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ΠΡΟΓΡΑΜΜΑ ΜΕΤΑΠΤΥΧΙΑΚΩΝ ΣΠΟΥΔΩΝ
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Μεταπτυχιακή Διπλωματική Εργασία

"ΑΝΤΙΘΡΟΜΒΩΤΙΚΗ ΑΓΩΓΗ ΣΤΑ ΟΞΕΑ ΣΤΕΦΑΝΙΑΙΑ ΣΥΜΒΑΝΤΑ.ΝΕΟΤΕΡΑ ΔΕΔΟΜΕΝΑ"

υπό

ΜΑΡΙΑ ΟΙΚΟΝΟΜΟΥ

Ειδικός Καρδιολόγος

Υπεβλήθη για την εκπλήρωση μέρους των

απαιτήσεων για την απόκτηση του

Διπλώματος Μεταπτυχιακών Σπουδών

«Θρόμβωση και Αντιθρομβωτική Αγωγή»

Λάρισα, 2025

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FACULTY OF MEDICINE
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MSc COURSE
THROMBOSIS AND ANTITHROMBOTIC TREATMENT

Master of Science Thesis

" ANTITHROMBOTIC TREATMENT IN ACUTE CORONARY SYNDROMES. LATEST DATA."

by

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Submitted to fulfil part of the

requirements for the acquisition of the

Diploma of MSc Studies in

“Thrombosis and Antithrombotic Treatment”

Larissa, 2025

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Acknowledgements

Upon the completion of this thesis, I feel the need to express my sincere gratitude to all those who have significantly contributed to my journey and to the successful completion of this endeavor.

First and foremost, I would like to extend my heartfelt thanks to Mr. Konstantinos Pappas, Director of the National Health System at the 2nd Cardiology Department of the University Hospital of Ioannina, as well as to Professor of Cardiology Mr. Grigorios Giamouzis, for their exceptional guidance, dedicated support, and valuable contribution to the scientific foundation of this work.

Special mention must be made of Professor of Cardiology Mr. Ioannis Kanonidis, who served as an important mentor during my cardiology residency at the Hippokration Hospital of Thessaloniki. His trust, encouragement, and the opportunities he provided played a vital role in my clinical and scientific development. His guidance, knowledge, and inspiring approach have left a profound mark on my professional path.

I warmly thank my husband, Georgios Dimitriadis, for his unwavering support, patience, and love, which have been a steadfast pillar throughout my studies and the writing of this thesis.

I am deeply grateful to my children, Eleftheria and Sarantis, for being an endless source of inspiration, strength, and joy, as well as to my parents, for their devotion, the values they instilled in me, and their enduring support at every step of my journey.

To all of you, I owe the completion of this important chapter in my life, and I thank you from the bottom of my heart.

Ευχαριστίες

Με την ολοκλήρωση της παρούσας διπλωματικής εργασίας, αισθάνομαι την ανάγκη να εκφράσω τις ειλικρινείς μου ευχαριστίες σε όσους συνέβαλαν καθοριστικά στην πορεία μου και στην επιτυχία του παρόντος εγχειρήματος.

Αρχικά, θα ήθελα να εκφράσω τις θερμότερες ευχαριστίες μου στον κ. Κωνσταντίνο Παππά, Διευθυντή Ε.Σ.Υ. της Β' Καρδιολογικής Κλινικής του ΠΓΝ Ιωαννίνων, καθώς και στον Καθηγητή Καρδιολογίας κ. Γρηγόριο Γιαμούζη, για την εξαιρετική καθοδήγηση, την αφοσιωμένη υποστήριξη και την πολύτιμη συμβολή του στην επιστημονική τεκμηρίωση της παρούσας εργασίας.

Ιδιαίτερη μνεία οφείλω στον Καθηγητή Καρδιολογίας κ. Ιωάννη Κανονίδη, ο οποίος αποτέλεσε σημαντικό μέντορα κατά την ειδικότητά μου στην Καρδιολογία στο Ιπποκράτειο Νοσοκομείο Θεσσαλονίκης με την εμπιστοσύνη, την ενθάρρυνση και τις ευκαιρίες που μου παρείχε να εξελιχθώ κλινικά και επιστημονικά. Η καθοδήγηση, η γνώση και η εμπνευσμένη του προσέγγιση άφησαν βαθύ αποτύπωμα στην επαγγελματική μου πορεία.

Θερμά ευχαριστώ τον σύζυγό μου, Γεώργιο Δημητριάδη, για την αμέριστη στήριξη, την υπομονή και την αγάπη του, που αποτέλεσαν ακλόνητο στήριγμα καθ' όλη τη διάρκεια των σπουδών και της συγγραφής της παρούσας εργασίας.

Ευχαριστώ από καρδιάς τα παιδιά μου, Ελευθερία και Σαράντη, για την αστείρευτη πηγή έμπνευσης, δύναμης και χαράς που μου προσφέρουν καθημερινά, καθώς και τους γονείς μου, για την αφοσίωσή τους, τις αξίες που μου ενστάλαξαν και τη διαχρονική τους υποστήριξη σε κάθε μου βήμα.

Σε όλους εσάς οφείλω την ολοκλήρωση αυτού του σημαντικού σταδίου της ζωής μου και σας ευχαριστώ βαθύτατα.

Περίληψη:

Τα οξέα στεφανιαία σύνδρομα (Acute Coronary Syndromes – ACS) παραμένουν μία από τις κυριότερες αιτίες καρδιαγγειακής θνησιμότητας παγκοσμίως. Η διαδερμική στεφανιαία παρέμβαση (Percutaneous Coronary Intervention – PCI) συνιστά την καθιερωμένη θεραπευτική στρατηγική πρώτης γραμμής σε ασθενείς με ACS, αποδεδειγμένα μειώνοντας τη θνησιμότητα και τα ποσοστά νοσηρότητας τόσο σε ελεγχόμενες μελέτες όσο και σε ρεαλιστικές συνθήκες καθημερινής κλινικής πρακτικής. Ωστόσο, παρά τη βελτίωση των κλινικών εκβάσεων, οι ασθενείς που υποβάλλονται σε PCI εξακολουθούν να διατρέχουν σημαντικό κίνδυνο υποτροπής μείζονων ανεπιθύμητων καρδιαγγειακών συμβαμάτων (Major Adverse Cardiovascular Events – MACE), όπως έμφραγμα του μυοκαρδίου, θάνατο και ισχαιμικά αγγειακά επεισόδια. Η χορήγηση αντιαιμοπεταλιακής και/ή αντιπηκτικής αγωγής συνιστά θεμέλιο λίθο της δευτερογενούς πρόληψης, μειώνοντας την επίπτωση συμβαμάτων που σχετίζονται με τη θρόμβωση του stent, την αναστένωση του αγγείου-στόχου και τη συστηματική αρτηριακή θρομβογένεση. Η διπλή αντιαιμοπεταλιακή αγωγή (Dual Antiplatelet Therapy – DAPT), που συνδυάζει ασπιρίνη με έναν αναστολέα του P2Y12 υποδοχέα, αποτελεί την καθιερωμένη θεραπευτική επιλογή μετά από PCI. Ωστόσο, η παρατεταμένη χορήγηση DAPT συνδέεται με αυξημένο αιμορραγικό φορτίο, συμπεριλαμβανομένων μείζονων ή απειλητικών για τη ζωή αιμορραγιών, γεγονός που δυνητικά επιβάλλει την πρόωρη διακοπή της θεραπείας και συνεπακόλουθα αυξάνει τον κίνδυνο θρόμβωσης του stent. Για την ελαχιστοποίηση του αιμορραγικού κινδύνου, έχουν προταθεί στρατηγικές τροποποίησης της διάρκειας της DAPT, όπως βραχυχρόνια χορήγηση (π.χ. ≤3 μηνών) ή στρατηγικές “de-escalation” της αγωγής, χωρίς ωστόσο να παραγνωρίζεται ο κίνδυνος ανεπαρκούς ισχαιμικής κάλυψης. Από την άλλη πλευρά, η άκριτη παράταση της DAPT πέραν των συνιστώμενων χρονικών πλαισίων μπορεί να οδηγήσει σε αποτρέψιμες αιμορραγικές επιπλοκές. Η ορθολογική προσέγγιση απαιτεί εξατομικευμένη σταδιοποίηση του αιμορραγικού και ισχαιμικού κινδύνου, ιδιαίτερα σε ασθενείς με υψηλό προφίλ κινδύνου και στους οποίους συνυπάρχει ανάγκη ταυτόχρονης χορήγησης από του στόματος αντιπηκτικής αγωγής (π.χ. σε μη βαλβιδική κολπική μαρμαρυγή). Η σύγχρονη κατεύθυνση της θεραπευτικής στρατηγικής εγκαταλείπει την προσέγγιση «one-size-fits-all» και υιοθετεί την έννοια της προσωποποιημένης ιατρικής, όπου η επιλογή και η διάρκεια της αντιθρομβωτικής αγωγής καθορίζονται με βάση πολυπαραγοντικά κριτήρια. Προς τούτο, έχουν αναπτυχθεί και επικυρωθεί πολυάριθμα εργαλεία πρόβλεψης και βαθμολόγησης κινδύνου, όπως τα σκορ PRECISE-DAPT, DAPT, και ARC-HBR, τα οποία συνδράμουν τους κλινικούς ιατρούς στη διαστρωμάτωση του κινδύνου και στη λήψη αποφάσεων βάσει αποδείξεων. Παρά ταύτα, η τελική κλινική απόφαση εξακολουθεί να βασίζεται στη σύνθεση της συνολικής κλινικής εικόνας, στην εμπειρία του θεράποντος ιατρού και στην εξατομικευμένη στάθμιση του αιμορραγικού έναντι του ισχαιμικού κινδύνου.

Λέξεις κλειδιά: αντιθρομβωτική αγωγή, από του στόματος αντιπηκτική αγωγή, δευτερογενής πρόληψη, διαδερμική στεφανιαία παρέμβαση, διαστρωμάτωση κινδύνου, διπλή αντιαιμοπεταλιακή αγωγή, εξατομικευμένη θεραπεία, ισχαιμικός κίνδυνος, κριτήρια arc-hbr, μείζονα ανεπιθύμητα καρδιαγγειακά συμβάματα, οξέα στεφανιαία σύνδρομα, σκορ precise-dapt, στρατηγική μείωσης έντασης της θεραπείας, θρόμβωση του στεντ, αιμορραγικός κίνδυνος.

Abstract:

Acute coronary syndromes (ACS) remain one of the leading causes of cardiovascular mortality worldwide. Percutaneous coronary intervention (PCI) is the established first-line therapeutic strategy in patients with ACS, demonstrably reducing mortality and morbidity rates in both controlled clinical trials and real-world clinical practice. However, despite the improvement in clinical outcomes, patients undergoing PCI continue to face a significant risk of major adverse cardiovascular events (MACE), such as myocardial infarction, death, and ischemic cerebrovascular events. The administration of antiplatelet and/or anticoagulant therapy constitutes a cornerstone of secondary prevention, reducing the incidence of events associated with stent thrombosis, target vessel restenosis, and systemic arterial thrombogenesis. Dual antiplatelet therapy (DAPT)—combining aspirin with a P2Y12 receptor inhibitor—is the standard therapeutic option following PCI. Nonetheless, prolonged DAPT is associated with an increased bleeding burden, including major or life-threatening bleeding events, which may necessitate premature discontinuation of therapy and subsequently increase the risk of stent thrombosis. To minimize bleeding risk, strategies modifying DAPT duration have been proposed, such as short-term administration (e.g., ≤3 months) or “de-escalation” approaches, though the risk of insufficient ischemic protection must not be overlooked. On the other hand, indiscriminate extension of DAPT beyond recommended time frames may lead to avoidable hemorrhagic complications. A rational approach requires individualized stratification of both bleeding and ischemic risk, particularly in high-risk patients and in those requiring concomitant oral anticoagulation (e.g., in non-valvular atrial fibrillation). The current direction in therapeutic strategy abandons the "one-size-fits-all" model and embraces the concept of personalized medicine, in which the selection and duration of antithrombotic therapy are guided by multiparametric criteria. To this end, several validated risk prediction and scoring tools have been developed, such as PRECISE-DAPT, DAPT, and ARC-HBR scores, which assist clinicians in risk stratification and evidence-based decision-making. Nonetheless, the final clinical decision remains dependent on the synthesis of the overall clinical picture, the physician’s experience, and the individualized balancing of bleeding versus ischemic risk.

Keywords: Acute Coronary Syndromes (ACS), Percutaneous Coronary Intervention (PCI), Dual Antiplatelet Therapy (DAPT), Major Adverse Cardiovascular Events (MACE), Stent Thrombosis, Bleeding Risk, Ischemic Risk, Risk Stratification, Oral Anticoagulation, Personalized Therapy, PRECISE-DAPT score, ARC-HBR criteria, De-escalation Strategy, Secondary Prevention, Antithrombotic Therapy

Abbreviations and Acronyms

ACC American College of Cardiology

ACS acute coronary syndromes

AF atrial fibrillation

AHA American Heart Association

AMI acute myocardial infarction

ASA acetylsalicylic acid

CABG coronary artery bypass grafting

CAD coronary artery disease

CCS Chronic coronary syndrome

CVD cardiovascular disease

CHD Coronary heart disease

CS cardiogenic shock

cTnI troponin I

DAPT dual antiplatelet therapy

DSMB data safety and monitoring board

ECG electrocardiogram

ESC European Society of Cardiology

LMWH low-molecular-weight heparin

MACE major adverse cardiac events

MACCE major adverse cardiac and cerebrovascular events

MI myocardial infarction

NACE net adverse clinical events

NSTE non-ST-elevation

PAD peripheral artery disease

PCI percutaneous coronary intervention

PPI proton pump inhibitor

STE ST-elevation

TAT Triple antithrombotic therapy

UA unstable angina

UFH unfractionated heparin

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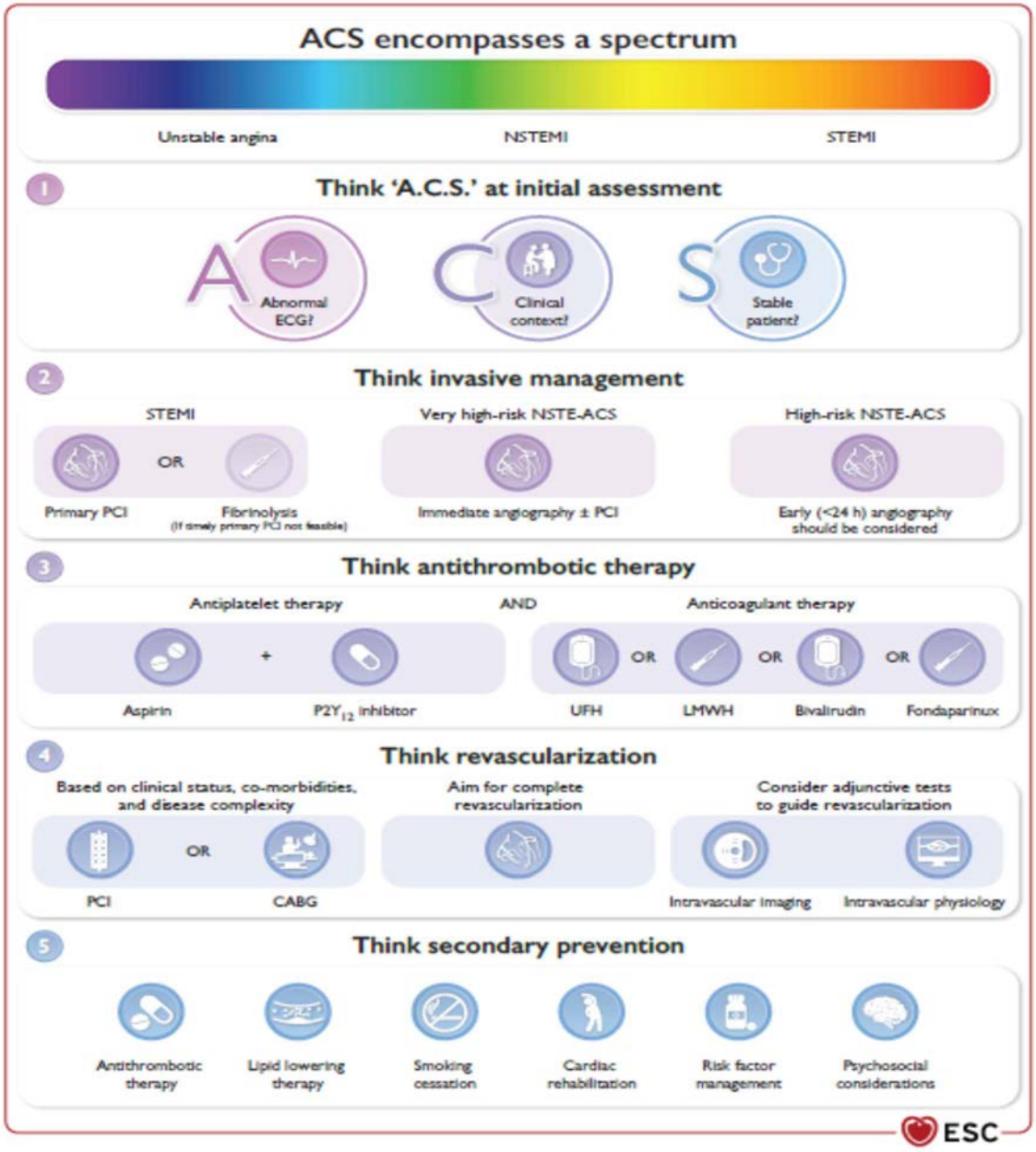
2.Introduction

Acute coronary syndromes (ACS) are most commonly triggered by the either rupture or erosion of an unstable atherosclerotic plaque within a coronary artery. This event typically leads to partial or complete thrombotic occlusion and/or distal microembolization, resulting in reduced myocardial blood flow and subsequent ischemia[1]. ACS encompasses three interrelated clinical entities: (1) ST-segment elevation myocardial infarction (STEMI), (2) non–ST-segment elevation myocardial infarction (NSTEMI), and (3) unstable angina. The initial evaluation and classification of ACS should be guided by the patient's clinical presentation, electrocardiogram (ECG) findings, and cardiac troponin (cTn) levels.

The major aspects of the management of patients with ACS:



2.1. Definition: Acute coronary syndromes

Acute coronary syndromes (ACS) represent a continuum of clinical conditions precipitated by acute myocardial ischemia and encompass a wide range of presentations, from unstable angina (UA) to non–ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). These conditions are typically characterized by recent changes in clinical symptoms such as chest pain or discomfort, which may occur with or without accompanying alterations on a 12-lead electrocardiogram (ECG) and with or without elevations in cardiac troponin (cTn) levels. The classification and diagnosis of ACS rely on a combination of clinical presentation, ECG findings, and cardiac biomarker analysis, most notably high-sensitivity troponin assays [2,3].

Patients presenting with suspected ACS may ultimately be diagnosed with either acute myocardial infarction (AMI) or unstable angina. The diagnosis of myocardial infarction is contingent upon the detection of myocardial necrosis, indicated by elevated cardiac troponin values, and is defined according to the Fourth Universal Definition of MI [4]. This consensus definition includes five types of MI, with type 1 MI—caused by a primary coronary event such as plaque rupture, erosion, or dissection—being the most prevalent in the setting of ACS [4,5].

In contrast, unstable angina is characterized by myocardial ischemia that occurs at rest or with minimal physical activity, without evidence of cardiomyocyte injury or necrosis. From a clinical perspective, it typically presents as newly developed severe chest pain, a worsening pattern of previously stable angina—in terms of frequency, intensity, or duration—or anginal symptoms that arise shortly after a recent myocardial infarction[3].

Importantly, while UA does not involve myocyte death (and hence lacks cTn elevation), it still signifies a high-risk state due to active ischemia and often shares a common pathophysiological substrate with MI—namely, atherosclerotic plaque instability and thrombosis [2,3].

ACS presentations vary widely, ranging from asymptomatic or minimally symptomatic patients to those with ongoing ischemic chest pain, hemodynamic compromise, cardiac arrest, or cardiogenic shock. Consequently, prompt and accurate triage is critical. Initial patient classification is typically based on ECG findings at the time of presentation. ST-segment elevation indicates a need for urgent reperfusion therapy, whereas its absence necessitates further risk stratification using biomarkers (especially cTn) and clinical features. Subsequent classification into NSTEMI or UA is then determined by the presence or absence of cardiac biomarker elevation [2,6].

Importantly, ACS is a dynamic clinical entity. Patients may evolve from one diagnostic category to another—for example, from UA to NSTEMI—during the

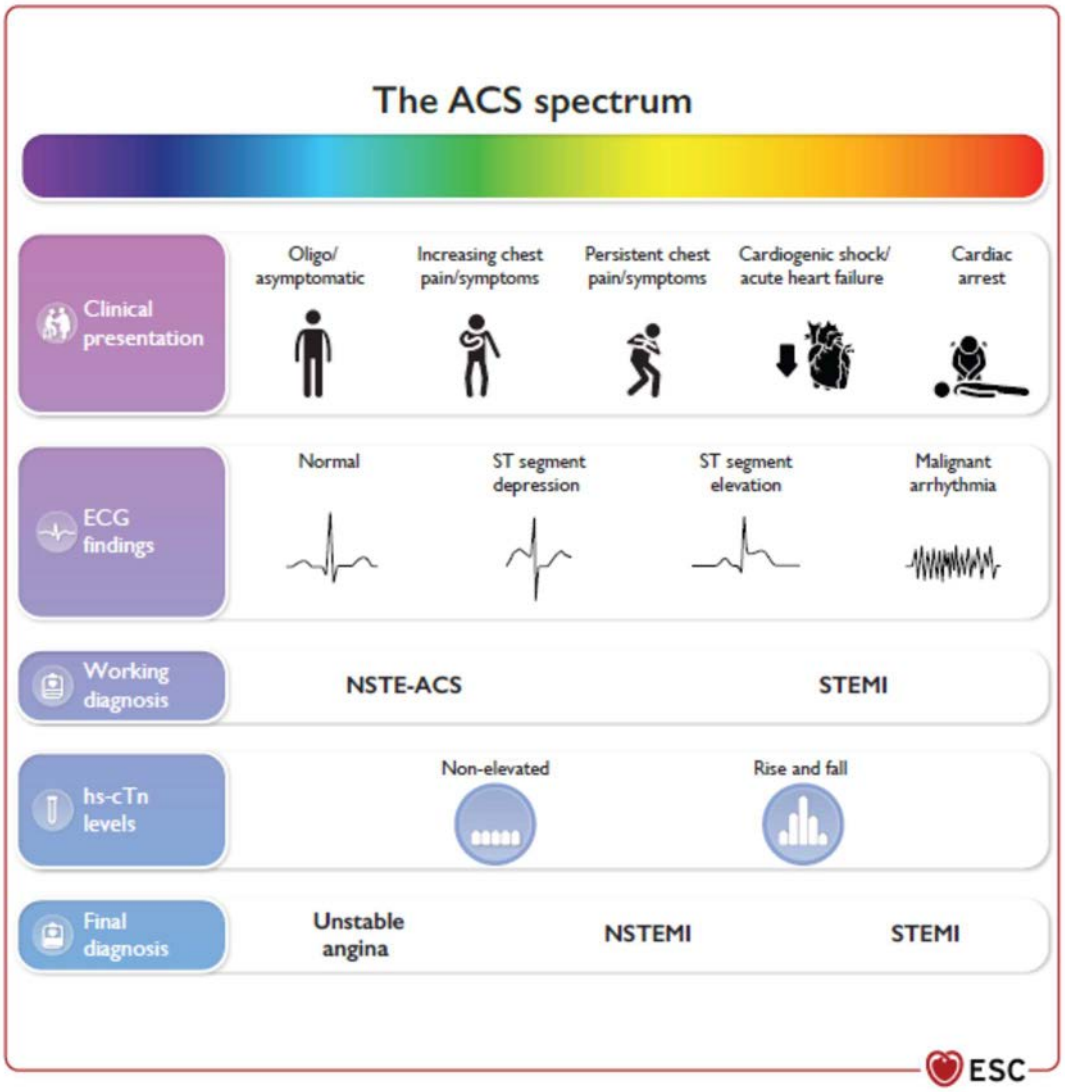
course of their initial evaluation and treatment, underscoring the need for continuous clinical monitoring and reassessment [2,5]. Despite initial differences in ECG and biomarker findings, once the acute phase is managed and patients are stabilized, the long-term therapeutic strategies—particularly in terms of secondary prevention—tend to converge. Therefore, a unified management approach is often applicable across the ACS spectrum, emphasizing the importance of antithrombotic therapy, lipid-lowering agents, lifestyle modification, and revascularization strategies where appropriate [2,3,7].

While closely interrelated, it is essential to distinguish between ACS and AMI. ACS refers broadly to the clinical manifestations of acute myocardial ischemia, encompassing both infarction and non-infarction syndromes. In contrast, AMI is a specific pathological diagnosis denoting cardiomyocyte necrosis in the context of acute ischemia [4]. This distinction is particularly important in clinical research and when applying treatment algorithms, as therapeutic goals may vary depending on whether the patient is experiencing reversible ischemia or irreversible myocardial injury [3,5].

Ultimately, the accurate identification and classification of ACS subtypes have profound implications for immediate and long-term management, influencing decisions regarding revascularization, antithrombotic strategies, and pharmacological therapies aimed at preventing recurrent events and improving survival [2,6,7].

Type 1*	**Caused by acute coronary atherothrombosis, usually precipitated by atherosclerotic plaque disruption (rupture or erosion) and often associated with partial or complete vessel thrombosis.**
Type 2	Caused by an imbalance between myocardial oxygen supply and demand unrelated to acute coronary atherothrombosis.
Type 3	Cardiac death, with symptoms of myocardial ischemia and presumed ischemic electrocardiographic changes or ventricular arrythmia, before blood samples for cardiac biomarkers can be obtained or increases in cardiac biomarkers can be identified and/or in whom MI is identified by autopsy.
Type 4	4a: Peri-PCI MI caused by a procedural complication and detected ≤48 h after PCI. 4b: Post-PCI MI caused by coronary stent or stent scaffold thrombosis. 4c: Post-PCI MI caused by coronary stent restenosis.
Type 5	Peri-CABG MI caused by a procedural complication detected ≤48 h after CABG surgery.

Types of Acute Myocardial Infarction According to the Universal Definition of Myocardial Infarction



2.2. Epidemiology of acute coronary syndromes

Cardiovascular disease (CVD) remains the leading cause of mortality and morbidity globally, with low- and middle-income countries carrying a disproportionate share of this burden[8,9]. Acute coronary syndromes (ACS) frequently represent the initial clinical presentation of underlying CVD. According to 2019 data, an estimated 5.8 million new cases of ischemic heart disease were reported across the 57 member countries of the European Society of Cardiology (ESC) [9].

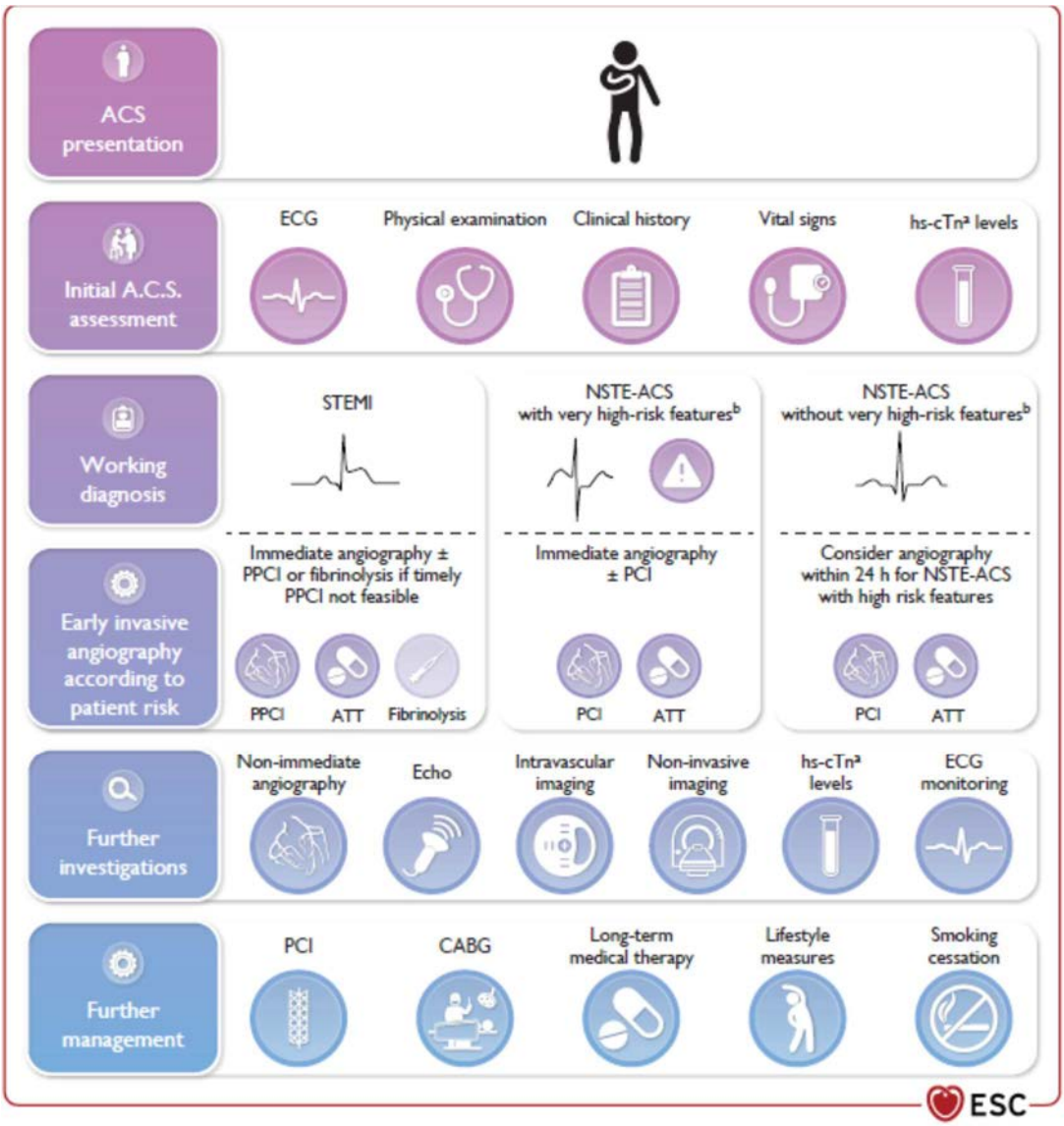
CVD continues to be the primary cause of death within ESC member states, accounting for approximately 2.2 million deaths in women and over 1.9 million deaths in men in the most recent year for which data are available. Among these, ischemic heart disease remains the predominant contributor, responsible for 38% of all CVD-related deaths in women and 44% in men [9].

Coronary heart disease (CHD) remains a major contributor to morbidity and mortality in the United States, affecting an estimated 15.5 million individuals. According to the American Heart Association, someone experiences a heart attack approximately every 41 seconds, underscoring the persistent burden of acute coronary events. Heart disease continues to be the leading cause of death in the country, accounting for nearly one in every five deaths. In addition to its impact on long-term outcomes, CHD is a primary driver of acute care utilization, with chest pain ranking among the most common reasons for emergency department visits. These figures reflect the significant clinical and societal burden of CHD and highlight the importance of timely diagnosis and evidence-based management strategies to improve patient outcomes[10].

A global review conducted in 2023 revealed notable sex- and region-based disparities in mortality associated with acute coronary syndromes (ACS). Mortality rates, including premature deaths (defined as occurring before age 70), were consistently higher in men than in women. In 2020, age-standardized mortality rates (ASMRs) for ACS were most elevated in lower-income regions of the world. This marked a significant shift from two decades earlier when the highest ASMRs were observed in high-income regions such as Europe, North America, and Oceania. Over the past 20 years, these higher-income regions have experienced substantial declines in ACS-related mortality, whereas mortality rates in parts of Asia, Latin America, and the Caribbean have remained relatively unchanged. In contrast, data from seven African nations showed a modest increase in ASMRs, suggesting a progressing epidemiological transition in these areas. Overall, while high-income countries recorded more than a 50% reduction in ACS-related ASMRs, lower-middle-income countries achieved reductions of less than 15%, highlighting a persistent global disparity in cardiovascular outcomes[11].

2.3. Triage & Diagnosis

An overview of the initial triage, management and investigation of patients who present with signs and symptoms potentially consistent with acute coronary syndrome by ESC.



A focused history and rapid clinical evaluation are the cornerstone of the assessment of patients presenting with suspected acute coronary syndrome (ACS). Timely identification of ACS is paramount, as early initiation of appropriate therapy significantly reduces morbidity and mortality. The diagnostic process should begin with a targeted clinical history emphasizing symptom characteristics, including onset, duration, and quality of chest discomfort, as well as associated symptoms such as dyspnea, diaphoresis, or syncope. This initial assessment helps to risk stratify patients and informs immediate management [2].

A 12-lead electrocardiogram (ECG) remains the most valuable initial diagnostic test and should be obtained and interpreted within 10 minutes of first medical contact. It plays a pivotal role in differentiating ST-elevation myocardial infarction (STEMI), which requires urgent reperfusion, from non–ST-elevation

ACS (NSTE-ACS), which may be managed with an early invasive strategy based on clinical risk [12]. ECG findings in NSTE-ACS are often subtle and may include transient ST-segment elevations, ST-segment depression, T-wave inversions, or nonspecific changes. ST-segment depression in leads V1–V3 may reflect posterior myocardial infarction and should prompt acquisition of posterior ECG leads (V7–V9). Additionally, in suspected inferior STEMI, right-sided leads (V3R–V6R) are essential for detecting right ventricular involvement, which has prognostic and therapeutic implications [3].

It is crucial to recognize that an initial non-diagnostic ECG does not exclude ACS. Ischemic ECG changes may be dynamic and evolve over time. Therefore, serial ECGs are recommended during the patient's emergency department (ED) stay, particularly if symptoms persist, recur, or clinical status changes. Comparison with prior ECGs is essential to identify new or evolving abnormalities. Clinicians must maintain a high index of suspicion in patients with ongoing symptoms and nondiagnostic ECGs [2].

In addition to ECG, cardiac biomarkers are integral to the diagnosis of myocardial infarction. Cardiac troponins (cTnI), specifically high-sensitivity cardiac troponin (hs-cTnI) assays, are the preferred biomarkers for detecting myocardial injury. It allows earlier and more accurate detection of even minor degrees of myocardial necrosis, due to its superior sensitivity and negative predictive value compared to conventional troponin assays[4]. A troponin concentration exceeding the 99th percentile of the upper reference limit (URL) indicates myocardial injury. However, elevated cTnI levels must be interpreted within the clinical context, as they can occur in both ischemic (Type 1 MI) and non-ischemic conditions (e.g., myocarditis, heart failure, pulmonary embolism). Notably, in patients with ECG-confirmed STEMI, immediate reperfusion therapy should not be delayed pending biomarker results [3].

Serial measurement of hs-cTnI values, typically 1–3 hours apart, is necessary to assess for a rising or falling pattern indicative of acute myocardial injury. Rapid diagnostic algorithms using troponin I have been validated and incorporated into clinical practice to facilitate early rule-in or rule-out of myocardial infarction, thus improving patient triage and resource allocation [3,4].

Given the wide clinical spectrum and varying prognoses among patients with ACS, accurate risk stratification is critical to guide the intensity of therapy and the timing of invasive procedures. Several validated clinical risk scores incorporate demographic, clinical, ECG, and biomarker data to estimate short- and long-term risks of death and recurrent ischemic events. The Global Registry of Acute Coronary Events (GRACE) score is one of the most robust and widely used tools for risk assessment in both NSTE-ACS and STEMI populations. It is superior in predicting mortality and other adverse outcomes compared to older scores [3]. The Thrombolysis in Myocardial Infarction (TIMI) score, while simpler and more accessible, also provides useful prognostic information and supports early decision-making, particularly in patients with NSTE-ACS [12]. These scores, however, are designed to complement—not

replace—clinical judgment. Their use helps standardize risk assessment, supports shared decision-making with patients, and informs therapeutic strategies including antithrombotic therapy, timing of angiography, and the need for intensive monitoring.

In summary, the evaluation of patients with suspected ACS requires a structured approach combining clinical history, timely ECG interpretation, and serial measurement of hs-cTnI. Together with validated risk scores such as GRACE and TIMI, these tools allow clinicians to stratify risk, tailor management strategies, and ultimately improve clinical outcomes.

Selected Risk Stratification Tools for Patients With ACS :

	GRACE Risk Score (2.0)[67]	TIMI Risk Score for Unstable Angina/NSTEMI*[4]	TIMI Risk Score for STEMI[5]
Target population	ACS	Unstable angina or NSTEMI	STEMI
Target outcome(s)	In-hospital, 6-mo, 1-y, 3-y, death or death/MI	14-d all-cause death, MI, or urgent revascularization	30-d all-cause death
Variables used	In-hospital risk score Age Killip class Systolic blood pressure Heart rate ST-segment deviation Cardiac arrest on admission Serum creatinine Elevated cardiac biomarkers	Age ≥65 y ≥3 risk factors for CAD Known coronary stenosis (≥50%) ST-segment deviation ≥0.5 mm ≥2 anginal events in prior 24 h Aspirin use in prior 7 d Elevated cardiac biomarkers (CK-MB or troponin)	Age (65-74 y/≥75 y) (2-3 points) Killip class II-IV (2 points)* Systolic blood pressure (<100 mm Hg, 3 points) Heart rate >100 bpm (2 points) Anterior ST-segment elevation or LBBB (1 point) Diabetes/hypertension/angina (1 point) Weight (<67 kg, 1 point) Time to treatment >4 h (1 point)

3. Antithrombotic therapy

Antithrombotic therapy constitutes a cornerstone in the therapeutic management of patients presenting with Acute Coronary Syndromes (ACS). The optimal selection, initiation timing, pharmacological combination, and duration of treatment should be individualized based on a comprehensive assessment of clinical, angiographic, and procedural parameters. Therapeutic decision-making necessitates a meticulous risk–benefit analysis, balancing the ischemic protection conferred by antithrombotic agents against the potential for hemorrhagic complications, including major or life-threatening bleeding events.

3.1. Acute Phase Antithrombotic Strategies

3.1.1. Oral Antiplatelet Agents

Antiplatelet agents are integral to the initial pharmacologic management of patients presenting with Acute Coronary Syndromes (ACS). The selection of an antiplatelet regimen should be guided by an individualized bleeding risk

assessment. Criteria for high bleeding risk (HBR) have been systematically defined by the Academic Research Consortium for High Bleeding Risk (ARC-HBR), with the presence of one major or two minor ARC-HBR criteria indicative of a high bleeding risk profile. The cumulative presence of multiple major criteria correlates with a stepwise increase in bleeding complications[13].

Aspirin therapy should be initiated promptly with an appropriate loading dose, followed by maintenance therapy. Current recommendations support a maintenance ASA dosage of 75–100 mg once daily[2]. Based on robust data from pivotal phase III trials, namely PLATO and TRITON-TIMI 38, dual antiplatelet therapy (DAPT) combining ASA with a potent P2Y12 receptor inhibitor (either prasugrel or ticagrelor) is advocated as the standard antithrombotic strategy in ACS[14,15]. Clopidogrel, due to its reduced and variable platelet inhibitory effects, should be reserved for cases where prasugrel or ticagrelor are contraindicated, unavailable, or in patients deemed at particularly high bleeding risk (e.g., meeting ≥1 major or ≥2 minor ARC-HBR criteria). Additionally, its use may be considered in elderly patients (e.g., aged ≥70 years)[13,16].

In patients with ACS undergoing percutaneous coronary intervention (PCI), prasugrel is generally preferred over ticagrelor, as demonstrated by the ISAR-REACT 5 randomized controlled trial—the largest direct comparison of 12-month DAPT with prasugrel versus ticagrelor. Among patients (predominantly treated with PCI) planned for an invasive strategy, prasugrel-based therapy (loading dose administered either immediately post-randomization in primary PCI or post-coronary angiography in NSTE-ACS) significantly reduced the composite endpoint of death, myocardial infarction, or stroke (6.9% vs. 9.3%; p = 0.006) without increasing bleeding events (4.8% vs. 5.4%; p = 0.46)[17]. Notable limitations include the open-label study design and underrepresentation of conservatively managed or CABG-treated patients.

Both aspirin and oral P2Y12 inhibitors achieve more rapid platelet inhibition when preceded by a loading dose. The concept of "pre-treatment" involves the administration of a P2Y12 inhibitor before coronary angiography, prior to anatomical delineation. Although theoretical benefits of pre-treatment in ACS exist, randomized controlled trials do not currently support a routine strategy in this context[18]. Pre-treatment may be particularly inadvisable in patients at high bleeding risk, including those on concomitant oral anticoagulation[19].

In patients with an initial diagnosis of ST-elevation myocardial infarction (STEMI) undergoing primary PCI (PPCI), pre-treatment with a P2Y12 inhibitor may be considered. Conversely, in patients with a working diagnosis of non-ST-elevation ACS (NSTE-ACS) scheduled for early invasive evaluation (<24 hours), routine pre-treatment prior to defining coronary anatomy is not recommended. In patients with anticipated delays to angiography (>24 hours), pre-treatment may be selectively considered, depending on the individual's bleeding risk profile[7,18]. For all ACS patients proceeding to PCI who have not

received pre-treatment with a P2Y12 inhibitor, a loading dose should be administered at the time of PCI.

Dosing Considerations for Oral Antiplatelet Therapy in Patients With ACS

Agent	Setting	Dosing Considerations
Aspirin	NSTE-ACS or STEMI	Loading dose 162-325 mg orally. Aspirin (nonenteric coated) should be chewed, when possible, to achieve faster onset of antiplatelet action. Loading dose should be administered for patients already on aspirin therapy. Maintenance dose 75-100 mg orally daily (nonenteric coated)
Clopidogrel	NSTE-ACS or STEMI without fibrinolytic	Loading dose 300 or 600 mg orally Maintenance 75 mg orally daily
	STEMI with fibrinolytic	Loading dose 300 mg orally if age ≤75 y; Initial dose 75 mg orally if age >75 y Maintenance 75 mg orally daily
Prasugrel	NSTE-ACS or STEMI without fibrinolytic, and undergoing PCI	Loading dose 60 mg orally Maintenance dose 10 mg orally daily if body weight ≥60 kg and age <75 y Maintenance dose 5 mg orally daily if body weight <60 kg or age ≥75 y (use caution)
Ticagrelor	NSTE-ACS or STEMI without fibrinolytic	Loading dose 180 mg orally Maintenance dose 90 mg orally twice daily

3.1.2. Intravenous antiplatelet agents

Peri-procedural intravenous antiplatelet agents include the P2Y12 receptor inhibitor cangrelor and glycoprotein (GP) IIb/IIIa inhibitors such as eptifibatide and tirofiban. The majority of clinical trials assessing the efficacy of GP IIb/IIIa inhibitors in ACS patients undergoing PCI were conducted prior to the widespread adoption of dual antiplatelet therapy (DAPT), particularly the early administration of a loading dose of a potent oral P2Y12 inhibitor[20,21]. Consequently, there is limited contemporary evidence supporting a routine role for GP IIb/IIIa inhibitors in patients with ACS undergoing planned coronary angiography[7].

However, selective use of GP IIb/IIIa inhibitors may be warranted as a bailout strategy in the presence of procedural complications, such as no-reflow phenomena or intraprocedural thrombotic events[22]. Additionally, their administration may be considered in high-risk PCI cases where patients have not received prior oral P2Y12 inhibitor therapy[23].

Recommendations for Intravenous Glycoprotein IIb/IIIa Inhibitors Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	**LOE**	**Recommendations**
2a	**C-LD**	1. In patients with ACS undergoing PCI with large thrombus burden, no-reflow, or slow flow, adjunctive use of an intravenous or intracoronary glycoprotein IIb/IIIa inhibitor is reasonable to improve procedural success and reduce infarct size.*[1,2]

Recommendations for Intravenous Glycoprotein IIb/IIIa Inhibitors (Continued)		
COR	**LOE**	**Recommendations**
3: Harm	**B-R**	2. In patients with ACS, glycoprotein IIb/IIIa inhibitors should not be administered routinely due to lack of ischemic benefit and increased risk of bleeding.[3-5]

*Adapted from the *2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.*[6]

Cangrelor is a direct-acting, reversible, and short-acting intravenous P2Y12 receptor inhibitor that has been evaluated in clinical trials for use during PCI in both chronic coronary syndrome (CCS) and acute coronary syndrome (ACS) settings. Comparative studies against clopidogrel included administration prior to PCI (CHAMPION PCI) and post-PCI (CHAMPION PLATFORM and CHAMPION PHOENIX)[23,24,25]. A meta-analysis of these trials demonstrated that while cangrelor conferred a reduction in major ischemic events, this benefit was offset by a corresponding increase in minor bleeding complications[26].

It is noteworthy that the ischemic benefit observed with cangrelor in CHAMPION PCI was diminished in cases where clopidogrel was administered prior to PCI[24]. Furthermore, clinical data regarding the concurrent use of cangrelor with other potent oral P2Y12 inhibitors such as ticagrelor or prasugrel remain limited[27].

Given its established efficacy in reducing periprocedural stent thrombosis in P2Y12 inhibitor–naïve patients, cangrelor may be considered as a selective option in ACS patients undergoing PCI who have not yet received a P2Y12 inhibitor. This includes clinical scenarios where oral administration may be impractical or delayed, such as in patients with cardiogenic shock or those receiving mechanical ventilation during emergent PCI[22].

Recommendation for Intravenous P2Y12 Inhibition Referenced studies that support recommendations are summarized in the Evidence Table.		
COR	**LOE**	**Recommendation**
2b	**B-R**	1. Among patients with ACS undergoing PCI who have not received a P2Y12 inhibitor, intravenous cangrelor may be reasonable to reduce periprocedural ischemic events.*[1-4]

*Reproduced from the *2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization.*[5]

3.1.3 Use of Anticoagulants

Anticoagulation constitutes a fundamental component of the early management of acute coronary syndromes (ACS), particularly in patients undergoing an invasive strategy. As such, parenteral anticoagulation is recommended for all ACS patients at the time of diagnosis[2]. Cross-over between different classes of anticoagulants, particularly between unfractionated heparin (UFH) and low-molecular-weight heparin (LMWH), should be avoided due to the risk of suboptimal anticoagulation or bleeding complications[28]. An exception applies to patients initially treated with fondaparinux for non-ST-elevation ACS (NSTE-ACS), in whom supplemental UFH is indicated upon transition to PCI to mitigate the risk of catheter thrombosis[29].

In general, anticoagulant therapy should be discontinued immediately following PCI, unless specific indications for extended anticoagulation exist—such as documented left ventricular aneurysm with thrombus or concurrent atrial fibrillation necessitating chronic oral anticoagulation[3]. In the specific context of STEMI patients undergoing PCI with bivalirudin, continuation with a full-dose post-procedural infusion is recommended to reduce thrombotic risk[21].

II. Anticoagulant drugs	
UFH	Initial treatment: i.v. bolus 70–100 U/kg followed by i.v. infusion titrated to achieve an aPTT of 60–80 s. During PCI: 70–100 U/kg i.v. bolus or according to ACT in case of UFH pre-treatment.
Enoxaparin	Initial treatment: for treatment of ACS 1 mg/kg b.i.d. subcutaneously for a minimum of 2 days and continued until clinical stabilization. In patients whose CrCl is below 30 mL per minute (by Cockcroft–Gault equation), the enoxaparin dosage should be reduced to 1 mg per kg o.d. During PCI: for patients managed with PCI, if the last dose of enoxaparin was given less than 8 h before balloon inflation, no additional dosing is needed. If the last s.c. administration was given more than 8 h before balloon inflation, an i.v. bolus of 0.3 mg/kg enoxaparin sodium should be administered.
Bivalirudin	During PPCI: 0.75 mg/kg i.v. bolus followed by i.v. infusion of 1.75 mg/kg/h for 4 h after the procedure. In patients whose CrCl is below 30 mL/min (by Cockcroft–Gault equation), maintenance infusion should be reduced to 1 mg/kg/h.
Fondaparinux	Initial treatment: 2.5 mg/d subcutaneously. During PCI: A single bolus of UFH is recommended. Avoid if CrCl <20 mL/min.

Parenteral anticoagulation is indicated in all patients with STEMI undergoing primary PCI (PPCI). Unfractionated heparin (UFH) remains the established standard of care in this setting, owing to its well-characterized efficacy and favorable risk–benefit profile[2]. Enoxaparin and bivalirudin may be considered as alternative options to UFH in selected patients[21]. Fondaparinux is not recommended for STEMI patients undergoing PPCI due to the risk of catheter thrombosis[30].

In patients with NSTE-ACS undergoing immediate or early invasive evaluation (with or without PCI), UFH is recommended as the anticoagulant of choice[3]. Enoxaparin should be considered as an alternative to UFH in these patients[31].

For patients with NSTE-ACS who are not expected to undergo early angiography, fondaparinux is recommended in preference to enoxaparin, provided that a bolus of UFH is administered at the time of PCI to prevent catheter thrombosis[29,30]. Enoxaparin should be considered when fondaparinux is unavailable or contraindicated[3].

3.2. Post-Revascularization Antithrombotic Therapy

Following percutaneous coronary intervention (PCI) for acute coronary syndromes (ACS), dual antiplatelet therapy (DAPT) remains the cornerstone of secondary prevention. The standard approach consists of a potent P2Y12 receptor inhibitor—either prasugrel or ticagrelor—in combination with low-dose ASA, continued for 12 months regardless of the type of stent implanted, provided there are no contraindications such as excessive bleeding risk[32]. This strategy is supported by robust clinical trial data and forms the basis of current guideline recommendations[2].

However, emerging evidence has emphasized the importance of personalizing DAPT duration and intensity based on the patient's individual risk profile, particularly the balance between ischemic risk (e.g., recurrent myocardial infarction, stent thrombosis) and bleeding risk. As a result, several alternative strategies have been proposed and evaluated, offering greater flexibility in clinical decision-making:

1. Shortened DAPT Duration (<12 months)

In patients identified as having a high bleeding risk (HBR), early discontinuation of DAPT—after 1 month or 3–6 months—followed by monotherapy (typically with a P2Y12 inhibitor or aspirin) may be considered[33]. This approach has been shown to reduce bleeding complications without significantly increasing the risk of ischemic events, particularly in those with stable clinical status, no recurrent ischemia, and uncomplicated PCI procedures. Trials such as STOPDAPT-2[34] and SMART-CHOICE[35] have contributed to this evidence base, although generalizability to all ACS populations is limited.

2. Prolonged DAPT Duration (>12 months)

For patients with a high ischemic risk—such as those with prior stent thrombosis, recurrent ACS, extensive coronary disease, or diabetes—and a low risk of bleeding, extending DAPT beyond the standard 12-month period may provide incremental protection against future ischemic events[36]. While this approach must be weighed carefully against the potential for bleeding, data from trials like PEGASUS-TIMI 54[37] suggest that extended DAPT may reduce the incidence of major adverse cardiac events (MACE) in select populations.

3. De-escalation Strategies

De-escalation involves switching from a potent P2Y12 inhibitor (prasugrel or ticagrelor) to clopidogrel after the initial high-risk period, usually beyond 30 days post-ACS. This strategy aims to maintain antithrombotic efficacy while reducing bleeding complications or addressing issues such as drug intolerance or cost[38]. De-escalation can be guided by clinical judgment or platelet function/genetic testing, as seen in the TROPICAL-ACS[39] and ANTARCTIC[40] trials. However,

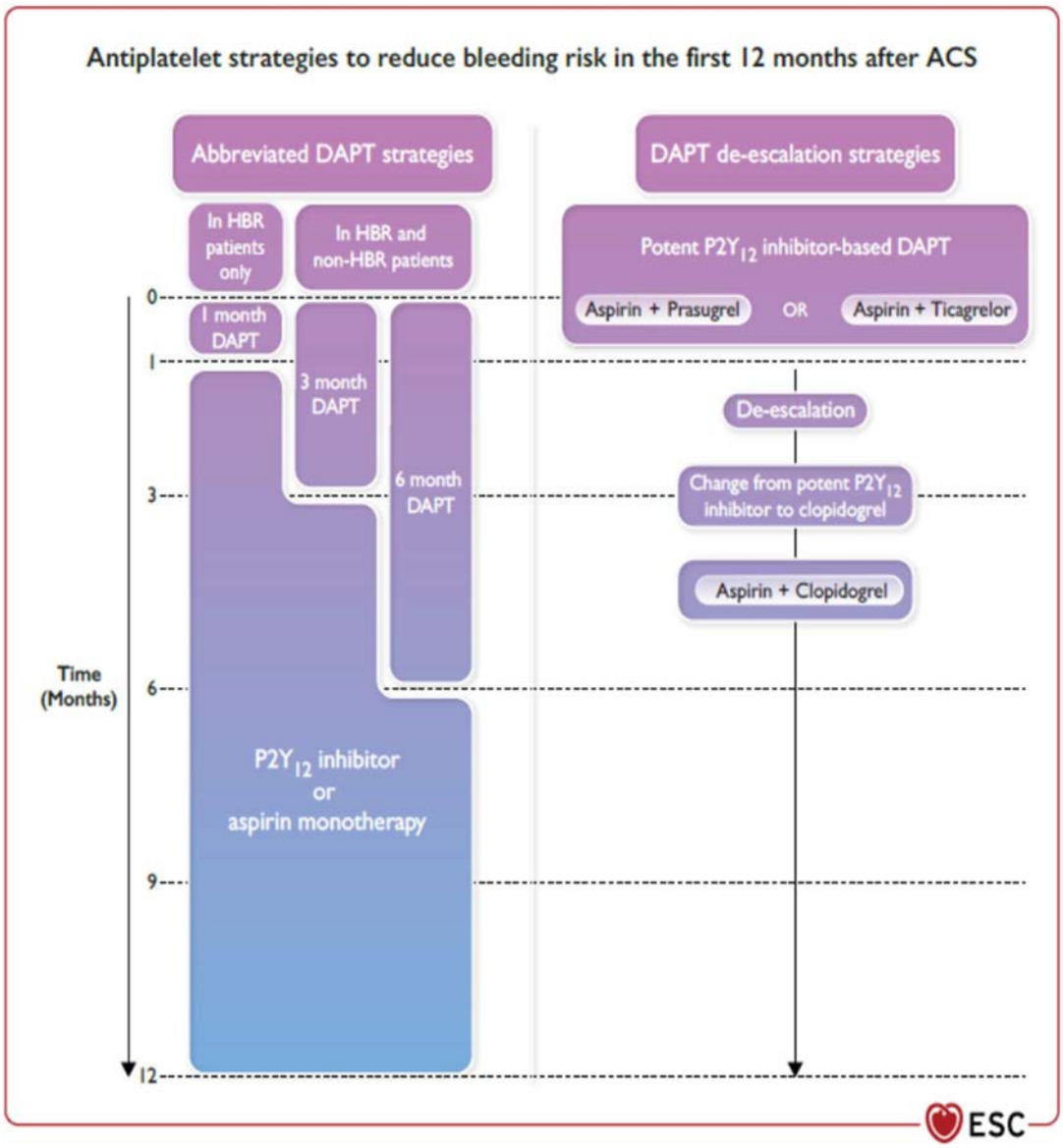
early de-escalation (i.e., within the first month post-ACS) is not recommended due to insufficient evidence supporting its safety and efficacy during the phase of heightened thrombotic risk.

4. Monotherapy Approaches

Recent studies have evaluated monotherapy with a P2Y12 inhibitor (typically ticagrelor or clopidogrel) after a brief period of DAPT in patients who remain event-free and are not at high ischemic risk. This strategy is based on the observation that long-term aspirin use may contribute disproportionately to bleeding risk, particularly gastrointestinal bleeding[41]. For example, the TWILIGHT trial demonstrated that discontinuation of aspirin after 3 months of DAPT and continuation of ticagrelor alone reduced bleeding events without compromising ischemic protection[42]. In HBR patients, monotherapy with either aspirin or a P2Y12 inhibitor as early as 1 month post-PCI may be considered, though supporting evidence remains modest[33].

The MASTER DAPT (Management of High Bleeding Risk Patients Post Bioresorbable Polymer Coated Stent Implantation with an Abbreviated Versus Standard DAPT Regimen) trial specifically evaluated the optimal duration of dual antiplatelet therapy in patients at high bleeding risk (HBR) who had undergone percutaneous coronary intervention (PCI) and remained free of ischemic events after one month. This randomized controlled study demonstrated that a shortened DAPT regimen—discontinuing one antiplatelet agent after one month—was not inferior to the conventional, longer-duration DAPT in terms of overall net adverse clinical events, which included both bleeding and ischemic outcomes, as well as major cardiovascular and cerebrovascular complications. Notably, the abbreviated approach led to a significant reduction in major and clinically relevant non-major bleeding events[33]. These results emphasize the importance of tailoring DAPT duration and intensity based on individual risk profiles, particularly for patients with an elevated risk of bleeding.

In summary, while a 12-month course of DAPT with a potent P2Y12 inhibitor and aspirin remains the default for ACS patients post-PCI, several alternative regimens tailored to patient-specific ischemic and bleeding risks are now supported by clinical trial evidence. These include both shortening and extending DAPT duration, de-escalation to clopidogrel, and early transition to monotherapy. Such personalized approaches aim to optimize outcomes by balancing thrombotic protection against the risk of bleeding complications.



Recommendations for alternative antithrombotic therapy regimens by ESC

Recommendations	Class[a]	Level[b]
Shortening/de-escalation of antithrombotic therapy		
In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, single antiplatelet therapy (preferably with a $P2Y_{12}$ receptor inhibitor) should be considered.[264,268–271,273,274,276,313,320]	IIa	A
De-escalation of $P2Y_{12}$ receptor inhibitor treatment (e.g. with a switch from prasugrel/ticagrelor to clopidogrel) may be considered as an alternative DAPT strategy to reduce bleeding risk.[279–282,321,322]	IIb	A
In HBR patients, aspirin or $P2Y_{12}$ receptor inhibitor monotherapy after 1 month of DAPT may be considered.[276,313]	IIb	B
De-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended.[238,323]	III	B
Prolonging antithrombotic therapy		
Discontinuation of antiplatelet treatment in patients treated with an OAC is recommended after 12 months.[324,325]	I	B
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention should be considered in patients with high ischaemic risk and without HBR[c].[314–318]	IIa	A
Adding a second antithrombotic agent to aspirin for extended long-term secondary prevention may be considered in patients with moderate ischaemic risk and without HBR[c].[314–318]	IIb	A
$P2Y_{12}$ inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment.[326,327]	IIb	A

3.3. Antithrombotic Approaches in Specific Clinical Scenarios

3.3.1. Management in ACS Patients Requiring Long-Term Oral Anticoagulation

A significant proportion of patients presenting with acute coronary syndromes (ACS) also have coexisting conditions that mandate long-term oral anticoagulation (OAC), most commonly atrial fibrillation (AF). The concurrent need for both antiplatelet and anticoagulant therapy introduces considerable complexity to the management of such patients. The therapeutic challenge lies in optimizing protection against ischemic events, such as stent thrombosis and

recurrent myocardial infarction, while minimizing the risk of bleeding, especially major bleeding events.

Traditionally, dual antiplatelet therapy (DAPT), consisting of aspirin and a P2Y12 inhibitor, has been the cornerstone of secondary prevention following percutaneous coronary intervention (PCI) in ACS patients. However, in individuals who also require long-term anticoagulation, DAPT alone is inadequate to prevent cardioembolic events. Consequently, triple antithrombotic therapy (TAT), which combines DAPT with an oral anticoagulant, was historically employed. While theoretically advantageous in terms of comprehensive thromboprophylaxis, TAT has consistently been associated with a substantial increase in bleeding risk, particularly gastrointestinal and intracranial hemorrhages, which in turn have been linked to increased morbidity and mortality[43,44].

Evidence from several pivotal clinical trials has revolutionized the approach to antithrombotic therapy in ACS patients with an indication for OAC. The WOEST (What Is the Optimal Antiplatelet and Anticoagulant Therapy in Patients with Oral Anticoagulation and Coronary Stenting) trial was among the first to challenge the routine use of TAT. It demonstrated that the use of dual therapy (OAC plus clopidogrel) significantly reduced bleeding complications without increasing thrombotic events compared to TAT[45]. This trial paved the way for further investigations involving direct oral anticoagulants (DOACs).

Four landmark randomized controlled trials—PIONEER AF-PCI, RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI—systematically examined the safety and efficacy of combining a DOAC with a P2Y12 inhibitor (primarily clopidogrel) versus TAT incorporating a vitamin K antagonist (VKA) and DAPT. Across these studies, dual therapy regimens consistently resulted in significantly lower bleeding rates without compromising the prevention of ischemic outcomes[46-49]. These findings have led to a paradigm shift in the standard of care, with dual therapy now considered the preferred approach in most cases.

While the reduction in bleeding with dual therapy is compelling, it is important to note that these trials were primarily powered for safety outcomes, and thus, ischemic endpoints such as stent thrombosis and myocardial infarction were relatively infrequent and underpowered for definitive conclusions. Some data suggest a slightly increased, though not statistically significant, incidence of stent thrombosis and myocardial infarction with dual therapy, especially with lower-dose anticoagulants or premature discontinuation of aspirin[48,49].

Meta-analyses of the available evidence have reinforced the clinical utility of dual therapy. These studies have shown that dual therapy significantly reduces the risk of major bleeding, including intracranial hemorrhage, when compared to TAT. However, the risk of ischemic events, particularly in high-risk populations, remains a concern[50,51]. For this reason, guidelines emphasize the importance of individual risk stratification using validated scoring systems, such as CHA2DS2-VASc for stroke risk and HAS-BLED or ARC-HBR for bleeding risk[52,53].

Current clinical guidelines advocate for a patient-centered, individualized approach to antithrombotic therapy in this complex patient population. The general recommendation is to initiate treatment with a short course of TAT using a DOAC at the full stroke prevention dose, in combination with aspirin and clopidogrel, particularly in patients at high ischemic risk. The duration of TAT should be minimized—ideally no longer than one week—after which aspirin is discontinued, and dual therapy with a DOAC and clopidogrel is continued for up to 12 months[52,53]. In patients at high bleeding risk, the duration of dual therapy may be shortened to 3-6 months, followed by DOAC monotherapy.

Importantly, the use of prasugrel or ticagrelor as part of a TAT regimen is generally discouraged due to the elevated bleeding risk associated with these agents. Clopidogrel remains the P2Y12 inhibitor of choice in combination with OAC. After completion of the dual therapy period, long-term antithrombotic management should consist of OAC monotherapy, provided the indication for anticoagulation persists.

In medically managed ACS patients who do not undergo coronary intervention, a similar strategy applies. Data from the AUGUSTUS trial and large observational registries support the safety and efficacy of dual therapy with a DOAC and clopidogrel in this subgroup[48,54]. These patients benefit from reduced bleeding risk without an apparent increase in ischemic complications, reinforcing the principle that aspirin can be safely omitted early in the course of treatment.

The AFIRE trial extended the evidence base by evaluating long-term antithrombotic therapy in patients with stable coronary artery disease and AF. The study demonstrated that rivaroxaban monotherapy was non-inferior to rivaroxaban combined with a single antiplatelet agent in preventing ischemic events and was associated with a lower risk of major bleeding[55]. These findings support the transition to DOAC monotherapy beyond 12 months in stable patients with ongoing indications for anticoagulation.

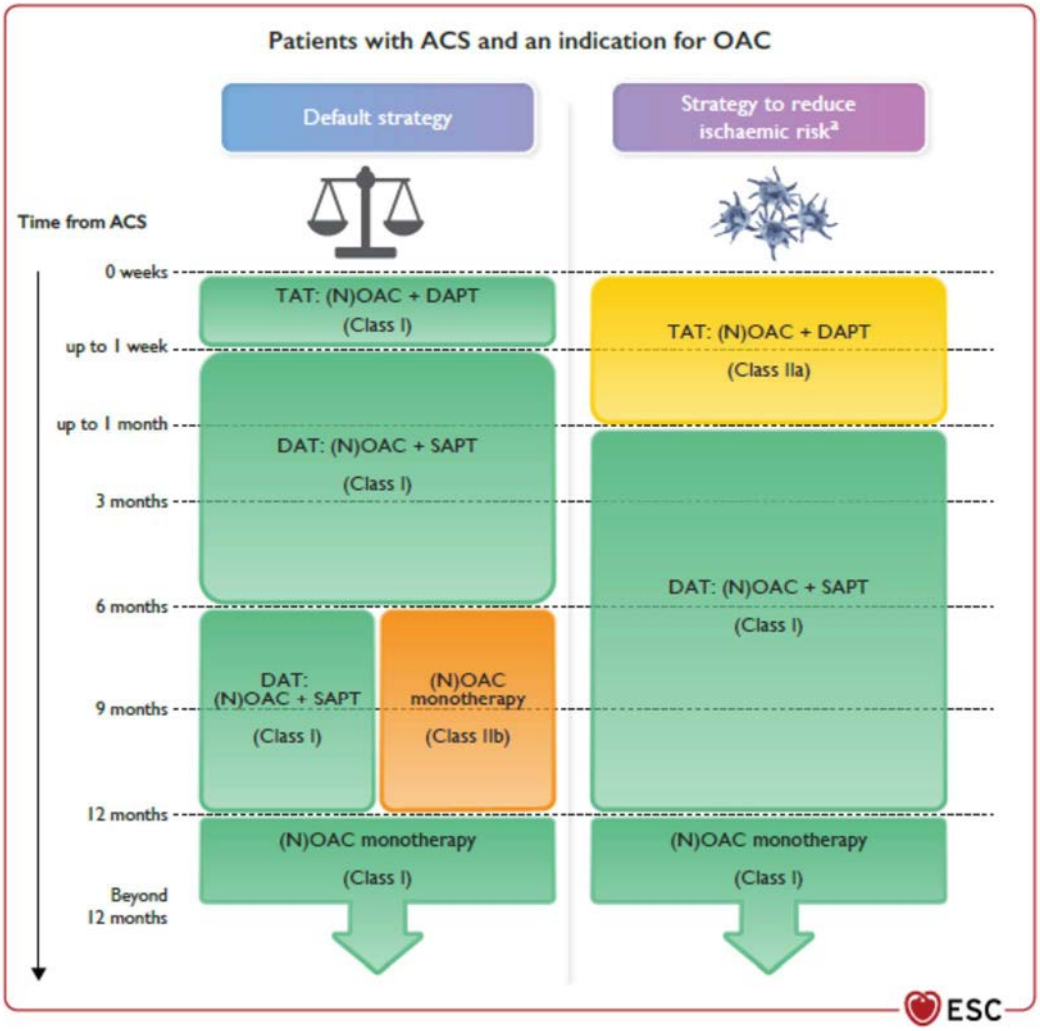
Additional measures are recommended to minimize bleeding risk. The use of radial artery access for PCI is strongly encouraged as it significantly reduces access-site bleeding complications[56]. Furthermore, proton pump inhibitors should be co-prescribed in patients receiving antithrombotic therapy, especially those with a history of gastrointestinal bleeding or at elevated risk[53].

For patients on VKA therapy, meticulous INR control is essential. Guidelines recommend targeting the lower end of the therapeutic range (INR 2.0–2.5) with a high time in therapeutic range (TTR ≥65–70%)[52]. Exceptions exist for patients with mechanical heart valves, particularly in the mitral position, where higher INR targets are warranted.

It is also crucial to reassess the need for continued OAC during the chronic phase of ACS management. OAC should be maintained only if a valid indication remains, such as AF with a CHA2DS2-VASc score ≥1 in men or ≥2 in women,

mechanical prosthetic heart valves, or a history of recurrent venous thromboembolism. If the indication no longer exists, discontinuation of anticoagulation may be considered, and the antithrombotic regimen can be simplified accordingly.

In conclusion, the management of antithrombotic therapy in ACS patients who require OAC is evolving from a generalized, protocol-driven approach toward a more nuanced, individualized strategy. The current evidence supports the use of DOAC-based dual therapy as the default strategy in most patients, with short-term TAT reserved for those at high thrombotic risk. Clinicians must continuously balance ischemic and bleeding risks, reassess therapeutic needs over time, and utilize contemporary trial data and guideline recommendations to guide optimal treatment decisions. This personalized approach is essential to improving clinical outcomes in this high-risk population.



3.3.2. Therapy Following Fibrinolytic Treatment

Primary percutaneous coronary intervention (PPCI) is the preferred method of reperfusion in patients presenting with ST-elevation myocardial infarction (STEMI), provided it can be performed promptly. However, when timely PPCI is not feasible, fibrinolytic therapy remains a well-established alternative. Administered within the first 12 hours of symptom onset, fibrinolysis offers a significant, time-dependent reduction in both mortality and morbidity. The greatest benefit is observed in patients who present early, particularly those with anterior infarctions and a low risk of bleeding[57,58].

The co-administration of ASA has been shown to enhance the efficacy of fibrinolytic therapy. An initial loading dose of 162–325 mg of aspirin, preferably chewed or administered intravenously, should be given as early as possible, followed by a daily maintenance dose of 75–100 mg orally starting from the next day[59]. The addition of clopidogrel to ASA further reduces the risk of cardiovascular events and all-cause mortality in patients undergoing fibrinolytic therapy for STEMI and is therefore recommended as part of the antiplatelet regimen[60]. Currently, there is insufficient evidence to support the use of ticagrelor or prasugrel in conjunction with fibrinolytic therapy in this patient population[61]. Moreover, glycoprotein (GP) IIb/IIIa receptor inhibitors have not demonstrated added benefit in terms of improving myocardial reperfusion or clinical outcomes when used alongside fibrinolytics and are associated with an increased risk of bleeding, making their use in this context generally unwarranted[62].

Parenteral anticoagulation is recommended following fibrinolysis and should be continued until revascularization, if performed. Among anticoagulants, enoxaparin has demonstrated a favorable net clinical benefit compared with unfractionated heparin (UFH) despite a higher incidence of major bleeding. In the ASSENT-3 trial (n = 6,095), enoxaparin was associated with improved outcomes in patients treated with thrombolysis[63]. This was further supported by the EXTRACT–TIMI 25 trial (n = 20,506), which showed a significant reduction in death and re-infarction at 30 days with enoxaparin compared to weight-adjusted UFH. In that study, dosing adjustments were made for older patients (≥75 years) and those with renal impairment (creatinine clearance <30 mL/min), and although non-cerebral bleeding events increased, the overall net benefit, defined as the absence of death, non-fatal MI, and intracranial hemorrhage, still favored enoxaparin[31].

Fondaparinux also demonstrated superior outcomes compared to placebo or UFH in the OASIS-6 trial, particularly among patients receiving streptokinase, showing reductions in both death and reinfarction rates[64]. Additionally, in a large trial involving streptokinase, bivalirudin given for 48 hours was associated with fewer reinfarctions than UFH, albeit with a modest, non-significant increase in non-cerebral bleeding. However, bivalirudin has not been evaluated in combination with fibrin-specific thrombolytic agents, and there is currently no

robust evidence supporting the use of direct thrombin inhibitors as adjunctive therapy during fibrinolysis[65].

Among pharmaco-invasive strategies, the combination of weight-adjusted intravenous tenecteplase, low-dose aspirin, oral clopidogrel, and an initial intravenous bolus followed by subcutaneous administration of enoxaparin until PCI, represents the most extensively investigated antithrombotic regimen, with a well-established evidence base supporting its safety and efficacy[66].

3.3.3. Antithrombotic Treatment in Non-Revascularized ACS Patients

Despite guideline recommendations favoring an invasive strategy for the management of acute coronary syndromes (ACS), a substantial proportion of patients are managed conservatively with pharmacological therapy alone.

In ACS patients who are treated medically without undergoing revascularization, the dual antiplatelet regimen of aspirin plus ticagrelor for up to 12 months has been shown to offer superior clinical outcomes compared to the combination of ASA and clopidogrel. This was supported by a prespecified subgroup analysis from the PLATO trial, which included 5,216 out of 18,624 patients initially planned for non-invasive treatment. Ticagrelor was associated with a significant reduction in composite ischemic outcomes, without a notable increase in bleeding events relative to clopidogrel.

Additionally, the combination of ASA and prasugrel may be considered a preferable alternative to aspirin and clopidogrel in patients who have undergone coronary angiography and have confirmed coronary artery disease. The TRILOGY-ACS (Targeted Platelet Inhibition to Clarify the Optimal Strategy to Medically Manage Acute Coronary Syndromes) trial enrolled 7,243 non–ST-segment elevation ACS (NSTE-ACS) patients under the age of 75 who were managed non-invasively. Overall, the incidence of the primary composite endpoint and major bleeding was comparable between the prasugrel and clopidogrel treatment arms. However, in a prespecified analysis of patients who underwent angiographic assessment, prasugrel resulted in lower rates of cardiovascular mortality, myocardial infarction, and stroke, without an excess risk of bleeding when compared to clopidogrel[68,69].

The 2023 European Society of Cardiology (ESC) Guidelines for managing acute coronary syndromes (ACS) recommend using dual antiplatelet therapy (DAPT) that includes a potent P2Y12 inhibitor—such as ticagrelor or prasugrel—together with aspirin. This recommendation applies even to patients ultimately diagnosed with ACS who are treated conservatively without reperfusion, provided there are no major concerns regarding bleeding risk, such as those outlined by the ARC-HBR criteria[32].

This treatment strategy is supported by strong clinical evidence showing that more potent P2Y12 inhibitors effectively lower the risk of recurrent ischemic

events across the full range of ACS presentations. Nevertheless, for patients who have a high risk of bleeding particularly older adults clopidogrel in combination with aspirin may be a safer alternative. This regimen tends to offer better tolerability with minimal reduction in efficacy[32,70]. Ultimately, treatment decisions should be tailored to the individual, using clinical judgment supported by established risk assessment tools.

4.Newest data in antithrombotic therapy

Key Recommendations in the 2025 Guideline for the Management of Patients with Acute Coronary Syndromes (ACS) by The American Heart Association (AHA), in collaboration with the American College of Cardiology (ACC) and other societies[71]:

1. Dual Antiplatelet Therapy (DAPT)

- **Preferred Agents**: For patients with ACS undergoing percutaneous coronary intervention (PCI), the combination of ASA with a potent P2Y12 inhibitor—either ticagrelor or prasugrel—is recommended over clopidogrel, unless contraindicated due to bleeding risk.
- **Duration**: A minimum of 12 months of DAPT is advised for most patients, balancing ischemic and bleeding risks.
- **Non-PCI Patients**: In non–ST-segment elevation ACS (NSTE-ACS) patients scheduled for delayed invasive strategies (>24 hours), pre-treatment with ticagrelor or clopidogrel may be considered to reduce major adverse cardiovascular events (MACE).

2. Strategies to Mitigate Bleeding Risk

- **Gastrointestinal Protection**: Proton pump inhibitors are recommended for patients at increased risk of gastrointestinal bleeding.
- **Monotherapy Transition**: For patients who have tolerated DAPT with ticagrelor, transitioning to ticagrelor monotherapy after ≥1 month post-PCI can be considered to reduce bleeding risk.
- **Anticoagulation Considerations**: In patients requiring long-term anticoagulation, discontinuation of ASA 1 to 4 weeks after PCI, with continuation of a P2Y12 inhibitor (preferably clopidogrel), is recommended.

3. Anticoagulant Therapy

- Parenteral anticoagulation is recommended during hospitalization for ACS patients, with the choice of agent (e.g., unfractionated heparin, enoxaparin, bivalirudin) tailored based on clinical context and bleeding risk.

Key Recommendations from the 2023 ESC Guidelines on ACS[72]:

1. **Dual Antiplatelet Therapy (DAPT):** For patients with ACS undergoing percutaneous coronary intervention (PCI), a combination of ASA and a potent P2Y12 inhibitor (ticagrelor or prasugrel) is recommended over clopidogrel, unless contraindicated due to high bleeding risk. In cases where PCI is not performed, DAPT duration and choice of agents should be tailored based on the patient's risk profile.
2. **DAPT Duration:** A standard duration of 12 months is advised for most patients. However, in patients with high bleeding risk, shorter durations (e.g., 3-6 months) may be considered. Conversely, extended DAPT beyond 12 months may benefit those with high ischemic risk and low bleeding risk.
3. **Monotherapy Transition:** After an initial period of DAPT, transitioning to monotherapy with a P2Y12 inhibitor (preferably ticagrelor) can be considered in patients who have tolerated DAPT without adverse events, aiming to reduce bleeding complications.
4. **Triple Antithrombotic Therapy:** In patients requiring oral anticoagulation (e.g., due to atrial fibrillation), triple therapy (ASA, P2Y12 inhibitor, and anticoagulant) should be limited to the shortest duration necessary, typically one month, followed by dual therapy (anticoagulant plus P2Y12 inhibitor) for up to 12 months, and then anticoagulant monotherapy thereafter.

Recommendations	Class[a]	Level[b]
Recommendations for antiplatelet and anticoagulant therapy in acute coronary syndrome		
If patients presenting with ACS stop DAPT to undergo coronary artery bypass grafting, it is recommended they resume DAPT after surgery for at least 12 months.	I	C
In older ACS patients, especially if HBR, clopidogrel as the $P2Y_{12}$ receptor inhibitor may be considered.	IIb	B
Recommendations for alternative antithrombotic therapy regimens		
In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, single antiplatelet therapy (preferably with a $P2Y_{12}$ receptor inhibitor) should be considered.	IIa	A
$P2Y_{12}$ inhibitor monotherapy may be considered as an alternative to aspirin monotherapy for long-term treatment.	IIb	A
In HBR patients, aspirin or $P2Y_{12}$ receptor inhibitor monotherapy after 1 month of DAPT may be considered.	IIb	B
In patients requiring OAC, withdrawing antiplatelet therapy at 6 months while continuing OAC may be considered.	IIb	B
De-escalation of antiplatelet therapy in the first 30 days after an ACS event is not recommended.	III	B

Recommendations in 2017 and 2020 versions	Class[a]	LoE[b]	Recommendations in 2023 version	Class[a]	LoE[b]
Recommendations for antiplatelet and anticoagulant therapy in STEMI					
A potent $P2Y_{12}$ inhibitor (prasugrel or ticagrelor), or clopidogrel if these are not available or are contraindicated, is recommended before (or at latest at the time of) PCI, and maintained over 12 months, unless there are contraindications such as excessive risk of bleeding.	I	A	Pre-treatment with a $P2Y_{12}$ receptor inhibitor may be considered in patients undergoing a primary PCI strategy.	IIb	B
Recommendations for long-term antithrombotic therapy					
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 ischaemic and bleeding risks.	IIa	A	In patients who are event-free after 3–6 months of DAPT and who are not high ischaemic risk, SAPT (preferably with a $P2Y_{12}$ receptor inhibitor) should be considered.	IIa	A

The evolving landscape of antithrombotic therapy in acute coronary syndrome (ACS) continues to be shaped by recent trials examining de-escalation strategies and novel agents aimed at optimizing ischemic protection while minimizing bleeding complications.

One notable contribution is the ULTIMATE-DAPT trial (2024), a multicenter, randomized, placebo-controlled study conducted across 58 sites in China, Pakistan, Italy, and the United Kingdom. The trial enrolled 3,400 patients who had undergone percutaneous coronary intervention (PCI) for ACS and completed one month of uneventful dual antiplatelet therapy (DAPT). Participants were randomized to either continue DAPT or switch to ticagrelor monotherapy for the subsequent 11 months. The primary bleeding endpoint—clinically relevant bleeding defined as BARC types 2, 3, or 5—occurred significantly less frequently in the ticagrelor monotherapy group (2.1%) compared to the continued DAPT group (4.6%), translating to a hazard ratio (HR) of 0.45 (95% CI, 0.30–0.66; $p < 0.0001$). Importantly, the composite endpoint of major adverse cardiovascular and cerebrovascular events (MACCE) was similar between the groups (3.6% vs. 3.7%; HR, 0.98; 95% CI, 0.69–1.39), establishing non-inferiority of ticagrelor monotherapy (p for noninferiority < 0.0001; p for superiority = 0.89). Subgroup analyses did not identify any significant interactions. Additionally, the net adverse clinical event rate (a composite of MACCE and any BARC bleeding) favored ticagrelor monotherapy (5.7% vs. 8.2%; $p = 0.007$), underscoring its potential role in reducing bleeding without compromising ischemic protection[73].

In contrast, the STOPDAPT-3 trial evaluated very early ASA discontinuation immediately following PCI. In this open-label, randomized study, 5,966 Korean patients undergoing PCI with the Xience everolimus-eluting stent were assigned to receive either DAPT (aspirin plus prasugrel) or prasugrel monotherapy at a low dose (3.75 mg/day). The study included both ACS and high bleeding risk populations. The 30-day results revealed that prasugrel monotherapy was not superior to DAPT in terms of bleeding reduction, and importantly, was associated with a numerically higher rate of cardiovascular

events, including a possible increased risk of subacute stent thrombosis. These findings raise concerns about premature de-escalation strategies immediately post-PCI, particularly in the ACS setting. Notably, among patients who underwent complex PCI, no significant differences were observed. Beyond 30 days, all patients transitioned to either aspirin or clopidogrel monotherapy, with no significant differences in ischemic or bleeding events observed through one-year follow-up[74].

Collectively, these trials provide important clinical insights. The ULTIMATE-DAPT trial supports the safety and efficacy of ticagrelor monotherapy initiated at one month post-PCI in select patients who remain free from adverse events, whereas the STOPDAPT-3 trial suggests that ultra-short DAPT (<1 month) may not be beneficial and could potentially increase harm. Thus, the current consensus continues to favor at least one month of DAPT post-PCI, particularly in ACS, before considering de-escalation.

Looking ahead, the Librexia-ACS trial represents a promising step in the pursuit of safer anticoagulant strategies. This ongoing Phase 3, double-blind, placebo-controlled trial aims to evaluate milvexian, a selective oral Factor XIa inhibitor, in combination with standard dual antiplatelet therapy in patients with recent ACS. Milvexian targets the intrinsic coagulation cascade upstream of thrombin generation, potentially offering effective ischemic protection without a proportional increase in bleeding risk. If successful, the trial may pave the way for a novel class of antithrombotic agents that challenge the existing paradigms of anticoagulation in ACS management[75].

5.Conclusions

Antithrombotic Therapy in ACS: A Shift Toward Individualized Management

Antithrombotic therapy remains a cornerstone of acute coronary syndrome (ACS) management, regardless of whether patients are treated invasively or conservatively. The therapeutic approach typically includes both antiplatelet and anticoagulant agents to reduce thrombotic risk during the acute phase and beyond.

Aspirin is universally recommended for all patients with ACS and should be initiated with a loading dose, followed by long-term administration at a maintenance dose. In addition to ASA, dual antiplatelet therapy (DAPT) is indicated, incorporating a P2Y12 receptor inhibitor for at least 12 months, unless contraindicated by bleeding risk considerations. Among the available P2Y12 inhibitors, prasugrel and ticagrelor are preferred over clopidogrel due to superior efficacy in reducing ischemic events. In patients undergoing percutaneous coronary intervention (PCI), prasugrel may offer additional benefit and is recommended over ticagrelor when no contraindications exist.

Routine pre-treatment with a P2Y12 inhibitor prior to coronary angiography is not advised in patients with non–ST-segment elevation ACS (NSTE-ACS), given the uncertain benefit and potential for harm. However, in ST-segment elevation myocardial infarction (STEMI) patients undergoing primary PCI (PPCI), early administration of a P2Y12 inhibitor may be considered to facilitate early platelet inhibition.

Parenteral anticoagulation is indicated in all ACS patients at the time of diagnosis and should be maintained through the invasive procedure. Discontinuation is generally appropriate immediately following completion of PCI, assuming hemostasis is secured.

A subset of ACS patients present with concomitant indications for long-term oral anticoagulation (OAC), most commonly atrial fibrillation. In these patients, a tailored approach is essential to balance thromboembolic and bleeding risks. The recommended default strategy involves short-term triple antithrombotic therapy (TAT) comprising aspirin, clopidogrel, and a non-vitamin K oral anticoagulant (NOAC) for up to one week. This is followed by dual antithrombotic therapy (DAT), typically consisting of a NOAC at the approved stroke prevention dose plus a single antiplatelet agent—preferably clopidogrel—for a duration based on bleeding and ischemic risk stratification.

Contemporary antithrombotic strategies in ACS are increasingly moving away from a "one-size-fits-all" model toward individualized treatment plans. This paradigm shift emphasizes the need to balance ischemic protection with bleeding avoidance, tailored to each patient’s clinical profile. A thorough assessment of both bleeding and thrombotic risks is essential to guide the optimal selection of agents and the duration of therapy. Several validated risk stratification tools, such as the PRECISE-DAPT and ARC-HBR criteria, have been developed to assist clinicians in making informed decisions regarding antithrombotic regimens. These tools support evidence-based personalization of therapy, aiming to enhance clinical outcomes while minimizing avoidable complications.

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