IN THE SUPERIOR COURT OF THE STATE OF DELAWARE

CAROL WOODY and JAKE WOODY Plaintiff, -against- BRISTOL-MYERS SQUIBB COMPANY and PFIZER INC., Defendants.	:	CA No.: **JURY TRIAL DEMANDED**

COMES NOW Plaintiff, CAROL WOODY, who by and through the undersigned counsel hereby submits this Complaint against Bristol-Myers Squibb Company and Pfizer Inc., for compensatory and punitive damages, and such other relief deemed just and proper arising from the injuries of CAROL WOODY as a result of her exposure to the prescription drug ELIQUIS®. In support of this Complaint, Plaintiff alleges the following:

COMPLAINT

COMMON ALLEGATIONS

Plaintiffs, at all times relevant hereto, were and are citizens and residents of the State of CALIFORNIA, who suffered personal injuries as a result of Plaintiff CAROL WOODY's use of Eliquis.

INTRODUCTION

1. This action involves claims of personal injury, economic damages, punitive damages, and other claims of damage arising from injuries sustained by the Plaintiff, CAROL WOODY, as a direct and proximate result of both the defective nature of defendants BRISTOL-

MYERS SQUIBB COMPANY and PFIZER INC. pharmaceutical product, Eliquis, also known as apixaban.

PARTIES

2. At all times hereinafter mentioned the Plaintiff, CAROL WOODY (herein referred to as "Plaintiff"), was a citizen and resident of the State of CALIFORNIA, County of San Joaquin.

3. At all times hereinafter mentioned, the Plaintiff, JAKE WOODY, was and is the spouse of CAROL WOODY.

4. Upon information and belief, at all times hereinafter mentioned, defendant, BRISTOL-MYERS SQUIBB COMPANY ("BMS"), was and is a corporation organized and existing under the laws of the State of Delaware with a principal place of business at 345 Park Avenue, New York, New York 10154. Its registered agent for service of process is: c/o CT Corporation System, 111 8th Avenue, New York, NY 10011. Defendant BMS is the holder of the approved New Drug Application ("NDA") for Eliquis as well as the supplemental NDA.

5. As part of its business, BMS was and is involved in the research, development, sales, and marketing of pharmaceutical products including Eliquis.

6. Defendant PFIZER was and is in the business of and did design, research, manufacture, test, advertise, promote, market, sell, and distribute the drug Eliquis for use as an oral anticoagulant.

7. At all relevant times, Defendant BMS was in the business of and did design, research, manufacture, test, advertise, promote, market, sell and distribute the drug Eliquis for use as an oral anticoagulant.

8. Upon information and belief, at all times hereinafter mentioned, defendant, PFIZER INC. ("Pfizer"), was and is a corporation organized and existing under the laws of the

State of Delaware with its principal place of business at 235 East 42nd Street, New York, New York 10017. Its registered agent for service of process is: c/o CT Corporation System, 111 8th Avenue, New York, NY 10011.

9. Defendant PFIZER was and is in the business of and did design, research, manufacture, test, advertise, promote, market, sell and distribute the drug Eliquis for use as an oral anticoagulant.

10. In 2007, Defendants entered into a worldwide collaboration to "commercialize" apixaban (Eliquis), which they have promoted as combining BMS's "long-standing strengths in cardiovascular drug development and commercialization" with PFIZER's "global scale and expertise in this field."

PLAINTIFF-SPECIFIC FACTUAL BACKGROUND

11. Plaintiff CAROL WOODY was prescribed Eliquis, also known as apixaban, because of a diagnosis of atrial fibrillation. On or about November 21, 2014, Plaintiff CAROL WOODY suffered severe physical, economic, and emotional injuries as a result of Eliquis including, but not limited to, Plaintiff suffering from internal bleeding.

12. Specifically, plaintiff suffered a severe gastrointestinal bleeding event, which required hospitalization. Her treatment for this injury required extensive blood transfusions and an extended hospitalizaion.

13. As a direct and proximate result of Defendants' conduct, Plaintiff suffered and incurred harm including severe pain and suffered personal injuries and incurred damages which include severe pain and suffering, medical expenses and other economic and noneconomic damages.

14. Defendants, BRISTOL-MYERS SQUIBB COMPANY and PFIZER INC., (hereinafter collectively referred to as "Defendants") designed, researched, manufactured, tested, advertised, promoted, marketed, sold and distributed Eliquis, as well as dealt with governmental regulatory bodies.

15. In written information about the safety and risks of Eliquis, Defendants negligently and fraudulently represented to the medical and healthcare community, including Plaintiff's prescribing doctor, the Food and Drug Administration (hereinafter referred to as the "FDA") , to Plaintiff and the public in general, that Eliquis had been tested and was found to be safe and effective for its indicated uses. Defendants concealed their knowledge of Eliquis' defects, from Plaintiff, the FDA, the public in general and the medical community, including Plaintiff's prescribing doctor.

16. These representations were made by Defendants with the intent of defrauding and deceiving the Plaintiff, the public in general, and the medical and healthcare community including Plaintiff's prescribing doctor, and were made with the intent of inducing the public in general, and the medical community in particular, to recommend, dispense and purchase Eliquis, all of which evinced a callous, reckless, willful, depraved indifference to health, safety and welfare of the Plaintiff herein. The Plaintiff and the prescribing physicians were not aware of the falsity of these representations.

FACTUAL ALLEGATIONS APPLICABLE TO ALL COUNTS

17. Atrial fibrillation is a common arrhythmia (abnormal heart beat) that increases the risk of blood clot formation, which gives rise to the potential for embolism and increased risk for stroke.

18. For generations, warfarin (Coumadin) has been prescribed for its anticoagulation

effect by inhibiting certain clotting factors within the coagulation cascade. Warfarin works by blocking clotting factors that rely on Vitamin K. Vitamin K is used by multiple clotting factors to help the blood clot.

19. Coumadin can be carefully monitored and dose-adjusted by way of regular, routine monitoring of the prothrombin time ("PT") and International Normalization Ratio ("INR"). Eliquis' anticoagulation effect, in contrast, cannot be monitored at all. Additionally, unlike Eliquis, which has no publicly known antidote, the anticoagulation effects of Coumadin are reversible with the administration of vitamin K and/or the administration of coagulation factors such as fresh frozen plasma.

20. All anticoagulants have a risk of bleeding. Without an antidote, a bleed can quickly become a life-threatening situation. If a patient presents to the emergency room with a bleed on warfarin, doctors have a variety of options to choose from depending on how quickly they need to reverse anticoagulation. Because warfarin is a vitamin K antagonist, a patient on warfarin presenting with bleeding can have the anticoagulation effects completely reversed within a very short amount of time by administering vitamin K.

21. Although warfarin is quickly reversible in the event of a bleed, one drawback is the amount of monitoring. Patients taking warfarin must be monitored every few weeks. Doctors test the amount of time it takes for a patient's blood to clot using the prothrombin time test. The prothrombin test measures the International Normalized Ration (INR). A high INR indicates a high risk of uncontrollable bleeding; a low INR indicates a high risk for blood clots. In addition, patients taking warfarin must follow a strict diet since many green, leafy vegetable contain high amounts of Vitamin K.

22. Given the inconvenience of warfarin and because the costs of warfarin

plummeted after generic manufacturers entered the market, pharmaceutical companies saw an opportunity for profit so Defendants and other pharmaceutical manufacturers began the race to develop an alternative to warfarin.

23. The first novel oral anticoagulant approved in the United States was Pradaxa (dabigatran) in 2010, followed by Xarelto (rivaroxaban) in 2011, Eliquis (apixaban) in 2012, and most recently, Savaya (edoxaban) in 2015. Defendants received FDA approval to market Eliquis in 2012 (NDA 202155).

24. Overall, dispensed outpatient prescriptions for NOACs increased by 6.8% to 11.1 million in the fourth quarter of 2015, compared to 2014 Q1. By the fourth quarter of 2015, the four novel anticoagulants had captured 34% of the market, leaving 66% to warfarin. Among the new agents, rivaroxaban (Xarelto) led, with 17.5% of dispensed outpatient prescriptions, but apixaban (Eliquis) prescriptions increased four-fold over the time period and now account for 11.8% of dispensed outpatient prescriptions. For Eliquis, this 11.8% market share represents a 446.2% increase.

25. At all relevant times, Defendants were in the business of and did design, research, manufacture, test, advertise, promote, market, sell and distribute Eliquis as a "new" or "novel" oral anticoagulant, also known as a Factor Xa inhibitor. Factor Xa is another factor on the coagulation cascade and forms the thrombin, which is required for blood to clot. By inhibiting Factor Xa, Eliquis prevents thrombin from forming, which prevents blood from clotting.

26. Eliquis has two dosages—2.5 mg and 5 mg—approved by the FDA to reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. The FDA, in March 2014, expanded the indicated use for the prophylaxis of deep vein thrombosis, which may lead to pulmonary embolism, in patients who have undergone hip or knee replacement. And in August 2014, the FDA label added that Eliqus is indicated for the treatment of DVT and PE,

and for the reduction in the risk of recurrent DVT and PE following initial therapy. Among the uses for which Defendants obtained permission to market Eliquis was in the treatment of atrial fibrillation. Approval of Eliquis was based in large part on clinical trials known as ARISTOTLE.

27. The ARISTOTLE study was conducted under the supervision and control of Defendants in various countries including China. However, Defendants' agents committed fraud in their conduct of the ARISTOTLE study, by concealing side effects which occurred in test users of Eliquis; a death which went unreported (whereas one purpose of the study was to study the rate of death in Eliquis users compared to others in Coumadin); loss of subjects to follow up; major dispensing errors including indicating that certain subjects were getting Eliquis when they were not; poor overall quality control; and changing and falsifying records, including records disappearing just before the FDA made a site visit, reportedly on the order of an employee of BMS. Based upon information and belief, Defendants, as means of cutting costs, chose incompetent and untrustworthy agents in China to conduct the ARISTOTLE study.

28. More specifically, Defendants and their agents committed fraud in their conduct of the ARISTOTLE study, by *inter alia*, concealing side effects that occurred in test users of Eliquis; concealing a death which went unreported (whereas one purpose of the study was to study the rate of death in Eliquis users compared to others on Coumadin); concealing loss of subjects to follow up; concealing major dispensing errors including indicating that certain subjects were getting Eliquis when they were not; having poor overall quality control; and changing and falsifying records, including records disappearing just before the FDA made a site visit, reportedly on the order of an employee of BMS (who was later terminated).

29. At a Feb. 9, 2012 meeting between the FDA and BMS-Pfizer executives, the FDA is reported to have characterized the conduct of Defendants as showing a pattern of inadequate supervision.

30. When the application by defendants to the FDA was pending, in 2012, Dr. Thomas Marcinak, a physician in the FDA who reviewed the data submitted by defendants in order to obtain approval to market Eliquis, objected to missing data from the ARISTOTLE study and recommended that the labeling which defendants were going to use with the drug should discuss the quality control problems in ARISTOTLE, the Chinese study. Dr. Marciniak concluded in a December 2012 memorandum that because vital data—primarily involving deaths—was missing from the trial, the data problems "destroy our confidence" that Eliquis reduces the risk of death.

31. The label fails to disclose other, post-approval studies which criticize the results of ARISTOTLE study, including the findings regarding frequency and severity of bleeds on Eliquis.

32. Instead of admitting the major errors and frauds involved in the ARISTOTLE study, Defendants misleadingly stated publicly that they were submitting "additional data" to the FDA, and to this date have never publicly acknowledged the missing and incorrect data submitted to the FDA, and to this date have never publicly acknowledged the missing and incorrect data submitted to the FDA, which would be of concern to prescribing physicians and the public.

33. After employees of defendants wrote and submitted an article based on the ARISTOTLE study for the New England Journal of Medicine, the article was reportedly attacked for its accuracy and omissions by the former editor-in-chief of that journal, Arnold Relman, M.D., including the failure to show that Eliquis was any more efficacious than low-cost warfarin.

34. Critically, there is no antidote to Eliquis, unlike warfarin. Therefore, in the event of hemorrhagic complications, there is no available or validated reversal agent or antidote, as there is for Coumadin.

35. Defendants now market Eliquis as a new oral anticoagulant treatment

alternative to warfarin (Coumadin), a long-established safe treatment for preventing stroke and systemic embolism. Defendants emphasize the alleged benefits of treatment with Eliquis over warfarin, in that Eliquis does not require periodic monitoring with blood tests, that Eliquis does not limit a patient's diet, and Eliquis has a set dose that fits all patients. But studies from 2014 and beyond have called into question all of these perceived advantages.

36. The U.S. label approved when the drug was first marketed in the U.S. and at the time Plaintiff was using in 2014 it did not contain an adequate warning regarding the lack of antidote, and the significance of a bleeding event for patients who began to bleed, or how to potentially stop any bleeding events.

37. After the drug was approved by the FDA in 2012, Defendants engaged in an aggressive marketing campaign for Eliquis, including extensive marketing directly to the public, via TV and print. The chief promotional aspect of the sales pitch was that Eliquis reduced the risk of stroke more effectively than warfarin, than Eliquis was safer than warfarin, and that unlike with Coumadin, the blood levels of the patient did not need to be monitored.

38. In the course of these direct-to-consumer advertisements, Defendants over promoted Eliquis as a "one-size-fits all dosage," overstated the efficacy of Eliquis with respect to preventing stroke and systemic embolism, overstated and misrepresented fact that Eliquis has less major bleeding and stroke risk than warfarin, failed to adequately disclose to patients that there is no drug, agent, or means to reverse the anticoagulation effects of Eliquis, and that such irreversibility would have life-threatening and fatal consequences.

39. In 2013 and 2014, Defendants aired several direct to consumer commercials, including, but not limited to, "Reasons,"[1] and "Photographer,"[2] both of which included assertions

[1] *See* https://www.ispot.tv/ad/72Se/eliquis-reasons

that Eliquis reduced the risk of stroke more effectively than warfarin, than Eliquis was safer than warfarin, and that unlike with Coumadin, the blood levels of the patient did not need to be monitored. These ads were designed to influence patients, including the Plaintiff, to make inquiries to their prescribing physician about Eliquis and/or to request prescriptions for Eliquis.

40. In 2015 and 2016, Defendants aired several direct to consumer television advertisements, including, but not limited to, the "Bringing my Best,"[3] "Fisherman,"[4] and "Go for My Best"[5] spots, all of which portray Eliquis as the "best" treatment for Afib and importantly, a better and *safer* alternative to Warfarin. These ads were designed to influence patients, including the Plaintiff, to make inquiries to their prescribing physician about Eliquis and/or to request prescriptions for Eliquis.

41. These ads overstated that Eliquis has less major bleeding risk and less stroke risk than Warfarin, and failed to adequately disclose to patients that there is no drug, agent or means to reverse the anticoagulation effects of Eliquis and that such irreversibility could have life-threatening and fatal consequences.

42. Defendants' marketing materials suggest that Eliquis represents a therapeutic simplification and therapeutic progress of anticoagulation therapy because it does not require dosage adjustments, does not requires patients to undergo periodic monitoring with blood tests and because there were no dietary restrictions.

43. In essence, the Defendants created a new drug, Eliquis, which is not better than warfarin from a safety perspective, and marketed it as a superior safety choice that required no

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[2] *See* https://www.ispot.tv/ad/7gVA/eliquis-photographer

[3] *See* https://www.ispot.tv/ad/ABoE/eliquis-bringing-my-best

[4] *See* https://www.ispot.tv/ad/AMeG/eliquis-fisherman

[5] *See* https://www.ispot.tv/ad/AJaT/eliquis-go-for-my-best

blood test monitoring. The idea of this apparently easier-to-use anticoagulant evidently appealed to physicians, who were subject to extreme marketing and promotion by the Defendants, but ignores patient safety.

44. Prior to Plaintiff's use of Eliquis, Plaintiff became aware of the existence of Eliquis and its general claims, based upon his prescribing physician's recommendation of the use of this medication.

45. Based upon information and belief, prior to Plaintiff's use of Eliquis, Plaintiff's prescribing physician would have received promotional materials and information from sales representatives of Defendants that Eliquis was just as or even more effective as warfarin (Coumadin) in reducing strokes in patients with non-valvular atrial fibrillation, and was more convenient, without also adequately informing prescribing physicians of potential risk of underdoing and overdoing due to the "one-size-fits-all" dosages, that there was no reversal agent that could stop or control bleeding in patients taking Eliquis, and overstated and misrepresented fact that Eliquis has less major bleeding than warfarin. Further, Defendants failed to adequately and accurately convey the length of time in which patients must be off of Eliquis prior to any procedure. This pharmaceutical lacks an appropriate safety shield which has become a standard in the pharmaceutical industry.

46. At all times relevant hereto, Defendants also failed adequately to warn emergency room doctors, surgeons, and other critical care medical professionals that unlike generally-known measures taken to treat and stabilize bleeding in users of warfarin, there is no effective agent to reverse the anticoagulation effects of Eliquis, and therefore no effective means to treat and stabilize patients who experience uncontrolled bleeding while taking Eliquis.

POST-APPROVAL DATA

47. After marketing Eliquis, Defendants became aware of many reports of serious hemorrhaging in users of its drugs, both as reported to the FDA and to them directly. Yet Defendants have not fully disclosed to the medical profession or patients which the incidence of such adverse reactions are.

48. Indeed, in its September 25, 2015 QuarterWatch publication (which covers data from Quarters 3 and 4 of 2014), the Institute for Safe Medication Practices ("ISMP") noted that the following NOAC adverse events were reported for 2014:

		Direct to FDA		Death outcome		Embolic-thrombotic*		Hemorrhage*	
Drug	Total	Number, %		Number, %		Number, %		Number, %	
Rivaroxaban	3,331	525	15.8%	379	11.4%	1129	33.9%	1,647	49.4%
Dabigatran	3,592	188	5.2%	752	20.9%	721	20.1%	2,709	75.4%
Apixaban	1,014	95	9.4%	108	10.7%	224	22.1%	492	48.5%

*Standardized MedDRA queries (SMQ), broad scope

49. Thus, for 2014, Eliquis (apixaban) produced 1,014 adverse event reports compared to approximately 3,400 each for Rivaroxaban (Xarelto) and Dabigatran (Pradaxa).[6]

50. Though the volume of reports for Eliquis (apixaban) in 2014 was lower compared to other NOACs, that was due to the lower volume of prescriptions for Eliquis. Critically, the ISMP noted that "the differences with rivaroxaban (Xarelto) in percentage of deaths and total hemorrhage cases were small." Indeed, 108 of those adverse events were a death outcome (10.7%), 224 thrombotic events (22.1%) and 492 hemorrhage events (48.5%). This is critical because real-world signal data from Xarelto was also found to have a much high incidence of adverse events than reported in the clinical studies.[7]

51. Subsequently, in 2015, Eliquis produced more than 6,000 adverse event reports.

[6] *See* Institute for Safe Medication Practices, Quarterwatch, Q3-4 2014, Sept. 21, 2015, **Exhibit A** at 12, *available at* https://www.ismp.org/QuarterWatch/pdfs/2014Q4.pdf.

[7] Frank Siebelt, Hans Seidenstuecker, and Christoph Steitz. "Reports of side-effects from Bayer's Xarelto grow: Spiegel," **Exhibit B.**

Again, the dominant report was hemorrhaging, with gastrointestinal hemorrhaging a close second.

52. Nor was it found that Eliquis was safer than Warfarin in terms of potential bleeding events, as the Defendants claim. "We also compared the three novel anticoagulants to warfarin as a reference drug, and used logistic regression to adjust for other differences in the drugs' reports . . . [t]he other two novel anticoagulants also had increased odds of embolic-thrombotic events compared to warfarin, but less so: dabigatran (OR 1.45 $p < 0.001$); and apixaban (OR 1.58 $p < 0.01$)." [8]

53. Thus, it was determined that the risk of a bleeding event was increased by 1.58 fold for a patient on Eliquis compared to a patient on the venerable warfarin blood thinner. The Eliquis label and promotional materials do not accurately reflect this heightened risk.

54. The ISMP also found that Eliquis, when used in conjunction with commonly used platelet inhibitors [aspirin, NSAIDs, and SSRIs, among others], show a significantly increased risk of bleeding events compared to the Defendants' prior clinical data (ARISTOTLE). Specifically:

> In the adverse event data, we found that concomitant therapy with platelet inhibitors while taking anticoagulants increased the odds of a hemorrhage event by threefold (OR 3.01 $p < 0.01$). The increased risk was found across **all three of the newer anticoagulants** and warfarin.[9]

55. Whether this newly available, post-approval information regarding a higher than indicated risk was submitted to the FDA is unknown. This three-fold increased risk factor for bleeding when Eliquis is used in conjunction with platelet inhibitor therapy is higher than what is indicated in the Eliquis label (*See* Eliquis Label, Sec. 7.3: Drug Interaction)(noting that data on

[8] *See* Institute for Safe Medication Practices, Quarterwatch, Q3-4 2014, **Exhibit A, at 12**, *available ai* https://www.ismp.org/QuarterWatch/pdfs/2014Q4.pdf.

[9] *Id.* (emphasis added).

combination apixaban and platelet inhibitor therapy was limited, and indicating an increased risk of bleeding from 1.8% to 3.4%, or less than a two fold increase).

56. Defendants will assuredly suggest that because the ISMP's data regarding concomitant therapy includes all three NOACs, *none* of the data is applicable or it is somehow skewed. But the ISMP makes it clear: this increased risk of bleeding when used in conjunction with anti-platlet therapy was found across **all three** NOACs, which includes Eliquis. The Eliquis label and promotional materials do not accurately reflect this heightened risk.

57. Additionally, Section 7.3 of the medication guide for Eliquis is not a warning. It does not advise how or when to use combination therapy with Eliquis. It does not advise how commonly bleeding events will occur.

58. Nowhere in the warning label are any clear and definitive guidelines for whether to use these new anticoagulant drugs at the same time when a patient is taking one or more of the platelet inhibitors.

59. Indeed, the ISMP called this lack of clinical guidance into question in its annual 2014 report, stating:

> The prescribing information for all three drugs contains no guidance on the concomitant use of antiplatelet agents other than a warning that an increased risk of bleeding was observed. The unsolved problem of combination therapy was further illustrated by the clinical trials in which lower doses of the three novel anticoagulants were tested in high-risk heart patients with Acute Coronary Syndrome (ACS) but only when added to the established treatments using platelet inhibitors. **The apixaban trial was stopped because of excess bleeding and no identifiable benefits**.[10]

60. Therefore, this post-approval signal data, culled from real world usage rather than the controlled patient population of the ARISTOTLE study, shows a higher than indicated risk of

[10] Institute for Safe Medication Practices, Quarterwatch, Q3-4 2014, **Exhibit A**, at 12, *available at* https://www.ismp.org/QuarterWatch/pdfs/2014Q4.pdf

a bleeding event with or without combination therapy.

61. Nor is the ISMP the only study to dispute the findings of the ARISTOTLE trial data. In May 2016, post-approval, the British Medical Journal ("the BMJ") published a meta-analysis on the Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation.[11] It was found that when limited to stroke, NOACs were not significantly different from warfarin in terms of the increased risk of a stroke occurring.[12] This is in direct contradiction to the ARISTOTLE data and Defendants' promotional materials to consumers and physicians.

62. Ultimately, these post-approval statistics indicated a higher than expected signal of bleeding events for Eliquis in comparison to the pre-approval clinical trials, including higher than reported death and hemorrhage events.

63. In 2015, JAMA published a report critiquing the ARISTOTLE study and Defendants' promotions and claims of the reduced mortality benefit of Eliquis when opposed to Warfarin. Specifically, JAMA noted that "A clinical site in China taking part in a large trial of apixaban, a novel anticoagulant, had apparently altered patient records. If one were to exclude the data from the patients at that site [the China site location that was the subject of the controversy detailed above], the claim of a statistically significant mortality benefit disappears."[13] Thus, Defendants' reliance on the ARISTOTLE study remains flawed.

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[11] *See Generally* Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study, *BMJ* 2016; 353:i3189, **Exhibit C**, *available at* http://www.bmj.com/content/353/bmj.i3189

[12] *Id.* at 1. ("The hazard ratios for dabigatran and apixaban (2.8% and 4.9% annually, respectively) were non-significant compared with warfarin . . . No significant difference was found between NAOCs and warfarin for ischaemic stroke.")

[13] Seife C. (2015), *JAMA Internal Medicine*, Research misconduct identified by the US Food and Drug Administration: out of sight, out of mind, out of the peer-reviewed literature at 570, **Exhibit D,** *available at*

64. The FDA itself is conducting a study only recently begun in November 2016, involving investigation into the strong adverse event signal connection between Eliquis and vasculitis.[14]

65. Despite the clear signals generated by this side effect data collected after Eliquis' 2012 FDA approval, Defendants failed to either alert the public, the FDA and the scientific community or perform further investigation into the safety of Eliquis.

POST-APPROVAL CLINICAL CONCERNS REGARDING ELIQUIS AND ITS LABELING

66. Since its release in 2012, three primary clinical questions regarding Eliquis and its clinical data have emerged: (1) the "one size fits all" method of prescribing, (2) the total silence and lack of guidance on the label regarding what steps to take if a patient suffers a bleeding event, and (3) what to do if an Eliquis patient needs emergent surgery.

A. Stopping Bleeding Events.

67. In general, since its approval in 2012, there has been a growing concern amongst physicians regarding the absence of guidance for dealing with the unstoppable bleeds of Eliquis. A 2014 study noted that "[a] concern among clinicians is a *virtual absence of guidance* from clinical trials for reversing the anticoagulant effects of these drugs in clinical settings such as life-threatening bleeding or a need for emergent procedures that carry bleeding risk."[15]

68. In 2013, because of the lack of clinical guidance from the label on treatment of bleeding for patients on Eliquis, a group of Australian physicians pooled their data and formed a

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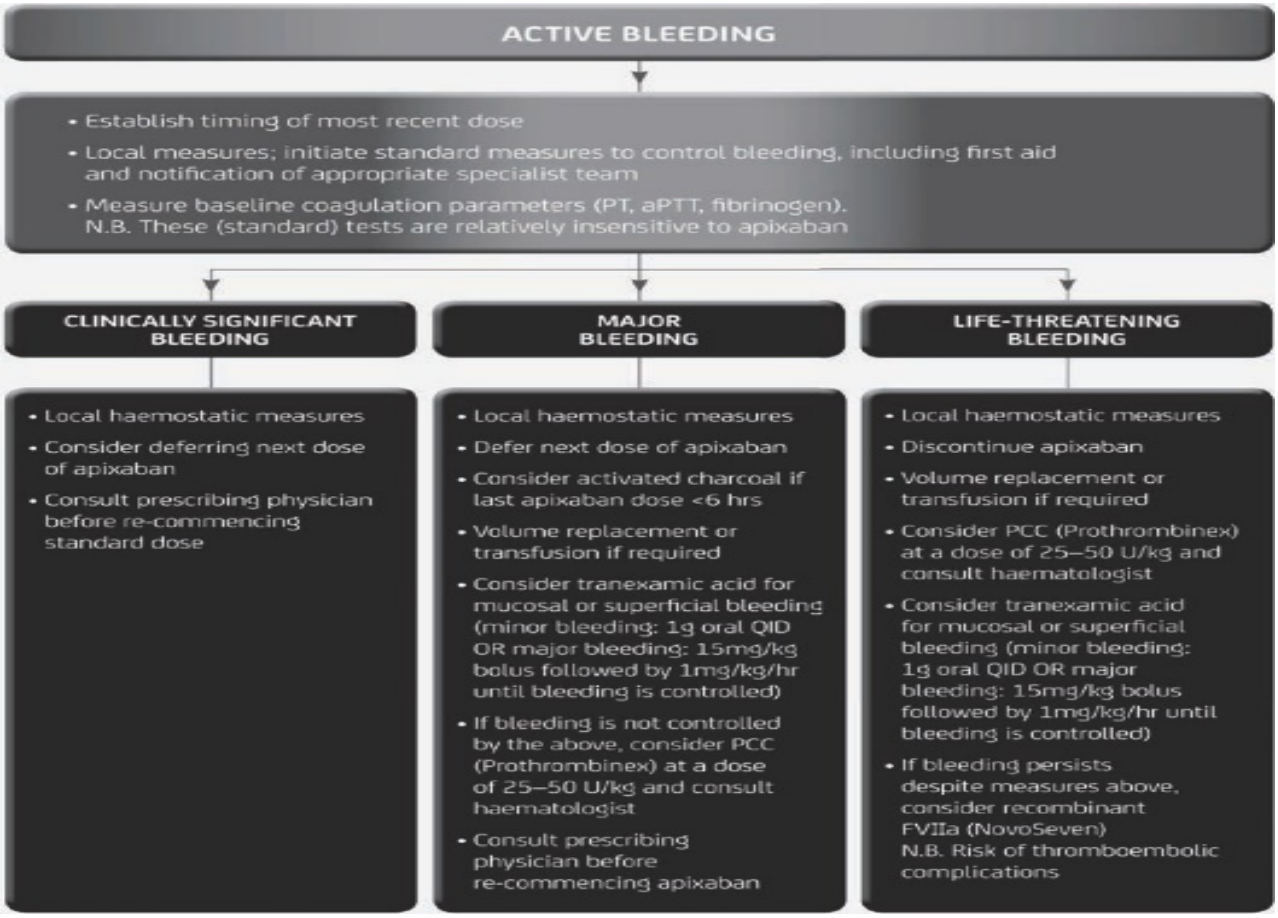
http://citeseerx.ist.psu.edu/viewdoc/download?doi=10.1.1.692.3512&rep=rep1&type=pdf.

[14] *See* http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm534355.htm

[15] *See* Jackson, Larry and Woody, Richard, Novel oral anticoagulants: pharmacology, coagulation measures, and considerations for reversal, *J. Thrombolysis* (2014) at 380, **Exhibit E**, at pp. 1.

consensus as to the methodology for the treatment of an Eliquis bleed[16]:



69. Despite a ballooning market share and a 400% increase in prescriptions of Eliquis in 2015, Defendants apparently cannot be bothered to detail specific information how to stop a potentially life threatening bleeding event in their clinical information.

70. To the extent the label does discuss these treatments, it states there is no experience with these potential avenues for treatment ("There is no experience with antifibrinolytic agents (tranexamic acid, aminocaproic acid) in individuals receiving

[16] *See* Ward, et al., Practical management of patients on apixaban: a consensus guide, **Exhibit F** at 4, *available at* https://thrombosisjournal.biomedcentral.com/articles/10.1186/1477-9560-11-27

apixaban…") or that these methods have not been evaluated in clinical studies ("Use of procoagulant reversal agents such as prothrombin complex concentrate, activated prothrombin complex concentrate, or recombinant factor VIIa may be considered but has not been evaluated in clinical studies.")(*See* Eliquis Label at Sec. 5.2). In short, physicians consider them potentially effective avenues to stop the serious injury or death of a patient from excessive bleeding, while Defendants cannot say either way.

71. Moreover, since the date Defendants received FDA approval to market Eliquis, Defendants made, distributed, marketed, and sold Eliquis without adequate warning to Plaintiff's prescribing physicians or Plaintiff that Eliquis was associated with and could cause life-threatening bleeding, presented a risk of life-threatening bleeding in patients who used it, and that Defendants had not adequately conducted complete and proper testing and studies of Eliquis with regard to severe side effects, specifically life threatening bleeding.

72. With no readily available reversal strategy, many patients, such as Plaintiff herein, have been substantially injured.

i. Antidotes or Lack Thereof.

73. An antidote for Eliquis bleeding events, not developed by defendants, was recently rejected by the FDA during phase III trials. No mention of this antidote is made. Defendants provided funding for the research and development of Portola Pharmaceuticals' AndexXa antidote to Eliquis bleeding.[17]

74. The FDA granted accelerated review of AndexXa.

75. However, in August 2016, the FDA rejected AndexXa's application for approval,

[17] *See Cardiology Today, FDA does not approve reversal agent for anticoagulation drugs,* August 18, 2016, **Exhibit G,** *available at* http://www.healio.com/cardiology/arrhythmia-disorders/news/online/%7B23c6c5c5-7a21-4fe3-825e-e59e1474ada8%7D/fda-does-not-approve-reversal-agent-for-anticoagulation-drugs

citing based on question marks associated with AndexXa's manufacturing and the need for additional review of various documents submitted by Portola.

76. It is unknown if AndexXa or any Eliquis antidote will ever be available. No warning or indication of this rejection was made in the label.

77. Nor is there any mention in the Eliquis label, medication guide or promotional material that a competing NOAC, Pradaxa, has an FDA approved antidote that is capable of stopping bleeding events.

78. Clinical studies found that with use of that antidote, praxbind, there was an immediate reduction in the amount of Pradaxa in the participants' blood (measured as unbound dabigatran plasma concentration) that lasted for a period of at least 24 hours.

79. Another trial included 123 patients taking Pradaxa who received this antidote due to uncontrolled bleeding or because they required emergency surgery. In this ongoing trial, based on laboratory testing, the anticoagulant effect of the Pradaxa was fully reversed in 89 percent of patients within four hours of receiving Praxbind.

80. The Eliquis label, packaging insert and marketing materials make no mention of this safer alternative NOAC.

B. "One (or two) size fits all" Dosing Concerns and Lack of Warning.

81. Significant Questions have also been as to the validity of the ARISTOTLE data and the Eliquis label regarding to the "one size fits all" dosing strategy. In the context of Daiichi's NOAC Savaysa, the FDA recently suggested that more tailored dosing would be beneficial to that drug, as well as all NOACs, including Eliquis. In a broader context, a 2015 study in the annals of hematology suggested that tailoring of dosage for each NOAC would be

beneficial.[18]

82. More critically, in February 2016, the British Medical Journal reported that both the European Medicines Agency ("EMA") and the FDA held meetings at the end of 2015 in order to discuss the need to measure blood levels (e.g. regularly monitor) of patients on NOACs and adjust the dose accordingly to maximize benefit and minimize harm to the patient.[19] Of course, such a change in therapy, although much safer, would negate one of the primary marketing advantages of Eliquis touted by Defendants—that no regular monitoring is required.

83. The BMJ further reported:

> A presentation to EMA last year by Robert Temple, deputy director for clinical science at the FDA's Center for Drug Evaluation and Research, suggests that the FDA believes there is a scientific argument for measuring the blood levels of these drugs and adjusting the dose. "Being too low leads to a stroke, a very bad outcome, and being too high leads to major bleeds, also bad, so that early optimization [of the dose] seems worthwhile[.]"[20]

84. The ISMP offered the same suggestion as early as 2014. "Also unanswered is whether apixaban safety could be further improved with individualizing the dose for each patient, as is done with warfarin." No mention of potential problems because of Eliquis' one size fits all dosing is mentioned in the label.

85. This is because the very nature of any anti-coagulant and its effect is to be "on edge." Too much anti-coagulation will cause excessive bleeding, while too little will not have the needed effect. That is why warfarin always required physicians to monitor the anti-coagulation level of each patient's blood. Further, as patients age or change over time, the needed dosage of warfarin would concurrently change.

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[18] *See* Schaefer, How to Choose Appropriate direct oral anticoagulant for patient with nonvalvular atrial fibrillation, **Exhibit H**, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4742513/

[19] *See British Medical Journal¸ Rivaroxaban: Can we Trust the Evidence?,* Feb. 6, 2016, at 181, **Exhibit I** *available at* http://www.bmj.com/bmj/section-pdf/914027?path=/bmj/352/8043/This_Week.full.pdf

[20] *Id.*

86. Eliquis is marketed as more convenient for patients because of its lack of regular monitoring, but that convenience does not make it safer. In fact it makes it less so. Because there are no monitoring requirements currently in place, in the hopes of being more convenient, virtually every patient is prescribed Eliquis to be taken twice per day. Therefore, the dosage for virtually all patients is not tailored to their specific needs, but instead fits into one of two "methods" of prescribing. Most A-Fib patients receive 5 mg of Eliquis to be taken twice per day. Certain other patients—those over 80, those weighing less than 132 lbs (61kg), or those who show a certain level of serum creatinine, the dose is 2.5 mg twice a day.

87. Those are the only two methods of dosing for Eliquis. This is in sharp contrast to warfarin, which tailors a specific dosage for every patient, and then monitors that dosage to ensure the correct amount of anti-coagulation is occurring.

88. Without a specifically tailored dose and regular monitoring, it is unclear if the correct and desire amount of anti-coagulation is occurring, leading to more bleeding events.

89. In sum, changing the method of monitoring to tailor the dosage of Eliquis seems to be a much safer alternative, and even the FDA believes specific patient tailoring may be needed to increase the safety of Eliquis to acceptable levels. But whether signal data regarding the above has been sent from Defendants to the FDA is unknown.

C. Surgery and Lack of Warnings or Data.

90. For a patient undergoing an emergency surgery, there is no guidance from defendants on how to approach measuring the level of anti-coagulation. Therefore, a patient requiring emergency surgery greatly increases their risk of complication if they are on Eliquis. No mention of this is made in the label.

91. Further, while the label does discuss the half-life of apixaban in a non-warning

context, certain studies indicate, in sharp contrast, that it is currently unknown what level of Eliquis would be considered safe for an elective surgery. "[A] 'safe' residual drug level of apixaban for surgery is presently unknown, and no test has been correlated with bleeding risk. As such, there is currently no known threshold at which apixaban patients' bleeding risk are able to be comparable to non-apixaban treated patients."[21]

92. Thus, despite the label's indication otherwise, it is unclear when a patient undergoing surgery may no longer be exposed to the higher risk of an Eliquis bleeding event, even after discontinuing using Eliquis.

93. Additionally, a patient who needs surgery may be exposed to a higher than indicated risk if bleeding occurs during the surgery. This is not indicated in the label. Again, this is newly available information and it is unknown if it has been disclosed to the FDA. But such information is not indicated in the label.

D. Miscellaneous Signal data and Failure to Warn.

94. Nor is any warning given that indicates that a patient using Eliquis who suffers a head injury may suffer an unstoppable, and potentially fatal, internal bleeding event. The only discussion of trauma is in the "patient medication guide," not officially part of the label, and certainly not a warning. The only mention of a head trauma is to say to call your physician immediately if a head trauma is suffered. But this is not a warning, nor does it explain or connect the supposed adequate bleeding warning to a potential head trauma.

95. No mention of an unstoppable bleed relating to a head injury is mentioned, nor is any mention made of the increased risk of a later than typical occurrence of a bleed mentioned. Thus, a patient could suffer a head trauma, not show immediate signs of internal bleeding, but

[21] *See* Ward, et al., Practical management of patients on apixaban: a consensus guide, **Exhibit F** at 4, https://thrombosisjournal.biomedcentral.com/articles/10.1186/1477-9560-11-27

develop such bleeding much later than expected while on Eliquis. The general bleeding warning, already inadequate, certainly does not cover this specific scenario.

96. Peer literature on this issue relating to Warfarin suggested that head trauma for a patient on Warfarin is not a concern once a CT-Scan is conducted and found to be clear. But for NOACs like Eliquis, where there is no method to measure the amount of anti-coagulation going on in a patient's system, there is believed to be a greater risk of a bleeding event occurring in the head even after a CT-Scan.

97. In sum, the warning label for Eliquis is inadequate. The original Eliquis label from December 2012 does not include a BLACK BOX warning for irreversible bleeding events, or that there is no antidote for such a bleeding event.

98. Importantly, warning labels as recently updated as July 2016 still do not include such a BLACK BOX or BOXED warning regarding unstoppable bleeding.

99. In contrast, Warfarin carries a black box warning of bleeding risk.

100. In addition to its failure to adequately and appropriately update its warning labels for the Eliquis product, Defendants have failed to issue a "Dear Doctor" letter that sufficiently outlines the dangers of prescribing and administering Eliquis to a patient.

101. The current warning is simply inadequate. The Defendants have failed and continue to fail in their duties to warn and protect the consuming public, including Plaintiff.

102. Even if the warnings were sufficient, which Plaintiff strongly denies, Eliquis still lacks any benefit sufficient to tolerate the extreme risk posed by the ingestion of this drug.

103. Eliquis is quite simply dangerous and defective as formulated and the Defendants should withdraw Eliquis from the market.

104. Therefore, Defendants' original and updated product labeling and prescribing

information for Eliquis:

a. failed to investigate, research, study, and define, fully and adequately, the safety profile of Eliquis;

b. failed to provide adequate warnings about the true safety risks associated with the use of Eliquis;

c. failed to provide adequate warning regarding the pharmacokinetic and pharmacodynamic variability of Eliquis and its complete effects on the degree of anticoagulation in patients of various populations;

d. failed to provide adequate warning that it is difficult or impossible to assess the degree and extent of anticoagulation in patients taking Eliquis;

e. failed to disclose in the "Warnings" section the significance of the fact that there is no drug, agent, or means to reverse the anticoagulation effects of Eliquis during an expanded timetable;

f. failed to advise prescribing physicians, such as the Plaintiff's physician, to instruct patients that there was no agent to reverse the anticoagulant effects of Eliquis;

g. failed to provide adequate instructions on how to intervene and stabilize a patient who suffers a bleed while taking Eliquis;

h. failed to provide adequate warnings and information related to the increased risks of bleeding events associated with aging patient populations of Eliquis users;

i. failed to provide adequate warnings regarding the increased risk of gastrointestinal bleeds in those taking Eliquis, especially, in those patients with a prior history of gastrointestinal issues and upset;

j. failed to provide adequate warnings regarding the need to assess renal functioning prior to starting a patient on Eliquis and to continue testing and monitoring of renal functioning periodically while the patient is on Eliquis;

k. failed to advise physicians to monitor their patients closely for signs of neurological impairment (meaning a potential stroke);

l. failed to provide adequate warnings regarding the increased risk of suffering a bleeding event, requiring blood transfusions in those taking Eliquis;

m. failed to provide adequate warnings regarding the need to assess hepatic functioning prior to starting a patient on Eliquis and to continue testing and monitoring of hepatic functioning periodically while the patient is on Eliquis;

n. failed to include a "BOXED WARNING" about serious bleeding events associated with Eliquis;

o. failed to include a "BOLDED WARNNG" about serious bleeding events associates with Eliquis;

p. Failed to appropriately warn about the connection between physical injuries, such as head trauma, and the initiation of bleeding events;

q. in their "Medication Guide" intended for distribution to patients to whom Eliquis has been prescribed, Defendants failed to disclose to patients that there is no drug, agent or means to reverse the anticoagulation effects of Eliquis and that if serious bleeding occurs, such irreversibility could have permanently disabling, life-threatening or fatal consequences;

r. failed to warn of the severity and duration of such adverse effects, as the warning given did not accurately reflect the symptoms or severity of side effects;

s. failed to warn regarding the need for more comprehensive, more regular medical monitoring to ensure early discovery and potentially serious side effects; and

t. failed to instruct how to adjust the dosage to the particular patient and instead stated misleadingly and inaccurately that one dosage fit all patients.

u. Failed to provide guidance on the concomitant use of antiplatelet agents, other than a limited interaction statement indicating that an increased risk of bleeding was observed during trials.

105. During the years since first marketing Eliquis in the U.S., Defendants modified the U.S. labeling and prescribing information for Eliquis, which included additional information regarding the use of Eliquis in patients taking certain medications. Despite being aware of: (1) serious, and sometimes fatal, irreversible bleeding events associated with the use of Eliquis; and

(2) more than 1,000 adverse event reports filed with the FDA in 2014 alone, including at least 100 deaths, Defendants nonetheless failed to provide adequate disclosures or warnings in their label as detailed in Paragraphs 1-105.

106. Despite the wealth of scientific evidence, Defendants have ignored the increased risk of the development of the aforementioned injuries associated with the use of Eliquis, but they have, through their marketing and advertising campaigns, urged consumers to use Eliquis without regular blood monitoring or instead of anticoagulants that present a safer alternative.

107. From the date Defendants received FDA approval to market Eliquis, Defendants made, distributed, marketed, and sold Eliquis without adequate warning to Plaintiff's prescribing physicians or Plaintiff that Eliquis was associates with and could cause life- threatening bleeding, presented a risk of life-threatening bleeding in patients who used it, and that Defendants had not adequately conducted complete and proper testing and studies of Eliquis with regard to severe side effects, specifically life threatening bleeding.

108. With no readily available reversal strategy, many patients, such as Plaintiff herein, have been substantially injured.

109. Despite the availability of this information, there is no indication of their usage in the warning label of Eliquis.

110. Upon information and belief, Defendants concealed and failed to completely well as its knowledge that they had failed to fully test or study said risk.

111. Defendants ignored the association between the use of Eliquis and the risk of developing life-threatening bleeding.

112. Defendants' failure to disclose information that they possessed regarding the failure to adequately test and study Eliquis for life-threatening bleeding risk further rendered

warnings for this medication inadequate.

113. By reason of the foregoing acts and omissions, Plaintiff has endured and continues to suffer emotional and mental anguish, loss of support, loss of services, medical and funeral expenses, and other economic and non-economic damages stemming from the injury of the Plaintiff, as a result of the actions and inactions of theDefendants.

FIRST CAUSE OF ACTION
MANUFACTURING DEFECT

114. Plaintiff incorporates by reference each preceding and succeeding paragraph as though set forth fully at length herein. Plaintiff pleads this Count in the broadest sense possible, pursuant to all laws that may apply pursuant to choice of law principles, including the law of the Plaintiff's resident State.

115. Eliquis was designed, manufactured, marketed, promoted, sold, and introduced into the stream of commerce by Defendants.

116. When it left the control of Defendants, Eliquis was expected to, and did reach the Plaintiff without substantial change from the condition in which it left Defendants' control.

117. Eliquis was defective when it left Defendants' control and was placed in the stream of commerce, in that there were foreseeable risks that exceeded the benefits of the product and/or that it deviated from product specifications and/or applicable federal requirements, and posed a risk of serious injury and death.

118. Specifically, Eliquis was more likely to cause serious bleeding that may be irreversible, permanently disabling, and life-threatening than other anticoagulants.

119. Plaintiff used Eliquis in substantially the same condition it was in when it left the control of Defendants and any changes or modifications were foreseeable by Defendants.

120. Plaintiffs and their healthcare providers did not misuse or materially alter their

Eliquis.

121. Defendants had a products liability duty to design, manufacture, and market products, including Eliquis, that were not unreasonably dangerous or defective, but which were safe for their users, including Plaintiff.

122. Defendants also had a products liability duty to provide adequate warnings and instruction for use regarding Eliquis. At the time of Plaintiff's injuries, Defendants' pharmaceutical drug Eliquis was defective and unreasonably dangerous to foreseeable consumers, including Plaintiff.

123. Defendants failed to exercise ordinary care in the design, manufacture, sale, labeling, warnings, marketing, promotion, quality assurance, quality control, and sale, distribution of Eliquis in that Defendants knew or should have known that the drugs created a high risk of unreasonable, dangerous side-effects and harm, including life-threatening bleeding, as well as other severe and personal injuries (including in some cases death) which are permanent and lasting in nature, physical pain, mental anguish, including diminished enjoyment of life.

124. The Defendants drug Eliquis was defective at the time of their manufacture, development, production, testing, inspection, endorsement, sale, and distribution, and at the time they left the possession of the Defendants, in that, and not by way of limitation, the products differed from the Defendants' intended result and intended design and specifications, and from other ostensibly identical units of the same product line.

125. At all times herein mentioned, the Defendants designed, researched, manufactured, tested, advertised, promoted, marketed, sold, and/or distributed Eliquis as hereinabove described that was used by the Plaintiff.

126. Defendants' Eliquis was expected to and did reach the usual consumers, handlers, and persons coming into contact with said product, including Plaintiff, without substantial

change in the condition in which it was produced, manufactured, sold, distributed, and marketed by the Defendants.

127. At those times, Eliquis was in an unsafe, defective, and inherently dangerous condition, which was unreasonably dangerous to users for its intended or reasonably foreseeable use, and in particular, the Plaintiff herein.

SECOND CAUSE OF ACTION
FAILURE TO WARN

128. Plaintiff incorporates by reference each preceding and succeeding paragraph as though set forth fully at length herein. Plaintiff pleads this Count in the broadest sense available under the law, to include pleading same pursuant to all substantive law that applies to this case, as may be determined by choice of law principles, regardless of whether arising under statute and/or common law.

129. Defendants failed to update warnings based on information received from product surveillance after Eliquis was first approved by the FDA and marketed, sold, and used in the United States and throughout the world.

130. Defendants are strictly liable for Plaintiff's injuries in the following ways in which they failed to adequately warn of the known dangers of Eliquis:

a. failed to investigate, research, study, and define, fully and adequately, the safety profile of Eliquis;

b. Failed to warn that it is believed that a more tailored dosing and blood test monitoring of Eliquis would increase safety and efficacy while reducing the risk of bleeding;

c. failed to provide adequate warnings about the true safety risks associated with the use of Eliquis;

d. failed to provide adequate warning regarding the pharmacokinetic and pharmacodynamic variability of Eliquis and its complete effects on

the degree of anticoagulation in patients of various populations;

e. failed to provide adequate warning that it is difficult or impossible to assess the degree and extent of anticoagulation in patients taking Eliquis, because even a blood test cannot determine the extent of anticoagulation occurring in a particular patient;

f. failed to disclose in the "Warnings" section the significance of the fact that there is no drug, agent, or means to reverse the anticoagulation effects of Eliquis during an expanded timetable;

g. failed to advise prescribing physicians, such as the Plaintiff's physician, to instruct patients that there was no agent to reverse the anticoagulant effects of Eliquis;

h. failed to provide adequate instructions on how to intervene and stabilize a patient who suffers a bleed while taking Eliquis;

i. failed to provide adequate warnings and information related to the increased risks of bleeding events associated with aging patient populations of Eliquis users;

j. failed to provide adequate warnings regarding the increased risk of gastrointestinal bleeds in those taking Eliquis, especially, in those patients with a prior history of gastrointestinal issues and upset;

k. failed to provide adequate warnings regarding the need to assess renal functioning prior to starting a patient on Eliquis and to continue testing and monitoring of renal functioning periodically while the patient is on Eliquis;

l. failed to advise physicians to monitor their patients closely for signs of neurological impairment (meaning a potential stroke);

m. failed to provide adequate warnings regarding the increased risk of suffering a bleeding event, requiring blood transfusions in those taking Eliquis;

n. failed to provide adequate warnings regarding the need to assess hepatic functioning prior to starting a patient on Eliquis and to continue testing and monitoring of hepatic functioning periodically while the patient is on Eliquis;

o. failed to include a "BOXED WARNING" about serious bleeding events associated with Eliquis;

p. failed to include a "BOLDED WARNNG" about serious bleeding events associates with Eliquis;

q. Failed to appropriately warn about the connection between physical injuries, such as head trauma, and the connection between that trauma and the initiation of a serious, and potentially fatal, bleeding event;

r. in their "Medication Guide" intended for distribution to patients to whom Eliquis has been prescribed, Defendants failed to disclose to patients that there is no drug, agent or means to reverse the anticoagulation effects of Eliquis and that if serious bleeding occurs, such irreversibility could have permanently disabling, life-threatening or fatal consequences;

s. failed to warn of the severity and duration of such adverse effects, as the warning given did not accurately reflect the symptoms or severity of side effects;

t. failed to warn regarding the need for more comprehensive, more regular medical and blood monitoring to ensure early discovery and potentially serious side effects; and

u. failed to instruct how to adjust the dosage to the particular patient and instead stated misleadingly and inaccurately that one dosage fit all patients.

v. Failed to provide guidance on the concomitant use of antiplatelet agents, other than a limited interaction statement indicating that an increased risk of bleeding was observed during trials.[22]

w. Indicated only a dangerous one-size fits almost all approach to doing instructions. For any separation of patient populations, it was grossly inaccurate and not representative of the true bleeding risks and dosage needs for these populations;

x. Failed to indicate that current, post-FDA approval signal data shows a much high risk for a bleeding event to occur than indicated in clinical studies;

y. failure to have tests available to determine and demonstrate

[22] The unsolved problem of combination therapy was further illustrated by the clinical trials in which lower doses of the three novel anticoagulants were tested in high-risk heart patients with Acute Coronary Syndrome (ACS) but only when added to the established treatments using platelet inhibitors. The Eliquis (apixaban) trial reviewing combination therapy with platelet inhibitors was stopped because of excess bleeding and no identifiable benefits.

therapeutic range;

z. Failure to advise testing for therapeutic range;

aa. Failure to provide a therapeutic range; and

bb. Failure to recommend testing and/or monitoring by providers for therapeutic range.

cc. Defendants failed to warn and place adequate warnings and instructions on Eliquis;

dd. Defendants failed to adequately give ***correct*** dosing instructions for different ages, renal impairments and weights, and instead gave inadequate dosing instructions for those populations ;

ee. Failed to warn that a safer NOAC with an effective, FDA approved antidote was available,

ff. Defendants failed to provide proper information as to the half-life of Eliquis and the amount of time that Eliquis should be discontinued prior to surgery;

gg. Defendants failed to provide proper warnings that the lack of a reversal agent can cause death; and

hh. Defendants failed to warn of the fraud and irregularities which occurred during the testing of Eliquis during the ARISTOTLE drug trials, and how such irregularities makes Defendants' data and claims unreliable.

131. By reason of the foregoing, Defendants have become strictly liable in tort to the Plaintiff for the marketing, promoting, distribution, and selling of a defective product, Eliquis, which Defendants placed on the market without adequate warnings. Defendants breached their duties by failing to provide a reasonably safe pharmaceutical and adequately warn of same. By virtue of the foregoing, Defendants are jointly and severally liable for Plaintiff's injuries.

132. A manufacturer exercising reasonable care would have updated its warnings on the basis of reports of injuries to individuals using Eliquis after FDA approval.

133. Plaintiffs used Eliquis for its approved purpose and in a manner normally intended and reasonably foreseeable by the Defendants.

134. Plaintiffs and Plaintiffs' healthcare providers could not, by the exercise of reasonable care, have discovered the defects or perceived their danger because the risks were not open or obvious.

135. Defendants, as the manufacturers and distributors of Eliquis, are held to the level of knowledge of an expert in the field.

136. The warnings that were given by Defendants were not accurate or clear, and were false and ambiguous.

137. The warnings that were given by the Defendants failed to properly warn physicians of the risks associated with Eliquis, subjecting Plaintiffs to risks that exceeded the benefits to the Plaintiffs. Plaintiffs, individually and through their physicians, reasonably relied upon the skill, superior knowledge and judgment of the Defendants.

138. Defendants had a continuing duty to warn Plaintiffs and their prescriber of the heightened dangers and inaccurate data associated with its product.

139. Had Plaintiffs or their healthcare providers received adequate warnings regarding the risks associated with the use of Eliquis, they would not have used it, used an NOAC with an antidote, or they would have used it with blood monitoring.

140. Defendants' inadequate warnings of Eliquis were acts that amount to willful, wanton, and/or reckless conduct by Defendants.

141. These aforementioned warning defects in Defendants' drug Eliquis were a proximate cause of Plaintiff's injuries.

142. As a result of the foregoing acts and omissions, Plaintiff was caused to

suffer serious and dangerous side effects including but not limited to, life-threatening bleeding, as well as other severe and personal injuries as well as physical pain and mental anguish, and diminished enjoyment of life, and financial expenses for hospitalization and medical care.

143. Defendants' conduct, as described above, was extreme and outrageous. Defendant's risked the lives of the consumers and users of their products, including Plaintiff, with knowledge of the safety and efficacy problems and suppressed this knowledge from the general public regarding the true risks of bleeding in different population. Defendants made conscious decisions not to redesign, re-label, warn or inform the unsuspecting consuming public. Defendants' outrageous conduct warrants an award of punitive damages.

THIRD CAUSE OF ACTION
PRODUCT LIABILITY- DESIGN DEFECT

144. At all times relevant hereto, Defendants designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, distributed and otherwise placed into the stream of commerce, pharmaceuticals, including Eliquis, for the sale to, and use by, members of the general public and specifically to Plaintiff. The Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by Defendants reached Plaintiff without substantial change and was ingested as directed.

145. The Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by Defendants was in an unreasonably and inherently dangerous, defective and unsafe condition, which was dangerous to others when it entered into the stream of commerce and was used by Plaintiff.

146. The Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by Defendants was defective in design and/or formulation, in that, when it left the hands of the Defendants, manufacturers and/or suppliers, the

foreseeable risks exceeded the benefits associated with the design or formulation of Eliquis.

147. The Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by Defendants was defective in design and/or formulation, in that, when it left the hands of the Defendants, manufacturers and/or suppliers, it was unreasonably dangerous, and it was more dangerous than an ordinary consumer would expect.

148. At all times relevant hereto, the Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by Defendants was, and still is, defective, unsafe and inherently dangerous and Defendants knew or should have known that Eliquis was, and still is, defective, unsafe and inherently dangerous, especially when used in the form and manner provided, directed, marketed and advertised by the Defendants.

149. Defendants, as manufacturers and distributors of pharmaceutical drugs, including Eliquis, are held to the level of knowledge of an expert in the field, and further, Defendants knew or should have known that warnings and other clinically relevant information and data which they distributed regarding the risks of irreversible bleeds and other injuries and death associated with the use of Eliquis were inadequate.

150. Defendants had and continue to have a duty to design and manufacture a product that was not unreasonable dangerous for its normal, usual and intended use.

151. Defendants designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed an unreasonably dangerous and defective prescription drug, Eliquis, which created an unreasonable risk to the health of consumers and to the Plaintiff, specifically; and Defendants are therefore strictly liable for the injuries sustained by the Plaintiff.

152. The Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by the Defendants reached their intended users in the

same defective and unreasonably dangerous condition in which it was manufactured.

153. The Plaintiff could not, by the exercise of reasonable care, have discovered Eliquis's defects herein and perceived its danger.

154. Defendants had and continue to have a duty to provide consumers, including Plaintiff and Plaintiff's physicians, with warnings and other clinically relevant information and data regarding the risks and dangers associated with Eliquis, as it became or could have become available to Defendants.

155. Defendants designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed an unreasonably dangerous and defective prescription drug, Eliquis, to health care providers empowered to prescribe and dispense Eliquis to consumers, including Plaintiff, without adequate warnings and other clinically relevant information and data.

156. As detailed above, through both omission and affirmative misstatements, Defendants misled the medical community about the risk and benefit balance of Eliquis, which resulted in injury to Plaintiff.

157. As noted above, Despite the fact that Defendants knew or should have known that Eliquis caused unreasonable and dangerous side effects, they continued to promote, market, label, advertise, distribute and sell Eliquis without stating that there existed safer and more or equally effective alternative drug products and/or providing adequate clinically relevant information and data and warnings regarding the adverse health risks associated with exposure to Eliquis.

158. The Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by the Defendants was defective due to inadequate postmarket surveillance and/or warnings because after Defendants knew or should have known of

the risks of serious side effects, the failed to provide adequate warnings to users and/or consumers of the product and continued to promote, market, advertise, distribute and sell Eliquis.

159. Defendants knew or should have known that consumers, including Plaintiff, would foreseeably and needlessly suffer injury as a result of Defendants' failures.

160. Defendants' defective design, manufacture, research, testing, advertising, promoting, marketing, labeling, sale, and distribution of Eliquis, as set forth herein, was done willfully, intentionally and with reckless disregard to the life and safety of Plaintiff and the general public.

A. Design Defect

120. Plaintiff incorporates by reference each preceding and succeeding paragraph as though set forth fully at length herein. Plaintiff pleads this Count in the broadest sense available under the law, to include pleading same pursuant to all substantive law that applies to this case, as may be determined by choice of law principles, regardless of whether arising under statute and/or common law.

121. At all times material to this action, Eliquis was designed, developed, manufactured, tested, packaged, promoted, marketed, distributed, labeled, and/or sold by Defendants in a defective and unreasonably dangerous condition at the time it was placed in the stream of commerce in ways which include, but are not limited to, one or more of the following particulars:

a. When placed in the stream of commerce, Eliquis contained unreasonably dangerous design defects and was not reasonably safe as intended to be used, subjecting Plaintiff to risks that exceeded the benefits of the subject product, including but not limited to permanent, personal, life-threatening injuries;

b. When placed in the stream of commerce, Eliquis was defective in design and formulation, making the use of Eliquis more dangerous than an ordinary consumer would expect, and more dangerous than other risks associated with the other medications and similar drugs on the market;

c. Eliquis's design defects existed before it left the control of the Defendants;

d. Eliquis was insufficiently tested;

e. Eliquis caused harmful side effects that outweighed any potential utility;

f. Eliquis was not accompanied by adequate instructions and/or warnings to fully apprise consumers, including Plaintiff herein, of the full nature and extent of the risks and side effects associated with its use, thereby rendering Defendants liable to Plaintiff; and

g. A feasible alternative design existed that was capable of preventing Plaintiff's injuries.

122. When it left the control of Defendants, Eliquis was expected to, and did reach Plaintiff without substantial change from the condition in which it left Defendants' control.

123. Eliquis was defective when it left Defendants' control and was placed in the stream of commerce, in that there were foreseeable risks that exceeded the benefits of the product and/or applicable federal requirements, and posed a risk of serious injury and death. There were conditions of Eliquis that rendered it unreasonably dangerous as designed, taking into consideration the utility of the product and the risk involved in its use.

124. Specifically, Eliquis was more likely to cause serious bleeding that may be irreversible, permanently disabling, and life-threatening more so than other anticoagulants as to patients in certain patient populations, including those with renal compromise, of a certain age and of certain weight. Additionally, Eliquis was designed with no reversal agent, so that in the event of a hemorrhagic bleed, there would be no method to reverse the bleeding, thus causing a potentially fatal bleeding episode. At all times herein mentioned, Eliquis was in a defective condition and unsafe, and Defendants knew or had reason to know that said product was defective and unsafe, especially when used in the form and manner as provided by the Defendants.

125. Eliquis as designed, researched, manufactured, tested, advertised, promoted, marketed, sold and distributed by Defendants was defective due to inadequate post-marketing surveillance and warnings because, after Defendants knew or should have known of the risks of serious side effects including, life-threatening bleeding, as well as other severe and permanent health consequences from Eliquis, they failed to provide adequate warnings to users or consumers of the product, and continued to improperly advertise, market and promote their product, Eliquis.

126. Eliquis was more likely to cause serious bleeding that may be irreversible, permanently disabling, and life-threatening more so than other anticoagulants.

127. The design defects render Eliquis more dangerous than other anticoagulants and cause an unreasonable increased risk of injury, including but not limited to life-threatening bleeding events.

128. The nature and magnitude of the risk of harm associated with the design of Eliquis, including risk of serious bleeding that may be irreversible, permanently disabling, and life- threatening is high in light of the intended and reasonably foreseeable use of Eliquis.

129. The risk of harm associated with the design of Eliquis are higher than necessary.

130. It is highly unlikely that Eliquis users and their prescribing physicians would be aware of the risks associated with Eliquis through either warning, general knowledge, or otherwise.

131. The intended or actual utility of Eliquis is not of such benefit to justify the risk of bleeding that may be irreversible, permanently disabling, and life-threatening.

132. Plaintiff used Eliquis in substantially the same condition it was in when it left

the control of Defendants and any changes or modifications were foreseeable by Defendants.

133. Plaintiff and her healthcare providers did not misuse or materially alter their Eliquis.

134. As a direct and proximate result of the use of Eliquis, Mrs. Matrazzo suffered serious physical injury (and death), harm, damages and economic loss, and Plaintiff will continue to suffer such harm, damages and economic loss in the future.

135. Defendants placed Eliquis into the stream of commerce with wanton and reckless disregard for public safety.

136. Eliquis was in an unsafe, defective, and inherently dangerous condition. Eliquis contains defects in its design which render the drug dangerous to consumers, when used as intended or as reasonably foreseeable to Defendants. The design defects render Eliquis more dangerous than other anticoagulants and cause an unreasonable increased risk of injury, including but not limited to life-threatening bleeding events.

137. Eliquis was in a defective condition and unsafe, and Defendants knew, had reason to know, or should have known that Eliquis was defective and unsafe, even when used as instructed.

138. The nature and magnitude of the risk of harm associated with the design of Eliquis, including the risk of serious bleeding that may be irreversible, permanently disabling, and life-threatening is high in light of the intended and reasonably foreseeable use of Eliquis.

139. It is highly unlikely that Eliquis users would be aware of the risks associated with Eliquis through either warnings, general knowledge or otherwise, and Plaintiff specifically was not aware of these risks, nor would Plaintiff have expected them.

140. Based on the foregoing, the Defendants are strictly liable to the Plaintiff for the

design, manufacture, research, testing, advertising, promoting, marketing, labeling, sale, and distribution of a defective product, Eliquis.

141. The foregoing defects in the drug Eliquis were a substantial factor in causing Plaintiff's injuries.

142. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff was caused to suffer serious and dangerous side effects, including severe and life-threatening bleeding, as well as other severe and personal injuries which were permanent and lasting in nature, physical pain, and mental anguish, diminished enjoyment of life, shortened life expectancy, and expenses for hospitalization.

143. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff suffered and incurred damages, including medical expenses; and other economic and non-economic damages flowing from the injuries of the Plaintiff.

144. Plaintiff pleads this Count in the broadest sense available under the law, to include pleading the same pursuant to all substantive law that applies to this case as may be determined by choice of law principles regarding or whether arising under statute and/or common law and reserves its rights to amend this cause of action or seek a court order to apply any applicable law of Plaintiff's home state.

FOURTH CAUSE OF ACTION
STRICT LIABILITY

161. At all times relevant hereto, Defendants designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, distributed and otherwise placed into the stream of commerce, pharmaceuticals, including Eliquis, for the sale to, and use by, members of the general public and specifically to Plaintiff.

162. The Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by Defendants reached Plaintiff without substantial change and was ingested as directed.

163. At those times, Eliquis was in an unsafe, defective, and inherently dangerous condition, which was dangerous to users, and in particular, the Plaintiff herein.

164. The Eliquis designed, researched, manufactured, tested, advertised, promoted, marketed, sold and distributed by Defendants was defective in design or formulation in that, when it left the hands of the manufacturer and/or suppliers, the foreseeable risks exceeded the benefits associated with the design or formulation of Eliquis.

165. The Eliquis designed, researched, manufactured, tested, advertised, promoted, marketed, sold and distributed by Defendants was defective in design and/or formulation, in that, when it left the hands of the Defendants manufacturers and/or suppliers, it was unreasonably dangerous, and it was more dangerous than an ordinary consumer would expect.

166. At all times herein mentioned, Eliquis was in a defective condition and unsafe, and Defendants knew or had reason to know that said product was defective and unsafe, especially when used in the form as provided by the Defendants.

167. Defendants knew, or should have known that at all times herein mentioned its Eliquis was in a defective condition, and was and is inherently dangerous and unsafe.

168. At the time of the Plaintiff's use of Eliquis, Eliquis was being used for the purposes and in a manner normally intended, namely to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, to reduce the risk of recurrence of DVT and/or PE, and for prophylaxis of DVT for patients undergoing hip and knee replacement surgery

169. Defendants, with this knowledge, voluntarily designed Eliquis in a dangerous condition for use by the public, and in particular the Plaintiff.

170. Defendants had a duty to create a product that was not unreasonably dangerous for its normal, intended use.

171. Defendants created a product unreasonably dangerous for its normal, intended use.

172. The Eliquis designed, researched, manufactured, tested, advertised, promoted, marketed, sold and distributed by Defendants was manufactured defectively in that Eliquis left the hands of Defendants in a defective condition and was unreasonably dangerous to its intended users.

173. The Eliquis designed, researched, manufactured, tested, advertised, promoted, marketed, sold and distributed by Defendants reached their intended users in the same defective and unreasonably dangerous condition in which the Defendants' Eliquis was manufactured.

174. Defendants designed, researched, manufactured, tested, advertised, promoted, marketed, sold and distributed a defective product which created an unreasonable risk to the health of consumers and to the Plaintiff in particular, and Defendants are therefore strictly liable for the injuries sustained by the Plaintiff.

175. The Plaintiff could not, by the exercise of reasonable care, have discovered Eliquis's defects herein mentioned and perceived its danger.

176. The Eliquis designed, researched, manufactured, tested, advertised, promoted, marketed, sold and distributed by Defendants was defective due to inadequate warnings or instructions as the Defendants knew or should have known that the product created a risk of serious and dangerous side effects including, life-threatening bleeding, as well as other severe and personal injuries which are permanent and lasting in nature and the Defendants failed to adequately warn of said risk.

177. The Eliquis ingested by Plaintiffs was in the same or substantially similar

condition as it was when it left the possession of Defendants.

178. Plaintiff did not misuse or materially alter their Eliquis.

179. Defendants are strictly liable for Plaintiffs' injuries in the following ways:

a. Eliquis as designed, manufactured, sold and supplied by the Defendants, was defectively designed and placed into the stream of commerce by Defendants in a defective and unreasonably dangerous condition;

b. Defendants failed to properly market, design, manufacture, distribute, supply and sell Eliquis;

c. Defendants failed to warn and place adequate warnings and instructions on Eliquis;

d. Defendants failed to adequately test Eliquis;

e. Defendants failed to provide timely and adequate post-marketing warnings and instructions after they knew of the risk of injury associated with the use of Eliquis, and,

f. A feasible alternative design and/or designs existed that was capable of preventing Plaintiff's injuries.

180. The Eliquis designed, researched, manufactured, tested, advertised, promoted, marketed, sold and distributed by Defendants was defective due to inadequate post-marketing surveillance and/or warnings because, after Defendants knew or should have known of the risks of serious side effects including, life-threatening bleeding, as well as other severe and permanent health consequences from Eliquis, they failed to provide adequate warnings to users or consumers of the product, and continued to improperly advertise, market and/or promote their product, Eliquis.

181. By reason of the foregoing, the Defendants have become strictly liable in tort to the Plaintiff for the manufacturing, marketing, promoting, distribution, and selling of a defective product, Eliquis.

182. Defendants' defective design, manufacturing defect, and inadequate warnings of

Eliquis were acts that amount to willful, wanton, and/or reckless conduct by Defendants.

183. That said defects in Defendants' drug Eliquis were a substantial factor in causing Plaintiff's injuries.

184. As a result of the foregoing acts and omissions, the Plaintiff was caused to suffer serious and dangerous side effects including, life threatening bleeding, as well as other severe and personal injuries which are permanent and lasting in nature, physical pain and mental anguish, and diminished enjoyment of life.

185. At all times relevant hereto, the Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by Defendants was, and still is, defective, unsafe and inherently dangerous and Defendants knew or should have known that Eliquis was, and still is, defective, unsafe and inherently dangerous, especially when used in the form and manner provided, directed, marketed and advertised by the Defendants.

186. Defendants, as manufacturers and distributors of pharmaceutical drugs, including Eliquis, are held to the level of knowledge of an expert in the field, and further, Defendants knew or should have known that warnings and other clinically relevant information and data which they distributed regarding the risks of irreversible bleeds and other injuries and death associated with the use of Eliquis were inadequate.

187. Defendants had and continue to have a duty to design and manufacture a product that was not unreasonable dangerous for its normal, usual and intended use.

188. Defendants designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed an unreasonably dangerous and defective prescription drug, Eliquis, which created an unreasonable risk to the health of consumers and to the Plaintiff, specifically; and Defendants are therefore strictly liable for the injuries sustained by the Plaintiff.

189. The Eliquis designed, manufactured, researched, tested, advertised, promoted,

marketed, labeled, sold, and distributed by the Defendants reached their intended users in the same defective and unreasonably dangerous condition in which it was manufactured.

190. The Plaintiff could not, by the exercise of reasonable care, have discovered Eliquis' defects herein and perceived its danger.

191. Defendants had and continue to have a duty to provide consumers, including Plaintiff and Plaintiff's physicians, with warnings and other clinically relevant information and data regarding the risks and dangers associated with Eliquis, as it became or could have become available to Defendants.

192. Defendants designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed an unreasonably dangerous and defective prescription drug, Eliquis, to health care providers empowered to prescribe and dispense Eliquis to consumers, including Plaintiff, without adequate warnings and other clinically relevant information and data.

193. As detailed above, through both omission and affirmative misstatements, Defendants misled the medical community about the risk and benefit balance of Eliquis, which resulted in injury to Plaintiff.

194. As noted above, Despite the fact that Defendants knew or should have known that Eliquis caused unreasonable and dangerous side effects, they continued to promote, market, label, advertise, distribute and sell Eliquis without stating that there existed safer and more or equally effective alternative drug products and/or providing adequate clinically relevant information and data and warnings regarding the adverse health risks associated with exposure to Eliquis.

195. The Eliquis designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, and distributed by the Defendants was defective due to inadequate

postmarket surveillance and/or warnings because after Defendants knew or should have known of the risks of serious side effects, the failed to provide adequate warnings to users and/or consumers of the product and continued to promote, market, advertise, distribute and sell Eliquis.

196. Defendants knew or should have known that consumers, including Plaintiff, would foreseeably and needlessly suffer injury or death as a result of Defendants' failures.

197. Defendants' defective design, manufacture, research, testing, advertising, promoting, marketing, labeling, sale, and distribution of Eliquis, as set forth herein, was done willfully, intentionally and with reckless disregard to the life and safety of Plaintiff and the general public.

198. Based on the foregoing, the Defendants are strictly liable to the Plaintiff for the design, manufacture, research, testing, advertising, promoting, marketing, labeling, sale, and distribution of a defective product, Eliquis.

199. The foregoing defects in the drug Eliquis were a substantial factor in causing Plaintiff's injuries.

200. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff was caused to suffer serious and dangerous side effects, including severe and life-threatening bleeding, as well as other severe and personal injuries which were permanent and lasting in nature, physical pain, and mental anguish, diminished enjoyment of life, shortened life expectancy, and expenses for hospitalization.

201. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff suffered and incurred damages, including medical expenses; and other economic and non-economic damages flowing from the injuries of the Plaintiff.

202. Plaintiff seeks all damages to which Plaintiff may be justly entitled.

FIFTHY CAUSE OF ACTION
NEGLIGENCE AND GROSS NEGLIGENCE

203. Plaintiff incorporates by reference each preceding and succeeding paragraph as though set forth fully at length herein. Plaintiff pleads this Count in the broadest sense available under the law, to include pleading same pursuant to all substantive law that applies to this case, as may be determined by choice of law principles, regardless of whether arising under statute and/or common law.

204. Defendants had a duty to exercise reasonable care in the design, manufacture, sale, labeling, warnings, marketing, promotion, quality assurance, quality control, and sale, distribution of Eliquis including a duty to assure that the product did not cause unreasonable, dangerous side-effects to users.

205. Defendants failed to exercise ordinary care in the design, manufacture, sale, labeling, warnings, marketing, promotion, quality assurance, quality control, and sale, distribution of Eliquis in that Defendants knew, or should have known, that the drugs created a high risk of unreasonable, dangerous side-effects and harm, including life-threatening bleeding, as well as other severe and personal injuries. Plaintiff suffered physical pain and mental anguish, and diminished enjoyment of life.

206. Defendants were well aware that if dosing instructions were not properly adjusted for age and information. Defendants' failure to provide a reasonably safe pharmaceutical, and Defendants' failure to adequately instruct or warn the users of the aforementioned dangers was negligent. Plaintiff's injuries and damages were a foreseeable, direct and proximate result of the negligence of Defendants.

207. Defendants, their agents, servants, and/or employees were negligent in the design, manufacture, sale, labeling, warnings, marketing, promotion, quality assurance, quality control,

and sale, distribution of Eliquis in that, among other things, they:

a. Failed to use due care in designing and manufacturing, and testing Eliquis (before placing it on the market) when Eliquis as used for treatment for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, reducing the risk of recurrence of DVT and/or PE so as to avoid the aforementioned risks to individuals;

b. Failed to analyze pre-marketing test data of Eliquis and convey the true risks of Eliquis based on the results of the testing conducted prior to placing Eliquis on the market;

c. As detailed above, failed to conduct sufficient post-marketing and surveillance of Eliquis in order to provide updated information to providers and patient populations, including currently available studies and adverse event information;

d. Failed to accompany the drug with proper warnings regarding all possible adverse side effects associated with its use, and the comparative severity and duration of such adverse effects, as well as the significance of the lack of a reversal agent for Eliquis. The warnings given did not accurately reflect the symptoms, scope or severity of the side effects; the warnings given did not warn Plaintiff and their healthcare providers regarding the need for blood monitoring, appropriate dose adjustments for various consumer groups, and further failed to fully and appropriately warn of the risk of serious bleeding that may be irreversible, and life-threatening, associated with Eliquis;

e. Failed to provide adequate training and instruction to medical care providers for the appropriate use of Eliquis;

f. Falsely and misleadingly overpromoted, advertised and marketed Eliquis as set forth herein including overstating efficacy, minimizing risk to influence patients, such as Plaintiff, to purchase and consume such product;

g. Manufacturing, producing, promoting, formulating, creating, and/or designing Eliquis without thoroughly testing it;

h. Manufacturing, producing, promoting, formulating, creating, and/or designing Eliquis without thoroughly testing it;

i. Not conducting sufficient testing programs to determine whether or not Eliquis was safe for use; in that Defendants herein knew or should have known that Eliquis was unsafe and unfit for use by reason of the dangers to its users;

j. Selling Eliquis without making proper and sufficient tests to determine the dangers to its users;

k. Negligently failing to adequately and correctly warn the Plaintiff, the public, the medical and healthcare profession, and the FDA of the dangers of Eliquis;

l. Failing to provide adequate instructions regarding safety precautions to be observed by users, handlers, and persons who would reasonably and foreseeably come into contact with, and more particularly, use, Eliquis;

m. Failing to adequately, sufficiently and properly test Eliquis;

n. Negligently advertising and recommending the use of Eliquis without sufficient knowledge as to its dangerous propensities;

o. Negligently representing that Eliquis was safe for use for its intended purpose, when, in fact, it was unsafe;

p. Negligently representing that Eliquis had equivalent safety and efficacy as other forms of treatment for patients taking blood-thinning medication;

q. Negligently designing Eliquis in a manner which was dangerous to its users;

r. Negligently manufacturing Eliquis in a manner which was dangerous to its users;

s. Negligently producing Eliquis in a manner which was dangerous to its users;

t. Concealing information from Plaintiff showing that Eliquis was unsafe, dangerous, and/or non-conforming with FDA regulations;

u. Improperly concealing and/or misrepresenting information from the Plaintiff, healthcare professionals (including Ms. Woody's prescribing physicians), and/or the FDA, concerning the severity of risks and dangers of Eliquis compared to other forms of treatment for blood-thinning; and,

v. Placing an unsafe product into the stream of commerce.

w. Defendants under-reported, underestimated and downplayed the serious dangers of Eliquis.

208. Defendants negligently compared the safety risk and/or dangers of Eliquis

with other forms of treatment of blood thinners.

209. Defendants were negligent in the designing, researching, supplying, manufacturing, promoting, packaging, distributing, testing, advertising, warning, marketing and sale of Eliquis in that they:

a. Failed to use due care in designing and manufacturing Eliquis so as to avoid the aforementioned risks to individuals when Eliquis was used for treatment for reducing the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation, reducing the risk of recurrence of DVT and/or PE, and for prophylaxis of DVT for patients undergoing hip and knee replacement surgery;

b. failed to accompany their product with proper and/or accurate warnings regarding all possible adverse side effects associated with the use of Eliquis;

c. Failed to accompany their product with proper warnings regarding all possible adverse side effects concerning the failure and/or malfunction of Eliquis;

d. Failed to accompany their product with accurate warnings regarding the risks of all possible adverse side effects concerning Eliquis;

e. Failed to warn Plaintiff and/or his physician of the severity and duration of such adverse effects, as the warnings given did not accurately reflect the symptoms, or severity of the side effects;

f. Failed to conduct adequate testing, including pre-clinical and clinical testing and post-marketing surveillance to determine the safety of Eliquis;

g. failed to warn Plaintiff and/or his physician, prior to actively encouraging the sale of Eliquis, either directly or indirectly, orally or in writing, about the need for more comprehensive, more regular medical monitoring than usual or of the risks of hemorrhagic events to ensure early discovery of potentially serious side effects;

h. Failed to provide full and appropriate dosing guidelines for all consumer groups;

i. Failed to warn that the lack of a reversal agent was likely to cause injury or death;

j. Failed to warn that it is believed that a more tailored dose of Eliquis would increase safety and efficacy while reducing the risk of bleeding;

k. Over promoted and inaccurately promoted the product;

l. Were otherwise careless and/or negligent.

210. Despite the fact that Defendants knew or should have known that Eliquis caused unreasonable, dangerous side-effects which many users would be unable to remedy by any means, Defendants continued to market Eliquis to consumers, including the medical community and Plaintiff.

211. Defendants knew or should have known that consumers such as Plaintiff would foreseeably suffer injury as a result of Defendants' failure to exercise ordinary care as described above, including the failure to comply with federal requirements.

212. It was foreseeable that Defendants' product, as designed, would cause serious injury to consumers, including Plaintiff.

213. As a direct and proximate result of Defendants' negligence, Plaintiff suffered serious physical injury, and the Plaintiffs will continue to suffer damages and economic loss in the future. Defendants are jointly and severally liable in negligence for Plaintiff's injuries and for general and special damages proximately caused by such negligence, in such amounts as shall be determined at trial.

214. Defendants' conduct, as described above, was extreme and outrageous. Defendants risked the lives of the consumers and users of their products, including Plaintiff, with the knowledge of the safety and efficacy problems and suppressed this knowledge from the general public. Defendants made conscious decisions not to redesign, re-label, warn, or inform the unsuspecting consuming public. Defendants' outrageous conduct constitutes gross negligence which warrants an award of punitive damages.

215. Plaintiff pleads this Count in the broadest sense available under the law, to include pleading the same pursuant to all substantive law that applies to this case as may be determined by choice of law principles regarding or whether arising under statute and/or common law and reserves its rights to amend this cause of action or seek a court order to apply any applicable law of Plaintiff's home state. WHEREFORE, Plaintiff demands judgment against all named Defendants, jointly and severally, for compensatory and punitive damages, together with interest, costs of suit, attorneys' fees and all such other relief as the Court deems proper.

SIXTH CAUSE OF ACTION
NEGLIGENCE – FAILURE TO WARN

216. Plaintiff incorporates by reference each preceding and succeeding paragraph as though set forth fully at length herein.

217. Defendants owed a duty to the general public, and specifically to Plaintiff, to exercise reasonable care to warn of the dangerous conditions and/or of the facts that made Eliquis likely to be dangerous.

218. Defendants owed a continuing duty to warn Plaintiff, prescribing physicians and the general public, of the dangers associated with Eliquis.

219. At all times relevant hereto, including the time period before Plaintiff ingested Eliquis, and during the time period in which he took Eliquis, Defendants knew or should have known that Eliquis was dangerous and created an unreasonable risk of bodily harm to consumers, including the Plaintiff.

220. The Defendants and their agents, servants and/or employees, breached their duty of care and were negligent by, but not limited to, the following acts, misrepresentations, and/or omissions:

a. Failing to provide proper, accurate or adequate warnings or labeling regarding

all possible adverse side effects and health risks associated with the use of Eliquis;

b. Failing to provide proper, accurate or adequate warnings or labeling regarding the comparative severity and duration of the adverse side effects and health risks associated with the use of Eliquis;

c. Failing to provide proper, accurate or adequate rate of incidence or prevalence of irreversible bleeds;

d. Failing to accompany their product with all proper, accurate or adequate warnings or labeling regarding all possible adverse side effects, health risks and/or rate of incidence or prevalence of irreversible bleeds associated with the use of Eliquis and the comparative severity and duration of same;

e. Failing to provide proper, accurate or adequate warnings regarding the need to assess renal functioning prior to starting a patient on Eliquis and to continue testing and monitoring of renal functioning periodically while the patient is on Eliquis;

f. Failing to provide proper, accurate or adequate warnings regarding the need to assess hepatic functioning prior to starting a patient on Eliquis and to continue testing and monitoring of hepatic functioning periodically while the patient is on Eliquis;

g. Failing to provide proper, accurate or adequate warnings to the Plaintiff, Plaintiff's physicians, the general public and the medical profession at large, that Eliquis's risk of harm was unreasonable and that there were safer and more effective alternative medications available to Plaintiff and other consumers;

h. Failing to provide proper, accurate or adequate warnings to the Plaintiff, Plaintiff's physicians, the general public and the medical profession at large, about the need for comprehensive, regular medical monitoring to ensure early discovery of potentially serious and/or fatal dangerous side effects associated with the use of Eliquis.

i. Failed to warn that it is believed that a more tailored dose of Eliquis would increase safety and efficacy while reducing the risk of bleeding;

221. Eliquis was defective and unreasonably dangerous when it left the possession of the Defendants in that it contained warnings insufficient to alert patients and prescribing physicians of the dangerous risks and reactions associated with Eliquis, including but not

limited to the prevalence of irreversible bleeding, and other serious injuries and side effects despite Defendants' knowledge of the increased risk of these injuries over other anticoagulation therapies available.

222. Eliquis was defective due to inadequate post-marketing warnings and instruction because Defendants knew or should have known of the risk and danger of serious bodily harm and or death from the use of Eliquis but failed to provide an adequate warning to patients and prescribing physicians of the product, knowing the product could cause serious injury and or death.

223. The warnings that were given by Defendants were not accurate, clear, complete, and/or were ambiguous.

224. The warnings, or lack thereof, that were given by Defendants failed to properly warn prescribing physicians of the risk of irreversible bleeding and other serious injuries and side effects, and failed to instruct prescribing physicians to test and monitor for the presence of the injuries for which Plaintiff and others had been placed at risk, as set forth herein.

225. Plaintiff, individually and through her prescribing physicians, reasonably relied upon the skill, superior knowledge, and judgment of Defendants.

226. Plaintiff was prescribed and used Eliquis for its intended purpose.

227. Plaintiff consumed the Eliquis as directed and without change in its form or substance.

228. Plaintiff could not have known about the dangers and hazards presented by Eliquis

229. Had Plaintiff received adequate warnings regarding the risks of Eliquis, he would not have used Eliquis.

230. Likewise, if Plaintiff's prescribing physicians received adequate warnings regarding the risks of Eliquis, Plaintiff's prescribing physicians would not have recommended, prescribed, dispensed, administered and/or relied on the drug, Eliquis.

231. Eliquis' ability to cause serious personal injuries and damages, such as those suffered by Plaintiff, was not due to any voluntary action or contributory negligence of Plaintiff.

232. As a direct and proximate result of Eliquis' defective, inaccurate, inadequate, incomplete and inappropriate warnings, Plaintiff has suffered severe physical injuries, harm, economic loss and damages as described herein.

233. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff was caused to suffer serious and dangerous side effects, including severe and life-threatening bleeding, as well as other severe and personal injuries which were permanent and lasting in nature, physical pain, and mental anguish, diminished enjoyment of life, shortened life expectancy, and expenses for hospitalization.

234. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff suffered and incurred damages, including medical expenses; and other economic and non-economic damages flowing from the injuries of the Plaintiff.

235. Plaintiff seeks all damages to which Plaintiff may be justly entitled.

236. Plaintiffs plead this Count in the broadest sense available under the law, to include pleading the same pursuant to all substantive law that applies to this case as may be determined by choice of law principles regarding or whether arising under statute and/or common law and reserves its rights to amend this cause of action or seek a court order to apply any applicable law of Plaintiff's home state.

SEVENTH CAUSE OF ACTION
BREACH OF EXPRESS WARRANTY

237. Plaintiff incorporates by reference each preceding and succeeding paragraph as though set forth fully at length herein.

238. Defendants designed, tested, manufactured, sold, distributed, marketed and promoted that Eliquis was were safe and efficacious for its intended uses. The Eliquis consumed by Plaintiff reached him without substantial change in its condition, and was used by Plaintiff as intended by Defendants. Defendants expressly and impliedly warranted that Eliquis was not unreasonably dangerous and instead were merchantable and fit for its intended use by Plaintiff. Further, Defendants expressly and impliedly warranted that Eliquis had been fully and adequately tested for long-term use and was, *inter alia,* safe to use in the treatment of atrial fibrillation.

239. At all times relevant hereto, Defendants designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, distributed and otherwise placed into the stream of commerce, the prescription drug, Eliquis.

240. Defendants expressly warranted in their labeling, product insert, materials disseminated to both Plaintiff and Plaintiff's physicians, and to the general public via direct to consumer advertising (as noted above) that Eliquis was safe and effective to Plaintiff and to other members of the general and consuming public.

241. Defendants expressly warranted that Eliquis was a safe and effective product to be used as a blood thinner, and did not disclose the extent of the risk that Eliquis could cause serious bleeding that may be irreversible, permanently disabling, and life-threatening. The representations made were not justified by the performance of Eliquis.

242. Defendants expressly warranted that Eliquis was safe and effective to use without the need for blood monitoring and dose adjustments.

243. Defendants marketed, promoted, sold, distributed and/or otherwise released into the stream of commerce, Eliquis as a safe and effective product.

244. Defendants expressly represented to Plaintiff, Plaintiff's physicians, the general public and the medical profession at large, that Eliquis was safe and fit for use for the purposes intended, that it was of merchantable quality, that it did not produce any dangerous side effects in excess of those risks associated with other forms of treatment for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, reducing the risk of recurrence of DVT and/or PE and for prophylaxis of DVT for patients undergoing hip and knee replacement surgery, that the side effects it did produce were accurately reflected in the warnings and that it was accurately tested and fit for its intended use.

245. Eliquis does not conform to those representations made by Defendants because it is not safe and has numerous serious side effects, including life-threatening and irreversible bleeding events.

246. The Defendants and their agents, servants and/or employees, breached their express warranty by, but not limited to, the following acts, misrepresentations, and/or omissions:

a. Designing, manufacturing, advertising, promoting, marketing, labeling, selling, distributing and otherwise placing into the stream of commerce, Eliquis in an defective and unreasonably dangerous condition;

b. Failing to warn and/or place accurate and adequate warnings and instructions on Eliquis, as described above;

c. Failing to adequately test Eliquis;

d. Failing to provide timely and adequate post-market warnings and instructions after they knew the risk of injury from Eliquis was higher than their pre-approval data showed.

e. Overpromoting and inaccurately promoting the Eliquis product as a safer alternative to warfarin and other anti-coagulants.

247. Members of the medical community, including Plaintiff's prescribing physicians, relied upon the representations and warranties of the Defendants for use of Eliquis in recommending, prescribing and/or dispensing Eliquis to their patients, including the Plaintiff.

248. Plaintiff, and other members of the general and consuming public were the intended third-party beneficiaries of the warranty.

249. Plaintiff relied on the representations and warranties of the Defendants that Eliquis was safe and effective when he took the medication.

250. Plaintiff's injuries were the direct and proximate result of the Defendants' breach of their express warranties.

251. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff was caused to suffer serious and dangerous side effects, including severe and life-threatening bleeding, as well as other severe and personal injuries which were permanent and lasting in nature, physical pain, and mental anguish, diminished enjoyment of life, shortened life expectancy, and expenses for hospitalization.

252. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff suffered and incurred damages, including medical expenses; and other economic and non-economic damages flowing from the injuries of the Plaintiff.

253. Defendants breached these warranties as Eliquis was not merchantable, was unfit for its intended use, and was unreasonably dangerous when comparing the benefits Eliquis to the risks associated with its use. As a direct and proximate result of these breaches of warranties, Plaintiff was injured.

254. Plaintiff pleads this Count in the broadest sense available under the law, to include pleading the same pursuant to all substantive law that applies to this case as may be determined by choice of law principles regarding or whether arising under statute and/or common law and reserves its rights to amend this cause of action or seek a court order to apply any applicable law of Plaintiff's home state. WHEREFORE, Plaintiff demands judgment against all named Defendants, jointly and severally, for compensatory and punitive damages, together with interest, costs of suit, attorneys' fees and all such other relief as the Court deems proper.

EIGHTH CAUSE OF ACTION
BREACH OF IMPLIED WARRANTY

255. Plaintiff incorporates by reference each preceding and succeeding paragraph as though set forth fully at length herein.

256. At all times relevant hereto, Defendants designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, distributed and otherwise placed into the stream of commerce, the prescription drug, Eliquis.

257. At all times that Defendants designed, manufactured, researched, tested, advertised, promoted, marketed, labeled, sold, distributed and otherwise placed into the stream of commerce, the prescription drug, Eliquis, they knew of its intended uses to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, reduce the risk of recurrence of DVT and/or PE and for prophylaxis of DVT for patients undergoing hip and knee replacement surgery.

258. Defendants impliedly represented and warranted Eliquis to Plaintiff, Plaintiff's physicians, the general public and the medical profession at large, that Eliquis was safe and of merchantable quality and was fit for use for the ordinary purposes for which the product was to be used, as set forth above.

259. Members of the consuming public, including consumers such as Plaintiffs, were intended third party beneficiaries of the warranty.

260. Eliquis was not merchantable and fit for its ordinary purpose, because it has a propensity to lead to the serious personal injuries described in this Complaint.

261. Eliquis does not conform to those representations and warranties made by Defendants because it is not safe, not of merchantable quality, not fit for its intended uses, and has numerous serious side effects, including life-threatening and irreversible bleeding events.

262. Defendants' implied representations and warranties were false, misleading, and inaccurate because Eliquis was unsafe, unreasonably dangerous, improper, not of merchantable quality, not fit for its intended uses and defective.

263. Members of the medical community, including Plaintiff's prescribing physicians, relied upon the implied representations and warranties of the Defendants for use of Eliquis in recommending, prescribing and/or dispensing Eliquis to their patients, including the Plaintiff.

264. Plaintiffs and Plaintiff's prescribing physicians reasonably relied on Defendants' representations that Eliquis was safe and free of defects and was a safe means of reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation, to treat Deep Vein Thrombosis ("DVT") and Pulmonary Embolism ("PE"), to reduce the risk of recurrence of DVT and/or PE, and for prophylaxis of DVT for patients undergoing hip and knee replacement surgery.

265. Plaintiff, and other members of the general and consuming public were the intended third-party beneficiaries of the warranty.

266. Plaintiff relied on the representations and warranties of the Defendants that Eliquis was safe and effective for treatment of non-valvular atrial fibrillation when he took the

medication.

267. Defendants' breach of their implied warranties of merchantability and fitness for a particular purpose were the direct and proximate result of the Plaintiff's injuries.

268. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff was caused to suffer serious and dangerous side effects, including severe and life-threatening bleeding, as well as other severe and personal injuries which were permanent and lasting in nature, physical pain, and mental anguish, diminished enjoyment of life, shortened life expectancy, and expenses for hospitalization.

269. As a direct and proximate result of the actions and omission of the Defendants described herein, Plaintiff suffered and incurred damages, including medical expenses; and other economic and non-economic damages flowing from the injuries of the Plaintiff.

270. Plaintiff seeks all damages to which Plaintiff may be justly entitled.

271. Plaintiffs plead this Count in the broadest sense available under the law, to include pleading the same pursuant to all substantive law that applies to this case as may be determined by choice of law principles regarding or whether arising under statute and/or common law and reserves its rights to amend this cause of action or seek a court order to apply any applicable law of Plaintiff's home state. WHEREFORE, Plaintiffs demand judgment against all named Defendants, jointly and severally, for compensatory and punitive damages, together with interest, costs of suit, attorneys' fees and all such other relief as the Court deems proper.

NINTH CAUSE OF ACTION
FRAUD/FRAUDULENT CONCEALMENT

272. Plaintiff incorporates by reference each preceding and succeeding paragraph as though set forth fully at length herein.

273. Prior to Plaintiff's use of Eliquis and during the period in which Plaintiff actually

used Eliquis, Defendants fraudulently suppressed material information regarding the safety and efficacy of Eliquis.

274. Defendants falsely and fraudulently represented to the medical and healthcare community, and to Plaintiff, the FDA, and the public in general, that said product, Eliquis, had been tested and was found to be safe and/or effective to reduce the risk of stroke and systemic embolism in patients required to take blood-thinning medications. Further, Defendants represented that the product had been adequately tested and evaluated in the ARISTOTLE study, and that the product was safe even though there was no reversal agent for the medication. Specifically, the fraudulent statements include, but are not limited to, the following:

a. Website – www.eliquis.com - https://www.eliquis.com/eliquis/hcp/stroke- risk-reduction-nvaf/efficacy - Defendants published "For patients with Nonvalvular Atrial Fibrillation (NVAF), Eliquis was proven effective in 2 Phase III studies." Defendants then cited to the "ARISTOTLE Study Primary Efficacy Endpoint" for justification of this representation as well as for its representation of its "superiority to warfarin." Defendants intentionally misled consumers and prescribers by citing to this highly flawed ARISTOTLE study. Specifically, in the ARISTOTLE study sponsored by Defendants, there were unreported or late-reported serious side effects, and then one of Defendant's site managers instructed individuals to alter and otherwise falsify records. Additionally, per the FDA, [Defendant] BMS employees knew of these "irregularities" and then withheld this data from the global BMS team. Additionally, during the allegedly double-blind study, 7.3% of apixaban versus just 1.2% of the warfarin group were alleged to have received incorrect medications or placebos. All of this data was fraudulently submitted to the FDA, and then Defendants used this fraudulent data to misrepresent the effectiveness of Eliquis when citing to the ARISTOTLE study in support of its claims of the medication's efficacy. As detailed above, the BMJ's findings dispute this data and no action has been taken on it.

b. Website-www.eliquis.com- https://www.eliquis.com/eliquis/hcp/stroke-risk-reduction-nvaf - Defendants published that "ELIQUIS Is the *ONLY* anticoagulant that demonstrated superiority in *BOTH* stroke/systemic embolism and major bleeding vs warfarin . . . ARISTOTLE was a Phase III, randomized, multinational, double-blind trial of 18,201 nonvalvular atrial fibrillation patients (ELIQUIS, n=9,120; warfarin, n=9,081) with 1 or more additional risk factors for stroke. Defendants then cited to the

ARISTOTLE Study for justification of this representation as well as for its representation of its "superiority to warfarin." Defendants intentionally misled consumers and prescribers by citing to this highly flawed ARISTOTLE study. Specifically, in the ARISTOTLE study sponsored by Defendants, there were unreported or late-reported serious side effects, and then one of Defendant's site managers instructed individuals to alter and otherwise falsify records. Additionally, per the FDA, [Defendant] BMS employees knew of these "irregularities" and then withheld this data from the global BMS team. Additionally, during the allegedly double- blind study, 7.3% of apixaban versus just 1.2% of the warfarin group were alleged to have received incorrect medications or placebos. All of this data was fraudulently submitted to the FDA, and then Defendants used this fraudulent data to misrepresent the effectiveness of Eliquis when citing to the ARISTOTLE study in support of its claims of the medication's efficacy. As detailed above, the BMJ's findings dispute this data and no action has been taken on it.

c. Website – www.eliquis.com – as archived on September 2, 2013 – Defendants published that "Eliquis had less major bleeding than warfarin" and also cited that "unlike warfarin," there is no routine monitoring required. As part of the support for these representations, Defendants then cited to the ARISTOTLE Study for justification of this representation as well as for its representation of its "superiority to warfarin." Defendants intentionally misled consumers and prescribers by citing to this highly flawed ARISTOTLE study. Specifically, in the ARISTOTLE study sponsored by Defendants, there were unreported or late-reported serious side effects, and then one of Defendants' site managers instructed individuals to alter and otherwise falsify records. Additionally, per the FDA, [Defendant] BMS employees knew of these "irregularities" and then withheld this data from the global BMS team. Additionally, during the allegedly double-blind study, 7.3% of apixaban versus just 1.2% of the warfarin group were alleged to have received incorrect medications or placebos. All of this data was fraudulently submitted to the FDA, and then Defendants used this fraudulent data to misrepresent the effectiveness of Eliquis when citing to the ARISTOTLE study in support of its claims of the medication's efficacy.

d. Dosing Guidelines – March 2014, as published by Defendants:

i. Page 3 – "No dose adjustment required in patients with mild, moderate, or severe renal impairment alone" – Defendants intentionally misled prescribing physicians and consumers to believe that even with moderate or severe renal impairment, Eliquis was safe, when in fact, it was not appropriate for such

patients;

ii. Page 4 – "Does not require routine monitoring using international normalized ration (INR) or other tests of coagulation" – Defendants intentionally misled prescribing physicians and consumers to believe that no routine monitoring is necessary. However, given the extreme bleeding risk in patient populations (some of which were not adequately studied), monitoring is required for some or all patient populations, as the EMA and FDA have been suggesting;

iii. Page 4 – While there is a section regarding the fact that "there is no established way to reverse the anticoagulant effect of apixaban, which can be expected to persist for at least 24 hours after the last dose," there is no

e. December 2012 – package insert for Eliquis, as published by Defendants –

i. Section 2.2 – recommended dosage is false, as the patient characteristics were inappropriate and should have been limited to one characteristic, instead of two of the listed characteristics;

ii. Section 5.2 – Bleeding. While there is a statement made that there is no reversal agent, Defendants withheld information and data that without the reversal agent, death could result;

f. March 2014 – package insert for Eliquis, as published by Defendants –

i. Section 2.2 – recommended dosage is false, as the patient characteristics were inappropriate and should have been limited to one characteristic, instead of two of the listed characteristics; and

ii. Section 5.2 – Bleeding. While there is a statement made that there is no reversal agent, Defendants withheld information and data that without the reversal agent, death could result.

275. These representations were made by said Defendants with the intent of defrauding and deceiving Plaintiff, the public in general, and the medical and healthcare community in particular (including Ms. Woody's prescribing physicians), and were made with the intent of inducing the public in general, and the medical and healthcare community in particular, to recommend, prescribe, dispense and/or purchase said product, Eliquis, all of which evinced a callous, reckless, willful, depraved indifference to the health, safety and welfare of the

Plaintiff herein.

276. At the time the aforesaid representations were made by the Defendants and, at the time Plaintiff used Eliquis, Plaintiff and his prescribing physicians were unaware of the falsity of said representations and reasonably believed them to be true.

277. In reliance upon said representations, Plaintiff was induced to and did use Eliquis, thereby sustaining severe and permanent personal injuries. Further, Plaintiff's prescribing physicians also acted in reliance upon said misrepresentations.

278. Defendants knew and were aware, or should have been aware, that Eliquis had not been sufficiently tested, was defective in nature, and/or that it lacked adequate and/or sufficient warnings. Moreover, Defendants knew or should have known that the recommended patient populations for dosing adjustments of Eliquis were inappropriate, and the failure to provide information that death can result from the lack of a reversal agent or the failure to monitor specific blood tests while on this medication is incomprehensible.

279. Defendants knew or should have known that Eliquis had a potential to, could, and would cause severe and grievous injury to the users of said product, and that it was inherently dangerous in a manner that exceeded any purported, inaccurate, and/or down-played warnings.

280. Defendants brought Eliquis to the market, and acted fraudulently, wantonly and maliciously to the detriment of Plaintiff.

281. At the time Defendants concealed the fact that Eliquis was not safe, Defendants were under a duty to communicate this information to Plaintiff, physicians, the FDA, the healthcare community, and the general public in such a manner that they could appreciate the risks associated with using Eliquis.

282. Defendants knew or should have known that Eliquis had a potential to, could, and would cause severe and grievous injury to the users of said product, and that it was inherently dangerous in a manner that exceeded any purported, inaccurate, and/or down-played warnings.

283. Defendants brought Eliquis to the market, and acted fraudulently, wantonly and maliciously to the detriment of Plaintiffs.

284. Defendants fraudulently concealed the safety issues associated with Eliquis including the need for blood monitoring and dose adjustments in order to induce physicians to prescribe Eliquis and for patients, including Plaintiffs, to purchase and use Eliquis.

285. Defendants, at all times relevant hereto, as detailed above, withheld information from the FDA which they were required to report.

286. Defendants had sole access to material facts concerning the defective nature of the product and its propensity to cause serious and dangerous side effects, and hence, cause damage to persons who used Eliquis, including the Plaintiff.

287. Plaintiff and his prescribing physicians relied upon the Defendants' outrageous untruths regarding the safety of Eliquis.

288. Plaintiff's prescribing physicians were not provided with necessary information by the Defendants, to provide an adequate warning to Plaintiff.

289. Eliquis was improperly marketed to Plaintiff and Plaintiff's prescribing physicians as the Defendants did not provide proper instructions about how to use the medication (including, but not limited to, failing to properly adjust dose requirements for all consumers and for failing to state that the lack of a reversal agent was likely to cause serious injury or death) and thus did not adequately warn about Eliquis's risks.

290. As a direct and proximate result of Defendants' malicious and intentional

concealment of material life-altering information from Plaintiff and Plaintiff's prescribing physicians, Defendants caused or contributed to Plaintiff's injuries.

291. It is unconscionable and outrageous that Defendants would risk the lives of consumers, including Plaintiff. Despite this knowledge, the Defendants made conscious decisions not to redesign, label, warn or inform the unsuspecting consuming public about the dangers associated with the use of Eliquis. Defendants' outrageous conduct rises to the level necessary that Plaintiff should be awarded punitive damages to deter Defendants from this type of outrageous conduct in the future and to discourage Defendants from placing profits above the safety of patients in the United States of America.

292. Defendants had a duty to disclose material information about serious side-effects to consumers such as Plaintiff.

293. Additionally, by virtue of Defendants' partial disclosures about the medication, in which Defendants touted Eliquis as a safe and effective medication, Defendants had a duty to disclose all facts about the risks associated with use of the medication, including the risks described in this Complaint. Defendants intentionally failed to disclose this information for the purpose of inducing consumers, such as Plaintiff, to purchase Defendants' dangerous product.

294. Had Plaintiff been aware of the hazards associated with Eliquis, Plaintiff would have employed appropriate blood monitoring, consumed a different anticoagulant with a better safety profile, or not have consumed the product that led proximately to Plaintiff's injuries.

295. Upon information and belief, Plaintiff avers that Defendants actively and fraudulently concealed information in Defendants' exclusive possession regarding the hazards associated with Eliquis, for the purpose of preventing consumers, such as Plaintiff, from

discovering these hazards.

296. Plaintiffs plead this Count in the broadest sense available under the law, to include pleading the same pursuant to all substantive law that applies to this case as may be determined by choice of law principles regarding or whether arising under statute and/or common law and reserves its rights to amend this cause of action or seek a court order to apply any applicable law of Plaintiff's home state. WHEREFORE, Plaintiffs demand judgment against all named Defendants, jointly and severally, for compensatory and punitive damages, together with interest, costs of suit, attorneys' fees and all such other relief as the Court deems proper.

TENTH CAUSE OF ACTION
NEGLIGENT MISREPRESENTATION

297. Plaintiffs repeat, reiterate and reallege each and every allegation of this Complaint contained in each of the foregoing paragraphs inclusive, with the same force and effect as if more fully set forth herein.

298. From the time Eliquis was first tested, studied, researched, evaluated, endorsed, manufactured, marketed and distributed, and up to the present, Defendants made misrepresentations to Plaintiffs, Plaintiffs' physicians and the general public, including but not limited to the misrepresentation that Eliquis was safe, fit and effective for human use. At all times mentioned, Defendants conducted sales and marketing campaigns to promote the sale of Eliquis and willfully deceived Plaintiffs, Plaintiffs' physicians and the general public as to the health risks and consequences of the use of Eliquis.

299. The Defendants made the foregoing representations without any reasonable ground for believing them to be true. These representations were made directly by Defendants, by sales representatives and other authorized agents of Defendants, and in publications and other written

materials directed to physicians, medical patients and the public, with the intention of inducing reliance and the prescription, purchase, and use of Eliquis.

300. Defendants had a duty to represent to the medical and healthcare community, and to the Plaintiff, the FDA, and the public in general that said product, Eliquis, had been tested and found to be safe and effective to reduce the risk of stroke and systemic embolism in patients with non-valvular fibrillation, to reduce the risk of recurrence of DVT and PE, and for prophylaxis of DVT for patients undergoing hip and knee replacement surgery.

301. The representations made by Defendants were, in fact, false in that Eliquis is not safe, fit and effective for human consumption as labeled, using Eliquis is hazardous to a patient's health and Eliquis has a serious propensity to cause serious injuries to users, including but not limited to the injuries suffered by Plaintiffs.

302. Defendants failed to exercise ordinary care in the representation of Eliquis, while involved in its manufacture, sale, testing, quality assurance, quality control, and distribution of said product into interstate commerce, in that Defendants negligently misrepresented Eliquis' high risk of unreasonable, dangerous side effects.

303. Defendants breached their duty in representing Eliquis' serious side effects to the medical and healthcare community, to the Plaintiff, the FDA and the public in general.

304. The foregoing representations by Defendants, and each of them, were made with the intention of inducing reliance and the prescription, purchase, and use of Eliquis.

305. In reliance on the misrepresentations by the Defendants, Plaintiffs were induced to purchase and use Eliquis. If Plaintiffs had known the truth and the facts concealed by the Defendants, Plaintiffs would not have used Eliquis. The reliance of Plaintiffs upon Defendants'

misrepresentations was justified because such misrepresentations were made and conducted by individuals and entities that were in a position to know all of the facts.

306. As a result of the foregoing acts and omissions, the Plaintiff was caused to suffer serious and dangerous side effects including life-threatening bleeding, as well as other severe and personal injuries which are permanent and lasting in nature, physical pain and mental anguish, diminished enjoyment of life, shortened life expectancy, expenses for hospitalization, loss of earnings and other economic and non-economic damages.

307. By reason of the foregoing, Plaintiffs have suffered injuries and damages as alleged.

308. As a result of the foregoing, Plaintiffs have been damaged in a sum that exceeds the jurisdictional limits of all lower courts that might otherwise have jurisdiction.

309. Plaintiffs plead this Count in the broadest sense available under the law, to include pleading the same pursuant to all substantive law that applies to this case as may be determined by choice of law principles regarding or whether arising under statute and/or common law and reserves its rights to amend this cause of action or seek a court order to apply any applicable law of Plaintiff's home state. WHEREFORE, Plaintiffs demand judgment against all named Defendants, jointly and severally, for compensatory and punitive damages, together with interest, costs of suit, attorneys' fees and all such other relief as the Court deems proper.

ELEVENTH CAUSE OF ACTION
VIOLATION OF CONSUMER PROTECTION LAWS

310. Plaintiffs repeat, reiterate and reallege each and every allegation of this Complaint contained in each of the foregoing paragraphs inclusive, with the same force and effect as if more fully set forth herein.

311. Defendants have a statutory duty to refrain from making false or fraudulent representations and from engaging in deceptive acts or practices in the sale and promotion of Eliquis pursuant to CALIFORNIA consumer protection laws, including, but not limited to, Cal. Bus. & Prof. Code § 17200, Cal. Bus. & Prof. Code § 17500, and Cal. Bus. & Prof. Code § 1750.

312. Defendants engaged in unfair, deceptive, false and fraudulent acts and practices in violation of CALIFORNIA law through its false and misleading promotion of Eliquis designed to induce Plaintiff to purchase and use Eliquis, including the following:

a. Representing that this good, Eliquis, has characteristics, ingredients, uses, benefits, or quantities that they do not have;

b. Advertising goods or services with the intent not to sell them as advertised; and,

c. Engaging in fraudulent or deceptive conduct that creates a likelihood of confusion or misunderstanding.

313. Defendants' conduct as described herein constituted unfair and deceptive acts and practices, including, but not limited to:

a. Publishing instructions and product material containing inaccurate and incomplete factual information.

b. Misrepresenting the nature, quality, and characteristics about the product; and

c. Engaging in fraudulent or deceptive conduct that creates a likelihood of confusion or misunderstanding.

314. Defendants misrepresented the alleged benefits of Eliquis, failed to disclose material information concerning known side effects of Eliquis, misrepresented the quality of Eliquis, and otherwise engaged in fraudulent and deceptive conduct which induced Plaintiff to purchase and use Eliquis.

315. Defendants uniformly communicated the purported benefits of Eliquis while failing to disclose the serious and dangerous side effects related to the use of Eliquis, its safety, its efficacy, and its usefulness. Defendants made these representations to physicians, the medical community at large, and to patients and consumers such as Plaintiff in the marketing and advertising campaign described herein.

316. Defendants' conduct in connection with Eliquis was impermissible and illegal in that it created a likelihood of confusion and misunderstanding, because Defendants misleadingly, falsely and or deceptively misrepresented and omitted numerous material facts regarding, among other things, the utility, benefits, costs, safety, efficacy and advantages of Eliquis.

317. Defendants' conduct as described above was a material cause of Plaintiff's decision to purchase Eliquis.

318. As a direct, foreseeable and proximate cause of Defendants' conduct in violation of CALIFORNIA law the Plaintiff suffered damages, including personal injuries, economic damages, and non-economic damages. Defendants' conduct was further wanton, egregious, and reckless so as to warrant the award of punitive damages.

319. As a result of the foregoing acts and omissions, the Plaintiff was caused to suffer serious and dangerous side effects including life-threatening bleeding, as well as other severe and personal injuries which are permanent and lasting in nature, physical pain and mental anguish, diminished enjoyment of life, shortened life expectancy, expenses for hospitalization, loss of earnings and other economic and non-economic damages.

320. By reason of the foregoing, Plaintiff has suffered injuries and damages as alleged.

321. As a result of the foregoing, Plaintiff has been damaged in a sum that exceeds the jurisdictional limits of all lower courts that might otherwise have jurisdiction.

322. Plaintiff pleads this Count in the broadest sense available under the law, to include pleading the same pursuant to all substantive law that applies to this case as may be determined by choice of law principles regarding or whether arising under statute and/or common law and reserves its rights to amend this cause of action or seek a court order to apply any applicable law of Plaintiff's home state.

323. Plaintiff demands that all issues of fact of this case be tried to a properly impaneled jury to the extent permitted under the law.

TWELFTH CAUSE OF ACTION
LOSS OF CONSORTIUM

324. Plaintiffs repeat, reiterate and reallege each and every allegation of this Complaint contained in each of the foregoing paragraphs inclusive, with the same force and effect as if more fully set forth herein.

325. Plaintiff, JAKE WOODY, was at all times relevant hereto the spouse of Plaintiff, and as such, lived and cohabitated with her.

326. By reason of the foregoing, Plaintiff, JAKE WOODY, has incurred significant expenses for medical care and will continue to be economically and emotionally harmed in the future.

327. By reason of the foregoing, Plaintiffs were caused to suffer, and Plaintiffs will continue to suffer in the future, loss of consortium, loss of society, affection, assistance, and conjugal fellowship, all to the detriment of their marital relationship.

328. Plaintiffs plead this Count in the broadest sense available under the law, to include pleading the same pursuant to all substantive law that applies to this case as may be determined by choice of law principles regarding or whether arising under statute and/or common law and reserves

its rights to amend this cause of action or seek a court order to apply any applicable law of Plaintiff's home state. WHEREFORE, Plaintiffs demand judgment against all named Defendants, jointly and severally, for compensatory and punitive damages, together with interest, costs of suit, attorneys' fees and all such other relief as the Court deems proper.

JURY TRIAL DEMANDED

329. Plaintiff demands that all issues of fact of this case be tried to a properly impaneled jury to the extent permitted under the law.

WHEREFORE, Plaintiffs demand judgment against each of the Defendants jointly and severally for such sums, including, but not limited to prejudgment and post-judgment interest, as would be necessary to compensate the Plaintiffs for the injuries Plaintiff has and or will suffer. Plaintiff further demands judgment against each of the Defendants for punitive damages. Plaintiff further demands payment by each of the Defendants jointly and severally of the costs and attorney fees of this action. Plaintiff further demands payment by each Defendant jointly and severally of interest on the above and such other relief as the Court deems just.

Napoli Shkolnik, LLC

By: /s/ James D. Heisman
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Attorney for Plaintiff

Dated: April 24, 2017

SUPERIOR COURT
CIVIL CASE INFORMATION STATEMENT (CIS)

COUNTY: N K S CIVIL ACTION NUMBER: _____

Caption: (Entire Caption) :CAROL WOODY and JAKE WOODY v. BRISTOL-MYERS SQUIBB COMPANY; and PFIZER, INC.,

Civil Case Code: CPRL

Civil Case Type: Products Liability
(See Reverse Side for Code and Type)

Name and Status of Party filing document:

CAROL WOODY and JAKE WOODY, Plaintiff

Document Type: (e.g.; Complaint; Answer with Counterclaim)

Complaint

Jury Demand: Yes X No _

Attorney Name(s):
James D. Heisman

Attorney ID(s):

2746

Firm Name:

Napoli Shkolnik, LLC

Address:

919 North Market Street, Suite 1801

Wilmington, DE 19801

Telephone Number:

302-330-8025

Fax Number:

(646) 843-7603

E-Mail Address:
JHeisman@NapoliLaw.com

Identify any related cases now pending in the Superior Court or any related cases that have been closed in this court within the last two years by caption and civil action number including Judge's initials:

Goodpaster N15C-12-119; Barb N 15C-12-213; Tobin N15C-12-048; Carr N16C-02-077; Hold N16C-02-150; Deitrich N16C-03-110; Daniels N16C-03-111; Carew N16C-04-019; Buck N16C-12-078 and Jackson N16C-05-123 AML

Explain the relationship(s):

Other unusual issues that affect Case Management:

The Prothonotary will not process the complaint, answer, or first responsive pleading in this matter for service until the case information statement (CIS) is filed. The failure to file the CIS and have the pleading processed for service may result in the dismissal of the complaint or may result in the answer or first responsive pleading being stricken.

SUPERIOR COURT CIVIL CASE INFORMATION STATEMENT (CIS) INSTRUCTIONS

CIVIL CASE TYPE

Please select the appropriate civil case code and case type (e.g., **CODE** - **AADM** and **TYPE** - **Administrative Agency**) from the list below. Enter this information in the designated spaces on the Case Information Statement.

APPEALS
AADM - Administrative Agency
ACER - Certiorari
ACCP - Court of Common Pleas
AIAB - Industrial Accident Board
APSC - Public Service Commission
AUIB - Unemployment Insurance Appeal Board

COMPLAINTS
CASB – Asbestos
CAAA - Auto Arb Appeal
CMIS - Civil Miscellaneous
CACT - Class Action
CCON - Condemnation
CCLD - Complex Commercial Litigation Division **(NCC ONLY)**
CDBT - Debt/Breach of Contract
CDEJ - Declaratory Judgment
CDEF - Defamation
CEJM - Ejectment
CATT - Foreign & Domestic Attachment
CFJG - Foreign Judgment
CFRD - Fraud Enforcement
CINT - Interpleader
CLEM - Lemon Law
CLIB - Libel
CMAL - Malpractice
CMED - Medical Malpractice
CPIN - Personal Injury
CPIA - Personal Injury Auto
CPRL - Products Liability
CPRD - Property Damage
CRPV - Replevin
CSPD - Summary Proceedings Dispute
CCCP - Transfer from CCP
CCHA - Transfer from Chancery

MASS TORT
CBEN - Benzene Cases
CPEL - Pelvic Mesh Cases
CPRA - Pradaxa Cases
CSER - Seroquel Cases

INVOLUNTARY COMMITMENTS
INVC- Involuntary Commitment

MISCELLANEOUS
MAGM - AG Motion - Civil/Criminal Investigations *
MADB - Appeal from Disability Board *
MAFF - Application for Forfeiture
MAAT - Appointment of Attorney
MGAR - Appointment of Guardianship
MCED - Cease and Desist Order
MCDR - Child Death Review
MCON - Civil Contempt/Capias
MCVP - Civil Penalty
MSOJ - Compel Satisfaction of Judgment
MSAM - Compel Satisfaction of Mortgage
MCTO - Consent Order
MIND - Destruction of Indicia of Arrest *
MESP - Excess Sheriff Proceeds
MHAC - Habeas Corpus
MTOX - Hazardous Substance Cleanup
MFOR - Intercept of Forfeited Money
MISS - Issuance of Subpoena
MLEX - Lien Extension
MMAN - Mandamus
MWIT - Material Witness *
MWOT - Material Witness - Out of State
MRAT - Motion for Risk Assessment
MROP - Petition for Return of Property
MCRO - Petition Requesting Order
MROD - Road Resolution
MSEL - Sell Real Estate for Property Tax
MSEM - Set Aside Satisfaction of Mortgage
MSSS - Set Aside Sheriff's Sale
MSET - Structured Settlement
MTAX - Tax Ditches
MREF - Tax Intercept
MLAG - Tax Lagoons MVAC
- Vacate Public Road
MPOS - Writ of Possession
MPRO - Writ of Prohibition

MORTGAGES
MCOM - Mortgage Commercial
MMED - Mortgage Mediation
MORT - Mortgage Non-Mediation (Res.)

MECHANICS LIENS
LIEN - Mechanics Lien

* Not eFiled

DUTY OF THE PLAINTIFF

Each plaintiff/counsel shall complete the attached Civil Case Information Statement (CIS) and file with the complaint.

DUTY OF THE DEFENDANT

Each defendant/counsel shall complete the attached Civil Case Information Statement (CIS) and file with the answer and/or first responsive pleading.

EFiled: Apr 24 2017 01:55PM EDT
Transaction ID 60509361
Case No. N17C-04-263 AML

EXHIBIT A

ISMP INSTITUTE FOR SAFE MEDICATION PRACTICES
QuarterWatch
Monitoring FDA MedWatch Reports

September 23, 2015 — Data from 2014 Quarters 3-4

ANNUAL REPORT ISSUE

Two tumor necrosis factor blockers lead overall report totals in 2014
Novel oral anticoagulant safety profiles diverge, but risks remain high
Atorvastatin (LIPITOR) accounts for most safety-related lawsuit reports

Executive Summary

This issue provides an overview of prominent drug safety issues as reflected in 833,076 adverse drug events reported to the U.S. Food and Drug Administration during 2014. For this annual review, we identify the drugs that account for the most reports overall and in key subgroups such as children, cases from legal claims, and reports indicating product problems. For each perspective it is important to consider both the insights revealed and the substantial limitations of the underlying data.

Although drug adverse effects are estimated to account for 100,000 to 200,000 patient deaths and 1 to 2 million hospitalizations each year, neither the FDA nor the Centers for Disease Control and Prevention publishes annual assessments of serious injury and death resulting from drugs in therapeutic use. Despite a world of proliferating digital data, the primary source for identifying injuries from therapeutic drugs remains the voluntary reports to the FDA's Adverse Event Reporting System (FAERS). The QuarterWatch™ assessment is based on publicly released excerpts of case reports submitted for the first time in 2014.

The Data Profile

The U.S. system for postmarket surveillance depends primarily on reports prepared by drug manufacturers. The types of reports that the FDA received in 2014 are described in Table 1. In 2014, manufacturers submitted 798,962 (95.9%) of the reports that the FDA received. The remaining 34,114 (4.1%) cases were submitted directly to the agency's MedWatch drug information program portal by consumers and health professionals. Any individual who desires to report an adverse drug event has the option of either submitting one directly to the FDA or contacting a drug manufacturer. Manufacturers, in turn, are required to report every adverse event they learn of through any channel that could range from a consumer help-line telephone contact to a refill reminder that was returned indicating the patient had died. The strength of the system is that it collects information from a wide array of sources that range from episodes observed by hospital pharmacists to legal claims

Table 1. Adverse drug event reports received by FDA in 2014

	Number,	%
Total (initial reports)	833,076	
Manufacturer	798,962	95.9%
Domestic, serious*	284,845	34.2%
Foreign, serious	218,309	26.2%
Domestic, not serious	295,808	35.5%
Direct to FDA	34,114	4.1%
Serious	25,038	3.0%
Not Serious	9,076	1.1%

*Includes death, disability, hospitalzation, life threatening, required intervention, and other serious injury.

for drug-induced injury filed in state and federal courts. Reporting events to the FDA is closed to no one.

Two Anti-TNF Products Post Most Injury Reports

In 2014, two similar biological products that inhibit a key element in the immune system–tumor necrosis factor (TNF)–accounted for the largest number of reports of injury received by the FDA in several different categories. The two drugs, adalimumab (HUMIRA) and etanercept (ENBREL), are approved to treat various autoimmune disorders, notably rheumatoid arthritis, Crohn's Disease, and forms of psoriasis. Counting all reports from all sources, adalimumab ranked 1st with 46,937 new reports and etanercept 2nd with 38,929 cases. For comparison, in 2014 we identified 1,604 therapeutic drugs with reports, with a median of 37 reports per drug. Only 168 drugs accounted for more than 1,000 reports each.

The primary focus of QuarterWatch is the subgroup of serious reports of domestic origin. By this measure etanercept ranked 1st (n = 7,752) and adalimumab 2nd (n = 6,081). Another category of interest is expedited reports about new, serious adverse events without full warnings in the prescribing information. Again etanercept ranked 1st and adalimumab 2nd. The two drugs were the primary suspect drugs in 1,809 patient deaths in reports from all sources.

Three factors combine to produce such large totals: 1) Larger patient exposure; 2) substantial toxicity; and 3) marketing and educational programs that increase the manufacturer's contact with patients and health professionals, causing the company to learn about more cases. In this report, we examine how all three factors contributed to the high event totals for these two anti-TNF products. Most adverse events were linked to the two drugs' immunosuppressant properties.

Contrast in Novel Anticoagulants' Safety Profiles

Rivaroxaban (XARELTO), dabigatran (PRADAXA), and apixaban (ELIQUIS) are "novel" oral anticoagulants approved from 2010-2012, and marketed as easier-to-use replacements for warfarin (COUMADIN), the high-risk standard treatment since the mid-1950s. All are approved to lower the risk of stroke in patients with atrial fibrillation, and most for use after hip and knee replacement surgery. Although rivaroxaban accounted for more direct reports to the FDA (mostly from health professionals) than any other drug, we expanded the focus to examine the safety profiles of all three novel anticoagulants. Key findings:

- Rivaroxaban emerged the winner of the race to replace warfarin, with more dispensed outpatient prescriptions than the other two drugs combined. We examine whether both hemorrhage events (too much anticoagulant) and blood clot related events (not enough anticoagulant) are linked to a disconnect between its once-a-day dosing and a terminal half-life of 5 to 9 hours.

- Dabigatran had the highest overall total of domestic, serious adverse event reports among the three, the largest total of reported severe hemorrhages, and the most patient deaths. The differences persisted after adjusting for patient exposure and other report characteristics. Previously, we have questioned whether a drug with a 5-fold variability of effect among patients getting the same dose was suitable for use in a single primary therapeutic dose. The 2014 data further illustrate our concerns.

- Apixaban was the third new anticoagulant to win FDA approval, but showed the strongest safety profile from several perspectives. Its twice-a-day dosing regimen was consistent with its 12-hour half-life. A lower dose for older and other high risk patients for bleeding was tested and found to reduce bleeding risk without loss of efficacy. And it accounted for the fewest reports and the fewest patient deaths both before and after adjusting for patient exposure.

Atorvastatin (LIPITOR) and Diabetes Lawsuits

A separate and distinct forum for evaluating drug safety exists in the U.S. court systems, where thousands of patient claims of injury for a drug are litigated at cost of millions of dollars in an elaborate process that may take years to complete. When legal claims reach a drug manufacturer they are also reported to the FDA as adverse events. In 2014, the biggest reported litigation target (n = 4,727) was the cholesterol-lowering drug atorvastatin (LIPITOR), and the issue was whether it causes diabetes in women.

Atorvastatin was the fourth most widely used therapeutic drug by the last quarter of 2014, accounting for 22 million dispensed outpatient prescriptions, according to IMS Health data, and approximately 11.4 million person-years of exposure. It has a proven clinical benefit established in mostly high-risk men where a large clinical trial showed it reduced the risk of cardiovascular events by 36%. But the chances of it benefiting any single patient were small: It took 33,000 person-years of observation to document the prevention of fewer than 60 cardiovascular events. If a relatively small risk were overlooked in the clinical studies it might tilt the balance of harm versus benefit.

Use of statins had escalated to one of the most widely used treatments in all of medicine when questions emerged about whether these drugs might also cause diabetes. A reexamination of 13 large clinical trials concluded that indeed treatment might increase the risk of diabetes by around 9%. The studies together suggested that all the statins shared roughly similar risks and benefits, although both might be higher for the most potent statins, rosuvastatin (CRESTOR) and atorvastatin. This was a concern but 9% seemed a small number compared to a 36% reduction in risk of cardiovascular events. But then a major gender gap was identified. The statin trials had largely enrolled men. Observational studies in women showed that the risk of diabetes with statin treatment was much higher – 48% in the largest study. And women had a lower risk of cardiovascular disease compared to men.

In the coming months, experts for both sides will dispute the nature and extent of the diabetes risk of atorvastatin in women. In a peculiar feature of mass tort litigation, much of the scientific evidence on which the competing experts rely often remains secret. In this report we examine other unusual characteristics of drug safety litigation cases in 2014. It is common for drug manufacturers to pay hundreds of millions of dollars in legal claims for a drug risk, and then claim the drug is not, in fact, responsible for the safety problem.

Additional Safety Perspectives

We identified signals of possible drug risks in other subgroups of reports. Among children under 18, somatropin (or recombinant human growth hormone) accounted for the most domestic, serious adverse event reports. In the oldest patients–those 75 years of age and older–denosumab (PROLIA), a twice-yearly injection to reduce the risk of bone fractures, accounted for the most reports and illustrated that it shared many of the safety issues of alendronate (FOSAMAX). A third subgroup was product quality complaints–most not indicating a serious outcome. Spiriva HandiHaler (tiotropium) accounted for the most complaints in 2014. Among estrogen/progestin products for women, the largest number of domestic, serious events reported was for MIRENA, an oral contraceptive intrauterine device (IUD) that releases levonorgestrel.

About QuarterWatch Data

Our findings should be interpreted in light of the known limitations of a reporting system that does not collect data systematically. The submission of an individual report does not in itself establish that the suspect drug caused the event described—only that an observer suspected a relationship. While the sheer numbers of case reports have scientific weight, because of variation in reporting rates, they reveal little about how frequently the events occur in the broader patient population. More complete disclaimers and descriptions of

our criteria are included in the Methods Summary section of this report. A disclosure statement expands our description of this project and its staff.

Conclusions

For our 2014 annual report issue the objective was to identify drug safety issues from different perspectives. Measured by sheer numbers of reports, the anti-TNF products place first, in part because of their potent effects on the immune system that increase the risks of invasive fungal and opportunistic bacterial infections, reactivation of hepatitis virus, and cancer. Intensive marketing and extensive patient contact by manufacturers or their agents also contribute to the high volume of reports.

The adverse event reports for oral anticoagulants confirm the evidence that long-term use remains one of the highest-risk drug treatments in older patients, with injury rates of 15-20% per year. As previously noted in this publication, bringing a new generation of oral anticoagulants to market based on ease of use rather than improved safety was a major wrong turn. In addition, two of the three novel anticoagulants have pharmacological profiles that raise questions about their simple, unmonitored dosing regimens. For dabigatran, a 5-fold variability in different patients getting the same dose creates risks in many patients that could be reduced by optimizing the dose for each patient. However, a reduced dose 110 mg dabigatran capsule and the most accurate blood-level test are not approved in the U.S. The short half-life of rivaroxaban means that once-a-day dosing results in higher maximum concentrations and higher bleeding risk on one hand, and an extended period each day when concentrations may be suboptimal for preventing stroke. Neither rivaroxaban nor dabigatran has lower recommended doses for older patients and most others with higher bleeding risks. At this point, apixaban appears to have avoided these drawbacks with a better safety profile. But the risks of bleeding are so high that individualizing the dose—as with warfarin—promises to improve the safety profile of this risky class of drugs.

The legal contest over the diabetes risks of atorvastatin provides new safety perspectives into the problems of drugs that are administered long-term for prevention of cardiovascular events. To discover after 20 years that one of the most widely used drug treatments in medicine might do more harm than good in a huge subgroup–low risk women–underscores the limited data that support the long-term use of this and other treatments for prevention. Also, the issues at stake illustrate that when a drug has a relatively small chance of providing a future benefit, even a small risk of harm can alter the balance of risk and benefit. Finally, drug safety issues that are addressed in the legal system identify problems that may need to be addressed by doctors, the FDA, and medical organizations. Whether cholesterol treatment guidelines for women are appropriate is one of them.

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Methods Summary

QuarterWatch monitors the safety of prescription drugs through analysis of adverse drug events reported to FDA by consumers and health professionals, either directly to the agency or through drug manufacturers. The agency releases computer excerpts for research use on a quarterly basis, and these case reports are our primary data source.[1] A full description of our methodology is available on the QuarterWatch pages of the ISMP web site. (http://www.ismp.org/QuarterWatch/detailedMethods.aspx)

The severity of the adverse event is classified by FDA regulation [2] as serious if the case report specified an outcome of death, disability, hospitalization, required intervention to prevent harm, was life threatening or had other medically serious consequences. Cases without these outcomes were classified as not serious.

In these data, the adverse events that occur are described by medical terms selected from the Medical Dictionary for Regulatory Activities (MedDRA), a terminology developed by the pharmaceutical industry to describe adverse events in clinical studies and postmarketing reports.[3] The MedDRA terminology also defines broader categories of adverse events that can include any of a list of more specific and related medical terms. We use these categories, called Standardized MedDRA Queries (SMQs), to identify possible cases of some adverse events. [4]

We also group adverse event terms using a MedDRA category called High Level Terms (HLTs) that combine several related but more specific medical terms. High Level Group Terms (HLGTs) combine several related HLTs and System Organ Classes combine the terms into 26 categories. The QuarterWatch database was updated in November 2014 to MedDRA version 17.1.

To provide a broader perspective on the adverse events reported, we assess the patient exposure to drugs on the basis of dispensed outpatient prescription data provided by IMS Health Inc. The data we rely on are an estimate of total non-governmental prescriptions dispensed through retail and mail channels. Our agreement with IMS includes the following disclaimer:

"The statements, findings, conclusions, views, and opinions contained and expressed in QuarterWatch are based in part on data obtained under license from an IMS Health Inc. information service called the National Prescription Audit™ for 2014 (All Rights Reserved). Such statements, findings, conclusions, views, and opinions are not necessarily those of IMS Health Incorporated or any of its affiliated or subsidiary entities."

In this report we also calculated person-years of exposure to provide an additional dimension to assessing the size of the patient population. A patient-year means a sufficient amount of drug dispensed to treat a patient for one year, even though in reality the patient population is larger because many will either start or stop the drug during the period of measurement. In addition, we used 4th quarter data to estimate person-years of exposure; it might over- or under-estimate exposure if there were major changes in prescription volume during the four quarters.

Events in QuarterWatch are attributed to the product identified as the primary suspect drug in the case report. The drug names are standardized to drug ingredient names based on the National Library of Medicine's RxNorm terminology.[5] When cited in the text, tables, or charts, the brand name of drugs used is the one most frequently indicated on the case reports but may account for a small or large share of the actual reports identified. Unless specified, QuarterWatch does not distinguish dose, route of administration, or extended release and other preparations.

Results

In 2014, the FDA received 833,076 new reports of adverse drug events, an increase of 12.7% from 2013. This total included 293,810 (35%) reports that indicated fatal, disabling or other serious injuries that occurred in the U.S. (excluding legal claims and clinical studies). These domestic reports inform the primary analysis for QuarterWatch. Another large category of reports is for domestic events that were not serious (n = 304,884). This category includes less severe reactions such as nausea, palpitations, and upset stomach, together with medication errors and product problem reports that did not result in a reported serious injury but have implications for drug safety. The non-serious reports increased by 2.1% from 2013 to 2014. The other large category is foreign reports of serious injuries submitted by drug manufacturers who also market the drug in other countries. In 2014 the FDA received 218,309 foreign reports of serious injury. The share of total reports from abroad has increased steadily over the last 10 years and now accounts for 42.7% of all serious injuries reported to the agency.

Serious injuries reported in the U.S. increased by 59,531 cases (25.4%) in 2014, leading all the report categories noted above. However, most of this increase was accounted for by an unusual episode described in a previous issue of QuarterWatch.[6] In spring of 2014 GlaxoSmithKline was required to submit more than 20,000 incomplete case reports for rosiglitazone (AVANDIA), a Type 2 diabetes drug. The cases resulted from a 2012 legal settlement for patients claiming the drug contributed to heart attacks and strokes. Although only a few hundred patients continue to take the drug in the U.S., it accounted for 34,284 reports of serious injury in 2014.

In the next sections of this report we identify the drug products that accounted for the largest number of reports in 2014 in different safety categories. Ranking 1st in a category does not immediately demonstrate that the suspect drugs have the highest risks, compared to all other therapeutic drugs. As previously reported, brand name drug manufacturers are the primary source for FAERS data, even though generic drugs accounted for 88% of all dispensed outpatient prescriptions in 2014.[7] Industry marketing and special FDA reporting requirements can increase the number of reports substantially, without necessarily indicating a safety problem. Nevertheless, sheer numbers have scientific weight and thousands of reports of serious injury, large legal actions, or product problems still serve to identify substantial safety problems warranting greater attention to minimize risks.

Two Anti-TNF Products Lead in 2014 Reports

Tumor necrosis factor (TNF) is a family of signaling proteins created by the immune system. They function primarily to destroy unwanted and abnormal cells in the inflammatory process. Genetically engineered proteins that inactivate TNF have been approved since 1998 to treat autoimmune disorders that include rheumatoid arthritis, severe psoriasis, and Crohn's disease. The two most widely prescribed biological products in this class—adalimumab (HUMIRA) and etanercept (ENBREL)–also account for the largest number of adverse event reports received by the FDA in 2014 in several different categories. Table 2 shows the totals.

Adalimumab ranked 1st and etanercept 2nd in 2014 in the number of total reports reaching the FDA. In the subset of reports of serious injuries occurring in the U.S. they also ranked at the top, etanercept 1st and adalimumab 2nd. They accounted for the most expedited reports from drug manufacturers about new, serious adverse events. And they were less prominent in direct reports to the FDA from consumers and health professionals with adalimumab ranking 9th and etanercept 11th.

To generate an unequalled number of adverse event reports over one year requires a combination of three factors: A substantial patient population, numerous toxic effects, and extensive manufacturer contact with patients and health professionals. In this case, all three factors contributed to the large case totals.

Exposure

In 2014 Q4, IMS Health data indicates that adalimumab accounted for 558,059 dispensed outpatient prescriptions, or approximately 250,000 person-years of exposure.* In terms of patient population this was moderate exposure; more than 250 drugs had larger patient populations in 2014. The etanercept patient population was similar, with 438,362 dispensed outpatient prescriptions and a patient exposure of approximately 185,000 person-years.

Table 2. Reports for 2 anti-tumor necrosis factor products, 2014

	ADALIMUMAB		ETANERCEPT	
	Number, %		Number,%	
Total	46,937		38,929	
Outcome				
Death	1,125	2.4%	684	1.8%
Serious	12,270	26.1%	11,818	30.4%
Not serious	33,542	71.5%	26,427	67.9%
Location				
U.S.	39,624	84.4%	34,149	87.7%
Foreign	7,313	15.6%	4,780	12.3%
Source				
Consumer	34,504	73.5%	9,091	23.4%
Health professional	12,303	26.2%	29,780	76.5%
Other/not stated	130	0.3%	58	0.1%
Report Quality*				
Reasonably complete	29,042	61.9%	28,113	72.2%
Minimally complete	30,841	65.7%	36,721	94.3%

* Reasonably complete = included age, gender and event date. Minimally complete = age, gender

Harmful Effects

Both drug products are administered with self-injection syringes. Both drugs also accounted for large numbers of injection site reactions, with more than 10,000 reported cases each in 2014. Practically all the injection site reaction cases were classified as not serious. In clinical studies, 20-40% of patients reported injection site reactions or pain. The anti-TNF drugs are also potent immunosuppressants with prominent warnings about the risk of opportunistic and other serious infections. Among serious and fatal injuries reported, 3,298 (24.6%) of the adalimumab cases indicated an infection, and 3,982 (31.9%) of etanercept cases. Anti-TNF products also carry Boxed Warnings about cancer risks, and cancer was frequently reported

* A person-year means one patient exposed for the entire period. In clinical practice, patient total is larger because some patients start and discontinue during the period.

in 2014. Serious injuries for adalimumab included 1,410 (10.5%) cases of cancer, including 197 reported cancer deaths. Etanercept serious injury cases included 1,253 cancer cases with 90 reported deaths. A third large group of serious adverse events involved hypersensitivity, with 1,438 cases for adalimumab and 1,465 for etanercept.

Patient Contacts

Available evidence shows that these two biological products are major revenue producers and are supported by extensive programs involving company contact with patients that could increase adverse event reporting. Adalimumab is the leading product of AbbVie, a spinoff of Abbott in 2011. Adalimumab accounted for $12 billion in sales in 2014. By some measures,[8] adalimumab ranked 1st in worldwide drug revenue. (Etanercept ranked 5th worldwide). AbbVie offers patients injection training kits, on-call nurse support, medication reminders, free travel packs, and syringe disposal. Amgen offers similar benefits for etanercept, as well as financial assistance and even a personal visit from an Amgen "Nurse-Partner." A month's supply of the drugs costs $3,000-$3,500, although patient out-of-pocket costs would likely be lower. Another indication that the two companies are in close contact with their patient populations is the high scores for the quality and completeness of their adverse event reports. Overall 92% of etanercept reports included both age and gender, compared to an industry in which only 62% of reports included that basic information. For AbbVie's adalimumab reports 63% included the basic information.

Conclusions

These unequalled totals of adverse event reports are a reminder that the prominent warnings about risks of cancer, infection, hypersensitivity, and other harms are not boilerplate to satisfy legal departments and regulators. These two drugs account for thousands of serious and life-threatening injuries reported each year and many thousands of reports about less severe harm. Because of these risks, the two drugs are intended for autoimmune disorders that are moderate to severe.

Other drugs accounting for very large numbers of total reports included rosiglitazone (n = 35,189), as noted previously, and estrogen/progestin products (n = 29,332) , a combined category that includes many different forms of oral contraceptives as well products for other related uses.

Safety Profiles for 3 Novel Anticoagulants

Our annual review for 2014 revealed that for one key indicator—direct reports to the FDA of serious injury—the anticoagulant rivaroxaban (XARELTO) led all other therapeutic drugs with 525 reports. Reports that health professionals and consumers submit directly to the FDA through the MedWatch portal are only 4% of the total. However, they provide signals of safety issues that are independent of manufacturer marketing and other patient contact programs that can skew results. Direct reports are also of higher quality. As we analyzed the reasons why rivaroxaban accounted for so many direct reports, a larger perspective emerged that illustrated the substantial health risks of anticoagulation therapy with both similarities to and differences from two similar novel anticoagulants–dabigatran (PRADAXA) and apixaban (ELIQUIS). Starting in 2010, the three drugs have been competing to replace the anticoagulant warfarin, first approved in 1956 and currently used by approximately 4 million patients at risk of blood-clot-related disorders after hip/knee replacement surgery or heart attacks or with atrial fibrillation.

Rivaroxaban Wins the Race to Replace Warfarin

By the close of 2014, rivaroxaban was the run-away winner in the race to replace warfarin. Data from IMS Health reveal that in the 4th Quarter of 2014 rivaroxaban accounted for more dispensed outpatient prescriptions than its other two competitors combined. As Table 3 indicates, however, warfarin remained the dominant treatment in this drug class.

Table 3. Dispensed oral anticoagulant prescripions 2014 Q4*

	Prescriptions	Person-years
Rivaroxaban	1,758,016	505,560
Dabigatran	560,887	252,780
Apixaban	609,301	231,618
Warfarin	80,266,745	3,944,233

Data from IMS Health National Prescription Audit

Safety vs. Ease of Use

More than a decade ago, as pharmaceutical company researchers assessed how to develop a new product that would be superior to warfarin, two clear choices were available. It was unlikely that any new product could substantially surpass warfarin for benefit in preventing serious and disabling blood-clot-related events. That is because anticoagulation by any drug lies on the razor's edge. Too much and the result is hemorrhage. Too little, and the drug fails to prevent heart attacks, strokes, pulmonary embolism, and other clot-related disorders. The next choice was safety. Warfarin, by a large margin, was the highest risk outpatient medical treatment in older patients,[9] accounting for one-third of all emergency room visits for the adverse effects of all therapeutic drugs. Most warfarin adverse events were for hemorrhages. A drug that substantially reduced warfarin bleeding events that could injure 16-20% of patients per year would be a major advance in drug safety.

The other possible advantage was ease of use. Administration of warfarin is challenging. It requires blood tests as frequently as every two weeks. Warfarin interacts with dozens of other drugs, even food. The same individual may need different doses over time. All three companies opted for ease of use over improved safety, and designed clinical trials based on the idea that periodic blood tests to establish an optimal dose were not required.

The Problem of Patient Variability

A high-risk drug where too much or not enough drug can lead to a medical emergency requires that the pharmacology and administration of the drug itself achieve reasonably uniform effects among patients, and over the full duration of the dose period. Although the facts were not fully understood until recently, two of the three new drugs had problems in basic pharmacology that raised questions about their suitability for simple dosing regimens without adjusting for each patient.

The Dabigatran Problem

As we have previously reported,[10] [11] before dabigatran was marketed, the manufacturer, Boehringer Ingelheim, and regulators had extensive pharmacokinetic/pharmacodynamic (PK-PD) data that raised questions about its suitability for use in a single primary therapeutic dose without blood-level monitoring. Because of problems metabolizing dabigatran, 17% of patients would get a sub-therapeutic dose and therefore minimal protection against stroke or heart attack. Because of 5-fold variability in blood levels among patients receiving the same dose, nearly half would receive more drug than needed, raising the risk of hemorrhage. The highest blood levels and excess anticoagulation were seen in older patients. However, older patients could not be protected by a reduced dose because the FDA rejected the company's request for a smaller dose for older patients.[11] FDA managers justified their decision to ban a lower dose, saying if approved too many doctors would worry about bleeding and use the lower dose.[12] Dose adjustment for older patients and a blood level test are available in most advanced nations, but not in the U.S. Safety concerns about dabigatran likely contributed to its decline in the U.S. market. Although it was the first of the new anticoagulants to be approved, dispensed outpatient prescriptions for dabigatran have declined 22% since mid-2012, according to data from IMS Health.

Rivaroxaban Single Daily Dose

For an ease-of-use claim, rivaroxaban had an advantage over the emerging competition. It was the only new anticoagulant with once-a-day dosing for most medical uses, instead of twice a day.[13] Whatever marketing advantage once-a-day dosing might provide, the PK-PD data shown in Table 4 clearly demonstrated that of the three new drugs, rivaroxaban was the poorest choice for a single dose.

Table 4. Anticoagulant half-life, dosing

	Half-life	Dosing
Rivaroxaban	5-9 hr	Once daily
Dabigatran	12-17 hr	Twice daily
Apixaban	12 hr	Twice daily
Warfarin	20-60 hr	Once daily

It is clear that once-a-day dosing for a drug with a terminal half-life of only 5-9 hours resulted in substantial peaks and troughs that could be avoided with twice-daily dosing. One head-to-head comparison showed that the peak dose of rivaroxaban was 16.9 times higher than the trough; with apixaban twice a day the peak was 4.7 times higher than the trough. [14] In addition, the problem was clearly identified by the FDA pharmacology staff prior to approval.[15]

No Worse than Warfarin

Despite these unfavorable characteristics in pharmacology studies, both dabigatran and rivaroxaban were approved for reducing the risk of stroke in atrial fibrillation patients on the basis of large clinical trials at the fixed-dose regimens. The results showed that overall, both drugs were no worse than warfarin.[16] [17] While FDA pharmacologists could and did assert that rivaroxaban10 mg twice a day had a better profile than 20 mg once a day, they also noted that "the clinical relevance was uncertain."[15] That was because only the once-a-day regimen had been tested in the pivotal clinical trial. As later safety questions arose about the safety of dabigatran in older patients, the FDA appeared to be satisfied with findings that the safety profile appeared to be no worse than warfarin—likely the highest risk outpatient treatment in older patients.

Apixaban in Contrast

Although apixaban was not approved until 2012–two years after dabigatran–the development plan appeared to avoid the limitations observed for rivaroxaban and dabigatran. Apixaban was tested in both once- and twice-daily regimens in patients following knee replacement surgery.[18] Twice a day was deemed safer and its advantages over a comparator were confirmed in a larger study.[19] In its longer-term trial in atrial fibrillation, older patients and others at higher risk for bleeding were given reduced dose. In the older patients getting the reduced dose, severe bleeding was reduced compared to warfarin but efficacy was retained.[20] At least partly because of these factors, the apixaban trial in atrial fibrillation was the only one to show a clear safety gain over warfarin, reducing severe hemorrhages by one-third, or 2.1% compared to 3.1%. On the other hand, apixaban approval was delayed because of FDA questions about the quality of the data in the pivotal trial.[21] Also unanswered is whether apixaban safety could be further improved with individualizing the dose for each patient, as is done with warfarin.

The Adverse Event Comparison

The strengths and weaknesses of the three new anticoagulants are also reflected in their serious adverse event profiles. The comparisons are shown in Table 5. While rivaroxaban led in the largest number of reports directly to the FDA, by most other measures dabigatran had a less favorable safety profile. In overall serious reports in the U.S., dabigatran had the largest number. After adjusting for differences in exposure, the difference with the more widely dispensed rivaroxaban was still greater, 14.1 serious injury reports per 1,000 person-years for dabigatran, compared to 6.6 for rivaroxaban, and 4.4 for apixaban. Examining the severity of the reported cases, the mortality rate for dabigatran events, at 20.9 % was about double that for the other two drugs.

Table 5. Domestic, serious reports for 3 anticoagulant drugs, 2014									
		Direct to FDA		Death outcome		Embolic-thrombotic*		Hemorrhage*	
Drug	Total	Number, %		Number, %		Number, %		Number, %	
Rivaroxaban	3,331	525	15.8%	379	11.4%	1129	33.9%	1,647	49.4%
Dabigatran	3,592	188	5.2%	752	20.9%	721	20.1%	2,709	75.4%
Apixaban	1,014	95	9.4%	108	10.7%	224	22.1%	492	48.5%
*Standardized MedDRA queries (SMQ), broad scope									

Rivaroxaban cases were notable in one area that would be expected, given its short half-life and once-a-day dosing. It had an excess of embolic-thrombotic events (or treatment failure) compared to the other two drugs. It had the largest number of these cases (n = 1,129) and the largest percentage of cases, 33.9% compared to 20.1% for dabigatran and 22.1% for apixaban.

Apixaban had the best adverse event safety profile by several measures. It had by far the fewest reports (n = 1,014), and the difference remained but was smaller after adjustment for prescription volume. It had the fewest direct reports to the FDA, the fewest deaths, and the lowest percentage of deaths. However, the differences with rivaroxaban in percentage of deaths and total hemorrhage cases were small.

We also compared the three novel anticoagulants to warfarin as a reference drug, and used logistic regression to adjust for other differences in the drugs' reports. The odds of a death outcome for dabigatran compared to warfarin were nearly 3 times higher (Odds Ratio 2.76, $p < 0.001$) after adjusting for patient age, the share of direct reports, and concomitant therapy with other blood-clot-inhibiting drugs. For rivaroxaban, embolic-thrombotic events (treatment failure) compared to warfarin were more likely to be reported (OR 2.73 $p < 0.001$), after adjustment for patient age and other clot-inhibiting medication. The other two novel anticoagulants also had increased odds of embolic-thrombotic events compared to warfarin, but less so: dabigatran (OR 1.45 $p < 0.001$); and apixaban (OR 1.58 $p < 0.01$).

Effect of Platelet Inhibitors

The adverse event data for 2014 raised questions about why no clear guidelines existed about when or even whether patients should take two different kinds of drugs that inhibited the formation of blood clots. The anticoagulants reduce blood clot formation by inhibiting the enzyme that triggers the formation of fibrin threads that help seal the platelets that aggregate to plug bleeding site. Aspirin, clopidogrel, and other non-steroidal anti-inflammatory drugs inhibit the aggregation of platelets. Low-dose aspirin was allowed in the large atrial fibrillation trials for all three drugs–and up to a 2-fold increased bleeding risk was observed among aspirin users.[16] [17][20] An FDA analysis of rivaroxaban showed that in a subgroup of patients with the highest levels of anticoagulation who were also taking aspirin,13.8% experienced severe bleeding.[15]

In the adverse event data, we found that concomitant therapy with platelet inhibitors increased the odds of a hemorrhage event by threefold (OR 3.01 $p < 0.01$). The increased risk was found across all three of the novel anticoagulants and warfarin. However, the 17% of patients on combined therapy had no greater risk of a death outcome ($p = 0.861$) and had a reduced risk of a blood clot/treatment failure event (OR 0.64 $p < 0.001$)

The prescribing information for all three drugs contains no guidance on the concomitant use of anti-platelet agents other than a warning that an increased risk of bleeding was observed. The unsolved problem of combination therapy was further illustrated by the clinical trials in which lower doses of the three novel anticoagulants were tested in high-risk heart patients with Acute Coronary Syndrome (ACS) but only when added to the established treatments using platelet inhibitors. The apixaban trial was stopped because of excess bleeding and no identifiable benefits.[22] Dabigatran development for ACS was stopped after a pilot study.[23] The FDA twice denied an ACS indication for rivaroxaban for ACS after two advisory committees voted that the evidence was not convincing that benefits outweighed the increased risk of bleeding.

Limitations

These adverse event report comparisons have limitations. Although all three anticoagulants are newer brand-name drugs, the adverse event reporting rates could be different. There were other differences among the drugs. Notably, rivaroxaban was used in younger patients, had more diverse indications, and had a larger share of reports from health professionals. Dabigatran had a substantially larger share of reports from consumers. However, we conducted sensitivity analyses to test whether these differences had an effect on the key findings and reported the adjusted odds ratios.

Conclusions

The need for steps to improve the safety of anticoagulant drugs is increasing. Although warfarin remains the most widely used oral anticoagulant drug, the introduction and marketing of three alternatives promising ease of use has increased dispensed prescriptions for these high-risk anticoagulants by 65% since 2010. In calendar quarters after 2010 it appeared that the new anticoagulants were mostly replacing warfarin. However, in the final two quarters of 2014 dispensed warfarin outpatient prescriptions were the highest since 2008.

Actions that could reduce bleeding risks have not been taken. There are limited guidelines for whether to use anticoagulants with platelet inhibitors in long-term use. The FDA has not taken action to reduce the bleeding risks of dabigatran through making a lower dose available for older patients, and blood level tests to identify patients with sub-therapeutic or unusually high blood levels. These risk-reduction tools are available in Europe, Canada, and elsewhere. The safety and efficacy of once-a-day dosing of rivaroxaban compared to twice-a-day dosing needs to be reassessed. It is time to move toward individualizing the dose for all long-term anticoagulant therapy.

Atorvastatin (LIPITOR) Leads Legal Claims

The FDA's adverse event report data form a crossroads between two systems: drug safety regulation through the FDA, and the legal system where thousands of patients pursue claims that they were injured by therapeutic drugs without adequate warnings. Litigation to resolve legal claims (for example whether varenicline (CHANTIX) caused suicidal behaviors and violence) can involve thousands of claimants and require a drug company to produce tens of millions of pages of scientific studies, emails and other documents. The company can demand medical records and other detailed information from every patient claiming to be injured. Both sides employ scientific experts to write lengthy reports with hundreds of citations. A judge (most often a federal judge) evaluates whether the experts have built their opinions on a solid scientific foundation. The net documentation available is usually more elaborate than the hundreds of thousands of pages of studies in a New Drug Application to the FDA and takes several years. Ultimately most legal claims are negotiated settlements, sometimes after trying a group of test cases, and sometimes without a single trial in open court. When drug manufacturers are sued for safety claims, they are required to file adverse event reports, which signal a safety problem important enough to be pursued in the legal system.

In 2014, the largest number of reported legal claims identified atorvastatin (LIPITOR) as the primary suspect. Atorvastatin, a cholesterol-lowering agent, is one of the most widely prescribed drugs in the world. In the 4th quarter of 2014, atorvastatin was the 4th most frequently dispensed outpatient drug in the U.S., accounting for an estimated 11.4 million person-years of exposure.

The Legal Issue: Diabetes

The medical need for atorvastatin is established primarily through a laboratory test of lipids, notably total cholesterol and low-density lipoprotein cholesterol (LDL-C), and the results of treatment are determined through changes in the laboratory test values. Unless adverse effects occur, no changes that a patient could detect are expected. The key medical evidence that this reduced cholesterol is beneficial with atorvastatin came through a long-term clinical trial that established that among patients (mostly men) with hypertension

and high cholesterol, the risks of future cardiovascular events was 36% lower than in a comparable group receiving a placebo.[24] But the chances of any one patient benefiting were small: It took 33,000 person-years of observation to document that treatment with atorvastatin in older high-risk men prevented fewer than 60 cardiovascular events.[24]

Treatment of the adult population with atorvastatin and other statins had been established for a decade when new evidence emerged that while statins lowered the risk of cardiovascular events they apparently increased the risk of diabetes. A trial in low-risk patients with another statin–rosuvastatin (CRESTOR)–showed an increased risk of newly diagnosed Type 2 diabetes.[25] This triggered a wave of research that involved reexamining large previous trials, possible mechanisms of action, and new observational studies. Studies combining 13 previous trials of statins with more than 1,000 patients showed a 9% increased risk of diabetes.[26] But there was an important problem: most earlier large statin trials had a large gender imbalance, enrolling 80% or more men. When investigators re-examined one of the largest clinical studies ever conducted in women, with more than 1 million person-years of follow-up, use of a statin was associated with a 48% adjusted increased risk of diabetes.[27] However, the study was retrospective and designed to monitor the effects of hormone replacement. Higher risk of diabetes for women was confirmed in a re-analysis of results women in cholesterol-lowering clinical trials.[28] While assessments varied, many concluded that the increased risks of diabetes were real, and higher for the more potent statins, rosuvastatin and atorvastatin. Among the results were a new warning from the FDA [29] and major litigation targeting atorvastatin.

Litigation Reported

In 2014, atorvastatin accounted for 4,727 reported legal cases, far more than any other therapeutic drug. (The contraceptive IUD Mirena (levonorgestrel) ranked 2nd with 721 cases.) All of the atorvastatin legal cases indicated the claim was Type 2 diabetes. Notably, 98% of the cases with gender data indicated women. Some cases indicated known complications of diabetes such as damage to the kidneys (n = 49), vision (n = 129) and nerves (n = 185). These cases, however, involve allegations that have yet to be proven through this legal process. However, the underling safety question is significant. Women have a lower risk of cardiovascular disease than men, and if proven to have a 2-3 times higher risk of diabetes, guidelines for treating women with cholesterol lowering drugs need to be reassessed.

When Contradictory Results Occur

In early 2015, lawyers announced the biggest provisional settlement in history for a drug still on the market.[30] The Japanese manufacturer Takeda Pharmaceutical Company offered $2.4 billion to settle 9,000 cases in which legal claimants alleged that pioglitazone (ACTOS) caused bladder cancer, contingent on the requirement that 95% of patients agreed to accept around $300,000 each. Eight cases were tried in court prior to the settlement offer, with plaintiffs winning five cases.

Whether pioglitazone causes bladder cancer was a question with conflicting answers among drug regulators and in observational studies. Pioglitazone was removed from the market in France and Germany in 2011 after a French study showed increased risk of bladder cancer.[31] The European Medicines Agency (EMA), which regulates the rest of Europe, let pioglitazone remain in limited use. The FDA required a warning on the label but did not restrict its use. As a result, patient exposure to pioglitazone in the U.S. remained substantial. In the 4th quarter of 2014, pioglitazone accounted for 1.4 million prescriptions and approximately 650,000 person-years of exposure.

In recent years drug companies have denied that the safety issue exists even while paying large sums of money in compensation. In the case of the proposed pioglitazone settlement, Takeda specifically stated the company "believes the claims made in this litigation are without merit, and does not admit liability."[32] Boehringer Ingelheim made a similar statement when it settled 4,000 lawsuits involving hemorrhages linked to dabigatran (PRADAXA) and agreed to pay $650 million. "We…believed from the outset that the plaintiffs' claims lacked any merit," the company said in a statement.[33] In a third example, Pfizer settled approximately 3,000 lawsuits for $300 million to settle claims that varenicline (CHANTIX) caused suicidal

behaviors, aggression, and other psychiatric side effects. In 2014 Pfizer tried to persuade the FDA to remove the prominent warning about psychiatric side effects, saying the scientific evidence did not support a safety problem for which it had paid damages to all the claimants. An FDA advisory committee rejected Pfizer's request to remove the Boxed Warning in an 18-1 vote.[34]

The final feature of drug safety actions in the legal system is the secrecy that surrounds much of the scientific information–and sometimes all of it–discovered and analyzed in litigation. In the dabigatran litigation the judge released a large group of documents requested by lawyers for the patients. But in the varenicline settlement the judge declined to release any documents. It is unfortunate that most of the scientific information uncovered in these intensive investigations lasting years remain under court seal.

Somatropin and Adverse Events in Children

From a drug safety perspective, children under 18 years of age have several characteristics that set them apart from other age groups. First, they are markedly healthier than adults, with mortality rates that are a fraction of those of middle-aged adults. For example, a 40-year-old-mother is 13 times more likely to die in the next year than her 10-year-old daughter.[35] As a result of good health and for other reasons, medication use is substantially lower for children under age 18 than for other age groups. Children under 18 make up 24% of the population and 19% of visits to the doctor, but only 7.3% of dispensed medications.

In 2014, somatropin (recombinant human growth hormone) accounted for the most serious adverse events reported in children under age 18 (n = 232). The anti-TNF drug infliximab (REMICADE) ranked next (n = 215), followed by the acne medication isotretinoin (ACCUTANE, others) (n = 164).

Somatropin was first approved in 1987 and is currently marketed under 10 brand names, Genotropin, Humatrope, Norditropin, Nutropin, Omnitrope, Saizen, Serostim, Valtropin, Zomacton and Zorbtive. Growth hormone is secreted by the pituitary gland in children, and in smaller amounts in adults. Somatropin was originally approved for a limited patient population of children who were proven to be deficient in growth hormone, or had other rare disorders that resulted in short stature. However, in 2003 the FDA greatly expanded the patient population when it approved somatropin in children who were short in stature for unknown reasons. [36]

At the time it triggered a debate about whether somatropin, which cost $20,000-$30,000 a year, should be used as a "lifestyle" drug because taller children might have higher self-esteem or increased social acceptance than shorter children. In addition, body builders and athletes used somatropin inappropriately to increase muscle mass.

Measuring the benefits of somatropin was challenging from the start because it required years of observation, and assessing additional growth beyond that which was occurring anyway. Further, clinical trials were small and many had no control or comparison group.[37] Also, skeptics worried that increased growth for a year or two might have little effect on final adult height. One meta-analysis of 10 clinical trials in children of short stature concluded that somatropin provided an average increase in adult height from 1.5 inches to 2.3 inches and cost $35,000 per inch of height gained.[38] The reason for various reviewers' concern about the poor quality of the benefit data could be seen in the pivotal clinical trial that won FDA approval for wider use in children who were short but had no identifiable endocrine disorder.[39] It enrolled only 71 patients, divided between somatropin and a placebo, and only 16 receiving somatotropin finished the trial. Because it measured final adult height, it took 12 years to complete. Open label trials were larger, but had no comparison group to assess adverse effects.

Adverse Events

In 2014, we identified 602 serious adverse events reported in the U.S. identifying somatropin as the primary suspect drug, including 232 with age data indicating age less than 18 years. Among cases indicating patient age, the median was 13 years, with one-quarter 9 years old or younger and one-quarter 17 or older. It

included 103 cases where the event required hospitalization, and 32 cases with an outcome of death. However in 24 of the 32 cases indicating a death, the report did not provide enough information to assess whether or not the drug was suspected of contributing to the death.

The most frequent specific adverse event reported was headache (n = 83), which ordinarily might be considered a non-serious event that occurs frequently in the absence of any drug therapy. However, 94% of cases were reported by health professionals, and headache was only one among a diverse group of symptoms that included joint pain, nausea, constipation, and vomiting. Another group of serious reports alleged that somatropin was apparently not working and were coded in these data as 72 cases of growth retardation. A third group of reports described cases of abnormal bone development including scoliosis (n = 30), limb asymmetry (n = 8) and abnormal bone development (n = 6). We also noted that a substantial share of children with reported serious adverse events were on multiple hormones or steroid drugs, including 24% also taking levothyroxine, a thyroid replacement, 19% taking hydrocortisone, and 6% taking testosterone.

Conclusions

Even though human growth hormone has been available for more than 25 years, the data about both benefits and risks are limited. The benefit in accelerated growth is hard to measure. The clinical trials were small and had many dropouts. Although treatment typically lasts several years, late onset adverse events are particularly difficult to assess. These data illustrate the need for more and better information about this hormone.

Other Perspectives

Reports in Older Patients

Denosumab (PROLIA), a biological product for high-risk women with osteoporosis, leads all other drugs in domestic reports of serious injury and death in patients 75 years age and older. We identified 2,982 reports in 2014 overall. The reports indicated the median age was 78 years; one-quarter of the patients were 86 years or older; and 77% were women. The same product, under the brand name XGEVA, is also approved for treatment with abnormally high calcium levels as a result of cancer. Xgeva reports accounted for 9.6% of the total. Denosumab blocks the effect of the bone cells that cause turnover, thereby increasing bone density, and is administered by health professionals as a twice-a-year injection.

The reports show that denosumab shares with the other major class of drugs for osteoporosis–the bisphosphonates–the risk of osteonecrosis of the jaw (n = 132). We also identified 275 cases of hypersensitivity. Other reports indicated adverse effects on mineral metabolism (hypocalcaemia, n = 74; vitamin D deficiency, n = 45). The denosumab reports also included 1,032 reports of patient deaths without information about whether a drug role was either suspected or investigated.

Reports of Estrogen Products

Monitoring serious adverse events associated with estrogen products is challenging because of the many different products, combinations, and uses. The largest number of reports of domestic serious injury was for MIRENA, an intrauterine contraceptive device (IUD) that releases levonorgestrel and can be used for up to 5 years.

In 2014 we identified 3,021 domestic reports of serious injury for Mirena, with a large majority indicating an IUD device injury including device dislocation (n = 1,131), uterine perforation (n = 8,790), genital hemorrhage (n = 745), and embedded device (n = 279). A single report could contain more than one of these terms. In addition to these cases, Mirena also ranked second in a separate tally of lawsuit-related cases, with 721 additional cases. Drugs that become litigation targets may also affect report totals outside of litigation because advertising for cases may increase awareness of the putative adverse effect.

Product Problem Reports

The Spiriva HandiHaler (tiotropium) accounted for the largest number of product problems reported in the U.S. in 2014, a total 843 reports. Product problems are monitored differently from other drug safety issues using the brand name to identify the product and including both serious and non-serious reports (but not foreign reports). The Spiriva report excerpts generally did not identify the specific nature of the product problem, with most indicating an unspecified "product quality issue." The Spiriva HandiHaler product was also involved in two recalls at the wholesale level, one in late 2013 because of possible foreign particles in the source material, and in spring of 2014 for a possible interaction of the powder with a lubricant on the capsule shell. The company told us that 9.6 million prescriptions were shipped in 2014 in the U.S. with 408 million capsules.

QuarterWatch Team and Funding Sources

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Thomas J. Moore serves as a part-time project director for QuarterWatch. He has developed and maintains the master adverse event database that serves as the primary data source for the publication and conducts the primary analysis for each issue. Mr. Moore receives an honorarium from ISMP for each issue, with the remaining work being on a volunteer basis. He is also a lecturer in the Department of Epidemiology and Biostatistics in The George Washington University School of Public Health and Health Services. Mr. Moore also conducts and publishes other independent studies in the peer-reviewed scientific literature and works as a consultant on drug safety issues, doing business under the name Drug Safety Research. He was a consulting expert to the Attorney General of the State of Texas in a Medicaid fraud lawsuit against Johnson & Johnson regarding the antipsychotic drug Risperdal (risperidone), and was an expert witness for the United States Army in connection with a criminal case involving Chantix (varenicline). He also worked as a consulting expert for plaintiffs in the civil litigation regarding Chantix. In 2013 he was a consulting expert for the plaintiffs in the Celexa and Lexapro Marketing and Sales Practices Litigation. He also conducts confidential assessments for attorneys inquiring about the safety profiles of drugs.

Curt D. Furberg, MD, PhD is a Professor Emeritus of Public Health Sciences at Wake Forest University School of Medicine and serves as senior medical adviser to QuarterWatch. He receives no compensation for his work in assessing scientific evidence, defining safety issues, shaping the written report, and communicating with the FDA and others about QuarterWatch findings. He continues to have a research role at Wake Forest and has published more than 450 peer-reviewed scientific articles. An expert on clinical trials of drug treatments, Dr. Furberg is author of a major textbook on that subject, and has worked for the National Institutes of Health and the pharmaceutical industry as an investigator in clinical drug research. In the past five years, has given expert testimony or depositions in cases involving COX-2 inhibitors, Fosamax (alendronate), and Chantix (varenicline). Dr. Furberg is a member of the British Medical Journal Advisory Board.

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Michael R. Cohen, RPh, MS, ScD (hon) is founder and President of ISMP and guides the overall policies and content of QuarterWatch. He also edits the other ISMP newsletters and is author of the textbook *Medication Errors*. He has served as an advisor and consultant to the FDA, and for his work in medication safety was recognized as a MacArthur Fellow by the John D. and Catherine T. MacArthur Foundation. Dr. Cohen receives a regular salary as president of ISMP and does not engage in outside consulting or legal testimony.

References

1. FDA Adverse Event Reporting System (FAERS). (2014) US Food and Drug Administration web site. URL: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/default.htm. Accessed 8 September 2015.

2. Code of Federal Regulations Title 21 314.80 Postmarketing reporting of adverse drug experiences. (2011) Food and Drug Administration. URL: http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?fr=314.80. Accessed 7 April 2014.

3. MedDRA MSSO. (2014) Introductory Guide MedDRA Version 17.1. Chantilly, VA: MedDRA Maintenance and Support Services Organization.

4. MedDRA MSSO. (2014) Introductory Guide for Standardised MedDRA Queries (SMQs) Version 17.1. Chantilly, VA: MedDRA Maintenance and Support Services Organization.

5. Unified Medical Language System: RxNorm. (2014) National Library of Medicine. URL: http://www.nlm.nih.gov/research/umls/rxnorm/. Accessed 23 April 2014.

6. Moore TJ, Furberg CD, Mattison DR, Cohen MR. (2015) QuarterWatch 2014 Quarter 2: New Safety Perspectives. Institute for Safe Medication Practices. URL: http://www.ismp.org/QuarterWatch/pdfs/2014Q2.pdf.

7. Caskey L, Lyle J, Antoli S, Cornwal MA. (2014) Medicine use and shifting costs of healthcare: A review of the use of medicines in the United States in 2013. Parsippany, NJ: IMS Institute for Healthcare Informatics.

8. Nisen M. (2015) The best selling prescription drugs in the world last year. Quartz.

9. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. (2011) Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 365: 2002–2012.

10. Moore TJ, Cohen MR, Mattison DR, Furberg CD. (2014) QuarterWatch 2013 Quarter 1: Perspective on Drug Hypersensitivity. Institute for Safe Medication Practices. URL: http://www.ismp.org/QuarterWatch/pdfs/2013Q1.pdf.

11. Moore TJ, Cohen MR, Mattison DR. (2014) Dabigatran, bleeding, and the regulators. BMJ 349: g4517.

12. Unger EF. (2010) Summary Review: Deputy Office Director Decisional Memo. NDA 22-512. Pradaxa dabigatran etexilate. US Food and Drug Administration web site. URL: http://www.accessdata.fda.gov/drugsatfda_docs/nda/2010/022512Orig1s000SumR.pdf. Accessed 27 May 2012.

13. Prescribing information for XARELTO (rivaroxaban) tablet, film coated [package insert]. (2014) Ridgefield, CT: Boehringer Ingelheim Pharmaceuticals, Inc.

14. Frost C, Song Y, Barrett YC, Wang J, Pursley J, et al. (2014) A randomized direct comparison of the pharmacokinetics and pharmacodynamics of apixaban and rivaroxaban. Clin Pharmacol 6: 179–187.

15. Sabarinath S, McDowell T. (2011) Clinical Pharmacology Review: NDA 202-438 Rivaroxaban (XARELTO). Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research.

16. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, et al. (2009) Dabigatran versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med 361: 1139–1151.

17. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, et al. (2011) Rivaroxaban versus Warfarin in Nonvalvular Atrial Fibrillation. N Engl J Med: 110810140021022.

18. Lassen MR, Davidson BL, Gallus A, Pineo G, Ansell J, et al. (2007) The efficacy and safety of apixaban, an oral, direct factor Xa inhibitor, as thromboprophylaxis in patients following total knee replacement. J Thromb Haemost 5: 2368–2375.

19. Lassen MR, Gallus A, Raskob GE, Pineo G, Chen D, et al. (2010) Apixaban versus enoxaparin for thromboprophylaxis after hip replacement. N Engl J Med 363: 2487–2498.

20. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, et al. (2011) Apixaban versus Warfarin in Patients with Atrial Fibrillation. N Engl J Med: 110827230022006.

21. Temple R. (2012) Complete Response NDA 202155 Eliquis (apixaban) tablets.

22. Alexander JH, Lopes RD, James S, Kilaru R, He Y, et al. (2011) Apixaban with Antiplatelet Therapy after Acute Coronary Syndrome. N Engl J Med 365: 699–708.

23. Oldgren J, Budaj A, Granger CB, Khder Y, Roberts J, et al. (2011) Dabigatran vs. placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J 32: 2781–2789.

24. Sever PS, Dahlöf B, Poulter NR, Wedel H, Beevers G, et al. (2003) Prevention of coronary and stroke events with atorvastatin in hypertensive patients who have average or lower-than-average cholesterol concentrations, in the Anglo-Scandinavian Cardiac Outcomes Trial--Lipid Lowering Arm (ASCOT-LLA): a multicentre randomised controlled trial. Lancet 361: 1149–1158.

25. Ridker PM, Danielson E, Fonseca FAH, Genest J, Gotto AM, et al. (2008) Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein. N Engl J Med 359: 2195–2207.

26. Sattar N, Preiss D, Murray HM, Welsh P, Buckley BM, et al. (2010) Statins and risk of incident diabetes: a collaborative meta-analysis of randomised statin trials. Lancet 375: 735–742.

27. Culver AL, Ockene IS, Balasubramanian R, Olendzki BC, Sepavich DM, et al. (2012) Statin use and risk of diabetes mellitus in postmenopausal women in the Women's Health Initiative. Arch Intern Med 172: 144–152.

28. Goodarzi MO, Li X, Krauss RM, Rotter JI, Chen Y-DI. (2013) Relationship of sex to diabetes risk in statin trials. Diabetes Care 36: e100–e101.

29. FDA Drug Safety Communication: Important safety label changes to cholesterol-lowering statin drugs. (2012) Food and Drug Administration web site. URL: http://www.fda.gov/Drugs/DrugSafety/ucm293101.htm. Accessed 25 August 2015.

30. Llamas M. (n.d.) Breaking News: Takeda Settles Actos Lawsuits for $2.37 Billion. DrugWatch.

31. Actions Taken on Actos® and Competact® by French Regulatory Authorities | Takeda Pharmaceutical Company Limited. (2011) Takeda web site. URL: https://www.takeda.com/news/2011/20110613_3871.html. Accessed 25 August 2015.

32. Takeda Agrees to Settle ACTOS Product Liability Lawsuits and Claims; Takeda Stresses Continued Commitment to ACTOS | Takeda Pharmaceutical Company Limited. (2015) Takeda web site. URL: http://www.takeda.com/news/2015/20150429_6975.html. Accessed 26 August 2015.

33. Boehringer Ingelheim announces comprehensive settlement of U.S. Pradaxa® (dabigatran etexilate) litigation. (2014) Boehringer Ingelheim web site. URL: http://www.boehringer-ingelheim.com/news/news_releases/press_releases/2014/28_may_2014_dabigatranetexilate.html. Accessed 26 August 2015.

34. Bhatt K, Parker R. (2014) Summary Minutes of the Joint Meeting of the Psychopharmacolgic Drugs Advisory Committee and the Drug Safety and Risk Management Advisory Committee, October 16, 2014. Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research.

35. Hoyert DL, Xu J. (2012) Deaths: preliminary data for 2011. Natl Vital Stat Rep 61: 1–65.

36. Parks M. (2008) Division Director Memo NDA 20-280/Supplement 60: Genotropin (recombinant human growth hormone) Indication: Idopathic Short Statute. Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research.

37. Loftus J, Heatley R, Walsh C, Dimitri P. (2010) Systematic review of the clinical effectiveness of Genotropin (somatropin) in children with short stature. J Pediatr Endocrinol Metab 23: 535–551.

38. Finkelstein BS, Imperiale TF, Speroff T, Marrero U, Radcliffe DJ, et al. (2002) Effect of growth hormone therapy on height in children with idiopathic short stature: a meta-analysis. Arch Pediatr Adolesc Med 156: 230–240.

39. Clinical Review: Humatrope (somatropin[rDNA orgin] for injection). (2003) Silver Spring, MD: Food and Drug Administration, Center for Drug Evaluation and Research.

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EXHIBIT B

HEALTH NEWS | Sun Sep 8, 2013 | 12:07pm EDT

Reports of side-effects from Bayer's Xarelto grow: Spiegel

Bayer faces a growing number of reports of suspected undesirable side-effects from its stroke prevention pill Xarelto, German magazine Der Spiegel reported, citing data from a federal authority.

There was a total of 968 cases of suspected undesirable side-effects related to Xarelto in the first eights months of 2013, including 72 cases of death, the magazine reported, citing Germany's Federal Institute for Drugs and Medical Devices (BfArM).

This compares to 750 cases of side-effects, including 58 cases of death, for the whole of 2012, the magazine said. BfArM said there was no clear proof of a correlation between the drug and side effects, the report said.

Jointly developed with U.S. peer Johnson & Johnson, Xarelto is one of Bayer's most important new drugs, expected to earn annual peak sales of more than 2 billion euros ($2.63 billion).

In the second quarter, Bayer made 219 million euros in sales from the anti-clotting pill, more than three times as much as during the same period last year.

When asked about the report on Sunday, a spokesman for Bayer said Xarelto's risk-benefit profile was still intact.

BfArM was not immediately available for comment.

(Reporting by Frank Siebelt, Hans Seidenstuecker and Christoph Steitz, editing by William Hardy)

NEXT IN HEALTH NEWS

CVS removes artificial trans fats from its food brands

CVS Health Corp said its pharmacy chain had removed artificial trans fats, which have been linked to rising rates of heart diseases, from its store-branded food products well ahead of a June 2018 federal deadline.

Thermo Fisher did not infringe genetic-testing patent, U.S. top court says

The U.S. Supreme Court on Wednesday cleared a subsidiary of biotech company Thermo Fisher Scientific Inc of infringing a genetic-testing kit patent held by Promega Corp, overturning a lower court's decision.

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EXHIBIT C

Comparative effectiveness and safety of non-vitamin K antagonist oral anticoagulants and warfarin in patients with atrial fibrillation: propensity weighted nationwide cohort study

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ABSTRACT

OBJECTIVE

To study the effectiveness and safety of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) dabigatran, rivaroxaban, and apixaban compared with warfarin in anticoagulant naïve patients with atrial fibrillation.

DESIGN

Observational nationwide cohort study.

SETTING

Three Danish nationwide databases, August 2011 to October 2015.

PARTICIPANTS

61678 patients with non-valvular atrial fibrillation who were naïve to oral anticoagulants and had no previous indication for valvular atrial fibrillation or venous thromboembolism. The study population was distributed according to treatment type: warfarin (n=35 436, 57%), dabigatran 150 mg (n=12 701, 21%), rivaroxaban 20 mg (n=7192, 12%), and apixaban 5 mg (n=6349, 10%).

MAIN OUTCOME MEASURES

Effectiveness outcomes defined a priori were ischaemic stroke; a composite of ischaemic stroke or systemic embolism; death; and a composite of ischaemic stroke, systemic embolism, or death. Safety outcomes were any bleeding, intracranial bleeding, and major bleeding.

RESULTS

When the analysis was restricted to ischaemic stroke, NOACs were not significantly different from warfarin. During one year follow-up, rivaroxaban was associated with lower annual rates of ischaemic stroke or systemic embolism (3.0% *v* 3.3%, respectively) compared with warfarin: hazard ratio 0.83 (95% confidence interval 0.69 to 0.99). The hazard ratios for dabigatran and apixaban (2.8% and 4.9% annually, respectively) were non-significant compared with warfarin. The annual risk of death was significantly lower with apixaban (5.2%) and dabigatran (2.7%) (0.65, 0.56 to 0.75 and 0.63, 0.48 to 0.82, respectively) compared with warfarin (8.5%), but not with rivaroxaban (7.7%). For the combined endpoint of any bleeding, annual rates for apixaban (3.3%) and dabigatran (2.4%) were significantly lower than for warfarin (5.0%) (0.62, 0.51 to 0.74). Warfarin and rivaroxaban had comparable annual bleeding rates (5.3%).

CONCLUSION

All NOACs seem to be safe and effective alternatives to warfarin in a routine care setting. No significant difference was found between NOACs and warfarin for ischaemic stroke. The risks of death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran compared with warfarin.

WHAT IS ALREADY KNOWN ON THIS TOPIC

The use of non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) has been increasing since their introduction

Based on data from clinical practice, however, limited evidence exists on effectiveness and safety of NOACs compared with warfarin

WHAT THIS STUDY ADDS

No significant difference in risk of ischaemic stroke was evident between NOACs and warfarin

Rivaroxaban was associated with a lower risk of ischaemic stroke or systemic embolism than warfarin, but with comparable major bleeding rates

Dabigatran and apixaban had non-significant hazard ratios compared with warfarin for ischaemic stroke or systemic embolism, whereas major bleeding rates were significantly lower with reference to warfarin

Introduction

Oral anticoagulant treatment with either vitamin K antagonists or non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) is essential for the prevention of stroke or systemic embolism and all cause mortality in patients with atrial fibrillation and one or more risk factors for stroke. The four currently available NOACs are dabigatran, rivaroxaban, apixaban, and edoxaban.[1-4] In clinical studies these drugs show similar efficacy and safety to warfarin, but with more convenience such as no requirement of meticulous dose adjustment to achieve optimal treatment. NOACs are therefore the preferred treatment option in some guidelines, especially where anticoagulation control with warfarin is suboptimal.[5]

A meta-analysis showed that NOACs at standard dose have a favourable risk-benefit profile compared with warfarin, with significant reductions in stroke or systemic embolism, intracranial haemorrhage, and mortality, but a similar major bleeding profile to warfarin, apart from increased gastrointestinal bleeding.[6] The relative efficacy and safety of NOACs were consistent across a wide range of patients.

Thus the use of NOACs in daily clinical practice has been increasing since their introduction.[7] Only large scale real world comparisons of a single NOAC versus warfarin have been published or presented. Evidence relating to the comparative effectiveness and safety of all oral anticoagulant drugs used in clinical practice is currently lacking.

We assessed and compared the effectiveness and safety of dabigatran, rivaroxaban, and apixaban compared with warfarin in clinical practice using a nationwide Danish cohort of patients with atrial fibrillation who were naïve to oral anticoagulants.

Methods

This study is based on data from three Danish nationwide databases: the Danish national prescription registry,[8] which holds information on purchase date, Anatomical Therapeutic Chemical (ATC) classification code, and package size for every prescription claimed since 1994; the Danish national patient register[9] established in 1977, which includes admission and discharge dates, and discharge diagnoses (international classification of diseases) for more than 99% of hospital admissions; and the Danish civil registration system,[10] with information on sex, date of birth, and vital and emigration status. Any individual in Denmark has a unique identification number, allowing linkage at individual level between databases.

Study population

We identified people with a first time purchase of a NOAC: apixaban (introduced 10 December 2012), dabigatran (1 August 2011), rivaroxaban (1 February 2012), as well as patients who started warfarin treatment (from 1 August 2011) up to 30 November 2015. All prescribed drugs in Denmark are partially reimbursed, based on a patient's level of drug expenses.

To study a cohort of patients treated for atrial fibrillation, we applied several criteria. We restricted the consumption of NOACs to standard doses (apixaban 5 mg twice daily, dabigatran 150 mg twice daily, and rivaroxaban 20 mg once daily). Warfarin is only available in 2.5 mg dose tablets in Denmark. We decided to focus our analyses on patients receiving standard dosages of apixaban, dabigatran, and rivaroxaban, because patients who receive reduced dosage regimens have more comorbidities and are of more advanced age (>80 years). Thus, comparisons across various dosing regimens and choices of antithrombotic agent could result in comparisons on mixed cohorts in terms of comorbidities, age, and concomitant treatment. Confining the analysis to patients receiving standard dosages only will thus allow for easier interpretation and a more robust comparison of cohorts. To establish a cohort of patients who were naïve to oral anticoagulant treatment, we excluded those who had used any oral anticoagulant within one year. We also excluded patients with hospital diagnoses indicating valvular atrial fibrillation (mitral stenosis or mechanical heart valves) or venous thromboembolism (pulmonary embolism or deep vein thrombosis) to narrow the included patients to only those who were likely to have been prescribed oral anticoagulants because of a diagnosis of atrial fibrillation in either hospital or general practice. The entire cohort comprised patients with atrial fibrillation. We also analysed a subgroup of patients who had been admitted to hospital with a diagnosis of atrial fibrillation.

Endpoints and variable definitions

Participants were followed until 30 November 2015 in the Danish national patient register for the occurrence of ischaemic stroke or systemic embolism and for ischaemic stroke separately (see supplementary table 1 for specific international classification of diseases, 10th revision codes). The outcome of ischaemic stroke has been validated, with a positive predictive value of more than 97%.[11] Because oral anticoagulants reduce the risk of both stroke and death, we included all cause mortality as a lone endpoint and as a combined endpoint with stroke.[12]

We recorded bleeding events as intracranial, major, gastrointestinal, and traumatic intracranial, reported in total as "any bleeding" and specific for intracranial and extracranial major bleeding. Extracranial major bleeding was defined as bleeding with anaemia, haemothorax, haematuria, epistaxis, and bleeding in the eye (see supplementary material for details).

Demographic data were obtained from the Danish civil registration system. Comorbidities and co-treatments (listed in table 1) were ascertained from the Danish national patient registry and the Danish national prescription registry (see supplementary table 1 for definitions of codes). We combined covariate information into the CHA_2DS_2VASc score[13] for assessing stroke risk, and a HAS-BLED score[14] as a measure of bleeding risk (see supplementary table 2 for definitions of scores).

Statistical analysis

To compare the risk of an endpoint between treatment groups we used time to event analysis, measuring risk time from initial prescription and until the relevant event, emigration, death, or end of follow-up, whichever came first. An intention to treat approach was applied for the analyses of all endpoints. The supplementary material shows the results of a continuous treatment analysis, by censoring follow-up if the patient was prescribed another treatment than that initiated.

We calculated crude incidence as the number of events divided by person time. Cox regression was used to compare event rates between the treatment groups, with warfarin as the primary reference. To deal with confounding by indication of treatment, we applied an inverse probability of treatment weighted analysis. Such an approach is suitable in situations with several treatment alternatives.[15,16] We used generalised boosted models, based on 10 000 regression trees, to calculate weights for optimal balance between the treatment populations.[17] The weights were derived to obtain estimates representing population average treatment effects. The underlying propensity models included the treatment predictors of age (continuous); binary indicators for sex; ischaemic stroke or systemic embolism or transient ischaemic attack; vascular disease; hypertension; diabetes; cancer; recent prescription of aspirin, β blockers, non-steroidal anti-inflammatory drugs, or statins; and CHA_2DS_2-VASc and HAS-BLED scores.

The treatments should be contrasted on comparable populations, and any patient must have a positive

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Table 1 | Participant characteristics according to treatment. Values are numbers (percentages) unless stated otherwise

Characteristics	NOAC			Warfarin	All	Maximum standardised difference*	
	Apixaban	Dabigatran	Rivaroxaban			Before	After
No in group				35 436	61 678	-	-
Women	39.7 (2522)	33.9 (4304)	43.1 (3100)	41.2 (14 598)	39.8 (24 524)	0.19	0.02
Median (interquartile range) age (years)	71.3 (65.8-77.2)	67.6 (62.0-72.4)	71.8 (65.7-78.9)	72.4 (64.7-79.8)	70.9 (64.3-77.7)	0.45	0.02
Age >65	78.2 (4967)	64.4 (8180)	77.7 (5590)	74.2 (26 295)	73.0 (45 032)	0.31	0.02
Age >75	33.7 (2140)	13.9 (1766)	38.1 (2737)	41.4 (14 655)	34.5 (21 298)	0.58	0.03
Previous atrial fibrillation diagnose	68.9 (4374)	70.0 (8889)	60.2 (4333)	51.5 (18 243)	58.1 (35 839)	0.38	0.02
Mean (SD) CHA_2DS_2VASc score†	2.8 (1.6)	2.2 (1.4)	2.8 (1.6)	2.8 (1.7)	2.7 (1.6)	0.39	0.02
Mean (SD) HAS-BLED score‡	2.3 (1.2)	2.0 (1.1)	2.2 (1.2)	2.2 (1.2)	2.2 (1.2)	0.25	0.01
Cancer	16.1 (1021)	11.8 (1495)	16.1 (1159)	16.5 (5862)	15.5 (9537)	0.13	0.02
Ischaemic stroke, or systemic embolism, or TIA	21.1 (1339)	13.2 (1674)	16.8 (1209)	14.8 (5241)	15.3 (9463)	0.22	0.03
Heart failure or LVD	15.9 (1009)	9.3 (1187)	12.6 (908)	10.4 (3699)	11.0 (6803)	0.13	0.03
Vascular disease	13.9 (882)	10.4 (1319)	12.2 (879)	18.1 (6407)	15.4 (9487)	0.21	0.02
Renal dysfunction	2.4 (155)	1.1 (145)	1.8 (131)	6.6 (2346)	4.5 (2777)	0.26	0.04
COPD	8.9 (564)	6.2 (787)	8.8 (636)	9.6 (3403)	8.7 (5390)	0.12	0.02
Previous bleeding	14.0 (886)	9.9 (1257)	12.8 (923)	11.8 (4185)	11.8 (7251)	0.13	0.02
Hypertension	48.8 (3099)	47.0 (5971)	48.6 (3492)	50.6 (17 932)	49.4 (30 494)	0.07	0.01
Diabetes	15.8 (1000)	13.8 (1754)	14.0 (1006)	15.6 (5513)	15.0 (9273)	0.05	0.03
Aspirin	37.8 (2400)	38.2 (4853)	38.3 (2751)	42.0 (14 895)	40.4 (24 899)	0.09	0.01
β blocker	38.6 (2450)	40.1 (5093)	38.9 (2801)	41.0 (14 518)	40.3 (24 862)	0.05	0.01
NSAIDs	22.4 (1422)	24.5 (3114)	22.1 (1586)	24.3 (8616)	23.9 (14 738)	0.06	0.01
Statins	40.6 (2577)	37.8 (4805)	38.4 (2764)	40.0 (14 181)	39.4 (24 327)	0.06	0.02

TIA=transient ischaemic attack; LVD=left ventricular dysfunction; COPD=chronic obstructive pulmonary disease; NSAIDs=non-steroidal anti-inflammatory drugs.
*Maximum standardised pairwise difference, before and after inverse probability of treatment weighting.
†Scores range from 0-9, reflecting risk of stroke in patients with atrial fibrillation not receiving anticoagulants (see supplementary table 2).
‡Scores range from 0-9, reflecting risk of bleeding in patients with atrial fibrillation receiving anticoagulants (see supplementary table 2).

probability for any treatment, hence substantial overlap between the scores for each treatment should be present. This was assessed by graphical inspection of the weight distributions.[16] We evaluated the balance between treatment populations by standardised differences of all baseline covariates, using a threshold of 0.1 to indicate imbalance.[18] Ordinary logistic regression was used to evaluate the association of baseline characteristics on treatment choice versus any of the alternatives.

We assessed the sensitivity of inclusion criteria and analytical method. The analyses were repeated by restricting to the cohort of patients with a hospital discharge diagnosis of atrial fibrillation either before or within 30 days of the first prescription of a NOAC. Selection bias could be suspected at introduction of dabigatran as this initial group may have had an excess of patients with special conditions making warfarin intractable. To avoid this potential bias we carried out an analysis where inclusion of patients using dabigatran was postponed to February 2012. We compared the results of the inverse probability of treatment weighted analysis with an ordinary crude and adjusted analysis as well as a standardised morbidity ratio weighted analysis, weighting the warfarin stratum with the expected odds of receiving treatment with a NOAC. To account for baseline differences and potential confounding we used the same covariates as for the propensity models to adjust the standardised morbidity ratio and the ordinary analyses. The results are provided in the supplementary material.

The analyses on the entire population were supplemented by stratified analyses on the populations younger and older than 65, as well as stratified according to previous experience of stroke, systemic embolism, or transient ischaemic attack. These two classifications represented primary and secondary prevention treatment groups, respectively.

Stata/MP version 14 and R version 3.1.1 was used for the statistical analysis. We considered a two sided P value of less than 0.05 to be significant.

Patient involvement

No patients were involved in setting the research question, the outcome measures, or the study design; there are no plans to actively involve patients in dissemination of the results. Ethical approval for observational studies using Danish nationwide registries is not required in Denmark.

Results

We identified 122 068 patients as new users of oral anticoagulant treatment, including 35 035 patients receiving one of the non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) with reduced doses, who were excluded. Overall, we excluded 25 355 patients with an indication for valvular atrial fibrillation or venous thromboembolism (see supplementary figure 1). The study population (n=61 678) was distributed according to treatment type: warfarin (n=35 436, 57%), dabigatran (n=12 701, 21%), rivaroxaban (n=7192, 12%), and apixaban (n=6349, 10%). Supplementary figure 2 shows

the progress of patients new to oral anticoagulants. The average follow-up was 1.9 years, with the shortest in the apixaban group (average 0.9 years), owing to its later introduction to the market.

Table 1 presents the baseline information of the initial study population before weighting. Patients who started dabigatran were slightly younger (<14% aged ≥75) and had fewer risk factors for stroke, as summarised by a CHA_2DS_2-VASc score of 2.2, than other groups (older, with >33% aged ≥75 and a CHA_2DS_2-VASc score of 2.8). More patients in the apixaban (69%) and dabigatran (70%) groups had a diagnosis of atrial fibrillation before (or in connection with) the initiation of treatment, compared with patients in the rivaroxaban and warfarin groups (60% and 52%, respectively). Patients treated with apixaban had a higher prevalence of previous ischaemic stroke, systemic embolism, or transient ischaemic attack (21%), whereas previous vascular disease was most prevalent among patients who started with warfarin. Patients treated with dabigatran had the lowest proportion of renal impairment (1.1%) in contrast with warfarin users (6.6%).

After the study populations had been weighted using the inverse probability of treatment weighted method, all baseline differences were less than 0.04 standardised differences at maximum. Inspection of individual propensity score distributions showed sufficient overlap between treatment populations to obtain valid comparisons (data not shown).

Baseline characteristics and treatment choices

Supplementary table 3 shows the odds ratios for treatment compared with any of the alternatives. The likelihood of apixaban use (contrasted to the three other alternatives) was increased (odds ratio >1.1) in the presence of previous ischaemic stroke, systemic embolism, or transient ischaemic attack; vascular disease; bleeding; and hospital confirmed atrial fibrillation, but it was reduced (odds ratio <0.9) by renal impairment and aspirin use. Choice of dabigatran was increased with a hospital diagnosis of atrial fibrillation but reduced if the patient was female, and had vascular disease, renal impairment, chronic obstructive pulmonary disease (COPD), heart failure, or cancer. The probability for selecting rivaroxaban was increased by female sex, previous ischaemic stroke, systemic embolism, or transient ischaemic attack, or bleeding but reduced by vascular disease, renal impairment, heart failure, or use of non-steroidal anti-inflammatory drugs. Treatment with warfarin was more likely if the patient was female, had vascular disease, hypertension, renal impairment, COPD, heart failure, or cancer, or used aspirin but less likely in patients with a confirmed hospital diagnosis of atrial fibrillation.

Ischaemic stroke and systemic embolism

During the first year of follow-up, 1702 ischaemic stroke or systemic embolism events were observed. Crude cumulative incidence curves for the endpoint (fig 1)

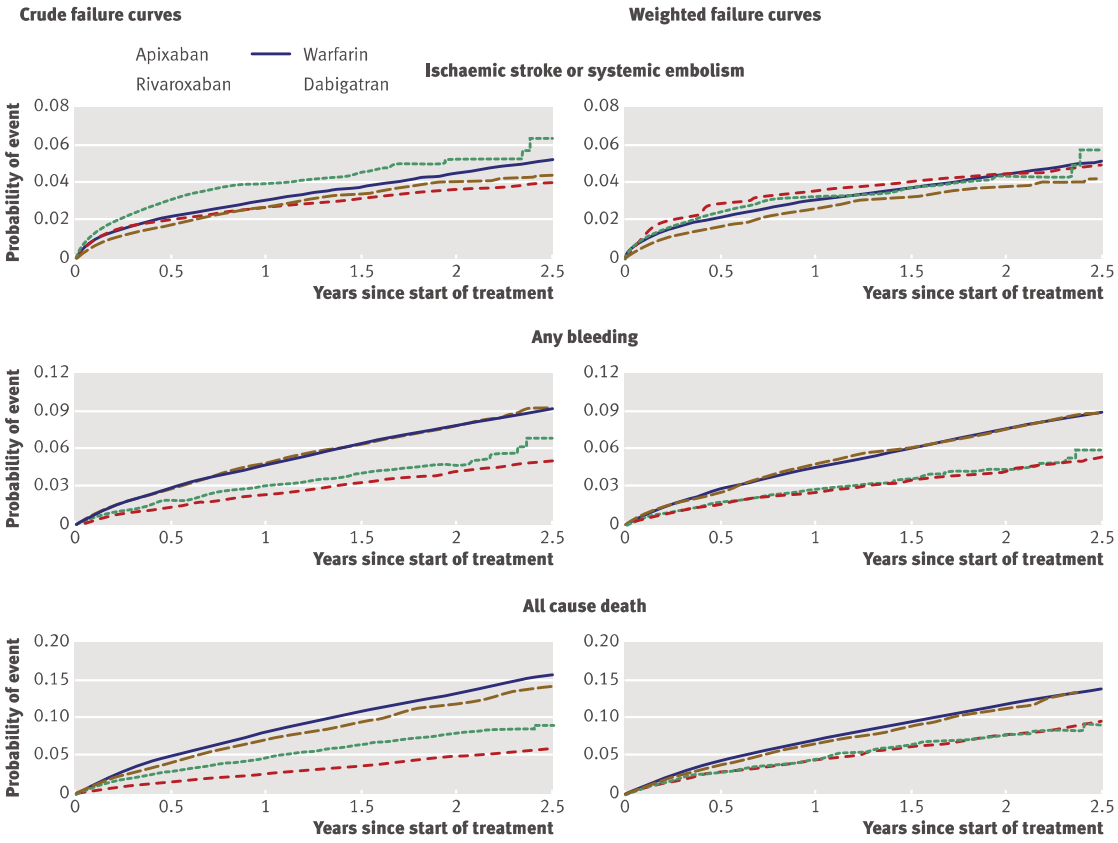

Fig 1 | Crude cumulative incidence curves of stroke, any bleeding, and all cause mortality according to initiated treatment. See supplementary material for corresponding curves for individual endpoints and for combined endpoints

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Table 2 | Number of events, and crude and weighted event rates according to initiated treatment

	Apixaban			Dabigatran			Rivaroxaban			Warfarin		
Variables	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†	Events	Crude rate*	Weighted rate†
One year follow-up:												
Ischaemic stroke or systemic embolism	210	4.86	3.92	327	2.77	3.73	161	3.04	2.89	1004	3.28	3.25
Ischaemic stroke	204	4.71	3.72	321	2.72	3.68	156	2.95	2.79	920	3.00	3.01
All cause mortality	232	5.23	5.01	319	2.66	4.62	413	7.69	7.02	2652	8.52	7.41
Ischaemic stroke, systemic embolism, or death	424	9.81	8.71	623	5.28	7.92	537	10.15	9.38	3483	11.39	10.28
Any bleeding	121	3.78	3.13	253	2.77	2.85	186	5.57	4.83	959	5.53	4.71
Major bleeding	90	2.80	2.29	203	2.22	2.04	149	4.44	3.92	725	4.16	3.58
Intracranial bleeding	15	0.46	0.40	19	0.21	0.22	14	0.41	0.31	118	0.66	0.55
2.5 years' follow-up:												
Ischaemic stroke or systemic embolism	225	4.08	3.32	441	1.84	2.32	201	2.34	2.21	1447	2.39	2.33
Ischaemic stroke	219	3.97	3.17	427	1.78	2.26	196	2.28	2.15	1337	2.20	2.17
All cause mortality	274	4.82	4.69	600	2.44	4.04	592	6.74	6.31	4469	7.17	6.20
Ischaemic stroke, systemic embolism, or death	473	8.58	7.75	992	4.13	6.10	733	8.53	8.03	5524	9.11	8.13
Any bleeding	143	3.52	2.90	461	2.48	2.67	252	4.60	4.09	1579	4.60	3.93
Major bleeding	109	2.67	2.15	376	2.01	2.02	200	3.63	3.27	1198	3.46	2.98
Intracranial bleeding	18	0.43	0.41	35	0.18	0.17	23	0.40	0.31	190	0.53	0.44

*Events divided by 100 person years.
†Inverse probability of treatment weighted and expressed as population average treatment rates per 100 years.

showed no distinct differences between the four treatments after applying weights. Weighted rates for ischaemic stroke or systemic embolism ranged from 2.9 to 3.9 per 100 person years among the NOACs and 3.3 specifically for warfarin (table 2).

When restricting the analysis to ischaemic stroke only, no significant differences were evident for the NOACs compared with warfarin across strata (fig 2, table 2). Rivaroxaban was associated with lower rates of ischaemic stroke or systemic embolism compared with warfarin: the hazard ratio at one year was 0.83 (95% confidence interval 0.69 to 0.99) and after 2.5 years was 0.80 (0.69 to 0.94, see supplementary fig 4a). When we restricted the analysis to patients with hospital diagnosed atrial fibrillation only or stratified according to age or primary or secondary stroke protection, the associations were similar, with hazard ratios between 0.79 and 0.86; statistical significance was not reached (fig 2).

The differences in rates of ischaemic stroke or systemic embolism were non-significant for apixaban and dabigatran compared with warfarin in the first year of treatment (fig 2).

Bleeding events

The cumulative incidence curves for the combined endpoint of any bleeding (fig 1) displayed comparable bleeding rates for warfarin and rivaroxaban, which were higher than for both apixaban and dabigatran. The incidence curves for the last two treatments overlapped. The weighted one year incidence rates were around five events per 100 person years for warfarin and rivaroxaban and three per 100 person years for apixaban and dabigatran (table 2).

Weighted Cox regressions yielded significantly lower hazard ratios with reference to warfarin for apixaban (0.63, 0.53 to 0.76) and dabigatran (0.61, 0.51 to 0.74, fig 3). After 2.5 years' follow-up these significant reductions remained (see supplementary figure 4b). The subgroup analyses (fig 3) showed consistency of these results, although the differences where less pronounced and non-significant for the secondary stroke prevention group.

The effect sizes for major bleeding were comparable to those for the overall combined bleeding endpoint (fig 3). The rate for dabigatran was significantly lower than for warfarin (0.50, 0.33 to 0.75) for the secondary stroke prevention group.

Intracranial bleeding was observed, with a one year weighted rate of 0.6 per 100 person years for warfarin; all NOACs had lower rates than warfarin. The main analysis showed lower rates for dabigatran (0.40, 0.25 to 0.65) and for rivaroxaban (0.56, 0.34 to 0.90) at one year follow-up (fig 2). The corresponding hazard ratios after 2.5 years' follow-up were 0.39 (0.27 to 0.56) and 0.66 (0.45 to 0.98, see supplementary figure 4b). The hazard ratios for apixaban ranged between 0.60 and 0.85 for all strata, with confidence intervals crossing unity.

Death

The cumulative incidence curves for warfarin and rivaroxaban overlapped and were higher than the overlapping curves for apixaban and dabigatran (fig 2). Table 2 shows the rates for death and the combined endpoint of ischaemic stroke, systemic embolism, or death. Death rates at one year follow-up were significantly lower for apixaban (0.65, 0.56 to 0.75) and for dabigatran (0.63, 0.48 to 0.82) compared with warfarin (fig 2). These differences remained consistent when stratified on subgroups.

The combined endpoint of ischaemic stroke, systemic embolism, or death displayed lower relative risks for all NOACs compared with warfarin, with general consistency in the entire cohort and the cohort of patients admitted to hospital (fig 2). After 2.5 years' follow-up, these differences were maintained (see supplementary figure 4a).

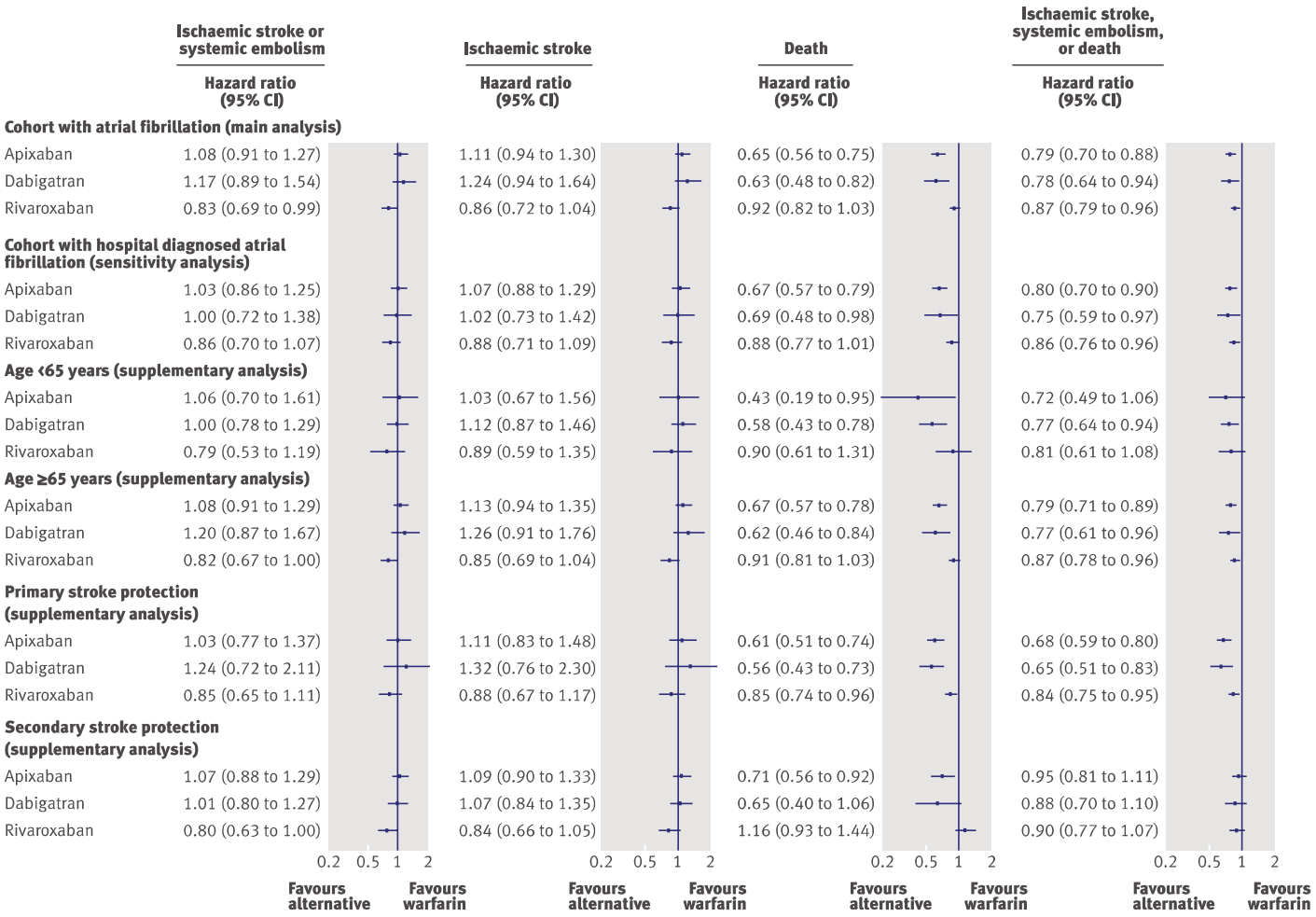

Fig 2 | Propensity weighted (inverse probability of treatment weighted) Cox hazard ratios for one year follow-up (intention to treat) for non-vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin for stroke and death endpoints. Supplementary material provides corresponding results for follow-up of 2.5 years and for continuous treatment analysis

Sensitivity analyses

The adjusted analyses, the standardised morbidity ratio weighted analysis, and the subgroup analyses on patients with confirmed atrial fibrillation agreed with the weighted analyses (see supplementary figures 5a and 5b). The results were not altered when the analyses were repeated under a continuous treatment approach (see supplementary figures 6a, 6b, 7a, and 7b). The exclusion of patients who started dabigatran during the first five months after its introduction in Denmark did not materially change the effect estimates and conclusions (results not shown).

Discussion

In this large comparative effectiveness and safety analysis of NOAC drugs and warfarin from routine care setting, we found that non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) are overall safe and effective alternatives to warfarin treatment.

We observed differential prescribing of different non-vitamin K antagonist oral anticoagulants (novel oral anticoagulants, NOACs) in relation to patient characteristics was evident. For example, dabigatran was preferentially prescribed in younger patients with a lower risk of stroke and less renal impairment. For ischaemic stroke only, no significant differences were evident (hazard ratios) between NOACs and warfarin; however, for the combined endpoint of ischaemic stroke or systemic embolism, rivaroxaban was associated with a lower risk than warfarin, with dabigatran and apixaban showing no significant differences. Apixaban and dabigatran were associated with a significantly lower risk of death compared with rivaroxaban or warfarin. The endpoints of any bleeding or major bleeding were significantly lower for apixaban and dabigatran than for rivaroxaban or warfarin; the last two drugs had similar profiles for bleeding risk.

Comparison with other studies

Some selective prescribing, as seen in this study, is perhaps unsurprising and consistent with other reports from small cohorts, often single centre studies.[19] With the availability of various NOACs, there is an opportunity to fit the particular NOAC to the patient's clinical profile.[20-22] Thus, dabigatran users were slightly younger than users of the other NOACs,

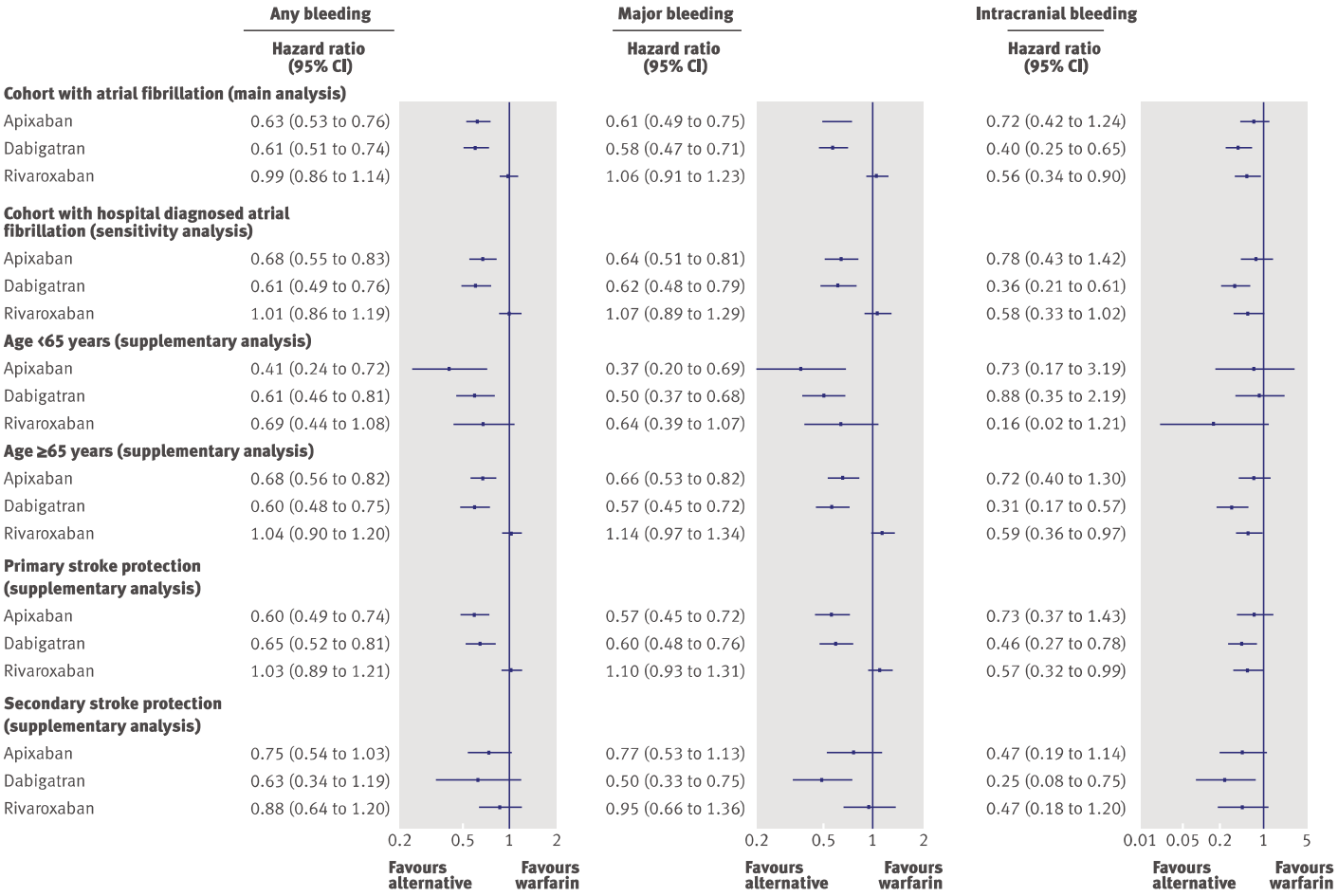

Fig 3 | Propensity weighted (inverse probability of treatment weighted) Cox hazard ratios for one year follow-up (intention to treat) for non-vitamin K antagonist oral anticoagulants (NOACs) compared with warfarin for bleeding endpoints. Supplementary material provides corresponding results for follow-up of 2.5 years and for continuous treatment analysis

but this may reflect our study focus on standard dose dabigatran (150 mg twice daily), which is not recommended for elderly patients (>80 years). NOACs were generally less used in patients with vascular disease, whereas warfarin was more commonly prescribed. This could reflect previous concerns of a numerical increase in cardiac ischaemic events with dabigatran treatment compared with warfarin, and the cardioprotective effect of warfarin.[23] The lower use of dabigatran in patients with renal impairment pertains to the caution with this NOAC, given its relative high renal excretion.[24] The higher use of rivaroxaban and apixaban in patients with previous ischaemic stroke or systemic embolism may possibly reflect the high proportion of such patients in their respective clinical trials.[2 3] In addition, throughout the past three to five years, NOACs have gained increasing attention, as healthcare authorities and caregivers learn the benefits and limitations of these new drugs. These include, for example, ease of being administered, continuous monitoring of renal function, and patient preferences. However, our analysis was not designed to take into account these facts and thus should be viewed in this perspective.

Our methodological approach accounted for such '"real world" selective prescribing through propensity weights.

In our analysis, mortality risks were similar in patients treated with warfarin and rivaroxaban, and higher than with apixaban or dabigatran. Mortality is a relevant endpoint in stroke prevention studies, and even in the historical trials, warfarin significantly reduced all cause mortality (by 26%) compared with placebo or control.[12] A meta-analysis of NOAC trials found a 10% reduction in all cause mortality with standard dose NOACs compared with warfarin.[25] Our analysis extends these observations, showing a differential effect of NOACs with a similar all cause mortality with rivaroxaban compared with warfarin, whereas dabigatran and apixaban had similar mortality that were significantly lower than warfarin. Indeed, mortality was not significantly different between rivaroxaban and warfarin in ROCKET-AF (the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation), whereas the mortality reduction was significant for apixaban (11% reduction) and borderline significant for dabigatran 150 mg twice daily

(10% reduction, P=0.05), compared with warfarin in their respective phase 3 trials.[2 26 27]

We found comparable bleeding rates for warfarin and rivaroxaban that were noticeably higher than for both apixaban and dabigatran. Apixaban and dabigatran both yielded statistically significantly lower risks for any bleeding or major bleeding with reference to warfarin, even after 2.5 years of follow-up. These associations remained present in most subgroups. Again, these data are consistent with the results of the NOAC phase 3 clinical trial. In ROCKET-AF, for example, the rates of major and clinically relevant non-major bleeding were similar for rivaroxaban and warfarin. Nevertheless, the validity of the data from the ROCKET-AF trial has recently been questioned owing to use of an inaccurate point-of-care device (Hemosense INratio; HemoSense, San Jose, CA).[28] A US Food and Drug Administration mandated post hoc analysis of the trial data examined bleeding outcomes in patients with chronic inflammation, acute inflammation, or hematocrit levels out of range.[29] Specifically for the outcome of major bleeding, treatment with rivaroxaban was favoured compared with warfarin (hazard ratio 0.87, 95% confidence interval 0.70 to 1.08) in the subgroup of patients with none of the conditions; whereas the hazard ratio in patients with any of the conditions was 1.18 (0.98 to 1.42). As discussed elsewhere,[28] these results are counterintuitive, as the patients with the mentioned conditions could have received a higher dose of warfarin due to the inaccurate point-of-care devices resulting in an increased risk of bleeding. Notwithstanding the trial results, biased or not, rivaroxaban displayed similar bleeding risks to warfarin. Our comparisons on relative bleeding risks contrasting rivaroxaban with warfarin using data from clinical practice support this observation. For dabigatran, the endpoint "all bleeding" was significantly lower with both doses of dabigatran versus warfarin, whereas dabigatran 150 mg twice daily was associated with a non-significant reduction in major bleeding compared with warfarin. For apixaban, all bleeding and major bleeding were significantly lower compared with warfarin in the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.[3] In their respective trials, all NOACs were associated with significantly decreased intracranial bleeding compared with warfarin, but our data did only yield significant results for dabigatran and rivaroxaban. This, however, might reflect the smaller number of events and the shorter follow-up for (especially) patients treated with apixaban.

Limitations of this study

The present study has several limitations, which mainly relate to the observational nature of the data. Some unmeasured and residual confounding is likely to persist. For example, the differences in stroke and bleeding could potentially be related to selective prescribing. Although we applied propensity weighting to account for baseline differences, we are unlikely to have captured the full extent and effect of different prescribing behaviour. We did not have access to information on time in therapeutic range among warfarin users; nor did we have information on laboratory, anthropometric, or socioeconomic factors. However, our sensitivity analyses did not change the conclusions from the main analyses, suggesting a limited potential for further adjustment for confounding within the setting of Danish administrative registry data. Our data also apply to a predominantly white European population, and differential efficacy and safety benefits are seen between people of Asian and non-Asian origin, which we were unable to investigate.[30 31] Finally, there is the risk of misclassification, and various limitations of comparative effectiveness studies of newly marketed drugs have been noted previously[32] that would also apply to the present study. Our analyses were not focused on direct comparisons of one NOAC agent against another; further research is warranted to establish comparative effectiveness and safety within the NOAC agent group. Moreover, in accordance with the described methods we chose to exclude patients treated with a non-standard (that is, reduced) dose of NOAC. It remains to be established whether each of the NOACs provide comparative effectiveness and safety compared with warfarin when prescribing a reduced dose of a specific NOAC drug.

Conclusions

All NOACs are generally safe and effective alternatives to warfarin in a clinical care setting. For ischaemic stroke, our weighted analysis suggests no significant differences between the NOACs and warfarin. The risks for death, any bleeding, or major bleeding were significantly lower for apixaban and dabigatran, compared with warfarin.

Contributors: TBL and had full access to all of the data in this study and takes responsibility for the integrity of the data and the accuracy of the data analysis. He is the guarantor. All authors contributed to the design; analysed and interpreted the data; drafted the article or revised it critically for important intellectual content; and approved the final version to be published.

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Competing interests: All authors have completed the ICMJE uniform disclosure form at ww.icmje.org/coi_disclosure.pdf and declare: TBL has served as an investigator for Janssen Scientific Affairs, LLC, and Boehringer Ingelheim and has served as a speaker for Bayer, Bristol-Myers Squibb/Pfizer, and Boehringer Ingelheim. PBN has served as a speaker for Boehringer Ingelheim. GYHL has served as a consultant for Bayer, Astellas, Merck, Sanofi, Bristol-Myers Squibb/Pfizer, Daiichi-Sankyo, Biotronik, Portola, and Boehringer Ingelheim and has served as a speaker for Bayer, Bristol-Myers Squibb/Pfizer, Boehringer Ingelheim, Daiichi-Sankyo, and Sanofi Aventis.

Ethical approval: Not required.

Data sharing: Not possible owing to legislation by the Danish government. The Danish Health Data Authority provided the data material.

Transparency: The lead author (TBL) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

1 Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51. doi:10.1056/NEJMoa0905561.
2 Patel MR, Mahaffey KW, Garg J, et al. ROCKET AF Investigators. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. *N Engl J Med* 2011;365:883-91. doi:10.1056/NEJMoa1009638.
3 Granger CB, Alexander JH, McMurray JJV, et al. ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2011;365:981-92. doi:10.1056/NEJMoa1107039.
4 Giugliano RP, Ruff CT, Braunwald E, et al. ENGAGE AF-TIMI 48 Investigators. Edoxaban versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2013;369:2093-104. doi:10.1056/NEJMoa1310907.
5 Camm AJ, Lip GYH, De Caterina R, et al. ESC Committee for Practice Guidelines-CPG Document Reviewers. 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation--developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;14:1385-413. doi:10.1093/europace/eus305.
6 Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. *Lancet* 2014;383:955-62. doi:10.1016/S0140-6736(13)62343-0.
7 Olesen JB, Sørensen R, Hansen ML, et al. Non-vitamin K antagonist oral anticoagulation agents in anticoagulant naive atrial fibrillation patients: Danish nationwide descriptive data 2011-2013. *Europace* 2015;17:187-93. doi:10.1093/europace/euu225.
8 Kildemoes HW, Sørensen HT, Hallas J. The Danish National Prescription Registry. *Scand J Public Health* 2011;39(Suppl):38-41. doi:10.1177/1403494810394717.
9 Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39(Suppl):30-3. doi:10.1177/1403494811401482.
10 Pedersen CB. The Danish Civil Registration System. *Scand J Public Health* 2011;39(Suppl):22-5. doi:10.1177/1403494810387965.
11 Krarup L-H, Boysen G, Janjua H, Prescott E, Truelsen T. Validity of stroke diagnoses in a National Register of Patients. *Neuroepidemiology* 2007;28:150-4. doi:10.1159/000102143.
12 Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. *Ann Intern Med* 2007;146:857-67. doi:10.7326/0003-4819-146-12-200706190-00007.
13 Gooley TA, Leisenring W, Crowley J, Storer BE. Estimation of failure probabilities in the presence of competing risks: new representations of old estimators. *Stat Med* 1999;18:695-706. doi:10.1002/(SICI)1097-0258(19990330)18:6<695::AID-SIM60>3.0.CO;2-O.
14 Pisters R, Lane DA, Nieuwlaat R, de Vos CB, Crijns HJGM, Lip GYH. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest* 2010;138:1093-100. doi:10.1378/chest.10-0134.
15 Robins JM, Hernán MA, Brumback B. Marginal structural models and causal inference in epidemiology. *Epidemiology* 2000;11:550-60. doi:10.1097/00001648-200009000-00011.
16 Stürmer T, Wyss R, Glynn RJ, Brookhart MA. Propensity scores for confounder adjustment when assessing the effects of medical interventions using nonexperimental study designs. *J Intern Med* 2014;275:570-80. doi:10.1111/joim.12197.
17 McCaffrey DF, Griffin BA, Almirall D, Slaughter ME, Ramchand R, Burgette LF. A tutorial on propensity score estimation for multiple treatments using generalized boosted models. *Stat Med* 2013;32:3388-414. doi:10.1002/sim.5753.
18 Austin PC. Some methods of propensity-score matching had superior performance to others: results of an empirical investigation and Monte Carlo simulations. *Biom J* 2009;51:171-84. doi:10.1002/bimj.200810488.
19 Lee SJ, Sayers M, Lip GYH, Lane DA. Use of non-vitamin K antagonist oral anticoagulants in atrial fibrillation patients: insights from a specialist atrial fibrillation clinic. *Int J Clin Pract* 2015;69:1341-8. doi:10.1111/ijcp.12712.
20 Shields AM, Lip GYH. Choosing the right drug to fit the patient when selecting oral anticoagulation for stroke prevention in atrial fibrillation. *J Intern Med* 2015;278:1-18. doi:10.1111/joim.12360.
21 Diener H-C, Aisenberg J, Ansell J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 2. *Eur Heart J* 2016;:ehv643; Epub ahead of print. doi:10.1093/eurheartj/ehw069.
22 Diener H-C, Aisenberg J, Ansell J, et al. Choosing a particular oral anticoagulant and dose for stroke prevention in individual patients with non-valvular atrial fibrillation: part 1. *Eur Heart J* 2016;:ehv643; Epub ahead of print. doi:10.1093/eurheartj/ehv643.
23 Lip GYH, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients?*Am J Med* 2010;123:785-9. doi:10.1016/j.amjmed.2010.01.031.
24 Heidbuchel H, Verhamme P, Alings M, et al. Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with non-valvular atrial fibrillation. *Europace* 2015;17:1467-507. doi:10.1093/europace/euv309.
25 Ruff CT, Giugliano RP, Antman EM, et al. Evaluation of the novel factor Xa inhibitor edoxaban compared with warfarin in patients with atrial fibrillation: design and rationale for the Effective aNticoaGulation with factor xA next GEneration in Atrial Fibrillation-Thrombolysis In Myocardial Infarction study 48 (ENGAGE AF-TIMI 48). *Am Heart J* 2010;160:635-41. doi:10.1016/j.ahj.2010.06.042.
26 Connolly SJ, Ezekowitz MD, Yusuf S, et al. RE-LY Steering Committee and Investigators. Dabigatran versus warfarin in patients with atrial fibrillation. *N Engl J Med* 2009;361:1139-51. doi:10.1056/NEJMoa0905561.
27 Connolly SJ, Eikelboom J, Joyner C, et al. AVERROES Steering Committee and Investigators. Apixaban in patients with atrial fibrillation. *N Engl J Med* 2011;364:806-17. doi:10.1056/NEJMoa1007432.
28 Cohen D. Rivaroxaban: can we trust the evidence?*BMJ* 2016;352:i575. doi:10.1136/bmj.i575.
29 Patel MR, Hellkamp AS, Fox KAA. ROCKET AF Executive Committee and Investigators. Point-of-Care Warfarin Monitoring in the ROCKET AF Trial. *N Engl J Med* 2016;374:785-8. doi:10.1056/NEJMc1515842.
30 Wang K-L, Lip GYH, Lin S-J, Chiang C-E. Non-Vitamin K Antagonist Oral Anticoagulants for Stroke Prevention in Asian Patients With Nonvalvular Atrial Fibrillation: Meta-Analysis. *Stroke* 2015;46:2555-61. doi:10.1161/STROKEAHA.115.009947.
31 Chiang C-E, Wang K-L, Lip GYH. Stroke prevention in atrial fibrillation: an Asian perspective. *Thromb Haemost* 2014;111:789-97. doi:10.1160/TH13-11-0948.
32 Schneeweiss S, Gagne JJ, Glynn RJ, Ruhl M, Rassen JA. Assessing the comparative effectiveness of newly marketed medications: methodological challenges and implications for drug development. *Clin Pharmacol Ther* 2011;90:777-90. doi:10.1038/clpt.2011.235.

Supplementary material

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EXHIBIT D

Original Investigation

Research Misconduct Identified by the US Food and Drug Administration

Out of Sight, Out of Mind, Out of the Peer-Reviewed Literature

Charles Seife, MS

IMPORTANCE Every year, the US Food and Drug Administration (FDA) inspects several hundred clinical sites performing biomedical research on human participants and occasionally finds evidence of substantial departures from good clinical practice and research misconduct. However, the FDA has no systematic method of communicating these findings to the scientific community, leaving open the possibility that research misconduct detected by a government agency goes unremarked in the peer-reviewed literature.

OBJECTIVES To identify published clinical trials in which an FDA inspection found significant evidence of objectionable conditions or practices, to describe violations, and to determine whether the violations are mentioned in the peer-reviewed literature.

DESIGN AND SETTING Cross-sectional analysis of publicly available documents, dated from January 1, 1998, to September 30, 2013, describing FDA inspections of clinical trial sites in which significant evidence of objectionable conditions or practices was found.

MAIN OUTCOMES AND MEASURES For each inspection document that could be linked to a specific published clinical trial, the main measure was a yes/no determination of whether there was mention in the peer-reviewed literature of problems the FDA had identified.

RESULTS Fifty-seven published clinical trials were identified for which an FDA inspection of a trial site had found significant evidence of 1 or more of the following problems: falsification or submission of false information, 22 trials (39%); problems with adverse events reporting, 14 trials (25%); protocol violations, 42 trials (74%); inadequate or inaccurate recordkeeping, 35 trials (61%); failure to protect the safety of patients and/or issues with oversight or informed consent, 30 trials (53%); and violations not otherwise categorized, 20 trials (35%). Only 3 of the 78 publications (4%) that resulted from trials in which the FDA found significant violations mentioned the objectionable conditions or practices found during the inspection. No corrections, retractions, expressions of concern, or other comments acknowledging the key issues identified by the inspection were subsequently published.

CONCLUSIONS AND RELEVANCE When the FDA finds significant departures from good clinical practice, those findings are seldom reflected in the peer-reviewed literature, even when there is evidence of data fabrication or other forms of research misconduct.

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Author Audio Interview at jamainternalmedicine.com

Supplemental content at jamainternalmedicine.com

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As part of the drug approval process, the US Food and Drug Administration (FDA) regularly inspects clinical trial sites involved in FDA-regulated research to determine the degree to which these sites conform to regulations. The FDA regulations intend to ensure, among other things, that scientists adhere to good clinical practice and that they protect the rights of human participants. Such inspections often yield useful information about the reliability and quality of the clinical data produced at a clinical trial site.

An FDA inspection typically involves officials visiting a trial site and auditing the records kept at that site. During the course of several days, the inspectors verify that, among other things, the investigators adhered to the trial protocol, the participants had given informed consent, and the research had been duly approved by an institutional review board. The inspectors may also audit the data comparing, for example, an investigator's progress notes in hospital records with data reported to the study sponsor to ensure that there are no irregularities.[1]

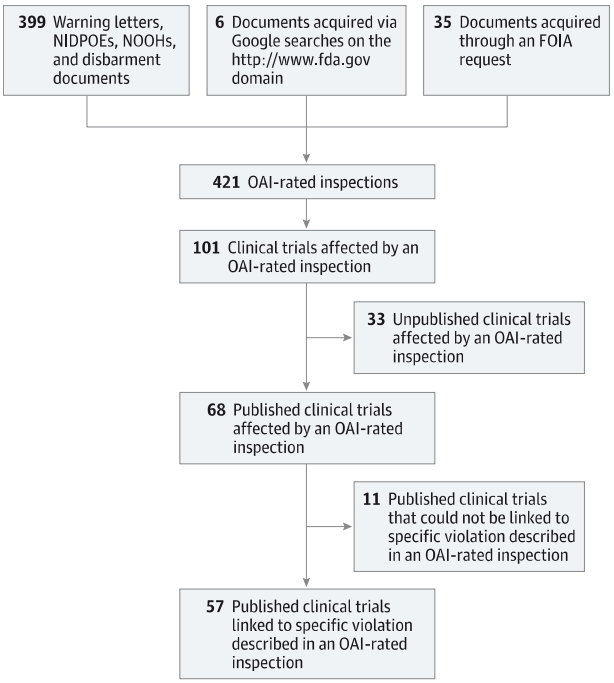
The FDA classifies its inspections in 1 of 3 ways, depending on the gravity of violations found. *No action indicated* indicates that there were no substantial violations. *Voluntary action indicated* means that inspectors have found violations of good clinical practice, but the nature and extent of those problems are not serious enough to require sanction. The most severe classification, *official action indicated* (OAI), is reserved for cases in which the inspection identified objectionable conditions or practices significant enough to warrant regulatory action.[2] In the 2013 fiscal year, approximately 2% of the 644 inspections of trial sites carried out by the FDA's Bioresearch Monitoring organization were classified as OAI.[3] The nature and extent of the OAI violations, which include submission of false information and failure to report adverse events to the appropriate bodies, often raise questions about the validity and accuracy of the clinical trial site's data. Consequently, the FDA typically excludes data from a site that received an OAI when judging the safety or efficacy of a new drug.

The goals of the present study were to identify publications describing clinical trials that the FDA had determined had an OAI violation, to describe the violations, and to determine whether the published article or any subsequent correction acknowledged the violation.

Methods

A multipronged approach was used to identify clinical trials with an OAI violation (**Figure**). The process began by attempting to identify clinical trial sites and principal investigators who had received an OAI violation. Although there is no public canonical list of OAI inspections, the FDA maintains a database containing the results of some of its inspections.[4] In July 2012, the database was searched for clinical investigators who had received an OAI. To obtain documents (form 483s and Establishment Inspection Reports) that provide details about a given inspection, Freedom of Information Act requests were made to the FDA. The request yielded documents related to 20 OAI-rated inspections, all dated before August 8, 2012, when the Freedom of Information Act request was submitted.

Figure. Relevant Clinical Trials



Identification of relevant clinical trials linked to specific violations described in an official action indicated (OAI)–rated inspection. Between October 7 and December 9, 2013, all warning letters that were issued to a clinical investigator after January 1, 1998, as well as all Notices of Disqualification Proceedings and Opportunity to Explain (NIDPOEs), Notices of Opportunity for a Hearing (NOOHs), and disbarment decisions that were on the US Food and Drug Administration's website, were reviewed. FOIA indicates Freedom of Information Act.

To supplement the data obtained from the searches of the FDA database, Google searches of the http://www.FDA.gov domain were performed. The most effective searches used combinations of phrases and their variants that were contained in documents describing OAI-rated inspections of clinical sites (eg, *classified as OAI*, *inspection summary*, *received an OAI*, *inspected*, *OAI classification*, and *inspection*). This strategy yielded documents related to 21 OAI-rated inspections.

The best source of documentation of OAI-rated inspections came from instances in which the FDA took regulatory action against clinical investigators. Such actions occur only when the failure to adhere to research regulations is considered particularly grave. In such cases, the FDA often issues 1 or more documents that detail the problems found in an inspection: warning letter, Notice of Disqualification Proceedings and Opportunity to Explain, Notice of Opportunity for Hearing, and official notification of disbarment or sanctions. Between October 7 and December 9, 2013, all warning letters that were issued to a clinical investigator after January 1, 1998 (letters regarding 298 inspections), as well as all Notices of Disqualification Proceedings, Notices of Opportunity for Hearing, and disbarment decisions that were on the FDA's website (documents concerning 82 inspections), were reviewed.

The 3 methods of search yielded 421 OAI-rated inspections. We then attempted to link the sites and investigators described in the related inspection documents to specific clinical trials. Heavy redactions in most of these documents prevented this linkage in most cases (eAppendix in the Supplement). However, whenever we were able to identify a clinical trial that received an OAI finding, we searched the peer-reviewed literature for any resultant publications. If such publications were found, they were independently reviewed by the author and by a second reader with the goal of identifying any written acknowledgment about the violations identified by the FDA. Agreement between the 2 reviewers was high ($\kappa = 0.85$). One article noted that data "were either missing, or were considered unreliable by the investigator due to problems collecting accurate data."[5(p3)] The 2 reviewers disagreed about whether the unreliability might have been an oblique reference to problems found during an inspection. However, the inspection documents[6] detailed failures to obtain informed consent, falsified information, misreporting the dosage of drugs for at least 7 patients, and failure to record data on 10 patients. After discussion, the reviewers concurred that the language in the article was not an acknowledgment of the inspection findings.

PubMed and Thomson-Reuters' Web of Science were searched for any corrections, retractions, expressions of concern, or other comments in which those violations might have been aired after the article was published. Food and Drug Administration-related documents obtained in this investigation are available.[7]

Results

General Findings

There were approximately 600 clinical trials mentioned in the documents we gathered; owing to redactions, most of these trials could not be identified. However, in some cases, key information was not redacted from the documents, allowing us to identify 101 trials in which at least one clinical trial site received an OAI grade on an inspection (Figure).

Of those 101 clinical trials, we identified 68 for which results had been published in the peer-reviewed literature, resulting in a total of 95 publications. For 11 of the clinical trials that had been published, the documents were not sufficiently detailed for us to prove that the violations described in the document were specific to the trial in question, so they were excluded from the primary analysis (**Table 1**).* For example, 1 warning letter[8] and 1 Notice of Disqualification Proceedings and Opportunity to Explain[9] detailed violations in 7 clinical trials of stem cell therapies, which then resulted in 4 publications.[10,35-37] Because of the redactions in those documents, there was ambiguity about which of the 7 trials was linked to which violation described in the documents. It was possible to tie specific violations to only 3 of the 4 published trials[38-40]; the fourth trial[41] was therefore excluded from analysis.

For each of the 57 remaining trials, 1 or more FDA inspections of a trial site had uncovered evidence of significant departures from good clinical practice, such as underreporting of adverse events, violations of protocol, violations of recruitment guidelines, and various forms of scientific misconduct.

In 22 of these trials (39%), the FDA cited researchers for falsification or submission of false information; in 14 (25%), for problems with adverse events reporting; in 42 (74%), for failure to follow the investigational plan or other violations of protocol; in 35 (61%), for inadequate or inaccurate recordkeeping; in 30 (53%), for failure to protect the safety, rights, and welfare of patients or issues with informed consent or institutional review board oversight; and in 20 (35%), for violations not otherwise categorized. Examples of uncategorized violations include cases in which the investigators used experimental compounds in patients not enrolled in trials, delegated tasks to unauthorized personnel, or otherwise failed to supervise clinical investigations properly.

The 57 clinical trials in our analysis resulted in 78 articles published in the peer-reviewed literature (**Table 2**). Of these 78 articles, only 3 publications (4%) included any mention of the FDA inspection violations despite the fact that for 59 of those 78 articles (76%), the inspection was completed at least 6 months before the article was published. Researchers are usually given a form 483 within a day of the inspection, with the form detailing any problems found by the inspector.

For the 3 articles that mentioned the inspection violations, 1 stated that 1 of the trial sites "was found to have allegedly entered fraudulent data and was dropped from participation."[121(p390)] (References 76 through 184 are listed in the eReferences in the Supplement.) The research misconduct involved falsified laboratory test results in a phlebotomy trial. In the second instance, the article noted that the data from 1 clinical trial site were excluded owing to "protocol adherence and data quality issues."[111(p78)] According to the FDA documents, the researcher apparently eliminated the blinding in a randomized protocol so she "could control drug treatment assignments"[168(p7)] of her patients; she was also cited for falsification of data in 2 other protocols. In the third instance, an article explained that data from several patients were excluded from the efficacy analysis because "site monitoring raised questions in regard to certain data at 1 study site."[65(p431)] The FDA documents[64] allege that none of the individuals enrolled at 1 study site had met the inclusion criteria and that the responsible researcher had fabricated chest radiographs of participants and committed other forms of misconduct.

In no other instance did we find acknowledgment of problems found during an FDA inspection. In addition, we were unable to identify any corrections, retractions, comments, or notifications of concern published after FDA identification of the violations.

Examples of Unreported Violations

To illustrate the importance of the unreported inspection violations, 4 cases cut examples are provided herein.

Case 1

A publication describing a stem cell trial in 26 patients with ischemic limbs stated that "all patients recognized and were aware of major clinical improvements in the treated (more is-

*References 12-16, 18-21, 24-26, 28, 29, 33, 34

Table 1. Clinical Trials and Publications With Possible but Not Definitive Instances of OAI-Rated Violations Excluded From the Primary Analysis[a]

Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name	Source Document/ Publication Affected	Falsification[b]	Protocol[c]	Record-keeping[d]	Safety[e]	Other[f]
Autologous stem cells	NCT00548613	2007-02-I	NIDPOE,[8] warning letter[9]/ Lasala et al[10]	...	...	...	P	Y
Bevacizumab	NCT00109070/ NCT00109226	AVF2107g/ AVF2192g	NIDPOE[11]/Scappaticci et al[12]	P	...	...	P	P
Bevacizumab	NCT00109070/ NCT00109226	AVF2107g/ AVF2192g	NIDPOE[11]/Kabbinavar et al[13]	P	...	...	P	P
Bevacizumab	NCT00109070/ NCT00109226	AVF2107g/ AVF2192g	NIDPOE[11]/Kabbinavar et al[14]	P	...	...	P	P
Docetaxel	...	TAX326	NIDPOE[11]/Belani et al[15]	P	...	...	P	P
Docetaxel	...	TAX326	NIDPOE[11]/Fossella et al[16]	P	...	...	P	P
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Gibofsky et al[18]	...	...	P	P	...
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Weaver et al[19]	...	...	P	P	...
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Markenson et al[20]	...	...	P	P	...
Etanercept	NCT00116714	Radius-1	NIDPOE[17]/Gibofsky et al[21]	...	...	P	P	...
Lumiracoxib	NCT00366938	...	NIDPOE,[22] form 483[23]/ Dougados et al[24]	P	P	...	...	...
Lumiracoxib	NCT00366938	...	NIDPOE,[22] form 483[23]/ Sheldon et al[25]	P	P	...	...	...
Naproxcinod	NCT00504127	...	NIDPOE,[22] form 483[23]/ Schnitzer et al[26]	P	P	...	...	...
Quetiapine	NCT00090324	112	Clinical Review[27]/ Findling et al[28]	...	...	...	...	...
Quetiapine	NCT00090311	149	Clinical Review[27]/ Pathak et al[29]	...	...	...	...	...
Telithromycin	...	3005	Form 483 and EIR,[30] NIDPOE,[31] NOOH[32]/ Luterman et al[33]	P	P	...	...	...
Telithromycin	...	3007	Form 483 and EIR,[30] NIDPOE,[31] NOOH[32]/ Zervos et al[34]	P	P	...	...	...

Abbreviations: ADE, adverse drug event; ellipses, not applicable; OAI, official action indicated; P, violation identified but no definitive link; Y, definitive link.

[a] None of the clinical trials listed herein had violations having to do with reporting of ADEs.

[b] Falsification and/or submission of false information.

[c] Protocol issues included failure to follow investigational plan and/or other violations of protocol.

[d] Record-keeping issues included inadequate and/or inaccurate records.

[e] Safety issues included failure to protect rights, safety, and welfare of patients and/or issues related to informed consent or institutional review board notifications.

[f] Other issues were violations not otherwise categorized.

chemic) leg, despite no significant clinical changes in the control (less ischemic) leg."[37(p381)] However, an FDA document[169] revealed that 1 patient had a foot amputated 2 weeks after administration of the stem cells. We found no correction or retraction.

Case 2

Eight of 16 FDA inspections of sites involved in a clinical trial of rivaroxaban,[170] a novel anticoagulant, had been rated OAI. These inspections had uncovered evidence of various transgressions, such as "systemic discarding of medical records,"[171(p3)] unauthorized unblinding, falsification, and "concerns regarding improprieties in randomization."[172(p211)] Consequently, the entire study, RECORD 4 (Regulation of Coagulation in Orthopedic Surgery to Prevent Deep-Venous Thrombosis and Pulmonary Embolism 4), was deemed unreliable by the FDA.[171] These problems are not mentioned in the article describing the study's results[142] or in other publications associated with the trial.[144,145]

Case 3

A researcher was caught falsifying documents in a number of trials,[173-176] in part because those falsifications led to the death of a patient undergoing treatment in a clinical trial comparing 2 chemotherapy regimens. The researcher had falsified laboratory test results to hide the patient's impaired kidney and liver function, and the first dose of the treatment proved to be fatal. The researcher pleaded guilty to fraud and criminally negligent homicide and was sentenced to 71 months in prison. Although this episode is described in detail in FDA documents[11,67] as well as court documents,[177] none of the publications in the peer-reviewed literature associated with the chemotherapy study in which the patient died[70-72,178] have any mention of the falsification, fraud, or homicide. The publications associated with 2 of the 3 other studies for which the researcher falsified documents also do not report on the violations.[68,73]

Case 4

A clinical site in China taking part in a large trial of apixaban, a novel anticoagulant, had apparently altered patient records. If one were to exclude the data from the patients at that site, the claim of a statistically significant mortality benefit disappears.[179] For this reason, among others, the FDA wrestled with whether it was appropriate to allow the manufacturer to claim a mortality benefit. None of this discussion appears in the literature. The claim for the mortality benefit, which has

Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
1[h]	Alogliptin	NCT00707993	SYR-322_303	Clinical inspection summary[42]/ Rosenstock et al[43]	...	...	Y	Y	Y	...
2	Amoxicillin/ clavulanic acid extended-release	...	25000/592	NIDPOE,[44] NOOH,[45] debarment order[46]/ File et al[47]	Y	...	Y	...	...	...
3	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Granger et al[38]	Y	Y	...	...	...	...
4[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Lopes et al[50]	Y	Y	Y	Y	Y	
5[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/McMurray et al[51]	Y	Y	Y	Y	Y	
6[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Wallentin et al[52]	Y	Y	Y	Y	Y	
7[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Garcia et al[53]	Y	Y	Y	Y	Y	
8[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Alexander et al[54]	Y	Y	Y	Y	Y	
9[h]	Apixaban	NCT00412984	ARISTOTLE	Clinical inspection summary,[48] medical review[49]/Alexander et al[55]	Y	Y	Y	Y	Y	
10[h]	Asenapine	NCT00145470	A7501008, P05844	Warning letter[56]/Szegedi et al[57]	...	...	Y	Y	...	...
11[h]	Autologous dendritic cells	...	1997-064	NOOH[58]/Redman et al[59]	...	...	Y	Y	...	...
12	Autologous stem cells	NCT00518401	2007-01-I	NIDPOE,[8] warning letter[9]/ Lasala et al[35]	...	...	...	...	Y	Y
13[h]	Autologous stem cells	NCT00721006	2008-01-II	NIDPOE,[8] warning letter[9]/ Lasala et al[37]	...	Y	...	...	Y	Y
14	Autologous stem cells	NCT00643981	2007-03-I	NIDPOE,[8] warning letter[9]/ Lasala et al[36]	...	...	Y	...	Y	Y
15	Autologous tumor cells	...	1995-243	NOOH[58]/Chang et al[60]	...	...	Y	Y	...	...
16[h]	Budesonide/ formoterol	NCT00206167	D5899C00001	NIDPOE[61]/Bleecker et al[62]	...	...	...	Y	...	...
17	Budesonide/ formoterol	NCT00206167	D5899C00001	NIDPOE[61]/Rennard et al[63]	...	...	...	Y	...	...
18[h]	Cd34+ cells	NCT00300053	ACT34-CMI	NIDPOE[64]/Losordo et al[65]	Y	Y	Y	Y	...	Y
19[h]	Cd34+ cells	NCT00300053	ACT34-CMI	NIDPOE[64]/Povsic et al[66]	Y	Y	Y	Y	...	Y
20[h]	Dfmo	NCT00003814	ILEX-DFMO341	NIDPOE,[67] NOOH[11]/Messing[68]	Y	...	Y	P	P	Y
21	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Ajani[70]	Y	...	Y	Y	Y	...
22	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Ajani[70]	Y	...	Y	Y	Y	...
23[h]	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Ajani et al[71]	Y	...	Y	Y	Y	...
24[h]	Docetaxel	NCT00290966	TAX325	NIDPOE,[11] NOOH,[67] NOOH [69]/ Van Cutsem et al[72]	Y	...	Y	Y	Y	...
25[h]	Docetaxel	...	TAX327	NIDPOE,[11] NOOH,[67] NOOH [69]/ Tannock et al[73]	Y	...	Y	Y	Y	...
26	Erlotinib	NCT00081614	AVF2938	Warning letter [74]/ Bukowski et al[75]	...	...	Y	...	Y	...
27[h]	Esomeprazole/ naproxen	NCT00527787	PN400-301	NIDPOE,[22] form 483[23]/ Goldstein et al[76]	Y	P	P	Y	...	...
28	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Gibofsky et al[18]	...	...	Y	Y	Y	...
29	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Weaver et al[19]	...	...	Y	Y	Y	...
30[h]	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Markenson et al[20]	...	...	Y	Y	Y	...
31[h]	Etanercept	NCT00116727	Radius-2	NIDPOE[17]/Gibofsky et al[21]	...	...	Y	Y	Y	...
32	Faropenem daloxate	...	100288	Form 483 and EIR,[77] warning letter,[78] warning letter[79]/ Upchurch et al[80]	...	...	Y	Y	P	...
33[h]	Ferric carboxymaltose	NCT00982007	1VIT09031	Warning letter[81]/ Onken et al[82]	...	...	Y	...	...	...
34[h]	Fondaparinux	NCT00038961	APOLLO	NIDPOE[83]/Turpie et al[84]	...	...	Y	Y	Y	Y

(continued)

Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections (continued)

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
35	Ibuprofen	NCT00225732	008a, CPI-CL-008	Warning letter,[85] clinical inspection summary[86]/ Southworth et al[87]	...	Y	Y	Y	...	Y
36[h]	Ibuprofen	NCT00225732	008b, CPI-CL-008	Warning letter,[85] clinical inspection summary[86]/ Kroll et al[88]	...	...	Y	Y	...	Y
37[h]	Indiplon	...	NBI34060-MR-0212	NIDPOE[89]/Lydiard et al[90]	Y	...	Y	Y	...	...
38[h]	Leuprolide acetate	...	...	Form 483,[91] EIR,[92] letter,[93] NIDPOE[94]/ Crawford et al[95]	Y	...	Y	Y	Y	Y
39[h]	Ly518674	NCT00133380	H8D-MC-EMBF	Warning letter[96]/ Nissen et al[97]	...	...	Y	P	P	Y
40[h]	Modified lymphocytes	...	1990-489	NOOH[58]/Chang et al[98]	...	...	Y	Y	Y	...
41	Modified lymphocytes	...	1995-318	NOOH[58]/DeBruyne et al[99]	...	...	Y	Y	...	...
42[h]	Nebivolol	NCT00200460	NEB302	NIDPOE[100]/Weiss et al[101]	Y	Y	Y	Y	...	Y
43	Ofloxacin	...	PRT002/ PRT003	NIDPOE,[102] NOOH,[103] proposal to debar/ NOOH,[104] debarment,[105] warning letter,[106] warning letter[107]/ Jones et al[108]	Y	...	Y	Y	Y	...
44[h]	Olanzapine	...	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/Tunis et al[111]	...	...	Y	...	P	...
45[h]	Olanzapine	...	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/ Ascher-Svanum et al[112]	...	...	Y	...	P	...
46[h]	Olanzapine	...	FID-US-HGGD/ 2325	NIDPOE,[109] Proposal to debar/ NOOH[110]/Faries et al[113]	...	...	Y	...	P	...
47[h]	Olanzapine	NCT00103571	F1D-US-HGLS	Warning letter[114]/Kinon et al[115]	...	...	Y	P	Y	...
48[h]	Oxycontin extended-release	NCT01559701	PTI-821-CM	NIDPOE[116]/Friedmann et al[117]	P	...	Y	Y	Y	...
49[h]	Paliperidone palmitate	NCT00111189	CR004198, R092670 PSY300	Warning letter[56]/ Kozma et al[118]	...	Y	Y	Y	Y	...
50[h]	Paliperidone palmitate	NCT00111189	CR004198, R092670 PSY300	Warning letter[56]/ Hough et al[119]	...	Y	Y	Y	Y	...
51[h]	Paroxetine	...	704	NIDPOE,[109] proposal to debar, NOOH[110]/Geller et al[120]	Y	...	Y	Y	Y	...
52[h]	Phlebotomy for atherosclerosis	NCT00032357	FeAST	NIDPOE,[11] NOOH,[67] NOOH[69]/ Zacharski et al[121]	Y	...	...	...	...	...
53[h]	Pomalidomide	NCT00072722	...	Warning letter [122]/ Amato et al[123]	...	...	P	P	Y	...
54[h]	Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Googe et al[127]	Y	...	Y	...	...	Y
55[h]	Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Gangaputra et al[128]	Y	...	Y	...	...	Y
56	Ranibizumab	NCT00445003	LRTforDME +PRP	Warning letter,[124] form 483 and EIR,[125] warning letter[126]/ Bhavsar et al[129]	Y	...	Y	...	...	Y
57[h]	Ranibizumab	NCT00891735	HARBOR	Warning letter[130]/ Busbee et al[131]	...	...	Y	Y	Y	...
58[h]	Reduced glutathione	...	...	Warning letter[132]/ Bishop et al[133]	...	...	...	...	Y	Y
59	Rivaroxaban	NCT00329628	RECORD 1	Compliance review,[134] medical review,[135] other review[136]/ Eriksson et al[137]	...	Y	Y	Y	...	...
60[h]	Rivaroxaban	NCT00332020	RECORD 2	NIDPOE,[48] Compliance review,[134] medical review,[135] other review[136]/ Kakkar et al[138]	Y	Y	Y	Y	Y	...

(continued)

Table 2. Clinical Trials and Publications Affected by Official Action Indicated–Rated Inspections (continued)

No.	Drug/Biologic/ Procedure	Clinical Trial No.	Other Protocol Name(s)	Source Document No./ Publication Affected[a]	Falsification[b]	ADE Reporting[c]	Protocol[d]	Record-keeping[e]	Safety[f]	Other[g]
61	Rivaroxaban	NCT00361894	RECORD 3	Compliance review,[134] medical review,[135] other review[136]/ Lassen et al[139]	...	Y		Y	Y	...
62[h]	Rivaroxaban	NCT00362232	RECORD 4	Compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Turpie et al[142]	Y	Y	Y	Y	Y	Y
63[h]	Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894	RECORD 1, 2, 3	Compliance review,[134] medical review,[135] other review[136]/ Eriksson et al[143]	Y	Y	Y	Y	Y	...
64[h]	Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894/ NCT00329628	RECORD 1, 2, 3, 4	NIDPOE,[48] compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Eriksson et al[144]	Y	Y	Y	Y	Y	Y
65[h]	Rivaroxaban	NCT00329628/ NCT00332020/ NCT00361894/ NCT00329628	RECORD 1, 2, 3, 4	NIDPOE,[48] compliance review,[134] medical review,[135] other review,[136] form 483,[140] EIR[141]/ Lassen et al[145]	Y	Y	Y	Y	Y	Y
66[h]	Rocuronium	NCT00124722	P05797	Warning letter,[146] letter[147]/ Pirotta et al[5]	...	...	...	P	Y	Y
67[h]	Rofecoxib	NCT00060476	2006_414, Formally P30A03LD, MK0966-201	NIDPOE[83]/ van Adelsberg et al[148]	...	...	P	...	...	Y
68[h]	Roflumilast	NCT00297102	BY217/M2-124	NIDPOE[61]/Calverley et al[149]	...	...	Y	Y	Y	Y
69[h]	Ropinirole	...	SKF-101468/ 191	NIDPOE[89]/Allen et al[150]	Y	...	Y	Y	...	...
70	Sodium oxybate	...	OMC-GHB-2	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrema Multicenter Study Group[154]	P	P	...	P	P	Y
71[h]	Sodium oxybate	...	OMC-GHB-3	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrema Multicenter Study Group[155]	P	P	...	P	P	Y
72[h]	Sodium oxybate	...	OMC-SXB-21	Form 483 and EIR,[151] NIDPOE,[152] medical review[153]/ US Xyrema Multicenter Study Group[156]	P	P	...	P	P	Y
73[h]	Thrombo-spondin-1	NCT00073125	...	Warning letter[122]/ Ebbinghaus et al[157]	...	...	P	P	Y	...
74[h]	Tramadol extended-release	NCT00348010	...	NIDPOE,[158] NOOH[159]/ Babul et al[160]	Y	Y	Y	Y	Y	...
75[h]	Tramadol extended-release	NCT00347685	...	NIDPOE,[158] NOOH[159]/ Pascual et al[161]	Y	Y	Y	Y	Y	...
76[h]	Valsartan	NCT00154271	CVAH631DUS02	NIDPOE[162]/ Everett et al[163]	Y	Y	Y	Y	Y	...
77[h]	Velimogene aliplasmid	NCT00044356	VCL-1005-208	Warning letter[164]/ Bedikian[165]	...	Y	Y	...	Y	...
78[h]	Zolpidem modified-release	...	EFC4529/ ZOLADULT	NIDPOE,[89] medical review[166]/ Roth et al[167]	Y	...	Y	Y	...	...

Abbreviations: ADE, adverse drug event; ellipses, not applicable; P, violation identified but no definitive link; Y, definitive link.

[a] References 76 through 167 are listed in the eReferences in the Supplement.

[b] Falsification and/or submission of false information.

[c] Violations having to do with reporting of ADEs.

[d] Protocol issues included failure to follow investigational plan and/or other violations of protocol.

[e] Record-keeping issues included inadequate and/or inaccurate records.

[f] Safety issues included failure to protect rights, safety, and welfare of patients and/or issues related to informed consent or institutional review board notifications.

[g] Other issues were violations not otherwise categorized.

[h] The article was published at least 6 months after the inspection was completed.

appeared in the literature since 2011,[50,52,180] consistently relies on the full data set, including data from the site at which the research misconduct allegedly occurred. This is true even for an article that was published[52] nearly 18 months after the alleged research misconduct was discovered. In addition, the mortality benefit analysis of the FDA-approved drug label as of August 31, 2014, is also based on the full data set[181] despite a recommendation from the FDA's Office of Scientific Investigation that data from not just the problematic site but 23 additional suspect Chinese sites be excluded.[182] Despite the fraudulent data, when all the suspect Chinese sites are excluded rather than just the one at which the evidence of alleged research misconduct was found, the mortality benefit becomes statistically significant at the $P = .05$ level once again.[182] One FDA analyst, commenting on the "data quality issues" in this clinical trial, complained about the agency's lack of transparency and poor handling of evidence of problems with trial data: Some of the responsibility for the data quality issues rests with us, the FDA: We have approved drugs ignoring similar data quality issues, granting superiority claims, and not discussing in the labels the data quality issues. We must stop doing this.[182(p19)]

Discussion

Our study has some limitations. The data are descriptive rather than quantitative. We do not know how many publications derive from trials that received an OAI finding or whether a full sample of such publications would show a higher or lower rate of acknowledging inspection violations. Our search strategy was limited by the information publicly available. For example, the FDA database of clinical inspections is infrequently updated. In addition, documents from certain time periods and certain regions of the country were harder to locate than others, indicating that our search was biased. Moreover, the records that the FDA makes available are incomplete and often heavily redacted. The nature of the redactions—and thus, our likelihood of linking a given document to a specific clinical trial—also varied depending on which FDA officer was performing the redaction and the year in which the redactions were performed. All of these limitations prevent generalization of our findings to the entire population of clinical trials. Finally, problems uncovered during inspections of clinical trial sites represent only a fraction of the departures from good clinical practice of which the FDA becomes aware. For example, the FDA sometimes learns of departures from good clinical practice through communications with and inspections of organizations sponsoring and responsible for conducting clinical trials; these instances were not part of our investigation.

Even though several inspection documents reviewed here described major violations of good clinical practice, including allegations of fabrication and other forms of research misconduct, it was rare that objectionable conditions or practices uncovered by the FDA were reflected in the peer-reviewed literature.

Of course, not all violations are of equal severity. When a clinical trial site receives an OAI, it does not mean that the violations need be acknowledged in an article or, if discovered after publication of the study, warrant a correction. Even in the case of data fabrication, there is occasional ambiguity. For example, in a clinical trial[183] of a drug administered via intravitreal injection, a researcher apparently fabricated images of patients' retinas. Although one might argue that an article in which those images were used as data[128] might require a correction, it is unclear whether another article that addresses the study's infection rates associated with intravitreal injections,[129] without relying on the retinal images to support the findings, would be similarly affected. Furthermore, data are sometimes excluded from peer-reviewed publications, occasionally without explanation. Consequently, in some of the articles (Table 2), tainted data might be handled properly, even if not explicitly remarked upon in the publication; it was not possible in the present study to determine how often this occurred.

Conclusions

The findings presented in this study should give us pause. This investigation has found numerous studies for which the FDA determined there was significant evidence of fraudulent or otherwise problematic data. Such issues raise questions about the integrity of a clinical trial, and mention of these problems is missing from the relevant peer-reviewed literature. The FDA does not typically notify journals when a site participating in a published clinical trial receives an OAI inspection, nor does it generally make any announcement intended to alert the public about the research misconduct that it finds. The documents the agency discloses tend to be heavily redacted. As a result, it is usually very difficult, or even impossible, to determine which published clinical trials are implicated by the FDA's allegations of research misconduct.

The FDA has legal as well as ethical responsibilities regarding the scientific misconduct it finds during its inspections. When the agency withholds the identity of a clinical trial affected by scientific misconduct, it does so because it considers the identity to be confidential commercial information, which it feels bound to protect.[184] However, failing to notify the medical or scientific communities about allegations of serious research misconduct in clinical trials is incompatible with the FDA's mission to protect the public health. Such allegations are relevant to include in the peer-reviewed literature on which physicians and other medical researchers rely to help them choose treatments that they offer to patients and other research participants.

To better serve the public health, the FDA should make unredacted information about its findings of research misconduct more readily available. The agency should make sure that any substantial evidence of misconduct is available to editors and readers of the scientific literature. One possible mechanism for this would be to use the national clinical trials database: any OAI inspection affecting a trial site should be promptly noted at http://www.clinicaltrials.gov. The FDA should also create a website or a publicly available database

that lists all OAI-rated inspections of clinical sites and provides links to copies of the relevant, unredacted, inspection-related documents.

The FDA should be more transparent about its findings of research misconduct; however, most of the burden for ensuring the integrity of the research in the peer-reviewed literature falls to the authors of the articles submitted to peer-reviewed journals. Currently, there is no formal requirement for authors seeking to publish clinical trial data to disclose any adverse findings noted during FDA inspections. Journals should require that any such findings be disclosed. Voluntary disclosures are never foolproof, but, as with conflict-of-interest statements, requiring authors and journals to be forthcoming about significant departures from good clinical practice will help raise the standard for the reporting of research toward greater transparency.

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REFERENCES

1. US Food and Drug Administration, Office of Good Clinical Practice. Information sheet guidance for IRBs, clinical investigators, and sponsors: FDA inspections of clinical investigators. June 2010. 2014. http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM126553.pdf. Accessed July 16, 2014.

2. US Food and Drug Administration, Office of Regulatory Affairs. Field management directive—establishment inspection reports conclusions and decisions; December 29, 2011. http://www.fda.gov/downloads/ICECI/Inspections/FieldManagementDirectives/UCM289084.pdf. Accessed March 8, 2014.

3. US Food and Drug Administration. Bioresearch monitoring (BIMO) Metrics–FY'13. http://www.fda.gov/downloads/ScienceResearch/SpecialTopics/RunningClinicalTrials/UCM381797.pdf. Accessed April 7, 2014.

4. The clinical investigator inspection list. http://www.accessdata.fda.gov/scripts/cder/cliil/index.cfm. Accessed July 2012.

5. Tirotta CF, Brandom B, Siddiqi MS, et al. Time course of rocuronium-induced neuromuscular blockade in pediatric patients: a phase III, randomized, dose-response study. *J Anesthe Clinic Res*. 2012;3:189. doi:10.4172/2155-6148.

6. Warning letter issued to Charles Cote, March 2, 2009 (document 8). http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm132595.htm. Accessed March 7, 2014.

7. FDA-inspection-related documents. Charles Seife website. http://www.charlesseife.com/fdadocuments.html. Accessed January 20, 2015.

8. Warning letter issued to TCA Cellular Therapy, LLC, August 15, 2011 (document 6). http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm268796.htm. Accessed March 7, 2014.

9. Notice of Initiation of Disqualification Proceedings and Opportunity to Explain. Issued to Gabriel Lasala, February 16, 2012 (document 5). http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/ucm132595.htm. Accessed March 7, 2014.

10. Lasala GP, Silva JA, Allers C, Minguell JJ. Combination cell therapy for the treatment of acute myocardial infarction. *Int J Cardiol*. 2012;157(2):293-294.

11. NIDPOE issued to James A. Holland, September 22, 2004 (document 60). http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm105756.htm. Accessed January 20, 2015.

12. Scappaticci FA, Skillings JR, Holden SN, et al. Arterial thromboembolic events in patients with metastatic carcinoma treated with chemotherapy and bevacizumab. *J Natl Cancer Inst*. 2007;99(16):1232-1239.

13. Kabbinavar FF, Wallace JF, Holmgren E, et al. Health-related quality of life impact of bevacizumab when combined with irinotecan, 5-fluorouracil, and leucovorin or 5-fluorouracil and leucovorin for metastatic colorectal cancer. *Oncologist*. 2008;13(9):1021-1029.

14. Kabbinavar FF, Hurwitz HI, Yi J, Sarkar S, Rosen O. Addition of bevacizumab to fluorouracil-based first-line treatment of metastatic colorectal cancer: pooled analysis of cohorts of older patients from two randomized clinical trials. *J Clin Oncol*. 2009;27(2):199-205.

15. Belani CP, Pereira JR, von Pawel J, et al; TAX 326 study group. Effect of chemotherapy for advanced non-small cell lung cancer on patients' quality of life: a randomized controlled trial. *Lung Cancer*. 2006;53(2):231-239.

16. Fossella F, Pereira JR, von Pawel J, et al. Randomized, multinational, phase III study of docetaxel plus platinum combinations versus vinorelbine plus cisplatin for advanced non-small-cell lung cancer: the TAX 326 study group. *J Clin Oncol*. 2003;21(16):3016-3024.

17. NIDPOE issued to Peggy Ann Garjian, August 25, 2008. http://www.fda.gov/downloads/regulatoryinformation/foi/electronicreadingroom/ucm143679.pdf. Accessed January 20, 2015.

18. Gibofsky A, Palmer WR, Goldman JA, et al. Real-world utilization of DMARDs and biologics in rheumatoid arthritis: the RADIUS (Rheumatoid Arthritis Disease-Modifying Anti-Rheumatic Drug Intervention and Utilization Study) study. *Curr Med Res Opin*. 2006;22(1):169-183.

19. Weaver AL, Lautzenheiser RL, Schiff MH, et al; RADIUS Investigators. Real-world effectiveness of select biologic and DMARD monotherapy and combination therapy in the treatment of rheumatoid arthritis: results from the RADIUS observational registry. *Curr Med Res Opin*. 2006;22(1):185-198.

20. Markenson JA, Gibofsky A, Palmer WR, et al. Persistence with anti-tumor necrosis factor therapies in patients with rheumatoid arthritis: observations from the RADIUS registry. *J Rheumatol*. 2011;38(7):1273-1281.

21. Gibofsky A, Palmer WR, Keystone EC, et al. Rheumatoid arthritis disease-modifying antirheumatic drug intervention and utilization study: safety and etanercept utilization analyses from the RADIUS 1 and RADIUS 2 registries. *J Rheumatol*. 2011;38(1):21-28.

22. NIDPOE issued to Howard W. Marker, January 29, 2009. http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM143608.pdf. Accessed January 20, 2015.

23. Form 483, EIR, and patient affidavits regarding Howard W. Marker, May 2, 2008. http://www.documentcloud.org/documents/1215430-68-marker483eirandaffadavits.html. Accessed January 21, 2015.

24. Dougados M, Moore A, Yu S, Gitton X. Evaluation of the patient acceptable symptom state in a pooled analysis of two multicentre, randomised, double-blind, placebo-controlled studies evaluating lumiracoxib and celecoxib in patients with osteoarthritis. *Arthritis Res Ther*. 2007;9(1):R11.

25. Sheldon E, Beaulieu A, Paster Z, Dutta D, Yu S, Sloan VS. Efficacy and tolerability of lumiracoxib in the treatment of osteoarthritis of the knee: a 13-week, randomized, double-blind comparison with celecoxib and placebo. *Clin Ther*. 2005;27(1):64-77.

26. Schnitzer TJ, Hochberg MC, Marrero CE, Duquesroix B, Frayssinet H, Beekman M. Efficacy and safety of naproxcinod in patients with osteoarthritis of the knee: a 53-week prospective randomized multicenter study. *Semin Arthritis Rheum*. 2011;40(4):285-297.

27. Clinical Review, NDA020639, May 11, 2009. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2011/020639Orig1s049OtherR.pdf. Accessed January 20, 2015.

28. Findling RL, McKenna K, Earley WR, Stankowski J, Pathak S. Efficacy and safety of quetiapine in adolescents with schizophrenia investigated in a 6-week, double-blind, placebo-controlled trial. *J Child Adolesc Psychopharmacol*. 2012;22(5):327-342.

29. Pathak S, Findling RL, Earley WR, Acevedo LD, Stankowski J, Delbello MP. Efficacy and safety of quetiapine in children and adolescents with mania associated with bipolar I disorder: a 3-week, double-blind, placebo-controlled trial. *J Clin Psychiatry*. 2013;74(1):e100-e109. doi:10.4088/JCP.11m07424.

30. Form 483 and EIR regarding C. Andrew DeAbate, June 27, 2000. http://www.documentcloud.org/documents/1215355-1-deabate483andeir.html. Accessed January 21, 2015.

31. NIDPOE issued to C. Andrew DeAbate, April 13, 2001. http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM144492.pdf. Accessed January 20, 2015.

32. NOOH issued to C. Andrew DeAbate, November 28, 2003. http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM144492.pdf. Accessed January 20, 2015.

33. Luterman M, Tellier G, Lasko B, Leroy B. Efficacy and tolerability of telithromycin for 5 or 10 days vs amoxicillin/clavulanic acid for 10 days in acute maxillary sinusitis. *Ear Nose Throat J*. 2003;82(8):576-580, 82-84, 586 passim.

34. Zervos MJ, Heyder AM, Leroy B. Oral telithromycin 800 mg once daily for 5 days versus cefuroxime axetil 500 mg twice daily for 10 days in adults with acute exacerbations of chronic bronchitis. *J Int Med Res*. 2003;31(3):157-169.

35. Lasala GP, Silva JA, Gardner PA, Minguell JJ. Combination stem cell therapy for the treatment of severe limb ischemia: safety and efficacy analysis. *Angiology*. 2010;61(6):551-556.

36. Lasala GP, Silva JA, Kusnick BA, Minguell JJ. Combination stem cell therapy for the treatment of medically refractory coronary ischemia: a phase I study. *Cardiovasc Revasc Med*. 2011;12(1):29-34.

37. Lasala GP, Silva JA, Minguell JJ. Therapeutic angiogenesis in patients with severe limb ischemia by transplantation of a combination stem cell product. *J Thorac Cardiovasc Surg*. 2012;144(2):377-382.

38. ClinicalTrials.gov. Combination Stem Cell Therapy for the Treatment of Severe Leg Ischemia. NCT00518401. http://clinicaltrials.gov/ct2/show/NCT00518401. Accessed March 7, 2014.

39. ClinicalTrials.gov. Combination Stem Cell Therapy for the Treatment of Severe Coronary Ischemia. NCT00643981. http://clinicaltrials.gov/ct2/show/NCT00643981. Accessed March 7, 2014.

40. ClinicalTrials.gov. Phase II Combination Stem Cell Therapy for the Treatment of Severe Leg Ischemia. NCT00721006. http://clinicaltrials.gov/ct2/show/NCT00721006. Accessed March 7, 2014.

41. ClinicalTrials.gov. Combination Stem Cell (MESENDO) Therapy for Utilization and Rescue of Infarcted Myocardium. NCT00548613. http://clinicaltrials.gov/ct2/show/NCT00548613. Accessed March 7, 2014.

42. Clinical inspection summary, NDA022271, February 3, 2012;128. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/022271Orig1s000OtherRedt.pdf. Accessed January 21, 2015.

43. Rosenstock J, Wilson C, Fleck P. Alogliptin versus glipizide monotherapy in elderly type 2 diabetes mellitus patients with mild hyperglycaemia: a prospective, double-blind, randomized, 1-year study. *Diabetes Obes Metab*. 2013;15(10):906-914.

44. NIDPOE issued to Kim C. Hendrick, May 11, 2006. http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM143707.pdf. Accessed January 20, 2015.

45. NOOH issued to Kim C. Hendrick, July 1, 2009. http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm259310.htm. Accessed January 21, 2015.

46. Debarment order regarding Kim C. Hendrick, August 4, 2009. http://www.circare.org/fdawls3/hendrick_20090804.pdf. Accessed January 20, 2015.

47. File TM Jr, Jacobs MR, Poole MD, Wynne B; 546, 547, 548, 549, 550, 551, 556, 557 and 592 Clinical Study Groups. Outcome of treatment of respiratory tract infections due to *Streptococcus pneumoniae*, including drug-resistant strains, with pharmacokinetically enhanced amoxycillin/clavulanate. *Int J Antimicrob Agents*. 2002;20(4):235-247.

48. NIDPOE issued to David Craig Loucks, August 18, 2009. http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM180531.pdf. Accessed January 20, 2015.

49. Clinical Inspection Summary, NDA202155, May 18, 2012:44-74. http://www.accessdata.fda.gov/drugsatfda_docs/nda/2012/202155Orig1s000OtherR.pdf. Accessed January 20, 2015.

50. Lopes RD, Al-Khatib SM, Wallentin L, et al. Efficacy and safety of apixaban compared with warfarin according to patient risk of stroke and of bleeding in atrial fibrillation: a secondary analysis of a randomised controlled trial. *Lancet*. 2012;380(9855):1749-1758.

51. McMurray JJ, Ezekowitz JA, Lewis BS, et al; ARISTOTLE Committees and Investigators. Left ventricular systolic dysfunction, heart failure, and the risk of stroke and systemic embolism in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Circ Heart Fail*. 2013;6(3):451-460.

52. Wallentin L, Lopes RD, Hanna M, et al; Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) Investigators. Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. *Circulation*. 2013;127(22):2166-2176.

53. Garcia DA, Wallentin L, Lopes RD, et al. Apixaban versus warfarin in patients with atrial fibrillation according to prior warfarin use: results from the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation trial. *Am Heart J*. 2013;166(3):549-558.

54. Alexander JH, Levy E, Lawrence J, et al. Documentation of study medication dispensing in a prospective large randomized clinical trial: experiences from the ARISTOTLE Trial. *Am Heart J*. 2013;166(3):559-565.

55. Alexander JH, Lopes RD, Thomas L, et al. Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial. *Eur Heart J*. 2014;35(4):224-232.

56. Warning letter issued to Saroj Brar, March 20, 2008. http://www.fda.gov/downloads/Drugs/.../ucm054138.pdf. Accessed January 20, 2015.

57. Szegedi A, Calabrese JR, Stet L, Mackle M, Zhao J, Panagides J; Apollo Study Group. Asenapine as adjunctive treatment for acute mania associated with bipolar disorder: results of a 12-week core study and 40-week extension. *J Clin Psychopharmacol*. 2012;32(1):46-55.

58. NOOH issued to Alfred E. Chang, October 9, 2003. http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM144539.pdf. Accessed January 20, 2015.

59. Redman BG, Chang AE, Whitfield J, et al. Phase Ib trial assessing autologous, tumor-pulsed dendritic cells as a vaccine administered with or without IL-2 in patients with metastatic melanoma. *J Immunother*. 2008;31(6):591-598.

60. Chang AE, Li Q, Bishop DK, Normolle DP, Redman BD, Nickoloff BJ. Immunogenetic therapy of human melanoma utilizing autologous tumor cells transduced to secrete granulocyte-macrophage colony-stimulating factor. *Hum Gene Ther*. 2000;11(6):839-850.

61. NIDPOE issued to Francisco Candal, March 2, 2011. http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM250107.pdf. Accessed January 20, 2015.

62. Bleecker ER, Meyers DA, Bailey WC, et al. ADRB2 polymorphisms and budesonide/formoterol responses in COPD. *Chest*. 2012;142(2):320-328.

63. Rennard SI, Tashkin DP, McElhattan J, et al. Efficacy and tolerability of budesonide/formoterol in one hydrofluoroalkane pressurized metered-dose inhaler in patients with chronic obstructive pulmonary disease: results from a 1-year randomized controlled clinical trial. *Drugs*. 2009;69(5):549-565.

64. NIDPOE issued to Alan Niederman, November 1, 2010. http://www.fda.gov/downloads/RegulatoryInformation/FOI/ElectronicReadingRoom/UCM239218.pdf. Accessed January 20, 2015.

65. Losordo DW, Henry TD, Davidson C, et al; ACT34-CMI Investigators. Intramyocardial, autologous CD34+ cell therapy for refractory angina. *Circ Res*. 2011;109(4):428-436.

66. Povsic TJ, Losordo DW, Story K, et al. Incidence and clinical significance of cardiac biomarker elevation during stem cell mobilization, apheresis, and intramyocardial delivery: an analysis from ACT34-CMI. *Am Heart J*. 2012;164(5):689-697.e3.

67. NOOH issued to Paul H. Kornak, May 4, 2009 (document 59). http://www.fda.gov/RegulatoryInformation/FOI

/ElectronicReadingRoom/ucm181014.htm. Accessed January 20, 2015.

68. Messing E, Kim KM, Sharkey F, et al. Randomized prospective phase III trial of difluoromethylornithine vs placebo in preventing recurrence of completely resected low risk superficial bladder cancer. *J Urol*. 2006;176(2):500-504.

69. NOOH issued to James A. Holland, June 1, 2009. http://www.fda.gov/RegulatoryInformation/FOI/ElectronicReadingRoom/ucm182805.htm. Accessed January 20, 2015.

70. Ajani JA. Docetaxel in combination for advanced gastric cancer. *Gastric Cancer*. 2002;5 (suppl 1):31-34.

71. Ajani JA, Fodor MB, Tjulandin SA, et al. Phase II multi-institutional randomized trial of docetaxel plus cisplatin with or without fluorouracil in patients with untreated, advanced gastric, or gastroesophageal adenocarcinoma. *J Clin Oncol*. 2005;23(24):5660-5667.

72. Van Cutsem E, Moiseyenko VM, Tjulandin S, et al; V325 Study Group. Phase III study of docetaxel and cisplatin plus fluorouracil compared with cisplatin and fluorouracil as first-line therapy for advanced gastric cancer: a report of the V325 Study Group. *J Clin Oncol*. 2006;24(31):4991-4997.

73. Tannock IF, de Wit R, Berry WR, et al; TAX 327 Investigators. Docetaxel plus prednisone or mitoxantrone plus prednisone for advanced prostate cancer. *N Engl J Med*. 2004;351(15):1502-1512.

74. Warning letter issued to Ronald Bukowski, March 30, 2009. http://www.propublica.org/documents/item/12449-fda-warning-letter-for-ronald-bukowski%0A. Accessed January 20, 2015.

75. Bukowski RM, Kabbinavar FF, Figlin RA, et al. Randomized phase II study of erlotinib combined with bevacizumab compared with bevacizumab alone in metastatic renal cell cancer. *J Clin Oncol*. 2007;25(29):4536-4541.

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Novel oral anticoagulants: pharmacology, coagulation measures, and considerations for reversal

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Abstract Novel oral anticoagulants (NOAC) provide an effective and, in some cases, superior alternative to traditional, oral vitamin K antagonists such as warfarin. These drugs differ in their pharmacokinetic and pharmacodynamics profiles, which is important for selecting the right drug for the right patient. A concern among clinicians is a virtual absence of guidance from clinical trials for reversing the anticoagulant effects of these drugs in clinical settings such as life-threatening bleeding or a need for emergent procedures that carry bleeding risk. In this review, we discuss NOAC, the role of coagulation assays to assess their systemic anticoagulants effects, and the available data supporting strategies designed to reverse or attenuate these effects.

Keywords Novel oral anticoagulants · Coagulation measures · Pharmacology

Introduction

The development of novel oral anticoagulants (NOAC) for the treatment of diseases ranging from atrial fibrillation to venous thromboembolism has led to a plethora of new drug options for physicians to consider for the management of their patients. While these new agents offer advantages to warfarin, the sheer number of new drugs, coupled with their distinct pharmacokinetic and pharmacodynamics profiles, make patient-specific selection a challenging task. In addition, the availability of effective options for systemic anticoagulation places immense responsibility on clinicians to understand the clinical trial data, pharmacologic profiles, and indications that support their evidence-based use in daily practice. The following review details the NOAC and includes emerging data on reversal strategies that not only influence laboratory coagulation measures, but potentially the clinical manifestations of bleeding as well.

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Oral anticoagulants

Warfarin

Warfarin is one of several hydroxy-coumarin compounds that prevents carboxylation of vitamin K dependent clotting factors II, VII, IX, and X. Warfarin is a racemic mixture of two equal enantiomers (S-warfarin and R-warfarin) administered as a sodium salt. The bioavailability of warfarin, taken once daily, approaches 100 % and its long half-life of 20–60 h and small volume of distribution are the end-result of tight binding to albumin [1]. The time to peak plasma concentration is approximately 72–96 h which explains its delayed anticoagulant effect [2]. Warfarin, a narrow therapeutic index drug, is dosed according to the INR (International Normalized Ratio). Warfarin inhibits vitamin K epoxide reductase (VKOR), which is required for carboxylation of vitamin K-dependent proteases and allows them to bind phospholipid surfaces. Cytochrome P450 metabolism of warfarin occurs in the liver and

excretion of the drug is predominantly renal [3]. Numerous drugs alter warfarin metabolism by affecting the cytochrome P450 enzyme complex through enzyme induction, enzyme inhibition, or decreased plasma protein binding. Treatment with warfarin requires dietary discretion, specifically foods containing large amounts of vitamin K.

Dabigatran

Dabigatran is the active form of the prodrug dabigatran etexilate that functions as a reversible, competitive, and direct thrombin active site inhibitor [4]. As a prodrug, dabigatran etexilate is cleaved by a hydrolytic reaction involving serum and liver serine esterases to the active form. This reaction occurs rapidly after intestinal absorption of the prodrug with peak concentrations of dabigatran being found in serum after 2–3 h. Dabigatran etexilate, after intestinal absorption and esterase-mediated hydrolysis, is not detected in plasma or feces and only traces amounts have been detected in the urine via mass spectrometry and liquid chromatography during in vivo assays [5]. Dabigatran is currently FDA approved for the management of patients with nonvalvular atrial fibrillation. In the RELY trial, dabigatran was given twice daily at a dose of either 110 mg or 150 mg for the prevention of stroke or systemic embolism. In the REMEDY trial, a 150 mg dose of dabigatran was employed to establish noninferiority compared with warfarin for the treatment of venous thromboembolism [6]. The FDA approved doses for patients with non-valvular atrial fibrillation is determined by estimated creatinine clearance (CrCl), 150 mg twice daily for patients with a CrCl >30 mL/min and 75 mg twice daily for patients with a CrCl of 15–30 mL/min [7]. Although the 75 mg dose has not been studied in clinical trials, its approval by the FDA was based on the pharmacokinetic and pharmacodynamic profile of the drug with respect to its predominant renal elimination and findings of the RELY trial which suggest that renal impairment is associated with a higher bleeding risk. Given the hydrophilic nature of dabigatran, it has poor intestinal absorption and a low oral bioavailability of 6.5 %. Peak plasma concentrations are reached within 2–3 h of administration and the circulating half-life is 12–17 h. Dabigatran follows first order kinetics, owing to its relatively high volume of distribution, plasma clearance, and elimination half-life [8]. The percentage of dabigatran bound to plasma proteins is approximately 35 %, irrespective of dabigatran serum concentration. The kidneys excrete more than 80 % of dabigatran with less than 10 % being excreted in the feces. Dabigatran is not metabolized by the CYP enzyme complex and subsequently has far fewer drug interactions than vitamin K antagonists. Dabigatran is a substrate for the P-glycoprotein (gp) efflux reverse transporter, an ATP-dependent pump that transports numerous substrates, including drugs across cell membranes. Co-administration of dabigatran and rifampin decreases dabigatran exposure given that rifampin is a strong inducer of P-gp. Similarly, dronedarone, a strong inhibitor of P-gp reverse transport increases plasma dabigatran concentrations. The most common adverse effects associated with dabigatran include bleeding, nausea, vomiting, dyspepsia, and diarrhea [4]. In the RELY trial, rates of dyspepsia (abdominal pain) were elevated (11.8 % with 110 mg BID, 11.3 % with 150 mg BID) compared with warfarin (5.8 %), presumably due to the tartaric acid content of the dabigatran etexilate capsule, which provides an acidic environment to aid in absorption and possibly high local drug concentrations within the gastrointestinal tract [4, 9]. Administration of dabigatran within meals can help mitigate this effect. The role of proton pump inhibitors in the treatment of dabigatran-induced dyspepsia and impact on absorption and plasma concentrations requires further investigation.

Rivaroxaban

Rivaroxaban is an oral, direct and competitive active site factor Xa inhibitor [10]. The drug is administered on a daily or twice daily dosing schedule, with the exact dosage being determined by indication and estimated creatinine clearance; typical dosages are 10, 15, and 20 mg [11]. Dose reductions are necessary for patients with an estimated CrCl of 15–50 mL/min. Because there is limited clinical experience in patients with CrCl <15 mL/min, rivaroxaban is contraindicated in these patients as well as those with severe hepatic disease. The bioavailability of rivaroxaban is between 80 and 100 % with serum concentrations peaking 2–4 h after oral administration [12]. The half-life is approximately 5–9 h, which is increased to 11–13 h for individuals greater than 75 years of age. Rivaroxaban is almost exclusively bound to plasma proteins, with greater than 90 % binding to albumin [12]. The CYP3A4/5 and CYP2J2 enzyme complexes as well as hydrolysis are responsible for the metabolism of rivaroxaban [12]. Sixty six percent of the drug is excreted in the urine with another 30 % excreted through the feces. Like dabigatran, rivaroxaban is a substrate for the P-gp efflux transporter, but unlike dabigatran it is hepatically metabolized and thereby possesses the potential for drug-drug interactions that can influence its metabolism. Drugs such as HIV protease inhibitors, azole antifungal agents, and macrolide antibiotics inhibit CYP3A4 and P-gp, causing increased rivaroxaban exposure. Drugs that are strong inducers of both P-gp and CYP3A4 reduce rivaroxaban's exposure. Rifampin, phenytoin, St. John's wort, and carbamazepine should not be concomitantly administered with rivaroxaban [13]. The most common side effects encountered include bleeding and nausea [12].

Apixaban

Apixaban, like rivaroxaban, is a competitive selective inhibitor of factor Xa that binds in a reversible fashion to the active site and inhibits factor Xa within the prothrombinase complex as well as free factor Xa [14]. Apixaban is highly protein bound (87 %) and has a small volume of distribution due to its limited extravascular distribution [13]. Apixaban reaches its peak plasma concentration in 3 h and has a variable half-life depending on the dosing frequency; apixaban's half-life is 8–11 h when administered twice daily and 12–15 h when given once daily [13]. The 5 mg twice daily dose is approved for the treatment of patients with non-valvular atrial fibrillation. A 2.5 mg twice daily dose is recommended in patients with 2 of 3 of the following: age $\geq$80 years; body weight $\leq$60 kg; or serum creatinine $\geq$1.5 mg/dL. Apixaban metabolism is multifactorial with combination of renal excretion, hydroxylation, and sulfation reactions accounting for the largest proportions [15]. Excretion of the drug occurs via multiple routes with renal excretion accounting for approximately 27 % of the total clearance and the majority being recovered in feces [15]. Apixaban metabolism is subjected to drug interactions with other compounds that induce or inhibit the CYP3A4/5 enzyme complex. Azole antifungal agents should be avoided or discontinued 14 days prior to the use of apixaban due to their potent inhibition of CYP3A4/5. Moderate inhibitors of CYP3A4/5 such as SSRI's, cimetidine, and diltiazem should be used with caution [13]. In addition, apixaban is a substrate for the P-gp efflux transporter, which may reduce the serum concentrations of certain drugs. Adverse reactions to apixaban include bleeding and nausea [14].

Edoxaban

Edoxaban is a competitive, active site inhibitor of factor Xa that binds reversibly to both factor Xa within the prothrombinase complex as well as free factor Xa. Edoxaban exhibits 10,000-fold greater selectivity for factor Xa relative to inhibition of thrombin making it a highly selective inhibitor of factor Xa [16]. The maximum serum concentration of edoxaban is achieved rapidly, reaching its peak approximately 1.5 h after oral administration [13]. The half-life is approximately 9–11 h with an oral bioavailability of 50 % when administered once daily [13]. 55 % of the drug is bound to plasma proteins and the volume of distribution is high compared to other NOACs. The anticoagulant effects of edoxaban are sustained for approximately 24 h. Elimination of edoxaban is primarily determined by two mechanisms, with one-third of the drug being eliminated renally and the remainder being excreted in the feces. Given its partial elimination via the kidneys, dose adjustments are necessary for individuals with a CrCl $\leq$50 mL/min. Edoxaban is a substrate for the P-gp efflux transporter and as such, drugs that inhibit P-gp can increase the serum concentration of edoxaban. Currently, edoxaban is being studied in phase III clinical trials to assess the safety and efficacy in prevention of stroke and systemic embolic events in patients with non-valvular atrial fibrillation and venous thromboembolism. The doses being studied for the prevention of stroke and systemic embolic events are 30 and 60 mg once daily.

Coagulation assays

A key factor in assessing the potential reversibility of NOAC is whether or not their anticoagulant effects can be detected by common coagulation assays and if so, can these assays provide a *quantitative* assessment of plasma concentration of the anticoagulant (Table 1).

Prothrombin time

The prothrombin time (PT) is traditionally used to assess the extrinsic clotting cascade and final common pathway, which includes tissue factor, factor VII, factor V, factor X, factor II, and fibrinogen. This test is routinely ordered in the hospital and in the outpatient setting as the principal method for monitoring vitamin K antagonists like warfarin. The PT is a ratio of the PT divided by control plasma. The International Normalized Ratio (INR) is the universal coagulation test specifically developed for monitoring vitamin K antagonist therapy. Despite the sensitivity of the INR to inhibition of vitamin K-dependent coagulation proteins, it does not correlate closely with plasma concentrations of warfarin. Similarly, the standard PT/INR assay does not quantify plasma concentration and is too insensitive to gauge the anticoagulant effect of direct thrombin inhibitors like dabigatran [17]. Patients on dabigatran can have normal to near normal PT/INR values with elevated dabigatran plasma concentrations. Although rivaroxaban does prolong the PT/INR in a more consistent fashion, this coagulation assay is *not* recommended for monitoring of rivaroxaban due to variability of response according to reagents used for this clinical assay [17]. Similar observations have been reported for apixaban and edoxaban (Fig. 1).

Activated partial thromboplastin time

The activated partial thromboplastin time (APTT) time globally assesses the intrinsic and final common pathway of coagulation. Clotting factors including factor II, factor V, factor VIII, factor IX and factor XI comprise the intrinsic

Table 1 Effect of oral anticoagulants on coagulation assays

Test	VKA's	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Prothromin time PT/INR	Sensitive marker. Dose dependent increase	Insensitive marker. Peak and trough levels of the drug may be associated with no change in INR	Causes dose dependent prolongation of PT/INR. Variable sensitivity due to lack of standard reagent	Causes dose dependent prolongation of PT/INR. Variable sensitivity due to lack of standard reagent	Causes dose dependent prolongation of PT/INR. Variable sensitivity due to lack of standard reagent
Activated partial thromplastin time (aPTT)	Variable sensitivity (non-linear)	Variable sensitivity (non-linear)	Dose-dependent increase but less sensitive than PT/INR	Dose-dependent increase but less sensitive than PT/INR	Dose-dependent increase but less sensitive than PT/INR
Chromogenic anti-Xa assay	Insensitive marker	Insensitive marker	Sensitive marker. Directly proportional to serum concentration	Sensitive marker. Directly proportional to serum concentration	Sensitive marker. Directly proportional to serum concentration
Thrombin time	Insensitive marker	Very sensitive marker.	Insensitive marker	Insensitive marker	Insensitive marker
Ecarin clotting time	Insensitive marker	Sensitive marker. Dose-dependent prolongation	Insensitive marker	Insensitive marker	Insensitive marker
Dilute thrombin time	Insensitive marker	Very sensitive marker	Insensitive marker	Insensitive marker	Insensitive marker
Chromogenic anti IIa	Insensitive marker	Very sensitive marker	Insensitive marker	Insensitive marker	Insensitive marker
Activated clotting time	Variable sensitivity	Variable sensitivity	Dose-dependent increase	Dose-dependent increase	Dose-dependent increase

clotting cascade. Any anticoagulant that affects the activity of these factors can influence the APTT, but the response varies by coagulation protein and reagent. Historically, the APTT has been viewed as a "one sided test" where in only prolonged values have clinical significance in terms of factor deficiency or the presence of inhibitors [18]. The APTT is a widely used coagulation assay that is available for use in both inpatient and outpatient clinical settings. The APTT is mildly and moderately sensitive to the anticoagulants effects of warfarin and dabigatran, respectively. Their relationship is non-linear, which means that the APTT can underestimate plasma concentrations at the low and high ends of the plasma concentration-APTT curves. The APTT is prolonged with administration of rivaroxaban in a dose-dependent manner, but this measure is comparatively less sensitive than the PT/INR assay. Similar to rivaroxaban, apixaban and e-doxaban demonstrate a dose-dependent increase in APTT but this increase is, in general, less sensitive to their factor Xa inhibitory effects than the PT/INR assay. The APTT can be used clinically for its general *qualitative* value (Fig. 2).

Ecarin clotting time

Although not routinely offered in most clinical coagulation laboratories, the ecarin clotting time (ECT) is an accepted coagulation assay for assessing the effect of direct thrombin inhibitors like hirudin. The ECT measures thrombin generation and is currently being used to assess both *qualitative* and *quantitative* measures of anticoagulant effect for dabigatran [19]. The ECT assay is insensitive to the effects of vitamin K antagonists, rivaroxaban, apixaban, and edoxaban [20]. Given the linear relationship between the ECT and dabigatran plasma concentrations, a normal value would supports a low plasma level.

Thrombin time and dilute thrombin time

The thrombin time (TT) is a coagulation assay that measures the polymerization of fibrinogen to fibrin in the presence of thrombin. Given factor Xa's proximal position in the coagulation cascade, inhibitors of factor Xa do not prolong the TT [20]. Similarly, VKA do not prolong the TT. In contrast, thrombin inhibitors prolong the TT in a linear, concentration-dependent fashion. Although the standard TT assay is used to *qualify* the presence of thrombin inhibitors, its ability to *quantify* the amount of anticoagulant in serum is limited due to the oversaturation of assay coagulometers by dabigatran concentrations in serum from individuals taking dabigatran for an extended duration [17]. The "dilute" TT, a modified version of the standard TT assay, has been used to quantify the amount of dabigatran in serum. A commercial dilute TT assay

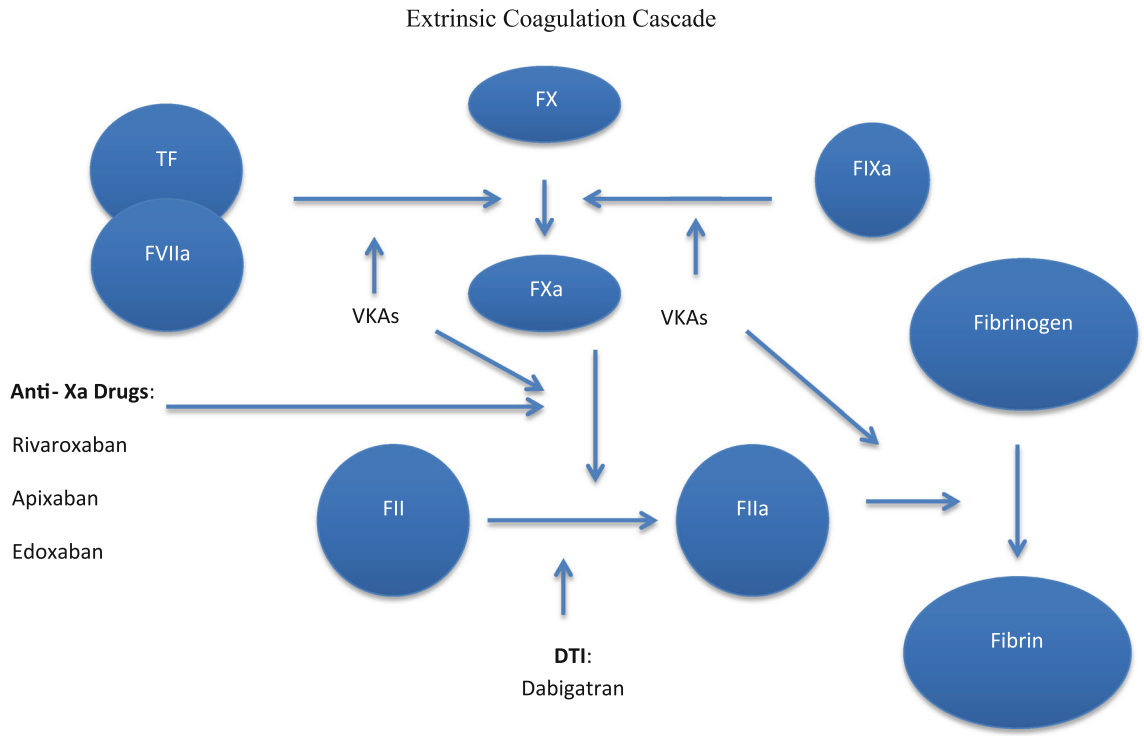

Fig. 1 Extrinsic coagulation cascade and sites of competitive, active-site inhibition by oral anticoagulants

(Hemoclot™ Thrombin Inhibitor Assay) is available for clinical use in circumstances where knowing the concentration of dabigatran is important, such as for consideration of invasive procedures or reversal strategies [17]. This test is licensed and approved for clinical use in the Europe and Canada, but is approved only for research purposes in the United States. Standard TT assays can be performed in most hospital and clinic settings throughout the country.

Chromogenic assays

Chromogenic assays have historically been used to measure heparin levels, specifically low molecular weight heparin (LMWH). This assay uses a chromophore-based compound that is chemically linked to a substrate for factor Xa [21]. The enzymatic activity of factor Xa cleaves the substrate, thereby releasing the chromogenic compound. This colored compound can be detected by a spectrophotometer and is directly proportional to the amount of factor Xa in serum. Inhibitors of factor Xa reduce cleavage of chromophore linked substrate producing less spectrophotometric activity [19]. Chromogenic assays are insensitive to the effects of VKA. Chromogenic assays can be used to assess factor Xa inhibitors such as rivaroxaban, apixaban, and edoxaban. A modified anti-Xa assay has been developed for rivaroxaban for the purposes of quantification of anticoagulant activity. The assay uses rivaroxaban-containing plasma calibrators to quantify plasma concentrations of rivaroxaban. This modified assay has been shown to be highly accurate and precise when compared to other quantification methods such as mass spectrometry [22]. The anticoagulant activity of apixaban and edoxaban can be quantified by using a chromogenic anti-Xa assay [23]. Dabigatran concentration can also be quantified using chromogenic assays. The anti-factor IIa assay uses thrombin's catalytic activity, in the presence of DTIs, to measure the amount of DTI contained within a sample. This assay is not approved for clinical use in the United States.

Prothrombinase-induced clotting time

The prothrombinase-induced clotting time is a plasma-based assay used for quantifying the anticoagulant activities of inhibitors to factor Xa and factor IIa. Plasma or serum is mixed with activated factor Xa, phospholipids, and Russells Viper Venom (RVV) to form the prothrombinase complex; RVV is an enzyme from the venom of *Daboia russelli,* that directly activates factor X in the presence of factor V and phospholipid. The prothrombinase complex activates factor II, which then converts fibrinogen to fibrin. The time to clot formation is recorded in seconds. Anticoagulants prolong the prothrombinase clotting time by inhibiting factor Xa or factor IIa, depending on the amount of anticoagulant present

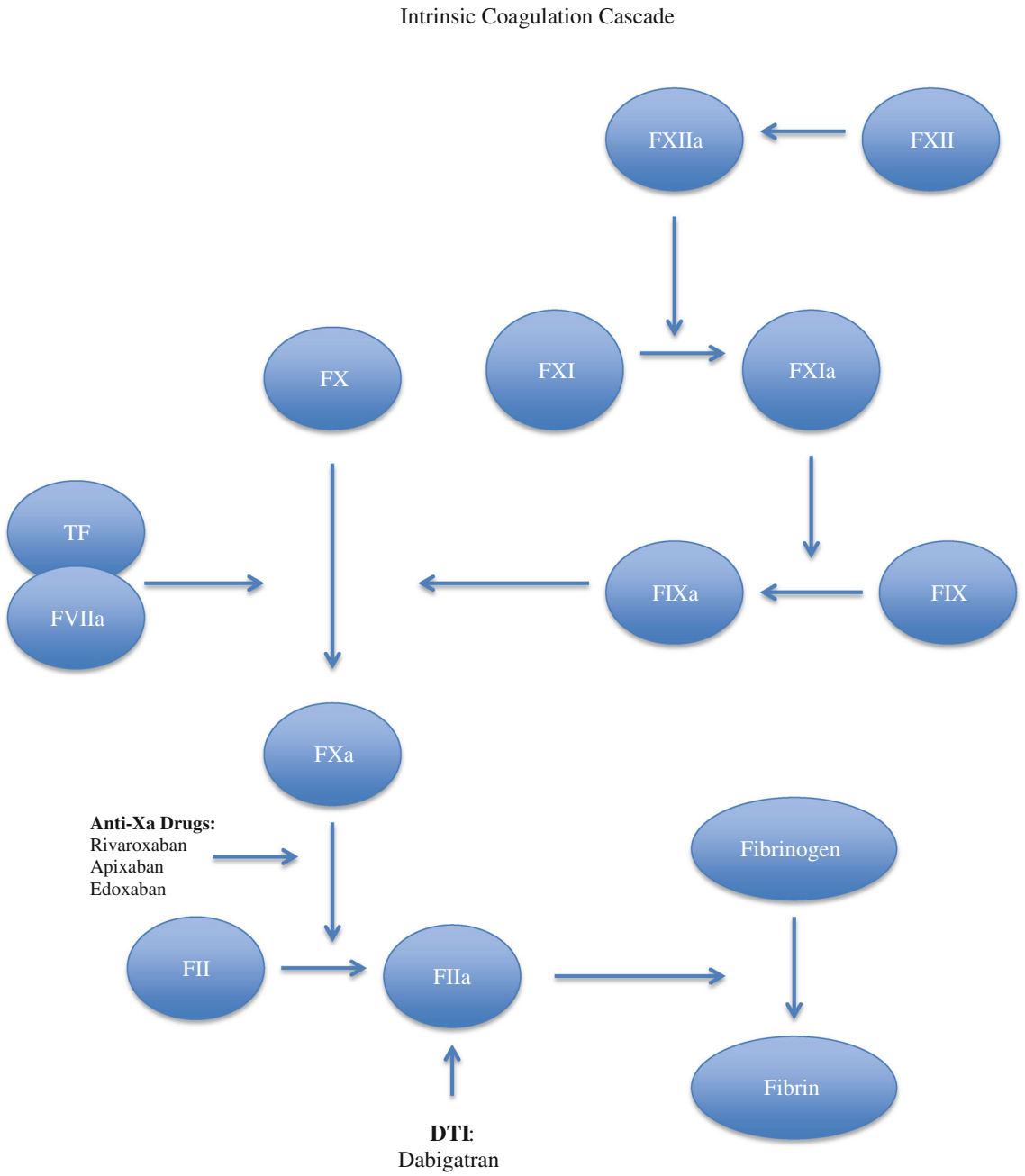

Fig. 2 Intrinsic coagulation cascade and sites of competitive, active site inhibition by novel oral anticoagulants

in the sample. This test is approved for laboratory use in Europe but not in the United States [24].

Dilute Russell's viper venom time

The dilute Russell's viper venom time (dRVVT), is an assay typically used for determining the presence of a circulating lupus anticoagulant, but given its sensitivity to factor II and factor X activity, there may be a role in monitoring the NOAC drugs [17].

Although several coagulation assays, including PiCT, ECT, anti-IIa assay, and dRVVT may correlate with NOAC concentrations, their role in the management of patients receiving these drugs has not been well delineated.

Reversal agents

The *reversal* of systemic anticoagulation achieved by drug therapy can be defined on the basis of coagulation

measures and its return to normal levels. This definition dictates that the coagulation measure itself is an accurate representation of drug concentration. The currently available reversal agents do *not* act as "antidotes" to specific oral anticoagulants but may attenuate their systemic pharmacodynamic effect by generating thrombin.

Prothrombin complex concentrates

Prothrombin complex concentrates (PCC) were developed in the 1970s to treat patients with inherited disorders of coagulation such as hemophilia A and B, but are now also used for patients with vitamin K antagonist-related bleeding [25]. PCC are purified products derived from a plasma pool that contains vitamin K-dependent coagulation proteins (factors II, VII, IX, and X). In addition to non-activated vitamin K-dependent coagulation proteins, PCC contains differing amounts of protein C and S, and in some preparations, antithrombin and low-dose heparin as well. These compounds are used with the goal of restoring hemostasis in the setting of major bleeding or excessive anticoagulation. PCC's can be divided into "4" factor concentrates (factors II, IX, X, and VII) or "3" factor concentrates (factors II, IX, and X). Four-factor PCC have been approved by the FDA and are commercially available only in Europe and Canada. The "activated" form of PCC (FEIBA®) contains variable amounts of factor II, factor IX, factor X, and protein C mainly in non-activated forms but with activated factor VII.

PCC is administered as an intravenous bolus with the dose determined on the difference between target and prior percentage of factors multiplied by the patient's body weight; the percentage of factors is based on INR values. While PCC can "reverse" the effects of systemic anticoagulants, by nature they are prothrombotic with the potential to cause thromboembolic events. Thromboembolic events, including acute coronary syndrome, disseminated intravascular coagulation, stroke, and venous thromboembolism have occurred with a reported incidence of 2 % [26]. During the manufacturing process of PCC, procedures are in place to inactivate and eradicate infectious agents such as viruses to decrease any potential for transmission.

Recombinant factor VII

NovoSeven® is recombinant active factor VIIa (rFVIIa) derived from human plasma and specifically used for promoting hemostasis by activating the extrinsic pathway of coagulation. Its original use was for patients with acquired hemophilias or for the prevention of bleeding in surgical interventions or invasive procedures in this patient population. NovoSeven® has been used "off label" in patients with vitamin K antagonist-associated bleeding. NovoSeven® activates conversions of factor X to factor Xa and factor IX to IXa. These activated factors, in the presence of factor Va, phospholipid, and calcium, convert prothrombin to thrombin, which in turn converts fibrinogen to fibrin. It has a half-life of 3–6 h in healthy subjects and is administered as an intravenous bolus injection. The drug is administered as a white, lyophilized white powder in single vials containing variable milligram dosages of rFVIIa per vial. While there are no absolute contraindications outside of hypersensitivity reactions, NovoSeven®'s use must be delicately weighed against potential risk. NovoSeven® has been linked to arterial thrombotic events, including myocardial ischemia, myocardial infarction, cerebrovascular ischemia, and stroke. Arterial thromboembolism was reported in 2 meta-analyses of placebo-controlled clinical trials in populations who "fell outside" of the approved indications of the drug [27, 28]. Thromboembolic complications have been demonstrated in clinical trials of patients with an approved indication as well, with an incidence of 0.28 % of bleeding episodes treated [29]. Administration of rFVIIa should be preceded by a detailed history and physical examination to evaluate for risk factors of vascular disease as well as abnormal cardiovascular and neurological examination findings. During and after administration of rFVIIa, physicians must be vigilant to assess for any signs or symptoms of compromised end-organ perfusion such as chest pain, headache, peripheral paresthesias, focal neurologic deficits, claudication, and decreased urine output.

Fresh frozen plasma

Fresh frozen plasma (FFP) consists of the fluid portion of human blood, which has been centrifuged, separated, and frozen solid at a temperature of −18 to −30 °C within 8 h of collection and then stored. One unit of FFP is the plasma taken from one unit of whole blood. FFP contains all coagulation factors in normal concentrations including antithrombin and von Willebrand factor. FFP is widely available and is the most common means of replacing depleted coagulation factors or urgently reversing an acquired coagulopathy. Given that FFP is blood group specific, ABO group testing is required prior to its administration. FFP has historically been used for active bleeding and/or elevated INR where reversal is needed prior to invasive procedures, surgery, or trauma. FFP pack volume can vary but is typically 200 mL. Limitations to the use of FFP include variable amounts of coagulation factors, risk of volume overload, the time required to thaw, and transmission of viral illnesses. The most serious consequence of FFP administration is the risk of transfusion related acute lung injury, which occurs with an incidence of 8–25 %.

Hemodialysis

Hemodialysis can be successful in the removal of compounds from circulation, particularly those that are not highly protein bound. In a situation where an overdose occurs or severe bleeding is apparent, hemodialysis could be effective in the removal of anticoagulants. A critical factor in determining whether a drug can be dialyzed is its protein binding within serum. Studies have demonstrated that hemodialysis can be affective in accelerating plasma clearance of dabigatran, which has relatively low plasma protein binding. For rivaroxaban, apixaban, and warfarin, which are highly bound to plasma proteins, dialysis will not accelerate plasma clearance. Edoxaban exhibits variable clearance by hemodialysis given that 55 % of the drug is protein bound in serum.

Activated charcoal

Oral activated charcoal has been studied in vitro and may be effective for decreasing dabigatran absorption [30]. Antifibrinolytic agents such as desmopressin may be useful as adjunctive therapy in patients with severe bleeding.

Cost considerations

Hemostatic agents, with the exception of FFP, are not available at all hospitals, including academic medical centers and cost is a legitimate consideration for their use. Recombinant factor VIIa is a cloned form of endogenous human hemostatic factor VII. Acquisition of a 1.2 mg vial cost approximately $1,400 USD. In addition, the drug is typically limited to large tertiary care centers. In comparison, fresh frozen plasma cost $35–$55 USD to acquire and is widely available throughout academic centers and community hospitals. Both 3- and 4-factor PCC are now available in the United States. PCC is administered on a unit per kilogram dosing scale with a dose of 25 U/kg costing $1,700 USD and a 40 U/kg dose costing approximately $2,600 USD. Vitamin K, for the treatment of warfarin-related bleeding or excess anticoagulation, is readily available in community and academic hospitals and is inexpensive compared to the cost of factor VIIa and PCC. Initiating hemodialysis introduces potential complexities, with additional consultation needed from a nephrologist, as well as the insertion of a large bore catheter to conduct the procedure. In addition, not all hospitals are equipped to perform hemodialysis.

Considerations for management of unwanted or excessive anticoagulation and bleeding

While anticoagulation decreases the risk of stroke and systemic embolic events in patients with atrial fibrillation, there are many questions about the risk and management of excess anticoagulation. The approval and rapid uptake of NOAC in some countries has not yet been matched by the formulation of consensus guidelines that include management strategies for their reversal. In addition, concerns surrounding the optimal management of bleeding complications stemming from NOAC have appeared in the medical literature and voiced by public consumers.

A discussion about the management of oral anticoagulant-associated bleeding logically begins with a summary of risk factors for bleeding complications and clinically differentiating emergent bleeding from non-emergent bleeding. Risk factors for bleeding complications from anticoagulant therapy include: excessive alcohol intake, renal insufficiency, recent trauma, increased age, uncontrolled hypertension, history of gastrointestinal bleeding, thrombocytopenia, and a history of stroke. Emergent bleeding can be classified as: bleeding from a major organ system or trauma-related bleeding in an individual taking oral anticoagulant therapy that results in acute hemodynamic compromise and possibly death. Indications for emergent reversal of anticoagulants should be considered for any of the following clinical scenarios including: intracranial hemorrhage, pulmonary hemorrhage, active gastrointestinal/genitourinary bleeding, bleeding related to trauma, or compartment syndrome [31]. In addition, emergent reversal of systemic anticoagulation should be considered for persons needing emergent invasive procedures, where the risk of bleeding and its consequences outweighs the potential benefit provided by the procedure.

Vitamin K antagonist

VKA prolong the PT, INR, and APTT; however, each coagulation assay can underestimate drug concentrations due not only to the variability of reagents used in clinical coagulation laboratories but also interactions with antibiotics, antiarrhythmic drugs, and diet. Vitamin K, FFP, rVIIa, and PCC shorten PT/INR values. Lubetsky et al. [32] showed that prolonged INR values could be reduced more rapidly with the administration of intravenous rather than oral vitamin K. Fredriksson et al. [33] found that patients with anticoagulant-related intracranial hemorrhage (ICH) due to warfarin or dicumarol had reductions in PT/INR values with the administration of intravenous vitamin K and PCC; normalization of PT/INR values was achieved more rapidly with the administration of PCC. In addition, Freeman et al. [34] demonstrated that rFVIIa reduced INR values in patients with warfarin-induced acute intracranial hemorrhage. The INR serves as a useful marker for bleeding risk in patients taking VKA. Fredriksson et al. [33] demonstrated that reversal of excessive anticoagulation was associated with improved signs and symptoms of

intracranial hemorrhage; however, clinical outcomes remain poor in a majority of patients.

Evidence based guidelines for the management of excessive warfarin and bleeding complications have been published by the American College of Chest Physicians [31]. For patients taking VKA with an elevated INR and no clinical evidence of bleeding, the recommendations are as follows:

- For patients taking VKA with INR's between 3.1 and 4.5 and no evidence of bleeding, the routine administration of vitamin K is *not recommended*. Omission of the next several doses of VKA and/or a dosage reduction is recommended.
- For patients taking VKA with INR's between 4.5 and 10 and no evidence of bleeding, the administration of vitamin K is *not recommended*. Omission of the next several doses of VKA and/or a dosage reduction is recommended. If a bleeding risk factor present, administration of oral vitamin K is recommended at a dose of 1–2.5 mg oral.
- For patients taking VKA with INR's between 4.5 and 10 and no evidence of bleeding, but pending dental extraction or surgical procedure, the administration of vitamin K is recommended at a dosage of 2–4 mg oral.
- For patients taking VKA with an INR >10 and no evidence of bleeding, the administration of vitamin K is recommended at a dosage 3–5 mg oral. All anticoagulants should be discontinued.

Patients with VKA associated major bleeding, the recommendations are as follows:

- For patients taking VKA with serious warfarin overdose (INR >20) or serious bleeding, anticoagulation with VKA should be discontinued. The administration of intravenous vitamin K at a dose of 5–10 mg is recommended as well as the use of coagulation factors in the form of FFP or PCC.
- For patients with life threatening bleeding, rapid reversal of systemic anticoagulation should be achieved with 4-factor PCC rather than FFP. In addition, the administration of 5–10 mg of intravenous vitamin K is recommended in addition to the use of coagulation factors.

Dabigatran

The American College of Chest Physicians Anticoagulation Guidelines detail pharmacokinetic and pharmacodynamic data for the optimal clinical use of dabigatran. The guidelines are explicit with regards to reversal strategies for this agent. The consensus statement underscores that there is "insufficient clinical experience to guide the management of major bleeding, suspected overdose, urgently needed surgery, or urgent invasive diagnostic procedure in patients taking this drug" [35]. Supportive measures such as fluid resuscitation, red blood cell transfusions, and rapid identification of the source of bleeding should be employed for any patient with bleeding complications. As discussed previously, dabigatran prolongs the PT, APTT, ECT, TT and dTT, prothrombinase-induced clotting time, and dRVVT. The ECT appears to be the most sensitive assay for a wide range of dabigatran concentrations given a concentration-dependent linear response observed in patients treated with dabigatran and prolongation of ECT [36]. PCC have not been shown to correct APTT, TT, or ECT prolongation following dabigatran in healthy volunteers [37]. Activated PCCs have been shown to correct thrombin generation parameters in patients taking single doses of dabigatran, but only when tested employing in vitro models [38]. rVIIa has no demonstrated efficacy for reversing dabigatran-induced prolongation of standard coagulation parameters in humans. There are no data regarding the administration of FFP for dabigatran-associated bleeding. In addition, no published reports exist detailing the effects of dabigatran on prolongation of either the prothrombinase-induced clotting time or dRVVT. Dabigatran has no antidote, but low plasma binding properties facilitate removal of the drug by hemodialysis. The ECT, while not widely available, is sensitive at all concentrations of dabigatran (and other DTI's) and may serve as an accurate and reproducible marker of not only dabigatran concentrations, but also bleeding risk. Zhou et al. [39] showed that increasing doses of dabigatran, correlated with increasing ECT and hematoma expansion in murine models. Human studies are needed to further demonstrate a relationship between prolonged coagulation assays and bleeding outcomes (Table 2).

Rivaroxaban

Similar to dabigatran, the guidelines from the American College of Chest Physicians do not provide specific management strategies for major bleeding in patients taking rivaroxaban. Administration of rivaroxaban prolongs the PT, APTT, anti-Xa chromogenic assay, prothrombinase-induced clotting time, and dRVVT. Anti-Xa chromogenic assays accurately reflect drug concentrations. Prothrombinase-induced clotting time and rivaroxaban show a concentration-dependent relationship [20]. PCC administration shortens PT prolongation following rivaroxaban administration in healthy human subjects [37, 40]. Activated PCCs have also been shown to correct thrombin generation parameters in patients taking single doses of rivaroxaban, but only in in vitro models [38]. To date, all human studies evaluating the role of rFVIIa in reversing prolonged coagulation parameters for patients on rivaroxaban have

Table 2 Considerations for reversal of novel oral anticoagulants

Agent	Coagulation assay	Reversal agent	Outcome measure
Dabigatran	Ecarin clotting time. Sensitive at a wide range of concentrations. Lacks FDA approval and limited availability. The hemoclot direct thrombin inhibitor assay is available and sensitive at relevant concentrations.	Consider 3 or 4 factor PCC's although data is limited with respect to reversing clinical bleeding. No efficacy for reversal of NOACs with rVIIa. Adjunctive agents include: activated charcoal and hemodialysis.	No studies using assays as surrogates for bleeding risk. Potential assays which show high sensitivity and linearity across varying concentrations include: ECT, anti-IIa and chromogenic assay.
Rivaroxban	Chromogenic anti-Xa assay. Accurate and reproducible. Readily available.	Consider 3 or 4 factor PCC's. Limited data on efficacy in patients with bleeding complications. No clear effect on bleeding outcomes.	Anti-Xa assay and PiCT are sensitive at vary concentrations and could prove to be a marker of bleeding risk.
Apixaban	Chromogenic anti-Xa assay. Accurate and reproducible. Readily available.	Consider 3 or 4 factor PCC's. Limited data on efficacy in patients with bleeding complications. No clear effect on bleeding outcomes.	Similar to all factor Xa inhibitors, PiCT and anti-Xa assays could serve as markers of bleeding given the high sensitivity of these assays.
Edoxaban	Chromogenic anti-Xa assay. Accurate and reproducible. Readily available.	Consider 3 or 4 factor PCC's. Limited data on efficacy in patients with bleeding complications. No clear effect on bleeding outcomes.	Similar to all factor Xa inhibitors, PiCT and anti-Xa assays could serve as markers of bleeding given the high sensitivity of these assays.

PCC prothrombin complex concentrates, *rVIIa* recombinant factor VIIa, *PiCT* prothrombinase induced clotting time

shown no effect [41]. To our knowledge, there are no data supporting FFP in patients with rivaroxaban-induced bleeding. Rivaroxaban does not have an antidote and high plasma protein binding precludes its effective removal by hemodialysis. There are currently no published data on the use of any coagulation assay as a surrogate marker for bleeding risk in patients receiving rivaroxaban.

Apixaban

Like other novel factor Xa inhibitors, apixaban prolongs the PT, APTT, prothrombinase-induced clotting time, anti-Xa chromogenic assay, and dRVVT. Anti-Xa chromogenic assays have shown promising results in quantifying apixaban concentrations. Becker et al. [23] identified a linear relationship between apixaban plasma concentrations and chromogenic anti-FXa levels among patients with acute coronary syndrome. Prothombinase-induced clotting time has not been studied with apixaban. Although in vitro studies have shown that PCC can increase thrombin generation in human serum containing apixaban, no human data exist regarding the use of PCC, rFVIIa, or FFP in the reversal of apixaban-induced prolongation of standard coagulation assays or bleeding [42].

Considering factor Xa inhibitors collectively as a class of drugs, PCC may reverse PT/INR prolongation in patients receiving apixaban, in a similar fashion to those taking rivaroxaban. No antidote exists for apixaban and given its high plasma protein binding, hemodialysis will not remove significant amount of the drug. To date, there are no published data supporting common coagulation measures as surrogate markers for bleeding risk.

Edoxaban

Although currently being evaluated in phase III clinical trials, several assumptions can be made regarding the reversal of edoxaban. Similar to other factor Xa inhibitors, edoxaban prolongs the PT/INR, APTT, prothrombinase-induced clotting time, and dRVVT. Activated PCC have been shown to correct PT prolongation induced by edoxaban, but only in in vitro studies [43, 44]. In vitro studies have also shown that rVIIa can shorten edoxaban-induced PT prolongation; but to date, no data exists for the use of rVIIa to treat edoxaban-induced bleeding in patients [43, 44]. No antidote exists for edoxaban and the amount of drug removed by hemodialysis may be relatively modest. There are currently no existing data evaluating individual coagulations assays for the purpose of conferring a measure of bleeding risk in patients taking edoxaban.

Concluding thoughts

For prescribers of NOAC, clinical judgment must be used to assess patients with and those at risk for bleeding complications. Although current national and international guidelines do not specify treatment algorithms for bleeding with NOAC, they do provide clear direction for VKA-associated bleeding and offer a general framework for management of anticoagulant-associated complications. The risks and benefits of reversal agents must be weighed carefully in the context of the severity of bleeding and inherent predisposition for thrombosis. More research is needed to sufficiently address the many lingering questions

that directly impact clinicians and their patients taking NOAC drugs.

Future directions

As we enter a new era in the management of thrombotic disorders, including atrial fibrillation, prescribing clinicians must be fluent in the pharmacology and appropriate use of the NOAC drugs. While demonstrating benefit, these agents are not without risk and bleeding will occur. Data derived from human studies or large scale, but sufficiently detailed registries are needed to assess the ability of hemostatic agents to impact clinical outcomes. Rapidly acting and target specific antidotes are currently under development for NOAC. Recombinant factor Xa, which is a catalytically and membrane inactive form of factor Xa is being developed as an antidote for factor Xa inhibitors. Animal studies have shown an 80 % decrease in blood loss after the administration this antidote [45]. A plasma-derived recombinant factor Xa antidote has been shown to reverse coagulation test abnormalities induced by rivaroxaban and apixaban [41, 45]. In addition, in vitro and *in vivo* studies in humans and animals, respectively, have shown potential efficacy of a monoclonal antibody targeted against dabigatran [46]. Thought leaders in cardiology, hematology, and anticoagulation management must continue to evaluate how to best quantify the degree of anticoagulation with the available coagulation assays and formulate guidelines for the management of patients with and those at risk for hemorrhagic complications.

References

1. Zehnder J, Katzung SM, Trevor A (2009) Basic and clinical pharmacology, 11th edn. McGraw-Hill Medical, New York
2. Kamali F, Wynne H (2010) Pharmacogenetics of warfarin. Annu Rev Med 61:63–75
3. Sanderson S, Emery J, Higgins J (2005) CYP2C9 gene variants, drug dose, and bleeding risk in warfarin-treated patients: a HuGEnet systematic review and meta-analysis. Genet Med 7:97–104
4. Connolly SJ, Ezekowitz MD, Yusuf S et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361:1139–1151
5. Blech S, Ebner T, Ludwig-Schwellinger E, Stangier J, Roth W (2008) The metabolism and disposition of the oral direct thrombin inhibitor, dabigatran, in humans. Drug Metab Dispos 36:386–399
6. Schulman S, Kearon C, Kakkar AK et al (2009) Dabigatran versus warfarin in the treatment of acute venous thromboembolism. N Engl J Med 361:2342–2352
7. Pharm. BI (2011) PRADAXA (*dabigatran etexilate)*: reducing risk of stroke from atrial fibrillation (Afib). Boehringer Ingelheim Pharmaceuticals, Inc, Ridgefield, CT
8. Ordovás Baines JP, Climent Grana E, Jover Botella A, Valero Garcia I (2009) Pharmacokinetics and pharmacodynamics of the new oral anticoagulants dabigatran and rivaroxaban. Farm Hosp 33:125–133
9. Hankey GJ, Eikelboom JW (2011) Dabigatran etexilate: a new oral thrombin inhibitor. Circulation 123:1436–1450
10. Patel MR, Mahaffey KW, Garg J et al (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365: 883–891
11. AG BSP (2011) Xarelto: summary of product characteristics. Bayer Pharma AG, Berlin
12. Kubitza D, Becka M, Voith B, Zuehlsdorf M, Wensing G (2005) Safety, pharmacodynamics, and pharmacokinetics of single doses of BAY 59-7939, an oral, direct factor Xa inhibitor. Clin Pharmacol Ther 78:412–421
13. Fareed J, Thethi I, Hoppensteadt D (2012) Old versus new oral anticoagulants: focus on pharmacology. Annu Rev Pharmacol Toxicol 52:79–99
14. Granger CB, Alexander JH, McMurray JJ et al (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365:981–992
15. Carreiro J, Ansell J (2008) Apixaban, an oral direct Factor Xa inhibitor: awaiting the verdict. Expert Opin Investig Drugs 17: 1937–1945
16. Zafar MU, Vorchheimer DA, Gaztanaga J et al (2007) Antithrombotic effects of factor Xa inhibition with DU-176b: phase-I study of an oral, direct factor Xa inhibitor using an ex-vivo flow chamber. Thromb Haemost 98:883–888
17. Favaloro EJ, Lippi G (2012) The new oral anticoagulants and the future of haemostasis laboratory testing. Biochemia medica : casopis Hrvatskoga drustva medicinskih biokemicara / HDMB 22:329–341
18. Ng VL (2009) Prothrombin time and partial thromboplastin time assay considerations. Clin Lab Med 29:253–263
19. Bates SM, Weitz JI (2005) Coagulation assays. Circulation 112:e53–e60
20. Miyares MA, Davis K (2012) Newer oral anticoagulants: a review of laboratory monitoring options and reversal agents in the hemorrhagic patient. Am J Health Syst Pharm 69:1473–1484
21. Tripodi A, van den Besselaar A (2009) Laboratory monitoring of anticoagulation: where do we stand? Semin Thromb Hemost 35:34–41
22. Asmis LM, Alberio L, Angelillo-Scherrer A et al (2012) Rivaroxaban: quantification by anti-FXa assay and influence on coagulation tests: a study in 9 Swiss laboratories. Thromb Res 129:492–498
23. Becker RC, Yang H, Barrett Y et al (2011) Chromogenic laboratory assays to measure the factor Xa-inhibiting properties of apixaban–an oral, direct and selective factor Xa inhibitor. J Thromb Thrombolysis 32:183–187
24. Castellone DD, Van Cott EM (2010) Laboratory monitoring of new anticoagulants. Am J Hematol 85:185–187
25. Colomina MJ, Diez Lobo A, Garutti I, Gomez-Luque A, Llau JV, Pita E (2012) Perioperative use of prothrombin complex concentrates. Minerva Anestesiol 78:358–368
26. Dentali F, Marchesi C, Pierfranceschi MG et al (2011) Safety of prothrombin complex concentrates for rapid anticoagulation reversal of vitamin K antagonists: a meta-analysis. Thromb Haemost 106:429–438
27. Hsia CC, Chin-Yee IH, McAlister VC (2008) Use of recombinant activated factor VII in patients without hemophilia: a meta-analysis of randomized control trials. Ann Surg 248:61–68
28. Hardy JF, Belisle S, Van der Linden P (2008) Efficacy and safety of recombinant activated factor VII to control bleeding in non-hemophiliac patients: a review of 17 randomized controlled trials. Ann Thorac Surg 86:1038–1048

29. Girolami A, Ruzzon E, Tezza F, Scandellari R, Vettore S, Girolami B (2006) Arterial and venous thrombosis in rare congenital bleeding disorders: a critical review. Haemophilia 12: 345–351
30. van Ryn J, Stangier J, Haertter S et al (2010) Dabigatran etexilate–a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 103:1116–1127
31. Holbrook A, Schulman S, Witt DM et al (2012) Evidence-based management of anticoagulant therapy: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e152S–e184S
32. Lubetsky A, Yonath H, Olchovsky D, Loebstein R, Halkin H, Ezra D (2003) Comparison of oral vs intravenous phytonadione (vitamin K1) in patients with excessive anticoagulation: a prospective randomized controlled study. Arch Intern Med 163: 2469–2473
33. Fredriksson K, Norrving B, Stromblad LG (1992) Emergency reversal of anticoagulation after intracerebral hemorrhage. Stroke 23:972–977
34. Freeman WD, Brott TG, Barrett KM et al (2004) Recombinant factor VIIa for rapid reversal of warfarin anticoagulation in acute intracranial hemorrhage. Mayo Clin Proc 79:1495–1500
35. Ageno W, Gallus AS, Wittkowsky A, Crowther M, Hylek EM, Palareti G (2012) Oral anticoagulant therapy: antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141:e44S–e88S
36. Samama MM, Guinet C (2011) Laboratory assessment of new anticoagulants. Clin Chem Lab Med 49:761–772
37. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M (2011) Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 124:1573–1579
38. Chan HHW, Atkinson HM, Goncharenko M, Berry LR, Chan AKC (2011) Reversal of dabigatran using recombinant activated factor VII and activated prothrombin complex concentrates in thromboelastography assay. J Thromb Haemost 9:576–577 (Abstracts of the XXIII Congress of the International Society on Thrombosis and Haemostasis, 57th Annual SSC Meeting, 2011)
39. Zhou W, Schwarting S, Illanes S et al (2011) Hemostatic therapy in experimental intracerebral hemorrhage associated with the direct thrombin inhibitor dabigatran. Stroke 42:3594–3599
40. Marlu R, Hodaj E, Paris A, Albaladejo P, Crackowski JL, Pernod G (2012) Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban: a randomised crossover ex vivo study in healthy volunteers. Thromb Haemost 108: 217–224
41. Siegal DM, Crowther MA (2013) Acute management of bleeding in patients on novel oral anticoagulants. Eur Heart J 34:489–498
42. Escolar G, Arellano-Rodrigo E, Reverter JC et al (2012) Reversal of apixaban induced alterations of hemostasis by different coagulation factor concentrates: studies in vitro with circulating human blood. Circulation 126(4):520–521 (Abstract from the Emerging Science Series)
43. Fukuda T, Honda Y, Kamisato C, Morishima Y, Shibano T (2012) Reversal of anticoagulant effects of edoxaban, an oral, direct factor Xa inhibitor, with haemostatic agents. Thromb Haemost 107:253–259
44. Morishima Y, Honda Y, Kamisato C, Furugohri T, Shibano T (2011) Reversal agents for edoxaban, a factor Xa inhibitor: effects of factor VIIa, anti-inhibitor coagulant complex, prothrombin complex concentrate, fresh plasma, and vitamin K. J Thromb Haemost 9:135
45. Lu GP, Luan P, Hollenbach S, Abe K, DeGuzman F, Siu G, Hutchaleelaha A, Inagaki M, Conley PB, Phillips DR, Sinha U (2009) Reconstructed recombinant factor Xa as an antidote to reverse anticoagulation by factor Xa inhibitors. J Thromb Haemost 7:309 (Abstracts of the XXIII Congress of the International Society on Thrombosis and Haemostasis, 57th Annual SSC Meeting, 2011)
46. Van Ryn J, Litzenburger T, Waterman A (2011) CanadaK, Hauel N, Kroe-Barrett R, Singh S, Park J. Dabigatran anticoagulant activity is neutralized by an antibody selective to dabigatran in in vitro and in vivo models. J Am Coll Cardiol 57:E1130

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REVIEW Open Access

Practical management of patients on apixaban: a consensus guide

Christopher Ward[1*], Greg Conner[2], Geoffrey Donnan[3], Alexander Gallus[4] and Simon McRae[5]

Abstract

Background: Atrial fibrillation (AF) is a common tachyarrhythmia in Australia, with a prevalence over 10% in older patients. AF is the leading preventable cause of ischaemic stroke, and strokes due to AF have a higher mortality and morbidity. Stroke prevention is therefore a key management strategy for AF patients, in addition to rate and rhythm control. Anticoagulation with warfarin has been an enduring gold standard for stroke prevention in NVAF patients. In Australia, three novel oral anticoagulants (NOACs), apixaban, dabigatran and rivaroxaban are now approved and reimbursed for stroke prevention in patients with non-valvular AF (NVAF). International European Cardiology guidelines now recommend either a NOAC or warfarin for NVAF patients with a CHA_2DS_2-VASc score ≥2, unless contraindicated. Apixaban is a direct factor Xa inhibitor with a 12-hour half-life and 25% renal excretion that was found in a large trial of NVAF patients to be superior to warfarin in preventing stroke or systemic embolism. In this trial population, apixaban also resulted in less bleeding and a lower mortality rate than warfarin.

Methods: Clinical experience with apixaban outside of clinical trials has been limited, and there is currently little evidence to guide the management of bleeding or invasive procedures in patients taking apixaban. The relevant currently available animal and *ex vivo* human data were collected, analyzed and summarized.

Results: This multi-disciplinary consensus statement has been written to serve as a guide for healthcare practitioners prescribing apixaban in Australia, with a focus on acute and emergency management.

Conclusions: The predictable pharmacokinetics and minimal drug interactions of apixaban should allow for safe anticoagulation in the majority of patients, including temporary interruption for elective procedures. In the absence of published data, patients actively bleeding on apixaban should receive standard supportive treatment. Quantitative assays of apixaban level such as chromogenic anti-Xa assays are becoming available but their utility is unproven in this setting. Specific antidotes for novel anticoagulants, including apixaban, are in clinical development.

Keywords: Apixaban, Novel oral anticoagulants, Bleeding, Perioperative management

Background

In Australia, three novel oral anticoagulants (NOACs) have been approved for the prevention of stroke in patients with non-valvular atrial fibrillation (NVAF) and one or more additional risk factors for stroke (prior stroke, prior transient ischaemic attack, prior systemic embolism, age ≥75 [or age ≥65 years associated with one of the following: diabetes mellitus, coronary artery disease, or hypertension], arterial hypertension requiring treatment, diabetes mellitus, heart failure ≥ New York Heart Association Class 2, decreased left ventricular ejection fraction or documented peripheral arterial disease). These are dabigatran, a direct thrombin inhibitor, and two direct factor Xa inhibitors, apixaban and rivaroxaban. All three are also approved in Australia for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone major orthopaedic surgery of the lower limb. Rivaroxaban is approved for the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE) and the prevention of recurrent venous thromboembolism. These novel oral anticoagulants have short half-lives (dabigatran 12-17 hrs, apixaban ~12 hrs, rivaroxaban 5-13 hrs), predictable

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pharmacokinetics and few drug-drug and drug-food interactions, compared to warfarin. In addition to their favourable pharmacokinetic profiles, dabigatran 110 mg and rivaroxaban have demonstrated similar rates of stroke and systemic embolism reduction to warfarin in NVAF patients, with dabigatran 150 mg and apixaban demonstrating a superior reduction in stroke and systemic embolism, compared to warfarin [1-3]. Additionally, dabigatran 110 mg and apixaban resulted in significantly less major bleeding, compared to warfarin [1,3]. Although specific antidotes for these agents are currently in development, the lack of a reversal strategy has raised concern among healthcare providers.

Methods

In the absence of robust clinical data for emergency and peri-operative management of patients receiving apixaban, an expert panel of Australian clinicians from the fields of cardiology, neurology and haematology convened to develop this practical consensus guide for apixaban management in Australia, utilising the currently available animal and *ex vivo* human data.

Results and discussion

About apixaban

Apixaban is a direct FXa inhibitor with rapid onset of action, a 12-hour half-life and only ~25% renal excretion [4,5]. Apixaban is indicated in Australia for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery and for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke. The recommended dose of apixaban for VTE prophylaxis is 2.5 mg BID. The recommended dose of apixaban for stroke prevention in non-valvular atrial fibrillation (NVAF) is 5 mg BID (2.5 mg BID if ≥2 of the following; ≤60 kg, ≥80 years, serum creatinine level ≥133 μm/L) [5].

The risk of stroke and bleeding must be assessed for each patient before commencing any anticoagulation therapy, including apixaban. Some of the patients excluded from the trials [3,6] had baseline characteristics that were associated with increased risk of bleeding (e.g. recent major bleeding, renal insufficiency [CrCl <25 ml/min], severe hepatic impairment, platelet count <100), and there are no or insufficient data on the use of apixaban in such patients. The clinical trials excluded aspirin doses >165 mg/day or dual anti-platelet therapy [3,6]. The concomitant use of apixaban with anti-platelet agents increases the risk of bleeding [7]. Apixaban should be used with caution when co-administered with NSAIDs (including acetylsalicylic acid) because these medicinal products typically increase the bleeding risk. A significant increase in bleeding risk was reported with the triple combination of apixaban, acetylsalicylic acid and clopidogrel in a clinical study in patients with acute coronary syndrome [8].

Laboratory measurement of apixaban

At present, there is no validated coagulation assay to measure apixaban effect. As a result of FXa inhibition, apixaban prolongs standard clotting tests such as prothrombin time (PT), activated partial thromboplastin time (aPTT) but with variability between reagents [9]. Increases in clotting times are small at best, and the PT may remain normal (ratio <1.2) at a therapeutic concentration of apixaban [9]. Therefore the PT and APTT are not recommended to assess the pharmacodynamic effects of apixaban [5].

Specialised clotting assays can be used to measure apixaban effects. Anti-FXa activity exhibits a close direct linear relationship with apixaban plasma concentration, reaching maximum values at the time of apixaban peak plasma concentrations. The relationship between apixaban plasma concentration and anti-FXa activity is linear over a wide dose range of apixaban [10]. Although treatment with apixaban at the recommended dose does not require routine laboratory monitoring, measurement of drug level by a chromogenic anti-FXa assay may be useful in exceptional situations where knowledge of the apixaban level may help to inform clinical decisions, e.g. overdose or emergency surgery [5]. Anti-Xa assays are generally available in large Australian teaching hospitals, but may not be routinely performed in smaller institutions or after hours. These assays may also be difficult to access in other countries, with significant delays in reporting. Diagnostic laboratories will need validated, commercial apixaban controls and calibrators to adapt their anti-Xa assays for apixaban. Although commercial research-use only apixaban-specific calibrators are currently available in Australia, a standard curve constructed with commercial LMWH standards was reported to show an equally strong correlation with apixaban plasma concentration ($r^2 = 0.89$) as one constructed with apixaban ($r^2 = 0.88$) [11]. A dilute prothrombin time (dPT), achieved by diluting the thromboplastin reagent in 100 mmol/L $CaCl_2$, has been proposed as an improved assay for factor Xa inhibitors [12]. This modification prolonged the PT measurements at therapeutic concentrations of apixaban and showed greater sensitivity than a standard PT [12]. However, others have found that dPT was no better than PT in terms of sensitivity [9], suggesting that further development of these assays is needed.

The delay between the last intake of the drug and the blood sampling should be considered when assessing apixaban levels, since assays are influenced proportionally to apixaban concentration [9].

Interactions with other medications

Apixaban is metabolized mainly by CYP3A4/5 and is a substrate of efflux transport proteins P-glycoprotein (P-gp) and Breast Cancer Resistance Protein [5]. Therefore, apixaban is contraindicated in patients who are receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp, such as azole-antimycotics or HIV protease inhibitors [5] e.g. ketoconazole, itraconazole, voriconazole, posaconazole or ritonavir.

No dose adjustment for apixaban is required when this is co-administered with less potent inhibitors of CYP3A4 and/or P-gp [5] such as diltiazem, naproxen, amiodarone, verapamil, clarithromycin or quinidine.

The concomitant use of apixaban with strong CYP3A4 and P-gp inducers may lead to reduced apixaban plasma concentrations. No dose adjustment for apixaban is required during concomitant therapy with such agents, however strong inducers of both CYP3A4 and P-gp should be co-administered with caution [5] e.g. rifampicin, phenytoin, carbamazepine, phenobarbital and St John's Wort.

Famotidine, a typical gastric acid suppressant, does not affect the pharmacokinetics of apixaban [13]. As such, increases in gastric pH due to other gastric acid modifiers (such as other H2-receptor antagonists, proton pump inhibitors, and antacids) or the presence of abnormally elevated gastric pH (e.g. achlorhydria) are unlikely to affect the pharmacokinetics of apixaban [13].

Starting apixaban

Prior to initiating apixaban, liver function and renal function testing should be performed. The European Society of Haematology 2012 guidelines recommend assessment of renal function (by calculated CrCl) be mandatory for all NOACs, with renal function being assessed annually in patients with normal (CrCl ≥80 mL/min) or mild (CrCl 50–79 mL/min) renal impairment, and 2–3 times per year in patients with moderate (i.e. creatinine clearance 30–49 mL/min) renal impairment [14].

Patients with impaired renal function (≤80 mL/min) were at higher risk for all cardiovascular events during the ARISTOTLE trial, and the incidence of major bleeding increased significantly with increasing renal dysfunction [15]. Apixaban was associated with less major bleeding compared with warfarin for three methods of glomerular filtration rate estimation (Cockcroft–Gault, Chronic Kidney Disease Epidemiology Collaboration and cystatin C) and stroke or systemic embolism occurred less frequently in patients assigned to apixaban than warfarin, regardless of renal function [15].

Switching from warfarin to apixaban

When switching anticoagulation from warfarin to apixaban, it is important to avoid using both drugs at therapeutic doses simultaneously; it is recommended that the INR is monitored daily after the cessation of warfarin, and that apixaban is not started until the INR is <2.0, typically approximately three days after cessation of therapeutic warfarin [3].

Switching from low molecular weight heparin (LMWH) to apixaban

As both agents have a similar rapid onset of FXa inhibition and effective half-life, switching anticoagulation from LMWH (e.g. enoxaparin) to apixaban, (and vice versa), can simply be done at the time of the next scheduled dose [5].

Switching from apixaban

An increased risk of stroke was observed during the transition from apixaban to warfarin in clinical trials in patients with non-valvular atrial fibrillation [16]. Discontinuation of apixaban prior to the onset of an effective antithrombotic effect of VKA could result in an increased risk of thrombosis. If anticoagulation with apixaban must be discontinued for any reason other than pathological bleeding, consider coverage with another anticoagulant.

Apixaban to warfarin

When converting from apixaban to warfarin, continue apixaban for 48 hours after the first dose of warfarin. After 2 days of co-administration of apixaban with warfarin, obtain an INR prior to the next scheduled dose of apixaban. Continue co-administration of apixaban and warfarin until the INR is ≥ 2.0.

Apixaban to low molecular weight heparin (LMWH)

As both agents have a similar rapid onset of FXa inhibition and effective half-life, switching anticoagulation from apixaban to LMWH (e.g. enoxaparin) and vice versa, can simply be done at the time of the next scheduled dose [5].

Bleeding management in patients receiving apixaban

In the ARISTOTLE study of apixaban in patients with atrial fibrillation, annual major bleeding events for apixaban compared to warfarin were 2.13% per year versus 3.09% per year ($p < 0.001$) [3]. Intracranial haemorrhage events were 0.33% per year for apixaban, compared to 0.80% per year for warfarin ($p < 0.001$) [3].

Spontaneous bleeding may occur with any anticoagulant. In the absence of published data regarding the treatment of patients with active bleeding while receiving apixaban, the following advice for general management of bleeding events is based on expert consensus (Figure 1).

- Establish the primary source of bleeding wherever possible, and secure haemostasis with local measures.

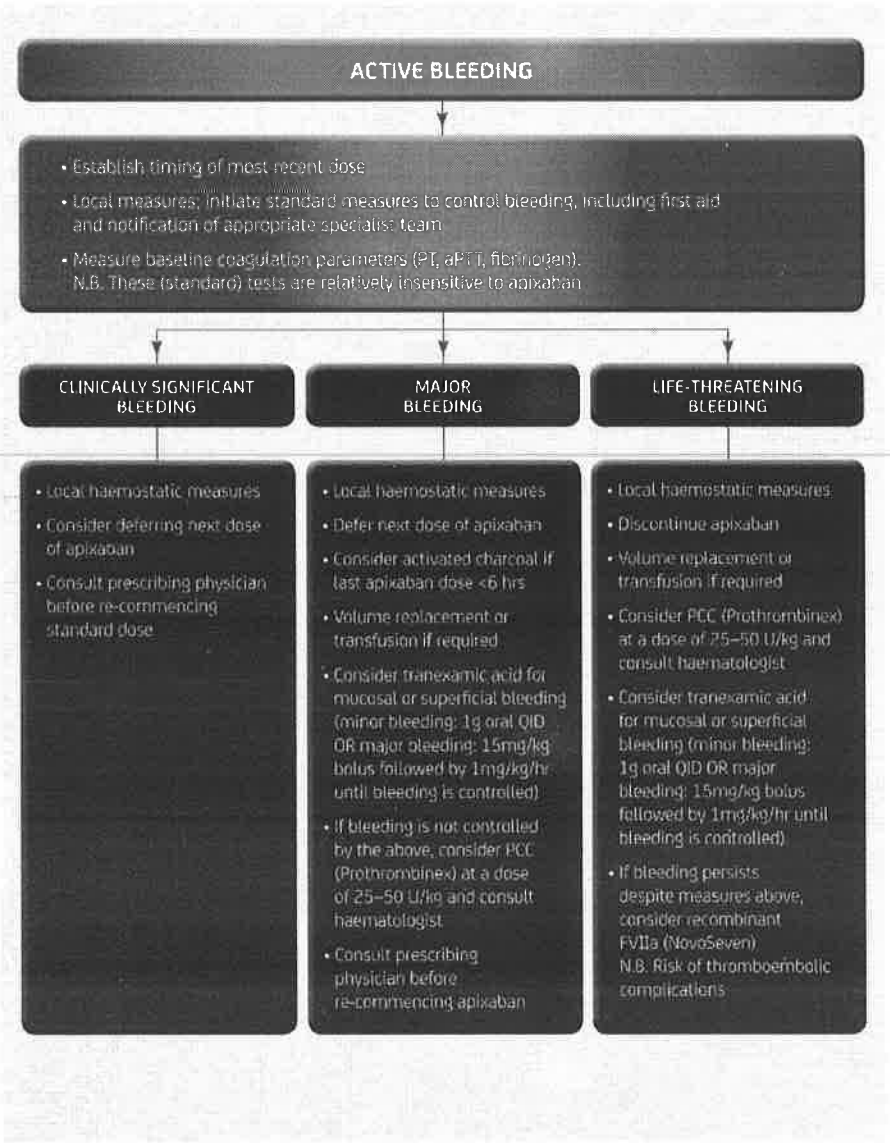

Figure 1 Considerations for the management of bleeding, based on expert consensus.

- Most cases of minor bleeding will resolve after cessation of drug, standard supportive treatment, including transfusion, mechanical compression and other local measures.
- If bleeding occurs within 6 hours of last apixaban dose, activated charcoal may reduce apixaban absorption, and hence anticoagulant effect [17]. This should also be considered soon after overdose or accidental ingestion.
- A specific antidote for apixaban is not currently available [5]. Two synthetic molecules are currently in early clinical trials for apixaban reversal. Andexanet alpha (PRT064445) is a truncated form of enzymatically inactive factor Xa, which can dose-dependently reverse the inhibitory activity and correct the prolongation of *ex vivo* clotting times by apixaban and other factor Xa inhibitors [18]. Another synthetic small molecule, aripazine (PER977), appears to have broad activity against the NOACs, reversing the anticoagulant activity of dabigatran, rivaroxaban, apixaban and edoxaban in rat bleeding models [19].
- Apixaban is highly (~87%) protein bound, and hence not expected to be dialyzable [5]. Based on studies of other factor Xa inhibitors in healthy volunteers, prothrombin complex concentrates (PCC) may reverse the anticoagulant effect, however the effect of PCC on clinical bleeding is not proven [20]. When apixaban (200 ng/ml) was added *in vitro* to

blood from healthy donors, PCC and activated PCC were more effective at improving thrombin generation than recombinant FVIIa (rFVIIa) [21].

- There is no clinical evidence examining the use of rFVIIa or bypassing agents (FEIBA) in bleeding patients receiving apixaban. In a rabbit model of apixaban-induced bleeding, neither rFVIIa nor PCC reduced blood loss from a standardised hepatosplenic injury, although rFVIIa did reverse prolongation of the prothrombin time and shortened skin bleeding time [22]. When apixaban (200 ng/ml) was added *in vitro* to blood from healthy donors, rFVIIa was more effective than PCC in restoring clotting times and thromboelastography parameters [21]. In animal, *in vitro* and healthy volunteer studies, these agents have partially reversed the anticoagulant effect of apixaban and other factor Xa inhibitors [23-26]. These agents can be considered for life-threatening bleeding, but carry a proven risk of thrombosis.
- There is no evidence to support the use of FFP, other than for volume replacement in case of major bleeding.

Peri-operative management in patients receiving apixaban

In stable patients, apixaban has a predictable half-life of 8-12 hours, which leaves residual activity of up to 50% at 12 hours and less than 25% at 24-hours after drug cessation [4]. This means that apixaban can be ceased for a shorter period of time than warfarin before invasive procedures, without the routine need to bridge with alternative anticoagulants such as heparin.

Planning for elective surgery or invasive procedures should involve balancing the intervention-associated bleeding risk and thrombotic risk associated with anticoagulant interruption in each individual. A "safe" residual drug level of apixaban for surgery is presently unknown, and no test has been correlated with bleeding risk. As such, there is currently no known threshold at which apixaban patients' bleeding risk are able to be comparable to non-apixaban treated patients [27].

In general, apixaban should be discontinued 2 to 3 days prior to elective surgery or invasive procedures [5], as outlined below and in Figure 2. There are small groups of people at higher risk of thrombosis (e.g. $CHADS_2 > 5$, recent TIA or stroke) where an individualised approach is needed to minimise the period of sub-therapeutic anticoagulation. A recent review of periprocedural use of antithrombotic therapy notes the importance of checking creatinine clearance in patients on rivaroxaban and apixaban, prior to cessation for high-risk procedures [28]. A longer period of pre-operative discontinuation, up to 5 days, can be considered for patients with renal or hepatic impairment or other conditions associated with decreased drug elimination. In this setting, "bridging" with LMWH has been proposed for patients with a high risk of thrombosis [27]. Given the predictable pharmacokinetics of apixaban, bridging with an alternative anticoagulant should not be required in the majority of cases.

Advice for assessing peri-procedural dosing

High bleeding risk

Procedures with a high risk of bleeding (e.g. neurosurgical, urological procedures, major abdominal or orthopaedic):

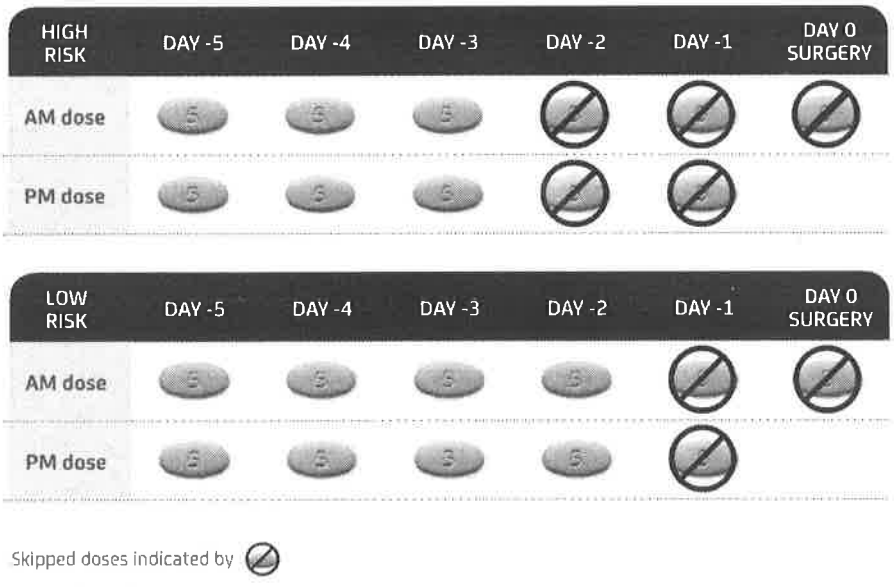

Figure 2 Perioperative dosing/elimination.

aim to achieve *no* residual apixaban effect at the time of the procedure; last dose of drug should be 3 days prior (5 missed doses including morning of surgery – Figure 2) [29].

Low bleeding risk

Procedures with a low risk of bleeding (e.g. inguinal hernia repair, percutaneous biopsy, dental extractions): aim to achieve *minimal-mild* residual apixaban effect at the time of the procedure; last dose of drug should be 2 days prior (3 missed doses including morning of surgery – Figure 2) [29].

Minimal bleeding risk

For selected procedures with minimal risk of bleeding (e.g. cataract surgery, skin cancer excision): therapeutic anticoagulation may be continued.

Re-commencing apixaban after surgery

Re-commence apixaban dosing only once surgical haemostasis has been secured (typically 24 hours after surgery) [29]. In general, caution should be exercised with re-instituting therapeutic anticoagulation within the first 48 hours after surgery. Where there is a risk of post-operative venous thrombosis and the bleeding risk is high, consider a reduced dose of 2.5 mg BID (recommended prophylactic dose) for the immediate post-operative period.

In patients with poor oral absorption or nil by mouth after surgery, parenteral anticoagulants may be needed until reliable oral absorption is established.

Neuraxial anaesthesia

Indwelling epidural or intrathecal catheters must be removed at least 5 hours prior to the first dose of apixaban. Experience with neuraxial blockade is limited and extreme caution is therefore recommended when using apixaban in this setting (see P.I.) [5].

Conclusions

- Apixaban is a direct FXa inhibitor indicated in Australia for the prevention of venous thromboembolic events (VTE) in adult patients who have undergone elective total hip or total knee replacement surgery (2.5 mg BID) and for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation and at least one additional risk factor for stroke (5 mg BID or 2.5 mg BID if ≥2 of the following; ≤60 kg, ≥80 years, serum creatinine level ≥133 um/L) [5].
- In the ARISTOTLE study of apixaban in patients with atrial fibrillation, annual major bleeding events for apixaban compared to warfarin were 2.13% per year versus 3.09% per year ($p < 0.001$). Intracranial haemorrhage events were 0.33% per year for apixaban, compared to 0.80% per year for warfarin ($p < 0.001$) [3].
- There is no standardised assay currently commercially available in Australia to measure apixaban effect. As apixaban minimally prolongs PT or aPTT, these clotting tests are not recommended to assess the pharmacodynamic effects of apixaban [5]. A chromogenic anti Xa assay or dilute PT assay may be useful, where knowledge of apixaban exposure is required [10-12].
- Apixaban is contraindicated in patients who are receiving concomitant treatment with strong inhibitors of both CYP3A4 and P-gp, however no dose adjustment for apixaban is required when co-administered with less potent inhibitors. No dose adjustment for apixaban is required during concomitant therapy with strong CYP3A4 and P-gp inducers, however they may lead to reduced apixaban plasma concentrations [5].
- A specific antidote for apixaban is not currently available, however specific anti-Xa inhibitor and universal novel oral anticoagulant antidotes are in clinical development [18,19].
- In the absence of published data regarding the treatment of patients with active bleeding while receiving apixaban, discontinue apixaban, apply standard supportive treatment and other local measures [5]. Activated charcoal may reduce apixaban absorption within 6 h of last dose [17].
- Apixaban is not expected to be dialyzable, however prothrombin complex concentrates (PCC) may reverse the anticoagulant effect and recombinant FVIIa or bypassing agents (FEIBA) can be considered for life-threatening bleeding. FFP will not reverse apixaban effect but can be used as volume replacement in case of major bleeding.
- Planning for elective surgery or invasive procedures should involve balancing the intervention-associated bleeding risk and thrombotic risk associated with anticoagulant interruption in each individual.

Abbreviations

APTT: Activated partial thromboplastin time; ASA: Acetylsalicylic acid; CrCl: Creatinine clearance; DVT: Deep vein thrombosis; FEIBA: Factor VIII inhibitor bypassing agent; FX: Factor X; INR: International normalized ratio; NOAC: Novel oral anticoagulants; NSAID: Non-steroidal antiflammatory drugs; NVAF: Non-valvular atrial fibrillation; PCC: Prothrombin complex concentrates; PE: Pulmonary embolus; PT: Prothrombin time; rFVIIa: Recombinant activated Factor VII; VTE: Venous thromboembolism.

Competing interests

The authors received honoraria and travel support from Pfizer Australia to review the literature and attend a working group meeting where this consensus statement was generated.

Authors' contributions
CW contributed to consensus statement and wrote the manuscript; GD contributed to consensus statement and reviewed the manuscript; ASG contributed to consensus statement and reviewed the manuscript; GC contributed to consensus statement and reviewed the manuscript; SM contributed to consensus statement and reviewed the manuscript. All authors read and approved the final manuscript.

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References

1. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, Pogue J, Reilly PA, Themeles E, Varrone J, Wang S, Alings M, Xavier D, Zhu J, Diaz R, Lewis BS, Darius H, Diener HC, Joyner CD, Wallentin L, the RE-LY Steering Committee and Investigators: **Dabigatran versus warfarin in patients with atrial fibrillation.** *N Engl J Med* 2009, **361**:1139–5.
2. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, Breithardt G, Halperin JL, Hankey GJ, Piccini JP, Becker RC, Nessel CC, Paolini JF, Berkowitz SD, Fox KA, Califf RM, and the ROCKET AF Steering Committee, for the ROCKET AF Investigator: **Rivaroxaban versus warfarin in nonvalvular atrial fibrillation.** *N Engl J Med* 2011, **365**:883–891.
3. Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, Al-Khalidi HR, Ansell J, Atar D, Avezum A, Bahit MC, Diaz R, Easton JD, Ezekowitz JA, Flaker G, Garcia D, Geraldes M, Gersh BJ, Golitsyn S, Goto S, Hermosillo AG, Hohnloser SH, Horowitz J, Mohan P, Jansky P, Lewis BS, Lopez-Sendon JL, Pais P, Parkhomenko A, Verheugt FW, *et al*: **ARISTOTLE Committees and Investigators: apixaban versus warfarin in patients with atrial fibrillation.** *New Engl J Med* 2011, **365**:981–992.
4. Frost C, Nepal S, Wang J, Schuster A, Barrett YC, Mosqueda-Garcia R, Reeves RA, Lacreta F: **Apixaban, an oral, direct factor Xa inhibitor: single-dose safety, pharmacokinetics, pharmacodynamics and food effect in healthy subjects.** *Br J Clin Pharmacol* 2013, **75**(2):476–487.
5. *ELIQUIS® (Apixaban) Approved Product Information.* Bristol-Myers Squibb Australia Pty Ltd and Pfizer Pty Ltd; 2013. http://www.bmsa.com.au/products/pages/Home.aspx.
6. Connolly SJ, Eikelboom J, Joyner C, Diener H-C, Hart R, Golitsyn S, Flaker G, Avezum A, Hohnloser SH, Diaz R, Talajic M, Zhu J, Pais P, Budaj A, Parkhomenko A, Jansky P, Commerford P, Tan RS, Sim K-H, Lewis BS, Van Mieghem W, Lip GYH, Kim JH, Lanas-Zanetti F, Gonzalez-Hermosillo A, Dans AL, Munawar M, O'Donnell M, Lawrence J, Lewis G, *et al*: **Apixaban in patients with atrial fibrillation.** *N Engl J Med* 2011, **364**:806–817.
7. Alexander JH, Lopes RD, James S, Kilaru R, He Y, Mohan P, Bhatt DL, Goodman S, Verheugt FW, Flather M, Huber K, Liaw D, Husted SE, Lopez-Sendon J, De Caterina R, Jansky P, Darius H, Vinereanu D, Cornel JH, Cools F, Atar D, Leiva-Pons JL, Keltai M, Ogawa H, Pais P, Parkhomenko A, Ruzyllo W, Diaz R, White H, Ruda M, *et al*: **Apixaban with antiplatelet therapy after acute coronary syndrome.** *N Engl J Med* 2011, **365**:699–708.
8. APPRAISE Steering Committee and Investigators, Alexander JH, Becker RC, Bhatt DL, Cools F, Crea F, Dellborg M, Fox KA, Goodman SG, Harrington RA, Huber K, Husted S, Lewis BS, Lopez-Sendon J, Mohan P, Montalescot G, Ruda M, Ruzyllo W, Verheugt F, Wallentin L: **Apixaban, an oral, direct, selective Factor Xa inhibitor, in combination with antiplatelet therapy after acute coronary syndrome.** *Circulation* 2009, **119**:2877–2885.
9. Douxfils J, Chatelain C, Chatelain B, Dogné J-M, Mullier F: **Impact of apixaban on routine and specific coagulation assays: a practical laboratory guide.** *Thromb Haemost* 2013, **110**(2):283–294.
10. Becker RC, Yang H, Barrett Y, Mohan P, Wang J, Wallentin LC, Alexander JH: **Chromogenic laboratory assays to measure the factor Xa-inhibiting properties of apixaban—an oral, direct and selective factor Xa inhibitor.** *J Thromb Thrombolysis* 2011, **32**:183–187.
11. Barrett YC, Wang Z, Frost C, Shenker A: **Clinical laboratory measurement of direct factor Xa inhibitors: anti-Xa assay is preferable to prothrombin time assay.** *Thromb Haemost* 2010, **104**:1263–1271.
12. Barrett YC, Wang Z, Knabb RM: **A novel prothrombin time assay for assessing the anticoagulant activity of oral factor Xa inhibitors.** *Clin Appl Thromb Hemost* 2012, **19**(5):522–528.
13. Upreti VV, Song Y, Wang J, Byon W, Boyd RA, Pursley JM, Lacreta F, Frost CE: **Effect of famotidine on the pharmacokinetics of apixaban, an oral direct factor Xa inhibitor.** *Clin Pharmacol: Advances and Applications* 2013, **5**:59–66.
14. Camm AJ, Lip GY, Caterina R, Savelieva I, Atar D, Hohnloser SH, G H, Kirchhof P, ESC Committee for Practice Guidelines (CPG): **2012 focused update of the ESC Guidelines for the management of atrial fibrillation.** *Eur Heart J* 2012, **33**:2719–2747.
15. Hohnloser SH, Hijazi Z, Thomas L, Alexander JH, Amerena J, Hanna M, Keltai M, Lanas F, Lopes RD, Lopez-Sendon J, Granger CB, Wallentin L: **Efficacy of apixaban when compared with warfarin in relation to renal function in patients with atrial fibrillation: insights from the ARISTOTLE trial.** *Eur Heart J* 2012, **33**:2821–2830.
16. Granger CB, Alexander JH, Hanna M, Wang J, Mohan P, Lawrence J, Hylek E, Ansell JE, Wallentin L, for the ARISTOTLE investigators: **Events after discontinuation of randomized treatment at the end of the ARISTOTLE trial [abstract].** *Eur Heart J* 2012, **33**(Abstract Supplement): 685–686.
17. Wang X, Tirucherai G, Pannacciulli, Wang J, Elsrougy A, Teslenko V, Chang M, Zhang D, Frost C: **Effect of activated charcoal on the pharmacokinetics of apixaban in healthy subjects [abstract].** *Clinical Pharmacol Ther* 2012, **91**(Suppl 1):s41.
18. Lu G, DeGuzman FR, Hollenbach SJ, Karbarz MJ, Abe K, Lee G, Luan P, Hutchaleelaha A, Inagaki M, Conley PB, Phillips DR, Uma S: **A specific antidote for reversal of anticoagulation by direct and indirect inhibitors of coagulation factor Xa.** *Nat Med* 2013, **19**(4):446–451.
19. Laulicht B, Bakhru S, Lee C, Baker C, Jiang X, Mathiowitz E, Costin J, Steiner S: **Small molecule antidote for anticoagulants [abstract].** *Circulation* 2012, **126**:A11395.
20. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M: **Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects.** *Circulation* 2011, **124**:1573–1579.
21. Escolar G, Arellano-Rodrigo E, Reverter JC, Villalta J, Sanz V, Molina P, Diaz-Ricart M, Galan AM: **Reversal of apixaban induced alterations of hemostasis by different coagulation factor concentrates: studies in vitro with circulating human blood [abstract].** *Circulation* 2012, **126**:520–521.
22. Martin AC, Le Bonniec B, Fischer AM, Marchand-Leroux C, Gaussem P, Samama CM, Godier A: **Evaluation of recombinant activated factor VII, prothrombin complex concentrate, and fibrinogen concentrate to reverse apixaban in a rabbit model of bleeding and thrombosis.** *Int J Cardiol* 2013, **168**:4228–4233.
23. Kaatz S, Kouides PA, Garcia DA, Spyropolous AC, Crowther M, Douketis JD, Chan AK, James A, Moll S, ORtel TL, Van Cott EM, Ansell J: **Guidance on the emergent reversal of oral thrombin and factor Xa inhibitors.** *Am J Hematol* 2012, **87**(Suppl 1):S141–S145.
24. Bauer KA: **Reversal of antithrombotic agents.** *Am J Hematol* 2012, **87**(Suppl 1):S119–S126.
25. Fukuda T, Honda Y, Kamisato C, Morishima Y, Shibano T: **Reversal of anticoagulant effects of edoxaban, an oral, direct factor Xa inhibitor, with haemostatic agents.** *Thromb Haemost* 2012, **107**:253–259.
26. Marlu R, Hodaj E, Paris A, Albaladejo P, Cracowski JL, Pernod G: **Effect of non-specific reversal agents on anticoagulant activity of dabigatran and rivaroxaban.** *Thromb Haemost* 2012, **108**:217–224.
27. Ferrandis R, Castillo J, de Andrés J, Gomar C, Gómez-Luque A, Hidalgo F, Llau JV, Sierra P, Torres LM: **The perioperative management of new direct**

oral anticoagulants: a question without answers. *Thromb Haemost* 2013, 110:515–522.
28. Baron TH, Kamath PS, McBane RD: **Antithrombotic therapy and invasive procedures.** *New Engl J Med* 2013, **368**:1079–1080.
29. Douketis JD: **Pharmacologic properties of the new oral anticoagulants: a clinician-oriented review with a focus on perioperative management.** *Curr Pharm Des* 2010, **16**:3436–3441.

doi:10.1186/1477-9560-11-27
Cite this article as: Ward *et al.*: **Practical management of patients on apixaban: a consensus guide.** *Thrombosis Journal* 2013 **11**:27.

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EXHIBIT G

FDA NEWS

FDA does not approve reversal agent for anticoagulation drugs

August 18, 2016

Portola Pharmaceuticals announced it received a complete response letter from the FDA that its reversal agent for Factor Xa inhibitor anticoagulants will not be approved at this time.

The agent, andexanet alfa (AndexXa), was developed for reversal of uncontrolled bleeding in patients treated with direct Factor Xa inhibitors such as apixaban (Eliquis, Bristol Myers-Squibb/Pfizer), edoxaban (Savaysa, Daiichi Sankyo) and rivaroxaban (Xarelto, Janssen Pharmaceuticals) and indirect Factor Xa inhibitors such as enoxaparin, according to a press release issued by the company. Factor Xa inhibitors are often used for stroke prevention in patients with nonvalvular atrial fibrillation and for treatment of deep vein thrombosis and pulmonary embolism.

There is no reversal agent for Factor Xa inhibitors approved in the United States; the FDA in 2013 designated andexanet alfa as a breakthrough therapy and in 2015 designated it as an orphan drug, both enabling expedited review.

According to the release, the FDA in the letter asked for additional information related to manufacturing and for more data supporting an indication for reversal of edoxaban and enoxaparin. The agency also wrote that it has not yet finalized its review of clinical amendments related to postmarketing studies, the company stated.

“Because AndexXa addresses an urgent unmet medical need, we and the FDA are committed to resolving the outstanding questions to determine the appropriate next steps,” **Bill Lis,** CEO of Portola, said in the release. “We plan to meet with the FDA as soon as possible.”

Disclosure: Lis is an employee of Portola Pharmaceuticals.

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EXHIBIT H

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REVIEW ARTICLE

How to choose appropriate direct oral anticoagulant for patient with nonvalvular atrial fibrillation

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Abstract The novel oral anticoagulants or direct oral anticoagulants (DOAC) are becoming more common in clinical practice for the prevention of stroke in non-valvular atrial fibrillation (NVAF). The availability of several agents with similar efficacy and safety for stroke prevention in NVAF patients offers more selection, but at the same time requires certain knowledge to make a good choice. This comparative analysis provides an appraisal of the respective clinical trials and highlights much of what remains unknown about four FDA-approved agents: dabigatran, apixaban, rivaroxaban, and edoxaban. It details how the DOACs compare to warfarin and to one another summarizes pharmacologic and pharmacodynamic properties, and drug interactions from the stand point of practical consequences of these findings. Common misconceptions and reservations are addressed. The practical application of this data is intended to help choosing the most appropriate agent for individual NVAF patient.

Keywords Direct thrombin inhibitors · Factor Xa inhibitors · Rivaroxaban · Dabigatran · Apixaban · Warfarin · Nonvalvular atrial fibrillation

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Introduction

In 2010, the FDA approved dabigatran for stroke prevention in patients with non-valvular atrial fibrillation (NVAF) and ended a long era of vitamin K antagonists (VKA) as the mainstay of oral anticoagulation for this indication [1]. Within the last 5 years, four direct oral anticoagulants (DOACs): dabigatran, rivaroxaban, apixaban, and edoxaban, were assessed in large phase III clinical trials, compared to either warfarin [2–5] or aspirin [6], for stroke prevention in patients with NVAF. Results of these trials have led to FDA approval of these agents, along with endorsement by a growing number of guidelines and regulatory bodies worldwide [7–20]. Although there are abundant data on DOAC efficacy and safety compared to warfarin, and a growing experience on their interaction with other medications, there is a general lack of knowledge of the application of these findings into clinical practice. In the end, choosing the most appropriate DOAC for an individual NVAF patient remains complicated. This review is intended to concentrate on useful practical implications of our knowledge about DOACs (formerly known as novel anticoagulants NOACs), and to resolve some misconceptions, and reservations regarding this group of anticoagulants to help in every day application of these agents.

Background

VKAs inhibit the carboxylation of all vitamin K-dependent procoagulant factors II, VII, IX, X, but also have the "off target" effect of inhibiting the natural anticoagulants, protein C, and protein S. In contrast, DOACs target specific proteins in the coagulation cascade. These targeted factors were well chosen given their central participation in the coagulation cascade. Factor Xa serves as the convergent enzyme where the

intrinsic and extrinsic pathways meet to form the final common pathway of prothrombin activation. It is estimated that one molecule of factor Xa is responsible for generating more than 1000 thrombin molecules [21]. Direct factor Xa inhibition (rivaroxaban, apixaban, edoxaban) turns off prothrombin activation upstream, thus limiting available thrombin. Moreover, unlike low molecular weight heparin or pentasaccharide therapy, direct factor Xa inhibitors have access to factor Xa sequestered within the prothrombinase complex. Targeting thrombin by dabigatran is also quite logical, as thrombin cleaves fibrinogen to fibrin as the final step of clot formation. Thrombin activates factor XIII, which stabilizes the developing clot. Moreover, thrombin self-amplifies its own generation by activating factors V and VIII, and is the most potent platelet activator.

General characteristics

There are several characteristics which distinguish DOACs, as a group, from VKAs. First, they have rapid onset of action (1–3 h) and, consequently, do not require "bridging" with parenteral anticoagulants. Second, there is no need for routine monitoring of anticoagulation. Third, they have similar (7–15 h) half-lives. Fourth, they are all, to some extent, partially eliminated by the kidney: 80 % of dabigatran, 50 % of edoxaban, 35 % of rivaroxaban, and 25 % of apixaban [5, 17]. Patients with impaired kidney function should therefore use these medications with caution. Despite similar elimination kinetics, the dosing frequency differs between the agents; dabigatran and apixaban are dosed twice daily while rivaroxaban and edoxaban are given once a day. Patients with busy schedule or compliance concerns might do better with agents dosed once a day. A summary of characteristics with meaningful, practical implications are provided (Table 1).

Providers should be aware of the characteristics that distinguish DOACs from one another. For example, only 6–7 % gastrointestinal absorption of dabigatran implies that slight fluctuations in absorption or elimination may have a profound impact on plasma levels. To reduce the impact of varying gastrointestinal acidity on pro-drug absorption, dabigatran is formulated with tartaric acid [22]. Therefore, breaking, chewing, or emptying the contents of the capsule is prohibited and the patients are instructed to swallow the capsule whole. Moreover, dabigatran capsules are susceptible to ambient moisture. Consequently, medication storage must be in the original bottle or blister package until use. The tartaric acid spherules may be responsible for a 5–10 % incidence of dyspepsia [2]. Patients with peptic ulcer disease, subtotal or total gastrectomy, or gastric bypass surgery should rather avoid dabigatran or use it with caution. It is also noteworthy that rivaroxaban at 15 and 20 mg doses must be taken with food because of higher bioavailability (from 66 to more than 80 %) [23]. The other DOACs do not have this requirement even though edoxaban has 6–22 % better [24] absorption when taken with food. Apixaban and rivaroxaban have similar bioavailability when administered in crushed form and therefore can be administered via a nasogastric tube [25]; no data are available yet on bioavailability of crushed tablets of edoxaban.

Although less frequent than warfarin, there are important drug interactions to consider. There are two main mechanisms by which drug interactions occur with DOACs which are clinically relevant (Table 1). The P-glycoprotein (P-gp) transporter system serves to secrete medication back into the intestinal lumen, bile, and urine, thus reducing drug exposure [26]. Medications which induce this system will, thereby, reduce drug exposure. Conversely, competitive inhibition will increase drug exposure. The hepatic cytochrome p450 CYP3A4 is the other important pathway in the metabolism of all DOACs, with the exception of dabigatran [20, 23, 24]. Medications that impact both P-gp and CYP3A4 pathways may influence the effect of DOACs [17–24]. Strong inducers to remember include carbamazepine, phenytoin, rifampin, St John's wort, and tipranavir/ritonavir which decrease circulating DOAC levels. Strong inhibitors include itraconazole, ketoconazole, lopinavir/ritonavir, indinavir, and voriconazole which increase DOAC levels. Such drugs should generally not be co-administered with DOACs [20, 26]. For apixaban,

Table 1 General characteristic of direct oral anticoagulants.

Characteristics	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Renal clearance (%)	80	35	25	50
Bioavailability (%)	pH dependent[a] 6–7	Food dependent[b] 66–≥80	Food independent 50	Food independent 62
Medication storage	In original bottle or blister package	Room temperature	Room temperature	Room temperature
Liver metabolism: CYP3A4 metabolism	No	Yes	Minor	Minor
Impacted by P-glycoprotein transporter system	Yes	Yes	Yes	Yes

[a] Ten milligram dose has oral bioavailability independent of food but 15 and 20 mg doses of rivaroxaban have achieved high bioavailability (≥80 %) when taken with food

[b] Tartaric acid added into the dabigatran capsule to ensure optimal and gastrointestinal pH independent absorption is responsible for 5–10 % incidence of dyspepsia

most of the hepatic clearance occurs without metabolism [27]. Therefore, the US package insert recommends reducing the dose of apixaban from 5 to 2.5 mg twice daily when co-administered with a strong CYP3A4 and P-gp inhibitors and to avoid apixaban use if the patient already requires a dose reduction due to other clinical cofounders (age >80, weight <60 kg, creatinine >1.5). The European package insert recommends avoiding apixaban use with a strong CYP3A4 and P-gp inhibitors. While changes in CYP3A4 do not appear to greatly impact edoxaban metabolism, caution is warranted until more definitive interaction data are available [28].

Information on dose adjustment and interaction of DOACs with commonly used cardiovascular medications in patients with NVAF are important to review (Table 2). Therapy should be tailored for each patient, not only taking into account coexisting medications but also comorbidities, including renal and liver function, general bleeding risk, and propensity for thrombosis.

Comparative efficacy and safety

In general, the clinical efficacy of DOACs in the four large clinical trials, enrolling over 70 thousand patients, was similar to warfarin [2–7, 29–34]. The "statistical evidence of superiority" of dabigatran over warfarin to prevent ischemic stroke relied on a very tight margin of 0.98 for 95 % confidence interval [0.76 (0.60–0.98), $p = 0.03$]. If one realizes that over 18 thousand patients were necessary to achieve this difference, the practical meaning of this superiority seems to be rather elusive. The real advantage of these new agents is the improved safety margin, particularly evident for apixaban and edoxaban.

General trial characteristics

To comprehend the combined results of these randomized trials, it is important to review the differences between studies (Table 3). The RE-LY study [2] was an open, blinded endpoint study that compared blinded doses of dabigatran 110 or 150 mg twice daily to open-label dose-adjusted warfarin. Local investigators were not blinded as to which drug was administered. The other three trials were double blinded, double-dummy trials comparing a once daily 20 mg dose of rivaroxaban (ROCKET AF) [3], twice daily, 5 mg dose of apixaban (ARISTOTLE) [4], and two doses (30 and 60 mg) of edoxaban, once daily (ENGAGE AF-TIMI) [5], respectively, to warfarin.

While doses of dabigatran were fixed, Xa inhibitor trials incorporated pre-defined criteria for dose reduction at randomization (Table 3). The ENGAGE-AF investigators also employed criteria for post-randomization edoxaban dose modifications. Edoxaban dosing, depending on the treatment arm and clinical characteristics, ranged from 60 to 15 mg daily [2–5].

Patients with severe renal failure were excluded from all of these trials. Each trial had pre-specified $CHADS_2$ scores for inclusion. The ROCKET AF and ENGAGE AF trials recruited patients with $CHADS_2$ score ≥2. Inclusion criteria for RE-LY and ARISTOTLE included scores ≥1 [2–5].

Table 2 Interaction of direct oral anticoagulants with commonly used cardiovascular medications

Medications	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Quinidine	Use with caution[a]	Use with caution[a]	No data	Use with caution[a]
Verapamil	Use with caution[a, b]	Minor effect	No data	Use with caution[a]
Amiodarone	Use with caution[a]	Use with caution[a]	No data	Use with caution[a]
Dronedarone	Avoid	Use with caution[a]	No data	50 % dose reduction[c]
Ranolazine	No effect	Use with caution[a]	No data	No data
Digoxin	No effect	Minimal effect	No effect	Minimal effect
Atorvastatin	Minimal effect	No effect	No data	No effect
Diltiazem	No effect	Use with caution[a]	Use with caution[a]	No data
Carvedilol	No effect	Minimal effect	No data	No data
Felodipine	Minimal effect	Use with caution[a]	No data	No data
Prazosin[d]	Avoid	Avoid	Avoid	Avoid

[a] "Use with caution" indicates that the effect on DOAC exists but does not require dose adjustment unless another interaction is present (concomitant use of other medication with additive interaction or CrCl 30–50 mL/min)

[b] European package insert and European Rhythm Association Practical Guide recommend using 110 mg dose of dabigatran

[c] American package insert does not require dose reduction

[d] Although the prescribing informations recommend that DOACs not to be administered in conjunction with the P-gp inducer like rifampin, studies have not been conducted with other P-gp-inducing medications like prazosin and, therefore, should be avoided, pending the availability of additional data

Table 3 Characteristics of phase III clinical trials of direct oral anticoagulants

Characteristics	RE-LY (dabigatran)	ROCKET AF (rivaroxaban)	ARISTOTLE (apixaban)	ENGAGE AF (edoxaban)
Design	Randomized, open label[a]	Randomized, DB/DD	Randomized, DB/DD	Randomized, DB/DD
Dosing	150 mg, 110 mg twice daily	20 mg daily	5 mg twice daily	60 mg, 30 mg daily
Dose adjustment/criteria	No	If CrCl 30–49 mL/min then 15 mg	If ≥2 factors: age ≥80 years, body weight <60 kg, creat ≥1.5 mg/dL then 2.5 mg	If CrCl 30–50 mL/min or weight ≤60 kg or potent P-gp inhibitor[b] then 50 % dose
CrCl exclusion	30 mL/min	30 mL/min	25 mL/min	30 mL/min
$CHADS_2$ score inclusion criteria	≥1	≥2	≥1	≥2
Primary efficacy endpoint	Stroke/TIA and SE	Stroke/TIA and SE	Stroke/TIA and SE	Stroke/TIA and SE
Primary safety endpoint	Major bleeding	Major plus CRNM bleeding	Major bleeding	Major bleeding
Trial size	18,113	14,264	18,201	21,105
Age (years), median (IQR)	72±9[c]	73 (65–78)	70 (63–76)	72 (64–78)
$CHADS_2$ (mean)	2.1	3.5	2.1	2.8
$CHADS_2$ ≥3 (%)	32	87	30	53
Heart failure	32	62	35	57
Stroke/TIA or SE	20[d]	55	19	28
Median follow-up (years)	2.0	1.9	1.8	2.8
Early discontinuation				
DOAC (%)	20.7/21.2	35.4	25.3	33.0/34.3
VKA (%)	16.6	34.6	27.5	34.4

CRNM clinically relevant non-major bleeding, *DB/DD* double blind, double dummy, *IQR* interquartile range, *DOAC* direct oral anticoagulant, *SE* systemic embolism, *TIA* transient ischemic attack, *VKA* vitamin K antagonist, *CrCl* creatinine clearance

[a] Patients were unblended with respect to dabigatran or warfarin assignment; however, all investigators, coordinating center members, the steering committee, the event adjudication committee, and the sponsor were blinded during event ascertainment and analyses

[b] Strong P-gp inhibitors such as dronedarone, quinidine, or verapamil

[c] Mean±SD

[d] No data on SE

The primary efficacy endpoint (stroke/TIA and systemic embolism) was identical for all four trials. The principal safety endpoint was major bleeding defined by the International Society for Thrombosis and Haemostasis (ISTH) criteria for all trials. The ROCKET AF trial included a combination of major, plus clinically relevant non-major bleeding [2–5].

Patients were followed for nearly 3 years in the ENGAGE AF trial and for about 2 years in the other three trials.

The median time spent within the therapeutic range for the warfarin arm was the highest in ENGAGE AF and the lowest in the ROCKET AF trial. The impact of warfarin management on the comparative analysis of DOACs efficacy and safety is discussed separately below.

Trial population characteristics

Differences in NVAF patient inclusion criteria, mainly $CHADS_2$ score, resulted in significant differences in clinical characteristics of the recruited populations (Table 3). These differences should be kept in mind when comparing thromboembolic and bleeding rates between studies. The mean $CHADS_2$ score was higher in ROCKET AF compared to RE-LY and ARISTOTLE trials. The mean $CHADS_2$ score was intermediate in the ENGAGE AF population. Nearly 90 % of participants in the ROCKET AF trial and 53 % of ENGAGE AF participants had a $CHADS_2$ score ≥3. In contrast, slightly less than one third of RE-LY and ARISTOTLE trial participants had $CHADS_2$ scores of similar severity. ROCKET AF and ENGAGE trials had the highest proportion of patients with CHF (about 60 %) compared to about one third in the other two trials. More than half of ROCKET AF patients had a history of prior stroke. By comparison, prior stroke was present in only 20–30 % of patients in the other three trials [2–5].

There are several practical implications of these differences worth considering. First, these study population differences limit inter-trial outcome comparisons. Neither efficacy nor safety of one agent can be indirectly compared to another. This is particularly true for rivaroxaban and the high $CHADS_2$ scores of ROCKET-AF. Second, meta-analyses must take into

account differences in patient risk characteristics to be useful for clinical application. Third, in low risk patients ($CHADS_2$ ≤2), clinicians can apply the results directly from RE-LY and ARISTOTLE.

Although dose adjustment was allowed at randomization in all three Xa inhibitor trials, practical application of these rules was quite different; only 5 % of ARISTOTLE trial participants had their dose reduced, compared to 21 % of patients in ROCKET AF, and 25 % of patients in the ENGAGE AF study. This indicates that dose adjustment of rivaroxaban and edoxaban was much better explored than apixaban, and this information should be discussed with the patient while deliberating on the choice of a DOAC for someone who would require dose modification. A post hoc analysis of RE-LY data showed that using 110 mg dose of dabigatran for NVAF patients ≥80 years of age or treated with verapamil (dose adjustment consistent with European label) further improved its overall net clinical benefit [35]. While this concept of "tailored dosing" for individual patients is attractive, the lack of direct trial data for dabigatran dose adjustments decreases the validity of this approach. Moreover, available formulations of dabigatran limit the applicability of this concept in the USA.

Co-administration of aspirin was allowed in all four clinical trials. The highest proportion of study participants taking aspirin was in ROCKET AF trial (35 %), followed by ENGAGE AF (29 %), ARISTOTLE (24 %), and RE-LY (21 %) trials. But the latter was the only study that allowed recruitment of patients on clopidogrel (5 % of participants) [2–6, 33]. The proportion of patients taking antiplatelet agents impacts the bleeding rate and needs to be included into any comparative analysis of safety outcomes. Furthermore, this may impact the decision of which anticoagulant to use for patients who require concurrent antiplatelet therapy.

Individual effectiveness and safety in relation to warfarin

The results of the DOAC trials are generally reported from an intention to treat perspective. From a trialists viewpoint, analyzing and reporting the results from an "intension to treat" perspective is statistically correct, ethically fair, and methodologically pure. Yet, in the end, the on-treatment event rates are what really matters, both to patients and practitioners alike, because it informs what happens when the medication is actually taken. From a patient perspective, an intention to treat analysis reflects information on what would happen if a patient is prescribed a DOAC, regardless of compliance.

The higher treatment discontinuation rates in the ROCKET AF and ENGAGE AF trials (over 30 %), compared to RE-LY and ARISTOTLE trials (over 20 %), analyzed with an intention to treat approach, would negatively impact thromboembolic rates for the former trials. This effect is compounded by the higher stroke risk population in ROCKET AF and ENGAGE AF, as well as the longer follow-up period in ENGAGE AF [2–6]. The effect of a higher, premature discontinuation rate of rivaroxaban and edoxaban on their relative efficacy can be appreciated by an on-treatment analysis. This approach shows superiority over warfarin for both rivaroxaban (HR 0.79, 0.66–0.96; $p = 0.02$) and edoxaban 60 mg (HR 0.79, 0.63–0.99; $p = 0.002$) for prevention of stroke and systemic embolization [7]. By the same reasoning, however, the higher discontinuation rates would favorably impact bleeding rates of rivaroxaban and edoxaban.

In the ENGAGE AF-TIMI 48 study, NVAF patients with creatinine clearance >95 mL/min had an increased rate of ischemic stroke with edoxaban 60 mg once daily compared to patients treated with warfarin. Therefore, the FDA restricted the use of this anticoagulant to those with creatinine clearance lower than 95 mL/min [13]. This restriction seems to have rather limited practical consequences as few NVAF patients have such a high creatinine clearance.

For prevention of systemic embolism only, rivaroxaban was superior to warfarin (in the "as treated" population, see Table 4) and the other DOACs were non-inferior or have no available data (dabigatran). Accordingly, for NVAF patient with the history of systemic embolization, rivaroxaban might be the preferred agent.

The principal efficacy outcome, used in all four trials, was a combination of stroke and systemic embolization that included the safety element of hemorrhagic stroke. This not only double counted medication effect and overestimated the net benefit of the DOACs but also provided misleading information. Proponents would argue that patients do not distinguish stroke types and might tend to lump hemorrhagic and ischemic strokes together. However, this endpoint may be deceptive when it comes to patient care. For the patient with a very high risk of thromboembolism and very low risk of bleeding, the DOAC with the best ischemic rather than global stroke reduction would be desired. In this case, only dabigatran at the higher dose of 150 mg twice a day was superior to warfarin to prevent ischemic stroke (Table 4). The lower dose of edoxaban, 30 mg, was the only DOAC that was inferior to warfarin. All other DOACs and other doses were non-inferior to warfarin [2–6].

The benefit-to-risk ratio of dabigatran 150 mg vs warfarin was less favorable in NVAF older than 75 years compared to younger individuals [33, 35, 36]. For this reason, dabigatran dose of 110 mg would be more appropriate for older patients. However, this dose of dabigatran is not approved in the USA. For elderly patients, the net benefit likely favors one of the factor Xa inhibitors.

Apixaban and both doses of edoxaban were associated with a significantly lower rate of major bleeding, while

Table 4 Clinical outcomes of clinical trials with direct oral anticoagulants (DOACs) in relation to warfarin

DOAC vs VKA HR (95 % CI)	RE-LY[a] (dabigatran) 110 mg 150 mg	ROCKET AF (rivaroxaban) 20 mg	ARISTOTLE (apixaban) 5 mg	ENGAGE AF-TIMI 48 (edoxaban) 30 mg 60 mg
Ischemic stroke	1.11 (0.89–1.40)[a]	0.94 (0.75–1.17)	0.92 (0.74–1.13)	***1.41 (1.19–1.67) $p < 0.001$***
	0.76 (0.60–0.98)[a] $p = 0.03$			1.00 (0.83–1.19)
Systemic embolism	Not reported	**0.23 (0.09–0.61) $p = 0.003$**	0.87 (0.44–1.75)	1.24 (0.72–2.15)
				0.65 (0.34–1.24)
Hemorrhagic stroke	**0.31 (0.17–0.56) $p < .0001$**	**0.59 (0.37–0.93 $p = 0.024$)**	**0.51 (0.35–0.75) $p < 0.001$**	**0.33 (0.22–0.50) $p < 0.001$**
	0.26 (0.14–0.49 $p < 0.001$			**0.54 (0.38–0.77) $p < 0.001$**
Major bleed	**0.80 (0.69–0.93) $p = 0.003$**	1.04 (0.90–1.20)	**0.69 (0.60–0.80) $p < 0.001$**	**0.47 (0.41–0.55) $p < 0.001$**
	0.93 (0.81–1.07) $p = 0.3$			**0.80 (0.71–0.91) $p < 0.001$**
Intracranial bleed	**0.31 (0.20–0.47) $p < 0.001$**	**0.67 (0.47–0.93) $p = 0.02$**	**0.42 (0.30–0.58) $p < 0.001$**	**0.30 (0.21–0.43) $p < 0.001$**
	0.40 (0.27–0.60) $p < 0.001$			**0.47 (0.34–0.63) $p < 0.001$**
Gastrointestinal bleed	1.10 (0.86–1.41)	***3.2 vs 2.2[b] $p < 0.001$***	0.89 (0.70–1.15)	**0.67 (0.53–0.83) $p < 0.001$**
	1.50 (1.19–1.89) $p < 0.001$			***1.23 (1.02–1.50) $p = 0.03$***
All-cause mortality	0.91 (0.80–1.03)	0.85 (0.70–1.02)	**0.89 (0.80–0.98) $p = 0.047$**	**0.87 (0.79–0.96) $p = 0.006$**
	0.88 (0.77–1.00) $p = 0.051$			0.92 (0.83–1.01)
Cardiovascular mortality	0.90 (0.77–1.06)[a]	0.89 (0.73–1.10)	0.89 (0.76–1.04)	**0.85 (0.76–0.96) $p = 0.008$**
	0.85 (0.72–0.99)[a] $p = 0.04$			**0.86 (0.77–0.97) $p = 0.013$**

Bold font indicates significantly better result of DOAC in relation to warfarin. Bold and italic font indicates significantly worse result of DOAC compared to warfarin

[a] RE-LY reported relative risk instead of hazard ratio (HR); ischemic or uncertain stroke instead ischemic stroke, and vascular mortality instead cardiovascular mortality

[b] Incidence/year (%), HR not reported

all the other DOACs were non-inferior to warfarin. All DOACs, except dabigatran dose of 150 mg, were associated with significantly lower rates of fatal bleeding. Hemorrhagic stroke rate and intracranial bleeding were significantly lower in all DOACs, at all doses, compared to warfarin. Only low dose edoxaban demonstrated a lower rate of gastrointestinal bleeding while dabigatran dosed at 150 mg, rivaroxaban, and edoxaban at 60 mg showed a significantly higher rate of gastrointestinal bleeding compared to the VKA arm; apixaban and dabigatran at 110 mg showed the same bleeding rate as warfarin [2–6].

Patients randomization to either apixaban or edoxaban experienced improved overall survival rates relative to warfarin-treated patients. A trend toward improved survival was noted for dabigatran and rivaroxaban. Cardiovascular death rates were significantly lower for dabigatran and edoxaban-treated patients [2–6].

Comparison of DOACs amongst themselves

The meta-analyses of DOACs as a whole group showed the following: better protection from stroke and systemic embolism, better safety from intracerebral hemorrhage, all-cause mortality, and vascular mortality compared to warfarin. Major bleeding and gastrointestinal bleeding rates were similar to warfarin [37, 38]. This global comparison to warfarin provides an endorsement for DOACs, but has minimal practical usefulness, as the individual patient will take just one agent of this group.

Several indirect, comparative analyses [31, 39–41] amongst DOACs were performed to identify agents with superior efficacy or safety from among the group. Such comparison, however, is seriously impacted by the differences in trial design, patient characteristics, and methods of outcome measurement [7, 42]. To compensate for these differences between trials, only NVAF patients with $CHADS_2 \geq 3$ were evaluated in one study [30]. This analysis showed that therapy with both doses of dabigatran, apixaban, and rivaroxaban had similar efficacy, but apixaban therapy was associated with a lower rate of major hemorrhage compared to dabigatran 150 mg and rivaroxaban. Very similar efficacy of dabigatran 150 mg, apixaban, and rivaroxaban were also reported when only NVAF patients with prior stroke (secondary prophylaxis) were analyzed [39].

In summary, indirect comparisons of DOACs, adjusted for patient characteristics, provide some meaningful additional information about these agents in the absence of direct comparisons, which are unlikely to be forthcoming. The reader must cautiously interpret these data given the methodological flaws associated with such comparisons.

Limitations of trials

Numerous exclusion criteria used in all four clinical trials of DOACs left clinicians with a considerable gap of knowledge about applicability of DOACs in important and commonly seen medical conditions. Patients with disabling stroke within the previous 6 months were excluded from dabigatran and rivaroxaban studies. The trial with apixaban excluded patients who suffered ischemic stroke within the previous 7 days; dabigatran and rivaroxaban within the previous 14 days, and edoxaban within the past 30 days. We have no data for DOACs used in patients with prior intracranial, intraocular, spinal, retroperitoneal or traumatic intra-articular bleeding, and in patients with hemoglobin Hb <10 g/dL or a platelet count <100,000 because they were excluded from all four clinical trials [2–5]. Adequate and well-controlled studies of DOAC use in pregnancy and pediatric populations are not yet available.

All four clinical trials showed lower risk of hemorrhagic stroke and intracranial bleed from DOAC therapy compared to warfarin [2–5, 42]. These results are dependent not only on DOACs "performance" but also warfarin arm safety data. Observational "real life" studies confirmed this favorable comparison [43, 44]. However, the "real life" risk of cerebral hemorrhage associated with warfarin [45], documented in a large Canadian registry, was significantly lower than the rate observed in the VKA arms of the DOAC clinical trials. These results, although obtained in a different cohort and clinical setting, might question the "undisputable superiority" of DOACs over warfarin for the risk of intracranial hemorrhage implied in the phase III clinical trials.

Dabigatran, used both for patients with NVAF and venous thromboembolism [46], was associated with increased risk of myocardial infarction. Additional analysis of the RE-LY study outcomes ordered by FDA [47] revealed 81 additional events in the study population including 4 clinically evident and 28 silent myocardial infractions (new Q waves on EKG). This study confirmed a trend toward an increased incidence of myocardial infarction in patients receiving dabigatran but the difference was no longer statistically significant both for 110 and 150 mg doses. Moreover, post-marketing investigations and clinical registries [43, 44] have not substantiated an increased rate of myocardial infarction in NVAF patients treated with dabigatran. It also needs to be highlighted that treatment with dabigatran resulted in significantly lower rates of cardiovascular death compared to warfarin [2].

Difficulty achieving therapeutic anticoagulation, dietary modifications, the necessity of blood collection, visits for INR assessment, and treatment counselling were among important factors responsible for suboptimal use of warfarin in patients with atrial fibrillation. Free of all these inconveniences, DOACs give hope for better compliance with oral chronic anticoagulation in patients with NVAF. However, the rate of discontinuation in all phase III trials was roughly the same for warfarin and DOACs. This suggests that adherence to DOACs is disheartening and might not be as good as expected. However, except for RE-LY, all other studies were double-dummy, so all patients were equally inconvenienced by blood testing and counselling. A "real life" assessment of adherence to DOAC therapy is needed to verify this expectation.

Controversies related to DOACs

DOACs reversal

For patients taking warfarin who are found to have prothrombin time-INR prolongation, reversal can be accomplished with fresh frozen plasma, prothrombin complex concentrate (PCC), and vitamin K. Although this approach has a long track record with general endorsement by medical professionals, there is little data showing clinical outcomes of "reversed" to "non-reversed" bleeders. Recently, reported lack of clinical benefit in warfarin-associated intracranial hemorrhage after anticoagulation reversal with PCC calls into question the clinical significance of this therapy [48]. Also, a study comparing patients with intracranial bleeding who were treated with dabigatran, and therefore not "reversed," compared to those with warfarin, for whom reversal of anticoagulant therapy was possible, did not show improved clinical outcomes with reversal [49]. Moreover, clinical outcome data of bleeding patients on apixaban, and those on warfarin, suggests indirectly that warfarin reversal may not be clinically beneficial [50].

PCC, highly purified concentrates of clotting factors, have been touted as potential reversal agents for patients taking oral direct factor Xa inhibitors. These concentrates are available as either three-factor or four-factor formulations. The four-factor formulation contains factors II, VII, IX, and X in addition to protein C and S. By comparison, the three-factor formulation does not contain factor VII, protein C, or protein S. In one study, a four-factor PCC was assessed in 12 healthy individuals given rivaroxaban 20 mg twice daily or dabigatran 150 mg twice daily. In this study, PCC was shown to normalize prolonged prothrombin times in those patients taking rivaroxaban, but not dabigatran [51]. In another double-blind, randomized, placebo-controlled, two-way crossover study, normal volunteers were given edoxaban 60 mg followed by four-factor PCC (10, 25, or 50 IU/kg) to determine impact on bleeding duration following skin punch biopsy [52]. In this study, a dose-dependent reversal of edoxaban's effects on bleeding duration, endogenous thrombin potential, and prothrombin time reversal were observed with complete reversal noted at the highest PCC dose. In a separate healthy volunteer study, the three-factor PCC was compared to the four-factor

PCC for reversal of rivaroxaban 20 mg twice daily [53]. In this study, only minimal normalization of the prothrombin time was achieved with either PCC; however, the three-factor PCC provided greater changes in thrombin generation. Recently, three-factor PCC was also evaluated for the ability to reverse the anticoagulation effects of edoxaban [54]. This study showed that although there was no apparent reversal of prothrombin time prolongation with three-factor PCC, endogenous thrombin potential was completely reversed. In summary, both the three-factor and four-factor PCCs likely work to some degree for reversal of the direct factor Xa inhibitors. Neither agent is likely to be effective for reversal of dabigatran. Based on our experience, we suggest judicious use of these agents given the propensity for thrombus induction.

Implementation of an antidote, defined as a substance that "neutralizes" or blocks the anticoagulant agent without changing any other components of the coagulation system, should theoretically limit the prothrombotic effect of its use. Several antidotes for DOACs such as idarucizumab, andexanet alfa, and aripazine have shown instantaneous or rapid normalization of coagulation measures in healthy volunteers and are currently evaluated in phase III clinical trials [55]. Recently, the safety of 5 g of intravenous idarucizumab was assessed in patients suffering a serious bleed or requiring an urgent procedure. This study showed that normalization of prolonged clotting tests could be accomplished in 88 to 98 % of the patients within minutes of administration [56]. Based on these data, idarucizumab has now been FDA approved for this indication.

Under circumstances of active bleeding or urgent/emergent surgery, management of these agents would ideally be guided by knowledge of circulating drug levels. Circulating drug levels can be measured directly or indirectly by assessing their impact on clot-based assays. Direct measurement of circulating drug levels is currently limited to academic medical centers. The dilute thrombin time assay supplemented by a specific, validated calibrator allows an indirect measurement of dabigatran plasma levels. Available data [57, 58] indicate that there might be increased bleeding risk if drug concentration at trough is >200 ng/mL. It was also reported [57] that prolongation of aPTT at trough exceeding two times the upper limit of normal range might be associated with excess bleeding risk. On the other hand, a normal aPTT in patients treated with dabigatran was used in a case of an urgent surgery to exclude any relevant residual anticoagulation effect of this DOAC [57]. Similarly, direct Xa inhibitors plasma concentration can also be measure by anti-FXa chromogenic assays using validated calibrators, but no data on threshold values for bleeding or thrombosis yet exist to apply this information into decision making [20]. Wide dissemination of these assays to general practice settings is therefore of principal importance in the effort to gain experience and achieve clinical applicability.

Labile INR and the relative effectiveness of DOACs

Relevant quality outcomes for anticoagulated patients include the frequency of hard events such as major bleeding and thromboembolism. For warfarin-managed patients, time spent within the therapeutic range is a well-established surrogate outcome which directly correlates with the stroke risk. The correlation with bleeding is variable [59]. The DOAC trials, like all previous multi-center, multinational trials of anticoagulation, showed wide variations in INR control between countries and sites. This has led to questions regarding the relevance of the overall findings for individual patients, or countries, with more refined anticoagulation management systems.

There is an assumption that poor management of warfarin therapy would favor both the efficacy and safety of DOACs and, conversely, more time spent within the therapeutic range would be associated with the loss of benefit of new anticoagulants. The interpretation of the relationships between time in therapeutic range (TTR) and treatment effect is complex and requires digestion before drawing firm conclusions. INR control during warfarin treatment is influenced by multiple patient-related factors such as age, sex, body weight, smoking, diabetes mellitus, liver failure, congestive heart failure, lung disease, prior experience with anticoagulation, and concomitant use of other medications, particularly amiodarone or dronedarone [59]. Other individual-related features, like cultural factors and education, significantly impact anticoagulation management. Furthermore, differences in socioeconomic status, healthcare systems, and quality of medical service have profound impact on the efficacy of anticoagulation management. All these factors have an impact not only on warfarin management, and therefore TTR, but also on efficacy and safety of DOACs. Blinded randomization should account for all of these variables, which are anticipated to be equally prevalent in both treatment arms. Redistributing study results based on individual TTR in the warfarin arm leads to redistribution of younger, better educated patients, with less comorbidities and greater access to sophisticated healthcare systems, into the cluster with better TTR values. Accordingly, the lower risk of stroke and bleeding becomes associated with better warfarin management. However, this "correction" does not happen in the DOAC arm. Thus, using individual TTR to adjust the effect of treatment violates principles of clinical and statistical analysis and annuls the advantages of randomization.

Analyses of the impact of TTR on comparative efficacy and safety of dabigatran [60], rivaroxaban [61], and apixaban [62] were performed using center-specific TTR, which better conserves a fair distribution of factors influencing treatment performance in both arms of the trial. This approach showed that the primary endpoints of efficacy and safety, in relation to warfarin, were consistent across a wide range of center

specific TTRs for dabigatran, rivaroxaban, and apixaban [60–62]. Apixaban showed similar efficacy and safety compared to warfarin across both center average TTR and individual TTR quartiles [62].

Taken together, these findings provide no clear evidence for an augmented net clinical benefit of DOACs among patients and populations with poor INR control during warfarin therapy. Conversely, it shows no clear evidence for the loss of benefit (and even potential harm) if replacing good INR management with DOACs. At our institution, we have been fortunate to consistently deliver high TTR for our warfarin-managed patients, and yet, the use of DOAC continues to rapidly expand.

Choosing a specific antithrombotic agent

To anticoagulate or not anticoagulate

The first step in this decision making process is to determine whether the patient requires an anticoagulant. The landscape of antithrombotic decision making for NVAF is rapidly evolving due, in part, to the introduction of CHA_2DS_2-VASc. This scoring tool qualifies more patients for anticoagulant therapy who were previously deemed low risk by the $CHADS_2$ scoring tool [63, 64]. In the past, anticoagulant therapy would have been recommended for 66 % of patients with NVAF [64]. Using this new scoring system, between 90 and 95 % of patients will qualify for anticoagulant therapy [65, 66]. The second major advance altering this landscape is the low bleeding rates associated with DOAC therapy. In the current climate, the vast majority of NVAF patients should be offered anticoagulant therapy. The question is not who should receive anticoagulant therapy, but rather who should not. Identifying the rare patient who is best served without antithrombotic therapy includes those with active bleeding, recurrent anticoagulant related bleeding, and those with a CHA_2DS_2-VASc score of 0. If the only CHA_2DS_2-VASc variable is female gender, then these patients also do not require anticoagulant therapy. If a NVAF patient had major bleeding on warfarin, anticoagulation often should not be completely eliminated as the therapeutic option until apixaban, or lower dose of dabigatran, or edoxaban is tried.

The traditional warfarin alternative for NVAF patients who are not suitable, not willing, or not requiring anticoagulation, has been aspirin. Compared to aspirin in the AVERROES trial, apixaban showed a similar major bleeding (1.4 vs 1.2 %, $p=0.57$) and intracranial bleeding rates (11 cases with apixaban vs 13 with aspirin), but significantly better protection from stroke (1.6 vs 3.7 %, $p<0.001$) [6]. These data suggest that antiplatelet therapy should not be offered for NVAF unless the patient refuses an anticoagulant or cannot afford apixaban [16, 20].

Tailoring anticoagulant choice

The next step in the decision making is to identify patient-specific factors, which would help tailor the anticoagulant choice (Table 5). For patients at increased risk of thromboembolism with acceptable bleeding risk, we prefer dabigatran 150 mg twice daily. This is the only antithrombotic agent shown to have superior efficacy in the reduction of ischemic stroke. The superiority rating noted for apixaban included a reduction in hemorrhagic stroke in the composite outcome. Therefore, for relatively young patients with good kidney function and no history of bleeding, but with the presence of left atrial appendage thrombus, dabigatran appears to be the best option. Apixaban does not offer a benefit over warfarin for this patient profile, as the risk of bleeding, including intracranial bleeding, is relatively low. In this case, edoxaban 30 mg will be the least attractive option as it is the only DOAC with higher ischemic stroke rates compared to warfarin.

For patients at increased risk of bleeding, we prefer apixaban whereby this agent provided a consistent reduction in bleeding outcomes regardless of the antithrombotic indication [4, 67]. Edoxaban would be a reasonable alternative choice.

Patients with NVAF and recurrent gastrointestinal bleeding pose a particular challenge. Edoxaban at the reduced dose of 30 mg could be considered in this clinical situation whereas this is the only preparation associated with a lower rate of gastrointestinal bleeding compared to warfarin [5]. Although edoxaban 60 mg is recommended for thromboembolism prevention in NVAF patients, current guidelines encourage a dose reduction in patients with high bleeding risk [17–20]. Dabigatran 150 mg, rivaroxaban, and edoxaban 60 mg should be avoided in these patients because they experienced a higher gastrointestinal bleeding rate compared to warfarin. Dabigatran 110 mg and apixaban were associated with gastrointestinal bleed rates similar to warfarin. Interestingly, dabigatran showed a similar proportion of upper and lower gastrointestinal bleeding, whereas rivaroxaban and apixaban use was associated with upper gastrointestinal bleeding in two thirds of cases [2–4]. It is speculated that high concentrations of active DOACs in feces explains the relatively high gastrointestinal bleeding rate of these medications. It is further postulated that the high concentration of the pro-drug dabigatran etexilate in the colon becomes activated to dabigatran by mucosal esterases, and consequently results in bleeding from this site [7]. For these combined reasons, we favor Xa inhibitors over dabigatran in patients with the prior episodes of lower gastrointestinal bleeding. This is particularly relevant for those patients who have undergone recent polypectomy.

Table 5 Clinical situation related preferences for the use of direct oral anticoagulants

Clinical situation	First choice	Second choice	Avoid
High thromboembolic and low bleeding risk	Dabigatran 150 mg	Apixaban, edoxaban 60 mg, rivaroxaban, dabigatran 110 mg	Edoxaban 30 mg
Low thromboembolic and high bleeding risk	Edoxaban 30 mg Apixaban	Edoxaban 60 mg Dabigatran 110 mg	Dabigatran 150 mg Rivaroxaban
Moderate thromboembolic and bleeding risk	Apixaban Edoxaban 60 mg Dabigatran 110 mg	Rivaroxaban Dabigatran 150 mg	Edoxaban 30 mg
High thromboembolic and bleeding risk	Apixaban	Rivaroxaban Edoxaban 60 mg Dabigatran 150 mg	Edoxaban 30 mg
Compliance concerns	Edoxaban 60 mg Rivaroxaban[a]	Edoxaban 30 mg	Dabigatran or apixaban
Moderate renal dysfunction[b]	Apixaban	Rivaroxaban Dabigatran 110 mg Edoxaban 60 or 30 mg	Dabigatran 150 mg

[a] Although dosing instruction recommends taking rivaroxaban with evening meal, in reality it means that it needs to be taken with food either in the morning or in the evening

[b] Creatinine clearance 30–44 mL/min (chronic kidney disease stage 3B). We remain hesitant to recommend any of these agents for CKD stages 4 or 5 until published safety data are available

For these patients, it would be reasonable to consider an alternate anticoagulant for the several week period of polypectomy site healing.

In the setting of chronic kidney disease, particularly those patients requiring dialysis, warfarin remains the first choice. Apixaban is FDA approved for patients with chronic kidney disease without a recommended dose adjustment regarding of CKD stage. Until further clinical experience is reported, we remain cautious regarding use of this drug for patients with end-stage renal disease.

Once daily dosing has been shown to improve compliance and adherence over medications requiring multiple daily dosing [68]. To promote adherence, we, therefore, would consider rivaroxaban or edoxaban.

For patients with significant dyspepsia, peptic ulcer disease, after vagotomy, gastric drainage procedure, antrectomy, subtotal or total gastrectomy, and after bariatric procedure, we suggest avoiding dabigatran which may increase symptoms of peptic ulcer and/or interfere with medication absorption. Because of limited gastrointestinal absorption of dabigatran (6–8 %), even minor fluctuations may have a profound impact on plasma levels.

Patients who had peripheral embolism as a thrombotic complication of NVAF might be treated preferentially with rivaroxaban as it is the only DOACs with improved efficacy for this type of event.

For patients older than 75 years, we prefer direct Xa inhibitors over dabigatran dose of 150 mg because of unfavorable benefit-risk balance for the latter in elderly.

When treating patients with significant coronary disease, we suggest avoiding dabigatran until more published experience is available.

For those patients who are already well-established on a stable warfarin regimen, there is no need to contemplate a change. An attractive option for streamlining this regimen is the addition of home INR monitoring which has been shown to improve safety, time in the therapeutic range, and patient satisfaction through increased flexibility and more frequent INR assessment [69].

Conclusion

Atrial fibrillation is commonly encountered in clinical practice, and some form of oral anticoagulation is indicated in almost all patients. Relative to warfarin, the clinical experience with DOACs has been limited and many questions remain. Providers must be familiar with the characteristics of these agents and the trials on which their use was established in order to counsel and care for the growing number of patients taking them. In general, DOACs have shown similar efficacy, with better safety, compared to warfarin for NVAF. This improved safety might further expand the proportion of NVAF patients who would benefit from anticoagulation therapy. Ultimately, patient-specific factors and shared decision making should guide anticoagulant selection.

Compliance with ethical standards

Conflict of interest Dr. Waldemar E. Wysokinski has received consultation fee from Daiichi Sankyo, Inc. and from Boehringer Ingelheim Pharmaceuticals Inc.

References

1. Press Announcements > FDA approves Pradaxa to prevent stroke in people with atrial fibrillation. Available at: http://www.fda.gov/newsevents/newsroom/pressannouncements/ucm230241.htm. Accessed July 8, 2014.
2. Connolly SJ, Ezekowitz MD, Yusuf S et al (2009) Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med 361 (12):1139–1151
3. Patel MR, Mahaffey KW, Garg J et al (2011) Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med 365(10): 883–891
4. Granger CB, Alexander JH, McMurray JJV et al (2011) Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365 (11):981–992
5. Giugliano RP, Ruff CT, Braunwald E et al (2013) Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med 369(22): 2093–2104
6. Connolly SJ, Eikelboom J, Joyner C et al (2011) Apixaban in patients with atrial fibrillation. N Engl J Med 364(9):806–817
7. Chan NC, Paikin JS, Hirsh J, Lauw MN, Eikelboom JW, Ginsberg JS (2014) New oral anticoagulants for stroke prevention in atrial fibrillation: impact of study design, double counting and unexpected findings on interpretation of study results and conclusions. Thromb Haemost 111(5):798–807
8. FDA approves Pradaxa to prevent stroke in people with atrial fibrillation [news release]. Silver Spring, MD: U.S. Food and Drug Administration; October 19, 2010. http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm230241.htm. Accessed October 12, 2013.
9. European Medicines Agency. Pradaxa. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000829/human_med_000981.jsp Accessed October 12, 2013.
10. FDA expands use of Xarelto to treat, reduce recurrence of blood clots [news release]. Silver Spring, MD: U.S. Food and Drug Administration; November 2, 2012.http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm326654.htm. Accessed October 12, 2013.
11. European Medicines Agency. Xarelto. http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000944/human_med_001155.jsp. Accessed October 12, 2013.
12. FDA approves Eliquis to reduce the risk of stroke, blood clots in patients with non-valvular atrial fibrillation [news release]. Silver Spring, MD: U.S. Food and Drug Administration; December 28, 2012.http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm333634.htm. Accessed February 16, 2014.
13. U.S. FDA approves Daiichi Sankyo's once-daily SAVAYSA™ (edoxaban) tablets for reduction of stroke risk in non-valvular atrial fibrillation and for the treatment of venous thromboembolism http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm429523.htm. Accessed January 17, 2015.
14. Kernan WN, Ovbiagele B, Black HR et al (2014) Guidelines for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. Stroke 45(7): 2160–2236
15. January CT, Wann LS, Alpert JS et al (2014) AHA/ACC/HRS guideline for the management of patients with atrial fibrillation: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the Heart Rhythm Society. Circulation 2014
16. Atrial fibrillation: the management of atrial fibrillation. National Institute for Health and Care Excellence. CG 180. http://www.nice.org.uk/guidance/CG180/ Published June 2014, Accessed August 2014.
17. Camm AJ, Lip GYH, De Caterina R et al (2012) 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. Eur Heart J 33(21):2719–2747
18. You JJ, Singer DE, Howard PA et al (2012) Antithrombotic therapy for atrial fibrillation: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141(2 Suppl): e531S–e575S. doi:10.1378/chest.11-2304
19. Skanes AC, Healey JS, Cairns JA et al (2012) Focused 2012 update of the Canadian Cardiovascular Society atrial fibrillation guidelines: recommendations for stroke prevention and rate/rhythm control. Can J Cardiol 28(2):125–136
20. Heidbuchel H, Verhamme P, Alings M et al (2015) Updated European Heart Rhythm Association Practical Guide on the use of non-vitamin K antagonist anticoagulants in patients with nonvalvular atrial fibrillation. Europace 17:1467–1507
21. Mann KG, Brummel K, Butenas S (2003) What is all that thrombin for? J Thromb Haemost 1(7):1504–1514
22. Stangier J (2008) Clinical pharmacokinetics and pharmacodynamics of the oral direct thrombin inhibitor dabigatran etexilate. Clin Pharmacokinet 47(5):285–295
23. Mueck W, Stampfuss J, Kubitza D, Becka M (2014) Clinical pharmacokinetic and pharmacodynamic profile of rivaroxaban. Clin Pharmacokinet 53(1):1–16
24. Mendell J, Tachibana M, Shi M, Kunitada S (2011) Effects of food on the pharmacokinetics of edoxaban, an oral direct factor Xa inhibitor, in healthy volunteers. J Clin Pharmacol 51(5):687–694
25. Song Y, Wang X, Perlstein I et al (2013) Bioavailability of apixaban solution formulation and crushed tablets via nasogastric tube. Clin Pharmacol Ther 93(supplement 1):S120–S121
26. Hellwig T, Gulseth M (2013) Pharmacokinetic and pharmacodynamic drug interactions with new oral anticoagulants: what do they mean for patients with atrial fibrillation? Ann Pharmacother 47(11): 1478–1487
27. Wang L, Zhang D, Raghavan N et al (2010) In vitro assessment of metabolic drug-drug interaction potential of apixaban through cytochrome P450 phenotyping, inhibition, and induction studies. Drug Metab Dispos 38:448–458
28. Chung N, Jeon H-K, Lien L-M et al (2011) Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. Thromb Haemost 105:535–544
29. Lega J-C, Bertoletti L, Gremillet C et al (2014) Consistency of safety and efficacy of new oral anticoagulants across subgroups of patients with atrial fibrillation. PLoS One 9(3):e91398

30. Schneeweiss S, Gagne JJ, Patrick AR, Choudhry NK, Avorn J (2012) Comparative efficacy and safety of new oral anticoagulants in patients with atrial fibrillation. Circ Cardiovasc Qual Outcomes 5 (4):480–486
31. Skjøth F, Larsen TB, Rasmussen LH, Lip GYH (2014) Efficacy and safety of edoxaban in comparison with dabigatran, rivaroxaban and apixaban for stroke prevention in atrial fibrillation. An indirect comparison analysis. Thromb Haemost 111(5):981–988
32. Dans AL, Connolly SJ, Wallentin L et al (2013) Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation 127(5):634–640
33. Eikelboom JW, Wallentin L, Connolly SJ et al (2011) Risk of bleeding with 2 doses of dabigatran compared with warfarin in older and younger patients with atrial fibrillation: an analysis of the randomized evaluation of long-term anticoagulant therapy (RE-LY) trial. Circulation 123(21):2363–2372
34. Majeed A, Hwang HG, Connolly SJ (2013) Management and outcomes of major bleeding during treatment with dabigatran or warfarin. Circulation 128:2325–2332
35. Lip GY, Clemens A, Noack H, Ferreira J, Connolly SJ, Yusuf S (2014) Patient outcomes using the European label for dabigatran. A post-hoc analysis from the RE-LY database. Thromb Haemost 111: 933–942
36. Dogliotti A, Paolasso E, Giugliano RP (2013) Novel oral anticoagulants in atrial fibrillation: a meta-analysis of large, randomized, controlled trials vs warfarin. Clin Cardiol 36(2):61–67
37. Miller CS, Grandi SM, Shimony A, Filion KB, Eisenberg MJ (2012) Meta-analysis of efficacy and safety of new oral anticoagulants (dabigatran, rivaroxaban, apixaban) versus warfarin in patients with atrial fibrillation. Am J Cardiol 110(3):453–460
38. Baker WL, Phung OJ (2012) Systematic review and adjusted indirect comparison meta-analysis of oral anticoagulants in atrial fibrillation. Circ Cardiovasc Qual Outcomes 5(5):711–719
39. Rasmussen LH, Larsen TB, Graungaard T, Skjøth F, Lip GYH (2012) Primary and secondary prevention with new oral anticoagulant drugs for stroke prevention in atrial fibrillation: indirect comparison analysis. BMJ 345:e7097
40. Lip GYH, Larsen TB, Skjøth F, Rasmussen LH (2012) Indirect comparisons of new oral anticoagulant drugs for efficacy and safety when used for stroke prevention in atrial fibrillation. J Am Coll Cardiol 60(8):738–746. doi:10.1016/j.jacc.2012.03.019
41. Li H-F, Zhao R-L (2013) Lack of stroke subtype information may hinder indirect comparison between the ROCKET-AF and other trials of new oral anticoagulants. J Am Coll Cardiol 61 (5):595–596
42. Chatterjee S, Sardar P, Biondi-Zoccai G, Kumbhani DJ (2013) New oral anticoagulants and the risk of intracranial hemorrhage: traditional and Bayesian meta-analysis and mixed treatment comparison of randomized trials of new oral anticoagulants in atrial fibrillation. JAMA Neurol 70(12):1486–1490
43. FDA Drug Safety Communication: FDA study of Medicare patients finds risks lower for stroke and death but higher for gastrointestinal bleeding with Pradaxa (dabigatran) compared to warfarin. Food and Drug Administration. http://www.fda.gov/drugs/drugsafety/ucm396470.htm. Accessed August 2, 2014.
44. Larsen TB, Rasmussen LH, Skjøth F et al (2013) Efficacy and safety of dabigatran etexilate and warfarin in "real-world" patients with atrial fibrillation: a prospective nationwide cohort study. J Am Coll Cardiol 61(22):2264–2273
45. Gomes T, Mamdani MM, Holbrook AM, Paterson JM, Hellings C, Juurlink DN (2013) Rates of hemorrhage during warfarin therapy for atrial fibrillation. CMAJ 185(2):E121–E127
46. Uchino K, Hernandez AV (2012) Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med 172:397–402
47. Connolly SJ, Ezekowitz MD, Yusuf S, Reilly PA, Wallentin L (2010) Randomized evaluation of long-term anticoagulation therapy investigators newly identified events in the RE-LY trial. N Engl J Med 363:1875–1876
48. Dowlatshahi D, Butcher KS, Asdaghi N et al (2012) Poor prognosis in warfarin-associated intracranial hemorrhage despite anticoagulation reversal. Stroke 43(7):1812–1817
49. Hart RG, Diener H-C, Yang S et al (2012) Intracranial hemorrhage in atrial fibrillation patients during anticoagulation with warfarin or dabigatran: the RE-LY trial. Stroke 43(6):1511–1517
50. Hylek EM, Held C, Alexander JH et al (2014) Major bleeding in patients with atrial fibrillation receiving apixaban or warfarin: the ARISTOTLE Trial (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation): predictors, characteristics, and clinical outcomes. J Am Coll Cardiol 63(20):2141–2147
51. Eerenberg ES, Kamphuisen PW, Sijpkens MK, Meijers JC, Buller HR, Levi M (2011) Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. Circulation 124(14): 1573–1579
52. Zahir H, Brown KS, Vandell AG et al (2015) Edoxaban effects on bleeding following punch biopsy and reversal by a 4-factor prothrombin complex concentrate. Circulation 131(1):82–90
53. Levi M, Moore KT, Castillejos CF et al (2014) Comparison of three-factor and four-factor prothrombin complex concentrates regarding reversal of the anticoagulant effects of rivaroxaban in healthy volunteers. J Thromb Haemost 12(9):1428–1436
54. Brown KS, Wickremasingha P, Parasrampuria DA et al (2015) The impact of a three-factor prothrombin complex concentrate on the anticoagulatory effects of the factor Xa inhibitor edoxaban. Thromb Res 136(4):825–831
55. Mo Y, Yam FK (2015) Recent advances in the development of specific antidotes for target-specific oral anticoagulants. Pharmacotherapy 35(2):198–207
56. Pollack CV Jr, Reilly PA, Eikelboom J, et al (2015) Idarucizumab for dabigatran reversal. N Engl J Med. Jun 22. [Epub ahead of print]
57. van Ryn J, Stangier J, Haertter S et al (2010) Dabigatran etexilate—a novel, reversible, oral direct thrombin inhibitor: interpretation of coagulation assays and reversal of anticoagulant activity. Thromb Haemost 103:1116–1127
58. Huisman MV, Lip GY, Diener HC, Brueckmann M, van Ryn J, Clemens A (2012) Dabigatran etexilate for stroke prevention in patients with atrial fibrillation: resolving uncertainties in routine practice. Thromb Haemost 107:838–847
59. Hylek EM, Go AS, Chang Y et al (2003) Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. N Engl J Med 349(11):1019–1026
60. Wallentin L, Yusuf S, Ezekowitz MD et al (2010) Efficacy and safety of dabigatran compared with warfarin at different levels of international normalised ratio control for stroke prevention in atrial fibrillation: an analysis of the RE-LY trial. Lancet 376(9745):975–983
61. Piccini JP, Hellkamp AS, Lokhnygina Y et al (2014) Relationship between time in therapeutic range and comparative treatment effect of rivaroxaban and warfarin: results from the ROCKET AF trial. J Am Heart Assoc 3(2):e000521
62. Wallentin L, Lopes RD, Hanna M et al (2013) Efficacy and safety of apixaban compared with warfarin at different levels of predicted international normalized ratio control for stroke prevention in atrial fibrillation. Circulation 127(22):2166–2176
63. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM (2010) Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based

approach: the Euro heart survey on atrial fibrillation. Chest 137(2): 263–272
64. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ (2001) Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA 285(22):2864–2870
65. Puurunen MK, Kiviniemi T, Schlitt A et al (2014) CHADS2, CHA2DS2-VASc and HAS-BLED as predictors of outcome in patients with atrial fibrillation undergoing percutaneous coronary intervention. Thromb Res 133(4):560–566
66. Friberg L, Rosenqvist M, Lip GYH (2012) Net clinical benefit of warfarin in patients with atrial fibrillation: a report from the Swedish atrial fibrillation cohort study. Circulation 125(19):2298–2307
67. Granger CB, Alexander JH, McMurray JJ et al (2011) ARISTOTLE Committees and Investigators. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med 365(11): 981–992
68. Kocurek B (2009) Promoting medication adherence in older adults … the rest of us. Diabetes Spectr 22:80–84
69. Bloomfield HE, Krause A, Greer N et al (2011) Meta-analysis: effect of patient self-testing and self-management of long-term anticoagulation on major clinical outcomes. Ann Intern Med 154 (7):472–482

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EXHIBIT I

this week

EMMA BROWN/BMA

GPs threaten mass resignation

GPs have threatened mass resignations from NHS contracts if the government fails to deliver a "rescue package" for general practice.

The BMA's General Practitioners Committee will ask for GPs' views about submitting undated resignations if a bailout plan isn't proposed within six months.

The move was supported by local medical committee (LMC) representatives after a debate at a special BMA conference in London on 30 January.

GPs could also be balloted on the work they would stop doing—to reduce workload and ensure safe and sustainable care—under a motion approved by the conference.

The General Practitioners Committee would also explore actions GPs could undertake without breaching their contracts.

James Murphy, of Buckinghamshire LMC, who proposed the motion, said that the profession needed to take action as hope was "fading fast" for general practice.

He said, "It feels like we are stuck on a permanent warlike footing, lurching from crisis to crisis with only sticking plaster solutions. I feel we are fighting for our very survival." He said that the motion would give BMA negotiators "the arsenal it needs to take on the battles ahead."

Naomi Beer, representing London Tower Hamlets LMC, agreed that the threat to canvass opinion on resignations would force the government and NHS England to take notice.

"We have to get the message through that we will not continue to work within an unsafe system created by others but where we take all the responsibility for failure," she said. "We are at a point where there is nothing to lose because they are killing us anyway. Threatening to resign is not giving up...it is saying we will not be party to this destruction anymore."

Anthony O'Brien, from Devon LMC, spoke against the motion. He warned that canvassing views on resignations would be "pointless" because there was very little chance of securing consensus. "We are here to discuss solutions. Mass unsigned resignations is not one. It won't work, you won't get people to sign up to it," he said.

Chaand Nagpaul, who chairs the General Practitioners Committee, backed the motion. "Let's all collectively do everything we can to safeguard our lives and the care we give to our patients," he said.

Matthew Limb, London

Cite this as: *BMJ* 2016;352:i646

GPs' representatives backed the motion that one doctor said would give BMA negotiators "the arsenal it needs to take on the battles ahead"

NEWS ONLINE

- BMA defends decision to end GPs' responsibility for care home residents
- *Lancet* retracts paper by disgraced Canadian researcher
- General practice is being "eroded" in Scotland, says RCGP

RIVAROXABAN
Can we trust the evidence

An investigation has uncovered the use of a faulty device in the key regulatory drug trial, casting doubt on the results. **Deborah Cohen** reports

Doctors and scientists are calling for an independent investigation into the key trial underpinning use of rivaroxaban to prevent ischaemic stroke in non-valvular atrial fibrillation after *The BMJ* found that a defective point of care device was used in the warfarin arm of the trial.

Doctors and scientists have also told *The BMJ* that the validity of the trial—called ROCKET-AF and published in the *New England Journal of Medicine* in 2011[1]—is in question until such independent analysis is done.

The drug was manufactured by Bayer and marketed in the United States by Janssen, part of Johnson and Johnson, and the companies relied on a single trial–ROCKET-AF—to gain approval from the US and European regulators. The trial included over 14 000 patients and found that rivaroxaban was non-inferior to warfarin for preventing ischaemic stroke or systemic embolism. There was no significant difference between groups in the risk of major bleeding—although intracranial and fatal bleeding occurred less often in the rivaroxaban group.

But there are now concerns about these outcomes. In a letter submitted to the *NEJM* (as yet unpublished) and shown to *The BMJ*, former cardiovascular and renal drug reviewer for the Food and Drug Administration (FDA), Thomas Marcinicak, says: "The care for the warfarin control arm patients [in ROCKET-AF] appears to have been compromised."

Earlier last year, *The BMJ* found that the point of care device used to measure international normalised ratio (INR) in patients taking warfarin in ROCKET-AF had been recalled in December 2014. An FDA class I recall notice (the most serious kind) said that certain INR devices could deliver results that were "clinically significantly lower" than a laboratory method. It added that Alere—the device manufacturer—had received 18 924 reports of malfunctions, including 14 serious injuries. The company confirmed to *The BMJ* that the fault went back to 2002, before the ROCKET-AF trial started.

A falsely low reading could mean that patients had their warfarin dose unnecessarily increased, leading to a greater risk of bleeding. In terms of the trial results, it could make rivaroxaban seem safer than it was in terms of the risk of bleeding and throws doubt on outcomes used to support the use of the world's best selling new oral anticoagulant.[2]

Back in September 2015, *The BMJ* asked the investigators named in the *NEJM* paper about the recall. They included researchers from Bayer, Johnson and Johnson, and the Duke Clinical Research Institute, which carried out the trial on behalf of the drug companies.

None of the authors responded, but a spokesperson for Johnson and Johnson contacted *The BMJ* to say that they were "unaware of this recall" and they took the journal's concerns "seriously." But it took months of probing by *The BMJ* before the companies, world drug regulators, and Duke began to investigate the problem in earnest.

Joining the dots

As for the regulators, when *The BMJ* contacted the European Medicines Agency in April 2015 and subsequently the FDA, both said they did not know that the recalled device had been used in ROCKET-AF. It's new territory for the regulators. What happens to a pivotal drug trial when a device used is found to be defective?

In November the EMA told *The BMJ* it was investigating, and the agency subsequently told journalists: "Due to the defect it is now thought that the INR device may have impacted the clotting results in some patients in the warfarin group."[4]

It would be nice to have some independent study carried out to give confidence in the use of this medicine
Guido Rasi, EMA

Executive director of EMA, Guido Rasi, also called for further independent investigation into direct oral anticoagulants. "It would be nice to have some independent study carried out to give confidence in the use of this medicine," he said.

The FDA also told *The BMJ* that it is "aware of concerns regarding the INR device and its use in the ROCKET-AF trial and is reviewing relevant data." It subsequently announced

DIRECT ORAL ANTICOAGULANTS

Rivaroxaban is a factor Xa inhibitor and belongs to a class of medicines known as the direct oral anticoagulants (DOAC), which also includes dabigatran, apixaban, and edoxaban. They have gained popularity in place of warfarin for the prevention of ischaemic stroke in non-valvular atrial fibrillation because routine blood monitoring is not required.[3]

that it will hold a public workshop about the safety and effectiveness" of point of care INR devices in March "to seek and identify potential solutions" to what it said were "scientific and regulatory challenges."

However, spokespeople for Johnson and Johnson and Bayer issued identical statements in December 2015: "We have conducted a number of sensitivity analyses. These sensitivity analyses confirm the results of the ROCKET-AF study and the positive benefit-risk profile of Xarelto (rivaroxaban) in patients with non valvular atrial fibrillation."

But what should happen amid the uncertainty?

Harlan Krumholz, professor of medicine (cardiology) at Yale University, says that the *NEJM* should place an "immediate expression of concern" on the paper to notify the medical community.

"The study should be considered of uncertain validity until a more thorough review can be done," he says, adding that there should be "an investigation by an independent group of experts to quickly determine if there are grounds for retraction."

The study should be considered of uncertain validity until a more thorough review can be done Harlan Krumholz

Concerns about warfarin control

Even before rivaroxaban was approved in Europe and the US in 2011 for use in non-valvular atrial fibrillation, regulatory officials raised concerns about the warfarin control in the ROCKET-AF trial. Two primary clinical FDA reviewers of the drug recommended that it should not be approved for the US market.

"ROCKET provides inadequate information to assess the relative safety and efficacy of Xarelto in patients whose warfarin administration can be well-controlled," they wrote in an FDA decisional memo—which outlines clinical reviewers' view on whether a drug should be approved.[5]

However, they were seemingly unaware that there are other reasons to be concerned about the adequacy of the warfarin control in the ROCKET-AF trial that have since emerged.

Lack of transparency over devices in trials

Currently, there is little public information about which diagnostic point of care devices are used in any of the direct oral anticoagulant trials (see box, facing page). They are not named in the published phase III trials. *The BMJ* became aware that the problematic device was used in the ROCKET-AF trial only by reviewing European regulatory documents in April last year.

Marciniak says that the *NEJM*, which published the trials for three of the direct oral anticoagulants, should rectify that.

"You should require that the devices used in trials are clearly and specifically identified in your publications," he wrote in his letter.

How has this come to happen?

In tracking the faulty recall and its potential effect on the outcomes of a global clinical trial, *The BMJ* has once again come across flaws in device regulation. A series of journal investigations have highlighted the lack of clinical data required by regulators for high risk implants, such as metal-on-metal hips, before they are put on the market.[8] They have also shown how slow regulators can be to act when problems do emerge and how oversight can be lacking on the performance diagnostic tests.[9 10]

In 2005, a warning letter from the FDA to HemoSense—the company that marketed the faulty device before Alere bought it—reprimanded them for failing to investigate "clinically significant erroneous" high and low INR results generated by the point of care device.

"Both high and low test [INR] results have the potential to cause or contribute to a death or serious injury, because: they may result in erroneous dosing and thus improper control of coagulation," the letter said.[11]

Despite these warning letters, the FDA cleared subsequent iterations of the device through its 510(k) regulatory system. This system requires makers of such devices to show only that the new version is "substantially equivalent," or similar, to one already on the market. It has been criticised by the likes of the Institute of Medicine for not providing enough evidence that a device is safe and effective.[12]

Johnson and Johnson, however, has lobbied against tightening up this aspect of device regulation and the need to provide more evidence.[13] But the lack of a regulatory requirement for the diagnostic accuracy of the device to be checked before it came on to the market has allowed the fault to creep through the system.

Alere has confirmed to *The BMJ* that the fault dates back to 2002 and it may occur in all devices and not just one batch. However, neither it nor the FDA responded to questions about why nothing had been done about the problem earlier.

Were the companies aware of any problems during the trial?

The BMJ asked Johnson and Johnson, Bayer, and Duke if any investigator complained to them about mismatched point of care and laboratory INR readings if someone had a bleed in the trial. *The BMJ* also asked if they had validated the device at any point before or during the trial. None responded to the questions.

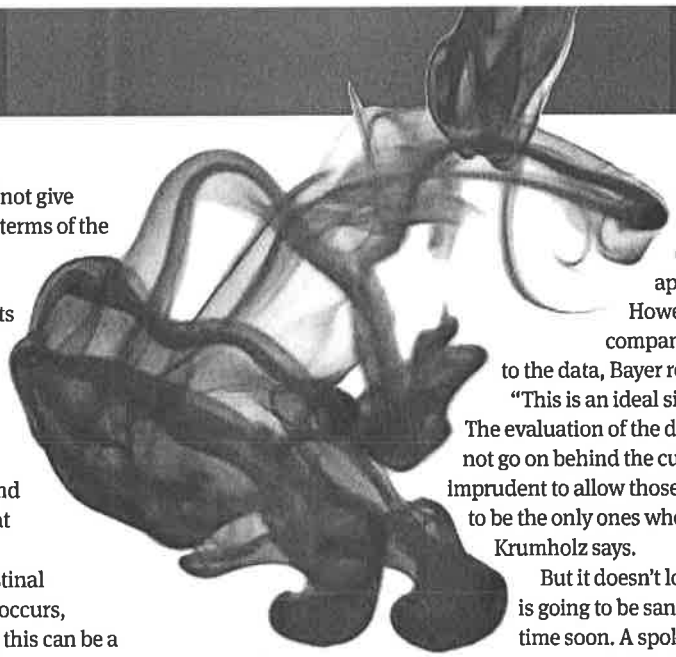
What next?

The EMA has told *The BMJ* that it has asked the companies for analyses and would consider any analyses by Duke too. During the trial INR at 12 and 24 weeks was measured at a central laboratory as well as with the point of care device. Powell says that "a comparison should be made between the defective point of care readings and the two sets of 'gold standard' central lab readings" as this would "determine whether this defective device undermined the integrity of the trial results."

It is not clear that this has happened. In December last year, Duke issued a press release with a summary report of the results of their "secondary analysis of the trial findings."

"The findings from the analysis are consistent with the results from the original trial and do not alter the conclusions of ROCKET-AF—rivaroxaban is a reasonable alternative to warfarin and is non-inferior for the prevention of stroke and systemic embolism with less intracranial hemorrhage and fatal bleeding," it said.

But Powell says this statement is "misleading" because of the lack of information.



Krumholz also thinks that this statement did not give enough information about what Duke found in terms of the major safety endpoint—major bleeds.

"The DCRI is among the most respected research institutions, but this statement suggests that they know important information that relates to the ROCKET-AF trial but are delaying in disseminating the information until it can be published," he says.

Hugo ten Cate, medical director of the Maastricht thrombosis anticoagulation clinic and coeditor in chief of *Thrombosis Journal*, says that major bleeds have serious consequences.

"Large bleeds mostly occur in the gastrointestinal tract and can be lethal if substantial blood loss occurs, especially in elderly subjects with comorbidity; this can be a devastating complication," he says.

Any changes to the ROCKET-AF trial will have a broader effect on the literature.

Carl Heneghan is an author on a forthcoming Cochrane Collaboration review of "direct thrombin inhibitors and factor Xa inhibitors for atrial fibrillation," which includes the ROCKET trial.

He has written to Duke to ask if the results for the main outcome measures in the reanalysis are the same as in the original published paper and, if not, what the differences are after the reanalysis.

A spokesperson for Duke did not answer the question but said that the ROCKET-AF executive committee "intends to publish a full description of its analysis as rapidly as possible."

You should require that the devices used in trials are clearly identified in your publications
Thomas Marciniak

Independent oversight

But given the lack of clarity over the outcomes and the methods used, is a reanalysis by Duke enough?

Marciniak is unequivocal. He says that he would not rely on any reanalyses done by Duke, Johnson and Johnson, or the FDA.

"Because they already missed the problems both in the trial and with the public marketing, I would not trust them to publish anything that is accurate—or that provides any details," he told *The BMJ*.

He added that the datasets need to be released as "the only solution that would lead to unbiased analyses."

But previous attempts to do this have been thwarted.

Krumholz has approached Johnson and Johnson for access to the trial data. His Yale University Open Data Access (YODA) project has an agreement with Johnson and Johnson to make all of the clinical trial data available for its approved products. However, although the company agreed to allow access to the data, Bayer refused.

"This is an ideal situation for data sharing. The evaluation of the data in this trial should not go on behind the curtain. And it seems imprudent to allow those who conducted the trial to be the only ones who can touch the data," Krumholz says.

But it doesn't look like the data release is going to be sanctioned by Bayer any time soon. A spokesperson for the company told *The BMJ* that this is because they have signed up to sharing information only on "study reports for new medicines approved in the US and the EU after January 1, 2014."

Good outcome for patients?

But in the end might this series of errors lead to a favourable outcome for the regulators—and perhaps patients?

At the end of 2015, both the EMA and the FDA held meetings to discuss the need to measure blood levels of direct oral anticoagulants and adjust the dose accordingly to maximise benefit and minimise harm—despite all the manufacturers claiming that this is not necessary. The meetings were held after *The BMJ* revealed that Boerhinger Ingelheim, manufacturers of dabigatran, withheld analyses from the regulators that showed how many major bleeds could be prevented by monitoring anticoagulant activity and adjusting the dose.[14]

A presentation to EMA last year by Robert Temple, deputy director for clinical science at the FDA's Center for Drug Evaluation and Research, suggests that the FDA believes there is a scientific argument for measuring the blood levels of these drugs and adjusting the dose.

"Being too low leads to a stroke, a very bad outcome, and being too high leads to major bleeds, also bad, so that early optimization [of the dose] seems worthwhile," he said adding that direct oral anticoagulants are "very good, but could probably be better."

But once a drug is on the market, regulators lack a mandate to act unless there are safety concerns. However, according to Powell, depending on the outcomes of any reanalysis of the ROCKET-AF trial, this might allow them to take action.

"After a drug is approved, it usually takes a safety signal to prompt significant action on the part of the FDA. It is this lack of safety signal that appears to be hindering the FDA in their desire to pursue tailored dosing for DOACs. If it turns out that the issue with the [INR] device changes the safety profile of rivaroxaban, this may constitute the safety signal necessary for the FDA to act in this regard," he said.

Deborah Cohen, associate editor, *The BMJ*
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DEVICES USED IN OTHER TRIALS

Given the lack of publicly available information about the point of care testing devices used in the other direct oral anticoagulant trials, *The BMJ* sought to find out what they are.

Lars Wallentin (right), corresponding author of the phase III ARISTOTLE trial (Apixaban versus Warfarin in Patients with Atrial Fibrillation)[6] said that the trials used the ProTime POC device made by International Technidyne Corporation, Edison, NJ, USA.

Daiichi-Sankyo, the manufacturers of edoxaban, also said that the ProTime POC device was supplied to all study sites in the Edoxaban versus Warfarin in Patients with Atrial Fibrillation Trial (ENGAGE AF)[7] and in its venous thromboembolism trial.

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IN THE SUPERIOR COURT OF THE STATE OF DELAWARE

CAROL WOODY and JAKE WOODY, Plaintiff, v. BRISTOL-MYERS SQUIBB COMPANY and PFIZER, INC., Defendants.	C.A. No.: JURY TRIAL DEMANDED

PLAINTIFFS' ANSWERS TO FORM 30 INTERROGATORIES

1. Give the name and present or last-known residential and employment address and telephone number of each eyewitness to the incident which is the subject of the litigation.

   ANSWER:

   To be supplemented, if applicable.

2. Give the name and present or last-known residential and employment address and telephone number of each person who has knowledge of the facts relating to the litigation.

   ANSWER:

   Plaintiffs, CAROL WOODY and JAKE WOODY, who may be contacted only through the undersigned counsel. Plaintiff's treating physicians. The names and contact information of said treating physicians will be supplied by plaintiff. To be supplemented, if applicable.

3. Give the names of all persons who have been interviewed in connection with the above litigation, including the names and present or last-known residential and employment addresses and telephone numbers of the persons who made said interviews and the names and present or last-known residential and employment addresses and telephone numbers of persons who have the original and copies of the interview.

   ANSWER: None.

4. Identify all photographs, diagrams, or other representations made in connection with the matter in litigation, giving the name and present or last-known residential and employment address and telephone number of the person having the original and copies thereof. (In lieu thereof, a copy can be attached.)

   ANSWER: None currently in possession.

5. Give the name, professional address, and telephone number of all expert witnesses presently retained by the party together with the dates of any written opinions prepared by said expert. If an expert is not presently retained, describe by type the experts whom the party expects to retain in connection with the litigation.

   ANSWER: Experts in epidemiology, Experts in blood clotting, FDA Regulatory Experts, Causation Experts, Damages Experts and other experts will be retained.

6. Give a brief description of any insurance policy, including excess coverage, that is or may be applicable to the litigation, including:
   a. The name and address of all companies insuring the risk;
   b. The policy number(s);
   c. The type of insurance;
   d. The amounts of primary, secondary, and excess coverage.

   ANSWER: Not Applicable

7. Give the name, professional address, and telephone number of all physicians, chiropractors, psychologists, and physical therapists who have examined or treated you at any time during the ten year period immediately prior to the date of the incident at issue in this litigation.

   ANSWER:

   To be supplemented.

NAPOLI SHKOLNIK, LLC

By: /s/ James D. Heisman
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IN THE SUPERIOR COURT OF THE STATE OF DELAWARE

CAROL WOODY and JAKE WOODY, Plaintiffs, v. BRISTOL-MYERS SQUIBB COMPANY and PFIZER, INC., Defendants.	C.A. No.: JURY TRIAL DEMANDED

PRAECIPE

PLEASE ISSUE Summons and Complaint through the Sheriff of New Castle County to the defendants at the addresses indicated herein:

BRISTOL-MYERS SQUIBB COMPANY
c/o The Corporation Trust Company
1209 Orange Street
Wilmington, DE 19801

PFIZER, INC.
c/o The Corporation Trust Company
1209 Orange Street
Wilmington, DE 19801

NAPOLI SHKOLNIK, LLC

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DATED: April 17, 2017

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IN THE SUPERIOR COURT OF THE STATE OF DELAWARE

CAROL WOODY and JAKE WOODY, Plaintiffs, v. BRISTOL-MYERS SQUIBB COMPANY and PFIZER, INC., Defendants.	C.A. No.: JURY TRIAL DEMANDED

SUMMONS

THE STATE OF DELAWARE,
TO THE SHERIFF OF NEW CASTLE COUNTY:

YOU ARE COMMANDED:

To summon the above defendant so that, within 20 days after service hereof upon defendant, exclusive of the day of service, defendant shall serve upon James D. Heisman, Esquire, plaintiffs' attorney, whose address is 919 N. Market Street, Suite 1801, Wilmington, DE 19801, an answer to the complaint (and, if an affidavit of demand has been filed, an affidavit of defense).

To serve upon defendant a copy hereof and of the complaint (and of the affidavit of demand if any has been filed by plaintiff).

Dated:

SUSAN A. HEARN
Prothonotary

_____
Per Deputy

TO THE ABOVE-NAMED DEFENDANTS:

In case of your failure, within 20 days after service hereof upon you, exclusive of the day of service, to serve on plaintiff's attorney named above an answer to the complaint (and, if an affidavit of demand has been filed, an affidavit of defense), judgment by default will be rendered against you for the relief demanded in the complaint (or in the affidavit of demand, if any).

SUSAN A. HEARN
Prothonotary

_____
Per Deputy