

Type 1 diabetes mellitus and coronary revascularization

Helene Mamet^a, Mark C. Petrie^{a,b} and Paul Rocchiccioli^a

Over the last three decades, trials of coronary revascularization have taken into account whether populations did or did not have diabetes. What has not been considered is whether or not patients with diabetes in these studies have type 1 or type 2 diabetes. 'Diabetes' appears to be largely used as a synonym for type 2 diabetes. The number of patients with type 1 diabetes has not been reported in most trials. Many questions remain unanswered. Do patients with type 1 diabetes have the same response to various modes of revascularization as those with type 2 diabetes? We know type 2 diabetes affects coronary endothelial function and the coronary artery wall but to what extent does type 1 diabetes affect these? Any response to revascularization does not just depend on the coronary artery but also on the myocardium. How does type 1 diabetes affect the myocardium? To what extent do patients with type 1 diabetes have viable or ischaemic myocardium or scar? What does 'diabetic cardiomyopathy' refer to in the context of type 1 diabetes? This manuscript reviews the evidence for revascularization in type 1 diabetes. We

Introduction

Much attention has been paid to the relative merits of coronary artery bypass grafting (CABG) and percutaneous intervention in patients with 'diabetes'. The term 'diabetes' however appears to have been used as a synonym for type 2 diabetes. Type 1 diabetes is widely recognized to have very different pathophysiology, natural history and associated comorbidities from type 2 diabetes [1]. This manuscript reviews the extent of the literature concerning type 1 diabetes and revascularization.

Type 1 diabetes and clinical trials of revascularization strategies

Trials including only patients with diabetes

Three trials of revascularization strategies have solely included patients with diabetes (Table 1). The largest of these, Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI-2D) [4], specifically excluded patients with type 1 diabetes (i.e. included only those with type 2 diabetes). The second largest, Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) [3], did not report how many patients had type 1 diabetes. The only other trial, Coronary Artery Revascularization in Diabetes (CARDia) [2], was the only trial to report the numbers with type 1 diabetes (4.9%). None of these trials reported subanalyses of the pros and cons of randomized

conclude that there has been a near absence of investigation of the pros and cons of revascularization in this population. Investigations to establish both the nature and extent of coronary and myocardial disease in these populations are necessary. Clinical trials of the pros and cons of revascularization in type 1 diabetes are necessary; many will declare that these will be too challenging to perform. *Cardiovasc Endocrinol Metab* 8:35–38 Copyright © 2019 Wolters Kluwer Health, Inc. All rights reserved.

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^aDepartment of Cardiology, Golden Jubilee National Hospital and ^bInstitute of Cardiovascular and Medical Sciences, University of Glasgow, Glasgow, UK

Correspondence to Paul Rocchiccioli, BSc (Med Sci), MBCHB (Hons), MD, Department of Cardiology, Golden Jubilee National Hospital, Agamemnon Street, Clydebank, Glasgow G81 4DY, UK
Tel: +44 141 951 5860; fax: +44 141 951 5859; e-mail: p.rocchiccioli@nhs.net

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strategies in type 1 diabetes. There will be those who suggest that trials specifically in patients with type 1 diabetes are too difficult to recruit because of the lower prevalence of type 1 versus type 2 diabetes. Caution should be used when extrapolating these results to guide the management of patients with type 1 diabetes until specific evidence in this population is available.

Trials with subgroup analyses of subgroups of patients with diabetes

Of the large trials with diabetes subgroups, only two stated how many patients had type 1 diabetes (Table 2). The Synergy between Percutaneous Coronary Intervention with Taxus and Cardiac Surgery trial [11] and Stent or Surgery trial [15] included a combined total of 30 patients with type 1 diabetes.

Type 1 diabetes and studies of revascularization strategies

In the absence of clinical trials, there are now emerging nonrandomized analyses attempting to shed some light on the relative merits of revascularization strategies in type 1 diabetes. In the largest to date (2546 patients with type 1 diabetes in Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies, SWEDE-

Table 1 Revascularization trials including patients with diabetes only

Trials	N	Randomization	Numbers of patients with type 1 diabetes	Analyses of outcomes by type 1 diabetes
CARDia [2]	510	CABG vs. PCI	4.9%	None
FREEDOM [3]	1900	CABG vs. PCI	Unknown	None
BARI-2D [4]	2368	CABG vs. PCI vs. medical therapy	None (type 2 diabetes only)	None

CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

HEART), CABG was associated with better outcomes than percutaneous coronary intervention [17].

International clinical practice guidelines and type 1 diabetes

The most recent international guidelines for revascularization (2018 guidelines on behalf of the European Society of Cardiology and European Association for Cardio-Thoracic Surgery) have several sections on ‘diabetes’ but make no mention of type 1 diabetes [18]. The lack of evidence is not acknowledged in the ‘gaps in evidence’ section. No previous international practice guideline has offered guidance on how revascularization in type 1 diabetes might be approached.

Coronary artery disease in type 1 diabetes

Coronary artery disease in diabetes is known to be characterized by endothelial dysfunction and extensive atherosclerotic changes [1]. These studies of coronary disease in diabetes have investigated patients with type 2 diabetes. Type 1 diabetes is anecdotally known to be associated with coronary artery disease but the prevalence and extent of disease is as yet unstudied. It is conceivable that patients with type 1 diabetes have very different coronary artery characteristics than those with type 2 diabetes in the context of the differing prevalence of comorbidities and presenting at different ages. The role of microvascular disease in coronary disease in patients with type 1 diabetes is unstudied.

Complications of percutaneous coronary intervention and coronary artery bypass grafting in type 1 diabetes

Patients with diabetes have a higher rate of one of the scourges of percutaneous coronary intervention: in-stent restenosis [19]. No study has reported on the rates of restenosis in type 1 diabetes with the vast majority of studies failing to report the proportion of patients with type 1 or type 2 diabetes. Similarly, patients with diabetes have a higher rate of graft occlusion following CABG [20]. ‘Diabetes’ in these studies has been used to mean type 2 diabetes. The rate of graft occlusion in patients with type 1 diabetes is unknown. Other unknowns regarding type 1 diabetes and percutaneous coronary intervention include the relative merits of dual antiplatelet therapy and rates of major and minor bleeding. Other unknowns with respect to CABG include the length of intensive care stay and sternal healing.

Myocardium and type 1 diabetes

In patients with type 2 diabetes and coronary artery disease, it is not only the coronary arteries that determine the pros and cons of revascularization but also the extent of disease of the myocardium. Myocardial disease in type 1 diabetes is largely unstudied. The prevalence of scar, ischaemia and viability is unknown. A very recent report from the DCCT has found that some patients with type 1 diabetes have cardiac autoantibodies [21]. Patients with elevated levels of these autoantibodies have a higher risk of subsequent cardiovascular events than those who do not. Findings such as this illustrate the unique nature of the cardiovascular disease in type 1 diabetes and emphasize that type 1 diabetes should be studied as a distinct entity. ‘Diabetic cardiomyopathy’ is a term that has been used to describe the effects of diabetes on the myocardium. As yet this term has primarily been used in the context of type 2 diabetes with very little debate or discussion as to how the myocardial changes of type 1 diabetes might sit within this construct [22].

The rising recognition of the pre-eminence of cardiovascular disease in diabetes

Diabetes and cardiology communities have been stirred to the opportunities of improving the outcomes of patients with diabetes following the remarkable reduction in cardiovascular events seen with sodium-glucose cotransporter 2 inhibitors and glucagon-like peptide-1 receptor agonists [23]. These trials have included patients with type 2 diabetes. The potential role of novel pharmacological strategies in type 1 diabetes is being considered. This enthusiasm should be expanded into improving the outcomes of patients with type 1 diabetes and coronary artery disease.

Type 1 diabetes is not the same as insulin-requiring diabetes

Some analyses of large clinical trials of revascularization in diabetes have presented results by insulin-requiring versus non-insulin-requiring diabetes. Not only is this a poor surrogate for type 1 diabetes, but it also fails to recognize those other forms of insulin-requiring diabetes including monogenic and secondary diabetes, and as such we recommend case report forms for clinical trials should be developed to explicitly capture whether the patient has type 1 or type 2 diabetes at baseline according to the American Diabetes Association criteria [24]. Inclusion and exclusion criteria should also be clear as to whether or not patients with type 1 diabetes are to be included.

Table 2 Revascularization trials with subgroup analyses of patients with diabetes

Trial	N	Randomization	Numbers of patients with type 1 diabetes	Analyses of outcomes by type 1 diabetes
EXCEL [5]	1905 (29% with diabetes)	CABG vs. PCI in left main disease	Unknown	None
NOBLE [6]	1201 (15% with diabetes)	CABG vs. PCI in left main disease	Unknown	None
BEST [7]	880 (41% with diabetes)	CABG vs. PCI	Unknown	None
MASS II [8]	611 (38% with diabetes)	Medical therapy vs. PCI vs. CABG	Unknown	None
STICH [9]	1212 (39% with diabetes)	Medical therapy vs. CABG in EF <35%	Unknown	None
PRECOMBAT [10]	600 (32% with diabetes)	CABG vs. PCI in left main disease	Unknown	None
SYNTAX [11]	1800 (25% with diabetes)	CABG vs. PCI	6% of diabetes had type 1 diabetes (n = 27)	None
COURAGE [12]	2287 (33% with diabetes)	Medical therapy vs. PCI	Unknown	None
OAT [13]	2166 (22% with diabetes)	Medical therapy vs. PCI	Unknown	None
RITA-2 [14]	1016 (9% with diabetes)	Medical therapy vs. PCI	Unknown	None
SOS [15]	988 (14% with diabetes)	CABG vs. PCI	3% had type 1 diabetes (n = 3)	None
ARTS-I [16]	1205 (17% with diabetes)	CABG vs. PCI	No	None

CABG, coronary artery bypass grafting; EF, ejection fraction; PCI, percutaneous coronary intervention.

The future

Future registries, clinical trials and international guidelines must address the large evidence gap in revascularization in type 1 diabetes. Diabetologists have appreciated for years that these two diseases are separate entities. Diabetes and cardiovascular communities need to come together to design achievable and informative clinical trials.

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Conflicts of interest

There are no conflicts of interest.

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