

Review

Comparison of different classes of drugs for Management of Acute Coronary Syndrome (ACS): A brief communication

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ABSTRACT

Acute coronary syndrome (ACS) is a class of conditions consisting of NSTEMI (non-ST-elevated myocardial infarction), STEMI (ST-elevated myocardial infarction), unstable angina, ranging from myocardial ischaemic states, as well as there is usually a mismatch with respect to both blood supply and blood demand marked by chest pain. Indian patients with ACS have a higher STEMI score than patients of established countries'. Since most of these patients were poor, they were less likely to receive adequate therapy and had a higher death rate of 30 days. In India, ACS patients appear to be young from low socioeconomic backgrounds and have higher ST-elevated MI rates than do patients of established countries'. In India, patients get late medical treatment and inadequate access to proven therapies. Hypertension, hyperlipidemia, diabetes, obesity, cigarette use and a family history of atherosclerotic disease are important risk factors attributed to ACS. Most of the general therapy for ACS focuses on reducing myocardial ischemia and pain suppression. Because of the time dependence of the condition, the onset of signs and arrival at the hospital for the treatment of ACS is very important. This time gap between the onset of symptoms and hospital appearance is larger in India relative to western countries. This paper will concentrate on ACS management and a brief on comparative study of various groups of drugs available with regard to clinical trials and guidelines, respectively.

Keywords Management, Acute coronary syndrome, therapies, Angina

INTRODUCTION

Acute coronary syndrome (ACS) is a class of conditions consisting of NSTEMI (non-ST-elevated myocardial infarction), STEMI (ST-elevated myocardial infarction), unstable angina, ranging from myocardial ischemic states, as well as there is usually a mismatch with respect to both blood supply and blood demand that is marked by chest pain.

Cardiac Biomarkers

The biochemical markers that increase in the blood stream when myocardial infarction or some other myocardial ischemia causes damage to the myocardium are cardiac biomarkers such as cardiac troponins. Increase in cardiac markers or biomarkers such as cardiac troponin T or I or CKMB (creatin kinase myoglobinulin fraction), which contributes to cardiac myocardial infarction. The increase in cardiac biomarkers does not suggest any underground myocardial necrosis process and the discrepancies between hypoxic and non-hypoxic causes cannot

be indicated (Thygesen *et al.*, 2012). Pathological conditions like heart failure, end-stage renal disease (ESRD), acute pulmonary embolism (APE) as well as myocyte inflammation are complicated by myocardial infarction/injury and contribute to an increase in cardiac biomarker levels (Korff, Katus, & Giannitsis, 2006). So for the diagnosis of myocardial infarction the cardiac troponins cannot be utilized alone there are multiple parameters to be utilized (Thygesen *et al.*, 2012). Nevertheless, cardiac troponin is a potential biomarker that has clinical usefulness and myocardium specificity. In general, the increase in levels of cardiac troponin is based on certain estimation assays and can be described as exceeding the 99th percentile of the standard reference population. It is mandatory to detect blood levels of cardiac troponins through cardiac troponin tests specifically designed to differentiate acute and chronic changes in cardiac troponin levels and may be associated with any underlying cardiac disease. With the onset of pain within six hours, blood levels of cardiac troponin owing to disrupted rise of cardiac biomarkers in the blood should be assessed in the initial scenario. The increase in cardiac troponins can be seen up to two weeks after myocardial necrosis, and the increase in cardiac biomarkers after cardiac pathology should be understood. CKMB should be measured if the cardiac troponin cannot be estimated (Thygesen *et al.*, 2012). The development of both CKMB and cardiac troponins during underlying pathology of acute coronary syndrome is optimal (Anderson *et al.*, 2007a; O'Gara *et al.*, 2013)

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Management of Acute Coronary Syndrome (ACS)

Emergency admission is the first procedure for patients suffering from ACS, where ECG and hemodynamic monitoring are carried out with due care and rapid treatment and venous access are put into place after following the patient (Verheugt, 1999). The general care focuses primarily on reducing myocardial ischemia, which can be minimized by antithrombotic therapy and pain suppression, which can be alleviated by nitroglycerin or morphine administration (Verheugt, 1999). When there is a total coronary blockade, like in transmural myocardial ischemia clot destruction (Weaver *et al.*, 1997) or clot lysis (White & Van de Werf, 1998) are mostly focused. The drugs that interfere with clot synthesis and production are recommended only in ACS that are non-transmural (Verheugt, 1999).

COMPARATIVE ANALYSIS OF DIFFERENT CLASSES OF DRUGS

1.1 Antithrombotic drugs

The central component of ACS treatment is to manage the threat of thrombosis by inhibiting the expression and accumulation of platelets that can be performed by antiplatelet therapy (Jneid *et al.*, 2012). Aspirin, glycoprotein IIb/III inhibitors as well as adenosine diphosphate P2Y₁₂ receptor antagonists are well-known antiplatelet interventions that serve an important part in the management of ACS (Cheng, 2013). A starting loading amount of aspirin 162-325 mg may be started following the ACS event unless contraindicated and aspirin at higher doses shows little benefit, so 81 mg daily is appropriate (Mehta *et al.*, 2010). The commonly used P2Y₁₂ antagonists in ACS management are clopidogrel, prasugrel, and ticagrelor (Comin & Kallmes, 2011; Jennifer N Smith, Jenna M Negrelli, Megha B Manek, Emily M Hawes, & Anthony J Viera, 2015). IIb/IIIa inhibitors have shown an overwhelming response, particularly in percutaneous coronary intervention (PCI), to reduce systemic complications of glycoprotein and are also active members of triple antiplatelet therapy, but unfortunately, there is an increasing incidence to bleeding (Jennifer N Smith *et al.*, 2015).

1.2 Clopidogrel

Clopidogrel and aspirin, referred to as dual antiplatelet therapy (DAPT), showed a substantial decrease in non-fatal myocardial infarction, cardiovascular mortality or stroke relative to placebo (P<.001), but increased odds of bleeding (Yusuf, 2001).

1.3 Prasugrel

Prasugrel functions by blocking the adenosine receptor, which is a useful agent for acute coronary syndrome (Spartalis *et al.*, 2017). The Prasugrel is extremely successful in reducing the rate of attacks of myocardial infarction, cardiovascular deaths, but the incidence of bleeding is a concern. For subjects that are more vulnerable to bleeding, caution should be taken when administering Prasugrel (Spartalis *et al.*, 2017).

1.4 Ticagrelor

By blocking the receptor of P2Y₁₂-adenosine diphosphate, ticagrelor demonstrates drastic inhibition of platelet aggregation in subjects with acute coronary syndrome (Wang *et al.*, 2018). The results showed that clopidogrel and ticagrelor had the same

protection and efficacy profile, while ticagrelor was a better choice for myocardial infarction, stroke and decreased bleeding incidence (Wang *et al.*, 2018).

1.5 Vorapaxar

Vorapaxar handles secondary thrombotic attacks better, but efficacy and protection are less prevalent in subjects with non-ST segment elevation and ACS segment elevation (Harskamp *et al.*, 2017). Although the clinical effects as well as protection of vorapaxar in non-ST segment elevation acute myocardial infarction was not significantly reduced by age, older subjects were more vulnerable to bleeding events (Armaganijan *et al.*, 2016).

2. Anticoagulants

NSTE-ACS has ample evidence that anticoagulation is effective in decreasing acute ischemic activities and that platelet inhibitor agents, when provided, have a synergistic effect (Eikelboom *et al.*, 2000). In a study, 14 randomized controlled trials studied aspirin alone versus aspirin in conjunction with warfarin in post-ACS subjects to track the occurrence of bleeding and ischaemic cases, respectively, and in this meta-analysis, targeting 2-3 normalized ratios, there was significant decrease in major adverse events consisting of non-fatal thromboembolic stroke, non-fatal MI, or all causes of death versus alone aspirin (P<.0001) (Jennifer N. Smith, Jenna M. Negrelli, Megha B. Manek, Emily M. Hawes, & Anthony J. Viera, 2015). Recommended doses approved/research for ACS, for medications acting at various levels of the clotting cascade and various anticoagulants for ACS with chronic renal disease and in normal renal disease are listed in table number 1.

3. Nitrates

Nitroglycerin is the most prevalent treatment used in acute myocardial ischemia, but tolerance grows rapidly (Verheugt, 1999). The mortality rate in the ISIS-4 trial was 5.3 percent, with 277 out of 5199 nitrates and 5.5 percent mortality, in which 285 out of 5199 placebo patients got placebo (Collins *et al.*, 1995; Miocardico, 1994).

4. β -blocker

Patients with ST-elevated myocardial infarction, unstable angina as well as non-ST-elevated myocardial infarction, except for patients with low cardiac output or any other contraindication to β -blockers, must be started in less than 24 hours, respectively (Jennifer N. Smith *et al.*, 2015). The key pharmacological role of β -blockers is to minimize cardiac load and demand for myocardial oxygen, and with regard to ACS, there are variable findings in which studies were performed to investigate the impact of β -blocker on mortality depending on the time and route of administration from the onset of ACS and the patient population (Chen, 2005; Dargie, 2001). In such a patient population, sufficient evidence is available to endorse β -blockers as part of normal treatment (Anderson *et al.*, 2007b; O'Gara *et al.*, 2013).

5. Calcium Channel Blockers (CCBs)

CCBs, especially verapamil or diltiazem, are recommended in patients with persistent ischemia without LVF (left ventricular dysfunction) and in patients unable to take β -blockers (Anderson *et al.*, 2007b; O'Gara *et al.*, 2013).

Table 1. Recommended doses for various anticoagulants in ACS with chronic kidney disease condition

Drug	Recommendations			References
	Normal Renal Functions /Stage 1-3 CKD (eGFR>30ml/min/1.73m ³)	Stage 4 CKD (eGFR 15-29ml/min/1.73m ³)	Stage 5 CKD (eGFR<15ml/min/1.73m ³)	(Roffi, Patrono, Collet, Mueller, Valgimigli, Andreotti, Bax, Borger, Brotons, & Chew, 2016)
Unfractionated heparin	Before coronary angioplasty 60-70 IU/kg iv(maximum 5000 IU) During PCI according to ACT or 70-100 IU/kg iv in patients not anticoagulated	No dose adjustment	No dose adjustment	(Roffi, Patrono, Collet, Mueller, Valgimigli, Andreotti, Bax, Borger, Brotons, Chew, <i>et al.</i> , 2016)
Enoxparin	1mg/kg s.c. twice a day	1mg/kg s.c. once a day	Not recommended	
Fondaparinux	2mg/kg s.c. once a day	Not recommended if eGFR<20ml/min/1.73m	Not recommended	
Bivalirudin	Bolus 0.75mg/kg iv	Not recommended	Not recommended	

ACT: Activated clotting time, PCI: Percutaneous coronary intervention, IU: international unit, eGFR: Estimated glomerular filtration rate, iv:intravenous, sc: subcutaneous, kg: kilogram

6. Renin-Angiotensin System inhibitors

ACE inhibitors (angiotensin-converting enzyme) in patients with ACS with pulmonary obstruction, left ventricular ejection fraction, heart failure, ST-segment elevation myocardial infarction, less than or equal to 40 percent with complete absence of ARB (angiotensin receptor blocker) contraindications must be administered in less than 24 hours, respectively (Anderson *et al.*, 2007b; O'Gara *et al.*, 2013). A wide range of ACE inhibitors showed a drop in mortality risk in patients with or without LVD (left ventricular dysfunction) upon myocardial infarction (Collins *et al.*, 1995; Køber *et al.*, 1995; Miocardico, 1994; Pfeffer *et al.*, 1992).

7. HMG coenzyme-A Reductase Inhibitors

It's also advised to start the statin class of drugs to patients with ACS (Anderson *et al.*, 2007b; Miocardico, 1994). About 3.9% reduction in risk of persistent MI, unstable angina requiring rehospitalization, high-intensity statin therapy stroke relative to low-intensity statin therapy after ACS event (Jennifer N. Smith *et al.*, 2015). American College of Cardiology and American Heart Association Guidelines recommended atorvastatin (about 40 mg daily), rosuvastatin (about 20 mg daily), which are high-intensity statins, for treatment of high cholesterol with ACS event (Jennifer N. Smith *et al.*, 2015; Stone *et al.*, 2014)

DISCUSSION

The principal goal of ACS therapy is to avoid thrombosis, restore coronary flow and reduce the need for myocardial oxygen. There is significant variance in the treatment procedures and thus the hospital service offered is determined by the type of hospital patient visit. A research performed in South Indian states showed that adherence to recommendations for STEMI care was poorer in government hospitals (Moser *et al.*, 2006). Patients enrolled at hospitals affiliated to medical colleges were more likely to undergo fibrinolytic treatment and beta blockers relative to the patients treated in non-teaching hospitals. Antiplatelet drugs, anticoagulants, beta adrenergic antagonists, calcium channel blockers, angiotensin-converting-enzyme (ACE) inhibitors, angiotensin receptor blocker (ARB) inhibitors, and glycoprotein

IIB/IIIa inhibitors are the medicines used to accomplish these targets. Revascularization by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) is carried out to restore coronary blood (Habel *et al.*, 2011). Among the medicinal products used for the treatment of ACS, antiplatelet medicinal products play an important role in the initial treatment and long-term management of ACS patients, especially with a conservative approach. Anticoagulant treatment is a central component of ACS patients' antithrombotic control. For about 60 years, unfractionated heparin (UFH) has been used for anticoagulant treatment. UFH has a treatment window that is small and holds the risk of bleeding. The dose response characteristics of UFH differ significantly among patients who need close control of the anticoagulant effect, resulting in higher laboratory and staff costs. Around six percent of ACS patients experience primary STEMI angioplasty. For reasons such as cost, primary PCI is not a feasible first option in India for reperfusion therapy (della Sopravvivenza nell'Infarto, 2005). Stents are widely used by revascularization for the treatment of patients with ACS. Bare metal stent (BMS) implantation appears to be associated with a substantial risk of in-stent restenosis, despite improved procedures and advancements in stent construction. The frequency of restenosis following BMS implantation is related to stent design, implantation procedure and, most notably, patient-related factors. A significant development in treating stent thrombosis has been the advent of drug eluting stents (DES). However, with reports of late and very late stent thrombosis being more frequent in DES recipients compared to BMS recipients, initial enthusiasm for DES implantation was reduced (Pancholy *et al.*, 2013).

CONCLUSION

Every year, millions of patients suffer from ACS, which is a life-threatening disease in today's world and is an important health issue. They also revolutionized our understanding of pathophysiology and other fields of ACS due to continuous improvement in medical technology, research, and innovations. Initial ACS treatment involves decreasing risk with appropriate prescribed medications, including DAPT, anticoagulants and

other recommended additions to therapies such as ACE inhibitors, ARB, beta-blockers, etc., and it is important to prescribe evidence-based therapies for long-term management.

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CONFLICT OF INTEREST

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REFERENCES

- Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, *et al.* ACC/AHA 2007 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction—Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) Developed in Collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons Endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiology*, 2007;50(7):652-726.
- Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, *et al.* ACC/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Writing Committee to Revise the 2002 Guidelines for the Management of Patients With Unstable Angina/Non-ST-Elevation Myocardial Infarction) developed in collaboration with the American College of Emergency Physicians, the Society for Cardiovascular Angiography and Interventions, and the Society of Thoracic Surgeons endorsed by the American Association of Cardiovascular and Pulmonary Rehabilitation and the Society for Academic Emergency Medicine. *J Am Coll Cardiology*, 2007;50(7):e1-e157
- Armaganijan LV, Alexander KP, Huang Z, Tricoci P, Held C, Van de Werf F, *et al.* Effect of age on efficacy and safety of vorapaxar in patients with non-ST-segment elevation acute coronary syndrome: Insights from the Thrombin Receptor Antagonist for Clinical Event Reduction in Acute Coronary Syndrome (TRACER) trial. *Am Heart J*, 2016;178:176-184.
- Chen Z. COMMIT (CLOpidogrel and Metoprolol in Myocardial Infarction Trial) collaborative group. Addition of clopidogrel to aspirin in 45,852 patients with acute myocardial infarction: randomised placebo-controlled trial. *Lancet (London, England)*, 2005; 366: 1607-1621.
- Cheng, JW. Updates in antiplatelet agents used in cardiovascular diseases. *Journal of cardiovascular pharmacology and therapeutics*, 2013;18(6):514-524.
- Collins R, Peto R, Flather M, Parish S, Sleight P, Conway M, *et al.* ISIS-4-A randomised factorial assessing early oral captopril, oral mononitrate, and intravenous magnesium sulphate in 58,050 patient with suspected acute myocardial-infarction. *Lancet (London, England)*, 1995;345(8951):669-685.
- Comin J. & Kallmes D. Clopidogrel (plavix). *American journal of neuroradiology*, 2011;32(11):2002-2004.
- Dargie, H. The CAPRICORN Investigators: Effect of Carvedilol on outcome after myocardial infarction in patients with left-ventricular dysfunction: the CAPRICORN randomised trial. *Lancet (London, England)*, 2001;357(9266):1385-1390.
- della Sopravvivenza nell'Infarto, S. Effects of reviparin, a low-molecular-weight heparin, on mortality, reinfarction, and strokes in patients with acute myocardial infarction presenting with ST-segment elevation. *JAMA*, 2005;293: 427-436.
- Eikelboom JW, Anand SS, Malmberg K, Weitz JI, Ginsberg JS. & Yusuf S. Unfractionated heparin and low-molecular-weight heparin in acute coronary syndrome without ST elevation: a meta-analysis. *The Lancet*, 2000;355(9219):1936-1942.
- Habel LA, Cooper WO, Sox CM, Chan KA, Fireman BH, Arbogast PG, *et al.* ADHD medications and risk of serious cardiovascular events in young and middle-aged adults. *JAMA*, 2011;306(24):2673-2683.
- Harskamp RE, Clare RM, Ambrosio G, Held C, Lokhnygina Y, Moliterno DJ, *et al.* Use of thienopyridine prior to presentation with non-ST-segment elevation acute coronary syndrome and association with safety and efficacy of vorapaxar: insights from the TRACER trial. *Eur Heart J Acute Cardiovasc Care*, 2017;6(2):155-163.
- Jneid H, Anderson JL, Wright RS, Adams CD, Bridges CR, Casey DE, *et al.* 2012 ACCF/AHA focused update of the guideline for the management of patients with unstable angina/non-ST-elevation myocardial infarction (updating the 2007 guideline and replacing the 2011 focused update): a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiology*, 2012;60(7):645-681.
- Køber L, Torp-Pedersen C, Carlsen JE, Bagger H, Eliassen P, Lyngborg K, *et al.* A clinical trial of the angiotensin-converting-enzyme inhibitor trandolapril in patients with left ventricular dysfunction after myocardial infarction. *New England Journal of Medicine*, 1995;333(25):1670-1676.
- Korff S, Katus HA & Giannitsis E. Differential diagnosis of elevated troponins. *Heart*, 2006;92(7):987-993.

Mehta SR, Tanguay JF, Eikelboom JW, Jolly SS, Joyner CD, Granger CB, *et al.* Double-dose versus standard-dose clopidogrel and high-dose versus low-dose aspirin in individuals undergoing percutaneous coronary intervention for acute coronary syndromes (CURRENT-OASIS 7): a randomised factorial trial. *Lancet (London, England)*, 2010;376(9748):1233-1243. doi: 10.1016/s0140-6736(10)61088-4

Miocardico, GIPIsdsNI. GISSI-3: effects of lisinopril and transdermal glyceryl trinitrate singly and together on 6-week mortality and ventricular function after acute myocardial infarction. *Lancet (London, England)*, 1994;343(8906):1115-1122.

Moser DK, Kimble LP, Alberts MJ, Alonzo A, Croft JB, Dracup K, *et al.* Reducing delay in seeking treatment by patients with acute coronary syndrome and stroke: a scientific statement from the American Heart Association Council on cardiovascular nursing and stroke council. *Circulation*, 2006;114(2):168-182.

O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Chung MK, De Lemos JA, *et al.* 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiology*, 2013;61(4):e78-e140.

Pancholy SB, Boruah P, Ahmed I, Kwan T, Patel TM & Saito S. Meta-analysis of effect on mortality of percutaneous recanalization of coronary chronic total occlusions using a stent-based strategy. *The American journal of cardiology*, 2013;111(4):521-525.

Pfeffer MA, Braunwald E, Moyé LA, Basta L, Brown Jr EJ, Cuddy TE, *et al.* Effect of captopril on mortality and morbidity in patients with left ventricular dysfunction after myocardial infarction: results of the Survival and Ventricular Enlargement Trial. *New England Journal of Medicine*, 1992;327(10):669-677.

Roffi M, Patrono C, Collet JP, Mueller C, Valgimigli M, Andreotti F, *et al.* 2015 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: Task Force for the Management of Acute Coronary Syndromes in Patients Presenting without Persistent ST-Segment Elevation of the European Society of Cardiology (ESC). *European Heart Journal*, 2016;37(3):267-315. doi: 10.1093/eurheartj/ehv320

Smith JN, Negrelli JM, Manek MB, Hawes EM & Viera AJ. Diagnosis and management of acute coronary syndrome: an evidence-based update. *Journal of the American Board of Family Medicine*, 2015;28(2):283-293.

Spartalis M, Tzatzaki E, Spartalis E, Damaskos C, Athanasiou A, Moris D & Politou M. The role of prasugrel in the management of acute coronary syndromes: a systematic review. *Eur Rev Med Pharmacol Sci*, 2017;21(20):4733-4743.

Stone NJ, Robinson JG, Lichtenstein AH, Merz CNB, Blum CB, Eckel RH, *et al.* 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic

cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *J of the American College of Cardiology*, 2014;63(25 Part B):2889-2934.

Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR. & White, HD. Third universal definition of myocardial infarction. *Glob Heart*, 2012;7(4):275-295.

Verheugt FW. Acute coronary syndromes: drug treatments. *The Lancet*, 1999;353:s20-s23.

Wang D, Yang XH, Zhang JD, Li RB, Jia M & Cui XR. Compared efficacy of clopidogrel and ticagrelor in treating acute coronary syndrome: a meta-analysis. *BMC Cardiovasc Disord*, 2018;18(1):018-0948.

Weaver WD, Simes RJ, Betriu A, Grines CL, Zijlstra F, Garcia E, *et al.* Comparison of primary coronary angioplasty and intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review. *JAMA*, 1997;278(23):2093-2098.

White HD & Van de Werf FJ. Thrombolysis for acute myocardial infarction. *Circulation*, 1998; 97(16):1632-1646. doi: 10.1161/01.cir.97.16.1632

Yusuf S. Clopidogrel in Unstable Angina to Prevent Recurrent Events Trial Investigators. Effect of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. *N Engl J Med*, 2001;345:494-502.