Progress in Cardiovascular Diseases 85 (2024) 2–13

Contents lists available at ScienceDirect

Progress in Cardiovascular Diseases

journal homepage: www.onlinepcd.com

Review Article

Stratified medicine for acute and chronic coronary syndromes: A patient-tailored approach

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ARTICLE INFO

Keywords:
Precision medicine
Stratified medicine
Acute coronary syndrome
Chronic coronary syndrome
INOCA
MINOCA

ABSTRACT

The traditional approach to management of cardiovascular disease relies on grouping clinical presentations with common signs and symptoms into pre-specified disease pathways, all uniformly treated according to evidence-based guidelines ("one-size-fits-all"). The goal of precision medicine is to provide the right treatment to the right patients at the right time, combining data from time honoured sources (e.g., history, physical examination, imaging, laboratory) and those provided by multi-omics technologies. In patients with ischemic heart disease, biomarkers and intravascular assessment can be used to identify endotypes with different pathophysiology who may benefit from distinct treatments. This review discusses strategies for the application of stratified management to patients with acute and chronic coronary syndromes.

Alphabetical list of abbreviations

ACS	Acute Coronary Syndrome
ACh	Acetylcholine
ARBs	Angiotensin Receptor Blockers
CAD	Coronary Artery Disease
CCBs	Calcium-Channel Blockers
CCS	Chronic Coronary Syndrome
CFR	Coronary Flow Reserve
CMR	Cardiac Magnetic Resonance
CMD	Coronary Microvascular Dysfunction
CVD	Cardiovascular Disease
CV	Cardiovascular
DAPT	Dual Antiplatelet Therapy
DPI	Dual-Pathway Inhibition
ECG	Electrocardiogram
HPR	High Platelet Reactivity
IHD	Ischemic Heart Disease
IMR	Index of Microvascular Resistance
INOCA	Ischemia and Non-Obstructed Coronary Artery
IVUS	Intravascular Ultrasound
LPR	Low Platelet Reactivity
LoF	Loss-of-Function
MACE	Major Adverse Cardiovascular Events
MI	Myocardial Infarction
MINOCA	Myocardial Infarction with Non-Obstructed Coronary Arteries
MVA	Microvascular Angina
NACE	Net Adverse Clinical Events
NSTE	Non-ST Elevation
OCT	Optical Coherence Tomography
PCI	Percutaneous Coronary Intervention
RCT	Randomized Controlled Trial
SCAD	Spontaneous Coronary Artery Dissection
STEMI	ST-Elevation Myocardial Infarction
TLR	Target Lesion Revascularization
VSA	Vasospastic Angina

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https://doi.org/10.1016/j.pcad.2024.06.003

Available online 25 June 2024

Introduction

Ischemic heart disease (IHD) still represents the leading cause of disability and mortality worldwide despite a > 50% reduction in IHD-related mortality over the last 50 years. This falling IHD-related mortality is associated with the implementation of international guidelines including early identification and treatment of traditional cardiovascular (CV) disease (CVD) risk factors.[1,2] The traditional approach to CVD relies on grouping patients presenting with common signs and symptoms into clinical pathways, such for stable angina. These large subpopulations are uniformly treated in accordance with evidence-based guidelines. This approach enables allocation of patients at scale to treatments shown to be effective and acceptably safe in clinical trials often involving large numbers of people. Emerging evidence mainly from other fields of Medicine, suggests that this approach may have, at least in part, exhausted improvements in clinical outcomes of patients with IHD. One of the reasons for this may be that most medical treatments are designed for the "average" patient, as in a "one-size-fits-all" approach, which may be efficacious in some patients but not in others. Yet, as a specific phenotype can be caused by different pathogenetic mechanisms, an effective treatment may require a targeted approach. For instance, the phenotype "anaemia" can be caused by iron deficiency or myeloproliferative disorders and clearly, the treatments are different.[3]

Precision medicine holds promise tailoring the right treatment to the right patient at the right time.[4] It combines data from time honoured sources (e.g., history, physical examination, imaging, laboratory) and those provided by multi-omics technologies (e.g., metabolomic, proteomic, next-generation sequencing analyses enabling genome, transcriptome, DNA-protein interaction profiling) to identify homogeneous subsets of patients and apply specific treatments.[5,6] Although other medical specialties such as oncology, haematology and immunology have been integrating these tools into diagnostic and therapeutic algorithms for decades, this integrative approach is not being widely applied in IHD[3]. Multiple factors contributed to slower precision medicine in IHD. Indeed, IHD encompasses a range of conditions with significant disease complexity and clinical heterogeneity, making the development of unified stratification approaches more challenging compared to other diseases (i.e., cancer). However, several adjunctive investigations including cardiac biomarkers, non-invasive and invasive diagnostic techniques are available in patients with IHD. These methods permit identification of specific pathogenic mechanisms on an individual patient basis, enabling the possibility of treatment stratification according to the disease process. If precision medicine is not yet ready for current clinical practice for IHD patients, a "stratified medicine" approach represents an initial step forward. 'Stratified medicine' is defined as the grouping of patients based on risk of disease or response to therapy by using diagnostic tests or techniques.[7] Of importance, stratified medicine in IHD has the potential to improve patients' outcomes by enabling an earlier and more accurate diagnosis as well as a timely and targeted treatment with potentially higher efficacy and fewer adverse effects. Furthermore, it could allow a more efficient allocation of healthcare resources by reducing unnecessary treatments and costs.

The purpose of this review is to provide updated evidence on potential strategies for the application of stratified medicine to the management of both patients with acute coronary syndrome (ACS) and chronic coronary syndrome (CCS).

Stratified Medicine in Patients with ACS

Although the considerable advances in terms of available technologies and knowledge of the underlying pathophysiologic mechanisms, the diagnostic and therapeutic algorithm of ACS patients is still largely based on the presence or absence of ST segment elevation at 12-lead surface electrocardiogram (ECG), a century-old technology,[8,9] even if new ECG systems have been developed aiming to improve user-friendliness and diagnostic accuracy in patients with IHD[10]. Furthermore, the current non-ST elevation (NSTE)-ACS and ST-elevation myocardial infarction (MI;STEMI) guidelines propose recommendations based on randomized controlled trials (RCTs) that mainly enrolled patients with obstructive coronary artery disease (CAD). On the other hand, one in eight patients with MI do not have obstructive CAD, and this condition is known as MI with non-obstructed coronary arteries (MINOCA). The diagnostic and therapeutic approaches for MINOCA are distinct and different.

Tailoring the Treatment of the Culprit Plaque in ACS

The occurrence of ACS has been traditionally identified with the destabilization of an atherosclerotic plaque leading to the thrombotic occlusion of a coronary artery.[11] Accordingly, ACS patients found with a culprit lesion at coronary angiography are uniformly treated with a one-size-fits-all approach consisting of timely percutaneous coronary intervention (PCI) with stent implantation and at least 1-year dual antiplatelet therapy (DAPT).[8,9] However, pathology studies and in vivo observations provided by intracoronary imaging have shown that three distinctly different pathogenetic mechanisms can lead to ACS in presence of obstructive CAD: plaque rupture, plaque erosion, and, rarely, eruptive calcified nodule.[12–14] The use of intracoronary imaging techniques, such as intravascular ultrasound (IVUS) or optical coherence tomography (OCT), allows this distinction as well as the identification of additional plaque features that can be used to tailor the optimal treatment (Table 1).[15,16]

Plaque rupture accounts for up to 50–60% of ACS and usually originates from the disruption of a thin-cap fibroatheroma (TCFA).[17] Plaque rupture has been traditionally considered the consequence of inflammatory mechanisms.[18] However, plaque rupture may occur even in the absence of systemic inflammatory activation and be the consequence of a local mechanical stress subsequent to a sympathetic nervous system activation with catecholamine surge (i.e., extreme emotional or physical triggers).[19–21] Furthermore, local changes in the equilibrium between esterified and free cholesterol might promote plaque rupture.[22] The distinction between plaque rupture with or without systemic inflammation could have important therapeutic implications. Indeed, patients with plaque rupture and systemic inflammation is likely the subgroup that may benefit from anti-inflammatory drugs.[23] In contrast, in the subgroup of plaque rupture without inflammation, intensive lipid-lowering treatment with statins and ezetimibe might interfere with cholesterol crystal formation.[24,25] Similarly, cyclodextrin could solubilize cholesterol thus limiting cholesterol crystal accumulation in plaques and inhibitors of cholesteryl ester hydrolase, an enzyme that converts cholesteryl esters to free cholesterol, might prevent cholesterol crystallization.[21,26] However, further evidence from randomized clinical trials is warranted before clear indications could be provided for clinical practice. Of note, the detection of plaque rupture as the mechanism of coronary instability may also have important prognostic implications, as patients with plaque rupture have a more aggressive phenotype of coronary atherosclerosis and are at increased risk of future CVD events compared to those with an intact fibrous cap, thus prompting a more aggressive therapy for secondary prevention.[27]

Plaque erosion is the underlying mechanism in 30–40% of ACS, especially in young individuals, women, and smokers.[28] A conservative strategy (antithrombotic therapy without stent implantation) may represent an appropriate treatment strategy when plaque erosion is identified as the underlying mechanism of ACS[29]. Such conservative approach can potentially translate in a reduction in both early (distal embolization and acute stent thrombosis) and late (in-stent restenosis, neoatherosclerosis, and late and very late stent thrombosis, endothelial dysfunction and related vasomotor disorders) complications deriving from stent implantation.[30,31] EROSION was the first study demonstrating the feasibility of a conservative approach with potent DAPT (aspirin and ticagrelor for 1-year) without stent implantation in ACS

Table 1
Tailoring the treatment of patients presenting with ACS according to the type of culprit lesion detected at OCT analysis.

Type of culprit lesion	Prevalence and pathogenetic features	Therapeutic implications
1) *Plaque rupture (PR)*	- Up to 60% of all ACS. - Fibrous cap discontinuity with a clear communication between the lumen and the inner core of a coronary plaque. PR usually originates from the disruption of a TCFA leading to the exposure a great amount of highly thrombogenic necrotic core and the formation of occlusive red thrombus. - Associated with a more aggressive phenotype of coronary atherosclerosis and an increased risk of future CV events. - The fissuring of the fibrous cap has been traditionally considered the consequence of inflammatory mechanisms leading to the weakening of its collagen structure. However, PR may occur even in the absence of systemic inflammatory activation as the consequence of a local mechanical stress (e.g., catecholamine surge) or local changes in the equilibrium between esterified and free cholesterol.	- Timely PCI with stent implantation and DAPT. - A more aggressive management of CV risk factors along with a more aggressive therapy for secondary prevention. - Anti-inflammatory drugs in patients with systemic inflammation. - Intensive lipid-lowering treatment with statins and ezetimibe, cyclodextrin and inhibitors of cholesteryl ester hydrolase in patients without evidence of systemic inflammation.
2) *Plaque erosion (PE)*	- Up to 30–40% of all ACS, especially in young, women, and smokers. - Attached thrombus overlying an intact plaque, luminal surface irregularity at the culprit without thrombus or attenuation of underlying plaque by thrombus without superficial lipid or calcification immediately proximal or distal to the site of thrombus. - Thrombus formation in PE is due to the apoptosis of superficial endothelial cells leading to denudation and is typically rich in platelets (white thrombus) and activated neutrophils. - PE is characterized by a lower plaque burden associated to less severe lumen obstruction with relatively preserved vascular integrity compared to PR.	- A conservative strategy (PCI without stent implantation) and DAPT may be feasible and potentially translate in a reduction in both early and late stent-related complications. - EROSION: no excess in MACE with a conservative strategy at 1-month, 1-year and 4-year follow-up. - EROSION III: OCT-guided conservative strategy showed no difference in the composite safety endpoint of thrombotic and ischemic events at 1-month and 1-year follow-up.
3) *Eruptive calcified nodule (CN)*	- Up to 5–10% of all ACS, especially in elderly patients or with chronic kidney disease, in heavily calcified vessels, particularly at hinge points of the right coronary artery. - Breaks in a calcified plate that disrupt the fibrous cap and are overlaid by thrombus. - Associated with higher rates of stent under expansion, poor apposition, or dissections immediately after PCI as well as worse long-term outcomes mainly due to higher rates of TLR.	- Adjunctive tailored approaches during PCI (i.e., aggressive pre-dilatation, cutting balloons, rotational or orbital atherectomy, laser therapy, or lithotripsy).

Abbreviations: ACS: acute coronary syndromes; OCT: optical coherence tomography; PR: plaque rupture; TCFA: thin cap fibroatheroma; CV: cardiovascular; PCI: percutaneous coronary intervention; DAPT: dual antiplatelet therapy; PE: plaque erosion; MACE: major adverse cardiovascular event; TLR: target lesion revascularization.

patients with plaque erosion, showing also no excess in major adverse cardiovascular events (MACE) up to 4-year follow-up.[32–34] The recent EROSION III study assessed whether OCT guidance vs angiographic guidance was associated with less stent implantation and better prognosis in STEMI patients. In the OCT arm, the reperfusion strategy was decided according to the underlying pathogenic mechanism and a conservative strategy was used in plaque erosion, plaque rupture without dissection and/or hematoma, and spontaneous coronary artery dissection (SCAD). The use of OCT significantly reduced (by 15%) the rate of stent implantation (primary endpoint) without difference in the exploratory (underpowered) composite safety endpoint of thrombotic and ischemic events at 1-month and 1-year.[35] A post-hoc analysis of DANAMI-3-DEFER trial demonstrated that STEMI patients randomized to deferred arm and treated without stent implantation during the index and the deferral procedure (if $\leq$30% residual stenosis, no significant thrombus and/or no visible dissection) had no significant differences in the primary (composite of all-cause mortality, recurrent MI and unplanned target vessel revascularization) and secondary endpoints (individual components of the primary endpoint, unplanned target lesion revascularization and hospitalization for heart failure) at long-term follow-up (3.4 years) compared to patients treated with conventional PCI and immediate stenting.[36] This study further supports the notion that selected ACS patients may undergo a positive healing process without the need of stenting, and the use of intravascular imaging could have potentially reinforced these results providing more detailed information about culprit lesion characteristics.

Finally, eruptive calcified nodule represents an infrequent cause of ACS (≈5–10%) and tends to occur in elderly patients or with chronic kidney disease, in heavily calcified vessels, particularly at hinge points of the right coronary artery.[37] The presence of calcified nodule and severe calcifications are associated with higher rates of stent under expansion, poor apposition, or dissections immediately after PCI as well as worse long-term outcomes mainly due to higher rates of target lesion revascularization (TLR).[38–40] The identification of calcified nodule as the underlying mechanism of ACS by OCT could guide adjunctive tailored approaches during PCI (i.e., aggressive pre-dilatation, cutting balloons, rotational or orbital atherectomy, laser therapy, or lithotripsy).[15,41]

Therefore, intracoronary imaging, especially OCT thanks to its very high-resolution (10–15 μm), represents a promising strategy for implementing stratified medicine in ACS (Fig. 1), although it is not routinely used by most interventional cardiologists due to a combination of factors, including cost, availability, and perceived lack of clinical benefit.

Circulating biomarkers are non-invasive and, potentially, economic tools that are routinely used in clinical practice to stratify patients and select treatments accordingly. The best example is the detection of increased serum levels of cardiac troponins to diagnose MI and direct NSTE-ACS towards an invasive management strategy.[9,42] Similarly, the identification of new circulating biomarkers for the distinction between the underlying mechanisms may direct ACS patients towards a standard vs. a conservative approach (i.e., PCI with stent implantation vs. DAPT

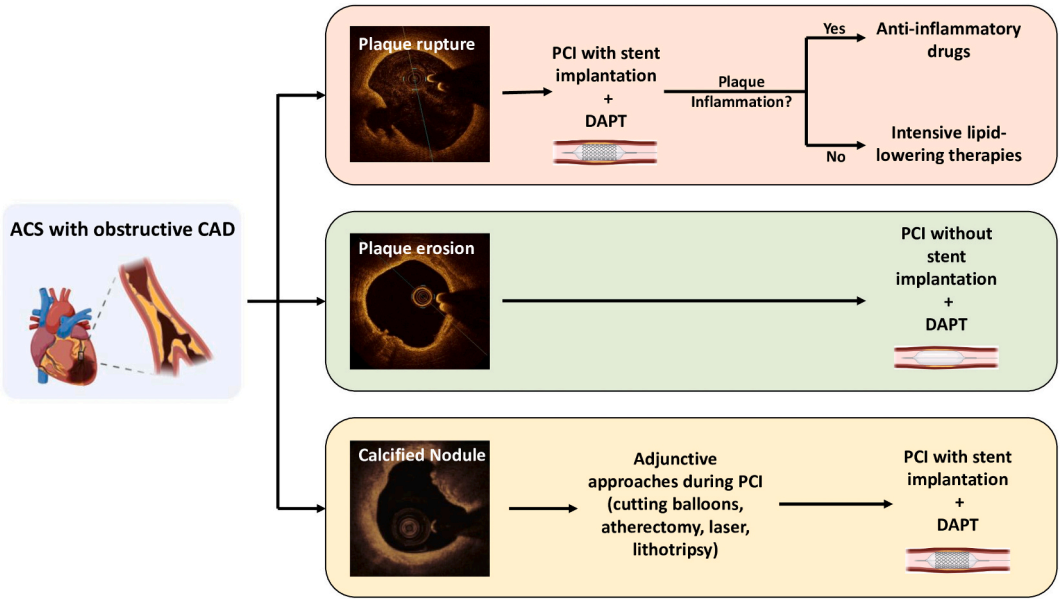

Fig. 1. Management of ACS with obstructive CAD according to the underlying pathogenetic mechanisms identified by OCT. *Abbreviations:* ACS: acute coronary syndrome; CAD: coronary artery disease; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; DAPT: dual antiplatelet therapy.

without stent).[43] Patients with plaque erosion demonstrate higher levels of systemic myeloperoxidase in peripheral blood that could also be detected in the accompanying intraluminal thrombus.[44] An alteration of hyaluronan metabolism has been recently demonstrated in plaque erosion, as the gene expressions of hyaluronidase 2 (an enzyme degrading high-molecular-weight hyaluronan into its proinflammatory 20-kDa isoform) and of CD44v6 splicing variant of hyaluronan receptor are significantly higher in plaque erosion patients compared to those with plaque rupture.[45] The ongoing PEPSii study (NCT04701385) will assess the differences of several circulating biomarkers (e.g., circulating endothelial cells, neutrophils, mitochondrial DNA, circulating endothelial progenitor cells and erosion-specific plasma biomarkers) between plaque rupture and plaque erosion assessed by OCT in patients presenting with NSTE-ACS. However, the integration of novel biomarkers into real-world practice faces several challenges, such as the need of validation in large population studies and standardization for their measurement, along with their practicality and affordability for routine clinical use.

Tailoring Antiplatelet Therapy after ACS

DAPT with aspirin and a P2Y12 inhibitor (clopidogrel, prasugrel or ticagrelor) for 12 months represents the standard of care for ACS patients, with the opportunity to tailor such regimen according to the bleeding and ischemic risks of the individual patient.[46] While prasugrel and ticagrelor are preferred over clopidogrel because their net clinical benefit, in patients at high bleeding risk (HBR) clopidogrel should be considered.[8] Moreover, DAPT duration may be shortened up to 1 month after ACS in HBR patients, or can be extended beyond 12 months in non-HBR patients at high ischemic risk.[8] However, many patients in clinical practice lie in a grey zone in which bleeding and ischemic risks largely overlap, making the optimal duration of DAPT a clinical conundrum.

Differences in individual response to P2Y12 inhibitors, particularly clopidogrel, carries clinical implications in patients undergoing PCI[47,48,49]. Approximately 30% of clopidogrel-treated patients, but <5% of those treated with prasugrel or ticagrelor, have inadequate platelet inhibition leading to high platelet reactivity (HPR), a modifiable marker of thrombotic risk.[50] Nevertheless, prasugrel and ticagrelor provide more potent platelet inhibition that leads to low platelet reactivity (LPR), a marker of bleeding risk[47]. Clopidogrel is a pro-drug that requires a 2-step biotransformation oxidative process by the hepatic cytochrome (CYP)P450 system to be activated with the CYP2C19 enzyme involved in both metabolic steps. Importantly, the gene responsible for CYP2C19 transcription is highly polymorphic, with carriers of loss-of-function (LoF) alleles associated with reduced generation of clopidogrel's active metabolite leading to high HPR rates and thrombotic complications. Clopidogrel response can be assessed by platelet function tests assessing the intensity of platelet inhibition or by genetic tests aiming at identifying LoF carriers of the CYP2C19 gene (i.e., alleles *2 and *3).[50] The use of prasugrel or ticagrelor is associated with increased bleeding without any reduction of ischemic events compared to patients with adequate response to clopidogrel, paving the way for a precision medicine approach based on a guided selection strategy of antiplatelet therapy in patients with an indication for the use of a P2Y12 inhibitor[47,49]. The aim of such approach would be to selectively administer a potent P2Y12 inhibitor (prasugrel or ticagrelor), which are not affected by LoF alleles, to clopidogrel non-responders, reducing the risk of bleeding associated with an unguided use of these more potent agents and, at the same time, overcoming the increased rate of ischemic events associated with clopidogrel non responsiveness.[50] To this extent, the impact on outcomes of such approach may vary according to the clinical setting in which it is implemented, ranging from a guided "escalation" or "de-escalation" of P2Y12 inhibiting therapy (Fig. 2).[50,51]

Among ACS patients, a guided approach generally leads to de-escalation of therapy, by identifying patients who are "clopidogrel responders" and fall within a range of platelet inhibition associated with a favourable balance between safety and efficacy. RCTs testing a guided de-escalation are relatively recent.[52] In 2016, the ANTARCTIC was the first study comparing a platelet function test-guided de-escalation to standard therapy in elderly ACS patients undergoing PCI and failed to show a reduction of net adverse clinical events (NACE).[53] Nevertheless, prasugrel 5 mg daily, and not 10 mg, was used in this trial as a standard therapy, potentially blunting the superior safety of a de-escalation strategy. Moreover, randomization was performed 14 days after PCI, thus excluding the period in which the risk of ischemic events is highest.[53] One year later, the TROPICAL-ACS trial overcoming some of prior trial design limitations met the composite primary endpoint for non-inferiority of NACE in ACS[54]. Furthermore, the POPular Genetics trial showed both the non-inferiority of the primary endpoint of NACE and a

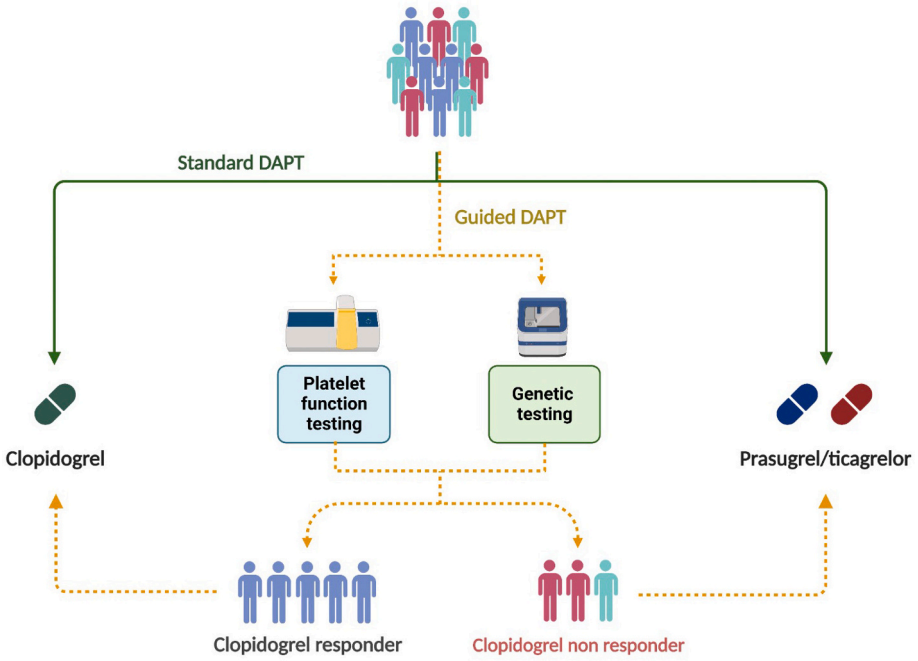

Fig. 2. Guided selection strategy of antiplatelet therapy in ACS and CCS (see text for more details). *Abbreviations:* PCI: percutaneous coronary intervention; DAPT: dual antiplatelet therapy; ACS: acute coronary syndrome; CCS: chronic coronary syndrome.

significant 22% reduction of the co-primary endpoint of major and minor bleeding at 12 months among STE-ACS patients randomized to either genotype-guided de-escalation or standard therapy (mainly ticagrelor) within 48 h after PCI[55]. Nevertheless, the use of a primary composite endpoint including both ischemic and bleeding outcomes and the non-inferiority design of these two trials, leading to a relatively low statistical power with respect to hard ischemic events (i.e., CVD death, MI, stent thrombosis, major bleeding and intracranial haemorrhage), represents an important limitation leading to the relatively weak recommendations on the use of platelet function testing or genetic guidance in guidelines (Class IIb, level of evidence A).[50,54,55] A recent comprehensive meta-analysis has overcome this limitation, showing that a strategy of guided de-escalation is associated with a 19% reduction of bleeding without any trade-off in ischemic events.[48] It is important to note that a significant difference in the evidence supporting a guided de-escalation in ACS between East Asians and non-East Asians exists. Indeed, the vast majority of trials testing this strategy has been primarily conducted in non-East Asians, while among East Asians these trials have primarily focused on the use of an unguided de-escalation 1-month after standard DAPT.

To date, three RCTs tested a guided escalation rather than a de-escalation of antiplatelet therapy: PHARMCLO, the trial by Al-Rubaish et al. and the TAILOR-PCI.[56–58] All these studies compared a genotype-guided antiplatelet therapy versus standard antiplatelet therapy. The first two found a significant reduction of MACE with guided compared to standard therapy (−42% and − 66%, respectively), while this reduction was consistent (−34%) but not statistically significant ($p = 0.06$) in the TAILOR-PCI, given the very ambitious 85% power to show a 50% reduction chosen for the primary endpoint and the lower-than-expected event rate. A recent network meta-analysis has described the comparative effects of a guided de-escalation versus prasugrel or ticagrelor, showing a guided de-escalation to be associated with the most favourable balance between safety and efficacy.[59]

Collectively, platelet function testing and genetic testing represents a promising strategy for implementing precision medicine in ACS and new evidence may impact future recommendations on the use of a guided selection of P2Y12 inhibiting therapy.

Tailoring treatment of MINOCA

MINOCA represents about 6–8% of all patients presenting with acute MI and is defined as the evidence of MI with normal or near normal coronary arteries in the absence of any alternative diagnosis for the clinical presentation (i.e., sepsis, pulmonary embolism, tachyarrhythmias, myocarditis and Takotsubo syndrome).[60] A variety of pathogenetic mechanisms may result in MINOCA, including non-obstructive unstable plaques, epicardial or microvascular coronary spasm, SCAD and coronary embolism.[61]

Advanced diagnostic techniques beyond coronary angiography and transthoracic echocardiography, the "gatekeeper" imaging exams performed in every MI patient, should be considered in MINOCA patients for risks stratification as well as for the choice of therapeutic approaches tailored to the underlying mechanism (Fig. 3). Intracoronary provocation testing with acetylcholine (ACh) is helpful for the diagnosis of underlying functional coronary alterations (i.e.: epicardial or microvascular spasm) as cause of MINOCA.[62,63] Moreover, the presence of a positive test portends a higher risk of future CVD events thus identifying a high-risk group of patients that may need a specific therapy and a closer follow-up.[64,65] Intracoronary imaging techniques (i.e., IVUS or OCT) have the potential to detect frequently unrecognized causes at coronary angiography (such as non-obstructive unstable plaques or SCAD). Cardiac magnetic resonance (CMR) in patients with troponin elevation allows the identification of the underlying aetiology as ischemic vs non-ischemic. Indeed, the differential diagnosis that CMR can delineate are MI (including a small embolic infarction), acute myocarditis mimicking MI, usually caused by Parvovirus B19, and Takotsubo syndrome.[66,67]

The management of MINOCA has a limited evidence-based, with few prospective RCTs. Accordingly, current guidelines do not specifically address the acute and long-term management of MINOCA, and the effects of secondary prevention treatments that are known to be beneficial in patients with obstructive CAD are uncertain in MINOCA. The results of a large observational study from the SWEDEHEART registry clearly demonstrated that a one-size-fits-all approach similar to patients with obstructive CAD may not be applicable to MINOCA, as a significantly lower rate of MACE (defined as all-cause mortality, hospitalization for

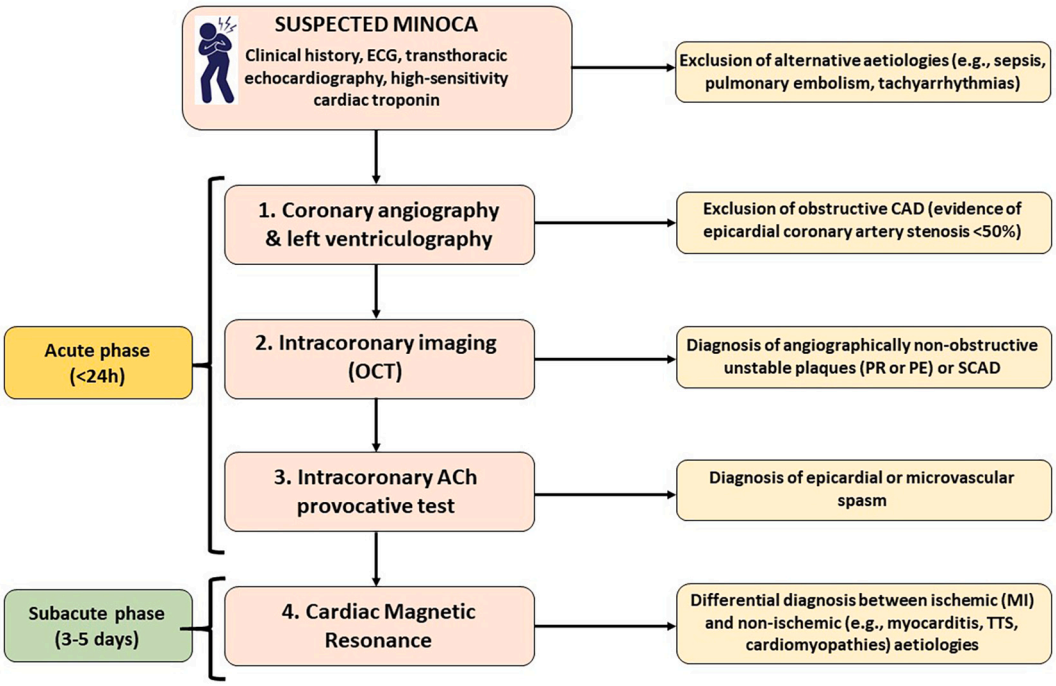

Fig. 3. Diagnostic algorithm of patients with suspected MINOCA aiming at uncovering the underlying aetiology. MINOCA: myocardial infarction with non-obstructed coronary arteries; ECG: electrocardiogram; CAD: coronary artery disease; ACh: acetylcholine; OCT: optical coherence tomography; PR: plaque rupture; PE: plaque erosion; SCAD: spontaneous coronary artery dissection; MI: myocardial infarction; TTS: Takotsubo syndrome.

MI, ischemic stroke, and heart failure) was associated with the use of statins and angiotensin converting enzymes inhibitors (ACEi)/angiotensin receptor blockers (ARBs), with a trend for a lower event rate with the use of beta-blockers, while DAPT failed to improve prognosis. Indeed, DAPT may be effective in patients in whom MINOCA is caused by a non-obstructive disrupted unstable plaque, while it may have no role in the presence of other pathogenetic mechanisms (i.e., coronary vasospasm).[68] Therefore, the treatment of MINOCA should be tailored according to the underlying specific aetiology (Table 2). If a non-obstructive unstable plaque is detected, the optimal treatment should be chosen as previously described (i.e., plaque rupture vs. plaque erosion). In patients with coronary vasospasm, non-dihydropyridine calcium-channel blockers (CCBs), such as verapamil and diltiazem, are considered the first choice. Nitrates (e.g., sublingual nitroglycerin) can be used for acute relief of angina symptoms during vasospastic episodes. However, not all patients with microvascular vasospasm respond well to nitrate therapy. In this regard, ACh rechallenge at the time of intracoronary provocative test might help to identify those patients who could benefit the most from nitrate therapy.[69] The optimal management of SCAD remains uncertain, as there are no RCTs providing definitive recommendations for revascularization strategies and pharmacotherapy in these patients. Due to the potential risk of exacerbating dissection and mural hematoma propagation, PCI is not routinely performed. However, it should be considered in high-risk scenarios such as ongoing ischemia, hemodynamic instability, ventricular arrhythmias, or left main/proximal vessel dissection.[70] Beta-blockers have shown significant reduction in the risk of recurrence.[71] Regarding the choice of optimal antiplatelet therapy, 12-months DAPT is recommended if PCI is performed.[8,9] Conversely, the role of DAPT in patients without PCI is still a matter of debate.[72] In case of coronary embolism, the patient should be screened for the source of embolic material and for systemic embolism, anticoagulation started if appropriate.[73]

In this context, the results coming from ongoing RCTs exploring the impact of a stratified medicine approach will likely impact future recommendations on the management of MINOCA. The PROMISE trial (NCT05122780) will assess if a precision medicine approach consisting of a comprehensive diagnostic work-up (including OCT imaging, intracoronary ACh provocation testing and CMR) and pharmacological treatment specifically targeting the underlying mechanism vs a standard approach consisting of routine diagnostic work-up and standard medical treatment for ACS can improve angina status and quality of life.[74] The StratMed-MINOCA trial will evaluate if an early risk stratification by coronary microvascular dysfunction (CMD, defined as index of microvascular resistance $\geq$25) coupled with cardio-protective mineralocorticoid antagonist (MRA) therapy using eplerenone could limit myocardial damage reflected by changes in N-terminal prohormone of brain natriuretic peptide (NT-proBNP) (primary outcome) and could have an impact on heart function evaluated at CMR and health-related quality of life (secondary outcomes) (NCT05198791).

Stratified medicine in CCS

Among patients with CCS, stratified medicine needs to be considered in two settings: antianginal treatment of patients with ischemia and non-obstructed coronary artery (INOCA) and antithrombotic treatment of patients with obstructive CAD.

Tailoring antianginal therapy in patients with INOCA

Management of INOCA is an unmet clinical need and largely encompasses patients with CMD and/or epicardial coronary vasospasm.[75,76] Around 50% of coronary angiograms for patients with typical angina and a positive stress test demonstrate non-obstructive CAD, which is higher in women compared with men.[77] Despite initially believed a benign condition, INOCA patients are at increased risk of CVD events compared with reference controls, with a significant impact on quality of life and healthcare related costs.[77–80]

Microvascular angina (MVA) is the clinical manifestation of CMD. The latter can result from: 1) structural microvascular remodelling leading to a fixed reduction of coronary flow reserve (CFR); 2) functional microvascular alterations responsible for impaired dilation in response to an increase of myocardial oxygen consumption and/or microvascular

Table 2
Tailoring the treatment of MINOCA according to the underlying specific aetiology.

Aetiology	Prevalence and pathogenetic features	Therapeutic implications
4) *Plaque rupture / Plaque erosion*	- Prevalence up to 40% of all MINOCA. - Even in the absence of obstructive CAD, both plaque rupture and plaque erosion can cause myocardial infarction through different mechanisms, including transient occlusive thrombosis with spontaneous thrombolysis, distal embolization, superimposed vasospasm, or a combination of these processes. - Prevalence ranging between 3 and 95% of all MINOCA.	- DAPT ± PCI (if evidence of unstable plaque) - Statins
5) *Epicardial or microvascular spasm*	- *Epicardial spasm:* presence of chest pain, ischaemic ECG changes and > 90% coronary vasoconstriction in any epicardial vessel during intracoronary provocative test with ACh. - *Microvascular spasm:* presence of chest pain, ischaemic ECG changes and < 90% coronary vasoconstriction in any epicardial vessel during intracoronary provocative test with ACh.	*Epicardial spasm:* - Non-dihydropyridine CCBs - Nitrates - Avoid beta-blockers *Microvascular spasm:* - Non-dihydropyridine CCBs - Nitrates (not effective in all patients)
6) *SCAD*	- Prevalence of up to 35% of all MINOCA, especially in young women. - Separation of intimal and media walls of coronary vessels, not iatrogenic or related to trauma. The affected artery can appear angiographically normal because of gradual tapering of the vessel.	- PCI (if ongoing ischemia, hemodynamic instability, ventricular arrhythmias or left main/ proximal dissection) + 12 months DAPT - Medical therapy with SAPT or DAPT - Beta-blockers (if clinically indicated to reduce the risk of recurrence)
7) *Coronary embolism / thrombosis*	- Abrupt filling defect of a distal coronary artery branch in patients with a hypercoagulable state or evidence of an embolic source (e.g., thrombophilic disorder, AF, mechanical valves, intraventricular thrombus, paradoxical thromboembolism, myxoma).	- Treatment of the underlying conditions - Long-term OAC if AF, persistent risk factors or recurrent events - 3 months OAC if reversible risk factors - OAC + SAPT/DAPT if PCI

Abbreviations: ACEi: Angiotensin Converting Enzyme inhibitors; ACh: acetylcholine; AF: atrial fibrillation; ARB: angiotensin receptor blockers; CAD: coronary artery disease; CCBs: calcium channel blockers; DAPT: dual antiplatelet therapy; ECG: electrocardiogram; MINOCA: myocardial infarction with non-obstructed coronary artery; OAC: oral anticoagulation; PCI: percutaneous coronary intervention; SAPT: single antiplatelet therapy.

spasm; 3) a combination of them.

Vasospastic angina (VSA) is the clinical manifestation of myocardial ischemia caused by dynamic epicardial coronary obstruction due to epicardial spasm.[81]

Key subgroups (endotypes) can be identified within the heterogeneous population of INOCA by performing a comprehensive invasive functional assessment, including measurement of CFR and microvascular resistance measurements (index of microvascular resistance - IMR), together with ACh provocation testing. The endotypes include MVA (evidence of CMD defined as any of abnormal CFR <2.0, IMR ≥25, or microvascular spasm), VSA (CFR ≥2.0, IMR <25 and epicardial spasm), and mixed type (both MVA and VSA, evidence of CMD and epicardial spasm).[82] The CorMicA was a randomized, controlled, blind clinical trial of stratified medicine in patients with angina. The intervention involved invasive coronary function tests (including ACh) and medical therapy linked to the endotype. The control arm involved standard, angiography-guided management. The study demonstrated that health-related quality of life may be improved by applying a strategy of adjunctive invasive testing (i.e., assessment of CFR, IMR, and ACh provocation testing) to identify endotypes that respond to specific therapies.[83,84] At the same time, the Cor-CTCA trial demonstrated that in patients with angina and unobstructive CAD, as defined by CT coronary angiography, a diagnosis informed by invasive functional assessment had no effect on long-term angina burden, whereas treatment satisfaction improved.[85] Moreover, further studies are ongoing in this field. The iCorMicA is a multicentre, next-stage trial that aims to add evidence in multiple geographies and clarify the external validity of the initial CorMicA trial undertaken in Scotland. The CorCMR clinical trial (NCT04805814) is a prospective, randomized, double-blind, multicentre clinical trial of stratified medicine guided by stress perfusion CMR in patients with chest pain and no obstructive CAD as defined by invasive coronary angiography. Further observational studies in different geographies are underway and of great interest to the community (NCT05164640, NCT05288361). However, despite several RCTs currently ongoing evaluating targeted investigations and therapy, available data for the management of INOCA are still lacking and recommendations are based on a few trials and largely on expert consensus. Moreover, to date, there are no disease-modifying therapies specific to INOCA.

Identifying the specific INOCA endotype is essential to personalize treatments and improve prognosis (Fig. 4).[8,77,86]

CCBs are particularly effective in both VSA and MVA due to microvascular spasm, and experts' consensus indicates CCBs as the first-line agents when the presence of vasomotor disorders is either suspected or documented.[81] In particular, CCBs demonstrated to effectively suppress anginal attacks and reduce the rate of MACE in patients with VSA.[87–90]

Long-acting nitrates may be helpful to reduce anginal episodes in VSA, but their efficacy in improving prognosis was not demonstrated.[91] Moreover, they may worsen anginal symptoms in MVA, probably due to a steal syndrome through regions of adequately perfused myocardium and/or to the coronary resistance vessels having blunted nitrate vasomotor responses as compared with large vessels.[92] Similarly, short-acting nitrates, although useful to treat acute anginal attacks, especially if an abnormal vasodilator reserve is present, are usually only partially effective.[93]

In patients with MVA due to an abnormal CFR and/or an increased IMR, beta-blockers, CCBs, and ACEi might be beneficial.[94] Beta-blockers are first line therapy in CMD, especially in patients with effort-induced angina and evidence of increased adrenergic activity, as they demonstrated to improve anginal symptoms likely by prolonging diastolic filling time and reducing metabolic demand.[8,95,96] However, beta-blockers may worsen anginal symptoms in VSA and should be avoided in these patients. Indeed, even cardioselective (i.e., with a greater affinity for β1-adrenoceptors as bisoprolol) beta-blockers will block the action of β2 adrenoceptors as the dosage increases. Blocking the vasodilator effects of β2 receptors leaves α-mediated vasoconstriction unopposed.[97] ACEi demonstrated to restore endothelial function and improve hyperaemic coronary blood flow in patients with hypertension and MVA as well as to improve CFR and reduce anginal symptoms in women with CMD.[98,99] Similar beneficial effects have been reported also with ARBs.[98] Statins demonstrated to reduce angina recurrence and the

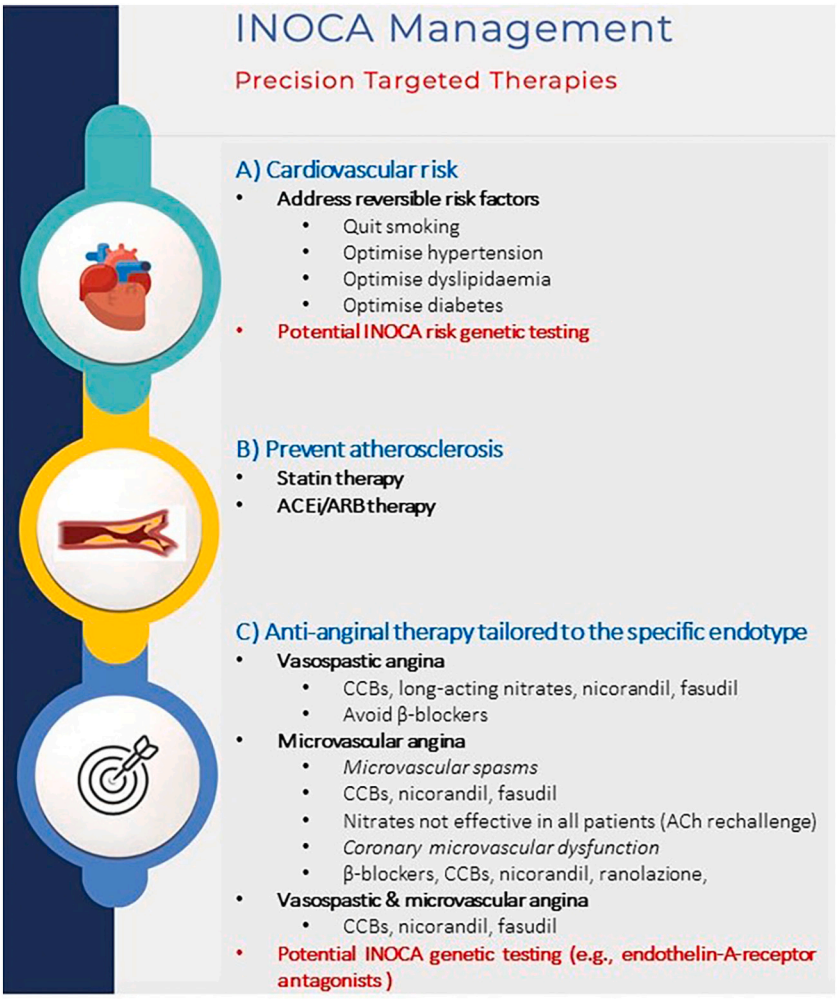

Fig. 4. Tailored Management of INOCA. *Abbreviations:* INOCA: ischemia with non-obstructed coronary arteries; ACEi: Angiotensin-converting enzyme inhibitors; ARB: angiotensin receptor blockers; CCBs: calcium channel blockers.

rate of MACE in patients with VSA as well as to improve endothelial dysfunction and CFR in patients with CMD, probably due to their anti-inflammatory and anti-oxidant properties.[100] Nicorandil, a vasodilator agent acting through nitrate and potassium channel activation, has been reported to reduce exercise induced myocardial ischemia in patients with CMD, suggesting a direct vasodilatory effect on the coronary microvasculature as well as preventing vasoconstriction.[101] Ranolazine, an inhibitor of the late inward sodium current that enhances myocyte relaxation and ventricular compliance by reducing intracellular calcium levels, demonstrated to improve anginal symptoms and myocardial perfusion reserve in patients with MVA and a severely reduced CFR due to an impaired vasodilation.[102] Fasudil, a selective Rho-kinase inhibitor, currently available only in Japan and China, demonstrated its efficacy in preventing coronary spasm and myocardial ischemia in patients with VSA and/or MVA due to microvascular spasm as well as to reduce microvascular resistances in patients with increased IMR.[103–105]

Genetic testing and subsequent direct targeted therapy are one of the key goals of precision medicine also in INOCA. In this regard, previous studies showed that genetic dysregulation of ET-1 might be implicated in causing CMD, as ET-1 is a potent vasoconstrictor acting on endothelin A receptors.[106] Potent and selective oral antagonists of endothelin-A-receptors might contrast the increased vasoconstrictive response of coronary microcirculation to ET-1. The ongoing PRIZE trial (NCT04097314) will evaluate whether the add-on treatment with endothelin-A-receptors antagonists could improve treadmill exercise times in patients with MVA and impaired exercise intolerance.[107]

Finally, clinicians are encouraged to adopt a broad approach to angina recalling that three main drivers contributing to INOCA vary for an individual patient (Fig. 5). Diffuse epicardial CAD or flush ostial side branch occlusions are common INOCA mimics that can be identified on careful review of angiographic images with consideration of advanced cardiac perfusion imaging (e.g., quantitative cardiac positron emission tomography - PET).[108] Systemic factors (pulse, blood pressure) and cardiac (non-coronary) factors are both relevant non-coronary contributors to myocardial ischaemia that should be addressed.

Tailoring antiplatelet therapy in patients with obstructive CAD

DAPT with aspirin and clopidogrel for 6 months represents the standard of care for CCS patients undergoing PCI[8]. Recent guidelines recommendations propose a shortening of DAPT down to 1 month for HBR patients, while DAPT may be prolonged, a dual-pathway inhibition (DPI, consisting in aspirin plus rivaroxaban 2.5 mg bid) strategy implemented, and the use of prasugrel or ticagrelor may be considered in non-HBR patients at high ischemic risk.[8] Nevertheless, clopidogrel remains the P2Y12 inhibitor of choice, despite an inadequate response in approximately 30% of patients.[50] The use of clopidogrel in non-responder may be of particular concern in patients at high ischemic risk due to procedural or clinical features, or in those in whom clopidogrel is used as monotherapy (e.g., 1–3 months after PCI or early after PCI in patients with atrial fibrillation treated with oral anticoagulant therapy) or in lieu of aspirin for secondary prevention.[109] However,

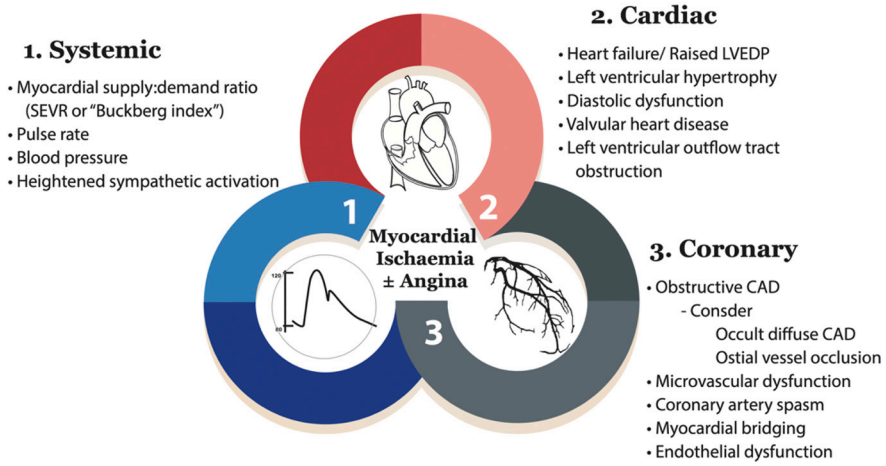

Fig. 5. Systemic, cardiac and coronary contributors to myocardial ischaemia, reproduced with permission (ref. 75). *Abbreviations:* SEVR: sub endocardial viability ratio; LVEDP: left ventricle end-diastolic pressure; CAD: coronary artery disease.

DAPT including prasugrel and ticagrelor may lead to an increased rate of bleeding events. The selective administration of prasugrel or ticagrelor in patients non-responding to clopidogrel assessed by platelet function testing or genetic tests with a guided escalation of antiplatelet therapy could reduce ischemic events without any trade-off in bleeding events (Fig. 2).[50] Nevertheless, the contrasting results from RCTs have resulted in the recommendation by guidelines for the implementation of platelet function testing or genetic tests in CCS only in specific high risk clinical scenarios.[50] In particular, early RCTs such as GRAVITAS and TRIGGER-PCI tested a guided escalation selectively among patients non-responding to clopidogrel, providing limited evidence on how this strategy compares to standard therapy in the totality of patients undergoing PCI[52]. On the other hand, the ARCTIC trial randomized 2440 patients to either guided escalation versus standard therapy and failed to show a benefit of a guided approach, but presented several pitfalls, such as the inadequate identification of clopidogrel non-responders and the use of strategies not effective in overcoming clopidogrel non-responsiveness.[110] On the contrary, the more recent PATH-PCI trial found a PFT-guided escalation (ticagrelor administered in patients with HPR) reduced NACE by 32% at 6 months compared to standard therapy (i.e., clopidogrel) among 2237 CCS patients undergoing PCI. Of note, there was no difference in the rate of major bleeding between groups.[111] A recent comprehensive meta-analysis including the totality of studies comparing a guided escalation versus standard therapy among patients undergoing PCI showed a strategy of guided escalation is associated with a 26% reduction of MACE, a 27% reduction of CV death, a 29% reduction of MI and a 38% reduction of stent thrombosis without any trade-off in bleeding events.[48]

Collectively, platelet function testing and genetic testing represents a promising strategy for implementing precision medicine also in CCS patients undergoing PCI and recent evidence may impact future guidelines to endorse such strategy. Finally, the recent advancements in the understanding of the interplay between platelets, coagulation and inflammation and its involvement in the pathophysiology of atherosclerosis and atherothrombosis, has represented the rationale for the implementation of a DPI strategy. Indeed, while studies testing prolonged intense DAPT have yielded modest ischemic benefit at the expenses of increased bleeding, several RCTs have compared the use of a DPI versus aspirin alone in patients with CVD with more promising results.[112] Among these, COMPASS randomly assigned 27,395 CCS patients to receive rivaroxaban 2.5 mg bid plus aspirin (DPI arm), rivaroxaban 5 mg bid alone, or aspirin alone.[111] DPI, but not rivaroxaban 5 mg bid alone, significantly reduced MACE compared with aspirin, but such benefit came at the expenses of increased major bleeding.[112] Therefore, DPI has shown promising results, but further research is warranted to identify patients in whom a DPI regimen may perform best, such as those with hypercoagulable status in which the synergistic use of antiplatelet and anticoagulant agents may be associated with an optimal balance between safety and efficacy.[113]

Conclusions and future directions

Stratified medicine of IHD patients defining endotypes combining diagnostic work with multi-omics including genetic testing represents a promising approach towards more personalized care (Central Illustration). While initial steps for implementing stratified medicine in IHD were taken several years ago and this concept is not new, there has been a significant step forward in recent years and additional research is required to improve patient characterization (i.e., through the implementation of omics technologies) and to identify new potential diagnostic or therapeutic targets. Efforts to personalize therapy and target the right patient at the right time should include further refinement of risk stratification tools including genetic risk scores and the integration of imaging studies to management decisions.

Funding

Ministero della Salute – Ricerca Finalizzata Grant number GR2019-1237019 awarded by Rocco A. Montone.

CRediT authorship contribution statement

Rocco A. Montone: Supervision. **Thomas J. Ford:** Supervision. **Mattia Galli:** Supervision. **Riccardo Rinaldi:** Supervision. **Adam Bland:** Supervision. **Andrew Morrow:** Supervision. **Dominick J. Angiolillo:** Supervision. **Colin Berry:** Supervision. **Juan Carlos Kaski:** Supervision. **Filippo Crea:** Supervision.

Declaration of competing interest

RAM, RR, AB, AM and FC have nothing to disclose.

MG has received speaker fees from Terumo, outside the present work.

DA has received payment as an individual for Consulting fee or honorarium from Abbott, Amgen, AstraZeneca, Bayer, Biosensors, Boehringer Ingelheim, Bristol-Myers Squibb, Chiesi, CSL Behring, Daiichi-Sankyo, Eli Lilly, Haemonetics, Janssen, Merck, Novartis, PhaseBio, PLx Pharma, Pfizer, Sanofi and Vectura. Institutional payments for grants from Amgen, AstraZeneca, Bayer, Biosensors, CeloNova, CSL Behring, Daiichi-Sankyo, Eisai, Eli-Lilly, Gilead, Idorsia, Janssen,

Matsutani Chemical Industry Co., Merck, Novartis, Osprey Medical, Renal Guard Solutions and the Scott R. MacKenzie Foundation.

JK has received payment of speaker's fees from Menarini Farmaceutica SRL and Servier.

TF is a consulting fee or honorarium from Abbott Vascular, Astra Zeneca, Boston Scientific, Boehringer Ingelheim, Biotronik and Novartis.

CB receives research funding from the British Heart Foundation grant (RE/18/6134217, BHF/FS/17/26/32744, PG/19/28/34310), Chief Scientist Office, EPSRC (EP/R511705/1, EP/S030875/1), European Union (754946–2), Medical Research Council (MR/S018905/1) and UKRI (MC/PC/20014). CB is employed by the University of Glasgow which holds consultancy and research agreements with companies that have commercial interests in the diagnosis and treatment of angina (Abbott Vascular, AstraZeneca, Boehringer Ingelheim, GSK, Menarini, Opsens, Siemens Healthcare and Valo Health.)

Acknowledgements

Figures created with BioRender.com

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