The myth of ‘stable’ coronary artery disease

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Abstract

Patients with known cardiovascular (CV) disease who have not suffered a recent acute event are often referred to as having ‘stable coronary artery disease (CAD)’. The concept of ‘stable’ CAD is misleading for two key reasons: the continuing risks of CV events over the longer term, and the diverse but powerful spectrum of risk characteristics. The risks of CV events are frequently underestimated and occur despite current standards of care for secondary prevention, including lifestyle changes, optimal medical therapy, myocardial revascularization, and use of antiplatelet agents to limit thrombosis. In dispelling the myth of ‘stable’ CAD, we explore the pathophysiology of the disease and the relative contribution of plaque and systemic factors to CV events. A broader concept of the vulnerable patient, not just the ‘vulnerable’ plaque, takes into account the diversity and future risks of atherothrombotic events. We also evaluate new and ongoing research into medical therapies aimed at further reducing the risks of CV events in patients with chronic but not ‘stable’ atherothrombotic disease.

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Keywords

Acute coronary syndrome; atherosclerosis; cardiovascular; coronary artery disease; myocardial infarction; peripheral artery disease

Key points

- The clinical label ‘stable’ coronary artery disease (CAD) needs to be reconsidered and more clearly defined, with chronic vascular disease including patient groups at substantial risk of future coronary events
- The risk of cardiovascular (CV) events in patients with chronic CAD is compounded by the presence of combined systemic and specific vascular risk factors
- Chronic CAD requires optimal medical therapy to mitigate the impact of modifiable risk factors and to reduce the risk of CV events (e.g. myocardial infarction, stroke, and CV death)
- Novel approaches may have the potential to further reduce the risk of adverse events, including profound lipid-lowering, inflammation-modifying agents, and novel antithrombotic combinations

- Recent advances demonstrate that chronic vascular risk is modifiable and has the potential to produce clinically worthwhile gains in the most susceptible patients
- The field will continue to evolve, with improved characterization of patients at the highest risk of vascular events

Introduction

Patients with known cardiovascular (CV) disease who have not suffered a recent acute event are often referred to as having ‘stable coronary artery disease (CAD)’. However, how stable is ‘stable CAD’? The term encompasses a diverse spectrum of patients. This includes patients with recurrent transient episodes of ischaemia induced by oxygen supply–demand imbalance in the presence of established coronary artery stenoses (i.e. stable angina and silent ischaemia), and those who have stabilized after an acute coronary syndrome (ACS), a phase that is often asymptomatic[1]. However, these apparently ‘stable’ patients are heterogeneous. CAD progression is dynamic and unpredictable and can unexpectedly lead to major adverse CV events (MACE; e.g. CV death, myocardial infarction [MI], and stroke)[1]. Of concern, patients remain at high risk of MACE despite adherence to current guideline-recommended secondary prevention therapies[2-6]. The probability of having MACE within 5 years of the onset of apparently stable angina ranges up to 35% depending on clinical variables that affect the risk (FIG. 1)[7]. This diversity of risk highlights the need to identify those patients at higher risk and to further optimize their therapeutic management. The all-embracing term ‘stable’ CAD masks those with chronic atherosclerotic disease and the amplified risk of adverse cardiovascular events.

This review aims to dispel the myth of ‘stable’ CAD by exploring our current understanding of CAD and to evolve the concepts from individual culprit or ‘vulnerable’ lesions toward the ‘vulnerable patient’ and the factors that identify such patients. This review will also identify indicators of advanced atherosclerotic disease, contributing to plaque instability, and risk factors that contribute to the systemic risk of thrombosis at sites of plaque erosion or rupture (e.g. diabetes, chronic kidney disease [CKD], etc.). Progress has been made in the development of risk stratification tools and there are implications for new therapies to optimize disease management. To avoid misconceptions around ‘stable’ CAD we apply the term ‘chronic CAD’ in place of ‘stable CAD’ in this review. By definition, the term ‘chronic’ characterizes an illness persisting for a long time or that is constantly recurring, i.e. the reality of long-term atherothrombotic disease.

Pathophysiology

The clinical manifestations of chronic CAD reflect the distribution and severity of vascular obstructive lesions. Both obstructive and non-obstructive lesions can lead to MACE and other significant CV events (e.g. unstable angina)[1,8]. Typically, such events are the result of

atherothrombosis with disruption of an atheroma (i.e. rupture or erosion), provoking the formation of a thrombus that can interrupt blood flow locally or embolize (FIG. 2A)[8]. The probability of CV events depends upon several factors, including the extent and severity of atherosclerosis (being a diffuse/systemic disease), vulnerability of plaques to disruption, and the likelihood of thrombus formation and propagation (FIG. 2B). CV risk factors (such as diabetes, CKD, hypertension, and hyperlipidaemia) heighten the probability of an event. Hence, the clinical presentation and significance of atherothrombosis is variable[1,9,10]. Furthermore, because atherothrombosis is a systemic condition, a patient with CAD may also be at risk of stroke from cerebrovascular artery disease or an acute limb event from peripheral artery disease (PAD), or vice versa. In the REACH registry (an international, prospective, observational study enrolling patients with established CAD, cerebrovascular disease, or PAD, or with at least three atherosclerotic risk factors), ~25% of patients had manifestations of thrombosis in more than one arterial bed[11].

Autopsy studies suggested that >70% of coronary thrombi develop superimposed on a ruptured atherosclerotic plaque[8]. In a minority of patients (23%) who survived an MI, plaque erosion was identified by optical coherence tomography as the responsible precursor[12]. Atherothrombosis provoked by erosion of calcified nodules is rare[13,14]. Extensive research has focused on improving the ability to detect rupture-prone plaques. Thin-capped fibroatheromas (TCFAs) have been linked with clinically relevant thrombotic events; for example, Kubo T *et al,* demonstrated that >80% of ruptured plaques that caused MI were TCFAs[12]. TCFAs have a large necrotic core covered by a thin fibrous cap and are accompanied by a loss of smooth muscle cells. Pro-inflammatory macrophages and other leukocytes may contribute to the degradation of the fibrous cap and its eventual rupture[8]. In the PROSPECT trial of patients with ACS who underwent three-vessel coronary angiography and intravascular ultrasound imaging after percutaneous coronary intervention (PCI), lesions associated with recurrent events were more likely to be characterized as TCFAs, compared with those not associated with recurrent events[15]. On the other hand, progress in secondary prevention measures, e.g. use of statins for lipid lowering, hypertension control, and smoking cessation, may have modified the characteristics of a typical atherosclerotic plaque, influencing the incidence of plaque rupture and increasing the incidence of erosion-induced thrombi.[16] This may explain the recently observed increase in non-ST-elevation MI and decrease in ST-elevation MI in countries such as the US[17,18], whereas ST-elevation MI still accounts for the majority of acute MI events in many low- and middle-income countries[19,20] albeit non-ST-elevation MI is on the increase in countries such as China [20].

Research has identified the contribution of non-culprit lesions and that of non-obstructive lesions (more prevalent than obstructive lesions). In the PROSPECT trial, MACE occurring during the 3-year follow-up was equally attributable to recurrence at the site of the culprit lesions versus non-culprit lesions (12.9% and 11.6%, respectively)[15]. Per lesion, obstructive lesions are more susceptible to rupture, but non-obstructive lesions are much more prevalent, and overall, they make a major contribution to the risk of ongoing vascular events[21]. A key reason why targeting individual lesions with revascularization may fail to improve prognosis is due to the systemic nature of atherothrombosis[22]. Furthermore, not all plaque ruptures are symptomatic, so subclinical or 'non-culprit' ruptures are often undiagnosed, and their importance underestimated[10]. One pathological study observed that repeated plaque ruptures that heal are frequently found in men who die suddenly[23]. Plaque morphology is dynamic, with longitudinal imaging studies demonstrating that plaques can gain and lose characteristics of vulnerability over a period of months[24]. These findings support the need to focus on the 'vulnerable patient', not just the 'vulnerable lesion', and they highlight the need for effective systemic secondary prevention strategies beyond the current standard of care.

Continued advancement in imaging techniques and other methods to measure baseline disease burden will likely assist in improving risk prediction models for MACE. These include intravascular (intravascular ultrasound, optical coherence tomography, and plaque elastography) and non-invasive imaging. The latter includes advanced computerized tomography (CT) imaging and novel studies using ^{18}F-fluoride positron emission tomography combined with CT imaging[25-27]. Inflammatory markers and genetic risk factors (e.g. the 9p21 locus) are associated with atherothrombotic risk and susceptibility to recurrent plaque rupture[28]. High-sensitivity cardiac troponin assays and newer biomarkers (including interleukins, growth factors, and thrombosis markers) can be used to predict the pre-test probability of obstructive CAD[29-32]. The finding of elevated high-sensitivity troponin in patients with chronic CAD reflects the instability of this condition, given that troponin is a marker of myocyte necrosis, and illustrates the possible contribution of coronary micro-emboli to the progression of disease in 'chronic' vascular patients (although elevated troponin levels can also be a manifestation of left ventricular dysfunction and other atherosclerotic processes)[33].

Current guideline recommendations

Guidelines from the European Society of Cardiology (ESC) and the American College of Cardiology/American Heart Association (ACC/AHA) provide a substantial set of measures to relieve symptoms of CAD and improve prognosis through prevention of CV events[1,34]. In line

with our current understanding of the pathophysiology of atherothrombosis, recommendations for the prevention of MACE encompass: 1) the control of CV risk factors to limit progression of atherosclerosis and stabilize existing plaques; and 2) the prevention of thrombus formation over ruptured or eroded plaques (FIG. 3).

The control of CV risk factors includes both lifestyle modifications and medical interventions, supported by patient education. Guidelines recommend smoking cessation, regular physical exercise, adopting a healthy diet, weight management, and psychosocial support[1,34-39]. Medical interventions for CV risk factors encompass lipid control, with statins recommended for all patients with CAD (other lipid-lowering therapies such as ezetimibe and approved PCSK9 monoclonal antibodies can be considered in select patients with intolerance or inadequate response to statins), and the use of an angiotensin-converting enzyme (ACE) inhibitor (or an angiotensin receptor blocker [ARB] as an alternative) to lower blood pressure in patients with CAD and hypertension, and therapies to improve CV outcomes in diabetes, and heart failure (HF)[1,34-37]. In cases that are unresponsive to medical therapy, the 2014 ESC/European Association for Cardio-Thoracic Surgery (EACTS) guidelines on myocardial revascularization state that revascularization can be used to improve symptoms in patients with any coronary stenosis >50% and is indicated for improved prognosis in patients with substantial stenosis/stenoses (>50%) that are anatomically or functionally significant, particularly if in the left main artery or in cases of 2- or 3-vessel disease[40]. Guidance from the AHA/ American College of Cardiology Foundation (ACCF) states that revascularization is indicated to improve prognosis in survivors of out-of-hospital cardiac arrest and ventricular tachycardia and in patients with left ventricular dysfunction[38]. In a recent review by Katritsis *et al,* it was noted that “the evidence base in revascularization for stable CAD is fragmentary”, and that “treatment recommendation should be formulated by a multidisciplinary approach from interventionalists, cardiac surgeons, and non-invasive cardiologists and from patients themselves”. Clinical judgement is especially important for patients who are not typical representatives of any clinical trial[41].

Antithrombotic agents are used in the prevention of thrombus formation, but the intensity of their use differs according to the clinical setting (MI or ACS, stent insertion, or chronic CAD). In current guidelines, antiplatelet agents are recommended to prevent the formation of coronary thrombus, specifically low-dose acetylsalicylic acid (ASA; aspirin) for medically managed patients with chronic CAD, with the $P2Y_{12}$ inhibitor clopidogrel recommended when ASA is not tolerated[1,34]. Dual antiplatelet therapy (DAPT) with a $P2Y_{12}$ inhibitor plus ASA is recommended in patients with chronic CAD for up to 1 year after coronary stent implantation, with ASA monotherapy used thereafter[42]. Data supporting a role for dual targeting of the

platelet and coagulation pathways of thrombosis in patients with chronic CAD have been published recently[4,43]; however, current guidelines precede the latest research in this area.

The persistent risk of events

Patients are still at high residual risk of MACE despite guideline-recommended therapy. This is clearly demonstrated by the incidence of MACE in the reference arms of randomized controlled trials (RCTs) attempting to optimize the therapeutic management of chronic CAD with intensified secondary prevention strategies. Examples include RCTs evaluating intensified antithrombotic strategies versus standard of care antiplatelet therapy (PEGASUS-TIMI 54[2], TRA 2°P-TIMI 50[3], and COMPASS[4]). In addition, the CANTOS trial, which evaluated the anti-inflammatory therapy canakinumab in patients with a history of MI and increased blood levels of high-sensitivity C-reactive protein (hsCRP), demonstrated a 4.5% annual risk of MACE in the placebo group receiving standard secondary prevention[5]. In the IMPROVE-IT trial, which evaluated the non-statin drug ezetimibe in patients following recent hospitalization for ACS, the 7-year risk of CV death, major coronary event (MI, unstable angina requiring hospitalization, or coronary revascularization) or non-fatal stroke was 35%[6]. Across these trials, baseline use of secondary prevention strategies was high, with ≥72% of patients receiving an ACE inhibitor/ARB, ≥92% a lipid-lowering therapy and ≥95% an antithrombotic therapy[2-6].

The persistent risk of CV events in patients with chronic CAD is also shown by registries and other large-scale observational data. In the REACH registry, consistent with the RCT data above, the 1-year incidence of MACE was 4.5% in the overall CAD population enrolled in the REACH registry (Table 1)[44]. In a retrospective cohort study of data from Swedish national registries, Jernberg *et al*. demonstrated that the risk of MACE persisted long after an index MI regardless of an absence of events for the first 12 months; the cumulative probability of subsequent MACE (after 12 months of surviving without recurrent MI or stroke; n=76,687) was 9% at 12 months and 20% at 36 months (FIG. 4)[45].

These data highlight the need to improve what we refer to as ‘optimal medical therapy’ for the secondary prevention of MACE in patients with chronic CAD. Patients with chronic CAD who are well-managed with current secondary prevention therapies (based on current guidelines) have a persistent risk of MACE, especially among those with multiple CV risk factors.

The heterogenous risk of events

As discussed in the 'Pathophysiology' section, two areas underpin a patient's risk of CV events: 1) the advanced/systemic nature of CAD, and 2) the presence of CV risk factors that impact on the progression and stability of atherosclerotic plaques and the risk of atherothrombosis (FIG. 2B). Advanced disease can be identified through the presence of stress-induced ischaemia (inferring obstructive disease), CT imaging, disease in multiple vascular beds, and prior revascularization as a marker of defined CAD[46]. Risk factors, including patient characteristics such as age and sex, and comorbidities including diabetes, CKD, HF, dyslipidaemia, and hypertension, can amplify the baseline CV risk, and the risk of atherosclerotic disease the risk of MACE. In turn, these factors increase the potential for thrombotic CV complications (Supple FIG. 1)[7,10,47]. The prevalence of important comorbidities has been demonstrated to be high among patients with chronic CAD (Table 2)[48]; a large database analysis demonstrated that comorbid disease is strongly associated with survival in patients with CAD[49].

Markers of advanced disease

'Stable' angina

Symptomatically 'stable' angina is defined as transient chest pain or tightness in the chest provoked by exertion or emotional stress that can be relieved by rest or administration of nitroglycerin[1]. Such symptoms are frequently the result of obstructive CAD, in which subclinical cycles of plaque disruption, thrombi formation, and subsequent healing can result in an accumulation of material over time and progressive lumen obstruction[8]. In the previously described REACH registry, 52% of patients with baseline documented chronic CAD had 'stable' angina, and the 4-year incidence of MACE in these patients was 16.3% compared with the 14.2% in patients without anginal symptoms. Furthermore, the difference in the risk of MI and stroke remained significant with adjustment for baseline characteristics, including use of ASA and statins[50].

History of cardiovascular events

The risk of recurrent events or death remains high in the first year following an event such as MI or stroke. In a retrospective analysis of data collected from the Singapore National Registry of Disease Office, the adjusted odds of recurrence of the same event within a year was 6.8% in patients with MI and 4.8% in patients with ischaemic stroke with the highest probability in the first 30 days following the index event. Mortality over the 1-year period was 31.7% and 17.1% in patients with MI and those with ischaemic stroke, respectively[51]. In an analysis of data from GRACE (a large, multinational registry enrolling patient with ACS), one-

third of MACE occurred in the first 4 days following the qualifying ACS event; however, 66% of deaths and 59% of reinfarctions took place subsequently in the 6-month follow-up period[52]. In the CAPRIE study, the risk of MACE was increased in the subgroup of patients with prior events compared with the overall population (23.8% and 15.2% at 3 years, respectively, in patients who received ASA)[53]. Such evidence supports the guideline-recommended use of DAPT for up to 1 year after an ACS event[42].

There is strong evidence, however, to support a persistent risk of MACE beyond 1 year after a CV event, both from observational studies[45,48,54] and RCTs[55-57] (FIG. 4). Such data underpin guideline recommendations to consider the use of DAPT beyond 1 year after an ACS event in patients who have tolerated DAPT without bleeding complications[42].

Disease in several vascular beds

As discussed in the 'Pathophysiology' section atherosclerosis is a progressive, systemic disease. Therefore, if one vascular bed is found to be affected, it is likely that the others are too. As such, disease in several vascular beds is common; for example, 24.8% of patients with CAD in the REACH registry had concomitant disease in other vascular beds[11]. This is associated with an increased risk of MACE and other significant CV events, as demonstrated in REACH[44,58] and the randomized PEGASUS-TIMI 54 trial, in which the residual risk of MACE with ASA was highest in patients with CV disease in more than one vascular bed versus the overall population (9.4% and 8.6%, respectively)[59]. As such, disease in more than one vascular bed has substantial prognostic power; for example, disease in both two and three vascular beds were found to be significant predictors of CV death and recurrent CV events at 20 months in a multivariable analysis used in the development of a risk stratification model based on REACH registry data (Table 2)[60].

Revascularization

Among patients with suspected chronic stable vascular disease, prior revascularization identifies those with defined vascular disease and is, therefore, a marker of disease severity. Crucially, these patients are still in need of medical secondary prevention strategies to reduce the risk of MACE. Several datasets provide examples of the high risk of MACE in revascularized versus non-revascularized patients (e.g. the CAPRIE[61,62] and TRA 2°P-TIMI 50[63] trials). Furthermore, a large database analysis demonstrated that the risk of operative mortality was doubled in patients who required a second coronary artery bypass grafting (CABG) procedure compared with those who required a first-time CABG procedure. In the long term (up to 6 years postoperatively), overall survival was significantly lower in patients undergoing a second CABG versus a first CABG[64].

Comorbidities

Type 2 diabetes mellitus

Type 2 diabetes mellitus (T2DM) is a common comorbidity in patients with atherosclerotic disease and was shown to be present in 38% of patients (with 4-years' follow-up data) in the REACH registry[65]. T2DM is a major risk factor for MACE because it is associated with a greater thrombotic predisposition; atherosclerosis is more widely and diffusely distributed in the coronary arteries of patients with T2DM, and atheromas have a greater inflammatory infiltrate and a larger necrotic core size[66]. In the REACH registry, T2DM was associated with a 27% increase in the relative risk of MACE (16.5% and 13.1% in patients with and without diabetes at 4 years, respectively)[65]. Similar trends were reported from analysis of data from the reference arms of the CAPRIE and TRA 2°P-TIMI 50 RCTs (evaluating intensified antiplatelet regimens)[67,68]. Of note, some evidence suggests that patients with extensive CAD and T2DM might benefit from prompt over-delayed revascularization. The BARI 2D trial demonstrated that among 381 patients with T2DM and CAD with high-risk angiographic characteristics intended for CAGB, the 5-year risk of death, MI and stroke was significantly reduced in patients randomized to receive rapid coronary revascularization relative to those assigned to deferred revascularization in a setting of coordinated medical therapy (24.8% and 36.8%, respectively; p=0.005)[69].

Chronic kidney disease

CKD is more prevalent in patients with chronic CAD compared with the general population. One-third of outpatients at risk of atherothrombotic events in the REACH registry had moderate-to-severe CKD, and just under one-quarter of patients in CLARIFY had CKD[70,71]. This is similar to an estimated global prevalence between 11% and 13% in the general medical population globally, with the majority of patients in stage 3 CKD[72]. This is because CKD is associated with accelerated CVD and a higher risk of MACE, mediated by factors including impaired clearance of pro-atherogenic cytokines and uremia-specific metabolites, and an increase in vascular calcification[73,74]. A patient with CKD is more likely to die from a CV-related cause than progress to end-stage kidney disease, with CVD accounting for more than 50% of mortality in patients with CKD[74].

Analyses of data from the REACH and FRENA registries demonstrated that CKD severity was an independent predictor of the extent and severity of vascular disease[70,75]. In the PEGASUS-TIMI 54 trial, the risk of MACE was 14.0% in patients with an estimated

glomerular filtration rate of <60 mL/min/1.73 m^2 compared with 9.0% in the overall population[76].

Heart failure

HF is the fastest-growing CV disease in terms of prevalence, affecting more than 60 million people worldwide, and it is associated with a substantial morbidity, mortality, and economic burden[77,78]. CAD is a major contributor to the development of HF; it is estimated that at least two-thirds of patients with HF have underlying CAD[79]. HF is also associated with an increased risk of MACE in patients with concomitant CAD. For example, in the REACH registry, congestive HF was associated with a ~70% increase in the risk of MACE[54].

Risk stratification

Comorbidities frequently occur together in patients with CAD (with many being independent risk factors for each other). An accumulation of CV risk factors elevates the risk of MACE and other manifestations of CAD such as HF. For example, patients with T2DM and HF have a particularly high risk of CV death[65]; patients with T2DM, congestive HF, and disease in more than one vascular bed have an elevated risk of MACE[65]; the coexistence of T2DM and hypertension significantly increases the risk of HF[80]; and following PCI, patients with T2DM have worse outcomes than those without T2DM[81,82].

Current guidelines recommend a pyramidal structure to prognostic assessment, to categorize patients into a high, intermediate, or low risk of all-cause death. In-sequence risk assessment is carried out by clinical evaluation, ventricular function, response to stress testing, and coronary anatomy[1]. As discussed previously in the ‘Pathophysiology’ section, only select high-risk patients are likely to benefit in terms of survival from revascularization. After revascularization, patients need to be managed with global CV risk control strategies and antithrombotic event prevention[40].

Several scores may be used to predict the risk of MACE in patients with established or suspected chronic CAD, but their use is limited in clinical practice (Table 1).

The concept of ‘personalized’ or ‘precision’ medicine has the potential to improve risk stratification and improve the application of secondary prevention therapies. These approaches may incorporate improved imaging, biomarkers, and genetic markers in conjunction with optimized therapeutic strategies[32]. However, the clinical impact of the use of

such methods is still unsettled and the era of precision medicine has not yet emerged for chronic CAD.

Optimizing the therapeutic management

Standard secondary prevention strategies are evolving to address the high residual risk of MACE observed in patients with chronic CAD despite their use. These advancements include the development of new antithrombotics, lipid-lowering drugs, and anti-inflammatory agents.

Antithrombotic therapy

Platelets have long been recognized as central to the development of arterial thrombosis[83,84]. Several RCTs have attempted to maximize reductions in the risk of MACE via intensified antiplatelet regimens (FIG. 5 and FIG. 6)[2,3,61,85]. Subgroup analyses have included those with a prior event[2,53,86], disease in more than one vascular bed[59,87], T2DM[67,68,88], and CKD[89]. Despite the incremental improvements in the prevention of vascular events with intensifying antiplatelet therapy, a substantial residual risk of MACE remained despite high use of additional secondary prevention medications (≥91% statins/lipid-lowering therapy; 74–90% ACE inhibitors/ARBs)[2,3,85]. Furthermore, there was an increased risk of major bleeding events and/or a lack of mortality benefit across these trials[2,3,61,85] (FIG. 5).

Attempts to further optimize antithrombotic strategies for chronic-phase CV disease are increasingly focused upon dual targeting of both the antiplatelet and coagulation pathways. Coagulation is now understood to play a key role in arterial clot stabilization and the amplification of the platelet activation by thrombin and the role of platelet thrombin receptors in coagulation are increasingly recognized. Hence, it is possible that synergies exist between platelet inhibition and anticoagulation[83]. The first trials to evaluate anticoagulants outside of the acute setting were focused on vitamin K antagonists (VKAs). Meta-analyses of such studies demonstrated a reduction in the risk of CV events with VKA therapy compared with ASA alone (e.g. the annual risk of recurrent MI was reduced by 44%)[90] and suggested improved efficacy benefits with VKA use compared with clopidogrel plus ASA therapy[91]. However, in these meta-analyses, the benefits were offset by a more than twofold increase in the incidence of major bleeding events[90,91]. The development of non-VKA oral anticoagulants (NOACs) led to trials of NOACs in patients with ACS (APPRAISE-2, ATLAS ACS 2 TIMI 51, and GEMINI ACS 1)[92-94] and with chronic CAD/PAD (COMPASS)[43].

The phase III APPRAISE-2 trial evaluated the addition of the Factor Xa inhibitor apixaban to standard antiplatelet therapy or the prevention of MACE in patients after acute ACS at high risk of a recurrent ischaemic event. However, the study was stopped early because apixaban, at a dose of 5 mg twice daily (bid; the full stroke prevention dose for patients with AF), was associated with a significant increase in the risk of major bleeding compared with placebo, without a significant reduction on the incidence of recurrent ischaemic events[92]. The excess bleeding risk with apixaban may have been attributable to the dose selection the inclusion of patients with a high risk of bleeding in the trial[95]. The phase III, double-blind ATLAS ACS 2 TIMI 51 trial evaluated two doses of rivaroxaban, 2.5 mg bid and 5 mg bid, in patients with a recent ACS (unlike in APPRAISE-2, these doses were much lower than those indicated for patients with AF)[93]. Both doses of rivaroxaban (with a background of ASA, or ASA plus clopidogrel or ticlopidine) significantly reduced the risk of MACE versus placebo at the expense of an increased risk of bleeding events (but not fatal bleeding events) versus placebo. The rivaroxaban 2.5 mg bid dose had improved safety outcomes over the rivaroxaban 5 mg bid dose[93]. These results led to European (but not North American) approval of the use of rivaroxaban 2.5 mg bid for the secondary prevention of CV events after an ACS in patients with elevated biomarkers (co-administered with ASA alone or in combination with DAPT [ASA plus clopidogrel or ticlopidine])[96,97].

As a result of the findings from ATLAS ACS 2 TIMI 51, it was hypothesized that removal of ASA, to avoid a triple therapy regimen of DAPT plus an anticoagulant, might reduce the risk of bleeding relative to DAPT alone (as seen in the WOEST trial in a post-PCI setting with VKA plus clopidogrel versus triple therapy)[94,98]. To investigate this hypothesis further, the double-blind, phase II GEMINI ACS 1 trial was conducted to evaluate the safety of rivaroxaban 2.5 mg bid compared with low-dose ASA with a background of $P2Y_{12}$ inhibitor therapy (clopidogrel or ticagrelor, at the investigators discretion) in patients with a recent ACS event[94,98]. Indeed, the risk of TIMI non-CABG clinically relevant bleeding was similar between treatment arms (5% with rivaroxaban versus 5% with ASA). Furthermore, the absence of ASA in the experimental arm had no observed impact on stent thrombosis (87% of patients had PCI for the index event). Conversely, a substantially higher risk of stent thrombosis has been observed when $P2Y_{12}$ inhibitors were stopped early after PCI for ACS[94]. A larger, more adequately powered trial would be needed to substantiate the findings from GEMINI ACS 1, and a better understanding of the intensity of antithrombotic therapy suitable for the transition from the acute to chronic setting is needed[94]. Of note, there are several ongoing studies evaluating antithrombotic regimens that exclude ASA in the setting of ACS (NCT03234114) and chronic CAD or PAD (NCT02567461; NCT02548650).

In the chronic vascular disease setting, rivaroxaban has been recently investigated in patients with chronic CAD or PAD in the phase III COMPASS trial[4,43,99]. The results of this newest study provided further support of the potential benefit of a low dose of the Factor Xa inhibitor rivaroxaban in combination with antiplatelet therapy in patients with atherothrombosis. In total, 27,395 eligible patients with chronic CAD or PAD were randomized to receive rivaroxaban 2.5 mg bid plus ASA 100 mg once daily (n=9152), rivaroxaban 5 mg bid (n=9117), or ASA 100 mg once daily (n=9126) in addition to guideline-recommended secondary preventative therapies. In patients receiving rivaroxaban 2.5 mg bid plus ASA, the risk of MACE was significantly reduced by 24% compared with those receiving ASA alone (4.1% and 5.4%, respectively; HR=0.76; p<0.001), supporting dual targeting of the platelet and coagulation pathways of thrombosis. Overall, the risk of major bleeding was increased by 70% in patients receiving rivaroxaban 2.5 mg bid plus ASA therapy versus those receiving ASA alone (3.1% and 1.9%, respectively; HR=1.70; p<0.001). Rates of fatal bleeding (0.2% and 0.1%, respectively) and ICH (0.3% and 0.3%, respectively) were low and similar between the treatment arms. Unlike the studies of intensified antiplatelet therapy mentioned previously (i.e. CHARISMA, PEGASUS-TIMI 54, and TRA 2°P-TIMI 50)[2,3,86], the COMPASS trial demonstrated a survival benefit with the addition of an anticoagulant[43]. In a pre-specified CAD subanalysis of the COMPASS data, the net clinical benefit outcome (defined as the composite of CV death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ) occurred in 4.7% of patients receiving rivaroxaban 2.5 mg bid plus ASA versus 6.0% in those receiving ASA alone (HR=0.78; p=0.0003). Results were consistent across a variety of patient subgroups, including patients with a history of MI, T2DM, and concurrent PAD[4]. In a subanalysis of data from 7470 patients with PAD or carotid artery disease (with or without CAD) enrolled in COMPASS, rivaroxaban 2.5 mg bid plus ASA reduced the risk of MACE and major adverse limb events including major amputation both as separate endpoints and as a combined composite outcome as follows: 6.3% and 2.4%, respectively; HR=0.54; p=0.0037[99]. The external validity of results from the COMPASS trial has been evaluated using data from the REACH registry. According to this analysis, a substantial number of evaluable patients enrolled in REACH (52.9%) would have been eligible for the COMPASS trial, demonstrating a sufficient level of external validity. COMPASS-eligible patients in REACH were at a significantly higher annualized risk of MACE than those enrolled in COMPASS (4.2% and 2.9%, respectively; p<0.001)[100].

Lipid-lowering agents

Statins are recommended for all patients with established CAD, with a treatment goal of LDL-C <1.8 mmol/L (<70 mg/dL) or >50% LDL-C reduction when the target level cannot be

reached. If the treatment goal is not reached, replacing or combining statins with other lipid-lowering therapies becomes an option[37]. One such therapy is ezetimibe, which inhibits cholesterol absorption in the gut. In the IMPROVE-IT trial, the addition of ezetimibe to simvastatin versus simvastatin alone significantly lowered average LDL-C levels (53.7 mg/dL and 69.5 mg/dL, respectively; $p<0.001$) and the composite risk of MACE and unstable angina requiring hospitalization and revascularization (Kaplan–Meier event rate at 7 years: 32.7% and 34.7%, respectively; $p=0.016$)[6].

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease involved in cholesterol homeostasis. PCSK9 binds to the LDL receptor complex inducing intracellular degradation, reducing serum LDL clearance. The subcutaneously injected PCSK9 monoclonal antibodies alirocumab and evolocumab are approved by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) for the treatment of hypercholesterolemia in patients with intolerance or inadequate response to statins, especially in patients at very high risk of CV events or in the case of familial hypercholesterolemia[37]. A recent meta-analysis of the long-term efficacy and safety of PCSK9 antibodies demonstrated significantly decreased LDL-C levels (mean difference: –50.23%; 95% confidence interval [CI] –56.65% to –43.82%) compared with no PCSK9 antibody treatment, and significant reductions in the rates of MI (relative risk [RR]=0.73; 95% CI 0.65–0.82), coronary revascularization (RR=0.79; 95% CI 0.73–0.87), and stroke (RR=0.81; 95% CI 0.68–0.96). There were no significant differences between the risk of treatment-emergent adverse events or serious treatment-emergent adverse events[101].

It has been demonstrated that the level of LDL-C correlated with a decreased risk of events, without a clear threshold[102]. Studies also demonstrated that plaque regression by 1% over 12 months can be achieved with LDL-C within the range of 36–70 mg/dL[103].

Anti-inflammatory agents

Research has suggested that inflammatory activity contributes to the vulnerability of plaque and that systemic inflammation may increase the risk of thrombosis at sites of plaque rupture or erosion[9]. Furthermore, biomarkers of inflammation, such as hsCRP and interleukin (IL)-6, are associated with an increased risk of CV events, independent of the cholesterol level. Statins have been shown to reduce C-reactive protein levels, and their anti-inflammatory effect has been demonstrated to contribute to the reduction of MACE in at-risk patients[5].

Canakinumab, an IL-1β inhibitor with proven anti-inflammatory effects, was assessed in the phase III CANTOS trial to evaluate the impact of lowering levels of hsCRP on the risk of MACE in patients with a history of MI and a persistent inflammatory response[5]. Canakinumab significantly reduced hsCRP levels from baseline, as compared with placebo, without reducing LDL-C levels, and the canakinumab 150 mg dose resulted in a significantly lower incidence of recurrent CV events compared with placebo (3.9% per year and 4.5% per year, respectively; HR=0.85; 95% CI 0.74–0.98; *p*=0.021). Canakinumab was associated with a higher risk of infection versus placebo but not all-cause mortality[5]. In contrast, in the CIRT trial of 4786 patients post MI or with multivessel CAD with either diabetes or metabolic syndrome, low-dose methotrexate (which targets a different component of the inflammatory pathway to canakinumab) did not reduce the levels of critical IL-1β to IL-6 to CRP pathway of innate immunity nor lower the risk of MACE as compared with placebo[104]. Nonetheless, further targeting of IL-1β and other inflammatory pathways might further improve the residual risk of MACE observed with current secondary prevention strategies.

Antidiabetic agents

Clinical trials of antidiabetic agents demonstrate that improvement in glycemic control does not automatically reduce CV risk; in fact, an increase in CV risk has been observed with some agents, and as a result the FDA has mandated that the risk of MACE be evaluated with new diabetic drugs[105]. Since then, several agents have been demonstrated to significantly lower the risk of MACE versus placebo in randomized controlled trials: the sodium-glucose co-transporter 2 antagonist empagliflozin in the EMPA-REG OUTCOME trial (10.5% vs 12.1%, respectively; HR=0.86; *p*=0.04)[35], the glucagon-like peptide-1 (GLP-1) receptor agonist liraglutide in the LEADER trial (13.0% vs 14.9%, respectively; HR=0.87; *p*=0.01)[106], and the long-acting GLP-1 receptor agonist semaglutide in the SUSTAIN-6 trial (6.6% vs 8.9%, respectively; HR=0.74; *p*<0.001)[107].

Conclusions

The clinical label ‘stable’ CAD needs to be reconsidered and more clearly defined as chronic coronary vascular disease, encompassing a diversity of patient groups including those at substantial risk of future coronary events. Chronic CAD requires optimal medical therapy to mitigate the impact of modifiable risk factors and to reduce the risk of CV events (e.g. MI, stroke, and CV death). Secondary prevention should include current guideline-indicated measures, such as lifestyle changes. Novel secondary prevention measures, which include profound lipid-lowering, inflammation-modifying agents and novel antithrombotic combinations, might have the potential to further reduce the risk of adverse events. The field

will continue to evolve with improved characterization of patients at the highest risk of vascular events, and could include novel imaging techniques to differentiate those with the highest risk plaque subtypes and use of novel systemic biomarkers of vascular disease. Recent advances demonstrate that chronic vascular risk is modifiable and that novel approaches in managing these risk factors has the potential to produce clinically worthwhile gains in the most susceptible patients to CV events.

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Tables

Table 1. Residual risk of MACE in patients with chronic CAD (data from registries)

Registry (patient population or subgroup)	% of the registry population	Residual risk of MACE
REACH registry		
Patients with CAD[11]	59.3%	4.5%
Patients with CAD and 'stable' angina[50]	52%	4-year incidence: 16.3% in patients with 'stable' angina versus 14.2% in patients without
Patients with CAD and a previous CV event[54]	48.4	4-year incidence: 18.3% in patients with a previous ischaemic event versus 12.2% without
Patients with CAD and concomitant disease in other vascular beds[11,44]	24.8%	1-year incidence: ~7.0% versus 4.5% in the overall CAD population
Patients with CAD and T2DM[65]	43.6%	4-year incidence: 16.5% in patients with T2DM versus 13.1% without
Patients at risk of atherothrombotic disease and CKD[70]	34.7% had moderate-to-severe CKD	1-year incidence: CV death ranged from 1.7% in patients with CrCl ≥90 mL/min to 3.8% in patients with a CrCl <30 mL/min (p-trend <0.01); the risk of non-fatal MI ranged from 1.0% to 2.0% (*p*-trend <0.01), and the risk of stroke from 1.5% to 2.0% (*p*-trend 0.1)
CAD and HF[54]	13.6%	71% increased risk of MACE (4-year data)
CLARIFY registry		
Patients with CAD and 'stable' angina[108]	20.0%	2-year incidence: 4.2% in patients with 'stable' angina versus 2.7% in patients without
Patients with CAD and a previous CV event[109]	59.7% of patients enrolled had a previous MI	NR
Patients with CAD and CKD[71]	22.1% of patients had an eGFR <60 mL/min/1.73 m^2	NR
FRENA registry		

Patients with CAD and CKD[75]	27.3% of patients had an eGFR <60 mL/min/1.73 m^2	Risk of MI: 1.38% per year in patients with eGFR >60 mL/min/1.73 m^2 versus 5.79% per year in patients with eGFR 30–60 mL/min/1.73 m^2 versus 18.8% per year in patients with eGFR <30 mL/min/1.73 m^2

CAD, coronary artery disease; CKD, chronic kidney disease; CrCl, creatinine clearance; CV, cardiovascular; eGFR, estimated glomerular filtration rate; HF, heart failure; MACE, major adverse cardiovascular events; MI, myocardial infarction; NR, not reported; T2DM, type 2 diabetes mellitus.

Table 2. Risk scores for predicting events in patients with atherothrombosis

	Risk factors	Outcome	Interpretation
REACH score* [60]	• Age • AF • ASA therapy • BMI • CHF • Country of residence • CV event <1 year • Diabetes mellitusNumber of vascular beds affected • Sex • Smoking status • Statin therapy	Risk of CV death and recurrent CV events at 20 months	**Example** Scores 0–8: <1% Score 10: 1.4% Score ≥26: >50%
Modified REACH score* [60,100]	• AF • Age • ASA therapy • BMI • CHF • Country of residence • CV event <1 year • Diabetes mellitus • Number of vascular beds affected • Sex • Smoking status • Statin therapy	Recurrent CV events	Scores range from 0 to >29 (low to high risk)
Updated GRACE score‡ [110] (https://www.mdcalc.com/grace-acs-risk-mortality-calculator)	• Age • Creatinine • Systolic blood pressure • Pulse • Cardiac arrest at admission (Yes/No)	Risk of death or death/MI following an initial ACS	**Example (following NSTEMI)** [111] Low (<4%) Intermediate (4–12%) High (>12%)

	• ST segmented deviation on EKG? (Yes/No) • Abnormal cardiac enzymes? (Yes/No) • Killip class (No CHF, rales and/or JVD, pulmonary oedema, cardiogenic shock)		
TRA 2°P score§[112]	• Age ≥75 years old • CHF • Diabetes mellitus • eGFR <60 • Hypertension • PAD • Prior stroke • Prior CABG • Smoking	Risk of MACE at 7 years	Low: 0–1 Intermediate: 2 High: ≥3 (maximum score =9)

*The number of points allocated per factor is categorical and full details are provided in Wilson *et al,* 2012 (e.g. there are 14 age categories allocated points ranging from 0 to 14)[60]; ‡the updated GRACE score generates absolute percentage risks[110] and the calculator is available online at: https://www.mdcalc.com/grace-acs-risk-mortality-calculator; §all risk factors are allocated 1 point[112].

ACS, acute coronary syndrome; AF, atrial fibrillation; ASA, acetylsalicylic acid; BMI, body mass index; CABG, coronary artery bypass grafting; CHF, congestive heart failure; CV, cardiovascular; eGFR, estimated glomerular filtration rate; EKG, electrocardiogram; JVD, jugular venous distention; MACE, major adverse cardiovascular events; MI, myocardial infarction; NSTEMI, non-ST-elevation myocardial infarction; PAD, peripheral artery disease.

Figure legends

Figure 1. Expected and observed probabilities of dying or sustaining myocardial infarction or disabling stroke in 5 years by tenth of risk score for patients with 'stable' angina[7].

Figure 2. A) The variable clinical manifestations of CAD[113]. B) The risk of thrombosis at the site of plaque rupture[10].
ACS, acute coronary syndrome; CAD, coronary artery disease.

Figure 3. Event prevention in patients with chronic CAD[1,34].
ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; ASA, acetylsalicylic acid; CAD, coronary artery disease.

Figure 4. The persistent risk of MACE after a CV event as demonstrated by observational[45,48,54] and RCT[55-57] data.
*Defined as non-fatal stroke, non-fatal MI, or CV death; [#]defined as CHD death, MI, or urgent coronary revascularization for MI.
ACS, acute coronary syndrome; CHD, congestive heart disease; CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction; RCT, randomized controlled trial.

Figure 5. Residual risk of MACE and bleeding events in patients with chronic CAD treated with various antithrombotic regimens (data from RCTs)[2,3,43,61,85].
ASA, acetylsalicylic acid; bid, twice daily; CAD, coronary artery disease; CV, cardiovascular; GI, gastrointestinal; ICH, intracranial haemorrhage; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease; RCT, randomized controlled trial.

Figure 6. The impact of different regimens in the context of proven secondary prevention regimens (ASA, lipid lowering, blood pressure, and ACE inhibitors)[2,3,43,61,85,114].
Patient eligibility was as follows. CAPRIE: patients with atherosclerotic vascular disease manifested as either recent ischaemic stroke, recent MI, or symptomatic PAD; CHARISMA: patients ≥45 years of age with multiple atherothrombotic risk factors and/or, documented CAD, cerebrovascular disease or symptomatic PAD; PEGASUS: patients with spontaneous MI 1–3 years before enrolment, ≥50 years old plus one additional risk factor (age ≥ 65 years, diabetes mellitus requiring medication, a second prior spontaneous MI, multivessel CAD, or

eCrCl <60 mL/min); TRA 2°P-TIMI 50: patients with a history of atherosclerosis, defined as a spontaneous MI or ischaemic stroke within 2 weeks to 12 months or PAD associated with a history of intermittent claudication in conjunction with either an ABI <0.85 or previous revascularization for limb ischaemia; COMPASS: patients who met the criteria for CAD and/or PAD (for patients with CAD and <65 years old were also required to have documentation of atherosclerosis involving ≥2 vascular beds or to have at least two additional risk factors).

ABI, ankle brachial index; ACE, angiotensin-converting enzyme; ASA, acetylsalicylic acid; ATT, Antithrombotic Treatment Trialists'; CAD, coronary artery disease; eCrCl, estimated creatinine clearance; MACE, major adverse cardiovascular events; MI, myocardial infarction; PAD, peripheral artery disease.