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The Great Debate: "Primary PCI for STEMI: an emergency!"

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On the opening day of EuroPCR 2014 the Great Debate saw chairman Thomas Cuisset and the four panellists Sajidah Khan, Maciej Lesiak, Flavio Ribichini and Julian Strange discussing "Primary PCI for STEMI: an emergency!". The topic was selected ahead of the session by the interventional cardiology community via a vote on the EuroPCR website. The session was designed to touch on the main and current controversies in delivering effective and timely primary PCI, with the panel selected from different countries to reflect the varied practice seen across the globe. Following a short case presentation of an acute STEMI patient, the debate started by discussing the vascular access site of choice for primary PCI. The speed of access and the importance of reducing bleeding complications were recognised as the most important factors in deciding access route. The learning curve to master radial access was also mentioned, but the evidence from the RIVAL study[1], which demonstrated a reduction in mortality in the radial STEMI group compared to femoral, was compelling. The general consensus in STEMI was that radial access was the preferred strategy driven by the reduction in both bleeding and access-site complications.

Although the radial approach reduces access-site complications substantially, there was recognition that the access site accounts for fewer than half of all bleeding events in STEMI patients. Since bleeding increases the risk of major adverse cardiovascular events (MACE), including cardiovascular death, all reasonable measures should be taken to avoid it. This may be particularly difficult in the setting of patients with high thrombotic risk where aggressive antithrombotic and antiplatelet therapy drives gastrointestinal, intracranial and other non-access-site bleeding. Multiple trials have aimed to assess the efficacy and safety of bivalirudin, a direct thrombin inhibitor, in replacing unfractionated heparin (UFH) combined with routine or bail-out infusion of glycoprotein (GP) IIb/IIIa inhibitors[2,3]. In the HORIZONS-AMI multicentre randomised trial, bivalirudin used instead of UFH plus routine GP IIb/IIIa inhibitor significantly reduced the rate of major bleeding (by 40%), which translated into a substantial reduction of cardiovascular death assessed at 30 days, as well as after three years. In the EUROMAX trial, a large randomised study of pre-hospital use of bivalirudin vs. heparin with bail-out GP IIb/IIIa inhibitor use in both arms, bivalirudin again proved to be safer and significantly reduced the bleeding rate by more than 50 percent, with no influence on mortality[3]. Both trials showed an increase in stent thrombosis in the bivalirudin group, although this did not translate into a higher risk of repeated infarction or cardiovascular death. Of note, PCI via the radial artery was performed in 47% of EUROMAX patients, and bivalirudin also significantly reduced bleeding among them.

These positive data have been challenged by the results of the HEAT-PPCI trial, recently presented during the annual ACC scientific session in Washington[4]. Akin to the other two, the trial compared bivalirudin with the use of UFH in STEMI patients treated with PPCI. GP IIb/IIIa inhibitors were used as a bail-out in both arms. To the surprise of the attendees, this single-centre, randomised trial showed no advantage of bivalirudin in the reduction of bleeding, and a substantial excess of MACE, including a fourfold increase in stent thrombosis. These results led to a heated debate during and after the session. Multiple issues were addressed, such as single site only, drug underdosing, no events adjudication, high rate of radial approach and bail-out GP IIb/IIIa use. What is more, shortly before the ACC session another bivalirudin trial was presented during the China Interventional Therapeutics meeting in Shanghai. The BRIGHT trial enrolled more than two thousand STEMI patients, and compared bivalirudin with heparin alone or heparin plus GP IIb/IIIa inhibitors. At 30 days, net adverse cardiovascular events were significantly reduced in patients receiving bivalirudin vs. UFH/GPI, and almost reached statistical significance compared against UFH monotherapy. Bleeding events were reduced in both bivalirudin arms by 50% to 60%.

During the Debate an increased risk of stent thrombosis observed in bivalirudin-treated patients was discussed. This phenomenon is confined to the acute phase, with the average time of occurrence being two to four hours after the procedure, and may be avoided by prolonged drug infusion at the same PCI dose. In practice, this means continuing the infusion to finish the vial already opened during the procedure. It is important to note that no excess in bleedings was observed with this strategy.

An important additional factor which may influence the occurrence of early stent thrombosis is the delayed effects of oral

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antiplatelet agents. New-generation drugs such as prasugrel and ticagrelor, which in healthy volunteers give the desired blocking effect within 30 minutes of administration, did not exhibit such a quick response in patients with acute myocardial infarction. As noted by Dr Lesiak, factors such as hypotension, vomiting and widespread use of morphine slow peristalsis and significantly delay the absorption of these drugs. Currently, primary PCI procedures are carried out very quickly and patients may leave the cathlab after just 30 minutes. Dr Strange noted that bivalirudin infusion stop at this point leads to a vulnerable window with the increased risk of stent thrombosis. Both Dr Ribichini and Dr Strange agreed that P2Y12 receptor blockers, including the new-generation ones, should be administered as early as possible, even though we do not yet have convincing evidence justifying their use in the pre-hospital phase, and despite the increased risk of bleeding complications. Additionally, this period of hyperreactivity could theoretically be covered by a GP IIb/IIIa inhibitor. However, this class of drug is rarely used in combination with bivalirudin except in the setting of very heavy thrombus burden or no-reflow. As mentioned by Dr Lesiak, another solution might be the use of a new intravenous P2Y12 receptor blocker cangrelor, which should gain approval in Europe later this year. This drug starts to act very quickly, straight after infusion, and will potentially be an excellent complement to the oral agents.

Another controversy that has recently been raised is the use of thromboaspiration (TA) as a routine adjunct to primary PCI. This procedure, recommended in current guidelines (class IIa, level of evidence B) has been shown to have no effect on 30-day mortality in a recent large multicentre randomised trial[5]. In the TASTE study, a total of 7,244 STEMI patients from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) were enrolled and randomised to TA or PCI only. The primary endpoint – death of any cause after 30 days – occurred in 2.8% of patients in the TA group and 3.0% of patients who received only PCI (p=NS). During the Debate a couple of issues regarding the study were discussed. Earlier, multiple randomised studies, registries and meta-analyses have consistently demonstrated that TA improves the flow in the infarct-related artery, enhancing myocardial perfusion and reducing infarct size or the size of microvascular obstruction detected by magnetic resonance imaging. The choice of all-cause mortality after 30 days for the primary endpoint is somewhat surprising, since none of the previous studies has shown significant mortality reduction in such a short time. The largest one (TAPAS), in contrast to its significant 12-month mortality reduction in the TA group, showed that the 30-day mortality was unaffected. Instead, it demonstrated significant improvement in important angiographic and ECG indicators of myocardial reperfusion[6]. It is unclear why the authors of TASTE neglected such simple measures: flow in the culprit vessel, ST-segment resolution or biomarker infarct size reduction. A further interesting issue is the number of subjects excluded from randomisation. During enrolment, 40% of patients presenting with STEMI were not randomised (a quarter of these patients underwent thromboaspiration). One of the reasons indicated by operators was the belief that thromboaspiration was definitely indicated, which meant that many of those who potentially might have benefited most were excluded! Although justified from an ethical standpoint, this strategy may have excluded the exact patient who may have driven the outcome of the study. Nevertheless, the TASTE study shows some positive trends towards reduction in the risk of recurrent MI and stent thrombosis at 30 days with thromboaspiration. While long-term clinical results from TASTE are awaited, all discussants agreed that this study would not influence their daily practice. Aspiration should be performed, in a proper manner, focusing on lesions where thrombus is angiographically visible or if there is no flow or slow flow after the culprit vessel has been wired. Following successful aspiration, ideally a stent should be directly implanted, since any additional vessel manipulation will increase the risk of distal embolisation. As for the stent choice, balloon-expandable drug-eluting stents are most commonly used, but there is more and more interest in the new devices such as self-expandable or mesh-covered stents. The use of bioabsorbable scaffolds is also promising, especially in young patients, but, considering the presence of thrombus and flow disorders, an adequate stent sizing may be difficult.

Returning to the initial case presentation where the patient had a non-culprit lesion in another vessel, the optimal strategy to deal with this disease was discussed. It is recognised that forty percent of non-shocked STEMI patients have multivessel disease, and the role of immediate multivessel PCI versus culprit only was debated. The PRAMI study[7] looked specifically at this point, comparing immediate complete revascularisation of any lesion greater than 50% versus symptom-led revascularisation of the non-culprit lesions. This UK multicentre study, published in the New England Journal of Medicine, was stopped early not only having reached the primary endpoints of death, myocardial infarction and refractory angina, but also displaying an excess number of events in the conservative arm. The study highlighted the importance of the non-culprit disease. Despite this, it was agreed by the panel that it had not changed their routine practice and did not actually reflect the current practice of assessing the functional significance of the non-culprit disease. What was interesting was the timing of non-culprit revascularisation with the final aim of all panellists to deliver complete revascularisation. For the critical lesion the timing was straightforward, with the patient receiving intervention during the same admission. In less critical lesions, practices varied, with some discharging patients and only offering PCI to those with evidence of functional significance on subsequent non-invasive testing. This strategy was compared to a staged in-patient fractional flow reserve driven PCI, the final choice being a pragmatic decision by the panellists and influenced by their own institutional policies.

In the last part of the Debate, the experts tried to find the answer to the question as to how to ensure the most effective reperfusion across the world. While in Europe and other developed countries primary PCI is the preferred strategy, in developing regions thrombolysis is still the only possible treatment option. This was best expressed by Sajidah Khan, who works in South Africa, who said that "The most powerful method of reducing mortality is to use

whatever method you have at hand to treat the patient within three hours, because that is the window of greatest opportunity for treatment to impact on survival and outcomes". The bulk of coronary artery disease mortality is shifting to middle and low income countries of Asia and Africa, and it is no coincidence that in these regions the availability of cardiac interventions is the lowest or none, with the number of cathlabs being less than one per million persons. This is why the maintaining of alternative strategies of reperfusion is so important. Thrombolysis is, of course, one of these strategies, and in some cases may be followed by late intervention. Numerous studies, including the recent STREAM Trial[8], have shown the equivalence between a pharmacoinvasive strategy and primary PCI if timely access to the cathlab is problematic. The timing of drug administration is critical. To achieve optimal effect, thrombolysis should be given pre-hospital. In the recently published five-year outcome of the French FAST-MI registry, pre-hospital administration of thrombolytics was associated with lower mortality compared with primary PCI, whereas in-hospital administration was associated with a trend towards higher five-year mortality[9]. In most European countries there are an overwhelming number of invasive centres that provide a very timely primary PCI service, so thrombolysis plays just a marginal role. The most important issues are an early diagnosis and a prompt direct transfer to a cathlab without any intermediate stops.

As expected, the Great Debate attracted the attention of many EuroPCR participants, who occupied the vast majority of the Main Arena. Lively discussion and excellent interaction between the experts and the audience made the debate a great show. It was impossible to answer all the questions, but the main objective was achieved: experts debating the most significant and controversial issues and, importantly, providing clear explanations based on their own experience in the treatment of patients with STEMI. These personal and practical comments will surely help attending physicians in making difficult decisions in their daily practice. In the current world the optimal management of acute myocardial infarction depends on the resources and geography, but early reperfusion, no matter how it is obtained, is the most important factor in determining patient outcome. Further components of the therapeutic process should be tailored to the individual patient.

Conflict of interest statement

The authors have no conflicts of interest to declare.

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