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Chapter

Is Coronary Artery Bypass Grafting (CABG) Surgery Still Preferable to Percutaneous Coronary Intervention (PCI) in View of Long-Term Outcomes among Diabetic Patients?

Ahmad Farouk Musa

Abstract

Coronary Artery Bypass Grafting (CABG) is the preferred revascularization modality among diabetic patients due to extensive coronary involvement and elevated risk of restenosis. Since drug-eluting stent significantly reduces restenosis, we expect it to narrow down the long-term benefit-gap between these two revascularization strategies. In our review, we compare the long-term outcomes of Percutaneous Coronary Intervention (PCI) to CABG in diabetic patients. While PCI can be a reasonable alternative to CABG at a low SYNTAX (Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery) score, an intermediate-high SYNTAX score makes CABG necessary. In left main stem occlusion, PCI and CABG demonstrated similar long-term outcomes. However, in cases of bifurcation or unprotected left main stem disease, revascularization is best done via CABG. Indeed, CABG is the main revascularization therapy in multivessel involvement—it lowers the risk of all-cause mortality, myocardial infarction and repeat revascularization at the expense of increased stroke. Glycaemic control, use of anti-platelet agents and feelings of disability are all factors that can potentially affect long-term outcomes. We expect hybrid coronary revascularization (HCR) involving both robotic surgery and PCI to be the future trend in treating diabetic patients with multivessel disease, although its clinical use needs further studies.

Keywords: Coronary Artery Bypass Grafting (CABG), Percutaneous Coronary Intervention (PCI), diabetic patients, long-term outcomes, hybrid coronary revascularization (HCR)

1. Introduction

Revascularization is the preferred treatment procedure in patients with coronary artery disease (CAD). Coronary Artery Bypass Grafting (CABG) and Percutaneous
Coronary Artery Bypass Grafting

Coronary Intervention (PCI), formerly known as Percutaneous Transluminal Coronary Angioplasty (PTCA), are the two methods of revascularization that are widely performed worldwide. Contrary to CABG, PCI is less invasive. Moreover, it has a shorter procedural time and duration of hospital stay. Nonetheless, it is associated with a higher risk of repeat revascularization.

About 25–30% of patients admitted with acute coronary syndrome (ACS) are reported to have underlying diabetes [1]. Compared to their non-diabetic counterparts, diabetic patients suffer from a significantly higher rate of mortality and adverse events [2–4]. While early revascularization could enhance their prognosis, [5] the long-term merits of utilising either CABG or PCI are yet to be conclusively established.

2. Aim

Our study aims to find out whether diabetic patients have a better long-term prognosis with PCI compared to CABG.

3. Methods

Using PubMed, MEDLINE, Cochrane and Embase database, we conducted a literature search dating from January 2010 to June 2020 to locate relevant articles. We used Medical Subject Heading (MeSH) terms such as “diabetes mellitus”, “Percutaneous Transluminal Coronary Angioplasty” and “Coronary Artery Bypass Surgery” to identify journal articles. We also cross-checked references to allow the selection of additional pertinent references.

Studies that were included fall into the following three categories: (1) they were published from January 2010 to June 2020; (2) they had a minimum duration of patient follow-up of five years; and (3) they involved revascularization of patients with Type 2 diabetes mellitus.

Studies that were excluded fall into the following four categories:

1. they were published as editorials, reviews and letters since they were prone to bias;
2. they involved other subtypes of diabetes such as Type 1 diabetes mellitus, Maturity-Onset Diabetes of the Young (MODY), Latent Autoimmune Diabetes of Adulthood (LADA) and impaired glucose tolerance, not to mention prediabetes states with a different mechanism of platelet dysfunction and thrombosis;
3. they are based on revascularization for diseases such as valvular heart disease, cardiogenic shock and arrhythmias, all of which are associated with different risks and complications; and
4. they involved repeat revascularization in patients with a history of CABG and PCI.

Based on the above inclusion and exclusion criteria, data extraction was performed. The primary endpoints were as follows: mortality rate, risk of myocardial infarction (MI), stroke and repeat revascularization.
4. Results

Regarding left main stem disease (LMSD), both CABG and PTCA arms yielded similar mortality and composite endpoints of all-cause mortality, myocardial infarction (MI) and stroke risk. Additionally, the CABG arm reported a lower risk of target vessel revascularization. Table 1 below describes the randomized controlled trials and observational studies of PTCA versus CABG that were included in our analyses.

<table>
<thead>
<tr>
<th>First author Year</th>
<th>Study design</th>
<th>Region</th>
<th>PTCA (n)</th>
<th>CABG (n)</th>
<th>Follow-up</th>
<th>All cause-mortality and adverse outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Left Main Stem Disease (LMSD)</strong></td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>
| Yu (2014) [6] | Retrospective study | China | PTCA: 143 | CABG: 131 | 7.1 years | All-cause mortality: Similar in both arms (HR: 0.752, 95% CI 0.380–1.489 p = 0.413)  
Death, myocardial infarction and stroke: Similar in both arms (HR: 0.794, 95% CI: 0.463–1.361 p = 0.401)  
Repeat revascularization: Higher in PTCA arm (HR: 2.112, 95% CI 1.102–4.048 p = 0.024) |
| Lee (2020) [7] | Multicentre, non-randomised trial | Korea | PTCA: 395 | CABG: 327 | 12 years | All-cause mortality: Similar in both arms (HR: 1.08, 95% CI 0.85–1.38 p = 0.54)  
Death, Q-wave MI, stroke: similar in both arms (HR: 1.25, 95% CI 0.97–1.61 p = 0.09)  
Repeat revascularization: Higher in PTCA arm (HR: 4.07, 95% CI 2.65–6.26 p < 0.0001) |
| **Multivessel disease (MVD)** |
| Onuma (2010) [8] | Population from ARTS I and ARTS II trial | 20 countries | PTCA: 159 | CABG: 96 | 5 years | All-cause mortality: Similar in both arms (HR:1.11, 95% CI 0.47–2.66 p = 0.81)  
MI: Similar in both arms (HR:1.19, 95% CI 0.38–3.76 p = 0.76)  
Stroke: Similar in both arms (HR:1.24, 95% CI 0.42–3.65 p = 0.70)  
Repeat revascularization: Lower in CABG arm (HR:0.31, 95% CI 0.16–0.62 p = 0.001) |
<table>
<thead>
<tr>
<th>First author</th>
<th>Year</th>
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<th>Region</th>
<th>PTCA (n)</th>
<th>CABG (n)</th>
<th>Follow-up</th>
<th>All cause-mortality and adverse outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Contini (2012)</td>
<td>[9]</td>
<td>Multicentre, non-randomised, open label ARTS-II trial</td>
<td>Italy</td>
<td>PTCA: 1466</td>
<td>CABG: 1419</td>
<td>5 years</td>
<td>All-cause mortality: Higher in PTCA arm (HR: 1.8, 95% CI 1.4–2.2, p &lt; 0.0001) MI: Higher in PTCA arm (HR: 3.3, 95% CI 2.4–4.6, p &lt; 0.0001) Stroke: Similar in both arms (HR: 0.8, 95% CI 0.5–1.2, p = 0.26) Repeat revascularization: Higher in PTCA arm (HR: 4.5, 95% CI 3.4–6.1, p &lt; 0.0001)</td>
</tr>
<tr>
<td>Kim (2012)</td>
<td>[10]</td>
<td>Single-centre prospective, non-randomised observational cohort study</td>
<td>Korea</td>
<td>PTCA: 489</td>
<td>CABG: 402</td>
<td>5.6 years</td>
<td>All-cause mortality: Similar in both arms (HR 1.01, 95% CI 0.77 to 1.33, p = 0.96) Repeat revascularization: Higher in PTCA arm (HR 3.69, 95% CI 2.64 to 5.17, p &lt; 0.001)</td>
</tr>
<tr>
<td>Moshkovitz (2012)</td>
<td>[11]</td>
<td>Retrospective study</td>
<td>Israel</td>
<td>PTCA: 271</td>
<td>CABG: 226</td>
<td>62 months</td>
<td>All-cause mortality: Higher in PTCA arm (HR:3.01, 95% CI 1.59 to 5.73, p &lt; 0.0001) Repeat revascularization: Higher in PTCA arm (HR:7.00, 95% CI: 3.1 to 15.70)</td>
</tr>
<tr>
<td>Freedom Study (2012)</td>
<td>[12]</td>
<td>Multicentre randomised trial</td>
<td>140 international centers</td>
<td>PTCA: 953</td>
<td>CABG: 947</td>
<td>2 to 6.75 years</td>
<td>All-cause mortality: Higher in PTCA arm (PTCA 16.3% vs. CABG 10.6%; p = 0.049) MI: Higher in PTCA arm (PTCA: 13.9% vs. CABG 6.0%; p &lt; 0.001) Stroke: Higher in CABG arm (PTCA:2.4% vs. CABG: 5.2%; p = 0.03) Repeat revascularization: Higher in PTCA arm (PTCA: 12.6% vs. CABG: 4.8%; p &lt; 0.001)</td>
</tr>
<tr>
<td>BEST Trial (2015)</td>
<td>[13]</td>
<td>Prospective, open-label, randomised trial</td>
<td>South Korea, China, Malaysia, Thailand</td>
<td>PTCA: 438</td>
<td>CABG: 442</td>
<td>1–5.2 years</td>
<td>All-cause mortality: Similar in both arms (HR: 1.34, 95% CI 0.77–2.34, p = 0.30) MI: Similar in both arms (HR:1.76, 95% CI 0.87–3.38, p = 0.11) Stroke: Similar in both arms (HR: 0.86, 95% CI 0.39–1.93, p = 0.72) Repeat revascularization: Higher in PTCA arm (HR: 2.09, 95% CI 1.28–3.41, p = 0.003)</td>
</tr>
</tbody>
</table>
In the case of multivessel disease (MVD), a significantly higher risk of repeat revascularization in patients undergoing PTCA was consistently reported in four observational studies and three randomised controlled trials. On the contrary, data regarding mortality rate, risk of myocardial infarction and stroke were inconsistent. We observed similar findings in Onuma’s [8] and Kim’s [10] study (Onuma: HR: 1.11, 95% CI 0.47–2.66, \(p = 0.81\); Kim: HR 1.01, 95% CI 0.77 to 1.33, \(p = 0.96\)). However, PTCA incurred a higher mortality risk in other studies. One such study is the FREEDOM Follow-On study [14] that reports the survival rate of patients in the FREEDOM trial with an extended follow-up period. The authors Farkouh et al. [14] concluded that only after the second year follow-up did the mortality curves begin to separate; they also noted increasing discrepancy as the follow-up duration was extrapolated. Meanwhile, the risk of myocardial infarction varied. While similar MI risk was observed in Onuma’s study [8] (HR: 1.19, 95% CI 0.38–3.76 \(p = 0.76\)) and BEST Trial [13] (HR: 1.76, 95% CI 0.87–3.58 \(p = 0.11\)), Contini’s [9] (HR: 3.3, 95% CI 2.4–4.6 \(p < 0.0001\)) and FREEDOM study [12] (PTCA: 13.9% vs. CABG: 6.0%; \(p < 0.001\)) reported a significantly higher risk in the PTCA arm. Likewise, Onuma’s [8] (HR: 1.24, 95% CI 0.42–3.65 \(p = 0.70\)), Contini’s study [9] (HR: 0.8, 95% CI 0.5–1.2 \(p = 0.26\)) and BEST Trial [13] (HR: 0.86, 95% CI 0.39–1.93 \(p = 0.72\)) documented comparable risk of stroke. But this was not the case in FREEDOM study [12] (PTCA:2.4% vs. CABG: 5.2%; \(p = 0.03\)).

SYNTAX trial [15] compared treatment outcomes of PTCA and CABG in patients with LMS and/or MVD with a follow-up duration of five years. Using Synergy Between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery (SYNTAX) score, subgroup analyses were performed to evaluate the adverse outcomes of each revascularization strategy. In SYNTAX trial, both groups demonstrated similar findings in Onuma’s [8] and Kim’s [10] study (Onuma: HR: 1.11, 95% CI 0.47–2.66, \(p = 0.81\); Kim: HR 1.01, 95% CI 0.77 to 1.33, \(p = 0.96\)). However, PTCA incurred a higher mortality risk in other studies. One such study is the FREEDOM Follow-On study [14] that reports the survival rate of patients in the FREEDOM trial with an extended follow-up period. The authors Farkouh et al. [14] concluded that only after the second year follow-up did the mortality curves begin to separate; they also noted increasing discrepancy as the follow-up duration was extrapolated. Meanwhile, the risk of myocardial infarction varied. While similar MI risk was observed in Onuma’s study [8] (HR: 1.19, 95% CI 0.38–3.76 \(p = 0.76\)) and BEST Trial [13] (HR: 1.76, 95% CI 0.87–3.58 \(p = 0.11\)), Contini’s [9] (HR: 3.3, 95% CI 2.4–4.6 \(p < 0.0001\)) and FREEDOM study [12] (PTCA: 13.9% vs. CABG: 6.0%; \(p < 0.001\)) reported a significantly higher risk in the PTCA arm. Likewise, Onuma’s [8] (HR: 1.24, 95% CI 0.42–3.65 \(p = 0.70\)), Contini’s study [9] (HR: 0.8, 95% CI 0.5–1.2 \(p = 0.26\)) and BEST Trial [13] (HR: 0.86, 95% CI 0.39–1.93 \(p = 0.72\)) documented comparable risk of stroke. But this was not the case in FREEDOM study [12] (PTCA:2.4% vs. CABG: 5.2%; \(p = 0.03\)).

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similar survival and other adverse outcomes rates. On the contrary, the PTCA group suffered a higher burden of repeat revascularization.

Referring to Figure 1, this study comprised ten studies (observational and randomised trials). It followed the rule of thumb regarding tests for funnel plot asymmetry: a minimum ten studies should be included in the meta-analyses. With fewer studies, the power of the tests is too low to tell apart chance from real asymmetry.

The Funnel Plot displayed a certain heterogeneity; only two studies were outliers. Conversely, Egger’s test confirmed the plot asymmetry. (Heterogeneity: ChiSq = 21.60; df = 9; p = 0.01, I² = 58%). This is not surprising since both observational and randomised trials were included. Moreover, publication bias cannot be ruled out since the funnel plot might have excluded smaller studies with negative outcomes.

Table 2 refers to one study-level pooled analyses and four meta-analyses which compared the rate of mortality and adverse outcomes of PTCA-DES vs CABG in diabetic patients with a minimum five-year follow-up.

<table>
<thead>
<tr>
<th>Author &amp; Year</th>
<th>Follow up (years)</th>
<th>RCT &amp; OS (n)</th>
<th>Number of patients (n)</th>
<th>All-cause mortality and adverse outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hakeem (2013)</td>
<td>2–5</td>
<td>RCT: 4</td>
<td>PTCA: 1539</td>
<td>All-cause mortality: Higher in PTCA arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td>OS: 0</td>
<td>CABG: 1513</td>
<td>(PTCA 14% vs. CABG 9.7%, RR 1.51, 95% CI 1.09 to 2.10, p = 0.01)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Total: 4</td>
<td>Total: 3052</td>
<td>MI: Similar in both arms</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(PTCA 10.3% vs. CABG 5.9%, RR 1.44, 95% CI 0.79 to 2.6, p = 0.23)</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Stroke: Lower in PTCA arm</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(PTCA 2.3% vs. CABG 3.8%, RR 0.59, 95% CI 0.39 to 0.90, p = 0.01)</td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Repeat revascularization: Higher in PTCA arm</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(PTCA 17.4% vs. CABG 8.0%, RR 2.15, 95% CI 1.0 to 3.40, p = 0.05)</td>
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</tbody>
</table>
The first systematic review and meta-analysis that reported the outcomes of PTCA-DES vs. CABG for MVD in diabetic patients was carried out by Hakeem [16]. Of the meta-analyses identified, Huang et al. [19] included the largest number of studies; their meta-analysis consisted of a total of 19 studies (four randomised controlled trials and 15 observational studies). Moreover, it included both randomised and non-randomised studies, making it the first systematic review and meta-analyses.
Coronary Artery Bypass Grafting

to do so. Meanwhile, Cui’s meta-analysis [20] involved three studies that compared the newer second-generation drug eluting stent (DES) Everolimus with CABG. It was also among the most recently published meta-analyses, besides having the longest period of follow-up and the highest number of diabetic patients (n = 17532).

Unlike randomised controlled trials and observational trials, meta-analyses consistently show that CABG confers a lower risk of all-cause mortality, myocardial infarction and repeat revascularization, albeit with a higher risk of stroke. We find two notable exceptions in Hakeem’s [16] and Verma’s [17] studies. In Hakeem’s [16] study, the risk of myocardial infarction was similar in CABG and PTCA arms (10.3% versus 5.9%, RR 1.44, 95% CI 0.79 to 2.6, \( p = 0.23 \)); however, the PTCA group displayed a trend towards higher risk of myocardial infarction. Hakeem et al. [16] attribute this phenomenon to the presence of VA CARDS trials which are responsible for the significant heterogeneity in the studies. It is noteworthy that, after excluding VA CARDs trial, MI risk attained statistical significance (RR 2.01, 95% CI 1.54 to 2.62, \( p < 0.0001 \)) without residual heterogeneity (\( I^2 = 0\% \); \( p = 0.83 \)). Similarly, in Verma’s study [17], the increase in risk of MI became significant (RR 0.57, 95% CI 0.41–0.78; \( p = 0.0004 \)) after VA CARDs study was excluded from the analysis (\( I^2 = 0\% \)).

Conversely, Huang et al. [19] excluded VA CARDs trial in their sensitivity analyses; they reported the presence of VA CARDs trial (inclusion: 8.5% DES vs. 4.6% CABG, RR 1.68, 95% CI 1.20—2.37, \( p = 0.003 \); exclusion: 8.6% DES vs. 4.3% CABG, RR 1.91, 95% CI 1.43–2.57, \( p < 0.0001 \)) did not alter the overall MI rate. Nonetheless, it is to be highlighted that Huang et al. [19] analysed a total of 14 randomised and non-randomised studies. This is in sharp contrast to Hakeem et al. [16] and Verma et al. [17] who only analysed four and eight randomised studies respectively in their meta-analyses.

5. Discussion

The past decade has witnessed the increasing prevalence of diabetes, with more than a two-fold rise seen in both genders [2]. About 25–30% of patients admitted with ACS suffered from diabetes [1]. Unfortunately, compared with their non-diabetic counterparts, post-myocardial infarction complications and deaths are higher in diabetic patients after CABG or PCI [3–5]. Indeed, compared to the non-diabetic population, diabetic patients have been shown to sustain a higher composite end point of death, stroke and MI after CABG (HR: 1.55; 95% CI: 1.04 to 2.31; \( p = 0.03 \)) or PTCA (HR: 1.53; 95% CI: 1.04 to 2.26; \( p = 0.03 \)) in a report analysis of EXCEL trial [21]. Moreover, diabetic patients, in contrast to healthy individuals, suffered a higher rate of wound infection, neurological and renal complications, and a higher risk of stroke and readmission following CABG; this is besides the increased rates of target lesion revascularization and reinfarction after PTCA [5]. Additionally, diabetic patients are afflicted with a number of comorbidities at diagnosis, which further deteriorated their prognosis [22, 23].

Indications for revascularization therapy did not differ between diabetic and non-diabetic patients [1]. However, according to a nationwide study [4], diabetic patients tend to avoid myocardial revascularization procedures as they fear post-procedural complications and death. Furthermore, the higher frequency of proximal stenosis and extensive involvement in diabetic patients entails a higher procedural risk; this makes revascularization a less attractive treatment option for ACS [4, 24].

Nonetheless, revascularization does have some merits for diabetic patients. Several studies show that early revascularization could benefit diabetic patients by reducing
the risk of adverse events [4, 25]. It was demonstrated in a meta-analysis [26] consisting of eight trials that early invasive strategy could reduce mortality rate by 36% (HR: 0.67, 95% CI: 0.45–0.99). Due to multivessel involvement and a higher risk of restenosis [5], CABG was likely the default treatment strategy for patients with diabetes in the past. Since Andreas Gruntzig introduced PTCA in 1977, notable advances have been made, which has significantly improved its success rate with a better safety profile [27]. The later introduction of drug-eluting stent (DES) drastically decreased the rate of restenosis of PTCA [27–30]. Despite these advances, whether PCI could replace CABG as an ideal treatment modality is yet to be determined.

The adverse outcomes of some treatments might not be obvious on a short-term follow-up. Additionally, the effects might alter in the long run. Long-term follow-up of patients is therefore essential. As an illustrative example, a study conducted by Pederson et al. [31] compared the cause of short-term and long-term mortality in patients treated with primary PTCA for ST segment elevation myocardial infarction. While it was shown that cardiac mortality remained the main cause of death within the first month of PTCA, the origin of death began to shift towards non-cardiac causes beyond the first month. Furthermore, Onuma et al. [8] documented that late stent and very late stent thrombosis constitute around two-thirds of stent thrombosis. To the best of our knowledge, the longest-term follow-up with regards to the outcomes of CABG and PTCA is 40 years [32]. Nonetheless, studies that follow up patients for such a long duration are few and limited. The merits of CABG significantly outweigh PTCA after four years of revascularization (pooled Absolute risk reduction = 6%), as Hakeem et al. [16] have observed. Hence, in our study, we settled on a five-year follow-up duration as the cut-off point.

When comparing the clinical outcomes of treatments of a disorder, randomised controlled trials (RCTs) are the gold standard. Yet, patients recruited in RCTs are usually specifically selected while those with multiple comorbidities are excluded; this does not reflect real-world clinical practice. Ironically, observational studies (OS) – which involve a significant level of selection, publication and treatment bias – closely mirror daily clinical practice in the hospital setting. Huang et al. [19] found that patients from observational studies enjoyed a considerably higher mortality benefit with CABG compared to their counterparts from randomised trials (Observational trials 9.6% vs. Randomised trials 11.9%, RR 0.81, 95% CI 0.71–0.92, p = 0.001). We can, therefore, infer that in the real setting, CABG is the desired choice of revascularization for patients with high risk profiles. Hence, it is essential to take into account the findings of both RCT and OS as demonstrated in our study; this allows us to determine the overall treatment effect of CABG and PTCA both clinically and statistically.

Studies — With respect to LMSD and/or MVD in diabetic patients, some notable studies are worth mentioning. The first study to demonstrate the survival advantage of CABG over PTCA among diabetic patients is the Bypass Angioplasty Revascularization Investigation (BARI) [33]. A total of 353 diabetic patients were analysed at 5-year follow up, revealing a two-fold risk of mortality rate related to PTCA. As a result, CABG was recommended as the optimal revascularization method in patients with diabetes. Though it is historically noteworthy, this study was conducted before DES and antiplatelet agents were introduced. Consequently, it has limited application to current clinical settings [5, 12, 34].

BARI study was followed by several other studies on diabetes and MVD disease that includes EAST trial, CARBI trial, RITA trial, ARTS trial, SYNTAX trial and CARDia Trial [5, 12]. We shall not discuss EAST trial, CARBI trial and RITA trial since they were too flawed for any meaningful conclusions. On the one
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hand, ARTS trial [35] was the first randomised trial that compared the five-year outcomes of patients with MVD treated with CABG instead of BMS. On the other hand, the first prospective randomised trial that evaluated coronary revascularization in diabetic patients was the CARDia trial [34]. Meanwhile, SYNTAX trial [15] utilised SYNTAX score to measure the extent of coronary vessels occlusion. ARTS trial, SYNTAX trial and CARDia trial consistently reported similar mortality rate coupled with excess major adverse cardiac and cerebrovascular events (MACCE) rate in the PTCA group; this called for repeat revascularization [6]. Regrettably, multiple recent studies [6, 17] have discredited these three trials as invalid on several grounds: the ARTS trial used historical control; the CARDia study was underpowered for primary composite outcome; and the SYNTAX trial involved a subgroup analysis of diabetic patients.

FREEDOM study [12] lasted from 2005 to 2010. It recruited a total of 1900 diabetic patients with MVD at 140 international centres; it was the largest prospective randomised trial. To evaluate any adverse outcomes, the patients were assigned to either CABG or PTCA with a follow-up period of between 2 to 6.75 years. This study recruited diabetic patients – high risk patients with a good distribution of SYNTAX scores coupled with optimal usage of medical therapy throughout follow-up. Consequently, it is regarded as the most outstanding trial to detect the safety and efficacy of revascularization therapies for diabetic patients with MVD. As a result, we included this study in most of the meta-analyses available. FREEDOM study is also the only study that we included in all the meta-analyses highlighted in our report. Indeed, FREEDOM Follow-On study [14] was published in 2019 with an extended median follow-up of 7.5 years to further evaluate the survival advantage of CABG over PTCA.

VA CARDS study is another study that was evaluated in numerous meta-analyses. Besides Luca’s study [18], all the meta-analyses mentioned above analysed VA CARDS study. VA CARDS study [16, 17, 36] aggressively searched for silent MIs that are assumed to be responsible for around one-third of the total MIs in diabetic patients. As such, following CABG, the risk of non-fatal MI was elevated drastically (CABG: 15% PCI:6.2%, HR: 3.32; 95% CI: 1.07 to 10.30). Nonetheless, we excluded this study since the follow-up duration did not meet our inclusion criteria.

BEST trial [13] compared Everolimus-eluting stent (EES) with CABG in patients with diabetes and MVD. Indeed, it represents one of the few randomised trials to do so. EES was demonstrated to be the most efficacious stent in terms of safety and efficacy thanks to its association with the lowest risk of stent thrombosis and repeat revascularization [28, 30, 37]. While evaluating how diabetic patients with MVD fared with CABG and EES for, Bangalore et al. [38] reported that EES provided comparable survival benefit to CABG (425 [10.50%] versus 414 [10.23%] events; HR = 1.12; 95% CI, 0.96–1.30; p = 0.16) and a lower risk of stroke (118 [2.92%] versus 157 [3.88%] events; HR = 0.76; 95% CI, 0.58–0.99; p = 0.04). However, this was at the expense of a higher risk of myocardial infarction (260 [6.42%] versus 166 [4.10%] events; HR = 1.64; 95% CI, 1.32–2.04; p < 0.0001) and repeat revascularization (889 [21.96%] versus 421 [10.40%] events; HR = 2.42; 95% CI, 2.12–2.76; p < 0.0001) driven by incomplete revascularization at long term. Nevertheless, it was demonstrated in BEST trial that CABG still outperformed PTCA even with EES. Due to inconsistencies in the current evidence, well-designed studies are required in the future for a more meaningful conclusion.

In LMSD, comparable adverse outcomes as well as mortality were observed in both CABG and PTCA [7, 39]. Indeed, a case could be made that the above studies were underpowered; they did not utilise Everolimus, the newer second-generation
drug-eluting stent. Two of the largest randomised trials that included Everolimus are NOBEL trial [40] and EXCEL trial [41] but, unfortunately, they were not powered to study diabetic patients exclusively. A subgroup analysis of EXCEL trial [21] revealed no difference in the composite risk of all-cause mortality, stroke and myocardial infarction between CABG and PTCA in diabetic patients at 3 years (PTCA 20.7% vs. CABG 19.3%; HR: 1.03; 95% CI: 0.71 to 1.50; \( p = 0.87 \)); however, the PTCA arm \( (p = 0.01) \) revealed a high risk of repeat revascularization. These results were consistent with our study findings. One exception is the higher all-cause mortality in the PTCA arm \( (p = 0.046) \) which included diabetic patients with high SYNTAX scores.

It should be highlighted that PCI as a substitute for CABG can only be indicated to selected LMSD patients. Patients with bifurcation lesions and unprotected LMSD yield better outcomes with CABG. Kappetein and Head [42] reported that CABG is the best treatment option for LMSD associated with bifurcation which incurs a higher risk of procedural complications, repeat revascularization and thrombosis. Yu’s study [6] found similar adverse effects and mortality in both PTCA and CABG arms of unprotected LMSD patients. Nonetheless, as an unprotected left main stem occlusion is highly associated with MVD, CABG is a more reasonable revascularization modality in this patient population [42].

For MVD, in terms of adverse outcomes and mortality, a large variation has been observed in the individual studies compared to the pooled analyses or meta-analyses. This phenomenon is alluded to various study designs, types of stents or grafting and inclusion and exclusion criteria. Hence, results from individual studies should be interpreted cautiously.

To summarise, long-term survival in MVD favours CABG. In their comprehensive meta-analysis of 14 randomised trials, Herbison and Wong [43] concluded that despite significant improvement of CABG and PTCA over the past 30 years, CABG, regardless of the types of stents used, still constantly outperformed PTCA by 30% difference in survival benefit particularly in diabetic patients. In another pooled analysis [44] of 10 randomised trials involving CABG and PTCA for diabetic patients with MVD, a significantly lower five-year mortality rate was observed in the CABG arm (12.3% versus 20.0%, HR 0.70, 95% CI 0.56 to 0.87, \( p = 0.014 \)).

Regarding adverse outcomes at long-term, it can be concluded from the above studies that, overall, CABG confer more benefits than PCI thanks to its ability to achieve complete revascularization and its lower rate of restenosis [45]. In Contini’s study [9], 85.6% of CABG as compared to only 51.3% of PTCA patients could undergo complete revascularization. Similarly, Farooq et al. [46] reported that in their study, angiographic complete revascularization was only achieved in 52.8% of PTCA as opposed to 66.9% of CABG patients. Worse, the presence of diabetes further complicates the burden of incomplete revascularization. Verma and Aronson et al. [17, 21] found that diabetic population tends to present with more progressive and diffuse coronary disease. In addition, they discovered that new lesions can also form easily in the revascularization sites as diabetes progresses.

Insofar as restenosis rate is concerned, target vessel revascularization remains an unwanted effect of PCI. Multivessel angioplasty carries a higher risk of restenosis at multiple independent sites while potentially worsening the overall treatment outcomes [5]. To complicate matters, the incidence of stent thrombosis is elevated significantly with the presence of diabetes and coronary artery disease, which markedly decreases the benefit of PCI in diabetic patients [11, 21]. Although it is a more invasive procedure [18], Aronson et al. [21] noted that CABG necessitates less reintervention among both diabetic and MVD patients.
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Despite its benefits, CABG carries a higher risk of stroke since antiplatelet agents are rarely used after CABG, and CABG itself is usually performed on-pump [20]. Noteworthy, in FREEDOM, 30 days after revascularization, aspirin was used 99.1% in PTCA versus 88.4% in CABG while thienopyridine was used only 98.4% and 24.6% for PTCA and CABG respectively [12, 17]. Abnormal platelets coupled with an enhanced platelet activity were observed in diabetic patients; this phenomenon leads to enhanced adhesion, activation and aggregation [47, 48]. Antiplatelet agents could therefore play a vital role in reducing the risk of thrombosis in the diabetic population. This theory is not baseless; a previous study suggested that for diabetes population afflicted with coronary artery disease, twice-daily aspirin regimen in lieu of once daily regimen could be more efficacious in hindering platelet production and platelet aggregation [49]. Given the lower frequency of antiplatelet use post CABG, a higher risk of stroke is therefore to be expected.

The utilisation of aortic manipulation in on-pump CABG is also associated with a higher risk of stroke. Aortic manipulation, it is postulated, causes atherosclerotic debris to occlude the blood vessels in the brain, with stroke as the end result. Moreover, prophylactic anti-platelet therapy might reduce the risk of stroke if provided weeks before CABG with aortic manipulation and on-pump CABG. Nonetheless, whether off-pump CABG could decrease the incidence of stroke remains debatable. On the one hand, a lower occurrence of stroke with off-pump CABG than on-pump CABG (adjusted odds ratio: 0.76, 95% CI 0.59 to 0.98, \( p < 0.001 \)) was observed in a retrospective analysis [50] of 30,426 patients undergoing CABG surgery in 2006 and 2007. On the other hand, comparable incidence of stroke with on-pump and off-pump CABG at 5-year follow-up (OR: 0.78; 95% CI: 0.56 to 1.10; \( p = 0.16; \) 2.2% vs. 2.8%) [51] was reported in a recent meta-analysis of 8145 patients in six studies. After evaluating the adverse outcomes of sirolimus eluting stent versus off-pump CABG in a non-randomised trial of 207 diabetic patients with MVD, Yamagata et al. [52] observed a significantly higher rate of cerebrovascular events following off-pump CABG (\( p = 0.035 \)) at 3 years. Based on this finding, it can be inferred that although the risk of stroke may decline with off-pump CABG, there was no significant change in the outcomes when compared with PTCA, if other factors remain unchanged. This hypothesis can only be validated by future well-designed studies.

*Effect of SYNTAX score* – SYNTAX score grades the complexity of coronary vessels in patients with CAD in order to determine the feasibility of CABG or PTCA [53]. Diabetes can increase the complexity of coronary lesions [54]. SYNTAX trial [15] revealed that revascularization benefits did not differ in patients with low-intermediate SYNTAX score. Conversely, among patients with intermediate-high SYNTAX score, the PTCA cohort with increasing SYNTAX score displayed increasing adverse events. Interestingly, this effect was more prominent in diabetic compared to non-diabetic individuals. We can therefore conclude that in diabetic patients, when the SYNTAX score is low, PCI can be recommended; however, when the SYNTAX score is high, CABG should be the default revascularization modality [1, 55]. This rule of thumb applies to both LMSD occlusion and MVD. Indeed, at high SYNTAX scores, a significant mortality difference was observed between CABG and PTCA in a subgroup analysis of EXCEL Trial [21] involving 554 diabetes patients. Although the EXCEL trial was underpowered for assessing mortality in diabetic patients, the trend towards improved survival could not be overlooked. Accordingly, in clinical decision making for patients with LMSD and MVD [1], the use of SYNTAX score is considered paramount. On a side note, VA CARDs trial [3] did not identify the effect of SYNTAX
score on the revascularization outcomes. Admittedly, that study was underpowered with a limited number of participants and follow-up duration.

**Confounding factors** – We need to consider several factors when determining the long-term adverse outcomes of CABG and PCI. Glycaemic control plays a pivotal role in altering the treatment outcomes of revascularization therapy. Of all parameters, the HbA1c value is of the utmost importance [56, 57]. Interestingly, HbA1c level has been found to be associated with spontaneous platelet aggregation, reflecting underlying hypercoagulable status in diabetes [58]. Harskamp and Park [59] noted that in a study conducted by Corpus et al. [60], when the HbA1c was above 7, the rate of target vessel revascularization after PTCA was enhanced significantly (34% vs. 15%, \( p = 0.02 \)). Moreover, a meta-analysis [61] of 16 studies also suggested that in diabetic patients receiving PTCA with a risk ratio of 1.18 (95% CI 1.10–1.27, \( p = 0.016; \Gamma^2 = 45.8\% \)), high HbA1c at baseline can independently increase the risk of major adverse cardiovascular and cerebrovascular events (MACCE). Similarly, it was revealed in an observational study [53] that the incidence of MACCE was significantly lower when HbA1c is below 7 (27.5% versus 37.4%; HR, 0.71; 95% CI, 0.52–0.97; \( p = 0.03 \)) which is accompanied by significant reduction of repeat revascularization (19.9% versus 29.5%; HR, 0.66; 95% CI, 0.47–0.93; \( p = 0.02 \)). It was found that this benefit was maximised when the residual SYNTAX score was above four.

Interestingly, potential determinants of mortality of PCI include psychological factors as well. A recent study [62] with a 12-year follow-up revealed that patients with higher feelings of being disabled one month after PCI had a significantly higher mortality rate (43.5% vs. 23.1%; HR = 2.53, 95% CI = 1.30–4.90, \( p = 0.001 \)). Due to the paucity of reliable data, future robust studies are required to determine the relationship between psychological states and PCI mortality.

It is known that diabetes can lead to a thrombotic state via various mechanisms [63]. Antiplatelet agents are crucial in minimising the risks of hypercoagulability. For several decades, aspirin and clopidogrel have been used as the standard antiplatelet regimens. However, newer antiplatelet agents (such as Ticagrelor and Prasugrel) appear to generate more favourable outcomes than the older medications, especially in diabetic patients [64, 65]. A meta-analysis [66] of seven randomised controlled trials involving 58,591 patients with ACS revealed that patients with Ticagrelor or Prasugrel had a significant decline in mortality (2.9% vs. 3.4%, \( OR = 0.87, 95\% CI = 0.79–0.95, p = 0.002 \)), recurrent myocardial infarction (4.2% vs. 5.2%, \( OR = 0.80, 95\% CI = 0.74–0.87, p < 0.0001 \)) and definite in-stent thrombosis (0.9% vs. 1.7%, \( OR = 0.52, 95\% CI = 0.43–0.63, p < 0.0001 \)) without an elevation of major bleeding complications (5% vs. 4.7%, \( OR = 1.06 95\% CI = 0.96–1.17, p = 0.25 \)). These findings corroborate the OPTIMUS trial [59] that demonstrated a greater inhibition of platelet activity by Prasugrel than Clopidogrel (89.3 vs. 27.7%, \( p = 0.0001 \)). Nonetheless, the clinical efficacy and safety of Ticagrelor and Prasugrel post revascularization therapy is yet to be proven to date. Hence, well-designed studies looking at this aspect are warranted.

### 6. Limitations

Despite our best effort to include similar studies and exclude studies which present significant heterogeneity from other studies, a number of variables still exist between the studies as a result of various inclusion and exclusion criteria and study designs. We also admit that definition of adverse outcomes, follow-up duration and
types of grafting which differ from one study to another can potentially affect the treatment outcomes. In addition, the aforementioned studies did not capture factors such as HbA1c level, SYNTAX score, treatment of diabetes and psychological factors. Moreover, only a limited number of studies were analysed since we excluded studies that are not published in English. Furthermore, since only a limited number of studies utilised EES, the results should be interpreted with caution when applied to the clinical setting where EES is widely performed. Robust studies utilising EES are warranted in the future. Lastly, several observational studies were recruited in our study where they posed inherent bias; nonetheless, it is unlikely that the results would differ considerably after exclusion of the observational trials.

7. Future directions

The coronary vessels of diabetic patients are lined with the more extensive and severe atherosclerotic plaque. This has given rise to hybrid coronary revascularization (HCR) [67]. HCR combines the essence of CABG and PCI to mitigate issues related to MVD [68]. In HCR, CABG is performed in the left anterior descending artery while PCI is utilised to open up the other occluded vessels [69, 70]. A robotic procedure is used for this minimally invasive CABG procedure where only small incisions rather than a midline incision are required. In this best-of-both-worlds strategy, a minimally-invasive off-pump left internal mammary graft is connected to the blocked left anterior descending artery, and a stent is then placed from the left main to the left circumflex artery.

HCR is safer and more effective than CABG or PCI. By avoiding sternotomy, cardiopulmonary bypass and most importantly, aortic manipulation, HCR is associated with a lower infection, transfusion and prolonged recovery rate and risk of stroke [62, 64, 71, 72]. Since diabetic patients are prone to more frequent infections with a slower healing rate, HCR would benefit them enormously.

HCR had a similar all-cause mortality (6.4% for HCR vs. 9.2% for CABG; \( p = 0.69 \)), myocardial infarction (4.3% vs. 7.2%; \( p = 0.30 \)) and repeat revascularization (37.2% vs. 45.4%; \( p = 0.38 \)), stroke (2.1% vs. 4.1%; \( p = 0.35 \)) and MACCE s (45.2% vs. 53.4%; \( p = 0.39 \)) in a randomised study [62] of 191 patients with MVD at five years. However, a trend towards better outcomes favours HCR instead of the conventional CABG. In a prospective study [61] at Fuwai Hospital in Japan, 120 diabetic patients were enrolled in the HCR arm and 240 patients in the off-pump CABG arm. A follow-up of MACCE events after three years reported a lower rate of stroke in the CABG arm (0% vs. 3.6% at 3 years; \( p = 0.046 \)).

We anticipate that HCR will be widely used in the near future [73]. Currently, there is insufficient evidence to guide the application of the procedures to diabetic patients [66, 67, 74]. Hence, future robust studies on long-term follow up are needed.

8. Conclusion

As an option in diabetic patients, revascularization is dictated by the complexity and nature of the coronary vessels involved. A low SYNTAX score favours PCI as an alternative to CABG. However, CABG is recommended at an intermediate-high SYNTAX score. Meanwhile, in multivessel involvement or complex CAD, CABG remains the mainstay of treatment. In left main stem occlusion, when the disease is
accompanied by bifurcation or is classified as unprotected left main stem disease, CABG could offer better treatment outcomes. Factors such as patient’s quality of life and cost effectiveness of therapy, coupled with other clinical factors and short-term clinical outcomes, should not be ignored in clinical decision making; these should be communicated clearly and effectively to patients in order to have their informed consent. The implementation of shared decision making is vital when formulating the best revascularization option; patients’ preferences, values and needs are to be respected and honoured.

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