Original Research Article

Study of efficacy and safety of drug eluting stent versus bare metal stent in ST elevation MI

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ABSTRACT

Background: The present study was conducted with the aim of determining whether drug-eluting stents are superior to uncoated stents in the setting of primary PCI in terms of occurrence of serious adverse cardiac events.
Methods: In this prospective, single blind, randomized study, 20 to 80 years old patients with acute myocardial infarction with ST-segment elevation with >30 minutes of chest pain and at least 1 mm of ST-segment elevation in at least two standard leads or a new LBBB or 2 mm of ST-segment elevation in at least two contiguous leads were included. Patients were randomly assigned to receive either drug eluting stent (DES) (Everolimus Eluting stent, Endevour-Medtronics) or bare metal stent (BMS, Cordis-Dx sonic) in a 1:1 ratio. During follow ups at 30 days and 12 months, all serious adverse cardiac events like death from cardiac or non-cardiac cause, recurrent MI, revascularization of target vessel, coronary artery bypass grafting (CABG) or other intervention to target or non-target vessel etc. were recorded and compared between groups.
Results: No significant differences were found between the two treatment groups for occurrence of adverse events during first 30 days after the intervention. At one year follow-up, trends were observed in favor of the DES group, none of the differences were significant.
Conclusions: No significant benefit was observed with the use of Everolimus-eluting stents in primary PCI for acute myocardial infarction with ST-segment elevation, in comparison with baremetal stents.

Keywords: Adverse events, Bare metal stent, Drug eluting stent, STEMI

INTRODUCTION

Worldwide, coronary artery disease (CAD) is the single most frequent cause of death and have been topping the cause of death charts globally in the last 15 years. Over seven million people every year die from CAD, accounting for 12.8% of all deaths.[1] They have been contributing to the all-cause mortality in a major way in India as well, for a while now.[2] Infact, in comparison with the people of European ancestry, CAD affects Indians at least a decade earlier and in their most productive midlife years.[3] The treatment approach of acute myocardial (MI) has undergone major revolution over years, with the recognition of intracoronary thrombosis as the final mechanism of vessel occlusion and the understanding that prompt re-establishment of vessel patency offers significant clinical benefits. Percutaneous coronary intervention (PCI) was introduced in 1977.[4] Experience with this approach, coupled with improved technology, has made it possible to treat increasingly complex lesions and also patients with a history of clinically significant cardiac disease, risk

factors for coronary artery disease, coexisting conditions, or anatomical risk factors.[5] PCI now is the preferred reperfusion strategy for patients presenting with acute myocardial infarction with ST-segment elevation (STEMI).[6] Compared with balloon angioplasty, routine implantation of bare-metal stents has been associated with improved clinical outcome mainly because of the decreased risk for re-intervention. Nevertheless, restenosis remains an important limitation of the use of bare-metal stents in patients with acute myocardial infarction.[7]

Drug-eluting stents effectively reduce restenosis while maintaining a good safety profile in many lesion and patient groups.[6,7] However, concerns have been raised with regard to the safety of drug-eluting stents in patients with acute myocardial infarction.[8,9] Data from long term follow-up studies have suggested that implantation of drug-eluting stents during primary PCI could be associated with an increased risk for stent thrombosis, which is associated with high morbidity and mortality rates.[9,10] Studies have not been consistent in showing the superior effectiveness of drug-eluting stents, at least in the settings studied. Moreover, most of them had insufficient power to assess the risk of rare adverse events. [11-13]

The aim of present study was to determine whether drug-eluting stents are superior to uncoated stents in the setting of primary PCI in terms of occurrence of serious adverse cardiac events.

METHODS

This prospective, single blind, randomized study was performed at a cardiac care equipped facility in central India over two years. Patients between 20 and 80 years of age with acute myocardial infarction with ST-segment elevation with >30 minutes of chest pain and at least 1 mm of ST-segment elevation in at least two standard leads or a new LBBB or 2 mm of ST-segment elevation in at least two contiguous leads were included in the study. Patients must have been admitted either within 12 hours of onset of symptoms or between 12 and 24 hours with evidence of continuing ischemia.

The patients were excluded if they had received thrombolytic therapy, infarction was caused by in-stent thrombosis/restenosis, there was contraindication to usage of aspirin, or clopidogrel or both, cardiogenic shock was evident before randomization, estimated life expectancy was less than 12 months, history of previous MI, previously documented left ventricular ejection fraction (LVEF) less than 30%, or patients were participating in another clinical trial, apart from refusal to consent for the study.

All such patients were administered aspirin (at least 300 mg) and clopidogrel (300mg) at arrival at the hospital. A glycoprotein IIb/IIIa inhibitor was administered at the

discretion of operator. A bolus of 5000 IU unfractionated heparin was administered before the procedure. Coronary angiography (CAG) was performed through either radial or femoral artery with the use of standard techniques.

The trial protocol required visualization of culprit lesion before randomization in order to determine whether angiographic selection criteria were met. Randomization was therefore performed either immediately after CAG if the infarct related vessel was spontaneously patent, or after reestablishing coronary artery blood flow by the placement of guidewire or by balloon angioplasty. Criteria for angiographic exclusion were previous PCI of infarct related vessel, excessive tortuosity or calcification, ostial or multiple region lesion, massive thrombus in the infract related artery, lesion at the bifurcation or left main CAD and severe multi-vessel disease necessitating surgical revascularization. Patients were randomly assigned to receive either drug eluting stent (DES) (Everolimus Eluting stent, Endevour-Medtronics) or bare metal stent (BMS, Cordis-Dx sonic) in a 1:1 ratio.

Stents were deployed with a minimum pressure of 12 atm. If dissection or incomplete coverage of lesion occurred during deployment, additional strength of same type as assigned stent were used. Final angiography was performed to obtain views similar to those obtained before procedure. Epicardial blood flow in the infarct related artery before and after stent implantation was determined according to TIMI classification.[14]

All the patients were prescribed aspirin 150 mg OD for lifetime, clopidogrel 150mg OD daily for at least 6 months followed by 75 mg OD for further 6 months. Clinical follow up was performed for each patient through-out hospital stay and 30 days and 12 months after the procedure. During follow up all serious adverse cardiac events like death from cardiac or non-cardiac cause, recurrent MI, revascularization of target vessel, coronary artery bypass grafting (CABG) or other intervention to target or non-target vessel etc. were recorded.

All the end points of the study were adjusted in a blinded fashion. The primary end point was the first occurrence of a serious adverse cardiac event at 12 months, including death from cardiac cause, recurrent myocardial infarction requiring hospitalization, and ischemia-driven revascularization of a target lesion. All deaths were considered to have been from cardiac causes unless a non-cardiac cause could be identified. Recurrent myocardial infarction was defined by the development of either pathological Q wave lasting for at least 0.4 second in at least two contiguous leads or an increase in the creatine kinase level to more than twice the upper limit of normal with an elevation of the creatine kinase MB isoenzyme.

A creatine kinase level of more than five times the upper limit of normal was required for the diagnosis of

myocardial infarction after bypass surgery. Patients who still had an elevation in cardiac enzymes received a diagnosis of re-infarction if there was an increase of at least 50% from the previous measurement. Revascularization of the target lesion was defined as ischemia-driven PCI of the target lesion owing to restenosis or re-occlusion within the stent or in the adjacent 5 mm of the distal or proximal segments and included CABG involving the infarct-related artery. Stent thrombosis was defined by the angiographic documentation of either vessel occlusion or thrombus formation within, or adjacent to, the stented segment. Stent thrombosis was categorized as acute (occurring within 24 hours after procedure), subacute (occurring 1 to 30 days after the procedure), or late (occurring more than 30 days after the procedure).

Student's t-test and fisher's exact test were used for the statistical analysis, performed using SPSS (version 16). The study was approved by the institutional ethics committee. All study participants provided written informed consent before enrollment.

RESULTS

A total of 259 patients who had myocardial infarction with ST-segment elevation during study period were screened by the mentioned selection criteria. Of these, 154 eligible patients were enrolled in the study as participants; 77 were randomly assigned to the Everolimus-stent group (DES) and 77 to the uncoated bare metal-stent group (BMS).

The most common reasons for exclusion from the study were an anticipated delay of more than 6 hours between the onset of symptoms and reperfusion, coronary anatomy that was not suitable for stent implantation, cardiogenic shock, fibrinolytic therapy, previous PCI and mechanical ventilation.

The mean age of participants was 61.0±12.0 years in DES group and 61.0±13.0 years in BMS group. In the DES group, out of 77 patients, 57 (73.9%) were male and in BMS group, out of 77 patients, 60 (78%) were male (p value- 0.26). The mean time from onset of chest pain to angioplasty was 3.00±1.70 hours in the DES group and 2.97±1.80 hours in the BMS group, the difference being statistically insignificant (p- 0.86). Various other baseline clinical variables like diabetes mellitus, hypertension, hypercholesterolemia, family History of CAD and history of smoking were evenly distributed in both the groups. (Table 1).

As for the baseline angiographic characteristics, approximately half the patients had multi-vessel disease, and in 50.1% of the cases, the left anterior descending coronary artery was the infarct-related artery. TIMI flow grade 2 or 3 was present in 29.3% of patients in the Everolimus-stent (DES) group and in 28.4% in the bare metal stent (BMS) group. Majority of the patients had an estimated lesion length between 10 mm and 19 mm.

The mean reference diameter was 3.13±0.43 mm in the Everolimus-stent (DES) group and 3.20±0.47 mm in the bare metal stent (BMS) group (P- 0.04) (Table 2).

The procedural characteristics were also well matched. The average length of stents was 19 mm in both groups. Glycoprotein IIb/IIIa receptor blockers were used in all the patients of both the groups. TIMI grade 3 flow was established in 93.2% of patients in the DES group, as compared with 96.1% of patients in the BMS group. (Table 3).

No significant differences were found between the two treatment groups for occurrence of events during first 30 days after the intervention. One patient (1.2%) in the BMS group developed subacute stent thrombosis on 3rd post procedural day leading to recurrent anterior wall myocardial infarction.

He subsequently underwent plain balloon angioplasty with GP IIb/IIIa blocker. Post procedure, this patient did not have any adverse event during the one year follow up. Patients were thoroughly evaluated again at one year follow-up. Although trends were observed in favor of the DES group, none of the differences were significant. (Table 4).

Table 1: Baseline clinical characteristics.

Characteristics	DES group [No. (%)]	BMS group [No. (%)]	P- value
Age (in years)	61±12	61±13	0.91
Male Sex	57 (73.9)	60 (78.00)	0.26
Diabetes Mellitus	8 (10.00)	9 (12.00)	0.44
Hypertension	24 (30.60)	25 (31.70)	0.80
Hypercholesterolemia	18 (23.20)	22 (27.80)	0.20
Family History of CAD	31 (40.30)	28 (35.60)	0.25
History of smoking	41 (53.20)	38 (49.80)	0.42
Time from Onset of Chest Pain to Angioplasty (hours) (Mean±SD)	3.00±1.70	2.97±1.80	0.86

Table 2: baseline angiographic characteristics.

Characteristics		DES group [No. (%)]	BMS group [No. (%)]	P- value
Coronary Artery Disease	1 vessel	44 (57.7)	40 (52.4)	0.20
	2 Vessel	21 (26.5)	25 (32.4)	0.11
	3 Vessel	12 (15.8)	12 (15.2)	0.91
Infarct Related artery				
Left anterior descending artery		38 (50.3)	39 (49.8)	0.94
Right coronary artery		34(41.6)	30 (38.2)	0.41
Left circumflex artery		5 (5.8)	8 (10.4)	0.04
TIMI flow grade	0	48 (62.3)	48(62.3)	1.00
	1	7 (8.4)	6(8.1)	1.00
	2	10 (13.20	11(15.5)	0.42
	3	12(15.5)	12(15.5)	1.00
Lesion length				
0-9 mm		10 (30.2)	12 (15.3)	0.49
10-19 mm		50(64.8)	47 (60.8)	0.36
20-29 mm		13 (16.1)	13 (16.80	0.83
> 30 mm		4 (5.8)	5 (6.8)	0.62
Proximal tortuosity		4 (5.5)	4 (5.5)	1.00
Calcified lesion		7 (9.00)	5 (16.10)	0.22
Reference diameter (Mean±SD)		3.13±0.43	3.20±0.47	0.04
Mean Luminal diameter (Mean±SD)		0.15±0.35	0.17±0.38	0.60
Stenosis (Mean±SD)		94.8±13.2	94.0±14.6	0.48

Table 3: Procedural characteristics.

Characteristics	DES group [No. (%)]	BMS group [No. (%)]	P value
Stent size (mm) (Mean±SD)	3.21±0.30	3.26±0.38	0.08
Stent length (mm) (Mean±SD)	19±5.6	19±5.5	0.71
Maximum balloon inflation pressure (Atm) (Mean±SD)	15.84±2.94	15.73±2.94	0.70
Final TIMI Flow grade			
0	0	0	-
1	0	0	-
2	4 (5.5)	2 (2.3)	0.06
3	73 (93.2)	75 (96.1)	0.15
Reference diameter (Mean±SD)	3.20±0.46	3.24±0.45	0.26
Luminal diameter (Mean±SD)	30.15±0.47	3.13±0.57	0.66
Residual stenosis (Mean±SD)	3.03±6.6	4.66±12.1	0.04

Table 4: Comparative assessment at 30 days and one year follow-up.

Event	30 days follow-up			12 months follow-up		
	DES group	BMS group	P value	DES group	BMS group	P value
Death from any cause	0	0	-	0	0	-
Death from cardiac cause	0	0	-	0	0	-
Recurrent myocardial infarction	0	1	0.75	0	1	0.75
Stent thrombosis	0	1	0.75	1	0	0.75
Restenosis	0	0	-	2	6	0.75
CABG of the target vessel	0	0	-	0	0	-
Ballooning of the target vessel	0	0	-	0	0	-
PTCA of the target vessel	0	0	-	0	0	-
Medical management of angina	0	0	-	0	0	-

DISCUSSION

With the present study, drug-eluting coronary-artery stents were compared with uncoated bare metal stents for primary PCI during acute myocardial infarction with ST-segment elevation to determine superiority assessed in terms of occurrence of serious adverse cardiac events.

The two groups were age and gender matched, with the other assessed co-morbidities and risk factors also being evenly distributed. There was no statistical difference between the mean time from onset of chest pain to angioplasty (3.00±1.70 hours in the DES group, 2.97±1.80 hours in the BMS group).

The procedural and baseline angiographic variables, detailed above, were comparable between the two groups, providing validity to subsequent observations. No death from cardiac or non-cardiac cause was recorded in patients from both the groups. The difference between two groups with respect to rate of occurrence of stent thrombosis was statistically not significant.

The incidence of stent thrombosis was observed to be particularly low; given the thrombotic environment at the time of stent placement, the potential for suboptimal stent deployment in the setting of PCI for acute myocardial infarction, and decreased blood flow in a vessel that supplies infarcted myocardium. There was significant reduction in restenosis rate in DES group (2 cases) compared to BMS group (6 cases). There was also a trend in favour of the Everolimus-stent group in the rates of almost all the observed adverse events, but no single end point reached statistical significance. In contrast, trials comparing these two types of stents in elective PCI have consistently showed significant benefit associated with the use of Everolimus-eluting stents.[15-17]

The statistical insignificance observed in the present study could be due to various reasons. Firstly, relatively smaller sample size could have rendered power of the study to be insufficient. The estimated relative reduction of serious adverse cardiac events by 31% is still considerably smaller than that observed in previous trials with drug-eluting stents, which has consequences for the cost–benefit profile of these stents.[8-11] Secondly, the study design did not include angiographic follow-up.

Recurrent stenosis observed during routine follow-up angiography could have led to re-intervention without symptoms or objective evidence of ischemia, thus increasing the event rate. Further, restenosis may have developed in some patients in the absence of ischemic symptoms, owing either to partial infarction or to a defective warning system. Thirdly, there may have been a difference in response to vascular injury in the setting of primary PCI, as compared with that of more elective procedures. The literature, however, shows that angiographic and clinical restenosis after primary PCI remains an important issue.[15-17] Fourthly, the study was performed in patients with relatively large infarct-related arteries in which there was a decreased risk of restenosis. Finally, continuing improvements in the design of stents and the lower thickness of struts may have been responsible for lower rates of restenosis in the bare metal stent group than in those reported previously.

The results of our study also differ from a series of retrospective analyses and one small, randomized trial evaluating the implantation of drug-eluting stents for myocardial infarction with ST-segment elevation.[8-11] Subgroup analysis of patients undergoing PCI with sirolimus-eluting stents for myocardial infarction in the Thoraxcenter Research Registry showed that the rate of serious adverse cardiac events at 300 days was reduced from 17.0% to 9.4% (p=0.02).[9] This pattern was repeated in a retrospective analysis from the Washington Hospital Center using the same stent type.[10] In the Single High-Dose Bolus Tirofiban and Sirolimus-Eluting Stent vs. Abciximab and Bare-Metal Stent in Myocardial Infarction (STRATEGY) trial involving 175 patients, the rate of death, re-infarction, or target-vessel revascularization at 8 months was reduced from 32% with an uncoated stent to 18% with a sirolimus-eluting stent.[11]

These event rates are among the highest reported for any trial of PCI, and the reasons for the high event rates are not entirely clear, although most of the patients in the STRATEGY trial underwent routine follow-up angiography and the mean reference-vessel diameter was considerably smaller than that the present trial. An additional feature of the STRATEGY trial was that by design, a different glycoprotein IIb/IIIa inhibitor was used in the two study groups, which confounded the interpretation.

No difference in the rates of stent thrombosis between the two study groups was observed, although the definition of stent thrombosis was conservative (since angiographic documentation was required). Delayed stent thrombosis occurred in one patient in the Everolimus-stent group and acute and subacute thrombosis occurred in three patients in the Baremetal-stent group. This incidence is low, given the thrombotic environment at the time of stent placement, the potential for suboptimal stent deployment in the setting of PCI for acute myocardial infarction, and decreased blood flow in a vessel that supplies infarcted myocardium. In a recent retrospective study from the Thoraxcenter, the incidence of stent thrombosis at 1 month (which was also defined on the basis of angiography) after primary PCI with the use of a drug-eluting stent was 2.9%.[18]

In conclusion, the present study did not show any significant benefit associated with the use of Everolimus-eluting stents in primary PCI for acute myocardial infarction with ST-segment elevation, as compared with bare metal stents with the same design.

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