

Diabetes mellitus and multivessel coronary artery disease: an ongoing battle for an ideal treatment strategy

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Already in the late 90s, Haffner *et al.* introduced diabetes mellitus (DM) as a coronary artery disease (CAD) equivalent condition (1). Several more recent similar investigations confirmed those earlier findings (2). Despite broad developments in pharmacotherapy and revascularizations techniques, the combination of DM and CAD still represents a major challenge for the clinician. The clinical guidelines advocate intensive medical therapy with lifestyle and pharmacologic interventions as the initial approach in patients with stable CAD (3,4). Contemporary, percutaneous coronary intervention (PCI) has become one of the most frequently performed therapeutic intervention in medicine. Revascularization for significant narrowed coronary lesions has been shown to improve ischemic endpoints (5). Whether optimal conservative therapy alone or in combination with revascularization strategies in stable CAD leads to more anti-ischemic benefit has been investigated extensively. In patients with DM, finding optimal treatment strategies are more crucial in view of the fact of their poor prognosis in comparison with non-diabetics (6,7). Multivessel CAD in patients with DM has been evaluated in the FREEDOM trial (8,9). Most patients had very extensive disease and CABG was superior regardless SYNTAX score. Event curves started to diverge beyond 2-year after randomization. Insulin treated patients fared worse than those not treated with insulin. Cardiovascular events were generally concordant to the

main study in the insulin treatment subgroups.

In a current sub-analysis of Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) trial (10), Ikeno *et al.* evaluated whether SYNTAX score predicted the effectiveness of coronary revascularization combined with medical therapy compared with medical therapy alone (11). The authors reported long-term outcome of 1550 patients with type 2 DM, stable CAD and no prior coronary revascularization. Most patients [1,219] had a low SYNTAX score (defined as ≤ 22), and 331 had a mid/high SYNTAX score (defined as ≥ 23). Mid/high SYNTAX score was significantly related to an increased risk of death (HR: 1.43; $P=0.03$) and myocardial infarction (MI) (HR: 1.44; $P=0.05$) after 5 years of follow-up. Among diabetics with low SYNTAX scores, medical therapy, PCI and CABG had all similar rates of major cardiovascular events (MACE), defined as the composite of all-cause death, MI and stroke. Diabetics with mid or high SYNTAX scores had a significant benefit of CABG as an addition to medical therapy. MACE was almost doubled among those who were assigned to medical therapy compared to those who received early revascularization through CABG (30.3% *vs.* 15.3%). This increase in MACE was mainly driven by higher rates of MI in medical therapy versus CABG. After multivariable adjustment for clinical risk factors, CABG in the mid/high SYNTAX patients was associated with a non-significant lower risk of death (HR: 0.70, $P=0.32$) and

a significant reduction in the risk of MI (HR: 0.21; $P=0.01$). Whereas, PCI among patients with a mid or high SYNTAX score, did not show significant reduction in MACE compared with medical therapy alone. Even more surprising in this stratum, patients randomized to PCI showed numerically higher rates of MACE compared to those assigned to medical therapy (35.6% *vs.* 26.5%, respectively, $P=0.12$) (11).

In recent years treatment of obstructive CAD by means of coronary intervention has been growing. With an expansion of the interventional area towards more effective and safer stents, less frequent short and long term complications were noted (12,13). Although the study of Ikeno *et al.* is subject to the limitations of post-hoc exploratory analysis, the results suggest that stable diabetic patients with low SYNTAX score (≤ 22) can safely be treated medically. However, for those with higher SYNTAX score (≥ 23) treatment with CABG provides long-term reduction in MACE. The study of Ikeno *et al.* is of huge importance since it shows that in patients with DM and CAD, high SYNTAX score might be helpful to distinguish between modes of treatment, conservative *vs.* revascularization. Moreover, the study shows that the reduction of MACE by CABG was mainly driven by fewer MI and by revascularization.

Despite these imperative findings, several limiting factors should be mentioned. First, the number of patients with high SYNTAX score was very low (207 randomized to medical therapy *vs.* CABG and 124 to medical therapy *vs.* PCI), which makes it difficult to compose a definitive conclusion. Second, BARI 2D excluded those patients with multivessel disease (MVD) involving left main stenosis which reduces the external validity of the results provided. Third, the BARI 2D study was conducted more than 10 years ago; since then, several advancements in both medical and revascularization therapy have changed the international practice guidelines. For instance, insulin sensitizing drugs, like glitazones, are of less frequent use since the results of a meta-analysis on rosiglitazone and higher association of pioglitazone with congestive heart failure (14,15). Also treatment goals for glycemic control have changed since publication of Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, Veterans Affairs Diabetes Trial (VADT) and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trial (16-18). Even target LDL-Cholesterol goals changed over that period towards goals of less than 70 mg/dL (19,20). Furthermore, revascularization using less invasive techniques e.g., off-

pump CABG and full arterial revascularization are used more often than in earlier years (36% off-pump for CABG treated patients in BARI 2D) (10); finally, patients referred to PCI were mostly treated with bare metal stents (BMS) (65%). Additionally, around 10% were treated via balloon angioplasty without implantation of stents. The remaining 34% were treated with 1st generation drug-eluting stents (DES) (10). Although safe, BMS were associated with a high rate of TLR (~16%) (21), 1st generation DES lowered the risk of revascularization. Unfortunately, a higher rate of late and very late stent thrombosis (21) mitigated the success of 1st generation DES and paved the way for the development of more efficient stent platforms and nontoxic polymers, biodegradable polymers or even polymer-free stents. These stents are considered in the current practice, especially in patients with DM (4,22).

The recently published multicenter randomized EXCEL trial (Evaluation of Xience versus Coronary Artery Bypass Surgery of Effectiveness of Left Main Revascularization) investigated the safety and efficacy of PCI of left main MVD in comparison to CABG (23). After 3 years follow-up, PCI with new generation everolimus eluting stent (EES) was non-inferior in reduction of MACE in comparison with CABG. Their results were evident in all subgroups analyzed. The event rates between PCI and CABG in patients with an intermediate SYNTAX score [23–32] were similar (17.6% *vs.* 16.5%; HR 1.02; 95% CI: 0.71–1.47). Even in patients with a high SYNTAX score (≥ 33), PCI was non-inferior to CABG (16.9% *vs.* 14.3%; HR 1.15; 95% CI: 0.71–1.87). Also patients with DM undergoing PCI had the same incidence rate of MACE compared to CABG (21.2% *vs.* 19.4%; HR 1.04; 95% CI: 0.70–1.55) (23). Despite these encouraging findings, results from long-term follow-up are currently not available. Therefore, treatment of DM patients with MVD and SYNTAX score of ≥ 23 remains the domain of cardiac surgery as primary treatment advice.

Meanwhile, a recent patient-level meta-analysis (24) documented a reduced long-term risk of mortality with CABG compared with PCI in non-diabetic patients with multivessel CAD (6.7% *vs.* 10.0%, $P=0.037$). The benefit of CABG over PCI was notably greater in patients with an intermediate to high (≥ 23) SYNTAX scores than in those with low (≤ 22) SYNTAX scores ($P=0.023$ *vs.* $P=0.662$).

Whether a strategy of initial medical therapy followed by PCI is better than prompt PCI in combination with medical therapy was investigated in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial (25). After a median follow-up of

4.6 years, medical therapy alone *vs.* PCI with medical therapy showed equivalent composite endpoint (death, MI and stroke) (19.0% *vs.* 18.5%; $P=0.62$). Also in all analyzed subgroups similar results were evident, including the subgroup analysis of diabetic patients. The primary endpoint rate in diabetic patients was 0.25% for PCI *vs.* 0.24% for medical therapy (HR 0.99; 95% CI: 0.75–1.32). Of note was the high rate of additional revascularization among patients primarily assigned to medical therapy compared to PCI (32.6% *vs.* 21.1%, respectively; $P<0.0001$). Furthermore, among 35,539 patients assessed for enrollment only 3071 met the inclusion criteria and finally 2287 patients were randomized. This high rate of ineligible patients raises the question of generalizability of the findings of the COURAGE trial (25).

With the knowledge gained by the analysis of Ikeno *et al.*, strong evidence to make a clear recommendation for the treatment of stable coronary artery disease in patients with DM is still pending. Future studies e.g., ISCHEMIA (International Study of Comparative Health Effectiveness with Medical and Invasive Approaches) will have to provide further evidence of the best approach for treatment of patients with multivessel disease. Finally a heart team approach in selection of ideal candidates for interventional or surgical revascularization is highly recommended to improve patient care and survival.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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