Anti-thrombotic options for secondary prevention in patients with chronic atherosclerotic vascular disease: what does COMPASS add?


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The publication of the recent COMPASS study1–3 raises key clinical questions:

• What is the potential for clinically worthwhile improvements in outcomes, in the context of currently proven secondary prevention measures?

• What are the therapeutic implications of atherothrombotic disease across different vascular territories?

• Can we extrapolate from studies in acute vascular disease to long-term chronic vascular disease?

• What does the COMPASS regimen add to current secondary prevention therapies for chronic arterial vascular disease?

• How do the benefits and risks of the combination of very low dose of rivaroxaban and aspirin compare with those seen with other anti-thrombotic combinations in patients with stable vascular disease?

• How does the new dual pathway anti-thrombotic therapy compare with the impact of other accepted pharmacological secondary prevention measures in stable vascular disease [hypertension control, reducing low density lipoprotein (LDL) cholesterol, angiotensin-converting enzyme (ACE) inhibitors]?

Is there potential for additional secondary prevention therapies?

For the prevention of ischaemic clinical events in those with chronic atherosclerosis (secondary prevention), current guidelines recommend lifestyle change (tobacco avoidance, a healthy diet, and regular exercise), drugs (LDL cholesterol lowering primarily with statins, beta-blockers, glucose control, angiotensin-converting enzyme inhibitors/blockers, and anti-platelet drugs), and coronary revascularization in high-risk individuals. These secondary prevention strategies are based on robust evidence and can substantially reduce cardiovascular (CV) complications. However, the residual risks of events due to cardiovascular disease (CVD) remain significant for patients with existing (CVD)4–6 even among populations with very high adherence to prescribed therapies. For example, among patients with multiple CV risk factors or established disease and well treated with secondary prevention therapies, contemporary studies indicate a 15–20% rate of CV death, myocardial infarction (MI), or stroke at 3 and 4 years, respectively.7,8

‘The implications of these observations are that there is scope for further improvement and potential opportunities for novel strategies’.

Atherothrombosis is a condition affecting multiple vascular territories (‘polyvascular disease’) with varying clinical therapeutic implications based on the vascular territories affected

Atherothrombotic disease underlies the diverse clinical manifestations that are determined by the vascular territory affected, the extent of vascular obstruction, and the characteristics of the perfused territory. Increased risks for vascular complications are observed in all vascular territories affected (coronary, cerebrovascular, or peripheral arteries), and the clinical complications are principally due to thrombotic obstructions of specific vessels.5,9–11
The pathophysiological mechanisms include the direct consequences of vascular obstruction to a coronary or peripheral artery, or the embolic consequences of disruption of an atheromatous or an intimal lesion with thrombosis and peripheral embolization.\textsuperscript{5,9--14} In addition, patients may sustain the late consequences of myocardial, cerebral, peripheral limb, and other vascular bed injury. Although the clinical presentation may be the result of vascular occlusion in one arterial vascular bed, subsequent events can be the result of occlusion of other vascular beds. For example, peripheral artery occlusion can present as intermittent claudication, but subsequent complications can occur in a coronary artery initiating an MI or in a cerebrovascular artery leading to a stroke.\textsuperscript{5,9--11} Many key risk factors are similar for these different clinical manifestations across vascular beds,\textsuperscript{6} and similar secondary prevention measures are recommended in guidelines.\textsuperscript{15,16} However, the impact of some therapies may differ depending on whether the primary clinical event is due to coronary, cerebrovascular, or peripheral artery disease (PAD). For example, the potent anti-platelet therapy, ticagrelor was clearly beneficial after an acute coronary syndrome (ACS) and in those with a history of MI\textsuperscript{7,18} but benefits have not been observed in patients with PAD\textsuperscript{19} or cerebrovascular disease.\textsuperscript{20}

‘The implications are that while atherothrombotic disease manifests across diverse arterial vascular territories, therapies may differ in their clinical impact on different arterial beds’.

Can we extrapolate from studies in acute vascular disease to long-term chronic stable vascular disease?

Several anti-thrombotic combinations have been tested in the context of an acute vascular event and in most instances following presentation with MI or ACS. These include combined anti-platelet therapies,\textsuperscript{21,22} more potent P2Y12 antagonists combined with aspirin,\textsuperscript{23,24} and other anti-thrombotic combinations.\textsuperscript{25--27} These treatments are administered during or soon after the acute vascular event, with continued treatment for 12 months or longer.\textsuperscript{17,18,20--28} In the context of an acute vascular event, thrombus may still be present in the artery, and there may be evidence of plaque disruption at more than one site. In addition, mechanical interventions (e.g. stents) require specific anti-thrombotic therapies. Although activation of platelets and of the coagulation pathways is implicated in thrombus formation in both acute and chronic settings, their relative contributions may differ. Potent anti-platelet combinations have been shown to be particularly effective in preventing stent thrombosis and in reducing vascular events during the in-hospital phase and in the early months after an ACS. However, they also increase bleeding both in the acute and long-term phases. For example, a meta-analysis of prolonged dual anti-platelet therapy (DAPT) showed an increase in major bleeding with DAPT (1.85% vs. 1.09%, risk ratio (RR) 1.73, \(P = 0.004\)).\textsuperscript{29} ‘This suggests that anti-thrombotic regimens designed for the acute phase (e.g. ACS) may not necessarily be optimal in terms of the balance of risk vs. benefit for chronic stable vascular patients’.

What does the COMPASS regimen add to current secondary prevention therapies for stable arterial vascular disease?

Single anti-platelet therapy (predominantly aspirin) is the currently accepted anti-thrombotic long-term therapy for patients with stable vascular disease\textsuperscript{15,16,30,31} and is used by the majority of patients.\textsuperscript{32} The concept of combining anti-platelet therapy and anti-coagulation is not new. For example, the WAVE study of warfarin and anti-platelet therapy vs. anti-platelet therapy alone in patients with chronic stable PAD did not reduce major adverse cardiovascular events (MACE) or major adverse limb events (MALE), but increased life threatening and intracranial bleeds.\textsuperscript{12} In a meta-analysis of 10 trials (5938 patients) of warfarin plus aspirin vs. aspirin in patients with recent MI, there was no impact on mortality, but MI [RR 0.56, confidence interval (CI) 0.48--0.69], and stroke (RR 0.46, CI 0.27--0.77) were reduced.\textsuperscript{13} However, there was an increased risk of major (RR 2.48, CI 1.67--3.68) and minor bleeding (RR 2.65, CI 2.14--3.69). Because of the increased bleeding risk, including that of intracranial haemorrhage (ICH), the lack of an effect on mortality, and the need for monitoring the intensity of coagulation, combined use of warfarin and aspirin in those with stable vascular disease has not been widely adopted in clinical practice.

Alternative or combined anti-platelet therapy?

Clopidogrel has been compared with aspirin in patients with stable CV disease in the CAPRIE study.\textsuperscript{33} In 19 185 patients with symptomatic atherosclerotic disease clopidogrel reduced the risk of MACE (CV mortality/MI/stroke) by 8.7% compared to aspirin (5.83% vs 5.32%; \(P = 0.043\)), but there was no reduction in mortality or stroke. The benefit of clopidogrel was most evident in the PAD subgroup but less clear among those with prior coronary or cerebrovascular disease. Additionally, there was no significant reduction in the secondary outcome of ischaemic stroke, MI, vascular death, or amputation (\(P = 0.076\)).\textsuperscript{33}

Clopidogrel plus aspirin was tested against aspirin in the CHARISMA trial.\textsuperscript{14} In 15 603 patients with clinically evident CV disease or CV disease risk factors without clinically evident disease, adding clopidogrel to aspirin did not significantly reduce the risk of stroke, MI, or CV death compared with aspirin alone (hazard ratio (HR) 0.93, CI 0.83--1.05).\textsuperscript{15} However, in a secondary analysis, among those with prior CV disease the combination of clopidogrel and aspirin produced a significant benefit in MACE (6.9% clopidogrel plus aspirin vs. 7.9% with aspirin plus placebo; RR 0.88; CI 0.77--0.998; \(P = 0.046\)).\textsuperscript{14} There were numerically more severe bleeds using the GUSTO criteria (1.7% vs. 1.5%), and fatal bleeds (0.3% vs. 0.2%) and significantly more moderate bleeds (2.1% vs. 1.3%, RR 1.62, CI 1.27--2.08; \(P < 0.001\)) among those treated with combination therapy.

The TRAP\textsuperscript{35} and PEGASUS\textsuperscript{16} trials were conducted more recently and in the context of more aggressive secondary prevention measures including widespread use of statins and ACE inhibitors.
In the TRA2P study, 26 449 patients with a history of MI, ischaemic stroke, or PAD were randomized to vorapaxar (2.5 mg daily) or placebo on background therapy of physician chosen single or dual anti-platelet therapies.\textsuperscript{24} Cardiovascular death, MI, or stroke occurred in 9.3% of the vorapaxar patients and 10.5% of the placebo patients (HR 0.87, CI 0.80–0.94; P = 0.001). GUSTO major or severe bleeding was significantly increased (4.2% vs. 2.5%, HR 1.66, CI 1.43–1.93, P < 0.001) and intracranial bleeds were significantly increased (1.0% vs. 0.5%, HR 1.94, CI 1.39–2.70, P < 0.001) among patients randomized to vorapaxar.\textsuperscript{34} In the PAD subgroup, vorapaxar reduced limb events including acute limb ischaemia and urgent revascularization.\textsuperscript{35}

In PEGASUS (21 162 patients who had an MI 1–3 years previously), either 60 mg b.i.d. or 90 mg b.i.d. of ticagrelor plus aspirin was tested against aspirin plus placebo. The 60 mg b.i.d. dose of ticagrelor decreased the risk of CV death, MI, or stroke. (HR 0.84, CI 0.74–0.95; P = 0.004) and similarly for the 90 mg b.i.d. dose of ticagrelor (HR 0.85, CI 0.75–0.96; P = 0.008) vs. aspirin and placebo.\textsuperscript{36} The rates of thrombosis in myocardial infarction (TIMI) major bleeding were higher with ticagrelor (2.3% with 60 mg, 2.6% with 90 mg) than with placebo (1.06% P < 0.001 for each comparison). Bleeding leading to study drug discontinuation and bleeding leading to transfusions were each increased three- to five-fold with the dual anti-platelet combinations (HR 3.08–5.79), but there was no significant difference in intracranial or in fatal bleeding.\textsuperscript{18,36} Ticagrelor (both doses combined) in the first year of treatment (HR 2.32, CI 1.75–3.07) but without a significant excess thereafter (Year 2: HR 1.19, CI 0.84–1.68; Year 3: HR 1.05, CI 0.63–1.75).\textsuperscript{3}

Overall implications of the COMPASS combined regimen in the context of current secondary prevention measures

Randomized trial evidence suggests that adding an anti-platelet agent or an anti-thrombin to aspirin may be of benefit in patients with stable CVD, particularly those with coronary artery disease (CAD) or PAD. On a review of the evidence one option is to use clopidogrel plus aspirin based on the CHARISMA trial.\textsuperscript{14} However, based on the magnitude of benefit in the trial data, the preferred options for clinicians to consider are the PEGASUS regimen (ticagrelor 60 mg b.i.d. plus low dose aspirin for patients who are 1–3 years post-MI and have high-risk features such as age, PAD, diabetes, chronic kidney disease, recurrent MIs, and multivessel disease),\textsuperscript{18,36} or the COMPASS regimen combining very low dose rivaroxaban and low dose aspirin in a broad range of stable CAD or PAD patients who have high-risk features.\textsuperscript{1–3} The latter regimen is particularly attractive given its impact on reducing CV mortality and all-cause mortality. It also markedly reduced MALE. The COMPASS regimen\textsuperscript{1–3} and ticagrelor 60 mg (PEGASUS)\textsuperscript{18} both reduced ischaemic strokes without significant increases in ICH. The combination of efficacy and mortality improvements with the dual pathway COMPASS regimen makes this option clinically attractive.
Anti-thrombotic strategies and risks of bleeding

More intensive anti-thrombotic regimens increase the risks of bleeding (Table 2) so more intensive anti-thrombotic therapy is not for all patients with stable vascular disease. Fatal bleeding and ICH are not significantly increased (except ICH in TRA2P) but other major bleeding – defined as GUSTO moderate or severe. The implications of the COMPASS results for clinical practice are worth considering. Patients with stable vascular disease and additional risk features have substantial rates of CV events over time, including deaths, strokes, MIs, and MALE. This is despite currently applied lifestyle and secondary prevention measures (Figure 2). Addition of anti-thrombotic therapy (generic clopidogrel or ticagrelor or vorapaxar or very low dose rivaroxaban) to aspirin (compared with aspirin alone) reduces major adverse cardiac events, but the magnitude of treatment effects differ by type of event prevented and the types of patients who benefit, with the respective strategies, and the bleeding risks also differ. What is unknown is how the various strategies would compare in trials where they are directly compared. Such trials are desirable given the magnitude of the global public health burden of CVD.

Future secondary prevention therapies may include profound LDL reduction with proprotein convertase subtilisin kexin 9 (PCSK9) inhibition and/or modification of inflammation in the vascular wall. Interventions to modify risks of thrombosis, to profoundly lower LDL cholesterol and to modulate inflammation are not necessarily independent, but combined therapies need to be evaluated, including their cost effectiveness.
Conclusions

The dual mechanism COMPASS regimen (low dose NOAC with rivaroxaban 2.5 mg b.i.d. plus low dose aspirin as an anti-platelet agent) is of at least similar or greater benefit to that seen in studies of other antithrombotic regimens in reducing the composite of CV death, MI, or stroke. Further, it reduced MALE and CV and total mortality. Although it increased the risk of bleeding, the net clinical benefit was favourable.

The dual mechanism COMPASS regimen is of comparable benefit to that seen with accepted secondary prevention regimens (aspirin, lipid lowering, blood pressure lowering, and angiotensin-converting enzyme inhibitors), and hence the potential clinical impact of using these proven drugs together is substantial.

The data from the respective trials need to be interpreted in the context of the populations included, the prevalent use of secondary prevention therapies and the increased use of such therapies over time. Caution must be exercised in cross trial comparisons, but the time trends in the reference arms of the trials suggest that the effects may be additive.

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