

## Review

## Reducing Type 1 Diabetes Mortality: Role for Adjunctive Therapies?

Jennifer R. Snaith,<sup>1,2,3,4,5</sup> Deborah J. Holmes-Walker,<sup>2,5</sup> and Jerry R. Greenfield<sup>1,3,4,\*</sup>

**Individuals with type 1 diabetes (T1D) frequently fail to achieve glycemic goals and have excess cardiovascular risk and premature death. Adjunctive agents may play a role in reducing morbidity, mortality, and the adverse sequelae of insulin treatment. A surge in type 2 diabetes drug development has revealed agents with benefits beyond glucose lowering, including cardiovascular risk reduction. Could these benefits translate to T1D? Specific trials for T1D demonstrate substantial hemoglobin (Hb)A1c reductions with sodium glucose cotransporter inhibitors (SGLTis) and glucagon-like peptide (GLP)1 agonists, and modest improvements with metformin, dipeptidyl peptidase-4 inhibitor (DPP4i), and pramlintide. Studies exploring cardiovascular risk reduction are warranted. This review synthesizes the emerging literature for researchers and clinicians treating people with T1D. Challenges in T1D research are discussed.**

## Type 1 Diabetes in Context

Type 1 diabetes (T1D; see [Glossary](#)) is characterized by insulin deficiency due to autoimmune destruction of pancreatic beta cells and globally constitutes 5–10% of the overall diabetes burden and the incidence is rising [1]. T1D is complicated by microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (coronary artery, cerebrovascular, and peripheral vascular) complications. Of all complications, cardiovascular (CV) disease is the chief contributor to the threefold higher mortality risk relative to the general population [2,3].

Intensive insulin treatment is the cornerstone of T1D management, but many individuals fail to achieve glucose targets [2,4]. There is a clear relationship between glycemic control and mortality risk and this risk remains double that of matched controls [hazard ratio (HR) 2.36] even for those with Hemoglobin A1c (HbA1c) <6.9% [2]. Even persons with near-target HbA1c often suffer dysglycemia, **glycemic variability (GV)**, and hypoglycemia; all major T1D management challenges that may have added implications for vascular health. HbA1c variability is a microvascular disease risk factor in T1D [5,6] and GV influences endothelial function [7]. An association between GV and macrovascular disease has not been clearly established, but in a cohort with diabetes (5.5% with T1D) admitted with myocardial infarction (MI), higher GV predicted future major adverse cardiac events (MACEs) [8]. Hypoglycemia may also affect the CV system by inducing vascular stress and is associated with nocturnal cardiac arrhythmias [9,10]. Severe hypoglycemia remains common, occurring in 11.8% of T1D at all levels of HbA1c [11].

Further T1D management challenges include obesity, overweight, and the development of **metabolic syndrome** [12]. These issues mirror trends in the general population [13] but is exacerbated by insulin-induced weight gain. Weight gain augments **insulin resistance (IR)**, a possible risk factor for atherosclerosis [12,14,15].

These clinical predicaments in T1D have prompted researchers to consider **adjunctive** therapeutic options with the goals of: (i) reduced hyperglycemia; (ii) weight reduction; (iii) delay in progression of complications; (iv) nephroprotection; (v) vascular protection; (vi) mortality reduction; and (vii) achievement of these goals without increased severe hypoglycemia or ketosis.

The aim of this narrative review is to provide a critical update on adjunctive agents considered for use in T1D. We explore the evidence base across multiple drug classes including Phase III randomized controlled trials (RCTs) where available. We also provide commentary regarding the challenges in conducting clinical trials and assessing CV risk reduction in T1D.

## Highlights

Therapies developed for use in T2D have cardiovascular and renal protective properties.

Clinical trials testing these agents in T1D assess their ability to mitigate side effects of insulin (weight gain and hypoglycemia) and improve achievement of glycemic goals. There is little focus on cardiovascular endpoints in current clinical trials.

Conducting clinical trials in T1D has unique challenges.

Adjunctive agents in T1D have potential to close morbidity and mortality gaps, but this is yet to be verified by the current evidence base.

<sup>1</sup>Diabetes and Metabolism, Garvan Institute of Medical Research, Sydney, NSW, Australia

<sup>2</sup>Department of Diabetes and Endocrinology, Westmead Hospital, Sydney, NSW, Australia

<sup>3</sup>Department of Diabetes and Endocrinology, St Vincent's Hospital, Sydney, NSW, Australia

<sup>4</sup>St Vincent's Clinical School, Faculty of Medicine, University of New South Wales, Sydney, NSW, Australia

<sup>5</sup>Faculty of Medicine, University of Sydney, Sydney, NSW, Australia

\*Correspondence: [j.greenfield@garvan.org.au](mailto:j.greenfield@garvan.org.au)



## Changing Landscape of Diabetes Research

The landmark Diabetes Control and Complications/ Epidemiology of Diabetes Interventions and Complications (DCCT-EDIC) Study was the first and only RCT to measure the mortality implications of an intervention in T1D. It demonstrated fewer microvascular complications and CV events ( $-42\%$   $P = 0.02$ ) with strict glucose targets (glucose 3.9–6.7 mmol/l before meals, peak  $<10.0$  mmol/l after meals) [16]. Although near-normal glucose targets became standard of care, this was at the expense of weight gain and hypoglycemia. Excessive weight gain from intensive insulin offsets the benefit of strict glucose targets [17].

T1D management has since progressed through new glucose monitoring technologies, insulin delivery devices, and noninsulin adjuncts are in trial phase. Although observational and controversial, promising data suggests that T1D **insulin pump** users have reduced fatal CV events and all-cause mortality compared with treatment with **multiple daily insulin injections (MDIs)**, possibly relating to reduced GV and/or hypoglycemia [18]. Therefore, the method of insulin delivery may be important and requires further study.

Research into noninsulin medications became popularized after a recent flurry of **type 2 diabetes (T2D)** drug approvals. Metformin, SGLTis, GLP1 agonists, DPP4is, and pramlintide have been considered for use in T1D but pramlintide is the only agent approved by the FDA.

In the past 10 years, the FDA has approved  $>17$  noninsulin therapies for use in T2D, including some with added CV and renal benefits. The 2008 post-glitazone FDA mandate that any glucose-lowering therapy must demonstrate CV safety was a historical milestone for diabetes research. New drugs were tested against a three-point MACE composite endpoint (death from CV causes, nonfatal MI, or nonfatal stroke). This revealed that some glucose-lowering therapies (GLP1 agonists and SGLT2is) were safe and could protect the CV system in high-risk individuals, even without diabetes (dapagliflozin) [19–26].

Ultra-large sample sizes became necessary to adequately power the capture of CV events. To date, up to 200 000 individuals have participated in T2D drug programs. This degree of resource investment is unmatched in T1D adjunct trials; the largest trial measured 1700 participants [27]. Not since the DCCT-EDIC study has there been a CV outcome trial in T1D, a striking contrast to T2D research. Over time, changes in diabetes management has enabled reduced standardized mortality ratios (SMR) relative to the general population but T1D mortality remains greater than T2D (T1D SMR 3.08 males, 3.46 females; T2D SMR 1.21 males, 1.22 females) [3]. To address this survival differential, adjunctive therapy **cardiovascular outcome trials (CVOTs)** may be the next frontier in T1D research, but this is not without major challenges.

## Challenges in Type 1 Diabetes Research

T1D CV research poses distinct challenges (Table 1). Lower disease prevalence, and limited capacity to enroll T1D patients at highest CV risk limit recruitment potential for CV trials. Since T1D has distinct pathophysiology, age of onset, clinical course, and metabolic environment (ketosis and hypoglycemia risk), results from studies in other disease populations may not be translatable; hence, dedicated studies are warranted.

Adjunct trials in T1D have so far focused on glycemic efficacy and safety rather than CV protection, although some trials have tested treatment effect on CV **surrogate measures** (Box 1). Surrogates enable reduced trial size, cost, and duration, but several factors affect their validity [28]. Of most importance is that surrogate endpoints must have an established association with true CV outcomes (requiring long trials). Furthermore, many CV surrogate tools are not validated in T1D, which may have unique atherosclerosis pathophysiology [29]. Altogether, these research barriers explain the fewer therapeutic options in T1D, and the difficulties in proving that an adjunct could improve CV mortality.

## Glossary

**Adjunct:** a therapy used alongside a primary treatment.

**Cardiovascular outcome trial (CVOT):** a clinical trial that focuses on cardiovascular endpoints.

**Diabetic ketoacidosis (DKA):** an acute state of hyperglycemia, ketosis, and acidosis arising from absolute or relative insulin deficiency.

**Glycemic variability (GV):** the degree of fluctuation between high (peaks) and low (nadir) glucose levels.

**Hemoglobin A1c (HbA1c):** a measure of hemoglobin glycation, a function of exposure to blood glucose.

**Insulin clamp:** hyperinsulinemic-euglycemic clamp is the gold standard measure of insulin resistance. It is a research method only.

**Insulin pump:** a mechanical device that provides the constant delivery of insulin through a cannula inserted under the skin; also referred to as continuous subcutaneous insulin infusion.

**Insulin resistance (IR):** a state in which a concentration of insulin produces a less than expected biological effect.

**Metabolic syndrome:** a complex cluster of interconnected factors; traditionally dyslipidemia, hypertension, abdominal adiposity, and dysglycemia arising from insulin resistance.

**Multiple daily insulin injection (MDI):** administration of insulin by three or more subcutaneous injections daily.

**Surrogate measure:** a measurement or marker that predicts a clinically meaningful outcome.

**Type 1 diabetes (T1D):** an autoimmune condition characterized by immune destruction of the insulin-producing beta cells of the pancreas.

**Type 2 diabetes (T2D):** a condition characterized by development of insulin resistance and/or gradual loss of the capacity of pancreatic beta cells to produce insulin.

**Table 1. Challenges in Conducting Cardiovascular Outcome Trials in T1D Research<sup>a</sup>**

Limitation	Discussion
Requirement for large sample sizes	<ul style="list-style-type: none"> <li>Conducting CVOTs in a reasonable time period necessitates high likelihood of event capture during the planned trial period. Studying individuals at highest CV risk enhances the ability to detect a treatment effect. Relative to T2D, T1D with highest CV risk (e.g., established CV disease) has lower absolute prevalence, resulting in relatively reduced recruitment potential</li> </ul>
Lack of generalizability	<ul style="list-style-type: none"> <li>Events in high risk populations may represent different pathophysiology (mechanistic changes in advanced CV disease vs changes in early disease), which may or may not change the likelihood of efficacy of the study drug. Results from studies of individuals with overt CV disease (secondary prevention) may not apply to the general T1D population in which the goal is to prevent CV risk (primary prevention) and would require separate study</li> <li>T1D is a heterogeneous disease: adult versus youth, age of diagnosis, C-peptide positivity, body mass index (BMI) status, presence of metabolic syndrome, ethnicity, and comorbidity are important factors. There may be lost opportunity to identify responders when homogenizing a heterogeneous group</li> </ul>
Prioritization of resources	<ul style="list-style-type: none"> <li>Lower relative prevalence of T1D compared with T2D, and competing priorities for resources leads to debate regarding appropriate resource allocation (clinical, financial, and professional resources)</li> <li>With lower disease prevalence there may be reduced interest from industry (lower perceived profits)</li> </ul>
Long follow-up time	<ul style="list-style-type: none"> <li>Atherosclerotic vascular disease has a long natural history, and CV benefits may manifest long after randomization of an intervention (DCCT-EDIC trial had appropriately long follow up)</li> <li>Durability of effect is also not detected unless long follow up periods are planned</li> <li>Surrogate measures can be used in place of hard clinical endpoints, but are not necessarily validated in T1D</li> </ul>
Safety	<ul style="list-style-type: none"> <li>There are added difficulties of safety monitoring in T1D (hypoglycemia, ketosis)</li> <li>Need for insulin dose adjustment (e.g., to prevent hypoglycemia) is an added factor in study design and follow up planning, increasing trial complexity. Blinding practices may be more difficult</li> </ul>

<sup>a</sup>Adapted from Cefalu et al. [30].

## Metformin

### Pathophysiology of Insulin Resistance in T1D

T1D is an IR state relative to normal controls, confirmed by **insulin clamp** studies [47,48]. There are multiple contributors to IR in T1D. Unique to insulin-treated individuals is IR arising from nonphysiological insulin delivery. Subcutaneous insulin requires hyperinsulinemia to suppress hepatic gluconeogenesis compared with portal insulin from a healthy pancreas. Chronic hyperinsulinemia leads to insulin receptor down-regulation, and low portal insulin levels reduce insulin-like growth factor (IGF)1 secretion, increasing growth hormone thereby exacerbating IR [49,50]. Glucotoxicity exacerbates IR but is not the main driver. Iatrogenic hyperinsulinemia plays a dominant role demonstrated by insulin clamps performed in T1D and glucokinase (GCK)-MODY (maturity onset diabetes of the young), selected as a hyperglycemia matched comparator group [51]. Factors that further increase IR include excess weight and transient pubertal factors [52].

IR may have detrimental vascular effects. In T1D, it predicts coronary artery calcification (CAC) volume ( $r = -0.42$ ,  $P < 0.0001$ ) [15], CAC progression [53], and hard coronary artery disease endpoints (MI, coronary artery disease death, or angiographically proven stenosis) [54]. T1D patients with higher IR had greater likelihood of micro- and macrovascular complications in DCCT participants [12]. Therefore, IR may be an under-recognized driver of atherosclerosis, either directly or indirectly, by augmentation of other CV risk factors.

### Lessons from T2D and Populations without Diabetes

Metformin is an inexpensive oral biguanide and the most frequently used noninsulin medication [4]. It suppresses liver gluconeogenesis, improves insulin-mediated glucose utilization, and reduces fatty acid oxidation; effects partly mediated by AMP-kinase activation [55]. Metformin can attenuate

cardiomyocyte mitochondrial dysfunction and has anti-inflammatory effects, which provides rationale for possible cardioprotective properties [56,57].

The evidence for CV protection is mixed across populations. In T2D, metformin was deduced to have CV benefit from a UK Prospective Diabetes Study (UKPDS) subanalysis in which metformin allocated obese T2D patients had reduced MIs ( $-39\%$   $P = 0.01$ ) compared with conventional treatment [58]. This effect persisted after 10 years of follow-up, suggesting sustained benefits [59]. The longer-term benefits of metformin were assessed in 390 insulin-treated T2D patients followed for 4.3 years [60]. This study failed to demonstrate the primary endpoint, an aggregate of micro- and macrovascular disease morbidity and mortality, but 40% fewer CV events were observed in the metformin group compared with placebo. There is little incentive for further trials with primary CV endpoints since metformin was approved years before the current era of mandatory CV safety assessment and is already in widespread use. Nonetheless, this signal towards CV protection has prompted RCTs in populations without diabetes with disappointing results. In individuals with established CV disease but without diabetes, metformin for 18 months did not reduce progression of mean carotid intima-media thickness (cIMT) (Box 1) [61]. Overall, metformin is not recommended for CV risk reduction outside of T2D, and CV protection in insulin-treated T2D cannot be extrapolated to T1D.

### Metformin in T1D

Metformin has been studied in T1D from both a glucometabolic and CV perspective. Studies have yielded inconsistent results regarding glycemia, lipids, weight, and insulin-dose reduction. A systematic review and meta-analysis of five RCTs noted insulin dose reduction ( $6.6$  U/day;  $P < 0.001$ ), but inconsistent HbA1c reduction and insufficient data to report effect on lipids [62]. At the time no trials included CV endpoints. Subsequent trials reported ongoing discrepant results. In adolescents, metformin reduces insulin requirements and weight with transient improvement in HbA1c, albeit not sustained beyond 3 months [63,64]. In T1D adults, metformin reduces weight, but with inconsistent lipid and HbA1c lowering [65–67]. Discrepant results may relate to population differences (pubertal status affecting IR), weight status, and the presence or absence of metabolic syndrome. Whether metformin is best suited to specific populations is unknown.

There have been three main T1D placebo-controlled metformin studies with a CV surrogate primary endpoint (Box 1). The REducing with METformin Vascular Adverse Lesions (REMOVAL) study, assessed the effects of metformin on atherosclerosis and is the largest and longest T1D metformin trial to date (Table 2) [66]. Adults with  $\geq 3$  CV risk factors were followed for 3 years with cIMT measurements. Metformin did not prevent the primary endpoint of progression of averaged mean far-wall cIMT, but the tertiary outcome, progression in maximal cIMT, was significantly reduced. Maximal cIMT was also studied in the DCCT/EDIC study, yet metformin achieved greater reductions than in the EDIC study ( $-0.039$  mm vs  $-0.013$  mm) [43]. This effect was not attributable to improved glycemia since HbA1c reduction was transient and minimal. The authors discuss that maximal rather than mean cIMT may be more reflective of advanced atherosclerotic disease. In the setting of no effect in the primary outcome, and positive results only in secondary and tertiary outcomes, these postulated CV benefits are hypothesis generating only.

Other smaller trials have tested metformin against various CV surrogate endpoints (Table 2). In T1D adults, metformin improved flow-mediated dilatation (FMD) without improving nitrate-mediated dilatation (NMD); both measures of endothelial function (Box 1) [65]. This effect was independent of metabolic improvements since there was no change in HbA1c or lipid profile, although weight was significantly reduced. Conversely, FMD and cIMT progression did not improve in 90 T1D adolescents receiving metformin for 12 months, but glyceryl trinitrate (GTN)-mediated dilatation, a secondary endpoint, did improve [64]. Other CV risk factors [weight, lipids, and blood pressure (BP)] were unchanged. Furthermore, another study determined that metformin improved insulin sensitivity, which correlated with magnetic resonance imaging (MRI)-measured aortic stiffness, a secondary outcome measure [67]. This was achieved with borderline weight reduction, and without a change in glycemia.

**Box 1. Vascular Health Surrogates Used in T1D Trials**

A surrogate marker is a measure that substitutes for a clinically meaningful outcome [31]. There are several surrogate measures used in CV research including measures of vascular dysfunction as a precursor to atherosclerosis, or imaging coronary calcium as a surrogate of established atherosclerosis [32–34]. They provide the advantage of noninvasive examination and detection of vascular abnormalities that occur early in the atherosclerotic process. In the case of predictors of CV events, it is important to consider the context in which surrogates have been validated and whether the context is translatable to T1D.

**FMD and NMD**

FMD is a measure of endothelium-dependent vasodilation, and NMD a measure of endothelium-independent vasodilatory ability. Both are endothelial function indices assessed by brachial artery ultrasound. Endothelial dysfunction correlates with angiographically measured coronary artery disease but is not specifically validated in T1D [35].

**Reactive Hyperemia Index (RHI)**

RHI is a measure of peripheral endothelial function. The brachial artery is occluded, then sensors placed on the index finger measure the extent of compensatory changes to blood flow after cuff deflation. RHI correlates with coronary endothelial function and predicts CV events [36].

**Pulse-Wave Velocity (PWV) and Augmentation Index (AIx)**

Arteriosclerotic vessels lead to stiffening of arterial walls, resulting in loss of vessel wall compliance and increased PWV [28]. Aortic arterial stiffness can be measured using various methods, but there are two main parameters: PWV and AIx.

PWV is calculated by measuring the arrival time of a pulse wave between two predetermined locations (e.g., carotid–femoral and brachial–ankle). There are various invasive (catheter), or noninvasive (oscillometry-, ultrasound-, or MRI-based) methods [37]. Stiff arterial walls have amplified PWV relative to elastic walls [38]. PWV predicts future CV events and all-cause mortality validated in patients with hypertension [39].

AIx is an index of pulse wave reflection. It is assessed by applanation tonometry of a peripheral artery (radial, carotid, or femoral). Normally, cardiac systole directs aortic pressure towards the peripheries but is partially reflected back towards the aorta, arriving during diastole. With increased arterial stiffness, the reflected wave returns early causing augmentation of systolic central pressure. AIx is independently associated with angiographically determined coronary artery disease [40] and is increased in T1D [41].

Phase-contrast MRI provides another direct measurement of aortic stiffness but is less widely used than tonometry-based methods.

**cIMT**

Ultrasound measurement of carotid wall thickness predicts carotid atherosclerotic disease and coronary events in general populations [42]. Notably, intensively treated T1D DCCT participants had reduced cIMT progression, with subsequent reduced CV events at 30 years follow up demonstrating cIMT was predictive of CV events in T1D [43,44].

**CAC**

CT measurement of coronary calcium assesses the degree of atherosclerotic plaque burden and predicts future MI and mortality in asymptomatic individuals with CV risk factors [45].

**Oxidative Stress**

Oxidative stress is thought to be part of the pathophysiology of vascular disease in diabetes [46]. Markers of vascular oxidative stress can be measured in urine (urinary prostaglandins and its metabolites) or in plasma. Oxidative stress markers have not been clearly correlated with CV outcomes.

Overall, these surrogate measures are not directly comparable between studies, nor necessarily indicative of clinically meaningful end points and results are inconsistent between studies. Improvements in vascular endpoints were independent of effects on glycemia. It is not clear if the effects of metformin in T1D are attributable to improvements in IR, or other pleiotropic effects of metformin, or if effects would be detected with longer term follow-up. The preliminary evidence for CV protection is not definitive, and dedicated trials with primary CV endpoints are warranted.

## SGLTis

### Lessons from T2D and Populations without Diabetes

Large clinical trials in T2D patients with high CV risk have shown that SGLT2 inhibition reduces CV events and heart failure (HF) admissions, modifies CV risk factors (HbA1c, weight, and BP), and provides nephroprotection [68–70]. In T2D with overt CV disease, empagliflozin and canagliflozin both demonstrated lower occurrence of MACEs; effects mostly driven by reduced HF hospitalizations and mortality [19,20]. In contrast, dapagliflozin did not lower MACEs, but enrolled a proportion of lower-risk T2D without evident atherosclerotic CV disease at baseline [21]. Dapagliflozin reduced HF admissions (prespecified primary outcome, composite with CV death), possibly reflecting reduced incident HF since most did not have HF at enrolment. Efficacy was detected earlier than usually seen with glucose-lowering therapies, raising the hypothesis that benefits could be seen in populations without diabetes. This was tested in the DAPA-HF (Dapagliflozin and Prevention of Adverse Outcomes in Heart Failure) trial in persons with a reduced ejection fraction but without diabetes [26]. There was a 26% reduction in the primary composite outcome (hospitalization or urgent visit resulting in intravenous treatment for HF or death from CV causes) compared with placebo. This magnitude was similar regardless of presence of diabetes, and ketoacidosis only occurred in diabetes. T1D was an exclusion criterion.

### Pathophysiological Basis for CV Protection

SGLTi mechanisms for glycemic benefit are well documented, yet mechanisms for nonglycemic benefits are not entirely understood. Normally, proximal renal tubular SGLT2 cotransporters remove glucose from glomerular filtrate to prevent urinary glucose excretion. In the presence of hyperglycemia, this reabsorption capacity is overwhelmed, leading to glucosuria. Patients with T1D develop a maladaptive increase in renal glucose transport, thereby exacerbating hyperglycemia [71]. This may be secondary to increased SGLT cotransporter expression, suggested in experiments performed in T2D, not T1D [72]. SGLT2is enhance glucosuria, thereby reducing hyperglycemia. SGLT1is further reduce hyperglycemia by blocking distal renal segment and small intestinal glucose absorption.

SGLTis have multiple actions relevant to the CV system but the generalizability to T1D is unclear. Glycosuric mechanisms lead to negative caloric balance, reduced fat mass, including epicardial fat, improving cardiac inflammation and fibrosis [73]. Natriuresis and related hemodynamic effects may lead to reduced sympathetic nervous system activation, plasma volume, and BP, thereby improving arterial stiffness. Generation of ketone bodies may also improve efficiency of myocyte oxygen consumption [73]. Evidence for the above changes in T1D is lacking but T1D-specific studies have confirmed renal hemodynamic changes including attenuated renal hyperfiltration and reduced intraglomerular pressure, which are relevant to defects in diabetic nephropathy and possible systemic flow on effects to the CV system. A small unblinded study in 42 patients with T1D treated with empagliflozin, 25 mg for 8 weeks, showed improvement in Alx (Box 1), and empagliflozin combined with metformin improves Alx and endothelial function [74,75]. The clinical significance of treatment effects on CV surrogates should be interpreted with caution, but these results provide important hypothesis generating exploratory data for future CV studies.

### SGLTi Trials in T1D

SGLTi research programs were developed in T1D in the context of promising glycemic effects in T2D. Several moderately sized Phase III clinical trials have been published in the last 5 years across three different products (Table 3): dapagliflozin (DEPICT), empagliflozin (EASE), and sotagliflozin (a dual SGLT1 and SGLT2 inhibitor – InTANDEM) [76–80,27]. Canagliflozin did not progress past Phase II trial

**Table 2. Metformin Trials in T1D with Outcome Measures Relevant to Vascular Health<sup>a</sup>**

Study	Design	Participants	Planned outcomes	Results	Refs
Pitocco et al. 2013	Metformin 850 mg thrice daily vs placebo 6 months	42 adults	Primary: endothelial function (FMD, NMD) Secondary: CGM parameters, glucometabolic (HbA1c, lipids, TDI), oxidative stress (urine PGF2 $\alpha$ )	<ul style="list-style-type: none"> <li>FMD improvement (+1.32% <math>P = 0.013</math>)</li> <li>Weight reduction (<math>- 2.27\text{kg}</math> <math>P = 0.012</math>)</li> <li>Increased oxidative stress</li> <li>No change: HbA1c, lipids, TDI, NMD</li> </ul>	[65]
Anderson et al. 2017	Metformin 2000 mg vs placebo 12 mo	90 adolescents (with BMI >50 <sup>th</sup> percentile)	Primary: FMD Secondary: GTN-mediated dilatation, carotid and aortic IMT HbA1c, TDI, BMI, lipid profile, eIS, and others	<ul style="list-style-type: none"> <li>Improved GTN mediated dilatation</li> <li>Reduced HbA1c (1.0% <math>P = 0.001</math>, mostly at 3 mo)</li> <li>Reduced insulin requirement (<math>-0.2</math> U/kg/d <math>P = 0.001</math>)</li> <li>Increased eIS</li> <li>No change: FMD, BMI, lipid profile</li> </ul>	[64]
Petrie et al. 2017	Metformin 2000 mg vs placebo 3 yr	428 adults	Primary: average mean fall wall cIMT Secondary: HbA1c, lipids, eGFR, weight, TDI, endothelial function (RHI) Tertiary: maximal cIMT	<ul style="list-style-type: none"> <li>Maximal cIMT (<math>-0.013</math> mm/yr <math>P = 0.0093</math>)</li> <li>HbA1c (<math>-0.13\%</math> <math>P = 0.0060</math>, mostly at 3 mo)</li> <li>Weight reduction (<math>-1.17</math> kg <math>P = 0.0001</math>)</li> <li>LDL cholesterol reduction (<math>-0.13</math> mmol/l <math>P = 0.0117</math>)</li> <li>eGFR increased (<math>+ 4.0</math> ml/min/1.73 m<sup>2</sup> <math>P &lt; 0.0001</math>)</li> <li>No change: mean cIMT, TDI, and RHI</li> </ul>	[66]
Bjornstad et al. 2018	Metformin 2000 mg vs placebo 3 months	48 adolescents	Primary: whole body insulin sensitivity (insulin clamps) Secondary: vascular health (cIMT – near and far wall, brachial distensibility, MRI-derived aortic PWV and WSS) Tertiary: glucometabolic measures (body composition, HbA1c, lipids, BP)	<ul style="list-style-type: none"> <li>Improved whole body insulin sensitivity</li> <li>Reduced aortic arterial stiffness distensibility – aortic WSS<sub>max</sub>, PSW, far-wall diastolic cIMT)</li> <li>Weight reduction (<math>-0.5</math> kg <math>P = 0.004</math>)</li> <li>Reduced fat mass (<math>-0.7</math> kg <math>P = 0.01</math>)</li> <li>No change: HbA1c, BP, lipids, brachial distensibility</li> </ul>	[67]

<sup>a</sup>Abbreviations: BMI, body mass index; CGM, continuous glucose monitoring; eGFR, estimated glomerular filtration rate; eIS, estimated insulin sensitivity (prediction model based on clinical parameters correlated with insulin clamp measurement) [26]; LDL, low-density lipoprotein; PGF2 $\alpha$ , prostaglandin F2 $\alpha$ ; TDI, total daily insulin dose; WSS, wall shear stress.

stage due to **diabetic ketoacidosis (DKA)** concerns (6% canagliflozin 300 mg vs placebo) [81], and DKA has proven to be the main factor limiting SGLTi approval and safety for widespread use in T1D. These trials were designed with HbA1c primary endpoints and have not studied CV health indices.

All trials studied cohorts with similar baseline characteristics – middle-aged T1D adults with suboptimal glucose control and long duration disease. Each demonstrated dose-dependent improvements

Table 3. Major Phase III SGLTi Trials in T1D

Study	Drug	Participants	Results	Refs
Dual SGLT1 and SGLT2 inhibitors				
Garg <i>et al.</i> 2017 InTANDEM 3	Sotagliflozin 400 mg vs placebo 24 wk investigator adjustment of insulin, no run-in insulin optimization	1402 Baseline characteristics: 43 yr, BMI 28, 20 yr diabetes, HbA1c 8.2%, 0.7 U/kg/d insulin	<ul style="list-style-type: none"> <li>• Reduced HbA1c (−0.46%, <math>P &lt; 0.001</math>)</li> <li>• Weight loss (−2.98 kg, <math>P &lt; 0.001</math>)</li> <li>• Lower SBP<sup>c</sup> (−3.5 mmHg, <math>P &lt; 0.001</math>)</li> <li>• Less TDI (−5.3 U/d, mostly bolus insulin <math>P &lt; 0.001</math>)</li> <li>• More DKA (3% vs 0.6% active vs placebo)</li> <li>• No difference severe hypoglycemia</li> </ul>	[76]
Buse <i>et al.</i> 2018 InTANDEM 1 North American cohort	Sotagliflozin 200 vs 400 mg vs placebo 52 wk 6 wk insulin optimization, investigator adjustment with external monitoring committee	793 Baseline characteristics: 46 years, BMI 29.7, 24 yr diabetes, HbA1c 7.6%, 0.73 U/kg/d insulin	<ul style="list-style-type: none"> <li>• Reduced HbA1c (−0.25% 200 mg, −0.31% 400 mg <math>P &lt; 0.001</math>)</li> <li>• Weight loss (−3.1 kg 200 mg, −4.3 kg 400 mg, <math>P &lt; 0.001</math>)</li> <li>• Less TDI (−6.2 U/d in 400 mg group, mostly bolus insulin <math>P &lt; 0.001</math>)</li> <li>• More DKA (3.4% 200 mg, 4.2% 400 mg, 0.4% placebo)</li> <li>• No difference severe hypoglycemia</li> <li>• CGM: increased TIR, reduced variability</li> </ul>	[77]
Danne <i>et al.</i> 2018 InTANDEM 2 European cohort	Sotagliflozin 200 vs 400 mg vs placebo 52 wk 6 wk insulin optimization with external monitoring committee	782 Baseline characteristics: 41 yr, BMI 27.8, 18 yr diabetes, HbA1c 7.8%, 0.74 U/kg/d insulin	<ul style="list-style-type: none"> <li>• Reduced HbA1c (−0.21% 200 mg, −0.32% 400 mg <math>P &lt; 0.001</math>)</li> <li>• Weight loss (−2.2 kg 200 mg, −2.9 kg 400 mg <math>P &lt; 0.001</math>)</li> <li>• Less TDI (−4.8 U/d 200 mg, −5.4 U/d 400 mg <math>P &lt; 0.001</math>)</li> <li>• More DKA (2.3% 200 mg, 3.4% 400 mg, 0% placebo)</li> <li>• CGM: increased TIR, reduced prandial glucose, reduced variability<sup>a</sup></li> </ul>	[78]
SGLT2is				
Dandona <i>et al.</i> 2018 DEPICT-1	Dapagliflozin 5 vs 10 mg vs placebo 52 wk (24 wk plus 28-wk extension)	833 Baseline characteristics: 42 yr, BMI 28, 20 yr diabetes, HbA1c 8.5%, 0.74 U/kg/d insulin	<ul style="list-style-type: none"> <li>• Reduced HbA1c (−0.33% 5 mg, −0.36% 10 mg)</li> <li>• Weight loss (−2.3 kg 5 mg, −3.6 kg 10 mg)</li> <li>• More DKA (4% 5 mg, 3.4% 10 mg, 1.9% placebo)</li> <li>• No difference severe hypoglycemia</li> </ul>	[79]
Mathieu <i>et al.</i> 2018 DEPICT-2	Dapagliflozin 5 vs 10 mg vs placebo 24 wk	813 Baseline characteristics: 43 yr, BMI 27, 19 yr diabetes, HbA1c 8.4%, 0.73 U/kg/d insulin	<ul style="list-style-type: none"> <li>• Reduced HbA1c (−0.37% 5 mg, −0.42% 10 mg, <math>P &lt; 0.0001</math>)</li> <li>• Reduced weight (−3.2% 5 mg, −3.7% 10 mg, <math>P &lt; 0.0001</math>)</li> <li>• Increased DKA (2.6% 5 mg, 2.2% 10 mg, 0% placebo)</li> <li>• No difference hypoglycemia</li> </ul>	[80]

(Continued on next page)

Table 3. Continued

Study	Drug	Participants	Results	Refs
Rosenstock et al. 2018 EASE	EASE-2: empagliflozin 10 vs 25 mg vs placebo 52 wk EASE-3: Empagliflozin 2.5 vs 10 vs 25 mg vs placebo 26 wk Pretreatment optimization	1707 Baseline characteristics: 45 yr, BMI 29, 22 yr diabetes, HbA1c 8.1%, 0.7 U/kg/d insulin Baseline characteristics: 43 yr, BMI 28, 20 years, diabetes, HbA1c 8.1%, 0.7 U/kg/d insulin	<ul style="list-style-type: none"> <li>• Reduced HbA1c (−0.39% 10 mg, −0.45% 25 mg, <math>P &lt; 0.0001</math>)</li> <li>• Reduced weight (−3.2 kg 10 mg, −3.6 kg 25 mg, <math>P &lt; 0.0001</math>)</li> <li>• Decreased TDI (−12% 10 mg, −12.9% 25 mg)</li> <li>• Increased DKA<sup>b</sup> (4.3% 10 mg, 3.3% 25 mg, 1.2% placebo)</li> <li>• Reduced HbA1c (−0.28% 2.5 mg, −0.45% 10 mg, −0.52% 25 mg, <math>P &lt; 0.0001</math>)</li> <li>• Reduced weight (−1.8 kg 2.5 mg, −3.0 kg 10 mg, −3.4 kg 25 mg, <math>P &lt; 0.0001</math>)</li> <li>• Decreased TDI (−6.4% 2.5 mg, −9.5% 10 mg, −10.7% 25 mg)</li> <li>• No increase in hypoglycemia</li> <li>• No increase DKA risk (0.8%) with 2.5 mg</li> </ul>	[27]

<sup>a</sup>Pooled analysis subsequently published [65].

<sup>b</sup>DKA events pooled from EASE-2 and EASE-3.

<sup>c</sup>Abbreviations: SBP, systolic blood pressure; TIR, time in range.

in HbA1c, weight loss and BP, echoing results seen in T2D. Despite evidence of metabolic improvements, risk–benefit evaluation has hindered FDA approval. Each study reported dose-dependent DKA risk, especially in insulin pump users; a group more at risk due to potential rapidity of interrupted insulin delivery. The only group without increased risk were subjects randomized to 2.5 mg empagliflozin in the EASE-2 study [27]. Therefore low-dose SGLTis may be a safer option. DKA diagnosis can be masked by relative euglycemia due to ongoing glucosuria. The FDA has issued warnings regarding euglycemic ketoacidosis in T2D, and the risk is foreseeable greater in T1D. Real-world DKA risks may be greater than reported in these studies, with less-stringent clinic follow-up arrangements. Recognizing risks and possible off-label use, protocols have been created suggesting risk mitigating strategies [82]. Reduced hypoglycemia revealed by *post hoc* analysis of sotagliflozin data is a risk–benefit (hypoglycemia vs DKA) discussion point [83]. Assessing capacity to improve CV mortality in T1D would necessitate investment in large clinical trials with a CV outcome focus in high risk populations for whom DKA risk can be minimized, a perceivably difficult research initiative.

## Incretins

### Pathophysiological Basis for CV Protection

Incretins are hormones secreted by the enteroendocrine cells in response to food, and are degraded by DPP4 enzyme. GLP1 regulates glucose levels by influencing insulin and glucagon secretion, gastric emptying, and satiety. These mechanisms provide possible rationale for use in T1D especially since exaggerated glucagon could be partially responsible for post prandial glucose excursions [84].

Incretin drugs are believed to have pleotropic effects but the exact actions of GLP1 on the CV system remain elusive. GLP1 receptors are located on atrial cardiomyocytes, coronary vascular smooth muscle cells, and macrophages, and GLP1 cleavage products may mediate mitochondrial signaling [85,86]. The only evidence supporting a possible CV effect in T1D was a small study demonstrating reversal of hypo- and hyperglycemia induced endothelial dysfunction (FMD) and oxidative stress after

Table 4. GLP1 Agonist and Pramlintide Trials in T1D<sup>a</sup>

Study	Design	Participants	Results	Refs
GLP1 agonist				
Mathieu et al. 2016 ADJUNCT ONE	Liraglutide 1.8 vs 1.2 vs 0.6 mg vs placebo 52 wk Treat to target insulin titration	1398 Baseline characteristics: 43 yr, 21 yr diabetes, BMI 29, HbA1c 8.1%, detectable fasting C-peptide 18% of cohort	<ul style="list-style-type: none"> <li>HbA1c reduction (–0.54% 1.8 mg, –0.49% 1.2 mg, –0.43% 0.6 mg, –0.34% placebo)</li> <li>Insulin dose reduction equivocal (–5% 1.8 mg, –2% 1.2 mg, +4% 0.6 mg, +4% placebo, mostly bolus insulin, insulin units/kg returned to baseline by 52 wk)</li> <li>Weight loss (–4.0 kg 1.8 mg, –2.7 kg 1.2 mg, –1.3 kg 0.6 mg, +0.9 kg placebo)</li> <li>Increased DKA (3 events 1.8 mg, 1 event 1.2 mg, 4 events 0.6 mg, no events placebo)</li> <li>No difference severe hypoglycemia (8.1% 1.8 mg, 6.2% 1.2 mg, 9.1% 0.6 mg, 10.6% placebo)</li> </ul>	[93]
Ahrén et al. 2016 ADJUNCT TWO	Liraglutide 1.8 vs 1.2 vs 0.6 mg vs placebo 26 wk Insulin dose adjustment capped	835 Baseline characteristics: 43 yr, 21 yr diabetes, BMI 28, HbA1c 8.1%, detectable fasting C-peptide 15% of cohort	<ul style="list-style-type: none"> <li>HbA1c reduction (–0.33% 1.8 mg, –0.22% 1.2 mg, –0.23% 0.6 mg, 0.01% placebo)</li> <li>Insulin dose reduction (reported as estimated treatment ratio compared with placebo 0.9 1.8 mg, 0.93 1.2 mg, 0.95 0.6 mg)</li> <li>Weight loss (5.1 kg 1.8 mg, –4.0 kg 1.2 mg, –2.5 kg 1.2 mg, –0.2 kg placebo)</li> <li>Increased hyperglycemia with ketosis (8.3% 1.8 mg, 6.2% 1.2 mg, 8.1% 0.6 mg, 4.4% placebo, mostly in C-peptide-negative group), 1 DKA event in 1.2 mg group</li> <li>Increased symptomatic hypoglycemia in 1.2 mg group (77.7% 1.8 mg, 83.7% 1.2 mg, 78.7% 0.6 mg, 78.6% placebo)</li> </ul>	[94]
Pramlintide				
Whitehouse et al. 2002	Pramlintide 30 µg s/c 4 times daily (re-randomized to 30 vs 60 µg at 20 wk if HbA1c reduction <1%) vs placebo 52 weeks	480 Baseline characteristics: 40 years, BMI 25, 17 yr diabetes, HbA1c 8.8%, (unclear baseline TDI)	<ul style="list-style-type: none"> <li>HbA1c reduction (–0.39% pramlintide vs –0.12% placebo)</li> <li>Weight reduction (–0.5 kg, +1 kg placebo)</li> <li>Maintained insulin requirements (+2.3% pramlintide, +10.3% placebo)</li> <li>No increase severe hypoglycemia</li> <li>Nausea (46.5% pramlintide, 21.9% placebo)</li> </ul>	[95]
Ratner et al. 2004	Pramlintide 60 µg sc 3 times daily vs 4 times daily (meal times plus snack) vs placebo 52 wk	651 Baseline characteristics: age 41 yr, BMI 26, 18 yr diabetes, HbA1c 8.9% (unclear baseline TDI)	<ul style="list-style-type: none"> <li>HbA1c reduction (–0.29% 3 times daily, –0.34% 4 times daily, +0.04% placebo)</li> <li>Weight loss (–0.4 kg 3 times daily, –0.4 kg 4 times daily, +0.8 kg placebo)</li> <li>Increased severe hypoglycemia (4-fold increase at 4 wk)</li> <li>Severe nausea (8.5% 3 times daily, 6.8% 4 times daily, 1.3% placebo)</li> </ul>	[96]
Edelman et al. 2006	Pramlintide 15–60 µg sc 3/4 times daily (escalated as	296 Baseline characteristics: age 41 yr, BMI 28, 20 yr diabetes, HbA1c 8.1%, TDI 65U (MDI) 47U (CSII)	<ul style="list-style-type: none"> <li>HbA1c no change</li> <li>Reduced insulin requirements (–12% pramlintide, +1% placebo)</li> </ul>	[97]

(Continued on next page)

Table 4. Continued

Study	Design	Participants	Results	Refs
	tolerated) vs placebo 29 wk Proactive 30–50% mealtime insulin dose reduction		<ul style="list-style-type: none"> <li>Weight loss (–1.3 kg pramlintide, +1.2 kg placebo)</li> <li>Increased severe hypoglycemia (event rate per patient year 0.57 pramlintide, 0.3 placebo)</li> <li>Nausea (63% pramlintide, 36% placebo)</li> </ul>	

<sup>a</sup>Abbreviations: CSII, continuous subcutaneous insulin infusion; sc, subcutaneously; TDI, total daily insulin.

GLP infusion. This suggests that GLP1 may protect endothelium function [87], but whether oral or injected GLP1 agonists have the same effect and prevent CV outcomes requires further study.

The evidence base for CV benefit is well established in T2D. Six GLP1 agonists have glycemic and weight benefit, and of these, liraglutide, semaglutide, albiglutide, and dulaglutide reduced three-point MACEs [88,89,22–25]. The large trial sizes (collectively >60 000 T2D patients studied) lasting 2–5 years is indicative of resources invested. It is possible that the observed effects related to CV risk factor improvement rather than an independent drug effect. Liraglutide and dulaglutide data also suggest added renal benefits. DPP4is neither reduce nor increase CV events in T2D, although the FDA added warnings about HF hospitalization risk in alogliptin and saxagliptin [90]. In populations without T2D, liraglutide did not improve HF outcomes in a cohort with established HF (59% T2D) [91]. A semaglutide CVOT in overweight or obese people without diabetes is underway (NCT03574597) to determine if benefits of GLP1 agonists carry over outside T2D, but no GLP1 agonist CVOTs are planned in T1D.

### Incretins in T1D

DPP4i and GLP agonist T1D drug trials have assessed suitability to improve glycemia. The evidence base for DPP4i in T1D is weak. A systematic review of six small RCTs (n = 12–125) did not demonstrate clear glycemic benefits and there are no data examining CV effects [92]. Regarding GLP1 agonists, only two large Phase III trials have been published in T1D, both liraglutide studies (Table 4) [93,94]. The addition of liraglutide to insulin reduces HbA1c, insulin dose requirement, and weight, but at the expense of increased hypoglycemia and ketosis in some dosage groups. Residual beta-cell function may be an important efficacy and safety factor. Subgroup analysis revealed greater glycemic efficacy in C-peptide-positive subjects (HbA1c –0.77% vs –0.27%) and higher DKA risk in C-peptide-negative subjects [93,94].

On balance, liraglutide may improve CV risk factors but is not recommended for use in T1D due to safety concerns. Exploratory studies examining the effect of GLP1 receptor agonism on CV measures may be of interest and more safely studied in T1D with residual beta cell function. The safety profile of other GLP1 agonists other than liraglutide has not been determined in T1D.

### Pramlintide

Pramlintide is an injected synthetic analog of amylin, a polypeptide hormone that is cosecreted with insulin. It complements the glucoregulatory effects of insulin by slowing gastric emptying, increasing satiety, and reducing postprandial glucagon release.

Several moderately sized Phase III clinical trials have demonstrated HbA1c reduction and weight loss, but increased hypoglycemia, nausea, and vomiting (Table 4) [95–97]. It is the only FDA-approved T1D adjunct for use in the USA; however, injection burden and gastrointestinal side effects have limited real-world use.

There is little evidence for effects on the CV system, although in a *post hoc* analysis of a small placebo-controlled randomized study in T1D (n = 18), meal-time pramlintide (with insulin) reduced oxidative

stress markers. This is likely from the effect of reduced prandial hyperglycemia though a direct effect of pramlintide is a theoretical possibility [98]. Whether pramlintide could improve long-term diabetes complications through reduced oxidative stress is yet to be explored.

### Concluding Remarks

There is an urgent need to find strategies to improve glycemia and reverse CV risk in T1D given the significant survival difference for individuals with T1D as compared with those without diabetes and even T2D individuals. There is growing enthusiasm amongst researchers to assess adjunctive medications for this role particularly given recent evidence for benefit of diabetes adjunctive therapies in people without diabetes [26].

Across classes, HbA1c reductions are most pronounced with SGLTis and GLP1 agonists but with issues of ketosis in both, and hypoglycemia with GLP1 agonists. Pramlintide is the only FDA-approved agent and provides marginal metabolic benefits but with the inconvenience of extra meal-time injections. There is preliminary evidence for improvement in CV surrogate measures in metformin, but results are mixed. Only two small studies in SGLTis and a single pramlintide and GLP1 agonist study have examined effects of these drugs on surrogates of vascular health. As the evidence stands, adjuncts may improve CV risk factors (weight, BP, and HbA1c), but this cannot be extrapolated to true CV risk reduction (see Outstanding Questions). Small pilot trials will remain insufficient to change practice and adequately powered RCTs will remain necessary, so long as safety is assured.

Overcoming issues concerning conduct of CV trials in T1D may require pragmatic solutions. Novel solutions include: (i) restricting target sample sizes by using adaptive trial designs and selecting focused high-risk individuals likely to experience a target endpoint (e.g., overweight T1D with established CV disease), but at the cost of generalizability; (ii) investing in validation of surrogate endpoints to avoid needing long trials for capture of endpoints with a long natural history (such as CV events); and (iii) ensuring that surrogate endpoints are valid in T1D.

The rationale for T1D adjuncts exceeds available evidence, and risks do not outweigh benefits. However, in this era of precision medicine, there may be a place for adjuncts in carefully selected populations. More robust data is required to make definitive conclusions and close the mortality gap in T1D.

### Acknowledgments

J.R.G. is partly supported by the Don Chisholm Fellowship. J.R.S. is supported by the University Postgraduate Award (University of New South Wales). We are thankful to the reviewers of this manuscript for their constructive feedback.

### References

- Patterson, C.C. et al. (2019) Trends and cyclical variation in the incidence of childhood type 1 diabetes in 26 European centres in the 25 year period 1989–2013: a multicentre prospective registration study. *Diabetologia* 62, 408–417
- Lind, M. et al. (2014) Glycemic control and excess mortality in type 1 diabetes. *N. Engl. J. Med.* 371, 1972–1982
- Harding, J.L. et al. (2014) Mortality trends among people with type 1 and type 2 diabetes in Australia: 1997–2010. *Diabetes Care* 37, 2579–2586
- Miller, K.M. et al. (2015) Current state of type 1 diabetes treatment in the U.S.: updated data from the T1D Exchange Clinic Registry. *Diabetes Care* 38, 971–978
- Kilpatrick, E.S. et al. (2008) A1C variability and the risk of microvascular complications in type 1 diabetes. *Diabetes Care* 31, 2198–2202
- Hirsch, I.B. (2015) Glycemic variability and diabetes complications: does it matter? Of course it does! *Diabetes Care* 38, 1610–1614
- Buscemi, S. et al. (2010) Glycaemic variability using continuous glucose monitoring and endothelial function in the metabolic syndrome and in Type 2 diabetes. *Diabetic Med.* 27, 872–878
- Gerbaud, E. et al. (2019) Glycemic variability is a powerful independent predictive factor of midterm major adverse cardiac events in patients with diabetes with acute coronary syndrome. *Diabetes Care* 42, 674–681
- Hanefeld, M. et al. (2016) Hypoglycemia and cardiovascular risk: is there a major link? *Diabetes Care* 39, S205–S209
- Frier, B.M. et al. (2011) Hypoglycemia and cardiovascular risks. *Diabetes Care* 34, S132–S137
- Weinstock, R.S. et al. (2013) Severe hypoglycemia and diabetic ketoacidosis in adults with type 1

### Outstanding Questions

Do adjunctive agents prevent cardiovascular events in T1D?

Is it safe to use a combination of adjuncts from different drug classes?

Is there a true benefit of insulin pump therapy over MDI for CV risk reduction?

Do surrogate measures of CV risk apply in T1D?

- diabetes: results from the T1D Exchange Clinic Registry. *J. Clin. Endocrinol. Metab.* 98, 3411–3419
12. Kilpatrick, E.S. et al. (2007) Insulin resistance, the metabolic syndrome, and complication risk in type 1 diabetes: “double diabetes” in the Diabetes Control and Complications Trial. *Diabetes Care* 30, 707–712
  13. Conway, B. et al. (2010) Temporal patterns in overweight and obesity in type 1 diabetes. *Diabetic Med.* 27, 398–404
  14. Rodrigues, T.C. et al. (2011) Obesity and coronary artery calcium in diabetes: the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study. *Diabetes Technol. Ther.* 13, 991–996
  15. Schauer, I.E. et al. (2011) Insulin resistance, defective insulin-mediated fatty acid suppression, and coronary artery calcification in subjects with and without type 1 diabetes. *Diabetes* 60, 306–314
  16. Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N. Engl. J. Med.* 329, 977–986
  17. Purnell, J.Q. et al. (2017) Impact of excessive weight gain on cardiovascular outcomes in type 1 diabetes: results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study. *Diabetes Care* 40, 1756–1762
  18. Steineck, I. et al. (2015) Insulin pump therapy, multiple daily injections, and cardiovascular mortality in 18 168 people with type 1 diabetes: observational study. *BMJ* 350, h3234
  19. Zinman, B. et al. (2015) Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. *N. Engl. J. Med.* 373, 2117–2128
  20. Neal, B. et al. (2017) Canagliflozin and cardiovascular and renal events in type 2 diabetes. *N. Engl. J. Med.* 377, 644–657
  21. Wiviott, S.D. et al. (2019) Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* 380, 347–357
  22. Marso, S.P. et al. (2016) Liraglutide and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* 375, 311–322
  23. Marso, S.P. et al. (2016) Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. *N. Engl. J. Med.* 375, 1834–1844
  24. Hernandez, A.F. et al. (2018) Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. *Lancet* 392, 1519–1529
  25. Gerstein, H.C. et al. (2019) Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. *Lancet* 394, 121–130
  26. McMurray, J.J.V. et al. (2019) Dapagliflozin in patients with heart failure and reduced ejection fraction. *N. Engl. J. Med.* Published online September 19, 2019. <https://doi.org/10.1056/NEJMoa1911303>
  27. Rosenstock, J. et al. (2018) Empagliflozin as adjunctive to insulin therapy in type 1 diabetes: the EASE Trials. *Diabetes Care* 41, 2560–2569
  28. Vlachopoulos, C. et al. (2015) The role of vascular biomarkers for primary and secondary prevention. A position paper from the European Society of Cardiology Working Group on peripheral circulation. *Atherosclerosis* 241, 507–532
  29. de Ferranti, S.D. et al. (2014) Type 1 diabetes mellitus and cardiovascular disease: a scientific statement from the American Heart Association and American Diabetes Association. *Diabetes Care* 37, 2843–2863
  30. Cefalu, W.T. et al. (2018) Cardiovascular outcomes trials in type 2 diabetes: where do we go from here? Reflections From a *Diabetes Care* Editors’ Expert Forum. *Diabetes Care* 41, 14–31
  31. Research, C. for D.E (2019) *Surrogate Endpoint Resources for Drug and Biologic Development*. <http://www.fda.gov/drugs/development-resources/surrogate-endpoint-resources-drug-and-biologic-development>
  32. Tardif, J.-C. et al. (2006) Vascular biomarkers and surrogates in cardiovascular disease. *Circulation* 113, 2936–2942
  33. Cohn, J.N. (2004) Surrogate markers for cardiovascular disease: functional markers. *Circulation* 109, IV-31–IV-46
  34. Greenland, P. et al. (2018) Coronary calcium score and cardiovascular risk. *J. Am. Coll. Cardiol.* 72, 434–447
  35. Neunteufl, T. et al. (1997) Systemic endothelial dysfunction is related to the extent and severity of coronary artery disease. *Atherosclerosis* 129, 111–118
  36. Rubinshtein, R. et al. (2010) Assessment of endothelial function by non-invasive peripheral arterial tonometry predicts late cardiovascular adverse events. *Eur. Heart J.* 31, 1142–1148
  37. Townsend, R.R. (2017) Arterial stiffness: recommendations and standardization. *Pulse (Basel)* 4, 3–7
  38. O’Rourke, M.F. and Gallagher, D.E. (1996) Pulse wave analysis. *J. Hypertens Suppl.* 14, S147–S157
  39. Laurent, S. et al. (2001) Aortic stiffness is an independent predictor of all-cause and cardiovascular mortality in hypertensive patients. *Hypertension* 37, 1236–1241
  40. Weber, T. et al. (2004) Arterial stiffness, wave reflections, and the risk of coronary artery disease. *Circulation* 109, 184–189
  41. Wilkinson, I.B. (2000) Increased augmentation index and systolic stress in type 1 diabetes mellitus. *QJM* 93, 441–448
  42. Lorenz, M.W. et al. (2007) Prediction of clinical cardiovascular events with carotid intima-media thickness: a systematic review and meta-analysis. *Circulation* 115, 459–467
  43. Nathan, D.M. et al. (2003) Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N. Engl. J. Med.* 348, 2294–2303
  44. Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group (2016) Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. *Diabetes Care* 39, 686–693
  45. Greenland, P. et al. (2004) Coronary artery calcium score combined with Framingham score for risk prediction in asymptomatic individuals. *JAMA* 291, 210–215
  46. Harrison, D. et al. (2003) Role of oxidative stress in atherosclerosis. *Am. J. Cardiol.* 91, 7A–11A
  47. DeFronzo, R.A. et al. (1982) Hepatic and peripheral insulin resistance: a common feature of type 2 (non-insulin-dependent) and type 1 (insulin-dependent) diabetes mellitus. *Diabetologia* 23, 313–319
  48. Cree-Green, M. et al. (2018) Youth with type 1 diabetes have adipose, hepatic, and peripheral insulin resistance. *J. Clin. Endocrinol. Metab.* 103, 3647–3657
  49. Catalano, K.J. et al. (2014) Insulin resistance induced by hyperinsulinemia coincides with a persistent alteration at the insulin receptor tyrosine kinase domain. *PLoS One* 9, e108693
  50. Salgin, B. et al. (2009) Effects of growth hormone and free fatty acids on insulin sensitivity in patients with type 1 diabetes. *J. Clin. Endocrinol. Metab.* 94, 3297–3305

51. Gregory, J.M. et al. (2019) Iatrogenic hyperinsulinemia, not hyperglycemia, drives insulin resistance in type 1 diabetes as revealed by comparison to GCK-MODY (MODY2). *Diabetes* 68, 1565–1576
52. Moran, A. et al. (1999) Insulin resistance during puberty: results from clamp studies in 357 children. *Diabetes* 48, 2039–2044
53. Bjornstad, P. et al. (2016) Estimated insulin sensitivity predicts incident micro- and macrovascular complications in adults with type 1 diabetes over 6 years: the coronary artery calcification in type 1 diabetes study. *J. Diabetes Complic.* 30, 586–590
54. Orchard, T.J. et al. (2003) Insulin resistance-related factors, but not glycemia, predict coronary artery disease in type 1 Diabetes: 10-year follow-up data from the Pittsburgh Epidemiology of Diabetes Complications study. *Diabetes Care* 26, 1374–1379
55. Bailey, C.J. and Turner, R.C. (1996) Metformin. *N. Engl. J. Med.* 334, 574–579
56. Chen, Q. et al. (2017) Metformin attenuates ER stress-induced mitochondrial dysfunction. *Transl. Res.* 190, 40–50
57. Hattori, Y. et al. (2015) Pleiotropic benefits of metformin: macrophage targeting its anti-inflammatory mechanisms. *Diabetes* 64, 1907–1909
58. UK Prospective Diabetes Study (UKPDS) Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet* 352, 854–865
59. Holman, R.R. and Matthews, D.R. (2008) 10-Year follow-up of intensive glucose control in type 2 diabetes. *N. Engl. J. Med.* 359, 1577–1589
60. Kooy, A. et al. (2009) Long-term effects of metformin on metabolism and microvascular and macrovascular disease in patients with type 2 diabetes mellitus. *Arch. Intern. Med.* 169, 616
61. Preiss, D. et al. (2014) Metformin for non-diabetic patients with coronary heart disease (the CAMERA study): a randomised controlled trial. *Lancet Diabetes Endocrinol.* 2, 116–124
62. Vella, S. et al. (2010) The use of metformin in type 1 diabetes: a systematic review of efficacy. *Diabetologia* 53, 809–820
63. Libman, I.M. et al. (2015) Effect of metformin added to insulin on glycemic control among overweight/obese adolescents with type 1 diabetes: a randomized clinical trial. *JAMA* 314, 2241
64. Anderson, J.J.A. et al. (2017) Effect of metformin on vascular function in children with type 1 diabetes: a 12-month randomized controlled trial. *J. Clin. Endocrinol. Metab.* 102, 4448–4456
65. Pitocco, D. et al. (2013) Metformin improves endothelial function in type 1 diabetic subjects: a pilot, placebo-controlled randomized study. *Diabetes Obes. Metab.* 15, 427–431
66. Petrie, J.R. et al. (2017) Cardiovascular and metabolic effects of metformin in patients with type 1 diabetes (REMOVAL): a double-blind, randomised, placebo-controlled trial. *Lancet Diabetes Endocrinol.* 5, 597–609
67. Bjornstad, P. et al. (2018) Metformin improves insulin sensitivity and vascular health in youth with type 1 diabetes mellitus: randomized controlled trial. *Circulation* 138, 2895–2907
68. Perkovic, V. et al. (2019) Canagliflozin and renal outcomes in type 2 diabetes and nephropathy. *N. Engl. J. Med.* 380, 2295–2306
69. Wanner, C. et al. (2016) Empagliflozin and progression of kidney disease in type 2 diabetes. *N. Engl. J. Med.* 375, 323–334
70. Wiviott, S.D. et al. (2019) Dapagliflozin and cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* 380, 347–357
71. Mogensen, C.E. (1971) Maximum tubular reabsorption capacity for glucose and renal hemodynamics during rapid hypertonic glucose infusion in normal and diabetic subjects. *Scand. J. Clin. Lab Invest.* 28, 101–109
72. Rahmoune, H. et al. (2005) Glucose transporters in human renal proximal tubular cells isolated from the urine of patients with non-insulin-dependent diabetes. *Diabetes* 54, 3427–3434
73. Ali, A. et al. (2019) SGLT2 inhibitors: cardiovascular benefits beyond HbA1c – translating evidence into practice. *Diabetes Ther.* 10, 1595–1622
74. Cherney, D.Z. et al. (2014) The effect of empagliflozin on arterial stiffness and heart rate variability in subjects with uncomplicated type 1 diabetes mellitus. *Cardiovasc. Diabetol.* 13, 28
75. Lunder, M. et al. (2018) Empagliflozin on top of metformin treatment improves arterial function in patients with type 1 diabetes mellitus. *Cardiovasc. Diabetol.* 17, 153
76. Garg, S.K. et al. (2017) Effects of sotagliflozin added to insulin in patients with type 1 diabetes. *N. Engl. J. Med.* 377, 2337–2348
77. Buse, J.B. et al. (2018) Sotagliflozin in combination with optimized insulin therapy in adults with type 1 diabetes: The North American inTandem1 Study. *Diabetes Care* 41, 1970–1980
78. Danne, T. et al. (2018) HbA1c and hypoglycemia reductions at 24 and 52 weeks with sotagliflozin in combination with insulin in adults with type 1 diabetes: The European inTandem2 Study. *Diabetes Care* 41, 1981–1990
79. Dandona, P. et al. (2018) Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes: the DEPICT-1 52-Week Study. *Diabetes Care* 41, 2552–2559
80. Mathieu, C. et al. (2018) Efficacy and safety of dapagliflozin in patients with inadequately controlled type 1 diabetes (the DEPICT-2 Study): 24-week results from a randomized controlled trial. *Diabetes Care* 41, 1938–1946
81. Henry, R.R. et al. (2015) Efficacy and safety of canagliflozin, a sodium–glucose cotransporter 2 inhibitor, as add-on to insulin in patients with type 1 diabetes. *Diabetes Care* 38, 2258–2265
82. Garg, S.K. et al. (2018) Strategy for mitigating DKA risk in patients with type 1 diabetes on adjunctive treatment with sglit inhibitors: a STICH protocol. *Diabetes Technol. Ther.* 20, 571–575
83. Danne, T. et al. (2019) Sotagliflozin added to optimized insulin therapy leads to lower rates of clinically relevant hypoglycemic events at any HbA1c at 52 weeks in adults with type 1 diabetes. *Diabetes Technol. Ther.* 21, 471–477
84. Behme, M.T. et al. (2003) Glucagon-like peptide 1 improved glycemic control in type 1 diabetes. *BMC Endocr. Disord.* 3, 3
85. Drucker, D.J. (2018) The ascending GLP-1 road from clinical safety to reduction of cardiovascular complications. *Diabetes* 67, 1710–1719
86. Ussher, J.R. and Drucker, D.J. (2014) Cardiovascular actions of incretin-based therapies. *Circ. Res.* 114, 1788–1803
87. Ceriello, A. et al. (2013) Glucagon-like peptide 1 reduces endothelial dysfunction, inflammation, and oxidative stress induced by both hyperglycemia and hypoglycemia in type 1 diabetes. *Diabetes Care* 36, 2346–2350
88. Pfeffer, M.A. et al. (2015) Lixisenatide in patients with type 2 diabetes and acute coronary syndrome. *N. Engl. J. Med.* 373, 2247–2257
89. Holman, R.R. et al. (2017) Effects of once-weekly exenatide on cardiovascular outcomes in type 2 diabetes. *N. Engl. J. Med.* 377, 1228–1239

90. Research, C. for D.E (2019) *FDA Drug Safety Communication: FDA Adds Warnings about Heart Failure Risk to Labels of Type 2 Diabetes Medicines Containing Saxagliptin and Alogliptin*. <http://www.fda.gov/drugs/drug-safety-and-availability/fda-drug-safety-communication-fda-adds-warnings-about-heart-failure-risk-labels-type-2-diabetes>
91. Margulies, K.B. et al. (2016) Effects of liraglutide on clinical stability among patients with advanced heart failure and reduced ejection fraction. *JAMA* 316, 500–508
92. Guo, H. et al. (2016) The efficacy and safety of DPP4 inhibitors in patients with type 1 diabetes: a systematic review and meta-analysis. *Diabetes Res. Clin. Pract.* 121, 184–191
93. Mathieu, C. et al. (2016) Efficacy and safety of liraglutide added to insulin treatment in type 1 diabetes: the ADJUNCT ONE Treat-To-Target randomized trial. *Diabetes Care* 39, 1702–1710
94. Ahrén, B. et al. (2016) Efficacy and safety of liraglutide added to capped insulin treatment in subjects with type 1 diabetes: the ADJUNCT TWO randomized trial. *Diabetes Care* 39, 1693–1701
95. Whitehouse, F. et al. (2002) A randomized study and open-label extension evaluating the long-term efficacy of pramlintide as an adjunct to insulin therapy in type 1 diabetes. *Diabetes Care* 25, 724–730
96. Ratner, R.E. et al. (2004) Amylin replacement with pramlintide as an adjunct to insulin therapy improves long-term glycaemic and weight control in Type 1 diabetes mellitus: a 1-year, randomized controlled trial. *Diabetic Med.* 21, 1204–1212
97. Edelman, S. et al. (2006) A double-blind, placebo-controlled trial assessing pramlintide treatment in the setting of intensive insulin therapy in type 1 diabetes. *Diabetes Care* 29, 2189–2195
98. Ceriello, A. et al. (2005) Effects of pramlintide on postprandial glucose excursions and measures of oxidative stress in patients with type 1 diabetes. *Diabetes Care* 28, 632–637