

Examining the Comparative Safety of Blood Thinners:

An Analysis Utilizing AdverseEvents Explorer



February 2014

Contents

Summary	3
Methods & Results	5
RxFilter™ Analysis	5
Table 1: Anticoagulants	7
Table 2: Antiplatelets	7
Disproportionality Analysis	8
Table 3: Anticoagulants	9
Table 4: Antiplatelets	9
RxScore™	9
Table 5: Anticoagulants: RxScores and Component Percentages	10
Table 6: Antiplatelets: RxScores and Component Percentages	11
Results Summary	11
Conclusion	13
Disclaimers	14
References	15
Appendix A – FDA-Approved Indications for each Drug	16
Appendix B – Adverse Event Search Terms Used	17

Summary

The pre-approval clinical trial process suffers from many limitations including: homogenous groups of patients, limited drug exposure times, ever-increasing exclusion criteria, lack of gender-specific analyses, inadequate testing of the elderly and different races, etc. All of these restrictions can result in very different reactions, especially with regard to side effects, in clinical trial subjects versus real-world consumer populations¹. Accordingly, the true side effect profile of a drug is almost never realized until many months, to years, after FDA approval^{2, 3}. In short, all FDA approved drugs have the potential to trigger various side effects not revealed during pre-approval investigations. For more detail please see a White Paper we recently produced, [“Post FDA-approval drug safety data: why they are vital and how they can be made accessible, actionable, and predictable.”](#)

Indeed, Adverse Events (AEs) from Food and Drug Administration (FDA) approved drugs are a major public safety concern. In fact, almost one million new AE reports are currently reported to the FDA each year, across ~2,000 approved drugs⁴.

Careful and continuous post-approval monitoring is therefore vital to the evaluation of a drug’s safety profile. That is exactly what we specialize in here at AdverseEvents.

Because of the noted limits of pre-approval safety processes, AdverseEvents believes that post-marketing side effect analysis can supply our clients with the real-world data they need to make informed coverage, formulary, and prescribing decisions.

To obtain such data, we leverage the FDA’s Adverse Event Reporting System (FAERS), a vast repository of over seven million post-marketing side effect case reports, across all FDA-approved drugs⁵. FAERS data (after extensive organization and cleanup via algorithms and our analysts) forms the cornerstone of our product offerings.

With regard to the widely used class of medications known as blood thinners (anticoagulants and antiplatelets) post-marketing side effects have been a concern for many years ([2006 Black Box Warning for Coumadin](#)). For a list of what each drug is FDA-approved for please see Appendix A.

Anticoagulant drugs prevent blood from clotting and are therefore prescribed to treat various thromboembolic disorders such as: Atrial Fibrillation (AF), pulmonary embolisms, and deep-vein thrombosis. AF represents the most common cardiac arrhythmia affecting approximately 1-2% of the world's population and is expected to affect an estimated 6-16 million people, in the US alone, by the year 2050^{6,7}. The risk of ischemic stroke is increased 4 to 5 fold in patients with AF⁸. The drugs are also prescribed to patients to prevent blot clot formation associated with surgical procedures.

Oral anticoagulants such as warfarin (**Coumadin**) and antiplatelets agents such as aspirin and clopidogrel (**Plavix**) have been on the market for decades. New orally active anticoagulants (NOACs) include dabigatran (**Pradaxa**), rivaroxaban (**Xarelto**), and apixaban (**Eliquis**).

NOACs are displacing the use of older drugs like Coumadin. Current opinion is generally that they work as well as Coumadin, have a better therapeutic index, more predictable pharmacokinetics, do not require sometimes complex dietary restrictions, and offer an improved safety profile via a reduction in major bleeding complications, particularly of the intracranial variety⁹. The other major advantage often cited in the press and in marketing campaigns is that, unlike Coumadin, NOACs do not require routine monitoring during their use. This latter point, however, has been called into question in the academic press, and allegedly even by internal researchers of the manufacturer of a popular NOAC, Pradaxa ([NY Times](#)).

A major danger for patients taking either NOACs or older drugs like Coumadin is that the medications greatly increase the time for blood to clot. Therefore, normally manageable bleeding from trauma, surgery, or other emergency situations, becomes a very serious concern for patients on these drugs. Coumadin, however, has an "antidote" that can be administered to a subject that is bleeding. The NOACs have no antidote, although efforts are underway to develop a drug that can restore normal clotting to a bleeding patient on an NOAC ([FierceBiotech](#)).

Antiplatelet drugs decrease platelet aggregation and alter platelet activation at sites of vascular damage and are accordingly prescribed to inhibit the formation of thrombi. These drugs are widely used to help prevent both cerebrovascular and cardiovascular disorders such as acute coronary syndrome¹⁰. New antiplatelet medications include ticagrelor (**Brilinta**) and prasugrel (**Effient**).

Given that blood-thinning drugs represent some of the most widely used medicines in the world and they are disproportionately used in both the elderly and other high-risk patient populations, we used our multiple analytic platforms to analyze post-marketing safety signals for drugs in this class.

The results from our analyses all point to the same general conclusions: 1) apixaban may be a safer choice within the anticoagulant class, and 2) prasugrel may have higher safety risks than the other two medications in its antiplatelet class.

Methods & Results

In order to better understand the post-approval safety data available on the class of blood thinner drugs, we conducted a detailed review of FAERS.

We subdivided the drug class into **anticoagulants** (warfarin (Coumadin), dabigatran (Pradaxa), rivaroxaban (Xarelto), and apixaban (Eliquis)) and **antiplatelets** (clopidogrel (Plavix), ticagrelor (Brilinta) and prasugrel (Effient)).

Utilizing the AdverseEvents Explorer platform, we analyzed the drugs with: 1) RxFilter (a big data analytic that optimizes FAERS and makes it user-friendly and fully searchable), 2) a disproportionality measure (mathematical analysis that compares “expected” versus “unexpected” rates of adverse events), and 3) the RxScore system (a proprietary algorithmic drug-safety ranking analytic).

RxFilter Analysis

In order to make FAERS data accessible to broad groups of healthcare professionals, AdverseEvents analyzes and categorizes the extensive database by using a combination of computer algorithms and in-house data analysis, called RxFilter. Our AdverseEvents Explorer platform makes FAERS data easy to search and understand¹¹ and feeds clean data into our other analytics.

RxFilter employs multiple processing steps, safeguards, and manual oversight. To import data from FAERS, RxFilter uses a framework of open source technologies such as Oracle MySQL, Python and PHP. Filtering processes

include: i) a system for automated name matching which corrects for drug name misspellings and incorrect data within major fields (i.e., the inclusion of dosages or routes of administration as part of the drug name field); ii) aggregation of generic and non-U.S. brand name drugs under a single brand name; iii) separation of “primary suspect” and “all suspect” designations, iv) removal of duplicate case reports; and v) identification of common adverse event and condition types.

Automated data pre-processing and scrubbing workflow provides an initial assignment of a ‘raw’ FDA FAERS drug name for approximately 98% of inputted data (within 6 hours of receipt of those data). Computationally, this automated matching process is accomplished by string searching and phonetic matching algorithms. Part of the human analysis side of RxFilter includes recovery and assignment of remaining data, and reassignment of automated matches when needed (which are then corrected for future quarterly uploads).

AdverseEvents Explorer, powered by RxFilter is the most thoroughly optimized, user-friendly, and fully searchable post-marketing drug safety database. It accurately standardizes and normalizes all reported side effects (from 1997 on) linked to over ~2,000 FDA approved drugs, enabling health plan administrators, health systems analysts, and pharmaceutical companies rapid access to FAERS information in order to supplement their own sources of drug safety data.

FAERS data was queried from a drug’s approval through the most recently available date. While most of the date ranges end at December 2012 (as that was the last FAERS download available), certain drugs have data through December 2013 because we had previously petitioned FDA, via a Freedom of Information Act (FOIA) request, for updated case reports on those specific drugs. FOIA requests are a routine service we provide for our clients, and our latest update on the process is detailed here (<http://www.adverseevents.com/foia/>). We do not believe that the inclusion of different ending dates affected the analyses presented here.

Top-level analysis of the blood thinner class of medications showed:

Table 1: Anticoagulants

Drug Name	Date Range	Primary Suspect Cases	Stroke* Cases (%)	Heart Attack* Cases (%)	Hospitalization Cases (%)	Death Cases (%)	Top 3 Adverse Events
apixaban (Eliquis)	Dec 2012- Dec 2013	1,031	54 (5.24%)	10 (0.97%)	212 (20.56%)	51 (4.95%)	Haemoglobin decreased, Ischaemic stroke, Haematoma
dabigatran (Pradaxa)	Oct 2010- Dec 2012	20,965	1,467 (6.99%)	324 (1.55%)	8,095 (38.64%)	2,529 (12.05%)	Gastrointestinal haemorrhage, Haemorrhage, Dyspepsia
rivaroxaban (Xarelto)	July 2011- Dec 2012	10,075	747 (7.41%)	107 (1.06%)	4,357 (43.25%)	1,115 (11.07%)	Pulmonary embolism, Deep vein thrombosis, Gastrointestinal haemorrhage
warfarin (Coumadin)	Nov 1997 [#] - Dec 2012	22,338	687 (3.08%)	228 (1.02%)	11,152 (49.92%)	1,841 (8.24%)	International normalised ratio increased, Gastrointestinal haemorrhage, Haemorrhage

**See Appendix B*

#Although warfarin was FDA-approved in 1954, our database begins 11/01/1997.

Table 2: Antiplatelets

Drug Name	Date Range	Primary Suspect Cases	Stroke* Cases (%)	Heart Attack* Cases (%)	Hospitalization Cases (%)	Death Cases (%)	Top 3 Adverse Events
clopidogrel (Plavix)	Nov 1997- Dec 2012	11,309	548 (4.85%)	545 (4.82%)	4,896 (43.29%)	2,218 (19.61%)	Death, Gastrointestinal haemorrhage, Anaemia
prasugrel (Effient)	July 2009- Dec 2012	1,917	90 (4.69%)	163 (8.50%)	973 (50.76%)	218 (11.37%)	Thrombosis in device, Chest pain, Death
ticagrelor (Brilinta)	July 2011- Dec 2013	2,263	69 (3.05%)	178 (7.87%)	854 (37.74%)	314 (13.88%)	Shortness of breath, Myocardial infarction (heart attack), Death

**See Appendix B*

Disproportionality Analysis

Data mining algorithms based on disproportionality can be used to estimate the relative frequency of an Adverse Event (AE) associated with the use of specific drug. The Reporting Odds Ratio (ROR) is a disproportionality measure commonly used by drug safety professionals to help identify drug-associated AEs that are reported more frequently than expected. The method compares expected reporting frequencies (based upon all drugs and all AEs in the FAERS database) with the amount of a given AE reported for a specific drug.

An ROR score of ≥ 1.0 indicates that there is a higher than normal reporting rate for a given AE / drug combination. While there is no widely accepted benchmark regarding the numerical level at which disproportionality analysis yields a “safety signal,” many in the drug industry assume that results above 2.0 warrant attention. We derived ROR and Confidence Intervals (CI) by the use of standard formulas¹², with the additional step of correlating the starting date of our calculations to each drug’s FDA approval date.

The tables below list the number of “primary suspect” case reports for each drug and how many of those reports fall into corresponding “Standardised MedDRA Queries” (SMQ) adverse event categories (as defined by MedDRA (<http://www.meddra.org/> and <http://www.meddra.org/how-to-use/tools/smq>)). SMQs are validated and standardized sets of MedDRA terms that are commonly used to support both safety signal detection and monitoring. SMQ categories can either be narrow or broad. We chose to use broad SMQs in our search in order to better capture generalizable safety risks between the drugs.

RORs and CIs were calculated for “primary suspect” cases reported from the drug’s approval date to the most recently available FAERS data.

Table 3: Anticoagulants

Drug	Approval Date	Primary Case Counts	All Case Counts	Haemorrhage Laboratory Terms* ROR (CI)	Haemorrhage terms (excl Laboratory Terms)* ROR (CI)	Embolic & Thrombotic Events (Arterial)* ROR (CI)	Embolic & Thrombotic Events (Venous)* ROR (CI)	Embolic & Thrombotic Events, Vessel Type Unspecified (Mixed Arterial & Venous)* ROR (CI)
apixaban (Eliquis)	Dec 2012	1,031	1,031	4.03 (1.98 - 8.21)	3.72 (3.23 - 4.28)	2.18 (1.56 - 3.05)	1.39 (0.96 - 2.04)	3.02 (2.35 - 3.87)
dabigatran (Pradaxa)	Oct 2010	20,965	21,963	8.04 (6.99 - 9.23)	8.43 (8.11 - 8.59)	2.03 (1.91 - 2.16)	1.90 (1.80 - 2.09)	3.64 (3.47 - 3.82)
rivaroxaban (Xarelto)	Jul 2011	10,075	10,431	8.99 (7.48 - 10.81)	8.39 (8.05 - 8.74)	2.01 (1.84 - 2.21)	13.46 (12.79 - 14.17)	5.59 (5.27 - 5.93)
warfarin (Coumadin)	Jun 1954	22,338	94,267	10.27 (9.21 - 11.45)	12.17 (11.85 - 12.49)	0.78 (0.72 - 0.85)	1.58 (1.45 - 1.71)	1.92 (1.81 - 2.03)

*See Appendix B

Table 4: Antiplatelets

Drug	Approval Date	Primary Case Counts	All Case Counts	Haemorrhage Laboratory Terms* ROR (CI)	Haemorrhage terms (excl Laboratory Terms)* ROR (CI)	Embolic & Thrombotic Events (Arterial)* ROR (CI)	Embolic & Thrombotic Events (Venous)* ROR (CI)	Embolic & Thrombotic Events, Vessel Type Unspecified (Mixed Arterial & Venous)* ROR (CI)
clopidogrel (Plavix)	Nov 1997	11,309	62,525	2.60 (1.95 - 3.46)	6.69 (6.43 - 6.95)	3.77 (3.56 - 4.00)	1.42 (1.25 - 1.61)	3.48 (3.27 - 3.69)
prasugrel (Effient)	Jul 2009	1,917	2,519	2.18 (0.98 - 4.87)	5.66 (5.12 - 6.25)	6.66 (5.91 - 7.52)	1.23 (0.90 - 1.68)	9.50 (8.51 - 10.61)
ticagrelor (Brilinta)	Jul 2011	2,263	2,481	1.78 (0.80 - 3.97)	4.56 (4.15 - 5.01)	4.24 (3.69 - 4.87)	0.43 (0.27 - 0.67)	5.87 (5.21 - 6.62)

*See Appendix B

RxScore

People are accustomed to counting on objective product ranking and scoring platforms such as Consumer Reports to guide their purchasing decisions. Drugs, however, have no similar platform, for either efficacy or safety.

Determining the overall safety risk of a drug necessarily involves the simultaneous assessment of several safety-related parameters. Choosing these

factors, and determining how to weigh their individual contribution within a ranking platform, needs careful consideration. Ideally, it should include safety information obtained from both pre- and post-approval sources. To paint a fair picture of the damage done by an AE, it would also need to factor in existing comorbidities that a patient was suffering from *before* a given drug was administered.

To meet these needs, we developed the “RxScore,” a proprietary algorithmic scoring model based predominantly on post-marketed safety data from over five million FDA Adverse Event Reporting System (FAERS) reports. RxScore is presented on a 100-point scale meant to reflect both the breadth and seriousness of side effect(s) by incorporating nine differentially weighted categories including FAERS fields such as “Outcome,” “Event Seriousness,” “Report Type,” and “Reporter Type,” a disproportionality measure, and existing FDA warnings and DEA risk classifications “Literature.” The score is also negatively adjusted by factoring in both “Indication Seriousness” and a patient’s existing comorbidities. A score of 100 indicates the highest potential adverse event risks. In order to highlight differences between the drugs in a class, the tables below list the total score as well as the “percent of maximum” that each drug had across individual components of the total RxScore.

Our RxScore analysis of blood thinner drugs yielded the following:

Table 5: Anticoagulants: RxScores and Percentage of Maximum for Score Components

Drug	RxScore	Outcome	Event Seriousness	Disproportionality	Literature	Reporter Type	Report Priority
warfarin (Coumadin)	67.56	41.08%	51.70%	28.76%	66.33%	51.32%	69.96%
dabigatran (Pradaxa)	67.15	37.85%	58.86%	17.76%	56.37%	73.43%	67.19%
rivaroxaban (Xarelto)	67.08	41.65%	55.67%	20.18%	56.37%	60.76%	91.95%
apixaban (Eliquis)	39.45	33.67%	25.23%	5.51%	56.37%	40.62%	66.60%

Table 6: Antiplatelets: RxScores and Percentage of Maximum for Score Components

Drug	RxScore	Outcome	Event Seriousness	Disproportionality	Literature	Reporter Type	Report Priority
prasugrel (Effient)	81.13	46.41%	72.07%	28.48%	66.33%	79.62%	98.76%
ticagrelor (Brilinta)	68.41	45.35%	53.29%	18.13%	66.33%	62.40%	83.12%
clopidogrel (Plavix)	63.82	49.27%	69.49%	16.90%	36.44%	55.31%	86.08%

Results Summary

RxFilter Analysis:

The top three most reported AEs for the anticoagulants varied, but “gastrointestinal hemorrhage” showed consistency by making the “top three” in three out of the four drugs. When we tallied anticoagulant case counts for “outcome,” we found that: dabigatran had 12% of its “primary suspect” cases listed as “death” compared with 11% for rivaroxaban and 8% for warfarin. “Death” for apixaban, however, was only reported 5% of the time. For “hospitalization,” dabigatran, rivaroxaban, and warfarin showed 39%, 43%, and 50%, respectively, while apixaban only had 21%.

For the antiplatelet drugs, notably, all three had “death” listed as a top 3 reported AE. “Death” was listed in 20% of clopidogrel cases and 11% and 14% of cases for prasugrel and ticagrelor, respectively. Hospitalization percentages were: clopidogrel (43%), prasugrel (51%), and ticagrelor (38%).

Disproportionality

When compared with three other anticoagulants, warfarin had elevated disproportionality results (10.2 to 12.1) for the hemorrhage-related categories, but it showed lower results (0.8 to 1.9) than its’ peers across embolic and thrombotic AE groupings. Both dabigatran and rivaroxaban had hemorrhage-related AEs in the 8.0 range. Apixaban, however, was in the 4.0 range. For embolic and thrombotic AE categories dabigatran and apixaban had similar DA results in the 1.4 – 3.0 range, while rivaroxaban showed higher results of 5.6 and 13.5.

For the antiplatelets, the two hemorrhage-related AE categories were similar across the three drugs, but the embolic and thrombotic groupings showed marked differentiation. For arterial-related events, prasugrel had a 6.7 result while clopidogrel and ticagrelor totaled 3.8 and 4.2, respectively. The unspecified mixed arterial and venous category showed DA results of 3.5 for clopidogrel and 5.9 for ticagrelor. Prasugrel, however, had a 9.5.

RxScore Analysis

Our RxScore analysis showed that warfarin, dabigatran, and rivaroxaban had similar total scores (~67 out of 100). Apixaban had relatively lower sub-scores for “event seriousness” and disproportionality, as well as a much lower total of 39.

For the antiplatelets, clopidogrel (64) and ticagrelor (68) had similar total scores. Prasugrel, however, had elevated “event seriousness” and disproportionality sub-totals and an overall score of 81.

Conclusion

Pre-marketing clinical trials are the established means for determining a drug's safety and efficacy during the approval process, but they are by no means perfect. When a new drug comes to market a more heterogeneous population uses it and, accordingly, real-world side effects begin to appear.

Accordingly, healthcare decision makers need safety tools that reflect a given medication's effects in these real-life populations. We believe that the use of the platforms discussed here meet such needs.

Using the methods outlined here we were able to detail real-world side effect data across the blood thinner class of medications, and particularly *within* the sub-categories of these drugs (anticoagulants and antiplatelets). Our review of post-approval data suggest disproportionately elevated reporting of certain adverse events such as various hemorrhagic, embolic, and thrombotic events linked to the use of blood thinners.

The results from our RxFilter, disproportionality, and RxScore analyses all point to the same general conclusions: 1) apixaban may be a safer choice within the anticoagulant class, and 2) prasugrel may have higher safety risks than the other two medications in its antiplatelet class.

Additionally, these data show specific post-marketing AE results that differ within each of the blood thinner sub-classes, and therefore may be important for healthcare providers, especially for those who prescribe these medications.

These results demonstrate our on-going and ever-evolving pursuit to provide our clients with the most up to date and relevant post-marketing safety information.

Disclaimers

Neither AdverseEvents, nor its officers or employees actively manage any account that holds a direct investment position (long or short) in any of the securities mentioned in this report.

Neither AdverseEvents, nor its officers or employees have been directly compensated by any party for the preparation of this report. AdverseEvents offers its services for sale to enterprise customers, including managed care organizations, financial institutions, pharmaceutical companies, and others.

The inclusion of a particular company, drug, class or indication in this report is determined wholly by our quantitative signaling and scoring systems along with our qualitative analysis work. The inclusion or exclusion of any drug, company, or indication has not and will not be influenced by any third party, including any clients of AdverseEvents.

In general, post-marketing data may be subject to biases such as underreporting, stimulated reporting, and confounding by comorbidities. An adverse event report does not definitively ascertain causality. A specific potential limitation to this analysis relates to the fact that warfarin has been on the market for so long that it is possible that physicians may under-report AEs for the drug because they assume all of its side effects are well-known and properly documented. Both the disproportionality measures and the RxScore method used herein, however, compare specific AEs for a drug with its overall AE reports, and therefore act as an internal control to help minimize such reporting influences.

References

1. Ahmad SR. Adverse drug event monitoring at the Food and Drug Administration. *Journal of general internal medicine*. 2003;18(1):57-60.
2. FDA. Follow-Up to the November 2009 Early Communication about an Ongoing Safety Review of Sibutramine, Marketed as Meridia. 2010. <http://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/DrugSafetyInformationforHeathcareProfessionals/ucm198206.htm>. Accessed February 2014.
3. FDA. Safety Information: Vioxx (rofecoxib). 2002. <http://www.fda.gov/Safety/MedWatch/SafetyInformation/SafetyAlertsforHumanMedicalProducts/ucm154520.htm>. Accessed February 2014.
4. FDA. Reports Received and Reports Entered into AERS by Year. 2012. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070434.htm>. Accessed February 2014.
5. FDA. Adverse Event Reporting System (FAERS) (formerly AERS). 1997. <http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Surveillance/AdverseDrugEffects/ucm070093.htm>. Accessed February 2014.
6. Parvez B, Darbar D. The "missing" link in atrial fibrillation heritability. *Journal of electrocardiology*. 2011;44(6):641-4. doi:10.1016/j.jelectrocard.2011.07.027.
7. Go AS, Hylek EM, Phillips KA, Chang Y, Henault LE, Selby JV et al. Prevalence of diagnosed atrial fibrillation in adults: national implications for rhythm management and stroke prevention: the AnTicoagulation and Risk Factors in Atrial Fibrillation (ATRIA) Study. *JAMA : the journal of the American Medical Association*. 2001;285(18):2370-5.
8. Gattellari M, Goumas C, Aitken R, Worthington JM. Outcomes for patients with ischaemic stroke and atrial fibrillation: the PRISM study (A Program of Research Informing Stroke Management). *Cerebrovascular diseases*. 2011;32(4):370-82. doi:10.1159/000330637.
9. Gomez-Outes A, Terleira-Fernandez AI, Calvo-Rojas G, Suarez-Gea ML, Vargas-Castrillon E. Dabigatran, Rivaroxaban, or Apixaban versus Warfarin in Patients with Nonvalvular Atrial Fibrillation: A Systematic Review and Meta-Analysis of Subgroups. *Thrombosis*. 2013;2013:640723. doi:10.1155/2013/640723.
10. Barker CM, Price MJ. Antiplatelet therapy in acute coronary syndromes. *Current cardiology reports*. 2008;10(4):327-33.
11. Hoffman KB, Overstreet, B.M., Doraiswamy, P.M. A Drug Safety ePlatform for Physicians, Pharmacists and Consumers based on Post-Marketing Adverse Events. *Drugs and Therapy Studies* 2013;3(e4).
12. Bate A, Evans SJ. Quantitative signal detection using spontaneous ADR reporting. *Pharmacoepidemiology and drug safety*. 2009;18(6):427-36. doi:10.1002/pds.1742.

Appendix A – FDA-Approved Indications for each Drug

Anticoagulants

Drug	Approved Indications
apixaban (Eliquis)	<ul style="list-style-type: none"> To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
dabigatran (Pradaxa)	<ul style="list-style-type: none"> To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation.
rivaroxaban (Xarelto)	<ul style="list-style-type: none"> To reduce the risk of stroke and systemic embolism in patients with nonvalvular atrial fibrillation. For the treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE).
warfarin (Coumadin)	<ul style="list-style-type: none"> For the prophylaxis and treatment of venous thrombosis and pulmonary embolism. For the prophylaxis and treatment of thromboembolic complications associated with atrial fibrillation and/or cardiac valve replacement. For the reduction in the risk of death, recurrent myocardial infarction, and thromboembolic events such as stroke or systemic embolization after myocardial infarction.

Antiplatelets

Drug	Approved Indications
clopidogrel (Plavix)	<ul style="list-style-type: none"> For the treatment of acute coronary syndrome in patients with non-ST-segment elevation ACS (unstable angina (UA)/non-ST-elevation myocardial infarction (NSTEMI)) and for patients with ST-elevation myocardial infarction (STEMI). To decrease the rate of cardiovascular death, myocardial infarction (MI), stroke, or refractory ischemia. To treat recent MI, recent stroke, or established peripheral arterial disease.
prasugrel (Effient)	<ul style="list-style-type: none"> For the reduction of thrombotic cardiovascular events (including stent thrombosis) in patients with acute coronary syndrome.
ticagrelor (Brilinta)	<ul style="list-style-type: none"> For the reduction of the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction) In patients treated with PCI, it also reduces the rate of stent thrombosis.

Appendix B – Adverse Event Search Terms Used

In tables 1 & 2, we aggregated MedDRA Preferred Terms into the following larger categories:

Stroke:
MedDRA Preferred Term: Basal ganglia stroke
MedDRA Preferred Term: Brain stem stroke
MedDRA Preferred Term: Cerebrovascular accident
MedDRA Preferred Term: Embolic stroke
MedDRA Preferred Term: Haemorrhagic stroke
MedDRA Preferred Term: Haemorrhagic transformation stroke
MedDRA Preferred Term: Ischaemic stroke
MedDRA Preferred Term: NIH stroke scale abnormal
MedDRA Preferred Term: NIH stroke scale score increased
MedDRA Preferred Term: Post procedural stroke
MedDRA Preferred Term: Stroke in evolution
MedDRA Preferred Term: Thrombotic stroke

Heart Attack
MedDRA Preferred Term: Acute myocardial infarction
MedDRA Preferred Term: Myocardial infarction
MedDRA Preferred Term: Post procedural myocardial infarction
MedDRA Preferred Term: Silent myocardial infarction

In tables 3 & 4, we used the following adverse event categories:

Standardised MedDRA Queries (SMQ)
SMQ: Haemorrhage laboratory terms
SMQ: Haemorrhage terms (excl laboratory terms)
SMQ: Embolic and thrombotic events, arterial
SMQ: Embolic and thrombotic events, venous
SMQ: Embolic and thrombotic events, vessel type unspecified and mixed arterial and venous