

Comparative outcomes of treatment initiation with brand versus generic warfarin: a Medicare cohort study

Desai RJ¹, Gopalakrishnan C¹, Dejene SZ¹, Sarpatwari AS¹, Levin R¹, Dutcher SK², Wang Z³, Wittayanukorn S³, Franklin JM¹, Gagne JJ¹
¹Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School, Boston, MA

²Office of Surveillance and Epidemiology, Center of Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

³Office of Research and Standards, Office of Generic Drugs, Center of Drug Evaluation and Research, Food and Drug Administration, Silver Spring, MD

Background and Objective

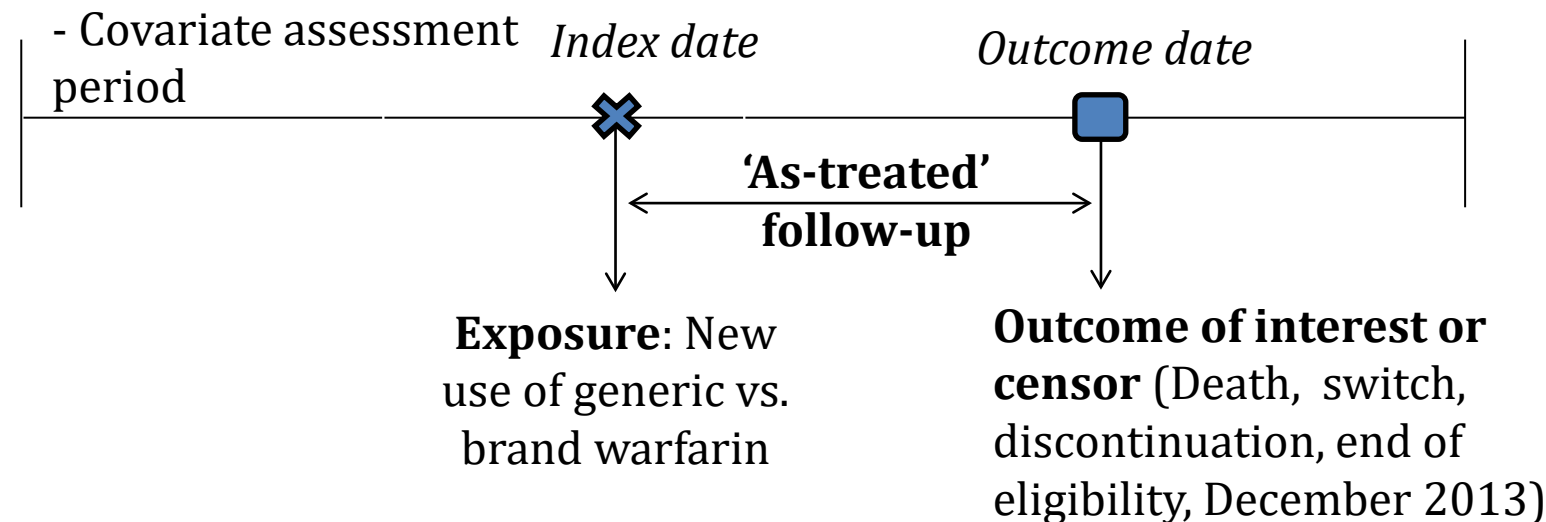
- Warfarin is a narrow therapeutic index (NTI) drug. The anticoagulant response to warfarin is exaggerated with advancing age, which might make the elderly more or less susceptible to adverse outcomes even with non-significant differences in bioavailability of the generic products compared to the brand according to the bioequivalence (BE) standard specific for warfarin.
- Therefore, the primary objective of this study was to compare effectiveness, safety, and mortality between brand and generic warfarin initiation in elderly patients.

Methods

Design: New user cohort study design

Data source: Medicare claims 2007-2013 linked with EHRs from two large Boston hospitals and American Community Survey data from the US Census Bureau

- 183 day baseline period
- Continuous enrollment required
- No use of drug allowed
- Covariate assessment



Endpoints

- Composite effectiveness outcome: Hospitalization for ischemic stroke, systemic embolism, pulmonary embolism, deep vein thrombosis
- Composite safety outcome: Hospitalization for major hemorrhage
- All-cause one-year mortality outcome

Confounding adjustment

- Propensity score (PS) fine-stratification weighting was used to account for 109 confounding variables derived from Medicare claims (demographics, indications, comorbid conditions, co-medications), EHRs (smoking, obesity, kidney function), and Census data (socioeconomic status).

Study cohort

Warfarin users in 2007-2013 with linked Medicare and EHR data
n=66,230

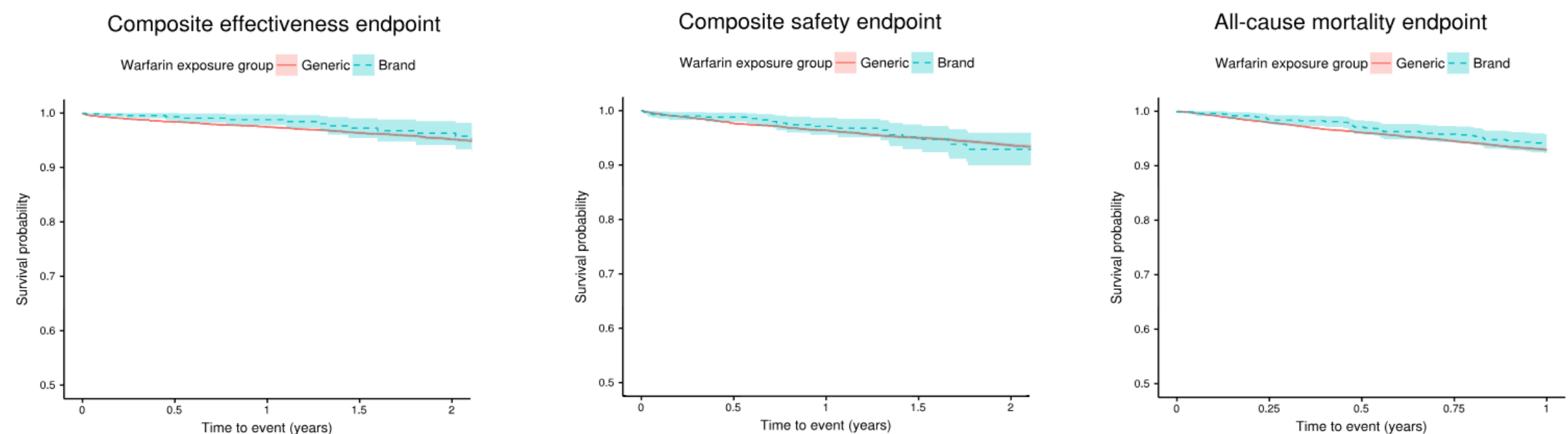
Enrolled in 6 month prior to the index date in fee-for-service Medicare parts A,B, and D
n= 52,513

New users of warfarin, age 65+ and sex-recorded
n=33,645
(755 brand, 32,890 generic warfarin)

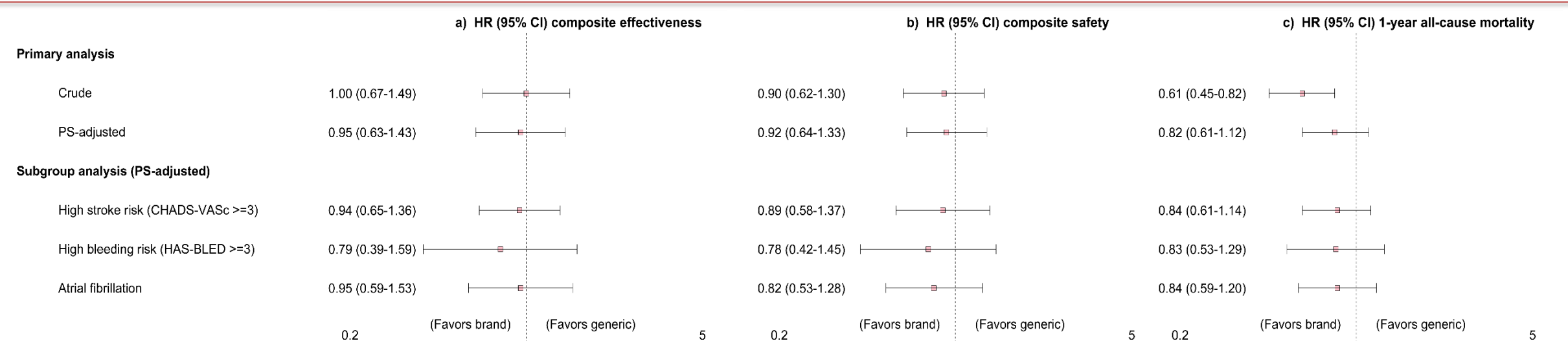
	Unadjusted			Propensity score adjusted		
	Brand initiators (n=755)	Generic initiators (n=32,980)	Std Diff	Brand initiators (n=753)	Generic initiators (n=32,656)	Std Diff
Age (Mean (SD))	77 (6.9)	77 (7.3)	4.1	77 (6.9)	77 (7)	0.4
White race (n (%))	726 (96.2)	30791 (93.6)	11.6	724 (96.1)	31383 (96.1)	0.2
Male gender (n (%))	363 (48.1)	14216 (43.2)	9.8	361 (47.9)	15712 (48.1)	-0.3
Indications for anticoagulation (n (%))						
Atrial fibrillation	553 (73.2)	18783 (57.1)	34.4	552 (73.3)	24100 (73.8)	-1.1
Valve disorders	155 (20.5)	4910 (14.9)	14.7	154 (20.5)	6756 (20.7)	-0.6
Deep vein thrombosis	93 (12.3)	6350 (19.3)	-19.2	93 (12.4)	4059 (12.4)	-0.2
Pulmonary embolism	49 (6.5)	3399 (10.3)	-13.9	49 (6.5)	2148 (6.6)	-0.3
Comorbid conditions and lifestyle factors (n (%))						
Acute myocardial infarction	34 (4.5)	2595 (7.9)	-14.1	34 (4.5)	1486 (4.6)	-0.2
Ischemic stroke/TIA	107 (14.2)	4529 (13.8)	1.2	107 (14.2)	4578 (14)	0.5
Chronic heart failure	187 (24.8)	9781 (29.7)	-11.2	187 (24.8)	8179 (25)	-0.5
Diabetes	222 (29.4)	10032 (30.5)	-2.4	222 (29.5)	9591 (29.4)	0.2
Acute renal disease	36 (4.8)	3658 (11.1)	-23.7	36 (4.8)	1626 (5)	-0.9
Chronic renal disease	105 (13.9)	6027 (18.3)	-12	105 (13.9)	4558 (14)	0
Obesity	59 (7.8)	4742 (14.4)	-21.1	59 (7.8)	2550 (7.8)	0.1
SES index (Mean (SD))	59 (4.3)	58 (5.5)	7	59 (4.4)	59 (5.1)	-0.1

Abbreviations: SD- standard deviation, SES- socioeconomic status, Std diff- standardized difference, TIA- transient ischemic attack

Adjusted survival plots



Hazard ratios for the primary and subgroup analyses



Conclusion

After controlling for confounding, we did not observe any significant differences in clinical outcomes between generic and brand warfarin, even among high risk subgroups defined based on indication, stroke risk, or bleeding risk. These results provide reassurance regarding the long-term clinical outcomes of generic products for a widely used NTI drug in a population that may be susceptible to adverse outcomes even with non-significant differences in bioavailability between brand and generic products according to the BE standard.