Cardiovascular disease and type 1 diabetes: prevalence, prediction and management in an ageing population

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***Abstract*:** Cardiovascular disease (CVD) is a major cause of mortality in type 1 diabetes mellitus (T1D). However, evidence of its risks and management is often extrapolated from studies in type 2 diabetic (T2D) patients or the general population. This approach is unsatisfactory given that the underlying pathology, demographics and natural history of the disease differ between T1D and T2D. Furthermore, with a rising life expectancy, a greater number of T1D patients are exposed to the cardiovascular (CV) risk factors associated with an ageing population. The aim of this review is to examine the existing literature around CVD in T1D. We pay particular attention to CVD prevalence, how well we manage risk, potential biomarkers, and whether the studies included the older aged patients (defined as aged over 65). We also discuss approaches to the management of CV risk in the older aged. The available data suggest a significant CVD burden in patients with T1D and poor management of CV risk factors. This is underpinned by a poor evidence base for therapeutic management of CV risk specifically for patients with T1D, and in the most relevant population – the older aged patients. We would suggest that important areas remain to be addressed, particularly exploring the risks and benefits of therapeutic approaches to CVD management in the older aged.

Keywords: Type 1 diabetes, older aged, older adults, elderly, ageing, cardiovascular disease, prevalence, risk factor, management, treatment

Introduction

Cardiovascular disease (CVD) is a major cause of mortality in type 1 diabetes mellitus (T1D) [Morrish *et al*. 2001]. The management of CVD in patients with T1D is, however, based on evidence that is at best sparse and often nonexistent. Frequently, management has been based on evidence extrapolated from studies in type 2 diabetes mellitus (T2D) or the general population [The National Collaborating Centre for Chronic Conditions, 2004]. This approach is unsatisfactory for a number of reasons. Firstly, there is emerging evidence that the pathogenesis of atherosclerosis in CVD differs between T1D and T2D and the nondiabetic population [Pajunen *et al*. 2000; Moreno *et al*. 2000]. Secondly, the age at which CVD becomes evident differs between T1D and T2D, compromising a reliance on therapies validated in older T2D patients. Thirdly, differences seen in the duration and natural history of CVD in patients with T1D and T2D raise the prospect of a need to initiate cardiovascular (CV) protective therapy earlier in T1D.

These considerations gain increasing importance in the context of a rising life expectancy in T1D [Miller *et al*. 2012; Lung *et al*. 2014]. As mortality from renal disease and acute metabolic complications fall (though not in all countries) [Pambianco *et al*. 2006], a greater number of T1D patients are exposed to the CV risk that associates with an ageing population. A recent cross-sectional survey undertaken by our group using data generated within a UK primary care setting identified a CVD prevalence of 40% in T1D patients aged over 65 years [Chapman *et al*. 2013].

This narrative review describes existing literature relating to CVD in T1D. Particular focus is applied to CVD prevalence, how well we manage

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risk, potential biomarkers in monitoring CVD, and the extent to which studies have included older aged participants (defined as aged over 65). We also discuss approaches to the management of CV risk in the older aged. Areas in which there is a paucity of available evidence are identified and a number of strategies suggested for improved research in to, and management of, T1D in older patients.

Methods

A literature search was undertaken using Medline (Ovid) and Embase (Ovid), with respective temporal limits of 1946 to March 2014 and 1974 to 1 April 2014. CVD, as defined by the British Heart Foundation, includes all diseases of the heart and circulation, including coronary artery disease (CAD), heart failure, congenital heart disease and stroke [British Heart Foundation, undated]. The search terms 'cardiovascular disease' (disease) and 'type 1 diabetes' (population) were used in the search. A total of 1765 papers were initially identified, 461 of which were duplicates.

The remaining 1304 manuscripts were subsequently screened by title. Review articles, conference abstracts and manuscripts with titles that were not relevant to CVD and T1D were removed. A total of 335 articles were subsequently reviewed and each was classified into 1 or more of 31 broad categories. We focused on 11 of these categories which were pertinent to the objective of this review (Table 1). A total of 99 papers from the 11 pertinent categories were included, in addition to 7 additional articles identified from the original search which were considered relevant and 30 papers identified through lateral searches. Flow chart 1 and Table 1 outline the search process of paper selection and the categories manuscripts were assigned to.

Prevalence of CVD in T1D

For clarity, we have described prevalence for CVD disease, CVD mortality and CVD risk factors in separate sections. Incidence rate ratio (IRR) describes the incidence rate (incident cases over the follow-up length) of the study population as a proportion of the incidence rate of the controls [Sedgwick, 2010]. Hazard ratio (HR) compares the rate of death or event in the study population with that of the controls across the follow-up period [Sedgwick, 2011]. The standardized mortality ratio (SMR) is a comparison of the number of observed death in the study population with the number of expected deaths based on age specific rates in a standard population [Public Health England]. The cohorts of commonly referenced studies are abbreviated and listed in Table 2.

CVD events are increased in T1D

There are a few established large T1D cohorts that provide valuable epidemiological data of CVD prevalence. Amongst these include the Pittsburgh Epidemiology of Diabetes Complication Study (EDC), the Finnish Diabetic Nephropathy Study (FinnDiane), the European Diabetes Prospective Complication Study (EURODIAB) and the Epidemiology of Diabetes Interventions and Complications study (EDIC, 1994) which is a long-term follow up of the Diabetes Control and Complications Trial cohort (DCCT, 1983–1993).

The EDC 1950–1980 cohort reported a CAD incidence density of 0.36 per 100 person-years (n = 906, baseline mean age 28, follow up censored in 2000) [Pambianco *et al*. 2006]. The FinnDiane followed 3110 T1D (baseline mean age 39) for a median of 5 years and found 269 (9%) patients had an incident CVD [Gordin *et al*. 2011]. At year 11 of the EDIC study, the CVD event rate was 0.38 and 0.80 per 100 patient-years in the intensive and conventional diabetes treatment group, respectively [follow up 17 years (mean), n = 593 and 589, mean age 45 at follow up] [Nathan *et al*. 2005].

Two large observational studies show higher rates of CVD in T1D compared with the general population. In the Scottish Registry Linkage Study (SRLS), data for T1D patients aged 20 and above were compared with the nondiabetic populations from the Scottish national surveys. This showed that the age adjusted IRR for first CVD event was 2.3 for men and 3.0 for women [Livingstone *et al*. 2012]. A separate study using the UK General Practice Research Database (GPRD) compared T1D patients with aged and sex-matched nondiabetic controls between 1992 and 1999. This study reported a HR for major CVD of 3.6 for T1D men and 7.7 for T1D women, with a mean age of 33 years in both groups [Soedamah-Muthu *et al*. 2006b].

The SRLS analysis found that the IRR of first CVD event for patients aged over 70 was 1.71 for

Table 1. Inclusion and exclusion criteria and the broad categories.

Inclusion criteria

- Papers related to epidemiology of CVD risk factors, incidence, and mortality
- Laboratory biomarkers for CVD risks

Exclusion criteria

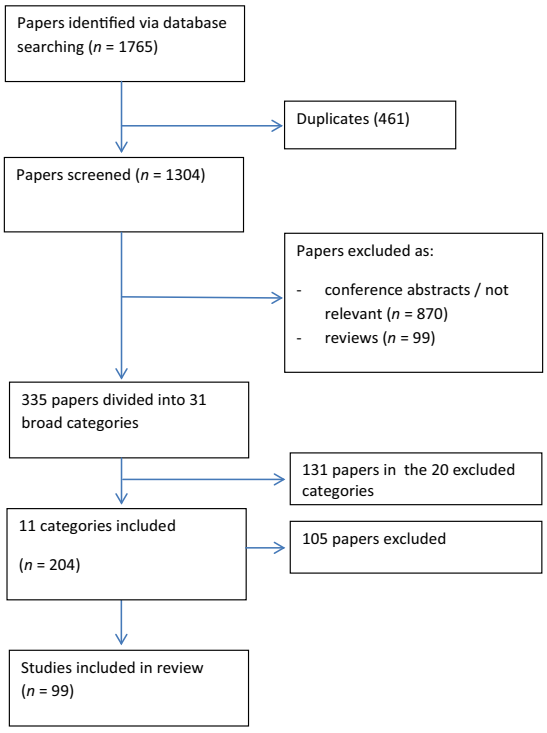
- Conference extract
- Review papers
- Similar results by the same author in a paper published at a later date
- Papers discussing mechanism or pathophysiology of CVD in T1D
- Papers discussing association of risk factors with CVD
- Animal models
- Imaging studies
- Study protocols
- Papers not available in English
- Microalbuminuria
- Full paper or abstract not available

All categories	Included categories
1. Cardiovascular autonomic disease	1. Epidemiology
2. Epidemiology	2. Lipid
3. Lipid	3. Laboratory
4. Laboratory	4. Medication
5. DCCT trial	5. Exercise
6. Cardiac and vessel function	6. Metabolic
7. Predictors	7. Glycaemic control
8. Rat models	8. Transplant
9. Medication	9. Hypertension
10. Coronary artery calcification	10. Gold medallist
11. Imaging	11. Intervention clinic
12. Exercise	
13. Artery stiffness	
14. Endothelium	
15. Metabolic	
16. EURODIAB	
17. Diet	
18. Search study	
19. Insulin resistance	
20. Intensive insulin regime	
21. Gender	
22. Children/adolescent	
23. Glycaemic control	
24. Transplant	
25. Hypertension	
26. CACTI study	
27. Gold medallist	
28. FinnDiane study	
29. Genetic	
30. Pittsburg study	
31. Intervention clinic	

CACTI, Coronary Artery Calcification in Type 1 Diabetes; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; T1D, type 1 diabetes.

men and 1.85 for women [Livingstone *et al.* 2012]. In the GPRD study, the major CVD HR for the age group 65–75 was 2.3 for men and 8.3 for women [Soedamah-Muthu *et al.* 2006b]. In both studies, the figures were lower than the younger age groups, likely reflecting the increasing risk of CVD with age in the general population.

The prevalence of CVD in T1D has also been reported in smaller observational studies within



Flowchart 1. Search strategy flow chart with 99 studies included in this review paper.

other worldwide populations. In a cohort of 209 Chinese with young-onset T1D (defined as diagnosis before age of 40; T1D participants' mean age was 27.8 years) in Hong Kong, the incidence of CVD was 0.6 per 1000 person years [Luk *et al.* 2014]. In comparison, the crude incidence rate of first CVD event for T1D aged 20–39 in the SRLS was 2.73 (men) and 1.76 (women) per 1000 person years [Livingstone *et al.* 2012]. In a small sample of 100 Saudi Arabian T1D patients, 4% (4/100) developed CV complications [Ammari, 2004].

In summary, CVD prevalence appears to be higher in T1D than the general population, particularly in younger women but this effect was not so pronounced in the older aged group.

CVD mortality is increased in T1D

Two large population based observational studies reported the SMR for CVD in T1D. The Allegheny County childhood onset T1D registry (onset age <18 years) reported a SMR of 12.9 [Secrest *et al.* 2010] in a cohort of 1075 T1D patients diagnosed between 1965 and 1979, with

Table 2. Abbreviations of the cohorts of commonly referenced studies.

Acronym	Short title of the study cohort	Reference
CLM	Castilla-La Mancha Multicentre Study	Sastre *et al.* [2012]
DCCT/EDIC	Diabetes Control and Complications Trial/ Epidemiology of Diabetes Interventions and Complications	Nathan *et al.* [2005
DPV	German Surveillance Database	Schwab *et al.* [2006]
EDC	The Pittsburgh Epidemiology of Diabetes Complication Study	Pambianco *et al.* [2006]
EURODIAB	EURODIAB Prospective Complication Study	Soedamah-Muthu *et al.* [2008]
FinnDiane	Finnish Diabetic Nephropathy Study	Gordin *et al.* [2011]
GPRD	UK General Practice Research Database	Soedamah-Muthu *et al.* [2006b]
IEMR	Cross-sectional study of cardiovascular disease risk factors in patients with type 1 diabetes at the Isfahan Endocrine & Metabolism Research Centre	Kalantari *et al.* [2007]
JMRH	Jamaica Major Referral Hospitals Study	Tulloch-Reid *et al.* [2009]
LAHDCA	Liverpool Aintree Hospital Diabetes Clinic Audit	Wallymahmed *et al.* [2005]
LDRDS	Lithuanian Type 1 Diabetes Register Database Study	Dobrovolskienė *et al.* [2013]
NCDQ	Norwegian Childhood Diabetes and Quality Project	Margeirsdottir *et al.* [2008]
NCDR	Norwegian Childhood Diabetes Registry	Skrivarhaug *et al.* [2006]
SRLS	Scottish Registry Linkage Study	Livingstone *et al.* [2012]
UHVGPD	University Hospitals Vienna and Graz Paediatric Department Study	Steigleder-Schweiger *et al.* [2012]

a mean age of 42.9 years old. Data for childhood-onset T1D from the Norwegian Childhood Diabetes Registry (NCDR) (n = 1906, onset age <15 years, diagnosed between 1973 and 1982, follow up till 2002) reported SMRs of 11 for men and 10 for women with T1D [Skrivarhaug *et al.* 2006]. A smaller Swiss study assessed mortality of patients with T1D and T2D compared with the general Swiss population between 1974 and 2005. There were 225 Swiss T1D patients with a mean age of 43 years old. This study reported a CVD SMR of 6.6; CVD SMR did not differ significantly between T1D and T2D [Allemann *et al.* 2009]. Finally, a New Zealand paper of 995 insulin-treated diabetics (including T2D) showed a CVD SMR of 4.48 in T1D diagnosed before the age of 30; the lower SMR in this paper could be due to a dilution effect of T1D with an older age of onset. In fact in the same paper, the CVD SMR was halved in T1D with onset age >30 years compared with <30 years [Florkowski *et al.* 2003].

CVD related deaths have also been reported as IRR, HR and annual mortality rate. In the SRLS, the IRR for CVD mortality related to T1D was 3.4 and 3.5 for men and women, respectively. The HR for CVD deaths in T1D was 7.4 in the GPRD study [Soedamah-Muthu *et al.* 2006b]. The annual mortality rate for CVD was 1.4 per 1000 person-years (n = 2787, baseline mean age 33, 7 years follow up) [Soedamah-Muthu *et al.* 2008].

CVD appears to be the predominant cause of death in adults with T1D. In the World Health Organization (WHO) multinational cohort, CVD accounted for 44% of T1D deaths [Morrish *et al.* 2001]. In a Danish study with 4821 T1D patients, CVD was the main cause of death [31% (125/402) and 30% (81/271) of all death for men and women, respectively] [Jørgensen *et al.* 2013]. This was also the case in the GPRD study [Soedamah-Muthu *et al.* 2006b].

Studies show that acute diabetic complications, such as ketosis and hypoglycaemia, are more likely to be the cause of death in the young, and CVD begins to predominate as patients become older. This was observed in a Japanese nationwide population-based cohort of 1385 T1D patients diagnosed between 1965 and 1979, where a lower mortality from acute diabetic complications and greater mortality from CVD was seen with increasing follow up. Here CVD was described as the main cause of death in those with more than 20 years' disease duration [Morimoto *et al.* 2013]. Similarly in the SRLS, the most common cause of death was diabetes [41% (51/123)] for the under 40s but circulatory disease [38% (349/907)] for those aged over 40 [Livingstone *et al.* 2012]. This trend is supported by the Allegheny study where acute diabetic complication was the main cause of death (73%) within the first 10 years of diagnosis and CVD was the leading cause of death (40%) after 20 years of T1D [Secrest *et al.* 2010]. Finally, in the NCDR study, acute diabetic complication and violent death was the main cause of death for under 30s but CVD accounts for the most death [30% (11/37)] for over 30s [Skrivarhaug *et al.* 2006].

Focusing on ischemic heart disease (IHD), the Diabetes UK cohort (23,000 T1D patients followed up till 2000) reported a IHD mortality rate that was higher than the general population across all age groups: the overall SMR for IHD was 4.5 (men) and 8.8 (women). Within this cohort, the SMR for IHD was exceptionally high in young women: female T1D patients at ages 20–29 had a SMR of 44.8 [Laing *et al.* 2003]. This gender difference for mortality was also seen in Huxley and colleagues' meta-analysis of 26 studies in T1D (n = 214114); the pooled women-to-men ratio of the SMR for fatal CVD and incident coronary heart disease was 1·86 and 2.54, respectively [Huxley *et al.* 2015].

Only the Diabetes UK cohort study showed data for older T1D, but this was for IHD: those aged 70–84 had IHD SMR of 2.2 for men and 5.3 for women. These figures are lower than the younger age bands and again likely reflect rising CVD risk with age in the general population, and the possibility that those with CVD are no longer alive to contribute to analyses.

One observational study from a tertiary centre in Australia found that there were more CVD death and risk factors in 354 young onset T2D (age of onset between 15 and 30 years) than the 470 young onset T1D observed [Constantino *et al.* 2013]. An 18-year observational study conducted in Finland involving 173 T1D and 834 T2D (aged 45–64 years at baseline) found that both types of diabetes had similar CVD mortality, although there was a 3–4 fold increase of risk in men and 10–13 fold increase for women. However, the impact of glycaemic control on CVD mortality was higher in T1D than in T2D: an increment of 1 unit (%) of glycated haemoglobin increased the risk of CV mortality by 52.5% [95% confidence

interval (CI) 28.4–81.3] in T1D and 7.5% (95% CI 4.3–10.8) in T2D [Juutilainen *et al.* 2008].

CV risk factors are increased in T1D

Whilst diabetes itself is a risk factor for CVD, a majority of T1D patient will have at least one further risk factor. The proportion who do so ranges from 69% in 27,358 T1D patients aged 0.25–26 years in a cross-sectional study from a German surveillance database (DPV) to 89% of 177 T1D patients with end stage renal failure and a mean age of 37 in a Spanish study [Schwab *et al.* 2006; Rueda *et al.* 2009]. The percentage of T1D patients with 3 or more CVD risk factors ranged from 2% in the DPV study to 15% in a Norwegian Childhood Diabetes and Quality Project (NCDQ) cohort (2658 T1D patients with mean age of 13) [Schwab *et al.* 2006; Margeirsdottir *et al.* 2008].

Managing CVD risk

Guidelines for CVD risk management have been proposed by major diabetes associations [American Diabetic Association, 2014; The National Collaborating Centre for Chronic Conditions, 2004; European Society of Cardiology (ESC) *et al.* 2013]. The American Diabetes Association (ADA) guidelines are outlined in Table 3. These do not recommend routine screening for CVD in patients with diabetes and suggest this does not provide any greater benefit than screening for and actively managing CVD risk factors. The approach to managing CV risk in patients with T1D is consequently comparable with that of the nondiabetic population.

Assessment therefore consists of measuring clinical risk factors, calculating risk from appropriate risk engines and actively enquiring about symptoms of CVD. Current risk engines for CVD risk in diabetes are largely based on data from studies of the general population. These risk engines include PROCAM (a cohort of working people) (http://www.chd-taskforce.com/procam_interactive.html) and QRISK®2 (a primary care population) (http://www.qrisk.org/) [Assmann *et al.* 2002; Hippisley-Cox *et al.* 2008]. The latter has the option to include T1D.

Achieving target glycated haemoglobin (HbA1c) in T1D

Target HbA1c achievement is generally low (Table 4). The percentage of T1D patients achieving HbA1c $< 7\%$ ranged from 13% (SRLS) to 26% in a multicentre outpatient based T1D study in Castilla-La Mancha, Spain (CLM; $n = 1465$, mean age 39) [Livingstone *et al.* 2012; Wallymahmed *et al.* 2005; Sastre *et al.* 2012]. A recent large observational study using regional and national T1D registries across 19 countries ($n = 324{,}501$) showed that only 28% of the people in the whole dataset had HbA1c $< 7.5\%$ [McKnight *et al.* 2014]. The overall prevalence of poor glycaemic control has been determined for paediatric patients in a number of cross-sectional studies. This is reported to range from 60.6% (HbA1c $>$ 7.5%) in a paediatric department in Austria (UHVGPD study; $n = 264$, mean age 13) to 91% (HbA1c $> 7\%$) of a small cohort of Caribbean youth with T1D in Jamaican major referral hospitals (JMRH; $n = 36$, mean age 18), respectively [Steigleder-Schweiger *et al.* 2012; Margeirsdottir *et al.* 2008; Tulloch-Reid *et al.* 2009].

In the older aged patient, the SRLS observed that the median HbA1c level for those aged over 60 was 8.1% (male) and 8.3% (female) [Livingstone *et al.* 2012].

Achieving target blood pressure in T1D

Estimates for the prevalence of hypertension vary between studies (Table 4). In paediatric T1D, the prevalence ranged from 7% in the NCDQ cohort (0.3% on antihypertensives) to 8% in the DPV study (2% on antihypertensives) and 21% in a Lithuanian T1D register database study (LDRDS; $n = 539$) [Margeirsdottir *et al.* 2008; Schwab *et al.* 2006; Dobrovolskienė *et al.* 2013]. For adults, this ranged from 8% in a group of Iranian T1D patients at the IEMR ($n = 219$; mean age 23), 13% in a UK consultant led T1D clinic (LAHDCA, $n = 218$, mean age 34) and 23% in the CLM study to 37% in over 40s in the SRLS [Kalantari *et al.* 2007; Wallymahmed *et al.* 2005; Sastre *et al.* 2012; Livingstone *et al.* 2012]. In the EDIC year 11 study, 38% and 41% of patients from the intensive treatment and conventional treatment group were hypertensive (>140/90 mmHg) [Nathan *et al.* 2005]. At baseline, 55% of the deceased *versus* 22% survivors in the EURODIAB study were hypertensive (>140/90 mmHg); 36 (35%) and 225 (8%) were on antihypertensives, respectively [Soedamah-Muthu *et al.* 2008].

In the SRLS, a greater proportion of older aged patients were prescribed antihypertensive medications (80% and 79% in over 60s compared with

Table 3. American Diabetes Association 2014 guidelines for type 1 diabetes management.

HbA1c	6.5–7.0%
Blood pressure	<140/80 mmHg
	may be appropriate to aim for lower 130/80 in individual cases
Lipids	LDL < 1.8–2.6 mmol/l.
	Triglyceride < 1.7 mmol/l.
	HDL cholesterol > 1.0 mmol/l (men), >1.3 mmol/l (women)
	Where there is pre-existing CVD, or multiple CVD risk factors, or when the patient is over 40 years of age, lipid lowering therapy should be considered.
Antiplatelet	Consider where there are multiple CVD risk factors, or where there has been previous CVD.
Smoking	Smoking cessation
Albuminuria	ACE inhibitors or ARBs if urinary albumin excretion >30 mg/24 hours
Other medical management	Known CVD: consider ACE inhibitor, aspirin and statin
	Prior myocardial infarct: beta blocker

ACE, angiotensin converting enzyme; ARB, angiotensin II receptor blocker; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; LDL, low density lipoprotein.

50% and 44% in those aged 40–59, men and women, respectively). Despite this, median blood pressure remained elevated in the older aged population when compared with younger persons. [Livingstone *et al.* 2012].

Achieving target lipids in T1D

Four studies have measured overall dyslipidaemia, two of which observed paediatric T1D patients. The CLM study of adult T1D patients found 35% had dyslipidaemia [Sastre *et al.* 2012]. In the EDIC year 11 study, 52% and 48% of patients from the intensive treatment and conventional treatment group had hyperlipidaemia; 34% and 33% were on a statin, respectively [Nathan *et al.* 2005]. From the DPV, 29% of paediatric T1D patients had dyslipidaemia, of whom only 0.4% were prescribed lipid lowering therapy [Schwab *et al.* 2006]. In a small US observational study, 50% of paediatric T1D patients were diagnosed with dyslipidaemia [Reh *et al.* 2011].

Prevalence of raised total cholesterol (>4.8 mmol/l) ranged from 22.3% in the LDRDS paediatric cohort to 55% of the LAHDCA cohort [Dobrovolskienė *et al.* 2013; Kalantari *et al.* 2007; Wallymahmed *et al.* 2005]. In a cohort of T1D patients aged over 60 years, the SRLS identified a median cholesterol level of 4.0 and 4.4 mmol/l in men and women, respectively, which was slightly lower than that of younger patients (4.4 and 4.8 mmol/l in men and women, respectively, aged 40–59) [Livingstone *et al.* 2012].

In the paediatric cohort, prevalence of high low density lipoprotein (LDL) (>2.5 mmol/l) ranged from 14.7% in the LDRDS to 67% in the small JMRH cohort [Dobrovolskienė *et al.* 2013; Tulloch-Reid *et al.* 2009; Margeirsdottir *et al.* 2008; Kalantari *et al.* 2007]. Amor and colleagues identified an improvement in the prevalence of target LDL (<2.5 mmol/l) from 26.3% in 1999 to 65.9% in 2009 in patients undergoing assessment for kidney–pancreas transplant [Amor *et al.* 2011].

The existing literature relating to high density lipoprotein (HDL) in patients with T1D is poor. The proportion of patients with HDL <1.1 mmol/l or <35 mg/dl (undesirable) ranged from 3.3% in a Colorado cohort studied by Maahs and colleagues [Maahs *et al.* 2007] and 4.1% in the LDRDS paediatric cohort [Dobrovolskienė *et al.* 2013] to 7% in the NCDQ cohort [Margeirsdottir *et al.* 2008] *versus* 23% in the IEMR cohort to 33% in the JMRH cohort [Kalantari *et al.* 2007; Tulloch-Reid *et al.* 2009]. Over 60s in the SRLS had median HDL of 1.4 mmol/l (men) and 1.7 mmol/l (women), which was similar to the younger age group [Livingstone *et al.* 2012].

Prevalence for high triglycerides (TG) ranged from 18% in the LDRDS and IEMR cohort to

Table 4. Achieving CVD risk targets in T1D.

Achieving target glycated haemoglobin (HbA1c) in T1D								
Study cohort / country of study cohort	Mean age of participants in years (SD)	Mean diabetes duration in years (SD)	Overall number of participants in the study	Number of participants contributing to the risk factor	Target HbA1c defined in the study	Mean BMI (SD), kg/m^2	Results	Reference
LAHDCA	34 (11.9)	14 (9.0)	218	215	<7.5%	n/a	Mean (SD) HbA1c was 9.7% (1.9) 17 (8%) had HbA1c <7.5% 126 (59%) had an HbA1c > 9%	Wallymahmed *et al.* [2005]
CLM	39.4 (13.5)	19.4 (10.6)	1465	n/a	n/a	n/a	Mean HbA1c was 7.8% 26% had HbA1c ⩽7%	Sastre *et al.* [2012]
SRLS	n/a	Median (IQR) 17.5 (9.3–27.0)	21,789	21,290	<7%	Median BMI 27	Median HbA1c was 8.5% 13% achieved the target 37% had Hb1Ac ⩾9%	Livingstone *et al.* [2012]
19 countries in Australasia, Europe and North America	n/a	n/a	324,501	324,501	n/a	n/a	7.1% had HbA1c < 6.5% 8.7% had HbA1c 6.5–6.9% 12.3% had HbA1c 7.0–7.4%	McKnight *et al.* [2014]
Paediatric cohort								
UHVGPD	12.5 (3.5)	4.6 (3.7)	264	n/a	<7.5%	20.4 (3.9)	Mean HbA1c = 7.85% 160 (60.6%) had HbA1c > 7.5%.	Steigleder-Schweiger *et al.* [2012]
JMRH	20 (8)	2.6 (2)	36	36	n/a	n/a	33 (91%) had HbA1c > 7%	Tulloch-Reid *et al.* 2009
NCDQ	13.1	5.7	1658	1658	<8.5% in 12 year-olds <8.0% in 6–12 year-olds <7.5% in >12 year-olds	20.2 (3.8)	Mean HbA1c was 8.2% 1149 (71.4%) above target level	Margeirsdottir *et al.* [2008]
Older aged cohort								
SRLS	n/a	n/a	1537 males 1427 females	2964	<7%	Median BMI 27 in over 60s	Median HbA1c 8.1% (men) and 8.3% (women) in over 60s	Livingstone *et al.* [2012]
Achieving target blood pressure (BP) in T1D								
Study cohort / country of study cohort	Mean age of participants in years (SD)	Mean diabetes duration in years (SD)	Overall number of participants in the study	Number of participants contributing to the risk factor	Target blood pressure defined in the study, mmHg	Mean BMI (SD), kg/m2	Results	Reference
Paediatric cohort								
NCDQ	13.1	5.7	1658	n/a	n/a	20.2 (3.8)	152 (6.9%) had BP above the 90th centile	Margeirsdottir *et al.* [2008]

Table 4. (Continued)

							4% had BP above the 95th percentile 0.3% on antihypertensives	
DPV	Range 0.5–26 years	n/a	27,358	n/a	n/a	See weight section	8.1% had systolic hypertension and 2.5% diastolic hypertension	Schwab *et al.* [2006]
LDRDS	n/a	n/a	539	n/a	n/a	13.4% overweight	2.1% on anti-hypertensive therapy 113 (21%) had arterial hypertension	Dobrovolskien *et al.* [2013]
Adult cohort								
IEMR	22.5 (10.3)	n/a	219	n/a	<120/80	n/a	17 (7.7%) had hypertension	Kalantari *et al.* [2007]
LAHDCA	34 (11.9)	14 (9.0)	218	213	SBP < 135 DBP < 85	n/a	28 (13%) above target SBP 8 (3.8%) above target DBP 52 (24%) were taking antihypertensives	Wallymahmed *et al.* [2005]
CLM	39.4 (13.5)	19.4 (10.6)	1465	n/a	n/a	n/a	23% were hypertensive	Sastre *et al.* [2012]
SRLS	n/a	17	21,789	n/a	BP < 130/80	Median BMI 27	60% (men) and 53% (women) were above target BP 37% aged over 40 had BP ⩾ 140/90 Median SBP: 130 mmHg (men) 132 mmHg (women) in age group 40–59	Livingstone *et al.* [2012]
EDIC						Year 11 BMI		Nathan *et al.* [2005]
- Intensive treatment	45 (7)	24 (5)	593	n/a		28.4 (6.9)	38% hypertensive	
- Conventional treatment	45 (7)	23 (5)	589	n/a	Hypertension defined as: >140/90	27.6 (4.5)	41% hypertensive	
EURODIAB	Baseline							
- Deceased	41 (11)	22 (12)	102	n/a		Men: 24.0 (2.9); women:23.5 (3.6)	56 (55%) hypertensive, 36 (35%) on antihypertensives	Soedamah-Muthu *et al.* [2008]
- Survived	32 (10)	14 (9)	2685	n/a	Hypertension defined as: >140/90 mmHg, or on antihypertensives	Men: 23.6 (2.6); women: 23.5 (3.0)	595 (22%) hypertensive, 225 (8%) on antihypertensives	
Older aged cohort								
SRLS	n/a	17	21,789	n/a	BP < 130/80	Median BMI 27 for over 60	Median SBP: 137 mmHg (men) and 138 mmHg (women) for over 60s 79.5% (men) and 79.4% (women) aged over 60 were on antihypertensives	Livingstone *et al.* [2012]

(Continued)

Table 4. (Continued)

Achieving target lipids in T1D								
Study cohort / country of study cohort	Mean age of participants in years (SD)	Mean diabetes duration in years (SD)	Overall number of participants in the study	Number of participants contributing to the risk factor	Target lipids defined in the study	Mean BMI (SD), kg/m^2	Results	Reference
CLM	39.4 (13.5)	19.4 (10.6)	1465	n/a	n/a	n/a	35% had dyslipidaemia.	Sastre *et al.* [2012]
DPV	n/a paediatric	n/a	27,358	19,359	n/a	See weight section	29% had dyslipidaemia 0.4% on lipid lowering treatment	Schwab *et al.* [2006]
USA	Median 14.3	6.4 (3.8)	46	n/a	n/a	Baseline BMI 22.8 (3.7)	50% had dyslipidaemia	Reh *et al.* [2011]
EDIC						Year 11 BMI		Nathan *et al.* [2005]
- Intensive treatment	45 (7)	24 (5)	593	n/a		28.4 (6.9)	52% hyperlipidaemia, 34% on statin	
- Conventional treatment	45 (7)	23 (5)	589	n/a	Hyperlipidaemia: defined as LDL >3.4 mmol/l or the use of lipid lowering agent	27.6 (4.5)	48% hyperlipidaemia, 33% on statin	
Cholesterol								
LDRDS	n/a	n/a	539	n/a	n/a	13.4% overweight	Hypercholesterolemia was diagnosed in 120 (22.3%)	Dobrovolskienė *et al.* [2013]
IEMR	22.5 (10.3)	n/a	219	n/a	Serum cholesterol <170 mg/dl	n/a	Hypercholesterolemia in 104 (47.4%)	Kalantari *et al.* [2007]
LAHDCA	34	14	218		Cholesterol <4.8 mmol/l	n/a	112 (54.6%) had a total cholesterol above target	Wallymahmed *et al.* [2005]
SRLS	n/a	Median (IQR) 17.5 (9.3–27.0)	21,789	21,290	n/a	Median BMI 27	41.7% were on a statin Median cholesterol was 4.4 mmol/l (men) and 4.8 mmol/l (women) in the 40–59 age group	Livingstone *et al.* [2012]
USA	13.6 (4.1)	4.5 (0.3)	360	360	Total cholesterol <200 mg/dl	BMI Z-score 0.62 (1.00)	16.9% had sustained raised total cholesterol ⩾ 200 mg/dl at follow up	Maahs *et al.* [2007]
LDL								
LDRDS	n/a	n/a	539	n/a	n/a	13.4% overweight	High LDL in 79 (14.7%)	Dobrovolskienė *et al.* [2013]
JMRH	18 (5)	3 (2)	36	n/a	n/a	n/a	24 (67%) had high LDL > 2.5 mmol/l 12 (33%) had low HDL <1.1 mmol/l	Tulloch-Reid *et al.* [2009]
NCDQ	13.1	5.7	1,658	1,658	n/a	20.2 (3.8)	453 (34.5%) had LDL > 2.6 mmol/l Only 0.2% of all the patients or 3% of those who should have been were receiving lipid lowering treatment	Margeirsdottir *et al.* [2008]

Table 4. (Continued)

Spain	37.4 (14.9)	24.7 (12.2)	270	n/a	n/a	23.2 (3.7)	Mean LDL was 105.06 mg/dl. LDL < 100 mg/dl increased from 26.3% in 1999–2000 to 65.9% in 2009–2010.	Amor *et al*. [2011]
HDL								
LDRDS	n/a	n/a	539	n/a	n/a	13.4% overweight	Decreased HDL in 22 (4.1%)	Dobrovolskienė *et al*. [2013]
NCDQ	13.1	5.7	1,658	1,658	>1.1 mmol/l	20.2 (3.8)	94 (6.9%) had HDL <1.1 mmol/l	Margeirsdottir *et al*. [2008]
IEMR	22.5 (10.3)	n/a	219	n/a	HDL > 35 mg/dl	n/a	HDL<35 mg/dl 22.8% (n = 50)	Kalantari *et al*. [2007]
JMRH	18 (5)	3 (2)	36	n/a	n/a	n/a	12 (33%) had low HDL <1.1 mmol/l	Tulloch-Reid *et al*. [2009]
USA	n/a	n/a	360	360	HDL > 35 mg/dl	BMI Z-score 0.62 (1.00)	3.3% had HDL <35 mg/dl	Maahs *et al*. [2007]
TG								
LDRDS	n/a	n/a	539	n/a	n/a	13.4% overweight	High TG in 96 (17.8%)	Dobrovolskienė *et al*. [2013]
IEMR	22.5 (10.3)	n/a	219	n/a	TG<150 mg/dl	n/a	Hypertriglyceridemia in 18.3% (n = 40)	Kalantari *et al*. [2007]
UHVGPD	12.5 (3.5)	4.6 (3.7)	264	n/a	Dyslipidaemia was defined as TG above 95th percentile	20.4 (3.9)	60 (22.7%) had raised triglycerides above target.	Steigleder-Schweiger *et al*. [2012]
Older aged cohort								
SRLS	n/a	n/a	Male: 1537 Female: 1427	2964		Median BMI 27	Median cholesterol of 4.0 mmol/l (men) and 4.4 mmol/l (women) aged over 60 Median HDL of 1.4 mmol/l (male) and 1.7 mmol/l (female) aged over 60 Median triglyceride levels of 1.2 mmol/l (male) and 1.1 mmol/l (female) aged over 60 72.8% male and 73.6% female over 60 on statins	Livingstone *et al*. [2012]
Smoking status in T1D								
Study cohort / country of study cohort	Mean age of participants in years (SD)	Mean diabetes duration in years (SD)	Overall number of participants in the study	Number of participants contributing to the risk factor	Mean BMI (SD), kg/m^2		Results	Reference
IEMR	22.5 (10.3)	n/a	219	n/a	n/a		15 (6.9%) smoke	Kalantari *et al*. [2007]

(Continued)

Table 4. (Continued)

SRLS	n/a	Median (IQR)	21,789	21,290	Median BMI 27		27.6% smoke overall	Livingstone *et al.* [2012]
		17.5 (9.3–27.0)						
CLM	39.4 (13.5)	19.4 (10.6)	1465	n/a	n/a		26% smoke	Sastre *et al.* [2012]
DPV	7.5 (2.5)	2.5 (2.3)	n/a	n/a	16% BMI > 90th centile		0.24% smoke	Schwab *et al.* [2006]
	13.7 (1.4)	4.9 (3.6)		n/a	20% BMI > 90th centile		10.5% smoke	
	18.5 (2.3)	8.2 (4.8)		n/a	25% BMI > 90th centile		34.8% smoke	
NCDQ	13.1	5.7	1658	n/a	20.2 (3.8)		2% smoke The mean age of the smokers was 17.4 years.	Margeirsdottir *et al.* [2008]
FinnDiane					n/a			Gordin *et al.* [2011]
- With incident CVD event	39 (12)	n/a	269	n/a			60% had history of smoking	
- No incident CVD event	38 (13)	n/a	2698	n/a			40% had history of smoking	
EDIC					Year 11 BMI			Nathan *et al.* [2005]
- Intensive treatment	45 (7)	24 (5)	593	n/a	28.4 (6.9)		14% current smoker at year 11 of EDIC study	
- Conventional treatment	45 (7)	23 (5)	589	n/a	27.6 (4.5)		11% current smoker at year 11 of EDIC study	
EURODIAB	Baseline							Soedamah-Muthu *et al.* [2008]
- Deceased	41 (11)	22 (12)	102	n/a	Men: 24.0 (2.9); women:23.5 (3.6)		32 (31%) current smokers	
- Survived	32 (10)	14 (9)	2685	n/a	Men: 23.6 (2.6); women: 23.5 (3.0)		835 (31%) current smokers	
Older aged cohorts								
SRLS	n/a	n/a	Male: 1537 Female: 1427	2964	Median BMI 27 for over 60		19.1% males and 15.4% females over 60 smoked	Livingstone *et al.* [2012]
Achieving a healthy diet in T1D								
Study cohort / country of study cohort	Mean age of participants in years (SD)	Mean diabetes duration in years (SD)	Overall number of participants in the study	Number of participants contributing to the risk factor	Target health diet defined in the study	Mean BMI (SD), kg/m^2	Results	Reference
NCDQ	13.1	5.7	1,658	Variable – see results	Moderate physical activity >1 hour/day Fat <30% of energy Fruit and vegetables >500 g/day	20.2 (3.8)	299/576 (51.9%) did moderate physical activity <1 hour/day 423/518 (82%) had fat >30% of energy intake 471/518 (91%) consumed <500 g fruit and vegetables /day	Margeirsdottir *et al.* [2008]

Table 4. (Continued)

European	33 (10)	15 (9)	533	n/a	n/a	Baseline BMI 23.6 (2.7) 7 year follow up BMI 24.7 (3.2)	European T1D patients consumed a high atherogenic diet. 2% achieved the recommended intake of dietary fibre 13% achieved the recommended intake of saturated fat	Soedamah-Muthu *et al.* [2013]
European	n/a	n/a	3250	n/a	n/a	n/a	The mean intake of natural dietary fibre was 17.3 g/day Fibre consumption was lowest in patients from Eastern European centres compared with patients from centres in southern and north-western Europe. The fibre density was highest in patients from southern Europe.	Toeller [2002]
Achieving target physical activity (PA) levels in T1D								
Study cohort / country of study cohort	Mean age of participants in years (SD)	Mean diabetes duration in years (SD)	Overall number of participants in the study	Number of participants contributing to the risk factor	Target physical activity levels defined in the study	Mean BMI (SD), kg/m^2	Results	Reference
European	32.7 (10.2)	n/a	3250	2185	n/a	None / mild PA group: 23.4 (2.8) Moderate/ vigorous PA group: 23.7 (2.8)	786 had none or mild PA once a week or more 1399 had moderate or vigorous PA once a week or more	Tielemans *et al.* [2013]
Finland	38.5 (12.3)	23.4 (12.8)	1945	1108 patients with normoalbuminuria	n/a	25.1 (3.5)	23% were sedentary 20.6% less than one session of exercise per week	Wadén *et al.* [2008]
Weight, body mass index (BMI) and the 'metabolic syndrome' in T1D								
Study cohort / country of study cohort	Mean age of participants in years (SD)	Mean diabetes duration in years (SD)	Overall number of participants in the study	Number of participants contributing to the risk factor	Target BMI defined in the study, kg/m^2		Results	Reference
LDRDS	n/a	n/a	539	n/a	n/a		72 (13.4%) were overweight	Dobrovolskienė *et al.* [2013]
JMRH	18 (5)	3 (2)	36	36	n/a		8 (22%) were overweight and 3 (8%) were obese in T1D.	Tulloch-Reid *et al.* [2009]

(Continued)

Table 4. (Continued)

NCDQ	13.1	5.7	1,658	1658	BMI > 95th percentile defined as obese	71 (4.4%) were obese	Margeirsdottir *et al.* [2008]
CLM	39.4 (13.5)	19.4 (10.6)	1465	n/a	n/a	15% were obese	Sastre *et al.* [2012]
UHVGPD	12.5 (3.5)	4.6 (3.7)	264	n/a	BMI > 90th percentiles = overweight	Mean BMI was 20.4 (3.9) 53 (20.1%) had BMI > 90th centile.	Steigleder-Schweiger *et al.* [2012[
DPV	7.5 (2.5)	2.5 (2.3)	n/a	n/a	n/a	16.4% had BMI above 90th percentile	Schwab *et al.* [2006]
	13.7 (1.4)	4.9 (3.6)				20.0% had BMI above 90th percentile	
	18.5 (2.3)	8.2 (4.8)				25.0% had BMI above 90th percentile	
EURODIAB	baseline					BMI: mean (SD)	Soedamah-Muthu *et al.* [2008]
- Deceased	41 (11)	22 (12)	102	n/a		Men: 24.0 (2.9); women:23.5 (3.6)	
- Survived	32 (10)	14 (9)	2685	n/a		Men: 23.6 (2.6); women: 23.5 (3.0)	
Paediatric Diabetes Consortium	3 months after diagnosis: 9.7 (3.7)	n/a	530	530		Baseline median BMI percentile 50%, increasing to 67% at 1 month	Gregg *et al.* [2015]
DCCT						Mean (SD) BMI percentile (%)	Baskaran *et al.* [2015]
- 1999	12.2 (2.2)	2.8 (1.5)	94	94		71 (21)	
- 2002	12.8 (2.3)	6.5 (3.5)	144	144		72 (21)	
- 2006	12.1 (1.9)	5.7 (3.3)	133	133		70 (22)	
- 2009	12.7 (2.5)	6.4 (3.2)	136	136		70 (23)	
Ethiopia	29.1 (12)	n/a	778	778		Mean BMI increased from 15.9 to 18.3 from 2000 to 2009	Abebe *et al.* [2013]
EDC	Baseline 29.1	n/a	n/a	629		Prevalence at baseline *versus* at 18years follow up	Conway *et al.* [2010]
						Obesity: 3.4% *versus* 22.7%	
						Overweight: 28.6% *versus* 46.0%	
Spain	39.7 (13.2)	16.7 (12.9)	91	n/a	n/a	29 (32%) had metabolic syndrome according to the NCEP-ATP III modified criteria	Chillarón *et al.* [2010]
FinnDiane	37 (12)	23 (12)	3783	n/a	n/a	Prevalence of metabolic syndrome at baseline was 44% from the FinnDiane study	Thorn *et al.* [2009]
England	46	21	1282	n/a	n/a	CVD risk factor targets were poorly achieved with only 0.7% of patients achieving all minimal dataset targets.	Syed *et al.* [2007]
						HbA1c and TC targets were those most poorly achieved	
SRLS	n/a	n/a	Male: 1537 Female: 1427	2964	n/a	Median BMI in over 60s was 27	Livingstone *et al.* [2012]

BMI, body mass index; CVD, cardiovascular disease; DBP, diastolic blood pressure; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; IQR, interquartile range; LDL, low density lipoprotein; n/a, not available; NCEP-ATP III, National Cholesterol Education Program-Adult Treatment Panel III; PA, physical activity; SBP, systolic blood pressure; SD, standard deviation; TC, total cholesterol; TG, triglycerides.

23% in the UHVGPD cohort [Dobrovolskienė *et al.* 2013; Kalantari *et al.* 2007; Steigleder-Schweiger *et al.* 2012]. In the SRLS over 60s cohort, the median triglyceride levels were 1.2 mmol/l (male) and 1.1 mmol/l (female), which was again similar to the younger age group [Livingstone *et al.* 2012].

The use of statins varied across age groups. In the NCDQ cohort, 0.2% T1D adolescents were prescribed statin therapy, contrasting with 6.4% (23/360) of paediatric T1D patients in Colorado, USA studied by Maahs and colleagues [Margeirsdottir *et al.* 2008; Maahs *et al.* 2007]. Within the SRLS, 41% of T1D patients were prescribed statins, although this figure was higher for older patients aged over 60 at 73% for males and 74% for females [Livingstone *et al.* 2012]. Data are summarized in Table 4.

Smoking status in T1D

The prevalence of smoking in T1D adult patients ranged from 7% in the IEMR study to 35% in the DPV study (Table 4) [Kalantari *et al.* 2007; Livingstone *et al.* 2012; Sastre *et al.* 2012; Soedamah-Muthu *et al.* 2008; Schwab *et al.* 2006]. In the FinnDiane cohort, 60% and 40% of T1D patients with incident CVD events and no CVD events smoked [Gordin *et al.* 2011]. A total of 14% and 11% of those who were in the intensive treatment and conventional treatment groups, respectively, were a current smoker at year 11 of the EDIC study [Nathan *et al.* 2005]. In the paediatric cohort, the NCDQ cohort identified that 3% of those ⩾12 years old reported smoking [Margeirsdottir *et al.* 2008]. For older aged patients, 19% male and 15% female T1D in the SRLS smoked, this was lower than the younger patients [Livingstone *et al.* 2012].

Achieving a healthy diet in T1D

In studies to date, there appear to be an overconsumption of fat and poor fibre consumption by patients with T1D (Table 4). In the NCDQ cohort, almost all study subjects had higher fat intake and lower fibre intake than recommended [Margeirsdottir *et al.* 2008]. Similar dietary pattern was observed in children aged under seven with T1D (n=24) in a small Swedish study [Sundberg *et al.* 2014]. In the EURODIAB study, European T1D patients consumed a high atherogenic diet, and very few patients achieved the recommended intake of dietary fibre (2%) and saturated fat (13%) [Soedamah-Muthu *et al.* 2013]. When comparing dietary patterns geographically, fibre intake was lowest in eastern Europe and highest in southern Europe [Toeller, 2002]. No study specifically observed the older age group.

Achieving target physical activity levels in T1D

Whilst studies have yet formally and objectively measured exercise and physical activity in T1D, a number of studies have analysed this subjectively (Table 4). The EURODIAB study quantified exercise through the use of questionnaires sent to over 2000 patients and showed that about a third undertook no or only mild physical activity [Tielemans *et al.* 2013]. Similarly, the Finnish Diabetic Neuropathy Study (FinnDiane) showed that 23% of people with T1DM were sedentary with a further 21% doing less than 1 session of exercise per week [Wadén *et al.* 2008]. A significant proportion of patients with T1D may therefore be considered physically inactive.

Weight, body mass index (BMI) and the 'metabolic syndrome' in T1D. A total of 13.4% of the children in the LDRDS and 22% of the JMRH adolescent cohort have been described as overweight [Dobrovolskienė *et al.* 2013; Tulloch-Reid *et al.* 2009]. The percentage of T1D patients classified as obese ranged from 4% of the NCDQ paediatric cohort to 15% of the CLM cohort [Margeirsdottir *et al.* 2008; Tulloch-Reid *et al.* 2009; Sastre *et al.* 2012]. A total of 20% of the UHVGPD cohort to 25% of young adults in the DPV study had a BMI > 90th centile [Steigleder-Schweiger *et al.* 2012; Schwab *et al.* 2006]. In the EURODIAB cohort, the baseline BMI for the deceased and the survivors were virtually the same; in those who survived the mean BMI was 24 [Soedamah-Muthu *et al.* 2008].

The Paediatric Diabetes Consortium's study of 520 T1D youth (mean age 10, median BMI percentile 50%) found that the largest increase in BMI was in the first 3 months post diagnosis of T1D and thereafter remained stable at 12 months, thus reflecting gain of weight lost before diagnosis [Gregg *et al.* 2015]. The DCCT group examined the temporal trends of overweight/obesity across 4 cohorts representing different time point over a decade (1999, 2002, 2006, 2009; n = 507, mean age 12.0–12.8, mean BMI percentile 70–72) and found that the prevalence of overweight/obesity was similar, ranging from 27% to 36% [Baskaran *et al.* 2015]. However, at a cohort level, the

Pittsburgh EDC group followed 589 T1D from 1986 to 1988 for 18 years and found that the prevalence of overweight and obesity increased by 47% and 7 fold, respectively (mean age 29, baseline prevalence of overweight and obesity 29% and 3%). Simultaneously, the use of intensive insulin regime increased from 7% to 82% and was quoted as a predictor of weight change [Conway *et al.* 2010].Similarly, a 10-year observational study at an Ethiopian hospital diabetes clinic reported that BMI increased from 16 to 18, although this remains in the underweight category (2000–2009, n = 778, mean age 29) [Abebe *et al.* 2013].

For the over 60s T1D patients, the median BMI was 27 in the SRLS; this was similar to the younger age groups [Livingstone *et al.* 2012] (see Table 4).

A Spanish hospital study showed that 32% of T1D outpatients had metabolic syndrome [Chillarón *et al.* 2010]. From the FinnDiane study, the prevalence of metabolic syndrome (by WHO definitions) at baseline was 44% [Thorn *et al.* 2009]. There were no data targeting the older aged group.

Whilst we accept that striving for prespecified targets may be inappropriate for some patients, these studies suggest that risk factors for CVD are suboptimally controlled in patients with T1D. We have previously shown in a UK single city multihospital study that targets of CVD risk factors were suboptimally recorded and only 0.7% of patients were achieving all minimal dataset target (total cholesterol, smoking, HbA1c) [Syed *et al.* 2007].

Biomarkers for CVD in T1D

Whilst the approach of managing CV risk through clinical assessment is simple, relatively straightforward and can be used in the clinical situation, there are a number of potential biomarkers for CVD in T1D that may prove to be useful. These are outlined in Table 5.

Management of CV risk in the older aged patient with T1D

There is a paucity of literature concerning effective strategies for the management of CV risk in the older aged patient with T1D. It appears on the basis of current evidence, however, that strategies should include tight control of both diabetes specific factors, such as blood glucose regulation, and the more general modifiable CV risk factors. The relative benefit afforded by targeting each of these risk factors remains unclear, with no single dominant factor predicting CV morbidity in patients with T1D and evidence to implicate the metabolic syndrome in its pathogenesis [Mäkinen *et al.* 2009; Thorn *et al.* 2009].

Interestingly, the Joslin 50-year medallist study provides evidence to suggest that there is a limit to the extent to which risk management strategies are effective in ageing patients with T1D [Sun *et al.* 2011]. Substantiating this, the authors provide evidence for a greater prevalence of CVD amongst patients with lower systolic blood pressure, mean arterial pressure, heart rate, total cholesterol and LDL, likely reflecting the use of pharmacological agents amongst these patients. Despite this, there is a clear link in the study between deranged lipids and CV risk, emphasizing a need for effective lipid management in aged patients with T1D. There is, in addition, further evidence within the Golden Years Cohort for genetically determined elevated HDL-cholesterol affording protection from large vessel disease in long-lived subsets of patients with T1D [Bain *et al.* 2003].

Taken together, these analyses of long-lived patients appear to suggest that HDL control may afford a significant therapeutic target for preventing CVD in ageing patients with T1D. There is, nevertheless, wider evidence amongst nonaged populations for a multifactorial approach to CV risk reduction in patients with T1D. Given that a number of these studies report extended follow up, albeit in younger patients than focused on in this review, their results are likely generalizable to an aged cohort.

Wallymahmed and colleagues provide evidence to suggest that lifestyle modifications may improve CV health within their randomized controlled trial comparing nurse-led CV risk factor intervention to routine care in patients with a mean age of 34.6 years [Wallymahmed *et al.* 2011]. In identifying positive impacts stemming from nurse-led intervention they do, however, note that much of the improvement seen was likely secondary to greater use of lipid-lowering or antihypertensive agents. It is additionally difficult to translate many of the lifestyle findings relating to young patients with T1D to their older aged counterparts. Chen and colleagues previously identified low physical activity to equate to decreased heart rate variability in children with T1D, for example, suggesting that strategies to improve exercise are important for preventing CVD [Chen *et al.*

Table 5. Potential biomarkers for CVD risk in T1D that has been investigated.

Name of biomarker	Function of biomarker	Studies
Asymmetric dimethylarginine (ADMA)	Competitive inhibitor of nitric oxide synthase and linked with endothelial dysfunction and insulin resistance.	ADMA levels above the median predicted fatal and nonfatal cardiovascular events in T1D with overt nephropathy adjusted HR 2.05, 95% CI 1.31 - 3.20, p=0.002) (p<0.001) [Lajer *et al*. 2008]. ADMA is marginally elevated in T1D with overt nephropathy compared with T1D with persistent normoalbuminuria (p<0.001) and significantly higher in patients with major cardiovascular events (p=0.05) [Tarnow *et al*. 2004]. Plasma ADMA concentrations were higher in T1D without any vascular complications than healthy controls (p<0.01) and higher ADMA levels are associated with CVD risk factors [Altinova *et al*. 2007]. In young T1D, there is no association between ADMA and endothelial dysfunction and levels are similar to healthy controls [Głowińska-Olszewska *et al*. 2010]. There is an inverse association between ADMA and HbA1c in T1D (p<0.001) in a longitudinal study [Marcovecchio *et al*. 2011]
Advanced glycation end product (AGE) and soluble receptor for advanced glycation end product (sRAGE)	Triggers inflammation and atheroma formation	T1D patients with CVD had higher levels of sRAGE than those without CVD (β=0.15, 95% CI 0.04–0.27) [Nin *et al*. 2009]. The incidence of fatal and nonfatal CVD increased with higher baseline levels of AGEs in T1D (HR=1.30, 95% CI 1.03–1.66) [Nin *et al*. 2011]. The AGE tetrahydropyrimidine was higher in T1D compared with healthy controls (p=0.03) but had no association with either micro or macro vascular complications [Van Eupen *et al*. 2013]. Baseline soluble RAGE was independently associated with CV mortality in T1D (Fine–Gray competing risks model: HR 1.06) [Thomas *et al*. 2011] The incident of fatal and nonfatal CVD increased with higher baseline levels of log-transformed sRAGE in T1D (HR 1.90, 95% CI 1.13–3.21 and 2.12, 95% CI1.26–3.57) [Nin *et al*. 2010]
Immune complexes of oxidized-LDL (oxLDL-IC) and advanced glycation end products-LDL (AGE-LDL-IC)	Taken up by macrophages leading to transformation into foam cells, the hallmark of artherosclerosis	oxLDL-IC and AGE-LDL-IC predicts progression of carotid intima -medial thickness progression [Hunt *et al.* 2013]
High-mobility group box 1 protein (HMGB1)	Released extracellularly from necrotic and immune cells and acts as a pro-inflammatory cytokine	In T1D with nephropathy and persistent normoalbuminuria, higher levels of $\log_e$ plasma HMGB1 were associated with a higher incidence of fatal and nonfatal CVD mortality (HR 1.55,95% CI 0.94–2.48 and HR1.86, 95% CI 1.18-2.9 respectively) in a 12 year follow up study [Nin *et al*. 2012a]. In T1D, higher serum HMGB1 are associated with greater prevalence and severity of albuminuria but not with cardiovascular disease [Nin et al. 2012b]
Osteoprotegerin (OPG)	Glycoprotein member of the TNF receptor family with a role in vascular calcification	In T1D with and without diabetic nephropathy, plasma OPG concentrations were increased in patients with CVD and correlated with HbA1c, systolic blood pressure and age. Plasma OPG was also significantly higher in T1D with nephropathy than without nephropathy (p<0.001) [Rasmussen *et al*. 2006]. High OPG levels predicted CV mortality in T1D with diabetic nephropathy [HR 4.88 95% CI 1.57–15.14] [Jorsal *et al*. 2008]. In the Finnish Diabetic Nephropathy T1D cohort of 1939 patients, OPG levels predicted incident CV events [HR 1.21, 95% CI 1.01–1.45, p=0.035] [Gordin *et al*. 2013].
Soluble CD40L (sCD40L)	Transmembrane portion of the TNF-alpha cytokine family that contributes to the atherosclerotic lesion progression	T1D with nephropathy had higher plasma sCD40L levels compared with T1D with normoalbuminuric (p=0.004). However sCD40L does not predict CVD [Lajer *et al*. 2010]. T1D is associated with increased serum CD40L levels (p=0.006), increased CD40L expression on platelets (p<0.001) and platelet–monocyte aggregation (p=0.005) compared with healthy controls [Harding *et al*. 2004].

(Continued)

Table 5. (Continued)

Name of biomarker	Function of biomarker	Studies
		T1D and T2D were found to have elevated sCD40L compared with healthy controls. SCD40L was also associated with *in vitro* adhesion molecules and monocyte chemo-attractant protein-1 release, impaired endothelial cell migration, more oxygen generation in monocytes and high levels correlated with HbA1C [Cipollone *et al*. 2005].
High sensitivity C-reactive protein (hsCRP)	An acute phase protein and marker of inflammation, predictive of coronary events and prognostic of myocardial infarction.	In young adolescent T1D patients, hsCRP was significantly associated with triglycerides, apolipoprotein B and both systolic and diastolic blood pressure [Karantza *et al*. 2008].
		hsCRP is significantly higher in T1D patients compared with healthy controls ($p<0.001$). Uncontrolled T1D had higher levels of hsCRP compared with controlled T1D ($p<0.000$). Hs-CRP correlated positively with total cholesterol ($p<0.0001$), LDL ($p<0.001$) and triglycerides ($p<0.0001$), whereas HDL showed a negative correlation ($p<0.0001$) [Fawaz *et al*. 2009].
Tumor necrosis factor α (TNF-α)	Cytokine regulating vascular adhesion molecules causing beta cell damage, insulin resistance and atherosclerotic lesions.	TNF-α is significantly higher in T1D than in healthy controls ($p<0.023$) with a significant positive correlation with HbA1c ($p<0.004$) and fructosamine ($p<0.049$) and a negative correlation with HDL cholesterol ($p<0.018$) and apolipoprotein A1 levels ($p<0.015$) [Lechleitner *et al*. 2000].
		Significant positive correlation of TNF-α with plasma levels of thiobarbituric acid reacting substances found in oxidative stress ($p<0.001$), which showed a positive correlation with the duration of diabetes ($p<0.008$) [Lechleitner *et al*. 2000].
		In normotensive T1D, TNF-α correlated significantly with pulse pressure [González-Clemente *et al*. 2005].
		Plasma TNF-α correlated with soluble vascular cell adhesion molecule 1 (sVCAM-1) ($p=0.008$), triglycerides ($p=0.021$) and diastolic blood pressure ($p=0.024$) in T1D [Mohamed-Ali *et al*. 2001].
Interleukin-6 (IL-6)	Inflammatory cytokine linked with myocardial injury, viral antigen presentation and cardiac hypertrophy.	Young T1D patients had significantly higher IL-6 levels compared with healthy controls ($p<0.05$) [Fawaz *et al*. 2009].
		Plasma concentrations of IL-6 were elevated in T1D compared with healthy controls ($p=0.016$), and in these patients IL-6 and soluble IL-6 receptor (sIL-6R) levels correlated with concentrations of soluble intracellular adhesions molecules 1 (sICAM-1), with $p=0.012$ and $p=0.04$, respectively [Mohamed-Ali *et al*. 2001].
Homocysteine (Hcy)	Amino acid stimulating atherosclerosis through endothelial damage.	The median for total Hcy level was greater in T1D children than healthy controls ($p<0.05$) [Dinleyici *et al*. 2006].
		Amongst T1D, total Hcy was significantly related to macroalbuminuria (adjusted OR=1.66, 95% CI 1.24–2.24), hypertension (adjusted OR=1.57, 95% CI 1.19–2.07) and decreased renal function [Soedamah-Muthu *et al*. 2005].
		There was no difference in total Hcy concentrations between T1D patients and controls [Atabek *et al*. 2006; Rossi *et al*. 2002; Pavia *et al*. 2000].
		Hcy levels were significantly lower among the diabetic male subjects than nondiabetic controls ($p=0.03$) [Al-Attas *et al*. 2009].
Endothelial progenitor cells (EPCs)	Produced in the bone marrow, expressing cell surface markers with the ability to differentiate and protect the endothelium	EPCs is significantly reduced in T1D children compared with healthy controls ($p<0.001$) [Hörtenhuber *et al*. 2013].
Adiponectin	Plasma protein that has anti-inflammatory and cardio-protective functions	Adiponectin concentrations were found to be higher in T1D children and adolescents compared with normal ranges [Galler *et al*. 2010].
		Adiponectin-mediated release of IL-6, CCL2 and CXCL8 is disturbed in T1D patients [Abke *et al*. 2006].
		Adiponectin Inversely predicted the incidence of coronary artery disease in T1D (HR=0.37, 95% CI 0.19–0.73, $p=0.004$) [Costacou *et al*. 2005].

Table 5. (Continued)

Name of biomarker	Function of biomarker	Studies
		No significant association of increased levels with vascular complications in T1D [Malecha-Jędraszek *et al*. 2012]
Vascular progenitor cells	Involved in vascular repair with the number of circulating progenitor cells inversely related to CVD	Circulating vascular progenitor cell number was reduced ($p<0.006$) and function impaired in 22 T1D with microalbuminuria compared with T1D without microalbuminuria [Dessapt *et al*. 2010].
Lipoprotein-associated phospholipase A_2 (Lp-PLA_2)	Macrophage derived pro-atherogenic enzyme linked with inflammation and oxidation	Lp-PLA_2 activity was significantly lower in T1D patients than in healthy controls ($p<0.0001$). High Lp-PLA_2 activity was also associated with progression of coronary calcification (OR=1.77 95%CI 1.08–2.91, p=0.02) [Kinney *et al*. 2011].
Nitrous oxide	Free radical with a protective function on the endothelial lining	Serum nitric oxide was significantly lower and IL-8 was significantly higher in T1D children compared with their healthy siblings [Lo *et al*. 2004]
Mannose-binding lectin (MBL)	Activates the complement system and may aggravate inflammation	T1D patients with cardiovascular disease had significantly elevated MBL levels (p=0.02). ($p<0.0001$) [Hansen *et al*. 2004].
Sialic acid (SA)	A monosaccharide reflecting atherosclerotic activity and may predict coronary heart disease	No significant difference between mean serum total SA of T1D children and healthy controls. However, a significant correlation was found between serum total SA and total cholesterol, triglyceride and apolipoprotein B [Moussa *et al*. 2004]
Soluble intracellular adhesion molecules (sICAM)	Play a key inflammatory role in early stages of atherosclerosis	sICAM-1 concentration was higher in T1D children than in healthy controls (p=0.04). High sICAM correlated with worse metabolic compensation and a family history of CVD [Gtowińska *et al*. 2003].
Soluble vascular cell adhesion molecule-1 (sVCAM-1) and solubleE-selectin	Soluble adhesion molecules	sVCAM-1 and sE-selectin has a positive association with CVD [Soedamah-Muthu *et al*. 2006a].
Albuminuria	Indicates proteinuria which is a risk factor for CVD	Triglyceride ($p<0.01$) and LDL cholesterol ($p<0.01$) levels were higher in macroalbuminuric T1D subjects compared with normoalbuminuric T1D subjects [Sibley *et al*. 1999].
Cystatin-C	Estimates renal function (renal disease is a CVD risk factor)	Increasing levels of cystatin C was associated with coronary atherosclerosis progression in T1D [Maahs *et al*. 2010b].
Heat shock protein (HSP)	HSP60 may have a role as an autoantigen in atherosclerosis; HSP70 protects against CVD.	Anti-HSP70 antibody levels were significantly greater in T1D with no micro/macro complications compared with T1D patients with complications, whereas anti-HSP60 antibody levels were smilar in both these groups. Anti-HSP70 levels were also associated with a 47% reduced odds ratio of micro/macrovascular complications [Gruden *et al*. 2009]
Bilirubin	Anti-atherogenic functions by preventing the formation of reactive oxygen species	Bilirubin level did not correlate with predictors of CVD in the diabetic population [Yeh *et al*. 2009].
YKL-40	A marker of inflammation and endothelial dysfunction	Median levels of serum YKL-40 were significantly higher in T1D with normoalbuminuria compared with healthy controls ($p<0.01$). Higher albuminuria was independently associated with increasing YKL-40 levels ($p<0.001$) [Rathcke *et al*. 2009].
Plasma alpha defensins	Antimicrobial peptides that have been shown to be proatherogenic	Baseline plasma alpha defensin was higher in T1D patients with nephropathy than without ($p<0.0001$). A baseline level of alpha defensins within the upper tertile compared with lower tertile significantly increased the CVD related morbidity and mortality to an adjusted HR of 2.8, 95% CI 1.3–5.9, p=0.006 [Joseph *et al*. 2008].
Hyaluronan	Hyperglycaemia-induced perturbation of hyaluronan metabolism, characterized by increased hyaluronidase	Plasma hyaluronan and hyaluronidase were significantly increased in T1D patients without micro/macrovascular complications compared with healthy controls . In univariate

(Continued)

Table 5. (Continued)

Name of biomarker	Function of biomarker	Studies
	activity with subsequent increased plasma hyaluronan levels, may indicate increased vascular vulnerability.	analysis, mean carotid intima-media thickness (surrogate marker for CVD) was associated with plasma hyaluronan. [Nieuwdorp *et al*. 2007].
N-terminal pro brain natriuretic peptide (NT-proBNP)	Traditionally been described as a marker of heart failure and left ventricular dysfunction.	Higher NT-proBNP concentrations (4th *versus* 1st quartile) were associated with macrovascular disease in 208 T1D patients in Denmark (OR 5.84, 95% CI 1.65–20.74) [Grauslund *et al*. 2010].
Combinations of inflammatory markers	Mean Z score calculated for: 1. C-reactive protein, IL-6, soluble intercellular adhesion molecule (sICAM-1) and secreted phospholipase A2 2. C-reactive protein, IL-6 and TNF-αlevels	1. The mean Z-score for inflammatory biomarkers was associated with the combined endpoint of CV mortality and morbidity with borderline significance after adjustment (HR 1.5, 95% CI 1.0- 2.3, p=0.051; 391 T1D patients; 199 had diabetic nephropathy, 192 had normoalbuminuria; mean age 41 and 43) [Astrup *et al*. 2008]. 2. The mean Z-score for the combined inflammatory markers are associated with CVD in T1D (p for trend <0.001) [Schram *et al*. 2005].
Combinations of endothelial dysfunction markers	Mean Z score calculated for a combination of endothelial dysfunction biomarkers: soluble vascular cell adhesion molecule 1, plasminogen activator inhibitor-1 and sICAM-1	The mean Z-score for endothelial dysfunction was associated with the combined endpoint of CV mortality and morbidity in unadjusted Cox regression (HR 1.7, 95% CI 1.2–2.3, p=0.001) [Astrup *et al*. 2008].

CI, confidence interval; CVD, cardiovascular disease; HbA1c, glycated haemoglobin; HDL, high density lipoprotein; HR, hazard ratio; LDL, low density lipoprotein; OR, odds ratio; T1D, type 1 diabetes; T2D, type 2 diabetes.

2008].It is not clear whether this is possible in an aged cohort with multiple comorbidities, many of which are likely to be musculoskeletal.

The putative impact of pharmacological agents in older aged patients is again unclear. This is further compounded by the lack of trials evaluating the impact of optimal blood pressure control or use of antihypertensive medications on CVD in T1D. The major clinical trials (UKPDS, HOT, ADVANCE) were conducted in the T2D cohort [UKPDS group 1998; Hansson *et al*. 1998; Patel *et al*. 2007]. Nevertheless, observations from the EDC cohort showed that higher blood pressure was associated with higher relative risks of CAD [Orchard *et al*. 2001]. Amongst the general population, there is an additional recognition that effective management of widened pulse pressure in older aged persons reduces CVD. Created by a concomitant rise in systolic blood pressure and fall in diastolic blood pressure, increases in pulse pressure are recognized to occur earlier in patients with T1D, indicating accelerated arterial stiffness and ageing [Rönnback *et al*. 2004; Gordin *et al*. 2012]. The additional recognition that pulse pressure predicts a first ever CVD event in patients with T1D, identified in a cohort with a mean age of 37 years, seems to support the need for effective blood pressure control in older aged patients [Gordin *et al*. 2011].

There were a few small studies from the literature search that evaluated nonconventional pharmacological treatment in T1D. Cavallo and colleagues evaluated the use of melatonin in lowering nocturnal diastolic blood pressure in 11 T1D and 10 healthy controls using a randomized placebo-controlled double-blind crossover study design and found a significant but marginal reduction in nocturnal diastolic blood pressure (17.8 mmHg *versus* 16.0 mmHg) [Cavallo *et al*. 2004]. Djurhuus and colleagues found that magnesium repletion lowered atherogenic lipid fraction in 10 magnesium depleted T1D patient, there was no randomization or control group [Djurhuus *et al*. 2001]. These studies did not target the older aged T1D patients, have small sample sizes and lack long-term data to support the efficacy in improving CVD risk or mortality.

Poor glycaemic control is predictive of CVD events in patients with T1D, as highlighted by the FinnDiane prospective multicentre study that demonstrated a strong association between HbA1c variability and CVD events [Wadén *et al*. 2009]. The relationship between glycaemic control and CV

health is, however, complex. In their 2010 analysis of 652 patients with T1D followed up over a period of 6 years, Maahs and colleagues identified that whilst good HbA1c control affords changes in fasting lipids, dyslipidaemia medications are nevertheless still required even in patients with well controlled diabetes in order to optimize CV health [Maahs *et al.* 2010a]. There is also some evidence to suggest that attempting to control blood glucose within too regimented a range might lead to adverse effects, though this is contested. Gruden and colleagues, for instance, argue that their analysis of 2181 T1D patients taken from the EURODIAB Prospective Complications Study suggests that severe hypoglycaemia does not increase the risk of CVD [Gruden *et al.* 2012]. Similarly, Eeg-Olofsson and colleagues highlight in their observational study of 7454 patients that, whilst CV risks increase with HbA1c levels, there is no J-shaped curve to indicate an increase risk resulting from hypoglycaemia [Eeg-Olofsson *et al.* 2010]. This linear relationship between HbA1c and CV health is further supported by a number of other authors reporting both observational studies and a meta-analysis [Wadén *et al.* 2009; Shankar *et al.* 2007; Selvin *et al.* 2004]. Somewhat conflictingly, an analysis published by Giménez and colleagues reported the opposite, with repeated severe hypoglycaemia increasing CV risk [Giménez *et al.* 2012]. This latter study is however a retrospective study and smaller than the EURODIAB studies.

Strategies to ameliorate the potential for CVD in older patients may additionally focus on oxidative stress, exposure to which arguably increases significantly with age. Costacou and colleagues have, for instance, identified that the anti-oxidant alpha-tocopherol provides protection against CAD in patients with T1D [Costacou *et al.* 2006]. Whilst this research was undertaken in a population with a mean age of 28 years, results were taken at a follow up of 10 years, suggesting an extended advantage to targeted antioxidant therapy which might extend into older age.

In their respective analyses of patients undergoing pancreas transplant alone, both Boggi and colleagues and Larsen and colleagues highlighted a number of improvements to independent CV risk factors, in addition to evidence to suggest directly improved left ventricular ejection fraction resulting from pancreatic transplantation [Boggi *et al.* 2012; Larsen *et al.* 2004]. Furthermore, combined pancreas and kidney transplantation for patients with T1D and end stage kidney disease (ESKD) has been associated with significantly lower mean arterial pressure, lower pulse pressure, lower LDL cholesterol and fewer required lipid-moderating medications which is likely secondary to a resultant lower atherosclerotic risk profile [Luan *et al.* 2007; Fiorina *et al.* 2001].

There are, finally, numerous reports within the literature concerning the proinflammatory state considered to accompany ageing. Inflammation in this context relates to a chronic overresponse that results in the accrual of cytokines and immune cells predisposing to atherosclerotic disease.

Whilst there is no direct evidence to link this state, often referred to under the umbrella term of 'inflammaging', to adverse events amongst aged patients with T1D, it is arguably implicated by work conducted within younger patient populations. González-Clemente and colleagues have, for instance, identified an association between interleukin (IL) 6 levels and lower heart rate variability, implying adverse outcomes stemming from raised cytokine levels [González-Clemente *et al.* 2007]. Although an untested hypothesis, it is possible that strategies to moderate inflammation amongst ageing patients may positively impact on CV morbidity and mortality.

Discussion

The available data suggest a significant CV burden in patients with T1D and poor management of CV risk factors. This is underpinned by a poor evidence base for therapeutic management of CV risk specifically for patients with T1D and in the most relevant population – the older aged patients. Whilst recent years have seen a decrease in CVD related mortality in patients with T1D [Miller *et al.* 2012], it still remains the leading cause of mortality and therefore significant further effort is required.

We would suggest that important areas remain to be addressed, particularly exploring the risks and benefits of therapeutic approaches to CVD management in the older aged. Thought will be required around the design of these studies. Clinical CVD outcomes (myocardial infarction, heart failure) may appear sooner than in a younger population because the older aged patients are more at risk and therefore studies could potentially be shorter and/or smaller. We also see greater risk of side effects associated with polypharmacy in the older aged patients and so dropout rates may be higher. The use of surrogate endpoints such as carotid intima thickness

and cardiac magnetic resonance imaging may provide useful information more quickly in the interim.

An important and urgent question relates to the benefits of blood pressure, lipid and glucose control in patients with T1D and at what age these benefits become significant. This is particularly relevant in the older aged patients where we risk committing them to many years of therapy against the risk of side effects and potentially minimal benefit.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this article.

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