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Updated antithrombotic strategies to reduce the burden of cardiovascular recurrences in patients with chronic coronary syndrome

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ABSTRACT

Despite recent achievements in secondary cardiovascular prevention, the risk of further events in patients with chronic coronary syndromes (CCS) remains elevated. Highest risk is seen in patients with recurrent events, comorbidities or multisite atherosclerosis. Optimising antithrombotic strategies in this setting may significantly improve outcomes. The higher the baseline risk, the higher the absolute event reduction with approaches using combined antithrombotic treatments. Tailoring such strategies to the individual patient risk appears crucial to achieve net benefit (i.e., substantial ischaemic event prevention at a limited cost in terms of bleeding). This paper focuses on antithrombotic and non-pharmacological approaches to secondary cardiovascular disease prevention in CCS. In particular, we critically review current evidence on the use of dual antithrombotic therapy, including the newest approach of aspirin plus low-dose anticoagulation and its net clinical outcome according to baseline risk.

1. Evolution of antithrombotic treatments for chronic coronary syndromes

Longterm antithrombotic therapy for chronic coronary syndromes (CCS) has evolved in the past 50 years. It started in the 1970s showing anti-ischaemic and survival benefits of oral anticoagulation with vitamin K antagonists over placebo [1]. It then evolved, in the 1980s and 1990s, showing anti-ischaemic benefits of single antiplatelet therapy (SAPT) - mainly aspirin – over placebo [2,3] and subsequently a roughly similar efficacy and safety profile of aspirin against another antiplatelet agent, the P_2Y_{12} inhibitor clopidogrel [4]. Longterm low-dose anticoagulation against aspirin was tested only in a primary prevention setting, showing overall similar anti-ischaemic effects against placebo and similar safety of one against the other [5]. Early studies of patients undergoing coronary angioplasty (receiving stents in only a minority of patients) reported superior ischaemic prevention with warfarin plus aspirin compared to aspirin alone, with acceptable enhanced bleeding risk, up to one year after the procedure [6]. Subsequent short-term trials in patients undergoing coronary stenting demonstrated unequivocal anti-ischaemic superiority and comparable safety of dual antiplatelet therapy (DAPT) versus warfarin plus aspirin up to 30 days [7,8]. More recent longterm strategies for patients undergoing percutaneous coronary intervention (PCI) have been twofold: on the one hand, the comparison of prolonged DAPT against aspirin alone [9–12] with superior ischaemic prevention afforded by DAPT counterbalanced, however, by an enhanced bleeding risk; on the other hand, the comparison of shortened DAPT durations followed by monotherapy with either aspirin or P_2Y_{12} inhibitor against standard treatment, resulting in improved safety [13–16]. A recent unique antithrombotic approach for CCS patients with or without prior PCI has compared low dose anticoagulation

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with a non-vitamin K antagonist oral anticoagulant plus aspirin (dual pathway inhibition) to aspirin alone, showing net clinical benefit with the combined antithrombotic strategy [17]. To date, longterm head-to-head comparisons of dual pathway inhibition vs. DAPT or of dual pathway inhibition vs. P_2Y_{12} inhibitor monotherapy are lacking. The main characteristics and findings of the fourteen major randomised trials that have tested the above longterm antithrombotic strategies in stable patients with CCS, or in mixed populations comprising both acute and chronic coronary syndrome patients, are reported in Table 1.

From a bird's eye view of such studies - conducted over five decades - it emerges that: a) a single antithrombotic agent (anticoagulant or antiplatelet) vs. none leads to clear reductions in the rates of myocardial infarction (MI) and death, with acceptable bleeding risks [1–3]; b) clopidogrel shows slightly superior efficacy over aspirin, but the aspirin dose of 325 mg daily tested in CAPRIE is not that currently used in Europe [4]; c) on top of SAPT, the risk of cardiovascular events during follow-up remains elevated, i.e., up to 20% at 3 years following an acute coronary syndrome (ACS) in observational, real-world investigations [18,19]; d) DAPT vs. SAPT decreases ischaemic events, but such benefit is counterbalanced by an increase in major bleeding events, including intracranial haemorrhages, in THEMIS [12] and a signal of increased all-cause mortality in the DAPT trial [10]. The latter highlight the importance of careful patient selection when prescribing DAPT to CCS patients, in addition to considering shorter DAPT durations to reduce bleeding events [13–16] or selecting alternative antithrombotic approaches such as dual pathway inhibition, in order to achieve an optimal benefit-to-risk balance (i.e., net benefit) [17].

2. ESC guidelines on chronic coronary syndromes: evidence supporting the recommendations

The 2019 European Society of Cardiology (ESC) guidelines on CCS recommend the addition of a second antithrombotic agent to aspirin for long-term secondary prevention in patients judged to be at high (class of recommendation IIa, level of evidence A) or moderate (IIb A) risk of ischaemic events and without high bleeding risk criteria [20]. High-ischaemic risk patients are defined as those with multivessel coronary artery disease (CAD) and at least one additional risk factor, such as diabetes mellitus, recurrent MI, peripheral artery disease (PAD) or renal failure, whereas moderate-risk patients as those with at least one of multivessel/diffuse CAD or diabetes mellitus, recurrent MI, PAD, chronic renal failure or heart failure. The 2019 recommendations represent a major change from the previous ESC guidelines on stable CAD released in 2013 [21] where, beyond recommending aspirin (or clopidogrel in the case of aspirin intolerance), it was stated that, in light of the CHARISMA and TRA-2P studies [11,22], there was insufficient evidence to systematically recommend combined antithrombotic therapy in this setting. Between the two guidelines, the pivotal randomised trials DAPT and PEGASUS [9,10] and subsequently COMPASS [17] were published. A post-hoc analysis of the DAPT trial showed greatest advantage of DAPT prolongation beyond one year from PCI (with clopidogrel or prasugrel added to aspirin) in patients with previous MI [23,24]. In PEGASUS, conducted in patients with prior MI, the benefit of ticagrelor 60 mg BID vs. placebo on top of aspirin treatment was mainly driven by a reduction in recurrent MI [9,25–28]. In a non-pre-specified post-hoc analysis, the greatest benefit in terms of major adverse cardiovascular events (MACE) prevention with aspirin plus ticagrelor was observed in the subgroup with $\leq$2 years from qualifying MI or $\leq$1 year from prior adenosine diphosphate receptor inhibitor treatment, where a significant 20% relative reduction of all-cause mortality has been reported [29]. This hypothesis-generating survival benefit was not evaluated or confirmed in subsequent prospective, randomised investigations. Based on DAPT trial and PEGASUS findings, current ESC guidelines recommend DAPT extension with clopidogrel or prasugrel or ticagrelor in post-MI patients who have tolerated one-year initial DAPT treatment [20]. However, in the DAPT trial, a significant interaction according to type of thienopyridine (i.e., lower protection from cardiovascular events with clopidogrel compared to prasugrel), stent type (i.e., lower protection with latest generation drug-eluting stents) and diabetes status (i.e., lower protection in diabetic patients) was present for the primary ischaemic endpoint, as well as a higher total mortality in patients receiving DAPT prolongation ($p = 0.050$) [10,23,24].

Multivessel CAD or PAD were the main inclusion criteria in the COMPASS trial [17,30]. Notably, CAD population was represented by patients with MI within 20 years, multivessel CAD, multivessel PCI or coronary bypass surgery. In the CAD cohort, the prevalence of PAD was 20%. The trial showed a favourable risk-to-benefit ratio with rivaroxaban at vascular dose (2.5 mg BID) plus aspirin vs. aspirin alone, leading to early trial termination for efficacy [17,30]. In COMPASS rivaroxaban reduced total, cardiovascular and coronary mortality [17,30,31] ESC guidelines state that the pre-specified thresholds for cardiovascular mortality and all-cause mortality were not met in COMPASS [20]. However, the COMPASS trial was stopped early, i.e., after a mean follow-up of 23 months, one year ahead of expectations; the interruption was due to overwhelming efficacy of the rivaroxaban/aspirin combination and, in light of the continuous divergence of the curves over time for ischaemic events, an underestimation of the real mortality benefit of dual pathway inhibition due to the premature trial interruption may be considered. Furthermore, as mentioned in the main COMPASS publication [17], 'an early stop of both antithrombotic treatment groups for efficacy had not been anticipated, and therefore a strategy for formal testing of secondary outcomes at the interim analysis was not pre-specified. Current ESC guidelines do not prioritise antithrombotic agents to be added to aspirin, placing them all in the same class of recommendation [20]. However, rivaroxaban at vascular dose plus aspirin may represent the only strategy for CAD patients without prior MI. Moreover, the high-ischaemic risk definition adopted by the ESC recommendations most closely reflect COMPASS enrolment criteria. Finally, the mortality reduction observed in COMPASS merits consideration by clinicians when choosing an antithrombotic drug to be added to aspirin in eligible CCS patients (Fig. 1), particularly if multisite atherosclerotic disease is present.

However, the term CCS includes a wide range of patients, i.e. from stable patients with remote history of CAD to those finishing standard DAPT at 12 months after ACS. This creates difficulties in evaluating the net benefit of different antithrombotic approaches, as in different scenarios their risk/benefit ratio can be different and current tools for stratifying ischaemic and bleeding risk cannot similarly perform. Finally, at 1 year after MI it may be different to continue DAPT in a patient already taking these drugs for several months with no side effects or to suggest a stable asymptomatic patient to start a new antithrombotic agent with potential side effects.

3. Tailoring antithrombotic strategies for chronic coronary syndromes to baseline risk

3.1. Cardiovascular protection of combined antithrombotic regimens according to ischaemic risk

Quantifying individual cardiovascular risk is difficult and is generally defined by the totality of factors associated with a higher incidence of recurrent cardiovascular events. A number of cardiovascular risk factors have been identified and effective treatments developed; however, there is a relevant inter-individual heterogeneity in response to risk factors and treatments, affecting both the efficacy and safety of therapeutic interventions.

After an acute cardiovascular event, certain patient subsets are at higher risk of recurrence. Available secondary coronary prevention trials indicate that the extent of atherosclerotic lesions (multivessel CAD or CAD plus concomitant PAD) with at least one additional risk factor (such as diabetes mellitus requiring medications, recurrent MI or chronic renal failure with eGFR 15–59 mL/min/1.73 m^2) are associated with higher

Table 1
Major randomised trials testing longterm antithrombotic treatments in chronic or mixed (acute and chronic) coronary syndrome patients.

Name	J & Yr	Blinding	Population type	No.	Randomisation arms	Follow-up	Main PEP & SEP results for A vs. B	Main safety results for A vs. B
Single anticoagulant or antiplatelet agent vs. none								
60 +	Lancet 1980	Double blind	age >60 yrs, on oral anticoagulant therapy at a mean of 6 yrs from MI	878	A: continued oral anticoagulant (acenocoumarin and phenprocoumon) B: placebo	2 yrs	Fewer recurrent MIs (p = 0.0001) and deaths (p = 0.017). Intracranial events, p = 0.18	Major extracranial bleeds: 27 in A vs. 3 in B (none fatal)
SAPAT	Lancet 1992	Double blind	Stable angina pectoris, no previous MI	2035	A: aspirin 75 mg od + sotalol B: placebo + sotalol	median 50 mo.	PEP of MI and sudden death: RRR 34%, 95% CI 24–49%, p = 0.003 SEP of vascular events, vascular death, any death, stroke: 22–32% reduction	Major bleeds including haemorrhagic stroke: 20 in A vs. 13 in B (NS)
ATT	Lancet 2009		Either CV risk factors or previous MI, stroke or transient cerebral ischaemia	112,000 (6860 previous vascular events)	A: aspirin B: placebo		Any serious vascular event 1. Primary prevention rate ratio 0.88, 95% CI 0.82–0.94, p = 0.0001 2. Secondary prevention rate ratio 0.81, 95% CI 0.75–0.87, p < 0.0001	More haemorrhagic strokes in all trials combined (p < 0.01) and major extracranial bleeds (p < 0.0001 in primary, p = 0.01 in secondary prevention trials)
One antiplatelet agent versus another								
CAPRIE	Lancet 1996	Double blind	Atherosclerotic vascular disease manifested as: i) recent ischaemic stroke ii) recent MI or iii) iii) symptomatic PAD	19,185 (>6300 in each group)	A: clopidogrel 75 mg od B: aspirin 325 mg od	mean 1.9 yrs	Composite of ischaemic stroke, MI, or vascular death RRR of 8.7%, 95% Cl 0.3–16.5, p = 0.043	Rash (578 vs 442), diarrhoea (428 vs 332), upper GI discomfort (1441 vs 1686), intracranial bleeds (34 vs 47), GI bleeds (191 vs 255), neutropenia (10 vs 16)
Single versus dual antiplatelet therapy								
CHARISMA	N Engl J Med 2006	Double blind	Chronic CV disease or multiple risk factors	15,603	A: daily clopidogrel 75 mg + aspirin 75–162 mg B: daily placebo + aspirin 75–162 mg	median 28 mo.	PEP of CV death, MI, or stroke: relative risk 0.93, 95% CI 0.83–1.05, p = 0.22 SEP of CV death, MI, stroke, hospitalised unstable angina, transient ischaemic attack or revascularisation: 16.7% vs 17.9%, relative risk 0.92, p = 0.04	Severe bleeding: 1.71% vs 1.3, p = 0.09
DAPT	N Engl J Med 2014	Double blind	Drug-eluting stent--------- placement; randomisation 12 months after PCI (58%—CCS as PCI-indication)	9961	A: daily aspirin 75–162 mg + clopidogrel 75 mg or prasugrel 10 mg B: daily aspirin 75–162 mg + placebo	30 mo. post PCI (18 mo. post randomisation)	PEP of stent thrombosis: 0.4% vs 1.4%, HR 0.29, 95% CI 0.17–0.48, p < 0.001 PEP of major adverse CV and cerebrovascular events: 4.3% vs 5.9%, HR 0.71, 95% CI 0.59–0.85, p < 0.001 SEP of death: 2.0% vs 1.5%, HR 1.36, 95% CI 1.00–1.85, p = 0.05	Moderate or severe bleeds: 2.5% vs. 1.6%, p = 0.001
PEGASUS	N Engl J Med 2015	Double blind	MI in the previous 1–3 years	21,162	A: ticagrelor 90 mg bid + aspirin A': ticagrelor 60 mg bid + aspirin B: placebo + aspirin	33 mo. median	PEP of composite of CV death, MI, stroke: HR A vs. B: 0.85, 95% CI 0.75–0.96, p = 0.008; HR A' vs. B: 0.84, 95% CI 0.74–0.95, p = 0.004 SEP of death: A vs. B HR 1.00, 95% CI 0.86–1.16, p = 0.99; A' vs. B HR 0.89, 95%CI 0.76–1.04, p = 0.14	TIMI major bleeds: 2.60% in A vs. 2.30% in A' vs. 1.06% in B (p < 0.001 for A or A' vs. B)

(*continued on next page*)

Table 1 (*continued*)

Name	J & Yr	Blinding	Population type	No.	Randomisation arms	Follow-up	Main PEP & SEP results for A vs. B	Main safety results for A vs. B
THEMIS	Lancet 2019	Double blind	Stable coronary artery disease, ≥ 50 yrs, type 2 diabetes, previous PCI or CABG or angiographic stenosis ≥ 50%, no prior MI or stroke	19,220	A: ticagrelor 90 mg (reduced to 60 mg mid-way) bid + aspirin 75–150 mg od B: placebo + aspirin 75–150 mg	3.3 yrs median	PEP of CV death, MI, or stroke: 7.7% vs. 8.5, HR 0.90, 95% CI 0.81–0.99, p = 0.04	TIMI major bleeds: 2.2% vs. 1.0%, HR 2.32, 95% CI 1.82–2.94, p < 0.001 Intracranial bleeds: 0.7% vs. 0.5%, p = 0.005
Shorter versus longer DAPT after PCI								
GLOBAL-LEADERS	Lancet 2018	Open-label	PCI; 53% wit CCS	15,968	A: 1 mo. DAPT→23 mo. ticagrelor B: 12 mo. DAPT→12 mo. aspirin	24 mo.	PEP of death or nonfatal Q-wave MI: 3.8% vs. 4.4%, p = 0.073	BARC bleeds 3 or 5: 2.0% vs. 2.1%, p = 0.77
STOPDAPT-2	JAMA 2019	Open-label	PCI; 62% with CCS	3045	A: 1 mo. DAPT→11 mo. clopidogrel B: 12 mo. DAPT	12 mo.	SEP of CV death, MI, any stroke or definite stent thrombosis: 1.96% vs. 2.51%, p = 0.34	Any TIMI bleed: 0.41% vs. 1.54%, p = 0.004
SMART-CHOICE	JAMA 2019	Open-label	PCI; 42% with CCS	2993	A: 3 mo. DAPT→9 mo. P2Y12inhibitor B: 12 mo. DAPT	12 mo.	PEP of death, MI, stroke: 2.9% vs.2.5%, non-inferiority p = 0.007	BARC bleeds 2–5: 2.0% vs. 3.4%, p = 0.02
TWILIGHT	NEJM 2019	Double blind	Randomisation 3 mo. after PCI and uneventful DAPT; 36% with CCS	7119	A: 12 mo. ticagrelor B: 12 mo. DAPT	15 mo. (12 mo. post-randomisation)	PEP of death, MI, stroke: 3.9% vs. 3.9%, non-inferiority p < 0.001	BARC bleeds 3 or 5: 1.0% vs. 2.0%, p < 0.001
Dual pathway inhibition versus single antiplatelet agent								
BAAS	Circulation 2000	Open-label	Randomisation >1 week before PCI (stenting in 35%); 88% with CCS	1058	A: 12 mo. coumarin + aspirin B: 12 mo. aspirin	12 mo.	Composite of death, MI, target-lesion revascularisation and stroke in A vs. B: 14.3% vs. 20.3% (relative risk 0.71, 95% CI 0.54–0.93)	Major bleeding or false aneurysms in A vs. B: 22 vs. 5
COMPASS	N Engl J Med 2017	Double blind	Stable atherosclerotic vascular disease	27,395	A: rivaroxaban 2.5 mg bid + aspirin 100 mg od	23 mo.	PEP of CV death, MI, or stroke: 4.1% vs. 4.9% vs. 5.4% in A vs. A' vs. B; p < 0.001 for A vs. B; p = 0.12 for A' vs. B	Major bleeds A or A' vs. B: p < 0.001
					A': rivaroxaban 5 mg bid	mean	SEP of death A vs. B: 3.4% vs. 4.1%, p = 0.01 (threshold p = 0.0025)	Fatal bleeds A or A' vs. B: NS
					B: aspirin 100 mg od		SEP stroke A vs. B: 0.9% vs. 1.6%, p < 0.001	Intracranial bleeds A vs. B: 0.3% vs. 0.3%, p = 0.60

Abbreviations: BARC = Bleeding Academic Research Consortium; bid = bis in die; CABG = Coronary artery bypass grafting; CCS = Chronic coronary syndrome; CI = Confidence interval; CV = Cardiovascular; DAPT = Dual antiplatelet therapy; GI = Gastro-intestinal; HR = Hazard ratio; MI = Myocardial infarction; mo. = month; No. = Number; NS = Non significant; od = once daily; PAD = Peripheral artery disease; PCI = Percutaneous coronary intervention; PEP = Primary endpoint; RRR = Relative risk reduction; SEP = Secondary endpoint; TIMI = Thrombolysis in Myocardial Infarction; vs. = versus; yrs = years.

recurrence risk [25–30,32,33] "More aggressive" antithrombotic strategies with prolonged DAPT or dual pathway inhibition have yielded enhanced efficacy in patients at higher baseline thrombotic risk [25–30,32–34]. Therefore, identifying populations where specific antithrombotic approaches are associated with increased absolute reduction of ischaemic complications, with limited or acceptable bleeding risk, is crucial to achieve greatest net benefit by implementing appropriate strategies.

In the PEGASUS trial, a greater reduction of MACE with aspirin plus ticagrelor vs. aspirin alone was observed in MI patients with concomitant PAD, who represented approximately 5% of the total population (4.1% absolute reduction of the primary ischaemic endpoint vs. 1.3% in the overall trial population), and in the subset with chronic renal failure (2.7% absolute reduction) [25,26]. Notably, adding ticagrelor to aspirin, the absolute reduction of MACE in patients with multivessel CAD or diabetes was slightly enhanced vs. the overall trial population (1.5% in both groups) [27,28]. In COMPASS, baseline renal function and diabetes were predictors of subsequent MACE. The combination of rivaroxaban plus aspirin vs. aspirin alone produced a consistent relative benefit for ischaemic events across the spectrum of baseline renal function and regardless of diabetes status [32]. The extent of atherosclerosis – both in the coronary and peripheral vessels – mirrors the burden of atherosclerotic disease: the greater the number of affected vessels, the higher the risk of plaque rupture causing a subsequent acute event, particularly with concomitant diabetes and reduced renal function. Both these conditions are associated with endothelial dysfunction, oxidative stress and a proinflammatory status [35,36], which further confer a prothrombotic diathesis and may trigger acute events, especially in the presence of disseminated atherosclerotic lesions. Notably, patients with PAD are at higher risk of cardiovascular events, including MI. Observational studies indicated that the risk of MI and cardiovascular death in patients with PAD is not dissimilar to that of patients with documented CAD [37]. Patients with PAD are also prone to major adverse limb events (MALE), in particular acute limb ischaemia and need for amputation [38]. It has

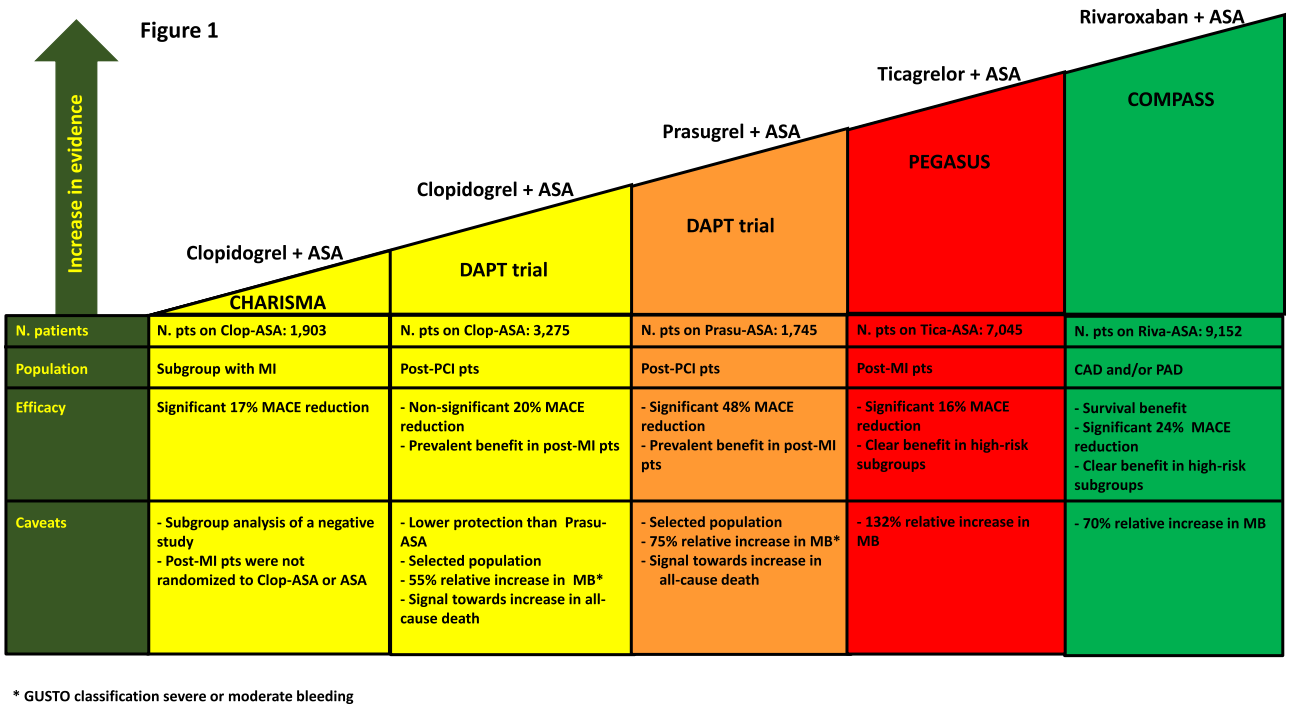

Fig. 1. Body of evidence from randomised studies of dual antithrombotic therapies vs. aspirin alone in CCS. ASA = Aspirin; MACE = Major adverse cardiovascular events; MB = Major bleeding; MI = Myocardial infarction; CAD = Coronary artery disease; CCS = Chronic coronary syndromes; PAD = Peripheral artery disease; PCI = Percutaneous coronary intervention; Pts = Patients.

been calculated that the annual incidence of major amputations in Western countries ranges between 120 and 500 per million, that in Western Europe the PAD-related mortality in 2010 reached 3.5 per 100,000 individuals (excluding stroke and MI), and that the years of life lost due to PAD is 31.7 years per 100,000 inhabitants [39–41]. Therefore, in patients with PAD, it is mandatory to reduce both MACE and MALE. A progressive, linear increase in MACE rates has been observed with the number of atherosclerotic vascular beds involved [37]. In COMPASS, the absolute reduction of MACE by rivaroxaban plus aspirin vs. aspirin alone was greatest in patients with concomitant CAD and PAD (2.7% reduction). In patients with polyvascular disease, dual pathway inhibition resulted in a 6.0% absolute risk reduction for the composite of MACE, acute limb ischaemia and total amputation and a 5.9% absolute risk reduction for the net clinical benefit outcome (i.e., the composite of cardiovascular death, stroke, MI, acute limb ischaemia, vascular amputation, fatal bleeding or symptomatic bleeding into a critical organ) [32,33]. Fig. 2 summarises different patient characteristics/risk-groups who might benefit from prolonged DAPT and those who might mostly benefit from the combination rivaroxaban at vascular dose plus aspirin.

Of note, conditions associated with a higher thrombotic risk may also predispose to bleeding complications (e.g., older age, diabetes or chronic renal failure). To assess the effects of antithrombotic approaches it appears crucial to balance expected protection from thrombotic events against the concomitant bleeding risk and to integrate this evaluation of overall "net clinical benefit" into daily clinical practice, by combining clinically-relevant efficacy and safety outcomes (i.e., MI, stroke, cardiovascular death, life-threatening and fatal bleeding) [42]. Assuming that "net clinical benefit" derives from the balance between efficacy (i.e., the entity of thrombotic risk reduction, with higher baseline risk corresponding to greater expected efficacy) and safety (i.e., the entity of bleeding risk caused, with lower baseline risk corresponding to higher expected safety), for secondary prevention antithrombotic approaches it is crucial to identify subgroups at higher thrombotic risk and/or at lower bleeding risk (Fig. 3).

3.2. Risk score stratification

Risk scores include multivariate models developed to estimate the individual probability of unwanted outcomes in clinical practice. A number of risk scores have been developed in the context of ACS for stratifying both the ischaemic (TIMI and GRACE) and the bleeding (CRUSADE and ACUITY) risk [43–47], but will not be discussed further. Notably, after an acute coronary event, major bleeding has a similar prognostic impact as spontaneous thrombotic events [48]. Beyond one year after ACS, randomised trials indicated that DAPT prolongation does not fit all patients; rather, those at high ischaemic risk without high bleeding risk are likely to benefit from a prolonged and intensified antithrombotic regimen. To facilitate risk stratification and maximise the net clinical benefit of antithrombotic therapies, individual scores for stabilised post-ACS patients have been elaborated. Some focus specifically on bleeding, others on ischaemic/thrombotic risk or on both ischaemic and bleeding outcomes.

In 2017, a focused ESC guideline suggested the use of ischaemic and bleeding risk scores for tailoring DAPT duration after ACS (recommendation IIb A) [49,50]. Main risk scores for patients with CCS are indicated in Table 2. An ischaemic risk score for patients with stable coronary disease and previous MI (TIMI Risk Score for Secondary Prevention - TRS2°P) was developed from a subgroup analysis of 8598 patients enroled in the TRA2°P-TIMI 50 trial. It includes nine clinical indicators and provided adequate discrimination for the composite endpoint of recurrent MI, ischaemic stroke and cardiovascular death. In particular, a high risk setting (i.e. ≥3 points) achieving the greatest benefit from adding vorapaxar to aspirin was selected. [22,51] The TRS2°P score has been recently validated in a multicentric observational study of 9618 patients, where its role as a stratification tool for ischaemic risk was confirmed, with c-statistic of 0.66 (vs 0.67 in the trial cohort) [52].

The DAPT score, derived from the DAPT trial, identified subgroups of patients in whom a DAPT prolongation beyond 12 months from ACS may be predominantly beneficial [53]. It was developed in 11,648 patients and validated in 8136 patients enroled in the PROTECT trial.

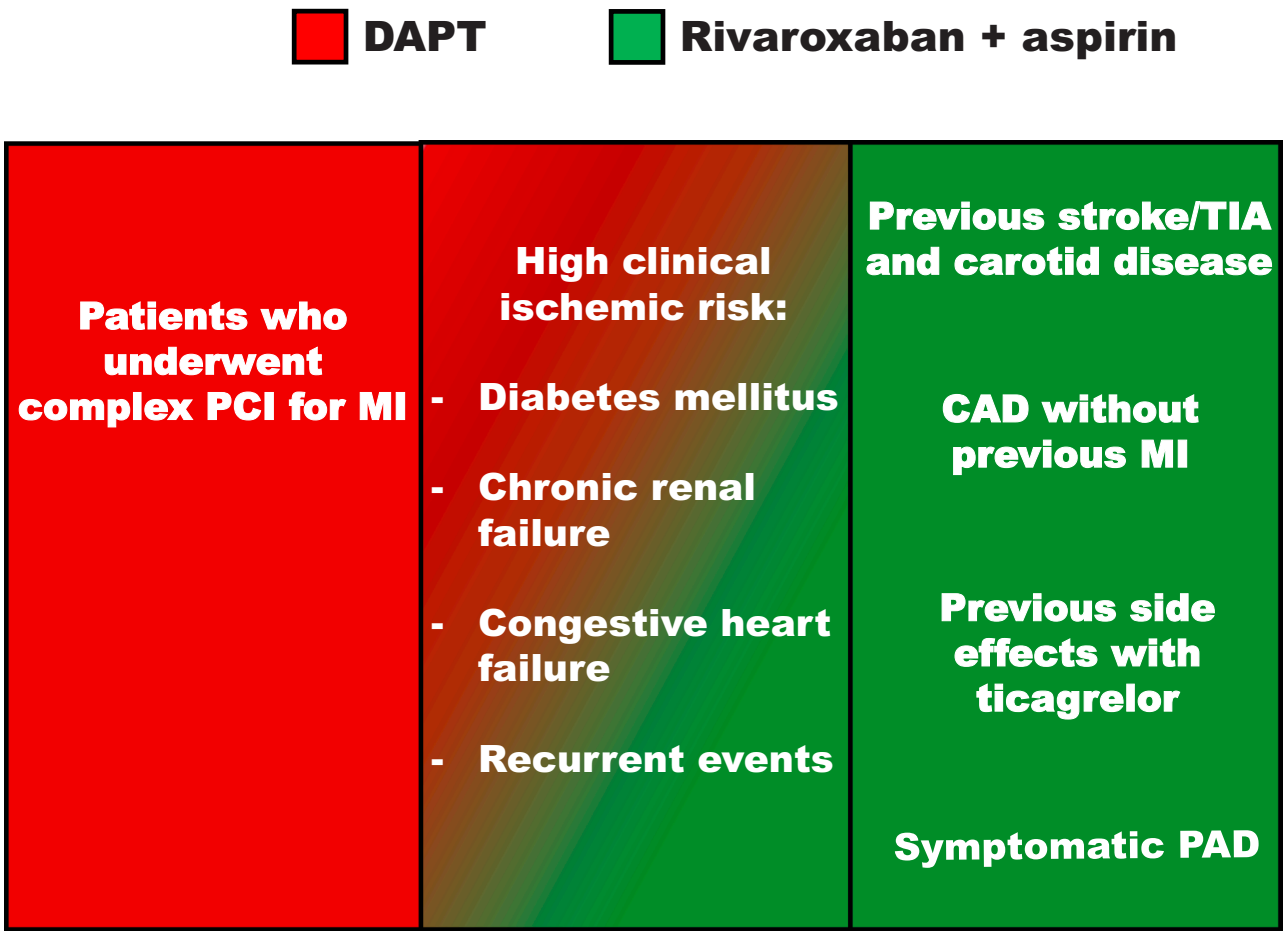

Fig. 2. Different patient characteristics/risk-groups who, in the absence of high bleeding risk, in the setting of CCS might benefit from prolonged DAPT and those who might mostly benefit from the combination rivaroxaban at vascular dose plus aspirin. * At least one of the following 3-vessel PCI, ≥3 stents implanted, ≥3 lesions treated, bifurcation, stent length >60 mm, chronic total occlusion CCS = Chronic coronary syndrome; DAPT = Dual antiplatelet therapy; MI = Myocardial infarction; PAD = Peripheral artery disease; PCI = Percutaneous coronary intervention; TIA = Transient ischaemic attack.

C-statistic for both ischaemic and bleeding events was moderate (0.70 and 0.68, respectively). This score includes nine variables and a value ≥ 2 indicates a significant benefit from DAPT prolongation (number needed to treat -NNT- to prevent an ischaemic event 34), with only a mild increase in bleeding risk (number needed to harm -NNH- to cause bleeding 272) [53].

The 2019 ESC Guidelines for the diagnosis and management of CCS underlined the importance of the bleeding risk assessment when adding a second antithrombotic drug to aspirin [20]; bleeding risk was defined high by at least one of: previous intracerebral haemorrhage or ischaemic stroke or other intracranial pathology; recent gastrointestinal bleeding or anaemia from possible gastrointestinal blood loss or other bleeding-prone gastrointestinal pathology; liver failure or bleeding diathesis or coagulopathy; extreme old age or frailty; chronic renal failure requiring dialysis or eGFR <15 mL/min/1.73 m^2. Of note, bleeding risk may be dynamic: predisposing factors may vary, have different weights in different patients, be modifiable, and differ according to type of antithrombotic drug and bleeding site. Thus, bleeding risk assessment is not a simple challenge.

The PRECISE-DAPT score focuses on bleeding risk and was developed to help clinicians identify those at higher bleeding risk who might benefit from shorter DAPT duration after coronary stenting (3–6 months vs. 12–24 months) [54]. It was validated mainly in patients treated with aspirin and clopidogrel, with modest predictive value on external validation in ACS patients undergoing PCI and receiving prasugrel or ticagrelor [55]. In a recent analysis of the PRECISE-DAPT datasets [56], the authors divided 14,963 subjects in high or non-high bleeding risk according to the PRECISE-DAPT score (≥25 or <25) and in high or non-high ischaemic/thrombotic risk according to PCI complexity (i.e. ≥3 stents implanted and/or ≥3 lesions treated, bifurcation stenting and/or stent length >60 mm, and/or chronic total occlusion revascularization). Notably, in patients at high bleeding risk, independently of ischaemic risk, DAPT was associated with increased bleeding complications without any significant reduction in mortality or MACE up to 2 years. Moreover, bleeding risk stratification was more relevant on prognosis than ischaemic/thrombotic risk stratification. Of note, here ischaemic/thrombotic risk was based on procedural features and did not include global patient evaluation (e.g., atherosclerosis burden or presence of diabetes). Recent data suggest that the CHA_2DS_2-VASc score (i.e., the clinically-oriented score validated to quantify thromboembolic risk in atrial fibrillation patients without anticoagulant therapy) may be able to stratify thrombotic risk even in an ACS population [57]. This demonstrates that a score evaluating global ischaemic risk may help identify patients at high risk of recurrence in whom intensified/prolonged antithrombotic therapy is beneficial. The identification of patients at high bleeding risk is crucial in specific subgroups, such as those needing combined antiplatelet and anticoagulant drugs, usually due to concomitant atrial fibrillation and PCI. To date, no risk score has been tested in this setting.

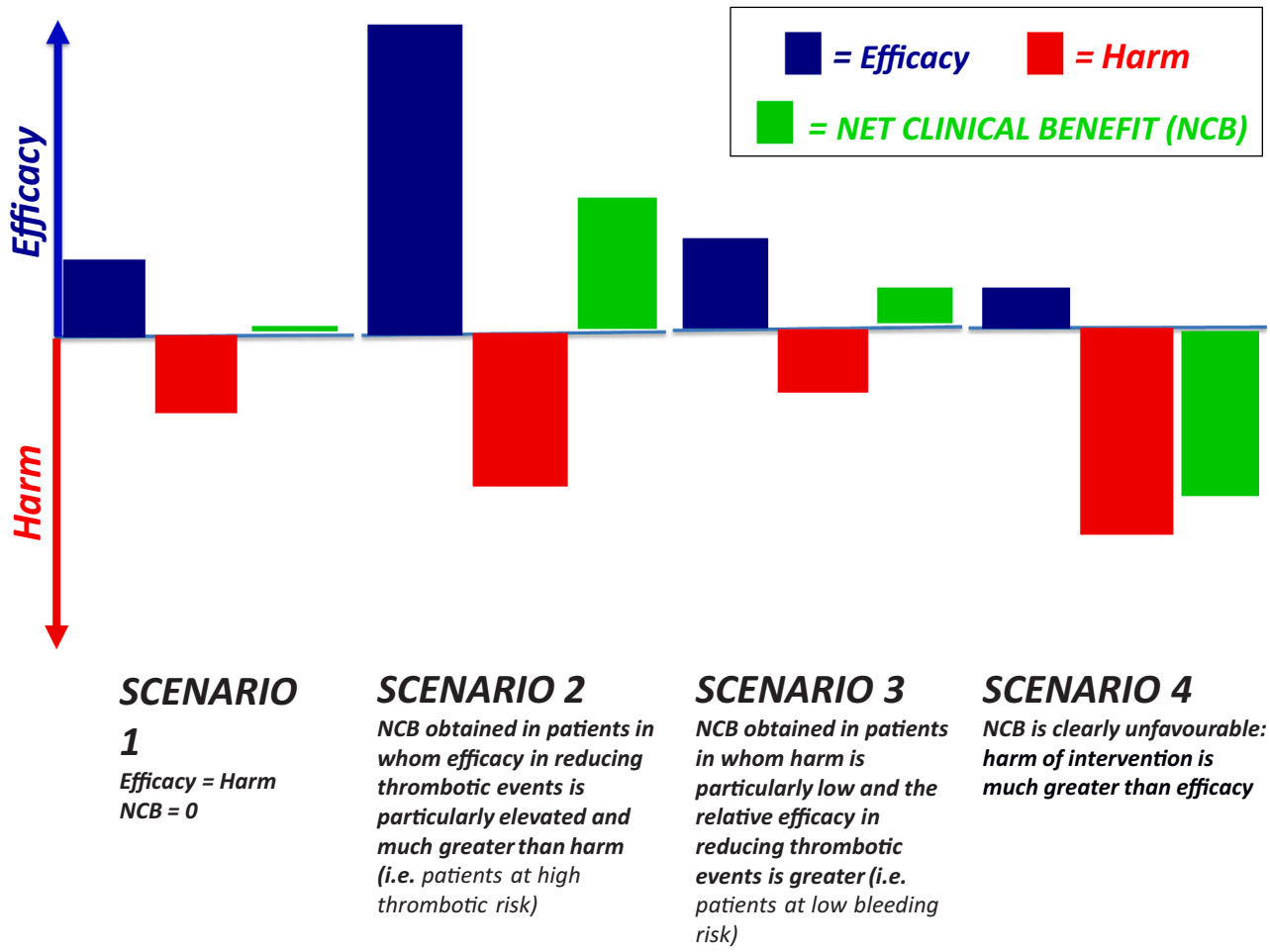

Fig. 3. Net clinical benefit (NCB). MODEL 1: efficacy of intervention (thrombotic events prevented) equals harm (bleeding events caused: NCB is null). MODEL 2: efficacy of intervention is much greater than harm: NCB is maximal. This model may be implemented in higher thrombotic risk subgroups: polyvascular disease; diabetes; recurrent events, impaired renal function. MODEL 3: intervention has moderately greater efficacy than harm: NCB is moderate. This model may be implemented in subgroups at lower bleeding risk, regardless of thrombotic risk. MODEL 4: harm of intervention is much greater than efficacy (NCB is clearly unfavourable).

4. How to balance antithrombotic ischaemic protection against bleeding risk for chronic coronary syndromes

4.1. Definition of bleeding across trials evaluating antithrombotic drugs in chronic coronary syndromes

A variety of bleeding definitions have been used in randomised trials on antithrombotic treatments in cardiology. The lack of standardisation hinders comparisons of safety endpoints and of safety-to-efficacy ratios across studies and across regimens, or even within a given trial, where the results may vary according to different bleeding definitions. Notably, in a recent analysis of patients with atrial fibrillation enroled in the ENGAGE AF-TIMI 48 trial, there was a >4-fold difference in the frequency of severe bleeding events using different bleeding scales [58].

Bleeding definitions across randomised trials on CCS have differed (Supplementary Table 1). Bleeding definitions include both laboratory parameters, such haemoglobin and haematocrit drops, and clinical events, i.e., bleeds in different sites, with varying haemodynamic consequences, need for transfusion or surgery. Each definition includes a different combination of elements ranking them into severity categories, which may vary across different definitions. Other potential limitations are related to heterogeneous populations and to the periods of original validation. For example, the TIMI major bleeding definition encompasses fatal bleeding, intracranial haemorrhage, haemoglobin drop ≥5 g/dL or haematocrit drop ≥15% [59]. Conversely, by the International Society on Thrombosis and Haemostasis (ISTH) scale, major bleeding encompasses fatal bleeding, symptomatic bleeding in a critical area/organ or bleeding causing a fall in haemoglobin ≥2 g/dL or leading to transfusion of ≥2 units of whole blood/red cells [60]. Thus, according to these different haemoglobin cut-offs, an ISTH major bleed may have lesser clinical relevance than a TIMI major bleed. This hinders the comparison across trials adopting different bleeding definitions, such as PEGASUS [5], where bleeding was computed according to TIMI definitions, vs. COMPASS, where a modified ISTH bleeding scale was considered and the incidence of major bleeding was approximately one-third lower using the standard vs. modified ISTH definition [61]. The GUSTO definition [59], adopted by the CHARISMA [11] and DAPT [10] trials, does not require changes in haemoglobin levels and therefore may refer to less objective criteria of bleeding severity. In order to harmonise various bleeding scales, the Academic Research Consortium standardised a classification for all cardiovascular bleeds, but, although validated, it has not been ubiquitously adopted [59].

4.2. Weighing the severity of bleeding events

Bleeding complications related to antithrombotic strategies have been associated with adverse outcomes, including higher risk of MI, stroke, stent thrombosis and death. The mechanisms underlying the increased morbidity/mortality associated with a bleeding event are in part explained by the bleeding severity, directly impacting on prognosis

Table 2
Main risk scores in patients with chronic coronary syndromes.

Score	Clinical setting	Variables included	Events included in outcome	Timing of outcome
Ischaemic and bleeding risk				
DAPT score	At least one year from STEMI/ NSTE-ACS	1. Age 2. Heart failure/ left ventricular dysfunction 3. Venous graft bypass 4. MI at the time of acute event 5. Previous MI or PCI 6. Diabetes mellitus 7. Stent diameter < 3 mm 8. Current smoking 9. Paclitaxel stent	MI or stent thrombosis; GUSTO moderate or severe bleeding	30 months after the index event
Bleeding risk				
PRECISE-DAPT	At the time of coronary stenting	1. Haemoglobin 2. White blood cells 3. Age 4. CrCl 5. Prior bleeding	TIMI major bleeding; any TIMI bleeding	1 year
Ischaemic risk				
TRS2°P	Previous MI in the last 12 months	1. Congestive heart failure 2. Arterial hypertension 3. Age ≥ 75 years 4. Diabetes mellitus 5. Prior stroke 6. Prior coronary bypass surgery 7. Peripheral artery disease 8. eGFR < 60 mL/min 9. Current smoking	Recurrent MI, ischaemic stroke, cardiovascular death	3 years

CrCl = Creatinine clearance; DAPT = Dual AntiPlatelet Therapy; eGFR = estimated Glomerular Filtration Rate; GUSTO = Global Strategies for Opening Occluded Coronary Arteries; MI = Myocardial infarction, NSTE-ACS = Non ST-segment elevation acute coronary syndrome; PCI = Percutaneous coronary intervention; PRECISE-DAPT = PREdicting bleeding Complications In patients undergoing Stent implantation and subsEquent Dual AntiPlatelet Therapy; STEMI = ST-segment elevation myocardial infarction; TIMI = Thrombolysis in Myocardial Infarction; TRS2°P = TIMI Risk Score for Secondary Prevention.

(particularly for intracranial haemorrhage), but they may also be related to consequent coronary events due to cessation of antiplatelet therapies, hypotension, adverse effects of hyper-adrenergic state, inflammatory and immunologic effects of transfusions. This was first demonstrated in the OASIS-5 trial [62] and subsequently confirmed. In particular, the WOEST trial [63], comparing SAPT vs. DAPT on top of warfarin in patients undergoing PCI, reported with the former antiplatelet approach a survival benefit that was most likely due to the large reduction in bleeding. A meta-analysis of phase III pivotal trials comparing non-vitamin K antagonist anticoagulants (NOACs) to warfarin in atrial fibrillation, showed that NOAC use was associated with lower mortality primarily through a decrease of fatal bleeding, especially intracranial, but also through a reduction in long-term consequences of bleeding episodes [64]. Finally, in the ENGAGE TIMI 48 trial [65], a strategy with low-dose edoxaban in patients with atrial fibrillation, despite a lower efficacy than warfarin in terms of ischaemic stroke prevention, significantly reduced mortality; this seems to be almost entirely due to a large reduction in all types of bleeding, both intracranial and extracranial.

Notably, data on post-ACS patients demonstrated that the mortality related to a bleeding event is lower than that related to a MI event for lower severity bleeds (BARC 2 and BARC 3a), but > 4-fold higher for higher severity bleeds (BARC 3c) [48]. A final consideration concerns the incidence of bleeding complications during antithrombotic treatments, which in patients with CCS may vary over time. Accordingly, in the rivaroxaban plus aspirin arm of the COMPASS study, the reduction of MACE vs. aspirin alone remained constant across the whole study period, whereas the relative increase in major bleeding was substantially greater in the first year of treatment (and was almost entirely restricted to the first two years of treatment) [61]. A similar, although less pronounced, pattern was observed with the combination of ticagrelor plus aspirin vs. aspirin alone in the PEGASUS trial [66].

4.3. Net clinical benefit of antithrombotic approaches in secondary cardiovascular prevention

As mentioned above, a composite outcome measure including both ischaemic and bleeding events, may be relevant in studies evaluating antithrombotic drugs. In patients with CCS, the net clinical outcome becomes even more important, as here the treatment is meant to reduce a chronic risk, rather than resolve an acute ischaemic event. However, a crucial point is how to appropriately the weight of ischaemic vs. bleeding events included in the net composite endpoint. To capture those events at higher prognostic weight in terms of mortality, more severe bleeds are here coupled to hard ischaemic cardiovascular complications. In particular, in COMPASS, the incidence of the net clinical endpoint (including cardiovascular death, stroke, MI, fatal bleeding, or symptomatic bleeding into a critical organ) was lower with rivaroxaban plus aspirin vs. aspirin alone (hazard ratio 0.80, $p < 0.001$) [67]; this advantage in the balance of ischaemic/haemorrhagic events probably accounted for the reduction in overall mortality observed with the former approach. Similarly, an analysis from the PEGASUS trial showed a significant 14% relative reduction of the net composite endpoint of cardiovascular death, MI, stroke, intracranial bleeding and fatal bleeding in the ticagrelor vs. placebo arm [9]. A practical approach on how to balance ischaemic protection against bleeding risk of antithrombotic treatments in secondary cardiovascular prevention is summarised in Fig. 4.

5. Longterm outcomes of chronic coronary syndromes: how to optimise the follow-up assessment

5.1. Planning a personalised programme

Despite significant improvements in stabilised ACS management, secondary prevention remains challenging [68]. The implementation of pharmacological and non-pharmacological interventions is still unsatisfactory, as a large number of patients have inadequate risk factor control after revascularisation and/or after ACS. Furthermore, the prevalence of co-morbidities, multivessel CAD, multivessel coronary revascularization or extra-coronary localisation of atherosclerosis, e.g. cerebrovascular and/or PAD, in patients with CCS is high. Such complexity requires a more accurate prognostic stratification, together with “more aggressive” secondary prevention strategies, and an appropriate use of evidence-based treatments to improve long-term outcomes is a priority [69].

Implementing on an individual basis healthy lifestyle behaviours and risk factors control decreases the risk of subsequent cardiovascular events and mortality in patients with CCS. This is additional to appropriate secondary prevention therapy. The time to educate and provide patients and caregivers with elements of coordinated care is limited during hospitalisation. Achieving favourable outcomes in post-ACS patients includes providing a safe transition to the post-acute care setting and long-term care by ensuring adequate planning and support [70,71].

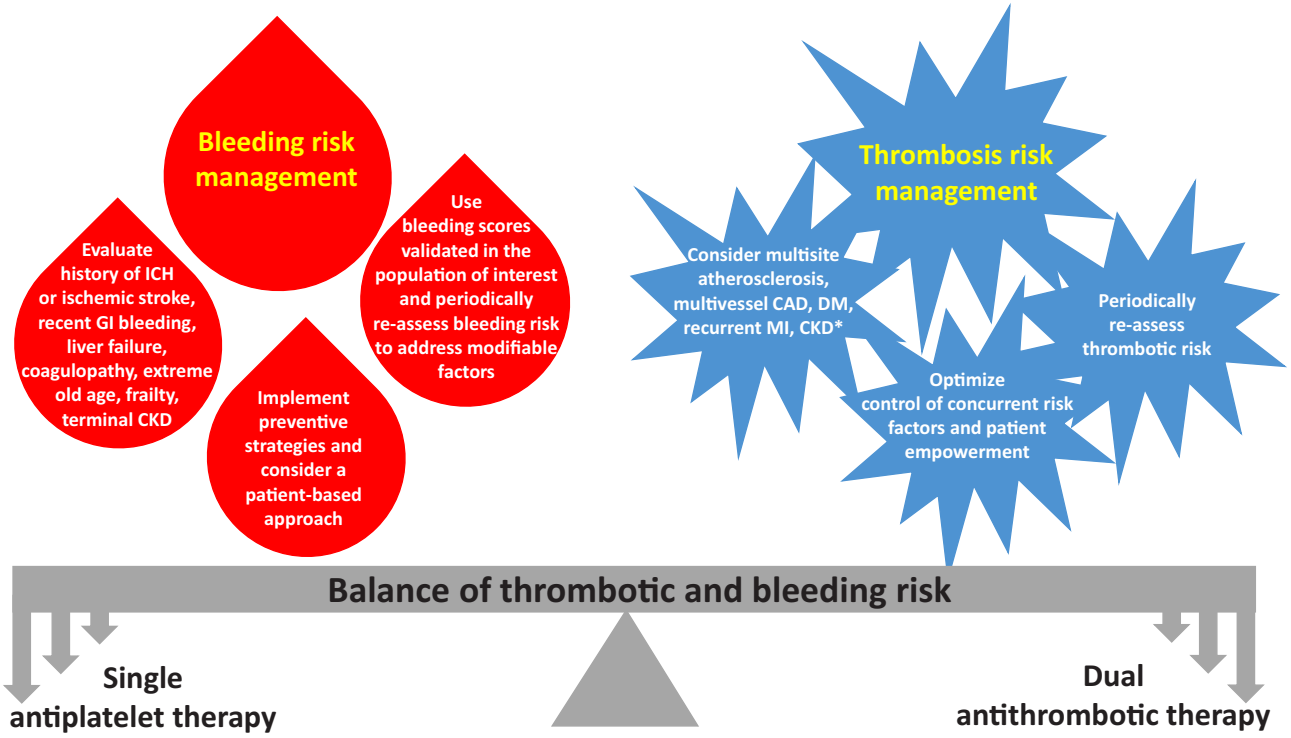

Fig. 4. Factors involved in the evaluation of the net clinical benefit of antithrombotic approaches for secondary cardiovascular prevention. * eGFR 15–59 mL/min/1.73 m^2 CAD = Coronary artery disease; CKD = Chronic kidney disease; DM = Diabetes mellitus; GI = Gastro-intestinal; MI = Myocardial infarction.

This is required for all patients, but is particularly needed for specific categories, including young patients after a first coronary event and high ischaemic risk profile [72], patients with high atherothrombotic burden or ventricular dysfunction, older patients with comorbidities and risk of disability [73,74], patients with lack of social support, low socioeconomic status and/or undetected depression or anxiety.

5.2. Cardiac rehabilitation and lifestyle intervention

Specialised, individualised prevention programmes should be delivered as Cardiac Rehabilitation (CR) [75]. Most patients after MI or revascularization are referred to CR. However, in European countries only a minority of patients are referred to CR for CCS, despite exercise-based CR and the involvement of a multidisciplinary team are strongly recommended for patients with CCS to achieve a healthy lifestyle and manage risk factors (Class 1 Level A) [20]. The potential benefits of referring patients with CCS to CR include decreased morbidity, lower rates of unplanned readmissions, healthy lifestyle behavioural choices and improved exercise capacity, especially in patients with a very high-risk profile [76]. When six or more risk factors are present in the same patient, a multidisciplinary assessment and a comprehensive patient-tailored programme are useful in reducing cardiovascular mortality, MI and cerebrovascular events [77]. Traditionally strategies for secondary cardiovascular prevention are stricter up to 1-year follow-up after the acute episode [78]. However, a later risk persists and cardiovascular events continue to occur, although at a lower rate, as do deaths from cardiovascular causes.

5.3. Cardiovascular health education and risk communication

Adherence to recommendations regarding smoking, diet and exercise is associated with a substantially lower rate of adverse events and a better prognosis [68,69]. Persistent smokers who did not diet or exercise have a 4-fold higher risk of cardiovascular events compared with never smokers who dieted and exercised [68,69]. The benefits of lifestyle modifications are additional to the beneficial effects conferred by drugs and interventions [79]. The education of patients with chronic cardiac diseases is known to influence their understanding and motivation to undertake lifestyle changes. However, across studies there were frequent reports of patients not receiving information or prescriptions related to their secondary cardiovascular prevention and detailed discussions about the potential of lifestyle change in reducing the risk of future coronary complications appear to be largely missing. An integral part of patient's education is the risk communication, often forgotten or transmitted in a confusing and conflictual way. The process of risk communication is extremely important for cardiovascular prevention activities, as it can be turned into actions by the patient him/herself generating healthy lifestyles [80].

5.4. Adherence to evidence-based secondary prevention therapies

Evidence-based treatments, especially for antithrombotic and lipid-lowering therapies, have been demonstrated to be effective in reducing cardiovascular events over the long term. However, medical adherence is a complex process and a well-documented unresolved issue in cardiovascular disease management [81]. Both disease and medication education should begin immediately throughout the hospital stay and must be reinforced in the post-acute care setting. It is not unusual for a patient with newly diagnosed ACS to be admitted with no home medication at baseline and to be discharged soon thereafter on "polypharmacy"; as the complexity of a medical regimen increases, adherence in the subsequent chronic phase of the disease declines. In the setting of CCS an adequate communication and education can improve treatment adherence, and therapeutic changes should be relayed to all parties (patient, caregivers, primary care) [82]. Fig. 5 summarises strategies to standardise and improve the follow-up assessment.

6. Conclusions

The risk of recurrent events in patients with CCS, especially in those

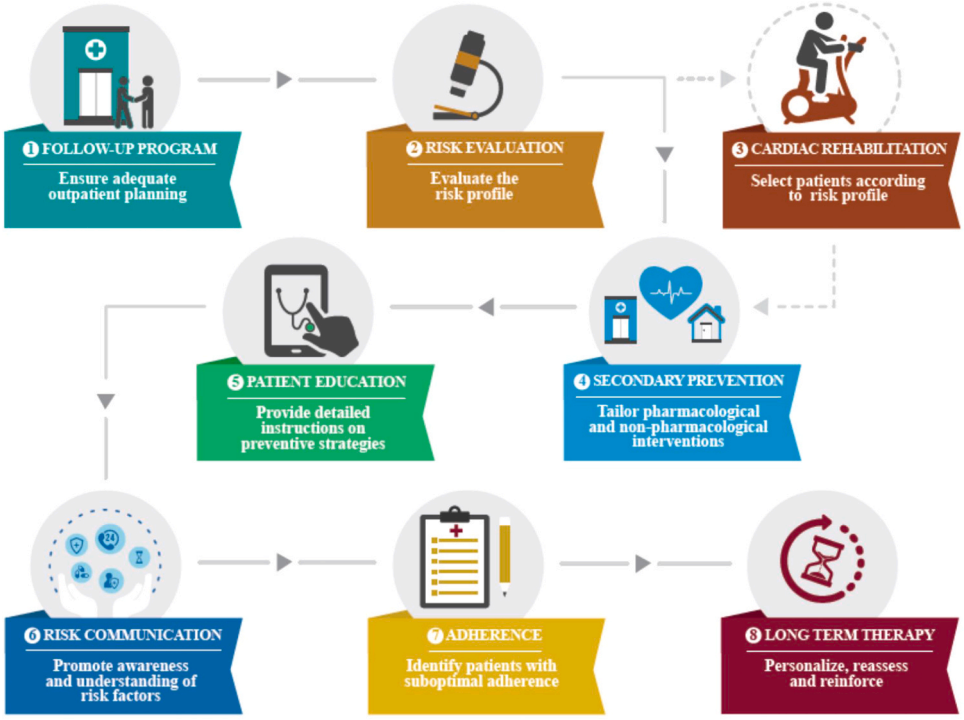

Fig. 5. Strategies to improve follow-up assessment in chronic coronary syndromes.

at higher thrombotic risk, remains elevated [18,83]. This risk may be significantly reduced by strategies including: a) interventions of global secondary cardiovascular prevention, although this was not the specific aim of the present paper; b) a careful stratification of baseline ischaemic and bleeding risks and its modification over time; c) tailoring of antithrombotic approaches to the individual risk, adopting a dual antithrombotic approach in patients potentially deriving the greatest net clinical benefit; d) optimal follow-up assessment through personalised programmes of non-pharmacological interventions and cardiovascular health education.

Disclosures outside the present work

Gi.Pa.: speaker/consultant fees from Abbott, Astra Zeneca, Sanofi, Amgen, Bayer, Pfizer, Bristol-Myers Squibb, Daiichi Sankyo, PIAM, Malesci, Sigma Tau, Chiesi, Menarini, Merck Sharp Dohme, Boehringer Ingelheim.

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G.P.P., C.G.: none.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.biopha.2021.111783.

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