

Supplementary Online Content

Schaefer JK, Li Y, Gu X, et al. Association of adding aspirin to warfarin therapy without an apparent indication with bleeding and other adverse events. *JAMA Intern Med*. Published online March 4, 2019. doi:10.1001/jamainternmed.2018.7816

eMethods. Supplemental Methods

eTable 1. Sensitivity Analysis Limiting Cohort to Patients Continuously on ASA or Not on ASA Throughout Follow-up

eTable 2. Sensitivity Analysis Limiting Cohort to Patients Without a History of CAD, CABG, PAD, or PCI, with ASA Use Defined at Enrollment

eTable 3. Sensitivity Analysis Limiting Cohort to Patients With Data on ACS/MI

eTable 4. Outcomes of Unmatched Patient Cohorts

eFigure 1. Study Schema

eFigure 2. Standardized Difference Plot

eFigure 3. Percent of Patients Without Recent Myocardial Infarction or Valve Replacement on Aspirin and Warfarin by Year

eFigure 4. Cumulative Incidence of Any Bleeding Over Time by Treatment

eFigure 5. Cumulative Incidence of ER Visits for Bleeding Over Time by Treatment

eMethods. Supplemental Methods

The Michigan Anticoagulation Quality Improvement Initiative (MAQI²) uses an online data collection tool with over 150 pre-defined data elements and a robust data dictionary. All data abstractors undergo training by the coordinating center and are regularly audited for accuracy and completeness. A new data form is completed for each interaction with the anticoagulation clinic (initial enrollment and every INR follow up or other interaction). The data form is designed to capture patients' latest co-morbidities and medications (including over-the-counter), as well as all bleeding and thrombotic adverse events. In particular, aspirin use is captured at a high rate as it is routine for anticoagulation clinic providers to assess for medications (e.g. aspirin) that may impact bleeding or stroke risk for warfarin-treated patients. These are documented in the anticoagulation clinic encounters from which much of the MAQI² data is manually abstracted.

The MAQI² Coordinating Center performs twice yearly audits at each participating site in which a random sample of patients is reviewed to ensure information in the MAQI² database matches information in site EMRs. Information verified at audits includes medications, co-morbidities, and adverse events.

eTable 1. Sensitivity Analysis Limiting Cohort to Patients Continuously on ASA or Not on ASA Throughout Follow-Up

	Warfarin+ASA N = 1273	Warfarin N = 1273	p-value
	Cumulative incidence at 1 year (95% confidence interval)	Cumulative incidence at 1 year (95% confidence interval)	
Thrombosis	0.020 (0.012 - 0.031)	0.022 (0.014 - 0.033)	0.52
Any bleeding	0.255 (0.228 - 0.284)	0.188 (0.166 - 0.212)	0.002
Major bleeding	0.060 (0.046 - 0.077)	0.031 (0.021 - 0.043)	0.002
ER for bleeding	0.132 (0.112 - 0.155)	0.091 (0.075 - 0.110)	0.005
AD for bleeding	0.084 (0.067 - 0.103)	0.047 (0.036 - 0.062)	0.001
Death (any cause)	0.047 (0.034 - 0.063)	0.041 (0.030 - 0.056)	0.51

In this sensitivity analysis, any patient who had a change in ASA status (e.g. started ASA part way through follow up) was excluded. Abbreviations: AD, hospital admission; ASA, acetylsalicylic acid or aspirin; ER, emergency room.

eTable 2. Sensitivity Analysis Limiting Cohort to Patients Without a History of CAD, CABG, PAD, or PCI, with ASA Use Defined at Enrollment

	Warfarin+ASA N = 990	Warfarin N = 990	p-value
	Cumulative incidence at 1 year (95% confidence interval)	Cumulative incidence at 1 year (95% confidence interval)	
Thrombosis	0.021 (0.012 - 0.034)	0.024 (0.015 - 0.036)	0.53
Any bleeding	0.248 (0.217 - 0.279)	0.169 (0.144 - 0.195)	<0.001
Major bleeding	0.052 (0.038 - 0.071)	0.022 (0.013 - 0.035)	0.002
ER for bleeding	0.121 (0.099 - 0.145)	0.078 (0.060 - 0.098)	0.002
AD for bleeding	0.077 (0.059 - 0.097)	0.032 (0.021 - 0.046)	<0.001
Death (any cause)	0.035 (0.022 - 0.051)	0.032 (0.020 - 0.048)	0.69

This sensitivity analysis used broader exclusion criteria. Any patient with a history of CAD, CABG, PAD, or PCI was excluded from analysis in order to generate a highly conservative cohort of patients with inappropriate ASA use. Abbreviations: AD, hospital admission; ASA, acetylsalicylic acid or aspirin; CABG, coronary artery bypass graft; CAD, coronary artery disease; ER, emergency room; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; VR, valve replacement

eTable 3. Sensitivity Analysis Limiting Cohort to Patients With Data On ACS/MI

	Warfarin+ASA N = 1406	No ASA N = 1406	p-value
	Cumulative incidence at 1 year (95% confidence interval)	Cumulative incidence at 1 year (95% confidence interval)	
Thrombosis	0.024 (0.016 - 0.034)	0.028 (0.019 - 0.038)	0.55
Any bleeding	0.255 (0.230 - 0.280)	0.201 (0.179 - 0.225)	0.003
Major bleeding	0.057 (0.045 - 0.072)	0.031 (0.022 - 0.043)	<0.001
ER for bleeding	0.128 (0.109 - 0.148)	0.092 (0.076 - 0.110)	0.002
ER for thrombosis	0.016 (0.010 - 0.025)	0.017 (0.011 - 0.026)	0.77
ER for ACS/MI	0.013 (0.007 - 0.020)	0.006 (0.003 - 0.013)	0.056
AD for bleeding	0.081 (0.066 - 0.098)	0.048 (0.037 - 0.061)	0.001
AD for thrombosis	0.022 (0.014 - 0.032)	0.020 (0.013 - 0.030)	0.85
AD for ACS/MI	0.013 (0.008 - 0.020)	0.006 (0.003 - 0.013)	0.056
Death (any cause)	0.038 (0.028 - 0.051)	0.037 (0.027 - 0.050)	0.766

In this sensitivity analysis, we only analyzed data for the time period where ACS and MI events were captured in the registry (January 2010-November 2015). Abbreviations: ACS, Acute coronary syndrome; AD, hospital admission; ASA, acetylsalicylic acid or aspirin; CABG, coronary artery bypass graft; CAD, coronary artery disease; ER, emergency room; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; VR, valve replacement.

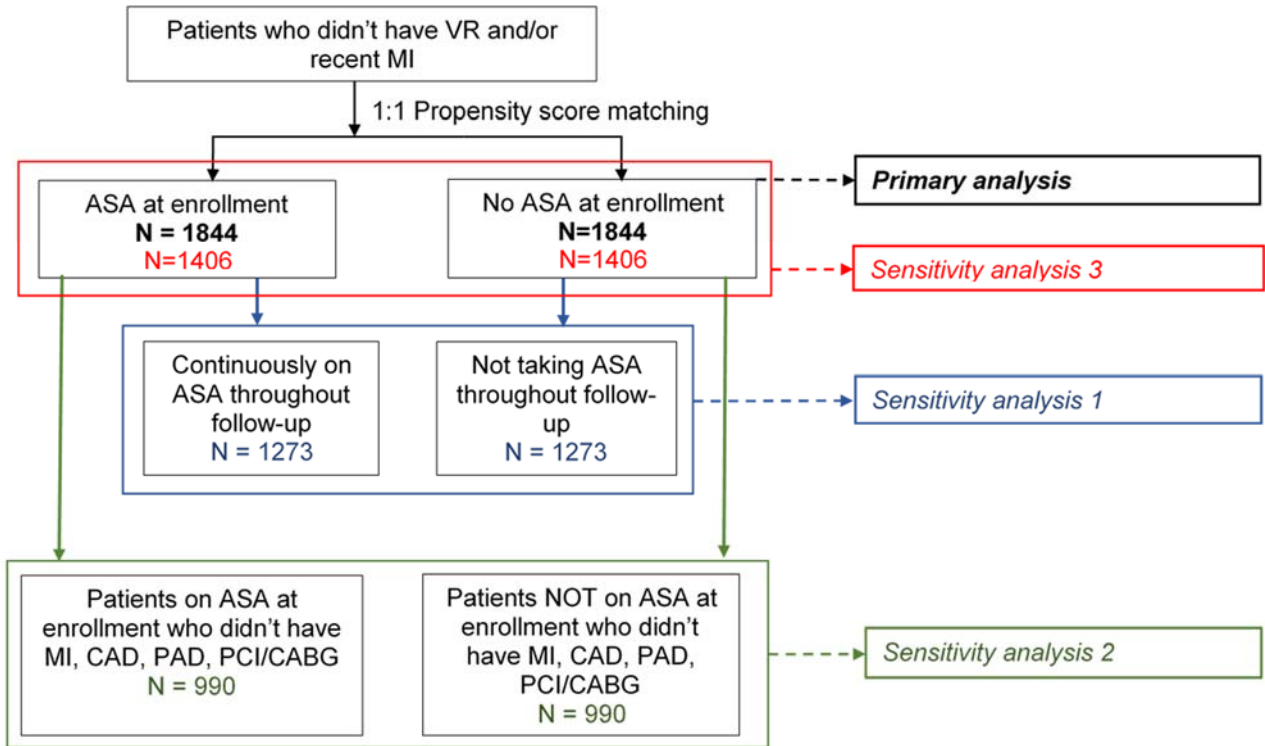
eTable 4. Outcomes of Unmatched Patient Cohorts

	Warfarin+ASA N=2453		No ASA N=4086		p-value (compare Cumulative Incidence) (Gray's test)	p-value (compare event rates) (Poisson)
	Cumulative incidence (95% CI) at 1 year	Event rate (# events/100 patient- years)	Cumulative incidence (95% CI) at 1 year	Event rate (# events/100 patient- years)		
Thrombosis	0.024 (0.0189 - 0.031)	2.7, ^a 1.9 ^b	0.029 (0.023 - 0.035)	3.5, ^a 2.4 ^b	0.21, ^a 0.11 ^b	0.29, ^a 0.26 ^b
Any bleeding	0.269 (0.249 - 0.288)	40.6, ^a 30.2 ^b	0.207 (0.193 - 0.222)	30.8, ^a 26.1 ^b	<0.001, ^a <0.001 ^b	<0.001, ^a <0.001 ^b
Major bleeding	0.060 (0.050 - 0.071)	6.7, ^a 5.0 ^b	0.032 (0.026 - 0.038)	3.6, ^a 3.6 ^b	<0.001, ^a <0.001 ^b	<0.001, ^a <0.001 ^b
ER for bleeding	0.138 (0.123 - 0.153)	18.4, ^a 14.6 ^b	0.095 (0.085 - 0.105)	11.9, ^a 10.6 ^b	<0.001, ^a <0.001 ^b	<0.001, ^a <0.001 ^b
ER for clotting	0.018 (0.013 - 0.024)	2.0, ^a 1.4 ^b	0.022 (0.017 - 0.028)	2.5, ^a 1.7 ^b	0.26, ^a 0.43 ^b	0.24, ^a 0.77 ^b
AD for bleeding	0.091 (0.078 - 0.104)	10.8, ^a 8.4 ^b	0.052 (0.045 - 0.061)	6.4, ^a 5.7 ^b	<0.001, ^a <0.001 ^b	<0.001, ^a <0.001 ^b
AD for clotting	0.021 (0.015 - 0.028)	2.4, ^a 1.7 ^b	0.021 (0.016 - 0.026)	2.4, ^a 1.7 ^b	0.98, ^a 0.89 ^b	1.0, ^a 0.97 ^b
Death (any cause)	0.047 (0.037 - 0.057)	4.3, ^a 4.1 ^b	0.0324 (0.0260 - 0.0398)	2.9, ^a 3.1 ^b	0.010, ^a 0.006 ^b	0.007, ^a 0.005 ^b

Abbreviations: AD, hospital admission; ASA, acetylsalicylic acid or aspirin; CI, confidence interval; ER, emergency room; coronary intervention; VR, valve replacement.

^a At 1 year.

eFigure 1. Study Schema



Abbreviations: ASA, acetylsalicylic acid or aspirin; CABG, coronary artery bypass graft; CAD, coronary artery disease; MI, myocardial infarction; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; VR, valve replacement.

eFigure 2. Standardized Difference Plot^a

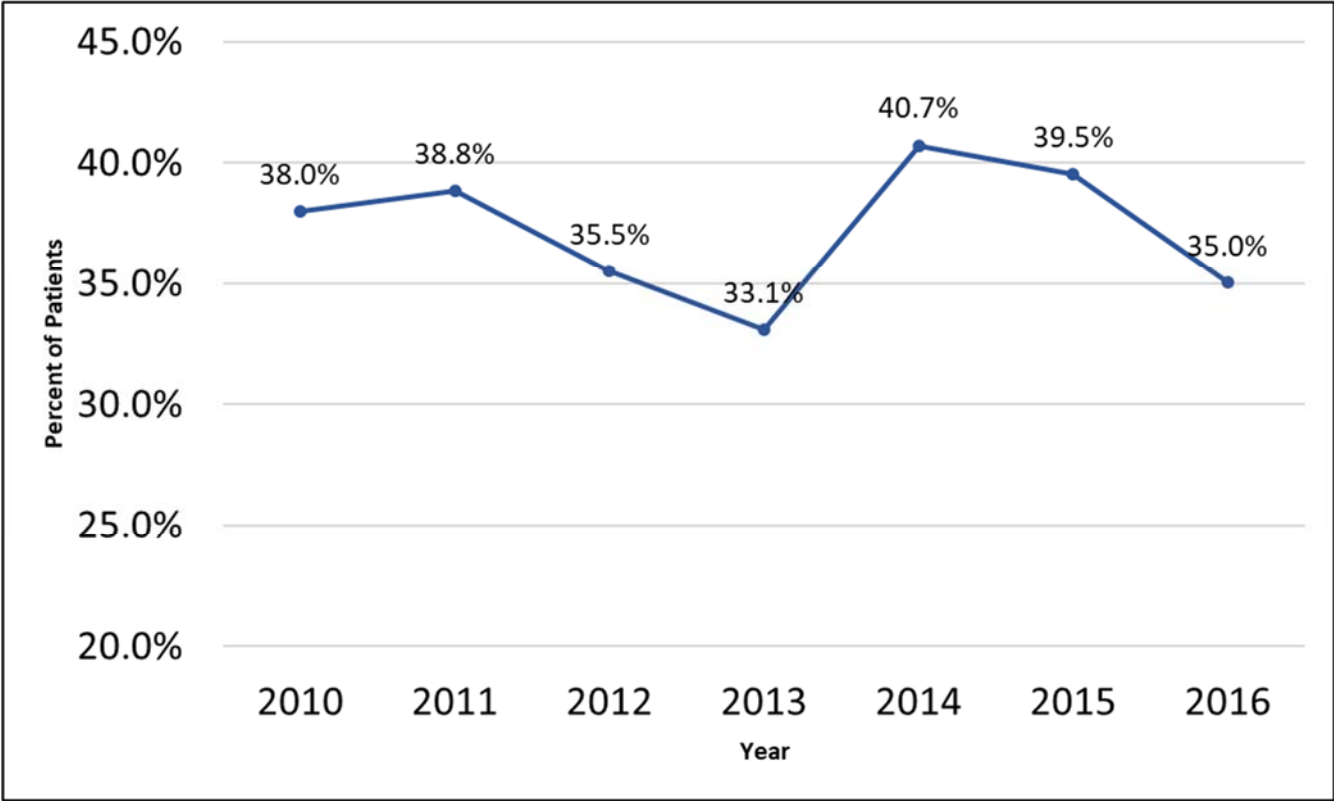


Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; Afib, atrial fibrillation; Aflutter, atrial flutter; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid or aspirin; BMI, body

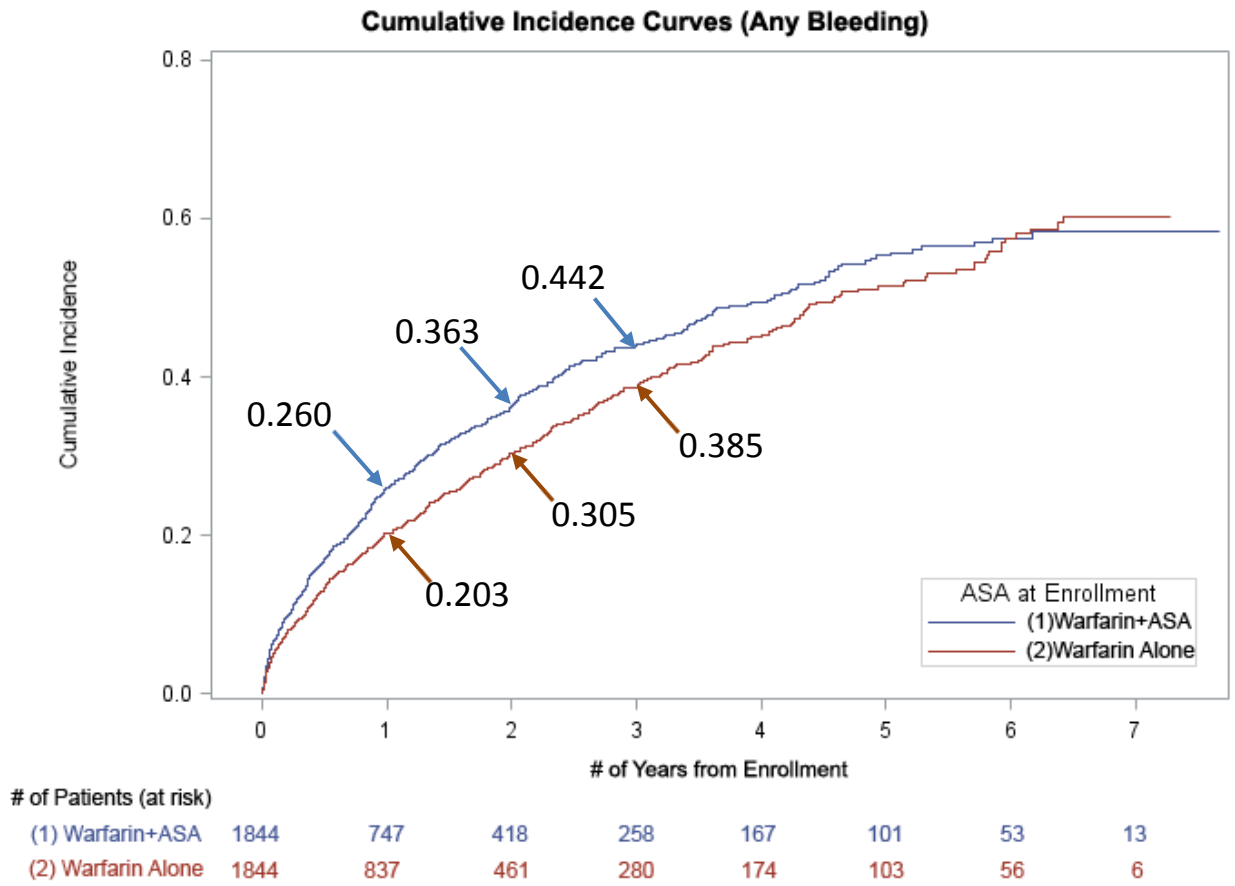
mass index; CABG, coronary artery bypass graft; CAD, coronary artery disease; CCB, calcium channel blocker; CHF, congestive heart failure; CVA, cerebrovascular accident; DM, diabetes mellitus; DVT, deep vein thrombosis; GIB, gastrointestinal bleed; LMW, low molecular weight heparin; MI, myocardial infarction; NSAID, nonsteroidal anti-inflammatory drug; PAD, peripheral arterial disease; PCI, percutaneous coronary intervention; PE, pulmonary embolism; TIA, transient ischemic attack; TTR, percent of time in the therapeutic range (INR 2-3).

^aAbsolute standardized differences in baseline covariates between patients treated with warfarin+ASA and those treated with warfarin monotherapy for atrial fibrillation or venous thromboembolism, before and after propensity score matching.

eFigure 3. Percent of Patients Without Recent Myocardial Infarction or Valve Replacement on Aspirin and Warfarin by Year



eFigure 4. Cumulative Incidence of Any Bleeding Over Time by Treatment



eFigure 5. Cumulative Incidence of ER Visits for Bleeding Over Time by Treatment

