

Coronary Heart Disease in Patients With Diabetes: Part II: Recent Advances in Coronary Revascularization

Colin Berry, Jean-Claude Tardif, and Martial G. Bourassa J. Am. Coll. Cardiol. 2007;49;643-656; originally published online Jan 25, 2007; doi:10.1016/j.jacc.2006.09.045

This information is current as of August 9, 2008

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Coronary Heart Disease in Patients With Diabetes

Part II: Recent Advances in Coronary Revascularization

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Although diabetic patients represent approximately one-quarter of all those undergoing revascularization, their outcomes after revascularization are usually worse compared with non-diabetic patients. We examined the recent advances in percutaneous and surgical revascularization that are relevant to the treatment of diabetic patients. A systematic review of publications in the past 5 years (2000 to 2005) relating to coronary revascularization in diabetes was undertaken. Early and mid-term follow-up of diabetic patients after revascularization indicates that the incidence of myocardial infarction and repeat revascularization are reduced in surgically treated patients compared with those treated by balloon angioplasty alone. Percutaneous coronary intervention (PCI) with bare metal stents has reduced the surgical advantage (for reintervention) in the early-mid-term; however, repeat revascularization in diabetic patients continues to be substantially higher after PCI. Advances in PCI include the use of drug-eluting stents and adjunctive drug therapies, such as abciximab. Glycemic control is an important determinant of outcome after revascularization in diabetic patients, and the impact of tight glycemic control after PCI is currently being investigated in the BARI 2D (Bypass Angioplasty Revascularization Investigation 2 in Diabetes). Improvements in PCI and coronary artery bypass graft surgery are leading to better results in diabetic patients, and clinical trials are presently comparing contemporary PCI with surgery. (J Am Coll Cardiol 2007;49:643-56) © 2007 by the American College of Cardiology Foundation

Patients with diabetes mellitus (DM) account for approximately one-quarter of all patients who undergo coronary revascularization procedures each year, and they experience worse outcomes compared with non-diabetic patients.

The clinical trials of percutaneous transluminal coronary angioplasty (PTCA) versus coronary artery bypass grafting (CABG) that included diabetic patients have been reviewed in this journal by Hammoud et al. (1). Since the publication of that article and other more recent reviews (2,3), longterm follow-up data from these trials and from a number of new trials have become available. Although surgical revascularization remains the recommended strategy for diabetic multivessel coronary heart disease (CHD), recent advances in percutaneous coronary intervention (PCI) have resulted in a changing paradigm for coronary artery revascularization in DM.

CABG Versus PTCA

Recent Findings From Previous Clinical Trials With Long-Term Follow-Up

The EAST (Emory Angioplasty versus Surgery Trial) Study. The EAST study was a single-center randomized comparison of a strategy of initial PTCA (n = 198; 49 [24.7%] DM) or CABG (n = 194; 41 [21.2%] DM) for patients with multivessel CHD (4) (Table 1).

The 8-year survival was 79.3% in the PTCA group and 82.7% in the surgical group (p = 0.40); however, survival tended to be greater in diabetic patients who underwent CABG (75.5%) compared with those who underwent PTCA (60.1%; p = 0.23). In the angioplasty group, diabetic subjects had a reduced survival rate compared with non-diabetic subjects (60.1% vs. 82.6%; p = 0.02). By 8 years, a repeat revascularization occurred in 26.5% of the CABG-treated patients and in 65.3% of the PTCA-treated patients (p < 0.001).

The BARI (Bypass Angioplasty Revascularization Investigation) Study. The BARI study was a National Heart, Lung, and Blood Institute-sponsored trial designed to compare long-term survival in patients with multivessel disease and severe angina or ischemia randomized to PTCA or CABG (1,5,6).

LONG-TERM SURVIVAL. The BARI 10-year follow-up results should be available soon; the current intention-to-treat analysis, however, is limited to 7 years (1,5–7) (Table 1).

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Manuscript received July 11, 2006; revised manuscript received September 7, 2006, accepted September 11, 2006.

Abbreviations	
and Acronyms	

- BMI = body mass index
- BMS = bare-metal stent CABG = coronary artery bypass grafting

CHD = coronary heart disease

CI = confidence interval

CKMB = creatine kinase isoenzvme MB

DES = drug-eluting stent

DM = diabetes mellitus

IMA = internal mammary artery

LAD = left anterior descending

LMS = left main stem

MACCE = major adverse cardiac and cerebrovascular events

MI = myocardial infarction

OR = odds ratio

PCI = percutaneous coronary intervention

PTCA = percutaneous transluminal coronary angioplastv

RR = relative risk

SES = sirolimus-eluting stent

SVG = saphenous vein graft TLR = target lesion

revascularization

TVR = target vesse revascularization

The survival advantage in the CABG group was largely confined to patients who had received an internal mammary artery (IMA) graft to the left anterior descending artery (LAD) (83.2%, n =140) compared with those who had received only saphenous vein grafts (SVGs) (54.5%, n = 33) (7). The difference between the 2 groups was explained by the 353 patients with treated DM for whom estimates of 7-year survival were 76.4% and 55.7% in those treated by CABG and PTCA, respectively (p = 0.001). At 5 years, the BARI study showed 15 excess deaths for every 100 diabetic patients revascularized by PTCA compared with CABG, and at 7 years this difference increased to >20. The predictors of mortality in BARI included insulin-treated DM, heart failure and renal failure, black race, and older age (8). The only significant interaction term for survival was insulin-treated DM (p = 0.042).

Primary End Point

Primary End Point

Results

⁼ollow-Up

Randomized

CABG noDM: 734 PTCA noDM: 742

25,200

Survival at 7 yrs

PTCA

Angina or severe ischemia CAD amenable to

or CABG

Inclusion and Exclusion Criteria

Randomization

Table 1

Period

1988-1991

BARI (1,6,7) Trial (Ref.)

Eligible

Primary End Point

CABG, DM: 180 PTCA, DM: 173

CABG all: 84.4% PTCA all: 80.9%

7.8 yrs*

Randomized Clinical Trials That Have Compared PTCA With Stents Versus Bypass Surgery in Patients With Multivessel CAD Deemed Suitable for Either Approach

M CABG: 76.4% PTCA: 55.7%

p = 0.0011

CABG-noDM: 86.4% PTCA-noDM: 86.8%

p = 0.043

CABG DM: 75.5%

8 yr: 60.1%‡

8-yr CABG: 82.7%

8-10.5 yrs

(DM: 41 [21.2%])

CABG: 194

842

Death, MI, or large

Multivessel CAD without previous revascularization,

1987-1990

EAST (4)

no LMS, chronic total occlusion (either multiple

or duration >8 weeks), and LVEF \leq 25%

ischemic defect

p = 0.55

PTCA: 79.3%

In the BARI study, CABG was associated with better survival in the randomized diabetic patients (n = 353) (9); however, in the registry patients (n =339), there was no difference (10). The different outcomes between the BARI study and registry might be explained by dif-

ferences in the characteristics of registry patients who had a selected revascularization strategy. For example, CABG registry patients had more extensive coronary artery disease and a lower left ventricular ejection fraction than PTCA registry patients, suggesting the latter group were lower risk.

REPEAT REVASCULARIZATION IN BARI. Repeat revascularization in CABG-treated patients was similar in diabetic patients and in non-diabetic patients (11.1% vs. 13.5%; p = 0.45) (7). In PTCA-treated patients, repeat revascularizations were much more common in diabetic patients than in non-diabetic patients (69.9% vs. 57.8%; p = 0.0078).

MECHANISMS TO EXPLAIN THE SURVIVAL BENEFITS OF CABG VERSUS PTCA IN DIABETIC PATIENTS IN THE BARI STUDY. The BARI investigators undertook a follow-up angiographic core laboratory analysis of all patients undergoing protocol-driven coronary angiography at years 1 and 5 (11). Patients who underwent repeat angiography because of

PTCA noDM: 9.4% CABG-noDM: 6.8% PTCA DM: 22.6% CABG-DM: 12.5% PTCA DM: 60.1% p = 0.23HR DM vs. noDM 2.19, PTCA: 10.9% p = 0.001CABG: 7.4% All: 9.2% p = 0.4 4 yrs* Stratified for 2- and 3-vessel CAD (125 [11.9%] DM (DM: 49 [24.7%]) (64 [11.9%] DM) 60 [12.3%] DM) Enrolled: 1,054 Randomized§ PTCA: 198 PTCA: 537 CABG: 488 23,047 at 3 yrs† **Nortality**

EF ≤35%, heart failure, stroke, or severe illness

LMS stenosis,

stenosis) and clinical evidence of ischemia.

No previous revascularization,

Multivessel CAD (\geq 2 vessels with \geq 2 50%

Age ≤76 yrs

1988 (for 53

CABRI (14)

months)

recurrent ischemia were also included in this analysis. The percentage of myocardium jeopardized represented the fraction of all terminal arteries with evidence of stenoses \geq 50% of the reference diameter. On multivariate analyses, DM conferred a 2-fold risk of an increased percentage of jeopardized myocardium during follow-up.

Diabetic patients had a greater mortality risk with acute Q-wave MI compared with non-diabetic patients, and Detre et al. (12) hypothesized that previous CABG might impact upon this risk. In this analysis, randomized and registry patients who underwent either CABG or PTCA were studied together (n = 1,512 [290 with DM]). Diabetic patients were more likely to be female and black and more likely to have a history of heart failure, hypertension, renal dysfunction, and peripheral vascular disease.

Coronary artery bypass grafting conferred a substantial protective effect for mortality in diabetic subjects with a Q-wave MI (adjusted relative risk [RR] of death 0.09; p <.001) (12). The protective effect of CABG was 7 times greater in diabetic patients who experienced a Q-wave MI compared with those who did not. In these patients, CABG reduced the risk of death but to a much lesser extent. Overall, the protective effect of CABG for a patient with an MI explained only about 50% of the overall reduction in mortality attributable to the procedure. The remaining benefit of CABG among the patients with DM was demonstrated by a further reduction in mortality during follow-up, perhaps a result of the reduction in the degree of chronic ischemia. This can probably be explained by the more extensive revascularization provided by CABG and the protection provided by these conduits with recurrent coronary events.

Incomplete revascularization is particularly important in DM, owing to the increased risk of restenosis and disease progression in PTCA-treated diabetic patients. In BARI, whereas the amount of jeopardized myocardium was greater in PTCA-treated (25%) compared with CABG-treated patients (20%; p = 0.01), late angina was predicted by myocardial jeopardy (odds ratio [OR]/10% increase 1.22, 95% confidence interval [CI] 1.09 to 1.36), severity of angina at baseline (OR 2.2, 95% CI 1.17 to 4.14), and a history of cigarette smoking (OR 1.91, 95% CI 1.09 to 3.35) but not treatment assignment. In other words, native CHD progression and CHD risk factors were more important than failed revascularization (13).

Results of registries (PTCA vs. surgery) with long-term follow-up. Although the BARI and CABRI (Coronary Angioplasty versus Bypass Revascularization Investigation) (14) studies demonstrated a lower mortality in CABG-treated diabetic patients and the EAST study also showed a trend in favor of bypass surgery (Table 1), this was not the case in a large European registry (15) (Fig. 1). Impaired long-term outcomes in CABG patients might be explained by late onset graft failure and heart failure (16). However, our interpretation of these registry reports (15,16) should



also account for the likelihood of selection bias, which usually influences the management of registry patients.

Relevance of PTCA versus surgery trials for contemporary practice. The findings from trials of PTCA versus surgery have provided major advances in our understanding of revascularization in diabetes (4,7,14). However, contemporary revascularization practices have made substantial progress, and this is particularly the case in PCI. Therefore, from the perspective of clinical decision making, the results of these trials are of historical interest only.

CABG Versus PCI With Bare-Metal Stents

The ARTS (Arterial Revascularization Therapy Study) trial compared outcomes from bypass surgery versus coronary stenting in patients with multivessel disease. In the ARTS trial (17) (Table 2), the reduced event-free survival at 1 year in diabetic patients treated with stenting as compared with diabetic patients treated with CABG (63.4% vs. 84.4%, p <0.001) and nondiabetic patients treated with stents (76.2%, p = 0.04) was due to a higher incidence of repeat revascularization (typically CABG). This difference was largely due to a lower rate of complete revascularization in patients who underwent PCI (70.5%), compared with those who had CABG (84.1%; p < 0.001). Conversely, diabetic and nondiabetic patients experienced similar 1-year event-free survival rates when treated with CABG (84.4% and 88.4%). The strategy of stenting was less costly than that of CABG regardless of diabetic status (17).

The 5-year mortality rate of diabetic patients in the stent group was 13.4% compared with 8.3% in the surgical group (RR 1.61, 95% CI 0.71 to 3.63). Within the stent group, the mortality of diabetic patients remained higher than that of nondiabetic patients (13.4% vs. 6.8%; p = 0.03), whereas

		That have c	ompareu r or with Ster	its versus bypass surgery in ratients	with multivess	er CAD Deemeu Juita	
Trial (Ref.)	Randomization Period	Primary End Point	Eligible	Number of Patients Randomized	Follow-Up	Primary End Point	Primary End Point in DM
ARTS (17)	April 1997– June 1998	Multivessel CAD	Freedom for 12 months after randomization, from MACCE	1,205 PCI = 600; DM = 112 (19%) CABG = 605; DM = 96 (16%)	1 yr	PCI: 73.8%; CABG: 87.8% p < 0.001	PCI: 63.4%; CABG: 84.4% p < 0.001
SOS (19)	1996-1999	Symptomatic multivessel disease	Repeat revascularization	988 PCI = 488 (DM = 68) CABG = 500 (DM = 74)	Median 2 yrs	PCI group: 101 (21%) CABG group: 30 (6%)	N/A
ERACI II (20,21	.) October 1996– September 1998	Multivessel CAD	MACE	450 (PCI = 225; CABG = 225) Diabetes 17.3% both groups	30 days, 1, 3, and 5 yrs	30-day PCI: 3.6% CABG: 12.3% p = 0.002 5-yr PCI: 34.7% CABG: 23.6% p = 0.013	Similar 30 days (PCI vs. CABG) outcomes in DM 5-yr mortality: PCI DM vs. PCI noDM: 10% vs. 6.4%; p = 0.663 CABG DM vs. CABG noDM: 10.2% vs. 11.8%; $p = 0.637$
AWESOME (22)	1995-2000	Medically refractory unstable angina and at least 1 high-risk feature for CABG LMS an exclusion criterion	Survival at 3 and 5 yrs	 454 (58%) randomized; 1,977 (1,650 [83%] physician-directed; 327 [17%] patient choice) entered into registry. DM = 32% (n = 144) in randomized patients, 27% (n = 89) in patient- and 32% (n = 525) in physician-directed registries, respectively. 93 physician-directed and 4 patient-directed diabetic patients received medical care. 	36 months, 5 yrs	Survival PCI (80%) and CABG (79%) groups NS	$\begin{array}{l} \mbox{Similar 3-yr survival rates DM: $n=67$ vs.}\\ n=81, 80\%$ vs. 73\%$, respectively;\\ DM: $n=155$ vs. $n=151, 79\%$ vs.}\\ 80\%$, respectively. 5 yr freedom from UA or repeat PCI/CABG in DM: CABG group 43\%$ vs. PCI group 23\%$ No other between-group differences at 5 yrs \\ \end{array}$

Table 2 Randomized Clinical Trials That Have Compared PCI With Stents Versus Bypass Surgery in Patients With Multivessel CAD Deemed Suitable for Either Approach

MACE = major adverse cardiac events (death, Q-wave MI, or stroke, and need for emergency or elective repeat revascularization); MACCE = major adverse cardiac and cerebrovascular events; N/A = not applicable; NS = not significant; other abbreviations as in Table 1.

the cardiac death rates were similar in diabetic (50%) and nondiabetic patients (38%). The mortality rates of diabetic and nondiabetic patients in the surgical group were similar (8.3% vs. 7.5%; p = 0.8). In the stent group, repeat revascularizations were much more frequent in diabetic (42.9%) compared with nondiabetic patients (27.5%; p =0.002), and this difference was reflected by the 5-year major adverse cardiac and cerebrovascular event (MACCE) rates of diabetic and nondiabetic patients (54.5% vs. 38.7%; p =0.003) (18).

At least 3 additional trials have compared PCI with bare-metal stents (BMS) versus bypass surgery in patients with multivessel CHD (19-22) (Table 2). The SOS (Stent Or Surgery) trial showed less repeat revascularization with CABG than with PCI overall at 2 years, but the diabetic subgroup was not analyzed separately (19). The 2 other trials showed mixed results (20-22), as shown in Table 2. Registry results: impact of PCI with stents in diabetes. Srinivas et al. (23) examined the impact of contemporary PCI in patients treated in the late 1990s compared with patients treated with PTCA without stents. The 904 BARI patients who had been randomized to PTCA were compared with 857 patients (23% with treated DM; 14% non-insulin-treated, 8% insulin-treated) with BARI randomization characteristics who were enrolled in the U.S. National Heart, Lung and Blood Institute (NHLBI) Dynamic Registry in 2 waves in 1997 to 1998 and in 1999 (23,24). A lower proportion of diabetic patients were randomized to BARI-PTCA (10%), compared with the BARI-Eligible Dynamic Registry (23%; p = 0.047). Glycoprotein IIb/IIIa inhibitor use in the Dynamic registry population was 24%. Bare-metal stents were used in 74% of the contemporary group compared with 1% in the BARI group. Compared with PTCA-treated patients, contemporary PCI-treated patients had a lower risk of subsequent CABG (hazard ratio [HR] 0.35, 95% CI 0.26 to 0.48, p = 0.001), PCI (HR 0.56, 95% CI 0.43 to 0.71, p = 0.001), or CABG/PCI (HR 0.41, 95% CI 0.33 to 0.51, p = 0.001) at 1 year.

CABG Versus PCI With Drug-Eluting Stents

Drug-eluting stents represent a major advance for the prevention of restenosis and repeat revascularization after PCI in diabetic patients (25–28) (Table 3). However, as in the SIRIUS (SIRolImUS-coated Bx Velocity stent) study (26), DM was an independent predictor of target lesion revascularization (TLR) (OR 1.54, 95% CI 1.04 to 2.27) in the paclitaxel-eluting TAXUS IV study (27) (Table 3).

Because diabetic patients did not represent a pre-specified subgroup in the SIRIUS (26) or TAXUS IV (27) studies, the role of DES for diabetic patients has been questioned (29). A thick strut BMS, used in the control group of these trials, is associated with a higher rate of restenosis compared with thin strut stents, and the relatively high BMS TLR rate observed in the DES trials probably enhanced the apparent anti-restenotic effects of the new DES. Furthermore, only a proportion of diabetic patients underwent angiographic follow-up in the TAXUS IV study (27). Repeat angiography can positively influence TLR, which might be higher than in studies with clinical follow-up only. This potential for bias might be particularly relevant for diabetic patients in whom restenosis might not be apparent, owing to silent ischemia (29). The DIABETES (Diabetes and Sirolimus-Eluting Stent) trial specifically assessed the effects of a sirolimus-eluting stent (SES) in DM (28). Notably, late loss at stent edges was similar in the SES and BMS groups. This might be explained by relative drug sparing at the edge of the stent, injury at the peri-stent zone, and geographic miss.

In the SIRTAX (SIRolimus- versus pacliTAXel-eluting stents) trial (30) (Table 3), the HR for MACCE was less in SES-treated patients compared with in paclitaxel-eluting stents (PES)-treated patients and this difference was more pronounced in DM. In the ISAR (In-Stent Angiographic Restenosis)-DIABETES trial (31) (Table 3), PCI with SES resulted in less in-segment restenosis in insulin-treated (p = 0.02) and non-insulin-treated (p = 0.03) diabetic patients. Although this trial was not powered to compare clinical events, its results suggest that SES might be preferred to PES for PCI in DM.

The SYNTAX (SYNergy between percutaneous coronary intervention with TAXus and cardiac surgery) (32) and COMBAT (COMparison of Bypass surgery and AngioplasTy using sirolimus stents in patients with unprotected left main coronary artery disease) (33) are ongoing trials of PCI with DES versus surgery that will provide more information on revascularization in DM.

Recommendations of Contemporary PCI Guidelines

Contemporary PCI guidelines place emphasis on the longterm survival benefit conferred by CABG for treatment of DM with multivessel disease. Clinician's judgment on the revascularization strategy remains an important factor. Although PCI with BMS have narrowed the gap with surgery, the effectiveness of PCI in CABG-eligible diabetic patients with stable or unstable multivessel disease (including proximal LAD disease) must be established by the on-going randomized trials (33–36) (Table 3) (American College of Cardiology/American Heart Association [ACC/AHA] guideline recommendation Class IIB; Level of Evidence: B) (37).

Invasive management in diabetic patients with unstable CHD is indicated on clinical need and should be guided by evidence of ischemia and by risk stratification (37). A recent meta-analysis that included 1,465 (18.9%) diabetic patients has confirmed that higher-risk unstable angina/non-ST-segment elevation MI patients (e.g., biomarker positive) benefit from a routine invasive strategy (38).

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Published and Ongoing Randomized Trials of PCI With Drug-Eluting Stents Versus Bare Metal Stents

Trial (Ref.)	Status	Inclusion and Exclusion Criteria	Primary End Point	Intervention	Number of Patients Randomized	Follow-Up	Primary End Point	Primary End Point in DM
BARI 2D (34)	Ongoing	Type 2 DM. ≥1 vessel amenable to revascularization (≥50% stenosis) Objective ischemia or typical angina with 70% stenosis in ≥1 artery Suitability for revascularization by at least 1 available method (does not require complete revascularization)	5-yr mortality	 Initial elective coronary revascularization combined with aggressive medical therapy, compared with an initial strategy of aggressive medical therapy alone Efficacy of a strategy of providing more insulin (endogenous or exogenous) vs. a strategy of increasing sensitivity to insulin (reducing insulin resistance) in the management of hyperglycemia, with a target HbA1c level of <7.0% for each strategy 	2,368	5 yrs	_	_
Cardia (35)	Ongoing	Diabetes. Multivessel CAD (≥2 stenotic coronary or 1 in which PCI suitability is unclear: e.g., bifurcation lesion involving proximal LAD) Consensus between a cardiologist and surgeon that adequate revascularization can be achieved	Death, non-fatal MI, or stroke within 1 yr	Optimal PCI includes the use of aspirin, clopidogrel, abciximab, and sirolimus-eluting stents in all patients Modern CABG is defined as ≥1 arterial conduit with a LIMA graft for the anterior native vessels and off-pump bypass at the surgical team's discretion	600 projected	1-5 yrs	_	_
FREEDOM (36)	Ongoing	Diabetes. Multivessel CAD (≥2 lesions in ≥2 major arteries), amenable to either PCI with DES or surgical revascularization.	All-cause mortality, MI, and stroke	Compares multivessel stenting using sirolimus-eluting stents with CABG Superiority trial	2,400 projected	5 yrs	_	_
COMBAT (33)	Ongoing	Inclusion: LMCA stenosis >50% (visual estimate); angina or documented ischemia amenable to both PCI or CABG; lesions outside LMCA amenable to both PCI or CABG Exclusion: previous PCI (<12 months); previous LMCA PCI; previous CABG; LVEF <20%; NYHA heart failure class III or IV	All-cause mortality, MI, and stroke at 2 yrs	Randomization stratified by diabetes	1,730 projected (1:1 SES vs. CABG)	5 yrs	_	_
SYNTAX (32)	Ongoing	Inclusion: stable or unstable angina or atypical presentation with ischemia; de novo lesion; 1 stenosis in all 3 major epicardial arteries supplying viable myocardium or significant LMCA stenosis or equivalent; reference diameter ≥1.5 mm Exclusion: previous PCI or CABG; 1- or 2-vessel CAD without LMCA disease	MACCE to 1 year	PCI with PES vs. CABG Randomization stratified by treated-DM. DM is a predefined subgroup (including by type, treatment, and hemoglobin A1c)	1,500 (750 per group)	5 yrs	_	_

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Table 3 Co	ontinued							
Trial	Status	Inclusion and Exclusion Criteria	Primary End Point	Intervention	Number of Patients Randomized	Follow-Up	Primary End Point	Primary End Point in DM
SIRIUS (25)	Published	Inclusion: stable or unstable angina and evidence of myocardial ischemia correlated with a de novo native coronary stenoses 50%–99% diameter, 15–30 mm in length, and 2.5–3 mm in diameter	Target vessel failure (composite of cardiac death, MI, and TVR) within 270 days of the index PCI	PCI with Cypher Stent (Cordis) vs. PCI with BMS (BxVelocity, Cordis)	SES (131/533 [25%]:DM) BMS (148/525 [28%]:DM)	270 days	All patients: SES: 8.6% BMS: 21.0% p < 0.001	SES: 12.2% BMS: 27.0% p = 0.003
TAXUS IV (27)	Published	Inclusion: single, de novo lesion estimated visually to be between 10 to 28 mm in length, with a reference vessel diameter 2.5–3.75 mm	TVR at 9 months	PCI with PES (Taxus, Boston Scientific) vs. PCI with BMS (Express, Boston Scientific)	PES: DM 23.4% (of total = 662) (7.7% insulin requiring) BMS: 25.0% (of total = 652) (8.3% insulin- requiring)	1 yr	PES: 4.7% BMS: 12% RR 0.39 p < 0.001	Paclitaxel: 11.3% BMS: 24% RR 0.53 p = 0.004
DIABETES (28)	Published	Insulin or non-insulin requiring treated DM Native vessel de novo lesion with a reference vessel diameter <4.0 mm by angiography Exclusion: LMS, ejection fraction <25%	In-segment late lumen loss at 270 days	PCI with SES (Cypher, Cordis) vs. PCI with BMS (standard stent)	SES (80; lesions 111) BMS (80; lesions 110)	270 days	_	$\begin{array}{l} \text{SES: } 0.06 \; (0.4) \\ \text{BMS: } 0.47 \; (0.5) \\ p < 0.001 \end{array}$
SIRTAX (30)	Published	Stable angina or an acute coronary syndrome Native vessel de novo lesion (>50%) with a reference diameter of 2.25-4 mm	MACE by 9 months	PCI with SES (Cypher, Cordis) vs. PCI with PES (Taxus, Boston Scientific)	SES: 503 (DM: 108 [21.5%]) PES: 509 (DM: 93 [18.3%])	9 months	$\begin{array}{l} \text{SES: 31 (6.2\%)} \\ \text{PES: 55 (10.8\%)} \\ \text{p} = 0.009 \end{array}$	SES vs. PES HR (95% Cl): 0.31 (0.12-0.78) DM vs. no DM p = 0.13
ISAR-DIABETES (3	31) Published	DM with angina or a positive stress test and a native vessel culprit lesion Exclusion: ST-segment elevation MI, LMS disease, restenosis NB. Pre-treatment with 600 mg of clopidogrel >2 h pre-procedure	Difference in mean n- segment late lumen loss at 9 months Trial designed to test non- inferiority of PES vs. SES	PCI with SES (Cypher, Cordis) vs. PCI with PES (Taxus, Boston Scientific)	SES: 125 PES: 125	196 days (median angiographic follow-up)	_	0.24 (0.09–0.39) mm SES superior to PES (p = 0.002)

BMS = bare-metal stent; DES = drug-eluting stent; LAD = left anterior descending; LIMA = left internal mammary artery; LMCA = left main coronary artery; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; RR = relative risk; PES = paclitaxel-eluting stent; SES = sirolimus-eluting stent; TLR = target lesion revascularization; TVR = target revascularization; other abbreviations as in Table 1.

Berry *et al.* Diabetes and Coronary Heart Disease: Part II

Mechanistic Insights to Explain Impaired Revascularization Outcomes in DM

Adverse Outcomes After Surgery

Postoperative complications. Compared with nondiabetic patients, early and long-term morbidity and mortality are higher in diabetic patients after CABG (39), with more postoperative complications, including wound infection (40).

In the ARTS trial, creatine kinase isoenzyme MB (CKMB) measurements were performed at 6, 12, and 18 h after CABG (41). A CKMB rise 1 to 3 times the upper limit of normal (ULN), 3 to 5 \times ULN, and > \times 5 ULN occurred in 42.9%, 7.5%, and 11.5% of patients (61.9% overall). Diabetes was an independent predictor of a reduced likelihood of CKMB elevation after CABG (OR 0.53, p = 0.01) (41), and the authors argued this might be due to reduced CK activity in diabetes. In a recent trial of the anti-inflammatory C5 complement inhibitor during CABG, 55.6% of the 785 patients who had full CKMB assessment had a postoperative CKMB concentration >×5 ULN (25 ng/ml) (42,43). Compared with placebo, pexelizumab reduced the incidence of MI at 30 days (RR reduction 18%; p = 0.04) but not the combined end point of 30-day death or MI (43). Myocardial infarction through day 4 predicted 30-day mortality.

Complications in the longer term. Angiographic analyses of diabetic patients in the BARI study demonstrated that despite smaller and more diseased native vessel targets, arterial and vein graft patency rates were similar after an average of 4 years' follow-up (44). Therefore, the worse survival of diabetic CABG patients compared with nondiabetic surgical patients in the BARI study (7) might be explained by non-cardiac complications (44).

Cognitive decline is common after CABG (45); however, whether this is a surgical complication or the natural history of cognitive function in CHD is controversial (46). Decline in cognitive function after CABG is not associated with DM (45). Stroke occurs more commonly in diabetic patients after CABG (17), and in the longer term, quality of life after CABG might be particularly reduced in DM (47). **Increasing burden of vein graft disease.** A recent CABG trial reported a similarly high 12-month incidence of death or SVG stenosis \geq 75% in diabetic (48.3%) and nondiabetic (44.2%) subjects (48). The 12-month mortality rate for the whole population was 3.2%. These revealing data illustrate strikingly high vein graft failure rates, even with contemporary practices.

Registry reports indicate that the prevalence of DM in PCI patients with prior CABG is rising. In the Mayo Clinic, DM was recorded in 16% (1979 to 1989), 28% (1990 to 1994), and 30% (1995 to 1998) of PCIs performed in patients with prior CABG (49). In the Washington Hospital Center, DM was recorded in 34% and 38% of PCIs performed in patients with prior CABG during 1990 to 1994 and 1995 to 1998, respectively (50). In patients with

DM who have recurrent ischemia despite medical therapy, redo CABG has a much higher risk than PCI, and PCI should be the preferred option (51). Diabetes is associated with in-hospital mortality after SVG PCI, and DM predicts TLR and late cardiac events (5).

Adverse Outcomes After PCI

Procedure-related and in-hospital outcomes. Although angiographic success after PCI occurs with a similar frequency in diabetic and nondiabetic subjects (52,53), procedural complications occur more frequently in DM (52,54). This can largely be explained by the higher risk profile in DM (54).

In the American College of Cardiology-National Cardiovascular Data Registry, the unadjusted in-hospital mortality rate in 100,292 PCI cases (26% DM) performed in 139 centers during 1998 to 2000 was higher in diabetic patients (1.8%) than in those without DM (1.3%; p < 0.0001) (52). Fewer diabetic patients had no adverse events in-hospital (96.2%) compared with nondiabetic patients (96.6%; p = 0.009), and mean length of stay was greater in diabetic patients (2.7 days) than in nondiabetic patients (2.4 days; p = 0.0001).

Renal dysfunction after PCI occurs more frequently in DM (55), and renal function should be checked in diabetic patients after PCI (37). Surprisingly, DM does not predict cardiac biomarker elevation after PCI (52,56).

Although diabetic patients undergo primary PCI less often and have a more adverse clinical profile than nondiabetic subjects, in-hospital mortality is comparable in both groups (57).

Long-term outcome after PCI. In the PRESTO (Prevention of REStenosis with Tranilast trial and its Outcomes), the largest contemporary restenosis trial to date, patients were stratified according to the presence (n = 2,694) or absence of diabetes (n = 8,798) (53). Compared with nondiabetic patients, diabetic patients were older (mean age 61.8 vs. 59.8 years; p < 0.01), more often had co-morbid health problems, and had more complex culprit stenoses (e.g., higher prevalence of restenosis, calcified lesions, and ACC/AHA type C lesions). Even after adjustment for other differences in baseline characteristics, DM predicted the 9-month rate of death (RR 1.87, 95% CI 1.31 to 2.68), target vessel revascularization (TVR) (RR 1.27, 95% CI 1.14 to 1.42), and the composite of death/MI and TVR (RR 1.26, 95% CI 1.13 to 1.40).

In other studies, DM has predicted MACCE (56,58) and mortality (23,54) in the longer term after PCI. The risk is greatest in insulin-treated DM (23). Furthermore, DM predicts mortality at 6 months after primary PCI (HR 1.53, 95% CI 1.03 to 2.26) (57).

Although PCI is generally preferable to repeat CABG, PCI for vein graft disease in DM might be particularly problematic (37). Insulin-treated DM is associated with calcific vein graft degeneration (59). Stent thrombosis. A recent European multicenter study included 2,229 consecutive patients (591 [27%] DM) who had undergone PCI with DES between April 2002 and January 2004 (60). At 9-months' follow-up, acute stent thrombosis had occurred in 29 patients (1.3%) of whom 15 had DM. Furthermore, DM was an independent predictor of acute stent thrombosis (HR 3.71, 95% CI 1.74 to 7.89). In-stent restenosis. Revascularization for restenosis is more common in diabetic patients than nondiabetic patients after PCI (53,54,61,62). In the PRESTO trial (53), 9-month restenosis rates were 39.8% and 32.4% in diabetic and nondiabetic patients, respectively (p < 0.01), and DM tended to be a multivariate predictor of restenosis (OR 1.22, 95% CI .97 to 1.54).

In 1 retrospective analysis of 3,090 (n = 418 [14%] with DM) clinical trial participants who had 6-month angiographic follow-up, restenosis occurred in 550 of 2,672 (20.6%) nondiabetic patients and 130 of 418 (31.1%) diabetic patients (p < 0.001) (62). Reduced body mass index (BMI) (OR 0.92, 95% CI 0.85 to 0.99), larger reference diameter before stenting (OR 0.38, 95% CI 0.20 to 0.70), and longer stented length of vessel (OR 1.03, 95% CI 1.00 to 1.06) were multivariate predictors of restenosis (62). Restenosis in DM is associated with excess intimal fibrosis and reduced cell content (63).

Disease progression. In the PRESTO trial (53), compared with nondiabetic patients, diabetic patients recorded a higher frequency of new lesions at 9 months (30% vs. 26%; p = 0.05). This difference was mainly due to the development of more new lesions in the treated vessel of diabetic patients (15% vs. 12%; p = 0.04) rather than in non-treated vessels (20% vs. 18%; p = 0.25).

Metabolic control and outcomes after PCI. In a casecontrol investigation of glycemic status in 179 diabetic and 60 nondiabetic patients undergoing elective PCI (64), HbA_{1c} >7% was a multivariate predictor of TVR at 12 months after PCI (OR 2.87, 95% CI 1.13 to 7.24) (Fig. 2). Diabetic patients with suboptimal glycemic control (HbA_{1c}



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>7%) were more often treated with insulin (54% vs. 27%), and insulin-treated patients had a higher rate of TVR, compared with non-insulin treated patients and control subjects (64) (Fig. 2). An HbA_{1c} >7% was a multivariate predictor of both cardiac repeat hospital stay (OR 2.44, 95% CI 1.05 to 5.66) and recurrent angina (OR 4.03, 95% CI 1.66 to 9.78). One other angiographic follow-up study of 217 PCI patients (n = 75 with DM) reported similar results (65).

In primary PCI, elevated admission blood glucose concentration (≥ 11 vs. <11 mmol/l) predicts early and longterm mortality (66).

BMI and Outcome After Revascularization in Diabetic Patients

Influence of BMI after PCI. Diabetes is common in obese patients (BMI \geq 30 kg/m²) undergoing revascularization (17% to 33%) (53,67–71), whereas low BMI is associated with advanced age, cigarette smoking, and peripheral vascular disease (67). Perhaps surprisingly, obesity is not associated with CHD severity (68,69).

There are conflicting reports about the influence of BMI on long-term outcome after PCI. In the ARTS trial, 3-year MACCE rates were similar in PCI patients who had a normal BMI (18.5 to 24.9 kg/m²; n = 168 [28%]), who were overweight (BMI 25 to 30 kg/m²; n = 307 [51%]), or who were obese (BMI >30 kg/m²; n = 124 [20%]): 30.4%, 37%, and 32%, respectively (p = 0.33) (70).

Reduced BMI is a predictor of restenosis in diabetic patients (62). If low BMI is related to an increased risk of either restenosis or disease progression, then it might be that such patients have short stature and small caliber coronary arteries (62,69), in which case low BMI might negate the metabolic advantage of reduced body fat (67). Small caliber arteries might be more common in diabetic patients (62), and reference diameter is a predictor of restenosis in diabetic patients after stenting (62).

Influence of BMI after surgical revascularization. In the ARTS trial, the 3-year MACCE rates for surgical patients who had a normal BMI (n = 169 [28%]), who were overweight (n = 299 [50%]), or who were obese (n = 136 [22%]) were 24%, 16%, and 11%, respectively (p = 0.008) (70). In a multivariate analysis that included diabetes, increasing BMI predicted a reduced rate of MACCE in surgical patients (HR 0.59, 95% CI 0.39 to 0.89). This observation was mainly due to a lower rate of repeat revascularization in obese patients.

By contrast, in the BARI trial, increasing BMI predicted all-cause mortality (adjusted p = 0.04) and cardiac mortality (adjusted p < 0.001) at 5 years (69). This finding might be explained by the adverse influence of cardiovascular risk factors, more prevalent in obese patients, on long-term outcomes after CABG (69).

Recent Developments in Diabetic Revascularization

In general, results of recent revascularization trials have been applied to diabetic patients on the basis of assumed efficacy after post hoc analyses and the absence of a negative interaction for diabetes status. We support current and future prospective revascularization trials (Table 3) exclusively in diabetic patients.

Advances in management of surgical patients. Continuous insulin administration to achieve tight glycemic control (e.g., plasma glucose concentration <150 mg/dl, 8.3 mmol/l) (72), improved use of secondary prevention therapies (73), and use of arterial conduits rather than SVGs are associated with improved outcomes after surgery.

Advances in PCI. Improved outcomes with contemporary PCI (24,37) are paralleled by increasing case complexity (24). Percutaneous coronary intervention is increasingly selected as a revascularization option in DM. The proportion of patients with DM treated by contemporary PCI has increased (25.8%) compared with earlier PTCA registries (13.5%) (23).

Antithrombotic Drug Therapy and Revascularization

Clopidogrel. In PCI-CURE (Clopidogrel in Unstable angina to prevent Recurrent Events) trial (74), of the 504 (38%) diabetic patients included, 32 (12.9%) of the clopidogrel-treated patients and 42 (16.5%) of the placebo-treated patients experienced cardiovascular death or MI during follow-up (HR 0.77, 95% CI 0.48 to 1.22). By contrast, in nondiabetic patients, a benefit in favor of clopidogrel was apparent (HR 0.66, 95% CI 0.50 to 0.87).

Diabetic patients are more likely to be resistant to the effects of aspirin (75) or to have dual platelet resistance to aspirin and clopidogrel (75). The question of whether anti-platelet resistance might contribute to adverse outcomes after PCI in DM merits further investigation.

Glycoprotein IIb/IIIa inhibitors. The results of recent glycoprotein IIb/IIIa inhibitor trials in PCI are shown in Table 4 (76–79). A meta-analysis demonstrated a survival advantage conferred by abciximab in DM (4.5% vs. 2.5%; p = 0.03) (80), and the 30-day mortality reduction associated with glycoprotein IIb/IIIa inhibitor in diabetic patients with non–ST-segment elevation acute coronary syndrome is greater in patients undergoing PCI (81).

The NHLBI Dynamic Registry indicated planned glycoprotein IIb/IIIa inhibitor therapy in diabetes might reduce the incidence of in-hospital death and death or non-fatal MI at 1 year after PCI (54). Abciximab might also be beneficial in clopidogrel-treated diabetic patients undergoing PCI (Table 4). The ISAR-SWEET trial prospectively tested the effect of abciximab in diabetic PCI patients who had been pre-treated with 600 mg of clopidogrel (79). Although the combined primary end point rates of death and MI at 1 year were similar in abciximab and placebo-

Table 4 Clinical Trials of Glycoprotein IIb/IIIa Inhibitor Therapy Involving Diabetic Patients

Trial (Ref.)	Randomization Period	Methods	Primary End Point	Patient Characteristics	Primary End Point Results	Primary End Point in DM	Long-Term Follow-Up
ESPRIT (76)	1999-2000	Efficacy and safety of a high-dose regimen of eptifibatide as an adjunct to elective coronary stenting.	48-h composite of death, non-fatal MI, urgent TVR, and bailout with glycoprotein IIb/IIIa inhibitor therapy	Eptifibatide (n = 1,040; 208 [20%] DM) or placebo (n = 1,024; 211 [21%] DM)	Eptifibatide: 6.6% Placebo: 10.5% RR 0.63 (95% Cl 0.47-0.84) p = 0.0015	Eptifibatide: 3.9% Placebo: 6.6% RR 0.58 (95% Cl 0.25-1.35) p = 0.20	1-yr follow-up, death or MI 8.0% eptifibatide group and 12.4% placebo group (HR 0.63, 95% Cl 0.48-0.83)
TARGET (77) Impact in diabetes (78)	1999-2000	Indication for non- emergent PCI in a native coronary artery or bypass graft; randomization to tirofiban or abciximab therapy for 12–18 h or 12 h, respectively; patients stratified according to diabetic status at enrolment	Composite of death, MI, or urgent TVR at 30 days	4,089 enrolled 1,117 (23%) with diabetes (503 [45%] insulin-treated): 560 tirofiban; 557 abciximab	Tirofiban group (7.6%); in the abciximab group (6.0%) Superiority of abciximab over tirofiban; p = 0.038)	35 (6.2%) tirofiban and 30 (5.4%) abciximab p = 0.54 Among insulin-treated DM: Tirofiban: 8.1% Abciximab: 3.1% p = 0.02	DM TVR rate (10.3%) at 6 months vs. non-DM (7.8%; p = 0.008) and trend to higher 1-yr mortality (2.5% vs. 1.6%; p = 0.056)
ISAR-SWEET (79)	January 2001 and October 2003	Elective PCI 600 mg of clopidogrel and 500 mg of aspirin at least 2 h before the procedure BMS	Death or MI at 1 yr	701 DM patients (351 abciximab and 350 placebo) 29% insulin-treated, 51% on oral hypoglycemic drugs only, and 20% on no diabetic therapy at all (with equal proportions in each group)	_	29 (8.3%) in abciximab and 30 (8.6%) in placebo), *TLR 23.2% abciximab and 30.4% placebo (p = 0.03)	-

*Follow-up angiography was performed at a median of 197 days (25th, 75th percentiles: 181, 220 days). Abbreviations as in Tables 1 and 3. treated patients (8.3% vs. 8.6%, p = 0.91), TVR was reduced by abciximab (79) (Table 4). Adjunctive glycoprotein IIbIIIa inhibitor therapy represents an advance for diabetic patients, particularly those undergoing complex PCI. Contemporary PCI guidelines recommend glycoprotein II/bIIIa inhibitors in patients with unstable CHD and in elective PCI patients with risk factors, such as diabetes (37).

Bivalirudin. The direct thrombin inhibitor, bivalirudin, is an emerging alternative to the combination of heparin and glycoprotein IIb/IIIa inhibitors during PCI. Further information in diabetic patients undergoing PCI is required before this drug can be recommended (37).

Impact of antidiabetic therapies on outcome after PCI. Thiazolidinedione drugs, such as rosiglitazone, are PPARgamma inhibitors that have pleiotropic effects, including improved insulin sensitivity and enhanced endothelial cell function. Recent studies suggest thiazolidinedione drugs have anti-restenosis effects after PCI (82,83).

Ongoing Interventional Trials in Diabetes

The BARI 2D trial is a 2×2 factorial trial, which will result in 50% of enrolled diabetic patients randomized to medical therapy or revascularization, and within each of these 2 groups an additional randomization will take place to insulin-providing or insulin-sensitizing agents (34) (Table 3). Other on-going trials include the CARDIA (Coronary Artery Revascularization in DIAbetes) trial (35) and the FREEDOM (Future REvascularization Evaluation in patients with Diabetes mellitus: Optimal Management of multivessel disease) trial (36) (Table 3).

Conclusions

In recent years, technical advances have resulted in greater capability for revascularization with PCI coupled with improved safety.

Although randomized clinical trials provide information intended to guide clinical activity, data arising from these trials are derived from highly selected populations that might not be fully representative of patients encountered in ordinary clinical practice. Subgroup analyses should be interpreted with caution. Common limitations of some of these revascularization trials with respect to DM include a lack of information about anti-diabetic therapy, glycemic status, and duration and control of DM (e.g., glycemic control or the presence of DM complications). Consequently, the effectiveness of PCI in diabetic patients with stable or unstable multivessel CHD (including the proximal LAD) is presently not supported by well established evidence and has a Class IIb/C recommendation (37).

On the basis of this and on previous information, one can reach several conclusions that might serve as guidelines for the contemporary invasive management of CHD patients with DM. In spite of a marked reduction of restenosis and TLR, with the use of BMS as compared with balloon angioplasty in the late 1990s and early 2000s, the outcome for diabetic patients was worse after PCI than after CABG surgery. Diabetes mellitus is also a predictor of worse outcome with CABG and might increase the risk for vein graft occlusion and stenosis.

In the current era of DES, DM remains an independent risk factor for restenosis and TLR. Conflicting results between clinical trials and their registries have created an imperative for trials of revascularization strategies in DM. The results of on-going randomized trials are awaited to inform us on the comparative efficacy of contemporary PCI and CABG in patients with diabetes. Finally, better risk factor control might decrease any difference between revascularization strategies.

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Colin Berry, Jean-Claude Tardif, and Martial G. Bourassa J. Am. Coll. Cardiol. 2007;49;643-656; originally published online Jan 25, 2007; doi:10.1016/j.jacc.2006.09.045

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