Emergency Medicine: Open Access

Shirotani et al., Emergency Med 2014, 4:6
DOI: 10.4172/2165-7548.1000220

Short Commentary Open Access

Current Problems in the Treatment of Acute Myocardial Infarction: For Better Reperfusion and Long-Term Benefits

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Received date: May 09, 2014, **Accepted date:** September 23, 2014, **Published date:** September 30, 2014

Summary

Coronary reperfusion for an occluded vessel with ruptured vulnerable plaque and clot burden in patients with acute myocardial infarction is now more easily performed due to the development of devices and techniques for percutaneous coronary intervention. However, even after successful coronary intervention, some patients may still have complications such as heart failure, stent thrombosis, or restenosis, which require revascularization in the long-term follow-up period and may affect their survival. Here, outstanding issues concerning primary percutaneous coronary intervention and patient medical care after reperfusion therapy are discussed.

Keywords: Acute myocardial infarction; Reperfusion therapy; Stent, Clot aspiration; Cell therapy

Abbreviations

AMI: acute myocardial infarction; BMS: bare metal stent; BVS: bioresorbable vessel scaffolding; DES: drug-eluting stent; FFR: fractional flow reserve; HCN: hyperpolarization and cyclic nucleotide; IRA: infarct-related artery; IVUS: intravascular ultrasonography; LAD: left anterior descending artery; LV: left ventricular or left ventricle; MACE: major adverse cardiac events; OCT: optical coherence tomography; PCI: percutaneous coronary intervention; ST: stent thrombosis; TLR: target lesion revascularization; TVR: target vessel revascularization

With the marked development of catheterization techniques and medical instruments as well as the supportive metallurgical engineering and biological, physiological, and pharmacological research, percutaneous coronary intervention (PCI) is able to treat patients not only by simple dilatation with ballooning, but also by easy scaffolding of stenotic lesions with metal stents [1]. Imaging devices provide more accurate assessment of lesion characteristics and severity than an angiogram, and often help interventionists decide how and how much they should dilate lesions.

Vulnerable plaque is considered to be an underlying pathological cause of acute myocardial infarction (AMI), characterized by a rapid progression to plaque rupture and high likelihood of thrombotic complications. This rupture-prone plaque, known as a thin-cap fibroatheroma, contains a large lipid core and a thin outer fibrous cap, which is infiltrated by macrophages [2]. The cap thickness is only <65 μm and visualization is possible using intravascular diagnostic techniques such as optical coherence tomography (OCT) with high-resolution images [3,4], or virtual-histology intravascular ultrasonography (IVUS); the latter which is able to visualize an abundant necrotic core (>10% of the cross-sectional area) in contact with the lumen, and a plaque-volume of greater than 40% through radiofrequency data analysis [5]. Non-invasive methods have also been developed to diagnose vulnerable plaque. One useful diagnostic modality is coronary computed tomographic angiography. A lipid core appearing as a "low-attenuation" plaque, positive vessel remodeling, and spotty calcification are the three typical features of vulnerability [6]. Magnetic resonance imaging using low molecular weight gadolinium is another method; the fibrous cap in the luminal surface can be visualized with good contrast to the inner necrotic lipid core, which has low signal intensity [7]. Vulnerable blood, prone to clot formation, is also believed to play an important role in the development of coronary blockage. Imaging rupture-prone vulnerable plaque will be of great help for both the presymptomatic detection of patients at risk for coronary events and the conclusive diagnosis of acute coronary syndrome in those with atypical chest symptoms.

Stents have enabled a much higher procedural success rate by compression and scaffolding of such culprit lesions, and excellent long-term patency has been achieved by using drug-eluting stents (DES). However, there still remain issues to be solved for better management of these patients, particularly those with very tight or calcified lesions, seriously depressed left ventricular (LV) function, or renal insufficiency. Primary PCI may be harmful due to complication with contrast-induced nephropathy, which is more frequent in AMI patients than in non-AMI patients (5.6% vs. 3.0%) [8]. AMI is reported to be a multivariate independent predictor of acute renal failure following PCI.

In PCI, DES have been reported to reduce the restenosis rate and target lesion or vessel revascularization (TLR or TVR) rate, and thereby major adverse cardiac events (MACE), compared to uncoated bare metal stents (BMS) [9-12]. However, it has also been reported that neoatherosclerosis, which may slowly develop in the stented segment with new lipid-laden atherogenic change over the stent struts, may limit blood flow, and hence diminish the advantage over BMS years after the procedure [13-15]. Whether this phenomenon holds true of second-generation DES, which is believed to have its polymers, antiproliferative agents, and stent platform improved, and have shown comparable or even better long-term outcomes with less frequent stent thrombosis (ST) [16-22], remains to be demonstrated. Whether these slow-developing stenotic changes may simply be delayed and develop over a longer interval of time with newer DES as "very late catch-up" remains unknown. Collection of 5-year follow-up data has just started [23].

In patients with AMI, emergency primary angioplasty to recanalize the occluded infarct-related artery (IRA) is currently regarded as the standard therapy for reducing cardiac mortality. In the balloon-only era, rapid closure of the infarct lesion often took place after balloon dilatation [24]. Stent implantation, by blocking lesion recoil, proved to be quite beneficial to overcome this phenomenon, avoiding time-

consuming repetitive balloon inflations until restoration of vessel patency. However, restenosis is still reported to be fairly frequent within a year of BMS implantation, particularly at the time of implantation in the proximal left anterior descending artery (LAD) compared with stenting in other coronary segments [25,26]. Currently, DES is used with more satisfactory TLR or TVR results during a 1- to 3-year follow-up period, although no significant difference in incidence of death or recurrent AMI has been observed between these two stent types [27-31]. Accumulated data, however, have instead shown a higher risk of ST in those treated with DES over a 1-year follow-up period [30-33]. Kalesan et al. [34] demonstrated in a meta-analysis that a year after AMI treatment, very late ST is significantly more likely to occur in patients receiving DES than in those with BMS placement. The large amount of intracoronary thrombus in patients with AMI may predispose them to stent malapposition due to stent undersizing or thrombus resolution. Stent malapposition at ruptured plaques has been confirmed on OCT images [35]; this may elevate the incidence of later ST, unless appropriate intimal coverage of the stent adluminal surface is achieved. This means that longer and more attentive management with steady antiplatelet treatment may be needed once patients with AMI are treated with DES. Recent studies showed that the frequencies of 5-year all-cause mortality, MACE, and overall ST were similar between those treated by DES and BMS, although DES significantly reduced TLR and TVR rates [36,37]. Surprisingly, DES was reported to increase cardiac mortality compared to BMS in one of those studies [37]. Even longer follow-up reports of DES placement, particularly for second-generation DES in AMI, are awaited. Self-expandable stents may be able to solve this problem by reducing malapposition and underexpansion, decreasing the risk of ST and restenosis [38]. The results are awaited from clinical trials using self-expandable stents in AMI [39].

Thrombus aspiration in primary PCI at the infarct lesion prior to coronary dilatation or stenting has been reported to reduce infarct size and 1-year mortality by improvement of myocardial perfusion [40-46]. However, the benefits of clot aspiration have been disputed by recent studies which demonstrated no reduction in the MACE rate in a longer 2- to 3-year follow-up period [47,48].

Bioresorbable vessel scaffolding (BVS) may be substituted for stents and may possibly require a shorter period of antiplatelet therapy [49,50]. There is much interest in how BVS interacts with clots and ruptured vulnerable plaque, and how it acts at bifurcating lesions when positioned over a side branch. Development of this device may also change the utilization of modalities which assist in judgment of the indication, lesion characteristics, and procedural endpoint among IVUS, OCT, and a pressure guidewire to measure fractional flow reserve (FFR). FFR has become an important modality to identify culprit lesions. The FAME study demonstrated that FFR measurement in patients with multivessel coronary artery disease can reduce mortality and AMI after two years compared to standard angiography-guided PCI, by deferring stent implantation in lesions showing FFR>0.80 in patients with stable angina and acute coronary syndrome [51,52].

The question of whether beta-blockers are able to additionally improve long-term clinical course remains to be further elucidated [53,54]. Beta-blockers are known to inhibit adverse arrhythmia [55] and are also known to improve LV contractility [56-58]. However, there are concerns regarding coronary vasoconstriction induction due to the beta-blocking effect on coronary vascular smooth muscle cells [59,60]. Coronary vasospasm is reported to be commonly induced early after AMI onset. Racial differences in its frequency were demonstrated by Pristipino et al. (2000) [61], in which Japanese patients showed more coronary vasospasm (80%) than Caucasians (still as high as 37% within 14 days of AMI onset) in spasm provocation test. A study with a small number of Japanese subjects reported that atenolol tended to increase provocative coronary vasospasm in both the IRA and non-IRA, although it did not reach statistical significance (Figure 1) [62].

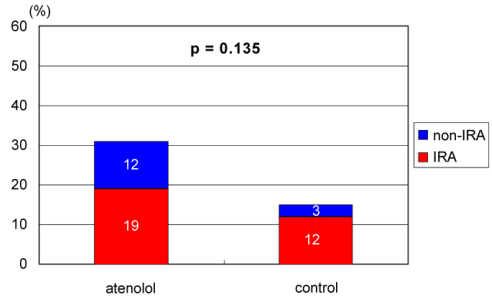

Figure 1: Frequency of inducible coronary vasospasm by ergonovine 4 weeks after AMI onset. IRA: infarct-related artery

We found that coronary vasoconstriction varied from 11% diameter stenosis to complete occlusion, and vasoconstriction with more than 60% diameter stenosis was more severe in the IRA than in non-IRA (Figure 2).

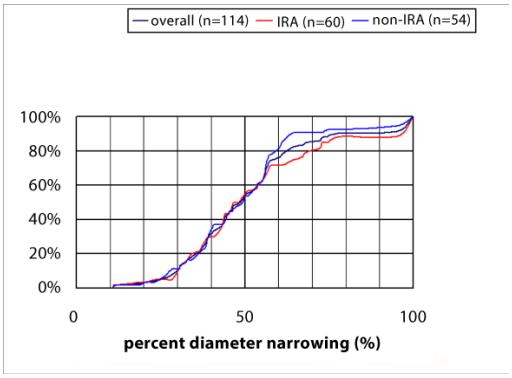

Figure 2: Cumulative frequency of percent diameter stenosis in the spasm provocation test in infarct-related artery and non-infarct-related artery. IRA: infarct-related artery

However, one of the adjusted multivariate predictors of vasospasm in non-IRA was the presence of rich collaterals to the infarct territory on the initial angiogram [63]. In such cases, special attention should be paid to avoid vasospasm in non-IRA, which supplies areas of preserved LV function remote from the infarct region, in order to prevent hemodynamic collapse. Thus, it is important to consider the possibility of beta-blockers inducing coronary spasm even after successful reperfusion. Their various cardiac effects need to also be taken into consideration, which diverge depending upon the pharmacological characteristics (e.g. beta1-adrenoceptor selectivity, intrinsic sympathomimetic activity) of each beta-blocking agent used. Their short- and long-term influence on AMI patients should be

evaluated in large-scale randomized trials, with attention paid to the agent(s) used and the racial background of subjects.

Anterior AMI involving the LAD is often associated, starting from its onset, with cardiac pump failure due to its broad supply of the myocardial area. It has also been reported that an anterior infarct is more likely to end with incomplete revascularization complicated with a no-reflow or slow flow phenomenon [64,65], which contributes to increase in infarct size and LV dysfunction [66,67]. As a consequence, a higher rate of reinfarction [66], ST [68], and mortality [25] can be anticipated. Thus, treatment of continuing heart failure is another issue which remains to be solved.

Percutaneous direct myocardial laser revascularization has been attempted to improve myocardial ischemia and thereby LV function by production of small myocardial channels in ischemic endocardial regions guided by electromechanical LV mapping. Although this treatment was helpful for increasing exercise duration and the time to onset of angina [69], it failed to improve LV ejection fraction [70].

A new type of pharmacological approach is generating much interest. The sinus node produces cardiac impulses via activation of I_f (funny) ionic current running through hyperpolarization and cyclic nucleotide (HCN)-gated channels. By selectively blocking these HCN channels, the heart rate has been reported to decrease by 20-30% without affecting ventricular contractility, peripheral vascular resistance, or intracardiac electrical conductance such as the PQ, QRS, and QT intervals [71]. This is in good contrast with beta-blockers and calcium channel blockers which influence multiple cardiovascular functions and may therefore induce adverse effects in patients with heart failure. Ivabradine, a selective I_f-pacemaker current blocker, was evaluated in heart failure patients with LV systolic dysfunction (ejection fraction <35%) in sinus rhythm with a heart rate >70bpm (SHIFT study). This placebo-controlled randomized study demonstrated that ivabradine significantly reduced composite of cardiovascular death and hospital admission for worsening heart failure [72]. With its beneficial anti-anginal and anti-ischemic effects [73], this agent may provide a favorable long-term clinical scenario and improved quality of life for patients after AMI.

Cell therapy is now becoming an attractive field in the treatment of chronic heart failure and restoration of LV function after AMI. Many attempts using a variety of cell origins (e.g. autologous bone marrow cells, peripheral blood stem cells) have been reported; however, the long-term beneficial effects remain controversial, including concerns about promoting intimal hyperplasia following coronary intervention [74-84]. New technologies such as surgical coverage of the damaged LV with a myocardial sheet produced by autologous cell culture or transformation of induced pluripotent stem cells [85,86] may emerge as promising therapeutic options. Together with basic translational research, rapid but solid development in this field is awaited with great hope and expectation.

A number of issues remain to be solved in the treatment of AMI. We hope that many exciting studies will be performed to develop new diagnostic and therapeutic methods. Such advancements will surely contribute to more efficient clinical practice to improve the long-term management of patients with AMI.

References

1. Lemos PA, Farooq V, Takimura CK, Gutierrez PS, Virmani R, et al. (2013) Emerging technologies: polymer-free phospholipid encapsulated sirolimus nanocarriers for the controlled release of drug from a stent-plus-balloon or a stand-alone balloon catheter. EuroIntervention 9: 148-156.
2. Naghavi M, Libby P, Falk E, Casscells SW, Litovsky S, et al. (2003) From vulnerable plaque to vulnerable patient: a call for new definitions and risk assessment strategies: Part I. Circulation 108: 1664-1672.
3. Patwari P, Weissman NJ, Boppart SA, Jesser C, Stamper D, et al. (2000) Assessment of coronary plaque with optical coherence tomography and high-frequency ultrasound. Am J Cardiol 85: 641-644.
4. Jang IK, Bouma BE, Kang DH, Park SJ, Park SW, et al. (2002) Visualization of coronary atherosclerotic plaques in patients using optical coherence tomography: comparison with intravascular ultrasound. J Am Coll Cardiol 39: 604-609.
5. Sánchez-Elvira G, Coma-Canella I, Artaiz M, Páramo JA, Barba J, et al. (2010) Characterization of coronary plaques with combined use of intravascular ultrasound, virtual histology and optical coherence tomography. Heart Int 5: e12.
6. Pundziute G, Schuijf JD, Jukema JW, Decramer I, Sarno G, et al. (2008) Evaluation of plaque characteristics in acute coronary syndromes: non-invasive assessment with multi-slice computed tomography and invasive evaluation with intravascular ultrasound radiofrequency data analysis. Eur Heart J 29: 2373-2381.
7. Briley-Saebo KC, Mulder WJ, Mani V, Hyafil F, Amirbekian V, et al. (2007) Magnetic resonance imaging of vulnerable atherosclerotic plaques: current imaging strategies and molecular imaging probes. J Magn Reson Imaging 26: 460-479.
8. Rihal CS, Textor SC, Grill DE, Berger PB, Ting HH, et al. (2002) Incidence and prognostic importance of acute renal failure after percutaneous coronary intervention. Circulation 105: 2259-2264.
9. Applegate RJ, Sacrinty MT, Kutcher MA, Santos RM, Gandhi SK, et al. (2009) Effect of length and diameter of drug-eluting stents versus bare-metal stents on late outcomes. Circ Cardiovasc Interv 2: 35-42.
10. Bangalore S, Kumar S, Fusaro M, Amoroso N, Attubato MJ, et al. (2012) Short- and long-term outcomes with drug-eluting and bare-metal coronary stents: a mixed-treatment comparison analysis of 117,762 patient-years of follow-up from randomized trials. Circulation 125: 2873-2891.
11. Applegate RJ, Sacrinty MT, Kutcher MA, Santos RM, Gandhi SK, et al. (2009) 3-year comparison of drug-eluting versus bare-metal stents. JACC Cardiovasc Interv 2: 231-239.
12. Tsai TT, Messenger JC, Brennan JM, Patel UD, Dai D, et al. (2011) Safety and efficacy of drug-eluting stents in older patients with chronic kidney disease: a report from the linked CathPCI Registry-CMS claims database. J Am Coll Cardiol 58: 1859-1869.
13. Kang SJ, Mintz GS, Akasaka T, Park DW, Lee JY, et al. (2011) Optical coherence tomographic analysis of in-stent neoatherosclerosis after drug-eluting stent implantation. Circulation 123: 2954-2963.
14. Nakazawa G, Otsuka F, Nakano M, Vorpahl M, Yazdani SK, et al. (2011) The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. J Am Coll Cardiol 57: 1314-1322.
15. Yonetsu T, Kato K, Kim SJ, Xing L, Jia H, et al. (2012) Predictors for neoatherosclerosis: a retrospective observational study from the optical coherence tomography registry. Circ Cardiovasc Imaging 5: 660-666.
16. Kedhi E, Gomes ME, Lagerqvist B, Smith JG, Omerovic E, et al. (2012) Clinical impact of second-generation everolimus-eluting stent compared with first-generation drug-eluting stents in diabetes mellitus patients: insights from a nationwide coronary intervention register. JACC Cardiovasc Interv 5: 1141-1149.
17. Simsek C, Räber L, Magro M, Boersma E, Onuma Y, et al. (2013) Long-term outcome of the unrestricted use of everolimus-eluting stents compared to sirolimus-eluting stents and paclitaxel-eluting stents in diabetic patients: the Bern-Rotterdam diabetes cohort study. Int J Cardiol 170: 36-42.
18. Jensen LO, Thayssen P, Hansen HS, Christiansen EH, Tilsted HH, et al. (2012) Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary

intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation 125: 1246-1255.

19. Räber L, Jüni P, Nüesch E, Kalesan B, Wenaweser P, et al. (2011) Long-term comparison of everolimus-eluting and sirolimus-eluting stents for coronary revascularization. J Am Coll Cardiol 57: 2143-2151.
20. Danzi GB, Chevalier B, Urban P, Fath-Ordoubadi F, Carrie D, et al. (2012) Clinical performance of a drug-eluting stent with a biodegradable polymer in an unselected patient population: the NOBORI 2 study. EuroIntervention 8: 109-116.
21. Klauss V, Serruys PW, Pilgrim T, Buszman P, Linke A, et al. (2011) 2-year clinical follow-up from the randomized comparison of biolimus-eluting stents with biodegradable polymer and sirolimus-eluting stents with durable polymer in routine clinical practice. JACC Cardiovasc Interv 4: 887-895.
22. Tada T, Byrne RA1, Simunovic I1, King LA1, Cassese S1, et al. (2013) Risk of stent thrombosis among bare-metal stents, first-generation drug-eluting stents, and second-generation drug-eluting stents: results from a registry of 18,334 patients. JACC Cardiovasc Interv 6: 1267-1274.
23. Gada H, Kirtane AJ, Newman W2, Sanz M3, Hermiller JB4, et al. (2013) 5-year results of a randomized comparison of XIENCE V everolimus-eluting and TAXUS paclitaxel-eluting stents: final results from the SPIRIT III trial (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 6: 1263-1266.
24. Shirotani M, Yui Y, Hattori R, Morishita H, Kawai C, et al. (1993) Emergency coronary angioplasty for acute myocardial infarction: predictors of early occlusion of the infarct-related artery after balloon inflation. Am Heart J 125: 931-938.
25. Shugman IM, Hee L, Mussap CJ, Diu P, Lo S, et al. (2013) Bare-metal stenting of large coronary arteries in ST-elevation myocardial infarction is associated with low rates of target vessel revascularization. Am Heart J 165: 591-599.
26. Calais F, Lagerqvist B, Leppert J, James SK, Fröbert O (2013) Proximal coronary artery intervention: stent thrombosis, restenosis and death. Int J Cardiol 170: 227-232.
27. Spaulding C, Henry P, Teiger E, Beatt K, Bramucci E, et al. (2006) Sirolimus-eluting versus uncoated stents in acute myocardial infarction. N Engl J Med 355: 1093-1104.
28. Sabate M, Cequier A, Iñiguez A, Serra A, Hernandez-Antolin R, et al. (2012) Everolimus-eluting stent versus bare-metal stent in ST-segment elevation myocardial infarction (EXAMINATION): 1 year results of a randomised controlled trial. Lancet 380: 1482-1490.
29. Garro N, Capodanno D, Cammalleri V, Tamburino C (2008) Very late thrombosis in acute myocardial infarction: drug-eluting versus uncoated stents. EuroIntervention 4: 324-330.
30. Assali A, Vaduganathan M, Vaknin-Assa H, Lev EI, Brosh D, et al. (2012) Comparison of late (3-year) registry data outcomes using bare metal versus drug-eluting stents for treating ST-segment elevation acute myocardial infarctions. Am J Cardiol 109: 1563-1568.
31. De Luca G, Dirksen MT, Spaulding C, Kelbaek H, Schalij M, et al. (2012) Drug-eluting vs bare-metal stents in primary angioplasty: a pooled patient-level meta-analysis of randomized trials. Arch Intern Med 172: 611-621.
32. Brodie B, Pokharel Y, Garg A, Kissling G, Hansen C, et al. (2012) Predictors of early, late, and very late stent thrombosis after primary percutaneous coronary intervention with bare-metal and drug-eluting stents for ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 5: 1043-1051.
33. Kukreja N, Onuma Y, Garcia-Garcia HM, Daemen J, van Domburg R, et al. (2009) The risk of stent thrombosis in patients with acute coronary syndromes treated with bare-metal and drug-eluting stents. JACC Cardiovasc Interv 2: 534-541.
34. Kalesan B, Pilgrim T, Heinimann K, Räber L, Stefanini GG, et al. (2012) Comparison of drug-eluting stents with bare metal stents in patients with ST-segment elevation myocardial infarction. Eur Heart J 33: 977-987.
35. Räber L, Zanchin T, Baumgartner S, Taniwaki M, Kalesan B, et al. (2014) Differential healing response attributed to culprit lesions of patients with acute coronary syndromes and stable coronary artery after implantation of drug-eluting stents: an optical coherence tomography study. Int J Cardiol 173: 259-267.
36. Musto C, Fiorilli R, De Felice F, Patti G, Nazzaro MS, et al. (2013) Long-term outcome of sirolimus-eluting vs bare-metal stent in the setting of acute myocardial infarction: 5-year results of the SESAMI trial. Int J Cardiol 166: 399-403.
37. Holmvang L, Kelbæk H, Kaltoft A, Thuesen L, Lassen JF, et al. (2013) Long-term outcome after drug-eluting versus bare-metal stent implantation in patients with ST-segment elevation myocardial infarction: 5 years follow-up from the randomized DEDICATION trial (Drug Elution and Distal Protection in Acute Myocardial Infarction). JACC Cardiovasc Interv 6: 548-553.
38. van Geuns RJ, Tamburino C, Fajadet J, Vrolix M, Witzenbichler B, et al. (2012) Self-expanding versus balloon-expandable stents in acute myocardial infarction: results from the APPOSITION II study: self-expanding stents in ST-segment elevation myocardial infarction. JACC Cardiovasc Interv 5: 1209-1219.
39. Giacchi G, La Manna A, Tamburino C, Capodanno D, Capranzano P, et al. (2014) Self-apposing STENTYS® stent in acute myocardial infarction. Minerva Cardioangiol 62: 59-70.
40. Liistro F, Grotti S, Angioli P, Falsini G, Ducci K, et al. (2009) Impact of thrombus aspiration on myocardial tissue reperfusion and left ventricular functional recovery and remodeling after primary angioplasty. Circ Cardiovasc Interv 2: 376-383.
41. Svilaas T, Vlaar PJ, van der Horst IC, Diercks GF, de Smet BJ, et al. (2008) Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 358: 557-567.
42. Sardella G, Mancone M, Canali E, Di Roma A, Benedetti G, et al. (2010) Impact of thrombectomy with EXPort Catheter in Infarct-Related Artery during Primary Percutaneous Coronary Intervention (EXPIRA Trial) on cardiac death. Am J Cardiol 106: 624-629.
43. Sardella G, Mancone M, Bucciarelli-Ducci C, Agati L, Scardala R, et al. (2009) Thrombus aspiration during primary percutaneous coronary intervention improves myocardial reperfusion and reduces infarct size: the EXPIRA (thrombectomy with export catheter in infarct-related artery during primary percutaneous coronary intervention) prospective, randomized trial. J Am Coll Cardiol 53: 309-315.
44. Vlaar PJ, Svilaas T, van der Horst IC, Diercks GF, Fokkema ML, et al. (2008) Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet 371: 1915-1920.
45. Moriel M, Matetzky S, Segev A, Medina A, Kornowski R, et al. (2014) Aspiration thrombectomy in patients with ST elevation myocardial infarction undergoing primary percutaneous coronary intervention (from the Acute Coronary Syndrome Israeli Survey 2010). Am J Cardiol 113: 809-814.
46. Kikkert WJ, Claessen BE, van Geloven N, Baan J Jr, Vis MM, et al. (2013) Adjunctive thrombus aspiration versus conventional percutaneous coronary intervention in ST-elevation myocardial infarction. Catheter Cardiovasc Interv 81: 922-929.
47. Vink MA, Dirksen MT, Tijssen JG, Suttorp MJ, Patterson MS, et al. (2012) Lack of long-term clinical benefit of thrombus aspiration during primary percutaneous coronary intervention with paclitaxel-eluting stents or bare-metal stents: post-hoc analysis of the PASSION-trial. Catheter Cardiovasc Interv 79: 870-877.
48. Nilsen DW, Mehran R, Wu RS, Yu J, Nordrehaug JE, et al. (2013) Coronary reperfusion and clinical outcomes after thrombus aspiration during primary percutaneous coronary intervention: findings from the HORIZONS-AMI trial. Catheter Cardiovasc Interv 82: 594-601.
49. Ormiston JA, Serruys PW, Onuma Y, van Geuns RJ, de Bruyne B, et al. (2012) First serial assessment at 6 months and 2 years of the second

generation of absorb everolimus-eluting bioresorbable vascular scaffold: a multi-imaging modality study. Circ Cardiovasc Interv 5: 620-632.

50. Muramatsu T, Onuma Y, García-García HM, Farooq V, Bourantas CV, et al. (2013) Incidence and short-term clinical outcomes of small side branch occlusion after implantation of an everolimus-eluting bioresorbable vascular scaffold: an interim report of 435 patients in the ABSORB-EXTEND single-arm trial in comparison with an everolimus-eluting metallic stent in the SPIRIT first and II trials. JACC Cardiovasc Interv 6: 247-257.
51. Pijls NH, Fearon WF, Tonino PA, Siebert U, Ikeno F, et al. (2010) Fractional flow reserve versus angiography for guiding percutaneous coronary intervention in patients with multivessel coronary artery disease: 2-year follow-up of the FAME (Fractional Flow Reserve Versus Angiography for Multivessel Evaluation) study. J Am Coll Cardiol 56: 177-184.
52. Sels JW, Tonino PA, Siebert U, Fearon WF, Van't Veer M, et al. (2011) Fractional flow reserve in unstable angina and non-ST-segment elevation myocardial infarction experience from the FAME (Fractional flow reserve versus Angiography for Multivessel Evaluation) study. JACC Cardiovasc Interv 4: 1183-1189.
53. Ozasa N, Morimoto T, Bao B, Furukawa Y, Nakagawa Y, et al. (2013) Î²-blocker use in patients after percutaneous coronary interventions: one size fits all? Worse outcomes in patients without myocardial infarction or heart failure. Int J Cardiol 168: 774-779.
54. Rochon PA, Tu JV, Anderson GM, Gurwitz JH, Clark JP, et al. (2000) Rate of heart failure and 1-year survival for older people receiving low-dose beta-blocker therapy after myocardial infarction. Lancet 356: 639-644.
55. Valle JA, Zhang M, Dixon S, Aronow HD, Share D, et al. (2013) Impact of pre-procedural beta blockade on inpatient mortality in patients undergoing primary percutaneous coronary intervention for ST elevation myocardial infarction. Am J Cardiol 111: 1714-1720.
56. Basu S, Senior R, Raval U, van der Does R, Bruckner T, et al. (1997) Beneficial effects of intravenous and oral carvedilol treatment in acute myocardial infarction. A placebo-controlled, randomized trial. Circulation 96: 183-191.
57. Senior R, Basu S, Kinsey C, Schaeffer S, Lahiri A (1999) Carvedilol prevents remodeling in patients with left ventricular dysfunction after acute myocardial infarction. Am Heart J 137: 646-652.
58. Poulsen SH, Jensen SE, Egstrup K (1999) Effects of long-term adrenergic beta-blockade on left ventricular diastolic filling in patients with acute myocardial infarction. Am Heart J 138: 710-720.
59. Robertson RM, Wood AJ, Vaughn WK, Robertson D (1982) Exacerbation of vasotonic angina pectoris by propranolol. Circulation 65: 281-285.
60. Tilmant PY, Lablanche JM, Thieuleux FA, Dupuis BA, Bertrand ME (1983) Detrimental effect of propranolol in patients with coronary arterial spasm countered by combination with diltiazem. Am J Cardiol 52: 230-233.
61. Pristipino C, Beltrame JF, Finocchiaro ML, Hattori R, Fujita M, et al. (2000) Major racial differences in coronary constrictor response between japanese and caucasians with recent myocardial infarction. Circulation 101: 1102-1108.
62. Shirotani M, Yokota R, Kouchi I, Hirai T, Uemori N, et al. (2010) Influence of atenolol on coronary artery spasm after acute myocardial infarction in a Japanese population. Int J Cardiol 139: 181-186.
63. Shirotani M, Yokota R, Kouchi I, Hirai T, Uemori N, et al. (2011) Quantitative assessment for angiographic results of coronary spasm provocation test performed among Japanese patients in the chronic stage of acute myocardial infarction. Kokyu To Junkan 59:625-629.
64. Ayhan E, Isik T, Uyarel H, Ergelen M, Cicek G, et al. (2013) The impact of NT-proBNP on admission for early risk stratification of patients undergoing primary percutaneous coronary intervention. Kardiol Pol 71: 165-175.
65. Caixeta A, Lansky AJ, Mehran R, Brener SJ, Claessen B, et al. (2013) Predictors of suboptimal TIMI flow after primary angioplasty for acute myocardial infarction: results from the HORIZONS-AMI trial. EuroIntervention 9: 220-227.
66. Kandzari DE, Tcheng JE, Gersh BJ, Cox DA, Stuckey T, et al. (2006) Relationship between infarct artery location, epicardial flow, and myocardial perfusion after primary percutaneous revascularization in acute myocardial infarction. Am Heart J 151: 1288-1295.
67. Palmerini T, Brener SJ, Genereux P, Maehara A, Della Riva D, et al. (2013) Relation between white blood cell count and final infarct size in patients with ST-segment elevation acute myocardial infarction undergoing primary percutaneous coronary intervention (from the INFUSE AMI trial). Am J Cardiol 112: 1860-1866.
68. Brugaletta S, Sabate M, Martin-Yuste V, Masotti M, Shiratori Y, et al. (2013) Predictors and clinical implications of stent thrombosis in patients with ST-segment elevation myocardial infarction: Insights from the EXAMINATION trial. Int J Cardiol 168: 2632-2636.
69. Kornowski R, Baim DS, Moses JW, Hong MK, Laham RJ, et al. (2000) Short- and intermediate-term clinical outcomes from direct myocardial laser revascularization guided by biosense left ventricular electromechanical mapping. Circulation 102: 1120-1125.
70. Salem M, Rotevatn S, Nordrehaug JE (2006) Long-term results following percutaneous myocardial laser therapy. Coron Artery Dis 17: 385-390.
71. Scicchitano P, Carbonara S, Ricci G, Mandurino C, Locorotondo M, et al. (2012) HCN channels and heart rate. Molecules 17: 4225-4235.
72. Scicchitano P, Cortese F, Ricci G, Carbonara S, Moncelli M, et al. (2014) Ivabradine, coronary artery disease, and heart failure: beyond rhythm control. Drug Des Devel Ther 8: 689-700.
73. Tardif JC, Ponikowski P, Kahan T; ASSOCIATE Study Investigators (2009) Efficacy of the I(f) current inhibitor ivabradine in patients with chronic stable angina receiving beta-blocker therapy: a 4-month, randomized, placebo-controlled trial. Eur Heart J 30: 540-548.
74. Tendera M, Wojakowski W, Ruzyo W, Chojnowska L, Kepka C, et al. (2009) Intracoronary infusion of bone marrow-derived selected CD34+CXCR4+ cells and non-selected mononuclear cells in patients with acute STEMI and reduced left ventricular ejection fraction: results of randomized, multicentre Myocardial Regeneration by Intracoronary Infusion of Selected Population of Stem Cells in Acute Myocardial Infarction (REGENT) Trial. Eur Heart J 30: 1313-1321.
75. Meyer GP, Wollert KC, Lotz J, Steffens J, Lippolt P, et al. (2006) Intracoronary bone marrow cell transfer after myocardial infarction: eighteen months' follow-up data from the randomized, controlled BOOST (BOne marrOw transfer to enhance ST-elevation infarct regeneration) trial. Circulation 113: 1287-1294.
76. Yousef M, Schannwell CM, Köstering M, Zeus T, Brehm M, et al. (2009) The BALANCE Study: clinical benefit and long-term outcome after intracoronary autologous bone marrow cell transplantation in patients with acute myocardial infarction. J Am Coll Cardiol 53: 2262-2269.
77. Meyer GP1, Wollert KC, Lotz J, Pirr J, Rager U, et al. (2009) Intracoronary bone marrow cell transfer after myocardial infarction: 5-year follow-up from the randomized-controlled BOOST trial. See comment in PubMed Commons below Eur Heart J 30: 2978-2984.
78. Kandala J, Upadhyay GA, Pokushalov E, Wu S, Drachman DE, et al. (2013) Meta-analysis of stem cell therapy in chronic ischemic cardiomyopathy. Am J Cardiol 112: 217-225.
79. Huikuri HV, Kervinen K, Niemelä M, Ylitalo K, Säily M, et al. (2008) Effects of intracoronary injection of mononuclear bone marrow cells on left ventricular function, arrhythmia risk profile, and restenosis after thrombolytic therapy of acute myocardial infarction. Eur Heart J 29: 2723-2732.
80. Sürder D, Manka R, Lo Cicero V, Moccetti T, Rufibach K, et al. (2013) Intracoronary injection of bone marrow-derived mononuclear cells early or late after acute myocardial infarction: effects on global left ventricular function. Circulation 127: 1968-1979.
81. Cao F, Sun D, Li C, Narsinh K, Zhao L, et al. (2009) Long-term myocardial functional improvement after autologous bone marrow mononuclear cells transplantation in patients with ST-segment elevation myocardial infarction: 4 years follow-up. Eur Heart J 30: 1986-1994.

82. Bolli R, Chugh AR, D'Amario D, Loughran JH, Stoddard MF, et al. (2011) Cardiac stem cells in patients with ischaemic cardiomyopathy (SCIPIO): initial results of a randomised phase 1 trial. Lancet 378: 1847-1857.

83. Kang HJ, Kim HS, Zhang SY, Park KW, Cho HJ, et al. (2004) Effects of intracoronary infusion of peripheral blood stem-cells mobilised with granulocyte-colony stimulating factor on left ventricular systolic function and restenosis after coronary stenting in myocardial infarction: the MAGIC cell randomised clinical trial. Lancet 363: 751-756.

84. Kang HJ, Kim MK, Lee HY, Park KW, Lee W, et al. (2012) Five-year results of intracoronary infusion of the mobilized peripheral blood stem cells by granulocyte colony-stimulating factor in patients with myocardial infarction. Eur Heart J 33: 3062-3069.

85. Miki K, Uenaka H, Saito A, Miyagawa S, Sakaguchi T, et al. (2012) Bioengineered myocardium derived from induced pluripotent stem cells improves cardiac function and attenuates cardiac remodeling following chronic myocardial infarction in rats. Stem Cells Transl Med 1: 430-437.

86. Sawa Y, Miyagawa S (2013) Present and future perspectives on cell sheet-based myocardial regeneration therapy. Biomed Res Int 2013: 583912.