Acetylsalicylic acid use in primary prevention in Canada: Insight from the Primary Care Audit of Global Risk Management (PARADIGM) study

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BACKGROUND: Acetylsalicylic acid (ASA) is of proven benefit in reducing cardiovascular (CV) events in both acute and chronic CV conditions. However, the role of ASA for the primary prevention of CV disease remains controversial, compounded by the risk of major hemorrhage with ASA therapy. Despite this, ASA remains frequently used in primary prevention.
METHODS: The PARADIGM study is an observational registry of 3015 healthy, middle-age Canadians, free of CV disease or diabetes, who underwent CV risk stratification. The present analysis assessed the use of ASA in this primary prevention cohort.
RESULTS: A total of 406 subjects (13.5%) were prescribed ASA by their primary care physician. Those prescribed ASA, compared with those who were not, were more likely to be older, of male sex, white Caucasian, past/current smokers, hypertensive and to have a family history of premature CV disease. Blood pressure, renal function, high-sensitivity C-reactive protein, waist circumference and body mass index were all discriminators of ASA use. The mean modified Framingham risk score was significantly higher for those prescribed ASA compared with those who were not. Importantly, only 44% of those prescribed ASA were at high risk according to Framingham risk score.
CONCLUSIONS: The contemporary use of ASA in primary prevention remains high. Several clinical and laboratory factors influence the decision to prescribe ASA. However, the majority of ASA use was noted in individuals at low and intermediate risk (versus those at high risk).

Key Words: *Acetylsalicylic acid; Cardiovascular disease; Primary prevention; risk stratification*

The ability of acetylsalycylic acid (ASA) to irreversibly inactivate platelet cyclooxygenase and, hence, prevent the synthesis of thromboxane A2, which promotes vasoconstriction and platelet aggregation, makes it an essential component of the management of cardiovascular disease (CVD). The benefits of ASA therapy in patients with a history of CVD are well established. ASA use in the secondary prevention of CVD results in an approximately 20% relative risk reduction (RRR) in CVD events including myocardial infarction and ischemic stroke, and approximately 10% RRR in CVD mortality and total mortality compared with placebo (1). In the secondary prevention population, the associated increase in gastrointestinal and intracranial bleeding associated with ASA use is offset by the absolute benefit obtained from a reduction in cardiovascular events. However, the role for routine ASA use in the primary prevention of CVD is less clear.

The most recent guidelines from the American College of Chest Physicians (ACCP [2]), American Heart Association (AHA [3]), US Preventive Services Task Force (4) and European Society of Cardiology (ESC [5]) recommend the selective use of ASA in the primary prevention of CVD in older patients (>50 years of age) and in those otherwise deemed to be at higher risk. Specifically, the ESC prevention guidelines indicate that in asymptomatic individuals, ASA use should only be considered when the 10-year risk of CVD mortality is >10% and blood pressure is controlled. Additionally, the Antithrombotic Trialists's Collaboration (ATTC) has indicated that in primary prevention without previous disease, ASA use is of uncertain net value as the reduction in occlusive events needs to be weighed against any increase in major bleeds (1,6,7). Similarly, the Canadian Cardiovascular Society antiplatelet therapy recommendations for primary prevention do not recommend the routine use of ASA to prevent ischemic vascular events for either men or women without evidence of manifest vascular disease, unless the individual's vascular risk is considered to be high and bleeding risk is low (8). Thus, at present, it remains unclear whether the routine use of ASA in the primary prevention of CVD is warranted given the significant risks that are associated with its chronic use.

The Primary Care Audit of Global Risk Management (PARADIGM) study is a registry of 3015 patients who at baseline were free of CVD or diabetes. These subjects were enrolled by Canadian primary care physicians with the aim of evaluating risk stratification practices and use of both classic and novel cardiovascular risk markers in cardiac risk assessment. In the present analysis, we analyzed the frequency of ASA use in the primary prevention of CVD in this cohort and the factors influencing physician practice.

METHODS

The PARADIGM study is an observational registry that prospectively enrolled 3015 healthy, middle-age adults undergoing cardiovascular risk assessment across Canada between March, 2009 and February, 2010 by 105 primary care physicians. Nine eligibility criteria included: males (>40 years of age) or females (>50 years of age) undergoing CVD risk assessment and able and willing to provide informed

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TABLE 1
Baseline clinical characteristics of the Primary Care Audit of Global Risk Management (PARADIGM) study population (n=3015)

Characteristics	
Age, years	56.3±8.4
Male sex, %	58.8
Caucasian, %	69.6
Hypertension, %	30.4
Treated hypertension, %	26.6
Systolic blood pressure, mmHg	126.6±14.0
Diastolic blood pressure, mmHg	78.5±9.1
Past or current smoking, %	34.7
Family history of premature cardovascular disease, %	24.3
Body mass index, kg/m^2	27.8±5.3
Waist circumference, cm	94.8±13.6
Medications at baseline, n (%)	
Acetylsalicylic acid	406 (13.5)
Angiotensin-converting enzyme inhibitor	327 (10.9)
Angiotensin receptor blocker	333 (11.0)
Beta-blocker	120 (4.0)
Calcium channel blocker	166 (5.5)
Diuretic	444 (14.7)

Continuous variables are expressed as mean ± SD

consent. Exclusion criteria included previous history of atherosclerotic disease (angina, myocardial infarction, transient ischemic attack, stroke, peripheral arterial disease or revascularization), a known high (≥20%) Framingham risk score (FRS) or diabetes. Patients who were currently or previously taking a lipid-lowering agent were also excluded from the study.

Assessment of risk factors and cardiovascular biomarkers

Each patient underwent a standard cardiovascular assessment, which included a detailed history and physical examination. Smoking status, self-reported ethnicity and family history of CVD were recorded. At the initial visit, body weight, height and waist circumference were measured and baseline medications were reviewed. Blood pressure (BP) measurements were performed in accordance with Canadian Hypertension Education Program recommendations (10). Laboratory investigations including a fasting lipid profile, fasting glucose, glycated hemoglobin (HbA1c), serum creatinine (to estimate glomerular filtration rate [eGFR]) and high-sensitivity C-reative protein (hsCRP) levels were performed by the primary care physician's local laboratory. The 10-year global cardiovascular risk score was calculated centrally for each patient using the FRS (ATP-III) (11). Individuals were assigned to either very low (<5%), low (5% to 9%), intermediate (10-% to 19%) or high (>20%) 10-year risk categories.

Statistical methods

Continuous variables are expressed as mean ± SD. Welch's *t* test, assuming unequal variances, was used to test the difference in means for continuous variables. The Fisher's exact test was used to test the difference in proportions from two independent samples for categorical variables. Categorical variables are presented as counts and percentages. Logistic regression was used for the multivariate analysis. Variables that appeared to be significant at 5% in the univariate analysis were selected in the multivariate model. All statistical tests were two-tailed, and P<0.05 was considered to be statistically significant.

RESULTS

The clinical characteristics of the entire PARADIGM cohort are presented in Table 1. The mean (± SD) age of the cohort was 56.3±8.4 years; 58.8% were male, 69.6% were Caucasian, 34.7% had a history of past/current smoking, 30.4% had a history of hypertension and 24.3% reported a family history of CVD. Of these 3015 participants, 406 (13.5%) were prescribed ASA for primary CVD prevention by their family physicians. Table 2 shows the general characteristics of the subjects who were prescribed ASA for primary prevention. Significant differences were noted between subjects who were prescribed ASA and those who were not. When compared with their counterparts, patients taking ASA were older (61.6±8.4 years versus 55.5±8.1 years (P<0.0001), more often male (P<0.001), more often Caucasian (88.9% versus 66.6%; P <0.0001), and more likely to be past or current smokers (43.8% versus 33.3%; P<0.001), hypertensive (60.8% versus 25.7%; P <0.00001) and to have a family history of premature CVD (30.9% versus 23.3%; P<0.01) (Table 2). Systolic and diastolic BP, serum creatinine, hsCRP levels, waist circumference (WC) and body mass index (BMI) were also significantly higher among ASA versus non-ASA users (all P<0.0005) (Table 2). However, low-density lipoprotein cholesterol (LDL-c) level, fasting blood glucose and HbA1c did not differ between the two groups (Table 2). In multivariate analysis, older age, male sex, the presence of hypertension, smoking, family history of CVD and an elevated BMI were independently associated with the use of ASA (Table 3). Individuals with a history of hypertension were 3.87 times more likely than nonhypertensive patients to be prescribed ASA (95% CI 3.38 to 5.43).

TABLE 2
Cardiovascular risk factors and overall Framingham risk scores in acetylsalicylic acid (ASA) and non-ASA users

	ASA		
Characteristic	Users (n=406)	Nonusers (n=2609)	P
Age, years	61.6±8.5	55.5±8.1	<0.0001
Male sex	255 (62.8)	1519 (58.2)	<0.001
Caucasian	361 (88.9)	1738 (66.6)	<0.00001
Hypertension	247 (60.8)	670 (25.7)	<0.00001
Past/current smoking	178 (43.8)	868 (33.3)	<0.001
Family history of CVD	125 (30.9)	607 (23.3)	0.002
BMI (>25 kg/m^2)	314 (77.3)	1764 (67.6)	<0.0005
BMI (>30 kg/m^2)	140 (34.5)	685 (26.3)	<0.0005
LDL-c, mmol/L	3.55±0.83	3.57±0.84	0.77
Fasting glucose, mmol/L	5.4±0.7	5.4±0.7	0.16
IFG (>6.1 mmol/L)	45 (11.1)	236 (9.0)	0.20
HbA1c, %	5.7±0.4	5.7±0.4	0.54
eGFR, mL/min/1.73m^2	72.7±16.5	78.1±15.7	<0.0005
hsCRP (>2.0 mg/L)	200 (49.3)	1052 (40.3)	<0.0005
Very low FRS (<5%), %	2.2	15.0	<0.00001
Low FRS (5% – 9%), %	15.8	32.6	<0.00001
Intermediate FRS (10% – 19%), %	37.7	33.3	<0.00001
High FRS (≥20%), %	44.3	19.1	<0.00001
Mean FRS, %	22.3±14.0	13.5±10.3	<0.00001

Data presented as n (%) unless otherwise indicated, continuous variables are expressed as mean ± SD. BMI Body mass index; CVD Cardiovascular disease; eGFR Estimated glomerular filtration rate; HbA1c Glycated hemoglobin; hsCRP High-sensitivity C-reactive protein; IFG Impaired fasting glucose; FRS Framingham risk score; LDL-c Low-density lipoprotein cholesterol

The use of aspirin was evaluated as a function of the calculated FRS. Individuals were assigned to either very low (<5%), low (5% to 10%), intermediate (10% to 20%) or high (>20%) 10-year risk categories. The mean modified FRS for those prescribed ASA was higher (22.3±14.0% ASA users versus 13.5±10.3% nonusers; P<0.00001) (Table 2). However, 44.3% of ASA users were in the high-risk category compared with 2.2%, 15.8% and 37.7% in the very low, low and intermediate risk groups, respectively (Table 2).

Stratification of the ASA-treated patients based on sex revealed no differences in the proportion of ASA-treated subjects, rates of smoking, presence of hypertension, presence of a family history of

TABLE 3
Risk factors independently associated with acetylsalicylic acid use following multivariate analysis

Characteristic	OR (95% CI)	P
Age	1.08 (1.06–1.09)	<0.00001
Male sex	1.63 (1.28–2.08)	0.00007
Caucasian	3.53 (2.50–4.99)	<0.00001
Hypertension	3.87 (3.06–4.91)	<0.00001
Family history of cardiovascular disease	1.44 (1.12–1.87)	0.00482
Body mass index	1.03 (1.00–1.05)	0.02407

CVD, BMI and hsCRP between men and women (Table 4). However, the mean FRS was lower in ASA-treated women than their male counterparts (14.4±8.0% versus 27.0±14.8%; P<0.00001). Significantly more ASA-treated women than men were in the low (34.4% versus 8.2%; P<0.00001) and intermediate (43.0% versus 34.5%; P<0.00001) FRS categories, and significantly more men were in the high FRS than women (57.3% versus 22.5%; P<0.00001) (Table 4).

TABLE 4
Differences in acetylsalicylic acid-treated subjects according to sex

Characteristic	Male (n=255)	Female (n=151)	P
Age, years	60.6±8.7	63.2±7.8	0.002
HDL-c, mmol/L	1.26±0.33	1.55±0.43	<0.00001
LDL-c, mmol/L	3.42±0.77	3.77 0.88	0.0001
HbA1c, %	5.6±0.4	5.9±0.4	0.0001
Smoking history, %	46.7	39.1	0.15
Hypertension, %	58.4	64.9	0.21
Family history of CVD, %	30.7	31.1	1.0
Body mass index, kg/m^2	29.4±5.4	28.5±6.4	0.17
hsCRP, mg/L	3.5±5.9	3.7±3.5	0.67
Low FRS (<10%)	8.2	34.4%	<0.00001
Intermediate FRS (10% to 19%), %	34.5	43.0%	<0.00001
High FRS (≥ 20%), %	57.3	22.5	<0.00001
Mean FRS, %	27.0±14.8	14.4±8.0	<0.00001

Continuous variables are expressed as mean ± SD. BMI Body mass index; CVD Cardiovascular disease; FRS Framingham risk score; HbA1c Glycated hemoglobin; HDL-c High-density lipoprotein cholesterol; hsCRP High-sensitivity C-reactive protein; LDL-c Low-density lipoprotein cholesterol

DISCUSSION

Although the value of ASA in the secondary prevention of cardiovascular events is widely accepted and endorsed by various national and international guidelines, the use of ASA in the primary prevention of cardiovascular events remains highly disputed (1,6,12-14). The American College of Chest Physicians provides a 2B recommendation for the use of ASA in the primary prevention of asymptomatic individuals >50 years of age. However, the AHA suggests that the use of ASA for cardiovascular prophylaxis is recommended only for patients whose risk is sufficiently high for the benefits to outweigh the risks associated with the treatment (a 10-year risk of 6% to 10%) (class 1 recommendation), which is similar to the recommendations of the ATTC and ESC respectively (1-3,5). The Canadian Cardiovascular Society antiplatelet therapy recommendations for primary prevention do not recommend the routine use of ASA to prevent ischemic vascular events for men or women without evidence of manifest vascular disease; however, they recommend that (8):

> ... in special circumstances in men and women without evidence of manifest vascular disease in whom vascular risk is considered high and bleeding risk low, ASA 75-162 mg daily may be considered.

Similarly, the US Preventive Services Task Force encourages physicians to participate in shared decision making with patients and to recommend ASA use for the prevention of CVD when its potential CVD benefit (myocardial infarction in men and stroke in women) outweighs the potential harm of gastrointestinal hemorrhage.

Raju and Eikelboom (6) recently reviewed and summarized the results of the four large meta-analyses addressing this issue. When used in primary prevention, ASA produces a nominally significant 6% reduction in all-cause mortality. Although ASA does not reduce cardiovascular mortality or cancer mortality, the pooled estimates for both of these outcomes are in favour of ASA, explaining the reduction in all-cause death. Furthermore, ASA use in primary prevention reduces the composite of major cardiovascular events by 10% to 13%, reduces nonfatal myocardial infarction by 19% to 23%, and ischemic stroke by 14%. However, ASA use in primary prevention is associated with a 32% to 36% increased risk for hemorrhagic stroke, a 31% to 66% increase in major bleeding and a 37% increase in gastrointestinal bleeding. From the perspective of net benefit, 314 to 384 individuals would have to take ASA for an average of 6.9 years to prevent one major cardiovascular event, at the cost of about three gastrointestinal or major bleeds.

In the ATTC meta-analysis, the estimated absolute benefit of ASA in primary prevention in individuals in the very low risk category (global 10-year risk <5%) is estimated to be 0.2%, with a 0.1% increase in the risk of bleeding (1). However, in a higher-risk population, it is estimated that ASA use may be associated with an absolute 2% risk reduction with a 1% absolute bleeding risk, a calculation that would favour ASA use. Clinicians are, therefore, faced with the difficult task of trying to help identify appropriate candidates for ASA therapy wherein the risk reduction outweighs the potential bleeding risks.

Most recently, the Japanese Primary Prevention Project (JPPP) trial evaluated the use of low-dose ASA in >14,000 Japanese subjects >60 years of age who had concomitant risk factors for CVD (15). The trial was terminated for futility after a median follow-up of five years, with no benefit observed with ASA in major atherosclerotic events, yet a significant excess of major bleeding.

The Primary Care Audit of Global Risk Management (PARADIGM) study was established to evaluate primary care physicians' knowledge and attitudes towards global risk assessment and treatment in an otherwise healthy middle-age population of Canadians, free of cardiovascular disease or diabetes. Several important observations emanate from these data. First, the use of ASA in primary prevention is relatively modest at 13.5%. Several clinical characteristics including advanced age, male sex, Caucasian ethnicity, hypertension, smoking, a family history of CVD, increased BMI or waist circumference, an elevated serum creatinine, an increased hsCRP level and a higher FRS were associated with ASA use in primary prevention in the univariate analysis. However, in the multivariate analysis, only age, male sex, Caucasian ethnicity, elevated BMI, hypertension and a family history of CVD were independent discriminators of ASA use.

When we examined the appropriateness of therapy by examining the distribution of ASA use among the various FRS subgroups, we noted an appropriate increase in ASA use in patients with higher CV risk. However, the majority of ASA use (55%) occurred in patients at low or intermediate risk, groups in which the risk:benefit ratio of ASA remains uncertain. Although this trend was seen in men and women, the magnitude was greater in women, in that approximately 80% of ASA use was in the low- and intermediate-risk groups.

In summary, we provide a contemporary analysis of ASA use in the primary prevention of CVD in a large number of otherwise healthy middle-age Canadians free of CVD or diabetes. Our assessment reveals fairly frequent use of ASA in low- and intermediate-risk patients, more so in women than in men. Given the uncertainty of benefit of ASA in this population, further studies and clarification of guidelines for the use of ASA in primary prevention are required.

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