Patients with diabetes mellitus represent roughly 25% of the nearly 1.5 million surgical and percutaneous coronary revascularization procedures performed annually in the United States. Typically, diabetic patients have an increased number of associated risk factors and therefore experience increased morbidity and mortality during and after revascularization compared with nondiabetic patients. Associated comorbidities in the diabetic population that may contribute to poorer outcomes include hypertension, dyslipidemia, systolic and diastolic heart failure, autonomic dysfunction, peripheral vascular disease, cerebrovascular disease, microvascular disease, a prothrombotic state, and nephropathy. These comorbidities must be considered carefully when one evaluates the diabetic patient as a candidate for revascularization.

A. Revascularization and Clinical Issues

Clinical Trials

The acute angiographic success rates for balloon coronary angioplasty (percutaneous transluminal coronary angioplasty [PTCA]) in diabetic patients (85% to 95%) have been comparable to those for nondiabetics; however, major adverse cardiac events are generally higher among patients with diabetes. A nearly 2-fold increase in 9-year mortality (36.9% versus 17.9%, \( P < 0.01 \)) was reported for diabetic patients compared with nondiabetic patients after PTCA in the National Heart, Lung, and Blood Institute registry. The increased incidence of restenosis and associated need for revascularization among diabetic patients after PTCA has led to speculation about the possible advantages of coronary bypass grafting (CABG) and novel percutaneous coronary intervention (PCI) techniques for this group.

The Bypass Angioplasty Revascularization Investigation (BARI) trial reported a highly significant difference in survival for randomized patients with treated diabetes and 2- or 3-vessel disease who underwent CABG compared with PTCA (76% versus 56%, \( P = 0.0011 \)), with substantially higher subsequent revascularization rates among the PTCA group (60% versus 13%, \( P < 0.001 \)). However, the benefits of CABG were seen only for those patients receiving at least 1 arterial conduit during CABG. In contrast to the findings for randomized patients in BARI, treated diabetic patients in the BARI registry did not differ significantly in long-term survival after PTCA compared with CABG. Although the reasons for this difference in outcomes are not entirely clear, the treated diabetics in the BARI registry had a higher educational level, were more physically active, were less likely to smoke cigarettes, and had a higher level of quality of life than their randomized counterparts, all findings that might be surrogates for better diabetic control. They were also less likely to have 3-vessel disease than randomized patients with diabetes in BARI or those in the registry who underwent CABG. Unlike the BARI randomized trial, the BARI registry and other nonrandomized retrospective studies have failed to confirm a worse survival rate for diabetic patients undergoing PTCA than for those having CABG, which suggests that among diabetics, physician selection for patients undergoing revascularization may be an important determinant in achieving comparable outcomes for CABG and PTCA.

Mechanisms

Several mechanisms, including decreased endothelial function, a prothrombotic state, increased intimal hyperplasia, increased negative remodeling, increased protein glycosylation, and increased vascular matrix deposition, have been postulated to account for the heightened vascular response and poorer outcome after PTCA among diabetics. A large body of experimental and clinical evidence suggests that hyperglycemia and hyperinsulinemia potentiate these negative mechanisms. Thus, it is postulated that tighter control of diabetes might contribute to more favorable outcomes, but confirmatory studies are lacking. The results of coronary intravascular ultrasound and histological analysis of atherectomy specimens suggest that the accelerated restenosis...
among diabetics may be caused both by a heightened proliferative response and by increased vascular matrix deposition. Serial intravascular ultrasound assessment in patients with hyperinsulinemia during glucose intolerance has revealed increased neointimal tissue proliferation after coronary stent implantation, which suggests an important causative role for insulin. Administration of troglitazone in a small number of non–insulin-dependent diabetic patients after stent implantation has been shown to reduce neointimal tissue proliferation.

**Stents and IIb/IIIa Platelet Receptor Antagonists**

The use of intracoronary stents has improved short- and long-term results for nondiabetic patients. However, among diabetics, most studies involving stents have been retrospective and small in patient number. The restenosis rates vary when stents are used in diabetic patients but generally are improved compared with those from PTCA; yet, they remain higher than those observed in nondiabetics. Restenosis is generally higher after stent placement in insulin-resistant diabetics. No data are available to determine whether diabetics with tight control of hyperglycemia have lower restenosis rates after stenting. The use of the IIb/IIIa platelet receptor antagonist abciximab has been shown to significantly reduce major cardiac events and target-vessel revascularization at 6 months among diabetic patients after stenting. These findings suggest abciximab may exert beneficial effects on the diabetic prothrombotic state and neointimal proliferation. Intracoronary vascular irradiation has also been shown to reduce restenosis after PTCA and when used as part of therapy for in-stent restenosis among diabetics. Thus, there are several therapies now available that may improve outcomes for treated diabetic patients over those reported by the randomized BARI trial. These include intracoronary stents, adjunct acute therapy with the platelet IIb/IIIa receptor antagonist abciximab, intracoronary vascular irradiation, tight control of diabetic hyperglycemia, pharmaco-coated stents, and aggressive medical therapies with statins and angiotensin converting enzyme inhibitors.

The current BARI 2D trial, which uses a 2×2 factorial design to compare tight diabetic control with insulin-providing versus insulin-sensitizing therapy with and without a revascularization procedure of choice, will contribute significantly to our understanding of the appropriate revascularization strategy for diabetic patients.

**B. Preconditioning and Altered Cardiovascular Responses in Diabetes**

Individuals with diabetes are at higher risk for angina, myocardial infarction, heart failure, and ventricular arrhythmia and have increased mortality after myocardial infarction and CABG surgery than the nondiabetic population. The factors that contribute to the increased risk are not fully understood. Because long-term prognosis is determined in large part by left ventricular function, more information is needed to understand the optimal strategies to prevent and treat coronary disease in diabetics and to preserve ischemic and revascularized myocardium. As pharmacological and molecular approaches are developed as adjuvant therapies to salvage ischemic myocardium, the unique physiological characteristics of the diabetic heart will need to be considered. Such characteristics may relate to changes in cellular metabolism, ion exchange, signaling pathways, and gene expression.

Thrombolytic therapy and PCIs that restore flow to occluded coronary arteries are effective in limiting the injury. However, studies showing reperfusion itself causes injury imply that additional myocardium is amenable to salvage. Several mechanisms of reperfusion-induced injury and ventricular dysfunction have been identified. These include “the oxygen paradox”; “the pH paradox”; intracellular Ca²⁺ loading; activation of lipases, proteases, endonucleases, and the signaling pathway leading to apoptosis; and neutrophil infiltration with associated vascular plugging, edema, and no reflow. Thus, preservation of cellular energetics and prevention of intracellular Na⁺ and subsequent Ca²⁺ loading during ischemia are expected to limit cellular injury. Two such approaches include ischemic preconditioning and inhibition of Na⁺/H⁺ exchange (NHE), because they limit ischemic and reperfusion injury in animal and human heart. Yet, limited information is available describing the efficacy of preconditioning and NHE inhibition to prevent ischemia/reperfusion injury in the diabetic heart.

**NHE and Ischemia/Reperfusion Injury**

Abrupt arrest of flow to the myocardium deprives ventricular myocytes of O₂ and substrate, causing the rapid inhibition of oxidative phosphorylation and a switch to anaerobic glycolysis for the production of high-energy phosphates. The transition from oxidative phosphorylation to anaerobic glycolysis has several important consequences. Cytosolic creatine phosphate and adenosine triphosphate (ATP) concentrations decrease rapidly. Intracellular pH (pHᵢ) falls as protons are produced during the hydrolysis of ATP and accumulated during the production of lactic acid. Likewise, extracellular pH (pHₑ) decreases as intracellular H⁺ molecules are delivered to the extracellular compartment by NHE, Na⁺/HCO₃⁻ cotransport, lactate transport, and lactic acid and CO₂ diffusion. Because certain glycolytic enzymes are inhibited by acidosis, the accumulation of intracellular H⁺ serves as a negative feedback mechanism to limit acidification of the cell. The fall of ATP and the accumulation of ADP, Pᵢ, and H⁺ decrease the free energy of hydrolysis of ATP available to the cell. Consequently, energy-dependent regulation of transmembrane ion gradients such as the Na⁺/K⁺ pump and sarcoplasmic reticulum Ca²⁺ cycling are inhibited. Taken together, all of these processes cause a net accumulation of intracellular Na⁺ (Na⁺ᵢ) and Ca²⁺ (Ca²⁺ᵢ), which are associated either directly or indirectly with cellular injury.

**Preconditioning**

Preconditioning is an adaptive process by which a previous ischemic event increases the tolerance of the heart to subsequent ischemia. Preconditioning does not prevent injury but delays the time to onset of irreversible ischemic/reperfusion injury. Benefits from preconditioning included a decrease in cellular necrosis and infarct size, ischemic contracture, cell-to-cell electrical uncoupling, posts ischemic contractile dys-
function, and arrhythmia. The beneficial effects of preconditioning were originally described by Murry and colleagues in 1986 when multiple brief episodes of ischemia decreased injury in reperfused ischemic canine hearts. Subsequently, this phenomenon was observed in many species and was found to have a biphasic response, with an early and late adaptation to ischemia. Preconditioning is stimulated by multiple triggers mediated by activation of G-protein-coupled receptors. These include adenosine A$_1$, adenosine A$_3$, bradykinin, opioid, angiotensin II, endothelin, a$_1$-adrenergic and muscarinic receptors, and reactive oxygen species and NO. Preconditioning is believed to occur in humans as suggested by studies in isolated human cardiac tissue or in exercise-induced ischemia, coronary artery syndromes, PCIs, and CABG surgery. Yet, there are few data to address the capacity of diabetic human heart to precondition, and what data do exist suggest that human diabetic myocardium precondition poorly.

For example, adenosine decreased infarct size by 67% in subjects with anterior infarction when used as an adjunctive therapy in combination with thrombolysis; however, the outcome in diabetic patients was not specified.

The cellular mechanism of preconditioning appears to involve the protein kinase C pathway and the opening of the mitochondrial ATP-dependent K channel (K$_{ATP}$). Importantly, protein kinase C is activated in diabetes, and the K$_{ATP}$ channel is the same channel modified by diabetes and blocked by sulfonylureas. Thus, several lines of evidence suggest an intrinsic impairment of diabetic myocardium to precondition and the possibility of an attenuation of preconditioning by sulfonylureas. Of note, a recent study showed that both diabetes and hyperglycemia attenuated the preconditioning-like effect of the K$_{ATP}$ channel opener diazoxide in ischemic canine heart.

### NHE Inhibition and Preconditioning in Diabetic Heart

Importantly, inhibition of the NHE decreased ischemic injury in diabetic heart. Two clinical studies have addressed the use of NHE inhibition to improve clinical outcome in coronary syndromes. Rupprecht and colleagues studied 100 patients with acute anterior infarction. When the NHE inhibitor cariporide was infused 10 minutes before PCI, left ventricular ejection fraction was preserved 3 weeks after the event, and the number of LV segments with severe hypokinesis was decreased. By contrast, the GUARD During Ischemia Against Necrosis (GUARDIAN) trial studied 11 590 subjects with coronary artery syndrome, including unstable angina, PCIs, non-ST-segment elevation myocardial infarction, and CABG. Cardiovascular events were shown to be decreased in CABG patients up to 6 months after surgery. Limited information is available about the outcome in diabetic patients because the studies were not powered to address the outcome in this population.

In animal studies, preconditioning and NHE inhibition are equivalent in their capacity to limit ischemia/reperfusion injury. Obviously, the degree of protection depends on many factors, not the least of which is the duration of ischemia. Gumina and colleagues recently showed that NHE inhibition and ischemic preconditioning had similar protective effects after 60 minutes of ischemia, but NHE inhibition was more effective when the ischemia interval increased to 90 minutes. Although added effects of NHE inhibition and ischemic preconditioning were not identified in this study, the possibility that different modalities like NHE inhibition and ischemic preconditioning could be additive or synergistic should be investigated. Whether the protective effect of NHE inhibition and preconditioning share a common pathway remains uncertain.

Ionic homeostasis is regulated differently in the diabetic heart. Glycolysis and NHE activity decrease, and the Na$^+$/Ca$^{2+}$ exchange activity decreases. Free fatty acids increase, and the capacity to scavenge reactive oxygen species increases.

An important question remains: Does NHE inhibition protect diabetic heart from ischemia/reperfusion injury? Although clinical data are not available, animal studies do indicate that NHE inhibition protects ischemic diabetic myocardium, as assessed by preservation of high-energy phosphates, as well as intracellular Na$^+$ and Ca$^{2+}$ loading, and it reduces cellular enzyme loss. Interestingly, diabetes alone reduced enzyme loss, a finding consistent with the view that diabetic myocardium is more tolerant of ischemia. However, this point is controversial and may depend on the species studied and the model of diabetes used. Additional studies, particularly in humans, will be necessary to determine the influence of the diabetic state on the magnitude of ischemia/reperfusion-induced injury.

Another important issue relates to the role of the microvasculature in ischemia/reperfusion injury. Accumulating clinical evidence implicates the microvasculature as an important site of injury and no reflow. Important questions to be answered include understanding the relative susceptibility of the endothelium, smooth muscle cells, and ventricular myocytes for the occurrence of reperfusion injury. To what extent is the injury caused by necrosis or apoptosis? What are the signaling pathways involved in these outcomes? In addition, does the endothelium precondition like ventricular myocardium? Recently, some relevant data have emerged from Frustaci and colleagues, who showed that cells isolated from left ventricular biopsies of diabetic patients with cardiomyopathy were more susceptible to injury. Importantly, the diabetic state increased the susceptibility to necrosis and apoptosis in ventricular myocytes and endothelial cells. Concomitant hypertension further increased the susceptibility to necrotic cell death in myocytes and endothelial cells but did not increase apoptosis. Tentatively, these differences are attributed to increased angiotensin II receptor sites and to oxidative stress in diabetic hearts that increases further with associated hypertension.

In summary, ionic regulation and metabolism during ischemia are affected by diabetes mellitus. The diabetic heart may be more tolerant of ischemia in certain animal-based experimental models. However, data do not exist in humans. Although this review has emphasized the role of preconditioning and NHE inhibition to protect ischemic and reperfused diabetic heart, other strategies are also being investigated. Adenosine receptor agonists, K$_{ATP}$ channel openers,
anti-integrins, antiselectins, and anticomplement molecules that target the preconditioning mechanism or inflammation are currently being assessed or planned. Additional work is necessary to define the role of these modalities in the treatment of diabetic patients. Pharmacological approaches to increase the tolerance of myocardium to ischemia and effectively reperfuse ischemic myocardium represent opportunities to preserve ventricular function in patients with coronary artery disease and may improve clinical outcome. As new clinical strategies to prevent the loss of ventricular muscle in acute coronary syndromes are developed and applied to the general population, the unique physiological response of the diabetic heart must be considered. More basic science is needed to more fully understand the effect of the prediabetic and diabetic state on metabolism, cellular energetics, gene expression, signal transduction, and channel function. Likewise, clinical studies should be designed to include, when possible, sufficient subjects with diabetes to have the statistical power to assess the influence of the diabetic state on the clinical end points.

**Recommendations**

On the basis of the available data and conference discussions, Writing Group VI proposes the following American Heart Association (AHA) initiatives, with potential collaborative partners as noted:

1. Develop programs and support research to implement aggressive medical therapy in diabetics undergoing revascularization. Potential collaborative partners: American College of Cardiology (ACC); American Diabetes Association (ADA); AHA Council on Clinical Cardiology; National Heart, Lung, and Blood Institute (NHLBI).
2. Advocate and support further research in diabetic patients to identify and more accurately assess the risk/benefit of PCI or CABG procedures. Potential collaborative partners: ACC, ADA, AHA Council on Clinical Cardiology, NHLBI.
3. Explore new strategies to improve the efficacy and safety of surgical revascularization, such as arterial conduits, off-pump revascularization, and concomitant medical therapy that includes glycemic control. Potential collaborative partners: National Institutes of Health (NIH), AHA targeted research, AHA Council on Cardio-Thoracic and Vascular Surgery, AHA Council on Clinical Cardiology.
4. Explore new strategies to improve the efficacy and safety of PCI, such as intravascular radiation therapy, coated stents, Ibll/IIa antagonists, and intensive medical therapy. Potential collaborative partners: NIH, AHA targeted research, AHA Council on Cardio-Thoracic and Vascular Surgery, AHA Council on Clinical Cardiology, industry.
5. Encourage clinical trials to determine the optimal timing of revascularization in the diabetic patient. Potential collaborative partner: NIH.
6. Encourage clinical trials to prespecify an adequate number of diabetic patients to allow subgroup analysis. Potential collaborative partners: NIH and industry.
7. Encourage and support research into novel imaging strategies to identify and characterize vascular wall abnormalities to better identify and assess the progression/regression of disease and the impact of therapy. Potential collaborative partners: NIH, AHA targeted research, AHA councils on Clinical Cardiology and Radiology.

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