CURRENT TOPIC

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Is there enough evidence for routine use of drug-eluting stents in acute myocardial infarction with ST segment elevation?

Da li ima dovoljno dokaza za rutinsko korišćenje stentova obloženih lekom u akutnom infarktu miokarda sa ST elevacijom?

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Introduction

Primary percutaneous coronary intervention (PPCI) is defined as angioplasty with or without stent implantation, with no prior or concomitant fibrinolytic therapy [1]. PPCI compared with medical therapy is a method of choice in the treatment of acute myocardial infarction with ST-segment elevation (STEMI), significantly reducing mortality and reischemia [1]. Implantation of bare metal stent (BMS) on the culprit lesion in STEMI is associated with a reduced incidence of target vessel revascularization (TVR), but is not associated with a reduced mortality and reinfarction compared to primary balloon dilatation of a culprit lesion [2]. Although some authors question the rate of restenosis of BMS in STEMI due to different patophysiological process, plaque rupture and formation of thrombus, restenosis in STEMI patients occurs in more than 20% of patients [2, 3]. The advantage of drug-eluting stents (DES) compared to BMS to prevent coronary restenosis in a variety of patients is proved in elective procedures [4, 5], while in the treatment of STEMI is still controversial, due to the lack of randomized studies with a duration of follow-up more than one year. Thus, at the moment there is a debate weather DES should be used in PPCI routinely.

STEMI is an independent stent thrombosis (ST) predictor both for BMS and DES especially when the complex lesions are treated (ostial and bifurcation lesions) [6–9]. This can be explained by prothrombotic state, hemodynamic changes (cardiogenic shock), stent apposition and insufficient expansion of the stent. Also, it is shown on autopsy that DES postpones endothelization of ruptured plaque, which is a primary cause of late ST, with persistent fibrin deposition compared to BMS [10]. Because of a longer duration of arterial healing of ruptured plaque (> 1 year) compared to stable plaque [8], safety of DES in STEMI patients cannot be determined in short term studies. Observational studies have indicated the existence of an increased risk in emerging late and very late (> 1 year) ST associated with the use of the first generation of DES [11], especially for indications that are different from those approved by the U.S. Food and Drug Administration (FDA) ("off-label" DES indications), which includes STEMI [12]. However, recent results from randomized trials, meta-analysis and registries, with short and intermediate duration of follow-up have demonstrated that the selection of the second generation of DES in STEMI is safe since there is no difference in mortality and reinfarction compared to the BMS group with a significant reduction in TVR.

Randomized studies using sirolimus-eluting stents

In a randomized prospective study, Single High Dose Bolus Tirofiban and Sirolimus Eluting Stent *vs* Abciximab and Bare Metal Stent in Myocardial Infarction (STRATEGY) [13], with follow-up of 8 months, the primary objectives (death, myocardial infarction, stroke and TVR) were significantly lower in the sirolimus-eluting stents (SES) group than in the BMS group (18% *vs* 32%, $p = 0.04$) primarily due to less TVR in the SES group compared to the BMS group (7% *vs* 20%, $p = 0.01$). The limitations of the study were: involvement of single center, small sample size (even though only 12% of consecutive patients were not enrolled in the study) and the same choice of stent and glycoprotein IIb/IIIa. To overcome the above limitations, the same group of authors presented the Multicentre Evaluation of Single High-

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Dose Bolus Tirofiban *vs* Abciximab With Sirolimus-eluting Stent or Bare Metal Stent in Acute Myocardial Infarction Study (MULTISTRATEGY) trial [14], where a sample of 745 patients were first randomly assigned to either abciximab or tirofiban and then to SES or BMS. After 8 months, major adverse cardiac events (MACE), composite of death of any cause, reinfarction, and clinically driven TVR, was significantly different in the SES compared to the BMS group (7.8% *vs* 14.5%, $p = 0.004$), also due to lower rate of TVR (3.2% *vs* 10.2%, $p < 0.001$) [14]. Composite endpoint of death, reinfarction and ST was comparable between the two groups at the end of 8 months follow-up [14]. ST did not differ significantly between the two groups even though dual antiplatelet therapy was given in SES group for at least 3 months and sensitive classification (definite/probable/possible) of ST was used [14].

Similar results were seen in the randomized Trial to Assess the Use of the Cypher Stent in Acute Myocardial Infarction Treated with Balloon Angioplasty (TYPHOON) study, which included 712 STEMI patients with a follow-up period of 12 months [15]. The primary endpoint-target vessel failure (defined as target-vessel-related death, reinfarction or TVR) was significantly reduced in the SES than in the BMS arm (7.3% *vs*14.3%, $p = 0.004$) which was again primarily due to reduced rates of TVR in the SES compared to the BMS group (5.6% *vs* 13.4%, $p < 0.001$) [15]. The rate of acute and subacute ST did not differ between the two arms after the first year of follow-up [15]. Recently the same group of authors presented that after 4 years there were no significant differences in definite or probable ST, freedom from reinfarction and cardiac death in the SES group compared to the BMS group, while freedom from target lesion revascularization (TLR) was significantly better in the SES group [16].

Randomized trials using paclitaxel-eluting stents in STEMI

The Paclitaxel-eluting Stents *vs* Bare Metal Stents in Myocardial Infarction with ST-segment Elevation (PASSION) study that included 619 STEMI patients randomized to paclitaxel-eluting stent (PES) or BMS [17], with a 12-month follow-up period, did not show a statistically significant difference in primary events (death, myocardial infarction, TVR) between PES and BMS groups (12.8% *vs* 8.8%, $p = 0.12$) [17]. TVR between the PES and BMS groups was not statistically significant (5.3% *vs* 7.8%), probably due to a low percentage of patients with diabetes (11%), more limited selection of angiographic characteristics (larger vessel diameter) and the absence of angiographic follow-up. The percentage of ST was not statistically significant between the PES and BMS groups after one year [17]. At 5 years, the occurrence of the composite of cardiac death, recurrent myocardial infarction, or TLR was comparable in the PES and BMS arm (18.6% *vs* 21.8%, $p = 0.28$), as also the incidence of definite or probable ST (4.2% *vs* 3.4%, $p = 0.68$) [18].

Safety and efficacy of PES stents in STEMI has been proved so in far the largest published randomized trial Harmonizing Outcomes with Revascularization and Stents in AMI (HORIZONS-AMI), involving 3006 STEMI patients [19]. After 12 months, the PES group compared to the BMS group had a significantly lower TLR (4.5% *vs* 7.5%, $p = 0.002$), and TVR (5.8% *vs* 8.7%, $p = 0.006$). The mortality and ST was similar between the PES and BMS group [19]. At 3 years, the major findings from the stent part of the trial were that the PES seemed safe in STEMI with a significantly lower ischaemia-driven TVR in the PES arm [20]. There were no significant differences in the rates of death, reinfarction, stroke [20]. ST was similar in both groups – around 5% [20]. In the intravascular ultrasound substudy of HORIZONS-AMI, it was shown that acute stent malapposition was similar in PES and BMS treated lesions, but late acquired stent malapposition was more common in PES treated lesions and it was due to positive remodeling and plaque/thrombus resolution [21]. However, either acute stent malapposition or late acquired stent malapposition were not associated with adverse cardiac events at one year [21]. A recent optical coherence tomography study shows that PES significantly reduces neointimal hyperplasia, but results in higher rates of uncovered and malapposed stent struts and different healing response of the ruptured plaque at a 13-month follow-up [22]. Still, studies are needed to determine the relationship between these optical coherence tomography observations and long-term adverse clinical events.

Randomized trials using the second generation of drug-eluting stents in STEMI

Since the first generation of SES and PES raised safety concerns after the first year [23, 24], second generation of DES brought novel improved biocompatible and biodegradable polymers [25], new antiproliferative agents and designs which might increase biocompatibility therefore improving long term efficacy and safety profile. Thus, patients with STEMI might benefit from the second generation of DES [26].

Drug Elution and Distal Protection in Acute Myocardial Infarction (DEDICATION) trial included 626 patients from the two centers [27]. The primary endpoint was the loss of luminal diameter in the infarct-related lesion determined using quantitative coronary angiography at 8 months. Stents implanted in the DES group were SES in 47%, PES in 40% and zotarolimus-eluting stents in 13% [27]. While the primary endpoint was in favor of DES (late lumen loss 0.06 ± 0.66 mm *vs* 0.47 ± 0.69 mm, $p < 0.001$), there was a strong tendency toward a higher cardiac death in the DES group (4.2% *vs* 1.6%, $p = 0.09$) [27]. TLR was lower in the DES arm (5.1% *vs* 13.1%, $p = 0.001$), while ST rates were similar in the two groups (2.0% *vs* 2.6%, $p = 0.72$) [27]. Inclusion criteria in this trial were less strict with a higher rate of patients with complex lesions, older patients, more stents per patient implanted and stented longer segments of the coronary arteries compared to the other studies [27]. After 3 years the rate of all-cause mortality was not statistically different while the cardiac death was significantly higher in DES group (6.1% *vs* 1.9%, $p = 0.01$) which was contrary to previous studies [28]. MACE was still significantly higher in the BMS arm (18.2% *vs* 11.5%, $p = 0.02$) due to a higher TVR [28].

The Evaluation of the Xience-V Stent in Acute Myocardial Infarction (EXAMINATION) trial presented novel data with the second generation of cobalt-chromium everolimus-eluting stent (CoCr-EES) in STEMI [29]. The author stated that "all-comers" design of the study with wide inclusion and less exclusion criteria will be a representative sample for "real world" population. Patients were randomized 1:1 on either CoCr-EES or BMS [29]. There were no differences in primary endpoint (all-cause death, reinfarction or revascularization), cardiac death and reinfarction between the two groups. Although the study failed to reach its primary endpoint, there were benefits in using EES since TVR and TLR were significantly lower in CoCr-EES compared to BMS arm, while definite ST was significantly higher in the BMS group (1.9% *vs* 0.5%, $p = 0.01$) [29]. However, this trial was not powered to show differences of ST and thus whether those findings are real or attributable to chance remain uncertain [29, 30]. Still, these results are similar to the result of recent meta-analysis that CoCr-EES had also reduced ST compared with BMS [30]. These results support the safety and efficacy of CoCr-EES in a representative sample of STEMI patients especially in preventing the early ST rate with the use of second generation DES [29]. A recent nonrandomized study, which evaluated the safety and effectiveness of the second generation of CoCr-EES in patients with acute myocardial infarction (AMI) with a patient without AMI showed at 1 year low clinical event rates in these two groups [31]. Comparing with elective procedures, the rates of ST at one year were 1.08% vs. 0.85% and late ST (30 days-1 year) were 0.31% *vs* 0.47%, (AMI *vs* non-AMI, all p = ns) [31]. Even though the sample size of AMI patients was small, low ST rates associated with CoCr-EES use in both non-AMI and AMI patients in this study are consistent with previous randomized controlled trials such as Clinical Evaluation of the XIENCE V Everolinus Eluting Coronary Stent System (SPIRIT) IV [32] and EXAMINATION [31].

A recent meta analysis has presented that CoCr-EES is associated with a significant reduction in definite ST compared with BMS and other first and second generation DES including PES, SES, resolute zotarolimus and phosphorylcholine polymer-based zotarolimus eluting stent at a 1-year follow-up [25]. In the same meta-analysis it was presented that only CoCr-EES showed a significant reduction of definite ST compared with BMS at a 2-years follow-up [25]. The authors stated that the results are consistent with the result of experimental studies, which compared EES with BMS, showing that a lower rate of ST in EES is due to the design and material (reduced stent strut thickness, use of a cobalt-chromium and platinum-chromium alloys instead of stainless steel) and durable, fluorinated and thromboresistant polymer [25]. It is of note, that even SES were also associated with significantly lower 1-year rates of definite ST compared to the BMS, but it was not maintained at 2 year follow-up [25]. However, larger and adequately powered randomized trials with longer follow-up in STEMI setting are needed to eliminate concerns of safety of these devices compared to BMS and with other DES.

The latest Comparison of Biolimus Eluted From an Erodible Stent Coating With Bare Metal Stents in Acute ST-Elevation Myocardial Infarction (COMFORTABLE AMI) trial included STEMI patients randomly assigned on a 1:1 basis to treatment with biolimus-eluting stents (BES) from a biodegradable polylactic acid polymer or BMS [33]. The primary endpoint of the study was the device-oriented composite of cardiac death, reinfarction, and ischemia-driven TLR at 1 year [33]. Major adverse cardiac events at 1 year occurred in 4.3% of patients receiving BES and 8.7% patients receiving BMS ($p = 0.004$) [33]. It was due to lower risk of target vessel reinfarction ($p = 0.01$) and ischemia driven TLR ($p = 0.001$) in patients receiving BES compared with those receiving BMS. The rates of cardiac death were not significantly different while ST occurred in 5 patients treated with BES and 12 patients ($p = 0.10$) treated with BMS [33]. The second generation DES–BES with biodegradable polymers provide controlled drug release with subsequent degradation of polymer contrary to durable polymer coatings for drug release of the first generation DES, which might be a trigger for the late ST [26, 34]. This might improve long-term clinical outcomes beyond 1 year by reducing the risk of ST by 80% compared to the first generation DES [26, 33, 34].

Similar to patients with stable angina, no randomized studies have demonstrated the effectiveness of DES in lowering the rates of cardiac death and myocardial infarction compared to BMS arms in STEMI patients. Also, current trials do not bring enough evidence concerning benefits of DES compared to BMS in STEMI patients as in the elective procedures when DES is proved to be more effective (long lesions, small vessels, diabetic patients). On the other hand, these randomized studies clearly indicate the safe use of DES in STEMI patients and a reduced TVR in the DES group, without a significant difference in cardiac death, reinfarction and ST after 1-year follow-up. Meta-analyses of these randomized studies also present that DES significantly reduce TVR compared to BMS, without an increase in death, reinfarction, or ST within 1 [35] and 2 years of the index procedure [25, 26, 37]. However, a long-term analysis at 3 to 5 years after the procedure showed that the use of the first generation DES in STEMI is associated with an excess of very late thrombotic complications [23] which occurred more likely in the DES group compared to the BMS arm.

The second generation DES might overcome very late thrombotic complication due to novel improved biocompatible and biodegradable polymers, new antiproliferative agents and designs, as a result patients with STEMI might benefit from these devices [25, 26, 34, 38]. Both Examination and Comfortable trials are not statistically powered neither have long-time follow-up to provide definite answer about safety of second generation DES. To be statistically powered to detect the difference in low-frequency events such as very late ST between available DES, there is a need for randomized trial which would include as many as 10,000 patients in STEMI setting. Consequently, the results from observational data, meta analysis and randomized trials between different DES devices in stable angina and acute coronary syndrome presented that second generation DES are more effective and

with increased safety compared with either BMS or the first generation of DES, which should lead to greatly improved outcomes in patient with AIM [24–26, 34, 39–41].

Conclusion

The efficacy of DES compared to BMS in reducing in-stent restenosis and repeat intervention within one year was shown in many randomized studies, registries and meta-analysis, therefore further studies comparing the efficacy of DES to BMS might not be needed in the setting of AMI. Although no significant difference in mortality, reinfarction and ST was shown in DES compared to BMS, late safety issues with DES are mostly related to the first generation of DES. Observational data, meta-analysis and randomized trials with the second generation of DES devices have showed better efficacy with increased safety compared with either BMS or the first generation of DES leading to the conclusion that the second generation of DES should be the "first choice" in STEMI setting.

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