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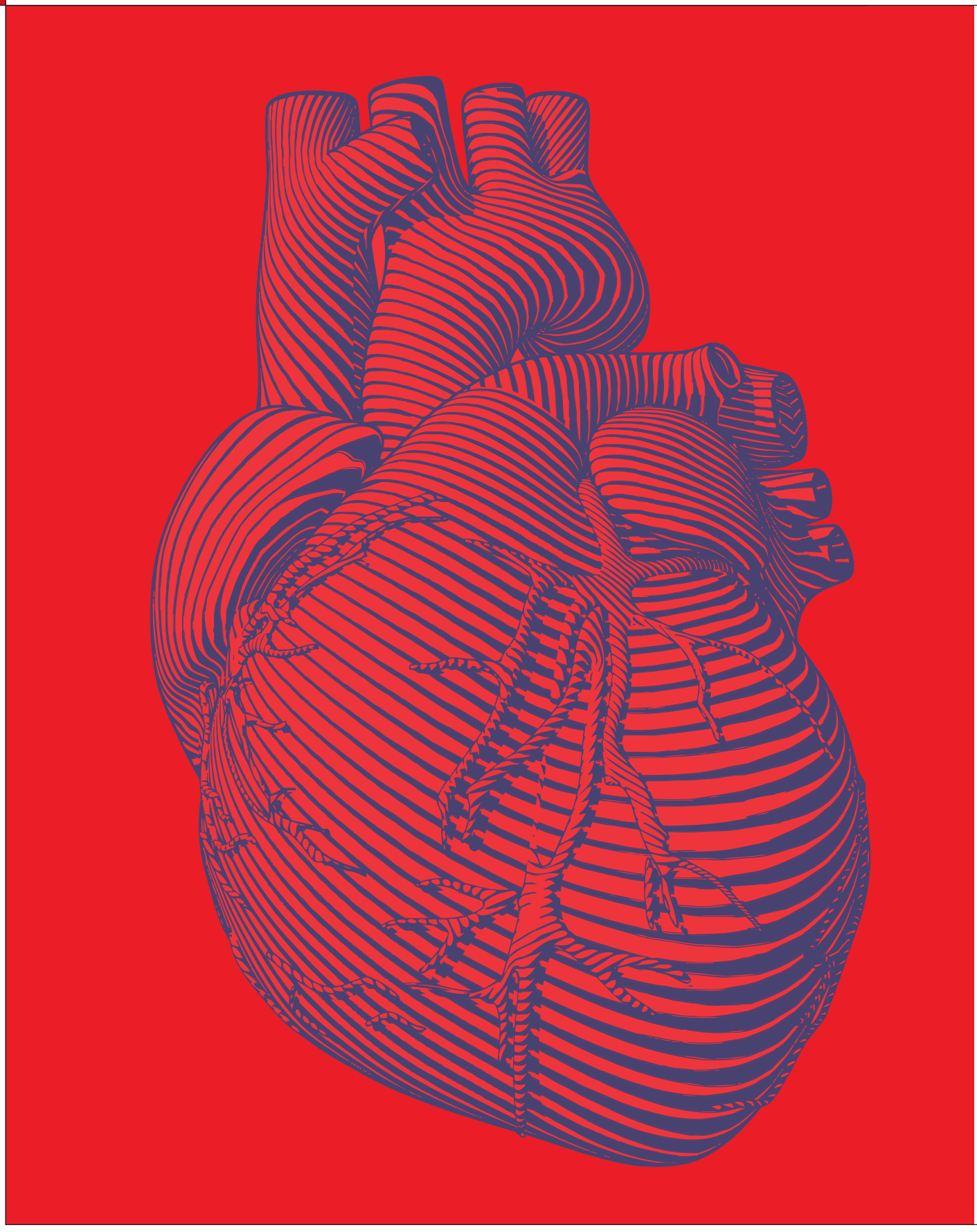

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Management strategies for STE-ACS

Abstract: Using guideline-driven interventions, NPs are well suited for management of ST-segment elevation (STE)-acute coronary syndrome (ACS). This second article in a two-part series on ACS management presents an updated overview to help NPs in applying evidence-based interventions while caring for patients with STE-ACS.

By Mohamed Toufic El Hussein, PhD, RN, NP and Jonah Hakkola

The first article in this two-part series focused on the management of non-ST-segment elevation (NSTE)-acute coronary syndrome (ACS).[1] In this second part, management of ST-segment elevation (STE)-ACS will be discussed including the current standards of care, such as the use of coronary interventions, beta-blockers, antiplatelets, anticoagulants, analgesics, ACE inhibitors, and statins.

Persistent electrocardiographic (ECG) STE-ACS reflects an ongoing transmural myocardial ischemia and necrosis.[2] Acute care NPs are in an ideal position to diagnose and manage STE-ACS by implementing guideline-driven medical interventions.[1]

Pathophysiology

STE-ACS is a subcategory of coronary artery disease, which involves atherosclerosis.[3] Coronary atherosclerosis includes an autoimmune response to elevated levels of low-density lipoprotein (LDL) cholesterol that contributes to accumulation of lipid-laden plaques within the walls of the coronary arteries.[4] Unstable plaques are characterized by a rich oxidized LDL core and a thin fibrous cap that may erode or even rupture when exposed to shearing forces or degradative enzymes from leukocytes.[4] The ruptured plaque triggers rapid formation of a thrombus that can completely obstruct the lumen of one of the coronary arteries resulting in STE-ACS.[4]

Diagnosis

The diagnosis of STE-ACS must be concluded within the first 10 minutes of the first medical contact using a 12-lead ECG, according to the 2019 focused update to the STE-ACS guideline by the Canadian Cardiovascular Society and Canadian Association of Interventional Cardiology (see *ECG changes commonly seen with STE-ACS*).[2,5]

Keywords: ACE inhibitor, anticoagulation, bare metal stent, beta-blocker, drug eluting stent, dual antiplatelet therapy, fibrinolysis, morphine, nitrate, oxygen, primary percutaneous coronary intervention, statin, ST-elevation acute coronary syndrome (STE-ACS), ST-elevation myocardial infarction (STEMI)

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ECG changes commonly seen with STE-ACS[2,6]

Men	<40 years: at least two contiguous leads with ST-elevation ≥2.5 mm in leads V_2-V_3 **and/or** ≥1 mm in the other leads. ≥40 years: at least two contiguous leads with ST-elevation ≥2.0 mm in leads V_2-V_3 **and/or** ≥1 mm in the other leads.
Women	At least two contiguous leads with ST-elevation ≥1.5 mm in leads V_2-V_3 **and/or** ≥1 mm in the other leads (regardless of age).

In addition to ST-elevation, the presence of pathologic Q waves on ECG with elevated cardiac troponin I (cTnI) and T (cTnT) blood levels above the 99th percentile upper reference limit are highly suggestive of STE-ACS.[2] Note that the use of an ECG as a singular diagnostic tool may not be sufficient to make a diagnosis of STE-ACS, as ST deviation can be present in other conditions, including acute pericarditis, left-ventricular hypertrophy, and left bundle-branch block among others.[2] Patients experiencing STE-ACS often present with diffuse chest pain that is nonreproducible on palpation, not positional nor worsened by the depth of inspiration (nonpleuritic).[2] In addition to chest pain, patients may experience diaphoresis, mandibular or epigastric discomfort, nausea, syncope, and unexplained fatigue.[2]

Treatment strategy

Coronary interventions

Coronary interventions are a mainstay in the management of STE-ACS, with strong recommendations that primary percutaneous coronary intervention (PPCI) be performed in patients with STE-ACS ideally within 90 minutes of first medical contact, or within 120 minutes for patients diagnosed in the field or in a non-PCI facility.[5] PPCI refers to emergent PCI (without prior fibrinolytic treatment) with a balloon, stent, or other approved device deployed into the infarct-related artery.[6] PPCI is the gold standard of reperfusion therapy and should be initiated within 12 hours of symptom onset, according to the Canadian guideline update.[5] In cases where access to PPCI in less than 120 minutes from first medical contact is not possible, fibrinolytic therapy should be initiated in the absence of contraindications (see *STE-ACS algorithm*).[5] Immediate transfer to a PCI-capable hospital is recommended postfibrinolysis, with angiography and PCI (if indicated) of the infarct-related artery within 2-24 hours of successful fibrinolysis.[6] In cases where fibrinolytic treatment has failed after implementation, a rescue PCI may be indicated, per the European Society of Cardiology guideline.[6] Absolute contraindications to fibrinolysis in STE-ACS according to the 2017 European Society of Cardiology guideline for STE-ACS include previous intracranial hemorrhage, ischemic stroke within the past 6 months, major trauma/surgery/head injury or gastrointestinal bleeding within the last month, bleeding disorders, aortic dissection, and noncompressible punctures within the past 24 hours.[6]

In a seminal quantitative review including 23 randomized controlled trials (RCTs), Keeley and colleagues concluded that PPCI was consistently superior to thrombolytic therapy (regardless of the thrombolytic agent) in reducing overall short-term death ($P = .0002$), nonfatal reinfarction ($P < .0001$), and stroke ($P = .0004$).[7]

The Danish Multicenter Randomized Study on Fibrinolytic Therapy versus Acute Coronary Angioplasty in Acute Myocardial Infarction (DANAMI-2) conducted by Andersen and colleagues randomized a total of 1,572 patients with STE-ACS to receive either fibrinolysis or PPCI.[8] At 30 days, there was a significant relative reduction in the composite outcome of death, clinical reinfarction, or disabling stroke at 30 days that included a 75% reduction to the relative risk of clinical reinfarction in favor of the PPCI group ($P < .001$).[8] In the 16-year follow-up of the same study, Thrane and colleagues determined that in comparison to fibrinolysis, patients who received PPCI had a lower rate of rehospitalization for myocardial infarction (MI) (19.0% versus 24.5%) and reduced cardiac mortality (18.3% versus 22.7%), and the average time of a main event (death or rehospitalization for MI) was postponed by an average of 12.3 months.[9]

Bare-metal stents vs. drug-eluting stents

In the context of PPCI for STE-ACS, there are strong indications for the placement of either a bare-metal stent (BMS) or the preferred drug-eluting stent (DES; (see *Drug-eluting stents vs. bare metal stents*).[6] Current guidelines indicate BMS for patients with high bleeding risk, potential nonadherence with dual antiplatelet therapy (DAPT), as well as if there is reason to anticipate invasive or surgical procedures within the next year.[2] DESs consist of three main components: a metal mesh (as seen with BMS), an antiproliferative drug (for example, sirolimus and paclitaxel in first-generation DESs or zotarolimus and everolimus in the preferred newer-generation DESs), and a polymer that coats the metal mesh and controls the rate of release of the drug (see *Drug-eluting stent*).[10] These antiproliferative drugs limit further growth of

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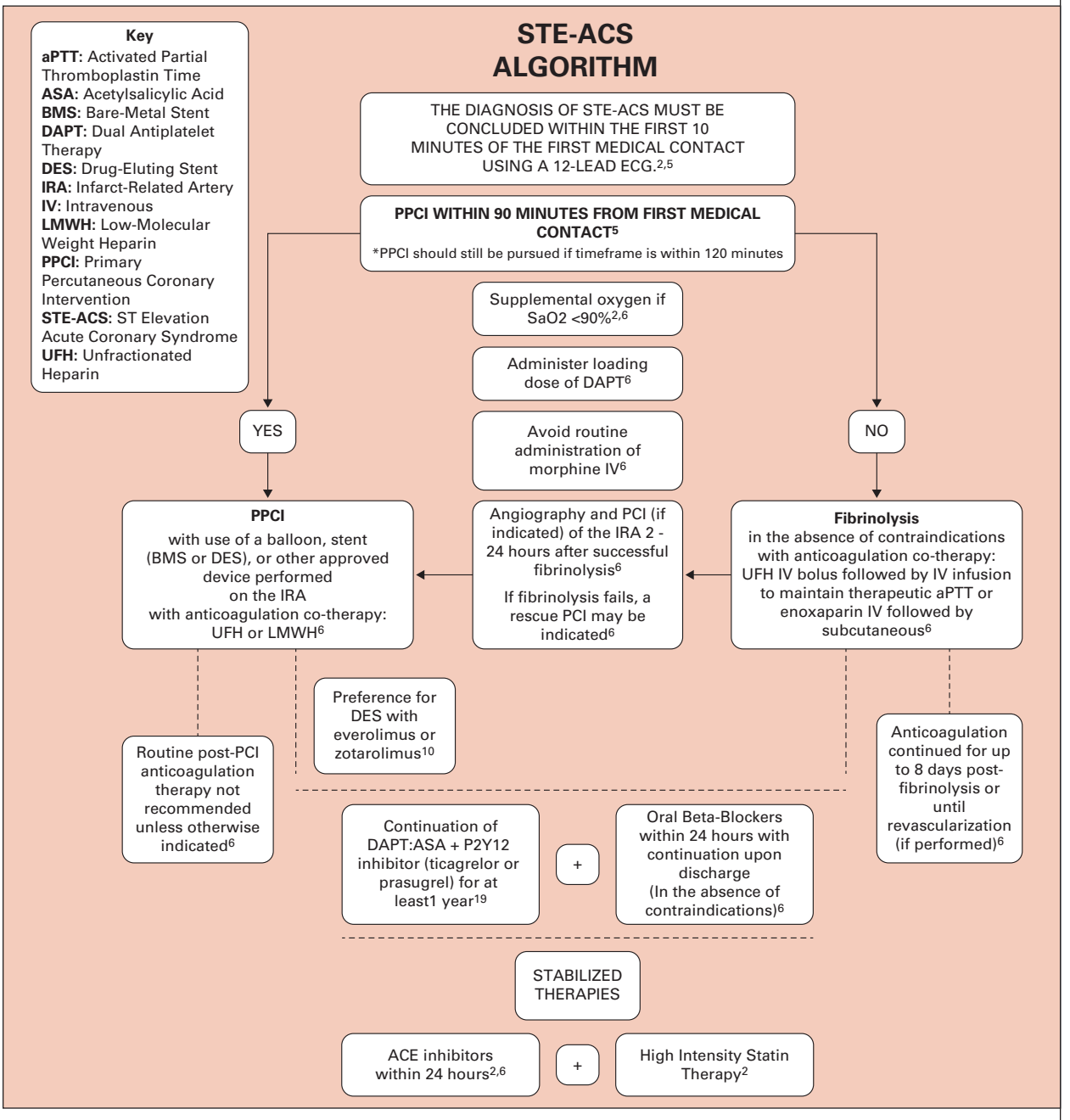

the neointima either through cytotoxic or cytostatic agents.[10] A DES is not recommended for patients who cannot tolerate or may be nonadherent to DAPT due to the increased risk of stent thrombosis if the patient discontinues one or both agents.[11] Stent thrombosis is a rare but life-threatening complication in patients post-PCI that can occur within 30 days (early stent thrombosis) or, more commonly, after 30 days (late stent thrombosis).[12] The exact triggering mechanism of stent thrombosis remains incompletely understood; however, recent data suggest a strong relation to the inflammatory process with the platelet-rich thrombus, which is composed of fibrin/fibrinogen fragments, erythrocytes, and inflammatory cells (namely neutrophils and eosinophils).[12]

Stent restenosis is another complication that may occur post-PCI wherein the stented vessel undergoes a lumen diameter reduction through neointimal proliferation; restenosis can also occur post-PCI if no stent is used through early elastic return or vascular remodeling.[13] Everolimus and zotarolimus are highly effective

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Drug-eluting stents vs. bare metal stents[2,6,13,16,17]

	Indications	Outcomes
Drug-Eluting Stents	• Patients with increased risk of restenosis (for example, left main coronary artery disease, small vessels, in-stent restenosis, bifurcations, diabetes) • Adherence to and toleration of dual-antiplatelet therapy	• Lower rates of definite stent thrombosis and target lesion revascularization (especially newer-generation DES) • Lower rates of all-cause mortality at 5 years
Bare-Metal Stents	• High bleeding risk • Nonadherence with or intolerance of dual-antiplatelet therapy • Anticipated invasive or surgical procedures within the next year	• Lower risk of reinfarction and target vessel revascularization when compared with balloon angioplasty

in reducing the occurrence of stent restenosis over first-generation DESs and BMSs.[13]

DES is ideal when the target artery is less than 3 mm or the lesion is longer than 15 mm.[10] Stents typically range in size from 2.25 mm to 4.00 mm in diameter and from 8 mm to 28 mm in length.[14] In comparison to balloon angioplasty, primary stenting has been associated with lower risks of both reinfarction and target vessel revascularization despite failing to reach significance with regard to lowering mortality.[6,15] However, note that balloon angioplasty without stent placement may still be used in select patients.[2] Newer-generation DESs are safer and more effective when compared with first-generation DESs in regard to lower risk of stent thrombosis and recurrent MI.[6] These newer DESs typically have decreased strut thickness alongside increased flexibility and enhanced biocompatibility, further reducing the occurrence of stent thrombosis and restenosis.[10]

The clinical Evaluation of the Xience-V stent in Acute Myocardial INfArcTION (EXAMINATION) trial was an RCT that examined clinical outcomes in patients with STE-ACS treated with everolimus-eluting stents (EESs), a second-generation DES, versus BMSs.[16] Patients with STE-ACS (N = 1,498) were randomly assigned to receive either an EES (n = 751) or a BMS (n = 747) and then the combined patient-oriented outcome of all-cause death, any MI, or any revascularization was assessed every year for 5 years.[16] At the 5-year follow-up, researchers concluded that the EES was statistically superior to a BMS as the patient-oriented endpoint had occurred in 21% of the EES group in comparison to 26% of the BMS group ($P = .033$).[16] Additionally, in Bønaa and colleagues' study (N = 9,013) comparing the long-term effects at 5 years of DES versus BMS, the authors found that DESs were superior to BMSs regarding rates of repeat revascularization ($P < .001$) and stent thrombosis ($P = .0498$).[17] Ninety-six percent of the DES group in this study had received either an everolimus- or zotarolimus-eluting stent.[17]

Antiplatelets, anticoagulants, oxygen, and analgesics

Antiplatelets. Antiplatelets are highly effective in inhibiting the progression of the clotting cascade and are first-line for the management of STE-ACS.[18]

The NP must ensure that an acetylsalicylic acid (ASA) loading dose is administered prior to PPCI; ASA therapy should be continued indefinitely.[6] Additionally, administration of a loading dose of a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor)—another antiplatelet—is recommended.[5] DAPT (ASA plus a P2Y12 receptor inhibitor) must be continued for at least 1 year post fibrinolysis and/or PCI.[6,19] While both clopidogrel and prasugrel are thienopyridine prodrugs causing irreversible P2Y12 receptor inhibition, prasugrel is more potent than clopidogrel, achieving greater inhibition of platelet aggregation.[11] Conversely, ticagrelor is a reversible nonthienopyridine P2Y12 receptor antagonist and does not require metabolic activation.[11]

Current guidelines prefer ASA alongside either ticagrelor or prasugrel over clopidogrel.[19] Schüpke and colleagues compared the primary end-point events (death, MI, and stroke) outcomes of ticagrelor versus prasugrel therapy in patients with suspected ACS (N = 4,018, 41% STE-ACS).[20] At 1 year, 9.3% of patients prescribed ticagrelor had undergone a primary end-point event compared with 6.9% in the prasugrel group ($P = .006$).[20] No significant difference in the occurrence of major bleeding events was noted ($P = .46$).[20] A prospective cohort study in Sweden (N = 45,073, 35.5% STE-ACS) evaluated ticagrelor (n = 11,954) versus clopidogrel (n = 33,119) therapy post-ACS with primary outcomes of all-cause death, MI, and stroke at 24 months.[21] Among

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patients who received ticagrelor, 11.7% experienced primary outcomes compared with 22.3% who received clopidogrel.[21] Bleeding outcomes requiring admission were similar between the groups, with ticagrelor posing a slightly higher risk for bleeding: 5.5% versus 5.2%.

Anticoagulants. Anticoagulation therapy (unfractionated heparin [UFH] or low-molecular-weight heparins [LMWHs] such as enoxaparin) should always be used during PPCI.[6] Following reperfusion therapy, the NP should initiate supportive anticoagulation therapy for up to 8 days postfibrinolysis or until revascularization (if indicated).[6] Routine anticoagulant therapy post-PCI is not recommended unless otherwise indicated (for example, atrial fibrillation, mechanical valves, or left ventricular thrombus).[6] For patients with STE-ACS who have received a fibrinolytic agent (such as tenecteplase), it is recommended to prescribe a UFH I.V. bolus followed by I.V. infusion to maintain a therapeutic activated partial thromboplastin time or to prescribe enoxaparin I.V. followed by subcutaneous.[5,22] Furthermore, if the patient undergoes PCI after fibrinolytic therapy with enoxaparin, additional enoxaparin must not be administered within 8 hours of prior dosage.[11]

The Acute Myocardial Infarction Treated with Primary Angioplasty and Intravenous Enoxaparin or Unfractionated Heparin to Lower Ischemic and Bleeding Events at Short- and Long-term Follow-up (ATOLL) trial was a randomized open-label trial that compared the effectiveness of UFH versus enoxaparin prior to PPCI in 910 patients presenting with STE-ACS.[23] The authors concluded that I.V. enoxaparin was associated with significantly reduced clinical ischemic outcomes ($P = .015$) for the endpoints of death, recurrent ACS, or urgent revascularization.[23]

Oxygen. The routine use of oxygen in the treatment of STE-ACS is common, yet current guidelines indicate that supplemental oxygen should only be initiated for patients with SaO2 < 90%.[2,6] Supplemental oxygen has no apparent clinical benefits and may increase the risk of further myocardial injury in patients with SaO2 ≥ 90% with evidence supporting that supplemental oxygen administered within the first 12 hours of STE-ACS can result in an increase in mean peak troponin I and creatine kinase ($P < .001$).[2,6,24] The effect of oxygen was examined in the DETermination of the role of Oxygen in suspected Acute Myocardial Infarction (DETO2X-AMI) trial, which compared the outcomes of normoxemic patients with STE-ACS who underwent PPCI and had received supplemental oxygen (n = 1,361) versus room air (n = 1,446).[25] At 1 year, no significant difference was observed in the composite endpoint of all-cause death, rehospitalization with MI, cardiogenic shock, or stent thrombosis between the two groups ($P = .27$).[25]

Drug-eluting stent

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Furthermore, new evidence suggests that oxygen therapy is not beneficial for analgesia within normoxemic conditions. Sparv and colleagues conducted a substudy of the DETO2X-AMI trial to determine the analgesic effect of moderate-flow oxygen therapy for patients with STE-ACS (n = 465).[26] No significant difference in peak level of pain was determined between the oxygen group versus the ambient-air group ($P = .97$).[26] These findings are further supported by the randomized Supplemental Oxygen in Catheterized Coronary Emergency Reperfusion (SOCCER) trial in which the authors examined the effects of supplemental oxygen on pain levels of patients with STE-ACS (N = 160).[27] Khoshnood and colleagues concluded no significant difference in pain levels from the time of randomization until PCI between the oxygen group versus the ambient-air group ($P = .183$).[27] Similar results were obtained by Zughaft and colleagues in the OXYPAIN trial, in which patients (N = 305) undergoing PCI with O2 saturations ≥ 95% were randomized to receive either oxygen supplementation or room air.[28] The patients then rated their pain using the Visual-Analog Scale.[28] The authors concluded that the use

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of supplemental oxygen during PCI is not effective for analgesic effects ($P = .12$) nor does it reduce myocardial injury as measured with troponin-*t* ($P = .46$).[28]

Analgesics

Morphine. Current guidelines suggest that NPs should avoid routine I.V. opioid (such as morphine) administration for patients with STE-ACS with the exception of extreme pain due to its interactions with P2Y12 inhibitors as well as its effects on BP and perfusion.[5,29] A meta-analysis and systematic review (11 studies, N = 10,476) by Batchelor and colleagues examining I.V. morphine use in patients undergoing PPCI for STE-ACS concluded that periprocedural morphine use may have an interaction with P2Y12 antagonists ticagrelor, clopidogrel, and prasugrel, but the authors were unable to identify any adverse short-term clinical outcomes.[29] This conclusion is further supported by Kubica and colleagues' review of I.V. morphine therapy's influences on clopidogrel, ticagrelor, and prasugrel absorption and effects.[30] The authors concluded that morphine delays and attenuates the action of P2Y12 antagonists in patients with STE-ACS.[30] Short-term outcomes have been identified by Furtado and colleagues' study examining the effects of concomitant clopidogrel and morphine therapy.[31] At 96 hours, patients treated with clopidogrel and morphine experienced higher rates of endpoints ($P = .026$) including composite of death, MI, recurrent ischemia, or thrombotic bailout.[31]

Given morphine's ability to alleviate some of the symptoms associated with STE-ACS, it remains the analgesic of choice for many practitioners. As morphine does not appear to enhance overall outcomes in patients with STE-ACS, the NP should remain cognizant of its interactions and possible adverse outcomes when used with P2Y12 inhibitors.

Nitrates. Nitrates, through the reduction of left ventricular preload and increase in coronary perfusion, are routinely used for the symptomatic control of myocardial ischemia in STE-ACS but should not be used as a diagnostic tool to determine the presence of an STE-ACS event.[11,32] Henrikson and colleagues established that there is no evidence that chest pain relief by nitroglycerin (NTG) is indicative of STE-ACS.[32] The researchers compared NTG's efficacy in relieving chest pain for patients undergoing active ACS to patients experiencing similar chest pain without active ACS and found no statistical difference ($P > .2$, [N = 459]).[32]

Current guidelines do not recommend the routine use of nitrates in the acute phase of STE-ACS.[6] The NP should exercise caution when prescribing nitrates to patients with hypotension, bradycardia/tachycardia, right ventricular infarction, or those who have used a phosphodiesterase type 5 inhibitor within the past 48 hours.[6]

Beta-blockers. Oral beta-blockers (BBs) are an integral component in the management of STE-ACS and should be initiated within 24 hours of all STE-ACS events in the absence of contraindications such as signs of acute heart failure, increased risk for cardiogenic shock, or evidence of a low output state.[6] Current guidelines recommend reassessing initial contraindications with the intent of determining subsequent eligibility after 24 hours.[11] Furthermore, it is recommended to continue BB therapy throughout hospitalization and upon discharge regardless of reperfusion therapy.[11,33] In cases where the patient is hypertensive or ischemic, the NP may initially administer I.V. BB followed by oral BB, which has been shown to independently limit myocardial ischemia-reperfusion damage.[6,34]

Early I.V. metoprolol for myocardial protection prior to reperfusion therapy for STE-ACS was studied by Pizarro and colleagues in the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial.[35] Patients in this trial were randomized to either receive metoprolol prereperfusion (n = 139) or not (n = 131).[35] MRI data 6 months after infarction was analyzed to determine outcomes, and showed significantly higher long-term mean left ventricular ejection fraction ($P = .025$) in patients who had received metoprolol therapy prereperfusion.[35]

Yang and colleagues compared the outcomes at approximately 1 year of patients with STE-ACS who had undergone PPCI who were prescribed BB therapy at hospital discharge (n = 6,873) versus those who were not (n = 1,637).[33] The authors established that the incidence of all-cause mortality in patients who received BB was 2.1% in comparison to 3.6% in the no-BB group ($P < .001$).[33] They concluded that the incidence of cardiac death was significantly lower for patients on a BB regimen versus those who were not ($P < .001$).[33]

The PLATE-BLOCK prospective randomized trial examined the effects of carvedilol versus metoprolol on platelet aggregation in patients with ACS (N = 111; 62% STE-ACS) receiving DAPT (ASA and ticagrelor).[36] At 30 days, carvedilol, a nonselective BB, significantly reduced residual platelet aggregation when compared

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with metoprolol, a selective beta-1 blocker ($P = .04$).[36] The NP's initiation of BB therapy is integral to the management of patients with STE-ACS to improve left ventricular ejection fraction and decrease mortality. The NP's choice to use a nonselective BB such as carvedilol may contribute to better antiplatelet therapy when compared with selective BBs like metoprolol.

Stabilized therapies

ACE inhibitors. Angiotensin-converting enzyme inhibitors (ACEi) are routinely prescribed to all patients with STE-ACS and are associated with a statistically significant reduction in 30-day mortality, particularly in patients with anterior infarction, post-MI left ventricular systolic dysfunction, and heart failure.[6,11] ACEi decreases afterload and myocardial oxygen demands, providing respite to the damaged tissue.[6] Typically, ACEi should be started postthrombolytic treatment and within 24 hours of STE-ACS event, provided the patient is not hypotensive, hyperkalemic, or in acute renal failure.[11]

Statins. Routine treatment with high-intensity statin therapy is recommended for all stabilized patients with STE-ACS.[2] This treatment strategy lowers the risk of coronary heart disease death, recurrent MI, stroke, and coronary revascularization.[2] Current guidelines from the Canadian Cardiovascular Society recommend high-dose statins as first-line treatment, with goals of LDL cholesterol less than 1.8 mmol/L (70 mg/dL) or greater than 50% reduction for patients with recent ACS.[37]

Conclusion

With the intent of maximizing positive patient outcomes, this article outlines guideline-directed treatment strategies in a concise and evidence-based manner. We acknowledge that STE-ACS may not affect all populations similarly due to sociodemographic factors, gender, and other determinants of health, with younger patients with STE-ACS having different risk profiles than patients older than 65 years of age.[38] As such, this article is not fully inclusive of all considerations in the management of STE-ACS. The NP should maintain an awareness of the unique needs of specific populations such as those previously on anticoagulation therapy prior to STE-ACS, those with heparin-induced thrombocytopenia, and individuals living with chronic kidney disease. Considering the various unique patient needs, referral to appropriate guidelines is encouraged, in conjunction with using clinical judgment for the treatment of STE-ACS to ensure patient-centered care and maximize positive outcomes. NP

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