Optimization of secondary prevention and risk stratification in patients with coronary heart disease

Bodde M.C.

Chapter 1.

General introduction and thesis outline

General introduction and thesis outline

Ischemic heart disease contributes, with almost 10 million deaths worldwide, for a substantial part to the total deaths in CVD.(1) In Europe, approximately 1.8 million died due to ischemic heart disease, which accounts for 20% of all deaths.(2) Ischemic heart disease is often caused by an acute coronary syndrome (ACS), which is the clinical manifestation of coronary artery disease. ACS can roughly be grouped in non-ST-segment elevation myocardial infarction (NSTEMI) and ST-segment elevation myocardial infarction (STEMI). A STEMI is caused by an occlusion of a coronary artery, which occurs when the blood flow is abruptly obstructed by a plaque rupture, erosion or fissuring which results in an obstructing thrombus.(3) This is clinically expressed by ischemic symptoms, and with new ST-segment elevation in 2 contiguous leads and often reciprocal ST-segment depression on the electrocardiogram (ECG). Confirmation of myocardial ischemic injury with elevated cardiac biomarkers is required for the diagnosis STEMI whereas in NSTEMI patients the symptoms of ischaemia is often represented with new or presumed new significant ST-T wave changes or left bundle branch block on 12-lead ECG.(4)

Development of atherosclerosis

Coronary artery disease is caused by the underlying pathological process of atherosclerosis illustrated in figure 1. Atherosclerosis starts early in life and often progresses silently for many years. Hypercholesterolemia is considered one of the main triggers of atherosclerosis. The increase is plasma cholesterol levels results in changes of the endothelial permeability that allow the migration of mainly low-density-lipoprotein-cholesterol (LDL-c) particles into the arterial wall.(3) This triggers an inflammatory reaction. Monocytes adhere to the endothelial cell and migrate in the sub endothelial space.(3) Here, monocytes require macrophage characteristics and incorporate oxidized LDL-c resulting in the formation of plaque-forming foam cells. Fatty streaks appear due to the local accumulation of serum lipoproteins in the vessel wall. Fatty streaks are the precursors of more advanced lesions characterized by the accumulation of lipid-rich necrotic debris and smooth muscle cells (SMCs). Such 'fibrous lesions' typically have a 'fibrous cap'.(5) Vulnerable plaques are characterized by the formation of a necrotic core and by thinning of the fibrous cap. This may result in a rupture of the cap exposing prothrombotic components to platelets and procoagulation factors leading to thrombus formation and clinical events such as N(STEMI).(6) The majority of coronary thrombi are caused by plaque rupture (55-65%), followed by erosions (30-35%), and last frequent from calcified nodules (2-7%)(7)

Treatment

At the beginning of the 20th century, a myocardial infarction (MI) was regarded as a rare condition not compatible with survival. In the first half of the 20th century, early mortality rates were high, around 30%, and for patients surviving the

acute phase, 'treatment' of a MI consisted of 4 weeks of bedrest and pain relief. However, by elucidating the natural history of the MI, physicians set the stage for huge advances that followed. These advances can be summarized into four categories; birth of the Coronary Care Unit (CCU), developments in pre-hospital care, myocardial reperfusion techniques and adjunctive pharmacotherapy.

The CCU is defined as probably the single most important advancement in the treatment of MI. The concept of the CCU was proposed in 1961 by Desmond Julian in *The Lancet*(8) and based on 4 principles. 1; the appreciation of the importance of arrhythmias as the principal cause of early death in MI, 2; the ability to monitor the ECG continuously, 3; the development of closed-chest cardiac resuscitation and 4; the delegation of the treatment of life threatening arrhythmias, to trained nurses in the absence of physicians.(9) Due to the developments of the CCU, early mortality was cut in half to approximately 15%.

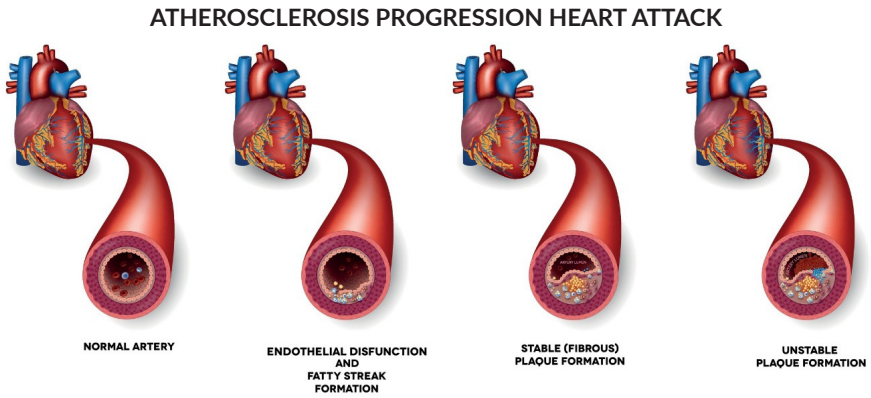

Figure 1. Cross-sectional view of atherosclerosis progression. The left figure shows a normal artery. Due to several stimuli, such as hypertension, smoking and hypercholesterolemia the endothelium begins to dysfunction, which results in an inflammation reaction with the formation of plaque-forming foam cells. Fatty streaks appear due to the local accumulation of serum lipoproteins in the vessel wall. As the atherosclerotic lesions progresses a fibrous cap with a necrotic core develops. When this fibrous cap thinness the plaque becomes unstable and is prone to rupture resulting in an acute occlusion of the artery due to thrombus formation.

Subsequently, it was early recognized that advances in prehospital care were necessary. Most deaths in patients with MI occur before the patient reached the hospital due to life threatening arrhythmias. In 1967, Pantridge designed the concept of a mobile CCU. These ambulances are equipped with ECG monitors, drugs and equipment for defibrillations and resuscitation(10) and have saved many lives. Furthermore, outcomes of patients suffering from MI are depending on the time taken to deliver definitive treatment. Evidence has shown that the

extent of myocardial salvage is greatest if patients are reperfused in the first 3 hours from the onset of symptoms.(11) The biggest delays are seen in the prehospital setting due to patient delay or system delay. Patient delay is the time from the onset of symptoms to contact with the emergency services. System delay is the time between contact with the emergency services to diagnosis and reperfusion treatment.

The use of dilating catheters for the treatment of atherosclerotic vascular disease was first described in 1964 by Charles Dotter and Melvin Judkins.(12) Building on their work, Andreas Gruentzig performed the first successful percutaneous transluminal coronary angioplasty (PTCA) in 1977.(13) However, a common complication of the PTCA was (late) restenosis which occurred in up to 30% of the treated coronary arteries.(14) It was theorized that devices could be placed inside the arteries as scaffolds to keep them open after a successful balloon angioplasty.(13) The first intracoronary stents were successfully deployed in coronary arteries in 1986.(15) Nowadays, primary percutaneous coronary intervention (pPCI) is the golden standard in STEMI patients.

Adjunctive pharmacotherapy after a MI consists of 5 medical therapies, defined as the 'golden five': Aspirin, a P_2Y_{12} inhibitor (e.g. prasugrel or ticagrelor or clopidogrel), ACE-inhibitor, betablocker and a statin. Platelet inhibition remains the core pharmacotherapy component in STEMI patients undergoing pPCI. Aspirin inhibits platelet dependent cyclooxygenase 1 (COX-1) enzyme and consequently preventing synthesis of thromboxane A_2 (TXA_2) which is a powerful promotor of platelet aggregation.(16) Major studies have indicated a central role for aspirin in patients with STEMI.(17-19) Clopidogrel, prasugrel and ticagrelor are P_2Y_{12} inhibitors. P_2Y_{12} receptor plays a key role in the platelet activation process. Adenosine diphosphate (ADP) interacts with the platelet P_2Y_{12} receptor stimulating activation of the glycoprotein IIb/IIIa (GPIIb/IIIa) receptor. In turn, activation of the GPIIb/IIIa results in enhanced platelet degranulation and thromboxane production, driving platelet aggregation.(20) Several trials showed a significant reduction of death using clopidogrel, prasugrel or ticagrelor in ACS patients undergoing PCI.(21-23)

Pump failure secondary to extensive myocardial damages emerged as the principal cause of death in patients surviving the life threatening arrhythmias. Preservation of the left ventricular function is a major predictive factor of prognosis. ACE inhibitors, blocks angiotensin converting enzyme that converts angiotensin I to angiotensin II. Decreased production of angiotensin II enhances natriuresis, lowers blood pressure, and prevents remodelling of smooth muscle and cardiac myocytes. Lowered arterial and venous pressure reduces preload and afterload. Treatment with ACE inhibitors is recommended in patients with systolic LV dysfunction or heart failure, hypertension, or diabetes and should be considered in all STEMI patients.(24, 25)

Beta blocker use decreases oxygen demand due to reduction in heart rate, blood pressure and contractility and can reduce remodelling and can improve left ventricular hemodynamic function.(26-28) The benefit of short-term treatment with oral beta blockers after STEMI is well established, although most of the data come from trials performed in the pre-reperfusion era.(29, 30)

3-hydroxy-3-methyl–glutaryl-coenzyme A (HMG-CoA) reductase inhibitors (usually addressed as "statins") induce an increased expression of LDL receptors (LDL-R) on the surface of the hepatocytes, which determines an increase in the uptake of LDL-C from the blood and a decreased plasma concentration of LDL-C and other apoB-containing lipoproteins, including TG-rich particles.(31, 32) The benefits of statins in secondary prevention have been unequivocally demonstrated.(33) Independent of baseline LDL-c level and baseline cardiovascular risk, a meta-analysis of 26 statin CV outcome trials, showed a 22% risk reduction in CV events per 1mmol/L reduction in LDL-c.(33) Next to the lipid lowering function of statins, they are well-known for their pleiotropic lipid lowering independent effect. Statins positively interfere with critical components of the atherosclerotic process, and have beneficial anti-inflammatory effects on the vascular wall and improve endothelial function.(34, 35) An overview of described pleiotropic mechanisms is provided in figure 2.

The last three decades, mortality rates decreased significantly due to these very successful treatments.(29, 33, 36-40) Current 1-year mortality rates are approximately 10%.(41, 42) In the Netherlands mortality rates have declined progressively since the 70's, with approximately 20.000 deaths to under the 5000 in 2017 (Figure 3).

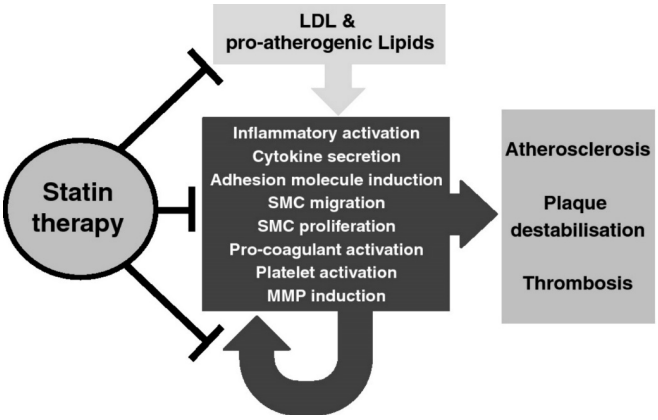

Figure 2. Pleiotropic effects of statins. The reduce hypercholesterolemia and directly attenuate the cellular precesses leading to atherosclerosis. The also break the positive feedback loop operative in the atherosclerotic process. SMC; smooth muscle cell, MMP; matrix metalloproteinase, LDL; low density lipoprotein. Source: *Babelova et al. Anti-atherosclerotic mechanisms of statin therapy*.(35)

Risk stratification and novel biomarkers

Although mortality rates have decreased significantly still a substantial amount of death occur with a wide variability between patients. Therefore it is essential to make an early assessment of short term risk. Readily available parameters in the acute phase before reperfusion have been identified for risk assessment and adjustment. (30) These parameters include older age, hypotension, Kilip class >1, anterior MI, peripheral vascular disease, initial serum creatinine level, elevated cardiac markers, cardiac arrest on admission and ST-segment deviation. All these risk factors are implemented in the GRACE risk score to assess the 6 months risk for death and can guide patient triage and management.(43)

The combination of clinical characteristic in combination with traditional cardiac biomarkers such as cardiac Troponin (cTn) and N-terminal pro-B-type natriuretic peptide (NTproBNP) have shown to improve risk prediction.(44, 45) However current risk prediction models provide only a rough estimate of individual risk. A multimarker strategy that captures a broader spectrum of disease may have added value since it can reveal novel relaease mechanisms and therefore potentioal therepeutic targets. Several biomarkers, such as growth differentiation factor-15 (GDF-15), galectin-3 (GAL-3) and suppression of tumorigenicity 2 (ST-2) have been studied in the recent years.(46) This thesis focusses on GDF-15 which is a systemic stress-responsive member of the transforming growth factor (TGF-β). (47) It is a relatively novel biomarker which is induced in the myocardium after ischemia and reperfusion and released due to heamodynamic stress.(48, 49)

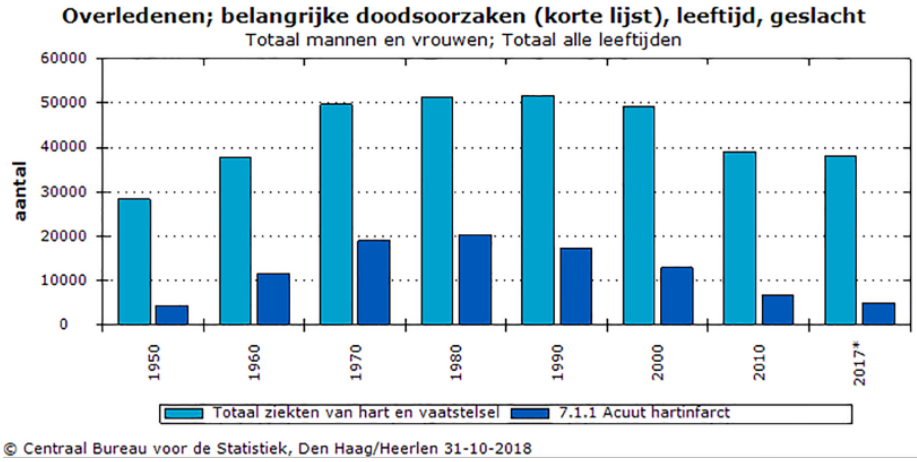

Figure 3. Number of deaths in the period 1950-2017 for cardiovascular disease and acute myocardial infarction separately. *Centraal Bureau voor de Statistiek, Den Haag/Heerlen, The Netherlands*(50)

Objective and outline of this thesis

The first objective of this thesis is to optimize the treatment in patients with STEMI or cardiovascular disease. Secondly, this thesis aims to improve risk stratification and identify high risk populations in STEMI patients. At last, a manuscript about a pre-hospital triage protocol was developed to manage the capacity in the cardiac emergency department.

Recent years have brought a significant amount of new results in the field of atherosclerosis. **Chapter 2** provides a background consisting of the current under-standing of the pathophysiology and treatment of atherosclerotic disease, followed by future perspectives on several novel classes of drugs that target atherosclerosis.

STEMI patients in the LUMC are treated according to the MISSION! MI protocol. Low risk patients are referred to the general practitioner (GP) after one year treatment according to the MISSION! MI protocol. In **chapter 3** the prognosis of STEMI patients referred to the GP after one year is assessed.

The current way to assess the risk of cardiovascular disease (CVD) is to measure conventional lipid and lipoprotein cholesterol fractions. Despite the success of statin treatment residual cardiovascular risk remains high. Therefore **chapter 4** studied the value of extensive serum apolipoprotein (apo) profiling and the risk of adverse events in patients with STEMI.

Identification of high-risk patients is essential for optimal monitoring and initiation of appropriate treatment to reduce risk of events. GDF-15 is a novel biomarker which can on top of other biomarkers improve risk stratification. **Chapter 5** investigated the additive prognostic value of GDF-15 levels at admission in STEMI patients on top of clinical characteristics and known cardiac biomarkers such as cTn and NTproBNP.

The introduction of high sensitivity assays (hs-cTn), which are up to 100 times more sensitive compared to the first-generation assays, permits the accurate determination of very low levels of circulating cardiac troponin. Elevated serum hs-cTn levels, even those within the normal range, are an emerging independent predictor of cardiovascular (CV) mortality in patients with and without CVD. **Chapter 6** sought to characterize the effect (magnitude and time of onset) of atorvastatin (ATOR) or rosuvastatin (ROSU) on hs-cTnI levels within the normal range in patients with stable CVD.

Hypercholesterolemia is a well-known risk factor for developing atherosclerosis and subsequently for the risk of a MI. Moreover, it might also be related to the extent of damaged myocardium in the event of a MI. **Chapter 7** aims to evaluate the association of baseline LDL-c level with infarct size in patients with STEMI after pPCI.

Chapter 8 is about the feasibility and efficacy of a novel pre-hospital triage protocol for use in the cardiac emergency department. Overcrowding in emergency department is a major public health problem and pre-hospital triage can help to allocate patients to the appropriate emergency department and thereby increase quality and efficacy of acute care in hospitals.

The final chapter includes a general summary, conclusions and future perspectives in English and in Dutch.

References

1. Global Health Estimates 2016: Deaths by Cause, Age, Sex, by Country and by Region, 2000-2016. Geneva, World Health Organization; 2018.: World Health Organization; [Available from: http://www.who.int/news-room/fact-sheets/detail/the-top-10-causes-of-death.
2. Townsend N, Wilson L, Bhatnagar P, Wickramasinghe K, Rayner M, Nichols M. Cardiovascular disease in Europe: epidemiological update 2016. European heart journal. 2016;37(42):3232-45.
3. Sakakura K, Nakano M, Otsuka F, Ladich E, Kolodgie FD, Virmani R. Pathophysiology of atherosclerosis plaque progression. Heart, lung & circulation. 2013;22(6):399-411.
4. Thygesen K, Alpert JS, Jaffe AS, Chaitman BR, Bax JJ, Morrow DA, et al. Fourth universal definition of myocardial infarction (2018). European heart journal. 2018.
5. Lusis AJ. Atherosclerosis. Nature. 2000;407(6801):233-41.
6. Virmani R, Kolodgie FD, Burke AP, Farb A, Schwartz SM. Lessons from sudden coronary death: a comprehensive morphological classification scheme for atherosclerotic lesions. Arteriosclerosis, thrombosis, and vascular biology. 2000;20(5):1262-75.
7. Libby P. Mechanisms of acute coronary syndromes and their implications for therapy. The New England journal of medicine. 2013;368(21):2004-13.
8. Julian DG. Treatment of cardiac arrest in acute myocardial ischaemia and infarction. Lancet (London, England). 1961;2(7207):840-4.
9. Braunwald E. Evolution of the management of acute myocardial infarction: a 20th century saga. Lancet (London, England). 1998;352(9142):1771-4.
10. Pantridge JF, Geddes JS. A mobile intensive-care unit in the management of myocardial infarction. Lancet (London, England). 1967;2(7510):271-3.
11. Gersh BJ, Stone GW, White HD, Holmes DR, Jr. Pharmacological facilitation of primary percutaneous coronary intervention for acute myocardial infarction: is the slope of the curve the shape of the future? Jama. 2005;293(8):979-86.
12. Dotter CT, Judkins MP. TRANSLUMINAL TREATMENT OF ARTERIOSCLEROTIC OBSTRUCTION. DESCRIPTION OF A NEW TECHNIC AND A PRELIMINARY REPORT OF ITS APPLICATION. Circulation. 1964;30:654-70.
13. King SB, 3rd, Schlumpf M. Ten-year completed follow-up of percutaneous transluminal coronary angioplasty: the early Zurich experience. Journal of the American College of Cardiology. 1993;22(2):353-60.
14. Holmes DR, Jr., Savage M, LaBlanche JM, Grip L, Serruys PW, Fitzgerald P, et al. Results of Prevention of REStenosis with Tranilast and its Outcomes (PRESTO) trial. Circulation. 2002;106(10):1243-50.
15. Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. The New England journal of medicine. 1987;316(12):701-6.
16. Patrono C, Bachmann F, Baigent C, Bode C, De Caterina R, Charbonnier B, et al. Expert consensus document on the use of antiplatelet agents. The task force on the use of antiplatelet agents in patients with atherosclerotic cardiovascular disease of the European society of cardiology. European heart journal. 2004;25(2):166-81.

17. Randomised trial of intravenous streptokinase, oral aspirin, both, or neither among 17,187 cases of suspected acute myocardial infarction: ISIS-2. ISIS-2 (Second International Study of Infarct Survival) Collaborative Group. Lancet (London, England). 1988;2(8607):349-60.
18. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ (Clinical research ed). 2002;324(7329):71-86.
19. Schwartz L, Bourassa MG, Lesperance J, Aldridge HE, Kazim F, Salvatori VA, et al. Aspirin and dipyridamole in the prevention of restenosis after percutaneous transluminal coronary angioplasty. The New England journal of medicine. 1988;318(26):1714-9.
20. Wallentin L. P2Y(12) inhibitors: differences in properties and mechanisms of action and potential consequences for clinical use. European heart journal. 2009;30(16):1964-77.
21. Mehta SR, Yusuf S, Peters RJ, Bertrand ME, Lewis BS, Natarajan MK, et al. Effects of pretreatment with clopidogrel and aspirin followed by long-term therapy in patients undergoing percutaneous coronary intervention: the PCI-CURE study. Lancet (London, England). 2001;358(9281):527-33.
22. Montalescot G, Wiviott SD, Braunwald E, Murphy SA, Gibson CM, McCabe CH, et al. Prasugrel compared with clopidogrel in patients undergoing percutaneous coronary intervention for ST-elevation myocardial infarction (TRITON-TIMI 38): double-blind, randomised controlled trial. Lancet (London, England). 2009;373(9665):723-31.
23. Cannon CP, Harrington RA, James S, Ardissino D, Becker RC, Emanuelsson H, et al. Comparison of ticagrelor with clopidogrel in patients with a planned invasive strategy for acute coronary syndromes (PLATO): a randomised double-blind study. Lancet (London, England). 2010;375(9711):283-93.
24. Yusuf S, Sleight P, Pogue J, Bosch J, Davies R, Dagenais G. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. The New England journal of medicine. 2000;342(3):145-53.
25. Fox KM. Efficacy of perindopril in reduction of cardiovascular events among patients with stable coronary artery disease: randomised, double-blind, placebo-controlled, multicentre trial (the EUROPA study). Lancet (London, England). 2003;362(9386):782-8.
26. Doughty RN, Whalley GA, Walsh HA, Gamble GD, Lopez-Sendon J, Sharpe N. Effects of carvedilol on left ventricular remodeling after acute myocardial infarction: the CAPRICORN Echo Substudy. Circulation. 2004;109(2):201-6.
27. Galcera-Tomas J, Castillo-Soria FJ, Villegas-Garcia MM, Florenciano-Sanchez R, Sanchez-Villanueva JG, de La Rosa JA, et al. Effects of early use of atenolol or captopril on infarct size and ventricular volume: A double-blind comparison in patients with anterior acute myocardial infarction. Circulation. 2001;103(6):813-9.
28. Hu K, Gaudron P, Ertl G. Long-term effects of beta-adrenergic blocking agent treatment on hemodynamic function and left ventricular remodeling in rats with experimental myocardial infarction: importance of timing of treatment and infarct size. Journal of the American College of Cardiology. 1998;31(3):692-700.

29. Freemantle N, Cleland J, Young P, Mason J, Harrison J. beta Blockade after myocardial infarction: systematic review and meta regression analysis. Bmj. 1999;318(7200):1730-7.
30. Ibanez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017 ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: The Task Force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). European heart journal. 2018;39(2):119-77.
31. Catapano AL, Graham I, De Backer G, Wiklund O, Chapman MJ, Drexel H, et al. 2016 ESC/EAS Guidelines for the Management of Dyslipidaemias. European heart journal. 2016;37(39):2999-3058.
32. Bergheanu SC, Bodde MC, Jukema JW. Pathophysiology and treatment of atherosclerosis : Current view and future perspective on lipoprotein modification treatment. Netherlands heart journal : monthly journal of the Netherlands Society of Cardiology and the Netherlands Heart Foundation. 2017;25(4):231-42.
33. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, et al. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. Lancet. 2005;366(9493):1267-78.
34. Tousoulis D, Psarros C, Demosthenous M, Patel R, Antoniades C, Stefanadis C. Innate and adaptive inflammation as a therapeutic target in vascular disease: the emerging role of statins. Journal of the American College of Cardiology. 2014;63(23):2491-502.
35. Babelova A, Sedding DG, Brandes RP. Anti-atherosclerotic mechanisms of statin therapy. Current opinion in pharmacology. 2013;13(2):260-4.
36. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet (London, England). 2003;361(9351):13-20.
37. Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. The New England journal of medicine. 2007;357(20):2001-15.
38. De Luca G, Suryapranata H, Stone GW, Antoniucci D, Tcheng JE, Neumann FJ, et al. Abciximab as adjunctive therapy to reperfusion in acute ST-segment elevation myocardial infarction: a meta-analysis of randomized trials. Jama. 2005;293(14):1759-65.
39. Dagenais GR, Pogue J, Fox K, Simoons ML, Yusuf S. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. Lancet (London, England). 2006;368(9535):581-8.
40. Indications for ACE inhibitors in the early treatment of acute myocardial infarction: systematic overview of individual data from 100,000 patients in randomized trials. ACE Inhibitor Myocardial Infarction Collaborative Group. Circulation. 1998;97(22):2202-12.

41. Fokkema ML, James SK, Albertsson P, Akerblom A, Calais F, Eriksson P, et al. Population trends in percutaneous coronary intervention: 20-year results from the SCAAR (Swedish Coronary Angiography and Angioplasty Registry). Journal of the American College of Cardiology. 2013;61(12):1222-30.
42. Pedersen F, Butrymovich V, Kelbaek H, Wachtell K, Helqvist S, Kastrup J, et al. Short- and long-term cause of death in patients treated with primary PCI for STEMI. Journal of the American College of Cardiology. 2014;64(20):2101-8.
43. Fox KA, Dabbous OH, Goldberg RJ, Pieper KS, Eagle KA, Van de Werf F, et al. Prediction of risk of death and myocardial infarction in the six months after presentation with acute coronary syndrome: prospective multinational observational study (GRACE). BMJ (Clinical research ed). 2006;333(7578):1091.
44. Bjorklund E, Jernberg T, Johanson P, Venge P, Dellborg M, Wallentin L, et al. Admission N-terminal pro-brain natriuretic peptide and its interaction with admission troponin T and ST segment resolution for early risk stratification in ST elevation myocardial infarction. Heart (British Cardiac Society). 2006;92(6):735-40.
45. O'Donoghue ML, Morrow DA, Cannon CP, Jarolim P, Desai NR, Sherwood MW, et al. Multimarker Risk Stratification in Patients With Acute Myocardial Infarction. Journal of the American Heart Association. 2016;5(5).
46. Salvagno GL, Pavan C. Prognostic biomarkers in acute coronary syndrome. Ann Transl Med. 2016;4(13):258.
47. Bootcov MR, Bauskin AR, Valenzuela SM, Moore AG, Bansal M, He XY, et al. MIC-1, a novel macrophage inhibitory cytokine, is a divergent member of the TGF-beta superfamily. Proc Natl Acad Sci U S A. 1997;94(21):11514-9.
48. Kempf T, Eden M, Strelau J, Naguib M, Willenbockel C, Tongers J, et al. The transforming growth factor-beta superfamily member growth-differentiation factor-15 protects the heart from ischemia/reperfusion injury. Circ Res. 2006;98(3):351-60.
49. Chan MM, Santhanakrishnan R, Chong JP, Chen Z, Tai BC, Liew OW, et al. Growth differentiation factor 15 in heart failure with preserved vs. reduced ejection fraction. Eur J Heart Fail. 2016;18(1):81-8.
50. Doodsoorzaken CBS [Available from: http://statline.cbs.nl/Statweb/publication/?DM=SLNL&PA=7052_95&D1=44&D2=a&D3=0&D4=0,10,20,30,40,50,60,l&HDR=G2,G1,G3&STB=T&CHARTTYPE=1&VW=T.