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Revascularization in type II diabetes: Challenges and evidence from clinical trials

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ARTICLE INFO

Article history:
Received 19 January 2015
Accepted 11 February 2015

1. Introduction

Though it lies at the other end of the spectrum, the challenge of revascularization in diabetics is huge. By 2030, the world authorities estimate that there will be 550 million patients with diabetes. In India, where the prevalence of diabetes is much greater, this is even more daunting. Coronary artery disease and diabetes are linked. Individuals with diabetes have a 2-fold increased risk for coronary artery disease and stroke, often undergo revascularization procedures, and have an increased risk of target vessel failure and need for repeat interventions.

Individuals with type 1diabetes, if well controlled, will not develop coronary disease at greater than patients who do not have diabetes. Thus, it is really type II diabetes that needs to be taken into consideration, especially with respect to accelerated atherosclerosis. The FREEDOM trial began over 10 years ago now. A challenging issue was restenosis, especially of the non-culprit lesions. It is the non-culprit lesions that progress over time and cause restenosis. The inflammation, the hyperglycemia, and insulin resistance that lead to all of the factors, increased tissue factor, increased inflammatory mediators, platelet dysfunction; along with impaired endothelial function all contribute to a whole different biology in the vessels. This contributes to stenosis in the non-culprit vessels.

Irrespective of stent or CABG, the issue of accelerated atherosclerosis persists. Since, FREEDOM trial was a trial of stent versus surgery there was some degree of selection bias. The scope of the discussion, with respect to the FREEDOM Trial, will include whether diabetes is important in decision making of PCI versus bypass, whether the stenting would have been better now with newer drug-eluting or bio-absorbable stents because this was the first generation drug-eluting stent studied in FREEDOM. This intervention is not "one size fits all", rather, it needs to be individualized.

Donald Cutlip and colleagues, in this particular study, highlighted the problems faced with bare metal stents. In the first year and a half, the events that are occurring are attributable to the target lesion, on which intervention was done. There was restenosis, repeat revascularization, and also stent thrombosis. But after the first year and a half, most of the events occur in the non-target lesion, for which no intervention was done. The lesion that didn't get any intervention becomes the lesion that is most responsible for the subsequent events (Fig. 1). Thus, a 1-year trial in revascularization may provide very different findings as compared to a 5-year trial. One of the messages in all of these clinical trials is long-term follow-up is incredibly important.

2. SYNTAX trial

The SYNTAX trial compared PCI with drug-eluting stents using the paclitaxel-coated stent (TAXUS) versus bypass surgery in about 2000 patients and a subgroup analysis of the diabetic subgroup was performed.

When we consider aspirin at discharge, 96% patients in the PCI group, and 88.5% patients in the bypass group went home on aspirin. So, the differences between the 2 arms in medical therapy of aspirin are apparent right away. These differences are relatively underrepresented; since one would expect much higher rates of aspirin prescription at discharge. If we consider statins, PCI patients were

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http://dx.doi.org/10.1016/j.jicc.2015.03.012
1561-8811/

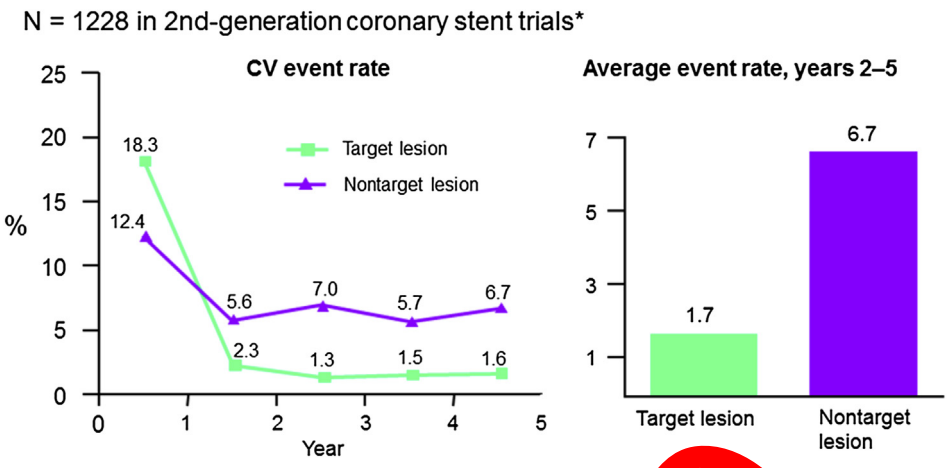

Fig. 1 – Disease progression in stented vs non-stented lesions and CV event
Source: Cutlip DE et al. Circulation. 2004; 110:1226–30

discharged 86.7% on a statin drug. Diabetics with aggressive multivessel coronary disease at the very end of the spectrum represent the highest risk levels; and only 87% in the PCI arm and 75% in the bypass arm are prescribed statin at discharge (Table 1). Thus we can see an overall underprescription of the most efficacious therapies. There can be plenty of discussions about the effectiveness of the ste used, but without optimal medical therapy, it may no be translated into clinical efficacy.

3. FREEDOM trial

FREEDOM tried to address the question in type 1 (5%) as well as type 2 (95%) diabetic patients with m essel d ease. Benefits of multivessel stenting, versus ypass on or of the coronary pump in multivessel coron y art y d se in diabetic patients were evaluated by his t STEMI patients were excluded. Patients with sta e coronary isease, with recent ACS and markers that we malized were included. The background therapy inclu d optim l aggressive medical therapy for al The baseline characteristics of the FREEDOM popul n n rand nization were as follows (Fig. 2). n FRE M, a pirin prescription even out to 5 years was % and equal the 2 arms. The use of clopidogrel was not as we balanced; at 1 year, 90% were still on clopidogrel in the PCI arm and this dropped to less than half in 5 years. In the bypass arm, patients actually continued on clopidogrel even out to 5 years, so we had 16% of people still on clopidogrel even on e bypass arm. Statin therapy is perhaps the most imp rtant in patients of type 2 diabetes. 90% of the patients re on a statin upto 5 years and equal between the 2 groups,

Table 1 – SYNTAX: ca iac-re ted medications given after the study procedu

Medication	PC (%)	CABG (%)	*p* Value
Any	98.9	98.6	0.62
Aspirin			
At discharge	96.3	88.5	<0.001
6 Mo after randomizatio	93.2	82.7	<0.001
Thienopyridine			
At discharge	96.8	19.5	<0.001
6 Mo after randomization	91.3	16.1	<0.001
Statin	86.7	74.5	<0.001
Beta-blocker	81.3	78.6	0.17
ACE inhibitor	55.1	44.6	<0.001
Angiotensin II–receptor antagonist	13.3	7	<0.001

Percentages are from the intention-to-treat analysis. ACE denotes angiotensin-converting enzyme, CABG coronary-artery bypass grafting, and PCI percutaneous coronary intervention.
Source: Serruys P et al. N Engl J Med 2009 March 5; 360:961–972

Characteristic	PCI/DES	CABG	P-value*
No. of Patients	953	947	
Age at randomization– yr	63.2 ± 8.9	63.1 ± 9.2	0.78
Male sex	73%	70%	0.08
Body mass index – gm/m^2	29.7 ± 5.4	29.8 ± 5.3	0.08
Duration of diabetes – yrs	10.1 ± 8.9	10.31 ± 9.0	0.49
Hemoglobin A1c - %	7.8 ± 1.7	7.8 ± 1.7	0.86
Current smoker	15%	17%	0.31
Previous myocardial infarction	26%	25%	0.56
Previous stroke	4%	3%	0.31
History of hypertension	85%	85%	0.75
Congestive heart failure	26%	28%	0.25
Hyperlipidemia	84%	83%	0.66
HDL cholesterol – mg/dL	38.9 ± 10.9	39.4 ± 11.4	0.34
Angina			0.25
Stable	68%	71%	
Unstable	32%	30%	
LV Ejection Fraction (< 30%)	0.8%	0.3%	0.28
LV Ejection Fraction (< 40%)	3%	2%	0.07
EuroSCORE	2.7 ± 2.4	2.8 ± 2.5	0.52
[Median (IQR)]	[1.9 (1.3, 3.1)]	[2.0(1.3, 3.3)]	
SYNTAX score	26.2 ± 8.4	26.1 ± 8.8	0.77
No. of lesions	5.7 ± 2.2	5.7 ± 2.2	0.33
Chronic total occlusion	6%	6%	0.99
Bifurcation	22%	21%	0.06

Fig. 2 – Baseline characteristics of patients enrolled into FREEDOM trial.