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Review

Urgent Revascularization Strategies in Patients With Diabetes Mellitus and Acute Coronary Syndrome

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ABSTRACT

The prevalence of diabetes mellitus (DM) is rising globally and in Canada. Besides being a risk factor for the development of coronary artery disease, DM is also a marker of poor prognosis in patients with acute coronary syndrome (ACS), increasing the risks for ischemic and bleeding complications. Patients with DM have a high prevalence of multivessel coronary artery disease (MVD) and robust evidence has supported coronary artery bypass surgery (CABG) as the optimal revascularization strategy in the setting of stable ischemic heart disease. In the acute scenario, particularly in patients with non–ST-segment elevation (NSTE) ACS (NSTE-ACS), there are many uncertainties regarding the best revascularization strategy. Most guidelines suggest an invasive and timely approach (that is,

RÉSUMÉ

La prévalence du diabète est en hausse tant dans le monde qu'au Canada. En plus d'être un facteur de risque de coronaropathie, le diabète est aussi un marqueur de pronostic défavorable chez les patients atteints du syndrome coronarien aigu (SCA) car il augmente les risques de complications ischémiques et hémorragiques. Chez les patients diabétiques, la prévalence de la coronaropathie plurivasculaire (CPV) est élevée, et des données probantes fiables montrent que le pontage aortocoronarien (PAC) est la stratégie de revascularisation optimale dans les cas de cardiopathie ischémique stable. Dans le scénario de la forme aiguë, en particulier chez les patients présentant un SCA sans élévation du segment ST (SCA-SSDST), de nombreuses incertitudes entourent le choix de la meilleure stratégie de

Diabetes mellitus (DM) is a major risk factor for coronary artery disease and approximately 30% of patients with an acute coronary syndrome (ACS) also have DM.[1] The prevalence of DM is especially rising in individuals with a non–ST-elevation (NSTE) ACS (NSTE-ACS),[2] which highlights the importance of understanding the best strategies to deliver coronary revascularization in this population. In the United States, it is estimated that only one-third of the patients with DM and multivessel coronary disease (MVD) undergo coronary artery bypass graft surgery (CABG) after an NSTE-ACS episode and the remaining patients either receive percutaneous coronary intervention (PCI) or medical therapy.[3] Because most of the evidence for coronary revascularization of patients with DM comes from studies in the stable ischemic heart disease (SIHD)[4] setting, in this article we review the literature regarding revascularization strategies in patients with SIHD and NSTE-ACS. Because of the differences in clinical presentation and prognosis, we also discuss the issues of revascularization in patients with an ST-segment elevation myocardial infarction (STEMI).

Prognosis of Patients With DM and ACS

DM is associated with a worse prognosis in patients with ACS, according to observational and experimental studies. In addition, ACS patients with DM have a higher proportion of MVD than non-DM patients,[1,5] which might contribute to the poorer prognosis. In the **Plat**elet Inhibition and Patient **O**utcomes (PLATO) trial, DM was associated with higher 1-year mortality (hazard ratio [HR], 1.84; 95% confidence interval [CI], 1.61-2.10; $P < 0.0001$) and major bleeding (HR, 1.41; 95% CI, 1.28-1.55; $P < 0.0001$) after an ACS.[6] In a pooled analysis of all diabetic patients included in the **T**hrombolysis **i**n **M**yocardial **I**nfarction (TIMI) group trials

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performing coronary catheterization within 72 hours after the onset of the NSTE-ACS) and make recommendations about choosing between percutaneous coronary intervention (PCI) or CABG on the basis of data for patients with stable ischemic heart disease. Recent observational and subgroup analyses suggest that CABG might be the preferential method of revascularization for patients with DM and MVD also in the NSTE-ACS setting; however, dedicated randomized clinical trials are lacking. Finally, in patients who present with an ST-segment elevation myocardial infarction, the initial revascularization method of choice is generally PCI, instead of fibrinolysis or CABG, and DM status most often does not influence this decision. The management of residual MVD after primary PCI for ST-segment elevation myocardial infarction, however, remains controversial.

revascularisation. La plupart des lignes directrices suggèrent une approche invasive et rapide (c'est-à-dire une coronarographie dans les 72 heures suivant l'apparition du SCA-SSDST) et font des recommandations sur le choix entre l'intervention coronarienne percutanée (ICP) et le PAC qui s'appuient sur des données portant sur des patients dont la cardiopathie ischémique est stable. Des analyses observationnelles et par sous-groupe récentes laissent croire que le PAC pourrait être la méthode de choix pour la revascularisation chez les patients atteints de diabète et de CPV dans le contexte d'un SCA-SSDST; toutefois, aucun essai clinique portant sur cette question n'a encore été mené. Finalement, chez les patients ayant subi un infarctus du myocarde avec élévation du segment ST, la méthode de choix de la revascularisation initiale est en général l'ICP plutôt que la fibrinolyse ou le PAC, et dans la plupart des cas, la présence ou l'absence de diabète n'a pas d'influence sur cette décision. Toutefois, la question de la prise en charge de la CPV résiduelle après une ICP primaire pour un infarctus du myocarde avec sus-décalage du segment ST fait toujours l'objet de controverses.

up to 2006, the 30-day and 1-year mortality rates were higher in patients with vs without DM (odds ratio [OR], 1.40; 95% CI, 1.26-1.56 for 30-day mortality and OR, 1.33; 95% CI, 1.20-1.48 for 1-year mortality).[1] In a report of the **E**uro **H**eart **S**urvey on **ACS-II** (EHS-ACS-II), DM was a predictor of 1-year mortality after an ACS (OR, 1.37; 95% CI, 1.09-1.71). Interestingly, patients with DM and NSTE-ACS experienced the worst long-term prognosis among all patients in this registry (Fig. 1).[7] Additionally, a meta-analysis involving 432,066 patients with DM (and more than 1 million without DM) reported higher early (OR, 1.66; 95% CI, 1.59-1.74; $P < 0.0001$) and late (6-12 months; OR, 1.86; 95% CI, 1.75-1.97; $P < 0.0001$) mortality rates for patients with DM, with the gap between diabetic and nondiabetic patients being stable in the past decades.[8] In Canada, DM is also an independent predictor of in-hospital mortality in patients with NSTE-ACS.[9]

Newly diagnosed DM is also associated with increased rates of death, stroke, and major bleeding in the ACS setting.[10] As well, hyperglycemia and increased glycemic variability seem to correlate with poor clinical outcomes in ACS patients, independently of the DM status.[11-13] Interestingly, poor glycemic control is also related to worse prognosis after a revascularization procedure in patients with DM, even in the SIHD setting. After CABG, glycemic control is associated with lower rates of wound infection and long-term mortality,[14] whereas PCI patients with hemoglobin A1c $\leq$ 7% at the time of the procedure have lower restenosis rates at 12 months.[15,16]

NSTE-ACS

Primary invasive vs conservative approach and timing of revascularization

Current clinical practice guidelines support the use of a primary invasive strategy (that is, routine referral for coronary angiography instead of noninvasive ischemic testing) for most patients with DM and an NSTE-ACS.[17-19] An observational study in the United States reported lower rates of in-hospital mortality using the invasive approach within 48 hours of hospital admission compared with usual care in patients with DM (2.2% vs 3.8%; OR, 0.57; 95% CI, 0.50-0.63; $P < 0.0001$).[20] In a meta-analysis invasive or conservative strategies were compared according to DM status in 9904 patients (18.1% with DM) and showed a greater reduction in myocardial infarction (MI) in diabetic patients (absolute risk reduction 3.7% vs 0.1%; P for interaction = 0.02), despite a lack of significant interactions in other end points.[21] Recent publications suggest that after long-term (more than 10 years) follow-up, the initial benefits of an invasive approach might no longer be relevant.[22]

When the decision to pursue an invasive approach is taken, the next step is choosing the optimal time frame for when an

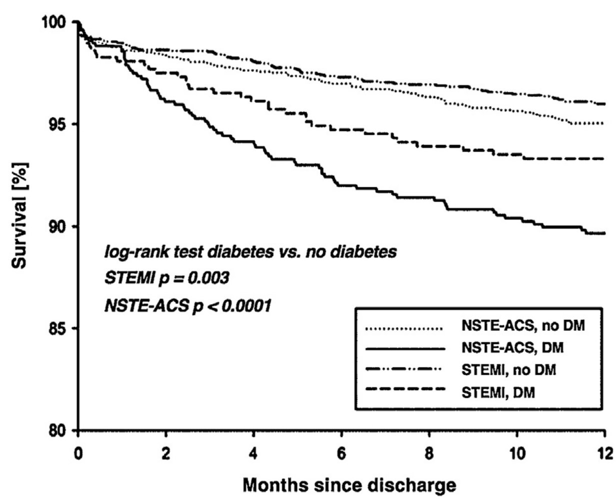

Figure 1. Kaplan-Meier survival curves after an acute coronary syndrome (ACS), according to the type of ACS (NSTE-ACS and STEMI) and DM status. Patients with DM who presented with NSTE-ACS had the higher mortality rates in the long term. Initial number of patients in each group: NSTE-ACS with no DM: 2241; NSTE-ACS with DM: 825; STEMI with no DM: 2346; STEMI with DM: 642. ACS, acute coronary syndrome; DM, diabetes mellitus; NSTE, non-ST segment elevation; STEMI, ST-segment elevation myocardial infarction. Data are from the **E**uro **H**eart **S**urvey on **ACS-II** (EHS-ACS-II). Modified from Hasin et al.[7] with permission from Elsevier.

NSTE-ACS patient should be referred to angiography and revascularization. The European Society of Cardiology and American College of Cardiology/American Heart Association guidelines for NSTE-ACS provide similar recommendations in this regard: DM is one of the factors that should prompt coronary angiography in the first 72 hours after admission for NSTE-ACS.[17-19] Despite these recommendations, studies on this topic present mixed results and in the United States, patients with DM might be less likely to be early referred to coronary angiography compared with non-DM patients.[23] A recent meta-analysis compared early (usually up to 24 hours) vs delayed coronary angiography in 5324 patients who presented with NSTE-ACS.[24] No significant differences in mortality or nonfatal MI rates were observed between the 2 groups, whereas in the diabetic subgroup (27.1% of the overall cohort) an early invasive strategy tended to a mortality benefit (HR, 0.67; 95% CI, 0.45-0.99; median follow-up, 180 days), although no significant interaction was detected (*P* interaction = 0.21; Fig. 2). In 2018, the **V**ery **Ear**ly vs **D**eferred **I**nvasive Evaluation Using **C**omputerized **T**omography (VERDICT) trial suggested similar rates of the composite of all-cause death, nonfatal recurrent MI, and hospital admission for refractory myocardial ischemia or heart failure after randomizing 2147 patients with NSTE-ACS to undergo coronary angiography in the first 12 hours after admission vs 48-72 hours. No interaction was found in the diabetic population (approximately 15% of all patients).[25]

Revascularization strategy

Evidence in SIHD. Current guideline recommendations about the optimal revascularization method (ie, PCI or CABG) in patients with diabetes after an ACS are extrapolated from evidence in DM patients with SIHD, because to date, no dedicated trials have evaluated this question in the ACS setting.[26]

In the **B**ypass **A**ngioplasty **R**evascularization **I**nvestigation (BARI) trial, 1829 patients with MVD were randomized; 65% of them who presented with unstable angina, to undergo either plain old balloon angioplasty or CABG and, after a follow-up of 5.4 years, survival in both groups was similar. A subanalysis including only patients with DM (19% of the overall trial population) showed a survival benefit for CABG compared with plain old balloon angioplasty (80.6% vs 65.5%; $P = 0.003$).[27] On the basis of these results, the **BARI 2 D**iabetes (BARI 2D) trial exclusively randomized patients with DM to coronary revascularization (PCI or CABG) vs medical therapy alone.[28] Approximately one-third of the PCI patients were treated with a drug-eluting stent (DES) and most (80%) of the procedures were single-vessel PCI. The 5-year survival rates (88.3% vs 87.8%; $P = 0.97$) and the composite of all-cause mortality, nonfatal MI, and nonfatal stroke (77.2% vs 75.9%; $P = 0.70$) were similar in both groups, but in a prespecified analysis, CABG resulted in lower rates of major cardiovascular events compared with medical therapy alone (22.4% vs 30.5%; $P = 0.01$), which was not observed in the PCI patients.[28]

The **Syn**ergy Between Percutaneous Coronary Intervention With **Tax**us and Cardiac Surgery (SYNTAX) trial reported a lower 5-year rate of all-cause mortality, MI, stroke, and repeat revascularization in patients with DM who underwent CABG vs PCI with a paclitaxel-eluting stent, a first-generation DES (29.0% vs 46.5%; $P < 0.001$).[29] Two other trials, the **C**oronary **A**rtery **R**evascularization in **Dia**betes (CARDia) trial and the U.S. Department of **V**eterans **A**ffairs - **C**oronary **A**rtery **R**evascularization in **D**iabete**s**

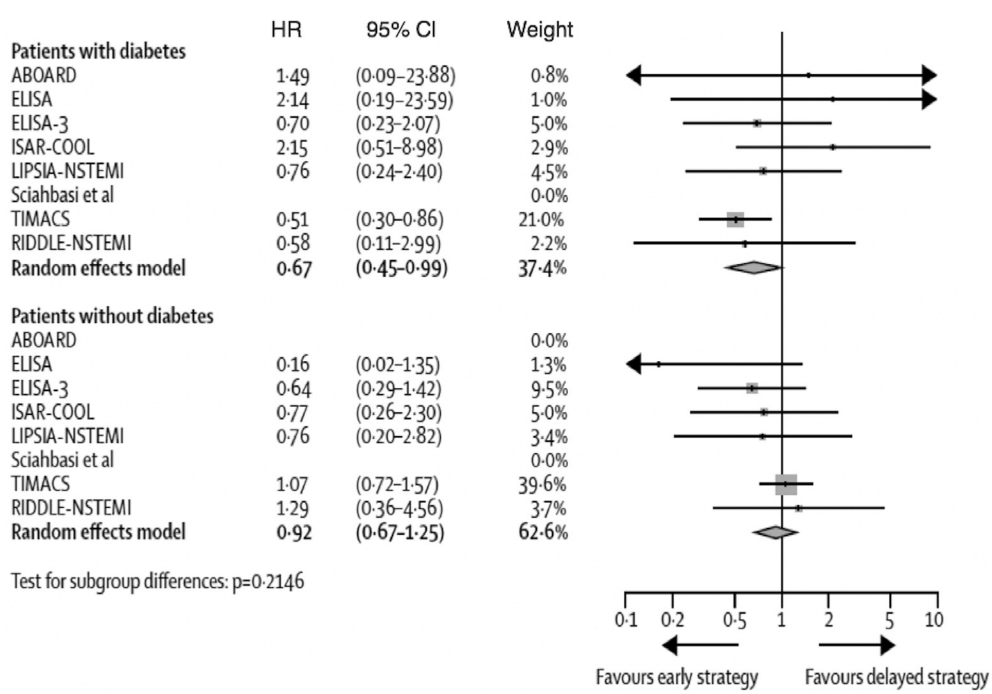

Figure 2. Mortality after an early invasive strategy vs a delayed invasive strategy in patients with and without DM after a non–ST-elevation acute coronary syndrome. Data from a meta-analysis of 8 trials and 5324 patients (27.1% with DM). CI, confidence interval; HR, hazard ratio. Reproduced from Jobs et al.[24] with permission from Elsevier.

(VA-CARDS) trial, attempted to compare revascularization strategies exclusively in patients with diabetes, but were stopped early because of slow enrollment, and not being able to provide a definite answer.[30,31]

The **F**uture **Re**vascularization **E**valuation in Patients With **D**iabetes Mellitus: **O**ptimal Management of **M**ultivessel Disease (FREEDOM) trial was the first international multicentre randomized clinical trial properly powered to compare hard clinical end points after PCI with a first-generation DES (paclitaxel or sirolimus) vs CABG in patients with DM, MVD, and without left main disease, in addition to optimal medical therapy.[4] A total of 1900 patients were randomized, after being considered eligible for PCI and CABG by the heart team. CABG was associated with a reduction in the primary outcome, a composite of all-cause mortality, nonfatal MI, and nonfatal stroke (18.7% vs 26.6%; $P = 0.005$) with a median follow-up of 3.8 years, as well as a lower rate of MI (6.0% vs 13.9%; $P < 0.001$). Of note, only 30.7% of the FREEDOM patients had a history of recent ACS. In a long-term follow-up of this trial (8 years), CABG led to lower all-cause mortality rates compared with PCI (18.3% vs 24.3%; $P = 0.01$).[32] In the FREEDOM trial, the SYNTAX score, commonly used to help guide revascularization decisions in the SIHD setting, had limited utility in patients with DM and MVD without left main disease.[33]

More recently, newer generations of DESs have been developed and questions have been raised about the safety and efficacy in patients with DM.[34,35] In 2014, a meta-analysis reported similar rates of repeat revascularization (relative risk [RR], 1.31; 95% CI, 0.74-2.29) and mortality (RR, 1.11; 95% CI, 0.67-1.84) in an indirect comparison of second-generation cobalt−chromium everolimus DES vs CABG in 24,015 patients with DM.[36] In a registry-based report with 8096 propensity-score matched diabetic patients with MVD, PCI with an everolimus DES was associated with similar rates of long-term mortality compared with CABG (HR, 1.12; 95% CI, 0.96-1.30; $P = 0.16$; up to 4 years of follow-up), but only if complete revascularization was attained.[37] The Randomized Comparison of Coronary Artery **B**ypass Surgery and **E**verolimus-Eluting **S**tent Implantation in the **T**reatment of Patients With Multivessel Coronary Artery Disease (BEST) trial compared CABG vs PCI with everolimus-eluting stents in 880 patients with MVD, 40% with DM. This study was stopped early because of slow recruitment and PCI noninferiority was not demonstrated for the composite of all-cause death, MI, and repeat revascularization at 2 years (7.9% in the CABG group vs 11.0% with PCI; $P = 0.32$ for noninferiority). Approximately 43% of all patients had unstable angina at enrollment and no differences in outcome rates were found in this subgroup (P value for interaction, 0.35). Conversely, in diabetic patients, a lower rate of the primary outcome was observed in the CABG group (9.1% vs 19.2%; $P = 0.007$; P value for interaction, 0.06), driven by lower rates of repeat revascularization.[38] A patient level pooled analysis was recently published by Head et al., including 11,518 patients, from 11 clinical trials, most of them mentioned in this review. PCI, compared with CABG, was associated with a higher risk of 5-year all-cause mortality in patients with DM and MVD (3266 patients; HR, 1.48; 95% CI, 1.19-1.84; $P = 0.0004$).[39]

Graft selection for CABG is still a matter of debate, especially in patients with DM. Because arterial conduits have better long-term graft patency, it is expected that long-term clinical outcomes will also be superior after a multiarterial CABG, compared with single arterial procedures. Conversely, the fear of sternal wound infection and mediastinitis, especially in the diabetic population, prevents a larger use of bilateral internal mammary artery (BIMA) in these patients.[40] In the absence of a dedicated trial in patients with DM, observational evidence support the use of BIMA, instead of single internal mammary artery (SIMA), with the latter being associated with lower long-term survival and similar perioperative complications, including sternal wound infection.[41] In the **Ar**trterial **R**evascularization **T**rial (ART), BIMA conferred no additional clinical benefit in the 5- or 10-year follow-up in a general population with MVD, or in the DM subgroup.[42,43] Concerning radial artery grafts, a recently published patient-level meta-analysis compared CABG with SIMA with radial graft vs SIMA with vein grafts and reported a 33% reduction in the composite of death, nonfatal MI, and nonfatal stroke with SIMA and radial graft at 60 months (HR, 0.67; 95% CI, 0.49-0.90; $P = 0.01$).[44] No interaction was observed in the DM subgroup (34.5% of the population; P interaction = 0.35). An observational study compared BIMA vs SIMA and radial graft in a propensity-matched diabetic cohort and reported similar rates of short- and long-term mortality and mediastinitis in both groups.[45] The ongoing **R**andomization **o**f Single vs **M**ultiple **A**rterial Grafts (ROMA; ClinicalTrials.gov identifier: NCT03217006) trial will contribute to the understanding of this topic.

Evidence in the ACS setting. CABG is still not widely used in patients with DM after an NSTE-ACS. Pandey and colleagues compared the use of different revascularization strategies in almost 30,000 patients with DM and MVD after an NSTE MI in the United States.[3] Only 36.4% of these patients underwent CABG after the ACS episode, whereas 46.2% underwent PCI and the proportion of PCI, but not CABG, significantly increased during the studied period. In patients with highly complex anatomy (eg, triple vessel disease patients with proximal left anterior descending artery involvement), no increase in PCI use was observed, and CABG is still the most used strategy.

A combined analysis, with individual data of the NSTE-ACS patients from the BEST, SYNTAX, and **Pre**mier of Randomized **Com**parison of **B**ypass Surgery versus **A**ngioplas**t**y Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease (PRECOMBAT) trials was recently published.[46] In all 1246 enrolled patients, CABG was associated with a significant reduction in the composite of all-cause mortality, MI, and stroke, compared with PCI (13.4% vs 18.0%; HR, 0.74; 95% CI, 0.56-0.98; $P = 0.036$), driven by a reduction in the rates of MI. When only patients with MVD (61%) were analyzed, the event rates were also higher in the PCI group, leading to a more pronounced risk reduction (14.0% vs 20.3%; $P = 0.035$). No interaction was found between DM status (34.7% of all patients) and outcomes ($P = 0.885$). Another study, including only patients with DM, MVD, and NSTE-ACS from the **A**cute **C**atheterization and **U**rgent **I**ntervention **T**riage Strateg**y** (ACUITY) trial, reported that CABG, compared with PCI, was associated with lower rates of the composite of all-cause death, MI, and repeat revascularization (17.3% vs 30.1%; $P = 0.01$), driven by lower rates of repeat revascularization.[47]

The largest study to date to compare CABG vs PCI in patients with diabetes and MVD in the ACS setting is a registry-based analysis of all revascularization procedures performed between 2007 and 2014 in the province of British Columbia, Canada.[26] In this work, Ramanathan and colleagues studied 3017 patients with DM and ACS, comprising 1966 PCIs and 1051 CABGs. Forty-three percent of the patients had triple vessel disease and 31.8% had proximal left anterior descending artery involvement. At 30 days, the rates of the composite of all-cause mortality, MI, and stroke (MACCE) were higher in the PCI group, as well as the rates of MI alone. In the long-term follow-up (from 31 days to 5 years), CABG was associated with reductions in rates of MACCE, the composite of MACCE and repeat revascularization, and all individual components of this combined end point, but stroke (Table 1). Interestingly, the benefits of CABG were observed even in the first month after revascularization, which differs from studies with SIHD patients. Table 2 shows a comparison of the MACCE event rates and risk reductions from these last 3 analyses (with ACS patients) and the FREEDOM trial.

The ideal time when CABG should be performed after an ACS is still not clear. A registry-based report assessed the influence on time to in-hospital CABG after an NSTE-ACS in the general population, from 2002 to 2008 in the United States. The proportion of patients with DM among those who underwent early CABG (up to 48 hours from admission) was 31.2%, vs 39.5% ($P < 0.001$) in the group who underwent late CABG (more than 48 hours; median time of 101.8 hours, interquartile range, 70.8-147.1). Other risk factors, such as hypertension, smoking, and congestive heart failure, were significantly associated with delayed CABG. In the light of this higher-risk profile, delaying CABG was not related to better in-hospital outcomes, including death (3.6% in the early CABG group vs 3.8% in the late CABG group, $P = 0.56$), MI, heart failure, and stroke.[48] Another single-centre observational study compared outcomes among 758 NSTE-ACS patients (47% with DM and 98.3% with MVD) treated with CABG according to the time between symptom onset and the beginning of the surgery (less than 24 hours, 24 hours to 72 hours, and > 72 hours). No difference was observed regarding in-hospital mortality rates and 5-year rates of death, MI, stroke, and repeat revascularization.[49] Actually, it seems that the operative risk of patients with ACS is mainly related to the presence of preoperative complications, such as cardiogenic shock or heart failure, rather than the time to surgery (in-hospital mortality of 12.5% for patients with preoperative complications vs 1.4% for those without).[50] It is still not clear if the use of fractional flow reserve (FFR) could lead to better outcomes in patients with an NSTE-ACS. FFR does not seem to be beneficial in guiding percutaneous revascularization of the culprit lesion in a general population with NSTE-ACS,[51] although results are mixed.[52] No study so far has examined the use of FFR to guide surgical revascularization in the ACS setting, but in the SIHD population current results do not seem promising.[53]

Possible mechanisms for CABG superiority. The mechanisms for explaining CABG superiority over PCI are not yet fully understood. Patients with DM usually have more diffuse atherosclerotic disease compared with the general population and lesions that are not angiographically significant might be responsible for cardiovascular events in the future[54]; CABG, but not PCI, is capable of bypassing multiple lesions.[55] Also, DM is related to higher rates of stent complications, such as stent thrombosis, neoatherosclerosis, and restenosis.[56] Graft loss after CABG might not alter the target vessel; however, stent thrombosis usually leads to loss of the target vessel. Therefore, one might speculate that patients with DM have a higher risk of stent complications, which are less poorly tolerated than patients without DM. Although CABG benefit is even more pronounced in the subgroup of patients with DM who suffer an MI in the post-CABG follow-up period,[57] none of the previous mechanisms seem to have a differential role in the SIHD or ACS settings and more studies are needed to clarify the pathophysiology behind the clinical evidence discussed so far.

ST-Elevation Acute MI

In patients with STEMI, DM status does not play a major role in guiding the initial decision of the most adequate revascularization strategy. When timely available and feasible, primary PCI is the preferred revascularization method, instead of fibrinolysis, and CABG should only be indicated in a small proportion of patients, usually after a failed or complicated PCI.[58,59] Revascularization should be offered as early as possible after the first medical contact and the same recommendations of the general population should be applied to patients with DM.[60-62]

Table 1. Event rates for selected clinical outcomes in patients with diabetes and multivessel coronary disease who underwent a revascularization procedure after an acute coronary syndrome

	30-day event rates			31-day to 5-year event rate		
	PCI	CABG	*P*	PCI	CABG	*P*
MACCE	8.2%	4.3%	< 0.01	33.4%	20.8%	< 0.01
Death	2.3%	1.2%	0.05	22.3%	12.4%	< 0.01
Stroke	0.8%	1.6%	0.04	5.8%	6.2%	0.97
Myocardial Infarction	6.1%	1.8%	< 0.01	17.6%	9.9%	< 0.01
Repeat revascularization		NA		22.6%	8.2%	< 0.01

Observe that, compared with PCI, CABG patients experienced lower rates of MACCE and MI, even in the first 30 days after the surgery.
CABG, coronary artery bypass graft; MACCE, major adverse cardiac or cerebrovascular event; PCI, percutaneous coronary intervention.
Data from a registry-based analysis from the province of British Columbia, Canada.[26]

Table 2. Comparison of the MACCE (comprised of all-cause mortality, myocardial infarction, and stroke) rates in a registry study,[26] a pooled analysis of 3 clinical trials,[46] a subanalysis of the ACUITY trial,[47] and a subgroup analysis of the FREEDOM trial[4]

	Description	N	Time	PCI, %	CABG, %	*P*
Ramanathan et al.[26]	Patients with DM, MVD, and ACS from a Canadian registry	3017	31 days to 5 years	33.4	20.8	< 0.01
Chang et al.[46]	Pooled analysis of the BEST, PRECOMBAT, and SYNTAX trials including patients with MVD and NSTE-ACS (34.7% with DM)	758	5 years	19.0	13.2	0.037
Ben-Gal et al.[47]	Subanalysis of the ACUITY trial including patients with DM, MVD, and NSTE-ACS	326	1 year	22.1	14.8	NA
Farkouh et al.[4]	Subgroup of patients with DM and MVD after an ACS in the FREEDOM trial	583	2 years 5 years	14.7 30.7	13.3 20.9	0.09

All analyses compared patients with DM and/or MVD who underwent a revascularization procedure (PCI or CABG) after an ACS. Times are maximum follow-up times when data on the event rates were collected. *P* values are for the comparison of CABG vs PCI. See text for a description of each study included in this table.

ACS, acute coronary syndrome; ACUITY, **A**cute **C**atheterization and **U**rgent **I**ntervention **T**riage Strateg**y**; BEST, Randomized Comparison of Coronary Artery **B**ypass Surgery and **E**verolimus-Eluting **St**ent Implantation in the **T**reatment of Patients With Multivessel Coronary Artery Disease; CABG, coronary artery bypass graft; DM, diabetes mellitus; FREEDOM, **F**uture **Re**vascularization **E**valuation in Patients With **D**iabetes Mellitus: **O**ptimal Management of **M**ultivessel Disease; MACCE, major adverse cardiac or cerebrovascular events; MVD, multivessel disease; NA, not available; NSTE, non-ST elevation; PCI, percutaneous coronary intervention; PRECOMBAT, **Pre**mier of Randomized **Com**parison of **B**ypass Surgery versus **A**ngioplas**t**y Using Sirolimus-Eluting Stent in Patients With Left Main Coronary Artery Disease; SYNTAX, **Syn**ergy Between Percutaneous Coronary Intervention With **Tax**us and Cardiac Surgery.

Because most patients with DM have MVD, an important question is whether all lesions or only the infarct-related artery should be treated urgently in the STEMI setting. The **Pre**ventive **A**ngioplasty in Acute **M**yocardial **I**nfarction (PRAMI) trial assigned 465 patients to undergo either preventive complete PCI revascularization (234 patients, 15% with DM) or infarct-artery only PCI (231 patients, 21% with DM). After a mean 23-month follow-up, preventive PCI significantly reduced the rates of the primary outcome, a composite of cardiac death, nonfatal MI, or refractory angina (HR, 0.35; 95% CI, 0.21-0.58; $P < 0.001$), which led to early termination of the trial. In the DM subgroup, a similar point estimate was found, without evidence of interaction (HR for DM patients, 0.39; 95% CI, 0.12-1.20; *P* for interaction = 0.50).[63] A meta-analysis with 3561 patients from 11 contemporary trials (including PRAMI) reported reduced risk of death or MI with complete revascularization, compared with culprit-only revascularization (RR, 0.76; 95% CI, 0.58-0.99; $P = 0.04$). Importantly, when performed at the same time of the primary PCI, as opposed to a staged procedure, complete PCI was also related to a mortality benefit (RR, 0.62; 95% CI, 0.39-0.97; $P = 0.03$) and diabetes did not influence outcomes in the meta-regression analysis ($P = 0.72$).[64] Similar results were also reported in another recent meta-analysis.[65] The Complete vs Culprit-only Revascularization to Treat Multi-vessel Disease After Early PCI for STEMI (COMPLETE; ClinicalTrials.gov identifier: NCT01740479) trial aims to compare staged PCI revascularization of all lesions vs revascularization of the culprit-lesion only in STEMI patients and will contribute to the understanding of this topic. No study has examined completion of revascularization early with PCI vs CABG after treatment of the culprit lesion. It is possible that the long-term benefits of CABG in the DM population might favour subsequent revascularization with CABG. Particularly in patients treated with fibrinolytic therapy, still broadly used in remote areas, CABG might be superior to PCI in short- and long-term follow-up.[66]

In patients with cardiogenic shock after a STEMI, early revascularization is advised, most commonly with PCI, and DM status does not influence this decision.[67] In the few patients with cardiogenic shock due to an ACS who are treated with CABG, DM is an independent predictor of prognosis, being associated with almost 40% increase in mortality after a mean follow-up of 2.8 years (HR, 1.39; 95% CI, 1.11-1.74; $P = 0.005$).[68] The **Culprit** Lesion Only PCI vs Multivessel PCI in Cardiogenic **Shock** (CULPRIT-SHOCK) trial reported lower rates of the 30-day composite of death and renal replacement therapy in 706 patients with post-MI cardiogenic shock and MVD who underwent culprit lesion-only PCI vs complete PCI revascularization (RR, 0.83; 95% CI, 0.71-0.96; $P = 0.01$). Approximately one-third of the patients had DM and, albeit no interaction was formally present ($P = 0.08$), non-DM patients tended to have a larger benefit with culprit lesion-only PCI (RR, 0.74; 95% CI, 0.61-0.91), whereas in the DM population the results were neutral (RR, 1.02; 95% CI, 0.81-1.28).[69]

Conclusions

Choosing the most adequate coronary revascularization method for patients with DM and MVD after the onset of an ACS is usually a challenging task, because of the lack of randomized evidence to guide the decision-making process. In the SIHD setting, CABG is the revascularization method of choice, as shown by a variety of clinical trials. Substudies of large clinical trials and registry-based analyses have suggested that CABG might also be the preferred revascularization method for patients with DM after an NSTE-ACS, resulting in lower rates of hard clinical end points compared with PCI. Randomized data are needed to corroborate these early results and to show the safety of the CABG procedure in the short-term horizon after an ACS. Because of the complexity of this subject, the heart team approach, which is already well established in the management of SIHD patients, should also be routinely implemented when making decisions about revascularization of patients with DM and MVD in the acute setting.

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