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Optimal approaches to diabetic patients with multivessel disease

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ABSTRACT

The pathophysiology of diabetes and systemic insulin resistance contributes to the nature of diffuse atherosclerosis and a high prevalence of multivessel coronary artery disease (CAD) in diabetic patients. The optimal approach to this patient population remains a subject of an ongoing discussion. In this review, we give an overview of the unique pathophysiology of CAD in patients with diabetes, summarize the current state of therapies available, and compare modalities of revascularization that have been investigated in recent clinical trials. We conclude by highlighting the importance of a comprehensive heart team approach to every patient while accommodating both patient preference and quality-of-life decisions.

Introduction

Diabetes has become a global pandemic in the 21st century, with a significant rise in prevalence in developed and developing countries. The number of individuals affected continues to increase as detrimental lifestyle choices become more common, including decreased physical activity and increased intake of saturated fats. A recent survey of worldwide prevalence of diabetes demonstrated a rate of 6.4% in 2010, affecting 285 million adults, and an expected rise to 7.7% in 2030 (439 million adults) [1]. Type II diabetes accounts for over 95% of the cases worldwide [2]. The distribution of diabetes in the population also varies by economic status and age, as the majority of diabetic patients are older than 60 in the developed world, and between 40 and 60 in the developing world. The prevalence of diabetes in the United States is approximately 8%, with a relative increase of over 60% over the past decade.

Insulin resistance, which often precedes diabetes mellitus by years or decades [3], contributes to the acceleration of atherosclerosis. Coronary artery disease (CAD) has the highest rate of mortality globally [4], and is very prevalent in adults with diabetes as compared to those without diabetes. By definition, multivessel CAD corresponds to at least two major epicardial coronary arteries with severe (>70%) stenosis. In a broad population of patients, about 50% of the patients in the CASS registry undergoing a coronary angiogram met this definition [5]. The pathophysiology of diabetes and systemic insulin resistance contributes to the nature of diffuse atherosclerosis and an even higher prevalence of multivessel CAD in diabetic patients.

The optimal approach to diabetic patients with multivessel coronary artery disease remains a subject of an ongoing discussion. The goal of this review is to understand the unique pathophysiology of CAD in patients with diabetes, summarize the current state of therapies available for managing diabetic patients with multivessel disease, and finally compare modalities of revascularization that have been investigated in recent clinical trials.

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Pathophysiology of CAD in diabetic patients

Diabetic patients with no evidence of CAD have an equal likelihood to experience a myocardial infarction (MI) as patients without diabetes with a history of prior MI [6]. The high-risk features of atherosclerotic plaques in diabetic patients stem from the heightened inflammatory milieu due to insulin resistance, dyslipidemia, hyperglycemia, and thrombophilia [2]. Insulin resistance contributes to both hyperglycemia and dyslipidemia, and platelets are hypercoagulable due to the overexpression of glycoprotein IIb/IIIa and an affinity towards aggregation, which lead to the final thrombotic event associated with endothelial dysfunction and plaque rupture.

The diffuse nature of atherosclerosis in diabetes, which is probably due to the systemic nature of the factors discussed above, portends a worse prognosis and a poorer response to revascularization. Intravascular ultrasound of arteries of diabetic patients has demonstrated that the arteries are less likely to undergo vascular remodeling, which is thought to be favorable for flow hemodynamics [7]. The nature of atherosclerotic plaques in diabetic patients also demonstrates increased and more diffuse endothelial dysfunction, more lipid-rich and macrophage-dense plaques with thin caps, more intracoronary thrombus formation and more chronic total occlusions with overall increase in atherosclerotic burden. Patients with diabetes have a limited ability to develop collaterals in response to severe coronary stenoses [8], but also they frequently have left main artery involvement and more chronic total occlusions. By optimizing the medical management of diabetes and CAD, there is a potential promise for improved outcomes after revascularization.

The history of coronary revascularization in diabetic patients with multivessel CAD is fascinating and underscores the need for well-conducted clinical trials to inform our practice.

Revascularization: PCI vs. CABG

PTCA era: Coronary artery bypass graft (CABG) vs. balloon angioplasty (PTCA)

There are no trials that compared PTCA with CABG in diabetic patients exclusively, but the Bypass Angioplasty Revascularization Investigation (BARI), which recruited a minority (19%, $N = 353$) of patients with diabetes out of the 1829 study participants, dramatically impacted clinical practice [9]. Overall, in patients with multivessel CAD and who were having angina or had evidence of ischemia, BARI reported similar rates of in-hospital mortality and 5-year overall survival. However, in the diabetic subgroup there was a statistically significant survival benefit associated with CABG at 5 years (rate of mortality 34.5% in the PTCA arm vs. 19.4% in the surgical arm; $p = 0.003$) and that persisted out to 10 years, with the majority of the surgical patients receiving an internal mammary artery (IMA) graft (81%). The diabetes story in BARI led to an NHLBI alert recommending the preferential consideration of CABG in diabetic patients with multivessel CAD.

Interestingly, the results of BARI were not reproduced in subsequent trials that compared angioplasty to surgery, as the Emory Angioplasty vs. Surgery (EAST) trial and the Coronary Angioplasty vs. Bypass Revascularization (CABRI) did not show a statistical difference in the diabetic subgroups [10,11]. The Randomized Intervention Treatment of Angina (RITA-1) trial, which had a trend towards higher mortality in patients with diabetes who underwent bypass surgery, was criticized for enrolling lower-risk diabetic patients, with a third of patients having single-vessel disease only [12].

Similar to BARI, these trials have an important historical value as hypothesis generating, but were performed in an era prior to coronary stent placement, and prior to the ubiquitous use of statins and optimal medical therapy with beta-blockers and dual-antiplatelet therapies.

BMS era: CABG vs. PCI with bare metal stenting (BMS)

The advent of bare metal coronary stents led to the design of the Arterial Revascularization Therapy Study (ARTS), which compared patients with multivessel CAD undergoing percutaneous coronary intervention (PCI) vs. CABG [13]. The trial demonstrated no significant increase in mortality in the diabetic subgroup of patients undergoing PCI with stenting as opposed to bypass surgery, with 89% use of an IMA and 3.5% use of a IIb/IIIa-inhibitor, but there was a trend towards improved survival with CABG (mortality rates 6.3% in the PCI arm vs. 3.1% in the surgical arm; $p = 0.294$). These findings were echoed in another bare metal stent (BMS) trial: mortality in the CABG group was 5.4% as compared to 17.6% in the PCI group within the diabetic patients of the SoS trial, with a hazard ration of 3.53 (1.14 to 10.95) favoring CABG in patients with diabetes [14]. In the MASS II study, there was a significant increase in mortality between years 2 and 5 in patients randomized to medical treatment as compared with patients treated with percutaneous intervention or CABG ($p = 0.039$); there was no statistically significant difference in mortality between angioplasty and surgery ($p = 0.7$) [15].

In the diabetic patients subgroups of BARI and ARTS, the rates of repeat revascularization were significantly higher in patients who underwent PTCA or bare metal stenting with a 6- to 7-fold increase in repeat revascularization rates at 1-year follow-up in ARTS and 7-year follow-up in BARI [9,16]. The predominant reason for the need for a repeat procedure in these trials was the high rate of restenosis in patients with diabetes due to mechanisms such as accelerated neo-intimal hyperplasia. In fact, the severity of restenosis correlated inversely with the degree of glycemic control, with optimal glycemic control associated with a lower rate of target vessel revascularization in patients with type II diabetes undergoing elective PCI [17]. The prospect of benefit of thiazolidinediones in reducing intimal hyperplasia was countered by significant adverse effects from this class of insulin-sensitizing agents, and their use in patients undergoing coronary revascularization fell dramatically. With persistently elevated rates of repeat revascularization procedures despite medical therapy, the advent of new technology that would reduce neo-intimal hyperplasia seemed crucial in this patient population.

DES era: CABG vs. drug-eluting stents (DES)

The introduction of drug-eluting stents (DES) in 2003 has led to a marked reduction in angiographic restenosis rates [18].