

Here we have estimated the downstream costs associated with post-marketing side effects for major anticoagulants by the use of: 1) Adverse Drug Reaction (ADR)-specific costs, 2) ADR case reports from FAERS, and 3) drug usage information.

Background

Pre-approval clinical trials results routinely do not correlate with real-world Adverse Drug Reactions (ADRs) in consumer populations. Therefore, a drug's true safety profile is not known until its marketing phase. Approximately 1,500,000 ADR reports are currently submitted to FDA's Adverse Event Reporting database (FAERS) each year. Substantial costs are associated with these ADRs. Healthcare organizations need improved methods to increase patient safety and lower downstream costs associated with ADRs.

Methods

FAERS was used to collect ADR data for each drug. Evaluate Pharma provided drug usage data. ICD-9 codes were mapped to serious MedDRA preferred terms (PTs). Individual PTs and patient outcomes were assigned costs based on AHRQ data. Non-serious terms and disease-related ADRs were ignored. Either the most costly "primary suspect" ADR or outcome cost was assigned to all eligible case reports for all drugs. Individual report costs were summed for each drug and then divided by exposure rates to obtain downstream costs per Rx. We mined the boxed warning, warnings, precautions, and adverse reactions sections of all prescription drug labels for AE terms. If an AE term is found in one or more of these sections of a given drug's label then it is considered "on-label."

Downstream costs

Drug Name	Total Costs (2010-2014)	Total Patients (2010-2014)	Downstream Costs Per Rx	N
dabigatran	\$319,469,822	5,013,910	\$22.00	23,143
rivaroxaban	\$153,358,800	1,685,640	\$13.38	10,623
apixaban	\$18,635,190	757,844	\$10.00	1,559
warfarin	\$48,979,352	16,702,728	\$2.33	3,603

Conclusions

ADRs are responsible for a huge cost burden for the healthcare industry. The method detailed here assigned AHRQ-derived cost data to post-market ADR case reports in order to calculate downstream costs of side effects and poor patient outcomes.

By quantifying the post-approval phase into downstream medical costs, the system can serve as a needed window into the real world profile of various anticoagulants.

Top 3 Costliest AEs

Drug Name	Primary Suspect Cases	Top 3 Costliest AEs			
		AE	N	Total Cost	%
apixaban	2,568	Haemorrhage	145	\$2,313,765	12.42%
		Cerebrovascular accident	95	\$1,411,510	7.57%
		Gastrointestinal haemorrhage	136	\$1,204,416	6.46%
dabigatran	32,101	Gastrointestinal haemorrhage	3,449	\$30,544,344	9.56%
		Haemorrhage	1,708	\$27,254,556	8.53%
		Cerebral haemorrhage	603	\$12,827,619	4.02%
rivaroxaban	14,018	Haemorrhage	635	\$10,132,695	6.61%
		Cerebral haemorrhage	373	\$7,934,829	5.17%
		Gastrointestinal haemorrhage	718	\$6,358,608	4.15%
warfarin	8,671	Haemorrhage	374	\$5,967,918	12.18%
		Subdural haematoma	112	\$2,087,344	4.26%
		Cerebral haemorrhage	91	\$1,935,843	3.95%

Non-labeled AEs that were reported more than expected are presented below. Reporting Odds Ratios (RORs) above 2.0 are highlighted. DME = Designated Medical Event (by FDA).

dabigatran

Adverse Event	ROR (CI)	Cases	RxSignal	DME?
Acute hepatic failure	0.83 (0.53 - 1.28)	20		✓
Acute respiratory failure	2.60 (2.06 - 3.29)	73	Active	✓
Cardiac failure acute	2.13 (1.33 - 3.40)	18	Active	
Colitis ischaemic	3.32 (2.46 - 4.48)	44	Active	✓
Colon cancer	3.89 (3.21 - 4.72)	108	Active	
Drug-induced liver injury	0.38 (0.19 - 0.76)	8		
Hepatitis acute	1.07 (0.63 - 1.80)	14	Watchlist	✓
Intestinal infarction	6.27 (3.78 - 10.4)	16	Active	✓
Oesophageal carcinoma	3.02 (2.03 - 4.50)	25	Active	
Renal failure	1.87 (1.70 - 2.04)	479	Watchlist	✓
Renal failure acute	2.90 (2.69 - 3.12)	752	Active	✓
Renal impairment	2.73 (2.45 - 3.04)	344	Active	✓
Sudden death	2.11 (1.62 - 2.75)	56	Active	✓

rivaroxaban

Adverse Event	ROR (CI)	Cases	RxSignal	DME?
Acute hepatic failure	1.62 (1.00 - 2.61)	17	Watchlist	✓
Acute respiratory failure	1.29 (0.79 - 2.10)	16	Watchlist	✓
Cardiac failure acute	2.15 (1.07 - 4.32)	8	Active	
Colitis ischaemic	1.18 (0.56 - 2.48)	7	Watchlist	✓
Colon cancer	1.12 (0.66 - 1.89)	14	Watchlist	
Drug-induced liver injury	4.14 (2.99 - 5.74)	37	Active	
Hepatitis acute	2.28 (1.32 - 3.94)	13	Active	✓
Intestinal infarction	4.31 (1.78 - 10.45)	5	Active	✓
Oesophageal carcinoma	1.63 (0.73 - 3.64)	6	Watchlist	
Renal failure	1.22 (1.03 - 1.45)	139	Watchlist	✓
Renal failure acute	1.43 (1.23 - 1.67)	167	Watchlist	✓
Renal impairment	3.03 (2.60 - 3.53)	168	Active	✓
Sudden death	2.06 (1.38 - 3.08)	24	Active	✓