Review Article

Antithrombotic Therapy for Acute Coronary Syndrome

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Acute coronary syndrome (ACS) encompasses a spectrum of cardiovascular emergencies, including unstable angina and myocardial infarction, that require immediate and effective management to reduce morbidity and mortality. Antithrombotic therapy, including antiplatelet and anticoagulant medications, is fundamental in ACS management. We sought to organize the current status of antithrombotic management of ACS, including the concept of high bleeding risk (HBR), in line with the clinical diagnostic flow. ACS is an ever-changing condition; therefore, its diagnosis and treatment are conducted in parallel. While primarily a coronary artery disease, the diagnosis of ACS also includes conditions such as myocardial infarction with nonobstructive coronary arteries as a working diagnosis. This review collates the mechanisms and classification of ACS, showing the diagnostic flow and the antithrombotic agents used at each stage. It discusses strategies for dual antiplatelet therapy (DAPT) duration and de-escalation in patients undergoing percutaneous coronary intervention and addresses the management of patients requiring oral anticoagulation alongside antiplatelet therapy, highlighting the shift toward dual therapy to reduce bleeding risk. Antithrombotic agents are key treatments for ACS, with various available options. Their mechanisms and the approved dosing regimens differ regionally, especially between Japan and other countries. This review synthesizes the regional availability of each agent and compares the latest recommendations from Japanese and international guidelines for ACS management. The field of antithrombotic therapy in ACS is dynamic, influenced by the findings of ongoing clinical trials and emerging evidence. Key considerations include balancing antithrombotic benefits against bleeding risks, particularly in patients with HBR. Recent studies have explored shorter DAPT durations and novel antithrombotic agents, offering new insights for diverse patient populations. In this review, we provide a comprehensive comparison of guidelines and insights from the neuro-interventional field to assist clinicians in making informed decisions regarding ACS management. As ACS management evolves, continued international, cross-sectional collaboration and research are essential to refine guidelines and improve clinical practice.

Keywords ▶ acute coronary syndrome, antithrombotic therapy, dual antiplatelet therapy, myocardial infarction

Introduction

Acute coronary syndrome (ACS), including unstable angina and myocardial infarction (MI), remains a leading cause of mortality and morbidity worldwide.[1)] Antithrombotic therapy, including antiplatelet and anticoagulant medications, is fundamental in ACS management; it reduces the risk of thrombus formation, a central pathophysiological process in ACS. Antithrombotic therapy in ACS primarily involves the use of antiplatelet agents, such as aspirin and purinergic receptor P2Y (P2Y12) inhibitors (e.g., clopidogrel and ticagrelor), alongside anticoagulants such as heparin. These agents act synergistically to prevent thrombus formation, mitigating the risk of acute ischemic events.

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This review discusses factors influencing plaque stability and the degree of myocardial injury. Plaques that are unstable and characterized by thin fibrous caps and large lipid cores have a higher propensity for rupture and a greater risk of ACS development. Disruption of such plaques exposes thrombogenic materials and triggers platelet adhesion. Platelet activation in response to agents such as thrombin or collagen involves the release of adenosine diphosphate (ADP), which activates the platelet P2Y12 receptor, and subsequently, the glycoprotein (GP) IIb/IIIa receptor, leading to platelet aggregation and thrombus formation. Therefore, inhibition of platelet activation and aggregation is a critical goal in the antithrombotic management of ACS.

The dynamism of this field, marked by ongoing clinical trials and emerging evidence, necessitates regular updates to clinical guidelines. While percutaneous coronary intervention (PCI) has become a popular treatment for ACS, neurointervention is another area where endovascular treatment and antithrombotic therapy are used to treat acute cerebrovascular disease. Both have a common goal of balancing bleeding and ischemia, and preventing the development of each disease as a consequence of antithrombotic therapy is also an important issue, requiring crosstalk between the 2 areas. In this context, it is vital for clinicians to stay abreast of the current recommendations. This review critically examines and compares the latest guidelines on antithrombotic therapy for ACS from Japanese and international bodies to distill key practices and identify areas of consensus and divergence.

Mechanism of ACS

The predominant cause of ACS is the disruption of atherosclerotic plaques, leading to thrombus formation and acute obstruction of coronary blood flow.[2] In the early stages of atherosclerosis, thickening of the arterial intima occurs due to the infiltration and accumulation of macrophages and lipids within the arterial wall.[3] As atherosclerotic plaques develop, the vessel wall may undergo positive remodeling, expanding to maintain the patency of the lumen. However, as the plaque advances, it can narrow the lumen, potentially leading to conditions such as effort angina. Inflammation is a critical component in both the development and progression of atherosclerosis. Within some atherosclerotic lesions, a necrotic core forms—laden with inflammatory cells and cholesterol crystals—known as fibroatheromas. Fibroatheromas, especially those with thin fibrous caps, are susceptible to rupture and are considered vulnerable plaques. The rupture of such plaques, followed by thrombus formation, is widely considered the primary cause of ACS (**Fig. 1**). Although plaque rupture is the most common cause, ACS can also result from plaque erosion, which involves thrombus formation despite the presence of an unruptured fibrous cap (**Fig. 1**). In addition, although infrequent, calcified nodules with eruptive features are another mechanism that leads to thrombus formation without plaque rupture or erosion.

Furthermore, ACS is diagnosed in up to 5%–25% of patients without significant epicardial coronary artery disease.[4] In such cases, ACS may be attributed to coronary artery embolism, spasm, dissection, arteritis, or myocardial bridging. Coronary artery embolism occurs due to atrial fibrillation (AF), impaired left ventricular wall motion, malignancy, or paradoxical embolism from a cardiac/extracardiac shunt. Coronary artery spasm is a transient constriction of the coronary arteries that reduces blood flow to the cardiac muscles. Spontaneous dissection of an epicardial coronary artery, termed SCAD, is a medical condition characterized by the development of an intramural hematoma or false lumen, which occurs independently of atherosclerotic, iatrogenic, or traumatic factors.[5] This formation can constrict the true arterial lumen, leading to the narrowing of the impacted artery. The clinical consequences of this narrowing range from acute to chronic coronary syndrome. In addition, the following conditions mimic coronary artery disease: Takotsubo cardiomyopathy, myocarditis, type II MI, and acute myocardial injury, as defined in the fourth universal definition of MI. Patients with these conditions may present with chest symptoms and myocardial injuries, which can be detected using cardiac biomarkers. However, rapid diagnosis and intervention, including PCI, are crucial for the treatment of ACS. Thus, to minimize time to treatment, ACS is often used as a working diagnosis, and we use various classifications for ACS management.

Clinical classifications of ACS

In clinical practice, stratifying and managing high-risk patients is essential. Accordingly, ACS is classified based on the electrocardiogram waveforms as ST-segment elevation MI (STEMI) or non-ST-segment elevation ACS (NSTE-ACS) (**Fig. 2**). Early intervention in STEMI, as evidenced by 12-lead electrocardiography, has been shown to reduce mortality rates. The diagnosis of MI necessitates the demonstration of myocardial injury, as exemplified by

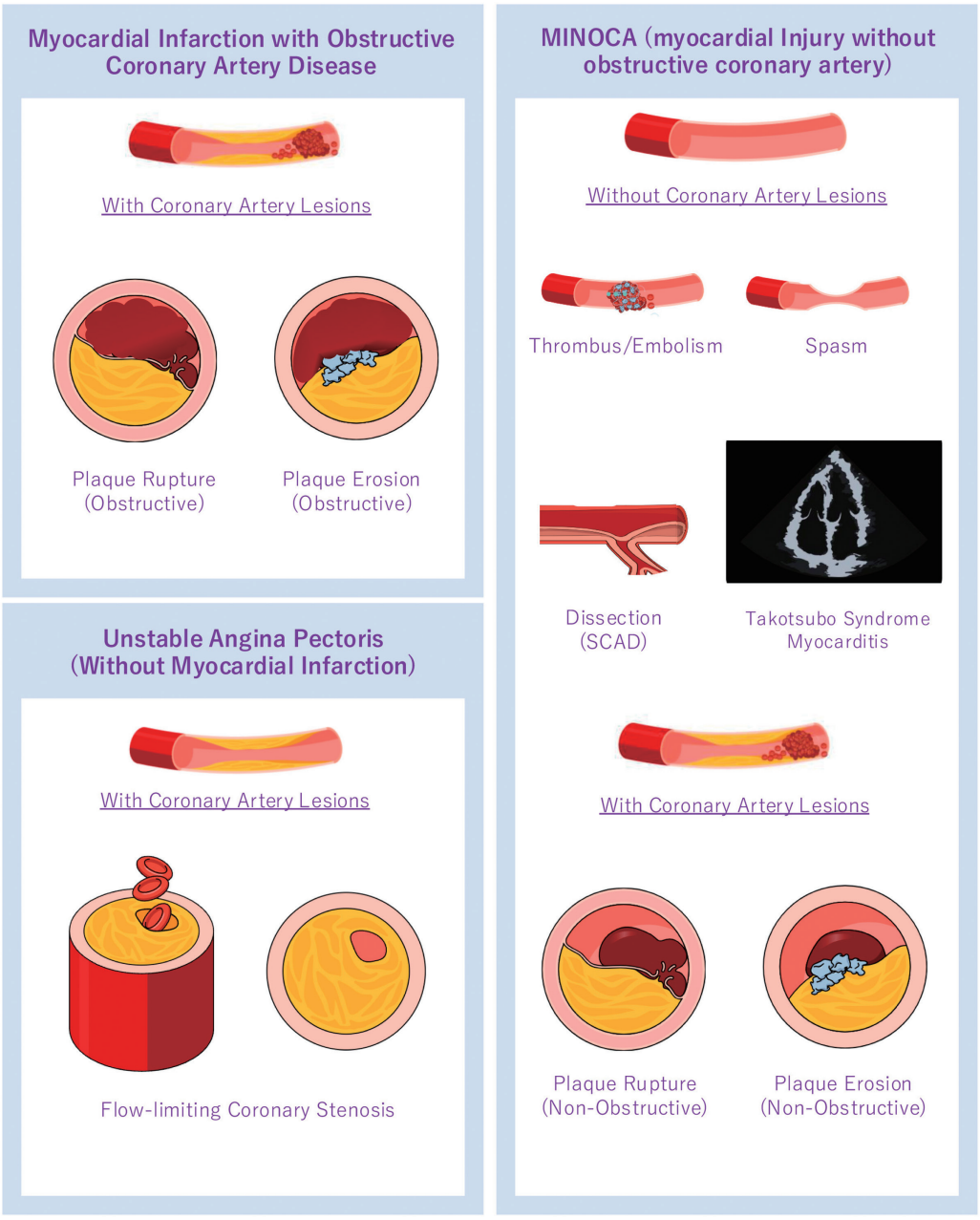

Fig. 1 Mechanisms and etiologies of ACS. The longitudinal and cross-sectional view of the artery shows schematic details of the lesion. ACS, acute coronary syndrome; SCAD, spontaneous epicardial coronary artery dissection

high-sensitivity troponins, making the classification more focused on rapid intervention rather than on defining MI in the absence of blood test results. Consequently, the concept of NSTE-ACS encompasses both non-ST-elevation MI (NSTEMI) with myocardial biomarker elevation and unstable angina without myocardial biomarker elevation. Patients with ST-segment elevation are often treated with early PCI, whereas in NSTE-ACS, risk stratification for ischemia, such as that using the Global Registry of Acute Coronary Events score, is possible. In patients with NSTE-ACS who are at a high risk of ischemia, early consideration of revascularization is often warranted.

MI with nonobstructive coronary arteries (MINOCA) as a "working diagnosis"

Another important aspect recently highlighted in the literature is MINOCA.[4] The concept of MINOCA was first coined by Beltrame in 2013.[6] This term was introduced to

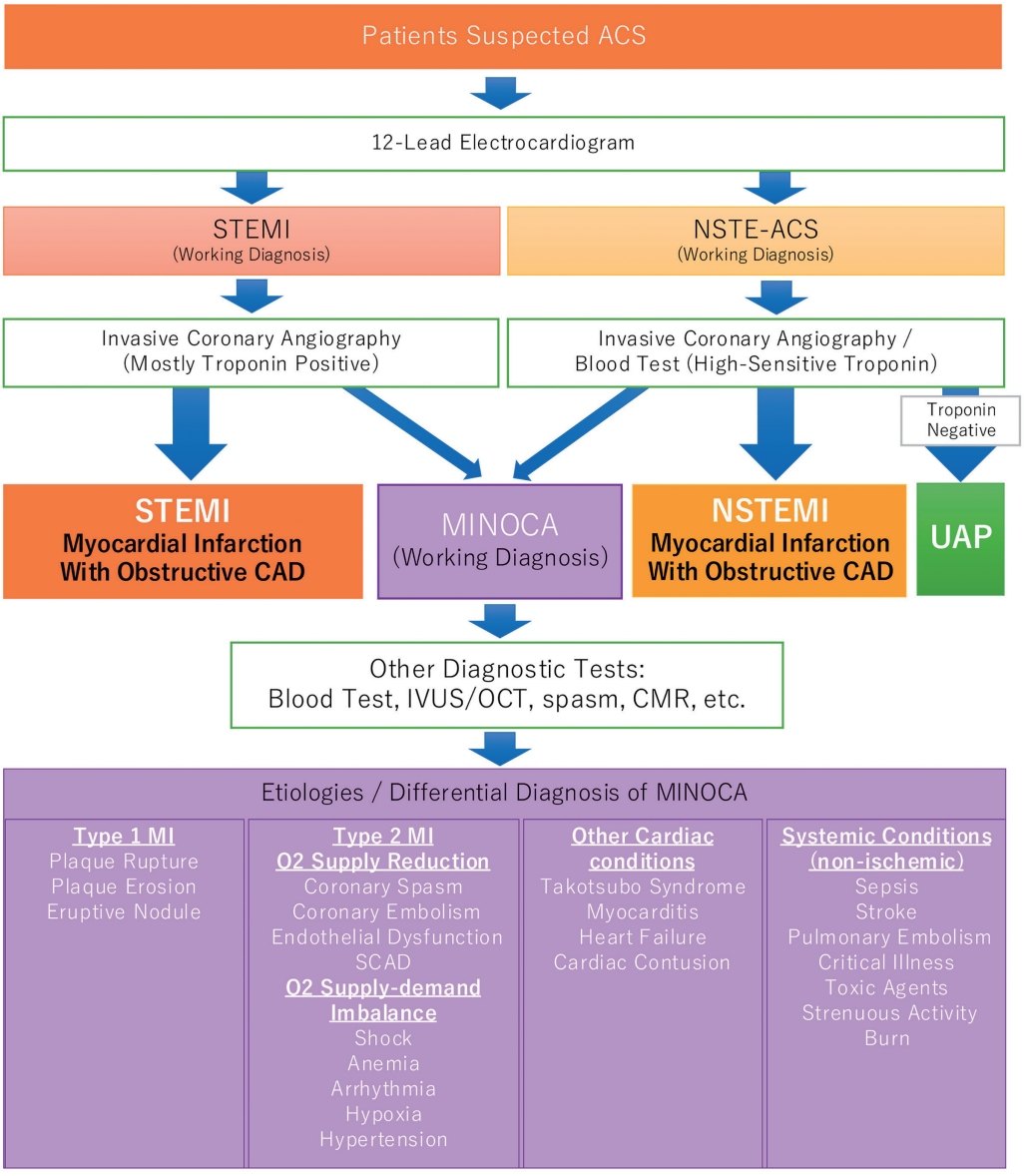

Fig. 2 Clinical diagnostic flow of ACS. ACS, acute coronary syndrome; CAD, coronary artery disease; CMR, cardiac magnetic resonance imaging; IVUS, intravascular ultrasound; MI, myocardial infarction; MINOCA, myocardial infarction with nonobstructive coronary arteries; NSTE-ACS, non-ST-segment elevation acute coronary syndrome; NSTEMI, non-ST-elevation MI; OCT, optical coherence tomography; SCAD, spontaneous epicardial coronary artery dissection; STEMI, ST-segment elevation myocardial infarction; UAP, unstable angina pectoris

supersede the previous term of MI with normal coronaries, which exclusively referred to patients without atherosclerosis in the epicardial vessels.[6] Etiologies for MINOCA can be divided into 2 categories: epicardial causes (epicardial spasm, or thrombus of extra-coronary origin) and microvascular causes (Takotsubo syndrome, myocarditis, microvascular spasm, or microvascular embolism). Diagnosis is established using invasive coronary angiography to evaluate the epicardial coronary artery in combination with intracoronary imaging, cardiac ventriculography, or cardiac MRI.[4]

Patients without occlusive coronary artery disease on coronary angiography are treated as MINOCA as a working diagnosis; however, the definition includes heterogeneous causes. Data from large MI registries suggest a prevalence of MINOCA of 5%–25%, but a recent study, involving a contemporary cohort of patients, reported a prevalence of 8.8%, which appears to reflect daily clinical experience.[7] Studies, including one that focused on women diagnosed with MI, have shown that multimodal imaging techniques, such as coronary optical coherence tomography and cardiac

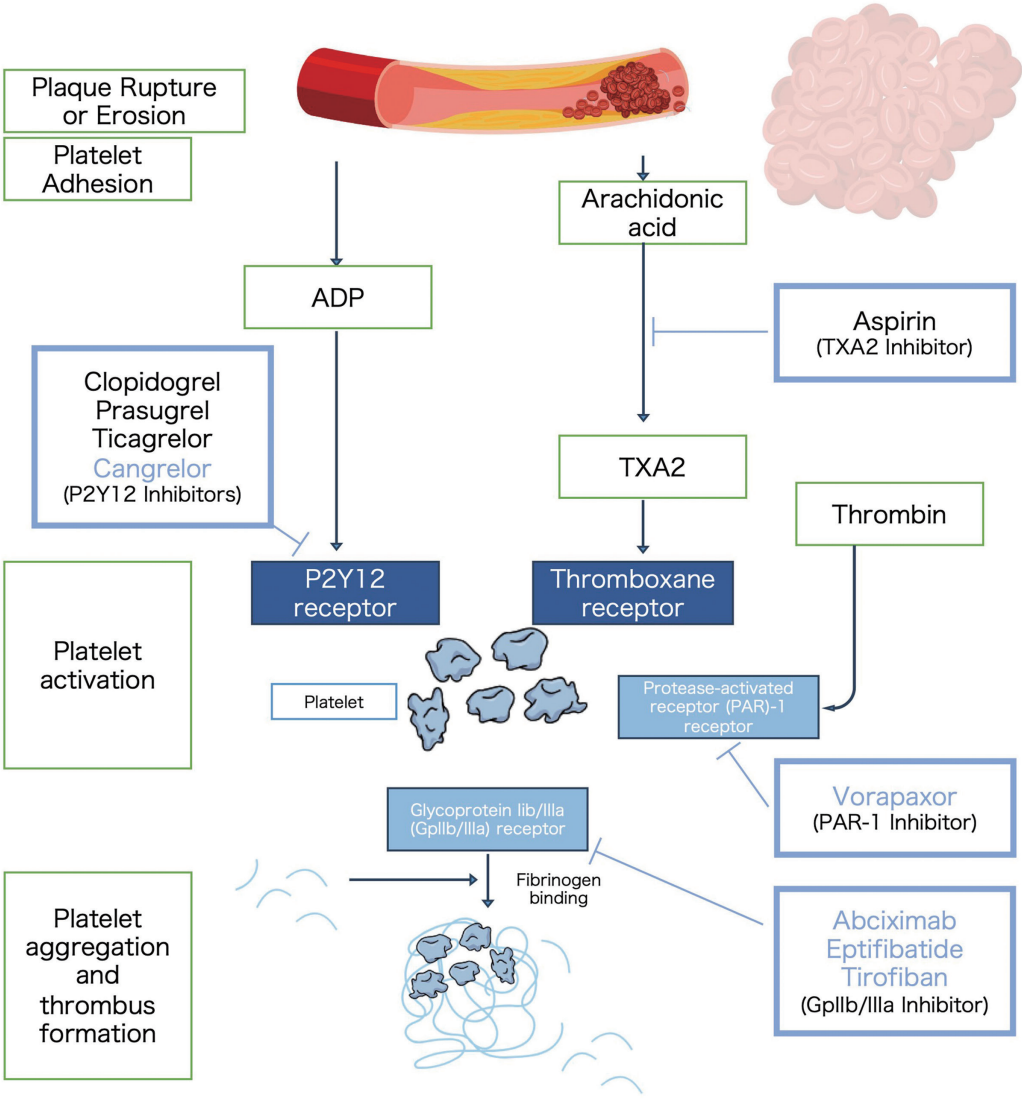

Fig. 3 Platelet aggregation process and effect sites of antiplatelet agents. ADP, adenosine diphosphate; P2Y12, purinergic receptor P2Y; TXA2, thromboxane A2

MRI, can identify the mechanism of MINOCA in a significant majority of cases. Representing approximately 10% of MI cases, MINOCA is clinically diagnosed after excluding other secondary causes of MI without coronary artery disease.

As mentioned previously, the diagnosis of ACS used in clinical practice includes a working diagnosis along the diagnostic and therapeutic pathways. Therefore, it is essential to note that the initial ACS diagnosis is not limited to coronary artery disease, and many conditions that cause myocardial damage can be treated as ACS. Recently, it has been suggested that the term "acute myocardial ischemic syndrome (AMIS)" be used instead of "ACS" to categorize these conditions.[8] This review summarizes the recommendations for each condition along with the diagnostic and treatment flow. Long-term antithrombotic strategies are also discussed along with current evidence.

Antithrombotic Therapy

Antithrombotic therapy is classified into antiplatelet and anticoagulant therapies based on the mechanism of action. Although the specific sites affected by each agent differ within the thrombotic and fibrinolytic cascades, they are broadly distinguished and used based on whether they have antiplatelet or anticoagulant effects (**Figs. 3** and **4**).

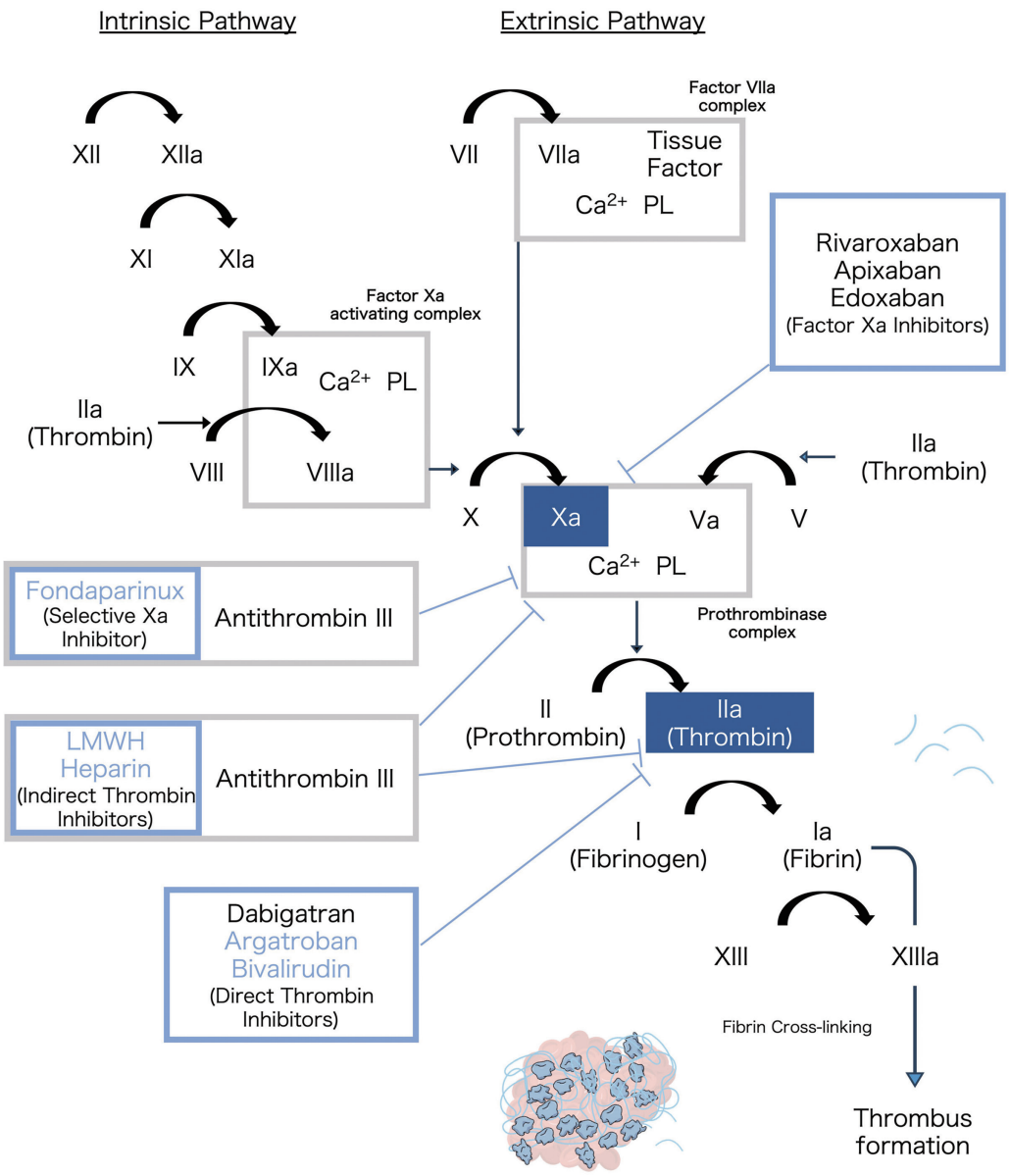

Fig. 4 Antithrombotic cascades and target sites of anticoagulant agents. LMWH, low-molecular-weight heparin; PL, phospholipid

Overview of antiplatelet agents in ACS

The agents used in antiplatelet therapy are classified according to their mechanism of action and include aspirin, ADP receptor blockers (P2Y12 inhibitors), protease-activated receptor-1 (PAR-1) inhibitors, and GP IIb/IIIa inhibitors (**Table 1** and **Fig. 1**). Aspirin binds to cyclooxygenase and inhibits thromboxane A2 formation. ADP receptor antagonists, including clopidogrel, prasugrel, ticagrelor, and cangrelor, bind to the P2Y12 receptor and inhibit platelet activation by ADP. GP IIb/IIIa inhibitors, including abciximab, eptifibatide, and tirofiban, bind to the GP IIb/IIIa receptor and inhibit the binding of platelets to fibrinogen. In Western countries, peri-interventional intravenous antiplatelet drugs include P2Y12 receptor inhibitors (cangrelor) and GP IIb/IIIa inhibitors (eptifibatide and tirofiban). However, there is no strong evidence of any additional benefit of the routine use of GP IIb/IIIa inhibitors in patients with ACS scheduled for coronary angiography. PAR-1 inhibitors, such as vorapaxar, bind to PAR-1 and inhibit thrombin-induced platelet activation. Vorapaxar was approved by the Food and Drug Administration for use in the USA, with indications for the reduction of thrombotic cardiovascular events in patients with a history of MI or peripheral arterial disease, and must be used in

Table 1 Available oral antithrombotic agents and approved doses for coronary artery disease

Drug	Aspirin	Clopidogrel	Prasugrel	Ticagrelor
Mechanism	Cyclooxygenase 1 inhibitor	P2Y12 antagonist, thienopyridine	P2Y12 antagonist, thienopyridine	P2Y12 antagonist, direct-acting reversible antagonist
Onset of action	30–40 min, enteric-coated: 3–4 hours	2–8 hours	30 min–4 hours	30 min–2 hours
Prodrug	No	Yes	Yes	No
Drug interaction with CYP enzymes	None	CYP2C19	CYP3A4/CYP2B6	CYP3A4
Known resistance (prevalence in the general population)	Yes, 5%–45%	Yes, 5%–44%	No	No
FDA approval (years)	Yes, NA	Yes, 1997	Yes, 2009	Yes, 2011
Loading dose/day	162–325 mg	600 mg (300 mg)	60 mg	180 mg
Maintenance dose/day	75–100 mg	75 mg	10 or 5 mg	90 mg × 2
CE mark approval (years)	Yes, NA	Yes, 1998	Yes, 2009	Yes, 2010
Loading dose/day	150–300 mg	600 mg (300 mg)	60 or 30 mg	180 mg
Maintenance dose/day	75–100 mg	75 mg	10 or 5 mg	90 mg × 2
PMDA approval (years)	Yes, NA	Yes, 2006	Yes, 2014	Yes, 2017
Loading dose/day	162–324 mg	300 mg	20 mg	180 mg
Maintenance dose/day	81 mg	75 mg	3.75 mg	90 mg × 2

CE, Conformité Européenne; CYP, cytochrome P450; FDA, Food and Drug Administration; NA, not applicable; P2Y12, purinergic receptor P2Y; PMDA, Pharmaceuticals and Medical Devices Agency

addition to standard-of-care antiplatelet therapy.[9] However, concerns about bleeding risks and other side effects necessitate further studies to determine its optimal use in clinical practice.

Overview of anticoagulant agents in ACS

The effects of oral and parenteral anticoagulants used for ACS by sites are shown in **Fig. 4**. Warfarin is a vitamin K antagonist (VKA) and has been widely used for oral anticoagulation therapy (OAC) in patients with specific clinical indications such as AF. However, owing to its variable effects among individuals, dose adjustment can be complex. Warfarin therapy requires frequent blood testing to ensure that the medication remains within the therapeutic range. Despite these challenges, its use is indispensable for patients with valvular AF, which is related to greater than moderate mitral valve stenosis, leading to left atrial low-flow status, or those fitted with mechanical prosthetic heart valves.

With advancements in OAC, non-VKAs (non-vitamin K oral anticoagulants [NOACs]), also known as direct oral anticoagulants (DOACs), have been introduced. Dabigatran directly inhibits thrombin, resulting in a rapid onset of action and renal excretion. Rivaroxaban, apixaban, and edoxaban selectively inhibit factor Xa. Rivaroxaban allows for once-daily dosing, and there are regional differences in approved doses (**Table 2**). These novel oral anticoagulants facilitate patient adaptation to treatment, as they require less frequent monitoring and have fewer dietary and drug interactions.

Intravenous anticoagulants include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), bivalirudin, and argatroban. UFH is a commonly used anticoagulant recommended for immediate anticoagulant effects when needed, especially during primary PCI in patients with STEMI. LMWH has predictable anticoagulant effects and can be used as an alternative to UFH. Argatroban, a direct thrombin inhibitor, is administered to patients at risk of heparin-induced thrombocytopenia (HIT). Bivalirudin is another direct thrombin inhibitor that may be selected for patients at risk of HIT and reduces the risk of major bleeding. In Japan, neither LMWH nor bivalirudin have been approved for the treatment of ACS.

High bleeding risk and OAC use

To optimize the antithrombotic therapy for ACS, a balance between thrombotic and bleeding risks is crucial. In

Table 2 Available oral antithrombotic agents and approved doses for atrial fibrillation in each region

Drug	Warfarin	Dabigatran	Rivaroxaban	Apixaban	Edoxaban
Mechanism	Vitamin K antagonist	Direct thrombin inhibitor	Factor Xa inhibitor	Factor Xa inhibitor	Factor Xa inhibitor
Time to response (hours)	24–72	1–3	2–4	3–4	1–2
Drug interaction with CYP enzymes	CYP2C9, CYP1A2, and CYP3A4	None	CYP3A4/5 and CYP2J2	CYP3A4/5	CYP3A4
FDA approval (years)	1954	2010	2011	2012	2015
Main dose/day	Tailored	150 mg × 2	20/15 mg	10 mg × 2	60 mg
Reduced dose/day	Tailored	110 mg × 2	15/10 mg	5 mg × 2	30 mg
CE mark	NA	2008	2008	2011	2015
Main dose/day	Tailored	150 mg × 2	20/15 mg	10 mg × 2	60 mg
Reduced dose/day	Tailored	110 mg × 2	15/10 mg	5 mg × 2	30 mg
PMDA approval	1962	2011	2012	2013	2011
Main dose/day	Tailored	150 mg × 2	15/10 mg	10 mg × 2	60 mg
Reduced dose/day	Tailored	110 mg × 2	15/10 mg	5 mg × 2	30/15 mg

CE, Conformité Européenne; CYP, cytochrome P450; FDA, Food and Drug Administration; NA, not applicable; PMDA, Pharmaceuticals and Medical Devices Agency

patients with ACS, the culprit lesion or the patient has a high thrombotic status; however, excessive use of antithrombotic agents can result in adverse events, such as severe bleeding. Numerous studies have been conducted on the state of ACS, the agents used for antithrombotic therapy, and their duration of use. The implementation of multiple scoring systems to assess bleeding risk has resulted in challenges when interpreting and comparing data across different studies due to variations in the criteria used.[10] Recently, the concept of high bleeding risk (HBR) has been advocated, and the latest guidelines from various countries recommend the selection of antiplatelet therapy after evaluating an individual patient's risk of bleeding and thrombosis. The Academic Research Consortium (ARC) took the initiative to devise a uniform definition of HBR in patients who have undergone PCI.[11] The establishment of the ARC-HBR criteria is anticipated to facilitate the design of clinical trials and the analysis of data pertaining to patients with HBR. The ARC encompasses a diverse group of experts, regulatory authorities, and corporate bodies from the USA, Europe, Japan, and South Korea. HBR has been defined within this framework as a Bleeding ARC (BARC) type 3 or 5 bleeding risk of ≥4% or an intracranial hemorrhage risk of ≥1% within the first year following PCI. Based on expert consensus, the ARC-HBR criteria outline 14 primary and 6 secondary factors (**Fig. 5A**). A patient is classified as having HBR if they meet at least 1 of the primary criteria or 2 secondary criteria.

The term "East Asian paradox" refers to the phenomenon observed in East Asian regions, including Japan, where there is a higher risk of bleeding and a lower risk of thrombosis compared with that in Western countries. Within the CREDO-Kyoto Registry Cohort-2, there was a notable incidence of bleeding complications classified as moderate or severe according to the Global Use of Streptokinase and tissue plasminogen activator (tPA) for Occluded Coronary Arteries criteria, particularly among patients who had peripheral vascular disease, heart failure, or lower body weight, with rates ranging from 10.1% to 14.2% within the first year.[12] This high incidence persisted at rates mostly ≥4% even in the absence of other risk factors, including those identified by the ARC-HBR criteria. When compared with the 2.6% incidence rate of bleeding complications in patients without HBR who did not meet any of the ARC-HBR major or minor criteria, the Working Group deduced that it would be justifiable to consider these factors as major criteria in the "Japanese version of HBR criteria" (**Fig. 5B**).

There are some differences between the ARC-HBR and the Japanese version of the HBR; however, OACs are prescribed to approximately 10% of patients with ACS, and OAC use is a major criterion in the assessment of both HBR criteria. The presence or absence of an indication

A ARC High Bleeding Risk

Major Criteria (Any 1 major)		Minor Criteria (Any 2 minor)
×	Age	Age ≥75 years
Anticipated use of long-term oral anticoagulation	Drug	×
×	Drug	Long-term use of oral NSAIDs or steroids
Severe or End-stage CKD (eGFR <30mL/min)	Kidney	Moderate CKD (eGFR 30–59mL/min)
Hemoglobin <11g/dL	Anemia	Hemoglobin 11–12.9g/dL for men and 11–11.9g/dL for women
Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent	Bleeding	Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion
Previous spontaneous ICH (at any time), Previous traumatic ICH within the past 12 months, Presence of a bAVM Moderate or severe ischemic stroke within the past 6 months	Brain	Any ischemic stroke at any time not meeting the major criterion
Liver cirrhosis with portal hypertension	Liver	×
Chronic bleeding diathesis	Bleeding	×
Moderate or severe baseline thrombocytopenia † (platelet count <100 × 109/L)	Platelet	×
Active malignancy within the past 12 months (excluding nonmelanoma skin cancer)	Malignancy	×
Nondeferrable major surgery on DAPT	Surgery	×
Recent major surgery or major trauma within 30 days before PCI	Surgery	×

B Japanese version High Bleeding Risk

Major Criteria (Any 1 major)		Minor Criteria (Any 2 minor)
×	Age	Age ≥75 years
Low body weight, Frailty	Physique	×
Anticipated use of long-term oral anticoagulation	Drug	Long-term use of oral NSAIDs or steroids
Severe CKD (hemodialysis)	Kidney	Moderate CKD (eGFR 30–59mL/min)
Hemoglobin <11g/dL	Anemia	Hemoglobin 11–12.9g/dL for men and 11–11.9g/dL for women
History of non-traumatic bleeding events	Bleeding	First non-traumatic bleeding within 6-12 months requiring hospitalization or transfusion
Previous spontaneous ICH (at any time), Previous traumatic ICH within the past 12 months, Presence of a bAVM Moderate or severe ischemic stroke within the past 6 months	Brain	Ischemic stroke not applicable to major criteria
Liver cirrhosis with portal hypertension	Liver	×
Chronic Bleeding Diatheses	Bleeding	×
Thrombocytopenia	Platelet	×
Active malignancy	Malignancy	×
Heart failure	Heart	×
Peripheral vascular disease	Vascular	×
Nondeferrable major surgery on DAPT	Surgery	×
Recent major surgery or major trauma within 30 days before PCI	Surgery	×

Fig. 5 List of clinical factors included in the ARC-HBR criteria and their comparison with the Japanese version of HBR criteria. (**A**) ARC-HBR classification. Ref. Urban et al.[11] (**B**) Japanese HBR classification. Ref. Nakamura et al.[14] ARC, Academic Research Consortium; bAVM, brain arteriovenous malformation; CKD, chronic kidney disease; DAPT, dual antiplatelet therapy; eGFR, estimated glomerular filtration rate; HBR, high bleeding risk; ICH, intracranial hemorrhage; NSAIDs, nonsteroidal anti-inflammatory drugs; PCI, percutaneous coronary intervention

for continued OAC use strongly influences the choice of antithrombotic therapy to be administered to patients with ACS.

Antithrombotic Therapy for ACS

Antithrombotic therapy for patients with ACS is generally administered before the exact diagnosis of MI, rather than at the exact diagnosis; therefore, adequate timely intervention is warranted. Accordingly, some patients do not have coronary occlusion. Additionally, the antithrombotic therapy recommendations should be tailored according to the patient's treatment strategies and etiologies.

Early antithrombotic therapy after diagnosis

Extensive studies have established the efficacy of aspirin in improving the prognosis of patients with AMI. Notably, the ISIS-2 trial demonstrated that aspirin alone could lower vascular-related mortality by 23%.[13] Aspirin is recommended at an initial loading dose and a maintenance dose in the long term for all patients with ACS, reflecting its beneficial effects (**Table 1**), which are not restricted to the immediate post-AMI phase; subsequent administration also results in reduced vascular-related mortality. The timeliness of aspirin administration is directly correlated with mortality improvement, thereby making it a critical early intervention for AMI, barring contraindications such as severe blood disorders, severe liver disorders, aspirin-induced asthma, or an established hypersensitivity to aspirin.

For all patients with ACS, a P2Y12 inhibitor is recommended in addition to aspirin. Prasugrel or ticagrelor is preferred over clopidogrel; however, other agents have not been recommended in recent guidelines.[14–16] In patients with STEMI undergoing PCI, clopidogrel reduces cardiovascular mortality, nonfatal MI, and overall mortality, with only a minor increase in major bleeding events. A loading dose of 300 mg clopidogrel before PCI, followed by a maintenance dose, is recommended to reduce cardiovascular events. This strategy is also beneficial in patients treated with fibrinolytic therapy or those without reperfusion therapy, as indicated by a reduction in vascular-related events compared with the placebo. It is uncertain whether pretreatment with oral P2Y12 receptor inhibitors before invasive coronary angiography improves the clinical outcomes in patients with NSTE-ACS. However, it may be considered for patients with STEMI who are undergoing primary PCI.

Antithrombotic therapy in coronary interventions

Primary PCI

Parenteral anticoagulation is recommended for patients with STEMI undergoing primary PCI, and, currently, UFH is the default choice of anticoagulant. In the context of STEMI treatment during primary PCI, alternatives to UFH include enoxaparin, which is an LMWH, and bivalirudin, which acts as a direct thrombin inhibitor. These alternatives are worth considering owing to their anticoagulant properties in this patient group. The ATOLL and BRIGHT-4 trials evaluated the efficacy of enoxaparin or bivalirudin and demonstrated favorable outcomes relative to UFH in patients with STEMI. However, more data are required to confirm the results, and these agents are not available in Japan.[17,18] Moreover, fondaparinux is not recommended in patients with STEMI undergoing primary PCI, as per the results of the OASIS-6 trial.[19]

Parenteral anticoagulation therapy is also recommended for patients with NSTE-ACS. In current European guidelines for patients with NSTE-ACS undergoing immediate or early angiography (±PCI if indicated), UFH is recommended, but enoxaparin should be considered an alternative to UFH. For patients with NSTE-ACS who are not anticipated to undergo early angiography, the guideline recommends fondaparinux (with a UFH bolus at the time of PCI) over enoxaparin, although enoxaparin should be considered if fondaparinux is not available.[16] Additionally, GP IIb/IIIa receptor antagonists are available for patients with no reflow or thrombotic complications in Western countries. However, in Japan, guidelines often recommend the use of UFH. This is partly because of the history of a higher incidence of hemorrhagic complications following the administration of newer parenteral anticoagulants in Japan, which has led to parenteral anticoagulants other than heparin not being approved.

UFH is recognized as the conventional treatment for patients with STEMI undergoing primary PCI owing to its positive risk/benefit ratio. However, robust evidence supporting the advantages of anticoagulation therapy prior to primary PCI is lacking. Certainly, in the European guidelines, discontinuation of parenteral anticoagulation should be considered immediately after an invasive procedure.[16] This finding seems valid even when patients experiencing slow-flow or no-flow are excluded from the analysis. Following the completion of the invasive procedure, discontinuation of parenteral anticoagulation therapy should be considered.

PCI with stenting

Backgrounds of stent choices in ACS

The use of coronary stents in PCI has significantly improved treatment outcomes by preventing acute-phase reocclusion and has also demonstrated favorable long-term results, making it the mainstream strategy for current PCI. Regarding antithrombotic therapy in the acute phase of PCI, the STARS trial showed the usefulness of using dual antiplatelet therapy (DAPT) in combination with aspirin and ticlopidine, not just aspirin alone or warfarin plus aspirin, in patients with Palmaz–Schatz bare-metal stents (BMSs).[20] Moreover, in the case of drug-eluting stents (DESs), which have been developed to prevent restenosis of BMSs, concerns have been raised regarding late stent thrombosis due to discontinuation of DAPT.[21] Previously, it was considered necessary to continue DAPT for over a year after PCI; however, the onset of bleeding complications, which significantly affect prognosis, and their higher incidence in patients undergoing DAPT have been noted. Recent generations of DESs are considered to have superior antithrombotic properties, and the efficacy and validity of shortening DAPT duration have been demonstrated in several trials.[22–24]

Regarding the choice of stents, there appears to be no reason to use BMSs in ACS. The COMFORTABLE-AMI and EXAMINATION trials demonstrated the clinical superiority of DES over BMS in reducing rates of reinfarction, target lesion revascularization (TLR), and stent thrombosis.[22,23] Compared with BMSs and first-generation DESs, new-generation DESs are associated with superior safety and improved efficacy. Reflecting the safety and efficacy of DESs, DES use is strongly recommended in preference to BMS to prevent ischemic events such as restenosis, MI, or acute stent thrombosis in the recent guidelines.[15,16]

Without OACs

According to the concept of HBR, the patient's condition, such as OAC use, should be considered. There are some randomized controlled trials (RCTs) regarding antithrombotic therapy in patients with ACS, excluding patients taking OACs. ACS is considered to have a high thrombotic risk; thus, DAPT is generally recommended for at least 1 year after coronary stenting in patients without OAC. However, the duration and components of the DAPT regimen remain debatable.

The STOPDAPT-2 ACS trial was a randomized trial that examined the possibility of shortening DAPT duration in 4169 patients with ACS. The results did not show non-inferiority for the primary endpoint (a composite of cardiovascular death, MI, definite stent thrombosis, stroke, and thrombolysis in MI [TIMI] major/minor bleeding) at 12 months in the 1-month DAPT group compared with that in the 12-month DAPT group. Furthermore, the incidence rate of cardiovascular events in the 1-month DAPT group was numerically increased compared with that in the 12-month DAPT group (hazard ratio [HR], 1.50; 95% confidence interval [CI], 0.99–2.26), and there was a 54% reduction in TIMI major/minor bleeding in the 1-month DAPT group compared to that in the 12-month DAPT group.[25] In a sub-analysis comparing the HBR and non-HBR groups in the STOPDAPT-2 trial, the effects of 1-month DAPT on the primary and major secondary endpoints were consistent in patients with HBR and non-HBR without any significant interactions. The benefit of 1-month DAPT in reducing major bleeding was numerically greater in patients with HBR.[26] The sub-analysis of the TWILIGHT trial examined the effect of ticagrelor monotherapy after 3 months of DAPT on bleeding and ischemic events in patients with and without NSTE-ACS who underwent PCI with DES. The results showed that ticagrelor monotherapy significantly reduced bleeding events compared with ticagrelor plus aspirin, especially in patients with NSTE-ACS, without increasing the risk of death, MI, or stroke.[27] Similarly, the TICO randomized multicenter trial involving 3056 patients with ACS treated with DES who switched to ticagrelor monotherapy after 3 months of DAPT showed a modest but significant reduction in net adverse clinical events, including major bleeding and cardiovascular events, compared to continuing ticagrelor-based 12-month DAPT.[28] Reflecting on these trial results, the current ACS guidelines allow for the shortening of the DAPT duration considering the balance of bleeding and ischemic risks, although there are some minor differences among the guidelines (**Fig. 6**).

Another approach to reduce bleeding risk is de-escalating DAPT. De-escalation of DAPT is often performed by changing the P2Y12 inhibitors from the potent ones, prasugrel or ticagrelor, to clopidogrel. Sometimes genetic testing or platelet function testing is performed to guide de-escalation of DAPT. Some RCTs were performed to assess the noninferiority of the de-escalation strategy relative to DAPT with prasugrel/ticagrelor, and their meta-analysis revealed lower bleeding risk without increased ischemic risk in the de-escalation group, irrespective of the guide testing.[29,30] The approved dose of ticagrelor and prasugrel

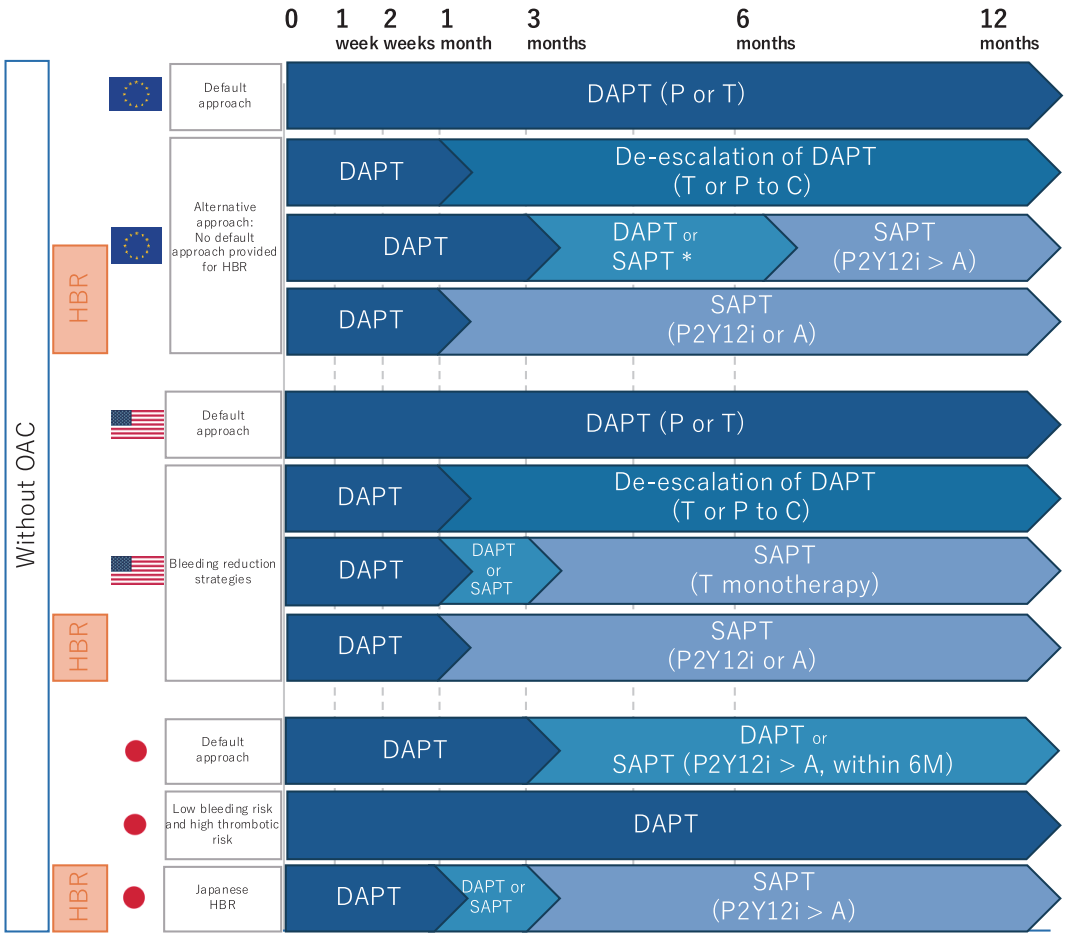

Fig. 6 Comparison of recommended DAPT duration as per regional guidelines in patients without OAC. *For Non-HBR: in patients at high ischemic risk and very low bleeding risk. For HBR: in patients not at high ischemic risk who are event-free after 3-6 months of DAPT. A, aspirin; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; M, month; OAC, oral anticoagulant; P, prasugrel; P2Y12i, purinergic receptor P2Y inhibitor; SAPT, single antiplatelet therapy; T, ticagrelor

varies according to the region; thus, careful consideration is required to apply the data, and more evidence is needed in light of the prevalence of carriers of the *CYP2C19* loss-of-function allele. Although we have scarce data regarding de-escalation in patients with ACS, reducing the dose of prasugrel or ticagrelor may be another option in patients with ACS. Currently, European guidelines do not recommend de-escalation of DAPT within 30 days after ACS.[16]

With OACs

Patients with AF, venous thromboembolism, mechanical prosthetic valve, thrombus in the left ventricle or atrium, left ventricular aneurysm, or thrombotic diathesis are indicated for OAC therapy to prevent thromboembolic events. The use of long-term OAC therapy, whether with a VKA or DOAC, after PCI is classified as a major criterion for HBR according to the ARC definitions published in 2019.[11] In patients receiving OAC therapy, their antithrombotic therapy should be tailored to minimize bleeding risk. Although no specific RCT has evaluated antithrombotic therapy in patients with ACS and OAC therapy, some RCTs that investigated minimizing bleeding risk in patients after PCI with maintenance therapy of OACs have included more than half of the patients with ACS in the entire population and are referenced in the current ACS guidelines.[14–16]

In the WOEST trial, researchers compared the efficacy and safety of dual therapy consisting of an OAC and clopidogrel versus triple therapy comprising an OAC along with DAPT.[31] The dual therapy regimen, consisting of an OAC plus a P2Y12 receptor inhibitor without aspirin, as investigated in the WOEST trial, showed a significantly lower incidence of bleeding events and did not increase ischemic events compared with the triple therapy regimen. This approach, now referred to as the "WOEST-like

regimen," has had a substantial influence on the subsequent strategies for antithrombotic therapy in clinical practice. Despite the influential findings of the WOEST trial, it had several limitations, such as a relatively small number of participants and the exclusive use of warfarin as an OAC. In the era of DOACs, 4 subsequent AF-PCI trials have been conducted that compare a WOEST-like regimen (dual therapy with a DOAC and a P2Y12 inhibitor without aspirin) with the traditional triple therapy regimen. The PIONEER AF-PCI trial revealed that the dual therapy group, which received 15 mg rivaroxaban in combination with 75 mg clopidogrel, experienced significantly fewer bleeding events compared with those in the triple therapy group.[32] Additionally, the rates of ischemic events were comparable between the 2 groups. It is important to recognize that the 15 mg dosage of rivaroxaban used in the PIONEER AF-PCI trial is considered a reduced dose in Western countries; however, it is the standard dose for certain indications in Japan (**Table 2**). The RE-DUAL PCI trial compared 2 doses of dabigatran (220 and 300 mg) with VKA therapy following PCI.[33] In this trial, the prescription of aspirin was limited to a duration of up to 3 months in the VKA group. The findings showed that both dabigatran groups exhibited superior outcomes in terms of reducing bleeding events compared with those in the VKA group. The AUGUSTUS trial was a study with a 2 × 2 factorial design that compared aspirin to placebo and warfarin to apixaban.[34] The findings of the trial showed that the rates of major or clinically relevant bleeding according to the International Society on Thrombosis and Haemostasis criteria were significantly lower in the apixaban group than in the warfarin group. Additionally, the aspirin group experienced twice the rate of major and clinically relevant bleeding compared with that in the placebo group. The primary efficacy endpoints of the AUGUSTUS trial were all-cause mortality and hospitalization. The results showed that apixaban 5 mg twice daily was more effective than warfarin in achieving these endpoints. However, the addition of aspirin did not offer any efficacy benefits over placebo. The ENTRUST-AF PCI trial demonstrated that dual therapy with edoxaban 60 mg once daily and clopidogrel was not inferior to warfarin triple therapy and tended to have a lower rate of bleeding endpoints.[35] Although these trials were not specifically designed to measure ischemic outcomes, pooled analyses suggested that the rates of mortality, MI, and stent thrombosis with dual therapy were comparable to those with triple therapy. All participants in these trials initially received triple therapy after PCI for a brief period before aspirin was discontinued. Subsequent analyses indicated that most stent thrombosis events occurred within the first 30 days after PCI. This finding suggests that extending aspirin therapy to 1 month after PCI can potentially mitigate the risk of stent thrombosis, particularly in patients at high risk for this complication. Taken together, these trials support the consideration of dual therapy with a DOAC and a P2Y12 inhibitor for patients with AF after PCI, with careful assessment of bleeding risk and the potential benefit of short-term continuation of aspirin therapy in certain high-risk individuals.

Although their mechanisms differ, it is generally accepted that anticoagulation therapy can fulfill the role of antiplatelet therapy; however, antiplatelet therapy cannot replace anticoagulation therapy in patients with ACS. Therefore, in patients receiving OACs, it is important to continue OACs with the indicated anticoagulation therapy and include the minimum necessary antiplatelet therapy, as required. In patients taking OAC, the current guideline recommends triple therapy at the time of PCI; however, rapid discontinuation of aspirin is recommended (**Fig. 7**).

Non-stenting PCI strategy: plain old balloon angioplasty (POBA) only, debulking devices, thrombus aspiration, and CABG

Although the long-term outcomes of PCI with stenting have been established, there are ongoing efforts to further improve PCI outcomes, including those of the non-stenting PCI strategy. Depending on the pathology of the obstructive coronary artery disease, good outcomes can be expected without stent placement if, after relieving the obstruction, the vascular endothelium is relatively preserved. Advancements in intravascular imaging have popularized PCI using intravascular ultrasound or optical coherence tomography, and the combined use of these imaging techniques during PCI improves clinical outcomes. Theoretically, under precise management using intravascular imaging, there is minimal concern regarding the progression of coronary dissection and acute occlusion.

To avoid long-term complications related to stenting, a strategy involving drug-coated balloon (DCB) angioplasty without stenting has also been proposed for patients with ACS. In the REVELATION trial, DCB-PCI vs. DES-PCI was investigated by randomizing 120 STEMI patients undergoing primary PCI. The primary endpoint of the target vessel fractional flow reserve at 9 months was not significantly different between the 2 groups.[36] In the PEPCAD NSTEMI trial, 210 patients were randomized,

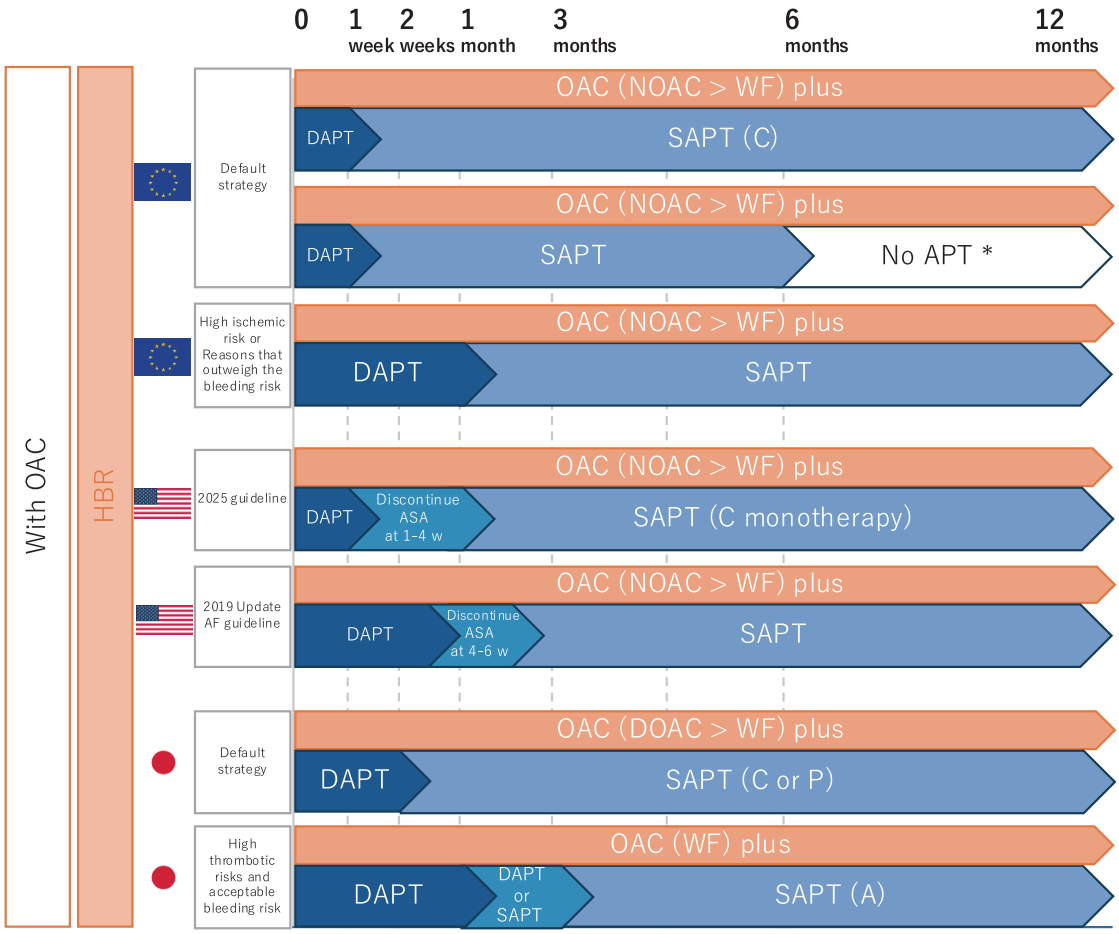

Fig. 7 Comparison of recommended DAPT duration as per regional guidelines in patients with OAC. When switching from short-term DAPT to monotherapy, P2Y12 inhibitor is considered as a single drug rather than aspirin. *In certain patients; for example, in patients with multiple HBR factors. A, aspirin; APT, antiplatelet therapy; C, clopidogrel; DAPT, dual antiplatelet therapy; HBR, high bleeding risk; NOAC, non-vitamin K oral anticoagulants; OAC, oral anticoagulant; P, prasugrel; P2Y12, purinergic receptor P2Y; SAPT, single antiplatelet therapy; w, weeks; WF, warfarin

and a DCB was compared with primary stent treatment by BMS or DES.[37] During a mean follow-up period of 9.2 months, DCB treatment was noninferior to treatment with a stent, with target lesion failure (primary study endpoint; defined as a combined clinical endpoint consisting of cardiac or unknown death, reinfarction, and TLR) rates of 3.8% vs. 6.6% (P = 0.53). In the REC-CAGEFREE I trial, 2272 patients with uncomplicated de novo coronary lesions, including STEMI or NSTE-ACS, were evaluated. DCB plus rescue stenting did not achieve noninferiority compared with the planned DES implantation in the assessment of a composite outcome comprising cardiovascular death, MI related to the target vessel, and TLR events at 24 months.[38] Despite the low use of intravascular ultrasound (IVUS) and optical coherence tomography (OCT) in this trial, the choice of opting for a non-stenting strategy for patients with ACS should be made with caution. It should also be noted that in clinical practice, non-stenting strategies may be chosen with the intention of shortening the DAPT period. Referring to practices from the era of POBA, a duration of DAPT within 1 month may be applied; however, data evaluating DAPT duration in patients with ACS and non-stenting treatment with DCB are limited. This non-stenting strategy can be applied to patients with MINOCA and the etiology is suitable for PCI, such as in patients with embolic sources treated by aspirating a thrombus or embolism. In patients treated with non-stenting strategies, such as conventional POBA and thrombus aspiration, and without coronary lesions, long-term DAPT may not be mandated; however, evidence is limited.

In patients with ACS treated by coronary artery bypass grafting (CABG), the role of antithrombotic therapy includes

other aspects different from those after PCI, such as surgical bleeding and graft patency. There are limited data on preoperative antithrombotic use. Patients who discontinue DAPT to undergo CABG surgery for ACS are advised to resume DAPT postoperatively. The DACAB trial enrolled 500 patients undergoing CABG and demonstrated the vein graft patency was highest in the DAPT group relative to the single antiplatelet regimen group.[39] The current guidelines recommend continuing DAPT for months following surgery.[15,16] There are no data to suggest the antithrombotic therapy of patients with ACS who undergo CABG when there is an indication for anticoagulation.

Antithrombotic therapy in patients with coronary artery disease, without reperfusion therapy

Current European Society of Cardiology (ESC) guidelines recommend the administration of a P2Y12 receptor inhibitor along with aspirin for 12 months in patients who are conclusively diagnosed with ACS and are not subjected to reperfusion therapy, provided that the patient is not at an HBR.[16] A sub-analysis of the PLATO trial for patients with ACS without revascularization has shown that DAPT combined with aspirin and ticagrelor for up to 12 months is more beneficial than aspirin and clopidogrel.[40] In patients with ACS not undergoing reperfusion therapy, the duration of DAPT up to 12 months remains a topic of ongoing investigation. For patients diagnosed with ACS who do not undergo reperfusion, a DAPT regimen that includes a potent P2Y12 inhibitor is considered a viable treatment unless the patient is predisposed to an elevated bleeding risk, as indicated by the ARC-HBR criteria.

Antithrombotic Therapy in Cases of MINOCA, without Epicardial Coronary Artery Involvement

In patients diagnosed with MINOCA without PCI-suitable lesions, the strength and duration of the antithrombotic therapy depend on the individual patient's status. Management should be considered separately for those with and without coronary artery lesions; however, evidence is lacking, and the current guidelines are based on data from conventional ACS with coronary artery lesions. In patients with MINOCA who are not suitable to undergo PCI, or in whom PCI may necessitate the placement of a stent or require prolonged antithrombotic therapy, careful evaluation of progressive myocardial ischemia is crucial during management with medical therapy and monitoring of their progress. If progressive ischemia is not observed during the acute phase, a specific duration of antithrombotic therapy is recommended. However, the evidence for these protocols in such patients remains limited. Therefore, treatment should be carefully tailored to the individual patient's situation and aligned according to the final established underlying diagnosis and disease-specific guidelines; however, data regarding MINOCA with cardiac reasons are limited.

Currently, data regarding antithrombotic therapy for MINOCA are limited. An observational study of the SWEDEHEART registry evaluated 9466 consecutive patients with MINOCA, among whom 66.4% were treated with DAPT. During the 4-year follow-up, DAPT had no significant effect (HR, 0.90; 95% CI, 0.74–1.08) on 1-year major adverse cardiovascular events (MACEs). DAPT was not associated with an increase in bleeding events (HR, 1.33; 95% CI, 0.73–2.42).[41] A post hoc analysis from OASIS-7 evaluated 23783 patients with MI and 1599 (6.7%) patients with MINOCA. From the 1-year follow-up data, they concluded that an intensive dosing strategy did not provide additional benefits or even a deleterious signal.[42] Kovach et al. evaluated 1986 patients with MINOCA, and 20% were treated with DAPT. They demonstrated that treatment with DAPT was not associated with a reduction in MACEs (HR, 1.02; 95% CI, 0.58–1.80) during the 1-year follow-up.[43] Current observational studies do not provide clear evidence of the benefits of antiplatelet therapy in patients with MINOCA. There is a keen interest in initiating specific prospective RCTs to evaluate the specificity, efficacy, and safety of various antiplatelet agents in patients with MINOCA with different underlying causes.

Crosstalk with Neurological Interventions and Coronary Interventions

Oral P2Y12 inhibitors: loading issues

Even though oral antiplatelet agents are loaded immediately after diagnosis in patients with ACS, it is important to note that this is not generally approved for acute cerebrovascular events. For stroke, the loading of ticagrelor or prasugrel is approved in the US or Europe, respectively, but the other drugs do not indicate loading for stroke in the instructions for use. Antiplatelet loading is primarily intended to prevent thrombus formation associated with atherosclerotic plaque disruption. However, because of the wide variety of causes of stroke, it is unlikely that antiplatelet loading is necessarily effective. Balancing the risk of hemorrhagic complications, starting at the usual dose,

would be a reasonable choice in patients with acute cerebrovascular events.

Antithrombotic therapy titration using platelet function or genetic testing

As mentioned previously, DAPT with a P2Y12 inhibitor is crucial, especially in patients requiring stenting. Although the prevalence of carriers of the *CYP2C19* loss-of-function allele differs according to the regions, we cannot predict the generation of clopidogrel's active metabolite. There is a concern regarding unintentionally high on-treatment platelet reactivity in patients with the *CYP2C19* loss-of-function allele. Even a minor thrombotic or bleeding event can result in severe neurological deficits in the neurointerventional fields; thus, periprocedural platelet function testing is often used to titrate antiplatelet therapy.

In the field of PCI for ACS, several RCTs failed to attest to the superiority of routine platelet function testing; the 2019 expert consensus document does not recommend routine platelet function testing or genotyping.[44] After that, the TAILOR-PCI trial assessed the genotype-guided selection of an oral P2Y12 inhibitor compared with conventional clopidogrel therapy without point-of-care genotyping on ischemic outcomes in patients with ACS or stable coronary artery disease carrying the *CYP2C19* loss-of-function allele and undergoing PCI.[45] The study found no statistically significant difference between the 2 approaches in terms of a composite endpoint, which included cardiovascular death, MI, stroke, stent thrombosis, and severe recurrent ischemia, based on the prespecified analysis plan and the study's power to detect treatment effects at 12 months. The potential benefits of utilizing platelet function or genetic testing to guide the de-escalation of oral P2Y12 receptor inhibitors following the initial month of therapy after PCI have yet to be definitively established. As recommended in the 2019 expert consensus, platelet function tests or genetic typing for tailoring antiplatelet therapy should be conducted in selective cases who require de-escalation or escalation of DAPT.[44]

Antithrombotic therapy for intracranial stents, in patients without atherosclerotic disease

Although antiplatelet therapy with P2Y12 inhibitors for those without ACS or who do not undergo PCI is off-label use, sometimes DAPT is implemented for patients with cerebral stenting, such as unruptured cerebral aneurysms, not only for patients with atherosclerotic arterial stenosis. The situation may be similar to the antithrombotic therapy for the patients with MINOCA, without atherosclerotic disease such as coronary dissection or embolism, and undergoing coronary stenting. Patients with unruptured cerebral aneurysms are also at risk for hemorrhagic complications, and careful judgment must be exercised when administering antiplatelet therapy. Appropriately designed RCTs are expected regarding the optimal regimen and duration of antiplatelet therapy in the treatment of unruptured cerebral aneurysms. Until then, the treatment strategy will need to be determined individually, considering each patient's risk factors. Sparse data are available for this field. However, the optimal antithrombotic therapy for those patients would be based on the etiology of the disease. We need more insight into the antithrombotic strategy for patients without atherosclerotic disease undergoing arterial stenting.

Future Perspectives: Potent Antithrombotic Therapy Options for ACS

Antiplatelet monotherapy after PCI

The no-DAPT regimen is considered a promising option in terms of its potential to reduce bleeding complications, which pose the greatest risk immediately after PCI. However, at present, it is considered reasonable to administer DAPT, including aspirin and a P2Y12 inhibitor, for at least 1 month after PCI. In the STOPDAPT3 trial, 6002 patients with ACS or HBR were randomized just before PCI after the confirmation of a suitable lesion for PCI and assigned to either aspirin-free prasugrel monotherapy or DAPT with aspirin and prasugrel.[46] The patients in both groups received a loading dose of prasugrel, and the patients in DAPT group also received a loading dose of aspirin if they were naïve to aspirin therapy. The dose of prasugrel was the approved one in Japan (loading 20 mg and maintenance 3.75 mg). At 1 month, the aspirin-free prasugrel monotherapy group was not superior to the DAPT group in terms of the coprimary bleeding endpoint (BARC type 3 or 5 bleeding, 4.47% and 4.71%, respectively; HR, 0.95; 95% CI, 0.75–1.20; *P* superiority = 0.66). The aspirin-free prasugrel monotherapy group was noninferior to the DAPT group in terms of the coprimary cardiovascular endpoint (4.12% and 3.69%, respectively; HR, 1.12; 95% CI, 0.87–1.45; *P* noninferiority = 0.01). There was an excess of any unplanned coronary revascularization (1.05% and 0.57%, respectively; HR, 1.83; 95% CI, 1.01–3.30) and subacute definite or probable stent thrombosis occurring between 24 hours and 1 month after

stenting (0.58% and 0.17%, respectively; HR, 3.40; 95% CI, 1.26–9.23) in the aspirin-free prasugrel monotherapy group compared with the DAPT group. Compared with the DAPT strategy, the aspirin-free strategy using low-dose prasugrel failed to demonstrate superiority for major bleeding within 1 month after PCI but was noninferior for cardiovascular events within 1 month after PCI. Post hoc analysis suggested that the reason might be the difference in the nature of bleeding that occurs within 1 month of PCI and that of bleeding that occurs after 1 month of PCI, or in the use of parenteral anticoagulants after PCI. In addition, the aspirin-free strategy was associated with a signal suggesting an excess of coronary events; furthermore, the signal was prominent in patients with ACS relative to patients with HBR. According to the STOPDAPT-3 study, the incidence of stent thrombosis in the aspirin-free prasugrel monotherapy group at 1 month was low: 0.47% for definite stent thrombosis and 0.71% for definite/probable stent thrombosis. Although there was no numerical increase in acute stent thrombosis occurring within 24 hours of stenting in the aspirin-free group relative to the DAPT group, there was a significant increase in the incidence of subacute stent thrombosis in the aspirin-free prasugrel monotherapy group. It appears that subacute stent thrombosis may be more influenced by antiplatelet therapy.[46] At present, it is considered reasonable to administer DAPT, including aspirin and a P2Y12 inhibitor, for at least 1 month after PCI.

Low-dose OACs after ACS

Several studies have investigated the additive value of DOACs in the long-term management of ACS after hospital discharge. The APPRAISE-2 trial, comparing standard-dose apixaban (5 mg twice daily or 2.5 mg twice daily for patients with renal disease) with placebo, was stopped early due to a significant increase in major bleeding, including intracranial hemorrhage, without notable differences in MACE.[47] The ATLAS ACS 2–TIMI 51 trial, investigating bleeding risks observed with standard-dose anticoagulants, tested low-dose rivaroxaban (2.5 or 5 mg of rivaroxaban) in patients with ACS, most of whom were on DAPT.[48] This trial found that low-dose rivaroxaban reduced the risk of death, MI, and stroke but increased major bleeding risks. The low-dose DOAC is not recommended in the current ACS guidelines; however, low-dose DOACs may be an option for patients with ACS. Nonetheless, regional or dosing differences in certification should be considered.

Advanced PCI techniques: non-stenting strategies and intracoronary imaging

The high safety profile of current DESs has been well-established; however, efforts to develop fully absorbable coronary devices have been made. The first generation of bioresorbable vascular scaffolds, designed to dissolve within the body, were initially introduced but later withdrawn from the market owing to concerns about scaffold thrombosis.[49] Incomplete apposition of struts breaking down during the degradation process in the body and thrombus formation at the same site are thought to be contributing factors. Despite this, the concept of artificial material that disappears from the vessel remains highly appealing, and improved versions are still being actively developed.[50] Although PCI is a well-established procedure, new treatments are still being developed, with ongoing optimization of therapy, including the use of intravascular imaging. These advancements hold promise for improved patient outcomes.

Conclusion

This review highlights the dynamic and nuanced nature of antithrombotic therapy for ACS. Since ACS is a rapidly evolving condition that requires prompt treatment initiation, antithrombotic therapy considered optimal in accordance with the working diagnosis should be performed during the acute phase. Although there is significant alignment among the regional guidelines, variations exist, influenced by genetic, demographic, and system-level factors. Going forward, a more personalized approach to antithrombotic therapy that integrates genetic and clinical data appears to be the trajectory of future guideline iterations. Continued studies will be pivotal in refining these guidelines to optimize patient outcomes in ACS.

Disclosure Statement

The authors declare that they have no conflicts of interest.

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