1

General introduction and thesis outline

H. Boden

ACUTE MYOCARDIAL INFARCTION

Ischemic heart disease results from acute or chronic inadequate supply of oxygen to the cardiac muscle. Generally, the underlying condition is coronary artery disease, referring to the pathological process of atherosclerosis in the coronary arteries. Coronary atherosclerosis initially develops without symptoms. It becomes clinically manifest as angina pectoris, acute coronary syndrome (ACS) or sudden cardiac death, when the patency of a coronary artery is impaired and consequently the flow of blood is jeopardized (**Figure 1**). ACS is a high-risk manifestation of coronary artery disease, ranging from unstable angina pectoris (UAP) and non-ST-elevation myocardial infarction (NSTEMI) to ST-elevation myocardial infarction (STEMI). Although rupture or erosion of a vulnerable atherosclerotic plaque frequently leads solely to progression of plaque volume, due to an unfortunate turn of events it might give rise to a cascade of inflammation, thrombus formation and partial or complete occlusion of the coronary artery resulting in acute ischemia or necrosis of the myocardium[1].

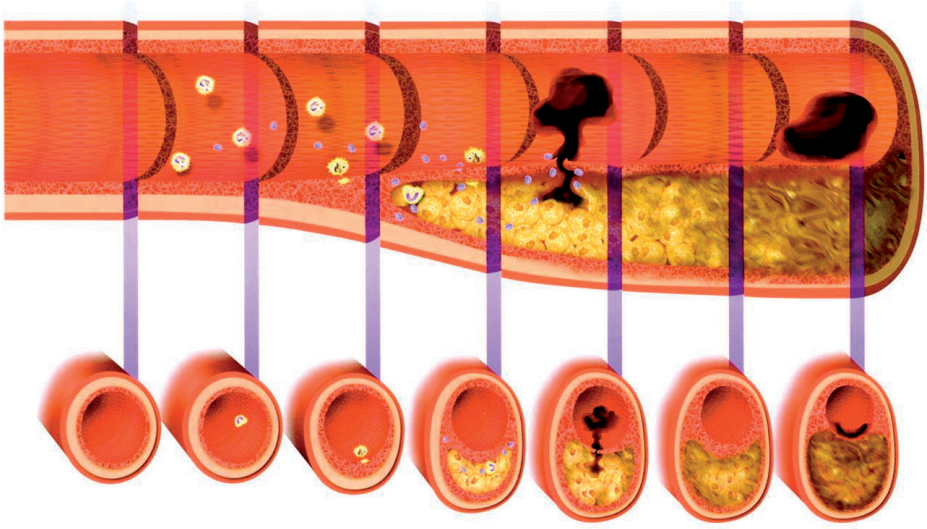

Figure 1. The development of an atherosclerotic lesion is depicted in time from normal artery to atheroma that causes clinical manifestations by thrombosis or stenosis.
Reprinted from Libby et al[2] with permission of Wolters Kluwer Health, Inc.

Ischemic heart disease represents a substantial part of the global burden of disease. According to recent data from the World Health Organization, the top 10 causes of death worldwide is led by ischemic heart disease and resulted in over 7 million deaths in 2012[3]. Additionally, coronary artery disease is the most common reason for cardiac hospitalization in the Western world and represents more than half of all cardiovascular events in

patients <75 years[4]. According to data from the National Health and Nutrition Examination Survey (NHANES) 2007-2010, the prevalence of coronary heart disease in the US alone is estimated at 15.4 million, including 7.6 million persons who suffered from an acute myocardial infarction (AMI)[4]. Future perspectives are that the prevalence in the US will increase by an estimated 18% in 2030[4]. In Europe, coronary artery disease accounts for 1.8 million deaths each year and is herewith the leading cause of death. In addition to the morbidity and mortality, the expenditure on ischemic heart disease is striking. Coronary artery disease costs the European Union an estimated €60 billion annually, of which slightly less than €20 billion is spent on direct health care related costs. On top of the health care expenses are the high costs due to production losses from 1) death and sickness in the working age population and 2) the informal care for patients with coronary artery disease[5]. Despite these disturbing reports, considerable progress has been achieved in both prevention and treatment of coronary artery disease. As a result, mortality rates have declined substantially during the last four decades[4;6-8]. Fatality rates for AMI separately have fallen as well, which is suggested to be driven by a decreased incidence of STEMI and a decline in mortality after NSTEMI[9]. In the Netherlands, mortality rates attributable to AMI were highest in the late 70's and early 80's with over 20,000 deaths per year but declined markedly to 5690 deaths in 2013 (**Figure 2**)[10].

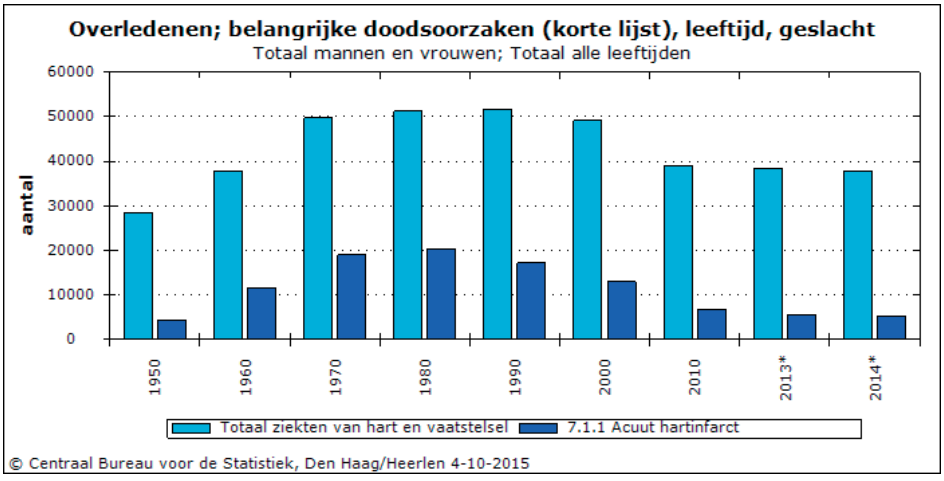

Figure 2. Number of deaths in the period 1950-2014 (sum of all age categories) for cardiovascular disease and acute myocardial infarction separately.
Centraal Bureau voor de Statistiek, Den Haag/Heerlen, The Netherlands[10]

Innovations in AMI care considered as important contributors to the reduction in early mortality included the introduction of the coronary care unit[11;12], fibrinolytic therapy[13], antiplatelet therapy[14;15], angiotensin-converting-enzyme (ACE) inhibitors[16;17] and me-

chanical revascularization[18;19]. Moreover, international guidelines were developed with recommendations for optimal AMI care, including strategies for early diagnosis, timely reperfusion and measures for secondary prevention[20-23]. Standardized guideline-based care programs were designed for implementation in daily clinical practice, such as the large-scale Guidelines Applied in Practice and Get With the Guidelines initiatives, but also smaller programs such as the regional Dutch MISSION! care program. These projects were proven to be strong tools to enhance adherence to evidence-based medicine and are likely to have contributed to improved outcome after AMI as well[24-27]. However, despite the evolving treatment modalities and accomplishments so far, ischemic heart disease and AMI remain major healthcare problems requiring attention.

TRENDS IN REPERFUSION

The field of invasive cardiology was already emerging in the 18th century when Stephen Hales performed the earliest documented cardiac catheterization by inserting brass pipes into the ventricles of a living horse[28]. Although there had already been performed several undocumented human procedures in the early 20th century, cardiac catheterization considered as the first in man was performed by – and on – Werner Forssmann in 1929[29]. From that time on, series of experiments by scientists such as Seldinger[30], Sones[31], Dotter and Judkins[32-34] eventually led to the introduction of percutaneous transluminal coronary angioplasty in 1977; the dilatation of an atherosclerotic coronary obstruction by local inflation of a balloon using a balloon-tipped catheter system (**Figure 3**)[35;36]. Primary angioplasty, currently most often referred to as primary percutaneous coronary intervention (PCI), is nowadays the preferred therapy to achieve restoration of coronary circulation in AMI patients[19].

The inception of balloon dilatation angioplasty for coronary artery disease was soon followed by the implantation of coronary stents in order to maintain lumen patency[37]. Although the implantation of a balloon-expandable coronary stent prevented acute vessel closure due to injury of the arterial wall, e.g. dissections, and substantially reduced the occurrence of restenosis, in-stent neointima hyperplasia and restenosis remained a major drawback of PCI[38;39]. Therefore, research focused on inventing a stent with the ability to inhibit or halt this process. The solution appeared – at least in part – to be found in a coated stent with local release of an antiproliferative agent; a drug-eluting stent (DES). DES were shown to significantly reduce the rate of angiographic restenosis and repeat PCI compared to a standard uncoated bare metal stent (BMS)[40-42]. Therefore, applications of DES were soon expanded to more complex lesions or conditions, such as STEMI. However, the use of DES has drawn attention with regard to the potential higher risk

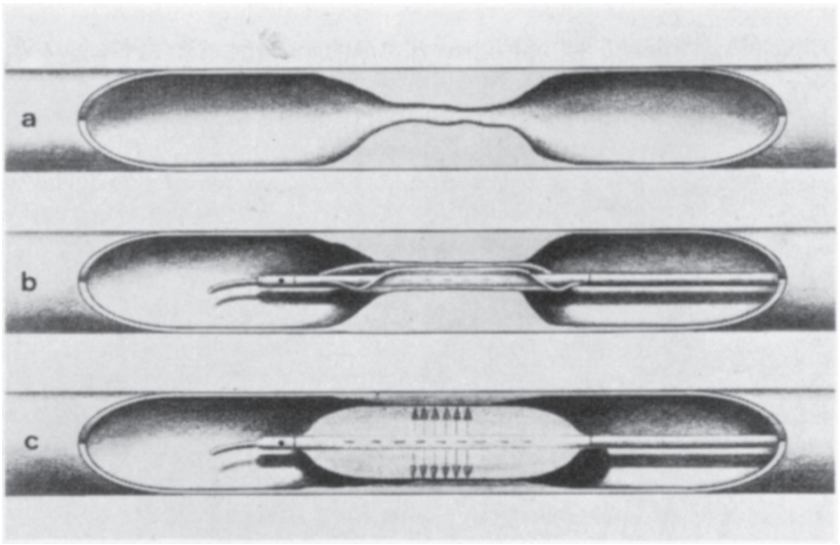

Figure 3. Percutaneous Transluminal Coronary Angioplasty.
a. Stenosis of the coronary artery; b. Introduction of a double lumen catheter with deflated balloon through a guiding catheter; c. Inflation of the balloon across the stenosis for enlargement of the lumen.
Reproduced with permission from Gruntzig et al [36], Copyright Massachusetts Medical Society.

of (very) late stent thrombosis (ST), particularly in the setting of STEMI[43-45]. Although stent thrombosis, universally defined according to the Academic Research Consortium (**Table 1**)[46], is a rare complication, it is associated with a poor prognosis[47-49].

Despite numerous randomized and observational studies, general agreement about the risk of stent thrombosis has not been made yet[50]. Suggested mechanisms for an increased risk for (very) late ST after DES implantation include stent mediated arterial injury, delayed arterial healing, poor endothelial strut coverage and an inflammatory environment, in particular in STEMI patients[51]. Additionally, late stent malapposition has been associated with very late ST and is much more commonly observed after the implantation of DES compared with BMS[52;53]. Second-generation DES, both durable- and biodegradable-polymer DES, were developed to overcome these presumptive problems, of which some appear successful so far[54-58]. However, given the concerns about very late events, research in the setting of STEMI with long-term follow-up is crucial and should be awaited for definite conclusions.

In addition to advances in mechanical revascularization, also achievements have been made in the field of antithrombotic therapy in order to prevent thrombotic events after AMI, such as novel $P2Y_{12}$ antagonists, direct thrombin inhibitors and factor Xa inhibitors.

Table 1. Criteria for definite, probable and possible stent thrombosis according to the Academic Research Consortium[46].

Definite stent thrombosis	**Probable stent thrombosis**	**Possible stent thrombosis**
Pathological confirmation: *Evidence of recent thrombus within the stent determined at autopsy or via examination of tissue retrieved following thrombectomy* Angiographic confirmation*: *The presence of an intracoronary thrombus that originates in the stent or 5 mm proximally or distally and one of the following criteria ≤ 48 hours:* - *Acute onset of ischemic symptoms at rest* - *New ischemic ECG changes that suggest acute ischemia* - *Typical rise and fall in cardiac biomarkers (refer to definition of spontaneous MI)* - *Non-occlusive thrombus† or occlusive thrombus‡*	Any unexplained death ≤ 30 days after stent implantation. Irrespective of the time after the index procedure, any MI that is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of ST and in the absence of any other obvious cause.	Any unexplained death > 30 days after stent implantation until end of trial follow-up.

* The incidental angiographic documentation of stent occlusion in the absence of clinical signs or symptoms is not considered a confirmed stent thrombosis (silent occlusion).
† Non-occlusive thrombus is defined as a (spheric, ovoid, or irregular) noncalcified filling defect or lucency surrounded by contrast material (on 3 sides or within a coronary stenosis) seen in multiple projections, or persistence of contrast material within the lumen, or a visible embolization of intraluminal material downstream.
‡ TIMI 0 or 1 intrastent or proximal to a stent up to the most adjacent proximal side branch or main branch (if originating from the side branch).

OBJECTIVE AND OUTLINE OF THIS THESIS

The purpose of this thesis was both to evaluate contemporary reperfusion strategies in the treatment of STEMI and the prognosis thereafter, including mechanical revascularization and antithrombotic therapy, as well as to address potential pitfalls associated with current STEMI treatment.

In the first part of this thesis, **Chapter 2** describes the long-term outcomes of the MISSION! Intervention Study, a prospective randomized controlled trial evaluating the clinical, angiographic and intravascular ultrasound (IVUS) results of a first-generation DES, i.e. sirolimus-eluting, compared with a BMS implantation in patients with STEMI.

Chapter 3 concerns long-term outcomes in mechanical revascularization as well. This chapter investigates the course of late stent malapposition, a well-known phenomenon after stent implantation, however particularly observed after DES, and likely involved in the multifactorial mechanism behind stent thrombosis.

Chapter 4 evaluates the clinical use of cardiac troponin, a specific indicator of myocardial necrosis, as a surrogate measure for infarct size and prognosis in patients after a first STEMI.

Although previous literature indicates a poorer prognosis for women after ACS when compared to men, conflicting results have been published on the influence of gender on survival after STEMI in particular. **Chapter 5** outlines the prognostic impact of gender on ischemic times and clinical outcomes after primary PCI.

To achieve improvement of the prognosis after ACS, management of these patients should involve multiple aspects of treatment. **Chapter 6** provides a comprehensive review about the integration of different approaches, novel tools for early recognition and diagnosis, a closely regulated AMI care system facilitating early reperfusion, and developments in antithrombotic agents.

Along with the increasingly aggressive antithrombotic therapy for prevention of thrombotic events after AMI, the risk of bleeding becomes a significant complication of therapy. **Chapter 7** studies the incidence, determinants and prognostic impact of major bleeding after treatment for STEMI.

Finally, a summery, conclusions and future perspectives are outlined in **Chapter 8**.

REFERENCE LIST

(1) Arbab-Zadeh A, Nakano M, Virmani R, Fuster V. Acute coronary events. Circulation 2012 Mar 6;125(9):1147-56.

(2) Libby P. Current concepts of the pathogenesis of the acute coronary syndromes. Circulation 2001 Jul 17;104(3):365-72.

(3) World Health Organization. The 10 leading causes of death in the world, 2000 and 2011. 1-7-2013. Ref Type: Online Source

(4) Go AS, Mozaffarian D, Roger VL, Benjamin EJ, Berry JD, Borden WB, et al. Heart disease and stroke statistics—2013 update: a report from the American Heart Association. Circulation 2013 Jan 1;127(1):e6-e245.

(5) Nichols M, Townsend N, Luengo-Fernandez R, Leal J, Scarborough P, Rayner M. European Cardiovascular Disease Statistics 2012. European Heart Network. 2012 Sep.

(6) Fox KA, Steg PG, Eagle KA, Goodman SG, Anderson FA, Jr., Granger CB, et al. Decline in rates of death and heart failure in acute coronary syndromes, 1999-2006. JAMA 2007 May 2; 297(17):1892-900.

(7) McGovern PG, Jacobs DR, Jr., Shahar E, Arnett DK, Folsom AR, Blackburn H, et al. Trends in acute coronary heart disease mortality, morbidity, and medical care from 1985 through 1997: the Minnesota heart survey. Circulation 2001 Jul 3; 104(1):19-24.

(8) Fox CS, Evans JC, Larson MG, Kannel WB, Levy D. Temporal trends in coronary heart disease mortality and sudden cardiac death from 1950 to 1999: the Framingham Heart Study. Circulation 2004 Aug 3;110(5):522-7.

(9) Yeh RW, Sidney S, Chandra M, Sorel M, Selby JV, Go AS. Population trends in the incidence and outcomes of acute myocardial infarction. N Engl J Med 2010 Jun 10;362(23):2155-65.

(10) Doodsoorzaken CBS. 21-6-2013. Ref Type: Online Source

(11) JULIAN DG. Treatment of cardiac arrest in acute myocardial ischaemia and infarction. Lancet 1961 Oct 14;2(7207):840-4.

(12) Goble AJ, Sloman G, Robinson JS. Mortality reduction in a coronary care unit. Br Med J 1966 Apr 23;1(5494):1005-9.

(13) Indications for fibrinolytic therapy in suspected acute myocardial infarction: collaborative overview of early mortality and major morbidity results from all randomised trials of more than 1000 patients. Fibrinolytic Therapy Trialists' (FTT) Collaborative Group. Lancet 1994 Feb 5;343(8893):311-22.

(14) 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 1988 Aug 13;2(8607):349-60.

(15) Yusuf S, Zhao F, Mehta SR, Chrolavicius S, Tognoni G, Fox KK. Effects of clopidogrel in addition to aspirin in patients with acute coronary syndromes without ST-segment elevation. N Engl J Med 2001 Aug 16;345(7):494-502.

(16) Pfeffer MA, Braunwald E, Moye LA, Basta L, Brown EJ, Jr., 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. The SAVE Investigators. N Engl J Med 1992 Sep 3;327(10):669-77.

(17) 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 Jun 9;97(22):2202-12.

(18) Zijlstra F, Hoorntje JC, de Boer MJ, Reiffers S, Miedema K, Ottervanger JP, et al. Long-term benefit of primary angioplasty as compared with thrombolytic therapy for acute myocardial infarction. N Engl J Med 1999 Nov 4;341(19): 1413-9.

(19) Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative

review of 23 randomised trials. Lancet 2003 Jan 4;361(9351):13-20.

(20) O'Gara PT, Kushner FG, Ascheim DD, Casey DE, Jr., 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 Cardiol 2012 Dec 12.

(21) Steg PG, James SK, Atar D, Badano LP, Blomstrom-Lundqvist C, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Eur Heart J 2012 Oct; 33(20):2569-619.

(22) Anderson JL, Adams CD, Antman EM, Bridges CR, Califf RM, Casey DE, Jr., et al. 2012 ACCF/AHA focused update incorporated into the ACCF/AHA 2007 guidelines for the management of patients with unstable angina/non-ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol 2013 Jun 11;61(23):e179-e347.

(23) Hamm CW, Bassand JP, Agewall S, Bax J, Boersma E, Bueno H, et al. ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: The Task Force for the management of acute coronary syndromes (ACS) in patients presenting without persistent ST-segment elevation of the European Society of Cardiology (ESC). Eur Heart J 2011 Sep 21.

(24) Mehta RH, Montoye CK, Gallogly M, Baker P, Blount A, Faul J, et al. Improving quality of care for acute myocardial infarction: The Guidelines Applied in Practice (GAP) Initiative. JAMA 2002 Mar 13;287(10):1269-76.

(25) Eagle KA, Montoye CK, Riba AL, DeFranco AC, Parrish R, Skorcz S, et al. Guideline-based standardized care is associated with substantially lower mortality in medicare patients with acute myocardial infarction: the American College of Cardiology's Guidelines Applied in Practice (GAP) Projects in Michigan. J Am Coll Cardiol 2005 Oct 4;46(7):1242-8.

(26) LaBresh KA, Ellrodt AG, Gliklich R, Liljestrand J, Peto R. Get with the guidelines for cardiovascular secondary prevention: pilot results. Arch Intern Med 2004 Jan 26;164(2):203-9.

(27) Liem SS. MISSION!: Optimization of acute and chronic care for patients with acute myocardial infarction. American Heart Journal 2007 Jan 1; 153(1):14e1-14e11.

(28) Mueller RL, Sanborn TA. The history of interventional cardiology: cardiac catheterization, angioplasty, and related interventions. Am Heart J 1995 Jan;129(1):146-72.

(29) Forssmann W. Die sondierung des rechten herzens. Klin Wochenschr 1929;8:2085-7.

(30) SELDINGER SI. Catheter replacement of the needle in percutaneous arteriography; a new technique. Acta radiol 1953 May;39(5):368-76.

(31) SONES FM, Jr., SHIREY EK. Cine coronary arteriography. Mod Concepts Cardiovasc Dis 1962 Jul;31:735-8.

(32) DOTTER CT, FRISCHE LH. Visualization of the coronary circulation by occlusion aortography: a practical method. Radiology 1958 Oct;71(4): 502-24.

(33) JUDKINS MP. Selective coronary arteriography. I. A percutaneous transfemoral technic. Radiology 1967 Nov;89(5):815-24.

(34) DOTTER CT, JUDKINS MP. TRANSLUMINAL TREATMENT OF ARTERIOSCLEROTIC OBSTRUCTION. DESCRIPTION OF A NEW TECHNIC AND A PRELIMINARY REPORT OF ITS APPLICATION. Circulation 1964 Nov;30:654-70.

(35) Hurst JW. The first coronary angioplasty as described by Andreas Gruentzig. Am J Cardiol 1986 Jan 1;57(1):185-6.

(36) Gruntzig AR, Senning A, Siegenthaler WE. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. N Engl J Med 1979 Jul 12;301(2):61-8.

(37) Sigwart U, Puel J, Mirkovitch V, Joffre F, Kappenberger L. Intravascular stents to prevent occlusion and restenosis after transluminal angioplasty. N Engl J Med 1987 Mar 19;316(12):701-6.

(38) Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. Stent Restenosis Study Investigators. N Engl J Med 1994 Aug 25;331(8):496-501.

(39) Serruys PW, de JP, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994 Aug 25;331(8):489-95.

(40) Rensing BJ, Vos J, Smits PC, Foley DP, van den Brand MJ, van der Giessen WJ, et al. Coronary restenosis elimination with a sirolimus eluting stent: first European human experience with 6-month angiographic and intravascular ultrasonic follow-up. Eur Heart J 2001 Nov;22(22): 2125-30.

(41) Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban HE, Perin M, et al. A randomized comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. N Engl J Med 2002 Jun 6;346(23):1773-80.

(42) Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. N Engl J Med 2003 Oct 2;349(14):1315-23.

(43) Stone GW, Moses JW, Ellis SG, Schofer J, Dawkins KD, Morice MC, et al. Safety and efficacy of sirolimus- and paclitaxel-eluting coronary stents. N Engl J Med 2007 Mar 8;356(10):998-1008.

(44) Kalesan B, Pilgrim T, Heinimann K, Raber L, Stefanini GG, Valgimigli M, et al. Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. Eur Heart J 2012 Apr;33(8):977-87.

(45) De LG, Dirksen MT, Spaulding C, Kelbaek H, Schalij M, Thuesen L, et al. Drug-eluting vs bare metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. Arch Intern Med 2012 Apr 23;172(8):611-21.

(46) Cutlip DE, Windecker S, Mehran R, Boam A, Cohen DJ, van Es GA, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007 May 1;115(17): 2344-51.

(47) Iakovou I, Schmidt T, Bonizzoni E, Ge L, Sangiorgi GM, Stankovic G, et al. Incidence, predictors, and outcome of thrombosis after successful implantation of drug-eluting stents. JAMA 2005 May 4;293(17):2126-30.

(48) Almalla M, Schroder J, Hennings V, Marx N, Hoffmann R. Long-term outcome after angiographically proven coronary stent thrombosis. Am J Cardiol 2013 May 1;111(9):1289-94.

(49) van Werkum JW, Heestermans AA, de Korte FI, Kelder JC, Suttorp MJ, Rensing BJ, et al. Long-term clinical outcome after a first angiographically confirmed coronary stent thrombosis: an analysis of 431 cases. Circulation 2009 Feb 17;119(6): 828-34.

(50) Finn AV, Nakazawa G, Kolodgie F, Virmani R. Drug eluting or bare metal stent for acute myocardial infarction: an issue of safety? Eur Heart J 2009 Aug;30(15):1828-30.

(51) Nakazawa G. Stent thrombosis of drug eluting stent: pathological perspective. J Cardiol 2011 Sep;58(2):84-91.

(52) Cook S, Wenaweser P, Togni M, Billinger M, Morger C, Seiler C, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation 2007 May 8;115(18):2426-34.

(53) Hassan AK, Bergheanu SC, Stijnen T, van der Hoeven BL, Snoep JD, Plevier JW, et al. Late stent malapposition risk is higher after drug-eluting stent compared with bare metal stent implantation and associates with late stent thrombosis. Eur Heart J 2010 May;31(10):1172-80.

(54) Hofma SH, Brouwer J, Velders MA, Van't Hof AW, Smits PC, Quere M, et al. Second-generation everolimus-eluting stents versus first-generation sirolimus-eluting stents in acute myocardial infarction. 1-year results of the randomized XAMI (XienceV Stent vs. Cypher Stent in Primary PCI for Acute Myocardial Infarction) trial. J Am Coll Cardiol 2012 Jul 31;60(5):381-7.

(55) Park KW, Kang SH, Velders MA, Shin DH, Hahn S, Lim WH, et al. Safety and efficacy of everolimus- versus sirolimus-eluting stents: a systematic

review and meta-analysis of 11 randomized trials. Am Heart J 2013 Feb;165(2):241-50.

(56) Kang SH, Park KW, Kang DY, Lim WH, Park KT, Han JK, et al. Biodegradable-polymer drug-eluting stents vs. bare metal stents vs. durable-polymer drug-eluting stents: a systematic review and Bayesian approach network meta-analysis. Eur Heart J 2014 May;35(17):1147-58.

(57) Dangas GD, Serruys PW, Kereiakes DJ, Hermiller J, Rizvi A, Newman W, et al. Meta-analysis of everolimus-eluting versus paclitaxel-eluting stents in coronary artery disease: final 3-year results of the SPIRIT clinical trials program (Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions). JACC Cardiovasc Interv 2013 Sep;6(9):914-22.

(58) Stefanini GG, Byrne RA, Serruys PW, De WA, Meier B, Massberg S, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J 2012 May;33(10):1214-22.