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Evidence Based Core Topics in Critical Care Medicine 2019



Ross Callum Freebairn
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CHAPTER 2

Adjunctive Therapies in Acute Myocardial Infarction

Harish MM, Atul Prabhakar Kulkarni

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INTRODUCTION

Acute coronary syndrome (ACS) is one of the leading causes of death among global population. Approximately one in seven deaths is secondary to coronary heart disease.[1]

Diagnostic and therapeutic modalities for acute myocardial infarction have vastly evolved over the last decades. Since this disease entity was first reported by Herrick in 1912, adjuvant and pharmacological modalities for the management of ACS have changed greatly and resulted in better pain relief and decreased mortality.[1]

MORPHINE

Morphine has been used as agent of choice for symptomatic relief of patients with chest pain. Morphine is given as injection for to patients with ongoing symptoms of chest discomfort and it is usually titrated till pain is relieved as per the individual need.[2]

In the studies which showed benefits with morphine also received aspirin, heparin, clopidogrel, diagnostic coronary angiography, and percutaneous coronary intervention (PCI).[1]

Patients not treated with morphine did not received even other optimal medical treatment. Morphine use may be an indicator of severity of myocardial infarction because it is usually prescribed for patients with acute pulmonary edema or refractory pain. However, this presumption was also determined to be untrue in many studies, since the analgesic effects may mask the severity of angina and result in misinterpretation of signs and symptoms, hiding true severity of the problem. Studies showed that morphine is associated with delayed activity of antiplatelet agents in patients presenting with ST-segment elevation myocardial infarction (STEMI).[1]

Owing to these negative findings, morphine administration has been recommended to be class IIb indication in the American Heart Association/American College of Cardiology (AHA/ACC) guidelines.[1]

Value is placed on its ability to relieve pain and distress, understanding that the evidence for its supposed benefit is lacking. Further research is required whether morphine really causes harm or not, as per data mentioned in some of the registry.[3]

Oxygen

Oxygen should be initiated only if the patient has breathlessness, hypoxemia (SpO_2 <94%), or signs of heart failure or shock. The use of pulse oximetry may be very useful in guiding oxygen therapy. However, it is important to understand that recent data suggests hyperoxemia is potentially harmful in uncomplicated myocardial infarction. Oxygen may have a distinct indication in other emergency situations along with ACS (e.g. water accidents, gas embolism etc.).[2]

The oxygen therapy is assumed to increase oxygen delivery to the ischemic myocardium and thereby limit progression of infarct size and its subsequent complications. The rationale for this practice is limited to experimental in

vitro data and small clinical studies.[4] However, high oxygen levels in the blood can cause coronary vasoconstriction and increase the production of reactive oxygen radicals, which can cause reperfusion injury.[5]

One of the most robust data pertaining to the use of oxygen is provided by the "Air Versus Oxygen in Myocardial Infarction" (AVOID) trial. This was a major multicenter, randomized controlled trial which compared the effects of the administration of oxygen (8 L/min) versus no supplemental oxygen in patients with STEMI and oxygen saturation more than or equal to 94% measured using a pulse oximeter. The primary endpoint was infarct size measured using troponin and cardiac enzyme assays. Secondary endpoints included recurrent myocardial infarction and cardiac arrhythmias. At 6-month follow-up the secondary endpoints were observed to be statistically significant favoring a no-oxygen strategy group. The overall incidence of in-hospital recurrent myocardial infarction and cardiac arrhythmias were more in the oxygen supplementation group (5.5% × 0.9%, P = 0.006 and 40.4% × 31.4%, P = 0.05).[6]

Recently, the "Determination of the Role of Oxygen in Suspected Acute Myocardial Infarction" ($DETO_2X$-AMI) trial included ACS patients with an oxygen saturation of more than or equal to 90% to receive oxygen supplementation versus inhalation of ambient air. The study showed no statistically significant difference in 1-year all-cause mortality observed among the groups. Non-ST-segment elevation myocardial infarction (NSTEMI) and STEMI AHA/ACC guidelines recommend the use of supplemental oxygen only when oxygen saturation is less than or equal to 90%.[7]

Nitrates

Intravenous or sublingual nitroglycerin administration was of probable useful only within 3 hours of the onset of symptoms in patients with infarction in the era prior to the advent of reperfusion therapy (based on extrapolation from other contexts). In the present situation no trial has specifically evaluated efficacy of nitrates in patients with acute myocardial infarction in the emergency department (ED) or prehospital settings. It is reasonable to consider the early administration of nitroglycerin only in selected group of patients without any contraindications, particularly if they have persistent pain even after antiplatelet and other anti-ischemic medications.[2]

However routine use of nitroglycerin is neither supported nor refuted by the evidence, may it be in the ED or prehospital setting in patients with a suspected ACS.

In specific situations like cocaine-associated chest pain lorazepam and nitroglycerin may be useful in the alleviation of chest pain.[8]

Aspirin

Aspirin is the single most important adjunctive therapy for ACS infarction. The major evidence for the efficacy of aspirin in decreasing mortality associated with ACS was demonstrated in the "Second International Study of Infarct Survival" (ISIS-2), in this patients were randomized to aspirin, streptokinase, a combination of the both, or placebo therapy. The mortality with use of aspirin was 23% in comparison with 25% for streptokinase and 41% for the combination of these agents relative to placebo. Aspirin acts by inhibiting platelet function by irreversible inactivation of platelet cyclo-oxygenase enzyme, which occurs within 15 minutes after a single 325-mg tablet has been chewed and swallowed. Aspirin-related allergy and thrombocytopenia are relative contraindications for its use. In patients with any of the relative contraindications, orally administered ticlopidine hydrochloride (250 mg twice a day) is a reasonable alternative agent, although no trials in acute infarction have been reported.[3,9] The use of enteric-coated aspirin is not suitable in the immediate treatment of acute myocardial infarction. Chewable aspirin should be the choice for all the patients with acute infarction or unstable angina except for those with the aforementioned contraindications.[9]

The early administration of aspirin as an antiplatelet dose of 300 mg is recommended in patients with suspected ACS when contraindications such as true anaphylaxis or bleeding disorder have been excluded. The patients should be advised to chew the tablet (which should not be enteric coated). Dissolvable aspirin is preferred at this acute condition.[9]

There is currently limited evidence to directly support the strategy of dispatcher directed or bystander administration of aspirin, however, it is considered to be a reasonable approach if the carer is able to exclude a history of true anaphylaxis or bleeding disorder.

Antiplatelet Agents

Clopidogrel: Clopidogrel is a thienopyridine group of drug that inhibits P2Y12 platelet receptor. The drug requires activation by a two stage biotransformation within the liver. This process is modulated by genetic polymorphisms, which results in variability in overall clinical effect. Benefit has been established when added to aspirin in non-ST elevation acute coronary syndrome (NSTEACS) patients, including those treated with PCI. Showed reductions in cardiovascular death, myocardial infarction and stroke but with an increase in major bleeding.[10] It should be considered that patients who have moderate to high risk

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NSTEACS and STEMI should receive clopidogrel in addition to the standard care (aspirin, anticoagulation and/or a reperfusion). The ideal dose in elderly has not yet been determined. However, in patients under the age of 75 years the loading dose of clopidogrel is 600 mg if PCI is planned or 300 mg if a noninvasive strategy with fibrinolysis is the planned treatment option.[11]

Prasugrel: Prasugrel is a newer thienopyridine agent that produces more rapid and consistent platelet inhibition than clopidogrel. In the clopidogrel naïve patient, prasugrel (compared to clopidogrel) reduced the incidence of myocardial infarction in patients with moderate to high risk NSTEACS and patients with STEMI planned for primary PCI. Prasugrel has been associated with a higher rate of bleeding complications in patients older than 75 years of age, those with a history of stroke or transient ischemic attack and body weight less than 60 kg. Prasugrel should not be given to patients with STEMI who have already received fibrinolysis. It may be used as an alternative to clopidogrel in patients with STEMI of less than 12 hours duration where PPCI is planned.[12]

In patients with NSTEMI, prasugrel may be administered after angiography when the coronary anatomy is known and the plan is to proceed to PCI.

The advised dose of prasugrel is 60 mg in place of clopidogrel, particularly when they are not at high risk from bleeding.

Ticagrelor is a pyrimidine derivative, which binds reversibly to the P2Y12 receptor without any biotransformation. Like prasugrel, it has a more rapid and consistent onset of action compared with clopidogrel, but other added advantage is its quicker offset of action so that recovery of platelet function is faster.[13]

Ticagrelor has showed some benefits compared to clopidogrel in patients with moderate-to-high risk NSTEACS (treated conservatively or invasively) and patients with STEMI planned for primary PCI (PPCI) in terms of a reduction in death from vascular causes and myocardial infarction. Overall there was no increase in major bleeding observed but an increase in minor bleeding was seen.[13]

The adverse effects of ticagrelor are dyspnea, increased frequency of mostly asymptomatic ventricular pauses, and asymptomatic increase in uric acid.

Ticagrelor can be an option for patients at moderate-to-high risk of ischemic events (e.g. troponin positive ACS), regardless of initial planned treatment strategy and including those pretreated with clopidogrel. The initial dose is 180 mg (loading dose) and then 90 mg twice daily. Ticagrelor may be used then in place of clopidogrel in patients with ACS.[14]

The risks and benefits of combinations of the newer antiplatelet agents are not established completely. When planned for switch over, these newer agents should not be used as combination. But these can be used with aspirin as combination safely.

Prehospital administration of these newer agents in the setting of STEMI in recent studies has shown no mortality benefit or harm.[14]

Vorapaxar: It is one of the most recent addition to the arsenal of antiplatelet agents. A high-affinity oral antagonist that selectively inhibits thrombin from activating platelets through the protease-activated receptor. Vorapaxar is indicated for the reduction of thrombotic cardiovascular events in patients with a history of myocardial infarction or with peripheral arterial disease (PAD). This novel agent was approved by the FDA in 2014 based on the results of a large, phase III randomized controlled trial. This trial included 26,449 patients with a history of myocardial infarction, ischemic stroke, or PAD who were randomly assigned to receive vorapaxar (2.5 mg daily) or placebo in addition to standard antiplatelet therapy for a median time of 30 months.[15] Vorapaxar showed a 1.2% absolute risk reduction in the primary composite endpoint of death from cardiovascular causes, myocardial infarction, or stroke as compared with placebo (hazard ratio (HR), 0.87; 95% confidence interval (CI), 0.80–0.94; P = -0.001, NNT 84 patients). Moderate-to-severe bleeding was more common in the vorapaxar group as opposed to the placebo group (4.2 vs 2.5%; HR, 1.66; 95% CI, 1.43–1.93; P = -0.001, NNH 58 patients).[16]

The role of vorapaxar in the management of ACS has not been fully established, needs further studies on this newer drug in the coming years.

Beta-adrenergic Blocking Agents

Beta-adrenergic blocking agents are the second most important adjunctive drug (next to aspirin) for acute infarction and for the other ischemic syndromes. The mechanisms by which beta-adrenergic receptor blockers decrease mortality is by reduction in myocardial oxygen consumption, an antagonism of arrhythmogenic and toxic biochemical effects of catecholamines, a possible direct effect on myocardial ventricular fibrillation threshold, and a decrease in the incidence of cardiac rupture.[17]

Although most benefits from beta-adrenergic blocking agents are derived during the first week, the continued advantage of decreased mortality has been substantiated to at least 5 years. The beneficial effects of the beta-adrenergic blockers are similar to all agents without intrinsic

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sympathomimetic activity. Some contraindications to the administration of these agents are gross congestive heart failure or pulmonary edema, asthma or severe bronchospastic airways disease, hypotension, and heart block greater than first degree.[17]

The presence of a mild degree of left ventricular failure or known severe left ventricular dysfunction is not an absolute contraindication, in such a setting, a short-acting drug for example, esmolol hydrochloride administered in an intravenous bolus of 0.5 μg/kg followed by infusion at 50 μg/kg/min should be considered. This therapy can be terminated if congestive heart failure worsens.[18]

Preferably, beta blockers should be administered at the time of admission, although benefits have been confirmed with later in-hospital administration as well.[19] In patients with absolute contraindications to beta blockade and with no evidence of left ventricular failure, the calcium channel blocker verapamil hydrochloride has been shown to be effective in secondary prevention of death and recurrent infarction. This agent, however, should be avoided in patients with poor LV contractility (EF <30%). Can be considered for late administration (>7 days) after initial assessment, and is also more likely to produce higher grades of atrioventricular block than beta blockers.[18]

Angiotensin-converting Enzyme Inhibitors

Another adjunctive pharmacologic agent now definitely shown to decrease mortality after myocardial infarction is the angiotensin-converting enzyme (ACE) inhibitor. Near about eight randomized trials of ACE inhibitors, given either selectively to patients with reduced left ventricular function (less than 45% ejection fraction) or nonselectively, have been performed, seven of these trials showed a significant reduction in postinfarct mortality.[18]

In two large recent mega trials "Gruppo Italiano per 10 Studio della Sopravvivenza nell'lnfarto Miocardico" (GISSI-3)[20] and the "Fourth International Study of Infarct Survival" (ISIS-4)[21] approximately 77,000 patients were randomly assigned to the use of captopril (ISIS-4) or lisinopril (GISSI-3), administered within 24 hours after onset of symptoms, versus placebo. Both trials demonstrated a statistically significant reduction in mortality (absolute numbers of 4–5 lives saved per 1,000 patients treated). Although such a benefit can be expected from the universal administration of these agents to all the infarct survivors, a much larger impact is evident with the selective use of these drugs.[20,21]

In a recent trial (SMILE—Survival of Myocardial Infarction Long-Term Evaluation) in which early oral administration of zofenopril was restricted to patients with anterior wall infarction, which was not treated with thrombolytic agents, a decrease in mortality of 41 lives saved per 1,000 patients treated was achieved, this is as same as that similar in magnitude to that attainable with thrombolysis itself.[22] Administration of ACE inhibitors helps in decreasing the blood pressure and ventricular wall stress, it has also been shown to have a useful effect on reducing late ventricular remodeling, which may help preserve left ventricular function.[11]

In addition, in the Survival and Ventricular Enlargement trial, the overall incidence of reinfarction was decreased, which shows a possible direct vascular action. In GISSI-3, 5 mg of lisinopril was administered orally in the beginning, followed by 5 mg after 24 hours, 10 mg after 48 hours, and then 10 mg daily. If the systolic blood pressure was less than 120 mm Hg at the time of initial assessment or within the first 3 days, a lower dosage of 2.5 mg daily was used. If the blood pressure declined below 100 mm Hg, a lower daily maintenance dose of 5 mg and temporary reductions to 2.5 mg/day were allowed. Administration of the drug was discontinued when blood pressure was less than 90 mm Hg. Contraindications to the administration of ACE inhibitors include confirmed prior allergic reactions and hypotension, as previously described.[20]

The optimal duration of therapy with these agents after infarction is not clearly defined, but like aspirin and beta-adrenergic blockers, the therapy may be continued indefinitely, especially if the patient has severe left ventricular dysfunction (ejection fraction of <45%) or in patients with moderate to severe mitral regurgitation. Care must be taken to avoid hypotension (systolic blood pressure of <90–100 mm Hg).

Heparin

Heparin binds to naturally occurring anticoagulation that is antithrombin and induces a conformational change, causing rapid inhibition of factor IIa (thrombin), factor IXa, and factor Xa, thus it prevents further thrombus propagation. An intravenous bolus of 60 units/kg produces a time to peak of 5–10 minutes and a half-life of 30–60 minutes.[23]

Heparin can be reversed by using protamine sulfate (1 mg per 100 units of heparin). For ACS, it is given in a bolus of 60 units/kg not exceeding 4,000 units, followed by a continuous infusion of 12–15 units/kg/hour, with monitoring of the activated partial thromboplastin time every 6 hours with a goal value of 50–70 seconds or 1.5–2.5 times control value. Side effects of heparin include thrombocytopenia, heparin-induced thrombocytopenia (a distinct condition), and bleeding.[23]

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The efficacy of unfractionated heparin was tested in ACS in the early 1990s. Oler et al. performed meta-analysis of six randomized trials and found a 33% lower rate of death in patients treated with heparin in addition to aspirin in ACS, as well less reported ischemic pain.[24,25]

Advantages of unfractionated heparin are that it has stood the test of time, rapid onset of action, is inexpensive, and can be rapidly reversed. The disadvantages are that it can have serious side effects, including heparin-induced thrombocytopenia, and is more likely to cause bleeding than the newer intravenous anticoagulants discussed below. Thus, its position as the main anticoagulant in ACS is being challenged in recent data.[15]

Enoxaparin (A Low-molecular-weight Heparin)

Enoxaparin is a low-molecular-weight heparin that inhibits factor IIa and factor Xa via antithrombin, roughly in a ratio of 1:3. It has a time to peak effect of 10 minutes when given intravenously and 3–5 hours when given subcutaneously. Its half-life is 4.5 hours, but it is longer in patients with renal dysfunction, requiring dose adjustments in this population.[24]

Its anticoagulant effect is partially reversible. If it is to be reversed between 0 hours and 8 hours after dosing, the recommended reversal regimen is 1 mg of protamine sulfate for every 1 mg of enoxaparin used. At 8–12 hours, it is 0.5 mg of protamine for every 1 mg of enoxaparin.

After 12 hours, no protamine is required. Compared with unfractionated heparin, enoxaparin has less plasma protein binding and a more consistent and predicted anticoagulant effect. Because of its high bioavailability, it can be administered as subcutaneous dosing also. Its greater anti-Xa activity inhibits thrombin generation more effectively, and it causes lower rates of thrombocytopenia and heparin-induced thrombocytopenia as compared to unfractionated heparin. de Lemos et al. found that, in ACS patients in whom an early conservative approach of medical management was planned, enoxaparin was more efficacious than unfractionated heparin and with a similar incidence of bleeding.[26]

A meta-analysis of 12 trials among 49,088 ACS patients, also found that enoxaparin had a net clinical benefit compared with unfractionated heparin in reducing rates of myocardial reinfarction and death despite of more bleeding.[27] The ESSENCE trial compared enoxaparin versus unfractionated heparin in 3,171 patients with ACS. It found fewer ischemic events with enoxaparin in the early phase, more minor bleeding, but no increase in major bleeding.[28]

Fondaparinux (A Factor Xa-inhibitor)

Fondaparinux is a synthetic pentasaccharide that indirectly inhibits factor Xa through the action of antithrombin. After a 2.5-mg subcutaneous dose, it has a time to peak concentration of 2 hours and a half-life of 17–21 hours.

The OASIS-5 (The Fifth Organization to Assess Strategies in Acute Ischemic Syndromes) trial compared fondaparinux and enoxaparin in 20,078 patients treated for NSTEACS. Although the rates of death, myocardial infarction, and refractory ischemia at 9 days were similar for both drugs, the fondaparinux group had a significantly (almost 50%) lower rate of bleeding at 30 days, translating into significantly fewer deaths at 30 days as compared enoxaparin. However, patients receiving fondaparinux who underwent PCI had a threefold higher rate of catheter-related thrombosis.[29]

The OASIS-6 trial compared fondaparinux versus usual care (placebo in those in whom unfractionated heparin was not indicated or unfractionated heparin was given for up to 48 hours followed by placebo for up to 8 days) among 12,092 patients with STEMI. There was a 1.5% absolute risk reduction in death and reinfarction without an increase in bleeding at 30 days, with trends persisting 6 months into the study. However, fondaparinux was not superior to heparin in the 3% of patients who underwent primary PCI.[30] As in OASIS-5, there was more catheter-related thrombosis in the fondaparinux group. Although the use of supplemental unfractionated heparin appears to have mitigated this risk, fondaparinux remains a less-than ideal option in the era of primary PCI for STEMI and has therefore found limited use in this group of patients.

It should, however, be considered in patients for whom a conservative strategy is planned, especially if bleeding risk is deemed to be high.

Oral Anticoagulants

Oral anticoagulants provide anti-ischemic benefit in selected patients with ACS—at the price of a higher risk of significant bleeding.

Warfarin

Warfarin was investigated in many trails like WARIS II, CARS, and CHAMP. WARIS II looked at the use of aspirin alone, warfarin alone, and aspirin and warfarin in combination. The rates of the primary endpoints of stroke, nonfatal infarction, and death were lower in the warfarin group.[31]

CARS trail found no difference in the rate of the primary endpoint of fatal infarction, nonfatal ischemic stroke, or cardiovascular death, with aspirin versus warfarin plus aspirin.[32]

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CHAMP trail also saw similar trends, i.e. no difference in the rate of death, recurrent myocardial infarction, or stroke with warfarin plus aspirin versus aspirin alone.[33]

All three studies showed increases in major bleeding with warfarin use. Putting all these trials into context, the significant net clinical benefit of dual antiplatelet therapy in the current era compared with the significant bleeding and questionable conflicting evidence supporting benefit with warfarin has limited its use in ACS patients.

Rivaroxaban (An Oral Factor Xa-inhibitor)

Rivaroxaban is a novel oral direct reversible factor Xa-inhibitor. The ATLAS ACS 2-TIMI 51 trial found rivaroxaban 2.5 mg or 5 mg to yield a significantly lower rate of the primary outcome of cardiovascular death, myocardial infarction, ischemic stroke, and in-stent thrombosis compared with placebo. Unfortunately rivaroxaban had significantly more major non-CABG bleeding and intracranial hemorrhage as compared to placebo.[34]

The dose used in this trial was much lower than the dose used in trials investigating the role of this drug in stroke prophylaxis in nonvalvular atrial fibrillation.

Apixaban (An Oral Factor Xa-inhibitor)

Apixaban is another direct factor Xa-inhibitor. The APPRAISE-2 trial compared apixaban 5 mg twice daily versus placebo in ACS. There was no difference in the rate of cardiovascular death, myocardial infarction, or stroke, like rivaroxaban, apixaban also had significantly more bleeding, prompting early termination of this study.[35]

Dabigatran (An Oral Thrombin Inhibitor)

Dabigatran is an oral direct thrombin inhibitor. The RE-DEEM trial compared four doses of dabigatran (50, 75, 110, and 150 mg twice daily) and placebo in ACS patients. The dabigatran groups showed dose related increase in bleeding. In addition, the rates of ischemic endpoints were no lower with dabigatran, although this trial was not powered to show differences in clinical events.[36]

CONCLUSION

Adjunctive therapy for acute myocardial infarction should include aspirin, beta-adrenergic blocking agents, and, in most patients, consideration of the use of ACE inhibitors, especially if left ventricular function is reduced. Heparin has an important adjunctive role in enhancing early vessel patency in patients who receive tissue-type plasminogen activator and in decreasing the frequency of re-occlusion of an infarct-related artery during any thrombolytic therapy. Heparin must also be administered to all patients who undergo primary angioplasty. Intravenously administered nitroglycerin and orally administered nitrates are not indicated in all the patients, its routine use should be avoided.

Calcium channel blockers for most patients with acute myocardial infarction. Currently, in the management of patients with acute myocardial infarction, the immediate goals are relief of pain from ischemia, assessment and stabilization of the hemodynamic status, and administration of reperfusion therapy, in conjunction with either thrombolytic agents or, when available, urgent direct angioplasty of the occluded infarct-related artery.

In addition to strategies for reperfusion, adjunctive pharmacologic therapy retains an important role in reducing mortality and morbidity from acute infarction.

REFERENCES

1. Alencar Neto J. Morphine, oxygen, nitrates, and mortality reducing pharmacological treatment for acute coronary syndrome: an evidence-based review. Cureus. 2018;10(1): e2114.
2. ARC. (2012). ANZCOR Guideline 14.2—ACS: Initial Medical Therapy. [online]. Available from https://resus.org.au/wpfb-file/anzcor-guideline-14-2-jan16-pdf/ [Accessed December, 2018].
3. Reeder GS. Concise review for primary-care physicians: Adjunctive therapy in the management of patients with acute myocardial infarction. Mayo Clin Proc. 1995;70:464-8.
4. Syed FA, Bett JH, Walters DL. Anti-platelet therapy for acute coronary syndrome: a review of currently available agents and what the future holds. Cardiovasc Hematol Disord Drug Targets. 2011;11:79-86.
5. Nicolau JC, Cohen M, Montalescot G. Differences among low-molecular-weight heparins: evidence in patients with acute coronary syndromes. J Cardiovasc Pharmacol. 2009;53:440-5.
6. Morrow DA, Braunwald E, Bonaca MP, et al. Vorapaxar in the secondary prevention of atherothrombotic events. N Engl J Med. 2012;366:1404-13.
7. Ganetsky VS, Hadley DE, Thomas TF. Role of novel and emerging oral anticoagulants for secondary prevention of acute coronary syndromes. Pharmacotherapy. 2014;34:590-604.
8. Reeder GS, Gersh BJ. Modern management of acute myocardial infarction. Curr Probl Cardiol. 1993;18:81-155.
9. Hansen JF. Danish Study Group on Verapamil in Myocardial Infarction. Treatment with verapamil during and after an acute myocardial infarction: a review based on the Danish Verapamil Infarction Trials I and II. J Cardiovasc Pharmacol. 1991;18(Suppl 6):S20-S25.
10. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. Gruppo Italiano per

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lo Studio della Sopravvivenza nell'infarto Miocardico. Lancet. 1994; 343:11151-22.
11. ISIS-4 (Fourth International Study of Infarct Survival) Collaborative Group. Presentation at the American Heart Association Meeting; Atlanta (GA): 1993.
12. Aslam MS, Sundberg S, Sabri MN, et al. Pharmacokinetics of intravenous/subcutaneous enoxaparin in patients with acute coronary syndrome undergoing percutaneous coronary interventions. Catheter Cardiovasc Interv. 2002;57:187-90.
13. De Lemos JA, Blazing MA, Wiviott SD, et al. Enoxaparin versus unfractionated heparin in patients treated with tirofiban, aspirin and an early conservative initial management strategy: results from the A phase of the A-to-Z trial. Eur Heart J. 2004;25:1688-94.
14. Murphy SA, Gibson CM, Morrow DA, et al. Efficacy and safety of the low-molecular weight heparin enoxaparin compared with unfractionated heparin across the acute coronary syndrome spectrum: a meta-analysis. Eur Heart J. 2007;28:2077-86.
15. Cohen M, Demers C, Gurfinkel EP, et al. A comparison of low-molecular weight heparin with unfractionated heparin for unstable coronary artery disease. Efficacy and Safety of Subcutaneous Enoxaparin in Non-Q-Wave Coronary Events Study Group. N Engl J Med. 1997;337:447-52.
16. Fifth Organization to Assess Strategies in Acute Ischemic Syndromes Investigators; Yusuf S, Mehta SR, et al. Comparison of fondaparinux and enoxaparin in acute coronary syndromes. N Engl J Med. 2006;354:1464-76.
17. Yusuf S, Mehta SR, Chrolavicius S, et al. OASIS-6 Trial Group. Effects of fondaparinux on mortality and reinfarction in patients with acute ST segment elevation myocardial infarction: the OASIS-6 randomized trial. JAMA. 2006;295:1519-30.
18. Hurlen M, Abdelnoor M, Smith P, et al. Warfarin, aspirin, or both after myocardial infarction. N Engl J Med. 2002;347:969-74.
19. Randomised double-blind trial of fixed low-dose warfarin with aspirin after myocardial infarction. Coumadin Aspirin Reinfarction Study (CARS) Investigators. Lancet. 1997;350:389-96.
20. Fiore LD, Ezekowitz MD, Brophy MT, et al. Department of Veterans Affairs Cooperative Studies Program Clinical Trial comparing combined warfarin and aspirin with aspirin alone in survivors of acute myocardial infarction: primary results of the CHAMP study. Circulation. 2002;105:557-63.
21. Mega JL, Braunwald E, Wiviott SD, et al. Rivaroxaban in patients with a recent acute coronary syndrome. N Engl J Med. 2012;366:9-19.
22. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011;365:699-708.
23. Oldgren J, Budaj A, Granger CB, et al. Dabigatran vs placebo in patients with acute coronary syndromes on dual antiplatelet therapy: a randomized, double-blind, phase II trial. Eur Heart J. 2011;32:2781-89.
24. Singh D, Gupta K, Vacek JL. Anticoagulation and antiplatelet therapy in acute coronary syndromes. Cleveland Clin J Med. 2014;81(2):103-14.
25. Oler A, Whooley MA, Oler J, et al. Adding heparin to aspirin reduces the incidence of myocardial infarction and death in patients with unstable angina. A meta-analysis. JAMA. 1996;276:811-5.
26. Meine TJ, Roe MT, Chen AY, et al. Association of intravenous morphine use and outcomes in acute coronary syndromes: results from the CRUSADE Quality Improvement Initiative. Am Heart J. 2005;149:1043-9.
27. Stub D, Smith K, Bernard S, et al. Air versus Oxygen in ST-Segment Elevation Myocardial Infarction. Circulation. 2015;131:2143-50.
28. Madias JE, Madias NE, Hood WB Jr. Precordial ST-segment mapping. 2. Effects of oxygen inhalation on ischemic injury in patients with acute myocardial infarction. Circulation. 1976;53:411-7.
29. Moradkhan R, Sinoway LI. Revisiting the role of oxygen therapy in cardiac patients. J Am Coll Cardiol. 2010;56:1013-6.
30. Hofmann R, James SK, Jernberg T, et al. Oxygen therapy in suspected acute myocardial infarction. N Engl J Med. 2017;377:1240-9.
31. Honderick T, Williams D, Seaberg D, Wears R. A prospective, randomized, controlled trial of benzodiazepines and nitroglycerine or nitroglycerine alone in the treatment of cocaine-associated acute coronary syndromes. Am J Emerg Med. 2003;21(1):39-42.
32. Yusuf S, Zhao F, Mehta SR, et al. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med. 2001;345:494-502.
33. Mehta SR, Bassand JP, Chrolavicius S, et al. Dose comparisons of clopidogrel and aspirin in acute coronary syndromes. N Engl J Med. 2010;363:930-42.
34. Nicolau JC, Cohen M, Montalescot G. Differences among low-molecular-weight heparins: evidence in patients with acute coronary syndromes. J Cardiovasc Pharmacol. 2009;53:440-5.
35. Reeder GS, Gersh BJ. Modern management of acute myocardial infarction. Curr Probl Cardiol. 1993;18:81-155.
36. Ambrosioni E, Borghi C, Magnani B. The effect of the angiotensin-converting-enzyme inhibitor zofenopril on mortality and morbidity after anterior myocardial infarction. The Survival of Myocardial Infarction Long-Term Evaluation [SMILE] Study Investigators). N Engl J Med. 1995;332:80-85.

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