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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Antithrombotic treatment strategies in patients with established coronary atherosclerotic disease

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Multiple guidelines and consensus papers have addressed the role of antithrombotic strategies in patients with established coronary artery disease (CAD). Since evidence and terminology continue to evolve, the authors undertook a consensus initiative to guide clinicians to select the optimal antithrombotic regimen for each patient. The aim of this document is to provide an update for clinicians on best antithrombotic strategies in patients with established CAD, classifying each treatment option in relation to the number of antithrombotic drugs irrespective of whether the traditional mechanism of action is expected to mainly inhibit platelets or coagulation cascade. With the aim to reach comprehensiveness of available evidence, we systematically reviewed and performed meta-analyses by means of both direct and indirect comparisons to inform the present consensus document.

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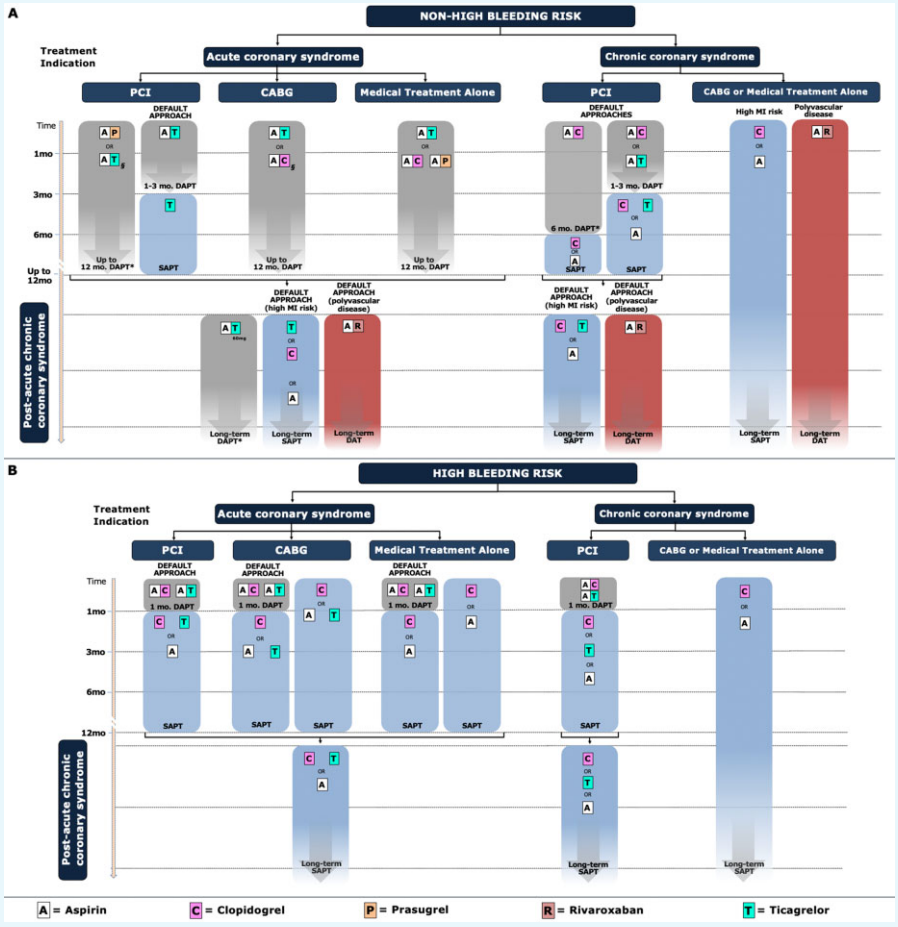
Graphical Abstract



Algorithm for antithrombotic treatment in patients with established CAD. Treatment preferences within each box are shown from above to below, whereas treatments within the same line are sorted in alphabetical order. Panels A and B refer to non-high bleeding risk (HBR) and HBR patients, respectively. HBR is defined according to the ARC-HBR criteria or a PRECISE-DAPT score ≥25. * for patients at high ischaemic risk and very low bleeding risk. § if the patient is not eligible for above shown treatment options. Box colours indicate composition of antithrombotic regimens (light blue: SAPT; grey: DAPT; and red: DAT). Abbreviations: ARC, Academic Research Consortium; CABG, coronary artery bypass grafting; CAD, coronary artery disease; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

Keywords Antithrombotic treatment • Coronary artery disease • Percutaneous coronary intervention • Acute coronary syndrome • Chronic coronary syndrome

Introduction

Multiple guidelines and consensus papers have addressed the optimal use of antithrombotic medications for patients with established coronary artery disease (CAD).[1–6] However, evidence and terminology continue to evolve, and a single comprehensive, updated document aimed at supporting clinicians in deciding which antithrombotic regimen to select throughout the entire spectrum of patients with established CAD is missing. The remit of this initiative is to systematically review and perform meta-analysis of the available evidence by means of both direct and indirect comparisons (separate manuscript) to further inform a consensus document on antithrombotic treatment strategies for secondary or tertiary prevention in patients with established CAD. The management of patients requiring anticoagulation has been recently addressed by multiple European Society of Cardiology (ESC) guidelines[5,7] and American consensus documents[8] and is therefore not addressed in this manuscript.

The 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes (CCSs)[9] suggested using the term CCS instead of stable CAD to highlight the progressive and dynamic nature of the disease and described its multiple manifestations, including CCS patients who never experienced a prior acute coronary syndrome (ACS) as well as those with stabilized CCS at 12 months after ACS. In recognizing the fact that the need for antithrombotic strategies may vary among CCS patients based on the presence or absence of prior myocardial infarction (MI),[10,11] the interpretation of the evidence and

clinical consensus statements have been provided separately for CCS patients with or without prior MI in this document. The present document distinguishes two types of CAD at onset, including ACS and CCS without prior MI, and discusses antithrombotic strategies stratifying patients based on revascularization modality [i.e. percutaneous coronary intervention (PCI), coronary artery bypass grafting (CABG), or no revascularization] and bleeding risk. In CCS patients without prior MI at onset who develop an ACS, the latter form of CAD should drive decisions for antithrombotic strategies. Patients with ACS at onset, or a secondary form of CAD, who remain stable per an arbitrary period of 12 months transition towards CCS with prior MI.

An overview of all investigated antithrombotic strategies and corresponding randomized clinical trials in patients with established CAD[12–78] is shown in *Table 1*.

Antithrombotic therapies have been traditionally classified based on the principal thrombotic target, either platelets (antiplatelet agents) or coagulation factors (anticoagulant agents). However, platelets and coagulation mutually influence each other. Anticoagulants, at lower than the standard dosing that is traditionally used to achieve conventional anticoagulation effects, prevent CAD-related ischaemic and fatal events not solely via an anticoagulation effect but likely by concomitantly modulating thrombin-mediated platelet activation.[79]

Against this background, multiple combinations of antiplatelet agents or antiplatelet and anticoagulant drugs, using various regimens, have been tested for the prevention of thrombotic events in patients with established CAD. Although some treatment combinations have lowered ischaemic risk compared with simpler regimens, combination therapy usually increases bleeding and always increases prescribing complexity. To better address this issue, the present document classifies each treatment option in relation to the number of antithrombotic drugs irrespective of whether the traditional mechanism of action is expected to mainly inhibit platelets or coagulation cascade. This document does not address antithrombotic treatments in primary prevention or in patients with incidental finding of non-obstructive CAD or with a high calcium score detected at coronary computed tomography for whom the risk/benefit of an antithrombotic therapy has never been clearly investigated. In this document, high bleeding risk (HBR) is defined based on Academic Research Consortium (ARC)-HBR criteria[80,81] or PRECISE-DAPT score[82,83] $\geq$25. Given the need for continuous monitoring of treatment tolerance and adherence together with the possible evolution of ischaemic and bleeding risks over time, active involvement of the primary care physician at the time of treatment implementation is warranted for shared decision-making and follow-up of these patients. An overview of consensus statements endorsed by this document regarding antithrombotic treatment strategies in patients with established coronary atherosclerotic disease after PCI, CABG or in medically managed patients, with or without HBR is provided in the graphical abstract.

Coronary and peripheral arterial diseases

A substantial and often underdiagnosed proportion of patients with CAD have peripheral artery disease (PAD).[84,85] These patients, often described as having 'polyvascular' disease, are at increased risk of thrombotic events.[86] This document includes the management of this subset of patients, while comorbidities other than PAD are not addressed in this document. Most data on concomitant PAD in patients with CAD are limited to a clinical history of the former. However, even subclinical PAD is a marker of increased risk in CAD patients particularly after revascularization.[87] CAD patients with concomitant PAD [diagnosed by a low ankle-brachial index (ABI) even in the absence of symptoms] are at increased risk of adverse cardiovascular events, and they have a larger absolute net benefit from intensified antithrombotic therapies than CAD patients without concomitant PAD.[17,88] Hence, the identification of subclinical PAD (e.g. by ABI measurement) can help to better stratify CAD patients and select the most suitable antithrombotic strategies. To better disseminate routine ABI measurement in cardiology practice, automated multi-cuff devices, which have been shown to have a high degree of correlation with the standard Doppler method,[89] can be considered as a first-line approach for subclinical PAD diagnosis. In the presence of an abnormal ABI, further confirmatory vascular work-up is suggested.

Consensus statements endorsed by this document regarding patients with CAD and PAD are provided in *Table 2*.

Acute coronary syndrome managed by percutaneous coronary intervention

Evidence-based treatment options are shown in *Figure 1* and the corresponding summary of evidence in the Supplemental material.

Single antithrombotic therapy

Aspirin monotherapy following PCI has been investigated mainly from 6 months onwards after dual antiplatelet therapy (DAPT)[90] among patients who were not deemed to be at HBR. Among HBR patients, aspirin monotherapy after a short course of DAPT is associated with lower bleeding risk compared with more prolonged DAPT, but it remains unclear if it preserves ischaemic risk as this treatment option has been investigated in a limited patient/selected population.[91–95] Among ACS patients at either low or unselected bleeding risk, aspirin monotherapy is associated with greater ischaemic risk than DAPT.[11,59,96] Clopidogrel monotherapy, compared with aspirin monotherapy after at least 6 months of DAPT without clinical events, is associated with greater net clinical benefit,[97] supporting the preference of the former over the latter treatment option. This evidence was generated in the context of an open-label trial (the HOST EXAM study) conducted in East Asian patients and generalizability to Western population remains to be established. However, an extended follow-up of this study confirmed a greater benefit of clopidogrel over aspirin monotherapy for up to 5 years.[98]

$P2Y_{12}$ inhibitor monotherapy following 1–3 months of DAPT has been investigated after PCI compared with DAPT prolongation.[28,29,70,99,100] Aggregate data meta-analyses of these studies are available[101] but suffer from limitations in quantifying the risks and benefits of aspirin withdrawal compared with DAPT. This is due to the inclusion of events occurring during the initial DAPT phase, which consisted of an identical treatment regimen in both experimental and control regimens. These limitations were addressed in two individual patient data meta-analyses that censored events occurring during the initial DAPT period, therefore appraising only the events that occurred during the experimental phase (i.e. when the two treatments started to diverge).[99,100] In the SIDNEY Collaboration, which included 14 628 patients, BARC 3 or 5 bleeding occurred less frequently with ticagrelor monotherapy than DAPT [hazard ratio (HR) 0.56, 95% confidence interval (CI) 0.41–0.75; $P < 0.001$].[99] The composite of all-cause death, MI, or stroke occurred in a similar number of patients in the ticagrelor monotherapy and DAPT-treated groups (HR 0.92, 95% CI 0.76–1.10; $P < 0.001$ for non-inferiority). In analyses of individual endpoints, ticagrelor was associated with lower risks of all-cause mortality (HR 0.71, 95% CI 0.52–0.96; $P = 0.027$) and cardiovascular mortality (HR 0.68, 95% CI 0.47–0.99; $P = 0.044$), possibly due to lower bleeding, taking into account the fact that

Table 1 **Studies testing different antithrombotic strategies in patients with established coronary artery disease**

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
AMIS, Schoenberger *et al.* (1980)[12]	CCS with prior MI (>12 months)	**Intervention:** ASA (*N* = 2267) **Control:** placebo (*N* = 2257)	**Efficacy:** death **Safety:** not available	−11.1%	−1.1%	Not applicable	Not applicable
ASCET, Pettersen *et al.* (2012)[13]	CCS and medical therapy without prior MI	**Intervention:** clopidogrel 75 mg (*N* = 499) **Control:** ASA (*N* = 502)	**Efficacy:** unstable angina, non-haemorrhagic stroke, MI, and death **Safety:** any bleeding	−3.8%	−0.4%	54.9%[a]	5.6%[a]
APPRAISE-2, Alexander *et al.* (2011)[24]	ACS and PCI, ACS and medical therapy	**Intervention:** apixaban 5 mg b.i.d. + standard antiplatelet therapy (*N* = 3705) **Control:** standard antiplatelet therapy (*N* = 3687)	**Efficacy:** CV death, MI, and ischaemic stroke **Safety:** TIMI major bleeding not related to CABG	5.1%	0.4%	61.5%[a]	0.8%[a]
ARCTIC, Collet *et al.* (2012)[35]	Phenotype-guided DAPT	**Intervention:** antiplatelet therapy guided by platelet function monitoring (*N* = 3705) **Control:** standard antiplatelet therapy (*N* = 3687)	**Efficacy:** death, MI, stroke, TIA, urgent coronary revascularization, and ST **Safety:** STEEPLE major bleeding	−11.3%	−3.5%	−30.3%	−1.0%
ATLAS ACS2-TIMI 51, Mega *et al.* (2012)[73]	ACS and PCI, ACS and medical therapy, ACS and CABG	**Intervention 1:** rivaroxaban 2.5 mg twice daily + DAPT (ASA + clopidogrel) (*N* = 5114) **Intervention 2:** rivaroxaban 5 mg twice daily + DAPT (ASA + clopidogrel) (*N* = 5115) **Control:** DAPT (asprin + clopidogrel) (*N* = 5115)	**Efficacy:** CV death, MI, or stroke **Safety:** TIMI major bleeding not related to CABG	R2.5 mg b.i.d. + DAPT vs. DAPT: 15.0%[a] R5 mg b.i.d. + DAPT vs. DAPT: 17.8%[a]	R2.5 mg b.i.d. + DAPT vs. DAPT: 1.6%[a] R5 mg b.i.d. + DAPT vs. DAPT: 1.9%[a]	R2.5 mg b.i.d. + DAPT vs. DAPT: 200%[a] R5 mg b.i.d. + DAPT vs. DAPT: 300%[a]	R2.5 mg b.i.d. + DAPT vs. DAPT: 1.2%[a] R5 mg b.i.d. + DAPT vs. DAPT: 1.8%[a]
CAPRIE, (1996)[46]	CCS with prior MI (>12 months)	**Intervention:** clopidogrel (*N* = 9599) **Control:** ASA (*N* = 9586)	**Efficacy:** CV death, MI, and ischaemic stroke **Safety:** severe bleeding	8.7%[a]	1.6%[a]	11%	0.2%

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
CARDIFF-I, Elwood *et al.* (1974)[57]	ACS and medical therapy	**Intervention** ASA ($N = 615$)	**Efficacy:** death	21.8%	2.1%	Not applicable	Not applicable
		Control: placebo ($N = 624$)	**Safety:** not available				
CARDIFF-II, Elwood *et al.* (1979)[68]	ACS and medical therapy	**Intervention:** ASA ($N = 832$)	**Efficacy:** death	16.9%	2.5%	Not applicable	Not applicable
		Control: placebo ($N = 850$)	**Safety:** Not available				
CARS, (1997)[76]	ACS and medical therapy	**Intervention 1:** 1 mg warfarin + ASA ($N = 2028$)	**Efficacy:** CV death, non-fatal MI, and non-fatal ischaemic stroke	1 mgW + A vs. A: −28.7%[a]	1 mgW + A vs. A: −2.6%[a]	1 mgW + A vs. A: 45%	1 mgW + A vs. A: 0.4%
		Intervention 2: 3 mg warfarin + ASA ($N = 3382$)	**Safety:** major bleeding	3 mgW + A vs. A: 3.9%	3 mgW + A vs. A: 0.4%	3 mgW + A vs. A: 73.9%[a]	3 mgW + A vs. A: 0.7%[a]
		Control: ASA ($N = 3393$)					
CASCADE, Kulik *et al.* (2010)[77]	CCS and CABG without prior MI	**Intervention:** ASA + clopidogrel 75 mg ($N = 46$)	**Efficacy:** SVG intimal hyperplasia; and MACE	MACE: 19.3%	MACE 1.7%	Not applicable	1.8%
		Control: ASA + ($N = 46$)	**Safety:** major bleeding				
Chesebro *et al.* (1982)[78]	CCS and CABG without prior MI	**Intervention:** ASA + dipyridamole ($N = 176$)	**Efficacy:** vein graft occlusion **Safety:** not available	57.1%	7%	Not applicable	Not applicable
		Control: ASA + placebo ($N = 184$)					
CDPA, (1974)[14]	CCS with prior MI (>12 months)	**Intervention**: ASA ($N = 727$)	**Efficacy:** death	30.1%	2.5%	Not applicable	Not applicable
		Control: placebo ($N = 744$)	**Safety:** not available				

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
CHAMP, Fiore *et al.* (2002)[15]	ACS and medical therapy	**Intervention**: warfarin (INR target 1.5–2.5) + ASA (*N* = 2522)	**Efficacy:** death	−1.7%	−0.3%	77.8%[a]	0.6%[a]
		Control: ASA (*N* = 2537)	**Safety:** major bleeding				
CHARISMA, Bhatt *et al.* (2006)[16]	CCS with prior MI (>12 months), CCS and medical therapy without prior MI	**Intervention**: clopidogrel 75 mg + ASA (*N* = 7802)	**Efficacy:** CV death, MI, and stroke	7%	0.5%	25%	0.3%
		Control: ASA (*N* = 7801)	**Safety:** GUSTO severe bleeding				
COMPASS, Eikelboom *et al.* (2017)[17]	CCS with prior MI (>12 months), CCS and PCI without prior MI, CCS and CABG without prior MI, CCS and medical therapy without prior MI	**Intervention 1:** rivaroxaban 2.5 mg twice daily + ASA (*N* = 9152)	**Efficacy:** CV death, MI, and stroke	R 2.5 mg b.i.d. + A vs. A: 24.1%[a]	R 2.5 mg b.i.d. + A vs. A: 1.3%[a]	R 2.5 mg b.i.d. + A vs. A: 63.2%[a]	R 2.5 mg b.i.d. + A vs. A: 1.2%[a]
		Intervention 2: rivaroxaban 5 mg twice daily (*N* = 9117)	**Safety:** modified ISTH major bleeding	R 5 mg b.i.d. vs. A: 9.3%	R 5 mg b.i.d. vs. A: 0.5%	R 5 mg b.i.d. vs. A: 47.4%[a]	R 5 mg b.i.d. vs. A: 0.9%[a]
		Control: ASA (*N* = 9126)					
CREDO, Steinhubl *et al.* (2002)[18]	CCS and PCI without prior MI	**Intervention**: clopidogrel 75 mg + ASA (*N* = 1053)	**Efficacy:** CV death, MI, and stroke	26.9%[a]	3.0%[a]	31.3%	2.1%
		Control: ASA (*N* = 1063)	**Safety:** TIMI major bleeding				
CRYSSA, Mannacio *et al.* (2012)[19]	CCS and CABG without prior MI	**Intervention**: clopidogrel 75 mg + ASA (*N* = 150)	**Efficacy:** SVG failure; MACCE	SVG failure:43.5%[a] MACCE: 49.5%	SVG failure: 5.7%[a] MACCE: 4.6%	0%	0%
		Control: ASA (*N* = 150)	**Safety:** major bleeding				

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
CURE, (2001)[74]	ACS and PCI, ACS and CABG, ACS and medical therapy	**Intervention**: clopidogrel 75 mg + ASA (*N* = 6259) **Control:** ASA (*N* = 6303)	**Efficacy:** CV death, non-fatal MI, and stroke **Safety:** major or minor bleeding	18.4%[a]	2.1%[a]	70%[a]	3.5%[a]
DACAB, Zhao *et al.* (2018)[20]	CCS and CABG without prior MI	**Intervention 1**: ticagrelor 90 mg b.i.d. + ASA (*N* = 168) **Intervention 2:** ticagrelor 90 mg b.i.d. (*N* = 166) **Control:** ASA (*N* = 166)	**Efficacy:** SVG patency; MACCE **Safety:** non-CABG-related bleeding	T90 mg + A vs. A SVG patency: −15.9%[a] MACCE: 66.7%	T90 mg + A vs. A SVG patency: −12.2%[a] MACCE: 3.6%	T90 mg + A vs. A 237%[a]	T90 mg + A vs. A 21.4%[a]
				T90 mg vs. A SVG patency: −8.2%[a] MACCE: 55.6%	T90 mg vs. A SVG patency: −6.3%[a] MACCE: 3.0%	T90 mg vs. A 34.4%	T90 mg vs. A 3.1%
DAPT study, Mauri *et al.* (2014)[21]	CCS with prior MI (>12 months), CCS and PCI without prior MI, CCS and medical therapy without prior MI	**Intervention**: P2Y12i (clopidogrel or prasugrel) + ASA (*N* = 5020) **Control:** ASA (*N* = 4941)	**Efficacy:** ST; MACCE (death, MI, or stroke) **Safety:** GUSTO moderate or severe bleeding	ST: 71%[a] MACCE: 27.1%[a]	ST: 1%[a] MACCE: 1.6%[a]	56.3%[a]	0.9%[a]
DES-LATE, Lee *et al.* (2014)[22]	CCS with prior MI (>12 months), CCS and medical therapy without prior MI	**Intervention**: Clopidogrel + ASA (*N* = 2531) **Control:** ASA (*N* = 2514)	**Efficacy:** CV death, MI, or stroke **Safety:** TIMI major bleeding	8.3%	0.2%	−21.4%	−0.3%

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
Elderly-ACS 2, Savonitto *et al.* (2018)[23]	ACS and PCI	**Intervention**: prasugrel 5 mg + ASA (*N* = 2531) **Control:** clopidogrel 75 mg + ASA (*N* = 2514)	**Efficacy:** death, MI, disabling stroke, or rehospitalization for CV causes or bleeding **Safety:** BARC 2, 3, or 5 bleeding	−2.4%	−0.4%	48.5%	1.3%
EXCELLENT, Gwon *et al.* (2012)[25]	ACS and PCI, CCS and PCI without prior MI	**Intervention**: 6-month DAPT (ASA + clopidogrel 75 mg) followed by ASA alone (*N* = 722) **Control:** 12-month DAPT (ASA + clopidogrel 75 mg) (*N* = 721)	**Efficacy:** TVF (CV death, MI, and TVR) **Safety:** TIMI major bleeding	−11.6%	−0.5%	−50.0%	−0.3%
Gao *et al.* (2009)[26]	CCS and CABG without prior MI	**Intervention**: clopidogrel + ASA (*N* = 95) **Control:** ASA (*N* = 102)	**Efficacy:** LIMA patency **Safety:** not available	−0.1%	−0.1%	Not applicable	Not applicable
GEMINI-ACS-1, Ohman *et al.* (2017)[27]	ACS and PCI, ACS and medical therapy	**Intervention**: rivaroxaban 2.5 mg b.i.d. + P2Y12i (clopidogrel 75 mg or ticagrelor 90 mg b.i.d.) (*N* = 1519) **Control:** ASA + P2Y12i (clopidogrel 75 mg or Ticagrelor 90 mg b.i.d.) (*N* = 1518)	**Efficacy:** CV death, MI, stroke, and definite ST **Safety:** TIMI non-CABG clinically significant bleeding	−5.5%	−0.3%	8.0%	0.4%
GLASSY, Franzone *et al.* (2019)[28]	ACS and PCI, CCS with prior MI (>12 months), CCS and PCI without prior MI	**Intervention**: ticagrelor 90 mg b.i.d. + ASA for 1-month followed by ticagrelor monotherapy (*N* = 3794) **Control:** ticagrelor or clopidogrel + ASA for 12-month followed by ASA monotherapy (*N* = 3791)	**Efficacy:** death, non-fatal MI, non-fatal stroke, urgent TVR **Safety:** BARC 3 or 5 bleeding	15.1%[a]	1.3%[a]	0%	0%

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
GLOBAL LEADERS, Vranckx *et al.* (2018)[29]	ACS and PCI, CCS with prior MI (>12 months), CCS and PCI without prior MI	**Intervention**: ticagrelor 90 mg b.i.d. + ASA for 1-month followed by ticagrelor monotherapy (*N* = 7980) **Control:** ticagrelor or clopidogrel + ASA for 12-month followed by ASA monotherapy (*N* = 7988)	**Efficacy:** death or new Q-wave MI **Safety:** BARC 3 or 5 bleeding	12.8%	0.6%	−3.8%	−0.1%
GRAVITAS, Price *et al.* (2011)[30]	Phenotype-guided DAPT	**Intervention**: high-dose clopidogrel + ASA (*N* = 1109) **Control:** standard-dose clopidogrel + ASA (*N* = 1105)	**Efficacy:** CV death, non-fatal MI, or ST **Safety:** GUSTO moderate or severe bleeding	0%	0%	−39.1%	−0.9%
HOST-EXAM, Koo *et al.* (2021)[97]	CCS and PCI, CCS with prior (>12 months) MI	**Intervention**: clopidogrel 75 mg (*N* = 2710) **Control:** ASA (*N* = 2728)	**Efficacy:** cardiac death, MI, stroke, readmission due to ACS, or definite/probable ST **Safety:** BARC 3–5 bleeding	32.7%[a]	1.8%[a]	−40%[a]	−0.8%[a]
I-LOVE-IT 2, Han *et al.* (2016)[31]	ACS and PCI	**Intervention**: 6-month DAPT (ASA + clopidogrel 75 mg) followed by ASA alone (*N* = 909) **Control:** 12-month DAPT (ASA plus clopidogrel 75 mg) (*N* = 920)	**Efficacy:** TLF (cardiovascular death, target vessel MI, or clinically indicated TLR) **Safety:** BARC ≥ 3 bleeding	−12.1%	−0.7%	71.4%	0.5%
ISAR-REACT 5, Schüpke *et al.* (2019)[32]	ACS and PCI	**Intervention**: ticagrelor 90 mg b.i.d. + ASA (*N* = 2012) **Control:** prasugrel 10 mg (5 mg in patients > 75yo or <60 kg) + ASA (*N* = 2006)	**Efficacy:** death, MI, or stroke **Safety:** BARC 3, 4, or 5 bleeding	−34.8%[a]	−2.4%[a]	12.5%	0.6%

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
ISAR-SAFE, Schüpke *et al.* (2014)[33]	ACS and PCI CCS and PCI without prior MI	**Intervention:** 6-month of ASA plus placebo (a total length of 6-month DAPT) (*N* = 1997) **Control**: 6-month of ASA + clopidogrel 75 mg (a total length of 12-month DAPT) (*N* = 2003)	**Efficacy:** death, MI, definite or probable ST, stroke, or TIMI major bleeding **Safety:** TIMI major bleeding	6.3%	0.1%	−33.3%	−0.1%
ISIS-2, (1988)[34]	ACS and medical therapy	**Intervention:** ASA (*N* = 8587) **Control**: placebo (*N* = 8600)	**Efficacy:** CV death **Safety:** major bleeding	20.3%[a]	2.4%[a]	0%	0%
ITALIC, Gilard *et al.* (2015)[36]	ACS and PCI; CCS with prior MI (> 12 months), CCS and PCI without prior MI	**Intervention**: 6-months DAPT (clopidogrel plus ASA) (*N* = 926) **Control:** 24-month DAPT (clopidogrel plus ASA) (*N* = 924)	**Efficacy:** death, MI, repeat emergency TVR, stroke, or TIMI major bleeding at 12 months **Safety:** TIMI major bleeding	−6.7%	−0.1%	Not applicable	−0.3%
IVUS-XPL, Hong *et al.* (2016)[37]	ACS and PCI	**Intervention**: 6-months DAPT (clopidogrel plus ASA) (*N* = 699) **Control:** 12-month DAPT (clopidogrel plus ASA) (*N* = 701)	**Efficacy:** the composite of cardiac death, MI, stroke, or TIMI major bleeding at 12 months **Safety:** TIMI major bleeding	−4.7%	−0.1%	−30%	−0.3%
LoWASA, Herlitz *et al.* (2004)[38]	CCS with prior MI (hospitalization for AMI within 42 days prior to randomization)	**Intervention**: ASA plus warfarin 1.25 mg (*N* = 1659) **Control**: ASA 75 mg (*N* = 1641)	**Efficacy:** (1) CV death, reinfarction, or stroke and (2) CV death **Safety:** serious bleeding	CV death, reinfarction, and stroke: 2.4% CV death: 9.5%	CV death, reinfarction, and stroke: 0.7% CV death: 1.5%	120%[a]	1.2%[a]
MASTER DAPT, Valgimigli *et al.* (2021)[91]	ACS and PCI, CCS and PCI	**Intervention:** abbreviated DAPT (*N* = 2295) **Control**: standard DAPT (*N* = 2284)	**Efficacy:** death, MI, stroke, or BARC 3 or 5 bleeding **Safety:** BARC 2, 3, or 5 bleeding	2.9%	0.2%	30.8%[a]	2.9%[a]

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
Mangano *et al.* (2002)[39]	CCS and CABG without prior MI	**Intervention**: ASA (*N* = 2999) **Control**: no ASA (*N* = 2023)	**Efficacy:** fatal and non-fatal events occurring >48 h after surgery and during the index hospitalization	Death from any cause: 88%[a] MI: 48%	Death from any cause: 9.4%[a] MI: 2.6%	Not applicable	Not applicable
NIPPON, Nakamura *et al.* (2017)[40]	ACS and PCI; CCS and PCI without prior MI	**Intervention**: 6-months DAPT (clopidogrel plus ASA) (*N* = 1654) **Control:** 18-month DAPT (clopidogrel plus ASA) (*N* = 1653)	**Efficacy:** NACCE (all cause death, MI, cerebrovascular events, and major bleeding events) from 6 to 18 months after DES implantation **Safety:** major bleeding (according to modified REPLACE-2 criteria)	−40%	−0.6%	0%	0%
One-month DAPT, Hong *et al.* (2021)[131]	CCS and PCI	**Intervention**: 1-month DAPT (clopidogrel + ASA) followed by ASA alone (*N* = 1507) **Control:** 6- to 12-month DAPT (clopidogrel plus ASA) (*N* = 1513)	**Efficacy:** CV death, myocardial infarction, TVR, stroke, or STEEPLE major bleeding **Safety:** STEEPLE major bleeding	10.8%	0.7%	32%	0.8%
OPTIDUAL, Helft *et al.* (2016)[41]	CCS with prior MI (>12 months)	**Intervention**: clopidogrel plus ASA for a further 36 additional months (total treatment duration with DAPT: 48 + 3 months) (*N* = 695) **Control:** ASA plus placebo (*N* = 690)	**Efficacy:** NACE (all-cause death, non-fatal MI, stroke, or ISTH major bleeding) **Safety:** ISTH major bleeding	22.7%	1.7%	0%	0%
OPTIMA-C, Lee *et al.* (2018)[42]	ACS and PCI; CCS and PCI without prior MI	**Intervention**: 6-months DAPT (clopidogrel plus ASA) (*N* = 683) **Control:** 12-months DAPT (clopidogrel plus ASA) (*N* = 684)	**Efficacy:** MACE (death, MI, and ischaemia-driven TLR) at 12-month follow-up **Safety:** TIMI major bleeding	−100%	−0.6%	0%	0%

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
OPTIMIZE, Feres *et al.* (2013)[43]	ACS and PCI; CCS and PCI without prior MI	**Intervention:** 3-month DAPT (clopidogrel plus ASA) (*N* = 1605) **Control:** 12-month DAPT (Clopidogrel plus ASA) (*N* = 1606)	**Efficacy:** NACCE (all-cause death, MI, stroke, and major bleeding) **Safety:** modified major REPLACE-2 and severe or life-threatening GUSTO bleeding	−3.4%	−0.2%	−33.3%	−0.3%
PEGASUS-TIMI 54, Bonaca *et al.* (2015)[44]	CCS with prior MI (>12 months)	**Intervention 1**: ticagrelor 90 mg b.i.d. (*N* = 7050) **Intervention 2:** ticagrelor 60 mg b.i.d. (*N* = 7045) **Control:** placebo (*N* = 7067) All pts treated with ASA	**Efficacy:** CV death, MI, or stroke **Safety:** TIMI major bleeding	T 90 mg vs. placebo: 13.1%[a] T 60 mg vs. placebo: 14%[a]	T 90 mg vs. placebo: 1.19%[a] T 60 mg vs. placebo: 1.27%[a]	T 90 mg vs. placebo: 145%[a] T 60 mg vs. placebo: 117%[a]	T 90 mg vs. placebo: 1.54%[a] T 60 mg vs. placebo: 1.24%[a]
PLATO, Wallentin *et al.* (2009)[45]	ACS and PCI; ACS and CABG; ACS and medical therapy	**Intervention:** ticagrelor 90 mg b.i.d. (*N* = 9333) **Control:** clopidogrel 75 mg (*N* = 9291)	**Efficacy:** death from vascular causes, MI, or stroke **Safety:** trial-defined major bleeding	16.2%[a]	1.9%[a]	3.6%	0.4%
POPular AGE, Gimbel *et al.* (2020)[47]	ACS and PCI; ACS and CABG; ACS and medical therapy	**Intervention**: clopidogrel 75 mg plus standard of care (*N* = 500) **Control:** ticagrelor 90 mg b.i.d. plus standard of care (*N* = 502)	**Efficacy:** net clinical benefit (all-cause death, MI, stroke, and PLATO major or minor bleeding) **Safety:** PLATO major or minor bleeding	15.6%	5%	−25%[a]	−6%[a]
POPular CABG, Willemsen *et al.* (2021)[119]	CCS and CABG without prior MI, ACS and CABG	**Intervention:** ticagrelor 90 mg b.i.d. + ASA (*N* = 249) **Control:** ASA (*N* = 247)	**Efficacy:** SVG occlusion at 1 year **Safety:** BARC 3–5 bleeding	4.9%	0.5%	0%	0%
PRAGUE-18, Motovska *et al.* (2018)[48]	ACS and PCI	**Intervention:** prasugrel 10 mg + ASA (*N* = 634) **Control:** ticagrelor 90 mg b.i.d. + ASA (*N* = 596)	**Efficacy:** CV death, non-fatal MI, or stroke **Safety:** any bleeding	−15.8%	−0.9%	−1.8%	−0.2%

Table 1 **Continued**

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
PRASFIT-ACS, Saito *et al.* (2014)[49]	ACS and PCI	**Intervention**: prasugrel 3.75 mg (*N* = 685) **Control:** clopidogrel 75 mg (*N* = 678)	**Efficacy:** MACE (CV death, non-fatal MI, and non-fatal ischaemic stroke) at 24 weeks **Safety:** TIMI major bleeding	20.3%	2.4%	−13.6%	−0.3%
PRODIGY, Valgimigli *et al.* (2012)[50]	ACS and PCI, CCS with prior MI (>12 months), CCS and PCI without prior MI	**Intervention**: 24 months of DAPT (*N* = 987) **Control:** 6 months of DAPT (*n* = 983)	**Efficacy:** death, MI, and cerebrovascular accident at 2 years **Safety:** BARC type 2, 3, or 5 bleeding	−1%	0.1%	111% [a]	3.9%[a]
RACS, Bernardi *et al.* (2007)[51]	ACS and PCI, CCS and PCI without prior MI	**Intervention:** ASA + 6-month clopidogrel (*N* = 502) **Control:** ASA + 1-month clopidogrel (*N* = 502)	**Efficacy:** death, MI, and stroke at 6 months **Safety:** any bleeding (modified TIMI criteria)	66%[a]	3.3%[a]	−58%	−0.88%
REAL/ZEST-LATE, Park *et al.* (2010)[52]	CCS with prior MI (>12 months)	**Intervention**: clopidogrel 75 mg + ASA (*N* = 1357) **Control:** ASA(*N* = 1344)	**Efficacy:** MI and death from cardiac causes **Safety:** TIMI major bleeding	−50%	−0.6%	100%	0.1%
REDUCE, De Luca *et al.* (2019)[53]	ACS and PCI	**Intervention**: 3 months of DAPT (*N* = 751) **Control:** 12 months of DAPT (*N* = 745)	**Efficacy:** all-cause mortality, MI, ST, stroke, TVR, and bleeding (BARC 2, 3, and 5) at 12 months **Safety:** BARC 2,3,5 bleeding	2.4%	0.2%	−16.7%	−0.5%
RESET, Kim *et al.* (2012)[54]	ACS and PCI, CCS and PCI without prior MI	**Intervention**: 3 months of DAPT with E-ZES (*N* = 1059) **Control:** 12 months of DAPT with other DES (*N* = 1058)	**Efficacy:** CV death, MI, ST, ischaemia-driven TVR, or bleeding at 12 months **Safety:** TIMI major or minor bleeding	0%	0%	−50%	−0.5%

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
SAPAT, Juul-Moller *et al.* (1992)[55]	CCS and medical therapy without prior MI	**Intervention:** ASA (*N* = 1099) **Control:** placebo (*N* = 1026)	**Efficacy:** non-fatal or fatal MI (during hospitalization) or sudden death **Safety:** major bleeding (trial-defined criteria)	33%[a]	4%[a]	58.3%	0.7%
SECURITY, Colombo *et al.* (2014)[56]	ACS and PCI, CCS and PCI without prior MI	**Intervention**: 6 months of DAPT (*N* = 682) **Control:** 12 months of DAPT (*N* = 717)	**Efficacy:** cardiac death, MI, stroke, definite or probable ST, or BARC type 3 or 5 bleeding at 12 months **Safety:** BARC type 3 or 5 bleeding	−21.6%	−0.8%	−45.4%	−0.5%
SMART-CHOICE, Hahn *et al.* (2019)[58]	ACS and PCI, CCS and PCI without prior MI	**Intervention**: DAPT for 3 months followed by $P2Y_{12}$ inhibitor monotherapy (*N* = 1495) **Control:** DAPT for 12 months (*N* = 1498)	**Efficacy:** MACCE (all-cause death, MI, or stroke) at 12 months after the index procedure **Safety:** BARC 2–5 bleeding	−16%	−0.4%	−41%[a]	−1.4%[a]
SMART-DATE, Hahn *et al.* (2018)[59]	ACS and PCI	**Intervention:** 6-month DAPT (*N* = 1357) **Control:** 12-month or longer DAPT(*N* = 1355)	**Efficacy:** All-cause death, MI, or stroke at 18 months **Safety:** BARC type 2–5 bleeding at 18 months	−12%	−0.5%	−30.7%	−1.2%
STOPDAPT-2, Watanabe *et al.* (2019)[60]	ACS and PCI, CCS and PCI without prior MI	**Intervention**: 1-month DAPT followed by clopidogrel monotherapy (*N* = 1523) **Control:** 12-month DAPT (ASA + clopidogrel) (*N* = 1522)	**Efficacy:** CV death, MI, ischaemic or haemorrhagic stroke, definite ST, TIMI major or minor bleeding at 12 months **Safety:** TIMI major or minor bleeding at 12 months	36.2%[a]	1.34%[a]	−73.4%[a]	−1.13%[a]

Table I Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
TALOS-AMI, Kim *et al.* (2021)[132]	ACS and PCI	**Intervention**: 1-month ASA + ticagrelor followed by 11-months ASA + clopidogrel ($N = 1349$) **Control:** 12-month DAPT (ASA + ticagrelor) ($N = 1348$)	**Efficacy:** CV death, MI, stroke, or BARC 2, 3, or 5 bleeding **Safety:** BARC 2, 3, or 5 bleeding	43.9%[a]	3.6%[a]	46.4%[a]	2.6%[a]
TAILOR-PCI, Pereira *et al.* (2020)[61]	Genotype-guided DAPT (ACS or CCS patients undergoing PCI with planned 12-month DAPT)	**Intervention:** genotype-guided DAPT (ASA + ticagrelor in CYP2C19 LOF carriers, ASA + clopidogrel in non-carriers) ($N = 2652$) **Control:** clopidogrel + ASA with genotyping after 12 months ($N = 2650$).	**Efficacy:** CV death, MI, stroke, ST, and severe recurrent ischaemia at 12 months in CYP2C19 LOF carriers **Safety:** TIMI major or minor bleeding in CYP2C19 LOF carriers	32.2%	1.9%	18.7%	0.3%
TenBerg *et al.* (2000)[62]	CCS and PCI without prior MI	**Intervention:** warfarin (started before PCI) + ASA ($N = 530$) **Control:** ASA ($N = 528$)	**Efficacy:** death, MI, TLR, and stroke at 1 year **Safety:** major bleeding (leading to hospitalization and/or death), blood transfusion or surgical intervention, and vascular complications	29.5%[a]	6%[a]	220%[a]	2.2%[a]
THEMIS, Steg *et al.* (2019)[63]	CCS and PCI without prior MI, CCS and medical therapy without prior MI	**Intervention:** ticagrelor plus ASA ($N = 9619$) **Control:** placebo plus ASA ($N = 9601$)	**Efficacy:** CV death, myocardial infarction, or stroke **Safety:** TIMI major bleeding	9.4%[a]	0.8%[a]	120%[a]	1.2%[a]
TICAB, Schunkert *et al.* (2019)[64]	ACS and CABG, CCS and CABG without prior MI	**Intervention**: ticagrelor 90 mg b.i.d. ($N = 946$) **Control:** ASA ($N = 947$)	**Efficacy:** CV death, MI, repeat revascularization, and stroke 12 months after CABG **Safety:** BARC $\geq$ 4 for periprocedural and hospital stay-related bleedings or BARC $\geq$ 3 for post-discharge bleedings	−18.2%	−1.5%	15.6%	0.5%

Table 1 Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
TICO, Kim *et al.* (2020)[65]	ACS and PCI	**Intervention**: 3-month DAPT followed by ticagrelor monotherapy 90 mg b.i.d. (*N* = 1527). **Control:** ticagrelor-based 12-month DAPT (*N* = 1529).	**Efficacy:** NACE (major bleeding, death, MI, ST, stroke, or TVR) at 12 months **Safety:** TIMI major bleeding	33.8%[a]	2%[a]	−43%[a]	−1.3%[a]
TREAT, Berwanger *et al.* (2019)[66]	ACS and PCI	**Intervention:** ticagrelor 90 mg b.i.d. (*N* = 1913) **Control:** clopidogrel 75 mg (*N* = 1886)	**Efficacy:** CV mortality, MI, or stroke at 12 months **Safety:** TIMI major bleeding	8.2%	0.6%	−16.6%	−0.2%
TRILOGY-ACS, Roe *et al.* (2012)[67]	ACS and medical therapy	**Intervention**: ASA + prasugrel 10 mg (*N* = 3620) **Control:** ASA + clopidogrel 75 mg (*N* = 3623)	**Efficacy:** MACE (CV death, non-fatal MI, or non-fatal stroke) **Safety:** GUSTO severe or life-threatening bleeding	81.8%	0.9%	0%	0%
TRITON-TIMI 38, Wiviott *et al.* (2007)[75]	ACS and PCI	**Intervention:** ASA + prasugrel (*N* = 6813) **Control:** ASA + clopidogrel (*N* = 6795)	**Efficacy:** CV death, MI, and stroke **Safety:** non-CABG related TIMI major bleeding	18.2%[a]	2.2%[a]	−33%[a]	−0.6%[a]
TROPICAL-ACS, Sibbing *et al.* (2017)[69]	Phenotype-guided DAPT	**Intervention:** 1-week prasugrel followed by 1-week clopidogrel and PFT-guided maintenance therapy with clopidogrel or prasugrel from day 14 after hospital discharge; (*N* = 1304) **Control:** prasugrel 10 mg (*N* = 1306)	**Efficacy:** net clinical benefit (CV death, MI, stroke, or BARC bleeding grade 2 or higher at 1 year after randomization) **Safety:** BARC bleeding grade 2 or higher	−28.6%	−2%	20%	1%
TWILIGHT, Mehran *et al.* (2019)[70]	ACS and PCI, CCS with prior MI (>12 months), CCS and PCI without prior MI	**Intervention**: 3-month DAPT followed by ticagrelor + placebo (*N* = 3555) **Control:** ticagrelor + ASA (*N* = 3564)	**Efficacy:** death from any cause, non-fatal MI, or non-fatal stroke **Safety:** BARC type 2,3,5 bleeding	0%	0%	−43.6%[a]	−3.1%[a]

Table I Continued

Study acronym; authors; year of publication	Characterization of study population	Study intervention (*N*)/control (*N*)	Key efficacy and safety endpoints	Primary efficacy endpoint		Primary safety endpoint	
				RRR	ARR	RRI	ARI
VACS, Goldman *et al.* (1988)[71]	CCS and CABG without prior MI	**Intervention 1:** ASA, 325 mg daily ($N = 154$). **Intervention 2:** ASA, 325 mg three times daily ($N = 155$). **Intervention 3:** ASA and dipyridamole (325 mg and 75 mg, combination three times daily ($N = 162$). **Intervention 4:** sulfinpyrazone, 267 mg three times daily ($N = 148$) **Control:** placebo ($N = 153$)	**Efficacy:** angiographic graft patency (within 60 days)	Rates of graft patency Int. 1: 93.5% Int. 2: 92.3% Int. 3: 91.9% Int. 4: 90.2% Comp: 85.2% ($P < 0.05$)	Not applicable	Not applicable	Not applicable
WARIS-II, Hurlen *et al.* (2002) [72]	CCS with prior MI	**Intervention 1:** warfarin ($N = 1216$) **Intervention 2:** warfarin plus ASA 75 mg ($N = 1208$) % **Control:** ASA alone ($N = 1206$)	**Efficacy:** death, non-fatal MI, and thromboembolic stroke	A + W vs. A: 25%[a]	A + W vs. A: 5%[a]	A + W vs. A: 283%[a]	A + W vs. A: 1.7%[a]
			Safety: trial specific non-fatal major bleeding	W vs. A: 16.5%[a]	W vs. A: 3.3%[a]	W vs. A: 350%[a]	W vs. A: 2.1%[a]

Main study results are presented as relative and absolute risk reduction (RRR and ARR) for the efficacy and relative and absolute risk increase (RRI and ARI) for the primary safety endpoint, as previously described by Bodemer *et al.* (*Med Decis Making* 2014; 34:615–626). Relative and absolute risk reductions or increases are presented as positive or negative numbers based on the risk of the outcome of interest. Specifically, positive ARR and RRR indicate that the risk of that outcome is reduced by study intervention, while negative ARR and RRR indicate that the active treatment arm increased the risk of the outcome. Conversely, positive RRI and ARI indicate that the risk of that outcome is increased by study intervention, while negative values indicate the active treatment is safer than the comparator.

[a]Statistically significant.

ACS, acute coronary syndrome; ARD, absolute risk difference; ASA/A, aspirin; b.i.d. , bis in die; BARC, Bleeding Academic Research Consortium; CABG, coronary artery bypass grafting; CI, confidence interval; CCS, chronic coronary syndrome; CV, cardiovascular; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; E-ZES, endeavor zotarolimus-eluting stent; GUSTO, Global Use of Strategies to Open Occluded Arteries; Hb, haemoglobin; HR, hazard ratio; INR, International Normalized Ratio; ISTH, International Society on Thrombosis and Haemostasis; LOF, loss of function; LIMA, Left Internal Mammary Artery; MACCE, major adverse cardiac and cerebrovascular events; MACE, major adverse cardiac events; MI, myocardial infarction; NACCE, net adverse clinical and cerebrovascular events; NACE, net adverse clinical events; P2Y12i, P2Y12 inhibitor; PCI, percutaneous coronary intervention; PLATO, Platelet Inhibition and Patient Outcomes; REPLACE-2, Randomized Evaluation in PCI Linking Angiomax to Reduced Clinical Events; R, rivaroxaban; RR, rate ratio; ST, stent thrombosis; STEEPLE, Safety and Efficacy of Enoxaparin in PCI Patients; an International Randomized Evaluation; SVG, saphenous vein graft; T, ticagrelor; TIA, transient ischaemic attack; TIMI, thrombolysis in myocardial infarction; TLF, target lesion failure; TVF, target vessel failure; TLR, target lesion revascularization; TVR, target vessel revascularization; W + A, warfarin + aspirin.

Table 2 Clinical consensus statements for PAD patients with established CAD

The presence of PAD in patients with CAD prompts considering an intensified antithrombotic treatment (e.g. clopidogrel instead of aspirin if single antiplatelet therapy is preferrable or aspirin and rivaroxaban 2.5 mg b.i.d or aspirin and ticagrelor 60 mg b.i.d. instead of single antiplatelet therapy with aspirin in patients not at high bleeding risk).

ABI, ankle-brachial index; b.i.d., bis in die; CAD, coronary artery disease; PAD, peripheral arterial disease.

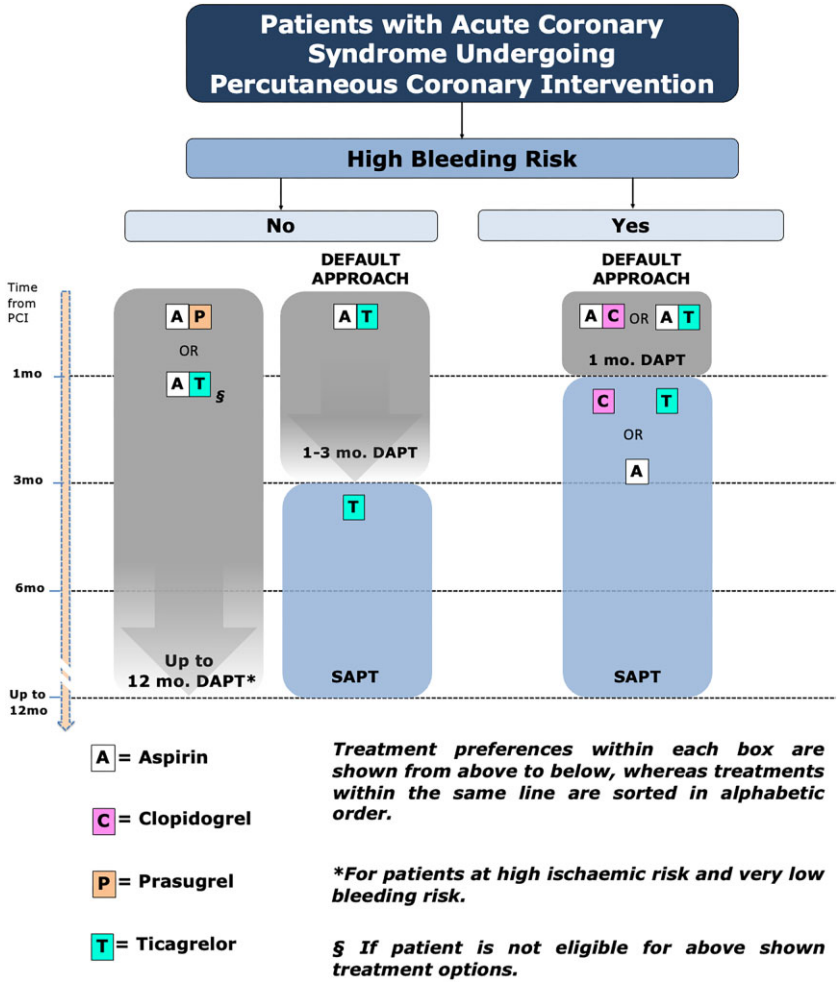


Figure 1 ACS managed by PCI. Treatment options for ACS patients managed by PCI, depending on bleeding and ischaemic risks. For detailed consensus statements, see *Table 3*. Box colours indicate composition of antithrombotic regimens (light blue: SAPT; grey: DAPT). Abbreviations: ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

the rates of MI, stent thrombosis, and stroke did not differ.[99] The treatment effect was consistent in ACS patients ($P_{interaction} = 0.51$), which represented slightly less than two-thirds of the study population. In the SIDNEY-2 Collaboration, consisting of data from 24 096 patients, the composite of all-cause death, MI, or stroke did not differ with $P2Y_{12}$ inhibitor monotherapy, including any of the three oral $P2Y_{12}$ inhibitors, or DAPT (HR 0.93, 95% CI 0.79–1.09; $P = 0.005$ for non-inferiority).[100] The treatment effect was consistent across all subgroups, including ACS (13 966 or 60%), but there was an interaction with sex ($P_{interaction} = 0.019$), suggesting that $P2Y_{12}$ inhibitor monotherapy is associated with a lower rate of all-cause death, MI, or stroke in females (HR 0.64, 95% CI 0.46–0.89), irrespective of the choice of $P2Y_{12}$ inhibitor monotherapy.[100] However, ticagrelor and prasugrel were over- and under-represented, respectively, among the newer $P2Y_{12}$ inhibitors, and clopidogrel monotherapy was only tested in Asian populations in comparison with the combination of aspirin and clopidogrel.[100] The STOPDAPT2-ACS trial enrolled 3008 ACS patients from Japan who were then combined with ACS patients included in the parent STOPDAPT2 trial ($n = 1161$). In the 4169 ACS patient cohort, non-inferiority for the composite of

cardiovascular death, MI, definite stent thrombosis, and stroke of 1-month DAPT with aspirin and clopidogrel followed by clopidogrel monotherapy was not shown compared with 1-year DAPT (HR 1.14, 95% CI 0.80–1.62; *P* for non-inferiority = 0.06) due to a significant excess of MI in the monotherapy arm (HR 1.91, 95% CI 1.06–3.44). However, the rate of BARC 3 or 5 bleeding was lower in the monotherapy arm (HR 0.41, 95% CI 0.20–0.83). The Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation With an Abbreviated vs. Standard DAPT Regimen (MASTER DAPT) trial recruited 4579 HBR patients, including 2211 (48.3%) patients with ACS who underwent 1-month DAPT after sirolimus-eluting biodegradable polymer stent implantation, followed by single antiplatelet therapy (clopidogrel in 53.9% of the patients, aspirin in 28.8%, ticagrelor in 13.6%, and prasugrel in 1.2%) or a more prolonged DAPT regimen of at least 3 months.[91] Non-inferiority for both net and major adverse cardiac and cerebral event endpoints was shown for the abbreviated DAPT arm, which was also associated with a lower risk of major or clinically relevant non-major bleeding (HR 0.68, 95% CI 0.55–0.84) and with consistent results among ACS patients.[91]

Evidence from the network meta-analysis (NMA), including PCI and/or ACS patients, focusing on 12-month treatment effects, suggests that ticagrelor monotherapy is associated with lower risks of mortality (HR 0.68, 95% CI 0.52–0.89) and MI (HR 0.69, 95% CI 0.50–0.95) compared with aspirin.[102] In comparison with 12-month DAPT with aspirin and clopidogrel, ticagrelor monotherapy is associated with a lower risk of mortality (HR 0.70, 95% CI 0.55–0.89) and a similar risk of MI and bleeding,[102] whereas clopidogrel monotherapy is associated with similar death or MI rates but lower bleeding (HR 0.62, 95% CI 0.40–0.96).[102]

Dual antithrombotic therapy

Since the publication of the PCI-CURE study,[103] DAPT has been the mainstay of antithrombotic treatment after PCI in patients with ACS. The TRITON-TIMI 38[75] and PLATO[45] trials established the superiority of prasugrel and ticagrelor over clopidogrel in aspirin-treated patients in terms of ischaemic outcomes. Both studies showed a similar reduction in the primary composite endpoint of cardiovascular death, MI, or stroke and a comparable increase in major non-CABG-related bleeding as compared with clopidogrel. In the TRITON-TIMI study, there was a slight, yet significant, excess of fatal bleeding with prasugrel, which led the Food and Drug Administration (FDA) to issue a black box warning on bleeding risk with prasugrel. The PLATO study found a significant reduction in cardiovascular mortality with ticagrelor.[45] In the PRAGUE-18, no significant differences in the primary composite net endpoint at 7 days were found among aspirin-treated ACS patients treated with prasugrel or ticagrelor.[104] The ISAR-REACT 5 is the largest head-to-head comparison of 1-year DAPT strategy with ticagrelor (administered 'upstream', before coronary angiography) as compared with DAPT with prasugrel (administered 'downstream', only after coronary anatomy was known) in patients with ACS treated with an invasive management.[32] In this study, prasugrel was associated with a reduction in the composite endpoint of cardiovascular death, MI, or stroke as compared with ticagrelor (HR 0.74, 95% CI 0.59–0.92), which was driven by a reduction in MI (HR 0.61, 95% CI 0.44–0.85).[32] Mortality and bleeding rates were similar between the two groups. Some aspects of this trial have been criticized, such as its open-label design and adherence to treatment assignment.[105] A NMA does not provide clear evidence of the superiority of prasugrel over ticagrelor.[106] DAPT duration should not exceed 1 month in HBR patients, irrespective of concomitant high-risk features, such as patients who underwent complex intervention[91,107,108] and should be preferably followed by $P2Y_{12}$ inhibitor monotherapy instead of aspirin.[97,99]

Triple antithrombotic therapy

In patients with a recent ACS, low-dose rivaroxaban [2.5 mg bis in die (b.i.d.)] for a mean of 13 months and up to 31 months was associated with lower risk of cardiovascular death, MI, or stroke (HR 0.84, 95% CI 0.72–0.97) compared with placebo in the ATLAS ACS 2- TIMI 51 trial, where most patients were on DAPT with aspirin and clopidogrel or ticlopidine.[73] The potential benefit of rivaroxaban with respect to ischaemic outcomes should be weighed against the increased risk of major (HR 3.46, 95% CI 2.08–5.77) and intracranial bleeding (HR 2.83, 95% CI 1.02–7.86).[73] Apixaban 5 mg b.i.d., mostly in combination with DAPT, was not associated with lower risk of cardiovascular death, MI, or ischaemic stroke (HR 0.95, 95% CI 0.80–1.11) but greater than two-fold major bleeding risk (HR 2.59, 95% CI 1.50–4.46) in the APPRAISE-2 trial, leading to premature study termination.[24] The NMA provides evidence that triple therapy with rivaroxaban 2.5 mg, aspirin, and clopidogrel is associated with lower mortality risk compared with aspirin and 12-month clopidogrel (HR 0.68, 95% CI 0.53–0.87), but with higher bleeding risk (HR 2.49, 95% CI 1.54–4.03).[102]

Consensus statements endorsed by this document regarding antithrombotic therapy in ACS patients undergoing PCI are provided in *Table 3*.

Acute coronary syndrome managed by coronary artery bypass grafting

Evidence-based treatment options are shown in *Figure 2* and summary of evidence in the Supplemental material.

Single antithrombotic therapy

Uninterrupted, low-dose aspirin reflects current best practice in most ACS patients while waiting for CABG and shortly (generally 24 h) after surgery.[1] Clopidogrel was associated with a lower risk of vascular death, MI or ischaemic stroke (HR 0.64, 95% CI 0.47–0.87) compared with aspirin in patients with prior CABG in the CAPRIE trial.[109] The prematurely interrupted TICAB trial, which included 31% of patients with ACS, failed to show superiority of ticagrelor monotherapy over aspirin monotherapy within 1 year after CABG.[64] Ticagrelor, clopidogrel, and prasugrel should be stopped 3, 5, and 7 days before CABG, respectively.

Dual antithrombotic therapy

The available evidence for dual antithrombotic therapy in ACS-CABG patients comes from subgroup analyses of ACS trials, which showed results consistent with the overall findings. The CURE trial first supported starting a second antiplatelet drug (clopidogrel) at hospital admission in addition to aspirin in ACS patients for the reduction of cardiovascular death, MI, or stroke [rate ratio (RR) 0.80, 95% CI 0.72–0.90],[74] including those undergoing CABG (RR 0.89, 95% CI 0.71–1.11), ($P_{interaction}$ = 0.53).[110] The PLATO trial showed a significant reduction in all-cause mortality (HR 0.49, 95% CI 0.32–0.77) and cardiovascular mortality (HR 0.52, 95% CI 0.32–0.85) with ticagrelor compared with clopidogrel in aspirin-treated patients undergoing CABG,[111] supporting the use of ticagrelor over clopidogrel in addition to aspirin for the first 6–12 months following surgery.

Triple antithrombotic therapy

In the ATLAS ACS 2-TIMI 51 trial, 60% of the overall ACS cohort underwent PCI or CABG.[73]

Table 3 Clinical consensus statements for ACS managed by PCI (without baseline indications for OAC)

Single antithrombotic therapy
Compared with 12-month DAPT, aspirin withdrawal after 1-to-3-month DAPT and continuation with $P2Y_{12}$ inhibitor in the form of: • ticagrelor monotherapy provides net benefit with reduced bleeding complications without increased risk of non-fatal or fatal ischaemic events; • prasugrel monotherapy has not been investigated and cannot, therefore, be supported; • clopidogrel monotherapy is associated with greater MI risk among patients who were not selected for being at HBR (e.g. based on ARC-HBR criteria or PRECISE-DAPT $\geq$ 25).[a]
Compared with $\geq$12-month DAPT, $P2Y_{12}$ inhibitor withdrawal after 3- or 6-month DAPT and continuation of aspirin is associated with greater MI risk among patients who were not selected for being at HBR (e.g. based on ARC-HBR criteria or PRECISE-DAPT $\geq$ 25).
Dual antithrombotic therapy
During the first year after PCI in ACS, DAPT with a newer $P2Y_{12}$ inhibitor (prasugrel or ticagrelor) is superior to DAPT with clopidogrel in terms of ischaemic outcomes and is therefore warranted.
Long-term DAPT, instead of $P2Y_{12}$ inhibitor monotherapy, remains justifiable in patients at high risk of recurrent ischaemic events[b] in whom the bleeding risk does not pose concerns.
One-month DAPT duration is warranted in HBR patients (e.g. based on ARC-HBR criteria or PRECISE-DAPT $\geq$ 25[83]).[c]
The combination of rivaroxaban 2.5 mg b.i.d. and a $P2Y_{12}$ inhibitor cannot be supported as a routine strategy without additional investigation.
The combination of rivaroxaban 2.5 mg b.i.d. with clopidogrel or ticagrelor may be justifiable following PCI in aspirin-intolerant patients who are not HBR.
Triple antithrombotic therapy
Triple antithrombotic therapy with rivaroxaban 2.5 mg b.i.d. in combination with aspirin and clopidogrel remains a therapeutic option in selected patients at high risk of thrombotic complications and low risk of bleeding.[d]

ACS, acute coronary syndrome; ARC, Academic Research Consortium; b.i.d., bis in die; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; MI, myocardial infarction; OAC, oral anticoagulation; PADs, peripheral arterial diseases; PCI, percutaneous coronary intervention.
[a]This evidence was generated in patients who underwent durable polymer everolimus-eluting stent implantation; consequently, these results may not extend to patients who receive other stent types.
[b]High ischaemic risk is defined as diffuse multivessel coronary artery disease with at least one of the following: diabetes mellitus requiring medication, recurrent MI, peripheral arteria disease, or chronic kidney disease with estimated glomerular filtration rate 15–59 mL/min/1.73 m^2.
[c]This evidence was generated in patients who underwent biodegradable polymer sirolimus-eluting stent implantation; consequently, these results may not extend to patients who receive other stent types.
[d]Such as patients in whom the use of ticagrelor and prasugrel is not an option, those with recurrent ischaemic events on prior use of ticagrelor or prasugrel in whom adherence to these drugs has been established, or patients in whom the early transition towards dual therapy with aspirin and rivaroxaban is envisioned.

The treatment effects of rivaroxaban, when mainly added to aspirin and clopidogrel, among CABG patients have not been separately reported.

Consensus statements endorsed by this document regarding antithrombotic therapy in ACS patients undergoing CABG are provided in *Table 4*.

Acute coronary syndrome managed by medical therapy alone

Evidence-based treatment options are shown in *Figure 3* and summary of evidence in the Supplemental material.

Single antithrombotic therapy

Aspirin reduces the odds of serious vascular events—defined as vascular death, MI, or stroke—by 25% as compared with no treatment in patients with prior MI.[112] The CAPRIE trial demonstrated greater ischaemic protection from clopidogrel than aspirin, without higher bleeding risk.[46]

Dual antithrombotic therapy

Among ACS patients who are medically managed without revascularization, the combination of aspirin and clopidogrel reduces the risk of cardiovascular death, MI, or stroke (RR 0.80, 95% CI 0.69–0.92) but increases the risk of major bleeding (RR 1.75, 95% CI 1.25–2.36) compared with aspirin alone.[110] The combination of ticagrelor and aspirin was associated with lower risk of cardiovascular death, MI, or stroke compared with aspirin and clopidogrel in the PLATO trial,[45] which was consistent in the medically managed population (HR 0.85, 95% CI 0.73–1.00; $P_{interaction} = 0.88$)[113] and across all ages.[114] The overall bleeding risks did not differ between ticagrelor and clopidogrel in medically managed ACS patients (HR 1.17, 95% CI 0.98–1.39; $P_{interaction} = 0.12$),[113] although observational data suggest that ticagrelor should be used cautiously in octogenarians.[115]

When low-dose rivaroxaban is combined with either clopidogrel or ticagrelor for the treatment of ACS patients who were, however, predominately treated with PCI, the risk of clinically significant bleeding is similar to the risk with aspirin and a $P2Y_{12}$ inhibitor without evidence of greater ischaemic protection.[27]

Triple antithrombotic therapy

ACS was managed medically in 55, 20, and 40% of the patients included in the APPRAISE-2,[24] ATLAS ACS-TIMI 46,[116] and ATLAS ACS 2-TIMI 51[73] trials, respectively. In the ATLAS ACS 2-TIMI 51, the use of low-dose rivaroxaban (2.5 mg b.i.d.) added to aspirin and clopidogrel was associated with a lower risk of cardiovascular death, MI, or stroke but considerably higher bleeding in the overall population.[73] However, the risks and benefits of triple therapy with rivaroxaban 2.5 mg b.i.d. in medically managed ACS patients have not been separately appraised in the published literature.

Consensus statements endorsed by this document regarding antithrombotic therapy in ACS patients managed by medical treatment alone are provided in *Table 5*.

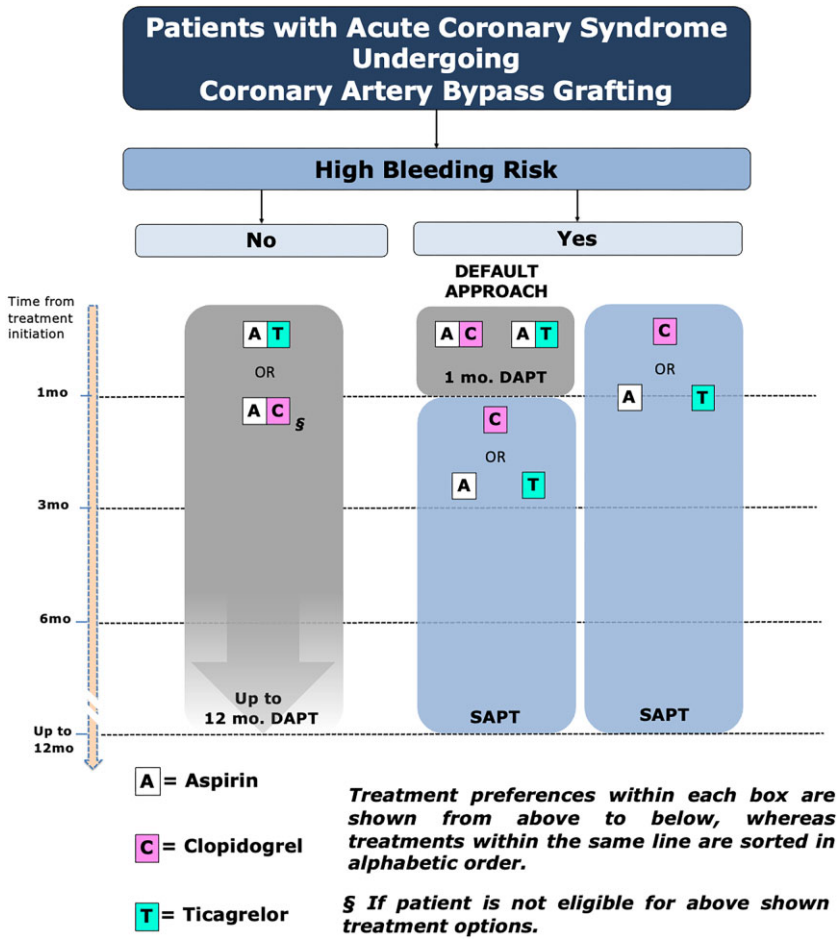


Figure 2 ACS managed by CABG. Treatment options for ACS patients managed by CABG, depending on bleeding risk. For detailed consensus statements, see *Table 4*. Box colours indicate composition of antithrombotic regimens (light blue: SAPT; grey: DAPT). Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.

Table 4 Clinical consensus statements for ACS managed by CABG (no baseline indications for OAC)

Single antithrombotic therapy
Single antithrombotic therapy does not represent the current standard of care unless it is justified by intolerance or contraindications to dual antiplatelet therapy, such as HBR (e.g. based on ARC-HBR criteria or PRECISE-DAPT $\geq$ 25).
If single antithrombotic therapy is selected, then clopidogrel is preferable over aspirin or ticagrelor.
Dual antithrombotic therapy
Dual antiplatelet therapy for up to 12 months provides greater ischaemic protection than aspirin alone, and represents the current standard of care, unless concerns over HBR prevail (e.g. based on ARC-HBR criteria or PRECISE-DAPT $\geq$ 25[83]).
The use of aspirin and ticagrelor provides greater ischaemic protection than aspirin and clopidogrel
Triple antithrombotic therapy
The treatment effects of rivaroxaban 2.5 mg b.i.d. on top of aspirin and clopidogrel in patients who underwent CABG are unknown.

ACS, acute coronary syndrome; b.i.d., bis in die; CABG, coronary artery bypass grafting; HBR, high bleeding risk; OAC, oral anticoagulation.

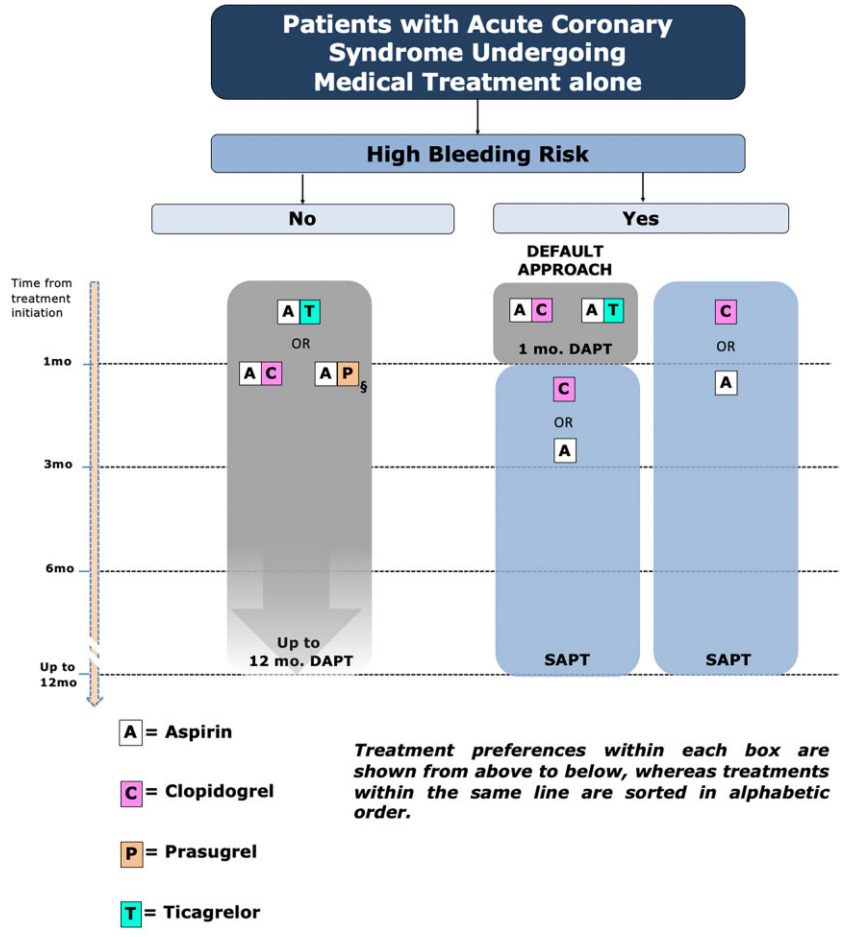


Figure 3 ACS managed by medical therapy alone. Treatment options for ACS patients managed by medical therapy alone, depending on bleeding risk. For detailed consensus statements, see *Table 5*. Box colours indicate composition of antithrombotic regimens (light blue: SAPT; grey: DAPT). § DAPT with aspirin and prasugrel is justifiable if clopidogrel and ticagrelor are not indicated, such as in patients receiving strong CYP3A inhibitors among patients with CAD confirmed by angiography. Abbreviations: ACS, acute coronary syndrome; DAPT, dual antiplatelet therapy; SAPT, single antiplatelet therapy.

Chronic coronary syndrome with prior (>12 months) myocardial infarction

Evidence-based treatment options are shown in *Figure 4* and summary of evidence in the Supplemental material.

Single antithrombotic therapy

Remote studies evaluated monotherapy with aspirin, clopidogrel, or warfarin in the context of CCS and prior MI are now historical. A 1994 meta-analysis showed that aspirin therapy, among ≈20 000 patients with a prior history of MI, reduced the odds of serious vascular events, defined as vascular death, MI, or stroke, by 25% as compared with no treatment.[117] A wide range of aspirin dosing regimens were evaluated and proved equally effective**.** In a comparison of clopidogrel vs. aspirin in the CAPRIE trial, among 8446 (44%) patients with prior MI, the relative risk reduction of vascular death, MI, or ischaemic stroke was 7.4% (95% CI −5.2 to 18.6%) with clopidogrel.[46] In that trial, the presence of polyvascular disease was associated with an increased benefit from clopidogrel over aspirin. In the WARIS-II trial,[72] though warfarin monotherapy showed benefit compared with aspirin in terms of a composite of death, non-fatal reinfarction, or thromboembolic cerebral stroke (RR 0.81, 95% CI 0.69–0.95), the warfarin strategy was associated with a four-fold higher annual rate of non-fatal major bleeding. In the more contemporary GLOBAL LEADERS trial (34% of patients with AMI at presentation and 23% of patients with prior MI before index procedure), ticagrelor monotherapy from 12 to 24 months after PCI was associated with borderline reduction of all-cause death or new Q-wave MI compared with aspirin.[29] A *post-hoc* landmark analysis of the GLOBAL LEADERS trial showed that ticagrelor monotherapy resulted in lower rates of the composite endpoint of all-cause death, any MI, or any stroke (HR 0.74, 95% CI 0.58–0.96), mainly driven by >40% lower MI risk at both unadjusted and adjusted analyses (HR 0.54, 95% CI 0.36–0.82).[118] The benefits with ticagrelor were consistent in patients with or without ACS at index PCI (*P* for interaction = 0.22). The rates of major bleeding were significantly higher with ticagrelor in the adjusted analyses (HR 1.89, 95% CI 1.03–3.45) but not in the unadjusted analyses (HR 1.80, 95% CI 0.99–3.30) and derived entirely from

Table 5 Clinical consensus statements for ACS managed by medical therapy alone (no baseline indications for OAC)

Single antithrombotic therapy
Single antithrombotic therapy does not represent the current standard of care unless it is justified by intolerance or contraindications to dual antiplatelet therapy, such as HBR (e.g. based on ARC-HBR criteria or PRECISE-DAPT $\geq$ 25[83]).
Aspirin provides greater ischaemic protection than no aspirin following acute MI.
Clopidogrel provides net benefit compared with aspirin.
Dual antithrombotic therapy
The combination of aspirin and ticagrelor for up to 12 months is warranted instead of aspirin and clopidogrel unless concerns over the bleeding risk prevail (e.g. based on ARC-HBR criteria or PRECISE-DAPT $\geq$ 25[83]).
The treatment duration of aspirin and ticagrelor or clopidogrel depends on treatment tolerance, side effects, and assessment of ischaemic vs. bleeding risks.
The combination of aspirin and prasugrel is justifiable if clopidogrel and ticagrelor are not indicated, such as in patients receiving strong CYP3A inhibitors if CAD has been confirmed by angiography.
The combination of rivaroxaban 2.5 mg b.i.d. with clopidogrel or ticagrelor requires further investigation.
Triple antithrombotic therapy
Triple antithrombotic therapy with rivaroxaban 2.5 mg b.i.d., aspirin, and clopidogrel has limited evidence in medically managed ACS patients.

ACS, acute coronary syndrome; b.i.d., bis in die; CAD, coronary artery disease; HBR, high bleeding risk; MI, myocardial infarction; OAC, oral anticoagulation; PCI, percutaneous coronary intervention.

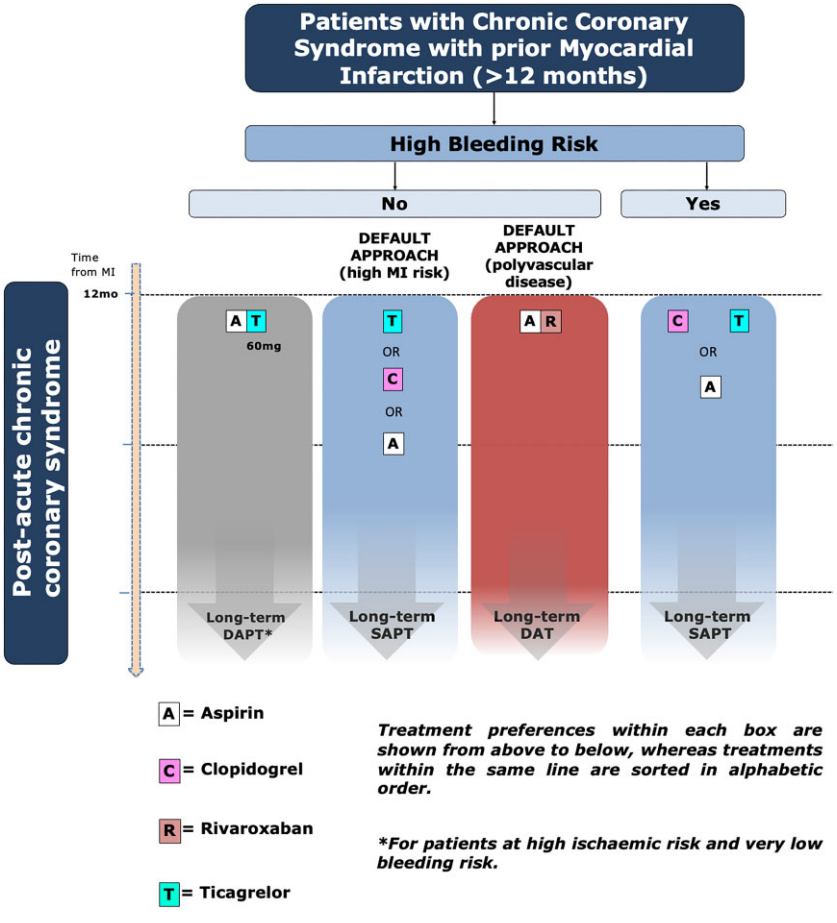


Figure 4 CCS with prior MI. Treatment options for CCS patients with prior MI (>12 months), depending on bleeding and ischaemic risks. For detailed consensus statements, see *Table 6*. Box colours indicate composition of antithrombotic regimens (light blue: SAPT; grey: DAPT; red: DAT). Abbreviations: CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; MI, myocardial infarction; SAPT, single antiplatelet therapy.

Table 6 Clinical consensus statements for CCS with prior (>12 months) MI (no baseline indications for OAC)

Single antithrombotic therapy
Aspirin therapy decreases the risk of ischaemic events compared with no aspirin.
Based on both direct and indirect evidence (ref. NMA), ticagrelor 90 mg b.i.d. decreases the risk of MI compared with aspirin.
Clopidogrel provides net clinical benefit compared with aspirin.
Dual antithrombotic therapy
Long-term DAPT, including the combination of aspirin and clopidogrel or aspirin and ticagrelor 90 mg, has not provided evidence of net clinical benefit in comparison with aspirin.
Long-term DAPT with aspirin and ticagrelor 60 mg b.i.d. is a therapeutic option for non-HBR patients (e.g. no ARC-HBR criterion or PRECISE-DAPT < 25) who are deemed at increased risk of ischaemic events, especially recurrent MI.[a]
Following completion of DAPT, a dual antithrombotic regimen consisting of aspirin + rivaroxaban 2.5 mg b.i.d. is a therapeutic option for patients with high ischaemic risk[a] who are non-HBR (e.g. no ARC-HBR criterion or PRECISE-DAPT < 25[83]) and is warranted especially among patients in whom the long-term risk of stroke prevails over the risk of recurrent MI, such as patients with prior stroke, or concomitant PAD or additional risk factors including diabetes, renal dysfunction, and heart failure, who did not experience recurrent coronary events over the last year(s).

ARC-HBR, Academic Research Consortium-high bleeding risk; b.i.d., bis in die; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy, HBR, high bleeding risk; MI, myocardial infarction; OAC, oral anticoagulation.
[a]High ischaemic risk is defined as diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, peripheral arteria disease, or chronic kidney disease with estimated glomerular filtration rate 15–59 mL/min/1.73 m^2.

patients with PRECISE DAPT < 25. In the Global Leaders Adjudication Substudy (GLASSY), an independent clinical event committee adjudicated investigator-reported and eventually unreported events of 7585 patients from the 20 top-enrolling participating sites. The 2-year co-primary efficacy endpoint occurred in 271 (7.14%) and in 319 (8.41%) patients in the experimental and conventional groups, respectively (RR 0.85, 95% CI 0.72–0.99; *P* for non-inferiority < 0.001; *P* for superiority = 0.0465).[28]

A landmark analysis of GLASSY showed that MI risk was significantly reduced with ticagrelor compared with aspirin from 12 to 24 months after PCI (HR 0.54, 95% CI 0.33–0.88), with consistent findings in patients with or without ACS at presentation, whereas major bleeding did not differ.

In the recent HOST-EXAM trial, 5530 patients, mainly after ACS (72%), were randomized to stop DAPT after a median duration of 382 days and continue with aspirin or clopidogrel.[97] The composite of all-cause death, MI, stroke, readmission due to ACS or major bleeding was reduced with clopidogrel (HR 0.73, 95% CI 0.59–0.90), mainly due to lower rates of the last two primary endpoint components.[97]

In the NMA, ticagrelor 90 mg monotherapy was associated with lower risk of MI (HR 0.54, 95% CI 0.32–0.92) compared with aspirin without higher bleeding risk.[102]

Dual antithrombotic therapy

The benefit of DAPT ($P2Y_{12}$ inhibitor plus aspirin) or a combination of aspirin with oral anticoagulation beyond 1 year after ACS was investigated in 11 trials, but interpretation of the accumulated evidence remains controversial. Several studies (CHARISMA,[16] DAPT,[21] DES-LATE,[22] ITALIC,[36] OPTIDUAL,[41] PRODIGY,[50] and REAL-ZEST LATE[52]) investigated the effectiveness of DAPT with clopidogrel, whereas only one trial tested DAPT using ticagrelor (PEGASUS-TIMI 54[44]); prasugrel was tested in a subset of patients in a trial (DAPT study)[21] (Supplemental material). One trial assessed a new oral anticoagulant (NOAC) in the management of CCS patients (COMPASS,[17] rivaroxaban). LoWASA[38] and WARIS-II[72] analysed an antiplatelet plus reduced-dose anticoagulant approach with coumadin.

The DAPT trial showed a significant reduction of stent thrombosis (HR 0.29, 95% CI 0.17–0.48) and major adverse cardiovascular and cerebrovascular events (HR 0.71, 95% CI 0.59–0.85) with DAPT compared with aspirin therapy alone.[21] The DAPT trial did not report the net impact of ischaemic outcomes and major bleeding (summation of these events does not show net benefit), and the first-generation drug-eluting stents (DES) were largely used in this trial.[21]

In the PEGASUS-TIMI 54 trial, twice-daily treatment with ticagrelor 90 mg (HR 0.85, 95% CI 0.75–0.96) or 60 mg (HR 0.84, 95% CI 0.74–0.95) in addition to aspirin 1–3 years after an MI reduced the risk of cardiovascular death, MI, or stroke[44]; however, the rates of major bleeding were more than two-fold higher with ticagrelor 90 mg (HR 2.69, 95% CI 1.96–3.70) or ticagrelor 60 mg (HR 2.32, 95% CI 1.68–3.21).[44] This therapeutic approach is justified for patients with a high ischaemic risk if at low risk of bleeding.

The data from the combination therapy of warfarin and aspirin should be interpreted with caution,[38,72] as NOACs have largely replaced warfarin, new generations of DES are routinely used, and the overall risk of coronary events has fallen in recent years.

The COMPASS trial assessed two strategies (rivaroxaban 2.5 mg b.i.d. plus aspirin or rivaroxaban 5 mg b.i.d. alone) compared with aspirin alone in patients with CCS and/or PAD (62% with a history of prior MI).[17] Among patients with CAD, rivaroxaban 2.5 mg and aspirin significantly reduced major adverse cardiac events (HR 0.76, 95% CI 0.66–0.86) vs. aspirin alone, at the cost of significantly increased risk of major bleeding (HR 1.70, 95% CI 1.40–2.05). There was a favourable net clinical benefit (HR 0.80, 95% CI 0.70–0.91), and all-cause deaths were numerically lower (HR 0.82, 95% CI 0.71–0.96) with rivaroxaban and aspirin dual therapy vs. aspirin alone. Subgroup analysis showed similar results in CAD patients with or without a history of MI ($P_{interaction}$ 0.93), irrespective of timing of prior MI. Patients with CAD and PAD had numerically higher absolute benefits from rivaroxaban and aspirin compared with aspirin alone. This trial showed no benefit of rivaroxaban 5 mg b.i.d. alone vs. aspirin alone.

In the NMA, the combination of aspirin and rivaroxaban 2.5 mg was associated with a large benefit for stroke reduction (HR 0.58, 95% CI 0.38–0.88) and ranked as the first treatment option for stroke prevention among the contemporary options to mitigate this endpoint.[102]

Consensus statements endorsed by this document regarding antithrombotic therapy in CCS patients with prior (>12 months) MI are provided in *Table 6*.

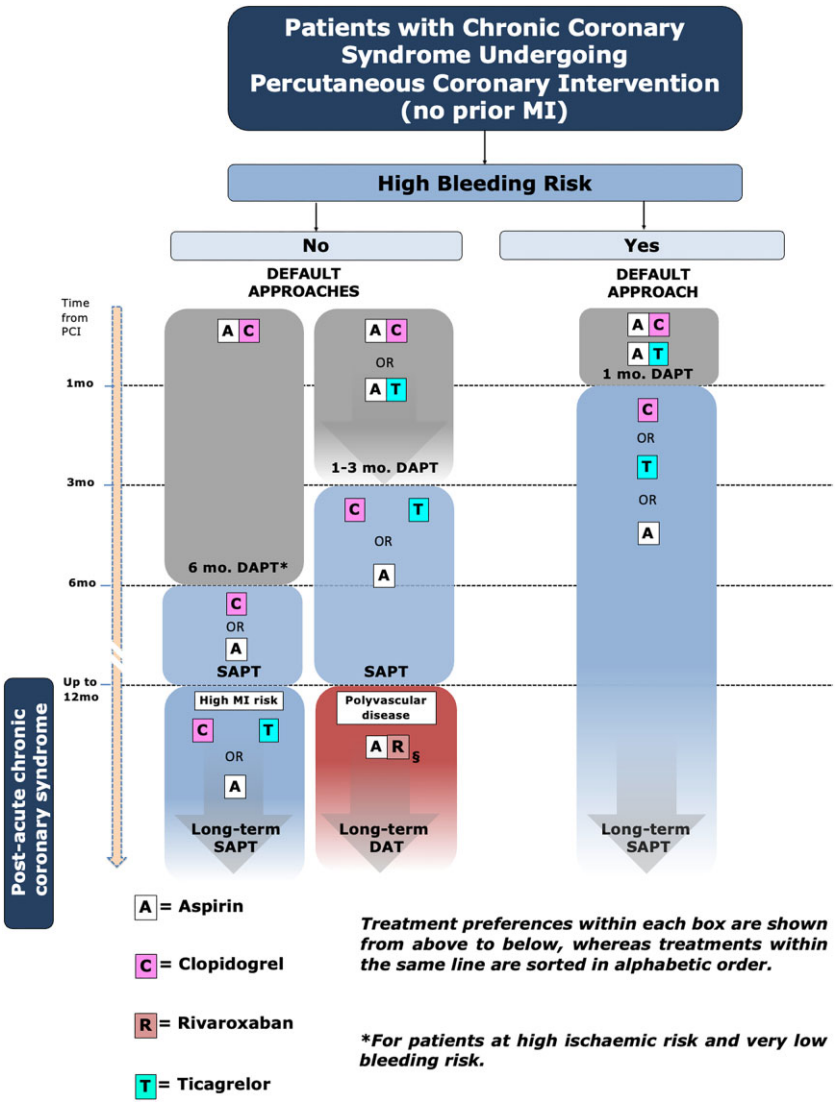


Figure 5 CCS managed by PCI without prior MI. Treatment options for CCS patients managed by PCI, depending on bleeding and ischaemic risks. For detailed consensus statements, see *Table 7*. Box colours indicate composition of antithrombotic regimens (light blue: SAPT; grey: DAPT; red: DAT). § After 1–3 month(s) of DAPT, if aspirin is continued in non-high bleeding risk patients in prevision of adding rivaroxaban 2.5 mg b.i.d at a later time point, an earlier administration of rivaroxaban in combination with aspirin after DAPT cessation is reasonable. Abbreviations: b.i.d, bis in die; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; MI, myocardial infarction; PCI, percutaneous coronary intervention; SAPT, single antiplatelet therapy.

Chronic coronary syndrome managed by percutaneous coronary intervention without prior myocardial infarction

Evidence-based treatment options are shown in *Figure 5* and summary of evidence in the Supplemental material.

Single antithrombotic therapy

The SIDNEY-2 collaboration included 22 974 (99%) patients who underwent PCI and compared oral $P2Y_{12}$ monotherapy after a 1-to-3-month course of DAPT with DAPT continuation for at least 12 months.[100] A total of 9339 (40.1%) patients had CCS, 13 966 (59.9%) had ACS, and overall prior MI was noted in 19.0% of the population. The composite of all-cause death, MI, or stroke occurred with similar rates in patients allocated to $P2Y_{12}$ monotherapy or DAPT at 1 year among CCS patients, which was consistent with the treatment effect observed among ACS patients ($P_{interaction} = 0.51$). Results remained consistent when clopidogrel monotherapy or monotherapy with newer $P2Y_{12}$ inhibitors, consisting of ticagrelor in 99% of the patients, was compared with DAPT. $P2Y_{12}$ monotherapy was associated with consistently lower risk of BARC 3 or 5 bleeding among CCS (HR 0.72, 95% CI 0.48–1.07) or ACS (HR 0.40, 95% CI 0.29–0.54) patients ($P_{interaction} = 0.057$).[100] However, the use of clopidogrel monotherapy was investigated exclusively in Asian patients in whom the use of intravascular imaging modalities was high. Recently, the HOST-EXAM

Table 7 Clinical consensus statements for CCS managed by PCI (no baseline indications for OAC)

Single antithrombotic therapy
Compared with 12-month DAPT, aspirin withdrawal after 1-to-3-month DAPT and continuation with $P2Y_{12}$ inhibitor in the form of ticagrelor or clopidogrel monotherapy provides net benefit with reduced bleeding complications and similar risk of non-fatal or fatal ischaemic events.
Compared with ≥12-month DAPT, $P2Y_{12}$ inhibitor withdrawal after 6-month DAPT and continuation of aspirin is associated with net benefit with reduced bleeding complications and similar risk of non-fatal or fatal ischaemic events.
Longer than 6-month DAPT duration remains justifiable in patients at high risk of recurrent ischaemic events[a] in whom the bleeding risk does not pose concerns.
Clopidogrel, after completion of DAPT, provides net clinical benefit compared with aspirin based on both direct and indirect comparisons.
The use of ticagrelor 90 mg b.i.d. monotherapy beyond 1 year is associated with lower risk of MI and similar bleeding compared with aspirin (based on direct and indirect comparisons).
Dual antithrombotic therapy
One-to-six-month DAPT followed by single antiplatelet therapy is the default approach following PCI. In HBR patients (e.g. ARC-HBR criteria or PRECISE-DAPT ≥ 25[83]), 1-month DAPT duration is warranted followed by single antiplatelet therapy.
Following completion of DAPT, the combination of aspirin and rivaroxaban 2.5 mg b.i.d. provides net clinical benefit in those with high ischaemic risk[a] who do not have a high bleeding risk and is especially warranted for those deemed at high risk for stroke (unless they have an indication for higher-dose anticoagulation such as atrial fibrillation), such as patients with prior stroke, or concomitant PAD or additional risk factors including diabetes, renal dysfunction, and heart failure.

ARC-HBR, Academic Research Consortium-high bleeding risk; b.i.d., bis in die; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; MI, myocardial infarction; OAC, oral anticoagulation; PCI, percutaneous coronary intervention.
[a]High ischaemic risk is defined as diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, peripheral arteria disease, or chronic kidney disease with estimated glomerular filtration rate 15–59 mL/min/1.73 m^2.

trial enrolled patients who maintained DAPT without clinical events for 6–18 months after PCI with DES. Patients were subsequently randomized to clopidogrel or aspirin monotherapy for 24 months. The study showed greater net benefit with clopidogrel than aspirin, mainly driven by lower rehospitalization for ACS and bleeding.[97] For long-term (>12 months) secondary prevention, the NMA suggests that ticagrelor (HR 0.54, 95% CI 0.32–0.92) but not clopidogrel monotherapy almost halved the risk of MI without a bleeding risk trade-off compared with aspirin monotherapy.[102]

Dual antithrombotic therapy

Most trials of DAPT duration included a mixed population of patients (CCS and ACS presentations), and a variable proportion had prior MI. Multiple studies have compared a shorter vs. a longer DAPT regimen, including ISAR-SAFE,[33] ITALIC,[36] NIPPON,[40] OPTIMA-C,[42] OPTIMIZE,[43] PRODIGY,[50] RESET,[54] SECURITY,[56] SMART CHOICE,[58] EXCELLENT,[25] OPTIDUAL,[41] and DAPT.[21] Overall, extended DAPT increased major bleeding about two-fold. In the DAPT trial (9961 patients), the benefits of reduced MI and stent thrombosis were approximately matched by the excess in major and fatal bleeding (the trend for excess mortality appears to be non-cardiovascular).[21] Net benefit (cardiovascular death/MI/stroke and major bleeding) has not been shown for prolonged DAPT. In summary, prolonged DAPT after PCI for non-ACS patients may only be justified for a selected population who received complex intervention in whom the ischaemic outweighs the bleeding risks.

THEMIS compared ticagrelor vs. placebo in aspirin-treated diabetic patients without prior MI.[63] The primary endpoint (CV death, MI, or stroke) was marginally lower in ticagrelor-treated patients (HR 0.90, 95% CI 0.81–0.99). There was no difference in cardiovascular death, but there was excess TIMI-major bleeding (HR 2.32, 95% CI 1.82–2.94), and the calculation of irreversible harm did not show benefit for ticagrelor in the trial as a whole.

COMPASS included patients with chronic vascular disease (CCS and/or PAD) and markers of increased vascular risk.[17] Rivaroxaban 2.5 mg b.i.d. plus aspirin significantly reduced the primary endpoint of CV death/MI/stroke (HR 0.76, 95% CI 0.66–0.86) compared with aspirin alone and demonstrated a net-clinical benefit (composite of CV death, MI, stroke, fatal bleeding, or symptomatic bleeding into a critical organ: HR 0.80, 95% CI 0.70–0.91). All-cause mortality was reduced using the nominal 0.05 statistical significance but did not meet the pre-defined alpha level of 0.0025 after correcting for multiplicity. In contrast to the findings with DAPT, the benefits seen with rivaroxaban were independent of prior MI. The patients that entered long-term trials of DAPT had tolerated DAPT without major bleeding complications. In contrast, patients in COMPASS had tolerated single antiplatelet therapy. Therefore, rivaroxaban 2.5 mg plus aspirin is an appealing treatment over aspirin alone in higher risk chronic vascular patients, independent of prior MI. These benefits have not been shown with full anticoagulation plus aspirin in patients with prior stenting,[119] nor with rivaroxaban 5 mg without aspirin. It is unknown whether reduced dosage of other NOACs will show similar benefits. In the NMA, the combination of aspirin and rivaroxaban 2.5 mg was associated with a large benefit for stroke reduction (HR 0.58, 95% CI 0.38–0.88) and ranked as the first treatment option for stroke prevention among the contemporary options to mitigate this endpoint.[102]

Consensus statements endorsed by this document regarding antithrombotic therapy in CCS patients treated with PCI (no prior MI) are provided in *Table 7*.

Chronic coronary syndrome managed by coronary artery bypass grafting without prior myocardial infarction

Evidence-based treatment options are shown in *Figure 6* and summary of evidence in the Supplemental material.

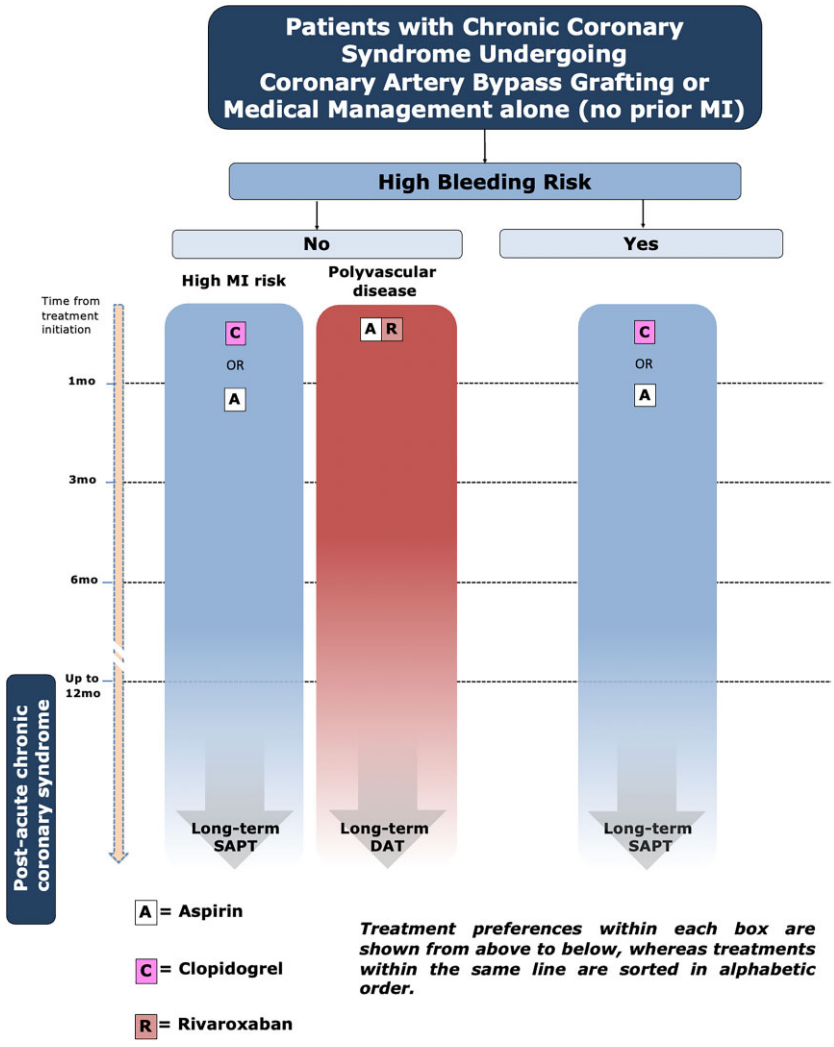


Figure 6 CCS managed by CABG or medical therapy alone (no prior MI). Treatment options for CCS patients managed by CABG, depending on bleeding risk. For detailed consensus statements, see *Table 8*. Box colours indicate composition of antithrombotic regimens (light blue: SAPT; red: DAT). Abbreviations: CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; DAT, dual antithrombotic therapy; MI, myocardial infarction; SAPT, single antiplatelet therapy.

Single and dual antithrombotic therapy

Focusing on graft patency as the primary endpoint, the majority of studies showed aspirin monotherapy to be effective and safe.[39,71,78] In contrast, DAPT studies included small study populations and reported heterogeneous results. Clopidogrel was associated with a lower risk of vascular death, MI or ischaemic stroke (HR 0.64, 95% CI 0.47–0.87) compared with aspirin in patients with prior CABG in the CAPRIE trial. The DACAB study, which assessed the effects of a combination of ticagrelor/aspirin on SVG patency, documented a significant increase in graft patency compared with aspirin alone (RR 0.48, 95% CI 0.31–0.74).[20] However, the results were not confirmed in the POPULAR CABG trial.[120] In the pre-specified COMPASS-CABG sub-study the combination of aspirin and rivaroxaban 2.5 mg b.i.d. did not affect graft patency compared with aspirin alone, but the treatment effect on reducing CV death/MI/stroke was consistent with the benefits shown in COMPASS overall.[121]

Consensus statements endorsed by this document regarding antithrombotic therapy in CCS patients treated with CABG (no prior MI) are provided in *Table 8*.

Chronic coronary syndrome managed by medical therapy alone without prior myocardial infarction

Evidence-based treatment options are shown in *Figure 6* and summary of evidence in the Supplemental material.

Single antithrombotic therapy

The SAPAT trial supports the use of low-dose aspirin in symptomatic patients with stable angina who do not have a history of prior MI.[55] It is uncertain whether aspirin provides net benefit in lower risk CCS

Table 8 Clinical consensus statements for CCS managed by CABG (no baseline indications for OAC)

Single antithrombotic therapy
Clopidogrel provides net benefit compared with aspirin.
The evidence for ticagrelor monotherapy is inconclusive.
Dual antithrombotic therapy
The benefits for DAPT after CABG have not been demonstrated.
The effect of aspirin and ticagrelor compared with aspirin monotherapy for preserving bypass patency remains unclear.
The combination of rivaroxaban 2.5 mg b.i.d. and aspirin, compared with aspirin monotherapy, is associated with lower ischaemic and higher bleeding risks and is therefore a reasonable treatment in patients in whom concerns over ischaemic events prevail over bleeding.
The combination of rivaroxaban 2.5 mg b.i.d. and aspirin compared with aspirin monotherapy has not been shown to preserve graft patency.

b.i.d., bis in die; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; MI, myocardial infarction; OAC, oral anticoagulation.

Table 9 Clinical consensus statements for CCS managed by medical therapy alone (no baseline indications for OAC)

Single antithrombotic therapy
Clopidogrel or alternatively aspirin monotherapy is warranted in symptomatic patients although the net benefit is uncertain in asymptomatic patients.
Rivaroxaban 5 mg b.i.d. monotherapy does not seem to provide benefit and confers a higher bleeding risk compared with aspirin monotherapy.
Dual antithrombotic therapy
The current evidence does not support the use of DAPT.
Long-term dual antithrombotic therapy (rivaroxaban 2.5 mg b.i.d. plus aspirin) provides net benefit in patients at high ischaemic risk[a] and low bleeding risk (e.g. no ARC-HBR criterion or PRECISE-DAPT < 25[83]).

ARC-HBR, Academic Research Consortium-high bleeding risk; b.i.d., bis in die; CCS, chronic coronary syndrome; DAPT, dual antiplatelet therapy; MI, myocardial infarction; OAC, oral anticoagulation.

[a] High ischaemic risk is defined as diffuse multivessel CAD with at least one of the following: diabetes mellitus requiring medication, recurrent MI, peripheral arteria disease, or chronic kidney disease with estimated glomerular filtration rate 15–59 mL/min/1.73 m^2.

Table 10 Clinical consensus statements for genotype-/phenotype-guided dual antiplatelet therapy

Genotype-based guidance
The current evidence does not support the routine selection of $P2Y_{12}$ receptor inhibitor treatment based on rapid genotype testing (e.g. de-escalation from prasugrel or ticagrelor to clopidogrel in non-carriers of loss-of-function alleles).
Phenotype-based guidance
The current evidence does not support the routine use of platelet function testing to guide antiplatelet therapy.

patients, such as those with incidental detection of non-obstructive CAD on imaging. Although the evidence is inconclusive, it is reasonable to use clopidogrel in CCS patients who are intolerant of aspirin on the basis of the CAPRIE trial[46] and experience in patients with prior MI. Based on the same trial, the coexistence of PAD in these patients would then prioritize clopidogrel over aspirin if single antiplatelet therapy is considered rather than dual antithrombotic therapy. Rivaroxaban 5 mg b.i.d did not reduce the composite of CV death, MI, and stroke compared with aspirin monotherapy and was associated with greater bleeding risk (HR 1.51, 95% CI 1.25–1.84).[17]

Dual antithrombotic therapy

A DAPT regimen consisting of aspirin and clopidogrel has not proved more beneficial than aspirin alone in this population, whereas results appeared more favourable with DAPT among patients with prior MI (CHARISMA[16]). In the THEMIS trial, among the 20% of medically managed patients, there was no evidence of benefit or net benefit with aspirin and ticagrelor compared with aspirin alone.[63] Rivaroxaban 2.5 mg plus aspirin significantly reduced the risk of CV death, MI, or stroke (HR 0.76, 95% CI 0.66–0.86), principally driven by reduced stroke,[17] and a significant net benefit was shown (HR 0.80, 95% CI 0.70–0.91).[17] Total mortality was reduced at a nominal *P*-value of 0.05, even if it did not reach predefined statistical significance. Findings were independent of the presence of prior MI.

Consensus statements endorsed by this document regarding antithrombotic therapy in CCS patients treated with medical therapy alone (no prior MI) are provided in *Table 9*.

Genotype- and phenotype-guided DAPT

In the POPULAR GENETICS trial,[122] including patients undergoing primary PCI, a *CYP2C19* genotype-guided strategy for selection of the $P2Y_{12}$ inhibitor was non-inferior to standard treatment with ticagrelor or prasugrel at 12 months with respect to a composite of thrombotic and bleeding events (*P*-value for non-inferiority < 0.001) and reduced the incidence of mostly minor bleeding (HR 0.78, 95% CI 0.61–0.98). However, a prior genetic sub-study of PLATO suggested superiority of ticagrelor over clopidogrel irrespective of the presence or absence of *CYP2C19* loss-of-function alleles.[123] Conversely, among *CYP2C19* loss-of-function allele carriers with ACS or CCS undergoing PCI, genotype-guided selection of DAPT did not reduce the incidence of combined thrombotic events compared with conventional clopidogrel therapy without point-of-care genotyping in patients with ACS and those with CCS.[61]

Despite initial promising data from observational[124] and small randomized studies,[125–128] no adequately powered randomized clinical trial demonstrated that the routine use of platelet function testing for guiding $P2Y_{12}$ inhibitor treatment improves clinical outcomes in patients with ACS or CCS undergoing PCI.[30,35,69,129] In the TROPICAL-ACS study, a guided de-escalation of antiplatelet treatment using platelet function testing was non-inferior to standard treatment with prasugrel at 1 year after PCI in terms of net clinical benefit.[69] Although the results of meta-analysis show favourable safety and efficacy outcomes associated with a guided selection of antiplatelet therapy by means of platelet function or genetic testing,[130] it remains unclear if these findings are reproducible outside the research setting, considering that routine use of platelet function testing for tailoring DAPT is not implemented in clinical practice.[131]

Consensus statements endorsed by this document regarding genotype- and phenotype-guided DAPT are provided in *Table 10*.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Disclaimer

In view of the short time interval between publication of the final version of this manuscript and the expected publication of the [2023 ACS Guidelines], which will largely overlap with the topics in this manuscript, EAPCI, ACVC and EAPC have decided that the manuscript will be published without the document subtitle of the unedited manuscript.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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