Title

Evidence for Preoperative Aspirin Improving Major Outcomes in Patients With Chronic Kidney Disease Undergoing Cardiac Surgery

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Review Article

Preventing Perioperative Major Adverse Cardiovascular Events in Patients with Diabetes

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ABSTRACT

Aim of review: Diabetes is a chronic and slowly progressing disease that has a tendency to develop rapidly deteriorating complications such as major adverse cardiovascular events (MACE), especially under the stress of surgery. While clinical strategy to prevent MACE is controversial and uncertain.

Method: We conducted a comprehensive review of current clinical strategies in preventing perioperative MACE, in particularly related to diabetic patients.

Results: The major findings are: 1) Current clinical studies have demonstrated that coronary artery bypass graft (CABG) is still a better therapy than percutaneous coronary intervention (PCI) on the ground of reducing repeat revascularization, myocardial infarction and death for most diabetic patients with left main-stem and multivessel coronary artery disease who require revascularization, however, it remains to be studied whether coronary revascularization before noncardiac surgery can protect diabetic patients from MACE; 2) There is lack of evidence that intensive or "tight" glycemic control perioperatively can reduce MACE, instead, a moderate or less stringent glucose management probably is safer for patients undergoing surgery;3) The recent results of clinical trials on beta- blockers appear to be disappointing in preventing MACE in surgical patients, including diabetic patients. Meanwhile, the perioperative therapy with statins, angiotensin- converting enzyme inhibitors or multifactorial interventions is promising in preventing MACE in diabetic patients.

Summary: Further studies targeted at preventing MACE in diabetic patients undergoing surgery are needed in order to fight this major health problem in perioperative medicine.

The prevalence of diabetes continues to soar worldwide. American adults diagnosed with diabetes have been markedly increased by 82.3% since the late 1990s, from 5.1% in 1997 to 9.3% in 2014 (1). Such rapid rising prevalence of diabetes has brought serious consequences for the population health. The major shift has been seen in the leading causes of death in the United States during the past 3 decades. While a precipitous decline in death rates was seen from stroke (63%) and heart disease (52%), a paradoxical increase in death rates was seen from diabetes (45%) (2), particularly among women (3).

The most common form of diabetes mellitus is type 2 diabetes. This disorder affects approximately 90% to 95% of the 14.6 million Americans diagnosed with diabetes and typically occurs later in life (4). The increasing prevalence of type 2 diabetes is mainly related to the rising prevalence of obesity, the relative-

ly low levels of physical activity and increasing age of the population in the United States. Due to the underlying metabolic defects of insulin production/action and the frequent co-existence of hypertension and dyslipidemia, type 2 diabetes has long been recognized as an independent risk factor for cardiovascular disease (CVD). In fact, CVD becomes virtually ubiquitous among diabetic patients as their age advances and consequently CVD and its complications represent the most common causes of morbidity and mortality in diabetic patients (4, 5). Thus, it may be appropriate to say, "diabetes is a CVD" (6).

Both the diabetes epidemic and the population aging have growing importance for the health care system, implying that more services especially surgical cares will be required for the treatment and management of chronic and acute health conditions associated with diabetes. It is estimated that the number of patients eligible for surgery will increase by 25% by 2020 (7), and among the patients with diabetes, more than 50% of them will undergo surgery at some time in their lives (8). Compared with nondiabetic patients undergoing surgery, diabetic patients are more likely to suffer serious complications perioperatively because many of these patients have severe coexisting diseases such as atherosclerotic disease, peripheral vascular disease and renal disease, and they are highly vulnerable to surgical stress due to the inherent metabolic and neural/hormonal abnormalities. Among the etiology of surgical complications, major adverse cardiovascular events (MACE) including cardiac dysfunction/failure, cardiac arrhythmias, myocardial infarction (MI), cerebral vascular events, and cardiac arrest represent major and common causes of morbidity and mortality in surgery, especially among ones undergoing major surgery (9-11). For example, about 3.9% of patients with risk of cardiac disease underwent noncardiac surgery experienced perioperative MACE (10).

Nevertheless, clinical strategies to prevent MACE are controversial and uncertain (12), furthermore, few studies have been targeted especially at clinical strategies to prevent MACE in diabetes. Therefore, the data from the clinical trials on diabetes and perioperative medicine gathered in this review are largely from the studies including a significant portion of diabetic patients or sub-group analyses.

Pathogenesis of MACE in Diabetic Patients

Previous studies have well demonstrated that patients with diabetes more frequently have left main coronary artery disease (CAD), generalized/multivessel atherosclerosis, and diffuse CAD (13). Also, diabetic patients have a larger amount of lipid-rich plaques or a greater atherosclerotic burden, which manifests itself by evolution of vulnerable plaques, with consequent predisposition to rupture and precipitation of acute coronary syndrome (ACS), and probably MACE too. However, despite extensive clinical and basic research, the mechanisms responsible for MACE remain enigmatic in surgical patients in general and become more puzzled in diabetic patients in particular. It is still largely unknown about the role of surgery-induced fluctuation of blood glucose, especially acute hyperglycemia in development of MACE, though some studies showed deleterious effects of acute hyperglycemia on endothelial function, thrombosis and inflammatory reaction (14).

Today, we recognize that most ACSs are caused by coronary luminal thrombosis, which is secondary to atherosclerotic plaque rupture or/and erosion. MACE probably also is caused by the similar mechanisms to the ones for ACS, but triggered by the extreme and complex surgical stress. Several lines of evidence support this hypothesis: Firstly, perioperative MI is preceded almost universally by long- rather than short-duration ST-segment changes, an indication of prolonged stress and myocardial ischemia (15, 16). Secondly, perioperative MIs are characterized by that most of them occur early after surgery and are preceded by episodes of increases in heart rate (17, 18). Thirdly, beta-adrenergic receptor blockers, due to their inherent role in blocking sympathetic activation, have been shown to reduce perioperative ischemia and the risk of MI and death in high-risk surgical patients (9, 18, 19). Fourthly, coronary plaque disruption is found in more than half of fatal perioperative MIs and considered as a primary cause of fatal perioperative MI (20-22). And finally previous studies demonstrated that tonic

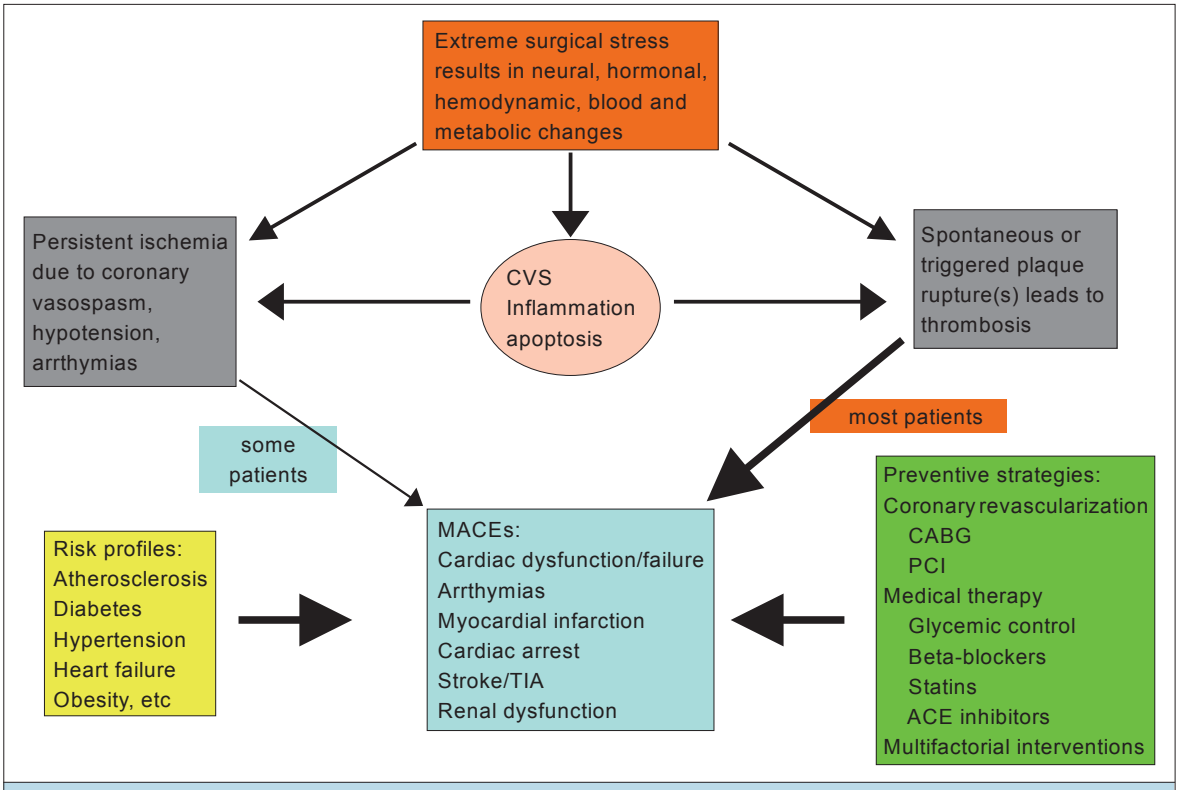

Figure. Proposed mechanisms for Perioperative Major Adverse Cardiovascular Events (MACEs).
The role of diabetes in pathogenesis of MACEs remains unclear but may be related to increased vulnerability of plaques.
CVS, cardiovascular system; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; ACE, angiotensin-converting enzyme; TIA, transient ischemic attack.

or chronic β-adrenergic activation provokes pro-inflammatory and proapoptotic changes in the mouse heart, indicating a close link between stress hormone (catecholamines) and inflammatory reaction, a key mechanism to provoke plaque rupture(s) (23, 24). Nevertheless, persistent myocardial ischemia secondary to coronary spasm, hypotension and arrhythmias may also result in MACE in some patients undergoing surgery (Figure).

Coronary Revascularization

Coronary revascularization techniques and medical therapy continue to progress in recent years, nevertheless the benefits of these therapies in diabetic patients are attenuated significantly by the underlying metabolic abnormalities and comorbidities. Currently, there is still lack of studies addressing specifically the prevention of perioperative MACE in diabetic patients, although some clinical trials have shown promising results in improving clinical outcomes and preventing CVD events in surgical patients in general (12).

Percutaneous Coronary Intervention vs. Coronary Artery Bypass Graft

Since Andreas Gruentzig performed the first coronary angioplasty on human in 1977, the tremendous growth has been witnessed in percutaneous coronary intervention (PCI) applications in patients with CAD, especially coronary stents with bare metal stents (BMS) in earlier years and drug-eluting stents (DES) in recent years. As increasing applications of PCI and its associated potential complications, it has sparked endless debate concerning the choice of PCI vs. coronary artery bypass graft (CABG) (25, 26). Overall, CABG is still superior to PCI including DES for most patients with multivessel and left mainstem CAD on two important grounds: reducing

repeat revascularization and relieving angina while PCI has advantage of less procedural risk, especially stroke. And it remains debating with respect to hard end points such as mortality (27, 28). However, the evidence from the meta-analyses (29, 30), registries (31, 32) and randomized clinical trials (RCT) (33, 34) showed a survival advantage for CABG over PCI.

In 2013, the landmark five-year results of Synergy between Percutaneous Coronary Intervention with TAXUS and Cardiac Surgery (SYNTAX) trial (35) have demonstrated that patients with complex left main (LM) or multivessel disease (MVD), i.e., high and intermediate SYNTAX scores ⩾23, will do better after CABG, and those with less complex LM/MVD, i.e., low SYNTAX scores ⩽22, fare equally well with either CABG or PCI (stents). As the SYNTAX trial (N= 1,800) concluded, CABG should remain the standard of care for patients with complex lesions (high or intermediate SYNTAX scores), while PCI is an acceptable alternative for patients with less complex lesion (low SYNTAX scores). These findings of the SYNTAX trial have been incorporated into the European Society of Cardiology (ESC)/European Association of Cardiothoracic Surgery (EACTS) Myocardial Revascularization Guidelines update in 2014 (36). Nonetheless, the search for the Holy Grail (a better coronary stent) by interventional cardiology continues in the ongoing EXCEL trial (37), in which the goal is to evaluate the stent (Xience) as a potential treatment option for select patients with high-risk LM disease. The benefits of CABG are even greater in diabetic patients as showed in BARI and FREEDOM trials (38, 39).

Coronary Revascularization before Noncardiac Surgery

The Coronary Artery Surgery Study (CASS, a prospective cohort study published in 1997) and CARP (a RCT published in 2004) trials are two major studies to compare coronary artery revascularization (CABG and PCI) with medical therapy before noncardiac surgery. In the CASS, Eagle and his colleagues (40) found that among 1, 961 patients undergoing higher-risk surgery, prior CABG was associated with fewer postoperative death and MIs compared with medically managed CAD. In the CARP trial, however, McFalls et al. (41) reported that patients with stable CAD undergoing vascular operations were randomly assigned to undergo coronary revascularization (CABG or PCI) or medical therapy, and after the vascular surgery there were no differences between the two groups in the incidence of MI or mortality. Of note, diabetic patients represented about 20% in either revascularization group or medical therapy group in the CARP trial.

Although published more than 17 years ago, the CASS provided evidence that CABG provides protection against adverse cardiac events for the patient undergoing major surgery as long as the graft(s) maintain patency. While the CARP was limited by: 1) the study excluded patients with symptoms of unstable coronary disease, left main CAD, aortic stenosis, or severe left ventricular dysfunction, which are Class I indications for CABG based on American College of Cardiology (ACC)/American Heart Association (AHA) guidelines for CABG surgery published in 2004 (42); and 2) the group of coronary revascularization in this study was mixed with 2 different techniques: CABG and PCI. However, several studies have already demonstrated a high incidence of cardiovascular complications when noncardiac surgery is performed shortly after PCI (43- 45). Actually, in the substudy of the CARP trial, Ward et al. compared clinical outcomes in the patients receiving CABG vs. PCI as prophylaxis for elective vascular surgery and found that compared with the patients with PCI (131 patients), the patients with CABG (91 patients) had fewer MIs despite more diseased vessels in the CABG group and tended to spend less time in the hospital after the vascular operation. The authors concluded that more complete revascularization was accounted for the intergroup differences (46).

Perioperative Medical Therapy

Glycemic Control

Intermediate-Term (Days) Glycemic Control

A study led by Van den Berghe et al. (47) in 2001 has provided the evidence to support beneficial effects of "tight" glycemic control, i.e., targeting normoglycemia (⩽110 mg/dl) in the surgical intensive care units (ICU) patients, where the

most patients were nondiabetic patients (13% patients were diabetics in the ICU). In this RCT, investigators have shown that intensive insulin therapy to maintain blood glucose ⩽ 110 mg/dl reduced morbidity and mortality among 1,548 patients in the surgical ICU. However, in another RCT including 1,200 patients in the medical ICU, the same group of investigators found that although intensive insulin therapy significantly reduced morbidity by the prevention of newly acquired kidney injury, accelerated weaning from mechanical ventilation and accelerated discharge from the ICU and the hospital, it failed to reduce in-hospital mortality (40.0% in the conventional-treatment group vs. 37.3% in the intensive-treatment group, P=0.33). In addition, in the subgroup of 433 patients who stayed in the ICU for less than three days, mortality was greater among those receiving intensive insulin therapy (56 patients died vs. 42 patients died in the conventional-treatment group, P=0.05). In contrast, among 767 patients who stayed in the ICU for three or more days, in-hospital mortality in the 386 who received intensive insulin therapy was reduced from 52.5% to 43.0% (P=0.09) (48).

In contrast, the landmark NICE SUGAR study (a large international, multicenter and randomized clinical trial, published in 2009) demonstrated that among critical ill adult patients (N=6,104), intensive glucose control (vs. conventional glucose control) led to increased risk of death, and a blood glucose target of 180 mg/dl or less resulted in lower mortality than did a target of 81-108 mg/dl (49).

Long-Term (Years) Glycemia Control

Several clinical trials have demonstrated that intensive glycemic control (target value of hemoglobin A1c < 6.0%) can reduce the risk of microvascular complications (diabetic retinopathy, nephropathy and neuropathy) in patients with type 2 diabetes (50, 51). However, it remains unclear about whether intensive glycemic control could reduce macorvascular complications (CVD events) (52).

Two large RCTs, the ACCORD and ADVANCE trials have reported different findings about whether intensive therapy vs. standard therapy (target value of hemoglobin A1c 7.0-7.9%) could reduce blood glucose and improve long-term outcomes in patients with type 2 diabetes (53). The ACCORD study enrolled 10,251 participants (54). During follow-up over an average of almost four years of treatment, the primary outcome, i.e., a composite of nonfatal MI, nonfatal stroke, or death from cardiovascular causes occurred in 352 patients in the intensive-therapy group, as compared with 371 in the standard- therapy group (hazard ratio [HR], 0.90; 95% confidence interval [CI], 0.78 to 1.04; P=0.16). At the same time, 257 patients in the intensive- therapy group died, as compared with 203 patients in the standard-therapy group (HR, 1.22; 95% CI, 1.01 to 1.46; P=0.04). This is a difference of 54 deaths, or about 3 per 1,000 participants each year. A higher death rate among diabetes patients treated aggressively to lower their blood sugar prompted the sponsor, National Institutes of Health (NIH) to halt one arm of a major study (53). In contrast, researchers from the ADVANCE trial enrolled 11,140 high-risk patients with type 2 diabetes and found after a median of 5 years of follow-up that there were no significant effects of the type of glucose control (intensive vs. standard) on major macrovascular events (HR with intensive control, 0.94; 95% CI, 0.84 to 1.06; P=0.32), death from cardiovascular causes (HR with intensive control, 0.88; 95% CI, 0.74 to 1.04; P=0.12), or death from any cause (HR with intensive control, 0.93; 95% CI, 0.83 to 1.06; P=0.28). However, major microvascular events were reduced (9.4% vs. 10.9% ; HR, 0.86; 95% CI, 0.77 to 0.97; P=0.01), primarily because of a reduction in the incidence of nephropathy (4.1% vs. 5.2%; HR, 0.79; 95% CI, 0.66 to 0.93; P=0.006) (55).

In an early report, the UKPDS trial (long-term intensive vs. standard therapy of blood glucose control) had similar findings to the ADVACE, showing that the achievement of nearly normal glycemic levels did not reduce major cardiovascular events in the short term (50). However, the UKPDS Group has recently found subsequent reduction in fatal and nonfatal macrovascular complications in a 10-year follow-up study (56).

More recently, the VADT trial randomized 1, 791 patients with type 2 diabetes. After a median 5.6 years follow-up, the investigators showed similar results to those in the ACCORD trial, i.

e., intensive glucose control had no significant effect on the rates of major CVD events or microvascular complications, while there were more CVD deaths in the intensive arm than in the standard arm (38 vs. 29, sudden death 11 vs. 4) though the difference was not statistically significant (57).

Despite the different results from these clinical trials (54-57), two common findings are as follows: 1) aggressively lowering blood sugar or near-normal glycemic control for about 3 to 5 years did not bring cardiovascular benefits and was potentially harmful in high-risk patients with type 2 diabetes, and 2) intensive glucose control was associated with an increased risk of severe hypoglycemia that plunged dangerously low and required assistance or hospitalization. On the basis of previous and latest clinical trials, American Diabetes Association (ADA), ACC and AHA issued a joint statement in 2009 that recommended an A1c goal of < 7% for most (nonpregnant) adults but also recognizing that less stringent A1c goals may be appropriate for certain patients for long-term glycemic control (52).

Short-Term (Hours) Glycemic Control

Gandhi et al. (58) conducted a RCT to compare intraoperative intensive insulin therapy (to maintain glucose levels between 80-100 mg/dl, N=199) with conventional glucose management (no insulin unless glucose levels > 200 mg/dl, N=201) in the patients undergoing cardiac surgery (the only RCT so far in addressing intraopeative glucose control). The trial results have shown that intensive insulin therapy during cardiac surgery did not reduce perioperative death or morbidity, instead, more deaths (4 deaths vs. 0, P=0.061) and strokes (8 strokes vs. 1, P=0.020) occurred in the intensive treatment group. Other studies (RCT or observational studies) have shown that periopeartive intensive glycemic control improve clinical outcomes (morbidity and mortality) in patients undergoing cardiac surgery (59, 60). Since the treatment regimens differed, however, between intraoperative vs. perioperative glycemic control, it is difficult to determine whether the beneficial effects of these 2 studies are due to intraoperative or postoperative interventions.

The above contrasting results leave us to ponder what role glycemic control plays in preventing MACE in diabetic patients. It also suggests that a "one recipe fits all" (tight glucose control for all) approach may be unwise since the patient populations and conditions are different markedly as seen in ICU, surgery and general medicine. Especially for surgical patients under general anesthesia, intensive/tight glucose control is associated with: 1) an increased risk of hypoglycemia and its serious complications because it is difficult to identify the symptoms associated with hypoglycemia under anesthesia or sedation (61, 62); 2) difficulty in achieving the goal during surgery due to the stress and various medications associated with surgery and anesthesia; 3) required substantial additional resources to achieve desired glycemic control perioperatively; and 4) lack of a reliable and precision mean to continuously monitor (only capable of measuring episodically at present) and control levels of serum glucose. And finally it is still to be determined on whether surgical stress-induced short-term and moderate elevation of blood sugar levels has some merits as an adaptive response (63) and a blunted response may simply implicate depressed physiological reserve in counterregulatory hormonal system, such as epinephrine, glucagon, cortisol, and growth hormone, while the intensive insulin therapy could further compromise the reserve, which otherwise would prevent hypoglycemia. As Goodarzi and Psaty (64) indicated recently, lowering glucose to control macrovascular disease in type 2 diabetes may be just "treating the wrong surrogate end point".

If clinical improvements of microvascular and macrovascular outcomes take years to become evident (56), a short time of glycemic control, such as during intraoperative or perioperative periods, probably would not produce significant effects on cardiovascular outcomes, instead, it may increase risk of hypoglycemia. More importantly, it remains unclear whether hyperglycemia is a primary cause for cardiovascular complications or simply a wrong surrogate endpoint. Obviously, further studies are certainly in need for the effectiveness of perioperative glycemic control.

Beta-blockers

2014 ACC/AHA Guideline Update on Periopera-

tive Cardiovascular Evaluation and Management of Patients undergoing Noncardiac Surgery (65) recommended: 1) Beta-blockers should be continued in patients undergoing surgery who have been on beta-blockers chronically (Level of Evidence: B); 2) Beta-blocker therapy should not be started on the day of surgery (Level of Evidence: B). The recommendations are mainly based on the studies as below.

In 1996, Mangano and colleagues (9) performed a RCT to investigate the effect of beta-blocker, atenolol, on patient outcomes (about 30% patients in this trial were diabetics) and concluded that in patients with risk for CAD who must undergo noncardiac surgery, treatment with atenolol during hospitalization can reduce mortality and the incidence of cardiovascular complications for as long as two years after surgery.

However, the findings of this early study could not be confirmed in the following studies (12). In 2006 DIPOM trial (the trial that was specifically targeted at diabetic patients perioperatively and enrolled 921 patients), perioperative beta-blocker (metoprolol started the evening before surgery for a maximum of 8 days) did not significantly affect mortality and cardiac morbidity in diabetic patients undergoing major noncardiac surgery during a median follow-up of 18 months (66). In 2008, Devereaux et al. (67) presented the results of the PeriOperative ISchemic Evaluation trial (POISE), which is a large RCT (included 8,351 patients, of them 29% were diabetics) designed to determine the impact of perioperative metoprolol (started acutely 2-4 hours before surgery and continued for 30 days) on the 30-day risk of major cardiovascular events. The results were mixed with significant reductions in the primary outcomes of cardiac death, nonfatal MI, and cardiac arrest (5.8% vs. 6.9%, HR 0.84, CI 0.70-0.99, P=0.04). There were also reductions in atrial fibrillation (2.2% vs. 2.9%, P=0.04) and the need for myocardial revascularization (0.3% vs. 0.6%, P=0.01). However, those beneficial effects were counterbalanced by an increase in death (3.1% vs. 2.3%, HR 1.33, CI 1.03-1.74, P=0.03) and stroke (1.0% vs. 0.5%, HR 2.17, CI 1.26-3.74, P=0.05). Other adverse effects included significant bradycardia (6.6% vs. 2.4%, P=0.0001) and hypotension (15.0% vs. 9.7%, P<0.0001). The results from the POISE highlight risk in assuming that a prophylactic therapy of the beta-blocker has benefit without substantial harm.

Probably, beta-blockers would be beneficial to only selected groups (again, not "one recipe fits all") of patients undergoing surgery, such as the patients with hypertension, tachycardia and congestive heart failure (CHF) or/and with certain genetic polymorphisms (68). More importantly, the potential benefits of beta-blockers in the patients can be achieved only with 1) a sensible dosing regimen that titrates doses individually and that minimizes hypotension and significant bradycardia; 2) a treatment protocol that has to be continued over a long periods of time before the surgery or potential cardiovascular events since "pleiotropic" effects of beta-blockers will take time to become effective (69).

Statins

Statin therapy is well established for prevention of cardiovascular events, including in diabetic patients. In primary prevention for diabetic patients, the Collaborative Atorvastatin Diabetes Study (CARDS trial, N=2,838) showed that atorvastatin 10 mg daily leads to a substantial reduction (37%) in major cardiovascular events in patients with type 2 diabetes with no history of cardiovascular disease and without high low-density lipoprotein (LDL)-cholesterol concentrations, and this drug also reduced the risk of stroke (48%) (70). In the secondary prevention, in GREACE substudy (approximately 15-25% of study participants who had diabetes), atorvastatin (vs. physicians' standard care) significantly reduced the relative risk of total mortality by 52% (P=0.049), coronary mortality by 62% (P=0.042), coronary morbidity by 59% (p<0.002) and stroke by 68% (P=0.046) (71). In the field of perioperative medicine, Hindler et al. (72) conducted a meta-analysis to evaluate the overall effect of preoperative statin therapy on postoperative outcomes and concluded that preoperative statin therapy can significantly reduce the risk of mortality for surgical patients (ranged from about 38% to 59% reduction). One small RCT (total 100 patients included) reported the effect of statin in patients undergoing noncardiac surgery (73).

Angiotensin- Converting Enzyme Inhibitors/Renin-Angiotensin System Blockers

The HOPE study examined whether angiotensin-converting enzyme (ACE) inhibitors have cardiovascular protective effects. In the HOPE, 3,577 individuals with diabetes received either ACE inhibitor, ramipril (up to 10 mg daily), or placebo. The study was stopped 6 months early after 4.5 years follow-up because of a consistent benefit of ramipril compared with placebo. Ramipril lowered the risk of the combined primary outcome by 25% (95% CI 12-36%, P=0.0004), MI by 22% (6-36%), stroke by 33% (10-50%), cardiovascular death by 37% (21-51%), total mortality by 24% (8-37%), and overt nephropathy by 24% (3-40%, P=0.027) (74). The ONgoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) trial showed that telmisartan reduces cardiovascular morbidity including MI and stroke in subjects with a broad spectrum of cardiovascular risk factors, including type 2 diabetes independent of reduction in blood pressure. It is the first study to show comparable reno- and cardioprotective effects between a renin- angiotensin system (RAS) blocker (telmisartan) and ramipril in a broad section of at-risk patients, on top of standard care (75). In a study with nearly half of the patients received ACE inhibitors were diabetics, preoperative ACE inhibitor therapy was associated with significant reductions in the risk of acute kidney injury (AKI), operative mortality, and septicemia in open-heart surgeries (76). In a retrospective cohort study, we have recently shown that preoperative use of rennin-angiotensin system inhibitors may have significant renoprotective effects for aging patients undergoing elective cardiac surgery (77). Other major clinical trials have shown that ACE inhibitors provide cardioprotective effects and should be used as first-line anti-hypertensive agents in all patients with diabetes (78, 79).

Conclusions

Diabetes is a chronic and slowly progressing disease that has a tendency to develop rapidly deteriorating complications such as serious cardiovascular events involving the heart, brain and/or kidneys, especially under the stress of surgery. Therefore, to prevent cardiovascular events like MACE, it would be better to consider the perioperative period as a time to adjust managements of patients based on severity and stability of their diseases, comorbidities and surgical conditions. When assessing and/or choosing various clinical strategies, the RCT (explanatory trials) has now become a "gold" standard for comparing different types of treatment for the disease. Nonetheless, it should be appreciated that even a superbly designed RCT may be limited by highly selected enrollment and thus the results of RCT may be not representative or be inapplicable to the entire populations. In this regard, observational studies (pragmatic trials), especially with a large database or registry, may reflect the picture of the real world and therefore complement the RCT (12). More importantly, pragmatic trials produce results that can be generalized and applied in routine practice settings (80). Major clinical trials to prevent perioperative MACEs in patients with diabetes are summarized in table.

In brief, it remains unclear about which treatment is the most effective one in preventing MACE and improving long-term outcomes in patients with significant CAD and diabetes undergoing major noncardiac surgery, i.e., prophylactic CABG vs. PCI vs. medical therapy. In addition, currently there is a lack of evidence that a short time or perioperative intensive glycemic control can reduce MACE. A moderate (less stringent) glucose management perioperatively appears to be more safe and feasible than tight glucose control. And finally, two major shifts have been seen in this research field. Firstly, it has been well demonstrated that qualitative and functional changes in the biologic characteristics of atherosclerotic plaques (stabilization), rather than mere shrinking of the stenosis, might underline the clinical improvement consistently found in the lipid-lowering statin trials (81). Therefore, a new therapeutic strategy, stabilization of atheroma has emerged and is aimed to prevent and reduce cardiovascular events (82). Secondly, recent studies have shown that multifactorial intervention, a therapeutic strategy targeting hyperglycemia, hypertension, dyslipidemia, microalbuminuria and behavior modification, not depending on any specific drug can

Table[#]. Major Clinical Trials to Prevent Perioperative MACEs in Patients with Diabetes.

Study	Patient profile and patients with DM (%)	Groups and patients number	Morbidity (%)	Mortality (%)	RR, HR or OR (95% CI)	Comments
			Periop MI			
CASS[40] 1997	CAD, undergoing high risk surgery (~10%)	CABG, N=964 Medical, N=582	0.8* 2.7	1.7* 3.3	Medical vs. prior CABG: OR 2.51 (1.41-4.46) for periop MI and death	A major study supports that prior CABG protects against MACE in the patients undergoing major surgery
CARP[41] 2004	CAD, undergoing vascular surgery (20%)	CABG or PCI N=258 Medical, N=252	12 14	22 23	CABG/PCI vs. medical: RR 0.98 (0.70-1.37) for the death at 2.7 years	The study is limited by excluding unstable or left main CAD, poor LV function, severe AS and mixing CABG with PCI
POISE[67] 2008	CAD or risk of CAD patients for surgery (29%)	Metoprolol, N=4147 Placebo, N=4177	4.2* 5.7	3.1* 2.3	Metoprolol vs. placebo: HR 1.33 (1.03-1.74) for 30 days mortality	The largest study on periop beta-blocker with mixed results
Durazzo et al.[73] 2004	Patients undergoing Vascular surgery (17%)	Atorvastatin, N=50 Placebo, N=50	6 16	2 4	N/A	At 6 month the combined end point including MI, angina, stroke and death was 8.0% vs. 26% in statin and placebo group respectively, P<0.031
Lazar et al.[59] 2004	Patients undergoing CABG with glycemic control (100%)	Intensive, N=72 Standard, N=69	0 2.8	1.7* 8.7	N/A	2 years follow-up for mortality
			Stroke			
Gandhi et al.[58] 2007	Patients undergoing cardiac surgery with glycemic control (20%)	Intensive, N=199 Conventional, N=201	4* 1	2 0	Intensive vs. conventional: RR 8.0 (1.0-63.7) for stroke	An only RCT with intraoperative control of glycemia
			Cardiac events			
DIPOM[66] 2006	DM patients undergoing major surgery (100%)	Metoprolol, N=462 Placebo, N=459	10 9.8	16 16	Metoporolol vs. placebo: HR 1.03 (0.74-1.42) for the death	A beta-blocker on DM patients with negative results. The median follow-up was 18 months
Mangano et al.[9] 1996	CAD or risk of CAD patients for surgery (32%)	Atenolol, N=99 Placebo, N=101	16.2* 31.6	10* 21	Atenolol vs. placebo: HR 0.5 (0.2-1.1) for the death	The data of morbidity and mortality were accumulated over 2 years

[#] All studies in this table are RCT except that the CASS study is an observational study.
*with significant difference vs. medical, placebo or standard/conventional group, respectively (P<0.05).
MACE, major adverse cardiovascular events; CAD, coronary artery disease; CABG, coronary artery bypass graft; PCI, percutaneous coronary intervention; periop, perioperative; MI, myocardial infarction; DM, diabetes mellitus; LV, left ventricular; AS, aortic stenosis; RR, relative risk; OR, odd ratio; HR, hazard ratio; CI, confidence interval.

markedly improve long-term outcomes in diabetic patients (83). Further studies are critically needed, especially large clinical (either RCTs or observational) studies aimed specifically at preventing MACE in diabetic patients. This review provides an insight into an increasing complex question: perioperative MACE and diabetes.

The authors claimed that this study has no relationship with industry.

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