# Applying contemporary antithrombotic therapy in the secondary prevention of chronic atherosclerotic cardiovascular disease

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For 4 decades, antithrombotic therapy with aspirin has been a cornerstone of secondary prevention for patients with chronic atherosclerotic cardiovascular disease (ASCVD). Unfortunately, despite the use of evidence-based therapies, patients with ASCVD continue to have recurrent major adverse cardiovascular events including death, myocardial infarction, and stroke—at a rate of approximately 2%-4% per year. To combat this continuing risk, several recent trials have evaluated the efficacy and safety of more intensive antithrombotic strategies through prolonged dual antiplatelet therapy (DAPT), combining a P2Y12 receptor antagonists and low-dose aspirin, or alternatively applying a dual pathway inhibition approach, combining low-dose non—vitamin K antagonist anticoagulant and low-dose aspirin. Both combination strategies have been shown to reduce recurrent ischemic events but at the cost of increased bleeding events. The clinical application of these antithrombotic strategies requires clinicians to assess and balance the risk of recurrent ischemic and bleeding events in an individual patient. Furthermore, clinicians may also need to adapt their antithrombotic strategies to achieve best patient outcomes, as ASCVD is a progressive disease and the risks of cardiovascular ischemic and bleeding events may shift over time. This state-of-the-art article reviews evidence from the trials and provides a practical approach to the application of DAPT and dual pathway antithrombotic therapy in the long-term management of patients with chronic ASCVD. (Am Heart J 2019;218:100-9.)

Atherosclerosis is a chronic vascular condition slowly progressing from minor fatty streaks and plaques in early adulthood to flow-limiting stenoses that eventually lead to tissue ischemia or to sudden acute vascular events following plaque disruption or erosion and subsequent thrombosis. At a population level, clinically documented coronary artery disease (CAD), peripheral arterial disease (PAD), and cerebrovascular disease are strong independent predictors of future cardiovascular events. With an estimated 423 million affected persons worldwide and nearly 18 million deaths each year, cardiovascular disease remains the single most common cause of morbidity and mortality, responsible for one third of deaths in people over the age of 35 years.[1] Cardiovascular disease is also a major economic burden, accounting for 55% of direct health care costs and an estimated 45% of population productivity loss in the United States.[2]

In patients with atherosclerotic cardiovascular disease (ASCVD) including CAD, peripheral vascular disease, and cerebral vascular disease, antithrombotic therapies, particularly aspirin, have been a cornerstone of secondary prevention (ie, after the occurrence of a clinical manifestation of the disease in the heart, peripheral vasculature, or brain) for >4 decades. Clinical trials in subjects with chronic cardiovascular disease demonstrate a yearly 2%-4% continuing risk of recurrent cardiovascular ischemic events of death, myocardial infarction, or stroke (MACE) annually with observational data demonstrating rates approximately double randomized trials in spite of the application of currently available medical therapies[3-7]. A number of alternative antiplatelet and anticoagulant therapies used alone or in combination have been tested to reduce this residual risk. In

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general, trials of more intensive antithrombotic therapy have demonstrated a trade-off, with a reduction in subsequent ischemic events but also increased risks for bleeding events. Identifying the best antithrombotic strategy for an individual patient requires clinicians to estimate and balance risks for recurrent ischemic events versus their risk for bleeding and address changes in these competing risks over time.

In this article, we critically review evidence regarding antithrombotic therapy in patients with ASCVD without atrial fibrillation and present clinicians with an approach to select the most appropriate strategy for their patients. We focus on long-term antithrombotic therapy in chronic CAD and take into account patient characteristics and temporal factors that may influence the choice between aspirin monotherapy, dual antiplatelet therapy (DAPT), and dual pathway inhibition (DPI) using low-dose oral non–vitamin K antagonist anticoagulant in combination with aspirin.

## Original oral antithrombotic trials

The first trials of chronic antithrombotic therapy for patients with ASCVD focused on vitamin K antagonists. As an example, the Warfarin Re-infarction Study (WARIS) demonstrated that, following a myocardial infarction, prolonged anticoagulation (average 37 months) with a therapeutic dose of a vitamin k antagonist could reduce death (RR 0.76, 95% CI 4%-44%, $P = .027$) and reinfarction (RR 0.66, 95% CI 19%-54%, $P = .0007$) relative to placebo but at a cost of 0.6% increased serious bleeding events each year of therapy.[8] Given the difficulties in monitoring vitamin k antagonists, the next set of trials tested antiplatelet therapy with aspirin. The AntiThrombotic Trialists (ATT) collaborative pooled the data from trials of antiplatelet therapy and demonstrated that aspirin produced a 20% reduction in major adverse cardiovascular events (RR 0.80, 95% CI 0.73-0.88) and a 10% reduction in mortality relative to placebo at a cost of increased hemorrhagic stroke (RR 1.39, 95% CI 1.08-1.78), fatal hemorrhagic stroke (RR 1.74, 95% CI 1.20-2.53), and gastrointestinal bleeding (RR 1.54, 95% CI 1.30-1.82).[9] Based on its low cost and ease of use, aspirin quickly became the dominant antithrombotic therapy for secondary prevention.[10]

### Elucidating residual risk in patients with chronic atherosclerotic cardiovascular disease

In spite of the application of aspirin and other secondary prevention therapies in patients with chronic cardiovascular disease, clinical trials and registries demonstrate a 2%-8% risk of recurrent cardiovascular events each year.[3-7] Evaluating individual risks of ischemic and bleeding events is challenging because risk depends on nonmodifiable patient characteristics (age and sex), comorbid medical conditions (diabetes, hypercholesterolemia, heart failure, renal insufficiency, etc), and temporal factors such as the time from the most recent acute ischemic event or revascularization procedure. In the REduction of Atherothrombosis for Continued Health (REACH) Registry, the occurrence of a recent ischemic event in the past year was associated with >70% increased risk of recurrent ischemic events (1.71 hazard ratio [HR], 95% CI 1.57-1.85, $P < .001$)[11]. Polyvascular disease, where an individual patient has atherosclerosis in at least 2 vascular territories (coronary, peripheral, and/or cerebral), was associated with a doubling (1.99 HR, 95% CI 1.78-2.24, $P < .001$) of the risk of adverse ischemic events.[11]

Various clinical scores have been developed to estimate the risk of ischemic and bleeding events and, their use is endorsed by guidelines.[12,13] Nonetheless, they are not consistently applied in clinical practice and may not accurately estimate an individual patient's risk. Although the typical major adverse cardiac end point of death, myocardial infarction, and stroke has reasonably consistent definitions across trials, the bleeding definitions used in trials vary, making comparisons challenging.[14] Furthermore, in most cases, the risk of ischemic events including death, myocardial infarction, or stroke is severalfold higher than that of a clinically significant bleeding event that permanently affect the patients' quality or quantity of life, most likely because risk factors for bleeding overlap with risk factors for ischemic events.[15]

### Contemporary antithrombotic strategies for secondary prevention

From the mechanistic perspective, increasing the intensity of antithrombotic therapy, by adding a second antiplatelet agent (DAPT) or a low-dose oral anticoagulant to an antiplatelet agent (dual pathway approach), is an attractive alternative to aspirin monotherapy to decrease the residual risk of ischemic events. The improvement in efficacy with these approaches needs to be balanced against the increase in bleeding to determine the net benefit for patients. Although all events (ischemic or bleeding) are meaningful to patients, the ultimate measure of the net clinical benefit is a reduction in all-cause mortality.

#### Antiplatelet strategies

*Dual antiplatelet therapy.* The Clopidogrel in Unstable Angina to Prevent Recurrent Events (CURE) trial established the combination of aspirin and the ADP receptor blocker clopidogrel as standard of care for the first year following a non–ST-elevation acute coronary syndrome (ACS).[16] This trial, plus supportive clinical investigation in patients with ST-elevation myocardial infarction, established the paradigm of DAPT for secondary prevention of coronary heart disease for the first year following an acute coronary syndrome.[17,18]

Among acute coronary syndrome patients managed with or without percutaneous coronary intervention (PCI), the Platelet Inhibition and Patient Outcomes

(PLATO) study found that the P2Y12 inhibitor ticagrelor, in combination with aspirin, reduced the risk of major adverse recurrent cardiovascular events (cardiovascular death, myocardial infarction, and stroke) compared with clopidogrel and aspirin over the first year (HR 0.84, 95% CI 0.77-0.92, $P < .001$).[19] Here, ticagrelor-based DAPT was associated with a reduction in death from vascular causes (HR 0.79, 95% CI 0.69-0.91) as well as all-cause death (HR 0.78, 95% CI 0.69-0.89). These results have led to ticagrelor being the preferred antiplatelet agent in combination with aspirin for the first year following an ACS event.

A series of trials investigated the optimal duration of DAPT in various patient populations. The Clopidogrel for High Atherosclerotic Risk and Ischemic Stablization, Management and Avoidance (CHARISMA) trial assigned 15,603 patients with multiple cardiovascular risk factors (21%) or documented atherosclerotic cardiovascular disease (78%) to clopidogrel 75 mg daily plus low-dose aspirin or placebo and low-dose aspirin for a median duration of 28 months.[20] Overall, there was no benefit observed in the rate of cardiovascular death, myocardial infarction, and stroke (clopidogrel 6.8% vs 7.3% placebo, RR 0.93, 95% CI 0.83-1.050, $P = .22$), with a trend to increased severe bleeding (clopidogrel 1.7% vs placebo 1.3%, RR 1.25, 95% CI 0.97-1.61, $P = .09$). In the large subgroup with symptomatic atherosclerotic cardiovascular disease, the primary end point was reduced (clopidogrel 6.9% vs placebo 7.9%, RR 0.88, 95% CI 0.77-0.998, $P = .046$) without an increase in GUSTO severe bleeding (clopidogrel 1.6% vs placebo 1.4%), although GUSTO moderate bleeding was increased (clopidogrel 2.1% vs placebo 1.3%, $P < .001$).

The Dual Antiplatelet Therapy (DAPT) study, which randomized 9,961 patients with a previous PCI and stent implantation who had already tolerated 12 months of DAPT therapy to aspirin monotherapy or prolonged DAPT with the combination of either clopidogrel or prasugrel and aspirin for 30 months.[4] DAPT prolongation was associated with a lower incidence of the co-primary end points with a 29% relative reduction in death, myocardial infarction, and stroke (4.3% vs 5.9%, HR 0.71, 95% CI 0.59-0.85, $P < .001$) and 71% reduction in stent thrombosis (0.4% vs 1.4%, HR 0.29, 95% CI 0.17-0.48, $P < .001$), although there was a 61% increase in GUSTO moderate or severe bleeding (2.5% vs 1.6%, $P = .001$). An unexpected and as yet unexplained finding in this trial was a borderline significantly increased risk of all-cause mortality with extended DAPT (RR 1.36, 95% CI 1.00-1.85, $P = .05$). This finding prompted a meta-analysis of 14 randomized trials involving 69,644 patients which demonstrated no reduction in mortality with clopidogrel-based DAPT (HR 1.05, 95% credible interval 0.96-1.19, $P = 0{\cdot}33$).[21] Another meta-analysis limited to patients with a prior myocardial infarction demonstrated a 15% reduction in cardiovascular death (2.3% vs 2.6%, RR 0.85, 95% CI 0.74-0.98, $P = .03$) with-long term DAPT but no reduction in all-cause mortality (0.92, 95% CI 0.83-1.03, $P = .13$).[22]

The Prevention of Cardiovascular Events in Patients with Prior Heart Attack Using Ticagrelor Compared to Placebo on a Background of Aspirin—Thrombolysis in Myocardial Infarction 54 (PEGASUS-TIMI 54) trial tested 2 doses of ticagrelor (90 mg twice daily and 60 mg twice daily) in combination with low-dose aspirin versus aspirin alone in 21,162 patients who were 1-3 years post–myocardial infarction.[5] This trial was designed to build on the observations from the PLATO trial and evaluate the optimal duration of aspirin and ticagrelor for long-term secondary prevention after myocardial infarction. Many patients enrolled had already discontinued DAPT at the time of enrolment (average 1.7 years post–myocardial infarction) and therefore had to reinitiate DAPT with ticagrelor. Both ticagrelor doses reduced the primary end point of cardiovascular death, myocardial infarction, and stroke (ticagrelor 90 mg twice daily, 7.85% vs 9.04%, HR 0.85, 95% CI 0.75-0.96, $P = .008$ and ticagrelor 60 mg twice daily, 7.77% vs 9.04%, HR 0.84, 95% CI 0.74-0.95, $P = .004$). There was no significant reduction in cardiovascular death in the intention-to-treat population (90 mg twice daily 2.94%, HR 0.87, 95% CI 0.71-1.06; 60 mg twice daily 2.86%, HR 0.83, 95% CI 0.68-1.01, placebo 3.39%). Although both regimens were not associated with increased risk in fatal bleeding or nonfatal intracranial hemorrhage, there was a greater than 2-fold increase in TIMI major bleeding (90 mg twice daily 2.60%, 60 mg twice daily 2.30% vs placebo 1.06%; $P < .001$ for each dose). Secondary analyses demonstrated consistent benefits in key patient subgroups, including those with diabetes, PAD, renal dysfunction, and known multivessel CAD, who also appeared to achieve the greatest absolute benefits.[23-27]

When the efficacy of ticagrelor (60 mg twice daily) was stratified by the time from myocardial infarction until randomization, those patients that were <2 years after the index event had a 23% reduction in cardiovascular death, myocardial infarction, and stroke (ticagrelor 7.8% vs placebo 9.7%, HR 0.77, 95% CI 0.66-0.90) and a 32% reduction in cardiovascular death (ticagrelor 2.5% vs placebo 3.7%, 95% CI 0.53-0.89). For those patients randomized >2 years after their myocardial infarction, the rate of cardiovascular death, myocardial infarction, and stroke was not reduced (ticagrelor 7.8% vs placebo 7.9%, 95% CI 0.79-1.17, $P$ interaction = .09), and similarly, there was no reduction in cardiovascular death (ticagrelor 3.3% vs placebo 2.8%, HR 1.12, 95% CI 0.81-1.54, $P$ interaction = .019).[28] These results combined with the previously discussed PLATO trial suggest that the major benefit of prolonged ticagrelor based DAPT is achieved over the first 2 years following myocardial infarction, with the strategy achieving a reduction in major adverse cardiovascular events and cardiac death compared to prior standards of care.

*P2Y12 monotherapy*. Dual antiplatelet therapy reduces the risk of stent-related and spontaneous ischemic events in patients with acute coronary syndromes or stable ischemic CAD undergoing PCI but at an increased risk of bleeding. In contrast to the previously discussed studies that assessed extended DAPT therapy to reduce ischemic events, several studies using various antiplatelet strategies have evaluated an abbreviated DAPT regimen followed by P2Y12-receptor monotherapy, attempting to sustain the benefit on reduced ischemic events while reducing the risk of bleeding events.[29-31]

The GLOBAL LEADERS trial (N = 15,968) compared 1 month of ticagrelor 90 mg twice daily in combination with aspirin followed by 23 months of ticagrelor 90 mg twice daily alone compared with ticagrelor 90 mg bid and aspirin for 12 months followed by aspirin alone for patients with an acute coronary syndrome (47% of patients enrolled), or clopidogrel 75 mg daily and aspirin for 12 months followed by aspirin alone in patients undergoing elective PCI (53% of patients enrolled).[30] Overall, there was no significant reduction in the efficacy primary end point of all-cause mortality and adjudicated new Q-wave myocardial infarction at 2 years (experimental arm 3.81% vs standard of care 4.37%, RR 0.87, 95% CI 0.75-1.01, $P = .073$), and there was no evidence for a difference in treatment effect for the prespecified subgroups with an acute coronary syndrome or PCI in stable CAD. The key safety end point of bleeding assessed by the Bleeding Academic Research Consortium criteria grade 3 or 5 occurred in 2.04% in the experimental arm and 2.12% in the standard-of-care arm (RR 0.97, 95% CI 0.78-1.20, $P = .77$). Compared to standard of care, this trial suggests that 1 month of DAPT followed by ticagrelor monotherapy was associated with sustained efficacy, although this important study failed to demonstrate the anticipated reduction in bleeding with the experimental strategy.

*Applying antiplatelet strategies*. The numerous trials of antiplatelet therapy have provided a wealth of information, but the various antiplatelet agents tested, abbreviated or prolonged DAPT duration, and mix of patients with acute coronary syndromes and PCI with stable CAD studied have created a challenge for clinicians to apply the results to their patients. Although the optimal duration of DAPT following elective nonurgent PCI is influenced by patient characteristics and PCI techniques and continues to be reviewed and debated, the totality of the current evidence suggests that, for many patients that undergo elective percutaneous revascularization, a shorter duration of clopidogrel-based DAPT (3-6 months) provides the best balance of ischemic and bleeding events.[32-34] Alternatively, in most patients with an acute coronary syndrome, evidence supports at least 1 year of treatment based on the results of the CURE and PLATO studies.[16,19] The PLATO results and subgroup analysis based upon the time from the index event in PEGASUS support a reduction in both the combined MACE end point as well as cardiovascular death with ticagrelor-based DAPT for the first 2 years following myocardial infarction with an apparent loss of effect thereafter, although subgroup analysis should be interpreted with caution. In those patients with higher predicted risk of stent thrombosis and recurrent myocardial infarction, prolonged DAPT should be considered and ideally tailored to the individual patient with specific considerations to be discussed.

## Dual antithrombotic pathway inhibition with aspirin and oral anticoagulants

Meta-analysis of trials comparing the combination of moderate-intensity vitamin K antagonist therapy (international normalized ratio, 2-3) and aspirin with aspirin alone in patients with a recent ACS demonstrated a 27% reduction (OR 0.73, 95% CI 0.63-0.84) in death, myocardial infarction, and stroke but a greater than 2-fold increase in major bleeding (OR 2.32, 95% CI 1.63-3.29), with no mortality reduction.[35] When the atrial fibrillation dose of apixaban (5 mg twice daily) was tested in the Apixaban for Prevention of Acute Ischemic Events 2 (APPRAISE-2) study in patients in the first year after ACS, a similar excess of bleeding prompted early termination of the trial.[36] Accordingly, the "standard" atrial fibrillation dose of oral anticoagulant therapy is not recommended for secondary prevention in patients with established ASCVD in the absence of a clinical indication.

The Anti-Xa Therapy to Lower cardiovascular events in addition to Aspirin with or without thienopyridine therapy in Subjects with Acute Coronary Syndrome (ATLAS) trial program assessed multiple doses of rivaroxaban in a large (N = 3,491) phase 2 dose-finding study, which led to the selection of reduced doses of rivaroxaban for evaluation in a phase 3 trial.[37,38] In 15,526 patients enrolled within 7 days after admission for ACS, rivaroxaban 2.5 mg bid or 5 mg bid compared with placebo and on a background of standard antiplatelet therapy (93% clopidogrel + ASA [DAPT] and 7% aspirin monotherapy) reduced cardiovascular death, myocardial infarction, and stroke (rivaroxaban 2.5 mg vs placebo: 9.1% vs 10.7%, HR 0.84, 95% CI 0.72-0.97, $P = .02$; rivaroxaban 5 mg bid versus placebo: 8.8% vs 10.7%, HR 0.85, 95% CI 0.73-0.98, $P = .03$). In addition, the lower rivaroxaban dose reduced cardiovascular death (2.7% vs 4.1%, HR 0.66, 96% CI 0.51-0.86, $P = .002$) and all-cause death (2.9% vs 4.5%, HR 0.69, 95% CI 0.53-0.87, $P = .002$), with no increase in fatal bleeding (0.1% vs 0.2%) or intracranial hemorrhage (0.4% vs 0.2%) but increased TIMI major bleeding (1.8% vs 0.6%, $P < .001$).[39]

The Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) trial randomized patients with chronic CAD, PAD, and cerebrovascular disease to the combination of rivaroxaban 2.5 mg bid and aspirin, rivaroxaban 5 mg bid alone, or aspirin alone. The combination of rivaroxaban 2.5 mg twice daily and

aspirin produced a 24% reduction (4.1% vs 5.4%, HR 0.76, 95% CI 0.66-0.86, $P < .001$) in cardiovascular death, myocardial infarction, and stroke; a 42% reduction in stroke (0.9% vs 1.6%, HR 0.78, 95% CI 0.44-0.76, $P < .001$); a 22% reduction in cardiovascular death (1.7% vs 2.2%, HR 0.78, 95% CI 0.64-0.96, $P = .02$); and an 18% reduction in all-cause mortality (3.4% vs 4.1%, HR 0.82, 95% CI 0.71-0.96, $P = .01$), whereas rivaroxaban 5 mg twice daily alone did not reduce the primary outcome (HR 0.90, 95% CI 0.79-1.03, $P = .12$).[3] The combination of rivaroxaban 2.5 mg twice daily and aspirin increased major bleeding (3.1% vs 1.9%, HR 1.70, 95% CI 1.40-2.05, $P < .001$) but did not increase fatal bleeding (0.2% vs 0.1%, HR 1.49, 95% CI 0.67-3.33, $P = .32$) or intracranial hemorrhage (0.2% vs 0.2%, HR 1.10, 95% CI 0.59-2.04, $P = .77$) events.

The COMPASS results were consistent in patients enrolled with CAD and in those with PAD.[40,41] Of the 24,824 patients with documented CAD, 17,028 had a prior myocardial infarction, including 1,238 who were enrolled within 1 year of their acute event and 8,520 enrolled greater than 5 years after their most recent MI.[41] Rivaroxaban 2.5 mg twice daily plus aspirin reduced the primary outcome by 26% (HR 0.74, 95% CI 0.65-0.86, $P < .0001$) and increased major bleeds by 66% (HR 1.66, 95% CI 1.37-2.03, $P < .0001$). The gastrointestinal tract was the most common source of bleeding source (HR 2.13, 95% CI 1.57-2.88), and there was no increase in fatal bleeding or symptomatic bleeding into a critical organ or surgical site requiring reoperation (HR 1.30, 95% CI 0.92-1.83). In subgroup analysis, the benefit of DPI therapy was consistent over the duration of the trial, whereas the risk of bleeding was significantly increased in the first year (HR 2.32, 95% CI 1.75-3.07) but not in year 2 (HR 1.19, 95% CI 0.84-1.68) or beyond (HR 1.05, 95% CI 0.63-1.75). Additionally, rivaroxaban 2.5 twice daily with aspirin reduced mortality by 23% when compared with aspirin alone (HR 0.77, 95% CI 0.65-0.90, $P = .0012$). The net clinical benefit achieved and the significant mortality reduction support the DPI strategy in the appropriate patient population with chronic CAD.

## Applying contemporary antithrombotic therapy in the secondary prevention of chronic atherosclerotic cardiovascular disease

Based on the aforementioned clinical trials, clinicians now have a choice of several antithrombotic strategies to decrease recurrent ischemic events in the long-term management of patients with chronic ASCVD. To apply these strategies to individual patients, clinicians need to consider several factors: (1) the estimated risk of cardiovascular ischemic and bleeding events using patient characteristics and coexistent comorbid medical conditions supported by available risk scores; (2) how their specific patient relates to the patient population enrolled in the clinical trials; and (3) temporal factors including the patient state at the time of clinical decision making (ie, time since the most recent acute ischemic event or PCI) as well as the duration of antithrombotic therapy tested in the clinical trials. Furthermore, the clinician may also need to transition between the specific antithrombotic strategies to achieve best patient outcomes as these factors change.

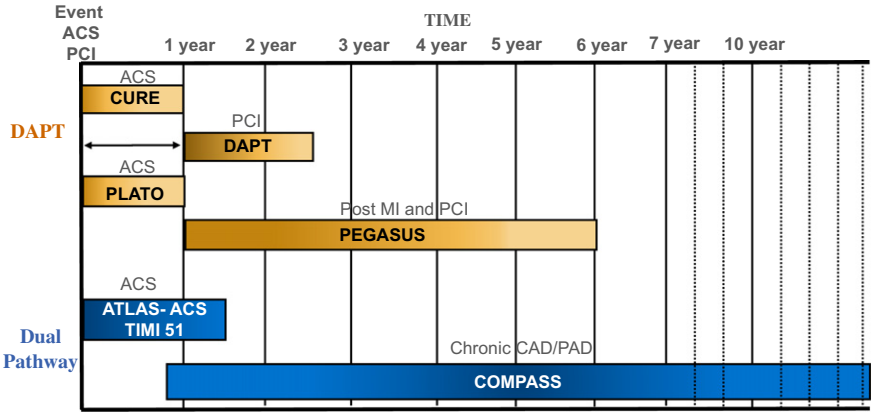
The availability of an expanded range of antithrombotic strategies for the long-term management of patients with CAD requires clinicians to determine an individual patient's risk of a recurrent ischemic event. This requires consideration of patient characteristics including age, occurrence of a recent cardiovascular ischemic event or PCI, the presence of multivessel CAD, established evidence of atherosclerosis in multiple vascular territories (CAD, PAD, and CVD), as well as comorbid medical conditions such as clinical heart failure, diabetes mellitus, and renal insufficiency (Table I). Bleeding risk should also be evaluated, recognizing that many of the factors that predict ischemic risk are also important determinants of bleeding risk (Table I). Balancing the risk and benefit of antithrombotic therapy for an individual patient is a clinical art which can be supported with knowledge of these clinical characteristics and the available risk scores. When assessing this balance, the clinician should acknowledge that the typical patient's risk of irreversible harm or a fatal bleeding event is typically less than that of a nonfatal or fatal ischemic event.[42] The clinician will

**Table I.** Clinical features associated with increased ischemic and bleeding risk.

| Features associated with increased ischemic risk | Features associated with increased bleeding risk |
|---|---|
| Polyvascular disease (CAD, PAD, CVD) | Previous major bleeding event |
| Heart failure | Anemia |
| Chronic kidney disease (creatinine clearance ≤60 mL/min) | Prior intracranial bleed |
| Diabetes mellitus | Patient frailty (advanced age) |
| Recent myocardial infarction | Concomitant medical therapy (anticoagulants, corticosteroids, NSAIDs, etc) |
| Multivessel CAD or multivessel revascularization | |
| Complex coronary stenting (2-stent bifurcation, extensive stenting, etc) | |

*NSAIDs*, nonsteroidal anti-inflammatory drugs.

**Figure 1**




This figure outlines the key clinical trials that had significant reductions in adverse clinical end points in secondary prevention of patients with chronic ASCVD. It attempts to illustrate the temporal characteristics for patient enrollment as well as the overarching antithrombotic strategies applied in the trials. DAPT studies are displayed with yellow bars and DPI is displayed in blue bars, with the bars shaded to reflect the patient distribution of randomization and follow-up.

need to discuss these potential complex competitive risks with their patients to support their informed choice.

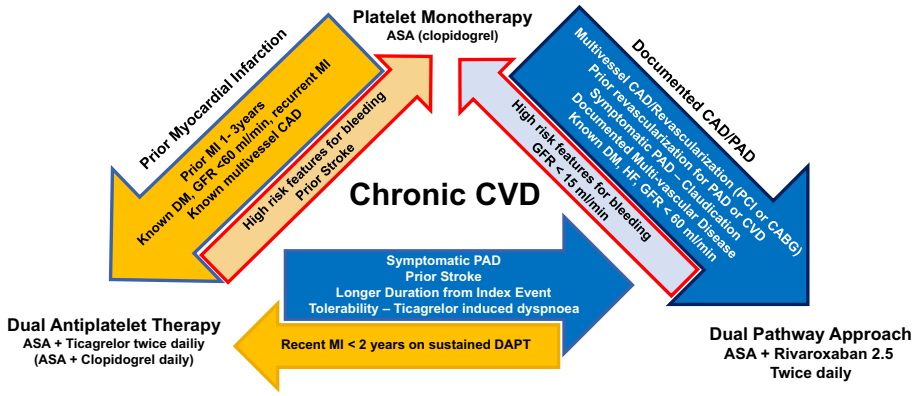
The patient populations enrolled, the timing of recruitment in relation to prior ischemic event or revascularization, and the antithrombotic treatment durations tested in the main trials discussed are displayed in Figure 1, and selected patient characteristics and randomized treatment discontinuation rates are presented in Table II. As noted, the patient populations enrolled varied across the 3 key trials because of the specific inclusion and exclusion criterion applied. The DAPT study assessed patients with a prior PCI who had tolerated 1 year of DAPT therapy, whereas PEGASUS enrolled only patient with a prior MI in the past 1-3 years (median of 1.7). In COMPASS, patients with chronic ASCVD including CAD and PAD were enrolled after DAPT therapy was no longer indicated, and included a broad range of patients from less than 1 year following an acute event to more than a decade from a previous event. (See Table II.)

Furthermore, the clinician will need to become skilled at applying transition strategies between these complementary therapies to optimize patient's long-term outcomes. Figure 2 demonstrates several factors that may influence a clinician's choices to transition between antithrombotic therapies in a patient with ASCVD. Features that support deescalating from more intense antithrombotic therapy to aspirin monotherapy include the occurrence of clinically relevant bleeding or the presence of high-risk bleeding characteristics or, alternatively, the lack of higher–ischemic risk clinical features. Sustained intensified antithrombotic therapy or indeed transitioning from aspirin monotherapy to DAPT or the

**Table II.** Key trials of anti-thrombotic therapy in chronic coronary syndrome patients.

| Trial | DAPT | PEGASUS | COMPASS |
|---|---|---|---|
| No. of patients (n) | 9961 | 21,162 | 27,395 |
| Key entry criteria | 100% Prior PCI (1 y of DAPT) | 100% Prior MI (1-3 y post) | CAD and PAD (chronic) |
| Age (y) | 62 | 65 | 68 |
| Women (%) | 25% | 24% | 22% |
| CAD (%) | 100% | 100% | 91% |
| PAD (%) | 6% | 5% | 27% |
| Diabetes (%) | 31% | 32% | 38% |
| Hypertension (%) | 75% | 78% | 75% |
| Heart failure (%) | 5% | NA | 22% |
| Prior stroke (%) | 3% | Excluded | 4% |
| Duration of randomized therapy | 30 m | 33 m | 23 m |
| Discontinuation rate (%) Placebo arm (ASA) | 20.3% | 21% | 15.7% |
| Discontinuation rate (%) Experimental arm | 21.4% | 28.7% Tic. 60 bid<br>32% Tic. 90 bid | 16.5%<br>Riva 2.5 bid |

**Figure 2**




This figure outlines clinical characteristics that may influence a clinician to treat a patient with chronic ASCVD with aspirin monotherapy, DAPT, or a dual pathway approach. In patients with lower risk of recurrent ischemic events, especially in the setting of an increased estimated risk of bleeding, aspirin monotherapy may be the most appropriate approach. In patients who have had a myocardial infarction within the past couple of years, especially if they have been tolerating ticagrelor-based DAPT, sustaining this therapy may be the optimal approach for the next 1-2 years. In patients with high risk of recurrent ischemic events, transition from ASA monotherapy to a DPI approach or transitions from DAPT to a DPI approach may be justified. If an individual patient is a candidate for either strategy, factors that may direct a clinician to ticagrelor-based DAPT would include a recent myocardial infarction (<2 years) and sustaining such therapy if they are tolerant. The dual pathway approach may be most appropriate in those with coexistent PAD, prior stroke, or a longer duration from the index event (especially beyond 3 years) or those intolerant of ticagrelor-based DAPT.

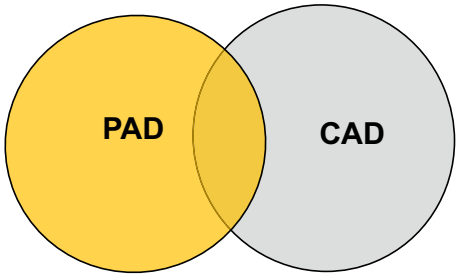
DPI approach would be reasonable in patients without prohibitive bleeding risk but an estimated increased risk of ischemic events. Once this clinical decision is made, the choice of DAPT or the dual pathway approach is influenced by the factors outlined in the preceding discussions and incorporates the patient's preference.

For many patients with chronic ASCVD, DAPT is not currently an evidence-based therapy, leaving practitioners to choose between aspirin monotherapy and the DPI approach. This population includes (1) those with isolated symptomatic or revascularized PAD or carotid artery disease, (2) those with chronic CAD beyond 3 years from a myocardial infarction, and (3) patients who have undergone coronary revascularization for stable angina (beyond the period of recommended DAPT (typically 3-6 months). These are indeed a large portion of the patient populations enrolled in COMPASS trial. Although an evidence-based purist might argue on the possibility of applying the DPI approach to all patients that meet the COMPASS eligibility/enrollment criteria, we recognize that novel therapeutic strategies are typically adopted slowly in real-world clinical practice. Acknowledging the shift in inertia required to intensify anticoagulant therapy in chronic ASCVD patients that are perceived to be clinically stable, Figure 3 provides clinicians with a schematic representation of several characteristics that may influence this decision. This figure is meant to be a tool to increase clinicians' awareness of contemporary antithrombotic strategies to reduce the risk of a recurrent ischemic events and death.

The additive benefit of DPI compared to aspirin monotherapy is similar if not greater than that achieved by other accepted therapies for secondary prevention that no physician would consider denying to an eligible patient. This includes aspirin compared to no antithrombotic therapy, lipid-lowering therapy with statins, and blood pressure control to existing evidence-based targets.

The various treatment options addressing specific patient populations with temporal factors including the time from the most recent ischemic event or revascularization are schematically presented in Figure 4. In certain instances, especially if the patient has had a major bleeding event or is at high risk of bleeding, downtitrating DAPT to aspirin monotherapy will be the most appropriate action for patients following an elective PCI (3-6 months) or following an ACS event (typically 12 months) (case scenarios A and E). In a significant proportion of patients with clinical predictors of increased ischemic risk and acceptable bleeding risk, it will be more appropriate to sustain DAPT for a prolonged period prior to converting to aspirin monotherapy (clinical scenario B and E). In these scenarios, once the clinician and patient have made the decision to prolong DAPT, the optimal duration remains unknown (shown diagrammatically with a tapering arrow), with the trials testing approximately 30 months of therapy, although the previously discussed stratified analysis by time from myocardial infarction in PEGASUS might suggest the duration of 2 years. Transitioning from DAPT to a DPI approach is another important option because this strategy

**Figure 3**




**Highest Ischemic Risk Patients**

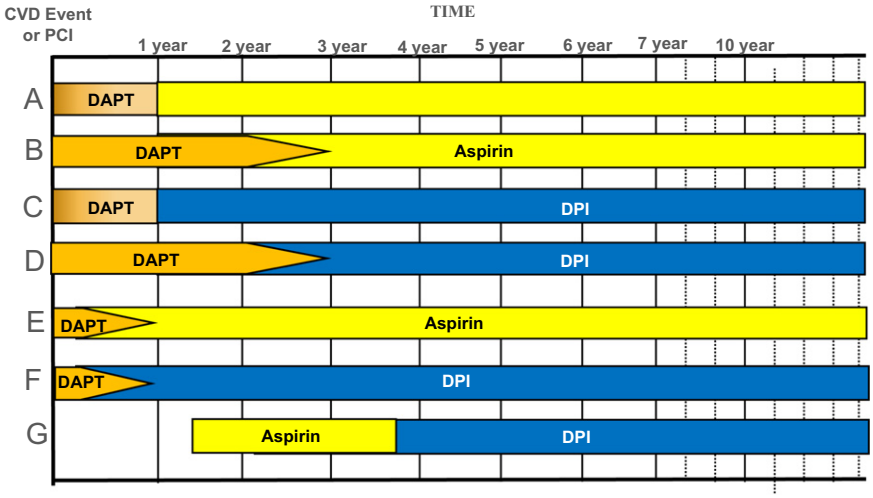
- Poly-vascular disease (CAD and PAD)
- CKD (eGFR <60 ml/min)
- Heart failure (ejection fraction >30%)
- Diabetes
- CV event within one year
- Multi-vessel CAD or revascularization

**Highest Bleeding Risk Patients**

- Previous major bleeding event
- Prior intracranial bleed
- Frailty (advanced age)
- Concomitant medical therapy
  (anticoagulants. NSAIDS, corticosteroids)
- Anemia

This figure is an awareness tool to facilitate practitioner's assessment of high-risk features in stable ASCVD that would impact the decision to transition from aspirin monotherapy to the dual pathway approach. It highlights the improvement in patients with isolated symptomatic or revascularized PAD—a group that has limited additional evidence-based therapies that result in reduction in MACE, MALE, and amputations. Additionally, to focused the clinician on those patients with multiple territories of atherosclerotic disease with the overlapping PAD and CAD circles. The right-hand panel defines patient populations with the largest absolute risk who would therefore achieve the largest absolute clinical benefit of dual pathway therapy. The clinician is reminded across the bottom of the figure to avoid the therapy in those with eGFR of less than 15 mL/min or those with perceived high bleeding risk.

**Figure 4**




The various antithrombotic transition strategies that clinicians will need to consider to optimize their patients' outcomes are schematically presented and discussed in the text. **A**, DAPT for 1 year followed by aspirin monotherapy for an ACS patient. **B**, DAPT extended beyond the first year for patients with selected characteristics consistent with increased stent thrombosis or recurrent ischemia followed by aspirin monotherapy (note the tapered arrows outline the various time points that the antithrombotic transitions could occur). Strategies C and D outline similar DAPT durations as A and B but in appropriate patients with increased ischemic risk and acceptable bleeding demonstrate transition from DAPT to a DPI approach. Strategies E and F apply to those patients under elective PCI where evidence supports 3-6 months of DAPT with transition to aspirin monotherapy (E) in those perceived to be at low risk of recurrent ischemic events or, alternatively, high bleeding risk or with transition to a dual pathway approach (F) if there is anticipated increased ischemic risk. Finally, the strategy demonstrated in G represents those patients with documented chronic ASCVD without a recent ischemic event or revascularization but are perceived to be at high risk of an ischemic event with transition from aspirin monotherapy to the dual pathway approach.

reduced the combined end point of major adverse cardiac events but also cardiovascular death and stroke with an acceptable bleeding risk and an attractive overall net clinical benefit (clinical scenario C, D, and F). Finally, in selected chronic ASCVD patients who present for routine follow-up, the clinician may consider transitioning from aspirin monotherapy to the dual pathway strategy. Again, once the clinician and patient implement the dual pathway approach, the optimal duration is unknown, with the COMPASS study showing consistent benefits of the strategy over time following randomization.

Once the antithrombotic strategy is determined, the decision needs to be reassessed with the passage of time and development of additional events or comorbidities that increase either the ischemic or bleeding risk.

### Residual questions and areas for future research

Although there has been extensive economic and intellectual investment into the role of antithrombotic management in patients with chronic ASCVD, there are still a number of unanswered questions. Despite 1 reasonably large dose-finding study, phase 2 investigations and 2 large phase 3 trials demonstrating the benefit of rivaroxaban 2.5 bid in cardiovascular disease patients, the "optimal dose" and mechanism of action remain a topic of discussion. Although rivaroxaban has been shown to have anti-inflammatory properties at this dose in animal models, it still seems prudent to consider most of the benefit to be related to direct anticoagulant effects. Regarding the "optimal dose," it would seem that by achieving significant reductions in MACE, stroke, CV death, all-cause death, as well as major adverse limb events and amputations in patients with PAD while not increasing fatal bleeding or nonfatal intracranial hemorrhage, rivaroxaban 2.5 bid in combination with aspirin has likely achieved the therapeutic "sweet spot." Additional definitive trials with clinically available as well as novel non–vitamin K oral anticoagulants proceeded by adequately powered phase 2 dose finding should be considered.

A second point of discussion that may indeed be controversial, is aspirin the optimal antiplatelet to administer in conjunction with low-dose oral anticoagulation to achieve the best balance of efficacy and safety. There have now been 2 large neutral trials that assessed ticagrelor versus aspirin in patient with stroke not requiring oral anticoagulation and ticagrelor versus clopidogrel in patients with PAD that demonstrated similar safety profiles of either platelet monotherapy. Might rivaroxaban 2.5 mg bid (or an alternative appropriately dosed oral anticoagulant) in combination with ticagrelor 60 mg bid, potentially even in a combination pill, further enhance chronic ASCVD patient outcomes? These questions are likely to remain for the moment purely speculative because the megatrials necessary to address these questions are likely not to be performed in the near future.

## Conclusions

The broad range of patients with chronic ASCVD are exposed to a significant ongoing risk of recurrent cardiovascular events including death. In conjunction with lifestyle interventions, cholesterol reduction, and blood pressure control, antithrombotic therapies remain a cornerstone of secondary prevention. The practicing clinician now has 3 key antithrombotic strategies that are complementary for secondary prevention in such patients. For many of them, aspirin monotherapy will remain the most appropriate therapy. However, for a substantial group of patients with increased ischemic risk and low to moderate bleeding risk, intensified antithrombotic therapy will safely reduce recurrent ischemic events. Clinicians will need to apply existing antithrombotic strategies appropriately including aspirin monotherapy, DAPT, and the DPI approach with rivaroxaban (2.5 mg twice daily) and low-dose aspirin and, in addition, will need to become skillful at switching between these complementary antithrombotic strategies.

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