Thieme

TH Open

Review Article

Current Strategies for Optimizing Antithrombotic Therapy in Patients with Chronic Coronary Syndrome: A Dynamic Approach

Abi Selvarajah[1], Enrico Fabris[2], Maarten A.H. van Leeuwen[1], Arnoud van't Hof[3,4,5], Rik Hermanides[1]

Affiliation addresses are listed at the end of the article.

ABSTRACT

Chronic coronary syndrome (CCS) represents a heterogeneous and dynamic manifestation of coronary artery disease characterized by persistent atherosclerotic burden and ongoing risk of atherothrombotic events. Antithrombotic therapy remains a cornerstone of secondary prevention in CCS, yet optimal treatment strategies have evolved substantially in recent years. The 2024 European Society of Cardiology (ESC) guidelines provide updated recommendations that reflect emerging evidence from randomized clinical trials and meta-analyses evaluating antiplatelet and anticoagulant strategies.

This narrative review summarizes key updates in the 2024 ESC CCS guidelines and the clinical evidence underpinning these changes. Contemporary management has moved beyond a uniform antithrombotic approach toward individualized treatment strategies based on ischemic and bleeding risk.

Single antiplatelet therapy remains the foundation of long-term management, although clopidogrel is now recognized as a Class I, Level A alternative to aspirin in selected patients. For patients undergoing percutaneous coronary intervention (PCI), the guideline maintains a default strategy of 6 months of dual antiplatelet therapy (DAPT) while providing stronger recommendations for abbreviated DAPT in patients at high bleeding risk. Emerging evidence supporting de-escalation strategies and early aspirin withdrawal following PCI has further contributed to risk-adapted treatment pathways. Conversely, in patients with persistently high ischemic risk and low bleeding risk, intensified strategies—including prolonged DAPT, ticagrelor-based therapy, or dual pathway inhibition with low-dose rivaroxaban and aspirin—may provide additional protection against recurrent ischemic events.

The updated recommendations underscore the importance of patient-centered risk stratification and periodic reassessment of ischemic and bleeding risk. Integrating clinical judgment with structured tools such as ARC-HBR and PRECISE-DAPT enables clinicians to tailor antithrombotic therapy in CCS, optimizing net clinical benefit in routine practice.

Keywords chronic coronary syndrome, antithrombotic therapy, optimization

received December 25, 2025 | **accepted after revision** April 20, 2026 | **article published online** 2026

Bibliography TH Open 2026; 10: a28597418 **DOI** 10.1055/a-2859-7418 **Art ID** THOpen-25-12-0051

Correspondence Abi Selvarajah MD, Department of CardiologyIsala Hospital, Dr. van Heesweg 2, 8025 AB Zwolle, Overijssel, the Netherlands, Email: a.selvarajah@isala.nl

Introduction

The term chronic coronary syndrome (CCS) has replaced the former designation "stable coronary artery disease (CAD)," reflecting a conceptual shift in how coronary atherosclerotic disease is understood. Rather than representing a static condition, CCS encompasses a dynamic and progressive disease continuum characterized by episodic plaque instability, thrombotic risk, and recurrent ischemic events. This updated terminology, introduced in the 2019[1] and reinforced in the 2024 European Society of Cardiology (ESC)[2] guidelines, emphasizes the need for long-term and adaptable strategies for secondary cardiovascular prevention.

Importantly, CCS does not exclusively refer to obstructive epicardial CAD. The concept encompasses a broad spectrum of underlying coronary pathologies—including obstructive macrovascular disease, diffuse atherosclerosis, coronary microvascular dysfunction, and vasomotor abnormalities—that may present with diverse clinical manifestations. While many patients remain clinically stable for prolonged periods, chronic coronary disease frequently progresses and may destabilize at any time, potentially resulting in an acute coronary syndrome (ACS). In this context, the term disease refers to the underlying coronary pathology, whereas the term syndrome reflects the clinical presentation resulting from that pathology.

Consequently, CCS represents a highly heterogeneous patient population. It includes individuals stabilized after ACS or coronary revascularization, patients with chronic ischemic left ventricular dysfunction, those with stable angina due to obstructive or

microvascular disease, and asymptomatic individuals in whom coronary disease is detected through imaging-based screening. Despite apparent clinical stability, these patients remain at persistent risk for myocardial infarction (MI), stroke, and cardiovascular death. Residual ischemic risk may persist for many years after the index event, whereas bleeding risk accumulates with more intensive antithrombotic therapy. A central challenge in CCS management therefore lies in balancing the prevention of atherothrombotic events with the avoidance of clinically relevant bleeding.

For decades, aspirin has served as the cornerstone of secondary prevention in CCS. Early randomized trials established its ability to reduce recurrent ischemic events with an acceptable safety profile, leading to its widespread adoption as single antiplatelet therapy (SAPT). However, contemporary evidence has increasingly challenged the exclusive role of aspirin as the default long-term strategy. The CAPRIE trial[3] demonstrated that clopidogrel was associated with a modestly lower incidence of MI, ischemic stroke, or vascular death compared with aspirin. More recent studies, including HOST-EXAM[4] and SMART-CHOICE 3,[5] have further evaluated alternative antiplatelet strategies in patients with CCS following percutaneous coronary intervention (PCI), raising the question of whether aspirin should remain the standard long-term therapy in all patients. Reflecting this evolving evidence base, the 2024 ESC CCS guidelines assign clopidogrel a Class I, Level of Evidence A recommendation for long-term SAPT in patients with prior MI or PCI.

Beyond SAPT, strategies aimed at addressing residual thrombotic risk have expanded. Approaches such as prolonged dual antiplatelet therapy (DAPT) or dual pathway inhibition (DPI) with low-dose rivaroxaban in combination with aspirin have demonstrated additional protection against ischemic events in selected high-risk populations, most notably in the COMPASS trial.[6] However, these strategies are associated with a higher incidence of major bleeding, highlighting the importance of careful patient selection and individualized risk assessment. Contemporary CCS management therefore increasingly relies on balancing ischemic and bleeding risks using validated clinical tools such as ARC-HBR[7] and PRECISE-DAPT.[8]

In this evolving therapeutic landscape, antithrombotic treatment in CCS can no longer follow a uniform "one-size-fits-all" approach. Instead, accumulating evidence supports a personalized strategy guided by clinical phenotype, prior revascularization status, burden of atherosclerotic disease, and individual bleeding susceptibility.

This narrative review aims to provide a clinically oriented overview of contemporary antithrombotic strategies in CCS. We summarize and critically discuss key randomized clinical trials, relevant meta-analyses, and the most recent ESC guideline recommendations. The review focuses on landmark studies that have shaped current practice, identified through targeted searches of major cardiology literature and guideline references, with the goal of providing a practical framework for tailoring antithrombotic therapy in patients with CCS.

Literature Search and Study Selection

This manuscript was designed as a narrative, clinically oriented review rather than a formal systematic review. The objective was to provide an illustrative but evidence-based overview of antithrombotic strategies in CCS, with emphasis on studies that have directly informed contemporary clinical practice and the 2019 and 2024 ESC guideline recommendations. Relevant literature was identified through targeted searches of PubMed/MEDLINE and guideline reference lists, focusing on randomized clinical trials, meta-analyses, and major consensus documents published in the field of antithrombotic therapy in CCS and PCI. Particular attention was given to landmark studies evaluating SAPT, DAPT, de-escalation strategies, oral anticoagulation (OAC), and DPI. Study selection was based on clinical relevance, methodological importance, and impact on current guideline recommendations rather than on a predefined systematic review protocol.

Key Updates in the 2024 European Society of Cardiology Chronic Coronary Syndrome Guidelines and the Supporting Evidence

The management of CCS has undergone further refinement in the 2024 ESC guidelines update regarding antithrombotic therapy. Compared with the 2019 ESC guidelines, the updated recommendations provide clearer and more structured guidance for the selection and duration of antithrombotic strategies in patients with CCS.

Single Antiplatelet Therapy

SAPT remains the cornerstone of long-term secondary prevention in patients with CCS without an indication for OAC. However, the 2024 ESC CCS guidelines introduce a more nuanced interpretation of SAPT options compared with the 2019 guidelines, particularly regarding the role of $P2Y_{12}$ inhibitor monotherapy.

In the 2019 ESC CCS guidelines, low-dose aspirin (75–100 mg once daily) was clearly recommended as the standard first-line antiplatelet therapy for secondary prevention in CCS (Class I, Level of Evidence A), regardless of a prior MI. For patients with aspirin intolerance, clopidogrel was recommended as an alternative therapy (Class I, Level of Evidence B), primarily supported by data from the CAPRIE trial.[3] Although other $P2Y_{12}$ inhibitors such as ticagrelor and prasugrel were discussed in the guideline, their role in CCS was largely limited to DAPT strategies or ACS settings rather than SAPT.

The 2024 ESC CCS guidelines maintain aspirin as a key therapy for long-term secondary prevention in patients with CCS (Class I, Level of Evidence A), based largely on the same robust evidence from historical trials and meta-analyses demonstrating a net reduction in ischemic events, despite a moderate increase in gastrointestinal bleeding risk. In contrast to the largely unchanged evidence base supporting aspirin, the 2024 update incorporates substantial new evidence regarding $P2Y_{12}$ inhibitor monotherapy, which has emerged from several contemporary randomized trials and meta-analyses. Recent state-of-the-art reviews further support this evolving paradigm, highlighting $P2Y_{12}$ inhibitor monotherapy as a potential alternative to aspirin in patients with atherosclerotic cardiovascular disease.[9] In particular, clopidogrel monotherapy is now more clearly recognized as an effective alternative SAPT strategy (Class I, Level of Evidence A). Evidence from studies such as HOST-EXAM[4] and recent individual patient-level meta-analyses[10] suggests that clopidogrel monotherapy

may provide improved protection against ischemic events compared with aspirin, while maintaining a similar overall bleeding risk and potentially reducing gastrointestinal bleeding. Importantly, extended follow-up data from the HOST-EXAM Extended study demonstrated that these benefits are sustained over the long term, with clopidogrel associated with a significantly lower incidence of composite ischemic and bleeding outcomes compared with aspirin during a median follow-up of approximately 5.8 years.[11] More recently, the SMART-CHOICE 3[5] trial further supported this concept by demonstrating that clopidogrel monotherapy after PCI was associated with a lower incidence of major adverse cardiovascular events compared with aspirin monotherapy, without an increase in major bleeding. These findings further strengthen the evidence supporting $P2Y_{12}$ inhibitor monotherapy as an alternative long-term antiplatelet strategy after PCI.

Another notable addition in the 2024 ESC CCS update is the discussion of ticagrelor monotherapy in selected patients, particularly after PCI. Evidence supporting this strategy is primarily derived from randomized trials such as GLOBAL LEADERS[12] and TWILIGHT,[13] which evaluated ticagrelor monotherapy following a short period of DAPT. However, these studies predominantly enrolled post-PCI populations and included a mixture of patients with ACS and CCS, limiting the direct applicability of their findings to the CCS population.

Importantly, the recent individual patient data meta-analysis by Gragnano et al.[14] specifically evaluated ticagrelor monotherapy across randomized trials and provided separate analyses for ACS and CCS populations. In this analysis, ticagrelor monotherapy was associated with a reduction in bleeding without an increase in ischemic events; however, the evidence in CCS remained less robust and was largely derived from subgroup data rather than dedicated CCS trials.

Reflecting these limitations, the 2024 ESC guidelines assign ticagrelor monotherapy a Class II, Level of Evidence B recommendation, indicating that it may be considered only in carefully selected patients following PCI.

Importantly, the clinical implication of the 2024 update is not the replacement of aspirin as the cornerstone therapy, but rather the recognition that alternative SAPT strategies—particularly clopidogrel monotherapy—may be appropriate in selected patients. This reflects a broader shift in contemporary CCS management toward individualized antiplatelet therapy based on ischemic and bleeding risk profiles, rather than a strictly aspirin-centered approach.

Dual Antiplatelet Therapy

The role of DAPT in patients with CCS is primarily confined to the post-PCI setting, as routine DAPT is not recommended for stable CCS patients without recent revascularization or an acute coronary event. Accordingly, both the 2019 and 2024 ESC CCS guidelines address DAPT predominantly in the context of secondary prevention following coronary stent implantation.

In the 2019 ESC CCS guidelines, a default duration of 6 months of DAPT consisting of aspirin and clopidogrel was recommended after PCI performed for CCS (Class I, Level of Evidence A). Clopidogrel was the preferred $P2Y_{12}$ inhibitor in this setting, reflecting the lack of evidence supporting the routine use of more potent $P2Y_{12}$ inhibitors in elective PCI for stable CAD. The guideline emphasized that premature discontinuation of the $P2Y_{12}$ inhibitor should be avoided, given the associated risk of stent thrombosis during the early healing phase after stent implantation. However, the exact timing that would constitute "premature" discontinuation was not clearly defined. At the same time, the guideline acknowledged that shorter DAPT durations of 1 to 3 months could be considered in patients at high bleeding risk, reflecting the relatively low incidence of late stent thrombosis with contemporary drug-eluting stents. As a result, while abbreviated DAPT strategies were mentioned, the minimum safe duration of therapy remained somewhat uncertain, and these strategies were presented cautiously.

The 2024 ESC CCS guidelines largely maintain the 6-month DAPT strategy as the default approach after PCI in CCS patients (Class I, Level of Evidence A), again recommending aspirin (75–100 mg daily) combined with clopidogrel (75 mg daily) as the preferred regimen. However, the updated guideline provides more explicit and stronger recommendations for abbreviated DAPT strategies, reflecting accumulating evidence from contemporary randomized trials. In particular, in patients at high bleeding risk without high ischemic risk, discontinuation of DAPT after 1 to 3 months followed by SAPT is now recommended (Class I, Level of Evidence A). In selected patients without high bleeding or ischemic risk, shortening DAPT to 1 to 3 months may also be considered (Class IIb, Level of Evidence B).

Conversely, in patients undergoing high thrombotic risk PCI, such as complex left main interventions, two-stent bifurcation techniques, suboptimal stent deployment, prior stent thrombosis, or known CYP2C19 loss-of-function polymorphisms, the temporary use of more potent $P2Y_{12}$ inhibitors such as ticagrelor or prasugrel in addition to aspirin may be considered during the early post-PCI phase, typically for the first month and up to 3 to 6 months.

Overall, while the default duration of DAPT remains unchanged, the 2024 ESC guidelines place greater emphasis on individualized treatment duration based on bleeding and ischemic risk, providing clearer guidance for abbreviated strategies that were previously described more cautiously in the 2019 document.

The Role of Anticoagulant Therapy in Chronic Coronary Syndrome Patients with and Without Atrial Fibrillation

In patients with CCS and concomitant atrial fibrillation (AF), long-term OAC remains the cornerstone of therapy for the prevention of cardioembolic stroke. Both the 2019 and 2024 ESC CCS guidelines recommend OAC in these patients, with direct OACs (DOACs) preferred over vitamin K antagonists in eligible individuals (Class I, Level of Evidence A).

Additional complexity arises in CCS patients with AF who undergo PCI as these patients require antithrombotic therapy to prevent both thromboembolic events and stent thrombosis. In the 2019 ESC CCS guidelines, early discontinuation of aspirin after uncomplicated PCI—typically within the first week—followed by dual therapy consisting of OAC and clopidogrel was suggested in patients in whom the bleeding risk outweighed the risk of stent thrombosis (Class IIa, Level of Evidence B). This approach was supported by emerging evidence from randomized trials demonstrating that dual therapy with an OAC and a $P2Y_{12}$ inhibitor reduces bleeding compared with prolonged triple therapy.

The 2024 ESC CCS guidelines further strengthen this strategy, now recommending early cessation of aspirin (≤1 week) after uncomplicated PCI, followed by dual therapy with OAC and clopidogrel for up to 6 months in patients without high ischemic risk and up to 12 months in those with higher ischemic risk, after which OAC monotherapy should be continued (Class I, Level of Evidence A). This upgrade reflects the growing body of evidence from randomized trials and meta-analyses demonstrating that minimizing exposure to triple antithrombotic therapy reduces bleeding without compromising ischemic protection.

De-escalation of Antithrombotic Therapy After Percutaneous Coronary Intervention in Chronic Coronary Syndrome

Although the ESC CCS guidelines do not include a dedicated subsection on de-escalation, this concept is embedded within the recommendations for antithrombotic therapy after PCI in patients with CCS. In this setting, de-escalation refers to strategies aimed at reducing the intensity or duration of antiplatelet therapy in order to lower bleeding risk while maintaining adequate protection against ischemic events. Importantly, these strategies apply primarily to antiplatelet agents, such as aspirin or $P2Y_{12}$ inhibitors. In contrast, when a long-term indication for OAC exists—such as AF—the anticoagulant component is generally maintained, and de-escalation typically involves modification of the accompanying antiplatelet therapy rather than withdrawal of OAC.

From a practical perspective, de-escalation after PCI has mainly been investigated in two forms. The first involves shortening the duration of DAPT. This strategy was evaluated in the MASTER-DAPT[15] trial, which enrolled patients at high bleeding risk undergoing PCI. Importantly, all patients initially received 1 month of mandatory DAPT following PCI before randomization. After this period, patients were randomized to either an abbreviated antithrombotic strategy or continuation of standard therapy. In the abbreviated arm, DAPT was discontinued after 1 month, and patients continued with SAPT—most commonly a $P2Y_{12}$ inhibitor—or OAC alone when indicated. This abbreviated strategy was noninferior to standard therapy with respect to ischemic outcomes while significantly reducing bleeding. A second de-escalation strategy involves early withdrawal of aspirin while maintaining $P2Y_{12}$ inhibitor monotherapy, rather than discontinuing DAPT immediately. This concept has been evaluated in several randomized trials conducted in post-PCI populations.

The GLOBAL LEADERS[12] trial investigated a strategy of 1 month of DAPT followed by ticagrelor monotherapy in an all-comer PCI population, including both ACS and CCS patients. Although superiority was not demonstrated, the study provided proof of concept for early aspirin withdrawal. The TWILIGHT[13] trial subsequently showed that discontinuation of aspirin after 3 months of DAPT followed by ticagrelor monotherapy significantly reduced bleeding without increasing ischemic events in high-risk PCI patients.

Importantly, these trials predominantly enrolled mixed populations of ACS and CCS patients and dedicated evidence in stable CCS populations remains limited. Supporting these findings, the SIDNEY-4[16] individual patient-level meta-analysis confirmed that $P2Y_{12}$ inhibitor monotherapy after a short course of DAPT was noninferior to standard 12-month DAPT for ischemic outcomes while significantly reducing major bleeding.

Taken together, these studies support the broader shift reflected in the 2024 ESC CCS guidelines toward risk-adapted antithrombotic therapy after PCI, where shortening DAPT or early withdrawal of aspirin may reduce bleeding risk once the early phase of heightened thrombotic vulnerability has passed. However, it should be noted that most trials evaluating these strategies enrolled mixed populations of ACS and CCS patients, and therefore, the evidence specifically in stable CCS populations remains more limited.

Extended and/or Intensified Antithrombotic Therapy

Despite optimal secondary prevention, patients with CCS remain at persistent risk of recurrent ischemic events due to the chronic and progressive nature of atherosclerotic disease. Consequently, strategies aimed at extended or intensified antithrombotic therapy have been explored in patients with high ischemic risk and acceptable bleeding risk. Two principal approaches have been investigated: prolongation of DAPT and DPI combining low-dose anticoagulation with antiplatelet therapy.

In the DAPT[17] trial, extending DAPT to 30 months after PCI significantly reduced the risks of stent thrombosis and MI compared with aspirin monotherapy. However, this benefit was accompanied by an increased risk of moderate or severe bleeding as well as a signal toward increased noncardiovascular mortality. These findings highlight the importance of careful patient selection, with prolonged DAPT offering the greatest net benefit in patients at high ischemic risk and low bleeding risk. Similarly, the PEGASUS-TIMI 54[18] trial demonstrated that long-term treatment with ticagrelor in addition to aspirin reduced the composite endpoint of cardiovascular death, MI, or stroke in patients with a prior MI 1 to 3 years earlier who also had additional high-risk characteristics. Importantly, the lower ticagrelor dose of 60 mg twice daily was associated with a more favorable safety profile and is therefore the preferred regimen for extended therapy. Additional evidence from the THEMIS[19] trial suggested that patients with diabetes and stable CAD, particularly those with a history of PCI, may derive ischemic benefit from long-term ticagrelor therapy despite an increased risk of major bleeding. Collectively, these studies indicate that prolonged DAPT may be beneficial in carefully selected patients with high ischemic risk and low bleeding risk. An alternative strategy for intensifying long-term antithrombotic therapy involves DPI, which combines low-dose anticoagulation with antiplatelet therapy. The most robust evidence supporting this approach in patients with CCS comes from the COMPASS[6] trial.

In COMPASS, the combination of low-dose rivaroxaban (2.5 mg twice daily) plus aspirin was compared with aspirin monotherapy in patients with stable atherosclerotic disease, predominantly CAD. This regimen resulted in a significant reduction in the composite endpoint of cardiovascular death, stroke, or MI, as well as a reduction in all-cause mortality. Although major bleeding was increased, this was not associated with a higher incidence of fatal or intracranial bleeding, supporting a favorable net clinical benefit. Importantly, the benefit of DPI in this study was most pronounced in patients with high ischemic risk features, including diabetes mellitus, peripheral artery disease, chronic kidney disease, and multivessel CAD. These findings established low-dose

rivaroxaban in combination with aspirin as an effective long-term secondary prevention strategy in carefully selected CCS patients with a high ischemic risk and low bleeding risk.

Reflecting this evidence, DPI has been incorporated into both the 2019 and 2024 ESC CCS guidelines. In the 2024 update, this strategy remains recommended (Class IIa) as one of the options for extended intensified antithrombotic therapy, alongside prolonged DAPT or ticagrelor-based strategies, within a more structured and individualized treatment framework.

Tailored Antithrombotic Strategies: Translating Guideline Updates into Clinical Practice

The 2024 ESC CCS guideline update reinforces a central principle of contemporary antithrombotic management: treatment selection in CCS should be individualized rather than protocol-driven. While aspirin has historically served as the default strategy for long-term secondary prevention, contemporary evidence shows that the optimal regimen depends on a careful assessment of ischemic risk, bleeding risk, prior MI, revascularization status, the presence or absence of AF, and the timing after PCI. In clinical practice, the challenge is therefore not simply to choose an antithrombotic regimen, but to identify which patients are most likely to benefit from treatment intensification, treatment shortening, or simplification.

For most patients with CCS without an indication for OAC and without recent PCI, long-term SAPT remains the preferred approach. In this setting, the 2024 guideline broadens the practical options by recognizing clopidogrel monotherapy as a Class I, Level A alternative to aspirin, particularly in patients with prior MI or prior PCI. This has direct clinical relevance, as it allows clinicians to move beyond a purely aspirin-centered approach in patients with gastrointestinal intolerance, previous bleeding concerns, or those in whom the overall balance between ischemic and bleeding risk may favor clopidogrel. At the same time, aspirin remains an entirely appropriate first-line therapy in many patients, especially where tolerance is good and bleeding risk is low.

In patients undergoing PCI for CCS, antithrombotic treatment becomes more dynamic and time-dependent. The default approach remains 6 months of DAPT with aspirin and clopidogrel, but the practical application of this recommendation is now more explicitly determined by bleeding and thrombotic risk. In patients at high bleeding risk, abbreviated DAPT for 1 to 3 months followed by monotherapy should be actively considered, and in selected cases, is now recommended. By contrast, in patients undergoing high thrombotic risk PCI, such as complex bifurcation stenting, left main PCI, prior stent thrombosis, or suboptimal stent deployment, temporary intensification with a more potent $P2Y_{12}$ inhibitor may be justified during the early postprocedural period. Thus, the duration and intensity of DAPT should be viewed as adjustable rather than fixed.

The concept of de-escalation is particularly relevant in this setting. In practical terms, de-escalation may involve either shortening DAPT itself or withdrawing aspirin early while maintaining $P2Y_{12}$ inhibitor monotherapy. These approaches are most relevant when the initial phase of heightened thrombotic risk has passed and bleeding risk becomes the dominant concern. However, the available evidence must be interpreted carefully, as much of it derives from mixed ACS/CCS populations rather than dedicated stable CCS cohorts. Therefore, in clinical practice, de-escalation should not be applied indiscriminately, but rather in patients in whom bleeding avoidance is a priority and ischemic risk is not excessive.

At the other end of the spectrum, some patients remain at persistently high ischemic risk despite apparent clinical stability. In such patients, treatment intensification may be appropriate if bleeding risk is low. This includes patients with prior MI, multivessel coronary disease, diabetes, chronic kidney disease, peripheral artery disease, or recurrent ischemic events despite standard therapy. In these patients, the 2024 ESC guidelines support consideration of extended intensified antithrombotic therapy, either through prolonged DAPT, the addition of ticagrelor 60 mg twice daily to aspirin in selected post-MI patients, or DPI with aspirin plus rivaroxaban 2.5 mg twice daily. Among these options, the COMPASS regimen has particular practical relevance for stable CCS patients with diffuse atherosclerotic burden and low bleeding risk. Importantly, however, intensification should never be considered a routine step-up strategy; rather, it should be reserved for patients in whom the anticipated ischemic benefit outweighs the incremental bleeding hazard.

In patients with concomitant AF or another indication for long-term OAC, treatment decisions must be made within a different framework. In such patients, OAC remains the foundation of therapy and should not be withdrawn simply as part of antithrombotic de-escalation. When PCI is performed, the contemporary approach favors very short triple therapy, followed by dual therapy with OAC and clopidogrel, and ultimately OAC alone. This is an important practical shift from older, more prolonged triple-therapy approaches and reflects the growing emphasis on minimizing bleeding without compromising protection against stent thrombosis or thromboembolism.

From a clinical perspective, the key message of the 2024 update is that antithrombotic therapy in CCS should be continuously re-evaluated rather than prescribed once and left unchanged. A patient initially treated with DAPT after PCI may later transition to SAPT, and subsequently, if ischemic risk remains high and bleeding risk remains acceptable, may even become a candidate for intensified long-term therapy. Conversely, a patient initially considered for prolonged therapy may require de-escalation if bleeding risk increases over time. Antithrombotic treatment in CCS should therefore be regarded as a longitudinal strategy that evolves with the patient's clinical course.

Ultimately, translating guideline recommendations into practice requires more than knowledge of trial data alone. It requires integration of patient phenotype, procedural characteristics, ischemic burden, prior events, and bleeding susceptibility into a tailored therapeutic decision. In this sense, the 2024 ESC CCS guidelines do not simply offer new recommendations; they formalize a broader shift toward precision-based secondary prevention, in which the optimal antithrombotic strategy is the one that best matches the individual patient's net clinical risk.

It is also important to recognize that patients enrolled in randomized clinical trials often differ substantially from those encountered in daily clinical practice. Elderly individuals, frail patients, and those with multiple comorbidities or polypharmacy are frequently underrepresented in clinical trials evaluating

antithrombotic therapy. In real-world populations, factors such as reduced physiological reserve, impaired renal function, drug–drug interactions, and adherence challenges may significantly influence both the efficacy and safety of antithrombotic regimens. In addition, competing risks related to noncardiovascular comorbidities may alter the overall net clinical benefit of intensified antithrombotic strategies. Therefore, guideline recommendations should be interpreted within the context of individual patient characteristics, emphasizing the importance of shared decision-making and individualized treatment selection in routine clinical practice.

Patient-Centered Risk Stratification and Net Clinical Benefit in Antithrombotic Therapy

Contemporary management of antithrombotic therapy in CCS increasingly relies on patient-centered risk stratification, in which therapeutic decisions are guided by the balance between ischemic protection and bleeding risk. This balance is often referred to as the net clinical benefit, reflecting the overall impact of antithrombotic therapy on major ischemic events—such as MI, stroke, or cardiovascular death—relative to the risk of clinically relevant bleeding. As illustrated in the previous sections, treatment strategies in CCS range from de-escalation approaches aimed at reducing bleeding risk to intensified regimens targeting residual ischemic risk, emphasizing the importance of individualized treatment selection.

Interpretation of the evidence supporting these strategies requires careful consideration of how outcomes are reported in randomized clinical trials. Many antithrombotic trials rely on composite endpoints, such as major adverse cardiovascular events, which typically combine cardiovascular death, MI, stroke, and sometimes repeat revascularization. While such composite outcomes improve statistical power, the individual components differ substantially in their prognostic relevance. Reductions in cardiovascular mortality or disabling stroke represent outcomes of clear clinical importance, whereas reductions in nonfatal MI or repeat revascularization may have a different impact on long-term prognosis. Similarly, bleeding outcomes range from minor bleeding events to life-threatening or fatal hemorrhage. Consequently, evaluation of the net clinical benefit of antithrombotic strategies should consider not only the composite outcome but also the relative contribution and clinical severity of individual endpoint components.

A structured assessment of bleeding risk is essential when tailoring antithrombotic therapy. The ARC-HBR criteria provide a widely adopted consensus definition of high bleeding risk in patients undergoing PCI. According to this framework, patients are considered to have high bleeding risk if at least one major or two minor criteria are present. Major criteria include conditions such as severe anemia, recent major bleeding, thrombocytopenia, advanced chronic kidney disease, or the need for long-term OAC, whereas minor criteria include advanced age, moderate renal impairment, or chronic use of nonsteroidal anti-inflammatory drugs. Identification of such patients is particularly relevant when considering abbreviated DAPT strategies or other de-escalation approaches.

In addition to qualitative definitions, quantitative bleeding risk prediction models may further support clinical decision-making. The PRECISE-DAPT score, which incorporates variables such as age, renal function, hemoglobin concentration, white blood cell count, and prior bleeding, has been validated to predict bleeding risk during DAPT after PCI. Patients with elevated PRECISE-DAPT scores appear to derive greater benefit from shortened DAPT durations, whereas those with lower scores may tolerate longer antithrombotic regimens.

Importantly, the translation of trial evidence into routine practice requires recognition of the heterogeneity of real-world CCS populations. Patients enrolled in randomized clinical trials are often younger and have fewer comorbidities than those encountered in daily clinical care. Elderly individuals, frail patients, and those with multiple chronic conditions or polypharmacy are frequently underrepresented in trials evaluating antithrombotic therapy. In routine practice, factors such as impaired renal function, increased bleeding susceptibility, drug–drug interactions, medication adherence, and competing noncardiovascular risks may substantially influence the overall net clinical benefit of antithrombotic strategies.

Taken together, these considerations highlight that risk stratification should not be viewed as a static assessment performed at a single time point. Rather, both ischemic and bleeding risks evolve over time and should be periodically reassessed throughout the course of disease. Integrating structured risk assessment tools such as ARC-HBR and PRECISE-DAPT, together with clinical judgment and patient-specific characteristics, allows clinicians to tailor antithrombotic therapy in a manner that maximizes ischemic protection while minimizing bleeding complications in patients with CCS.

Discussion

The expanding body of evidence supporting contemporary antithrombotic strategies in CCS highlights the growing complexity of treatment decision-making in this population. While randomized clinical trials have provided the foundation for current guideline recommendations, translating these findings into clinical practice requires careful interpretation of trial outcomes, thoughtful patient selection, and consideration of real-world clinical circumstances.

One important consideration is the reliance of many antithrombotic trials on composite endpoints, such as major adverse cardiovascular events, which often combine cardiovascular death, MI, stroke, and occasionally repeat revascularization into a single outcome measure. Although composite endpoints increase statistical efficiency, the individual components differ substantially in clinical relevance. Reductions in cardiovascular mortality or disabling stroke represent outcomes with clear prognostic importance, whereas reductions in nonfatal MI or repeat revascularization may have a different impact on long-term prognosis and quality of life. Similarly, bleeding endpoints encompass a broad spectrum ranging from minor bleeding to life-threatening or fatal hemorrhage. Consequently, interpretation of treatment effects and assessment of the net clinical benefit of antithrombotic strategies should consider not only the composite outcome but also the relative contribution and clinical severity of individual endpoint components. In addition, the generalizability of randomized clinical trial data to everyday clinical practice warrants careful consideration.

Another important consideration in routine practice is the presence of competing noncardiovascular risks, such as malignancy, advanced frailty, or progressive chronic disease, which may influence the overall net clinical benefit of intensified antithrombotic strategies. For example, the potential ischemic benefit of prolonged or intensified therapy may be attenuated in patients with limited life expectancy or high bleeding susceptibility. Therefore, risk stratification tools should be viewed as supportive instruments rather than substitutes for clinical judgment.

Taken together, these considerations emphasize that antithrombotic therapy in CCS should be viewed as a dynamic and individualized strategy, requiring periodic reassessment of both ischemic and bleeding risks over time. Integrating evidence from randomized trials with patient-specific characteristics and real-world clinical considerations remains essential for optimizing therapeutic decision-making in this complex patient population.

Conclusion

Antithrombotic therapy remains central to secondary prevention in CCS, yet contemporary management increasingly requires a personalized approach that balances ischemic protection against bleeding risk. The 2024 ESC CCS guidelines reflect a shift toward risk-adapted treatment strategies, incorporating new evidence supporting $P2Y_{12}$ inhibitor monotherapy, abbreviated DAPT after PCI, and intensified approaches in selected high-risk patients. At the same time, real-world clinical decision-making must account for patient heterogeneity, comorbidities, frailty, and competing risks that are often underrepresented in randomized clinical trials. Ultimately, optimizing antithrombotic therapy in CCS requires integration of guideline recommendations, structured risk stratification tools, and individualized clinical judgment to achieve the greatest net clinical benefit.

What is Known About This Topic?

- Antithrombotic therapy is a cornerstone of secondary prevention in patients with CCS.
- Recent clinical trials and ESC guidelines support more individualized antithrombotic strategies based on ischemic and bleeding risk.
- Both de-escalation and intensified antithrombotic approaches have been investigated to optimize net clinical benefit.

What Does This Paper Add?

- This review summarizes key updates from the 2024 ESC guidelines on antithrombotic therapy in CCS.
- The paper provides a practical overview of contemporary strategies including P2Y12 inhibitor monotherapy, abbreviated DAPT, and dual pathway inhibition.
- It highlights the importance of dynamic, patient-centered risk stratification, and individualized treatment selection in routine clinical practice.

Author Affiliations

1 Department of Cardiology, Isala Hospital, Zwolle, Overijssel, the Netherlands
2 Department of Cardiology, University of Trieste, Trieste, Italy
3 Department of Cardiology, University Medical Center Maastricht, Maastricht, the Netherlands
4 Cardiovascular Research Institute Maastricht (CARIM), Maastricht University, Maastricht, the Netherlands
5 Department of Cardiology, Zuyderland Medical Centre, Sittard-Geleen, the Netherlands

Statements and Additional Information

Conflict of Interest The authors declare that they have no conflict of interest.

Data Availability Statement This study is based on previously published data, which are cited in the reference list.

Contributors' Statement A.S.: conceptualization, investigation, visualization, writing original draft, writing review and editing. E.F.: writing review and editing. M.A.H.V.L.: supervision, writing review and editing. A.v.H: supervision, writing review and editing. R.H.: conceptualization, supervision, writing review and editing.

References

1 Knuuti J, Wijns W, Saraste A, et al. ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2020;41(03):407–477
2 Vrints C, Andreotti F, Koskinas KC, et al. ESC Scientific Document Group. 2024 ESC guidelines for the management of chronic coronary syndromes. Eur Heart J 2024;45(36):3415–3537
3 CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet 1996;348 (9038):1329–1339
4 Koo BK, Kang J, Park KW, et al. HOST-EXAM investigators. Aspirin versus clopidogrel for chronic maintenance monotherapy after percutaneous coronary intervention (HOST-EXAM): an investigator-initiated, prospective, randomised, open-label, multicentre trial. Lancet 2021;397(10293):2487–2496
5 Choi KH, Park YH, Lee JY, et al. SMART-CHOICE 3 investigators. Efficacy and safety of clopidogrel versus aspirin monotherapy in patients at high risk of subsequent cardiovascular event after percutaneous coronary intervention (SMART-CHOICE 3): a randomised, open-label, multicentre trial. Lancet 2025;405(10486):1252–1263
6 Eikelboom JW, Connolly SJ, Bosch J, et al. COMPASS Investigators. Rivaroxaban with or without aspirin in stable cardiovascular disease. N Engl J Med 2017;377 (14):1319–1330
7 Urban P, Mehran R, Colleran R, et al.Defining high bleeding risk in patients undergoing percutaneous coronary intervention. Circulation 2019;140 (03):240–261
8 Costa F, van Klaveren D, James S, et al. PRECISE-DAPT Study Investigators. Derivation and validation of the predicting bleeding complications in patients undergoing stent implantation and subsequent dual antiplatelet therapy (PRECISE-DAPT) score: a pooled analysis of individual-patient datasets from clinical trials. Lancet 2017;389(10073):1025–1034
9 Galli M, Ten Berg J, Valgimigli M, et al.Aspirin or P2Y12 inhibitor monotherapy in atherosclerotic cardiovascular disease? Eur Heart J 2026;47(05):558–573
10 Gragnano F, Cao D, Pirondini L, et al. PANTHER Collaboration. P2Y12 inhibitor or aspirin monotherapy for secondary prevention of coronary events. J Am Coll Cardiol 2023;82(02):89–105
11 Kang J, Park KW, Lee H, et al.Aspirin versus clopidogrel for long-term maintenance monotherapy after percutaneous coronary intervention: the HOST-EXAM Extended Study. Circulation 2023;147(02):108–117
12 Vranckx P, Valgimigli M, Jüni P, et al. GLOBAL LEADERS Investigators. Ticagrelor plus aspirin for 1 month, followed by ticagrelor monotherapy for 23 months vs aspirin plus clopidogrel or ticagrelor for 12 months, followed by aspirin monotherapy for 12 months after implantation of a drug-eluting stent: a multicentre, open-label, randomised superiority trial. Lancet 2018;392(10151):940–949

13 Mehran R, Baber U, Sharma SK, et al.Ticagrelor with or without aspirin in high-risk patients after PCI. N Engl J Med 2019;381(21):2032–2042

14 Gragnano F, Valgimigli M, Mehran R, et al.Ticagrelor monotherapy after percutaneous coronary intervention: an individual patient data meta-analysis of randomized trials. Eur Heart J 2024;45(39):3360–3372

15 Valgimigli M, Frigoli E, Heg D, et al. MASTER DAPT Investigators. Dual antiplatelet therapy after PCI in patients at high bleeding risk. N Engl J Med 2021;385 (18):1643–1655

16 Valgimigli M, Hong SJ, Gragnano F, et al. Single Versus Dual Antiplatelet Therapy (Sidney-4) collaborator group. De-escalation to ticagrelor monotherapy versus 12 months of dual antiplatelet therapy in patients with and without acute coronary syndromes: a systematic review and individual patient-level meta-analysis of randomised trials. Lancet 2024;404(10456):937–948

17 Mauri L, Kereiakes DJ, Yeh RW, et al. DAPT Study Investigators. Twelve or 30 months of dual antiplatelet therapy after drug-eluting stents. N Engl J Med 2014;371(23):2155–2166

18 Bonaca MP, Bhatt DL, Cohen M, et al. PEGASUS-TIMI 54 Steering Committee and Investigators. Long-term use of ticagrelor in patients with prior myocardial infarction. N Engl J Med 2015;372(19):1791–1800

19 Steg PG, Bhatt DL, Simon T, et al. THEMIS Steering Committee and Investigators. Ticagrelor in patients with stable coronary disease and diabetes. N Engl J Med 2019;381(14):1309–1320