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CARDIOVASCULAR DISEASE AND STROKE (P PERRONE-FILARDI AND S. AGEWALL, SECTION EDITORS)

Acute Revascularization in ST-Segment-Elevation Myocardial Infarction

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Abstract We briefly and comprehensively present some of the novel findings in the field of revascularization therapy and management of ST-segment-elevation myocardial infarction (STEMI). We highlight the latest evidence-based advancements in the pharmacological and mechanical treatment of patients who presented with STEMI. Since the last updates to the international guidelines (American College of Cardiology/American Heart Association and the European Society of Cardiology) were published in 2011 and 2012, there have been changes and several important studies have presented their final outcomes. We also highlight some controversial approaches as part of the current debates in the cardiology community. In addition, we share our recent experience in the field of biodegradable scaffold stents as a treatment strategy in STEMI.

Keywords Acute revascularization · Myocardial infarction · Percutaneous coronary intervention · Fibrinolysis · Antiplatelet therapy · Balloon angioplasty · Stenting · Direct stenting · Bioresorbable vascular scaffold · Biodegradable stent · Multivessel disease · Bypass grafting

Introduction

Coronary heart disease (CHD) is leading cause of morbidity and mortality in the USA and Europe. This led to more than 20 years of unremitting effort by the medical community to change the organization and priorities of health care and to redirect research and investments toward the field of cardiovascular treatment and care. As a consequence of that effort, we are witnessing a decrease in mortality, which is a milestone of contemporary health care. Multiple novel findings from various randomized clinical trials and meta-analyses have helped to establish and refine current evidence-based treatment of acute coronary syndromes (ACS).

The era of reperfusion therapy is marked by significant evolution of devices and treatment approaches (invasive treatment and pharmacological agents). Clinical trials have confirmed a reduction of restenosis and target lesion revascularization by use of drug-eluting stents (DES), without increasing the risk of stent thrombosis. That led to the preferential use of DES in most percutaneous coronary interventions (PCI), including in patients who presented with ST-segment-elevation myocardial infarction (STEMI). Despite the excellent outcomes achieved with modern DES, associated with very low risk of stent thrombosis, work is continuing in the field of fully biodegradable scaffolds. Improving anticoagulation and antiplatelet medication and optimizing treatment strategies is still one of the main goals of contemporary cardiology.

ACS: Morbidity and Mortality

According to heart disease statistics [1] published in an updated report from the American Heart Association, CHD was an underlying cause of death in approximately one in every six deaths in the USA in 2010. Approximately 80 % of people who die of CHD are older than 65 years. According to data from the US National Registry of Myocardial Infarction, from 1990 to 2006 in-hospital acute myocardial infarction (AMI) mortality declined from 10.4 to 6.3 %, and particularly for STEMI, it declined from 11.5 to 8.0 %. In addition, the percentage of ACS or myocardial infarction patients with ST-segment elevation appears to be declining. In an analysis of 46,086 hospitalizations for ACS in the Kaiser Permanent Northern California study, the percentage of myocardial infarction patients with ST-segment elevation decreased from

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47.0 to 22.9 % between 1999 and 2008 [2]. In Europe, the annual incidence of hospital admission of patients with AMI is about 1,900 per million population, with an STEMI incidence of about 800 per million. The in-hospital mortality of all consecutive STEMI patients ranges between 4.2 and 13.5 % [3]. The tendency of decreasing mortality is confirmed by reports from different national registries, such as Fast-MI in France [4] and ALKK in Germany.

Organization and Emergency Treatment of Patients with AMI

According to European Society of Cardiology (ESC) guidelines for the management of AMI in patients presenting with STEMI [5], reperfusion should be performed as early as possible. For patients presenting in PCI-capable hospitals, the time delay (door-to-balloon time) should be less than 60 min from the first medical contact (FMC), with a maximum delay of 90 min after FMC (according to the American College of Cardiology Foundation/American Heart Association) [5]. This led to ongoing effort to optimize emergency and clinical care. The European Association of Percutaneous Cardiovascular Intervention, EuroPCR, and the ESC Working Group on Acute Cardiac Care, in collaboration with EUCOMED, launched the Stent for Life Initiative. The mission is to improve the delivery and patient access to the lifesaving indications of primary PCI (pPCI), thereby reducing the morbidity and mortality. The benefit of implementation of pPCI as early as possible for patients presenting with STEMI compared with reperfusion by thrombolytic treatment is proved and enshrined in the clinical guidelines. Direct transfer from the FMC site to the nearest PCI-capable hospital, bypassing the nearest non-PCI-capable hospital, is essential to minimize the time delays. Catheterization laboratory staff work must be organized to provide an immediate PCI service 24 h a day, 7 days a week [6]. In a comparison of patients with pre-hospital-ECG-diagnosed STEMI undergoing emergency department evaluation and those bypassing the emergency department, a recently conducted study shows significant shorter reperfusion time, numerically lower mortality rates, and lower frequency of heart failure and shock on presentation [7]. An interesting paradox was demonstrated by Cancannon et al. [8]. They show that in some regions in the USA, the PCI-capable hospitals are duplicative and the increase in their number has not increased access to PCI for patients with STEMI. Public campaigns, emergency medical services organized as networks, according to infrastructure and geographical features, and improving treatment protocols are still some of the main topics and definitely will have further impact on overall clinical outcomes.

Fibrinolytic Therapy: Indications, Fibrinolysis Versus PCI, and Role of PCI After Fibrinolysis

Since pPCI was shown to be better than thrombolytic therapy at reducing overall short-term death, nonfatal reinfarction, and stroke, including the long-term events [9], it became the preferred and recommended treatment strategy in the setting of STEMI [5]. However, many STEMI patients present in a non-PCI-capable hospital for different reasons (health care organization, climate or traffic condition, geographical features, etc.) and do not receive mechanical reperfusion in the recommended timeframe. In patients with sudden (less than 12 h) onset of symptoms and without contraindications, when pPCI cannot be performed within 90–120 min from FMC, fibrinolytic therapy is recommended. All patients treated with fibrinolytic therapy in a non-PCI-capable hospital or before admission to a hospital must be transferred to a PCI-capable hospital for rescue PCI or routine coronarography [5, 11]. The outcomes from this pharmacoinvasive strategy were proved to be noninferior and comparable to those obtained with transfer for primary angioplasty. However, fibrinolysis was associated with a slightly increased risk of intracranial bleeding [10, 11].

Considering antiplatelet therapy as an addition to fibrinolytic therapy in STEMI, the newer $P2Y_{12}$ receptor antagonists (prasugrel and ticagrelor) have not been studied. The Combination of aspirin and clopidogrel is recommended. The use of parenteral anticoagulation during and after fibrinolytic therapy is improving coronary patency [5].

Stenting Versus Plain Old Balloon Angioplasty

A prospective, randomized trial by Suryapranata et al. [12] shows that primary stenting can be applied safely and effectively in selected patients with AMI, with a significant reduction in recurrent myocardial infarction and subsequent target-vessel revascularization compared with balloon angioplasty. Long-term follow-up, performed by Sasao et al. [13], shows that after 1 year in the stent group (17.1 %), compared with the plain old balloon angioplasty (POBA) group (39.0 %), there was a significantly lower incidence of the combined clinical end points (death, nonfatal myocardial infarction, coronary artery bypass graft surgery, repeat coronary angioplasty of the target lesion and nonculprit lesions, congestive heart failure, and cerebrovascular events). After 5 years' follow-up, there were no significant differences in mortality, congestive heart failure, myocardial infarction, or cerebrovascular events between the stent and POBA groups. However, the incidence of the combined clinical end points in the stent group (34.1 %) was significantly lower than that in the POBA group (61.0 %). The main reason for the difference in the rate of events between the stent and POBA groups was the higher incidence of target lesion revascularization in the POBA group, due to

restenosis or reocclusion of the infarct-related artery (IRA) at 1 year compared with the stent group. It remained unchanged at 5 years.

These findings, as well as those of previous studies, suggest that the long-term outcome of patients with AMI treated by successful primary stenting is superior to that of patients treated with optimal (stent-like) primary balloon angioplasty without stenting.

Direct Stenting Versus Balloon Predilatation in STEMI

According to the ESC guidelines, stent implantation during pPCI in patients with STEMI was approved as the preferred revascularization strategy. Möckel et al. [14] compared direct stenting with conventional stent implantation with balloon predilatation. This large study based on the Harmonizing Outcomes with Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial shows that direct stenting compared with conventional stenting was associated with a significantly lower rate of all-cause death (1.6 % vs 3.8 %) and stroke (0.3 % vs 1.1 %), with nonsignificant differences in the rates of target lesion revascularization, myocardial infarction, stent thrombosis, and major bleeding. The death rate at 1 year remained significantly lower in the direct-stenting group.

Previous smaller studies have suggested that direct stenting in STEMI is feasible and may result in less distal embolization with reduced microcirculatory dysfunction and no reflow [15]. Also, direct stenting is associated with decreased use of balloons and is equivalent to the standard technique in terms of 6-month clinical outcomes when performed on selected coronary lesions without significant calcification [16].

DES Versus Bare Metal Stents

The safety and efficacy of different stent types in STEMI patients is still a hot topic. A recently published meta-analysis of Palmerini et al. [17] compared the various stent types [first-generation and second-generation DES and bare meal stents (BMS)] for patients with STEMI, and provided evidence that confirmed the superiority of DES over BMS. In total, 12,453 randomized patients were analyzed. The risk of 1-year cardiac death, myocardial infarction, and stent thrombosis with second-generation everolimus-eluting stents (EES) compared with BMS was assessed as significantly lower. That was apparent as early as at 30 days' follow-up as the rates of early stent thrombosis were significantly lower with EES compared with BMS and first-generation paclitaxel-eluting stents. This was maintained up to 2 years' follow-up. However, early-generation DES compared with BMS for STEMI have clearly reduced the need for target vessel revascularization, but have been associated with an increased risk of very late stent thrombosis, prompting further discussions and raising concerns about their safety [18].

New-Generation DES

In the last few years we have witnessing dynamic evolution of stent systems. New-generation DES are using novel antiproliferative agents and modern platforms, which provide better deliverability and flexibility, as well as novel drug carrier systems, including biodegradable scaffolds. A number of studies are investigating their safety and effectiveness.

Park et al. [19] demonstrated the superiority of second-generation EES compared with sirolimus-eluting stents by the reduction in the risk of target vessel revascularization and stent thrombosis, with no significant differences in the risk of cardiac death or myocardial infarction. Consistent results with EES were recently demonstrated in another multicenter, randomized controlled trial—EXAMINATION [20]. This compares the implantation of EES with a cobalt–chromium stent with the same metallic platform but not containing any drug or polymer in patients with STEMI.

The safety and efficacy of second-generation EES versus zotarolimus-eluting stents was recently investigated by analyzing the EXCELLENT and RESOLUTE-Korea registries [21]. Both types of stents showed comparable outcomes at 1 year of follow-up, including the risk of stent thrombosis.

The recently published final 3-year report of the RESOLUTE international study [22], evaluating the safety and effectiveness of zotarolimus-eluting stents compared with EES, shows a total very late stent thrombosis rate of 1.1 % through 3 years. The rate of cardiac death and target vessel myocardial infarction was 7 %, a result consistent with the results of previously reported trials.

The early clinical outcomes from studies investigating the use of biodegradable scaffolds in patients with STEMI are encouraging (see the next section).

Biodegradable Vascular Scaffold Stents in STEMI

In a recent published meta analysis, biodegradable polymer DES appear superior to paclitaxel-eluting stents and sirolimus-eluting stents for definite stent thrombosis, but are inferior to cobalt–chromium EES for long-term safety (definite stent thrombosis). Also, the mortality rate was increased in the biodegradable vascular scaffold stent (BVSS) group [23].

Implantation of BVSS in patients with STEMI has not been well studied. Nevertheless, early outcomes are already available. The prospective multicenter study Prague-19 suggest that BVSS implantation in acute STEMI is feasible and safe

and could be potentially used in a larger proportion of patients. The short-term clinical outcomes are encouraging, but will require longer follow-up [24•, 25].

The future outcomes from studies comparing the safety and efficacy of new-generation DES with a durable polymer and with a biodegradable scaffold will be important.

Multivessel Disease in STEMI (PCI of a Noninfarct Artery at the Time of pPCI in Patients with STEMI)

Depending on the baseline characteristics of the study population, the rate of multivessel artery disease in patients presenting with STEMI is 41–67 %. Despite current guidelines on the management of STEMI, which recommend PCI only on the IRA (or culprit artery) in hemodynamic stable patients [26], "real-life" treatment strategies still differ widely, and the decision-making is very complex and should be individualized. A review article from 2011 very comprehensively summarizes the international experience, from an aggressive approach, which treats all significant lesions in the acute phase of pPCI, through the intermediate approach with staged procedures with pPCI on the culprit artery and other lesions treated later during the hospital stay or within the first month following discharge to a conservative approach with pPCI only of the IRA and medical treatment of significant lesions of the noninfarct arteries [27••]. Nevertheless none of the current studies is large enough to provide a definite answer, and the findings are controversial. Toma et al. [28] identified all subjects in the APEX-AMI trial with multivessel disease who underwent PCI in a non-IRA. The outcomes show that intervention on the nonculprit artery at the time of a pPCI procedure is associated with worse clinical outcome, including a twofold increase in the rate of 90-day death. According to the ESC guidelines in patients with cardiogenic shock in the presence of multiple, critical (90 % or more) stenoses or highly unstable lesions, and if there is persistent ischemia after PCI of the supposed culprit lesion, multivessel PCI is justified [26].

Nevertheless, Wald et al. [29] enrolled 465 patients with acute STEMI and multivessel disease, 234 of which received preventive PCI. After the completion of PCI in the infarct artery, patients were randomized to undergo no further PCI procedures or to undergo immediate preventive PCI in non-IRA with a major stenosis of more than 50 %. The finding suggests that the use of "preventive" PCI immediately after PCI in the infarct artery is superior over not performing this additional procedure. However, the findings do not address the question of immediate versus delayed (staged) preventive PCI before discharge [28]. Several related studies are currently ongoing. One such study is led by D. Wood (http://clinicaltrialsfeeds.org/clinical-trials/show/NCT01065103), and another is led by O. Hlinomaz, and L. Groch (the PRAGUE-13 study), but no results are available.

Dual Antiplatelet Therapy Regimens

The currently preferred dual antiplatelet therapy (DAPT) in patients with ACS consists of ticagrelor, prasugrel, and clopidogrel (class I recommendation) in combination with aspirin. Priority is given to the first two ADP-receptor blockers, but prasugrel is recommended only in patients undergoing PCI (ESC guidelines). Several large trials are comparing the different antiplatelet agents.

The TRITON-TIMI 38 trial shows that in patients with STEMI undergoing PCI, prasugrel is superior and more effective than clopidogrel for prevention of ischemic events. Prasugrel was associated with a significant risk reduction in the primary (cardiovascular death, nonfatal myocardial infarction, or stroke) and secondary (target vessel revascularization and stent thrombosis) end points, albeit with significant increase in the rates of major bleeding, life-threatening bleeding, and fatal bleeding. Rapid inhibition of platelet aggregation is desirable for pPCI in patients with STEMI; therefore, a loading dose of 60 mg prasugrel, followed by 10 mg prasugrel daily, than loading dose of 600 mg clopidogrel, followed by 75 mg daily, makes prasugrel the preferred treatment if there is no history of prior stroke or transient ischemic attack and in patients younger than 75 years of age [30]. The reason is that prasugrel achieves faster, more consistent, and greater inhibition of ADP-induced platelet aggregation.

Ticagrelor is the first reversibly binding orally administered $P2Y_{12}$ receptor antagonist. The PLATO trial demonstrated that treatment with ticagrelor compared with clopidogrel reduced the risk of death resulting from vascular causes, myocardial infarction or stroke, and stent thrombosis during 12 months without increasing the overall risk of major bleeding. Steg et al. [31] analyzed a subgroup of patients from the PLATO trial with STEMI treated with pPCI. The outcomes show that the effects of ticagrelor compared with clopidogrel were consistent with those seen in the overall PLATO trial, but with a higher rate of stroke. The rate of major bleeding was similar.

The duration of DAPT after STEMI treated by pPCI with implantation of a DES should be at least 12 months. Despite official recommendations, the risk as opposed to the benefit of prolonged DAPT remains controversial. Valgimigli et al. [32] in their meta-analysis that compares prolonged DAPT (12–24 months) with short-term DAPT (6–12 months) found no significant difference in ischemic end points, including the composite of cardiac and noncardiac death and myocardial infarction with or without stroke. Also, there was no reduction of definite/probable stent thrombosis in the long-term DAPT

group. In addition, they found a twofold higher rate of major bleeding events and stroke in the long-term DAPT group.

Periprocedural Drug Therapy: Bivalirudin Versus Unfractioned Heparin/Glycoprotein IIa/IIIb

With the optimization of devices for mechanical treatment of coronary arteries, there has been a significant improvement in the adjunctive pharmacological therapy.

Antiplatelet therapy is playing an important role not only in the long-term management of CAD, but also as a periprocedural therapy. The use of glycoprotein IIb/IIIa inhibitors is narrowing, and is acceptable only in high-risk STEMI patients with a high thrombus burden [33]. Still in discussion is the optimal administration route (intracoronary versus intravenous). According to the results of the AIDA STEMI trial, intracoronary administration as compared with intravenous administration of abciximab does not result in a difference in the combined end point of death, reinfarction, or congestive heart failure [34].

HORIZONS-AMI is a large randomized clinical trial, and together with other studies has consistently suggested the superiority of bivalirudin over combination therapy with unfractioned heparin (UFH) and glycoprotein IIa/IIIb inhibitors as adjunctive therapy in patients with STEMI. According to the results of this trial, bivalirudin treatment was associated with reduced rates of major bleeding, mortality, and reinfarction, including the 3-year follow-up [35]. That approach received a class 1b recommendation in the American College of Cardiology Foundation/American Heart Association guidelines. However, the study compares bivalirudin alone with the combination of unfractioned heparin and glycoprotein IIa/IIIb inhibitors. In contrast, a retrospective analysis from Sweden's SCAAR database revealed no benefit from using monotherapy with bivalirudin, rather than unfractioned heparin. Several randomized trials are under way, but no results are available (VALIDATE–SWEDEHEART, HEAT–PPCI), but surely they will be essential.

Cangrelor is useful as a short-acting intravenously administered ADP-receptor blocker in more specific clinical situations. For example, in patients waiting to undergo open-heart surgery, cangrelor has been shown to result in consistent platelet inhibition without a significant increase in bleeding. As compared with clopidogrel administered immediately before or after PCI, cangrelor significantly reduced the rate of periprocedural complications of PCI, including stent thrombosis, without a significant increase in severe bleeding [36].

The Role of Coronary Artery Bypass Graft Surgery in STEMI

Timely coronary reperfusion is one of the main goals in the treatment of patients with STEMI. Coronary angiography as a first-line treatment strategy also identifies patients eligible for coronary artery bypass grafting (CABG) revascularization during the acute and subacute phase of STEMI. Rarely, the coronary anatomy is unsuitable for PCI, and CABG is used as the primary reperfusion therapy either in the acute phase or after cardiopulmonary stabilization [37]. More often in clinical practice, CABG is used as a definitive or adjunctive revascularization strategy after pPCI. Indication criteria are defined in the international guidelines. Fourteen years ago, Stone et al. [38] reported 11 % of patients required CABG during hospitalization. Today the proportion is only 5.5 %. However, CABG is playing a major role and is an integral component, especially in a high-risk group of STEMI patients with severer coronary findings and hemodynamic instability. Despite a high incidence of surgical complications, the clinical outcomes from a study by Gu et al. [37] show excellent 30-day and 1-year follow-up results. Nikolsky et al. [39] analyzed a cohort of patients with ACS and prior CABG from the ACUITY trial. They were treated with early invasive strategy and a contemporary antithrombin regimen (bivalirudin), but had a substantially worse prognosis than patients without prior CABG, especially if PCI or (repeat) CABG was required. In addition, bivalirudin monotherapy was acceptable treatment, but did not improve their prognosis.

Future Treatment Strategies in STEMI

What changes can be expected in STEMI treatment during next 5–10 years? The greatest room for improvement of patient outcomes still lies in improved logistics: (1) the knowledge of the population of AMI symptoms should be improved to allow very early (within the first 1–2 h) reperfusion therapy; (2) the networks of emergency services, smaller hospitals, and PCI centers should be organized effectively (e.g., the population per center should be between 300,000 and one million, and patients with a ECG diagnosis of STEMI should always be transported directly to the catheterization laboratory). Technological improvements may include biodegradable vascular scaffolds, very safe DES (allowing early interruption of aggressive antithrombotic therapies), improved thrombectomy devices (may be cardiologists may learn here from neuroradiologists), etc. Improvements in pharmacotherapy will come with refined antithrombotic strategies both in the acute phase and in the long term. And last, but not least, further improvements in prevention and in early diagnosis (in the phase of unstable angina or non-STEMI) will certainly further decrease the numbers of STEMI patients, thus improving overall outcomes of all ACS.

Conclusion

Even with the decreased rate of mortality, the optimal treatment strategy for patients presenting with STEMI still remains a challenge. Direct transportation to PCI-capable hospitals, bypassing the emergency department, and performing mechanical reperfusion as early as possible have brought about significant improvements in outcomes. Fibrinolytic therapy followed by rescue PCI or routine coronarography is the recommended reperfusion therapy in cases when pPCI cannot be performed. Concerning the safety and efficacy of the different stent types, there have also been serious advances. Different studies have confirmed the superiority of DES over BMS. However, research is continuing in the field to find better antiproliferative agents and modern platforms, including fully biodegradable scaffolds. Despite the guideline recommendations, optimal adjunctive pharmacological therapy is still a hot topic. New-generation oral antiplatelet therapy shows significant advancement in the acute phase and in long-term treatment, and the administration of glycoprotein IIb/IIIa inhibitors is narrowing. Regarding the outcomes of different clinical trials, administration of bivalirudin remains controversial. The indication of surgical revascularization as an adjunctive or definitive revascularization strategy is defined in the guidelines. However, more effective prehospital and clinical management together with expansion of the knowledge of the population will definitely bring future benefits.

Compliance with Ethics Guidelines

Conflict of Interest XPetko Prodanov declares that he has no conflict of interest.

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