

Appendix: Comparative Risk of Gastrointestinal Bleeding with Dabigatran, Rivaroxaban and Warfarin

Table A1. ICD9-CM code used to define study outcomes

Primary Outcome	ICD-9-CM codes
Gastrointestinal (GI) bleeding	455.2, 455.5, 455.8, 456.0, 456.20, 530.7, 530.82, 531.0-531.6, 532.0-532.6, 533.0-533.6, 534.0-534.6, 535.01-535.61, 537.83, 562.02, 562.03, 562.12, 562.13, 568.81, 569.3, 569.85, 578.0, 578.1, and 578.9(1)
Secondary Outcome (appendix)	ICD-9-CM codes
Stroke	433.x1, 434.x1, or 436 in any hospital discharge diagnosis position without a primary discharge diagnosis of rehabilitation (<i>ICD-9-CM</i> code V57) or any additional diagnoses of subarachnoid hemorrhage (<i>ICD-9-CM</i> code 430), intracerebral hemorrhage (<i>ICD-9-CM</i> code 431), or trauma (<i>ICD-9-CM</i> codes 800-804 and 850-854).(2, 3)

Table A2. Pharmacological Factors Assessed in the Model: Inducers and Inhibitors of Warfarin

Inducers and Inhibitors of Warfarin	Specifics	
Inhibitors of Warfarin	CYP2C9 inhibitors	amiodarone, capecitabine, cotrimoxazole, etravirine, fluconazole, fluvastatin, fluvoxamine, metronidazole, miconazole, oxandrolone, sulfipyrazone, tigecycline, voriconazole, zafirlukast
	CYP1A2 inhibitors	acyclovir, allopurinol, caffeine, cimetidine, ciprofloxacin, disulfiram, enoxacin, famotidine, fluvoxamine, methoxsalen, mexiletine, norfloxacin, oral contraceptives, phenylpropanolamine, propafenone, propranolol, terbinafine, thiabendazole, ticlopidine, verapamil, zileuton
	CYP3A4 inhibitors	alprazolam, amiodarone, amlodipine, amprenavir, aprepitant, atorvastatin, atazanavir, bicalutamide, cilostazol, cimetidine, ciprofloxacin, clarithromycin, conivaptan, cyclosporine, darunavir/ritonavir, diltiazem, erythromycin, fluconazole, fluoxetine, fluvoxamine, fosamprenavir, imatinib, indinavir, isoniazid, itraconazole, ketoconazole, lopinavir/ritonavir, nefazodone, nelfinavir, nilotinib, oral contraceptives, posaconazole, ranitidine, ranolazine, ritonavir, saquinavir, telithromycin, tipranavir, voriconazole, zileuton
Inducers of Warfarin	CYP2C9 inducers	aprepitant, bosentan, carbamazepine, phenobarbital, rifampin
	CYP1A2 inducers	montelukast, moricizine, omeprazole, phenobarbital, phenytoin
	CYP3A4 inducers	armodafinil, amprenavir, aprepitant, bosentan, carbamazepine, efavirenz, etravirine, modafinil, nafcillin, phenytoin, pioglitazone, prednisone, rifampin, rufinamide

Table A3. ‘Intent to Treat’ Events and Adjusted Hazards of GI Bleeding Events (Censoring on End of Enrollment)

	Events per 100 Patient-Yrs.		Dabigatran vs Warfarin Bleeding	Events per 100 Patient-Yrs.		Rivaroxaban vs Warfarin Bleeding
Atrial Fibrillation	Dabigatran	Warfarin	Hazard Ratio* (95% CI)	Rivaroxaban	Warfarin	Hazard Ratio* (95% CI)
Total Bleeding Events	1.21 (1.03, 1.43)	1.75 (1.52, 2.02)	0.75 (0.60, 0.94)•	2.45 (2.02, 2.96)	2.76 (2.32, 3.29)	0.94 (0.72, 1.23)
Upper GI Bleeding Events	0.75 (0.60, 0.92)	1.11 (0.93, 1.33)	0.71 (0.55, 0.94)•	1.57(1.24, 1.99)	1.60 (1.27, 2.02)	1.02 (0.73, 1.44)
Lower GI Bleeding Events	0.47 (0.36, 0.61)	0.64 (0.51, 0.81)	0.84 (0.58, 1.22)	0.88 (0.64, 1.21)	1.16 (0.88, 1.52)	0.82 (0.53, 1.27)
Non-Atrial Fibrillation						
Total Bleeding Events	1.57 (0.96, 2.55)	1.65 (1.04, 2.62)	1.02 (0.51, 2.04)	0.74 (0.59, 0.94)	1.21 (1.01, 1.44)	0.64 (0.47, 0.86)
Upper GI Bleeding Events	1.08 (0.60, 1.94)	1.19 (0.69, 2.05)	1.02 (0.44, 2.35)	0.48 (0.36, 0.64)	0.74 (0.59, 0.93)	0.68 (0.46, 1.00)
Lower GI Bleeding Events	0.49 (0.20, 1.18)	0.46 (0.19, 1.10)	1.01 (0.29, 3.50)	0.26(0.18, 0.36)	0.47 (0.36, 0.63)	0.58 (0.34, 0.97)•

*Hazard Ratio Adjusted for those covariates significant at the <0.05 level.

•Significant at the <0.05 level

Table A4. Events and Adjusted Hazards of Stroke Events

	Events per 100 Patient-Yrs. (95% CI)		Dabigatran vs Warfarin Stroke	Events per 100 Patient-Yrs. (95% CI)		Rivaroxaban vs Warfarin Stroke
Atrial Fibrillation	Dabigatran	Warfarin	Hazard Ratio* (95% CI)	Rivaroxaban	Warfarin	Hazard Ratio* (95% CI)
Total Stroke Events	0.74 (0.53, 1.05)	0.72 (0.51, 1.01)	1.03 (0.63, 1.68)	0.64 (0.41, 1.00)	0.67 (0.44, 1.05)	0.95 (0.51, 1.79)

*Hazard Ratio Adjusted for those covariates significant at the <0.05 level.

Figure A1. Standardized Differences for Baseline Covariates Comparing Dabigatran to Warfarin among AF Cohort (Pre-Match and Post-Match Sample)

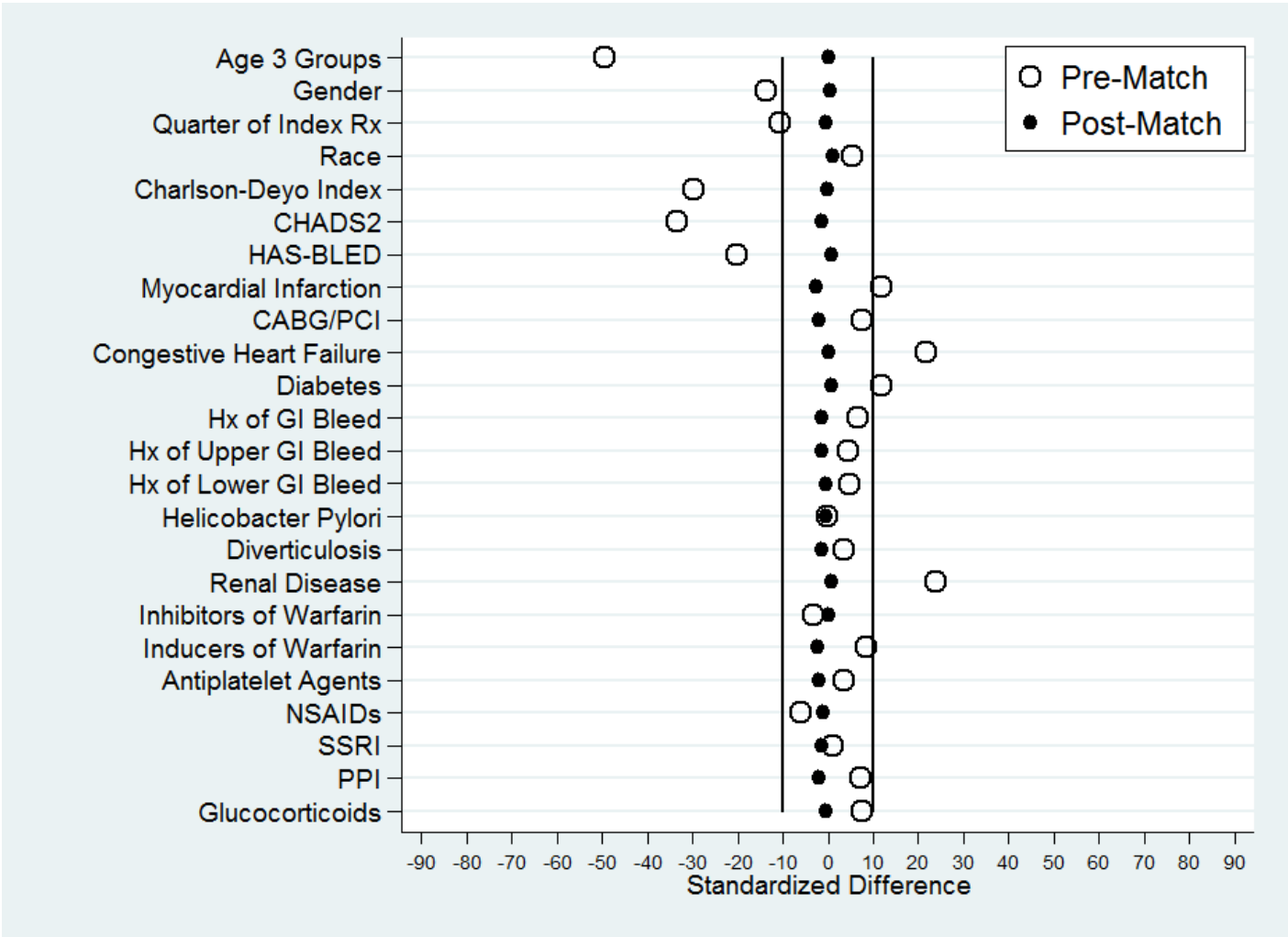


Figure A2. Standardized Differences for Baseline Covariates Comparing Dabigatran to Warfarin among Non-AF Cohort (Pre-Match and Post-Match Sample)

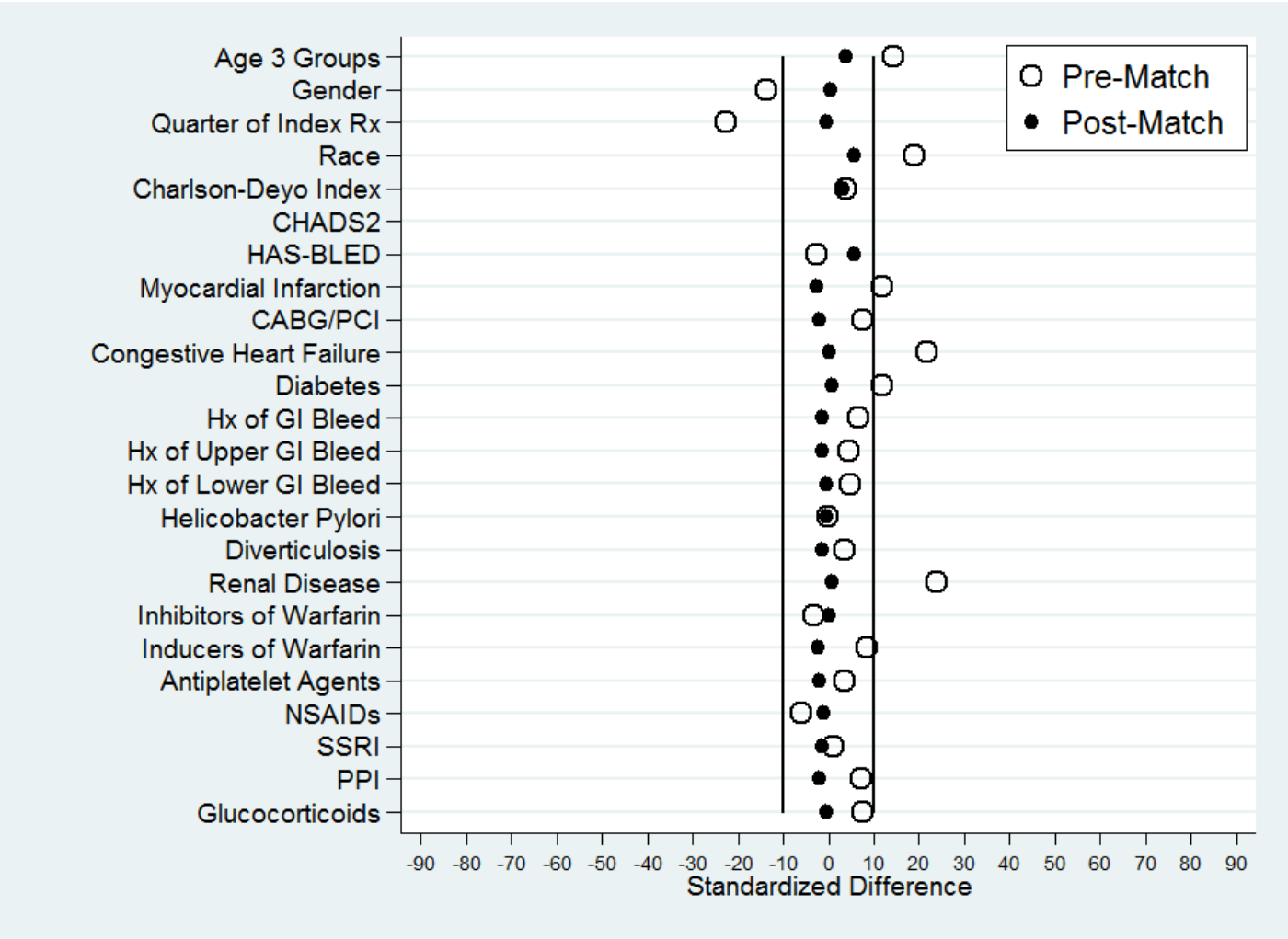


Figure A3. Standardized Differences for Baseline Covariates Comparing Rivaroxaban to Warfarin among AF Cohort (Pre-Match and Post-Match Sample)

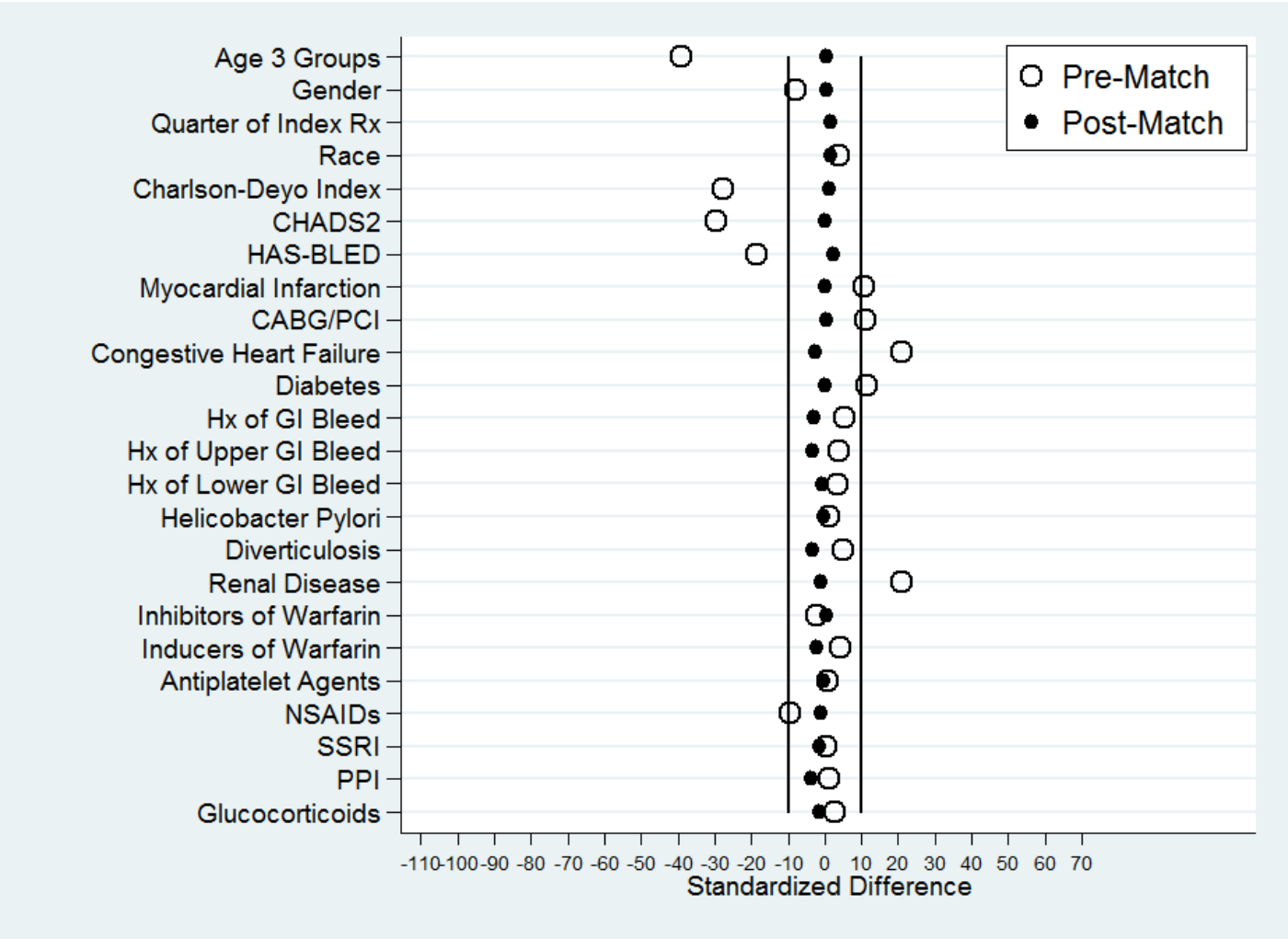


Figure A4. Standardized Differences for Baseline Covariates Comparing Rivaroxaban to Warfarin among Non-AF Cohort (Pre-Match and Post-Match Sample)

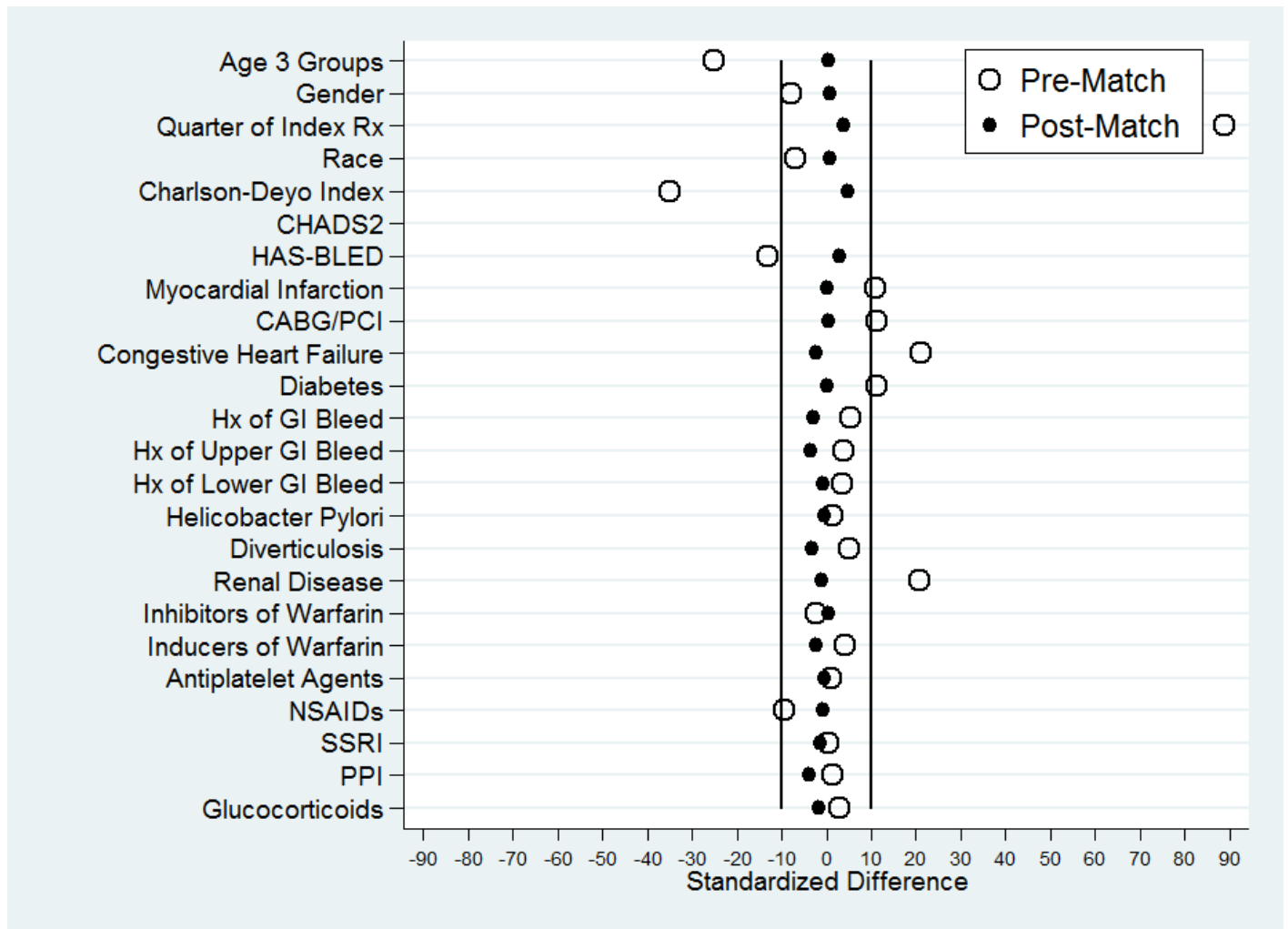


Figure A5. Dabigatran vs. Warfarin Non-AF Patients: Treatment Effect by Age

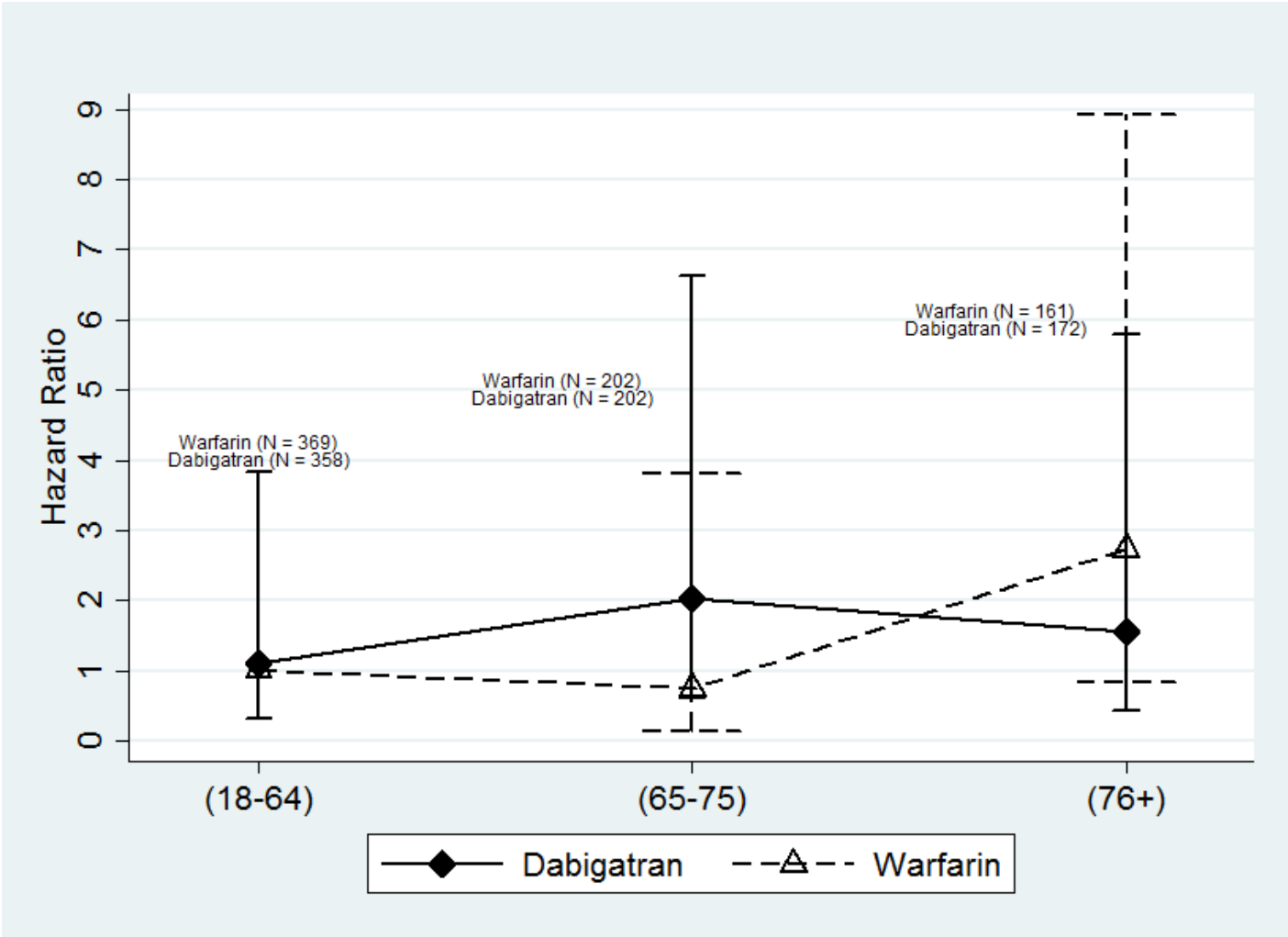
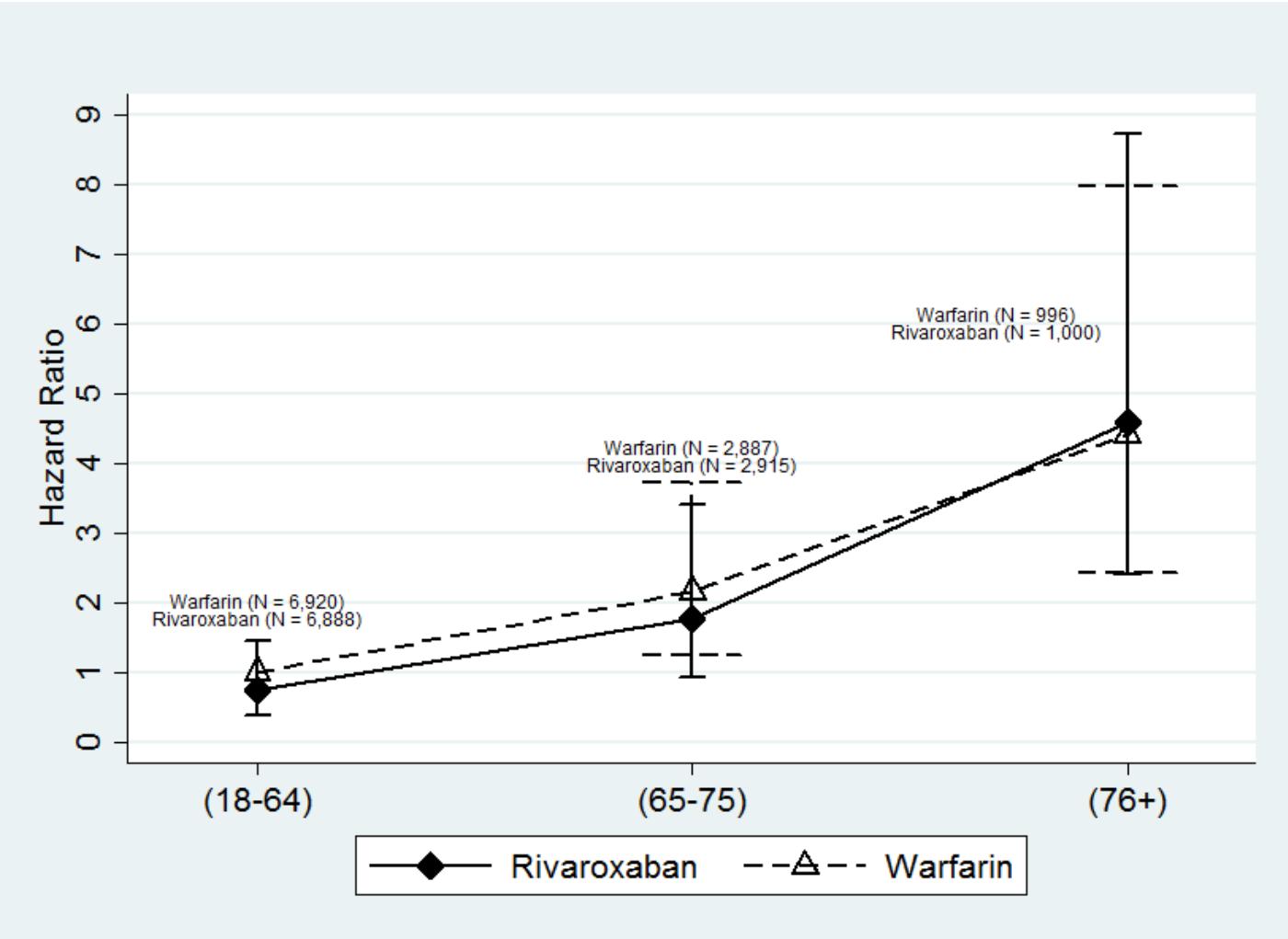


Figure A6. Rivaroxaban vs. Warfarin Non-AF Patients: Treatment Effect by Age



Figures A7-A10 represent unadjusted incident GIB rates per 100 Patient Years by Age Group

Figure A7. Histogram GI Bleed Events: AF Dabigatran vs Warfarin

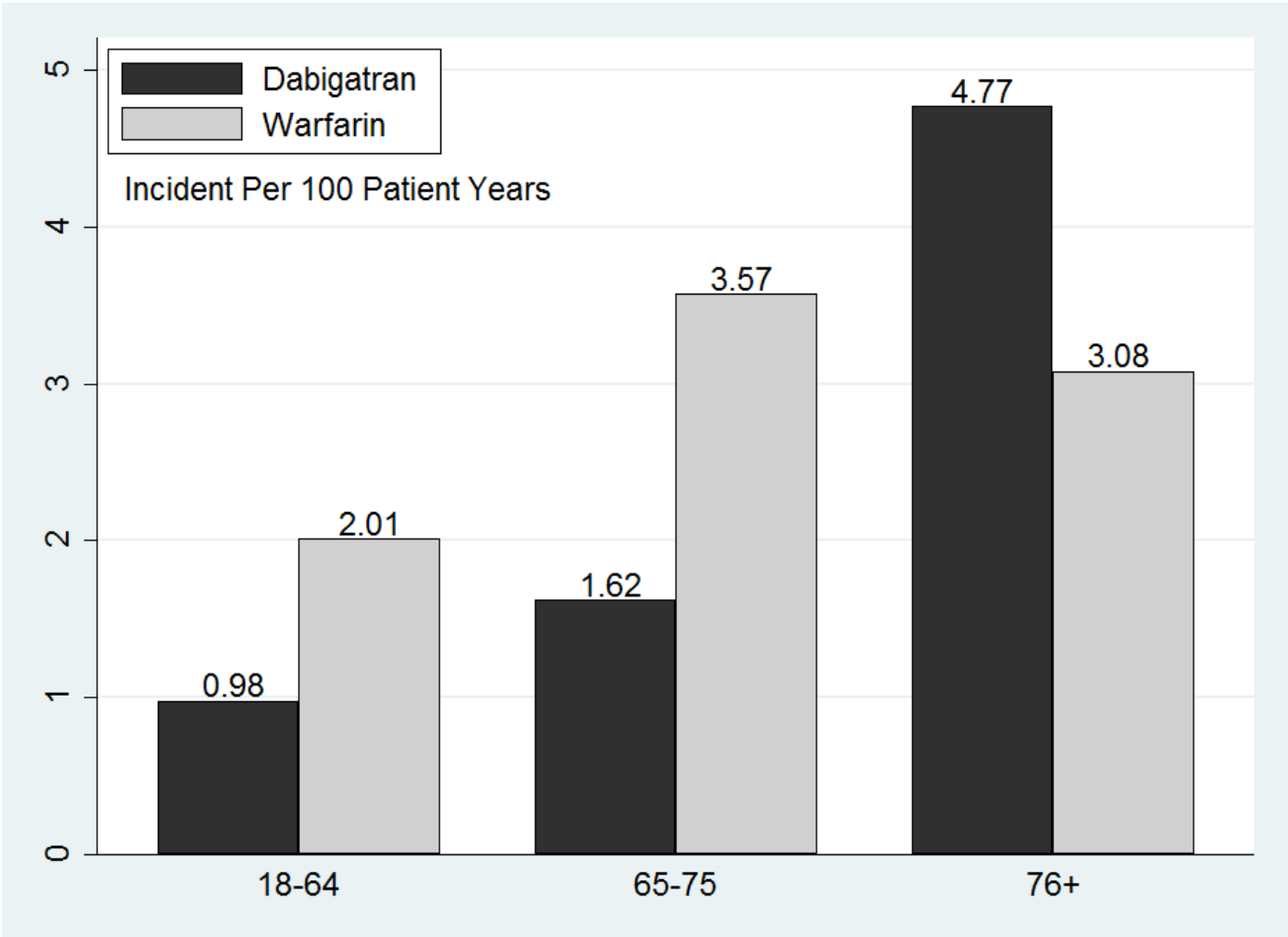


Figure A8. Histogram GI Bleed Events: Non-AF Dabigatran vs Warfarin

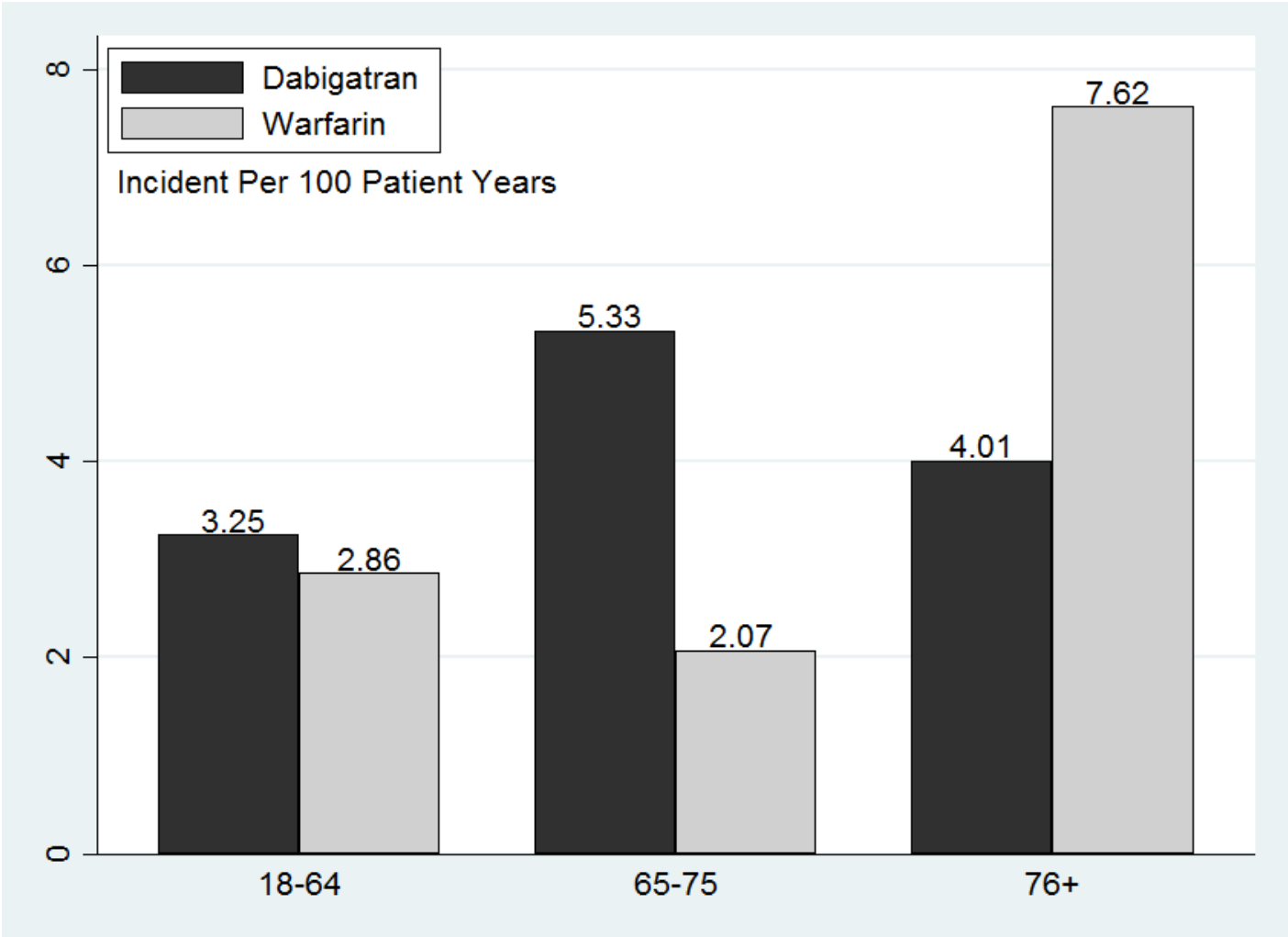


Figure A9. Histogram GI Bleed Events: AF Rivaroxaban vs Warfarin

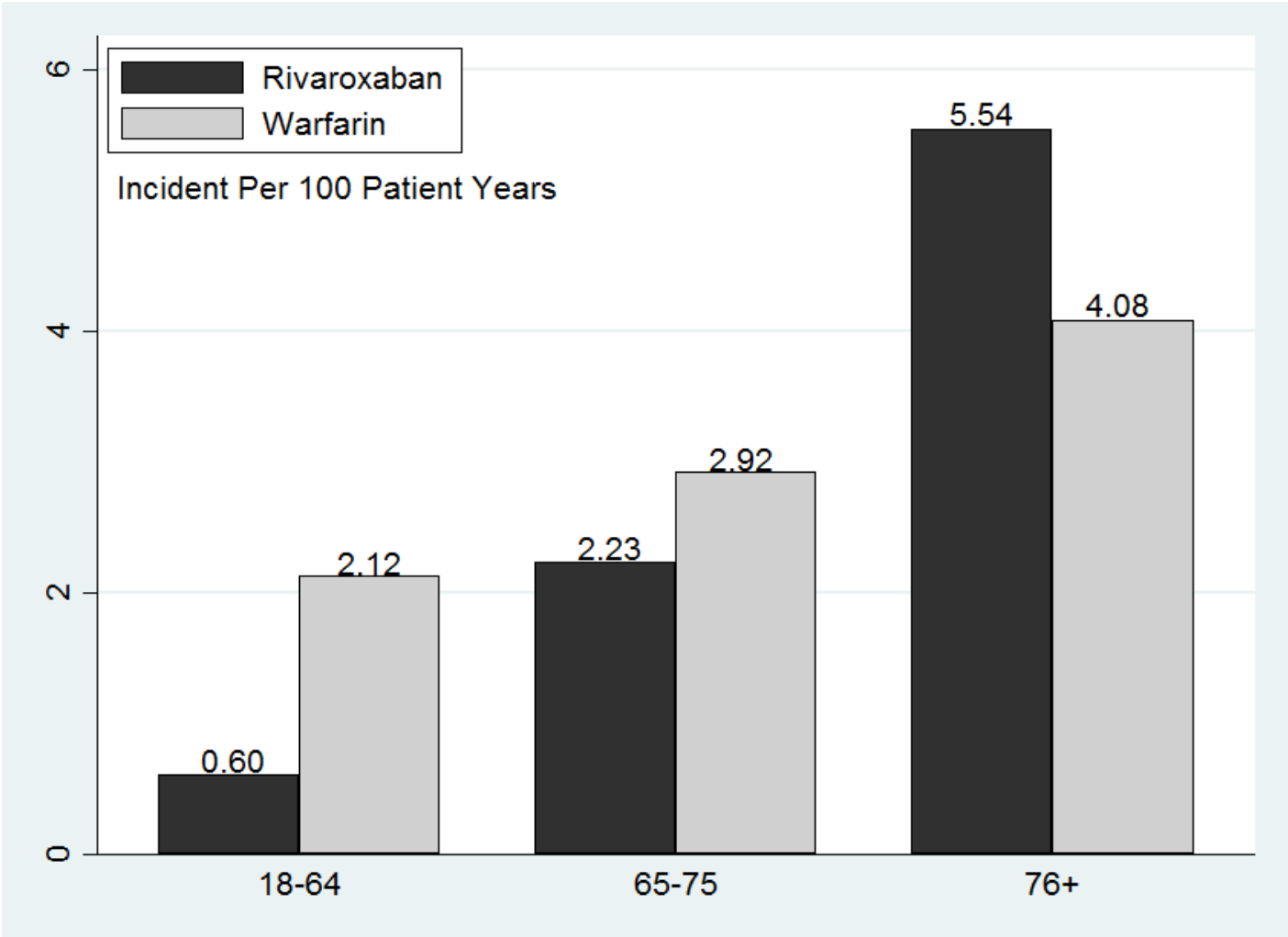
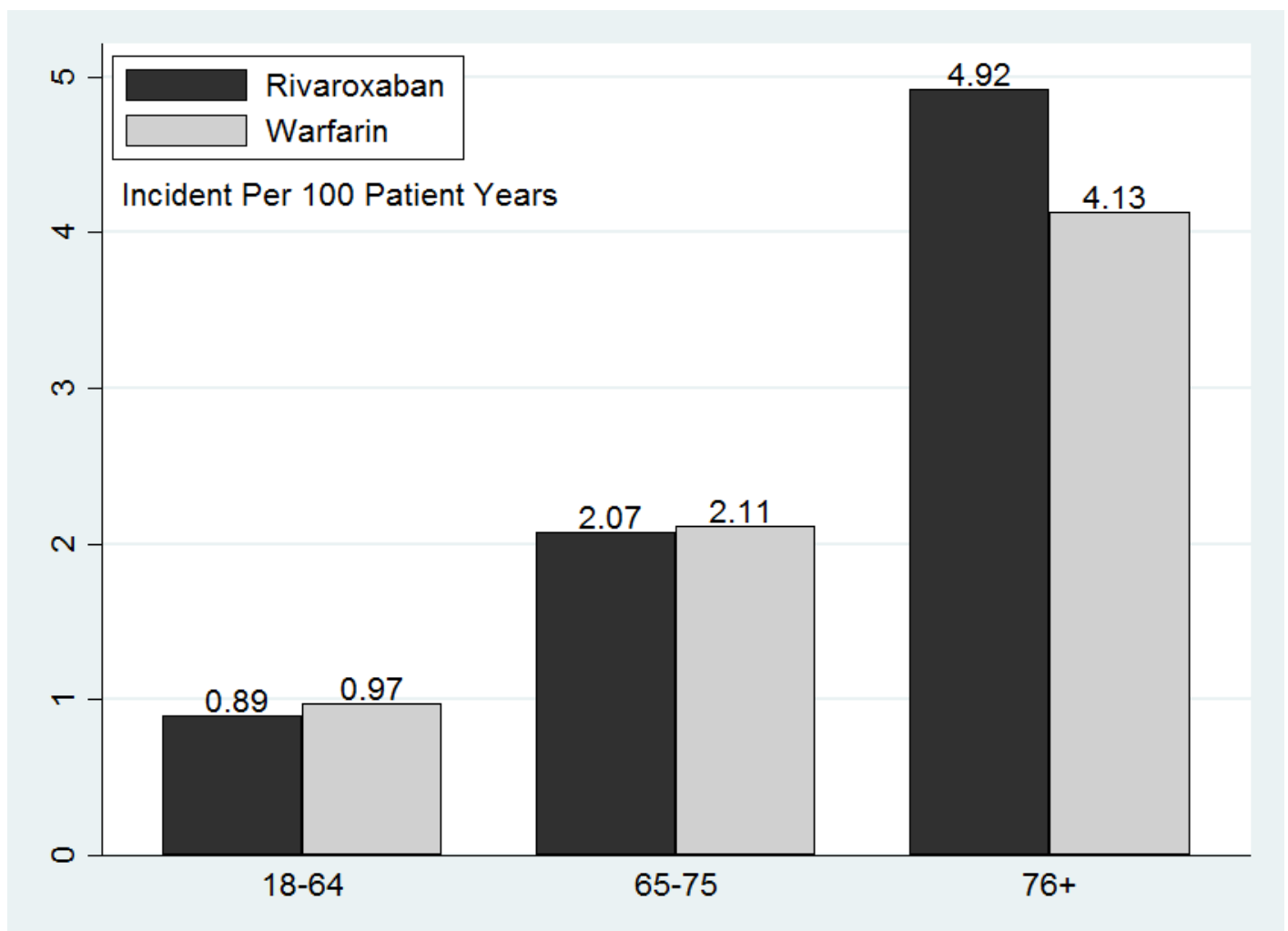


Figure A10. Histogram GI Bleed Events: Non-AF Rivaroxaban vs Warfarin



1. Mini-Sentinel Medical Product Assessment: A Protocol For Assessment of Dabigatran. 2014 [updated March 18, 2014]; Available from: http://www.mini-sentinel.org/work_products/Assessments/Mini-Sentinel_Protocol-for-Assessment-of-Dabigatran.pdf.
2. Gialdini G, Nearing K, Bhavé PD, Bonuccelli U, Iadecola C, Healey JS, et al. Perioperative atrial fibrillation and the long-term risk of ischemic stroke. *Jama*. [Research Support, N.I.H., Extramural Research Support, Non-U.S. Gov't]. 2014 Aug 13;312(6):616-22.
3. Tirschwell DL, Longstreth WT, Jr. Validating administrative data in stroke research. *Stroke*. [Comparative Study Research Support, Non-U.S. Gov't Research Support, U.S. Gov't, P.H.S. Validation Studies]. 2002 Oct;33(10):2465-70.