

# Percutaneous Revascularisation in Diabetic Patients with Coronary Artery Disease

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**CHEN and LAU: Percutaneous Revascularisation in Diabetic Patients with Coronary Artery Disease.** Diabetic patients with coronary artery disease are associated with an unfavourable long-term outcome. Surgical revascularisation on top of medical therapy has been shown to confer survival benefit in patients with multivessel and left main disease. With the emergence of the percutaneous approach of revascularisation, several clinical trials have been conducted to compare these two modalities of treatment. Consistent results were demonstrated in the diabetic subgroup that coronary artery bypass grafting is superior to balloon angioplasty in preventing late adverse cardiac event. With the advancement of percutaneous technique using coronary stenting as the predominant mode of catheter-based revascularisation, the latest comparison trial showed that stenting is a comparable alternative but is associated with a higher incidence of repeat revascularisation than bypass surgery. However, the debate is not yet settled because of the promising results of platelet glycoprotein IIb/IIIa antagonists and drug-eluting stents in improving the safety and efficacy of percutaneous intervention. It remains to be proven by ongoing clinical trials the best revascularisation strategy for diabetics with multivessel coronary disease. (*J HK Coll Cardiol* 2002;10:114-119)

*Coronary artery disease, diabetes mellitus, revascularisation*

## 摘要

患有冠狀動脈疾病的糖尿病病人，其長期預後不理想。對於該類共並發有多發性血管疾患和以此為主要症狀的病人，外科血管再通的治療將給他們的生存帶來益處。隨著經皮血管再通技術的興起，一些臨床研究對比了二種治療方法。過去的研究結果一致表明在糖尿病組對於預防晚期心臟不良事件中，運用冠狀動脈搭橋術要優於氣囊血管形成術。隨著經皮穿刺技術的提高，冠脈支架已成為基於導管技術的血管再通的優越手段。最近的臨床對比研究表明，支架技術是可供選擇的治療手段，但它比冠狀動脈搭橋術則需要更多的反復血管再通。然而對此的爭論並未了結，原因在於血小板糖蛋白 IIb/IIIa 拮抗劑誘入結果和藥物洗脫支架在經皮介入治療的安全性和有效性的提高。期待進一步的臨床實驗以證實患有冠狀動脈疾病的糖尿病病人血管再通的最佳方案。

關鍵詞：冠狀動脈疾病 糖尿病 血管再通

Following randomised clinical trials (RCTs) in the 70's that showed the benefits of coronary artery bypass graft (CABG) over medical treatment alone

in certain subsets of patients with multivessel coronary artery disease (CAD) and left main stem disease, CABG has been regarded as the "standard" treatment for these patients. With improvements in expertise and technology, percutaneous transluminal coronary angioplasty (PTCA) evolves from the treatment of simple, focal, proximally located lesions in a single vessel to those complex anatomic subsets previously tackled only by cardiac surgeons.

In the late 1980's, six RCTs were undertaken to compare PTCA and CABG as the revascularisation

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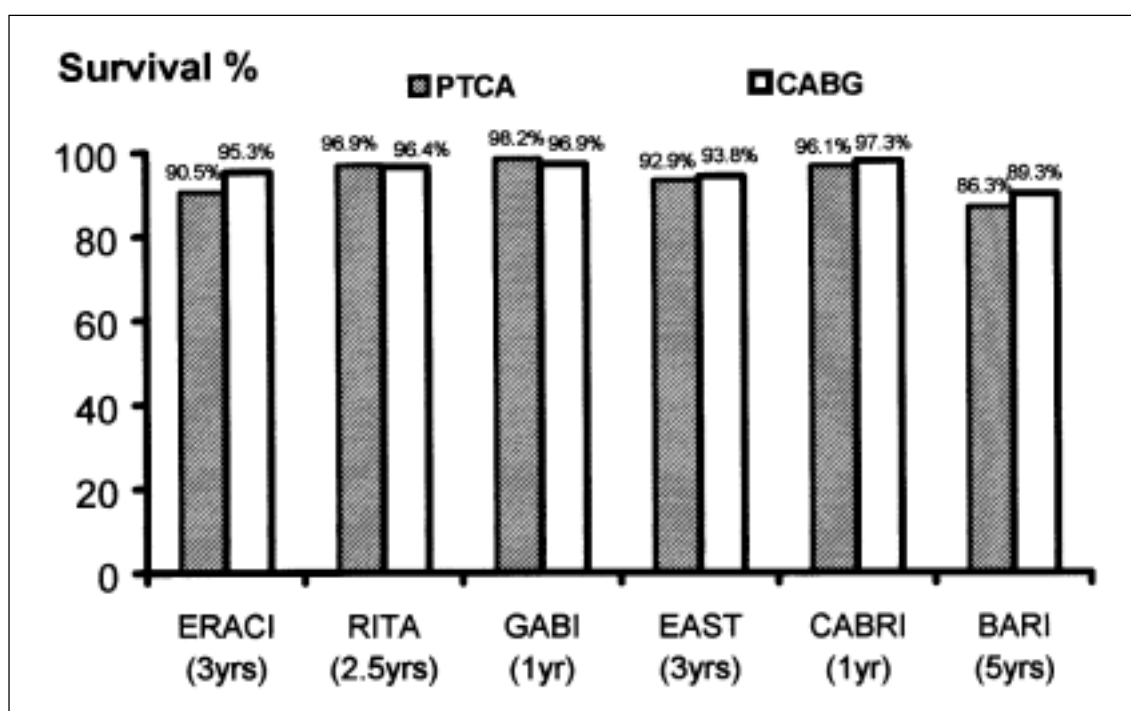
Received May 15, 2002; revision accepted June 7, 2002

procedure in patients with multivessel CAD. The main results were consistent among the trials. Mortality was not significantly different between the two modalities of treatment (Figure 1). Fewer repeat revascularisations and recurrent angina were achieved by CABG. A trend of reduction of myocardial infarction (MI) was seen in patients undergoing PTCA.<sup>1-6</sup> However, there are two exceptions to the overall trial results. The Bypass Angioplasty Revascularization Investigation (BARI) trial showed that treated diabetics had a distinct survival advantage with CABG. The benefit was seen 6 months after randomisation and the survival curve continued to diverge up to 7 years of follow-up. Survival was 76.4% for the CABG group and 55.7% for the PTCA group at 7 years ( $p=0.0011$ ).<sup>7</sup> The

Emory Angioplasty Versus Surgery Trial (EAST) also showed a trend of better survival among diabetics treated with CABG. Eight-year survival was 75.5% in the CABG group and 60.1% in the PTCA group.<sup>8</sup>

### Poor Outcome of Diabetics After Revascularisation

Diabetes mellitus is associated with the early initiation and accelerated progression of coronary atherosclerosis. Diabetics constitute a significant proportion of patients requiring revascularisation for the treatment of advanced coronary artery disease. Patients with diabetes are at increased risk of adverse outcome after PTCA. In the early era of balloon



**Figure 1.** Survival of diabetic patients with multivessel coronary artery disease after percutaneous transluminal coronary angioplasty or coronary artery bypass graft surgery in randomized controlled trials. BARI = Bypass Angioplasty Revascularization Investigation; CABG = Coronary Artery Bypass Graft; CABRI = Coronary Angioplasty versus Bypass Revascularisation Investigation; EAST = Emory Angioplasty versus Surgery Trial; ERACI = Argentine Randomized Trial of Percutaneous Transluminal Coronary Angioplasty versus Coronary Artery Bypass Surgery in Multivessel Disease; GABI = German Angioplasty Bypass Surgery Investigation; RITA = Randomised Intervention Treatment of Angina; PTCA = Percutaneous Transluminal Coronary Angioplasty.

angioplasty, diabetic patients had more in-hospital mortality or myocardial infarction (MI) compared with patients without diabetes. The long-term outcome is also plagued by increased risk of restenosis, contributing to greater rates of mortality, MI, and repeat revascularisation.<sup>9,10</sup>

The presence of diabetes is also associated with a higher event rate after CABG.<sup>11</sup> Diabetic patients have more rapid disease progression in saphenous vein grafts and in native vessels whether grafted or not.<sup>12</sup> Diabetes is also an independent risk factor of late mortality after CABG.<sup>13</sup>

Metabolic and haematologic derangements contribute to the increased incidence of adverse cardiac events after revascularisation in diabetics.<sup>14</sup> Platelets are more often activated with increased aggregability, enhanced secretion of vasoconstrictive agents, and greater mitogenic activity. Fibrinogen, factor VII and plasminogen activator inhibitor-1 levels are increased while antithrombin III activity is reduced. Diabetes is associated with endothelial dysfunction and excessive smooth muscle cell proliferation and extracellular matrix formation.<sup>15</sup>

The reasons for the inferiority of PTCA compared with CABG for coronary revascularisation in diabetics are usually attributed to a high restenosis rate, incomplete revascularisation, and progression of atherosclerosis. Improvements in the techniques of both percutaneous and surgical techniques have made it necessary to re-examine this issue from time to time. This is especially true for percutaneous intervention as changes in practice are occurring rapidly over the last few years.

### **Stenting: Improvement over Balloon Angioplasty**

Balloon angioplasty is largely replaced by coronary stent implantation as the predominant modality of percutaneous revascularisation because of the advantages of reduction in emergency CABG and restenosis.<sup>16,17</sup> CABG has also undergone changes with the routine use of arterial conduits that has better long-term patency.<sup>18</sup> The Arterial Revascularization Therapy Study (ARTS) was undertaken to compare contemporary percutaneous and surgical revascularisation for the treatment of patients with

multivessel CAD. In the diabetic subgroup, the 1-year incidence of the individual components or the composite of death, MI, or stroke was similar between the two groups. The main difference was the increased need for repeat revascularisation in the stent group (14.3% vs 3.1%;  $p < 0.001$ ).<sup>19</sup> Although the reintervention rate has been reduced by ~50% compared with balloon angioplasty results in prior comparison trials, coronary stenting in diabetics is still associated with a high rate of restenosis and the resulting need for repeat revascularisation, confirming the results of retrospective series which reported poorer outcomes of diabetics after stent implantation compared to nondiabetics.<sup>20,21</sup> Moreover, the mortality was 6.4% for the stent group and 3.1% for the surgery group, although not reaching statistical significance. From the BARI and EAST experience, a longer follow-up may unmask the mortality difference between the two groups.

### **Platelet Glycoprotein IIb/IIIa Antagonist: Reduction in Mortality and Repeat Revascularisation**

Another important advance in percutaneous revascularisation emerges from the use of platelet glycoprotein (GP) IIb/IIIa antagonists. In particular, abciximab has been shown to reduce ischaemic cardiac events following balloon angioplasty, arterectomy, and stent implantation.<sup>22-24</sup> In the Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial (EPISTENT) diabetic substudy, the 6-month target vessel revascularisation (TVR) rate was significantly reduced from 16.6% in the stent-placebo group to 8.1% in the abciximab-stent group.<sup>25</sup> Angiographic analysis showed a significant decrease in the late loss index. The data are suggesting an anti-restenotic effect of abciximab which may be related to its non-specific inhibitory effects on integrin receptors including IIb/IIIa,  $\alpha_v\beta_3$  and Mac-1, which have been implicated in the thrombotic and proliferative response leading to neointima formation after arterial injury.<sup>26-29</sup> In addition to TVR reduction, evidence of mortality reduction was observed in the EPISTENT trial when abciximab was used as adjunct during coronary stenting.<sup>30</sup> Meta-analysis of Evaluation of 7E3 for the Prevention of Ischemic

Complications (EPIC), Evaluation in PTCA to Improve Long-term Outcome with abciximab GP IIb/IIIa blockade (EPILOG), and EPISTENT demonstrated a survival benefit in diabetic patients receiving abciximab during elective or urgent percutaneous intervention. A 44% mortality reduction at 1 year from 4.5% to 2.5% was found.<sup>31</sup> The combination of abciximab and stenting should be considered in diabetic patients undergoing percutaneous revascularisation because of the significant reduction in mortality, MI and re-intervention and should be adopted for future comparison trials.

### **Drug-eluting Stents: Reduction of Restenosis; Complete Revascularisation**

Enormous efforts have been invested in the attempt to reduce restenosis soon after the inception of PTCA. Among the numerous devices and drugs that have been tested, stents were shown in the early 1990s to be the first device capable of reducing restenosis compared with balloon angioplasty. The improved but still disappointing rate of in-stent restenosis (ISR) especially in diabetic patients was the impetus for continued effort to overcome this enemy of percutaneous revascularisation. Although proven to be an effective treatment for ISR, vascular brachytherapy was disappointingly unsuccessful in diminishing restenosis when applied to de novo lesions after coronary angioplasty or stenting.<sup>32</sup> Following early promising results of reduction in restenosis in animal models,<sup>33-35</sup> a pilot study with the sirolimus-eluting stent was shown to achieve 0% ISR up to 1-year angiographic follow-up in 29 patients.<sup>36</sup> The dramatic result of ISR reduction was recently joined by the Randomised double-blind study with the Sirolimus-eluting Bx Velocity™ balloon expandable stent in the treatment of patients with de novo native coronary artery lesions (RAVEL) which showed again no ISR at 6 months in patients receiving sirolimus-eluting stents. The diabetic subgroup in RAVEL is no exception to this remarkable anti-restenotic effect of sirolimus. The ISR was 0% in the sirolimus-eluting stent group versus 42% in the bare stent group.<sup>37</sup> Many other medications including paclitaxol and actinomycin-

D are being tested in clinical trials of drug-eluting stents. The TAXUS I trial using paclitaxol-eluting NIR™ stents also demonstrated a promising 0% ISR.<sup>38</sup> When the safety and efficacy are confirmed by longer-term follow-up, the new era of percutaneous revascularisation will begin. Small vessels, long lesions, bifurcations, and unprotected left main stenosis can be confidently tackled by drug-eluting stents with little hindrance from the worry of restenosis. A more complete revascularisation comparable to CABG may be achieved by the percutaneous approach. With development in the technology of detecting vulnerable plaques,<sup>39</sup> e.g. optical coherence tomography, thermography, elastography, those haemodynamically insignificant but unstable lesions may be prophylactically stented for the prevention of future coronary events from plaque disruption.

### **Conclusion**

Advances in interventional cardiology will most likely impact upon the shortcomings of catheter-based revascularisation in diabetics. Equipped with GP IIb/IIIa antagonists and drug-eluting stents, interventional cardiologists are ready again for another comparison trial with CABG. The ARTS-2 is underway to compare percutaneous revascularisation incorporating these improvements with CABG in patients with multivessel disease. The best revascularisation strategy for diabetic patients with multivessel CAD remains to be elucidated by ongoing clinical trials.

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