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REVIEW

Advances in the available pharmacotherapy for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation

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ABSTRACT

Introduction: Non-ST-segment elevation acute coronary syndromes (NSTE-ACS), including non-ST-segment-elevation myocardial infarction (NSTEMI) and unstable angina, represent a leading cause of mortality worldwide, with important socio-economic consequences. NSTEMI accounts for the majority of acute coronary syndromes and usually develops on the background of a nonocclusive thrombus. We searched for relevant literature in the field in PubMed and clinicaltrials.gov as of July 2022.

Areas covered: A number of pharmacotherapies are currently available for treatment and secondary prevention, mainly including antithrombotic, lipid-lowering and anti-inflammatory drugs. Pretreatment with aspirin, anticoagulant and statin therapy is of key importance in the preprocedural phase, while pretreating with an oral $P2Y_{12}$ inhibitor is not routinely indicated in patients undergoing early invasive management. For patients undergoing percutaneous coronary revascularization, pharmacotherapy essentially consists of antithrombotic drugs, which should be carefully selected. Finally, antithrombotic, lipid-lowering and anti-inflammatory drugs are important components of long-term secondary prevention after a NSTE-ACS.

Expert opinion: This article reviews the evidence supporting recommendation on pharmacotherapy in patients presenting with a NSTE-ACS. Several randomized clinical trials are still ongoing and are expected to further inform scientific knowledge and clinical practice, with the final aim to improve the treatment of NSTE-ACS patients.

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1. Introduction

More than seven million cases of acute coronary syndrome (ACS) are diagnosed every year, representing a leading cause of mortality worldwide, with prominent social and economic implications [1]. Based on the presence or absence of persistent elevation of the ST segment at the electrocardiogram, ACS can be categorized into ST-segment elevation myocardial infarction (STEMI) and non-ST-segment elevation ACS (NSTE-ACS). The latter includes non-ST-segment-elevation myocardial infarction (NSTEMI) and unstable angina (UA), two entities that differ for the degree of myocardial injury (i.e. increased cardiac biomarkers in NSTEMI, but not in UA). NSTEMI is the most frequent type of acute myocardial infarction (MI) and accounts for the majority of ACS, usually on the background of a nonocclusive coronary thrombus [2].

Multiple pathophysiological mechanisms and cardiovascular risk factors contribute to the development of NSTE-ACS, which calls for a comprehensive and multitargeted treatment approach, including drug therapy, with or without myocardial revascularization [3,4]. A number of pharmaceutical agents are currently available for the management (i.e. treatment and secondary prevention) of NSTE-ACS, including antithrombotic, lipid-lowering, and anti-inflammatory drugs [3,4]. In addition, pharmacotherapies usually administered for treating myocardial ischemia and heart failure (e.g. beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers or mineralocorticoid receptor antagonists) can have a role, but their description goes beyond the scope of this review.

We searched for relevant literature in the field in PubMed (MEDLINE) and clinicaltrials.gov as of July 2022. In this review, we prioritized evidence stemming from trials enrolling only NSTE-ACS patients; however, since many trials also including patients with STEMI are of key importance in supporting current recommendations, we also mentioned them as appropriate. This article reviews current knowledge and advances in the field of pharmacotherapy for patients with NSTE-ACS.

2. Clinical scenarios and pathophysiology

The clinical presentation of NSTE-ACS usually varies based on the time from symptoms onset and the hemodynamic status. Beyond the classic chest pain, atypical presentations (e.g. epigastric pain, gastroenteric symptoms, or isolated dyspnea and fatigue) are more frequent in the elderly, in women, or in patients with diabetes mellitus or chronic kidney disease [5,6].

Approximately two thirds of ACS are caused by the rupture of a lipid-laden coronary plaque, resulting into occlusive (STEMI) or non-occlusive (NSTEMI) thrombosis [7]. Plaque erosion is the second most common mechanism of ACS (~25%), with a platelet-rich thrombus developing on a denuded endothelial surface [8]. Calcific nodules represent another cause of ACS (~5%): consisting

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Article highlights

- Non-ST-segment elevation acute coronary syndromes (NSTE-ACS) are a leading cause of morbidity and mortality, requiring a comprehensive and multitargeted treatment approach, including drug therapy, with or without myocardial revascularization.
- NSTE-ACS patients require prompt pharmacological intervention (i.e. before angiography and percutaneous coronary intervention [PCI]) with antiplatelet and anticoagulant drugs. Pretreatment with aspirin, a parenteral anticoagulant and a statin is indicated as part of the preprocedural management of NSTE-ACS.
- Antithrombotic drugs are the main components of intraprocedural therapy of NSTE-ACS, potentially including both antiplatelet (e.g. glycoprotein IIb/IIIa inhibitors or cangrelor) and anticoagulant drugs (e.g. unfractionated heparin, low-molecular-weight heparin or bivalirudin).
- After PCI for NSTE-ACS, long-term secondary prevention strategies are of the utmost importance to improve clinical outcomes and prevent further adverse events. These strategies include antithrombotic therapy, lipid-lowering agents and anti-inflammatory drugs.
- Novel approaches in cardiovascular secondary prevention are gaining importance, including the adoption of dual antiplatelet therapy modulation strategies and the use of new drugs (e.g. selatogrel, inclisiran, bempedoic acid).

This box summarizes key points contained in the article.

of nodular calcification protruding into the lumen with superimposed thrombus, they are associated with a high incidence of major adverse cardiovascular events (MACE) [9]. Coronary vasospasm (~1-5%), spontaneous coronary artery dissection (~1-4%) and coronary embolism (~1-3%) are additional causes of ACS [10–12]. In addition, ~6% of MI consists of MI with nonobstructive coronary arteries (MINOCA), which is more common in women and non-Caucasians [13–16]. Finally, also the unbalance between oxygen demand and supply to the heart (e.g. sustained tachyarrhythmia, severe bradyarrhythmia, severe hypertension, respiratory failure, shock, severe anemia or hypotension) can cause a MI [17].

Targeting these mechanisms, antithrombotic drugs and lipid-lowering agents are currently the cornerstones of treatment and secondary prevention of NSTE-ACS [2,4]. Additionally, anti-inflammatory therapy is gaining momentum in selected patients at high residual risk of cardiovascular events. Since the majority of suspected or established NSTE-ACS patients are referred to invasive management, we will discuss the available pharmacological options with respect to the time of coronary angiography and percutaneous coronary intervention (PCI), which is the most frequent revascularization modality in this setting.

3. Pharmacotherapy before percutaneous coronary intervention

NSTE-ACS patients require prompt pharmacological intervention (i.e. before angiography and PCI) with antiplatelet and anticoagulant drugs (Table 1). Statin pretreatment has also been advocated [4].

3.1. Antiplatelet therapy

3.1.1. Evidence on preprocedural antiplatelet therapy

The administration of any drug when the coronary anatomy is unknown is usually termed pretreatment [4]. Patients presenting with NSTE-ACS are usually pretreated with aspirin and parenteral anticoagulation. Differently from aspirin pretreatment [18], oral $P2Y_{12}$ inhibitor pretreatment has been debated over time (Table 2). Advantages of pretreatment in determining adequate platelet inhibition at the time of PCI and thus reducing the ischemic burden have to be balanced with an increase in the risk of bleeding, particularly in patients with alternative diagnoses (e.g. MINOCA), requiring surgery (e.g. coronary artery bypass grafting or surgery for aortic dissection) or at high bleeding risk (HBR), such those fulfilling one major or two minor criteria of the Academic Research Consortium – HBR (ARC-HBR) definition [19, 20]. In addition, the pharmacokinetics of the most potent $P2Y_{12}$ inhibitors (i.e. prasugrel or ticagrelor) is characterized by a faster onset of action, which allows for the administration of an effective loading dose after coronary angiography and immediately before PCI [21].

The PCI-CURE trial is a substudy of the CURE trial where 2,658 NSTE-ACS patients undergoing PCI randomly received pretreatment and long-term clopidogrel (i.e. for 9 months) versus placebo (i.e. no-pretreatment) and four-week clopidogrel [22]. Clopidogrel pretreatment followed by long-term therapy reduced one-year MACE compared with placebo (4.5% vs. 6.4%; relative risk [RR] 0.70; 95% confidence interval [CI] 0.50 to 0.97; p = 0.03) [22]. However, the median time from pretreatment to PCI was ~ six days, which clearly limits the applicability of these findings to contemporary practice in NSTE-ACS patients undergoing an early invasive strategy. In the CREDO trial, 2,116 undergoing or at high likelihood of elective PCI were allocated to receive clopidogrel 300 mg loading dose or placebo three-to-24 hours before PCI: pretreatment did not reduce the risk of MACE at 28 days compared to placebo (6.8% vs. 8.3%; relative reduction 18.5%; 95% CI −14.2% to 41.8%; p = 0.23), but signals for a time-to-treatment interaction were noted in a subgroup analysis showing a numerically larger reduction of MACE in patients pretreated more than six hours before PCI (relative reduction 38.6%; 95% CI −1.6% to 62.9%; p = 0.051) [23].

These trials were followed by a number of neutral or negative investigations of pretreatment. The ARMYDA-5 PRELOAD trial enrolled 409 patients undergoing PCI (39% with ACS) to randomly compare the administration of a 600 mg loading dose of clopidogrel four-to-eight hours before PCI or immediately before PCI: despite the evidence of increased platelet reactivity without pretreatment, there was no between-group difference in 30-day MACE (10.3% pretreatment vs. 8.8% no-pretreatment; p = 0.72), with similar rates of bleeding and vascular complications (7.8% vs. 5.4%; p = 0.42) [24]. The ACCOAST trial randomized 4,033 NSTE-ACS patients to prasugrel pretreatment two-to-48 hours before angiography or matching placebo; despite some advantages in platelet reactivity inhibition, pretreatment with prasugrel compared with no-pretreatment did not impact on MACE at seven (10.0% vs. 9.8%; hazard ratio [HR] 1.02; 95% CI 0.84 to 1.25; p = 0.81) or 30 days (10.8% vs. 10.8%; HR 1.00; 95% CI 0.83 to 1.20; p = 0.98). However, the trial was terminated just before completion because of increased rates of major bleeding with pretreatment at both seven (1.3% vs. 0.5%; HR 2.95; 95% CI 1.39 to 6.28; p = 0.003) and 30 days (2.8% vs. 1.5%; HR 1.97; 95% CI 1.26 to 3.08; p = 0.002) [25]. These results were consistent regardless of the timing of pretreatment with respect to coronary angiography [26]. Following the direct and indirect evidence available on ticagrelor and prasugrel pretreatment in the PLATO and ACCOAST trials [25,27], a small trial enrolling 213

Table 1. Dose regimens of available antithrombotic drugs for NSTE-ACS patients.

	Administration route	Loading dose	Maintenance dose	Dose adjustment
Antiplatelet drugs – aspirin				
Aspirin	Oral	150–300 mg (oral) or 75–250 mg (intravenous)	75–100 mg once daily	
Antiplatelet drugs – $P2Y_{12}$ inhibitors				
Clopidogrel	Oral	300–600 mg	75 mg once daily	
Prasugrel	Oral	60 mg	10 mg once daily	5 mg once daily for patients ≥75 years old or <60 Kg
Ticagrelor	Oral	180 mg	90 mg twice daily	60 mg twice daily after 12-month DAPT
Cangrelor	Intravenous	Bolus of 30 µg /Kg	4 µg/Kg/min for at least 2 hours or the duration of PCI (whichever is longer)	
Antiplatelet drugs – GP IIb/IIIa receptor inhibitors				
Abciximab	Intravenous	Bolus of 0.25 mg/Kg	0.125 µg/Kg/min (maximum 10 µg/min) for 12 hours	
Eptifibatide	Intravenous	Double bolus of 180 µg/Kg (second bolus after 10 minutes)	2 µg/Kg/min up to 18 hours	Infusion rate of 1 µg/Kg/min if CrCl <50 ml/minute; not indicated if CrCl <30 ml/min
Tirofiban	Intravenous	Bolus of 25 µg/Kg over 3 minutes	0.15 µg/Kg/min up to 18 hours	Dose should be halved if CrCl <30 ml/min
Anticoagulant drugs				
UFH	Intravenous	Bolus of 70–100 U/Kg	-	Bolus of 50–70 U/Kg if associated with GPI
Enoxaparin	Intravenous	Bolus of 0.5 mg/Kg	-	Increased time between doses if CrCl <30 ml/min
Bivalirudin	Intravenous	Bolus of 0.75 mg/Kg	1.75 mg/Kg/hour for up to 4 hours	Infusion of 1.4 mg/Kg/h if CrCl <60 ml/min; not indicated if CrCl <30 ml/min
Fondaparinux	Subcutaneous	-	2.5 mg once daily (only before PCI)	Not indicated if CrCl <30 ml/min
Rivaroxaban	Oral	-	2.5 mg twice daily (on top of aspirin)	Not indicated if CrCl < 15 ml/min

Abbreviations: CrCl, creatinine clearance; DAPT, dual antiplatelet therapy; ESRD, end-stage renal disease; GPI, glycoprotein IIb/IIIa receptor inhibitors; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; U, units; UFH, unfractionated heparin.

Table 2. Randomized clinical trials of $P2Y_{12}$ inhibitor pretreatment for NSTE-ACS.

Trial	Population	Revascularization strategy	Pretreatment group	Control group	Primary outcome	Results
PCI CURE 2001	Patients with NSTE-ACS (n = 2,658)	GDMT CABG PCI 100%	Clopidogrel (300 mg LD, 75 mg MD) six-to-10 days before PCI	Placebo	Thirty-day cardiovascular death, MI, or urgent target-vessel revascularization	4.5% vs. 6.4%; relative risk 0.70; 95% CI 0.50 to 0.97; p 0.03
CREDO 2002	Patients undergoing elective PCI or with high likelihood of undergoing PCI (n = 2,116)	GDMT CABG PCI 100%	Clopidogrel (600 mg LD, 75 mg MD) three-to-24 hours before PCI	Placebo	One-year incidence of the composite of death, MI, or stroke. Death, MI, or urgent target vessel revascularization at 28 days	8.5% vs. 11.5%; relative risk reduction 26.9%; 95% CI 3.9% to 44.4%; p 0.02 6.8% vs. 8.3%; relative risk reduction 18.5%; 95% CI −14.2% to 41.8%; p 0.23
ARMYDA-5 PRELOAD 2010	Patients with ACS or CCS (n = 409)	GDMT CABG PCI 100%	Clopidogrel (600 mg LD, 75 mg MD) four-to-eight hours before PCI	Clopidogrel (600 mg LD, 75 mg MD) after angiography, prior to PCI	Thirty-day cardiovascular death, MI, or urgent target-vessel revascularization	10.3% vs. 8.8%; p 0.72
ACCOAST 2013	Patients with NSTE-ACS (n = 4,033)	GDMT 25% CABG 6% PCI 69%	Prasugrel (30 mg LD and additional 30 mg if PCI indication was confirmed; 10 or 5 mg MD)	Placebo	Seven-day MACE	10.0% vs. 9.8%; HR 1.02; 95% CI 0.84 to 1.25; p 0.81
Bonello et al. 2015	Patients with NSTE-ACS (n = 213)	GDMT CABG PCI 100%	Ticagrelor (180 mg LD as soon as possible; 90 mg twice daily MD)	Prasugrel (60 mg LD once coronary anatomy is known; 10 mg MD)	Rate of periprocedural myonecrosis (i.e. increase of >5 times the 99th percentiles in troponin-negative patients or a 20% increase in troponin-positive patients)	19.8% vs. 38.3%; p 0.03
ISAR-REACT 5 2020	Patients with ACS (n = 4,018)	GDMT 20% CABG 3% PCI 77%	Ticagrelor (180 mg LD, 90 mg twice daily MD) given as soon as possible after admission and before PCI	Prasugrel (60 mg LD, 10 mg daily MD) given as soon as possible in STEMI or at the time of PCI in NSTEMI patients	One-year incidence of the composite of death, MI, or stroke	9.3% vs. 6.9%; HR 1.36; 95% CI 1.09 to 1.70; p 0.006
DUBIUS 2020	Patients with NSTE-ACS (n = 1,449)	GDMT 24% CABG 7% PCI 69%	No pretreatment; in case of PCI, repeat randomization to ticagrelor (180 mg LD, 90 mg twice daily MD) or prasugrel (60 mg LD, 10 mg daily MD)	Pretreatment with ticagrelor (180 mg LD, 90 mg twice daily MD)	NACE at 30 days	2.9% vs. 3.3%; absolute risk reduction −0.46%; 95% CI −2.87 to 1.89; p 0.50

Results are presented by reporting the effect of interventional strategy versus reference treatment. Abbreviations: ACS, acute coronary syndrome; CABG, coronary artery bypass grafting; CCS, chronic coronary syndrome; CI, confidence interval; GDMT, guideline-directed medical therapy; HR, hazard ratio; LD, loading dose; MACE, major adverse cardiovascular event; MD, maintenance dose; MI, myocardial infarction; NACE, net adverse cardiovascular event; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; STEMI, ST-segment elevation myocardial infarction.

NSTE-ACS patients compared ticagrelor pretreatment and prasugrel at the time of PCI in terms of periprocedural myonecrosis (i.e. increase of cardiac troponin): patients in the ticagrelor group had less periprocedural myonecrosis than those on prasugrel (19.8% vs. 38.3%; p = 0.03), without differences in MACE (4.0% vs. 5.0%; p = 1.00) and major bleeding (7.0% vs. 8.0%; p = 1.00) [28]. Similarly, the ISAR-REACT 5 trial enrolled 4,018 ACS patients to compare ticagrelor (180 mg loading dose as soon as possible) and prasugrel (60 mg loading dose at randomization in STEMI, and treatment initiation postponed until coronary anatomy was known in NSTEMI): at one year, the incidence of MACE was higher with ticagrelor than with prasugrel (9.3% vs. 6.9%; HR 1.36; 95% CI 1.09 to 1.70; p = 0.006), without difference in major bleeding (5.4% vs. 4.8%; HR 1.12; 95% CI 0.83 to 1.51; p = 0.46), therefore supporting prasugrel with a downstream loading dose over routine pretreatment with ticagrelor [29]. Notably, these results were confirmed in a subgroup analysis of NSTE-ACS patients only [30]. Finally, the DUBIUS trial randomized NSTE-ACS patients to a downstream strategy (i.e. no pretreatment and, in case of PCI, second randomization to ticagrelor or prasugrel) or an upstream strategy (i.e. pretreatment with ticagrelor) [31]. The trial was prematurely stopped for futility after the enrolment of 1,449 patients, showing no difference in terms of net adverse cardiovascular events (NACEs) at 30 days (2.9% vs. 3.3%; absolute risk reduction −0.46%; 95% CI −2.87 to 1.89; p = 0.50) [31].

A meta-analysis of 13,226 patients from seven randomized clinical trials (RCTs) showed that pretreatment compared to no-pretreatment was not associated with a difference in 30-day MACE (odds ratio [OR] 0.95; 95% CI 0.78 to 1.15), MI (OR 0.90; 95% CI 0.72 to 1.12) and cardiovascular death (OR 0.79; 95% CI 0.49 to 1.27), while increasing 30-day major bleeding (OR 1.51; 95% CI 1.16 to 1.97; number needed to harm 63) [32].

Importantly, the EARLY trial randomized 709 NSTE-ACS patients who did not receive pretreatment to very early (i.e. within two hours) or delayed (i.e. 12-to-72 hours) angiography: compared to delayed angiography, very early angiography was associated with lower rates of the composite of death or ischemic events at one month (4.4% vs. 21.3%; HR 0.20; 95% CI 0.11 to 0.34; p < 0.001) [33]. These findings should discourage the association of no pretreatment and delayed coronary angiography.

Glycoprotein IIb/IIIa inhibitors (GPIs) can theoretically also be used before PCI. A meta-analysis of 31,402 NSTE-ACS patients not referred to early PCI from six randomized trials showed that GPI were associated with lower rates of death or MI, with an increase in major bleeding as compared to placebo or active control [34]. However, no evidence supports upstream GPI in contemporary patients referred to early angiography and treated with potent $P2Y_{12}$ inhibitors, and therefore this practice is discouraged by current recommendations [35, 36].

3.1.2. Guideline recommendations

Latest guidelines by the European Society of Cardiology (ESC) on NSTE-ACS recommend aspirin pretreatment for all patients with an initial oral loading dose of 150 to 300 mg or an intravenous dose of 75 to 250 mg (class of recommendation [COR] I, level of evidence [LOE] A) [4].

By contrast, routine pretreatment with an oral $P2Y_{12}$ inhibitor is contraindicated in patients in whom coronary anatomy is not known and for whom an early invasive management is planned (COR III, LOE A), whereas it may be considered in patients not referred to an early invasive strategy and without HBR characteristics (COR IIb, LOE C) [4].

Finally, GPIs are not recommended for upstream use (i.e. before coronary anatomy is known) (COR III, LOE A) [4].

In ACS patients undergoing PCI, North-American guidelines for coronary revascularization recommended aspirin and $P2Y_{12}$ inhibitor loading doses (COR 1, LOE B-R), preferably ticagrelor or prasugrel (COR 2a, LOE B-R), without any recommendation supporting pretreatment [37].

3.2. Anticoagulant therapy

3.2.1. Evidence on preprocedural anticoagulation

Anticoagulation aims to inhibit thrombin generation and clot stabilization, and its use if supported by evidence of improved outcomes with unfractionated heparin (UFH) or low-molecular-weight heparin (LMWH) versus no use in patients with NSTE-ACS [38].

The SYNERGY trial randomized 10,027 NSTE-ACS patients to subcutaneous enoxaparin or intravenous UFH. There was no difference in 30-day death or MI (14.0% for enoxaparin vs. 14.5% for UFH; OR 0.96; 95% CI 0.86 to 1.06), with increased major bleeding with enoxaparin (9.1% vs 7.6%; p = 0.008) [39].

Fondaparinux is an alternative option for selected patients (i.e. medically treated or in case of constraints for early invasive evaluation). The OASIS-5 trial randomized 20,078 ACS patients to fondaparinux or enoxaparin for a mean of six days: fondaparinux was noninferior to enoxaparin for the composite of death, MI, or refractory ischemia at nine days (5.8% vs. 5.7%; HR 1.01; 95% CI 0.90 to 1.13) while reducing major bleeding (2.2% vs. 4.1%; HR 0.52; 95% CI 0.44 to 0.61; p < 0.001) [40].

3.2.2. Guideline recommendations

The ESC guidelines on NSTE-ACS recommend parenteral anticoagulation for all NSTE-ACS patients at the time of diagnosis (COR I, LOE A) [4]. In particular, UFH is the first choice in patients undergoing PCI (COR I, LOE A), while fondaparinux is indicated in patients not undergoing early angiography (COR I, LOE B) [4].

3.3. Statins

3.3.1. Evidence on statins before PCI

Pre-treatment with a high-intensity dose of statins has been associated with a reduction in the risk of MACE and contrast-associated acute kidney injury after PCI [41, 42]. In the MIRACL trial, 3,086 NSTE-ACS patients were randomized to atorvastatin or placebo: pretreatment with statin reduced 16-week MACE compared to placebo (14.8% vs. 17.4%, RR 0.84, 95% CI 0.75 to 1.00; p = 0.048), mainly driven by reduced rates of recurrent ischemia requiring revascularization (6.2% vs 8.4%; RR 0.74; 95% CI 0.57 to 0.95; p = 0.02) [41]. Similarly, the ARMYDA-ACS trial compared atorvastatin and placebo before PCI in 171 NSTE-ACS patients: 30-day MACEs were reduced with statin pretreatment (5% vs. 17%; p = 0.01), mainly driven by a reduction in MI (5% vs. 15%; p = 0.04) [43]. Conversely, the SECURE-PCI trial (n = 4,191) showed that two loading doses of atorvastatin 80 mg did not reduce the rate of 30-day MACE compared with placebo (6.2% vs. 7.1%; HR 0.88; 95% CI 0.69 to

1.11; p = 0.27) [44]. However, signals of benefit were noted in a subgroup analysis of patients who ultimately underwent PCI (adjusted HR 0.72; 95% CI 0.54 to 0.97; p = 0.03) [45].

In a meta-analysis of 3,146 statin-naïve patients undergoing PCI from 14 trials, statin pretreatment was associated with a 56% reduction in periprocedural MI (OR 0.44; 95% CI 0.35 to 0.56; p < 0.001); of note, a sensitivity analysis showed a significant reduction only in NSTE-ACS patients (OR 0.18; 95% CI 0.07 to 0.47; p < 0.001) [46].

In addition, the ARMYDA-RECAPTURE trial randomized 383 PCI patients already on statin to receive a 40 mg loading dose of atorvastatin or placebo 12 hours before PCI. The administration of a loading dose was associated with lower rates of 30-day MACE (3.7% vs. 9.4%; OR 0.50, 95% CI 0.20 to 0.80; p = 0.037), particularly among NSTE-ACS patients (3.3% vs. 14.8%; RR reduction 82%; p = 0.027) [47].

3.3.2. Guideline recommendations

The 2019 ESC guidelines on dyslipidemias recommend routine pretreatment or loading with statin (on a background of chronic therapy) in patients undergoing PCI (COR IIa, LOE B) [48].

4. Pharmacotherapy during percutaneous coronary intervention

4.1. Antiplatelet therapy

4.1.1. Evidence on intraprocedural antiplatelet therapy

Antiplatelet drugs for intraprocedural use include oral $P2Y_{12}$ inhibitors, the intravenous $P2Y_{12}$ inhibitor cangrelor and GPIs (i.e. abciximab, eptifibatide and tirofiban) (Table 1). In patients undergoing early angiography, oral $P2Y_{12}$ inhibitors are usually administered after coronary anatomy is known, with other drugs reserved to specific high-risk patients or scenarios or with a bailout role in case of thrombotic complications.

In patients undergoing early angiography (i.e. who did not receive $P2Y_{12}$ pretreatment), a loading dose of an oral $P2Y_{12}$ inhibitor should be usually administered during the procedure [4].

Cangrelor is an intravenous, reversible, short-acting $P2Y_{12}$ inhibitor characterized by a potent and rapidly reversible effect [49]. The CHAMPION PCI (n = 8,877) and CHAMPION PLATFORM (n = 5,362) trials randomly compared cangrelor (bolus of 30 μg/kg plus infusion of 4 μg/kg per minute) with clopidogrel (in patients undergoing PCI for any indication) or placebo (in NSTE-ACS), respectively. Both trials were stopped early for futility, concluding with no difference in the rate of death, MI or ischemia-driven revascularization at 48 hours [50, 51]. However, in the CHAMPION PLATFORM trial, cangrelor was associated with reduced mortality (0.2% vs. 0.7%; OR 0.33; 95% CI 0.13 to 0.83; p = 0.02) and stent thrombosis at 48 hours as compared to placebo (0.2% vs. 0.6%; OR 0.31; 95% CI 0.11 to 0.85; p = 0.02) [51]. Finally, the CHAMPION PHOENIX trial compared cangrelor and clopidogrel (600 or 300 mg loading dose) in 11,145 PCI patients who were $P2Y_{12}$ inhibitor-naïve: compared with clopidogrel, cangrelor reduced the composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours (adjusted OR 0.78; 95% CI 0.66 to 0.93; p = 0.005), without any significant difference in severe bleeding (0.16% vs. 0.11%; OR 1.50; 95% CI 0.53 to 4.22; p = 0.44) [52]. A pooled analysis of patient-level data from the three CHAMPION trials (n = 24,910) showed that cangrelor reduced the incidence of the composite of death, MI, ischemia-driven revascularization, or stent thrombosis at 48 hours (3.8% vs. 4.7%; OR 0.81; 95% CI 0.71 to 0.91; p < 0.001) and stent thrombosis (0.5% vs 0.8%; OR 0.59; 95% CI 0.43 to 0.80, p < 0.001), with increased bleeding (17.5% vs. 13.5%; OR 1.35; 95% CI 1.26 to 1.45; p < 0.001) but no difference in severe or life-threatening bleeding (0.2% vs. 0.2%; OR 1.22; 95% CI 0.70 to 1.22; p = 0.488) [53].

The evidence on GPI is scarce for patients treated with prasugrel or ticagrelor, and for those referred to early coronary angiography. However, GPIs have a residual bailout role in case of thrombotic complications and slow flow, particularly in highly complex PCI or in patients not pretreated with $P2Y_{12}$ inhibitors [4].

4.1.2. Guideline recommendations

ESC guidelines on NSTE-ACS recommend administering a loading dose of ticagrelor (COR I, LOE B), prasugrel (COR I, LOE B) or clopidogrel (COR I, LOE C) to patients proceeding to PCI [4]. Cangrelor is recommended in $P2Y_{12}$ inhibitor-naïve patients undergoing PCI to prevent intra- and postprocedural stent thrombosis (COR IIb, LOE A) [4]. The use of GPI is indicated for bailout reasons, particularly if there is evidence of no-reflow or thrombotic complications (COR IIa, LOE C) [4]. North-American guidelines yielded identical recommendations on GPI in bailout (COR 2a, LOE C-LD) and cangrelor (COR 2b, LOE B-R) [37].

4.2. Anticoagulant therapy

4.2.1. Evidence on intraprocedural anticoagulant therapy

Anticoagulants that can be used during PCI include UFH, enoxaparin and bivalirudin (Table 1). In a meta-analysis of 30,966 patients from 23 studies, enoxaparin significantly reduced the incidence of death (RR 0.66; 95% CI 0.57 to 0.76; p < 0.001; number needed to treat 60) and major bleeding (OR 0.80; 95% CI 0.67 to 0.95; p = 0.009; number needed to harm 83) compared to UFH [54].

Further investigations explored the role of bivalirudin. The MATRIX trial randomized 7,213 ACS patients to either bivalirudin or UFH, showing no difference in 30-day MACE (10.3% vs. 10.9%; RR 0.94; 95% 0.81 to 1.09; p = 0.44) and NACE (11.2% vs. 12.4%; RR 0.89; 95% CI 0.78 to 1.03; p = 0.12). More recently, a subgroup analysis of the VALIDATE-SWEDEHEART trial (n = 3,001) compared bivalirudin and UFH in patients undergoing PCI with radial access and with limited use of GPIs, showing no difference in six-month NACE (12.1% vs. 12.5%; HR 0.96; 95% CI 0.78 to 1.18; p = 0.69) [55]. Later meta-analyses showed that, compared with UFH, bivalirudin was associated with similar or higher risks of ischemic events, with less bleeding, partly explained by an increased use of GPIs with UFH [56, 57].

The OASIS-5 trial supported the use of fondaparinux in ACS; however, a significantly higher rate of catheter thrombosis was noted in the fondaparinux group as compared to

enoxaparin (0.9% vs. 0.4%; RR 3.59; 95% CI 1.64 to 7.84; p = 0.001), therefore questioning the role of fondaparinux during PCI [40].

4.2.2. Guideline recommendations

The ESC guidelines on NSTE-ACS recommend parenteral anticoagulation for all patients during PCI (COR I, LOE A). Intravenous enoxaparin should be considered in patients pretreated with subcutaneous enoxaparin (COR IIa, LOE B), while bivalirudin may be considered as an alternative to UFH (COR IIb, LOE A) [4]. Crossover of anticoagulants is not recommended (COR III, LOE B), with the only exception of adding a single bolus of UFH in patients previously treated with fondaparinux and proceeding to PCI, with the aim to reduce the risk of catheter thrombosis [4].

North-American guidelines recommend UFH for anticoagulation in patients undergoing PCI (COR 1, LOE C-EO) [37]. In patients treated with upstream subcutaneous enoxaparin, UFH should not be used (COR 3-Harm; LOE B-R), while intravenous enoxaparin should be preferred (COR 2b, LOE B-R) [37]. In particular, an intravenous bolus of enoxaparin (0.3 mg/Kg) should be administered if only one dose of subcutaneous enoxaparin was administered or if the last subcutaneous dose was administered eight-to-12 hours earlier; conversely, no additional enoxaparin is needed if patients have received at least two doses and the last dose of subcutaneous enoxaparin was administered within the previous eight hours.

5. Pharmacotherapy after percutaneous coronary intervention

After PCI, a multitargeted secondary prevention therapy is recommended for all NSTE-ACS patients. In particular, one or more antithrombotic drugs and lipid-lowering agents are of crucial importance to reduce the risk of further events and to slow disease progression down. In addition, other classes of drugs (e.g. anti-inflammatory agents) should be considered.

5.1. Antiplatelet therapy

5.1.1. Evidence on antiplatelet therapy after PCI

Dual antiplatelet therapy (DAPT) is usually indicated for 12 months after PCI for NSTE-ACS, irrespective of the stent type. Although clopidogrel, prasugrel and ticagrelor are all oral $P2Y_{12}$ inhibitors approved for use in NSTE-ACS patients undergoing PCI (Table 1), in the absence of contraindications, prasugrel and ticagrelor are preferred over clopidogrel in light of their superior efficacy [27,58]. DAPT in ACS patients can be modulated by three major strategies, namely prolonged DAPT, short DAPT and DAPT de-escalation [4].

The DAPT study randomized 9,961 patients one year after PCI to receive DAPT (aspirin plus clopidogrel or prasugrel) or aspirin plus placebo for additional 18 months: compared to standard DAPT, prolonged DAPT reduced the rates of stent thrombosis (0.4% vs. 1.4%; HR 0.29; 95% CI 0.17 to 0.48; p < 0.001) and MACE (4.3% vs. 5.9%; HR 0.71; 95% CI 0.59 to 0.85; p < 0.001) while increasing moderate or severe bleeding (2.5% vs. 1.6%; difference 1.0; 95% CI 0.4 to 1.5; p = 0.001) between 12 and 30 months [59]. In the PEGASUS-TIMI 54, high-risk patients with a MI one-to-three year before (21,162) were randomized to ticagrelor 90 mg twice daily, ticagrelor 60 mg twice daily or placebo on top of aspirin; compared to placebo, both doses of ticagrelor reduced the incidence of three-year MACE (7.85% for ticagrelor 90 mg vs. 7.77% for ticagrelor 60 mg vs. 9.04% for placebo; HR for ticagrelor 90 mg vs. placebo 0.85; 95% CI 0.75 to 0.96; p = 0.008; HR for ticagrelor 60 mg vs. placebo 0.84; 95% CI 0.74 to 0.95; p = 0.004), with higher rates of major bleeding (2.60% for ticagrelor 90 mg vs. 2.30% for ticagrelor 60 mg vs. 1.06% for placebo; HR for ticagrelor 90 mg vs. placebo 2.69; 95% CI 1.96 to 3.70; p < 0.001; HR for ticagrelor 60 mg vs. placebo 2.32; 95% CI 1.68 to 3.21; p < 0.001) [60]. Collectively, prolonged DAPT reduced MACE at the price of increased bleeding, underscoring the need for careful patient selection (i.e. patients at high ischemic and low bleeding risks) when deciding to prolong DAPT.

Strategies for bleeding risk mitigation include shortening DAPT duration and de-escalating to a lower potency regimen [61,62]. In early trials of short DAPT (Figure 1), stopping the $P2Y_{12}$ inhibitor at six months after PCI was compared to longer durations of DAPT (12-to-24 months): short DAPT did not increase ischemic events, with the exception of MI in the SMART-DATE trial (1.8% vs. 0.8%; HR 2.41; 95% CI 1.15 to 5.05; p = 0.02), enrolling East-Asian ACS patients [63–69]. Subsequent trials tested shorter DAPT durations (i.e. three or four months) followed by aspirin monotherapy, collectively showing noninferiority of short DAPT to standard DAPT with respect to MACE, with a note of caution due to the generally small sample sizes and large noninferiority margins [70–73]. Another approach was tested in three trials investigating $P2Y_{12}$ inhibitor monotherapy after three-month DAPT [74–76]. Compared to standard DAPT, short DAPT reduced the incidence of MACE in the SMART-CHOICE trial (2.5% vs. 2.9%; difference 0.4%; one-sided 95% CI -∞ to 1.3%; p = 0.07 for noninferiority), while the TWILIGHT and TICO trials showed decreases in clinically relevant bleeding (4.0% vs. 7.1%; HR 0.56; 95% CI 0.45 to 0.68; p < 0.001) and NACE (3.9% vs. 5.9%; difference −1.98%; 95% CI −3.50% to −0.45%; HR 0.66; 95% CI 0.48 to 0.92; p = 0.01), respectively [77–79]. Finally, two RCTs investigated an even shorter DAPT duration (i.e. one month) followed by aspirin or clopidogrel monotherapy, showing noninferiority (or even superiority) to standard DAPT in terms of NACE [80,81]. However, these findings were not confirmed in the ACS setting by a post-hoc analysis of the One-Month DAPT trial (aspirin monotherapy) or by the STOPDAPT-2 ACS trial (clopidogrel monotherapy) [82,83]. In the GLOBAL LEADERS trial, ticagrelor monotherapy after one-month DAPT did not overcome standard DAPT in terms of death or Q-wave MI (3.81% vs. 4.37%; rate ratio 0.87; 95% CI 0.75 to 1.01; p = 0.073) [84]; this finding was also confirmed in a subgroup analysis of ACS patients, where there were however signals for advantages in net clinical benefit with ticagrelor monotherapy [85–87]. Interestingly, in the GLASSY substudy, featuring endpoint adjudication by an independent clinical event committee, ticagrelor monotherapy was noninferior (but not superior) to standard DAPT in terms of death or Q-wave MI (7.14% vs. 8.41%; rate ratio 0.85; 95% CI 0.72 to 0.99; p < 0.001 for noninferiority; p = 0.0465 for superiority, with a one-sided type I error of 2.5%) [88]. More recently, the MASTER DAPT trial randomized 4,434 HBR patients to discontinue DAPT immediately (by either stopping aspirin or $P2Y_{12}$ inhibitor) or to continue it for at least two additional months; short DAPT was noninferior to

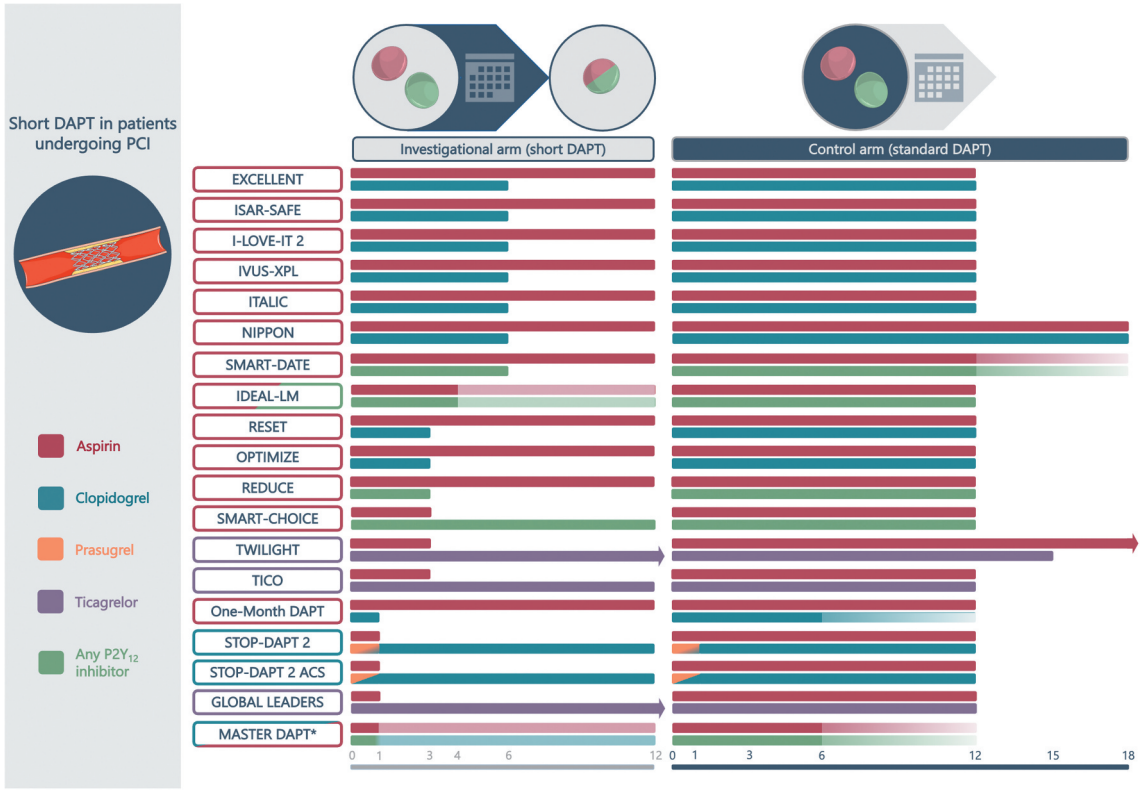

Figure 1. Strategies of short DAPT in patients undergoing PCI Durations of dual antiplatelet therapy (DAPT) in both investigational and control arms of randomized trials of short DAPT in percutaneous coronary intervention (PCI) patients are illustrated. Shadows represent the possibility for a drug to be interrupted at a moment of choice by the investigators within the protocol-mandated timeframe*.
In particular, in the MASTER DAPT trial, patients of the short DAPT group were administered one-month DAPT followed by monotherapy (with aspirin or clopidogrel) up to one year (or at least six months if oral anticoagulation coexists); patients in the control group were treated with DAPT at least for six months (or three months if oral anticoagulation coexists) followed by monotherapy with aspirin or a $P2Y_{12}$ inhibitor (i.e. clopidogrel or any $P2Y_{12}$ inhibitor in patients with or without concomitant oral anticoagulation) thereafter. Part of the figure was generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.
Abbreviations: DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

continued DAPT with regards to NACE (7.5% vs. 7.7%; absolute difference −0.23 %; 95% CI −1.80 to 1.33; p < 0.001 for noninferiority) and MACE (6.1% vs. 5.9%; absolute difference 0.11%; 95% CI −1.29 to 1.51; p = 0.001 for noninferiority), with a significant reduction in major or clinically relevant nonmajor bleeding (6.5% vs. 9.4%; absolute difference −2.82%; 95% CI −4.40 to −1.24; p < 0.001) [89].

DAPT de-escalation, unguided or guided by platelet function testing or genotyping, can be obtained with $P2Y_{12}$ inhibitor dose reduction or switching from prasugrel or ticagrelor to clopidogrel (Figure 2). Trials of unguided de-escalation showed benefits in terms of bleeding compared with standard DAPT, without any increase in ischemic events [90–93]. The only trial of genotype-guided de-escalation was conducted in STEMI patients, while two trials investigated de-escalation guided by platelet function testing, showing no difference between de-escalation and standard DAPT in NACE, MACE and bleeding [94, 95]. A meta-analysis of 69,746 patients from 19 trials showed that unguided de-escalation was associated with less major or minor bleeding (HR 0.48; 95% CI 0.33 to 0.72), without increasing MACE (HR 0.82; 95% CI 0.53 to 1.28) compared to guided de-escalation, without any difference for the type of guidance [96]. Guided de-escalation was also superior to standard therapy in a meta-analysis of 11 randomized trials and three observational studies, showing reductions in MACE, cardiovascular death, MI, stent thrombosis and minor bleeding [97]. In addition, a network meta-analysis of 15 trials showed that a guided selection of $P2Y_{12}$ inhibitor (either by genotyping or platelet function testing) reduced MACE, MI and stent thrombosis, without increasing the rate of bleeding as compared to a routine use of potent $P2Y_{12}$ inhibitors in ACS patients [98].

In a network meta-analysis of 50,602 ACS patients from 29 RCTs, the indirect comparison between DAPT de-escalation and short DAPT showed that, despite no difference between the two strategies in all-cause death (risk ratio 0.98; 95% CI 0.68 to 1.43), DAPT de-escalation reduced the risk of NACE (risk ratio 0.87; 95% CI 0.70 to 0.94) while increasing major bleeding (risk ratio 1.54; 95% CI 1.07 to 2.21) [99].

Finally, two trials with vitamin K antagonists and four with direct oral anticoagulants investigated the optimal duration and composition of antithrombotic therapy in PCI or ACS patients with an established indication for long-term oral anticoagulation, supporting a short period of triple therapy, followed by dual antithrombotic therapy (an antiplatelet agent plus an oral anticoagulant) and ultimately by anticoagulation alone [100–105]. A Bayesian network meta-analysis of 10,969 patients from the four landmark trials of direct oral anticoagulants showed a reduction in the risk of bleeding, without a

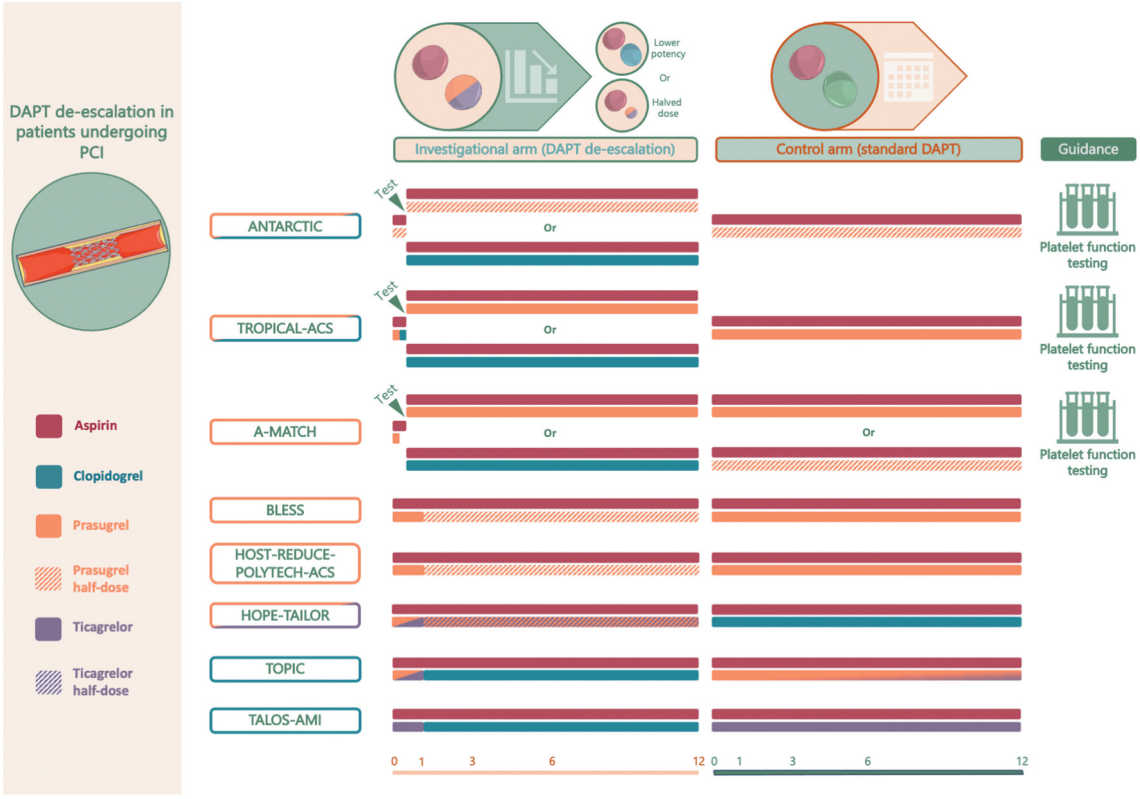

Figure 2. **Strategies of DAPT de-escalation after an ACS** Strategy of dual antiplatelet therapy (DAPT) de-escalation in randomized trials enrolling acute coronary syndrome patients (not ST-segment elevation myocardial infarction only) are illustrated. Shadows represent the possibility for a drug to be interrupted at a moment choice by the investigators within the protocol-mandated timeframe. Part of the figure was generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 unported license.
Abbreviations: DAPT, dual antiplatelet therapy; PCI, percutaneous coronary intervention.

parallel increase in MACE with dual therapy as compared to triple therapy in patients requiring anticoagulation undergoing PCI or presenting with ACS [106].

5.1.2. Guideline recommendations

ESC guidelines on NSTE-ACS recommend DAPT with aspirin and a $P2Y_{12}$ inhibitor for 12 months after PCI (COR I, LOE A) [4]. When the ischemic risk prevails over the bleeding risk, adding a second antithrombotic to aspirin (i.e. prolonged DAPT or dual pathway inhibition [DPI] as described below) is indicated (COR IIa, LOE A and COR IIb, LOE A in patients at high and moderate ischemic risk, respectively) [4]. This strategy is also endorsed by North-American guidelines [37].

In HBR patients, short DAPT by discontinuing the $P2Y_{12}$ inhibitor three months after PCI (COR IIa, LOE B) or by withdrawing aspirin at three-to-six months should be considered (COR IIa, LOE A) [4]. Furthermore, DAPT de-escalation, either unguided or guided, may be considered in patients unsuitable for potent platelet inhibition (COR IIb, LOE A) [4]. Short DAPT (one-to-three months) is also recommended by North-American guidelines for selected HBR patients, with subsequent $P2Y_{12}$ inhibitor monotherapy (COR 2a, LOE A) [37].

Finally, in ACS or PCI patients with an established indication for oral anticoagulation, guidelines recommended a very short period (i.e. one week) of triple therapy (COR I, LOE A), followed by dual therapy with a direct oral anticoagulant and an antiplatelet agent, preferably clopidogrel (COR I, LOE A) up to 12 months, and anticoagulant monotherapy thereafter (COR I, LOE B). In this setting, North-American guidelines recommend aspirin discontinuation after one-to-four weeks, maintaining a $P2Y_{12}$ inhibitor and a direct oral anticoagulant (COR 1, LOE B-R) [37].

5.2. Anticoagulant therapy

5.2.1. Evidence on anticoagulation after PCI

In the last few years, anticoagulation with low-dose rivaroxaban has been proposed as a long-term secondary prevention strategy (Table 1) [107]. In the ATLAS ACS 2-TIMI 51 trial, 15,526 patients on DAPT with aspirin and clopidogrel due to a recent ACS were randomized to rivaroxaban 2.5 mg twice daily, rivaroxaban 5 mg twice daily or placebo for a mean of 13 months and up to 31 months: rivaroxaban was superior to placebo in reducing MACE (9.1% for rivaroxaban 2.5 mg vs. 8.8% for rivaroxaban 5 mg vs. 10.7% for placebo; HR for rivaroxaban 2.5 mg vs. placebo 0.84; 95% CI 0.72 to 0.97; $p = 0.007$; HR for rivaroxaban 5 mg vs. placebo 0.85; 95% CI 0.73 to 0.98; $p = 0.01$); only rivaroxaban 2.5 mg reduced the occurrence of all-cause death (2.9% vs. 4.5%; HR 0.66; 95% CI 0.51 to 0.86; $p = 0.005$) and cardiovascular death (2.7% vs. 4.1%; HR 0.68; 95% CI 0.53 to 0.87; $p = 0.004$) as compared to placebo; both doses of rivaroxaban increased the incidence of bleeding (1.8% for rivaroxaban 2.5 mg vs. 2.4% for rivaroxaban 5 mg vs. 0.6% for placebo; HR for rivaroxaban 2.5 mg vs. placebo 3.46; 95% CI 2.08 to 5.77; $p < 0.001$; HR for rivaroxaban 5 mg vs.

placebo 4.47; 95% CI 2.71 to 7.36; p < 0.001) [108]. The COMPASS trial randomized 27,395 patients with stable atherosclerotic vascular disease to receive either i) DPI with rivaroxaban 2.5 mg twice daily plus aspirin, ii) rivaroxaban 5 mg twice daily, or iii) aspirin alone; while rivaroxaban 5 mg twice daily failed in significantly improving cardiovascular outcomes (likely as the result of premature termination of the trial leading to less events), DPI reduced MACE (4.1% vs. 5.4%; HR 0.76; 95% CI 0.66 to 0.86; p < 0.001) and NACE (4.7% vs. 5.5%; HR 0.80; 95% CI 0.70 to 0.91; p < 0.001) at a mean follow-up of 23 months, despite an increase in major bleeding (3.1% vs. 2.8%; HR 1.70; 95% CI 1.40 to 2.05; p < 0.001) compared to aspirin alone [109]. These findings were confirmed in a subgroup analysis including only patients with coronary artery disease [110].

5.2.2. Guideline recommendations

The ESC guidelines on NSTE-ACS recommend the discontinuation of parenteral anticoagulation immediately after PCI (COR IIa, LOE C) [4]. Rivaroxaban 2.5 mg twice daily is recommended on top of aspirin and clopidogrel in ACS patients with no prior stroke or transient ischemic attack who are at high ischemic and low bleeding risks [4]. Rivaroxaban 2.5 mg twice daily is also recommended on top of aspirin in patients with an ischemic risk prevailing over the bleeding risk (COR IIa, LOE A and COR IIb, LOE A in patients at high and moderate risk of ischemic events, respectively) [4].

5.3. Lipid-lowering therapy

5.3.1. Evidence on lipid-lowering therapy after PCI

Several strategies can be adopted on top of statins for secondary prevention in PCI patients [111]. In the IMPROVE-IT trial, 18,144 ACS patients were randomized to ezetimibe or placebo on top of simvastatin: at seven years, ezetimibe was superior to placebo in reducing MACE (32.7% vs. 34.7%; absolute risk difference 2.0%; HR 0.936; 95% CI 0.89 to 0.99; p = 0.016) [112].

Different trials have been conducted to investigate the role of omega-3 fatty acid for secondary prevention of patients with cardiovascular disease, with contentious results. A meta-analysis of 38 trials showed that these compounds positively affected cardiovascular outcomes [113].

Evolocumab and alirocumab are subcutaneous monoclonal antibodies inhibiting proprotein convertase subtilisin/kexin type 9 (PCSK9). In the FOURIER trial, 27,564 patients with atherosclerotic cardiovascular disease already on statin were randomized to evolocumab or placebo; at 48 weeks, compared to placebo, evolocumab reduced the incidence of MACE (9.8% vs. 11.3%; HR 0.85; 95% CI 0.79 to 0.92; p < 0.001) [114]. These results were also confirmed in a pre-specified subgroup analysis of patients with a recent MI (within 12 months) of the FOURIER trial [115]. Similarly, the ODYSSEY-OUTCOMES trial randomized 18,924 patients with previous ACS to alirocumab or placebo; at a median follow-up of 2.8 years, MACE were reduced with compared to placebo (9.5% vs. 11.1%; HR 0.85; 95% CI 0.78 to 0.93; p < 0.001), driven by a reduction in mortality (3.5% vs. 4.1%; HR 0.85; 95% CI 0.73 to 0.98) [116]. Alirocumab was also recently tested on top of statin in the randomized PACMAN-AMI trial: the two non-infarct-related arteries of 300 patients undergoing PCI for MI were serially studied with intravascular ultrasound, near-infrared spectroscopy, and optical coherence tomography; at 52 weeks, alirocumab was associated with significantly greater coronary plaque regression compared with placebo [117].

Two trials investigated the role of inclisiran, a small interfering ribonucleic acid that inhibits translation of PCSK9. Patients with atherosclerotic cardiovascular disease (n = 1,561) or a risk equivalent (n = 1,617) were enrolled in the ORION-10 and ORION-11 trials, respectively, and were randomized to subcutaneous inclisiran every six months or placebo on top of statin; after 510 days,

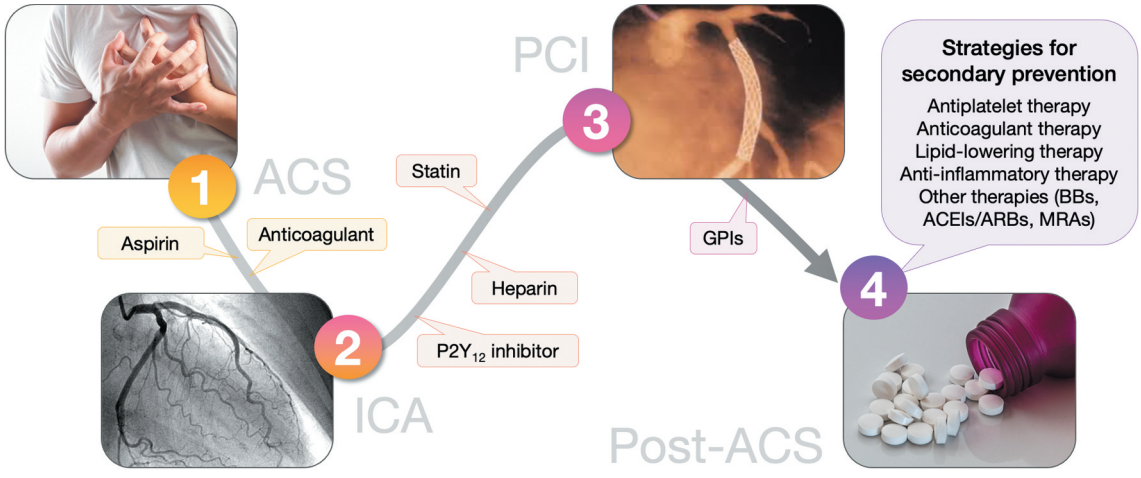

Figure 3. **Antithrombotic therapies and secondary prevention strategies for NSTE-ACS patients** Main pharmacotherapies for NSTE-ACS patients are presented through different stages of the management of such patients (i.e. from symptoms onset to long-term secondary prevention after PCI). In the first phase (i.e. acute event, on the left of the figure), a loading dose of aspirin and a parenteral anticoagulant should be administered, following by other antithrombotic agents and statins, which are recommended before PCI; additional drugs (e.g. GPI) can be considered during PCI in case of thrombotic complications. Finally, a number of pharmacotherapies are recommended as a secondary prevention strategy for the long-term management of NSTE-ACS patients (on the right of the figure).
Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ACS, acute coronary syndrome; ARB, angiotensin II receptor blocker; BB, beta-blocker; GPI, glycoprotein IIb/IIIa inhibitor; ICA, invasive coronary angiography; MRA, mineralocorticoid receptor antagonist; NSTE-ACS, non-ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

Table 3. Guideline recommendations for pharmacotherapy before and during percutaneous coronary intervention.

PHARMACOTHERAPY BEFORE PERCUTANEOUS CORONARY INTERVENTION		
Antiplatelet therapy		
Aspirin is recommended for all patients without contraindications at an initial oral loading of 150–300 mg (or 75–250 mg intravenously)	I	A
In patients undergoing PCI, a loading dose of aspirin, followed by daily dosing, is recommended to reduce ischemic events	1	B-R
Routine pretreatment with an oral $P2Y_{12}$ receptor inhibitor is contraindicated in patients in whom coronary anatomy is not known and for whom an early invasive management is planned	III	A
Pretreatment with a $P2Y_{12}$ receptor inhibitor may be considered in patients with NSTE-ACS who are not planned to undergo an early invasive strategy and do not have a high bleeding risk	IIb	C
In patients with ACS undergoing PCI, a loading dose of $P2Y_{12}$ inhibitor, followed by daily dosing, is recommended to reduce ischemic events	1	B-R
In patients with ACS undergoing PCI, it is reasonable to use ticagrelor or prasugrel in preference to clopidogrel to reduce ischemic events, including stent thrombosis	2a	B-R
Treatment with GPI in patients in whom coronary anatomy is not known is not recommended	III	A
Anticoagulant therapy		
Parenteral anticoagulation is recommended for all patients, in addition to antiplatelet treatment, at the time of diagnosis	I	A
UFH is recommended in patients undergoing PCI	I	A
In cases of medical treatment or logistical constraints for transferring the patient to PCI within the required time frame, fondaparinux is recommended and, in such cases, a single bolus of UFH is recommended at the time of PCI	I	B
Statins		
Routine pretreatment or loading (on a background of chronic therapy) with a high-dose statin should be considered in patients undergoing PCI for an ACS or elective PCI	IIa	B
PHARMACOTHERAPY DURING PERCUTANEOUS CORONARY INTERVENTION		
Antiplatelet therapy		
Prasugrel is recommended in $P2Y_{12}$ receptor inhibitor-naïve patients proceeding to PCI	I	B
Ticagrelor is recommended irrespective of the planned treatment strategy (invasive or conservative)	I	B
Clopidogrel is recommended only when prasugrel or ticagrelor are not available, cannot be tolerated, or are contraindicated	I	C
Cangrelor may be considered in $P2Y_{12}$ receptor inhibitor-naïve patients undergoing PCI	IIb	A
In patients undergoing PCI who are $P2Y_{12}$ inhibitor naïve, intravenous cangrelor may be reasonable to reduce periprocedural ischemic events	2b	B-R
GPI should be considered for bailout if there is evidence of no-reflow or a thrombotic complication	IIa	C
In patients with ACS undergoing PCI with large thrombus burden, no-reflow, or slow flow, intravenous GPI are reasonable to improve procedural success	2a	C-LD
Anticoagulant therapy		
Parenteral anticoagulation is recommended for all patients, in addition to antiplatelet treatment during revascularization procedures	I	A
In patients undergoing PCI, administration of intravenous UFH is useful to reduce ischemic events	1	C-EO
Intravenous enoxaparin should be considered in patients pretreated with subcutaneous enoxaparin	IIa	B
In patients on therapeutic subcutaneous enoxaparin, in whom the last dose was administered within 12 hours of PCI, UFH should not be used for PCI and may increase bleeding	3: Harm	B-R
In patients treated with upstream subcutaneous enoxaparin for unstable angina or NSTE-ACS, the use of intravenous enoxaparin may be considered at the time of PCI to reduce ischemic events	2b	B-R
Bivalirudin may be considered as an alternative to UFH	IIb	A
Crossover of UFH and low-molecular-weight heparin is not recommended	III	B

Blue and black fonts signals for recommendations from North-American and European guidelines, respectively. Abbreviations: ACS, acute coronary syndrome; GPI, Glycoprotein IIb/IIIa inhibitors; NSTE-ACS, Non-ST-segment elevation acute coronary syndrome; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

inclisiran reduced low-density lipoprotein cholesterol (LDL-c) levels by ~50% [118].

Bempedoic acid, an oral inhibitor of adenosine triphosphate citrate lyase, was investigated in the CLEAR Harmony trial: 2,230 patients with either or both atherosclerotic cardiovascular disease or heterozygous familial hypercholesterolemia were randomized to bempedoic acid or placebo (2:1 ratio) on top of maximally tolerated statin therapy; at week 12, bempedoic acid significantly reduced mean LDL-c by ~16% compared to placebo [119]. A similar reduction of LDL-c was shown in patients at high risk of cardiovascular disease in the CLEAR Wisdom trial [120].

5.3.2. Guideline recommendations

The European guidelines set the goals for LDL-c reduction at 50% from baseline and target levels <55 mg/dL (COR I, LOE A) [4, 48]. If the ACS was a recurrence within two years, the target might be lowered to <40 mg/dL (COR IIb, LOE B) [4].

Initiation or continuation of a high-dose statin therapy is recommended in all ACS patients, regardless of initial cholesterol values (COR I, LOE A) [48]. If the LDL-C goal is not achieved after four-to-six weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended (COR I, LOE B); if this combination is not enough to reach the goal after four-to-six weeks, the addition of a PCSK9 inhibitor is recommended (COR I, LOE B) [4, 48]. PCSK9 inhibi-

Table 4. Guideline recommendations for pharmacotherapy after percutaneous coronary intervention.

PHARMACOTHERAPY AFTER PERCUTANEOUS CORONARY INTERVENTION		
Antiplatelet therapy		
In patients with NSTE-ACS treated with coronary stent implantation, DAPT with a $P2Y_{12}$ receptor inhibitor on top of aspirin is recommended for 12 months unless there are contraindications such as excessive risk of bleeding	I	A
Adding a second antiplatelet agent to aspirin for extended long-term secondary prevention should be considered in patients with a high risk of ischemic events and without increased risk of major or life-threatening bleeding	IIa	A
Adding a second antiplatelet agent to aspirin for extended long-term secondary prevention may be considered in patients with moderately increased risk of ischemic events and without increased risk of major or life-threatening bleeding	IIb	A
After stent implantation with high risk of bleeding, discontinuation of $P2Y_{12}$ receptor inhibitor therapy after three months should be considered	IIa	B
After stent implantation in patients undergoing a strategy of DAPT, stopping aspirin after 3–6 months should be considered, depending on the balance between the ischemic and bleeding risk	IIa	A
De-escalation of $P2Y_{12}$ receptor inhibitor treatment may be considered as an alternative DAPT strategy, especially for ACS patients deemed unsuitable for potent platelet inhibition	IIb	A
In selected patients undergoing PCI, shorter-duration DAPT (one-to-three months) is reasonable, with subsequent transition to $P2Y_{12}$ inhibitor monotherapy to reduce the risk of bleeding events	2a	A
In patients with AF, after a short period of TAT (up to one week), DAT is recommended as the default strategy using a DOAC at the recommended dose for stroke prevention and a single oral antiplatelet agent (preferably clopidogrel)	I	A
In patients with AF who are undergoing PCI and are taking OAC, it is recommended to discontinue aspirin treatment after one-to-four weeks while maintaining $P2Y_{12}$ inhibitors in addition to a DOAC or warfarin to reduce the risk of bleeding	1	B-R
Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months	I	B
Anticoagulant therapy		
Discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure	IIa	C
Adding rivaroxaban 2.5 mg twice daily to aspirin for extended long-term secondary prevention should be considered in patients with a high risk of ischemic events and without increased risk of major or life-threatening bleeding	IIa	A
Adding rivaroxaban 2.5 mg twice daily to aspirin for extended long-term secondary prevention may be considered in patients with moderately increased risk of ischemic events and without increased risk of major or life-threatening bleeding	IIb	A
Lipid-lowering therapy		
In all ACS patients without any contraindication or definite history of intolerance, it is recommended that high-dose statin therapy is initiated or continued as early as possible, regardless of initial LDL-C values	I	A
If the LDL-C goal is not achieved after four-to-six weeks with the maximally tolerated statin dose, combination with ezetimibe is recommended	I	B
If the LDL-C goal is not achieved after four-to-six weeks despite maximal tolerated statin therapy and ezetimibe, the addition of a PCSK9 inhibitor is recommended	I	B
For ACS patients whose LDL-C levels are not at goal, despite already taking a maximally tolerated statin dose and ezetimibe, the addition of a PCSK9 inhibitor early after the event (during hospitalization for the ACS event if possible) should be considered	IIa	C
Anti-inflammatory therapy		
Low-dose colchicine (0.5 mg once daily.) may be considered in secondary prevention of cardiovascular disease, particularly if other risk factors are insufficiently controlled or if recurrent events occur under optimal therapy	IIb	A

Blue and black fonts signals for recommendations from North-American and European guidelines, respectively. Abbreviations: ACS, acute coronary syndrome; AF, atrial fibrillation; DAPT, dual antiplatelet therapy; DAT, dual antithrombotic therapy; DAOC, direct oral anticoagulant; LDL-C, low density lipoprotein cholesterol; NSTE-ACS, Non-ST-segment elevation acute coronary syndrome; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; PCSK9, proprotein convertase subtilisin/kexin type 9; TAT, triple antithrombotic therapy; UFH, unfractionated heparin.

tors should be considered early (i.e. during hospitalization for ACS) in patients not meeting the goal of LDL-C despite being already on maximally tolerated statin and ezetimibe (COR IIa, LOE C) [48].

5.4. Anti-inflammatory therapy

5.4.1. Evidence on anti-inflammatory therapy after PCI

Inflammation is part of the 'residual cardiovascular risk,' defined as the remaining risk after optimal treatment of traditional risk factors [121].

The CANTOS trial randomized 10,061 patients with previous MI and high-sensitivity C reactive protein ≥2 mg/L to three different doses of canakinumab (a monoclonal antibody targeting interleukin 1ß) or placebo; at a median follow-up of 3.7 years, canakinumab 150 mg reduced the risk of MACE as compared to placebo (3.86 vs. 4.50 events per 100 patient-years; HR 0.85; 95% CI 0.74 to 0.98; p = 0.021), but increased fatal infections (0.31 events/100 patient-years for combined canakinumab doses vs. 0.18 events/100 patient-years for placebo; p = 0.02) [122].

Trials investigating colchicine in stable coronary artery disease patients showed significant reductions in ischemic events; however, there were signals for increased non-cardiovascular death with colchicine [123, 124]. The COLCOT trial randomized 4,745 patients within 30 days after a MI to colchicine 0.5 mg daily or placebo; at a median follow-up of 22.6 months, colchicine reduced the composite of cardiovascular death, resuscitated cardiac arrest, MI, stroke, or urgent revascularization compared with placebo (5.5% vs. 7.1%; HR 0.77; 95% CI 0.61 to 0.96), while showing higher rates of pneumonia (0.9% vs. 0.4%; p = 0.03) [125].

The COPS trial randomized 795 ACS patients to 12-month colchicine or placebo; at one year, there was no difference in the composite of all-cause death, ACS, unplanned revascularization, or non-cardioembolic ischemic stroke (6.1% vs. 9.5%; HR 0.65; 95% CI 0.38 to 1.09; p = 0.10), while colchicine was associated with higher all-cause (HR 8.20; 95% CI 1.03 to 65.61; p = 0.018) and non-cardiovascular death (HR 3.09; 95% CI 0.32 to 29.71; p = 0.023)

Table 5. Main ongoing randomized clinical trials of pharmacological strategies including patients presenting with NSTE-ACS.

Trial name (clinicaltrials.gov ID)	Investigated strategy	Population	Investigational strategy	Control strategy	Primary outcome(s)	Expected completion
SOS-AMI NCT04957719	Antiplatelet agents (pretreatment)	Patients with confirmed diagnosis of acute myocardial infarction (n = 14,000#)	Selatogrel 16 mg self-injection	Placebo self-injection	Death or MI seven days after self-injection; BARC type 3 or 5 bleeding within two days from self-injection	2025
DAPT-SHOCK-AMI NCT03551964	Antiplatelet agents	Patients with ACS complicated by initial cardiogenic shock (n = 304)	Intravenous cangrelor	Oral ticagrelor	One-month MACE; periprocedural inhibition of ADP-induced platelet aggregation	2024
SWITCH SWEDEHEART NCT05183178	Antiplatelet agents	Patients with ACS undergoing PCI (n = 16,000)	Prasugrel	Ticagrelor	One-year MACE	2025
OPTIMIZE-APT NCT05418556	Antiplatelet agents (short DAPT)	Patients with ACS undergoing imaging-guided PCI (n = 3,944)	Three-month aspirin plus ticagrelor or prasugrel followed by nine-month ticagrelor or prasugrel monotherapy*	One-year DAPT (aspirin plus clopidogrel, prasugrel or ticagrelor, according to clinical setting)	One-year BARC type 2, 3 or 5; one-year NACE; one-year MACE	2028
TARGET-FIRST NCT04753749	Antiplatelet agents (short DAPT)	Patients with ACS undergoing PCI (n = 2,246)	Clopidogrel, prasugrel or ticagrelor after one-month DAPT	DAPT with aspirin plus any $P2Y_{12}$ inhibitor	One-year NACCE; one-year BARC 2, 3 or 5 bleeding	2024
ULTIMATE-DAPT NCT03971500	Antiplatelet agents (short DAPT)	Patients with ACS undergoing PCI (n = 3,486)	Ticagrelor plus matching placebo after one-month DAPT	DAPT with aspirin plus ticagrelor	One-year clinically relevant bleeding; one-year MACCE	2024
STOPDAPT-3 NCT04609111	Antiplatelet agents (short DAPT)	Patients undergoing PCI with ACS or at high risk of bleeding (n = 3,110)	Prasugrel before PCI, followed by clopidogrel one month after PCI	DAPT with aspirin and prasugrel, followed by aspirin monotherapy at one month	One-month BARC 3 or 5 bleeding; one-month MACCE	2024
NEO-MINDSET NCT04360720	Antiplatelet agents (short DAPT)	Patients with ACS undergoing PCI (n = 3,400)	One-year prasugrel or ticagrelor monotherapy	One-year DAPT with aspirin and prasugrel or ticagrelor	One-year MACE; one-year BARC type 2, 3, or 5 bleeding	2024
EASTYLE NCT04755387	Antiplatelet agents (de-escalation)	Patients with ACS undergoing PCI (n = 2,000)	In-hospital ticagrelor 90 mg bid, followed by ticagrelor 60/45 mg bid for 12 months	Ticagrelor 90 mg bid	One-year NACCE; one-year clinically significant bleeding	2024
MATE NCT04937699	Antiplatelet agents (de-escalation)	Patients with ACS undergoing PCI (n = 2,856)	DAPT with aspirin and ticagrelor for one month, followed by ticagrelor monotherapy for five months, and then clopidogrel monotherapy up to one year	DAPT with aspirin plus ticagrelor	One-year NACCE	2025
VERONICA NCT046554052	Antiplatelet agents (de-escalation)	Patients undergoing PCI due to ACS and with low on-treatment platelet reactivity (n = 634)	DAPT with clopidogrel for 11 months	DAPT with prasugrel or ticagrelor for 11 months	One-year NACE	2023
DAN-DAPT NCT05262803	Antiplatelet agents (de-escalation)	Patients low-responders to clopidogrel for CYP2C19 loss-of-function with ACS (n = 2,808)	DAPT with clopidogrel or prasugrel/ticagrelor according to CYP2C19 genotyping for three or six months, followed by aspirin monotherapy.	Six-month DAPT with prasugrel or ticagrelor	One-year BARC type 2, 3, or 5 bleeding; one-year NACE; one-year MACE	2025

(*Continued*)

Table 5. (Continued).

Trial name (clinicaltrials.gov ID)	Investigated strategy	Population	Investigational strategy	Control strategy	Primary outcome(s)	Expected completion
ELECTRA-SIRIO NCT04718025	Antiplatelet agents (de-escalation)	Patients with ACS (n = 4,500)	One-month DAPT with aspirin and ticagrelor 90 mg bid for 30 days, followed by aspirin and ticagrelor 60 mg bid up to 12 months (group one); DAPT with aspirin and ticagrelor 90 mg bid for 30 days, followed by DAPT with aspirin and ticagrelor up three months and finally ticagrelor 60 mg bid plus placebo up to 12 months (group two)	DAPT with ticagrelor 90 mg bid and aspirin for 12 months	One-year major bleeding; one-year MACE	2023
EVOLVE-MI NCT05284747	Lipid-lowering agents	Patients with STEMI or NSTEMI (n = 4,000)	Evolocumab every two weeks on top of standard of care	Standard of care	MACE at the end of the study (approximately 3.5 years)	2027

* This strategy refers to ACS patients only; in CCS patients, the investigational arm consists of one-month DAPT with aspirin and clopidogrel, followed by clopidogrel monotherapy for 11 months.
# Sample size refers to randomized patients; the primary endpoint will be evaluated only in those self-injecting selatogrel.
Abbreviations: ACS, acute coronary syndrome; ADP, adenosine diphosphate; BARC, bleeding academic research consortium; bid, bis in die (twice daily); DAPT, dual antiplatelet therapy; ID, identification number; LDL-c, low-density lipoprotein cholesterol; MACE, major adverse cardiovascular event; n, number of patients; MACCE, major adverse cardiac and cerebrovascular event; NACE, net adverse cardiovascular event; NACCE, net adverse cardiac and cerebrovascular events; NCT, clinicaltrials.gov identifier; NSTE-ACS, non-ST-segment acute coronary syndrome; NSTEMI, non-ST-segment elevation myocardial infarction; .STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention.

[126]. A small trial randomized 249 ACS patients to colchicine 0.5 mg daily or placebo for 6 months, therefore confirming the benefit of colchicine in MACE reduction (6.7% vs. 21.7%; HR 1.64; 95% CI 1.31 to 2.05; p = 0.001) [127].

A meta-analysis of 11,594 patients with stable coronary artery disease or ACS showed that colchicine reduced the incidence of MACE compared with placebo (HR 0.68; 95% CI 0.54 to 0.81), with no significant differences in safety endpoints [128].

5.4.2. Guideline recommendations

The 2021 ESC guidelines on cardiovascular prevention recommend colchicine (0.5 mg once daily) for secondary prevention, particularly if other risk factors are insufficiently controlled or in case of recurrent events under optimal therapy (COR IIb, LOE A) [129].

6. Conclusions

Patients presenting with NSTE-ACS require a multitargeted approach to reduce the risk of further complications and mortality, regardless of whether myocardial revascularization is indicated. A number of options are currently available for treatment and secondary prevention of NSTE-ACS, mainly including antithrombotic therapy, lipid-lowering agents, and anti-inflammatory drugs. Combining these drugs is crucial to improve clinical outcomes of NSTE-ACS patients, but several factors should be considered, particularly with regards to the individual patient risk profiles and specific treatment objectives. Randomized trials and societal guidelines inform the optimal pharmacological management of NSTE-ACS patients; however, further studies are expected to provide relevant information, especially on novel therapeutical targets and drugs as well as patient selection.

7. Expert opinion

Pharmacotherapy for NSTE-ACS patients is intended to treat acute manifestations and to prevent the development of further ischemic events. Different drugs can be adopted, including antithrombotics, lipid-lowering agents, anti-inflammatory drugs (Figure 3). Guideline recommendations are summarized in Table 3 and Table 4. Several relevant randomized trials are ongoing, aiming at fulfilling current gaps in knowledge with regards to many aspects of such pharmacotherapy (Table 5).

In the preprocedural phase, the management of NSTE-ACS is centered around pretreatment, which carries some drawbacks, including an increased risk of bleeding in the case of antithrombotic therapy. While pretreating with aspirin, an anticoagulant and a statin is supported by solid evidence, pretreatment with oral $P2Y_{12}$ inhibitors has been more debated: early studies showed promising results that were not confirmed by more recent trials [22–25, 28, 29, 31]. Of note, different strategies have been adopted depending on the specific $P2Y_{12}$ inhibitor (i.e. no pretreatment with prasugrel), therefore contributing to some difficulty in disentangling the effects of the drug from those of the strategy. Importantly, the evidence on $P2Y_{12}$ inhibitor pretreatment was derived in the setting of patients undergoing invasive management,

while its role in case of delayed coronary angiography is more debated. A different strategy for pretreatment will be investigated by the SOS-AMI trial (NCT04957719), which will randomize 14,000 MI patients to a subcutaneous $P2Y_{12}$ inhibitor (selatogrel 16 mg) or placebo for self-injection even before the first medical contact in case of ACS recurrency; the primary ischemic and bleeding outcomes will be evaluated at very short term (from two to seven days) only among patients accomplishing self-injection. Following the results of the ISAR-REACT 5 trial, the comparison of prasugrel and ticagrelor is another interesting area of research: the SWITCH SWEDEHEART trial (NCT05183178) is a stepped wedge cluster trial in which administrative regions in Sweden act as clusters: all the regions were initially using ticagrelor for ACS patients and, every nine months, a region switches from ticagrelor to prasugrel in a randomized order; the primary outcome will be the composite of death, MI or stroke at one year and will target enrollment of 16,000 ACS patients [130].

The main drugs used during PCI are represented by parenteral antiplatelet agents (i.e. GPIs and cangrelor) and anticoagulants (i.e. UFH, LMWH, bivalirudin). In the era of potent $P2Y_{12}$ inhibitor, GPIs are not indicated for upstream use and their role is current limited to bailout use in case of thrombotic intraprocedural complications; another potential application is bridging therapy in patients undergoing surgery shortly after PCI with stent implantation [131]. Cangrelor is increasingly used in $P2Y_{12}$ inhibitor-naïve patients, particularly in case of high risk of thrombotic complications to reach a more rapid and potent onset of platelet inhibition; in addition, cangrelor has also a rapid offset of action that allows for its use as a bridging therapy in patients referred for cardiac or noncardiac surgery requiring DAPT interruption [131,132].

After PCI, antithrombotic, lipid-lowering and anti-inflammatory drugs are recommended to reduce further the risk of thrombotic complications. DAPT can be modulated based on the individual ischemic and bleeding risk profiles [133,134]. Although a number of studies have been conducted for each strategy, optimal modalities of DAPT modulation remains an area of uncertainty. Indeed, several options are available, including shortening DAPT to three or to one month, by either withdrawing aspirin or stopping the $P2Y_{12}$ inhibitor, and de-escalating to halved dose of $P2Y_{12}$ inhibitor or to a lower potency drug (i.e. from prasugrel or ticagrelor to clopidogrel) that can be either unguided or guided by platelet function testing or genotyping. Whether any of these strategies should be prioritized is currently unknown, but differential benefits and drawbacks of each strategy should be considered. DAPT de-escalation seems to confer a higher degree of ischemic protection but it increases the bleeding risk as it still consists of the combination of two antiplatelet drugs; therefore, it is indicated in ACS patients to avoid the effects of full-dose potent $P2Y_{12}$ inhibitors (i.e. prasugrel or ticagrelor) while preserving benefits of DAPT in the prevention of thrombotic complications [99]. A few trials on different de-escalation strategies are still ongoing (Table 5). Conversely, short DAPT consists of an early transition to a monotherapy regimen, primarily aimed to reduce the risk of bleeding: its use was demonstrated to be safe also in terms of ischemic protection in the setting of chronic coronary syndromes, while several concerns arose with shortest (i.e. one-month) DAPT durations in ACS patients [82,83]. Ongoing trials are investigating short DAPT regimens (Table 5), including an upstream $P2Y_{12}$ inhibitor monotherapy: the NEO-MINDSET trial (NCT04360720) will compare a monotherapy with prasugrel or ticagrelor (i.e. aspirin stopped the day of PCI) with one-year standard DAPT in ACS patients; similarly, the STOPDAPT 3 trial (NCT04609111) will enroll ACS or HBR patients to investigate prasugrel monotherapy started before PCI followed by clopidogrel monotherapy at one month as compared to one-month DAPT with aspirin and prasugrel followed by aspirin monotherapy.

Finally, novel approaches in cardiovascular secondary prevention are gaining importance, including the use of inclisiran and bempedoic acid (which have become available for clinical use) and anti-inflammatory drugs, mainly colchicine (Table 5).

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