Prevention of Vascular Events in High-risk Individuals: Optimal Use of Antiplatelet Therapies in Primary Care

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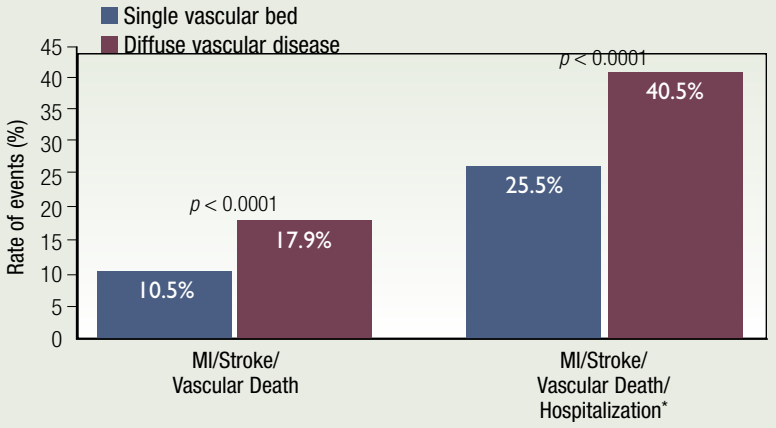
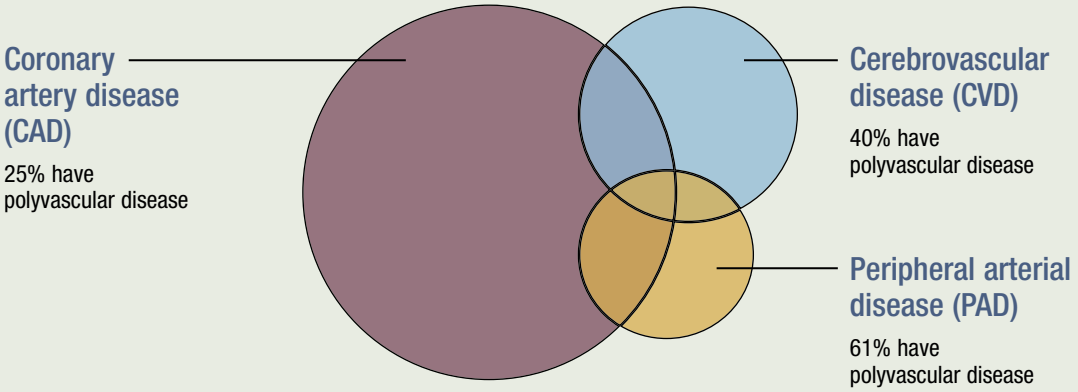
Given Canada's aging population, the number of people living with atherosclerotic disease (*i.e.*, coronary artery disease [CAD], cerebrovascular disease, and/or peripheral arterial disease [PAD]) will continue to rise over the next 20 to 25 years. Included in this group will be a substantial and growing population of patients who have survived a major atherothrombotic event (*e.g.*, myocardial infarction [MI], stroke). With the healthcare system already straining to keep up with current demands, optimal prevention measures for people with atherosclerotic disease—who are at very high risk of primary or recurrent events—is essential not only to prolong survival for these individuals, but also to reduce the burden on the healthcare system.

FIGURE 1 REACH 3-year Event Rates: Single Vascular Bed vs. Diffuse Vascular Disease[4]



*Hospitalization for another type of vascular event or vascular procedure.

FIGURE 2 Prevalence of Polyvascular Disease in the REACH Registry[5]



Evidence-based medicine has provided healthcare practitioners with a variety of proven therapies that can help prevent events in patients who have existing atherosclerotic disease. Depending on the type of event targeted, these may include beta-blockers, inhibitors of the renin-angiotensin system (*i.e.*, ACE inhibitors or ARBs), lipid-lowering medication and antiplatelet therapy. This last type of therapy is the focus of this review. Antiplatelet therapy is indicated for all patients with atherosclerotic disease, regardless of the location (coronary, cerebrovascular or peripheral circulation). While these agents (*e.g.*, aspirin, clopidogrel) may be initiated by specialists in hospital, patients will usually be managed over the long term by their primary care providers. It is therefore the responsibility of primary-care practitioners to ensure that their patients are receiving optimal antiplatelet therapy, optimize the regimen if necessary, and ensure continued adherence to the optimal regimen over the long term. The REACH registry and other studies[1,2] have demonstrated that, while most Canadians with atherosclerotic disease do receive antiplatelet therapy, there is still a large minority that are not receiving these potentially life-saving medications.

It is the responsibility of primary-care practitioners to ensure that their patients are receiving optimal antiplatelet therapy, optimize the regimen if necessary, and ensure continued adherence to the optimal regimen over the long term.

This review outlines the scope of the problem in preventing atherothrombotic events, presenting recent data from the Reduction of Atherothrombosis for Continued Health (REACH) registry documenting the high rate of events in high-risk patients. It also includes a discussion of the evidence for antiplatelet therapy in general, with a focus on clopidogrel as an important component of optimal antiplatelet therapy for many high-risk patients.

THE SCOPE OF THE PROBLEM: HIGH RISK OF EVENTS IN PATIENTS WITH VASCULAR DISEASE (REACH REGISTRY DATA)

The most up-to-date epidemiologic data for atherothrombotic events, in Canada and around the world, come from the REACH registry. The goal of this registry is to compile an international data set to extend knowledge of atherothrombotic risk factors and ischemic events in the outpatient setting.[3] The registry includes data on 67,888 patients from 5,587 different physician practices in 44 countries across six major regions worldwide (Latin America, North America, Europe, Asia, the Middle East, and Australia).[4] To be included in the registry, patients had:

- proven symptomatic atherosclerotic disease in the cerebrovascular, coronary or peripheral circulation; OR
- at least three atherothrombotic risk factors, from among the following:
  – diabetes treated with hypoglycemic agents;
  – evidence of diabetic nephropathy;
  – ankle-brachial index [ABI] ≤ 0.9;

Clinical Considerations

■ Patients with "stable" vascular disease are not so stable.

- Over 3 years, the symptomatic REACH population (*i.e.,* those with a history of coronary, cerebrovascular or peripheral arterial disease, regardless of how remote) had an average annual major vascular event rate of 4%. Put in terms of 10-year risk, this is double the 20% rate we consider to be high-risk by Framingham calculation standards.

■ Patients with a history of atherothrombosis should be receiving "triple therapy."

- Statin, RAAS inhibition with ACEI or ARB, and antiplatelet therapy each reduce the risk of major vascular events by 25%. Unless clearly contraindicated, all secondary-prevention patients should receive life-saving "triple therapy."

■ Patients with atherothrombotic disease in one vascular bed are likely to have it in other beds as well.

- 25%, 40% and 61% of REACH subjects with coronary, cerebrovascular and peripheral arterial disease, respectively, had atherothrombosis in another bed.
- The presence of diffuse vascular disease roughly doubles the risk of future events. There is evidence that such patients may benefit from more aggressive antiplatelet therapy.

■ Patients with symptomatic peripheral arterial disease are at extremely high risk of heart attack and stroke.

- PAD is under-diagnosed and under-treated. Clinicians should be diligent to screen for symptoms of intermittent claudication.
- Patients with symptoms of leg pain should be evaluated with a careful history, physical exam and measurement of ankle-brachial index (ABI).

■ Despite the use of drugs to treat dyslipidemia, hypertension and diabetes, many secondary-prevention patients are not where they need to be.

- Achieving guideline targets will reduce the incidence of major vascular events and microvascular disease.
- Physicians must remain diligent in continuing to add pharmacologic and non-pharmacologic strategies to achieve these targets. In the Canadian healthcare system, this is largely the mandate of primary care.

■ Lifestyle changes are important, too.

- The following measures are evidence-based risk-reduction strategies:
  - sodium restriction to a maximum of 1500 mg/day;
  - 60 minutes daily of moderate exercise;
  - weight control to a BMI of 18.5 to 25;
  - smoking cessation; and
  - alcohol consumption of < 14 standard drinks/week in men or < 9 standard drinks/week in women.

■ The benefit of dual antiplatelet therapy with aspirin + clopidogrel depends on the clinical situation.

- There is clear benefit in patients with a history of acute coronary syndrome regardless of the type of ACS or the use of medical or interventional management.
- There is no benefit in long-term secondary stroke prevention.
- There is no benefit in patients without a clear history of an atherothrombotic event.

■ Low-dose aspirin monotherapy is an example of "less is more."

- Low-dose aspirin monotherapy (81 mg) provides the same benefit as higher doses (325 mg), with a lower risk of bleeding.
- If your patient is taking > 81 mg of apirin daily for vascular protection, consider switching to the lower dose.

■ Antiplatelet therapy should not be stopped for trivial reasons.

- Easy bruising, subconjunctival hemorrhage, epistaxis and most surgical or dental procedures are not good reasons to stop antiplatelet drugs.

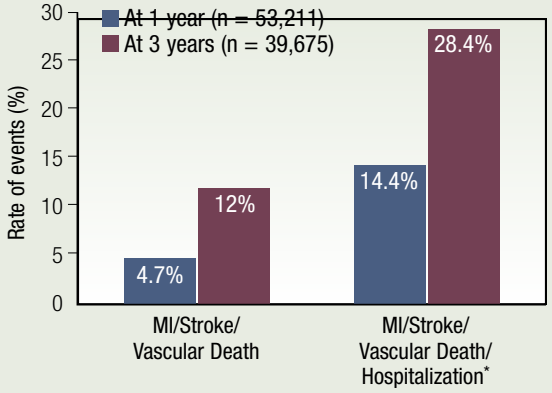
– presence of at least one carotid plaque as evidenced by intima-media thickness [IMT] twice that of neighboring sites;
– asymptomatic carotid stenosis ≥ 70%;
– systolic blood pressure (BP) ≥ 150 mmHg despite therapy for at least three months;
– dyslipidemia currently treated with medication;
– current smoking; and
– age 65 years or older for men and 70 years or older for women.

The data collected upon entry into the registry included medical history, risk factors, demographic information, and management. Clinical events were recorded during the four-year follow-up period. REACH was a non-interventional registry and did not test any specific medications or procedures.

Baseline data. Approximately 40% of the REACH registry's recruiting physicians were primary-care practitioners; a further 30% were internists and the remainder were cardiologists, neurologists, angiologists, vascular surgeons, endocrinologists and others.[3]

Analysis of the baseline data for the 67,888 patients in the REACH registry illustrated the systemic nature of atherosclerotic disease, in that there was a considerable

FIGURE 3 Incidence of Major Clinical Events at 1 and 3 Years Among Symptomatic REACH Patients[4]



*Hospitalization for another type of vascular event or vascular procedure.

TABLE 1 Medication Use at Baseline and 3 Years Among Symptomatic REACH Patients[4]

Medication[a] (%)	Baseline	3 Years
≥ 1 antihypertensive	90.9	91.1
≥ 1 antithrombotic	92.4	92.1
Aspirin alone	56.6	56.9
Aspirin + other antiplatelet	14.5	12.8
Other antiplatelet alone	13.6	14.2
Oral anticoagulant	12.9	13.5
≥ 1 lipid-lowering drug	72.9	75.9
Statin	68.3	71.9
Diabetic patients with ≥ 1 antidiabetes drug[b]	87.3	84.6

[a]Denominators may vary due to missing data.
[b]Percentage calculated from 14,282 diabetic patients at baseline and 10,628 at 3 years.

subgroup with diagnosed disease in more than one arterial bed. Approximately two-thirds had diagnosed disease in one arterial bed, 16% had diagnosed polyvascular disease (or diffuse vascular disease) and 18% were enrolled based on risk factors alone (Figure 2).[5] Of note, the actual prevalence of diffuse vascular disease was likely higher, since patients with one diagnosis or those with only risk factors were not necessarily evaluated for disease in other vascular beds.

> … the proportion of patients enrolled by primary-care physicians was substantially higher in the Canadian cohort (74.7%) than in the overall REACH cohort. Therefore, REACH subjects are likely to be representative of the types of patients that most Canadian primary-care physicians see on a daily basis.

Canadian REACH cohort. Of the patients in the REACH registry, 1,976 are Canadian. The demographic and clinical characteristics of this subset of patients were published as a separate paper in the *Canadian Journal of Cardiology* in 2009.[1] The characteristics of the cohort were reported to be similar to other, larger registries of Canadian patients, and the proportion of patients enrolled by primary-care physicians was substantially higher in the Canadian cohort (74.7%) than in the overall REACH cohort. Therefore, REACH subjects are likely to be representative of the types of patients that most Canadian primary-care physicians see on a daily basis.

REACH GLOBAL DATA

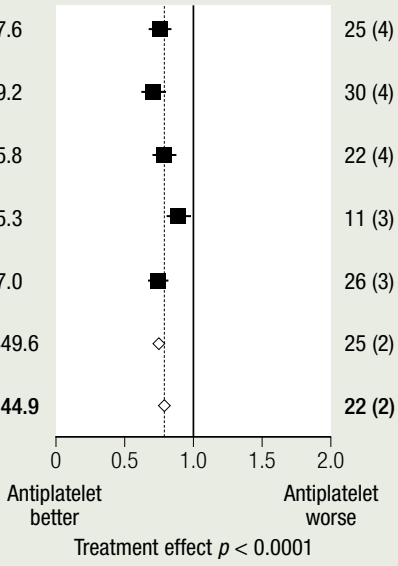
Risk of events over three years. Three years after the REACH cohort was fully enrolled, investigators examined the data for the large subset of patients with established vascular disease at baseline who had available three-year data (n = 32,247). The primary event assessment was incidence of the composite of MI, stroke and vascular death. Other assessments included the rates of hospitalization for vascular events other than those in the primary composite outcome. The investigators also assessed medication use during that period. The assessments were carried out for this whole group of patients and were also conducted on subgroups divided by baseline disease characteristics.

Three-year clinical event data. For the primary composite endpoint, the incidence rate was 4.7% at one year; in the three-year analysis, this had grown to 12.0% (Figure 3). When hospitalizations were added to the composite, the rate was 14.4% at 1 year and 28.4% at 3 years (Figure 3).

Of note, the risk of events was significantly higher among the subset of patients with diagnosed diffuse vascular disease compared to those who were diagnosed

FIGURE 4 Effects of Antiplatelet Therapy on Vascular Events in Five High-risk Categories: Antithrombotic Trialists' Collaboration[6]

Category of trial	No. of trials with data	No. (%) of vascular events: Allocated antiplatelet	No. (%) of vascular events: Adjusted control	Observed-expected	Variance	% odds reduction (SE)
Previous myocardial infarction	12	1,345/9,984 (13.5)	1,708/10,022 (17.0)	-159.8	567.6	25 (4)
Acute myocardial infarction	15	10,07/9,658 (10.4)	1,370/9,644 (14.2)	-181.5	519.2	30 (4)
Previous stroke/transient ischemic attack	21	2,045/11,493 (17.8)	2,464/11,527 (21.4)	-152.1	625.8	22 (4)
Acute stroke	7	1,670/20,418 (8.2)	1,858/20,403 (9.1)	-94.6	795.3	11 (3)
Other high risk	140	1,638/20,359 (8.0)	2,101/20,543 (10.2)	-222.3	737.0	26 (3)
Subtotal: all except acute stroke	188	6,035/51,494 (11.7)	7,644/51,736 (14.8)	-715.7	2,449.6	25 (2)
All trials	**195**	**7,705/71,912 (10.7)**	**9,502/72,139 (13.2)**	**-810.3**	**3,244.9**	**22 (2)**



Heterogeneity of odds reductions between:
5 categories of trial: $x^2 = 21.4$, df = 4; $p = 0.0003$
acute stroke vs. other: $x^2 = 18.0$, df = 1; $p = 0.00002$

with vascular disease in only one arterial bed. For the primary composite endpoint, the three-year incidence rate was 10.5% for those with single-bed vascular disease and 17.9% for those with diffuse vascular disease (absolute increased risk 7.3%, $p < 0.0001$; Figure 1). For the composite endpoint of MI/stroke/vascular death/hospitalization, the three-year event rates were 25.5% for those with diagnosed single-bed vascular disease and 40.5% for those with diffuse vascular disease ($p < 0.0001$; Figure 3).

Analysis of three-year data for the Canadian REACH subgroup is in progress.

CARDIOVASCULAR RISK IS STILL UNDERTREATED IN HIGH-RISK PATIENTS

The three-year event rates for patients who were symptomatic at entry into the REACH registry (12% for MI/stroke/vascular death and 28.4% for MI/stroke/vascular death/hospitalization) illustrate the high rate of cardiovascular risk in these patients. This is despite treatment with a number of risk-reduction therapies at baseline and at three years (Table 1).

Some of this high risk could likely be attenuated by more universal use of proven interventions. For example, current tobacco use among patients with diagnosed vascular disease was quite high (14.4%). Smoking cessation efforts for that subgroup would likely yield significant benefits in terms of risk reduction. In terms of medication, statin use was reported in only 69.4% of patients in the overall REACH population.[5] Antiplatelet therapy also appeared to be suboptimally used: approximately 15% of patients were not receiving any antiplatelet agent at baseline, and a similar rate was observed at three years (Table 1). The majority of those treated with antiplatelet therapy were receiving aspirin alone.

Additionally, even among patients receiving therapy, there was evidence of inadequate treatment. While more than 90% of the registry's hypertensive population was receiving antihypertensive therapy, half of the population had elevated BP at baseline.[5]

It is interesting to note that, at baseline, among the Canadian REACH subset, these statistics were somewhat better than in the overall cohort (although there is still a care gap that remains to be addressed). In the Canadian subgroup, the use of antihypertensive, antiplatelet and lipid-lowering therapies was significantly higher than in the overall REACH population. The control of risk factors was also better: more Canadian

FIGURE 5 Clopidogrel vs. Aspirin (CAPRIE): Annual Incidence Rate of MI, Ischemic Stroke, Vascular Death[7]

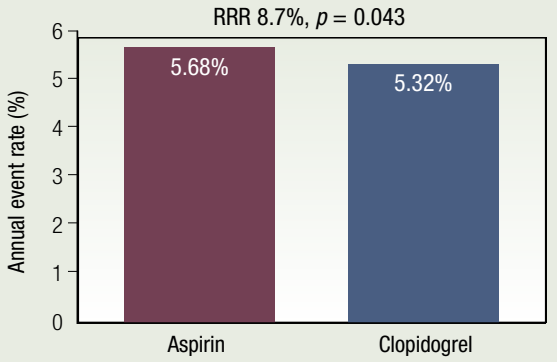
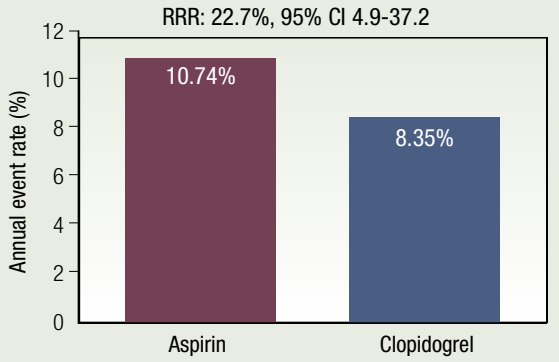


FIGURE 6 Clopidogrel vs. Aspirin (CAPRIE): Annual Incidence Rate of MI, Ischemic Stroke, Vascular Death Among Patients with Diffuse Vascular Disease[7]



patients were at target levels for total cholesterol and BP at baseline compared to the overall REACH cohort.[1]

EVIDENCE FOR PROTECTIVE EFFECT OF ANTIPLATELET AGENTS

One of the shortcomings of treatment patterns identified in the REACH registry was suboptimal antiplatelet therapy. The use of aspirin alone was observed in 56.6% of symptomatic patients at baseline, another antiplatelet alone in 13.6%, and aspirin + another antiplatelet in 14.5%. This left 15.3% not receiving any antiplatelet therapy. Although some of these patients may have contraindications, this points to a significant care gap.

The Antithrombotic Trialists' Collaboration. The fact that more than 15% of REACH patients with established vascular disease were not receiving antiplatelet therapy at baseline should be recognized as significant undertreatment. The evidence showing vascular protection with these agents is clear. The Antithrombotic Trialists' Collaboration published a systematic overview of studies evaluating an antiplatelet regimen vs. control (n = 135,000) or evaluating one antiplatelet regimen vs. another (n = 77,000) in high-risk patients (with acute or previous vascular disease or some other predisposing condition).[6] For the primary composite outcome measure of non-fatal MI, non-fatal stroke, or vascular death, allocation to antiplatelet therapy reduced the risk by about 25% compared to controls. In terms of the individual components of the composite, there were reductions of approximately 33% for non-fatal MI, approximately 25% for non-fatal stroke, and approximately 17% for vascular mortality. The benefits of therapy were seen regardless of the primary high-risk condition for which the antiplatelet therapy was being used (Figure 4).

> The CAPRIE investigators reported that, for patients with diffuse vascular disease (MI + PAD or stroke), the annual event rates were 8.35% and 10.74% for clopidogrel and aspirin, respectively (statistically significant relative risk reduction of 22.7%).

CAPRIE. The fact that aspirin continues to be used as the primary antiplatelet therapy is a reflection of the hurdles of the healthcare system, while evidence suggests that clopidogrel could be seen as the first-line treatment of choice for most patients with established vascular disease. The Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study[7] was designed to assess the efficacy of clopidogrel compared to aspirin in reducing the risk of a composite outcome of ischemic stroke, MI, or vascular death. The trial population consisted of 19,185 patients with established vascular disease (*i.e.*, divided into similarly sized groups with recent ischemic stroke, recent MI, or symptomatic PAD). The subjects were followed for one to three years (mean 1.9 years).

The investigators reported that there was a 5.32% annual event rate for patients treated with clopidogrel, compared to a 5.83% annual rate with aspirin (relative risk reduction of 8.7% in favor of clopidogrel; $p = 0.043$; Figure 5). There were no major safety differences reported between treatment groups. Furthermore, the CAPRIE investigators reported that, for patients with diffuse vascular disease (MI + PAD or stroke), the annual event

rates were 8.35% and 10.74% for clopidogrel and aspirin, respectively (statistically significant relative risk reduction of 22.7%; Figure 6).[7]

Subsequent analysis of the CAPRIE cohort also revealed that, among patients who had previously experienced an event, the relative risk reduction (secondary prevention) in favor of clopidogrel was more substantial and remained statistically significant (relative risk reduction of 14.9%; $p = 0.04$).[8]

Combination antiplatelet therapy. In several different populations of patients with established vascular disease, the combination of clopidogrel and aspirin has proven to be superior to aspirin alone for preventing events. The best evidence is for patients who have experienced an acute coronary syndrome (ACS: acute MI or unstable angina), with or without percutaneous coronary intervention (PCI). Results from several studies (*e.g.,* CURE,[9] PCI-CURE,[10] PCI-CLARITY,[11] COMMIT[12]) have shown statistically significant reductions in subsequent cardiovascular events in these high-risk groups with the combination of aspirin and clopidogrel compared to aspirin alone. It should be acknowledged, however, that these trials were conducted in patients who primarily had CAD.

CONCLUSIONS

Patients with established vascular disease are at very high risk for vascular events, as illustrated by the three-year data from the REACH registry. Certain subgroups have been identified that are at even greater risk, the most striking of which are those patients with diffuse vascular disease (*i.e.,* diagnosed vascular disease in more than one arterial bed). These patients have approximately double the risk of experiencing a major event compared to those with diagnosed disease in only one vascular bed.

While Canadian physicians are doing well in terms of widespread use of proven risk-reduction therapies, there is still considerable room for improvement. Smoking cessation is of paramount importance in this population and should be aggressively targeted. Pharmacotherapy should also be optimized, including adjusting regimens to reach established national targets for hypertension, dyslipidemia, and diabetes.

The REACH data also indicate that antiplatelet therapy is being suboptimally used. Aspirin monotherapy remains the most commonly prescribed antiplatelet regimen, despite evidence that clopidogrel may offer superior protection, particularly for patients with diffuse vascular disease. In clinical trials over the past decade, the combination of aspirin and clopidogrel has consistently proven to be more effective than aspirin monotherapy for the prevention of major vascular events for the first year following ACS including ST-elevation MI (STEMI) and non-ST-elevation MI (NSTEMI) with or without PCI.

Atherothrombosis is a major cause of morbidity and mortality, around the world and in Canada. To reduce the burden of atherothrombotic events on patients and on the healthcare system, Canadian physicians need to continue to employ optimal risk-reduction strategies, including effective use of the best possible antiplatelet regimens.

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