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Review Article

Interventions in type 2 diabetes mellitus and cardiovascular mortality–An overview of clinical trials

Benjamin Burggraaf *, Manuel Castro Cabezas

Department of Internal Medicine, Center for Diabetes and Vascular Medicine; Franciscus Gasthuis, Rotterdam, The Netherlands

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ABSTRACT

Diabetes mellitus type 2 (T2DM) has been associated with an increased cardiovascular risk. Improving glycaemia or other traditional cardiovascular risk factors may reduce cardiovascular risk in patients with T2DM. However, single risk intervention in T2DM has not provided convincing evidence in the reduction of cardiovascular risk. The aim of this paper is to provide an overview of clinical trials involving reduction of cardiovascular outcomes in patients with T2DM.

Trials with glucose lowering therapies have shown conflicting results. Intensive therapy to reduce glycaemia has shown some benefit on composite cardiovascular endpoints but these benefits take a longer period to emerge. Recent studies with empagliflozin and glucagon-like peptide-1 (GLP-1) agonists show promising results, but the mechanisms are most likely not mediated by improved glycaemia, given the relatively rapid effects. Both LDL-cholesterol and blood pressure reduction have been proven by large meta-analysis to reduce both cardiovascular events and mortality in all patients with T2DM. Treatment of microalbuminuria and anti-platelet therapy have only been proven in diabetic patients with increased cardiovascular risk.

Classical lifestyle interventions have been disappointing with respect to cardiovascular outcome, possibly due to limited weight reduction. So far, the strongest evidence lies on bariatric surgery and a multifactorial intervention to reduce mortality and cardiovascular events in the long term.

1. Introduction

Patients with type 2 diabetes mellitus (T2DM) have a well-established increased risk of cardiovascular disease (CVD) [1–3]. In fact, CVD is the major cause of death in these patients [4]. In 2013, worldwide 387 million people were diagnosed with diabetes and this number is expected to rise to 600 millions by the year 2030 [5].

In the early 1930s, the first studies were published showing an association between T2DM and CVD [6]. The famous Framingham Heart Study reported in 1979 that diabetic patients had a two- to threefold increased risk of clinical atherosclerosis [7]. In 1998, Haffner et al. published a classic paper reporting that patients with T2DM, but without a history of myocardial infarction, had a similar risk of myocardial infarction compared to patients with a previous myocardial infarction [8]. Two years later these data were confirmed in patients hospitalized for unstable angina pectoris or myocardial infarction [9]. This led to intensification of treatment and prevention of cardiovascular disease in patients with T2DM. However, later studies showed some contradicting results [10, 11]. A meta-analysis from the Emerging Risk Factors Collaboration, with 102 prospective studies and 698,782 patients, showed an adjusted HR of 2.00 for coronary heart disease in diabetic patients. Associated risk factors were female gender, lower BMI and younger age (40–59 years) [12]. Other studies also found an higher cardiovascular risk in females compared to males, indicating that the so called "female-advantage" is lacking in diabetic patients [13]. Importantly, clustering of traditional cardiovascular risk factors as hypertension, LDL-cholesterol and obesity is frequently seen in patients with T2DM [14].

For a long time, it was believed that improving glycemic conditions and traditional risk factors would lower cardiovascular risk in T2DM. The last decade, a large number of studies were published dealing with this issue. This paper intends to provide an overview of a historical perspective and recent clinical trials with glucose lowering interventions and cardiovascular risk modification aiming to reduce cardiovascular risk in patients with T2DM.

2. Interventions aiming to reduce cardiovascular mortality in T2DM

2.1. Blood glucose management (Table 1)

Elevated blood glucose levels have been associated with higher cardiovascular risk [8], thus it was believed that managing blood glucose levels should lead to a decrease in cardiovascular events. Many trials have been performed, and results have been controversial.

* Corresponding author at: Franciscus Gasthuis, Department of Internal Medicine, Center for Diabetes and Vascular Medicine, PO Box 10900, 3004 BA Rotterdam, The Netherlands.
E-mail address: b.burggraaf@franciscus.nl (B. Burggraaf).

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Table 1
Randomized, controlled, cardiovascular outcome trials in patients with T2DM aiming at blood glucose reduction

	Population	N	Follow up	Intervention	Outcome	
					Events	Mortality
UKDPS [16,17], 1998	T2DM	3867	Median 10 years	Intensive (sulfonylurea/ insulin or in overweight metformin) versus conventional glucose lowering strategy (diet restriction)	Myocardial infarction RR 0.84 (p = 0.052)	All-cause mortality RR 0.94 (p = 0.44)
	T2DM and obesity	342			Myocardial infarction RR 0.61 (p = 0.01)	All-cause mortality RR 0.64 (p = 0.011)
Post-trial follow-up [18], 2008		3277	10 year post-trial		Myocardial infarction: sulfonylurea/insulin RR 0.85 (p = 0.01), metformin RR 0.67 (p = 0.005)	All-cause mortality: sulfonylurea/insulin RR 0.87 (p = 0.007), metformin RR 0.73 (p = 0.002)
DIGAMI 1 [35], 1997	T2DM after myocardial infarction	620	Median 3.4 years	Intensive (>24 hour insulin infusion followed by multidose insulin) versus routine anti-diabetic therapy		Overall mortality RR 0.72 (95%-CI 0.550.93)
Post-trial follow-up [36], 2014			Mean 7 years			Overall mortality HR 0.83 (95%-CI 0.700.98)
DIGAMI 2 [37], 2005	T2DM after acute myocardial infarction	1253	Mean 2.1 years	Intensive (acute insulin infusion follow by 1: insulin-based glucose control or 2: standard glucose control) versus usual metabolic control		1: All-cause mortality HR 1.03 (95%-CI 0.79-1.34) 2: All-cause mortality HR 1.23 (95%-CI 0.89-1.69)
Post-trial follow-up [38], 2011		1145	Median 4.1 years			1: All-cause mortality HR 1.17 (95%-CI 0.90-1.52) Cardiovascular mortality HR 1.19 (95%- CI 0.86-1.64) 2: All-cause mortality HR 1.12 (95%-CI 0.86-1.46) Cardiovascular mortality HR 1.32 (95%- CI 0.97-1.81)
PROactive [23], 2005	T2DM and macrovascular disease	5238	Median 34.5 months	Pioglitazone 15-45 mg versus placebo	Composite of all-cause mortality, nonfatal myocardial infarction, or stroke HR 0.84 (95%-CI 0.72-0.98) Composite of death of any cause, nonfatal myocardial infarction, stroke, acute coronary syndrome, leg amputation, coronary revascularization, or revascularization of the leg HR 0.90 (95%-CI 0.80-1.02)	All-cause mortality HR 0.83 (95%-CI 0.65-1.06)
Post-trial follow-up [24], 2016		3606	Mean 7.8 years		Composite of all-cause mortality, non- fatal myocardial infarction, or stroke HR 0.98 (95%-CI 0.89-1.07) Composite of death of any cause, nonfatal myocardial infarction, stroke, acute coronary syndrome, leg amputation, coronary revascularization, or revascularization of the leg HR 0.96 (95%-CI 0.88-1.04)	All-cause mortality HR 0.93 (95%-CI 0.84-1.04) Cardiovascular mortality HR 0.91 (95%- CI 0.80-1.05)
DREAM [22], 2006	Impaired fasting glucose	5269	Median 3 years	Rosiglitazone 8 mg versus placebo	Composite of myocardial infarction, stroke, cardiovascular death, heart failure, new angina and revascularisation HR 1.37 (95%-CI 0.97-1.94)	All-cause mortality HR 0.91 (95%-CI 0.55-1.49) Cardiovascular mortality HR 1.20 (95%- CI 0.52-2.77)
Dargie et al [28], 2007	T2DM and heart failure	224	52 weeks	Rosiglitazon 4 mg versus placebo		All-cause mortality HR 1.50 (95%-CI 0.49-4.59) Cardiovascular mortality HR 1.13 (95%- CI 0.30-4.25)
ACCORD [39], 2008	T2DM	10251	Mean 3.5 years; stopped due to higher mortality intensive group	Intensive (targeting HbA1c <6.0%) versus standard (HbA1c 7.07.9%) therapy	Composite nonfatal myocardial infarction, nonfatal stroke, or death cardiovascular causes HR 0.90 (95%-CI 0.78-1.04)	All-cause mortality HR 1.22 (95%-CI 1.01-1.46) Cardiovascular mortality HR 1.35 (95%- CI 1.04-1.76)
Post-trial follow-up [40], 2016		8601	Mean 7.7 years		Composite nonfatal myocardial infarction, nonfatal stroke, or death cardiovascular causes HR 0.95 (95%-CI 0.87-1.01)	All-cause mortality HR 1.01 (95%-CI 0.92-1.10) Cardiovascular mortality HR 1.20 (95%- CI 1.03-1.40)
ADVANCE	T2DM	11140	Median 5 years	Intensive (gliclazide + other drug to	Composite of death from any cardiovascular	All-cause mortality

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