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ORIGINAL INVESTIGATIONS

Frequency and Practice-Level Variation in Inappropriate Aspirin Use for the Primary Prevention of Cardiovascular Disease

Insights From the National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence Registry

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CME Objective for This Article: After reading this article, the reader should be able to: 1) state the current recommendations for aspirin use in primary prevention of cardiovascular disease (CVD); 2) identify, using cardiovascular disease risk algorithms, patients in whom the bleeding use associated with aspirin therapy may outweigh its anti-ischemic benefits; and 3) describe practice-level variation in potentially inappropriate use of aspirin therapy for primary CVD prevention.

CME Editor Disclosure: *JACC* CME Editor Ragavendra Baliga, MD, FACC, has reported that he has no financial relationships or interests to disclose.

Author Disclosures: Dr. Nambi was a national monitor for a study sponsored by Anthera Inc.; coinvestigator on a provisional patent filed by Baylor College of Medicine and Roche Diagnostics on the use of biomarkers in heart failure prediction; performed research collaboration with GE and Tomtec; and is a member of the regional advisory board for Sanofi. Dr. Alam is a member of the advisory board for AstraZeneca. Dr. Ballantyne has received grant/research support (all significant and all paid to the institution [not individual]) from Abbott, Amarin, Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi-Synthélabo, National Institutes of Health, and the American Heart Association; and served as a consultant for Abbott, Aegerion, Amarin, Amgen, Cerenis, Esperion, Genzyme, Kowa, Merck, Novartis, Pfizer, Resverlogix, Regeneron, Roche, and Sanofi-Synthélabo (the funding from Merck and Pfizer were significant, and others were moderate in amount). Dr. Virani has received grant/research support (all significant and paid to the institution [not individual]) from the Department of Veterans Affairs, the American Diabetes Association, and the American Heart Association. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Frequency and Practice-Level Variation in Inappropriate Aspirin Use for the Primary Prevention of Cardiovascular Disease

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ABSTRACT

BACKGROUND Among patients without cardiovascular disease (CVD) and low 10-year CVD risk, the risks of gastrointestinal bleeding and hemorrhagic strokes associated with aspirin use outweigh any potential atheroprotective benefit. According to the guidelines on primary prevention of CVD, aspirin use is considered appropriate only in patients with 10-year CVD risk ≥6% and inappropriate in patients with 10-year CVD risk <6%.

OBJECTIVES The goal of this study was to examine the frequency and practice-level variation in inappropriate aspirin use for primary prevention in a large U.S. nationwide registry.

METHODS Within the National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence registry, we assessed 68,808 unique patients receiving aspirin for primary prevention from 119 U.S. practices. The frequency of inappropriate aspirin use was determined for primary prevention (aspirin use in those with 10-year CVD risk <6%). Using hierarchical regression models, the extent of practice-level variation using the median rate ratio (MRR) was assessed.

RESULTS Inappropriate aspirin use frequency was 11.6% (7,972 of 68,808) in the overall cohort. There was significant practice-level variation in inappropriate use (range 0% to 71.8%; median 10.1%; interquartile range 6.4%) for practices; adjusted MRR was 1.63 (95% confidence interval [CI]: 1.47 to 1.77). Results remained consistent after excluding 21,052 women age ≥65 years (inappropriate aspirin use 15.2%; median practice-level inappropriate aspirin use 13.8%; interquartile range 8.2%; adjusted MRR 1.61 [95% CI: 1.46 to 1.75]) and after excluding patients with diabetes (inappropriate aspirin use 13.9%; median practice-level inappropriate aspirin use 12.4%; interquartile range 7.6%; adjusted MRR 1.55 [95% CI: 1.41 to 1.67]).

CONCLUSIONS More than 1 in 10 patients in this national registry were receiving inappropriate aspirin therapy for primary prevention, with significant practice-level variations. Our findings suggest that there are important opportunities to improve evidence-based aspirin use for the primary prevention of CVD. (J Am Coll Cardiol 2015;65:111–21) © 2015 by the American College of Cardiology Foundation.

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those of the authors and do not necessarily represent the views of the Department of Veterans Affairs.Dr. Nambi was a national monitor for a study sponsored by Anthera Inc.; coinvestigator on a provisional patent filed by Baylor College of Medicine and Roche Diagnostics on the use of biomarkers in heart failure prediction; performed research collaboration with GE and Tomtec; and is a member of the regional advisory board for Sanofi. Dr. Alam is a member of the advisory board for AstraZeneca. Dr. Ballantyne has received grant/research support (all significant and all paid to the institution [not individual]) from Abbott, Amarin, Amgen, Eli Lilly, GlaxoSmithKline, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi-Synthélabo, National Institutes of Health, and the American Heart Association; and served as a consultant for Abbott, Aegerion, Amarin, Amgen, Cerenis, Esperion, Genzyme, Kowa, Merck, Novartis, Pfizer, Resverlogix, Regeneron, Roche, and Sanofi-Synthélabo (the funding from Merck and Pfizer were significant, and others were moderate in amount). Dr. Virani has received grant/research support (all significant and paid to the institution [not individual]) from the Department of Veterans Affairs, the American Diabetes Association, and the American Heart Association. All other authors have reported that they have no relationships relevant to the contents of this paper to disclose.

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Cardiovascular disease (CVD) has been the leading cause of death in the United States for the past century and is the underlying cause of death in 32.3% of people (1). Therefore, emphasis has been placed on the primary and secondary prevention of this disease (2). Aspirin use is recommended for secondary prevention in patients with pre-existing CVD (3), and it is recommended for primary prevention in patients without CVD who have a moderate to high 10-year risk of developing CVD (2,4). However, in patients without CVD and a low 10-year CVD risk, there is no proof that aspirin use is associated with a reduction in adverse cardiovascular events. In this primary prevention population, the increased risk of gastrointestinal bleeding and hemorrhagic strokes associated with aspirin use outweighs any potential benefit from CVD risk reduction (5).

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Based on these findings, the American Heart Association (AHA) guidelines on primary prevention of CVD and stroke in 2002 (6) recommended aspirin for patients with 10-year coronary and stroke risk ≥10%. The U.S. Preventive Services Task Force recommendation on aspirin use for prevention of CVD from 2009 (4) advised an approach of weighing the benefit of preventing CVD against the risk of increased gastrointestinal bleeding and hemorrhagic strokes, with recommendations to use aspirin if 5-year coronary heart disease (CHD) risk is ≥3% (10-year CHD risk of ≥6%). The recent AHA/American Stroke Association guidelines for primary prevention of stroke in 2011 (7) recommend aspirin use for primary prevention if 10-year CVD risk is at least 6% to 10% (Class I; Level of Evidence: A). Thus, aspirin use for primary prevention would be considered appropriate in patients with 10-year CVD risk ≥6%. Given the risk of gastrointestinal bleeding and hemorrhagic strokes, aspirin use for primary prevention in patients at low risk of cardiovascular events (10-year CVD risk <6%) would be potentially inappropriate.

The U.S. Food and Drug Administration also recently issued a public advisory against the general use of aspirin for the primary prevention of heart attacks and strokes (8). This decision followed its denial of a request to change professional labeling to allow marketing of aspirin for primary prevention of heart attacks.

Accordingly, we examined the frequency and practice-level variation in inappropriate aspirin use for primary CVD prevention in a national cohort of patients enrolled in the American College of Cardiology's National Cardiovascular Disease Registry's Practice Innovation and Clinical Excellence (PINNACLE) registry.

ABBREVIATIONS AND ACRONYMS

AHA = American Heart Association

CHD = coronary heart disease

CI = confidence interval

CVD = cardiovascular disease

MI = myocardial infarction

MRR = median rate ratio

PINNACLE = Practice Innovation and Clinical Excellence

METHODS

STUDY POPULATION. The PINNACLE registry, launched in 2008, is a prospective, office-based, outpatient quality improvement registry of CVD patients seeking care in U.S. cardiology practices. Site participation in this initiative is voluntary, with data collected at the point of care for 100% of patients with coronary artery disease, heart failure, atrial fibrillation, and hypertension at each practice. The majority of sites provide data via electronic health records (9–14). Periodic global edit checks are conducted on all records to identify outliers in performance rates and ineligible instance totals before submission to the Centers for Medicare & Medicaid Services.

COHORT DEVELOPMENT AND DEFINITIONS. From the PINNACLE registry, patients receiving aspirin from 119 practices (21.9% were solo practices) between January 12, 2008, and June 15, 2013, were identified. Because a patient may have had multiple outpatient visits during the study interval, we used information from the most recent outpatient visit for each patient.

Patients were excluded if they were receiving aspirin for secondary prevention (i.e., history of myocardial infarction [MI], percutaneous coronary intervention, coronary artery bypass graft surgery, peripheral arterial disease, prior stroke, prior transient ischemic attack, atrial fibrillation, unstable angina, systemic embolism, heart transplant, prior cardiovascular surgery) or were receiving concomitant warfarin, clopidogrel, ticlopidine, or an aspirin/extended-release dipyridamole combination.

Because observational and clinical trial data indicate that a woman's risk for ischemic stroke typically exceeds her risk for CHD (15), the 10-year CVD risk (as opposed to a CHD risk calculator) was evaluated in all patients. We used the Framingham general CVD risk assessment tool, which has been well validated. The variables used in the Framingham 10-year CVD risk calculator include age, sex, hypertension, diabetes, cigarette smoking, total and high-density lipoprotein cholesterol levels, systolic blood pressure, and treatment of hypertension. The outcome calculated is an individual patient's 10-year risk of CVD events, which includes CHD events (coronary death, MI, coronary insufficiency, and angina), cerebrovascular events (ischemic stroke, hemorrhagic stroke, and transient

ischemic attack), peripheral arterial disease, and heart failure (16).

OUTCOMES

Inappropriate aspirin use was defined as aspirin therapy in patients with documentation in the data collection form of current aspirin use along with a 10-year risk of a CVD event <6%. All remaining patients were classified as appropriately receiving aspirin therapy for primary prevention. Because aspirin dose is not routinely collected in the PINNACLE registry, we evaluated aspirin use as a categorical (yes/no) variable.

The following outcomes were studied: 1) frequency of inappropriate aspirin use for primary CVD prevention in the entire registry; and 2) extent of practice-level variation in inappropriate aspirin use for primary CVD prevention. We also assessed temporal trends for inappropriate aspirin use for primary CVD prevention in the PINNACLE registry.

STATISTICAL ANALYSIS. For analyses pertaining to the frequency of inappropriate use, the number of patients who were receiving aspirin inappropriately was divided by the total number of patients who were receiving aspirin for primary CVD prevention. We then compared the baseline characteristics between patients receiving inappropriate versus appropriate aspirin therapy for primary prevention by using Student *t* tests for continuous variables and chi-square tests for categorical variables. Annual rates of inappropriate aspirin use since 2008 were then evaluated.

We subsequently determined inappropriate aspirin use for each practice with >30 patients receiving aspirin for primary prevention; descriptive plots were used for these analyses. The number of patients receiving inappropriate aspirin therapy at each practice was divided by the number of patients receiving aspirin for primary CVD prevention at that practice. Practice characteristics were then compared, stratified according to practice prescription rates above and below the median combined rate of inappropriate aspirin use; Student *t* tests were used for continuous variables and chi-square tests were used for categorical variables.

To further examine the extent of practice-level variation in inappropriate aspirin use, multivariable hierarchical regression models were constructed to determine the median rate ratio (MRR) for inappropriate aspirin use for primary CVD prevention. Two-level hierarchical models were used to adjust for clustering of patients within practices, with the individual practices modeled as a random effect and patient characteristics as fixed effects within each practice (17). This approach allowed us to control for confounding between practices because the use of hierarchical models ensured that patients with similar baseline characteristics were compared with each other from the same practice. The following covariates were included in the model: provider type (physician vs. nurse practitioner) and practice region (West, Northeast, Midwest, and South). The resultant MRR provides an estimate of the effect size of the practice on the outcome and can be interpreted as the likelihood that 2 randomly chosen practices would differ in treatment of "identical" patients. For example, an MRR of 1 suggests no practice-level variation and similar treatment at 2 randomly chosen practices for identical patients, whereas an MRR of 1.50 suggests a 50% likelihood of differing treatment (e.g., inappropriate vs. appropriate) for identical patients receiving care at 2 randomly chosen practices. Based on previous literature, an MRR >1.2 indicates clinically significant practice-level variation (10,18).

The 2011 AHA update to the guideline for CVD prevention in women (15) recommends aspirin use for primary prevention as Class IIa (Level of Evidence: B) for use in women ≥65 years of age, when the benefit of ischemic stroke and MI prevention is likely to outweigh the risk of gastrointestinal bleeding and hemorrhagic stroke. In addition, aspirin for primary prevention was recommended by the American Diabetes Association (19) for patients with diabetes in patients who were >40 years of age with additional risk factors. Lastly, statin use can alter cholesterol levels and, therefore, 10-year CVD risk. Given these recommendations, sensitivity analyses were also performed by excluding: 1) women ≥65 years of age; 2) patients with diabetes; and 3) patients receiving statin therapy. The frequency and practice-level variation of inappropriate aspirin use were then re-evaluated.

As secondary analyses, we also examined whether the frequency of inappropriate aspirin use at a practice was associated with either the overall frequency of aspirin use or the frequency of aspirin use for secondary CVD prevention at that practice by using the Spearman correlation coefficient. For all analyses, the null hypothesis was evaluated with a 2-sided significance level of 0.05. All analyses were performed by using SAS version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

The study flow diagram is shown in **Figure 1**. From the PINNACLE registry, we evaluated 9,538,255 patient

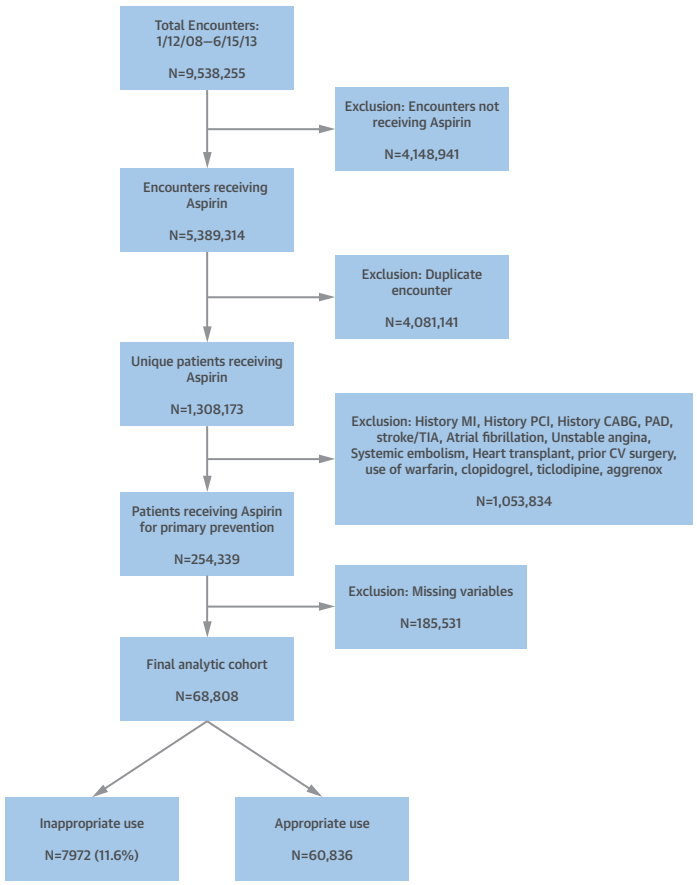
encounters between January 12, 2008, and June 15, 2013. After exclusions due to patients not receiving aspirin, multiple encounters for the same patient, history of MI, percutaneous coronary intervention, coronary artery bypass graft surgery, peripheral arterial disease, prior stroke or transient ischemic attack, atrial fibrillation, unstable angina, systemic embolism, heart transplant, prior cardiovascular surgery, or because these patients were receiving concomitant warfarin, clopidogrel, ticlopidine, or aspirin/extended-release dipyridamole, a total of 254,339 patients were determined to be receiving aspirin for primary prevention. Of these patients, 10-year CVD risk could not be calculated in 185,531 (72.9%) due to missing variables. Thus, the final cohort included 68,808 patients receiving aspirin for primary CVD prevention in whom the 10-year CVD risk could be calculated.

Of the total cohort, 7,972 patients (11.6%) had a calculated 10-year CVD risk <6% and were thus receiving aspirin inappropriately. The majority of these patients were female (79.7%); the frequency of inappropriate aspirin use was 16.6% (6,353 of 38,349) among female subjects and 5.3% (1,619 of 30,459) among male subjects. The annual trend of inappropriate aspirin use decreased from 14.5% in 2008 to 9.1% in 2013 (**Figure 2**).

Baseline characteristics of patients with inappropriate aspirin use compared with those with appropriate use are summarized in **Table 1**. Patients receiving aspirin inappropriately were younger (49.9 vs. 65.9 years). A larger proportion of patients in the appropriate group were male; had diabetes, hypertension, or dyslipidemia; and were smokers. These findings were not surprising because increased age and male sex carry a higher weight while calculating 10-year CVD risk using the Framingham general CVD risk calculator. Patients receiving aspirin for an inappropriate indication were less likely to be prescribed angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, diuretics, or statins. Mean 10-year CVD risk in the inappropriate aspirin group was 4.0% versus 24.5% in the appropriate group ($p < 0.001$).

Practice-level variation in inappropriate aspirin use is shown in the **Central Illustration**. The median practice-level frequency for inappropriate aspirin use was 10.1%. There was significant practice-level variation in inappropriate aspirin use, with a range of 0% to 71.8% (interquartile range: 6.4%). MRR for inappropriate aspirin use was 1.63 (95% confidence interval [CI]: 1.47 to 1.77), indicating significant variation in inappropriate aspirin use across practices.

FIGURE 1 Details of Cohort Development



The study population was initially selected to allow analysis of prevalence and temporal trends of inappropriate aspirin use for primary prevention of cardiovascular disease (CVD). Patients were excluded for duplicate encounters, receiving aspirin for secondary prevention, or inability to calculate 10-year CVD risk due to missing variables. Patients were then classified as receiving aspirin inappropriately for primary CVD prevention if 10-year CVD risk was <6% and those receiving aspirin appropriately if 10-year CVD risk was ≥6%. CABG = coronary artery bypass graft; CV = cardiovascular; MI = myocardial infarction; PAD = peripheral arterial disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.

The MRR of 1.63 suggests that between 2 "identical" patients treated at 2 randomly chosen practices, 1 patient was 63% more likely to receive aspirin inappropriately than another patient with similar characteristics because of the practice where they were receiving care.

To further evaluate practice characteristics associated with inappropriate aspirin use, practices above or below the median inappropriate aspirin use were evaluated. Interestingly, the number of physicians or the number of providers in a practice and the duration of participation in the PINNACLE registry were

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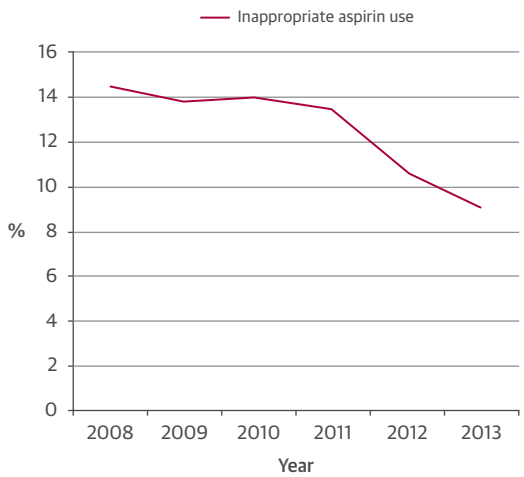
FIGURE 2 Annual Trend of Inappropriate Aspirin Use in the PINNACLE Registry



The annual inappropriate aspirin use for primary prevention decreased from 14.5% in 2008 to 9.1% in 2013. PINNACLE = Practice Innovation and Clinical Excellence.

TABLE 1 Comparison of Baseline Characteristics of Patients With Inappropriate or Appropriate Aspirin Use for Primary CVD Prevention

	Inappropriate (n = 7,972)	Appropriate (n = 60,836)	p Value
Age, yrs	49.9 ± 11.3	65.9 ± 11.8	<0.001
Male	1,619 (20.3)	28,840 (47.4)	<0.001
Race			
White	3,936 (49.4)	32,534 (53.5)	<0.001
Black	535 (6.7)	3,593 (5.9)	<0.001
Hispanic	106 (1.3)	644 (1.1)	<0.001
Provider type			0.132
Physician	7,591 (96.2)	57,788 (96.5)	
Nurse practitioner	251 (3.2)	1,679 (2.8)	
Other	52 (0.7)	438 (0.7)	
Insurance type*			
Private	5,444 (68.3)	35,347 (58.1)	<0.001
Medicare	1,130 (14.2)	30,467 (50.1)	<0.001
None	521 (6.5)	2,239 (3.7)	<0.001
Comorbidities			
Diabetes	344 (4.3)	13,753 (22.6)	<0.001
Hypertension	4,689 (58.8)	51,817 (85.2)	<0.001
Dyslipidemia	5,465 (68.6)	50,136 (82.4)	<0.001
Tobacco use	1,631 (20.5)	30,024 (49.4)	<0.001
Medications			
Angiotensin-converting enzyme inhibitor	1,474 (18.5)	22,428 (36.9)	<0.001
Angiotensin receptor blocker	808 (10.1)	13,588 (22.3)	<0.001
Beta-blocker	2,406 (30.2)	28,168 (46.3)	<0.001
Calcium-channel blocker	726 (9.1)	13,738 (22.6)	<0.001
Diuretic	1,662 (20.8)	23,846 (39.2)	<0.001
Statin	3,789 (47.5)	37,104 (61.0)	0.001

Values are mean ± SD or n (%); percentages were calculated from available data.
*Patients can have >1 type of insurance.
CVD = cardiovascular disease.

higher in practices above the median compared with the practices below the median practice-level rates of inappropriate aspirin use (Table 2).

There was modest regional variation noted in inappropriate aspirin use. The proportion of patients receiving inappropriate aspirin therapy for primary CVD prevention in the Northeast, Midwest, South, and West were 11.4%, 12.2%, 11.3%, and 10.6%, respectively ($p < 0.001$).

Our results remained consistent after excluding 21,052 women ≥65 years of age: inappropriate aspirin use 15.2% (range 2.0% to 29.4%); median practice-level inappropriate aspirin use 13.8% (interquartile range: 8.2%); and adjusted MRR 1.61 (95% CI: 1.46 to 1.75). Similar results were found after excluding 14,097 patients with diabetes: inappropriate aspirin use 13.9% (range 0% to 71.8%); median practice-level inappropriate aspirin use 12.4% (interquartile range: 7.6%); and adjusted MRR 1.55 [95% CI: 1.41 to 1.67). After excluding 40,893 patients receiving statin therapy, results were as follows: inappropriate aspirin use 14.9% (range 2.4% to 29.6%); median practice-level inappropriate aspirin use 14.5% (interquartile range: 7.7%); and adjusted MRR 1.44 (95% CI: 1.31 to 1.55).

There was no correlation between a practice's frequency of inappropriate aspirin use for primary CVD prevention and the overall frequency of aspirin use at that practice (Spearman correlation coefficient 0.112; p = NS). Similarly, there was no correlation between a practice's frequency of inappropriate aspirin use for primary prevention and its use of aspirin therapy for secondary prevention (Spearman correlation coefficient 0.025) at that practice (p = NS).

DISCUSSION

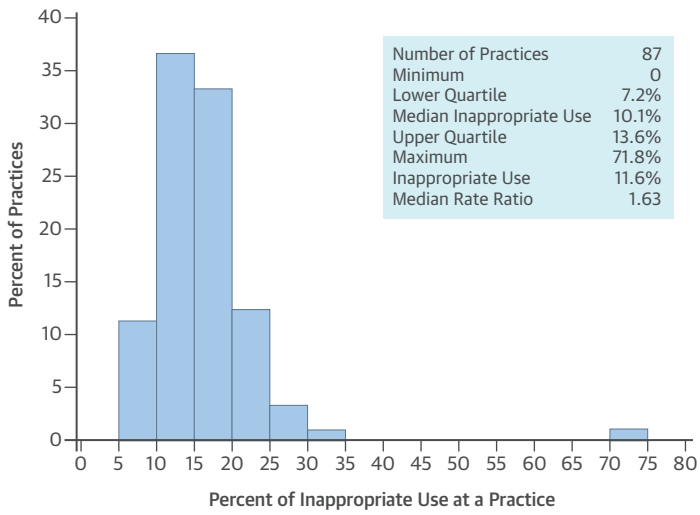
Our data provide an overview of contemporary use of aspirin for primary prevention in a national registry of U.S office-based patients with CVD. We found that 11.6% of patients were receiving aspirin for primary CVD prevention with a 10-year CVD risk <6%. There was also significant practice-level variation, with an MRR of 1.63 (Central Illustration). Our results provide an important benchmark for inappropriate aspirin use for primary CVD prevention in contemporary outpatient U.S. practices.

Approximately 36% of the adult U.S. population (>50 million people) take aspirin regularly for CVD prevention (20). In patients with pre-existing CVD, the benefits of aspirin use for prevention of MI, stroke, and cardiovascular death are well established, with >90% of these patients receiving aspirin at hospital discharge (1). However, the role of aspirin for primary prevention of cardiovascular events is less clear. There are patients who would be considered high risk for adverse cardiovascular events due to the presence of multiple cardiovascular risk factors in whom the benefit of aspirin in preventing cardiovascular events would potentially outweigh bleeding risk. However, patients who are at low risk for cardiovascular events could be harmed by aspirin use due to an increased risk of major bleeding.

For defining the cutoff benefit with use of aspirin for primary CVD prevention, we used multiple guideline recommendations on aspirin use for primary CVD prevention (4,6,7) and ascertained the most conservative cutoff for inappropriate use from these guidelines as 10-year CVD risk <6%. Because women's risk for ischemic stroke typically exceeds their CHD risk, we evaluated the 10-year CVD risk (as opposed to a CHD risk calculator) in all patients by using the Framingham general CVD risk calculator. It could be argued that the Framingham risk score was developed and validated in epidemiologic cohorts derived from the general population and thus has inherent limitations in its application to patients receiving care in cardiology practices. Cardiovascular practices enrolling patients in the PINNACLE registry are more likely to manage patients with CVD or those with increased risk of CVD. However, we stipulate that after excluding patients with CVD (as we did in the present study), patients seeking care for primary CVD prevention in a U.S. cardiology practice should be treated in a manner similar to a patient seeking care for the same reason in a primary care practice. This care would entail assessing a patient's 10-year CVD risk followed by instituting appropriate therapy to mitigate that risk. Furthermore, because 72.9% of our patients had missing variables to ascertain 10-year CVD risk, it is possible that cardiologists may be preconditioned to seeing patients with a high burden of CVD and thus have a low threshold to use aspirin for primary CVD prevention, which at times may be inappropriate.

The anti-ischemic benefits of aspirin for primary prevention are reportedly sex-specific (5). In women, the benefit is mainly driven by ischemic stroke reduction with the use of aspirin. The Women's Health Study found a significant decrease in major cardiovascular events, ischemic stroke, and MI in the subgroup of women ≥65 years of age who were using aspirin. Thus, the 2011 AHA update to the guideline for CVD prevention in women (15) assigns aspirin use for primary prevention a Class IIa (Level of Evidence: B) recommendation for use in women ≥65 years of age along with a Class III recommendation (Level of Evidence: B) for the routine use of aspirin in healthy women <65

CENTRAL ILLUSTRATION U.S. Cardiology Practice-Level Variation in Inappropriate Aspirin Use



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Inappropriate aspirin use frequency was 11.6% (7,972 of 68,808) in the overall cohort. There was significant practice-level variation in inappropriate use (range 0% to 71.8%; median 10.1%; interquartile range: 6.4%) for practices; adjusted median rate ratio was 1.63 (95% confidence interval: 1.47 to 1.77).

TABLE 2 Practice Characteristics by Median Rates of Inappropriate Aspirin Use

	Inappropriate Aspirin Use Below Median (n = 43)	Inappropriate Aspirin Use Above Median (n = 44)	p Value
No. of physicians	8.0 (2.0–17.0)	13.0 (6.5–22.5)	0.04
No. of providers	9.0 (2.0–17.0)	15.0 (6.5–27.5)	0.03
Months of PINNACLE registry participation	15.6 (7.7–36.1)	23.8 (13.7–45.4)	0.03
Practice location			0.77
Urban	31 (79.5%)	32 (82.1%)	
Rural	8 (20.5%)	7 (17.9%)	

Values are median (interquartile range) or n (%). Data are from sites with >30 patients receiving aspirin for primary cardiovascular disease prevention (87 practices).

PINNACLE = Practice Innovation and Clinical Excellence.

years of age. Given these recommendations, we performed sensitivity analyses by excluding women ≥65 years of age and found similar results with respect to the frequency and practice-level variation in inappropriate use of aspirin for primary prevention.

Diabetes is known to increase the risk of developing cardiovascular events 2- to 4-fold (21). The American Diabetes Association thus recommends aspirin for primary prevention in patients with diabetes who are >40 years of age and have additional risk factors (19). However, the randomized controlled trials of aspirin for primary prevention in patients with diabetes have not shown a decrease in cardiovascular events with use of aspirin (22,23). Our sensitivity analyses after excluding diabetic patients in our cohort produced results that are consistent with the study's main findings.

Another factor to consider is the increase in statin use over time. Statins are now recommended for primary prevention in patients at 10-year risk of atherosclerotic CVD ≥7.5% according to the American College of Cardiology/AHA guideline on the treatment of blood cholesterol (24). It is important to note that most patients in the randomized controlled trials of aspirin versus placebo for primary prevention were not receiving statin therapy. The temporal trend of increasing statin use could further decrease MI and ischemic stroke risk and thereby further minimize any incremental benefit associated with aspirin therapy for primary CVD prevention (25). In our cohort, 59.4% of patients were receiving statin therapy. It is unclear if there is any additional benefit to using aspirin for primary prevention in patients already receiving statin therapy, while potentially increasing their risk of major bleeding. However, to confirm our results, a sensitivity analysis was performed by excluding patients receiving statin therapy, and similar results were produced.

An additional consideration is the dosing of aspirin for primary prevention. An association between higher doses of aspirin and an increased risk of bleeding has been confirmed in multiple studies, whereas no similar association has been shown between dose and anti-ischemic efficacy of aspirin (20). Thus, data are most supportive of a 75- to 100-mg daily dose of aspirin (4,20). It is possible that some of the 7,972 patients receiving aspirin inappropriately in our study could be receiving higher doses. However, information on medication dosages is not routinely collected in the PINNACLE registry, and we were therefore unable to evaluate the appropriateness of aspirin doses in our patient population.

Our results have important implications for quality measurement and improvement. As noted by an Institute of Medicine (IOM) report (26), effective care delivery denotes "providing services based on scientific knowledge to all who could benefit and refraining from providing services to those not likely to benefit." Although most current performance measures incorporate measures of care delivery in those likely to benefit from a particular therapy (e.g., provision of aspirin or statins in patients with coronary artery disease), our results indicate that measures that pertain to refraining from providing therapy to those not likely to benefit or those who could be harmed by a particular therapy are also needed to capture this important aspect of care.

The AHA/American College of Cardiology Foundation 2009 performance measures for the primary prevention of CVD in adults have designated aspirin

TABLE 3 Comparison of Baseline Characteristics Between Included Patients (in Whom 10-Year CVD Risk Could Be Calculated) and Excluded Patients due to Missing Variables (in Whom 10-Year CVD Risk Could Not Be Calculated)

	Included Participants (n = 68,808)	Excluded Participants (n = 185,531)	p Value
Age, yrs	64.0 ± 12.8	63.7 ± 14.1	<0.001
Male	30,459 (44.3)	80,918 (43.6)	0.003
Race			
White	36,470 (88.7)	87,135 (88.5)	0.335
Black	4,128 (10.0)	9,578 (9.7)	0.076
Hispanic	750 (2.8)	1,998 (3.8)	<0.001
Provider type			<0.001
Physician	65,379 (96.4)	173,171 (96.7)	
Nurse practitioner	1,930 (2.8)	4,609 (2.6)	
Other	490 (0.7)	1,211 (0.7)	
Insurance*			
Private	40,791 (65.7)	103,517 (64.4)	<0.001
Medicare	31,597 (45.9)	83,443 (45.0)	<0.001
None	2,760 (4.4)	5,962 (3.7)	<0.001
Comorbidities			
Diabetes	14,097 (20.5)	35,428 (19.1)	<0.001
Hypertension	56,506 (82.1)	139,196 (75.0)	<0.001
Dyslipidemia	55,601 (80.8)	89,249 (48.1)	<0.001
Tobacco use	31,655 (46.0)	81,374 (43.9)	<0.001
Medications			
Angiotensin-converting enzyme inhibitor	23,902 (34.7)	61,747 (33.3)	<0.001
Angiotensin receptor blocker	14,396 (20.9)	33,439 (18.0)	<0.001
Beta-blocker	30,574 (44.4)	78,016 (42.1)	<0.001
Calcium channel blocker	14,464 (21.0)	35,844 (19.3)	<0.001
Diuretics	25,508 (37.1)	63,648 (34.3)	<0.001
Statin	40,893 (59.4)	87,609 (47.2)	<0.001

Values are mean ± SD or n (%); percentages were calculated from available data. *Patients can have >1 type of insurance.

Abbreviation as in Table 1.

use for internal quality improvement but not for accountability and public reporting (2). They recommended that a 10-year CVD risk assessment with a risk score be conducted in all adults ≥40 years of age every 5 years. In the present study, we were unable to calculate the 10-year CVD risk in 185,531 (72.9%) patients receiving aspirin for primary prevention mainly due to missing cholesterol values in 96.9% of these patients. To address this important issue, we compared the baseline characteristics between included patients (in whom 10-year CVD risk could be calculated) and patients excluded due to missing variables (in whom 10-year CVD risk could not be calculated) (**Table 3**). Overall, these 2 groups were numerically comparable except that patients with missing variables were less likely to have hypertension and dyslipidemia. These results indicate that if 10-year CVD risk had been available, then the calculated 10-year CVD risk may have been slightly lower in these excluded patients compared with those included, thereby potentially increasing the frequency of inappropriate aspirin use even further. These analyses also suggest that there is much work to be done to educate practitioners and practices about the need to ascertain risk by using well-validated methods before initiating medications, such as aspirin, for primary CVD prevention.

Of note, there was a significant difference between practices above and below the median practice-level frequency of inappropriate aspirin use with respect to their duration of participation in the PINNACLE registry. The mean duration of participation in the PINNACLE registry was higher (23.8 months) for practices above the median practice-level frequency of inappropriate aspirin use compared with those practices that were below the median practice-level frequency of inappropriate use (15.6 months). This finding suggests a lack of audit and feedback to practices with higher inappropriate aspirin use. Future efforts that focus on incorporating the delivery of both appropriate and inappropriate evidence-based management of CVD risk factors could address this gap. In addition, because aspirin is available over the counter, patient and public education (similar to the U.S. Food and Drug Administration advisory against the general use of aspirin for primary CVD prevention) will play a key role in avoiding inappropriate use.

Finally, there is a suggestion that aspirin could be used for the prevention of colorectal cancer and to decrease mortality from colorectal cancer (27,28). However, the U.S. Preventive Services Task Force recommends against routine use of aspirin to prevent colorectal cancer in those at average risk for this disease (29). Some clinicians may be more convinced by the available evidence of the non-CVD benefits of aspirin, which could also partially explain the practice-level variations in aspirin use.

STUDY LIMITATIONS. First, aspirin use for primary prevention was self-reported. Because aspirin is available over the counter with no need for prescriptions, aspirin use could be underreported, and the rates of inappropriate use in patients with 10-year risk for CVD <6% could be higher. Second, our study was conducted among cardiology practices participating in the PINNACLE registry. Therefore, these practices may be highly motivated for quality improvement, and the rates of inappropriate use of aspirin for primary prevention could be higher in nonparticipating practices. Furthermore, the majority of patients seek preventative care for CVD in primary care practices, where the frequency of inappropriate aspirin use may be different. Third, we did not examine ischemic or bleeding outcomes associated with the inappropriate use of aspirin for primary prevention in this study because those outcomes are not routinely collected in the PINNACLE registry. Fourth, the dose of aspirin was not collected in the registry, and analysis pertaining to aspirin dose could therefore not be performed. Fifth, due to missing variables (mainly missing cholesterol values), we were unable to calculate the 10-year CVD risk in 72.9% of patients receiving aspirin for primary prevention, although our analyses comparing patients who had missing and nonmissing data show broadly comparable populations. Finally, because aspirin is available over the counter, patient (rather than provider) preferences could be partly driving inappropriate use of aspirin for primary CVD prevention.

CONCLUSIONS

More than 1 in 10 patients in this national registry were inappropriately receiving aspirin for primary CVD prevention, with significant variation observed across practices. Our findings suggest that there are important opportunities to improve evidence-based use of aspirin for primary CVD prevention.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Aspirin use for primary prevention of CVD must consider several clinical factors, including the patient's overall risk of harm and benefit. Aspirin use is indicated for primary prevention in patients with 10-year CVD risk ≥6% to 10%.

COMPETENCY IN INTERPERSONAL & COMMUNICATION SKILLS: Because aspirin is available over the counter, patient choice (rather than provider recommendation) may be contributing to inappropriate aspirin use for primary prevention. It is important to discuss the risks and benefits of aspirin use with patients.

TRANSLATIONAL OUTLOOK 1: Additional research in methods to decrease practice-level variation and prevent inappropriate aspirin use for primary prevention in patients with low 10-year CVD risk needs to be conducted.

TRANSLATIONAL OUTLOOK 2: The benefit of aspirin use for the primary prevention of CVD in patients receiving statin therapy must be evaluated.

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