# Systematic Review of Therapies for Stable Coronary Artery Disease in Diabetic Patients

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Diabetes mellitus is a significant risk modifier for stable coronary artery disease, causing patients to have more extensive and diffuse lesions. Opposing treatment strategies remain a matter of debate. A multiple database search was conducted and outcomes, lesion, and patient characteristics were compared. Overall mortality, cardiac death, major adverse cardiovascular and cerebrovascular events, and need for revascularization were higher with percutaneous coronary intervention than with coronary artery bypass graft surgery. Multivessel disease and high Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) scores were associated with better outcomes for coronary artery bypass graft surgery.

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Cardiovascular disease in patients with diabetes mellitus is associated with higher morbidity and mortality, accounting for as many as 65% of deaths in this population [1]. It remains the seventh leading cause of death, with estimated annual health care costs of $174 billion [2, 3]. Diabetic patients have poorer outcomes and higher revascularization rates after both percutaneous coronary intervention (PCI) and surgery [4, 5].

The coronary artery lesions in diabetic patients are more extensive and diffuse. There is altered lipid metabolism owing to insulin resistance and endothelial dysfunction, resulting in a propensity for involvement of medium and small vessels, accelerated atherosclerosis, increased vessel wall reactivity, and plaque complications. Insulin resistance increases endothelial fatty acid oxidation and reduces the prostacyclin synthetase and endothelial nitric oxide synthase activity [6]. Endothelium dysfunction, formation of advanced glycation end products, generation of reactive oxygen species, systemic inflammation, and accelerated atherosclerosis are among other phenomena that lead to poorer outcomes for diabetic patients [7]. Diabetic patients have more comorbidities with obesity, increased risk of infection and sternal dehiscence, problems with conduits, and vasculopathy-associated organ dysfunction. Cardiovascular disease remains the leading cause of death among diabetic patients, with a 68% mortality rate due to heart disease or stroke.

There has been a constant evolution of therapies with strides in medical management, next generation drug-eluting stents (DES), and greater use of arterial conduits in surgical revascularization. Awareness and strategies for medical management are more refined now compared with previous decades, with greater emphasis on control of hemoglobin 1Ac, hyperlipidemia, hypertension, and other modifiable risk factors such as smoking and obesity, and a greater use of statins and dual antiplatelet agents.

This review compares treatment strategies—medical therapy, PCI, and coronary artery bypass graft surgery (CABG)—for stable coronary artery disease (CAD) in diabetic patients to help guide treatment decisions by a heart team.

## Material and Methods

A PubMed, MEDLINE, and clinicaltrials.gov database search was performed using the following key terms: coronary revascularization, diabetes mellitus, coronary artery bypass graft surgery, percutaneous coronary intervention, and angioplasty. Randomized clinical trials (RCTs), metaanalyses, and reviews that included diabetic patients with stable CAD from 2005 to 2013 were analyzed. Acute patient studies including ST-segment elevation myocardial infarction and urgent revascularization, previous surgeries, or percutaneous intervention were excluded. A total of eight RCTs and three RCT subanalyses were found that stratified diabetic subgroups into medical therapy, PCI, or CABG (Fig 1). The main characteristics of the trials [8–22] are summarized in Table 1. Endpoints of mortality and major adverse cardiovascular and cerebrovascular events (MACCE) were compared between trials and further stratified by lesion and patient characteristics (Tables 2 and 3) [8, 14–18, 21, 23–27]. Statistical significance was determined by a p value of less than 0.05. Data were collected from the cohorts and stratified by

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## Abbreviations and Acronyms

| | | |
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| ACCORD | = | Action to Control Cardiovascular Risk in Diabetes |
| ADVANCE | = | Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation |
| ARTS | = | Arterial Revascularization Therapies Study |
| BARI | = | Bypass Angioplasty Revascularization Intervention |
| BARI 2D | = | Bypass Angioplasty Revascularization Intervention 2 Diabetes |
| BMS | = | bare-metal stent |
| CABG | = | coronary artery bypass graft surgery |
| CAD | = | coronary artery disease |
| CARDiA | = | Coronary Artery Revascularization |
| COURAGE | = | Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation |
| DEAR | = | Diabetic Argentina Registry |
| DES | = | drug-eluting stent |
| DIABETES | = | Diabetes and Sirolimus-Eluting Stent |
| FREEDOM | = | Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease |
| LAD | = | left anterior descending artery |
| MACCE | = | major adverse cardiovascular and cerebrovascular event |
| MASS II | = | Medicine, Angioplasty and Surgery Study II |
| MI | = | myocardial infarction |
| PCI | = | percutaneous coronary intervention |
| PES | = | paclitaxel-eluting stent |
| PTCA | = | percutaneous transluminal coronary angioplasty |
| RCT | = | randomized controlled trial |
| RR | = | relative risk |
| SCORPIUS | = | Sirolimus-Eluting Stent in the Treatment of Diabetic Patients With De Novo Native Coronary Artery Lesions |
| SES | = | sirolimus-eluting stent |
| SIRIUS | = | Sirolimus Drug-Eluting Stent Versus Bare-Metal Stent |
| SYNTAX | = | Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery |
| VA CARDS | = | Veterans Affairs Coronary Artery Revascularization in Diabetes Study |
| VADT | = | Veterans Affairs Diabetes Trial |

outcome and further analyzed by years of follow-up. Odd ratios were calculated by the Cochran-Mantel-Haenzel method, and Forest plots were constructed for MACCE and overall mortality with Review Manager (version 5.3; Cochrane Collaboration, Copenhagen, Denmark).

## Results

### Trial Characteristics Early Versus Late

Earlier trials—Bypass Angioplasty Revascularization Intervention (BARI), Bypass Angioplasty Revascularization Intervention 2 Diabetes (BARI 2D), Medicine, Angioplasty and Surgery Study II (MASS II)—compared medical therapies against revascularization in small subsets of suboptimally managed, low-risk patients, without analysis of lesion characteristics. The study designs of Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) and Future Revascularization Evaluation in Patients With Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) were an important departure from these trends. Direct comparisons are difficult because of innate differences in the trial design, different time periods, cohort characteristics, power considerations, and evolution of both PCI and surgical techniques. Later trials were better designed for stratification of lesion severity and risk profile of patients.

### Medical Therapy Versus Revascularization

The BARI 2D trial did not show a significant survival difference between revascularization and medical therapy (88.3% vs 87.8%, respectively; $p = 0.97$) nor insulin sensitizing versus insulin provision approaches (88.2% vs 87.9%, respectively; $p = 0.7$). Mortality was the same for medical treatment groups in CABG and PCI at 5 years [21]. The MASS-II study also did not show any benefit of initial PCI (angioplasty and bare-metal stents [BMS] only) to optimal medical therapy for stable CAD. Coronary artery bypass graft surgery had significantly fewer MACCE and nonfatal myocardial infarction (MI) in both the BARI-2D and the MASS-II studies as compared with medical therapy alone [22]. Later trials stressed the need for optimum medical therapy as important adjunct to PCI and CABG in the comparison of these modalities.

### Bare-Metal Stents Versus Drug-Eluting Stents

Late lumen loss, MACCE, and subsequent revascularization were significantly reduced in the sirolimus-eluting stent (SES) arm ($p < 0.001$) in the Diabetes and Sirolimus-Eluting Stent (DIABETES) trial and the Sirolimus-Eluting Stent in the Treatment of Diabetic Patients With De Novo Native Coronary Artery Lesions (SCORPIUS) study [8, 10]. No significant difference in mortality, cardiac death, repeat MI, or stent thrombosis was reported. Lower MACCE with SES was due to a lower target lesion revascularization (49% BMS vs 34% DES, $p < 0.02$). The DES performed better than the BMS in trials comparing the two; however, there was no survival benefit.

### Trials of PCI Versus CABG

The differences in overall mortality, cardiac mortality, repeat revascularization, and MACCE rates are shown in Figures 2 through 5. The Arterial Revascularization Therapies Study (ARTS) reported a significantly higher mortality rate (13.4% PCI vs 6.8% CABG, $p = 0.03$), MACCE, and repeat revascularization rates at 5 years