Blood Pressure and Cardiovascular Disease in Type 1 Diabetes: an Exploration of Prediction and Control

by

Jingchuan Guo

MPH, University of Pittsburgh, 2016

MD, Peking University, China, 2014

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This dissertation was presented

by

Jingchuan Guo

It was defended on

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and approved by

Maria M Brooks, PhD, Professor, Departments of Epidemiology and Biostatistics
Graduate School of Public Health, University of Pittsburgh

Tina Costacou, PhD, Associate Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Matthew F Muldoon, MD, Professor, Heart and Vascular Institute
School of Medicine, University of Pittsburgh

Ashely I Naimi, PhD, Assistant Professor, Department of Epidemiology
Graduate School of Public Health, University of Pittsburgh

Dissertation Director: Trevor J Orchard, MD, Distinguished Professor
Department of Epidemiology, Graduate School of Public Health, University of Pittsburgh

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Jingchuan Guo, PhD

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Abstract

This dissertation provides, in a type 1 diabetes (T1D) cohort followed for 25 years, a comprehensive examination of both blood pressure (BP) as a cardiovascular disease risk predictor and the role of the renin-angiotensin system (RAS) inhibition in reducing cardiovascular risk. Data are from the Pittsburgh Epidemiology of Diabetes Complications (EDC) Study of childhood-onset diabetes.

First, we observed that all five BP indices (systolic [SBP], diastolic [DBP], pulse [PP], mean arterial [MAP] and mid-blood pressure [MidBP]) predicted incident coronary artery disease (CAD) independently of other risk factors. Although PP was less effective in the entire cohort, its prognostic significance improved, and became comparable to SBP, in participants age 35 years and older and/or with poor glycemic control. This likely reflects an early onset of glycation-included vascular stiffening in T1D.

Second, using time-weighted variables that reflected long-term exposure to high BP from youth throughout midlife, we found dose-gradient associations of SBP, DBP and MAP with CAD outcomes, beginning at approximately 120, 80 and 90 mmHg, respectively. This suggests a lower BP goal (i.e.,120/80 mmHg) is needed than currently recommended (140/90 mmHg) for young T1D adults.

In the third analysis, an examination of the RAS inhibition effect on CAD outcomes in T1D, appropriate statistical methods (inverse probability treatment weight, marginal structural

model, and causal mediation analysis) were used under a causal-inference framework. RAS inhibitors, but not β blockers or calcium channel blockers, reduced CAD risk, though the results did not reach statistical significance. Mediation analysis indicated that cardiovascular protective effect of RAS inhibitors was partially achieved through pathways beyond lowering BP and urinary albumin, the two prominent effects of this antihypertensive class. Though not significant, these findings suggest a greater potential for RAS inhibitors to offer superior cardioprotection, compared to β blockers and calcium channel blockers, in T1D.

Overall, the dissertation findings have contributed to filling some critical gaps in our understanding of the magnitude of cardiovascular risk associated with BP and how to effectively control hypertension in T1D. This body of work thus has important public health relevance, given the enormous contribution of cardiovascular disease to T1D mortality and morbidity.

Table of Contents

List of Tables

List of Figures

1.0 Introduction and Background

Not only are diabetes and hypertension two of the most common diseases, but they also share a remarkable overlap in the underlying pathophysiological pathways of end-organ damage. In the United States, approximately three-quarters of the diabetes patients also have hypertension [1], and an estimated 18 million Americans are affected by both conditions [2]. Moreover, the coexistence of diabetes and hypertension accelerates the course of end-organ damage [3]. Previous results showed that 35-75% of diabetes complications could be attributed to elevated blood pressure (BP) [4]. Hypertension increases the risk of cardiovascular disease by 50% in patients with diabetes [5]. Hypertension management remains a concern in the diabetes population, including optimal BP targets and choices of antihypertensive agents. The answers to these questions are particularly elusive with regard to type 1 diabetes (T1D). This review focuses on evidence and knowledge gaps of hypertension and BP control in T1D.

1.1 Diabetes Classification, Natural History and Epidemiology

According to the American Diabetes Association (ADA), diabetes is "a group of metabolic diseases characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both" [6]. All forms of diabetes are chronic and progressive, leading to large vessel, small vessel, and/or neuropathic complications. Diabetes has been a substantial burden in the United States because of its high and rising prevalence, as well as its implications for both long-term health and economics [7,8].

1.1.1 Diagnosis and Classification

The primary clinical manifestation and diagnostic feature of diabetes is hyperglycemia [9]. The ADA diagnostic cut-offs are listed in **Table 1**[10]. The presence of one or more of the following four criteria may confirm the diagnosis of diabetes: 1) glycated hemoglobin (HbA1c) ≥ 6.5%, 2) Fasting plasma glucose (FPG) ≥ 126 mg/dL, 3) two-hour plasma glucose in the 75g oral glucose tolerance test (OGTT) ≥ 200 mg/dL, and 4) random plasma glucose ≥ 200 mg/dL in patients with hyperglycemic symptoms (polyuria, polydipsia, or unexplained weight loss) or hyperglycemic crisis. In prediabetes, which usually manifests as impaired glucose tolerance (IGT) and/or impaired fasting glucose (IFG), blood glucose is higher than normal but it does not reach the threshold of a diabetes diagnosis [6].

To address the distinct etiologies of different forms of diabetes, the ADA guidelines now recommend a four-category classification, comprising type 1 and type 2 diabetes mellitus, gestational diabetes mellitus, and other specific forms of diabetes [6]. These are described below:

- T1D features the autoimmune-mediated destruction of pancreatic β-cells [11], resulting in absolute insulin deficiency. It accounts for about 5% of diabetes cases.
- Type 2 diabetes is featured as having glucose-specific insulin secretion defects and/or insulin resistance [12]. It accounts for over 90% of diabetes cases.
- Gestational diabetes mellitus is glucose intolerance that is first identified in the second or third trimester of pregnancy. In the United States, gestational diabetes mellitus affects about 7% of pregnant women [13].
- Specific types of diabetes may present with symptoms similar to those of type 1 or type 2 diabetes, but they have diverse causes, such as monogenic diabetes syndromes (e.g.,

maturity-onset diabetes of the young [MODY]), pancreatic disorders, drug-induced effects, and transplantation related diabetes.

1.1.2 Natural History of Diabetes

Expert consensus from the ADA, the Juvenile Diabetes Research Foundation (JDRF), the European Association for the Study of Diabetes, and the American Association of Clinical Endocrinologists concluded that hyperglycemia due to pancreatic β-cell dysfunction or destruction is the unifying feature of all forms of diabetes regardless of distinct pathophysiological pathways [14]. Hyperglycemia of all forms of diabetes subsequently leads to the risk of developing complications, although disease progression rates may vary.

A natural history model of T1D was proposed in 1986 by Eisenbarth [15] and subsequent findings have improved the understanding of the autoimmune mechanism as well as the potential triggering effects of genetic and environmental factors in the disease pathogenesis [16]. In genetically susceptible individuals, some environmental factors (possibly infections and chemicals) may trigger a self-autoimmune reaction, which results in the progressive destruction of pancreatic β-cells. In the early phases, although the progressive destruction of β-cells and the serological positivity of circulating autoantibodies have been initiated, sufficient pancreatic β-cell function is still preserved to maintain a normal blood glucose level. In this phase, the persistent presence of multiple islet autoantibodies might be predictors of the risk of clinical hyperglycemia and diabetes in the future [17]. In the following disease phases, the β-cell destruction continues, leading to the subsequent loss of insulin production and then the elevation of blood glucose. Overt diabetes eventually develops when most β-cells are lost.

T1D staging was recently updated based upon the natural history of the disease (**Table 2**) [14,18]. Stage 1 is characterized by the presence of islet β-cell autoimmunity, which is indicated by the serological positivity of multiple autoantibodies with normal glucose status and the absence of symptoms. Stage 2 is characterized by the presence of islet β-cell autoimmunity with impaired glucose status and the absence of symptoms. Stage 3 is the onset of overt diabetes [18].

The presence of β-cell-targeting autoantibodies reflects the exposure to β-cell autoantigens [19]. The GAD65 and/or insulin autoantibodies usually appear in the first order, and the IA-2 and/or ZNT8 autoantibodies appear in the second or third order [19]. Because autoantibodies can be present in the first stage of the disease [14,18], their detection offers opportunities for early screening and diagnosis prior to the onset of diabetic ketoacidosis. Indeed, screening studies to detect autoantibodies in newborns or children have been conducted in several European counties and the United States. The follow-up visits have suggested a decreased incidence of diabetic ketoacidosis in these screening cohorts, mainly resulting from the earlier start of treatment [20–22].

Genetic susceptibility in T1D has been extensively studied over the past several decades. More than 60 genetic variants have been found to be associated with the disease [23]. The link between the human leukocyte antigens (HLA) region and T1D was first described in the 1970s [24] and it remains the greatest contributor to genetic susceptibility to the disease [25]. The HLA region localized on chromosome 6 (6p21.31) and the class II DR-DQ antigens are particularly strongly associated with T1D [25,26]. Interestingly, the direction of the association---either susceptible to or protective against---in the development of T1D is dependent on the particular DR-DQ haplotypes [25,27,28]. European data showed that the HLA-DR3-DQ2 and HLA-DR4-DQ8 haplotypes were detected in approximately 90% of Caucasian children diagnosed with T1D [28,29]. Multiple non-HLA risk loci were identified to be linked to T1D based on the advancements in genotyping

methodologies in recent decades [30]. In addition to the HLA region, the insulin gene (INS) and the PTPN22 gene are the two loci that are the most susceptible to T1D [25].

The pathophysiological pathway that leads to the loss of β-cell mass and/or function is less well understood in type 2 diabetes. Defective insulin secretion in the background of insulin resistance is thought to be the central pathogenesis of the onset and progression of the disease [14,31]. In the initial phase, individuals at risk of type 2 diabetes (e.g., obese individuals and first-degree relatives) may exhibit reduced insulin sensitivity compensated by increased insulin secretion in pancreatic islet β-cells, which usually leads to hyperinsulinemia. Overtime, the compensatory hyperinsulinemia is no longer able to cope with the further decrease in insulin sensitivity, which results in increased blood glucose in the background of hyperinsulinemia. The β-cell function progressively declines over time, which eventually leads to overt hyperglycemia. As indicated by the glucose status, a three-stage classification is now used for type 2 diabetes: normal glucose, prediabetes (IGT and/or IFG) and diabetes [6]. Intervention in the stage of prediabetes may reduce the risk of progression to diabetes [32,33] as well as the risk of all-cause mortality [34,35].

1.1.3 Epidemiology of Diabetes

The prevalence of diabetes have increased dramatically in recent years [36]. Globally, the number of diabetes cases increased over 12-fold (from 30 to 382 million) in the recent half-century from 1964 [37] to 2013 [36]. According to the International Diabetes Federation (IDF), the total health expenditure for diabetes was 673 billion US dollars [8].

The United States has the third largest patient population of diabetes in the world [38]. According to statistics from the National Health and Nutrition Examination Survey (NHANES) [39], the age-standardized diabetes prevalence among adults ≥ 20 years of age increased from 9.8% in

the period 1988 -1994 to 10.8% in 2001-2002 and to 12.4% in 2011-2012. The prevalence of diabetes was projected to rise to 25% by 2050 [40].

The most recent National Diabetes Report published by the Centers for Disease Control and Prevention (CDC) [1] documented that 23.1 million U.S. individuals were diagnosed with diabetes in 2015, including 193,000 children and adolescents ≤20 years of age. Between 2001 and 2009, the prevalence of type 1 and type 2 diabetes in youth increased by 21.1% and 30.5%, respectively [41].

The health, social, and economic impacts of diabetes continue to increase in the United States. Diabetes is the seventh leading underlying cause of mortality [42] in the nation. The estimated total economic cost of diabetes increased from $174 billion in 1997 [43], $132 billion in 2002[44], to $245 billion in 2012 [45].

1.2 Type 1 Diabetes (T1D) and Complication Burdens

Type 1 diabetes (T1D) is a common chronic disorder among children [46]. The United States has the largest T1D population and the highest diabetes-related health expenditures in the world [47]. According to the NHANES 1999-2010, T1D affected approximately a million people in the nation [48]. Despite advances in healthcare, the mortality rate of T1D remains two to four times greater than that seen in the general population [49,50]. Because the negative impact of the disease continues to increase and prevention remains elusive in T1D, the effective control of the risks of complications is critical.

1.2.1 Mortality in T1D

Mortality in T1D has decreased in recent years [51,52]. However, excess mortality remains in the contemporary T1D population [53]. The major cause of death has shifted from acute to chronic diabetes complications, especially cardiovascular disease [51,54,55].

1.2.2 Cardiovascular Disease in T1D

Cardiovascular disease is the leading cause of death in long-standing T1D, which accounts for over 60% of all-cause mortality in type 1 patients with more than 20 years of diabetes duration [56]. Although the prevention and delay of microvascular complications [57] have been notably improved in recent years, cardiovascular complications in T1D remain high in [47]. Typically, cardiovascular events occur more than 10 years earlier in T1D patients compared to the non-diabetic population [58]. The Pittsburgh Epidemiology of Diabetes Complications (EDC) Study reported an incidence of 0.98% per year for major coronary artery disease (CAD) in T1D individuals between 28 and 38 years of age [59], whereas the annual incidence of myocardial infarction in the general population was 0.1% in the age group 35- 44 years [60], suggesting an approximate 10-fold increase in cardiovascular risk in young adults with T1D [61]. Another striking finding from the EDC cohort showed that young T1D adults at age 30 - 39 and 40 - 44 years had 33 and 19 times increased risk of cardiovascular mortality, respectively [62].

1.2.3 Chronic Kidney Disease in T1D

Epidemiological data of T1D kidney disease vary among cohorts. A review published in 2013 reported that over 30 years, the cumulative incidence of overt nephropathy and end-stage renal disease were 11 - 32% and 3.3 - 7.8%, respectively [63]. A striking finding in the EDC cohort suggested that the 50-year cumulative incidences of overt nephropathy and end-stage renal disease were 72% and 60%, respectively [64]. Another report of the EDC study documented that the death rates of T1D individuals without kidney disease were similar to the age-matched general population, implying that the excess deaths in the T1D population were mainly attributed to renal complications [65].

1.3 Blood pressure (BP) and Hypertension

Hypertension is considered as a hemodynamic disorder with a chronic elevation of arterial pressure and leads to premature morbidity and mortality via target organs damage (**Table 3**) [66]. Hypertension remains the most common risk factor of death and disability according to the 2015 Global Burden of Diseases [67]. The number of people affected worldwide increased from 600 million to 1 billion between 1980 and 2008 [68]. The lifetime risk of hypertension was found to be 90% in individuals over 55 years of age [69]. Most hypertension cases (90 - 95%) that have no apparent cause are categorized as essential (primary) hypertension. About 5 - 10% of the hypertensive population have an identifiable cause, which are referred to as secondary hypertension [70].

1.3.1 Pathophysiology of Essential Hypertension

The maintenance of arterial pressure is dependent on the balance of cardiac output and systematic vascular resistance [71]. The pathogenesis of essential hypertension remains elusive. Impaired renal sodium excretion might cause the increased concentration of calcium in the smooth muscle cells in arteries, leading to an increased vascular tone [72,73]. Both mechanisms, renal sodium excretion and vascular tone, are fundamental in BP regulation, which may be affected by various genetic and environmental factors [73]. Several additional physiological factors are thought to be involved in BP regulation mechanisms, including the circulating and intrarenal renin-angiotensin system (RAS), the autonomic nervous system, endothelial dysfunction as well as vasoactive and inflammatory substances (e.g., bradykinin, endothelin, nitric oxide, arterial natriuretic peptide, ouabain, and cytokines adhesion molecules)[71–77]. In the context of elevated BP, these factors worsen pathophysiological changes, including damage to the arterial wall and abnormal blood flow, and facilitate a prothrombotic state, which subsequently results in target organ damage [78,79].

1.3.2 Hypertension Diagnosis and Classification

According to the American Heart Association (AHA) ideal cardiovascular health criteria, BP less than 120/80 mmHg was identified as one of the seven components of ideal cardiovascular health [80]. The most recent classification update from the AHA is displayed in **Table 4** [81], which shows that normal BP is defined as < 120/80 mmHg [81]. However, the 2018 ADA continued the cutoff of 140/90 mmHg [82].

1.3.3 BP Components

Several BP components, such as systolic (SBP) and diastolic (DBP) pressure, mean arterial pressure (MAP), pulse pressure (PP) and mid-blood pressure (MidBP), have shown predictive values of adverse vascular outcomes, (**Table 5**) [83–85]. The SBP and DBP represent the maximum and minimum pressures of large arteries within one cardiac cycle. Both SBP and DBP remain the primary indices for hypertension diagnosis, classification, and intervention evaluation [86–88]. In the general population, DBP rises until 50 - 60 years of age and then becomes constant or even declines, whereas SBP increases with age [73]. The results of the Framingham Heart Study suggested that DBP was the strongest risk factor for adverse cardiovascular outcomes in individuals less than 50 years old, and its prognostic value diminished with age [89,90]. In comparison, SBP maintains its predictive value of cardiovascular disease, which is superior in elderly individuals over 60 years old [90–92]. Guidelines have recommended SBP as the primary index of antihypertensive therapy evaluation [66,88,93].

BP has both steady and pulsatile components [94,95]. The steady component is estimated by MAP, reflecting an average pressure load over a cardiac cycle [94]. PP is used to estimate the pulsatile component, which represents BP fluctuation and is mainly affected by the stiffness of large arteries [94]. MAP is a predictor of adverse cardiovascular outcomes [83,84], but its discriminatory power diminishes with age because of the respective changes in SBP and DBP [89]. In contrast, the changes in SBP and DBP with age result in a significant increase in PP.

MidBP is calculated as the average of SBP and DBP. MidBP has been shown to be a strong predictor of cardiovascular outcomes, and it might even be superior to other single BP measures (i.e., SBP , DBP, and PP) [96]. The possible explanation is that this index incorporates information

on both SBP and DBP. It is also possible that the average may reflect the halving of the random measuring errors that affect SBP or DBP [96].

1.3.4 Epidemiology of Hypertension

Hypertension is the most frequent cause of death and disability in the world, even exceeding tobacco use and obesity [67]. Hypertension results in more than 9 million deaths worldwide every year, which is as many as all infectious diseases combined [97]. The global burden of hypertension increased substantially from 1995 to 2005: an increase of 11% in prevalence rates; an increase of 7% in related death; and an increase of 43% in associated loss of disability-adjusted life-years (DALY) [98].

In the United States, one in three to four adults has hypertension [99], according to a threshold ≥ 140/90 mm Hg or the use of antihypertensive medications. The overall prevalence of hypertension is 29.0% (approximately 90.0 million people are affected), which increases progressively with age from 7.3% at 18 - 39 years of age to 32.2% at 40 - 59 years of age, and 64.9% in those 60 years of age and older. Compared with women, men have a higher prevalence among those aged 18 - 39 years old (8.4% men vs. 6.1% women) and those aged 40 - 59 years old (34.6% vs. 29.9%), but not in those aged 60 and older (63.1% men vs. 66.5% women) [99]. Among different races and ethnicities, black adults of both genders have the highest prevalence of hypertension (41.2%) compared with whites (28.0%), Asians (24.9%) and Hispanics (25.9%).

1.3.5 High BP as a Cardiovascular Risk Factor

Hypertension remains one of the most important risk factors of cardiovascular disease, which is more common than diabetes, smoking, and dyslipidemia [66,67]. It has been estimated that, at the global level, hypertension accounts for about one-half of cardiovascular diseases [100]. The Multiple Risk Factor Intervention Trial (MRFIT) [101] was one of the first studies with a large sample size to demonstrate a dose-dependent association of high BP with cardiovascular risk. The Coronary Artery Risk Development in Young Adults (CARDIA) study reported that elevated BP was significantly associated with the heavier burden of coronary artery calcification [102,103] in young and middle-aged adults. Evidence from randomized control trials (RCTs) demonstrated that antihypertensive therapy reduced the risk of cardiovascular events. A recent meta-analysis of 123 randomized control trails among over 600,000 hypertensive individuals demonstrated that every decrease of 10 mmHg in SBP was associated with a 20% reduction in cardiovascular risk [104]. A subsequent network meta-analysis of 42 antihypertensive therapy randomized control trails confirmed the above findings, showing that a mean SBP of 120 - 124 mmHg reduced cardiovascular risk by 29% compared with a mean SBP of 130 - 134 mmHg; by 42% compared with a mean SBP of 140 - 144 mmHg; by 54% compared with a mean SBP of 150 - 154 mmHg; and by 64% as compared to a mean SBP higher than 160 mmHg [105]. The cumulative evidence derived from the available studies supported a causal link between raised BP and cardiovascular risk.

1.4 BP Measurement Methodologies

Two basic techniques are available for BP measurement in clinical settings: the auscultatory and oscillometric methods. The auscultatory method is applied using mercury sphygmomanometers, aneroid, or hybrid devices. The advantages and disadvantages of these methods are listed in **Table 6**.

The Korotkoff method of auscultatory measurement has been used since it was developed over a century ago [87]. A cuff is wrapped around the upper arm, which is then inflated and deflated. The cuff is inflated until the pressure exceeds the SBP to ensure that the brachial artery is occluded. With the gradual deflation of the cuff, the pulsatile blood flow reappears in the brachial artery, producing sounds that can be heard through a stethoscope [106]. The Korotkoff sounds, which are thought to be generated by the reestablished pulsatile flow, have been classified in five phases [106]. SBP is determined by the onset of the first phase. There was controversy in the past regarding the use of the fourth or fifth phase for recording DBP. The detection of the fourth phase tends to be more difficult and subjective than that of the fifth phase. Hence, the general consensus now is to use the fifth phase [87]. Notably, the fifth phase may be heard nearly to a level of 0 mmHg in some children, and the fourth phase should be recorded under such a circumstance [106].

The mercury auscultatory technique using the Korotkoff sounds, has been the gold standard [87]. Nevertheless, it is important to note that observer error is the major limitation of this technique. The terminal digit preference is the most common source of this error [87,107–109]. Indeed, digital bias frequently occurs when the observer recognizes a particular BP threshold value [87].

The Hawksley random-zero sphygmomanometer (RZS), which is a modification of the standard mercury manometer, was designed to reduce digital bias by eliminating the terminal digit preference [110]. However, the use of RZS devices was discontinued because of the inherent technical

issue of under-recording the BP values compared with the standard mercury sphygmomanometer [111,112]. Nevertheless, in the past, the RZS was widely implemented in epidemiological studies. Recent studies have compared the RZS and the automated oscillometric device to obtain corrections between these two methods [113].

The use of automated oscillometric devices has increased mainly because of the advantages of eliminating observer error, decreasing the white-coat effect, and increasing measurement frequency. It should be noted that in difference brands of oscillometric devices different algorithms are applied in BP readings, which are kept confidential by the manufacturers. Thus, the BP measuring values may not be comparable across different brands of devices.

BP levels fluctuate physiologically over time, which is due to the regulation mechanisms of the cardiovascular system [114]. In addition to these physiological fluctuations, the levels of BP are influenced by various internal and external factors, such as environmental conditions (e.g., noises), emotions, and physical activities. Hence, a BP measured in a single visit may not be sufficiently representative of an individual' s usual BP status [115]. More than 40 years ago, the Hypertension Detection and Follow-up Program (HDFP) started using a two-screen protocol for the detection of hypertension [116]. In their study, participants with elevated BP at the first screening required a second screening for repeated BP measurements to confirm the diagnosis of hypertension. Since then, repeated readings for elevated BP have been widely recommended in the guidelines for hypertension diagnosis [87].

1.5 Hypertension in T1D

Hypertension, which is a strong predictor of microvascular and macrovascular diseases, affects over 40% of T1D patients as early 30 years of age [117]. Although high BP is modifiable, it remains a poorly treated risk factor of adverse health outcomes in the contemporary T1D population [118].

1.5.1 Epidemiology of Hypertension in T1D

High BP is a common finding in T1D, and is involved in the pathogenesis of diabetes complications [119]. However, the epidemiological data on hypertension in T1D are limited and mainly from Europe [120–127] and a few are from the United States [117,128,129]. Over 20% of T1D patients less than 18 years old were affected by raised BP, and this proportion increases with age and diabetes duration [124,127]. A striking finding from a recent systematic review demonstrated that hypertension occurred in almost one in two young adults with T1D between 18 and 30 years old [130]. Hypertension in T1D individuals is generally thought to have an approximately 1.5- to 2-fold greater prevalence than that seen in the general population [131]. In individuals with T1D, BP not only rises at an early age but also develops a deleterious pattern in later life, showing a greater elevation in SBP and an earlier fall in DBP [124].

In T1D, high BP was generally thought to be a manifestation of underlying nephropathy. Hence, the presence of hypertension was thus thought to be a consequence of nephropathy of T1D and manifested only in the subgroup of patients who had already developed diabetic nephropathy [121,132]. Nørgaard et al. showed that hypertension prevalence was similar between normoalbuminuric T1D patients and non-diabetic individuals [133], indicating that BP would not be

elevated in T1D before the development of nephropathy. However, recent data demonstrated that T1D individuals, even in the absence of microalbuminuria, exhibited a remarkably increased BP than age-matched non-diabetic controls did [124]. This findings suggests that hypertension can occur in T1D patients even in the absence of renal impairment [124].

1.5.2 Pathophysiology of Hypertension in T1D

Type 1 and type 2 diabetes have distinct biological mechanisms and thus the pathophysiological pathways of hypertension at least partially differ between the two types. Different from type 2 diabetes, BP usually rises after the occurrence of T1D, thus, hyperglycemia (HbA1c and diabetes duration) plays a particularly crucial role in the pathogenesis of hypertension, primarily via hyperglycemia-induced RAS overstimulation, as well as the development of advanced glycated end products [2,134]. The Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study has demonstrated that intensive insulin therapy decreased the risk of hypertension in T1D [128], suggesting the essential effect of glycemic load on hypertension pathogenesis in T1D. Another common characteristic of hypertension in T1D is that hypertension coexists much more frequently with microalbuminuria, suggesting that the increased renal reabsorption of sodium and the impaired renal excretion of sodium is a likely contributor to BP elevation [135]. Moreover, long-term insulin therapy often leads to weight gain [136,137], which is another major contributor to raised BP. Given the diabetes onset age is usually much younger in type 1 population, the basis of the pathophysiology differs between the two types of diabetes. Therefore, for evidence of hypertension management in the middle-aged and older type 2 population is not likely to be directly extrapolated to individuals with T1D.

1.5.3 Renal Complications

Over the past 30 years, hypertension has been extensively studied in conjunction with the renal complications of diabetes [131,138,139]. High BP may be both a cause and a consequence of diabetic nephropathy [131]. Traditionally, the development of diabetic nephropathy was based on the albuminuria-centric model; raised albuminuria has been the gold standard of both the screening and diagnosis of diabetic nephropathy. Elevated BP in T1D has been frequently observed to follow the initiation of microalbuminuria [140]. The EDC study also found that high BP was a predictor of microalbuminuria in T1D [141], which indicated the major role of hypertension in the albuminuria-centric model. However, intriguing findings from the most recent studies suggested that a significant renal decline may start in the normoalbuminuric phase. The presence of albuminuria does not always reflect the declining glomerular filtration rate (GFR) [142,143]. Thus, Krolewski et al. [144] proposed a new paradigm of T1D nephropathy in which an early GRF decline is the primary disease progression that leads to impaired renal function. It should be noted that BP remains an independent predictor of the new paradigm T1D nephropathy. A 10 mmHg increase in SBP may lead to a 30% increased risk of renal function decline [143,145].

Because of the close interaction between hypertension and diabetic kidney disease, BP control is of paramount importance in preventing and slowing the decline of renal function in T1D. The antagonism of RAS has been the mainstay therapy used for BP control and albuminuria reduction. Nevertheless, several specific issues remain to be resolved in T1D, such as the optimal BP target to minimize the risk of renal function decline, whether the reduction of albuminuria per se leads to the prevention and/or slower progression of renal decline, and whether the use of RAS inhibiting agents prevent the development of renal decline in ways other than lowering BP and reducing albuminuria.

1.5.4 Cardiovascular Complications

Elevated BP in T1D can begin in childhood, and it causes excess cardiovascular risk at an early age. Schwab et al. [146] reported that an elevated SBP, but not lipid profile, was significantly correlated with carotid intima-media thickness in T1D children, supporting the greater importance of BP than dyslipidemia in early arteriosclerosis.

Although BP is modifiable, it remains a poorly treated risk factor in the contemporary T1D population [118]. A recent series of studies have developed multivariable prediction models of atherosclerotic cardiovascular complications in T1D, which may help to understand the effects of BP on cardiovascular outcomes [147–150]. These four studies, which were published between 2010 and 2016, are summarized in **Table 7**. These studies proposed fully developed and valid models of cardiovascular risk prediction in contemporary T1D populations [151]. SBP was a significant predictor in all these predictive models except the male participants in the EDC cohort. According to the authors, the absence of BP in the subgroup of EDC males might be explained by a close link between high BP and albuminuria, such that the BP effect was subsumed [151]. Additionally, in these models, BPs predicted cardiovascular outcomes in both short- and long-term periods (from 5 years to 27 years), which implied a preservation effect of BP, thus showing the importance of continuing research on BP control.

In the past two decades, RCTs have been conducted examine whether vigorous BP control decreases cardiovascular risk and to determine the ideal BP goals in diabetes. The Hypertension Optimal Treatment (HOT) randomized trial demonstrated that strict BP control with a DBP target <80 mmHg compared with <90 mmHg was especially beneficial in the subgroup with diabetes, showing an over 50%-reduced risk of major cardiovascular events [152]. In the Systolic Hypertension in Europe (Syst-Eur) trial, aggressive BP control was associated with a 63% decrease in the risk

of overall cardiovascular outcomes in diabetic individuals [153]. However, the Action of Control Cardiovascular Risk in Diabetes (ACCORD) trial, which was recently conducted in older T2D individuals (mean age = 66 years), failed to show cardiovascular benefits except for incident stroke when the intensive BP control target was <120/80 mmHg versus <140/90 mmHg [154]. Intriguingly, a secondary analysis of the ACCORD [155] and a meta-analysis [156] both suggested that a SBP <130 mmHg was more favorable in the diabetes population than the more conservative goal of <140 mmHg [86].

It should be noted that the existing trials were conducted exclusively in the type 2 population. Therefore, the findings are not useful for individuals with T1D. However, a few observational studies in the T1D population showed a lower risk of cardiovascular events with lower BP levels (**Table 8)** [157–159]**.** Orchard et al. examined the ideal BP threshold and T1D compilation outcomes using data on the Pittsburgh EDC 10-year follow-up cohort [158]. A baseline BP ≥ 130/90 mmHg increased, on average, the risk of CAD more than 5 times compared with BP ≤ 110/80 mmHg. Surprisingly, SBP from120 - 129 mmHg also exhibited a 2.5-times increased risk versus the reference level <110 mmHg. A DBP of 80 - 89 mmHg exhibited a more than two-fold risk of CAD compared to the reference level of < 80 mmHg. Similarly, a dose-gradient relationship of BP beginning from 120/70 mmHg with adverse cardiovascular outcomes was observed in both a World Health Organization (WHO) multinational study [157] and a study by Sibal et al. [159]. These findings strongly support that more intensive control of BP may offer additional cardiovascular benefits in T1D. However, several limitations should be noted with respect to these studies [157–159]. Only baseline BPs were examined in all of these three studies although longitudinal changes in BPs have been shown to be significant predictors of cardiovascular complications in T1D beyond baseline pressure levels [150]. A maximum follow-up of only 12 years was undertaken.

In addition, the models only allowed for a limited number of covariates (e.g., age and diabetes duration).

Another important issue is whether a certain class of antihypertensive agents confers superior cardiovascular benefits on other classes in this high-risk population. In addition to underlying renal benefits, the antagonism of RAS has been thought to be particularly important in diabetes patients because it decreased the risk of myocardial infarction and death in type 2 diabetes [160,161]. Recent overviews of systematic reviews and meta-analyses with regard to the choice of antihypertensive agents in diabetes concluded that no particular antihypertensive agent class exhibited more cardioprotective benefits than the others did [162,163]. Thus, evidence in T1D is still lacking. As mentioned previously, hyperglycemia in T1D was found to play a substantial role in the pathogenesis of hypertension and premature arterial stiffening via the overstimulation of the RAS, shedding light on the hypothesis that the inhibition of RAS may confer additional cardiovascular benefits beyond lowering BP in T1D. Future studies are recommended to examine the effects of RAS inhibitors on cardiovascular endpoints in T1D.

1.5.5 Cognitive Impairment

The increased prevalence of cognitive dysfunction has been consistently observed in individuals with T1D compared to that seen in the general population [164–167]. The EDC study reported that the prevalence of clinically relevant cognitive impairment was 28% in middle-aged T1D individuals (mean age = 49 years) [165], which was comparable with the general population aged 85 years or older [168]. The pathogenesis of impaired cognition in T1D remains poorly understood. Evidence suggested a linkage between chronic hyperglycemia and cognitive function decline [165,169,170]. Microvascular complications in T1D, such as diabetic retinopathy [171–173] and distal symmetric

polyneuropathy [174,175], have also been shown to be associated with cognitive impairment, thus supporting the assumption of a microvascular basis of cognitive complications in diabetes [176].

Hypertension has been shown to be an independent predictor of cognitive impairment [177–180]. The Atherosclerosis Risk in Communities (ARIC) study suggested that hypertension was associated with faster cognitive decline, and antihypertensive intervention slowed the decline of cognition during a 20-year follow-up in the general population [181]. An association between hypertension and cognitive dysfunction in T1D was also observed in both cross-sectional [171,174] and prospective studies [170,173]. The DCCT/EDIC cohort study and small studies showed that hypertension was a strong risk factor of impaired cognitive function [170,171,174]. Furthermore, Ryan et al. observed an inversely linear association between SBP and cognitive efficiency score in T1D [173]. In contrast, a recent study by Nunley et al. failed to show the association between high BP and clinically relevant cognitive impairment in T1D [165]. The authors explained that BP might be evaluated at the same time as the implementation of cognition tests in their study, which failed to establish a temporal association between these two conditions [165].

In summary, studies focusing on impaired cognitive performance are urgently needed in this high-risk population. Hypertension is a modifiable risk factor. Future comprehensive studies are needed to assess the ways in which BP trajectories and antihypertensive interventions individually and/or synergistically influence cognitive performance in T1D.

1.5.6 Other Complications

Hypertension is an independent risk factor of peripheral arterial disease, and it is associated with two to three times the excess risk in diabetes [182,183]. Findings from the United Kingdom Prospective Diabetes Study (UKPDS) suggested that every 10 mmHg increase in SBP led to a 25% increased

risk of peripheral arterial disease [184]. Data from the Heart Outcomes Prevention Evaluation (HOPE) trial suggested that angiotensin converting enzyme (ACE) inhibitors were beneficial for peripheral arterial disease prevention beyond lowering BP [185] in T2D. The results of the EDC cohort showed that hypertension in T1D was independently associated with peripheral arterial disease [186]. Unfortunately, there is scant evidence regarding the effects of BP control and antihypertensive intervention on peripheral arterial disease outcomes in T1D.

Diabetic retinopathy is an important cause of vision impairment in the young and middle-aged population [187,188]. Unfortunately, almost all people with T1D are affected by diabetic retinopathy in their lifetime [189]. The presence of hypertension might be a risk factor of incident diabetic retinopathy. The results of Wisconsin Epidemiology of Diabetic Retinopathy cohort study suggested that hypertension in T1D was associated with the more than 70% increased risk of incident proliferative retinopathy [190]. However, the Wisconsin cohort study and others failed to show the association of high BP with the disease progression of diabetic retinopathy [190]. A recent Cochrane meta-analysis of clinical trials [191], including five trials with 4,036 T1D patients (Chase [192]; DIRECT Prevent 1 [193]; DIRECT Protect 1 [193]; EUCLID [194]; and RASS [195]), suggested that the antihypertensive therapy was associated with an 18% reduced risk of incident diabetic retinopathy but had no effect on the retinopathy progression during 1.5 to 3 years of the follow-up. Interestingly, the EDC study found an association of high BP with the progression of retinopathy in a subgroup with T1D nephropathy [196], which suggests that high BP may affect the progression of retinopathy particularly in patients with advanced microvascular damage.

Hypertension has been identified as a risk factor of diabetic neuropathy in T1D [197] . The EDC study was the first to report a cross-sectional association between hypertension and diabetic neuropathy [198]. Subsequently, hypertension was suggested to be the strongest predictor of distal

symmetric polyneuropathy in the follow-up study [199]. Later, the EURODIAB cohort confirmed EDC's findings that hypertension was strongly associated with diabetic neuropathy after adjusting for age and diabetes duration in T1D [200]. However, evidence is lacking regarding the effects of the antihypertensive intervention on diabetic neuropathy in T1D.

1.6 Antihypertensive Clinical Trials in T1D

In the past 30 years, many clinical trials have been conducted to examine the effects of antihypertensive agents on lowering BP and/or target-organ protection in the diabetes population. It is not surprising that fewer prospective clinical trials have been conducted on T1D than on T2D. A review of the relevant RCTs conducted on T1D is provided in **Table 9** [201–208]. It should be noted that trials that did not include hypertensive participants, and trials with a sample size of less 50 participants were excluded. Among the eight trials that were identified all (i) were conducted more than a decade ago, (ii) recruited T1D individuals in the presence of renal impairment (either microalbuminuria or overt nephropathy), and (iii) focused on only renal outcomes. Of the eight studies, six [201,205–209] were conducted to examine the renal protective abilities of ACE inhibitors versus a placebo, and the remaining two were conducted to examine intensive versus regular BP control [202,204]. The remarkable reduction of urinary albuminuria with the ACE inhibitor therapy compared to the placebo was found in all six studies, and changes in urinary albuminuria were observed to be parallel to the changes in BP [201,205–209]. Similarly, in both studies, in the intervention of intensive versus standard BP controls, the group with more rigid BP control showed significant reductions in urinary albuminuria [202,204] compared with the group with regular BP control. Despite favorable changes in both urinary albuminuria and BP during the study periods, the renal function

indicators, including GFR and creatinine clearance, did not exhibit parallel changes in most of these trials. Indeed, only one study identified a significantly increased creatinine clearance with the captopril intervention versus placebo in T1D individuals with overt nephropathy [201]. Another trial by Sawicki et al. suggested that a BP control of less than 140/90 mmHg was associated with the decreased risk of a composite outcome of all-cause mortality and the need for renal replacement [202]. However, they failed to show an association with the single endpoint of the "need for renal replacement therapy."

In summary, these trials demonstrated that the administration of the ACE inhibitor in T1D with raised albuminuria led to both albuminuria reduction and lowered BP. The results of these major trials have led to the promotion of RAS inhibitors as the first-line choice for treating hypertension in patients with diabetes. In contrast, there has been no strong evidence showing a favorable change in renal function with the intervention of RAS inhibitors in this patient group. Because of the nature of clinical trials, the intervention and follow-up periods were short compared with patient conditions in the real world. Thus, the long-term effect of RAS inhibitors remains elusive in this group of patients. Additionally, a BP goal of 140/90 mmHg in the early trails might not be sufficient to maximize benefits based on the evidence from previous observational studies [210,211].

1.7 Gaps in Knowledge and Significance

Hypertension affects over 40% of the T1D population as early as their 30s [117]. Effective BP control may reduce as much as 75% of the risk of CAD in T1D [158] and subsequently reduce approximately over a half billion U.S. dollars of health expenditure per year [212,213]. However, the current

knowledge about optimizing BP management in this high-risk population remains insufficient. Several questions, such as when intervention should start, what BP level should be targeted, and which agents to choose, are still unanswered.

Practical guidelines have frequently been changed regarding the BP control goals. The current ADA recommendations have raised the BP target to 140/90 mmHg for the diabetes population regardless of the type [214]. The evidence was mostly derived from trials that focused on the middle-aged and older T2D population, such as the ACCORD trial. In the ACCORD trial, the aggressive SBP goal of less than 120 mmHg versus a goal of less than 140 mmHg did not improve cardiovascular outcomes or mortality [154]. However, the Systolic Blood Pressure Intervention Trial (SPRINT) demonstrated that a SBP goal of less than 120 mmHg versus less than 140 mmHg significantly reduced the risk of major cardiovascular events and all-cause mortality in a group of participants with high cardiovascular risk but without diabetes [215]. The SPRINT findings reinforced the importance of vigorous BP control in high-risk groups, which has implications for the diabetes population because it carries a substantially greater cardiovascular risk than the general population does.

The findings of an early clinical trial of T1D patients suggested that a strict BP goal with a MAP target of 92 mmHg compared with 107 mmHg might offer renal benefits in reducing urinary albumin [204]. Recently, a few prospective longitudinal studies of T1D cohorts suggested that lower BP levels (<110–120/70–80 mmHg) were associated with a lower risk of adverse cardiovascular and renal outcomes [157–159,210,211]. Despite the observational nature of these studies, the results were encouraging because they considered a BP target lower than the currently recommended 140/90 mmHg, which may benefit the T1D population by further decreasing morbidity and mortality.

Not only does the pathogenesis of hypertension differ in individuals with T1D and T2D but also the onset of T1D occurs at a much earlier age, suggesting that findings in the T2D population may not be directly extrapolated to the T1D population. Thus, there is a great need to identify BP goals in this patient population.

In addition to BP regulation, RAS was found to be involved in the pathophysiological pathways of inflammation, oxidative stress, fibrosis remodeling, and end-organ damage [216]. This finding suggests that RAS inhibitors may offer additional benefits beyond lowering BP. However, the cumulative evidence from recent head-to-head comparison clinical trials and associated meta-analyses demonstrated that RAS inhibitors were not better than other antihypertensive classes (i.e., calcium-channel blockers, β receptor blockers, and thiazides) in diminishing the cardiovascular risk [217–219]. The most recent hypertension guidelines [86,220] recommend any class of antihypertensive medications in diabetes patients; RAS inhibitors are preferred only in those with raised albuminuria.

It should be noted that the existing trial results were derived exclusively from samples of middle-aged or older T2D patients, and evidence of antihypertensive recommendations is still largely lacking in T1D patients. Indeed, hyperglycemia-induced RAS overstimulation was found to play a crucial role in the pathogenesis of hypertension particularly in T1D [2,134], suggesting that the pharmacological effects of RAS inhibitors might be potentially exaggerated in T1D.

The results of a few observational studies suggested that RAS inhibitors might have additional cardioprotective benefits beyond lowering BP in T1D individuals. The EDC study found that ACE inhibitors, but not calcium-channel blockers, had a significant inverse association with mortality [221]. Additionally, the Coronary Artery Calcification in Type 1 Diabetes (CACTI) study showed that RAS inhibition treatment was associated with a lower risk of coronary artery

calcification progression in young adults with T1D [222]. These findings are encouraging because they imply the cardiovascular benefits of RAS inhibitors in addition to lowered BP in T1D individuals. Future studies are needed to evaluate the effects of RAS inhibitors on hard cardiovascular endpoints as well as their effectiveness compared with other antihypertensive classes.

Major gaps persist in the knowledge regarding effective BP control in T1D. Although the causes of poor complication outcomes are multifactorial, the focus on BP is important because the association is plausible, modifiable, and has important implications for long-term health outcomes. Filling the critical gaps in our understanding of the effects of BP and hypertension on adverse complications outcomes in T1D could have positive effects on clinical practice.

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1.8 Tables

Table 1 Diabetes Diagnostic Cut-offs

Diagnostic criteria [10]	Fasting plasma glucose (mg/dL)	2-hour plasma glucose in the 75g oral glucose tolerance test (mg/dL)	Random plasma glucose (mg/dL)	HbA1c (%)
Normal	<100	<140		<5.7
Prediabetes	100-125 (IFG)			5.7-6.4
		140-199 (IGT)		
Diabetes	≥ 126	≥ 200	≥ 200 [a]	≥6.5

[a] In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis
(Adapted from Chamberlain et al [10])

Table 2 Staging of T1D

Stage [14,18]	**Stage 1**	**Stage2**	**Stage3**
Feature	• Autoimmunity Normoglycemia • Presymtomatic	• Autoimmunity • Dysglycemia • Presymtomatic	• New-onset hyperglycemia • Symtomatic
Diagnostic criteria	• Multiple autoantibodies • No IGT or IFG	• Multiple autoantibodies • Dysglycemia: IFG and/or IGT • FPG 100-125 mg/dL • 2-g PG 140-199mg/dL • HbA1c 5.7-6.4% or ≥10% increase in HbA1c	• Clinical symptoms • Diabetes by standard criteria

PG: plasma glucose, IFG: impaired fasting glucose, IGT: impaired glucose tolerance
(Adapted from Skyler et al[14])

Table 3 Target Organ Damage of Hypertension

Target organ damage of hypertension [66]
• Heart disease
✓ Left ventricular hypertrophy
✓ Angina or prior myocardial infarction
✓ Prior coronary revascularization
✓ Heart failure
• Stroke or transient ischemic attack
• Chronic kidney disease
• Peripheral arterial disease
• Retinopathy

(Adapted from Chobanian et al [66])

Table 4 Classification of Hypertension (AHA 2017)

BP Classification [81]	**SBP mmHg**	**DBP mmHg**
Normal	<120	<80
Elevated	120-139	80-89
Stage 1 hypertension	130-139	80-89
Stage 2 hypertension	≥140	≥90

AHA: American Heart Association; BP indicates blood pressure; DBP, diastolic blood pressure; SBP, systolic blood pressure
(Adapted from Whelton et al [81])

Table 5 Estimation of Different BP Indices

Blood pressure index	**Definition/Estimation**
Systolic blood pressure (SBP)	Maximum pressure in large arteries of the systemic circulation during one cardiac cycle.
Diastolic blood pressure (DBP)	Minimum pressure in large arteries of the systemic circulation during one cardiac cycle.
Pulse pressure (PP)	PP=SBP-DBP
Mean arterial pressure (MAP)	MAP=DBP + 1/3 *(SBP+DBP)
Mid-blood pressure (MidBP)	MidBP=1/2*(SBP+ DBP)

Table 6 Pros and Cons of BP Measurement Methodologies

Techniques [87,223]	**Pros**	**Cons**
Auscultatory Mercury devices	• Gold standard with a high stability over time • Simple design of device with negligible difference in the accuracy between brands • Widely used in clinical studies	• Observer error • Environmental issue for the use of mercury
Auscultatory Aneroid devices	Avoid the use of mercury	• Inaccuracy issues of the devices • Require frequent calibration • Observer error
Auscultatory Hybrid devices	• A combination of the main benefits of electronic and mercury technique, including avoiding the use of mercury and minimizing terminal digit preference	• Inaccuracy issues of the devices • Require individual validation of devices
Oscillometric	• Less susceptible to external noise and placement location of the cuff • Avoiding Observer error • Decrease impact of white coat • increasing the measuring frequency	• Difference in BP measurements between devices from different manufacturers • Potential error inherent in the oscillometric technique • Epidemiological studies have mostly used auscultatory methods for the BP measurement

Table 7 BP and Cardiovascular Risk Prediction in T1D

Study	Follow-up time	Outcomes	Findings
U.S. Pittsburgh EDC cohort [147] **2010**	14 years	CAD death or non-fatal MI	Men: No Women: Baseline SBP
Swedish national diabetes registry [148] **2011**	5 years	CVD death, or non-fatal MI, or stroke, or unstable angina, or revascularization	Baseline SBP
Denmark Steno Type 1 Risk Engine [149] **2016**	5 years	Ischemic heart disease or stroke, heart failure or peripheral vascular disease	Baseline SBP
U.S. DCCT/EDIC cohort [150] **2016**	27 years	CHD death, non-fatal MI or stroke	Baseline and time-updated mean of SBP

DCCT/EDIC: Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study, EDC: Pittsburgh Epidemiology of Diabetes Complications Study, SBP: systolic blood pressure
(Adapted from the Orchard et al. [151])

Table 8 Observational Studies of BP Threshods and Cardiovascular Outcomes in T1D

Source and publication year	Participants features and sample size	Age, years Mean (SD)	Follow-up	Statistical analysis and covariates	CVD Outcomes	Relative risk of BP
U.S. Pittsburgh EDC cohort **Orchard et al** [158] **2001**	T1D adults 18 years or older N=598	NA	up to 10 years	Cox model Covariate: age or HbA1	CAD	Baseline SBP (mmHg): <110: ref 110-119: HR=1.8 (p<.01) 120-129: HR=2.5 (p<.05) ≥130: HR=5.6 (p<.001) Baseline DBP (mmHg): <80: ref 80-84: HR=1.4 85-89: HR=2.0 ≥90: HR=4.2 (p<.01)
WHO multinational study **Fuller et al** [157] **2001**	T1D patients N=1260	Male: 44.4 (6.1) Female: 44.5 (6.2)	up to 12 years	Cox model Covariate: age	fatal and non-fatal MI	Baseline SBP (mmHg) for Male: <120: ref 120-139: HR=1.4 140-159: HR=1.3 160-179: HR=3.6 ≥180: HR=4.1 HR(95%CI) per SD: 1.4 (1.1-1.8) Bassline SBP (mmHg) for Female: <120: ref 120-139: HR=1.5 140-159: HR=2.0 160-179: HR=4.4 ≥180: HR=1.9 HR(95%CI) per SD: 1.4 (1.1-1.9)
					fatal and non-fatal stroke	Baseline SBP (mmHg) for Male: <120: ref 120-139: HR=1.1 140-159: HR=1.6 160-179: HR=2.2

Table 8 Continued

						≥180: HR=4.5 HR(95%CI) per SD: 1.5 (1.1-2.0) Baseline SBP (mmHg) for Female: <120: ref 120-139: HR=0.8 140-159: HR=3.1 160-179: HR=2.1 ≥180: HR=8.1 HR(95%CI) per SD: 1.8 (1.3-2.5)
				Cox model Covariate: age, diabetes duration, total cholesterol, smoking, proteinuria, retinopathy and ECG abnormalities	CVD mortality	Baseline SBP (mmHg) for Male: HR(95%CI) per SD: 1.4 (1.1-1.8) Baseline SBP (mmHg) for Female: HR(95%CI) per SD: 1.5 (1.1-2.0)
U.K. **Sibal et al** [159] **2006**	T1D patients aged of 17-76 years N=363	39 (13)	up to 9 years	Cox model Covariate: age	Composite endpoint of macrovascular diseases, including ischemia heart diseases, peripheral artery diseases and cerebrovascular diseases	Baseline SBP (mmHg): <=118: ref 119-130: HR=2.99 (p=.087) 131-142: HR=3.79 (p=.042) ≥143: HR=5.21 (p=.010) Baseline DBP (mmHg): ≤70: ref 71-78: HR= 0.86 79-84: HR= 0.90 ≥85: HR=1.81 (p=0.07)

CAD: coronary artery disease, CI: confidence interval CVD: cardiovascular disease, DBP: diastolic blood pressure, ECG: electrocardiogram, HR: hazards ratio, SBP: systolic blood pressure, SD: standard deviation, WHO: World Health Organization

Table 9 Randomized Control Trials of BP Contorl in T1D

Source and publication year	Features of T1D subjects	N	Intervention (I)	Control (C)	Age (mean (SD))	Baseline blood pressure (mean, mmHg)	Follow-up	Primary outcomes	Other outcomes	Major findings
U.S. Lewis et al [201] 1993	overt nephropathy	409	Captopril (n=207)	Placebo (n=202)	35 (7) (I) 34 (8) (C)	137/85 (I) 140/86 (C)	4 years	Creatinine clearance	Combined endpoint of death, dialysis and kidney transplant	Captopril group had slower decline in creatinine clearance
Germany Sawicki et al [202] 1995	Hypertension and overt nephropathy	91	Intensified hypertension control with goal of <140/90 mmHg (n=45)	Routine hypertension therapy (n=46)	35.8 (8.6) (I) 37.2 (10.5) (C)	154/92 (I) 143/87 (C)	5 years	Combined endpoint of all-cause mortality and the need for renal replacement therapy	Single endpoint of all-cause mortality or the need for renal replacement therapy	Intervention group had significantly lower risk of combined endpoint of all-cause mortality and the need for renal replacement therapy, but not the need for renal replacement therapy alone
Europe, U.S., Canada and Asia Microalbuminuria Captopril	Micro-albuminuria	225	Captopril (n=116)	Placebo (n=119)	31.8 (I) 32.5 (C)	122/77 (I) 122/77 (C)	2 years	AER	1. Creatinine clearance 2. Incidence of hypertension	Captopril reduced risk of AER progression, but not the decline of creatinine clearance

Table 9 Continued

Study Group [208] 1996										
Europe EUCLID Study Group [209] 1997	norm- or micro-albuminuria	530	Lisinopril (n=265)	Placebo (n=265)	31.8 (I) 32.5 (C) (median)	122/79 (I) 121/80 (C) (median)	2 years	AER		Lisinopril slowed the progression of AER
U.S. Lewis et al [204] 1999	Overt nephropathy	128	Intensive BP control with goal of MAP ≤92 mmHg (n=62)	Standard BP control with goal of MAP 100-107 mmHg (n=66)	37 (7) (I) 37 (8) (C)	95 (I) 97 (C) (MAP)	2 years	GFR measured by iothalamate clearance	1. AER 2. Combined endpoint of death or ESRD	BP control group had lower urinary protein, but similar GFR changes
U.K. ATLANTIS Study Group [205] 2000	Micro-albuminuria	134	Ramipril (n=88)	Placebo (n=46)	40(12) (I) 40(12) (C)	133/77 (I) 130 /76 (C)	2 year	AER	1. GFR 2. BP	Ramipril reduced risk of AER progression, but there was no significant difference of GFR between Ramipril and placebo group
Denmark Poulsen et al 2001[206]	Micro-albuminuria	58	Lisinopril (n=33)	Placebo (n=25)	34.9(1.8) (I) 38.5(10.4) (C)	124/83 (I) 129 /79 (C)	2 years	AER	1. BP 2. Renal filtration fraction	Lisinopril slowed the progression of AER, and the change of AER were positively correlated with FF only in lisinopril group

Table 9 Continued

Japan Katayama et al [207] 2002	Raised albuminuria	79	Imidapril(Im) (n=26) Captopril(Ca) (n=26)	Placebo (Pl) (n=27)	36.2 (6.7) (Im) 30.9 (8.5) (Ca) 33.4(7.9) (Pl)	129.3/79.8 (Im) 125.5/76.0 (Ca) 126.7/78.1 (Pl)	30 months	AER		Both imidapril and captopril were significantly associated with less increase in AER compared to placebo

AER: albumin excretion rate, BP: blood pressure, GFR: glomerular filtration rate, MAP: mean arterial pressure, SD: standard deviation

Inclusion criteria: (1) including hypertensive patients, (2) sample size >50

2.0 Paper I: Relative Importance of Different BP Components in Type I Diabetes

2.1 Introduction

High BP is a major modifiable risk factor of cardiovascular disease [96,224] that displays a series of distinct changes with increasing age [89]. SBP progressively increases with age [89], whereas DBP generally declines after 50 or 60 years of age . The prognostic importance of SBP as a cardiovascular disease risk factor increases with age [90], while the predictive value of DBP declines or reverses with age [225]. The levels of MAP, along with its predictive values, also decline with older age given this diverging pattern of SBP and DBP [89]. The age-related changes of SBP and DBP result in an increase in PP with age, which appears to constitute a surrogate marker of arterial stiffness and vascular aging [226]. Collectively, the prognostic significance of these different BP measures are altered by aging. However, their comparative roles in T1D remains unknown, which is particularly important given that "accelerated aging" has been suggested in this high risk population [227–229]. SBP has been recommended as the primary measure reflecting cardiovascular risk in current hypertension guidelines [81]. DBP and MAP may carry further value for risk prediction at younger ages. PP is an independent determinant of adverse cardiovascular outcomes especially in older people but appeared less informative than the other BP measures in the general population [96].The degree to which similar relationships exist in people with T1D is still unclear.

Since hyperglycemia and insulin resistance are associated with greater stiffening of arteries and premature vascular aging, PP may be more informative for risk prediction in the diabetes population [230,231]. However, very few studies have tested the relative importance of PP

compared with other BP measures in diabetes, and previous data were exclusively from the older aged type 2 diabetes population [91,232]. High BP can affect T1D individuals as early as in their childhood [146]. Compared to the non-diabetes population, individuals with T1D experience an elevated SBP at all ages and an earlier decline in DBP, resulting in an premature increase in PP [124]. However, the discriminatory abilities of different BP indices for cardiovascular risk have not been established in the T1D population. The objective of this study, therefore, is to assess and compare the relative predictive utilities of different BP variables for CAD in T1D.

2.2 Methods

2.2.1 Study Population

Participants were from the Pittsburgh EDC Study, which has previously been described in detail [233]. In brief, this is a prospective longitudinal cohort study of childhood-onset (<17 years of age) T1D, diagnosed between 1950 and 1980 at Children's Hospital of Pittsburgh. There were 658 eligible participants who were initially examined between 1986 and 1988. Subsequent clinical assessments, including resting BP measurements, took place biennially for 10 years, with further examinations at the 18- and 25-year follow-up visits. Importantly, the EDC cohort has been shown to be epidemiologically representative of the T1D population in Allegheny County, Pennsylvania [234]. There were 605 participants who were free from CAD at the study entry and these were selected for the present analysis.

2.2.2 Ascertainment of Cardiovascular Outcomes

Cardiovascular disease status was evaluated biennially from the baseline visit. CAD was defined as EDC physician-diagnosed angina; myocardial infarction confirmed by Q-waves on an electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records; angiographic stenosis ≥ 50%; revascularization; or ischemic electrocardiograph (ECG) changes (Minnesota codes 1.3, 4.1–4.3, 5.1–5.3, and 7.1).

2.2.3 Measurement of BP

BP was measured by a random-zero sphygmomanometer for the initial 10 years of the study and subsequently by an aneroid device. At each clinic visit, BP was measured three times by trained and certified research staff, after the participant had been peacefully sitting for five minutes in a quiet room, according to the Hypertension Detection and Follow-up Program protocol [235]. PP was defined as the difference between SBP and DBP, MAP was calculated as the sum of one third of the SBP and two thirds of the DBP, and MidBP was quantified as the average of the SBP and DBP.

2.2.4 Measurement of Covariates

Demographic and medical history information was obtained through biennial questionnaires beginning at study initiation. Participants self-reported all medication use via questionnaires. Antihypertensive medication use was identified using the Anatomical Therapeutic Chemical Classification System/Defined Daily Dose (ATC/DDD) index. An ever-smoker was defined as

someone who had smoked at least 100 cigarettes in a lifetime. BMI was calculated as weight in kilograms divided by the square of height in meters. HbA1 was obtained by ion-exchange chromatography (Isolab, Akron, OH, USA) for the first 18 months, and the subsequent 10 years by automated high-performance liquid chromatography (Diamat, BioRad, Hercules, CA, USA). Results from the two methods were highly correlated (r=0.95). HbA1c was subsequently obtained using the DCA 2000 analyzer (Bayar, Tanytown, NY, USA) for assessments beyond the first 10 years. The DCA and Diamat assays were also highly correlated (r=0.95). Before being used in the analysis, all glycosylated hemoglobin values were converted to DCCT-aligned HbA1c using regression equations derived from duplicate assays [236]. Total cholesterol was determined enzymatically [237]. High-density lipoprotein (HDL) cholesterol was obtained enzymatically with a precipitation technique (heparin and manganese chloride) using a modified version of the Lipid Research Clinics method [238]. Non-HDL cholesterol was estimated from total cholesterol minus HDL cholesterol. Urinary albumin was measured by immunonephelometry [239].

2.2.5 Statistical Analysis

Baseline characteristics of the study population were examined; categorical variables were presented as a percentage (number) and continuous variables as a mean (standard deviation [SD]) or median (1st and 3rd quantiles), as appropriate.

Cox proportional hazard models were constructed to estimate the associations of each baseline BP measure with incident CAD, adjusting for sex, age, age at diabetes onset, HbA1c and antihypertensive use. In all of the Cox models, time was measured as time since the study entry (i.e. time 0 = date of study entry). The adjusted hazards ratios (HR) with 95% confidence intervals (CIs) were presented. To evaluate whether the predictive abilities of BP measures vary

at different ages or glycemic levels, stratified analysis was conducted by age < 35 and ≥ 35 years and by HbA1c < 9 and ≥ 9%, respectively. The age cut-off of 35 years is based on previous findings that PP showed a steep rise from the 30s to 40s in T1D [124]; the HbA1c cut-off of 9% was close to the median of baseline HbA1c in this cohort. In addition to stratified analysis, the interaction effect of different age and HbA1c groups on the association of BP with outcome events were tested and then plotted (model-based interaction plot) [240]. The predictive ability of each baseline BP measure was also assessed using the C-statistic method by Uno et al. [241]; all pairwise comparisons were tested.

Cox proportional hazard models with time-varying BP measures were also created, adjusting for sex, age, age at diabetes onset, HbA1c, and time-varying antihypertensive medication use. The interaction tests and stratified analyses were also conducted by different baseline age (< vs ≥ 35 years) and HbA1c (< vs ≥ 9 %) groups, respectively.

The least absolute selection and shrinkage operator (LASSO)-penalized Cox regression [242] was also employed for variable selection, allowing for all four BP measures (SBP, DBP, PP, and MAP) and a wide range of potential baseline risk factors (age, sex, age at diabetes onset, ever smoker, BMI, pulse rate, HbA1c, urinary albumin excretion rate, HDL and non-HDL cholesterol, white blood cells (WBC), and antihypertensive use). The optimal penalty parameter was determined using the 10-fold cross-validation method. The considerations of using LASSO regression were as follows: 1) penalized regression handles multicollinearity between predictors by imposing a penalty factor in the estimation of coefficients [243,244] and 2) LASSO, as one of the most widely-used penalized models, is applicable for both low- and high-dimensional data and has been shown to be superior to the stepwise technique [245].

The assessment of improvement in model fit of the combination of BP variables (SBP and DBP, MAP and PP, or SBP and PP) vs a single BP variable was conducted using the likelihood-ratio χ^2 test. The combined MAP and PP was tested as the MAP and PP reflects two distinct BP characteristics, the steady and pulsatile components, receptively [95]. PP has been suggested to be more informative for cardiovascular risk prediction in the diabetes population [230,231], and SBP has been recommended as the primary BP measure in current guidelines [81]. Thus, we indented to test whether risk prediction might be improved with the combination of SBP and PP.

A two-sided $p<0.05$ was considered significant. The analyses were performed with SAS v 9.4 (SAS Institute, Cary, NC) and R version 3.5.1 (R core team, Vienna, Austria).

2.3 Results

Baseline characteristics are shown in **Table 10**. Among 605 eligible participants without known CAD at baseline, mean age and diabetes duration were 27 and 19 years, respectively. During the 25 years of follow up, 219 (36.2%) incident CAD cases were identified. The Pearson correlation coefficients of different baseline BP measures were 0.72 (SBP vs DBP), 0.68 (SBP vs PP), 0.90 (SBP vs MAP), 0.95 (SBP vs MidBP), -0.02 (DBP vs PP), 0.95 (DBP vs. MAP), 0.90 (DBP vs MidBP), 0.28 (PP vs MAP), 0.41 (PP vs MidBP), and 0.99 (MAP vs MidBP).

Age-specific means of BPs were calculated among CAD cases and non-cases, comprising all BP values from the baseline to the last available measure, prior to the event occurrence for cases or at the end of the follow up for non-cases (**Figure 1).** CAD cases experienced a higher SBP and a higher PP than non-cases across all age groups; the differences of BP between cases

and non-cases became greater with older age. The DBP increased until late 30s and early 40s and started falling thereafter; the CAD cases showed a decline in DBP 10 years earlier than seen in non-cases.

Controlling for sex, age, age at diabetes onset, HbA1c levels, and antihypertensive medication use, the HRs (95% CI) associated with one increment in SD for CAD risk were 1.35 (1.17, 1.56) for SBP; 1.30 (1.12, 1.51) for DBP; 1.20 (1.03, 1.39) for PP; 1.35 (1.17, 1.56) for MAP; and 1.36 (1.18, 1.57) for MidBP (**Table 11**). In an analysis stratified by baseline age < vs ≥ 35 years, PP was not significantly associated with CAD at age < 35 years (HR [95%CI]: 1.07 [0.88, 1.29], p value =0.508), but PP became the strongest BP predictor in those aged 35 years or older (HR [95%CI]: 1.51 [1.16, 1.96], p value =0.002). In a stratified analysis by baseline HbA1c < vs ≥9%, the HR of PP associated with CAD was statistically significant, and the effect size was similar to that of other BP measures (HR [95%CI]: 1.32 [1.01, 1.72], p value=0.044) in those with worse glycemic control; however, the association was less powerful and non-statistically significant (HR [95%CI]: 1.14 [0.94, 1.38], p value=0.177) in those with better glycemic control.

The effect modification was significant for HbA1c (HR: 1.41, p value=0.023) and was marginally significant for age (HR: 1.29, p value=0.093) on the association of PP with CAD outcomes (**Figure 2**). No significant interaction effect was found for the other four BP measures (SBP, DBP, MAP, and MidBP) in this analysis **(Table 12).**

Consistently, although the C-statistic value was significantly lower for PP compared to the other four BP indices in the entire cohort, PP performed similarly to that of other indices in those with higher HbA1c levels (≥ 9%) or at an older age (≥ 35 years) (**Table 11**).

In the analysis of Cox proportional model with time-varying covariates (**Table 13**), the associations of time-varying BP measures with incident CAD displayed a similar pattern as that of baseline measures. Overall, PP was less powerful as a determinant of CAD risk compared to the other BP measures. The association of PP with CAD was significant in those with higher HbA1c levels >9 % (HR [95%CI]:1.49 [1.14, 1.96], p value =0,004), but not seen in those with HbA1c < 9%, while, the association of PP with CAD was not statistically significant in either age group, baseline age < or ≥ 35 years. Consistently, the interaction of "PP x HbA1c" was positively significant (p value=0.027), but not for "PP x age". There was no evidence of interaction effect for the other four time-varying BP measures (data not shown).

Table 14 shows the baseline risk factor selection for the prediction of CAD using a LASSO-Cox model for overall participants as well as subgroups of different age and glycemic levels. Allowing for a wide range of potential risk factors as well as four BP measures (SBP, DBP, PP, and MAP), SBP was retained in the model after LASSO selection in the entire cohort, and the two subcohorts with HbA1c < and ≥ 9%. Consistent with the conventional Cox models, PP exerted an important role in CAD risk prediction for those over 35 years of age and in those with an HbA1c of over 9%. As expected, MAP, compared to other BP measures, showed a stronger effect in the younger group.

A model with combined SBP and DBP or combined SBP and PP, was not remarkably superior to a model with a single SBP for CAD risk prediction. A model with combined MAP and PP, was not remarkably superior to a model with a single MBP (**Table 15**).

2.4 Discussion

This study presents a comprehensive comparison of the CAD risk prediction of five BP measures in a cohort with long duration T1D. We observed a fall of DBP at late 30s and early 40s in this group of participants, leading to an early rise in PP. This early fall in DBP occurred approximately 20 years earlier in these T1D individuals than that seen in the general population [89]. Significant positive baseline and time-varying associations were observed between each BP measure (SBP, DBP, PP, MAP, and MidBP) and incident CAD in the entire study cohort after adjusting for age, sex, glycemic burden and antihypertensive treatment. Although the relative magnitudes of the associations appear similar among the SBP, DBP, MAP, and MidBP measures, SBP tends to be more effective overall since it remained in the CAD prediction models after LASSO selection among a wide range of potential risk factors in the entire cohort. PP appears to be inferior to the other four BP measures, but becomes comparable in those aged 35 years or older and in those with worse glycemic control. Of note, PP was the only BP measure that was retained after LASSO selection in the subcohort with older age (> 35 years). Not surprisingly, MAP seems more informative than the other measures at younger ages as it was the only one retained in the model after LASSO selection in the subgroup of age < 35 years. Compared to a single measure, no significant benefit was observed for predicting CAD risk using a combination of the measures of SBP and DBP, MAP and PP or SBP and PP.

To our knowledge, very few studies have previously presented such a comprehensive evaluation of different BP measures in the T1D population, especially incorporating both baseline and time-varying BP measures. The current observations of the relative importance of different BP variables for cardiovascular risk prediction, in general, are in line with findings from people with type 2 diabetes [91,246] and the general population [96,247]. Collectively, no

remarkable difference has been found between the different BP measures, but SBP appears to be a more informative and reliable predictor in different settings and populations compared to other BP indices. Consistent with reports from the Framingham Heart Study [248] and secondary analysis of the ADVANCE trial [91], we observed a small improvement of prognostic significance with combined BP measures versus a single measure. However, no convincing evidence is shown that combined SBP and DBP or combined SBP and PP is superior to SBP or that combined MAP and PP is superior to MAP.

Stiffening of the arterial wall as a sign of vascular aging is thought to be a complex process involving collagen overproduction and accumulation, elastin fiber degradation, vascular smooth muscle cell proliferation, and vascular calcification [249]. Increased cardiovascular risk in diabetes is at least partially explained by glycation-induced accelerated vascular aging, such as advanced glycated end products (AGE), cross-linking, and decreased turnover of collagen on the arterial wall, leading to a decline of artery elasticity [250,251]. An increased PP results from age-related stiffening of the large arteries [252], leading to increasing interest in the role of PP in contributing to cardiovascular risk, particularly in diabetes [231]. According to the current study, T1D individuals have an increased SBP across all ages compared to the non-diabetes population, and also have a sharp rise of PP as early as the third and fourth decade of life. We found a weaker, but significant association of PP with incident CAD in the entire cohort, in line with the results of other T1D studies, such as the EURODIAB study [213] and the FinnDiane study [253]. Our observations extend previous findings by showing that PP is a powerful determinant for CAD risk particularly in those 35 years or older and/or with poorer glycemic control. These findings strongly support the hypothesis that vascular aging is accelerated by glycation mediated changes in this high-risk population.

The 2017 ADA position paper "Diabetes and Hypertension" [254] states that a higher PP (> 60 mmHg, systolic hypertension in association with low DBP) in older people with diabetes may result in an increased risk of adverse cardiovascular outcomes. Our findings suggest that, in T1D individuals, PP may start playing an important role from an early age, i.e., late 30s, in predicting cardiovascular disease. An increased PP may not only be a marker of cardiovascular risk but also reflect a diseased state of stiffened arteries. Thus, studies focusing on premature vascular aging in T1D may open a window for us to better understand the pathogenesis of general vascular aging that is typically occurred at older ages in the general population.

This EDC Study is a well-characterized T1D cohort with an extended follow-up duration. Different BP measures for CAD risk prediction were examined using both baseline single time-point and time-varying variables, along with age and HbA1c stratified analyses. Advanced statistical methods (e.g., LASSO regression) were employed to further confirm the study findings. Several limitations of the current work should also be noted. Our sample consisted primarily of white T1D individuals and therefore may not be representative of other ethnic or racial groups. The cohort was relatively young at study entry, which allowed us to observe a long disease course of T1D. However, some types of outcome events, such as stroke and cause-specific mortality, were relatively rare even at the 25-year follow up, which have limited our ability to fully evaluate different classes of cardiovascular outcomes.

2.5 Conclusion

In a group of individuals with childhood-onset T1D, we observed that an early fall of DBP beginning from late 30s, leads to an early rise of PP. All five studied BP measures (SBP, DBP,

PP, MAP and MidBP) are independent predictors of CAD in the entire cohort. The current study supports SBP to be a primary BP determinant of cardiovascular risk, especially considering its reliability and convenience in the implementation of its measurement in clinical settings. Although PP is less effective for risk prediction in CAD in the entire cohort, its prognostic significance may improve and become comparable to SBP in those aged 35 years or more or those under poor glycemic control, reflecting an early onset of glycation-induced vascular stiffening in T1D. PP may be necessary to incorporate into the clinical evaluation in T1D, especially in those over 35 years old and/or in poor glycemic control.

2.6 Tables and Figures

Table 10 Baseline Characteristics of the Overall Study Participants

Variables [a]	Data
Age, yrs	27.2 (7.7)
Age at diabetes onset, yrs	8.2 (4.1)
Diabetes duration, yrs	19.0 (7.4)
Female, %(n)	49.8 (301)
SBP, mmHg	112.9 (14.7)
DBP, mmHg	72.5 (10.8)
PP, mmHg	40.4 (10.3)
MAP, mmHg	85.9 (11.3)
MidBP, mmHg	92.7 (11.9)
Antihypertensive medication use, %(n)	12.9 (78)
Hypertension, %(n)	14.4 (87)
Pulse rate, beats/min	78 (10)
HbA1c, %	8.8 (1.5)
Ever smoker, %(n)	37.2 (225)
BMI, kg/m^2	23.5 (3.2)
High WHR [1], %(n)	4.8 (29)
AER, µg/min	14.4 (7.2, 101.7)
Raised albuminuria, %(n)	44.4 (269)
Total cholesterol, mg/dL	189.6 (41.0)
Non-HDL cholesterol, mg/dL	135.6 (41.0)
HDL cholesterol, mg/dL, Male	49.5 (9.8)
HDL cholesterol, mg/dL, Female	58.4 (12.9)

Categorical variables were presented as percentage (number) and continuous variables as mean (SD) or median (1^{st} and 3^{rd} quantiles)

[a] High WHR was defined as >1 in men or > 0.85 in women

AER: urinary albumin excretion rate, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, MAP: mean arterial pressure, MidBP: mid-blood pressure, PP: pulse pressure, SBP: systolic blood pressure, SD: standard deviation, WHR: waist-hip ratio

Table 11 Hazard Ratios and C Statistics of Different BP Indices for CAD Prediction

BP measure	Cox model		C-statistics
	HR (95% CI) Per SD	p value	C-statistic (95%CI)
Overal	n=605, events=219		
SBP	1.35 (1.17, 1.56)	<0.001	0.791 (0.747, 0.823)*
DBP	1.30 (1.12, 1.51)	<0.001	0.784 (0.746, 0.822)*
PP	1.20 (1.03, 1.39)	0.021	0.770 (0.729, 0.810)
MAP	1.35 (1.17, 1.56)	<0.001	0.789 (0.747, 0.831)*
MidBP	1.36 (1.18, 1.57)	<0.001	0.788 (0.748, 0.828)*
Stratified by age			
	Baseline age < 35 years n=500, events=150		
SBP	1.30 (1.09, 1.56)	0.004	0.760 (0.705, 0.815)
DBP	1.32 (1.12, 1.58)	0.002	0.773 (0.719, 0.827)*
PP	1.07 (0.88, 1.29)	0.508	0.748 (0.691, 0.805)
MAP	1.34 (1.13, 1.60)	0.001	0.770 (0.713, 0.826)*
MidBP	1.34 (1.12, 1.60)	<0.001	0.767 (0.712, 0.823)
	Baseline age ≥ 35 years n=105, events=69		
SBP	1.40 (1.08, 1.81)	0.012	0.658 (0.567, 0.749)
DBP	1.09 (0.79, 1.51)	0.600	0.638 (0.540, 0.736)
PP	1.51 (1.16, 1.96)	0.002	0.661 (0.567, 0.754)
MAP	1.26 (0.94, 1.70)	0.126	0.642 (0.549, 0.735)
MidBP	1.32 (0.99, 1.75)	0.059	0.649 (0.557, 0.741)
Stratified by HbA1c			
	Baseline HbA1c < 9 % n=380, events=141		
SBP	1.35 (1.12, 1.62)	0.001	0.751 (0.696, 0.806)*
DBP	1.37 (1.13, 1.66)	0.001	0.768 (0.715, 0.822)*
PP	1.14 (0.94, 1.38)	0.177	0.731 (0.678, 0.784)
MAP	1.39 (1.16, 1.68)	<0.001	0.774 (0.710, 0.838)*
MidBP	1.39 (1.16, 1.67)	<0.001	0.773 (0.710, 0.835)*
	Baseline HbA1c ≥ 9 % n=225, events=78		
SBP	1.32 (1.04, 1.68)	0.023	0.840 (0.780, 0.900)
DBP	1.18 (0.93, 1.50)	0.164	0.836 (0.773, 0.898)
PP	1.32 (1.01, 1.72)	0.044	0.838 (0.786, 0.890)
MAP	1.25 (0.99, 1.58)	0.064	0.839 (0.792, 0.887)
MidBP	1.27 (1.01, 1.61)	0.044	0.838 (0.782, 0.890)

*p<0.05 compared to PP. p>0.05 for the rest of pairwise comparisons between different blood pressure measures (SBP, DBP, PP, MAP, and MidBP)

BP: blood pressure, CAD: coronary artery disease, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, MAP: mean arterial pressure, MidBP: mid-blood pressure, PP: pulse pressure, SBP: systolic blood pressure

Table 12 Interactions of BP with Age, and with HbA1c in CAD Prediction Models

Interaction term	HR (95%CI)	p value
Age (< vs ≥ 35years) x BP		
SBP	0.874 (0.675, 1.132)	0.307
DBP	0.800 (0.591, 1.083)	0.149
PP	1.293 (0.958, 1.745)	0.093
MAP	0.828 (0.630, 1.090)	0.179
MidBP	0.838 (0.642, 1.094)	0.193
HbA1c (< vs ≥ 9%) x BP		
SBP	1.127 (0.871, 1.458)	0.365
DBP	0.937 (0.708, 1.241)	0.652
PP	1.410 (1.049, 1.897)	0.023
MAP	1.004 (0.772, 1.306)	0.977
MidBP	1.038 (0.801, 1.344)	0.779

BP, age (or HbA1c), and their interaction term (e.g., BP x Age) were in the model for testing

BP: blood pressure, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, MAP: mean arterial pressure, MidBP: mid-blood pressure, PP: pulse pressure, SBP: systolic blood pressure

Table 13 Time-varying BP Indices Associated with Incident CAD

BP measure	Model [a]	HR (95%CI) [b]	p value
SBP	Overall	1.99 (1.48, 2.67)	<0.001
	Age < 35 yrs	2.22 (1.53, 3.23)	<0.001
	Age ≥ 35 yrs	1.67 (1.01, 2.77)	0.045
	HbA1c < 9 %	1.84 (1.25, 2.72)	0.002
	HbA1c ≥ 9 %	2.49 (1.54, 4.05)	<0.001
DBP	Overall	2.00 (1.48, 2.69)	<0.001
	Age < 35 yrs	2.43 (1.68, 3.51)	<0.001
	Age ≥ 35 yrs	1.42 (0.86, 2.36)	0.175
	HbA1c < 9 %	2.29 (1.57, 3.34)	<0.001
	HbA1c ≥ 9 %	1.82 (1.09, 3.02)	0.021
PP	Overall	1.19 (1.01, 1.41)	0.041
	Age < 35 yrs	1.18 (0.94, 1.48)	0.164
	Age ≥ 35 yrs	1.21 (0.93, 1.57)	0.156
	HbA1c < 9 %	1.05 (0.83, 1.32)	0.677
	HbA1c ≥ 9 %	1.49 (1.14, 1.96)	0.004
MAP	Overall	2.37 (1.71, 3.29)	<0.001
	Age < 35 yrs	2.77 (1.86, 4.11)	<0.001
	Age ≥ 35 yrs	1.77 (0.98, 3.19)	0.058
	HbA1c < 9 %	2.54 (1.66, 3.89)	<0.001
	HbA1c ≥ 9 %	2.50 (1.44, 4.33)	0.001
MidBP	Overall	2.37 (1.70, 3.29)	<0.001
	Age < 35 yrs	2.71 (1.82, 4.03)	<0.001
	Age ≥ 35 yrs	1.84 (1.02, 3.33)	0.043
	HbA1c < 9 %	2.43 (1.58, 3.73)	<0.001
	HbA1c ≥ 9 %	2.65 (1.54, 4.57)	<0.001

[a] Adjusted for sex, age, age at diabetes onset, HbA1c, and time-varying antihypertensive use
[b] Per SD increase

BP: blood pressure, CAD: coronary artery disease, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, MAP: mean arterial pressure, MidBP: mid-blood pressure, PP: pulse pressure, SBP: systolic blood pressure

Table 14 Baseline Risk Factor Selection for CAD Prediction using LASSO-Cox Model

Risk factors	β Coefficient				
	Overall	Subset age < 35 yrs	Subset Age ≥ 35 yrs	Subset HbA1c < 9%	Subset HbA1c ≥ 9%
SBP	0.168	.	.	0.033	0.081
DBP	.	.	.	.	.
PP	.	.	0.247	.	0.128
MAP	.	0.153	.	0.147	.
Age	0.717	0.526	.	0.588	0.801
Age of diabetes onset	-0.192	-0.177	-0.172	-0.207	-0.151
Female	.	.	.	.	.
Ever smoking	0.137	0.073	0.219	0.075	0.192
BMI	0.024	0.108	.	.	.
Pulse rate	.	.	.	.	.
HbA1c	.	.	.	.	.
Urinary AER	0.197	0.191	0.075	0.212	0.155
HDLc	-0.134		-0.388	-0.085	-0.125
non-HDLc	0.208	0.230		0.214	0.167
WBC	0.090	0.082	0.030	0.066	0.094
Antihypertensive use	0.098	0.078	0.107	0.042	0.179

AER: urinary albumin excretion rate, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, HDLc: high density lipoprotein cholesterol, LASSO: least absolute shrinkage and selection operator, MAP: mean arterial pressure, MidBP: mid-blood pressure, PP: pulse pressure, SBP: systolic blood pressure, WBC: white blood cell counts

Table 15 Combined BP versus Single BP Indices in CAD Prediction

Comparison		Likelihood ratio test	
Model 1	Model 2	$\Delta\chi^2$	p value
Overall			
SBP+DBP	SBP	0.63	0.426
	DBP	5.01	0.025
	PP	11.21	<0.001
	MAP	1.08	0.299
	MidBP	0.23	0.633
MAP+PP	SBP	0.63	0.426
	DBP	5.01	0.025
	PP	11.21	<0.001
	MAP	1.08	0.299
	MidBP	0.23	0.633
	SBP+DBP	0.00	>0.999
SBP+PP	SBP	0.63	0.426
	DBP	5.01	0.025
	PP	11.21	<0.001
	MAP	1.08	0.299
	MidBP	0.23	0.633
	SBP+DBP	0.00	>0.999
	MAP+PP	0.00	>0.999
HbA1c < 9%			
SBP+DBP	SBP	1.88	0.170
	DBP	1.82	0.178
	PP	9.88	0.002
	MAP	0.04	0.834
	MidBP	0.08	0.767
MAP+PP	SBP	1.88	0.170
	DBP	1.82	0.178
	PP	9.88	0.002
	MAP	0.04	0.834
	MidBP	0.08	0.767
	SBP+DBP	0.00	>0.999
SBP+PP	SBP	1.88	0.170
	DBP	1.82	0.178
	PP	9.88	0.002
	MAP	0.04	0.834
	MidBP	0.08	0.767
	SBP+DBP	0.00	>0.999
	MAP+PP	0.00	>0.999
HbA1c ≥ 9%			
SBP+DBP	SBP	0.29	0.588
	DBP	3.39	0.066
	PP	1.49	0.223
	MAP	1.93	0.165
	MidBP	1.33	0.249
MAP+PP	SBP	0.29	0.588
	DBP	3.39	0.066
	PP	1.49	0.223
	MAP	1.93	0.165

Table 15 Continued

	MidBP	1.33	0.249
	SBP+DBP	0.00	>0.999
SBP+PP	SBP	0.29	0.588
	DBP	3.39	0.066
	PP	1.49	0.223
	MAP	1.93	0.165
	MidBP	1.33	0.249
	SBP+DBP	0.00	>0.999
	MAP+PP	0.00	>0.999
Age < 35 years			
SBP+DBP	SBP	2.69	0.101
	DBP	0.71	0.399
	PP	10.07	0.002
	MAP	0.03	0.860
	MidBP	0.41	0.525
MAP+PP	SBP	2.69	0.101
	DBP	0.71	0.399
	PP	10.07	0.002
	MAP	0.03	0.860
	MidBP	0.41	0.525
	SBP+DBP	0.00	>0.999
SBP+PP	SBP	2.69	0.101
	DBP	0.71	0.399
	PP	10.07	0.002
	MAP	0.03	0.860
	MidBP	0.41	0.525
	SBP+DBP	0.00	>0.999
	MAP+PP	0.00	>0.999
Age ≥ 35 years			
SBP+DBP	SBP	3.21	0.073
	DBP	8.93	0.003
	PP	0.02	0.877
	MAP	6.88	0.009
	MidBP	5.71	0.017
MAP+PP	SBP	3.21	0.073
	DBP	8.93	0.003
	PP	0.02	0.877
	MAP	6.88	0.009
	MidBP	5.71	0.017
	SBP+DBP	0.00	>0.999
SBP+PP	SBP	3.21	0.073
	DBP	8.93	0.003
	PP	0.02	0.877
	MAP	6.88	0.009
	MidBP	5.71	0.017
	SBP+DBP	0.00	>0.999
	MAP+PP	0.00	>0.999

DBP: diastolic blood pressure, MAP: mean arterial pressure, MidBP: mid-blood pressure, PP: pulse pressure, SBP: systolic blood pressure.

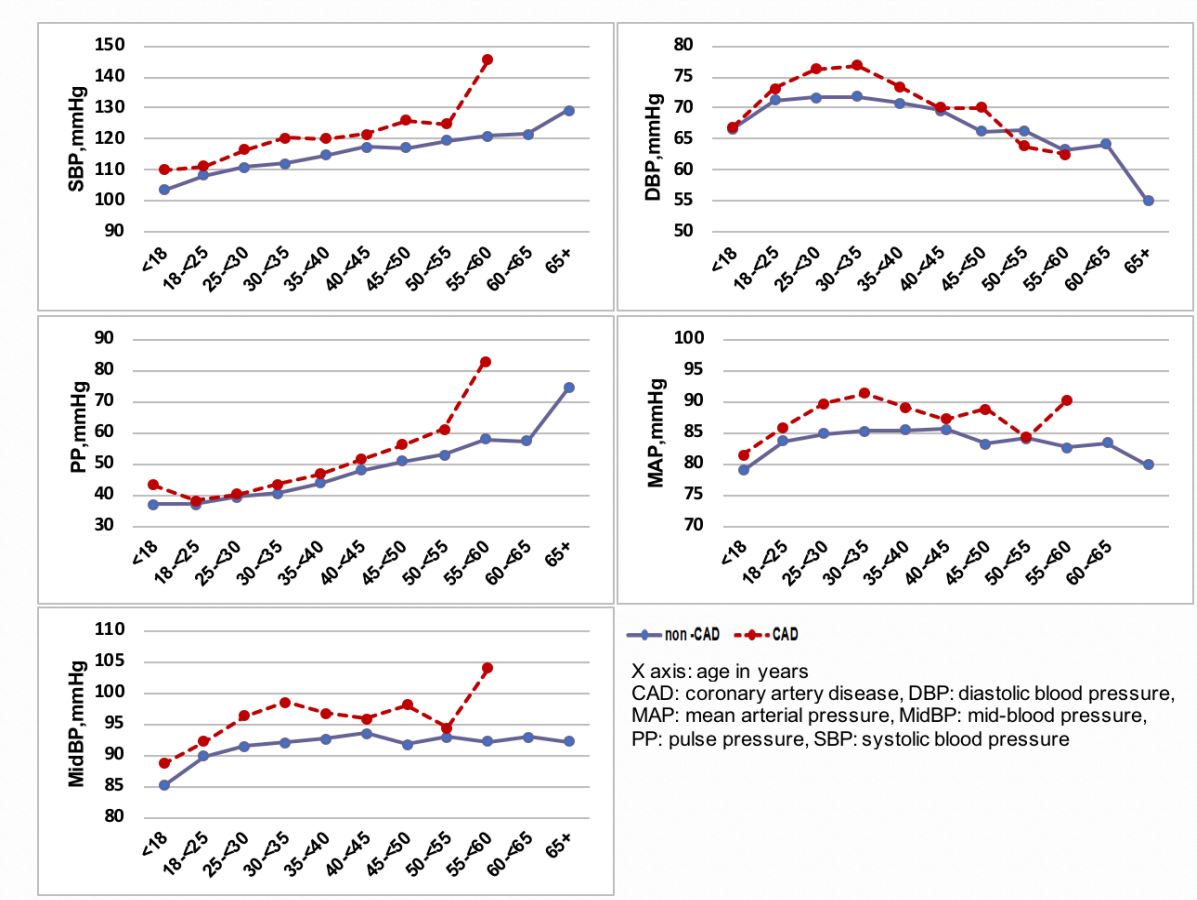


Figure 1 Age-specific Means of BP Indices between CAD Cases and Non-Cases

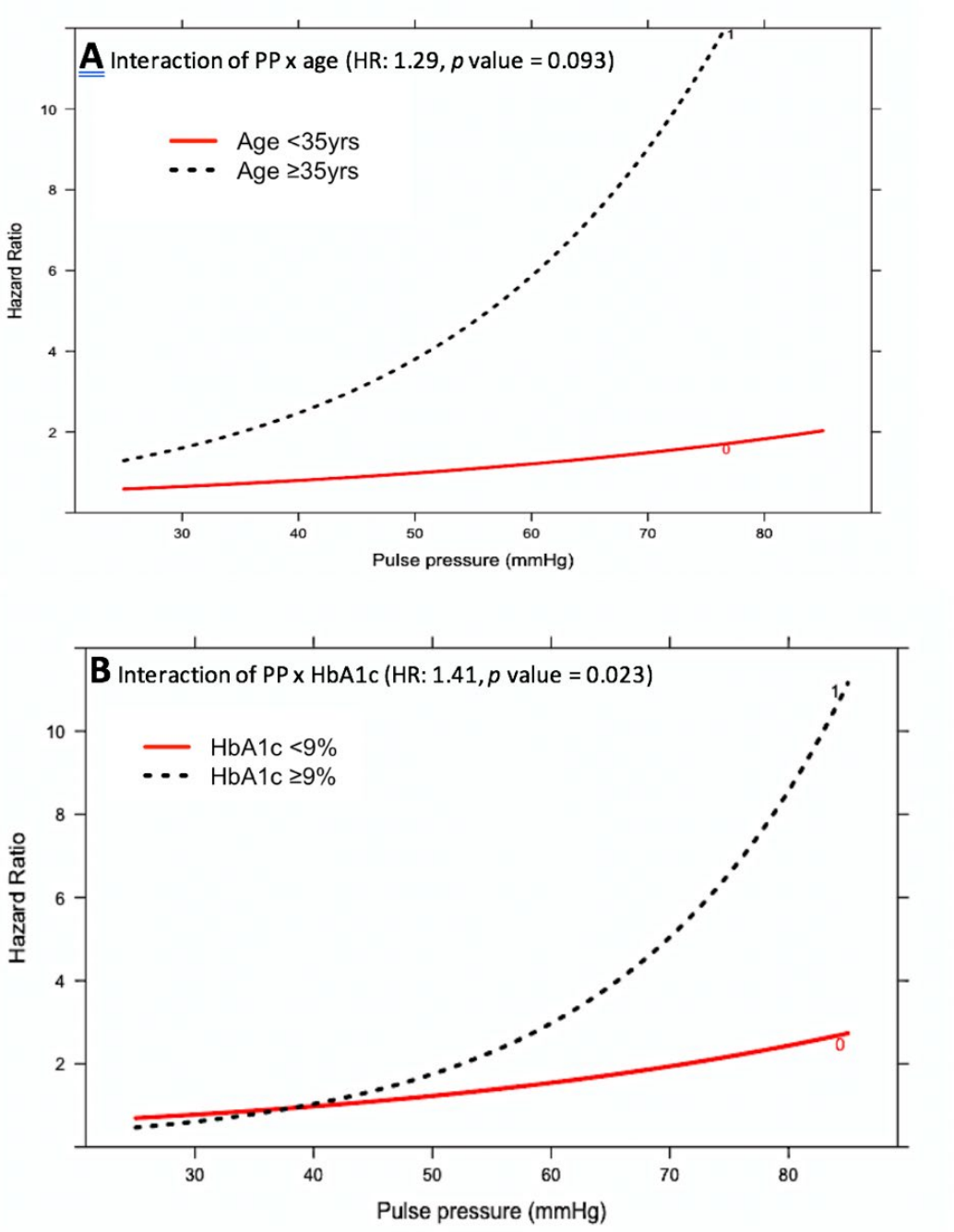


Figure 2 Model-based Interaction Effect of Age and HbA1c on the Association of PP with CAD Outcomes

CAD: coronary artery disease, HbA1c: hemoglobin A1c, PP: pulse pressure

3.0 Paper II: Optimal BP Goals in Young Adults with Type 1 Diabetes

3.1 Introduction

Individuals with T1D carry a substantially greater cardiovascular risk, especially at younger ages, than the general population. The Pittsburgh EDC Study has shown that young adults with childhood-onset T1D exhibit more than a 30-fold higher risk of cardiovascular mortality compared to age- and sex-matched individuals in the general population [62]. BP begins to rise at an early age in T1D individuals such that hypertension (defined as BP ≥140/90 mmHg or the use of BP lowering mediations) affects over 40% of these individuals as early as in their 30s [117]. However, very few studies have examined the impact of chronic exposure to elevated BP, from an early phase in life, on cardiovascular outcomes in this high-risk population. Long term exposure to glycaemia has been widely shown to be associated with diabetes complications, including cardiovascular disease [255,256]. Nonetheless, the relative importance of chronic exposure to high BP versus hyperglycemia for diabetes complication outcomes remains unknown.

Although high BP is modifiable, it continues to be a poorly treated risk factor for adverse health outcomes in the contemporary population of individuals with T1D [118]. Currently, the major guidelines recommend a BP target of 130/80 (AHA 2017) [81] or 140/90 mmHg (ADA 2018) [257] in diabetes populations based on evidence exclusively in middle-aged or older type 2 diabetes populations. However, not only may the pathogenesis of hypertension differ between individuals with T1D compared with those with type 2 diabetes but also the onset of the condition occurs at a much earlier age in the former group [5]. Unfortunately, there is an absence of clinical trial-based evidence regarding the optimal BP targets in T1D. A few observational studies of T1D have

reported that a lower BP threshold (i.e., less than 110 or 120 mmHg) was associated with a lower cardiovascular risk [157–159], however, usually only a single baseline BP measure was examined. These limited studies and the lack of BP lowering clinical trials indicate an insufficiency of data regarding the BP management targets in T1D.

The primary aim of the study was, therefore, to determine optimal BP goals in terms of minimizing cardiovascular risk in young adults with long duration childhood-onset T1D. In addition, we examined the relative importance of long-term glycemic and BP exposures for cardiovascular risk prediction in T1D.

3.2 Methods

3.2.1 Study Population

The Pittsburgh EDC Study is a prospective cohort of individuals with childhood-onset T1D, who were diagnosed prior to 17 years of age [233]. The participants were seen at diagnosis, or within one year of diagnosis, at the Children's Hospital of Pittsburgh between 1950 and 1980. Though clinic based, this cohort has been shown to be epidemiologically representative of the T1D population in Allegheny County, Pennsylvania [234]. There were 658 eligible participants examined at study entry (baseline) between 1986 and 1988. Participants were then assessed biennially by surveys for 25 years, and biennially by examination for the first 10 years and again at 18 and 25 years [59]. Of these participants, 605 were free from CAD at study entry and thus comprised the study population of the present analysis. Participants were followed up to their first CAD event, death, or the 25th year of the EDC cohort (2011–2014).

3.2.2 Coronary Artery Disease Definition

The CAD status was evaluated biennially from baseline to the end of the follow-up period. A CAD event was defined as new-onset angina diagnosed by an EDC physician, myocardial infarction confirmed by Q-waves on an electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, angiographic stenosis ≥ 50%, revascularization, or ischemic ECG changes (Minnesota codes 1.3, 4.1-4.3, 5.1-5.3, and 7.1).

3.2.3 Assessment of BP

BP was measured by a random-zero sphygmomanometer for the initial 10 years of the study and subsequently by an aneroid device. At each clinic visit, BP was measured three times by trained and certified research staff, after the participant had been peacefully sitting for five minutes in a quiet room, according to the Hypertension Detection and Follow-up Program protocol [235]. The average of the second and third readings was used in the analysis. MAP was calculated as the sum of one third of the SBP and two thirds of DBP.

The cumulative BP (mmHg-year) was determined as a sum of the products of average BP (mmHg) from two consecutive follow-up visits multiplied by the time interval (year) between the two visits; that is, cumulative BP = ([BP1 + BP2] / 2) × (time2 - time1) + ([BP2 + BP3] / 2) × (time3 - time2)… [258]. This cumulative variable increases as time progresses over the follow-up period. The time-weighted BP (mmHg) was then obtained by dividing cumulative BP by the total follow-up time: time-weighted BP = cumulative BP / ([time2 - time1]+ [time3 - time2]+…) [259]. This weighted variable is time-invariant and reflects the entire observed follow-up period, i.e., from baseline to the first CAD event if a case, to death or the 25th year follow-up if a non-case.

3.2.4 Measurement of Covariates

Demographic and medical information was self-reported via questionnaires. Clinical exams were conducted by trained personnel using standardized protocols. An ever smoker was defined as a person who had smoked at least 100 cigarettes in his or her lifetime. The body mass index (BMI) was calculated as weight in kilograms divided by the square of height in meters. Participants self-reported all medication use biennially since the study baseline. The medication class was determined using the ATC/DDD code.

HbA1 was measured by ion-exchange chromatography (Isolab, Akron, OH, USA) for the first 18 months, and the subsequent 10 years by automated high-performance liquid chromatography (Diamat; Bio-Rad, Hercules, CA, USA); the results of the two methods were highly correlated (r = 0.95). For follow-up beyond 10 years, HbA1c was measured with the DCA 2000 analyzer (Bayer, Tarrytown, NY, USA). The DCA and Diamat assays were also highly correlated (r = 0.95). The values were then converted to DCCT - aligned HbA1c using regression equations derived from duplicate assays [236]. The time-weighted HbA1c was also calculated, using the same method as that for BP measures.

Total cholesterol was determined enzymatically [237]. HDL cholesterol was measured by a precipitation technique (heparin and manganese chloride) using a modified version of the Lipid Research Clinics method [238]. Non-HDL cholesterol was determined as total cholesterol minus HDL cholesterol. Urinary albumin was determined by immunonephelometry [239]. Raised albuminuria was defined as an urinary albumin excretion rate (AER) >20 μg/min (30 mg/24h) in at least two of three validated timed biennial urine collections [64].

3.2.5 Statistical Analysis

Demographics and baseline clinical characteristics were compared by time-weighted BP levels (< vs ≥ 120/80 mmHg) and between CAD incident cases and non-cases. In these comparisons, the Chi-square test or Fisher's exact test were used for the dichotomous variables and the Student t-test or the nonparametric Wilcoxon test were used for the continuous variables, as appropriate.

The cumulative SBP, DBP and MAP were calculated at each follow-up visit until the first occurrence of a CAD event for cases or the end of the follow-up for non-cases. Each time-updated cumulative BP variable (i.e. time-varying) was included in a Cox model to assess the association between the cumulative BP and incident CAD. The models were adjusted for covariates that have previously been demonstrated to be important predictors of CAD in the Pittsburgh EDC cohort [147] or those that were found to be significantly associated with outcome events in the univariate analyses. Specifically, the final models were adjusted for age, sex, diabetes duration, current use of antihypertensive medications, ever smoking, raised albuminuria, updated mean BMI, HbA1c, HDL and non-HDL cholesterol.

Cox models including time-weighted BP measures (time-invariant) were constructed to examine a dose-gradient association between the categorized BP and incident CAD. The time-weighted SBP (<110, -<120 [reference], - <130, <140, ≥140 mmHg), DBP (<60, -<70 [reference], - <80, <90, ≥90 mmHg) and MAP (<80, -<90 [reference], - <100, <110, ≥110 mmHg) were categorized into 5 groups and tested. Model 1 was adjusted for age, diabetes duration, sex and current antihypertensive use. Model 2, the fully adjusted model, was further adjusted for time-weighted HbA1c, ever smoking, raised albuminuria, and updated mean BMI, HDL and non-HDL cholesterol.

Sensitivity, specificity, and the area under the receiver operating characteristic curve (AUC) were then summarized by different BP cut-points [260]. The Youden's index criterion [261] was also applied to select the optimal cut-offs.

To evaluate the relative importance of long-term exposure to elevated BP versus hyperglycemia in T1D, we subsequently stratified the participants into four groups by time-weighted BP and time-weighted HbA1c: Group 1 (reference group, SBP/DBP < 120/80 mmHg and HbA1c < 8%), Group 2 (high BP only, SBP/DBP ≥ 120/80 mmHg and HbA1c < 8%), Group 3 (high HbA1c only, SBP/DBP < 120/80 mmHg and HbA1c ≥ 8%), and Group 4 (both, SBP/DBP ≥ 120/80 mmHg and HbA1c ≥ 8%). Cox models were built to estimate the hazard ratios among these groups controlling for the same set of covariates described above. A similar risk stratification strategy was also applied to time-weighted MAP (< vs ≥ 90 mmHg) and HbA1c (< vs ≥ 8%). The cut-offs of 120/80 mmHg for SBP/DBP and 90 mmHg for MAP were established according to a significantly increased risk for these thresholds in the prior analyses of the dose-gradient associations between time-weighted BP categories and incident CAD, as well as the best cut-offs determined by the AUC and Youden index criteria. Similarly, the time-weighted HbA1c showed a remarkably increased risk from 8% according to the analysis of the time-weighted HbA1c categories and incident CAD. In addition to risk stratification analysis, the interaction effects of high BP (< vs ≥ 120/80 mmHg) with HbA1c and the high MAP (< vs ≥ 90mmHg) with HbA1c were also tested within the Cox models; model-based interaction plots were then displayed.

In addition, to understand the potential impact on CAD outcome of the two different BP cutoffs, 120/80mmHg and 140/90 mmHg, the population attributable risk fraction (PARF) was estimated for each of these two cutoffs, using the equation $PARF = (P * [I_{Exposed} - I_{Unexposed}])$

/ I_{total}, where P = prevalence of a given risk factor, $I_{Exposed}$ = event incidence rate in the Exposed population, $I_{Unexposed}$ = event incidence rate in the unexposed population, and I_{total} = Incidence rate in the total population. In this case, a PARF represents the percentage of CAD cases in this T1D cohort that can be attributed to ≥120/80 mmHg, and ≥140/90 mmHg, respectively.

In the exploratory sensitivity analysis, we examined the association of high BP (time-weighted SBP/DBP ≥ 120/80 mmHg, or time-weighted MAP ≥ 90 mmHg) with incident CAD in the subgroups who were never treated and who were ever treated with antihypertensives.

A two-sided P <0.05 was considered significant. Analyses were performed using SAS v 9.4 (SAS Institute, Cary, NC) and R version 3.5.1 (R Core Team, Vienna, Austria).

3.3 Results

Among the 605 EDC participants who were free from clinical CAD at study entry, the mean age and diabetes duration were 27 and 19 years, respectively. The average age of diabetes onset was eight years. Of all the participants, half of the cohort were females; 13% took antihypertensive medications at baseline (**Table 16**).

There were 219 (36.2%) individuals who experienced at least one CAD event over 25 years follow up. Compared to participants without incident CAD, those who developed CAD were more likely to be older, have a longer duration of diabetes, smoke, take antihypertensive medications, have raised albuminuria, and have higher BMI, higher levels of BP and non-HDL cholesterol at baseline (**Table 16**).

The time-weighted SBP, DBP, and MAP were all approximately normally distributed with the respective means (SD) of 116.3 (13.7), 72.3 (9.6) and 87.0 (10.1) mmHg. Overall, the incidence

rates of CAD progressively increased as time-weighted BP increased (all p trends <0.01) (**Figure 3**). At 2, 4, 6, 8, 10, 18 and 25 years of follow-up, the mean (SD) cumulative BP values were 235(52), 497(82), 704(98), 933(116), 1144(134), 2104(198), and 2830(261) mmHg-years for SBP, and 150(34), 316(53), 447(62), 590(71), 723(83), 1307(139) and 1735(170) mmHg-years for DBP (**Figure 5**).

The time-updated cumulative SBP, DBP and MAP were separately examined in three Cox models. Over the follow-up period, all these three cumulative BP measures independently and significantly predicted the risk of incident CAD after adjusting for age, sex, diabetes duration, ever smoking, raised albuminuria, antihypertensive use, updated mean BMI, HbA1c, HDL and non-HDL cholesterol. The adjusted Hazard ratio (HR) (95% CI) of incident CAD per 500 mmHg-years increase in cumulative SBP, DBP and MAP were 1.3 (1.04, 1.7), 1.5 (1.02, 2.2) and 1.4 (1.03, 2.0), respectively (**Table 17**).

The dose-gradient association of each time-weighted BP measure (SBP, DBP, and MAP) with incident CAD is presented in **Table 18**. In the fully adjusted model (Model 2), compared to SBP within 110 to <120 mmHg, the HR (95%CI) associated incident CAD for <110, 120 to <130, 130 to <140, and ≥140 mmHg was 1.1 (0.7, 1.6), 1.6 (1.1, 2.3), 1.9 (1.2, 3.0) and 2.6 (1.6, 4.5), respectively. For DBP, with 60 to <70 mmHg as the reference group, the HR (95%CI) in the groups for <60, 70 to <80, 80 to <90, and ≥90mmHg was 0.9 (0.5, 1.7), 1.8 (1.2, 2.7), 4.5 (2.9, 6.9) and 5.6 (3.0, 10.3), respectively. Compared to MAP within 80 to < 90mmHg, the HR (95%CI) for <80, 90 to <100, 100 to<110, and ≥110 mmHg was 0.9 (0.6, 1.4), 2.5 (1.7, 3.5), 2.9 (1.8, 4.9) and 8.5 (4.3, 16.8), respectively.

The results of sensitivity, specificity, and AUC by different cut-off points of the time-weighted BPs are summarized in **Table 19**. Among the cut-offs ≥110, ≥120, ≥130 and ≥140

mmHg, a SBP cut-off ≥120 mmHg provided the highest AUC (0.614) with a sensitivity of 48% and a specificity of 75%. In evaluating DBP with cut-offs ≥60, ≥70, ≥80, and ≥90 mmHg, the cut-off point with the highest AUC (0.605) was ≥80 mmHg. A MAP ≥90 mmHg showed the best discrimination ability (AUC: 0.621) compared to cut-offs ≥80, ≥100, and ≥110 mmHg. According to the Youden index criterion, the optimal cut-off points for SBP, DBP and MAP were 116.1, 78.6, and 91.4 mmHg, respectively.

In the risk stratification analysis (**Table 20**), compared to participants with a time-weighted BP <120/80 mmHg, a higher BP ≥120/80 mmHg carried almost doubled increased risk of CAD (HR [95%CI]): 1.9 [1.4, 2.6]) in the fully adjusted model. When the participants were categorized into four groups according to time-weighted BP (< vs ≥ 120/80 mmHg) and time-weighted HbA1c (< vs ≥ 8%), the high BP only group (≥ 120/80 mmHg and <8%) (HR: 2.0 [1.06, 3.9]) had a similar hazards ratio as the high HbA1c only group (<120/80mmHg and ≥8%) (HR: 1.6 [0.97, 2.8]) for CAD risk prediction (**Figure 4 and Table 20**). In the risk stratification analysis by MAP (< vs ≥ 90 mmHg) and HbA1c (< vs ≥ 8%), the high MAP only group (≥ 90 mmHg and <8%) tended to carry higher CAD risk than the high HbA1c only group (<90mmHg and ≥8%) though the two 95% CIs were largely overlapping (3.4 [1.8, 6.5] vs 1.9 [1.1, 3.2]).

In the tests for interaction, both of the two interaction terms, high BP (< vs ≥ 120/80 mmHg) x HbA1c (HR: 0.851, p value=0.111) and MAP (< vs ≥ 90 mmHg) x HbA1c (HR: 0.786, p value=0.018) showed negative β coefficients (**Figure 6**).

In the sensitivity analyses (**Table 21**), a high BP ≥120/80 mmHg, vs <120/80 mmHg, was associated with a significantly increased risk in both subgroups who were never (HR: 2.3 [1.3, 4.1]) and ever (HR: 2.7 [1.7, 4.1]) treated with antihypertensives over the study period. (Dose-gradient association of time-weighted HbA1c and CAD was displayed in **Table 22.)**

As BP changes with age, and the duration exposure to diabetes is an important measure of diabetes burden, both age and diabetes duration were adjusted in our primary analyses. However, age and diabetes duration are highly correlated (r=0.84) in this childhood onset T1D cohort, it may be inappropriate to have both in the same model. Therefore, models adjusted for age, but not diabetes duration, were also constructed (**Appendix A Table 26 - 29**). These models yielded similar results as those with adjustment of both variables as stated above.

According the PARF calculations (**Figure 7**), compared to the BP cutoff 140/90 mmHg (PARF=19.1%), the cutoff 120/80 mmHg (PARF: 37.4%) identified a further 18.3% CAD cases in this type 1 cohort.

3.4 Discussion

In the current study, long-term cumulative BP exposure independently predicted the risk of CAD in individuals who were living with T1D since their childhood. A dose-gradient association was also observed between time-weighted BP and incident CAD. Time-weighted SBP and DBP, approximately starting from 120 and 80 mmHg, strongly predicted the CAD risk in this group of individuals with childhood-onset T1D. Compared with participants with reasonably good control of both BP and glycaemia (time-weighted SBP/DBP <120/80 mmHg and time-weighted HbA1c < 8%), the magnitude of the risks associated with incident CAD in the high BP only group (≥120/80 mmHg and <8%) were comparable to the hyperglycemia only group (<120/80 mmHg and ≥8%). In aggregate, these results suggest that chronic exposure to higher BP from youth/young adulthood through midlife plays an important role in the development of CAD in individuals with long duration T1D. Furthermore, chronically elevated BP and HbA1c showed a comparable

magnitude of effect on long-term CAD risk prediction, indicating BP control is at least as equally important as glycemic control is for cardiovascular risk reduction in T1D.

This study is unique in its provision of information about how chronically elevated BP in young to midlife affects cardiovascular outcomes in T1D. Both time-updated cumulative BP exposures (mmHg-year) and time-weighted (mmHg) BP measures were utilized in the present work to quantify long-term BP exposure. A time-weighted BP accounts for the amount of time that a participant has been exposed to a given BP level. Hence, it may better reflect the true exposure over time than a BP obtained on a single occasion (i.e., at baseline or current) or a simple average of multiple measures over time, i.e., an updated mean. Indeed, a most recent report from Lifetime Risk Pooling Project cohorts reported an improvement of atherosclerotic cardiovascular disease risk prediction using the 5 or 10 years cumulative SBP in comparison with using the current SBP [262].

Although several previous studies have shown the importance of cumulative BP exposure on adverse health outcomes, their data were exclusively collected from the general population [102,259,262–265]. BP rises at a much earlier age in T1D individuals than in the general population [124]. The prevalence of hypertension (≥95th percentile) can be as high as over 16% in T1D youth even less than 18 years of age [126]; over 40% were affected by hypertension (≥140/90mmHg or the use of BP lowering medications) in their early-mid adulthood [117]. In the present study, we have examined the effects of cumulative BP burden on adverse cardiovascular events in T1D individuals during young ages through midlife as well as its importance relative to chronic glycemic exposure.

Although the existing trial-based evidence did not support the benefit of a lower BP target (i.e., <120 mmHg) among individuals with type 2 diabetes (e.g., the ACCORD trial) [154], we believe it is inappropriate to simply extrapolate the findings in older type 2 population to the younger type

1 population. A few observational studies [157–159] conducted within T1D cohorts have shown a decreased cardiovascular risk at lower BPs levels even within the normal range as denoted by the current ADA recommendations (<140/90 mmHg) [257]. A prior report from the Pittsburgh EDC Study demonstrated that a baseline BP over 130/90 mmHg carried more than a five-fold greater risk of CAD than a BP of 110/80 mmHg after adjusting for age [158]. A similar dose-gradient relationship of BP (beginning at 120/70 mmHg) with adverse cardiovascular outcomes was also observed in a multinational study conducted by the World Health Organization [157] and a study by Sibal et al [159] in the U.K. In these prior reports, however, only baseline BPs were examined, a limited number of covariates were adjusted for in the risk prediction models (i.e., sex and age), and the follow-up periods were relatively short. The findings of the present study expand those of previous studies by providing data based on a cohort in which the follow-up period was up to 25 years, using a time-weighted BP and an adjustment for a wide range of potential risk factors.

We also conducted exploratory sensitivity analyses in subgroups who were never and ever treated with antihypertensive medications, respectively. A high BP (SBP/DBP >120/80 mmHg or MAP >90 mmHg) was consistently shown as an independent predictor of incident CAD in both subgroups, reflecting the inadequacy of BP control even in treated T1D individuals. Moreover, in our test of discrimination ability of different BP cut offs, the sensitivity was improved by 37% when the SBP cut-off was lowered from 140 to 120 mmHg, and by 24% when the DBP cut-off was lowered from 90 to 80 mmHg. In addition, according to the PARF estimation, a BP cutoff of 120/80 mmHg was able to identify a further 18% of CAD events than the 140/90 mmHg cutoff in this T1D cohort, nearly doubling the PARF. Collectively, these findings support a much lower BP target than 140/90mmHg, in order to fully reduce cardiovascular risk seen in the young T1D individuals.

The recent results from the DCCT/EDIC study suggested that a BP threshold of 120/70 mmHg was associated with the risk of adverse renal outcomes [211] in individuals with T1D. The results of our study were reasonably consistent with these findings as we found a threshold of 120/80 mmHg to be associated with incident CAD. Although we also observed that DBP was significantly associated with CAD risk beginning at 70 mmHg based on the Cox models, the AUC value was highest at the cut-off 80 mmHg. Overall, our observational data and those of others may provide support for conducting clinical trials in T1D individuals to further test the hypothesis that tighter BP control benefits this high-risk population.

The clinical management of T1D has traditionally focused on glycemic control [256]. In the current study, chronically elevated BP in participants who already had reasonably good glycemic control was independently associated with the increased risk of CAD, and the magnitude of effect was comparable to that seen in those who had poor glycemic control but reasonably good BP. This suggests that these two modifiable risk factors are similarly important in cardiovascular risk prediction in individuals with long standing T1D. It is not surprising that the relative risk was further increased in those who were exposed to both elevated BP and HbA1c. Indeed, animal studies have suggested a positive interaction between hyperglycemia and high BP on the progression of atherogenesis [266]. Intriguingly, we however found a "negative" interaction effect between high BP and HbA1c, such that the impact of BP is greater in those with lower HbA1c levels. We think these findings have major clinical implications, emphasizing the need for initial focus on glycaemia control when very high, but as HbA1c approaches high normal range, an increasing focus on BP becomes critical.

Our findings suggest that a BP management goal of < 120/80 mmHg is associated with minimal CAD risk. Because of the lack of interventional randomized trials with clinical outcomes

in BP management goals in T1D, observational evidence from an epidemiologically representative and well-characterized type 1 cohort, such as the EDC Study, could be important and helpful for clinical recommendation development. Thus, if BP trials are not going to be conducted in this high-risk population, it would seem reasonable to strengthen the ADA recommendations by embracing a lower goal of 120/80 mmHg for young and middle-aged adults with childhood-onset T1D.

The strengths of our investigation include the well-characterized cohort of childhood-onset T1D with standardized measurements, the long follow-up period over 25 years, and the application of cumulative and time-weighted BP measures that are able to reflect long-term exposure to high BP. Over the entire study period, BP measurement has been conducted by trained and certified research staff, strictly following the standard protocol [235].

However, we also recognize a number of limitations. We have to note that the cumulative BP exposure in the current analysis does not represent the entire history of disease, i.e. from the diagnosis of T1D. The EDC Study is a historical prospective T1D cohort and thus participants were already exposed to the disease for certain amount of time prior to study entry (mean baseline diabetes duration: 19 years). Due to the absence of pre-baseline data, we are unable to accurately estimate the BP exposure in this left censored period (from diabetes diagnosis to study baseline). However, when we arbitrarily estimated the pre-baseline cumulative BP exposure as the product of baseline BP with baseline diabetes duration (BP1 × [time at study baseline - time at diabetes diagnosis]) and added it into the current cumulative BP measure, the results were consistent regarding the optimal BP cut-offs associated with minimal CAD risk (data not shown). In addition, because of the observational nature of the study, our interpretation of the results might not reflect the direct casual effects of lower BP target on outcome endpoints. Our sample consists primarily

of white T1D individuals and therefore may not be representative of other ethnic or racial groups. Finally, these findings only focus on CAD events; the effects of BP and glycemia on other clinical outcomes was not addressed.

3.5 Conclusion

Long term cumulative BP exposure is an independent predictor of incident CAD among people with long duration childhood-onset T1D. Time-weighted BP analyses also suggest that a BP of 120/80 mmHg maximally predicts CAD events over 25 years follow up. Chronically elevated BP and glycaemia are similarly important in predicting cardiovascular endpoints. These findings raise the need for those setting treatment guidelines to consider lower goals (120/80mmHg) than now exist (140/90mmHg), especially for young adults with childhood-onset T1D as in the EDC cohort. In the absence of any pending or existing direct evidence from clinical outcome trials, which sadly do not seem likely to be conducted, such review should be take place sooner than later.

3.6 Tables and Figures

Table 16 Study Participant Characteristics by Time-weighted BP

Variables	Total	Time-weighted BP (mmHg)		Incident CAD	
	N=605	< 120/80 (n=387)	≥ 120/80 (n=218)	Non-cases (n=386)	Cases (n=219)
Age, years	27.2 (7.7)	25.7 (7.5)	29.8 (7.4) **	24.8 (7.2)	31.3 (6.8) **
Age at diabetes onset, years	8.2 (4.1)	8.0 (4.1)	8.5 (4.0)	8.1 (4.2)	8.3 (3.8)
Diabetes duration, year	19.0 (7.4)	17.7 (7.1)	21.3 (7.4) **	16.7 (6.6)	23.0 (7.1) **
Female, %(n)	49.8 (301)	57.1 (221)	36.7 (80) **	51.0 (197)	47.5 (104)
SBP, mmHg	112.9 (14.7)	106.3 (8.7)	124.6 (16.1) **	109.9 (12.3)	118.1 (17.1) **
DBP, mmHg	72.5 (10.8)	68.1 (7.9)	80.2 (11.1) **	70.8 (9.8)	75.5 (12.0) **
PP, mmHg	40.4 (10.3)	38.1 (8.1)	44. 4 (12.4) **	39.1 (9.6)	42.7 (10.7) **
MAP, mmHg	85.9 (11.3)	80.9 (7.2)	95.0 (11.6) **	83.8 (9.8)	89.7 (13.0) **
Antihypertensive use, %(n)	12.9 (78)	5.7 (21)	26.6 (57) **	7.6 (28)	23.0 (50) **
Hypertension, %(n)	14.4 (87)	3.6 (14)	33.5 (73) **	7.8 (30)	26.0 (57) **
Pulse rate, beats/min	78 (10)	76.9 (9.1)	80.5 (10.6) **	77.4 (9.8)	79.6 (9.7) *
HbA1c, %	8.8 (1.5)	8.7 (1.5)	8.8 (1.6)	8.8 (1.5)	8.7 (1.5)
Ever smoker, %(n)	37.2 (225)	36.2 (140)	39.0 (85)	30.3 (117)	49.3 (108) **
BMI, kg/m^2	23.5 (3.2)	23.2 (3.2)	24.1 (3.2) **	23.2 (3.2)	24.0 (3.2) **
High WHR [a], %(n)	4.8 (29)	5.0 (19)	4.6 (10)	5.2 (20)	4.2 (9)
AER, μg/min	14 (7, 102)	11 (6, 25)	10 (12, 985) **	11 (7, 42)	39 (9, 470) **
Raised albuminuria, %(n)	44.4 (269)	29.7 (115)	70.6 (154) **	36.5 (141)	58.5 (128) **
Non-HDLc, mg/dL	135.6 (41.0)	128.0 (36.7)	149.6 (46.4) **	127.6 (38.8)	149.9 (42.9) **
HDLc in male, mg/dL	49.5 (9.8)	50.1 (9.9)	48.7 (9.7)	50.8 (10.0)	47.3 (9.0) **
HDLc in female, mg/dL	58.4 (12.9)	58.4 (12.6)	58.6 (13.7)	58.9 (13.0)	57.5 (12.5)

Categorical variables were presented as percentage (number) and continuous variables as mean (SD) or median (1st and 3rd quantile)
[a] high WHR defined as >0.9 in men or > 0.85 in women
*p < 0.05, ** p < 0.01 between comparisons of time-weighted BP < vs ≥ 120/80 mmHg, and CAD non-cases vs cases
AER: urinary albumin excretion rate, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, MAP: mean arterial pressure, PP: pulse pressure, SBP: systolic blood pressure, SD: standard deviation, WHR: waist-hip ratio

Table 17 Time-updated Cumulative BPs (mmHg-Years) and CAD

	Model for SBP		Model for DBP		Model for MAP	
Variables[a]	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Cumulative BP (per 500 mmHg-years)	1.3 (1.04, 1.7)	0.025	1.5 (1.02, 2.2)	0.042	1.4 (1.03, 2.0)	0.031
Age	1.4 (1.01, 1.9)	0.041	1.4 (1.04, 1.9)	0.028	1.4 (1.03, 1.9)	0.033
Diabetes duration	1.7 (1.3, 2.3)	<0.001	1.7 (1.3, 2.3)	<0.001	1.7 (1.3, 2.3)	<0.001
Female	1.4 (0.9, 1.9)	0.069	1.4 (0.9, 2.0)	0.055	1.4 (0.9, 1.9)	0.059
Ever smoking	1.1 (0.7, 1.3)	0.915	1.1 (0.7, 1.4)	0.971	1.1 (0.7, 1.3)	0.952
BMI	0.9 (0.7, 1.02)	0.083	0.9 (0.7, 1.02)	0.080	0.9 (0.7, 1.02)	0.080
HbA1c	1.3 (1.04, 1.5)	0.016	1.3 (1.04, 1.5)	0.018	1.3 (1.04, 1.5)	0.017
non-HDL cholesterol	1.6 (1.4, 1.9)	<0.001	1.6 (1.4, 2.0)	<0.001	1.6 (1.4, 2.0)	<0.001
HDL cholesterol	0.8 (0.7, 0.94)	0.010	0.8 (0.7, 0.95)	0.012	0.8 (0.7, 0.95)	0.011
Raised albuminuria	2.5 (1.8, 3.6)	<0.001	2.6 (1.8, 3.6)	<0.001	2.5 (1.8, 3.6)	<0.001
Current antihypertensive use	0.4 (0.3, 0.6)	<0.001	0.4 (0.3, 0.6)	<0.001	0.4 (0.3, 0.6)	<0.001

Per SD increase if a continuous variable, unless specified

[a]BMI, HbA1c, and lipids (non-HDLc, HDLc and triglycerides) were updated means (time- invariant) in the models

BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CI: confidence interval, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, HDLc: high density lipoprotein cholesterol, HR: hazard ratio, MAP: mean arterial pressure, SBP: systolic blood pressure, SD: standard deviation

Table 18 Dose-Gradient Associations of Time-weighted BPs and CAD

	Model 1		Model 2	
	HR (95% CI)	p value	HR (95% CI)	p value
SBP, mmHg				
<110	0.9 (0.6, 1.3)	0.558	1.1 (0.7, 1.6)	0.801
110 to <120	ref		ref	
120 to <130	1.7 (1.1, 2.5)	0.013	1.6 (1.1, 2.3)	0.027
130 to <140	2.3 (1.4, 3.7)	<0.001	1.9 (1.2, 3.0)	0.011
140+	3.3 (2.0, 5.5)	<0.001	2.6 (1.6, 4.5)	<0.001
DBP, mmHg				
<60	1.1 (0.6, 1.9)	0.813	0.9 (0.5, 1.7)	0.825
60 to <70	ref		ref	
70 to <80	1.9 (1.3, 2.8)	<0.001	1.8 (1.2, 2.7)	0.002
80 to <90	5.9 (3.9, 8.9)	<0.001	4.5 (2.9, 6.9)	<0.001
90+	9.2 (5.2, 16.3)	<0.001	5.6 (3.0, 10.3)	<0.001
MAP, mmHg				
<80	0.9 (0.6, 1.3)	0.556	0.9 (0.6, 1.4)	0.718
80 to <90	ref		ref	
90 to <100	2.9 (2.1, 4.2)	<0.001	2.5 (1.7, 3.5)	<0.001
100 to <110	4.1 (2.6, 6.6)	<0.001	2.9 (1.8, 4.9)	<0.001
110+	13.9 (7.2, 26.9)	<0.001	8.5 (4.3, 16.8)	<0.001

Model 1: Adjusted for age, sex, diabetes duration, and current use of antihypertensive medications
Model 2: Model 1+ time-weighted HbA1c, ever smoking, updated mean BMI, HDL and non-HDL cholesterol, and raised albuminuria
BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CI: confidence interval, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, HR: hazard ratio, MAP: mean arterial pressure.

Table 19 Sensitivity, Specificity and AUC by Different Cut-offs of Time-weighted BPs

BP (mmHg)	Sensitivity	Specificity	AUC	p value for AUC comparison
SBP				
≥110	0.7534 (0.6895, 0.8082)	0.4378 (0.3886, 0.4870)	0.5956 (0.5578, 0.6335)	0.336
≥120	0.4795 (0.4110, 0.5479)	0.7487 (0.7047, 0.7902)	0.6141 (0.5745, 0.6537)	ref
≥130	0.2557 (0.2008, 0.3151)	0.9119 (0.8834, 0.9379)	0.5838 (0.5516, 0.6160)	0.075
≥140	0.1142 (0.0776, 0.1598)	0.9637 (0.9430, 0.9819)	0.5389 (0.5159, 0.5620)	<0.001
Optimal cutoff by Youden Index criteria :116.1 mmHg	0.5753 (0.5069, 0.6417)	0.6891 (0.6403, 0.7350)	0.648 (0.601, 0.695)	/
DBP				
≥60	0.9315 (0.8995, 0.9635)	0.0777 (0.0518, 0.1036)	0.5036 (0.4817, 0.5256)	<0.001
≥70	0.6530 (0.5890, 0.7169)	0.4896 (0.4404, 0.5415)	0.5683 (0.5278, 0.6088)	0.068
≥80	0.3288 (0.2690, 0.3882)	0.8808 (0.8472, 0.9119)	0.6048 (0.5697, 0.6399)	ref
≥90	0.0868 (0.0500, 0.1233)	0.9741 (0.9585, 0.9896)	0.5304 (0.5101, 0.5507)	<0.001
Optimal cutoff by Youden Index criteria :78.6 mmHg	0.3699 (0.3058, 0.4375)	0.8523 (0.8129, 0.8862)	0.611 (0.563, 0.660)	/
MAP				
≥80	0.8128 (0.7580, 0.8630)	0.2694 (0.2254, 0.3135)	0.5411 (0.5070, 0.5752)	<0.001
≥90	0.4749 (0.4064, 0.5388)	0.7668 (0.7254, 0.8083)	0.6209 (0.5816, 0.6602)	ref
≥100	0.1872 (0.1370, 0.2374)	0.9482 (0.9249, 0.9689)	0.5677 (0.5395, 0.5959)	0.003
≥110	0.0594 (0.0274, 0.0913)	0.9948 (0.9870, 1.0000)	0.5271 (0.5110, 0.5432)	<0.001
Optimal cutoff by Youden Index criteria :91.4 mmHg	0.4384 (0.3712, 0.5068)	0.8187 (0.7765, 0.8558)	0.633 (0.585, 0.681)	/

AUC: area of under receiver operating curve, BP: blood pressure, CAD: coronary artery disease, DBP: diastolic blood pressure, MAP: mean arterial pressure, SBP: systolic blood pressure

Table 20 Risk Stratification by Time-weighted BPs and Time-weighted HbA1c for CAD Risk Prediction

	Model 1		Model 2	
	HR (95% CI)	p value	HR (95% CI)	p value
SBP/DBP				
BP≥120/80 vs. <120/80	2.4 (1.8, 3.3)	<0.001	1.9 (1.4, 2.6)	<0.001
BP<120/80, and HbA1c<8	ref		ref	
BP≥120/80, and HbA1c<8	2.3 (1.3, 4.3)	0.007	2.0 (1.06, 3.9)	0.033
BP<120/80, and HbA1c≥8	2.2 (1.4, 3.6)	0.002	1.6 (0.97, 2.8)	0.071
BP≥120/80, and HbA1c≥8	5.8 (3.5, 9.7)	<0.001	3.3 (1.9, 6.0)	<0.001
MAP				
MAP≥90 vs. <90	3.5 (2.6, 4.7)	<0.001	2.6 (1.6, 3.5)	<0.001
MAP<90, and HbA1c<8	ref		ref	
MAP≥90, and HbA1c<8	4.6 (2.5, 8.4)	<0.001	3.4 (1.8, 6.5)	<0.001
MAP<90, and HbA1c≥8	2.6 (1.6, 4.2)	<0.001	1.9 (1.1, 3.2)	0.016
MAP≥90, and HbA1c≥8	8.5 (5.1, 14.1)	<0.001	4.9 (2.7, 8.7)	<0.001

Model 1: Adjusted for age, sex, diabetes duration, and current use of antihypertensive medications
Model 2: Model 1+ ever smoking, updated mean BMI, HDL and non-HDL cholesterol, and raised albuminuria

BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CI: confidence interval, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, HR: hazard ratio, MAP: mean arterial pressure

Table 21 Stratified Analysis of Time-weighted BPs and CAD by Antihypertensive Use

	Subgroup of **never** treated with antihypertensives (n=223, events=89)		Subgroup of **ever** treated with antihypertensives (n=382, events=130)	
	HR (95% CI)	p value	HR (95% CI)	p value
BP ≥ 120/80 vs. <120/80	2.3 (1.3, 4.1)	0.007	2.7 (1.7, 4.1)	<0.001
MAP ≥ 90 vs. <90	2.6 (1.5, 4.7)	0.001	4.0 (2.5, 6.3)	<0.001

Adjusted for age, sex, diabetes duration, ever smoking, time-weighted HbA1c, and updated mean BMI, HDL and non-HDL cholesterol, and raised albuminuria

BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CI: confidence interval, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, HR: hazard ratio, MAP: mean arterial pressure

Table 22 Dose-gradient Association of Time-weighted HbA1c and CAD

	Model 1		Model 2	
HbA1c, %	HR (95% CI)	p value	HR (95% CI)	p value
<7	ref		Ref	
7-<8	1.3 (0.6, 2.8)	0.441	1.6 (0.7, 3.3)	0.251
8-<9	2.1 (1.06, 4.4)	0.033	2.1 (1.0, 4.3)	0.0497
9-<10	2.8 (1.4, 5.7)	0.005	1.9 (0.9, 3.9)	0.094
10+	3.9 (1.9, 8.0)	<0.001	2.2 (1.04, 4.7)	0.041

Model 1: Adjusted for diabetes duration, sex
Model 2: Model 1+ time-weighted SBP, ever smoking, updated means BMI, HDL and non-HDL cholesterol, and raised albuminuria

BMI: body mass index, CAD: coronary artery disease, CI: confidence interval, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, HR: hazard ratio, SBP: systolic blood pressure

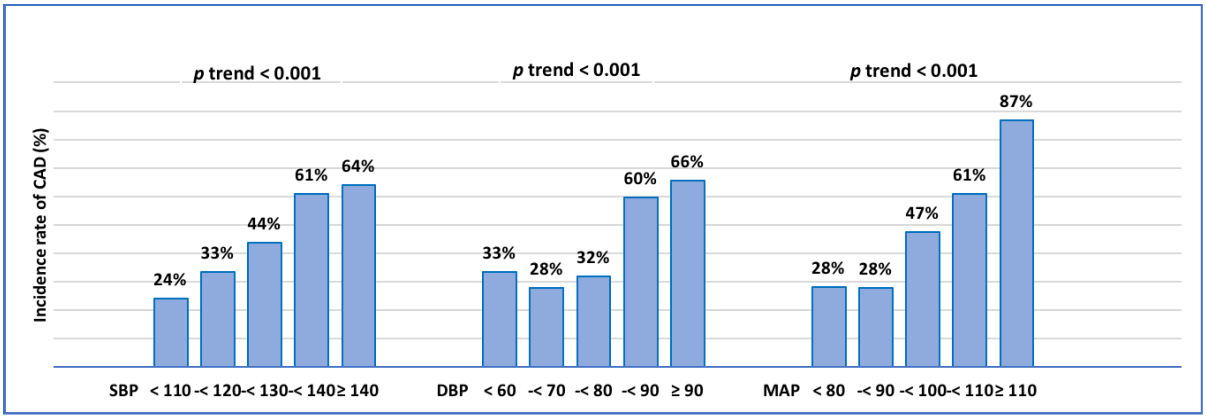


Figure 3 CAD Incidence Rate by Categorized Timed-weighted BPs

Chi-square test was used
CAD: coronary artery disease, DBP: diastolic blood pressure, MAP: mean arterial pressure, SBP: systolic blood pressure

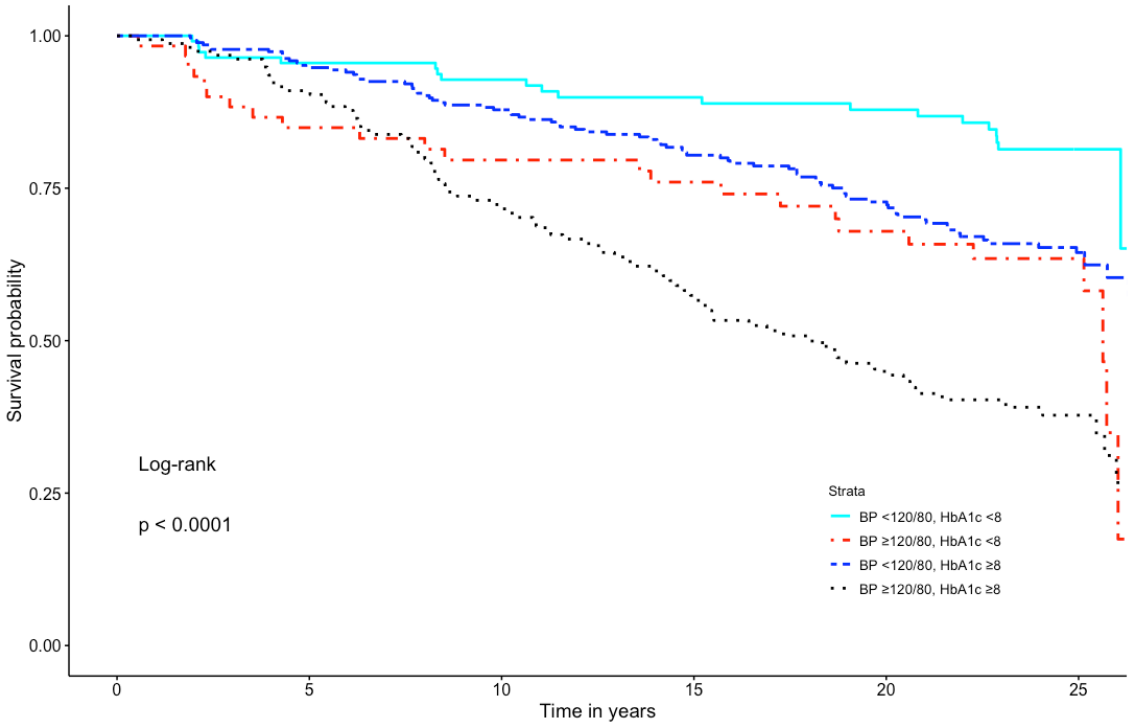


Figure 4 Risk Stratified Kaplan-MeierSurvival Curves for CAD Risk Prediction

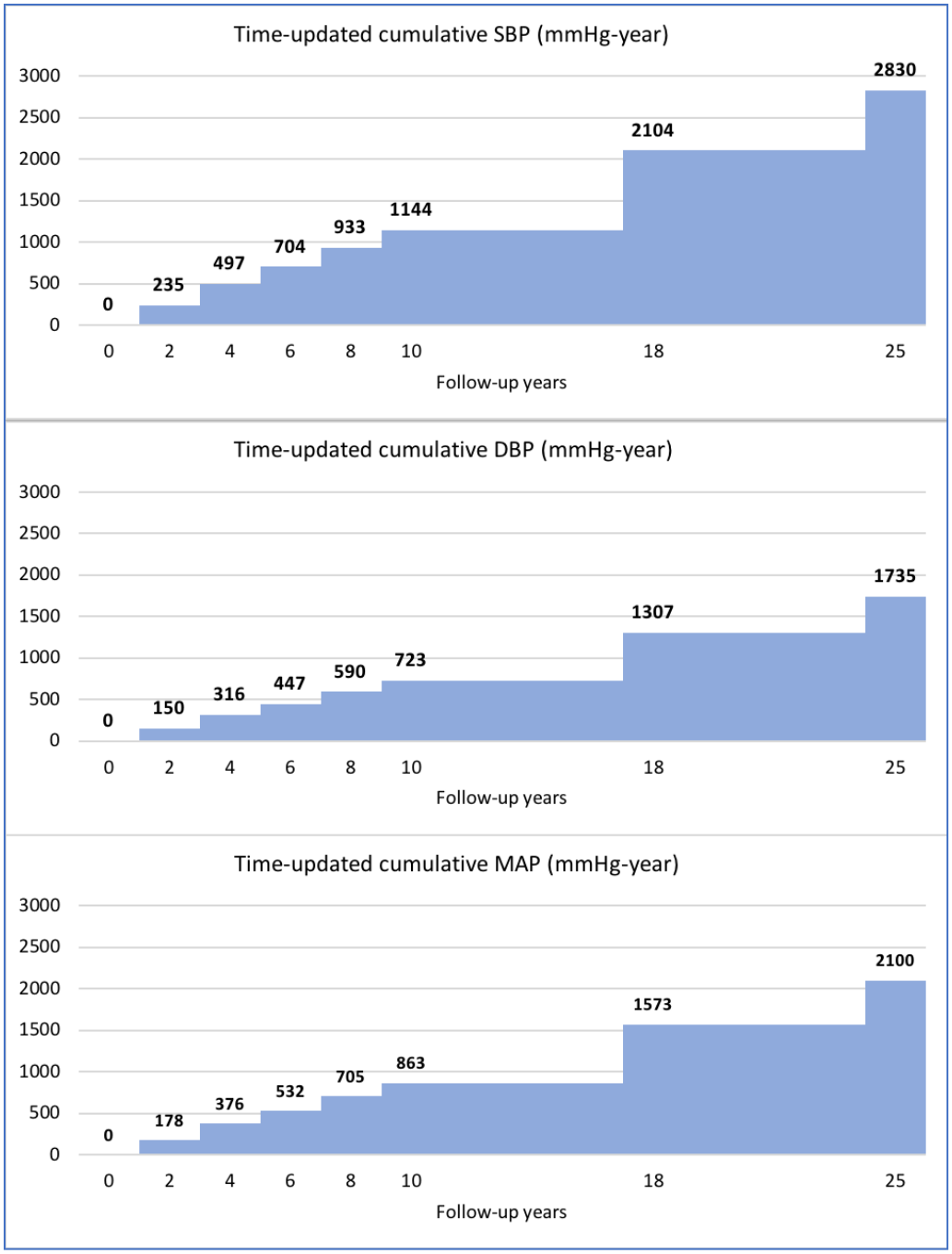


Figure 5 Time-updated Cumulative BPs (mmHg-Years) over the Follow-up

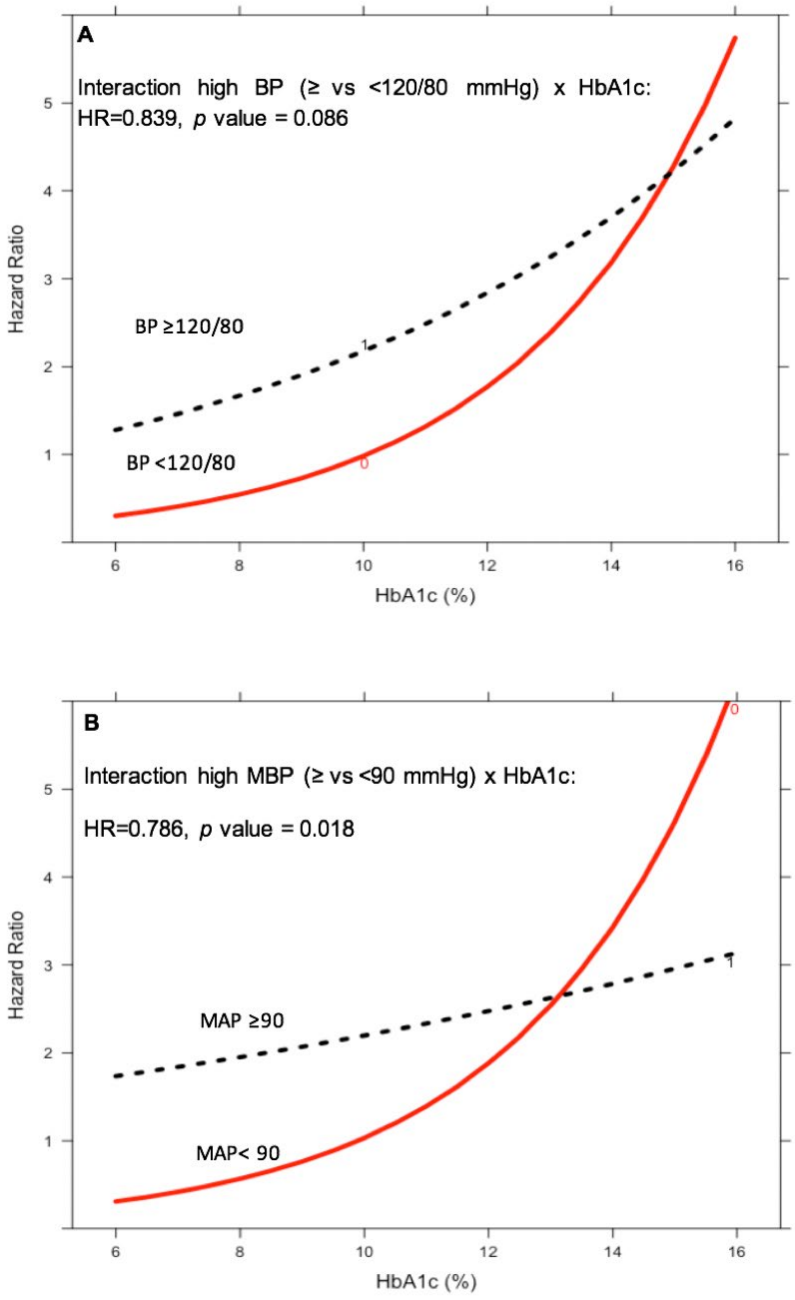


Figure 6 Model-based Interaction Plot between Time-weighted BP and HbA1c

BP: blood pressure; CAD: coronary artery disease, MAP: mean arterial pressure

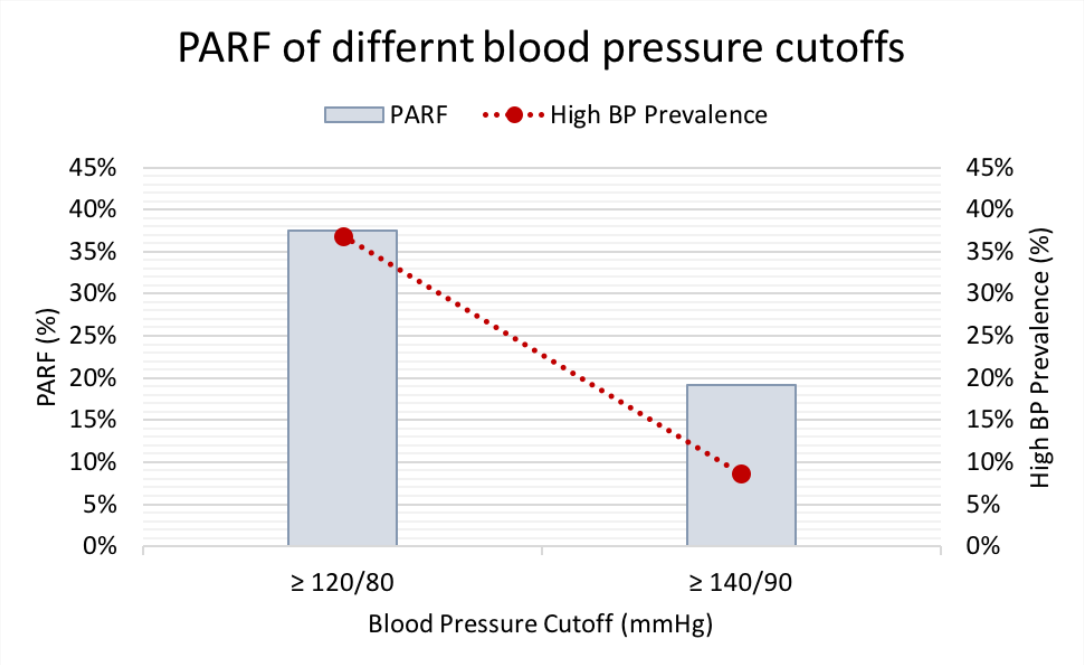


Figure 7 Population Attributable Risk Fraction (PARF) Estimation

4.0 Paper III: RAS Inhibition Effect on CAD Outcomes in Type I Diabetes

4.1 Background

T1D confers a high risk for cardiovascular disease [62,267]. Although the prevention and delay of microvascular complications have improved notably because of diabetes healthcare advances in recent years [47,57], risk of cardiovascular complications remains high [267]. A prior report from the Pittsburgh EDC Study has shown that cardiovascular disease is the leading cause of death in individuals who have lived with T1D over 20 years, accounting for over 60% of all-cause mortality [56].

RAS inhibition treatment (i.e., angiotensin-converting enzyme [ACE] inhibitors or angiotensin receptor blockers [ARBs]), is known to reduce proteinuria in addition to BP regulation [201,205–209], and is usually the first-line recommendation of antihypertensive therapy in diabetes patients with elevated BP. However, hypertension guidelines [86,220,257,268] have recently changed to recommend any class of antihypertensive agents for diabetes patients, with a preference for RAS inhibitors only in the presence of raised albuminuria. This guideline change is mainly based on evidence from recent head-to-head comparison clinical trials and associated meta-analyses, which have shown RAS inhibitors are not superior to other antihypertensive classes (thiazides, calcium channel blockers, and β receptor blockers) for decreasing cardiovascular risk [217,218]. It is important to note that this evidence was derived mostly from middle-aged or older type 2 diabetes patients who were already on antihypertensive treatment, and therefore may not be generalizable to younger people with T1D.

Unfortunately, clinical trial-based evidence of antihypertensive treatment recommendations in T1D is strikingly lacking and thus the question of whether RAS inhibition treatment reduces cardiovascular disease risk in the T1D population remains unanswered. While two observational analyses have indicated that the use of RAS inhibitors might be associated with decreased coronary artery calcification progression [222] or cardiovascular events [150], these studies were not primarily aimed to test the effect of RAS inhibition on cardiovascular outcomes. Also, they used common conditional models for treatment effect estimation, which, given the observational nature of the data, make statistical inferences of the treatment effect on the outcome, subject to observed and unobserved confounding factors [269]. Confounding by indication is a particular concern for the analysis of treatments like RAS inhibition.

The aim of the present study was, therefore, to rigorously evaluate the effect of RAS inhibition treatment (ACE inhibitors and/or ARBs) on incident CAD in individuals with T1D participating in the Pittsburgh EDC Study of childhood-onset T1D. Both most recent (time-invariant, the last value before the event or end of follow up) and time-varying RAS inhibition treatment effects were considered. In addition, we explored two potential pathways for RAS inhibition to affect CAD, the direct and indirect paths mediated by BP and albuminuria. To minimize the confounding effects in this observational study, inverse probability of treatment weighting based on a propensity score was employed in Cox models, testing the association between RAS inhibition treatment and CAD outcomes.

4.2 Methods

4.2.1 Study Population

Participants in this analysis were from the Pittsburgh EDC Study, which has previously been described in detail [233]. In brief, this is a historical prospective longitudinal cohort study of childhood-onset (<17 years of age) T1D, diagnosed between 1950 and 1980 at Children's Hospital of Pittsburgh. There were 658 eligible participants, who were initially examined between 1986 and 1988 (baseline). Subsequent clinical assessments took place biennially for the first 10 years, with further examinations at the 18- and 25-year follow-up visits. Since baseline, self-reported surveys were undertaken biennially to obtain updated information from the participants, including demographic and medical history, reproductive health, healthcare, and life styles. The EDC cohort has been shown to be epidemiologically representative of the T1D population in Allegheny County, Pennsylvania [234]. Of the 658 EDC participants, 605 were free from CAD at the start of the study and were selected for the present analysis. Participants were followed until the first occurrence of CAD, death, or 25th year of the study (2011-2014).

4.2.2 Ascertainment of Cardiovascular Outcomes

CAD was defined as myocardial infarction that was confirmed by Q-waves on an electrocardiogram (Minnesota codes 1.1 or 1.2) or hospital records, angiographic stenosis of ≥ 50%, revascularization, EDC physician-diagnosed angina, or ischemic ECG changes (Minnesota codes 1.3, 4.1–4.3, 5.1–5.3, and 7.1).

4.2.3 Medication Use Assessment

Participants self-reported medication use through biennial questionnaires for the entire duration of the EDC Study. Antihypertensive classification was identified using the ATC/DDD index, which comprises RAS inhibitors (ACE inhibitors and/or ARBs), β receptor blockers, calcium channel blockers, diuretics, and other types of antihypertensives. At each follow-up, a dichotomous indicator (yes/no) was created for each antihypertensive class.

4.2.4 Risk Factors Measurement

BP was measured by certified personnel according to the Hypertension Detection and Follow-up Program protocol [235] in a sitting position using the right arm after a participant had sat quietly for 5 min with an appropriate-sized cuff. The measurement was conducted by a Hawksley random zero sphygmomanometer in the initial 10 years of the study and by aneroid devices in the subsequent follow up visits. An average of the second and third readings was recorded for data analysis. Pulse rate (beats/min) was determined by palpitating the radial pulse for 30s and multiplying by two. BMI was calculated as the weight in kilograms divided by the square of the height in meters. An ever-smoker was determined as someone who had smoked at least 100 cigarettes in his/her lifetime. Hypertension was defined as a SBP ≥140 mmHg, a DBP ≥90 mmHg, or the use of BP lowering medications. A high waist-hip ratio (WHR) was defined as WHR >0.1 in men or >0.85 in women. Overt nephropathy was defined as urinary AER > 200 μg/min (300 mg/24h) in at least two of three validated timed urine collections. Onset of end stage renal disease (ESRD) was determined as starting dialysis or undergoing kidney transplantation.

HbA1 was measured by ion-exchange chromatography (Isolab, Akron, OH, USA) for the first 18 months, and the subsequent 10 years by automated high-performance liquid chromatography (Diamat; Bio-Rad, Hercules, CA, USA); the results of the two methods were highly correlated (r = 0.95). For follow-up beyond 10 years, HbA1c was measured with the DCA 2000 analyzer (Bayer, Tarrytown, NY, USA). The DCA and Diamat assays were also highly correlated (r = 0.95). The values were then converted to DCCT - aligned HbA1c using regression equations derived from duplicate assays [236]. Total cholesterol and triglycerides were determined enzymatically [237,270]. HDL cholesterol was obtained enzymatically with a precipitation technique (heparin and manganese chloride) using a modified version of the Lipid Research Clinics method [238]. Non-HDL cholesterol was defined as total cholesterol minus HDL cholesterol. An Ectachem 400 Analyzer (Eastman Kodak Co.) was used to measure serum creatinine. The estimated GFR was obtained using the CKD-EPI creatinine equation [271]. Urinary albumin was measured by immunonephelometry [239]. Urinary AER was calculated for each of the three, timed, urine samples (24-hour, overnight, and 4-hour collections obtained over a two-week period); the median of the three AERs was used in the analyses. There were 615 EDC participants having the haptoglobin genotype tested (haptoglobin 1/1, 2/1 and 2/2). For 486 participants having DNA sample, the haptoglobin was genotyped by an amplification method [272,273]; for the other 129 participants without DNA but with stored blood samples available, haptoglobin phenotype was assessed using an Elisa test [274].

4.2.5 Statistical Methods

Both baseline and most recent clinical characteristics of the study participants were examined, by status of incident CAD (cases vs non-cases) and most recent RAS inhibition treatment (users vs

non-users), respectively. Categorical variables were presented as a percentage (number) and continuous variables as a mean (SD) or median (1^{st} and 3^{rd} quantiles), as appropriate. The prevalence rates of antihypertensive use (RAS inhibitors only, other classes only, and both) were calculated by study cycle. The prevalence rates of using RAS inhibitors at each cycle were then calculated for CAD cases and non-cases, respectively. All prevalence rates were estimated according to antihypertensive usage before the first CAD occurrence.

We first analyzed the effect of the most recent RAS inhibition treatment, as a time-invariant variable, on incident CAD. The status of most recent RAS inhibition treatment was determined by the most recent medication usage information prior to the first CAD event occurrence for cases or at the end of the follow up for non-cases. The exposure-outcome association was assessed using an inverse probability treatment weighed (IPTW) Cox proportional hazard model with robust variance. The IPTWs of participants were calculated using the inverse of the estimated probability of receiving RAS inhibition treatment based on a multiple logistic regression model. Specifically, the model included covariates: age, sex, diabetes duration, college education (yes/no), family history of myocardial infarction, haptoglobin genotype (1/1, 2/1 and 2/2), baseline and most recent smoking status, most recent hypertension and renal disease status (overt nephropathy and/or ESRD), most recent WHR, SBP, PP, HbA1c, non-HDL and HDL cholesterol, triglycerides, WBC, GFR, urinary AER and historical use of RAS inhibitors. All covariates in this model were time-invariant, obtained from the last collection prior to the most recent RAS inhibition treatment. The IPTWs were stabilized by the marginal probability of the most recent use of RAS inhibitors. Of the 605 participants without known CAD at baseline, 565 had the haptoglobin genotype results and thus were included in the analyses of most recent RAS inhibition treatment (CAD events=207).

Mediation analysis using natural effect models [275,276] was subsequently employed to evaluate the mediation effect of BP and urinary albumin on the association of RAS inhibition treatment with CAD outcomes. The total effect was the sum of the direct and indirect effects; the mediated proportion was calculated as the ratio of indirect effect over total effect (mediated proportion = indirect effect / total effect). In this scenario, as the BP and urinary albumin levels were interdependent, the mediation effects of the two factors were tested individually and together. Specifically, SBP and urinary AER were used as mediators to be examined per 10 mmHg and per 1 log-unit (μg/min) change, respectively. A parametric survival model with a Weibull distribution to the follow-up time was employed during the mediation analysis, adjusting for the full set of covariates, as described above. The CIs of total, direct, and indirect effects were obtained via 5000 bootstrap repetitions. Simplified directed acyclic graph is shown in **Figure 8.**

Additionally, a marginal structural model with robust variance was employed to estimate the long term average effect of time-varying RAS inhibition treatment on CAD outcomes controlling for time-varying confounders [277]. The model-based inverse probability of the RAS inhibition treatment and the censoring status of participants were estimated using logistic regression models. Age, sex, diabetes duration, college education (yes/no), family history of myocardial infarction, haptoglobin genotype (1/1, 2/1 and 2/2), time-varying smoking, hypertension, and renal disease status (over nephropathy and/or ESRD), time-varying WHR, SBP, PP, HbA1c, non-HDL and HDL cholesterol, triglycerides, WBC, GFR and urinary AER were included in the models for inverse probability estimation. Weights were stabilized before being applied into the final exposure-outcome model.

Prior to the application of marginal structural models, missing data were handled using multiple imputations by chained equations (MICE) [278,279] for all variables that were included in the

analyses. A total of 50 datasets were imputed and analyzed; the results were subsequently pooled using Rubin's combination rules [280].

Of the 605 participants with up to 8 clinic visits (baseline, follow-up year 2, 4, 6, 8, 10, 18, and 25), the CAD outcome status was completely documented. There were 11.8%, 21.0%, and 25.3% of missing values for time-varying RAS inhibition treatment status, SBP, and urinary AER, respectively. The WHR had the highest missing rate of 50.0%, as it was not examined in three clinic visits (year 4, 6, and 8). Among the remaining covariates included in the analysis, the missing rates were no higher than 28.1% (WBC).

Two-sided tests were performed with a 5% level of significance. SAS 9.4 (SAS Institute, Carry, NC) and R 3.5.1 (R Core Team, Vienna, Austria) were utilized for statistical analysis.

4.3 Results

The mean age and diabetes duration of the 605 EDC Study participants free of CAD at study entry were 27 and 19 years, respectively; half of the cohort were females. There were 219 (36.2%) participants who experienced at least one CAD event during the follow-up period. Compared to participants without incident CAD, those who developed CAD were more likely to be older and less educated, have a longer duration of diabetes, smoke, take antihypertensive medications, have family history of myocardial infarction, have hypertension and/or renal disease, and have higher BMI, higher levels of BP, non-HDL cholesterol and urinary AER, and lower GFR at baseline **(Table 23).** In the primary analysis of time-varying RAS inhibition effect, participants were censored at their first loss to follow-up, and thus 192 CAD events were included in the final analysis. Sensitivity analysis that included all the CAD events (n=219) were conducted (only

participants who never came back were censored) and the results were similar as in the primary analysis (**Appendix B**).

Of all the participants, 42.3% (256) were most recent users of RAS inhibitors. The most recent participant characteristics are displayed in **Table 24**. Compared to non-users, RAS inhibitor users were less likely to smoke, more likely to be hypertensive and concurrently use other classes of antihypertensive medications and have higher BMI and BP and lower WBC levels.

The overall prevalence rate of antihypertensive use increased with longer follow-up time. RAS inhibitors have become the dominate treatment since the early 1990s (EDC Study cycle 3) (**Figure 9**). When examined retrospectively by CAD event status, cases had a higher prevalence rate of taking RAS inhibitors compared to non-cases over the entire follow up period (**Figure 10**).

In the weighted Cox model, most recent RAS inhibition treatment was associated with a 20% lower risk for incident CAD events compared to being untreated, though the results were not statistically significant (HR [95%CI]: 0.80 [0.54, 1.18]). Most recent use of β receptor blockers (HR [95%CI]: 0.92 [0.47, 1.79]) and calcium channel blockers (HR [95%CI]: 1.07 [0.63, 1.84]) did not show a clear protective effect on CAD outcomes **(Figure 11).**

In the mediation analysis **(Table 25)**, an increase of 10 mmHg in SBP and 1 log-unit (μg/min) in urinary AER explained 45% of the beneficial effect of RAS inhibition on CAD outcomes. Using the parametric survival model, the estimated total effect of RAS inhibition treatment was associated with a reduction in CAD events of 17% (HR [95%CI]: 0.83 [0.73, 0.96]). Of the total 17% risk reduction, 8% was mediated by BP and urinary albumin (HR [95%CI]: 0.92 [0.75, 1.07]); while the direct effect reduced the risk by a further 9% (HR [95%CI]: 0.91 [0.79, 1.05]). When SBP (per 10 mmHg) and urinary AER (per 1 log-unit [μg/min]) were individually

tested, the mediation proportion of the total effect attributable to each factor was 38.2% and 21.9%, respectively.

Finally, in the analysis of time-varying RAS inhibition treatment, using marginal structural modelling (**Figure 12**), the average effect of RAS inhibition decreased the CAD risk by 53% over the follow up period, again non-significantly (HR [95%CI]: 0.47 [0.15, 1.44]). Using the same analytical strategies, treatment with β receptor blockers (HR [95%CI]: 0.96 [0.20, 4.69]) or calcium channel blockers (HR [95%CI]: 1.16 [0.34, 3.99]) did not show an attenuation in CAD risk.

Sensitivity analyses with different model specifications were conducted and the results were presented in the Appendix B (**Table 30 and Table 31**).

4.4 Discussion

We used an observational study cohort of individuals with long standing T1D to evaluate the effect of RAS inhibition treatment on CAD outcomes. The IPTW-based modeling with robust variance was employed to reduce confounding in the association between treatment initiation and clinical outcomes. A trend indicating that RAS inhibition was associated with a clinically meaningful risk reduction for adverse cardiovascular outcomes was observed in the current analysis. A mediation analysis also showed that BP and albuminuria explained half of the association between RAS inhibitors and CAD events. These results suggest that RAS inhibition treatment may protect against adverse cardiovascular outcomes in individuals with T1D, although the association did not reach statistical significance.

RAS inhibitors have been demonstrated to reduce urinary albumin in addition to BP regulation [201,205–209]. Both high BP and albuminuria are independent risk factors of cardiovascular disease in the T1D population [151], and hence a major benefit of RAS inhibition would be anticipated. This large anticipated effect was not seen in the current analyses, though the results are consistent with a small effect. The CACTI study [222] reported a significant interaction effect between RAS inhibition treatment (ACE inhibitors and/or ARBs) and albuminuria on coronary artery calcification progression, showing that the positive association of albuminuria with coronary artery calcification progression was repressed by RAS inhibition treatment. This suggests that the cardiovascular protective value of RAS inhibitors is partially mediated by proteinuria reduction. In addition, a recent report from the DCCT/EDIC study, which exclusively examined many cardiovascular risk factors in their long-term follow up of this T1D cohort, showed the most recent RAS inhibition treatment was associated with a decreased risk of major atherosclerosis cardiovascular events [150]. It should be noted, however, that these prior studies were not primarily aimed to examine the effect of RAS inhibition treatment. Moreover, only standard modeling methods were employed without addressing confounding by indication between those who were treated and untreated in the statistical analysis.

Our study is consistent with results obtained from prior studies [150,222], and extends them by investigating the effect of RAS inhibition treatment on cardiovascular outcomes using IPTW-based modeling, a widely accepted statistical method used with observational data to better allow a causal interpretation of the exposure-outcome associations [281]. Moreover, the present analysis is unique for evaluating not only the most recent but also the long-term treatment effect of RAS inhibition over 25 years of follow up. We found the magnitude of risk reduction was greater in the evaluation of long-term RAS inhibition than it was in the analysis of most recent RAS inhibitor

use (CAD risk reduced by 29% vs 18%), suggesting that the cumulative beneficial impact on cardiovascular endpoints for continuing RAS inhibition in T1D individuals may increase with longer term treatment.

Although the point estimates derived from the present analyses consistently suggest a decreased cardiovascular risk for RAS inhibition treatment in this study, the wide CIs when using the robust variance for CI estimation, prohibit significant conclusions. In the analysis of the association between most recent RAS inhibition treatment and CAD outcomes, the 95% CI were close to borderline by using IPTW and robust variance estimation and became narrower and reached statistical significance when using the G-computation based method with a parametric survival model and bootstrap variance estimation (the total effect in the mediation analysis as shown in **Table 25**). The discrepancy of the two CIs as well as the slightly different point estimates may be explained by the two fundamentally different methods, the inverse probability based, and G-computation based methods. A much wider 95% CI, crossing over 1, was obtained from the test of the average effect of time-varying RAS inhibition on outcome events using the marginal structural model, and the bootstrap variance estimation did not show improvement (data not shown). The relatively small sample size, particularly when using time-varying predictors with multiple time points of measurement, resulted in an underpowered analysis and thus wide CIs. Furthermore, multiple imputations were employed to handle the missing data prior to the marginal structural modeling, and this may have increased the variability of the data. Consequently, these findings need to be confirmed in future studies with a larger sample size.

We are unable to conclude that RAS inhibition treatment has a causal effect on cardiovascular outcomes through the present study; however, we believe that our results, taken together with others [150,222], are encouraging and have important clinical implications, highlighting

the potential cardiovascular benefits of long-term RAS inhibition treatment in this high risk population. These findings support the need for interventional clinical trials to test the effect of the targeted-organ protection of RAS inhibition treatment in T1D.

One of the unique aspects of the present study is that we present a causal mediation analysis, which suggests that RAS inhibition treatment associated with decreased cardiovascular risk was only partially achieved through the pathways of lowering BP and urinary albumin excretion. This supports the hypothesis that RAS inhibition provides additional cardiovascular benefit beyond BP regulation and albumin excretion reduction. As stated above, a prior report from the CACTI study suggested the cardiovascular protective effect of RAS inhibitors was attained by reducing albuminuria [222], results which we have confirmed in this analysis by utilizing a formal mediation analysis. Indeed, animal evidence support that, in addition to BP regulation, RAS is involved in the pathophysiological pathways of oxidative stress, chronic inflammation, and fibroblast activation, leading to fibrosis, remodeling and then end-organ damage [216]. Furthermore, a reinforcing feedback cycle between RAS and hyperglycemia has been previously proposed based on animal studies [282]: the activation of RAS contributes to insulin resistance and altered glucose homeostasis, leading to hyperglycemia which further increases angiotensin II synthesis. Collectively, we think the present results are plausible and intriguing, indicating that RAS inhibition treatment might be superior to other classes of antihypertensives for targeted-organ protection, particularly in T1D individuals who are usually chronically exposed to hyperglycemia since the very early phase of life.

In addition to RAS inhibitors, we also tested the effects of β blockers and calcium channel blockers on CAD outcomes and did not observe a cardiovascular protective effect of these two antihypertensive classes in this cohort, which is in line with previous T1D studies [150,221]. Only a

small proportion of participants received non-RAS inhibition antihypertensive treatment alone in this cohort, which limits our ability to conduct a head-to-head comparison. However, these results suggest that RAS inhibition treatment might be superior to other classes of antihypertensive medications (β blockers and calcium channel blockers) for cardiovascular protection.

The observed treatment rates of antihypertensive medications progressively increased with longer follow up, which can be explained by increasing age and the disease course of diabetes over time. RAS inhibitors have been the dominant antihypertensive treatment since the early 1990s in this T1D population, which is consistent with the trial-based evidence supporting an albuminuria reduction effect of RAS inhibition over the last two decades. It is not surprising that the CAD cases had a higher treatment rate with RAS inhibitors as compared with non-cases even before the occurrence of CAD events, reflecting a confounding by indication bias. This emphasizes the importance of using appropriate statistical methods, as in the current analyses, to address the confounding effect between initiation of treatment and the risk of clinical outcomes, to draw valid statistical inferences.

This study was conducted within a well-characterized, epidemiologically representative, and long-term follow-up cohort of childhood-onset T1D. The analysis has focused on the association of RAS inhibition treatment with CAD outcomes in individuals who have lived with T1D since childhood. Being a longitudinal cohort with multiple follow-ups, the EDC Study has offered the opportunity to evaluate the long term effect of RAS inhibition treatment in this patient population. Appropriate statistical methods (i.e., IPTW and marginal structural modeling) were utilized to minimize the effect of differences between treated and untreated participants to obtain a causal interpretation of the findings. Moreover, the study is unique by conducting a causal

mediation analysis to estimate the direct effect of RAS inhibition on cardiovascular outcomes in addition to the indirect effect that was mediated by BP and albuminuria.

Several limitations of the present study should also be noted. Due to the observational nature of the study and the presence of unmeasured confounding, we are unable to definitively conclude that there is a causal effect of RAS inhibition treatment on CAD outcomes. The application of the IPTW approach should, however, have partially accounted for differences between participants who were treated and untreated with RAS inhibitors. The study is likely to be underpowered because of a relatively small sample size leading to wide confidence intervals. Lastly, the interpretation of the mediation analysis results warrants caution in a time-to-event study design, as the mediator effect might be underestimated as the occurrence of the event has a truncation effect on the mediator process [283].

4.5 Conclusion

RAS inhibition treatment was not statistically associated with CAD benefit in current IPTW based analyses, however, it tended to be associated with a decreased risk of CAD in individuals with long-standing T1D, and the beneficial effect appeared to be increased with longer term treatment. It was also evident that the cardiovascular protective effect of RAS inhibitors was only partially explained by lowering BP and albumin excretion, indicating that RAS inhibition may provide cardiovascular benefits beyond BP regulation and albuminuria reduction. Our study suggests that clinical trials of RAS inhibition treatment on clinical complication outcomes in the T1D population may be warranted.

4.6 Tables and Figures

Table 23 Baseline Characteristics of Participants by RAS Inhibitor Use Status

Baseline characteristics	Total	Most recent use of RAS inhibitors		Incident CAD	
	N=605	No (n=349)	Yes (n=256)	Non-cases (n=386)	Cases (n=219)
Age, years	27.2 (7.7)	27.2 (8.0)	27.2 (7.4)	24.8 (7.2)	31.3 (6.8) **
Age at diabetes onset, years	8.2 (4.1)	8.3 (4.0)	8.1 (4.1)	8.1 (4.2)	8.3 (3.8)
Diabetes duration, year	19.0 (7.4)	18.9 (7.6)	19.1 (7.2)	16.7 (6.6)	23.0 (7.1) **
Female, %(n)	49.8 (301)	50.4 (176)	48.8 (125)	51.0 (197)	47.5 (104)
College education, %(n)	42.6 (258)	41.8 (146)	43.8 (112)	47.7 (184)	33.8 (74) **
Family history of MI, %(n)	41.3 (248)	40.3 (139)	42.8 (109)	32.6 (124)	56.6 (124) **
Haptoglobin 1/1	11.5 (65)	10.6 (35)	12.8 (30)	12.3 (44)	10.1 (21)
Haptoglobin 2/1	46.0 (260)	43.6 (144)	49.4 (116)	47.2 (169)	44.0 (91)
Haptoglobin 2/2	42.5 (240)	45.8 (151)	37.9 (89)	40.5 (145)	45.9 (95)
Ever smoker, %(n)	37.2 (225)	40.7 (142)	32.4 (83) *	30.3 (117)	49.3 (108) **
BMI, kg/m^2	23.5 (3.2)	23.4 (3.3)	23.7 (3.1)	23.2 (3.2)	24.0 (3.2) **
High WHR[a], %(n)	4.8 (29)	4.1 (14)	5.9 (15)	5.2 (20)	4.2 (9)
Hypertension, %(n)	14.4 (87)	11.5 (40)	18.4 (47) *	7.8 (30)	26.0 (57) **
SBP, mmHg	112.9 (14.7)	111.5 (14.0)	114.7 (15.6) **	109.9 (12.3)	118.1 (17.1) **
DBP, mmHg	72.5 (10.8)	71.6 (11.3)	73.7 (10.2) *	70.8 (9.8)	75.5 (12.0) **
PP, mmHg	40.4 (10.3)	39.9 (9.2)	41.0 (11.5)	39.1 (9.6)	42.7 (10.7) **
HbA1c, %	8.8 (1.5)	8.8 (1.5)	8.7 (1.5)	8.8 (1.5)	8.7 (1.5)
Non-HDLc, mg/dL	135.7 (41.7)	135.9 (43.0)	135.5 (39.8)	127.6 (38.8)	149.9 (42.9) **
HDLc in men, mg/dL	49.5 (9.8)	48.8 (9.5)	50.4 (10.1)	50.8 (10.0)	47.3 (9.0) **

Table 23 Continued

HDLc in women, mg/dL	58.4 (12.9)	57.1 (12.2)	60.4 (13.6) *	58.9 (13.0)	57.5 (12.5)
Triglycerides, mg/dL	82 (60, 121)	83 (62, 126)	80 (58, 118)	76 (57, 108)	93 (70, 141) **
WBC, x1000/m^3	6.6 (1.9)	6.7 (1.9)	6.4 (1.9) *	6.4 (1.8)	6.9 (2.0) **
GFR, mL/min per 1.73 m^2	103.8 (30.8)	103.3 (32.4)	104.5 (28.4)	108.3 (30.1)	95.9 (30.4) **
AER, µg/min	14 (7, 102)	15 (7, 115)	14 (8, 97)	11 (7, 42)	39 (9, 470) **
Over nephropathy/ESRD, %(n)	22.6 (137)	23. 5 (82)	21.5 (55)	14.5 (56)	37.0 (81) **
Antihypertensive use, %(n)	13.3 (78)	11.8 (40)	15.4 (38)	7.6 (28)	23.0 (50) **
RAS inhibitors,	2.9 (17)	0.6 (2)	6.1 (15) **	1.6 (6)	5.1 (11) *
β blockers, %(n)	3.3 (19)	3.9 (13)	2.5 (6)	2.2 (8)	5.1 (11)
Calcium channel blockers, %(n)	0.3 (2)	0.3 (1)	0.4 (1)	0.6 (2)	0 (0)

Categorical variables were presented as percentage (number) and continuous variables as mean (SD) or median (1^{st} and 3^{rd} quantile)

[a] High WHR defined as >1.0 if men or > 0.85 if women

*p < 0.05, ** p < 0.01 between comparisons

AER: urinary albumin excretion rate, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, DBP: diastolic blood pressure, ESRD: end stage renal disease, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, PP: pulse pressure, RAS: renin angiotensin system; SBP: systolic blood pressure, SD: standard deviation, WBC, white blood cell count, WHR: waist-hip ratio

Table 24 Most Recent Characteristics of Participants

Most recent collection	Total	Most recent use of RAS inhibitors		Incident CAD	
	N=605	No (n=349)	Yes (n=256)	Non-cases (n=386)	Cases (n=219)
Follow-up time, years	17.8 (8.0)	16.0 (8.5)	20.3 (6.5) **	20.8 (6.7)	12.5 (7.3) **
Age, years	43.9 (8.6)	42.2 (8.7)	46.2 (8.0) **	45.4 (8.7)	41.2 (7.8) **
Current smoker, %(n)	17.7 (107)	20.9 (73)	13.3 (34) *	13.2 (51)	25.6 (56) **
BMI, kg/m^2	26.1 (4.5)	25.4 (4.3)	26.9 (4.7) **	26.5 (4.7)	25.3 (4.2) **
High WHR[a], %(n)	17.9 (108)	16.1 (56)	20.3 (52)	20.1 (77)	14.2 (31)
Hypertension, %(n)	44.0 (266)	31.0 (108)	61.7 (158) **	42.2 (163)	47.0 (103)
SBP, mmHg	117.9 (17.1)	115.8 (15.5)	120.7 (18.7) **	115.4 (15.7)	122.2 (18.5) **
DBP, mmHg	71.2 (11.6)	70.8 (11.7)	71.8 (11.4)	70.0 (10.7)	73.4 (12.7) **
PP, mmHg	46.6 (14.4)	45.0 (13.1)	48.9 (15.8) **	45.4 (13.4)	48.8 (15.8) **
HbA1c, %	8.7 (1.8)	8.7 (1.8)	8.6 (1.8)	8.4 (1.8)	9.0 (1.6) **
Non-HDLc, mg/dL	136.3 (42.2)	138.7 (43.5)	133.0 (40.2)	129.0 (41.5)	149.1 (40.5) **
HDLc in male, mg/dL	49.3 (11.4)	49.1 (11.7)	49.7 (12.3)	51.0 (11.7)	46.6 (10.4) **
HDLc in female, mg/dL	61.1 (15.4)	59.8 (14.5)	63.0 (16.5)	61.5 (15.5)	60.4 (15.3)
Triglycerides, mg/dL	84 (61, 123)	88 (61, 134)	82 (57, 117)	78 (55, 113)	100 (71, 152) **
WBC, x1000/m^3	7.1 (2.2)	7.3 (2.2)	6.8 (2.0) **	6.8 (2.0)	7.5 (2.3, 5.9) **
GFR, mL/min per 1.73 m^2	90.0 (30.6)	90.5 (31.2)	89.3 (29.7)	92.4 (29.2)	85.6 (32.4) *
AER, μg/min	15 (6, 158)	13 (6, 144)	20 (6, 191)	10 (5, 60)	64 (11, 489) **
Over nephropathy/ESRD, %(n)	35.4 (198)	33.4 (109)	38.2 (89)	27.9 (97)	47.9 (101) **
Concurrent use of β blockers, %(n)	11.2 (68)	8.9 (31)	14.5 (37) *	11.1 (43)	11.4 (25)
Concurrent use of calcium channel blockers, %(n)	12.2 (74)	10.6 (37)	14.5 (37)	12.4 (48)	11.9 (26)
Concurrent use of any antihypertensive class other than RAS inhibitors, %(n)	29.6 (179)	22.6 (79)	39.1 (100) **	28.0 (108)	32.4 (71)

Categorical variables were presented as percentage (number) and continuous variables as mean (SD) or median (1st and 3rd quantile)

[a] High WHR defined as >1.0 if men or > 0.85 if women

*p < 0.05, ** p < 0.01 between comparisons

AER: urinary albumin excretion rate, BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, DBP: diastolic blood pressure, ESRD: end stage renal disease, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, PP: pulse pressure, RAS: renin angiotensin system; SBP: systolic blood pressure, SD: standard deviation, WBC, white blood cell count, WHR: waist-hip ratio

Table 25 Mediation Effect of BP and Albuminuria on the Association of Most Recent RAS Inhibition with CAD

RAS inhibition effect	Total	Direct	Indirect
Mediated by SBP (per 10 mmHg) and urinary AER (per 1 log[AER])			
HR (95%CI)	0.83 (0.73, 0.96)	0.92 (0.79, 1.05)	0.91 (0.75, 1.07)
Mediation proportion	100%	55.2%	44.8%
Mediated by SBP (per 10 mmHg)			
HR (95%CI)	0.83 (0.73, 0.96)	0.90 (0.79, 1.02)	0.94 (0.76, 1.11)
Mediation proportion (%)	100%	61.8%	38.2%
Mediated by AER (per 1 log [AER])			
HR (95%CI)	0.83 (0.73, 0.96)	0.88(0.77, 1.00)	0.95 (0.79 1.14)
Mediation proportion (%)	100%	70.5%	29.5%

CAD: coronary artery disease, CI: confidence interval, HR: Hazard ratio, RAS: renin–angiotensin system, SBP: systolic blood pressure

The CIs were obtained using 5000 bootstraps

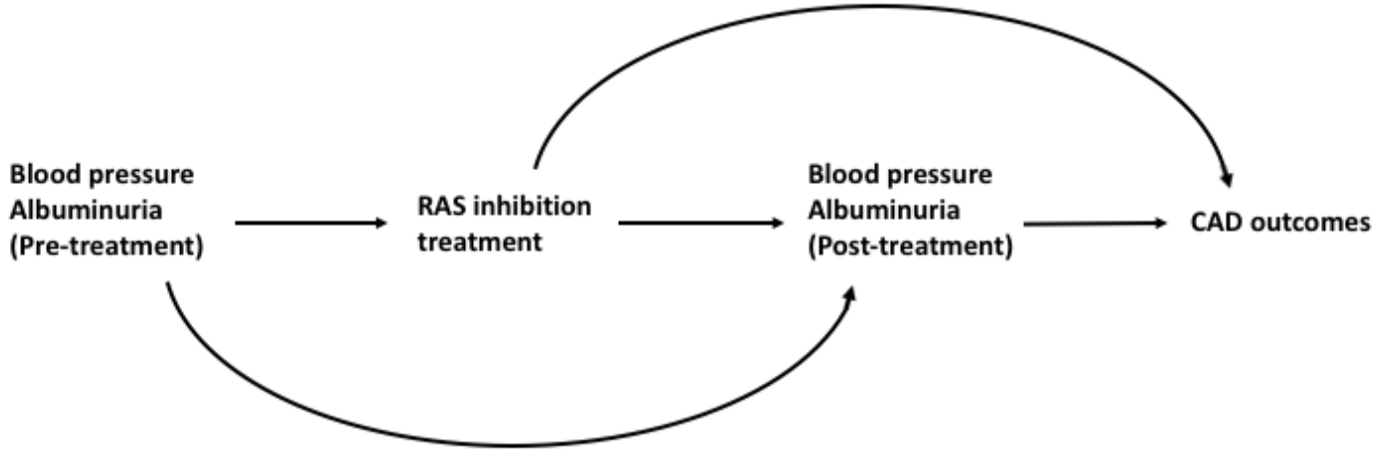
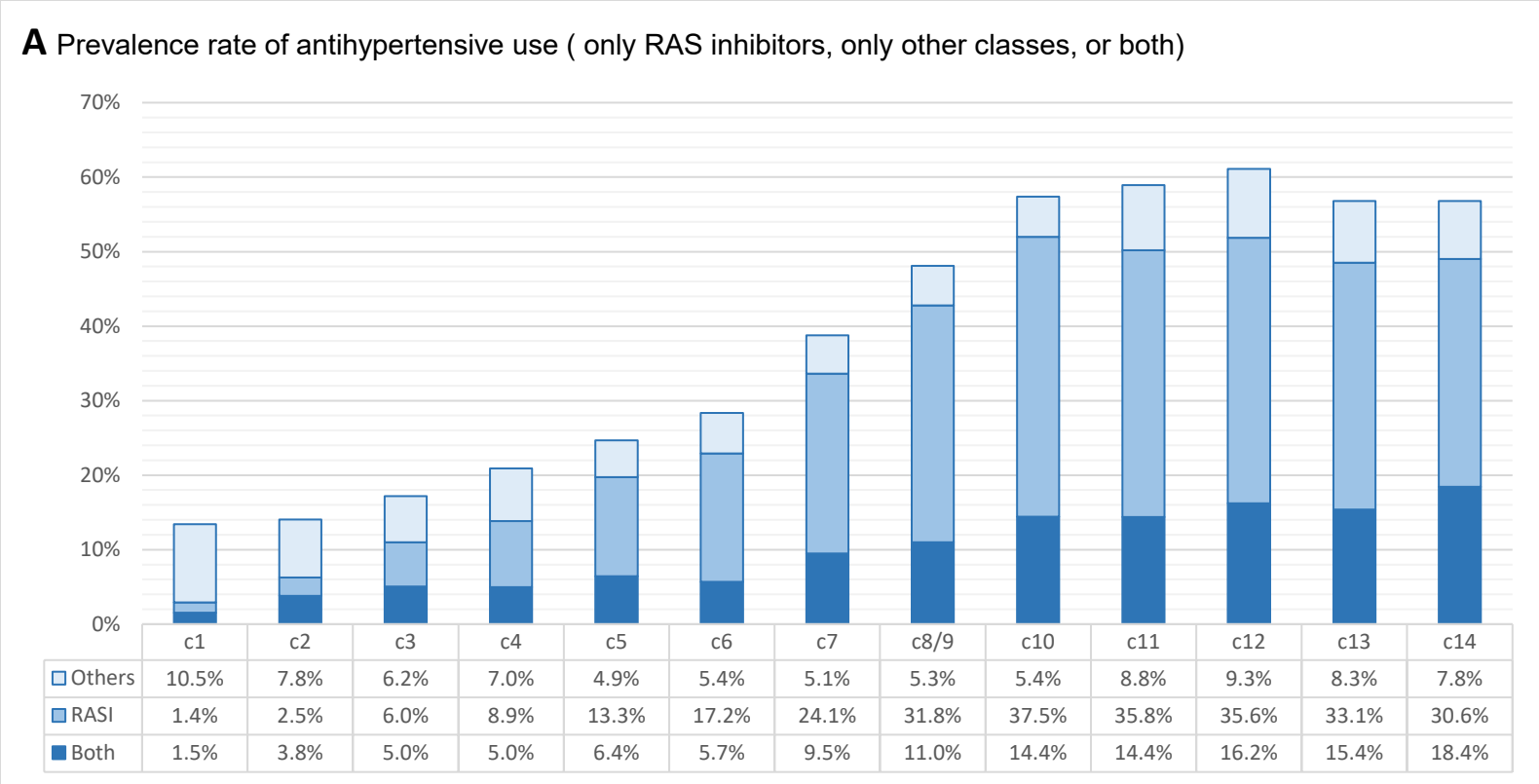


Figure 8 Simplified Directed Acyclic Graph to Illustrate the Association of RAS Inhibitors with CAD

CAD: coronary artery disease, RAS: renin–angiotensin system

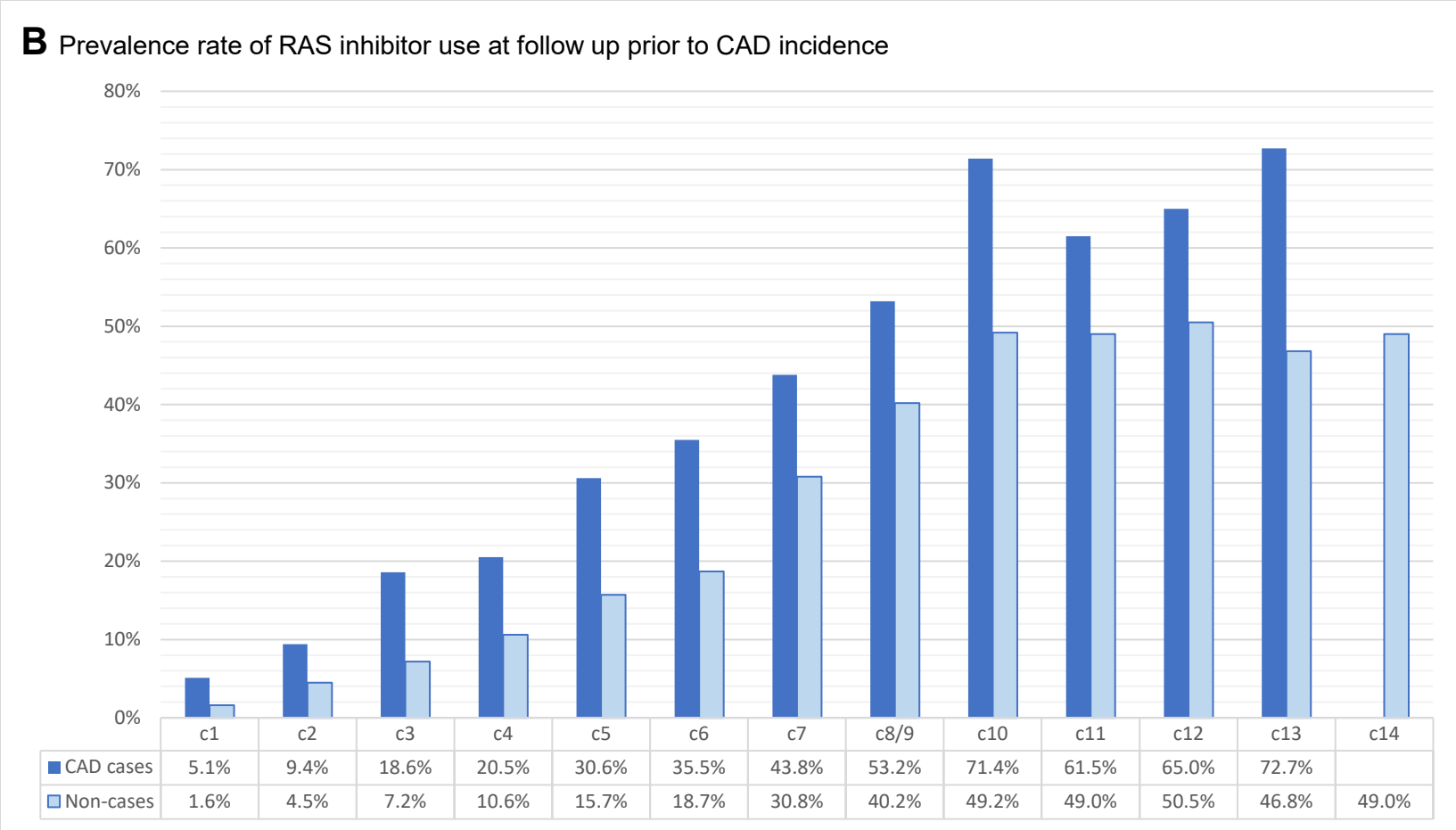


	c1	c2	c3	c4	c5	c6	c7	c8/9	c10	c11	c12	c13	c14
Others	10.5%	7.8%	6.2%	7.0%	4.9%	5.4%	5.1%	5.3%	5.4%	8.8%	9.3%	8.3%	7.8%
RASI	1.4%	2.5%	6.0%	8.9%	13.3%	17.2%	24.1%	31.8%	37.5%	35.8%	35.6%	33.1%	30.6%
Both	1.5%	3.8%	5.0%	5.0%	6.4%	5.7%	9.5%	11.0%	14.4%	14.4%	16.2%	15.4%	18.4%

Figure 9 Prevalence of Antihypertensive Use over the Fullow-Up

CAD: coronary artery disease, RASI: renin–angiotensin system inhibitors

C1: 1986-1988, C2: 1988-1990, C3: 1990-1992, C4: 1992-1994, C5: 1994-1996, C6: 1996-1998, C7: 1998-2000, C8/9: 2000-2004, C10: 2004-2006, C11: 2006-2008, C12: 2008-2010, C13: 2010-2012, C14: 2012-2014



	c1	c2	c3	c4	c5	c6	c7	c8/9	c10	c11	c12	c13	c14
CAD cases	5.1%	9.4%	18.6%	20.5%	30.6%	35.5%	43.8%	53.2%	71.4%	61.5%	65.0%	72.7%	
Non-cases	1.6%	4.5%	7.2%	10.6%	15.7%	18.7%	30.8%	40.2%	49.2%	49.0%	50.5%	46.8%	49.0%

Figure 10 Prevalence of RAS Inhibitor Use Prior to CAD Incidence

CAD: coronary artery disease, RASI: renin–angiotensin system inhibitors

C1: 1986-1988, C2: 1988-1990, C3: 1990-1992, C4: 1992-1994, C5: 1994-1996, C6: 1996-1998, C7: 1998-2000, C8/9: 2000-2004, C10: 2004-2006, C11: 2006-2008, C12: 2008-2010, C13: 2010-2012, C14: 2012-2014

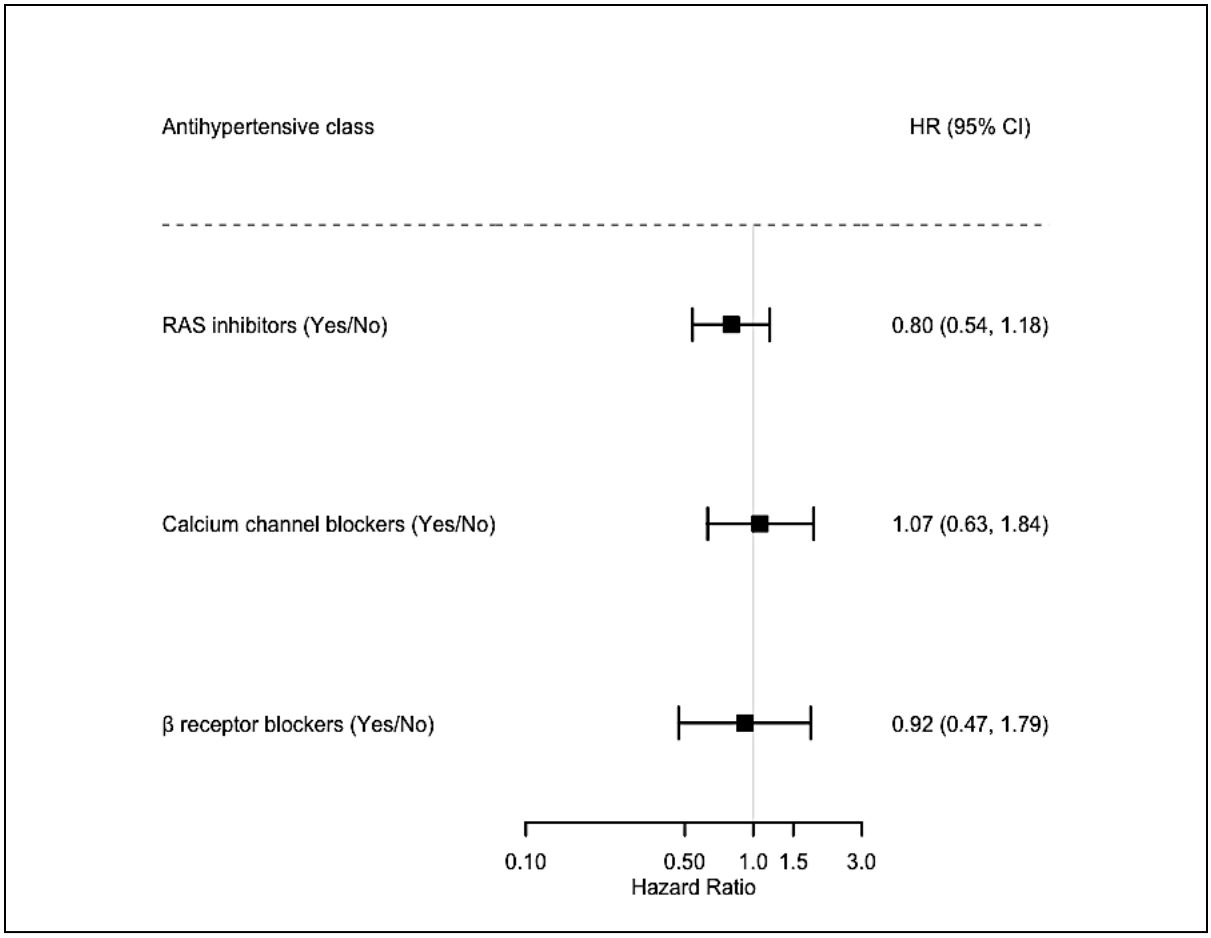


Figure 11 The Effect of Most Recent RAS Inhibition Treatment on CAD

CAD: coronary artery disease, CI: confidence interval, HR: hazard ratio, RAS: renin–angiotensin system

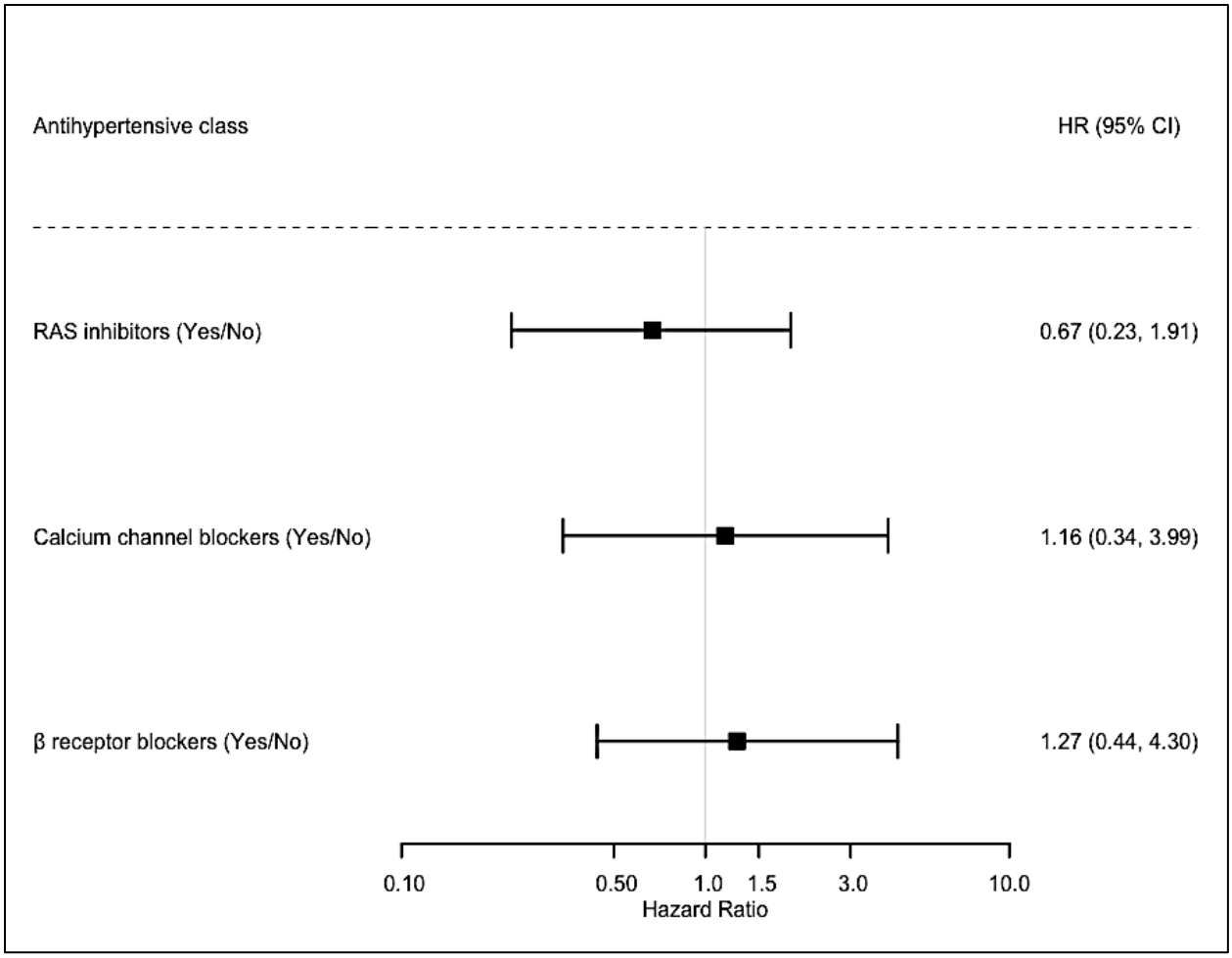


Figure 12 The Average Effect of Time-varying RAS Inhibition Treatment on CAD

CAD: coronary artery disease, CI: confidence interval, HR: hazard ratio, RAS: renin–angiotensin system

5.0 Contextual Discussion of Research Findings

5.1 Introduction

The findings of this dissertation reflect a comprehensive examination of risk prediction and control of BP on cardiovascular complication outcomes in T1D. Our first objective was to assess the comparative predictive utilities of different BP indices (SBP, DBP, PP, MAP, and MidBP) on CAD outcomes. We have demonstrated that all five BP indices are independent predictors of incident CAD in the EDC Study cohort of T1D with a long term follow up and diabetes duration. Although PP is less effective for cardiovascular risk prediction in the entire cohort, its prognostic significance improves and becomes comparable to SBP in age 35 years and older and/or with poor glycemic control. This likely reflects an early onset of glycation-included vascular stiffening in T1D.

Our second objective was to determine optimal BP targets that were associated with minimal cardiovascular risk among young adults with T1D, in an effort to provide evidence for developing BP management recommendations for this high-risk population. Notably, there is absence of high-quality data to guide BP goals in T1D. Using time-weighted variables that reflect a long-term exposure to high BP from youth throughout midlife, we have found dose-gradient associations of SBP, DBP and MAP with CAD outcomes, beginning at approximately 120, 80 and 90 mmHg, respectively. Furthermore, our data have shown BP may play an even more important role for cardiovascular risk prediction in those T1D individuals with lower glycaemia exposure. This suggests a lower BP goal (i.e., 120/80mmHg) may be needed than currently recommended (140/90mmHg) for young T1D adults.

Our third objective was to examine the effect of RAS inhibition treatment (ACE inhibitors and/or ARBs) on long term CAD outcomes in T1D. To obtain a causal interpretation of the exposure-outcome association in an observational study, appropriate statistical methods (propensity score based IPTW, marginal structural model, and causal mediation analysis) have been utilized under a causal-inference framework. In this analysis, RAS inhibitors, but not β blockers or calcium channel blockers, tended to reduce the CAD risk in T1D, though the results did not reach statistical significance. Any beneficial effect of RAS inhibition appeared to increase with longer term treatment. Mediation analysis indicated the cardiovascular protective effect of RAS inhibitors is partially achieved through pathways beyond lowering BP and urinary albumin, the two prominent effects of this class of antihypertensive therapy. These findings indicate that long term RAS inhibition treatment may offer superior cardioprotection for individuals with long standing T1D.

5.2 Major Findings

5.2.1 Predictive Utilities of Different BP Components

SBP is recognized as the primary predictor of cardiovascular risk, which has been supported by studies in both the general population [248,284,285] and the type 2 diabetes population [231]. The present study extends previous work to the T1D population and confirms that, among five BP indices (SBP, DBP, PP, MAP and MidBP), SBP is a preferred predictor of cardiovascular risk in this patient population. A recent position paper by the ADA [254] indicated that DBP might be a strong determinant of cardiovascular disease in adults less than 50 years, according to the findings in the

general population from the Framingham heart study [89]. However, in the ADA paper, there was an absence of prior evidence regarding the T1D population. Our study fills this gap in the research by providing evidence derived from a group of young T1D individuals with a mean baseline age of 27 years. SBP is shown to be a strong determinant relative to other BP measures in our analyses of the entire study cohort, i.e., only SBP was retained in the final model among all five BP indices with LASSO modelling for risk factor selection. In addition, we observed an early decrease in DBP beginning in the late 30s, which further supports SBP, in relation to DBP, as a preferred predictor of cardiovascular risk in T1D individuals even in their early adulthood. Furthermore, the reliability of DBP appears to be inferior to SBP with regard to measurement [87]. It's been controversial as to whether DBP should be determined by the fourth or fifth Korotkoff sound, although the current guidelines support the fifth phase. In addition, there are situations in which the fifth Korotkoff cannot reliably be determined for identifying the DBP, i.e., in pregnant women and children [87]. Taken together, we consider SBP to be a primary predictor for cardiovascular risk in T1D, relative to DBP, MAP, MidBP and PP.

5.2.2 Temporal Change in BP Reflects Accelerated Vascular Aging in T1D

As a sign of vascular aging, arterial stiffness contributes to an increase in SBP and a decrease in DBP in older individuals, resulting in an increase in PP [90,286]. In the general population, age-related impaired vascular compliance, as indicated by lowering DBP [89] along with widening PP [89], was observed by age 50 and 60 years and was found to increase cardiovascular risk [225,287]. However, the temporal change in BP in the aging process has not been well described in people with long lasting T1D. In this work, we have characterized temporal changes in different BP components from young adulthood throughout middle-age in a cohort of individuals who was living with the

T1D since their childhood. SBP progressively increases according with age. Moreover, there is an early decrease in DBP beginning in the late 30s and early 40s, leading to an early rise in PP. When examined retrospectively by incident CAD status, CAD cases experience not only a higher SBP across all ages but also a decline in DBP 10 years earlier than seen in the non-cases.

In sum, these findings are an important contribution to our in-depth understanding of the magnitude of the accelerated vascular aging process and its impact on cardiovascular outcomes in people with long-standing T1D. Our results suggest that the vascular aging process in this group of T1D individuals is accelerated by 20-30 years compared to the general population in whom DBP decreases and PP rises beginning in the fifth and sixth decades [89]. More importantly, this accelerated vascular aging is shown to be related to adverse cardiovascular outcomes in this high-risk population. We believe these findings partially explain the substantially high risk of premature cardiovascular events in the T1D population as early as in their 30s and 40s [62].

We subsequently found that PP is a strong determinant of CAD outcomes particularly in people aged 35 years and older and/or in those who have poor glycaemia control. This finding further supports that premature vascular aging is a risk factor of CAD in T1D individuals, beginning in the third or fourth decade of life. Our results are consistent with previous mechanistic studies, suggesting the pathogenesis of premature stiffening in vessel walls in diabetes has been related to the extra exposure to glycation [250,251]. These results also support the DCCT's findings that CAD risk can be reduced by intensive glycemic control in T1D [256]. Although the tests of model fit improvement were not statistically significant with combined SBP and PP versus a single SBP measure in this cohort, the collective findings implicate PP as a useful marker for vascular aging and cardiovascular risk in T1D individuals aged 35 years and older, especially considering its ease of measurement in clinical settings.

5.2.3 High BP is a Important Risk Factor

In line with previous studies on T1D [147–150], we have demonstrated that high BP plays an important role in the development of CAD in this patient population. These results are highly consistent in examining different BP variables, such as single time-point baseline values, time-weighted values, and cumulative exposures calculated in mmHg-years. Our results have indicated the inadequacy of BP control in real-world clinical settings in the modern T1D population. Indeed, a previous EDC report [118] has examined the change of predictors of major complication outcomes in two subcohorts of the study separated by 10 years (diabetes diagnosed in 1960-1969 and 1970-1979, respectively) but otherwise comparable in terms of age and diabetes duration. The study demonstrated that hyperglycemia, high cholesterol and smoking were significant predictors only in the earlier diagnosed subcohort but not in the later diagnosed one. Only hypertension was consistently shown to be a strong predictor in both subcohorts, suggesting it remains a poorly treated risk factor in the contemporary T1D population. Interestingly, another recent EDC report [288] looked at the achievement of concurrent ADA recommendations of different cardiovascular risk factors, and showed that attainment rate of BP goals remained high throughout the EDC follow-up (89.7% at baseline and 87.4% at 25-year follow-up). Taking together, it seems that T1D individuals have experienced a good compliance regarding BP control according to concurrent guidelines; meanwhile, studies consistently demonstrated that high BP remains a major cardiovascular risk factor in same cohort. This apparent paradox leads us to believe that the currently recommended BP goals may not be low enough to minimize cardiovascular risk in young adults with T1D. High BP is modifiable, and it is relatively easy and economical to manage. It is thus upsetting that it has remained a poorly treated risk factor for adverse health outcomes in this high-risk population.

Our results regarding the interaction between BP and HbA1c are also intriguing and clinically meaningful. We have found that high BP is a more powerful predictor of CAD outcomes in participants with lower glycaemia exposure than in those with higher glycaemia exposure. These results might partially explain the remaining increased cardiovascular risk in T1D individuals, even in those with effective glycemic control [267]. These findings also indicate the importance of BP control in so-called "lower risk" groups, such as individuals with good glycaemia control. An initial focus on glycemia control is necessary when very high, but as HbA1c approached the high normal range, an increasing focus on BP becomes critical.

5.2.4 A Lower BP Goal than Currently Recommended is Needed in T1D

The current ADA recommendation of BP target 140/90 mmHg [254,257] is based on trial results derived exclusively from type 2 diabetes patients in middle age and older [154]. Although a tighter BP control may be considered for younger adults with T1D according to the recommendations, there has been an absence of clinical trial-based evidence in guiding BP targets in younger T1D individuals. Because diabetes onset is earlier in people with T1D than in those with type 2 diabetes, the disease has a significantly larger impact on life expectancy and cardiovascular risk in the former population [56,147]. Therefore, we believe the evidence based on the general population or type 2 diabetes population should not be simply extrapolated to young T1D adults. One of the major findings in this work is that SBP and DBP, approximately starting at 120 and 80 mmHg, respectively, are associated with a substantially increased risk of CAD outcomes. The cardiovascular risk was doubled in participants with BP ≥ 120/80 mmHg compared with those < 120/80 mmHg, even in the fully adjusted models. In an exploratory, sensitivity, analysis of those who reported having "never" or "ever" taken antihypertensive medications, a BP ≥ 120/80 mmHg,

vs < 120/80 mmHg, was consistently and significantly associated with an increased risk of CAD. These findings suggest inadequate BP management in both untreated and treated T1D individuals in whom CAD risk might have been reduced if they had been adequately treated.

Combined, our results suggest that the currently recommended BP target of 140/90 mmHg may be too high for maximal cardiovascular protection in the young to middle-aged T1D population. Instead, our findings suggest that a BP management goal of <120/80 mmHg may be associated with minimal CAD risk. Because of the lack of interventional randomized trials with clinical outcomes in BP management goals in T1D, observational evidence from an epidemiological representative and well-characterized T1D cohort, such as the EDC Study, could be important and helpful for clinical recommendation development. If BP trials are not going to be conducted in this high-risk population, it would seem reasonable to strengthen the ADA recommendations to embrace a lower goal of 120/80 mmHg for young and middle-aged adults with T1D.

5.2.5 RAS Inhibition Offers Direct Cardioprotection

In the last part of our work, we conducted an exploratory analysis to evaluate the effect of RAS inhibition treatment (ACE inhibitors and/or ARBs) on CAD outcomes in T1D. A trend indicating that RAS inhibition is associated with a clinically meaningful risk reduction for adverse cardiovascular outcomes was observed in the current analysis, and the RAS inhibitors offer direct cardioprotection beyond the recognized pathways of BP control and albuminuria reduction. Although the main results are not statistically significant, and we are unable to definitively conclude that there is a causal effect of RAS inhibition treatment on CAD outcomes, we do think

these findings have clinical relevance, in that they shed light on RAS inhibitors as a potential prioritized choice of antihypertensive therapy in T1D individuals.

According to a meta-analysis of the data collected in 19 randomized trials in the diabetes population, RAS inhibition treatment (ACE inhibitors and/or ARBs), in the absence of albuminuria, was not found to afford superior cardioprotection compared to other antihypertensive agents [217]. Notably, all these trials enrolled only type 2 diabetes participants. Thus, the evidence may not be generalizable to younger TD1 individuals. It is disappointing that the Adolescent T1D Cardio-Renal Intervention Trial (AdDIT) did not show a reduction in urinary albumin in T1D adolescents [289]. In addition, in the AdDIT trial, ACE inhibitors did not significantly lower SBP z scores, and also failed to show significant effects on subclinical cardiovascular markers, i.e., carotid intima-media thickness and asymmetric dimethylarginine. However, we could not use these results to indicate the long-term effect of RAS inhibition treatment on clinical outcomes of targeted organs in this patient population.

By developing a causal inference framework and utilizing appropriate statistical methods to address confounding by indication between those who were treated and untreated, we have investigated the likelihood of a casual association of RAS inhibition treatment with CAD outcome and the two potential pathways to link the exposure and outcome. Although this part of our work has not been fully explored at this stage (alternate outcome evaluation, e.g., major atherosclerotic cardiovascular events [MACE]), we hope the applications of causal inference and the implications of the results will eventually be informative in developing clinical guidelines for this high-risk population. Because of the high costs and practical difficulties of conducting a randomized trial in a rare disease population for examining chronic outcomes, studies such as ours could be valuable and helpful to provide information in guiding clinical practice.

5.3 Strengths

The present study was conducted using existing data from the Pittsburgh EDC Study of childhood-onset T1D. The EDC Study is based on a well-characterized prospective longitudinal observational cohort with good representativeness of the T1D population in Allegheny County, Pennsylvania [234]. BP measurement was conducted by trained and certified research staff, strictly following the Hypertension Detection and Follow-up program Protocol [235]. Diabetes complications were assessed biennially; more than 150 risk markers were assayed at various time points over the follow-up period. Overall, the EDC cohort has been an extremely valuable source of research on T1D complications. In particular, the long-term follow-up of the study with multiple surveys and exams has allowed us to evaluate the risk of long-term exposure to high BP as well as the long-term effects of RAS inhibition treatment on the CAD outcomes. In addition, no previous study, to our best knowledge, has conducted a similar comprehensive evaluation of BP with adverse cardiovascular outcomes in a T1D cohort, including the predictive utilities of different BP measures, optimal BP thresholds associated with minimal cardiovascular risk, as well as how BP, as a cardiovascular risk factor, interacts with hyperglycemia. Because of the absence of trial-based evidence, the above information has major clinical implications for BP management in this high-risk population. Propensity score method has been employed in examining the effect of RAS inhibition treatment on CAD outcomes, which allows the study to achieve some of the characteristics of randomized clinical trials by minimizing the effect of differences between treated and untreated participants. This method has controlled for the measured confounding factors. It is important to note that, however, unlike randomized trials, propensity score analyses have the limitation that remaining unmeasured confounding factors may still be present.

5.4 Limitations

The present work has several limitations. Since participants in the EDC Study cohort were mainly Caucasian, the results may not be generalizable to other races and ethnicities. Due to the observational nature of the study and the presence of unmeasured confounding, we are unable to definitively conclude that there is a causal effect of RAS inhibition treatment on CAD outcomes. However, we think this association is likely to be causal in examining causality by using the Bradford Hill criteria [290]. The association of RAS inhibition treatment with CAD outcomes has met six of the nine Hill's criteria, including consistency (results were in line with previous studies [150,222]), specificity (studied in T1D population), temporality (RAS inhibition treatment information was collected prior to the event occurrence), dose-gradient (the effect size was increased with longer term therapy), biological plausibility and coherence (animal studies support the direct cardioprotection of RAS inhibition beyond lowering BP [216]). Moreover, being observational, we could not evaluate the risk benefit ratio of the lower BP targets, medication use, and adverse side effects. Some of the analyses (i.e., marginal structural models) are likely to be underpowered because of a relatively small sample size leading to wide confidence intervals. Although the EDC Study has been followed over 25 years, the cohort is still relatively young. We, therefore, have limited power to examine specific cardiovascular outcomes at this point in time, such as stroke, cardiovascular mortality, myocardial infarction, and "softer" outcomes (e.g., angina or coronary stenosis >50%). However, we have used a rigorous assessment of CAD events and have previously demonstrated that this is a valid outcome for evaluation of risk prediction models [147].

5.5 Future Research

Several research questions still remain to be answered with regard to BP management in the T1D population. Hypertension begins to affect T1D individuals at a young age [125,126]. However, very few previous studies reported the ways in which BP from youth throughout young adulthood is related to complication outcomes in this population. In future research, we intend to evaluate the trajectories and the magnitude of risk of elevated BP for complication outcomes in a subgroup of the EDC cohort with a baseline age < 27 years. This is a comparable age group to the Life For A Child (LFAC) program, a global health program which has been focusing on helping T1D children in resource-limited countries. This younger group tends to have a shorter diabetes duration at baseline, which offers us the opportunity to study individuals from an early phase of diabetes. It is also of greater direct relevance to the youth onset nature of the EDC cohort as baseline measures are available at a young age. The current series of studies has focused on a composite CAD outcome of soft and hard events. An outcome of MACE, which has been a standard endpoint measured in randomized clinical trials, should also be examined in the further research, especially on the evaluation of BP management goals and the effects of RAS inhibition treatment. Furthermore, a comparative effectiveness analysis based on large datasets is needed to directly compare the effects of RAS inhibitors and other classes of antihypertensive medications.

5.6 Public Health and Clinical Implications

The United States has both the largest T1D population and the highest diabetes-related health expenditures in the world [47]. T1D has affected approximately a million people in the nation

according to the NHANES of 1999-2010 [48]. Cardiovascular disease is the leading cause of death in long standing T1D [56]. Advances in diabetes care over the past couple of decades have resulted in a remarkable improvement in the prevention and delay of microvascular complications [57] as well as mortality [52]. However, the risk of cardiovascular complications remains high in T1D [62]. Although the causes of poor cardiovascular outcomes are multifactorial, we have focused on BP because this association is plausible and modifiable. It also has substantial clinical implications for long term healthy outcomes. Importantly, there are still major gaps in knowledge on effective BP control in this high-risk population to optimize cardiovascular health.

We have demonstrated SBP to be a reliable and powerful predictor of cardiovascular risk in T1D; PP starts rising when T1D individuals reach their late 30s and has shown strong prognostic significance on cardiovascular outcomes in age 35 and older. We also have found PP is particularly effective in risk prediction in those who have a higher glycemia exposure. Although no statistically significant improvement of model fit was observed for the combined BP measure of SBP and PP versus a single SBP in this cohort, these findings raise the possibility that, in addition to SBP, PP may also be helpful to incorporate into the clinical evaluation in the T1D population, for those who are over 35 years of age and/or have poor glycaemia control.

Even though high BP has consistently been identified as a strong and independent cardiovascular risk factor in the T1D population [147–150], there still is a lack of trial-based evidence to guide BP management goals. We have found the SBP and DBP below the thresholds of 120 and 80 mmHg, respectively, are associated with minimal cardiovascular risk. Our findings, from an epidemiological representative and longitudinal T1D cohort, raise the need for those settling treatment guidelines to consider lower goals (120/80mmHg) than now exist (140/90mmHg), especially for young adults with childhood-onset T1D as in the EDC cohort. Indeed, using the

PARF calculation, we have found that a BP cutoff 120/80 mmHg, compared to the cutoff 140/90 mmHg, is able to identify a further 18% CAD events in this TD cohort, or nearly doubling of the PARF.

Very limited evidence has documented whether or not RAS inhibition treatment affords superior cardioprotection in T1D. A preference for RAS inhibitors was only recommended in the presence of raised albuminuria according the current ADA guidelines. Our current results have supported that RAS inhibition treatment tends to reduce cardiovascular risk in individuals having long-standing T1D, and the beneficial effect seems enhanced with longer term treatment. Moreover, we have found evidence that RAS inhibitors might offer cardiovascular benefit beyond BP control and albuminuria reduction in this patient population. These findings add important information to the understanding of how RAS inhibition affects cardiovascular health. The results also implicated interventional clinical trials of RAS inhibitors in the T1D population may be warranted.

In aggregate, this body of work has therefore demonstrated a comprehensive examination of risk prediction and control of BP on cardiovascular outcomes in T1D. Our findings from a representative and long-term follow-up study cohort have contributed to filling some of the critical gaps in the understanding of the magnitude of risk of high BP associated with adverse cardiovascular outcomes as well as its management in relation to minimal risk. Our results thus have important implications in clinical practice and preventive medicine, emphasizing the importance of effective BP control for further reduction in cardiovascular risk in this high-risk population.

Appendix A Supplemental Materials of Paper II

Table 26 Time-updated Cumulative BPs (mmHg-years) with CAD (Adjutment for Age but not Diabetes Duration)

	Model for SBP		Model for DBP		Model for MAP	
Variables[1]	HR (95% CI)	p value	HR (95% CI)	p value	HR (95% CI)	p value
Cumulative BP (per 500 mmHg-years)	1.3 (1.03, 1.6)	0.027	1.5 (0.99, 2.1)	0.054	1.4 (1.02, 1.9)	0.038
Age	2.2 (1.9, 2.6)	<0.001	2.3 (1.9, 2.7)	<0.001	2.3 (1.9, 2.6)	<0.001
Female	1.3 (0.9, 1.9)	0.099	1.4 (0.9, 1.9)	0.083	1.3 (0.9, 1.9)	0.088
Ever smoking	1.04 (0.8, 1.4)	0.801	1.1 (0.8, 1.4)	0.741	1.05 (0.8, 1.4)	0.761
BMI	0.9 (0.7, 1.04)	0.127	0.9 (0.7, 1.04)	0.128	0.9 (0.7, 1.04)	0.126
HbA1c	1.3 (1.02, 1.5)	0.033	1.2 (1.01, 1.5)	0.037	1.2 (1.01, 1.5)	0.035
non-HDL cholesterol	1.6 (1.4, 2.0)	<0.001	1.6 (1.4, 2.0)	<0.001	1.6 (1.4, 2.0)	<0.001
HDL cholesterol	0.8 (0.7, 0.96)	0.017	0.8 (0.7, 0.97)	0.020	0.8 (0.7, 0.96)	0.019
Raised albuminuria	2.5 (1.8, 3.6)	<0.001	2.6 (1.8, 3.6)	<0.001	2.5 (1.8, 3.6)	<0.001
Current antihypertensive use	0.4 (0.3, 0.6)	<0.001	0.4 (0.3, 0.6)	<0.001	0.4 (0.3, 0.6)	<0.001

Per SD increase if a continuous variable, unless specified

BMI, HbA1c, and lipids (non-HDLc, HDLc and triglycerides) were updated means (time- invariant) in the models

BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CI: confidence interval, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, HDLc: high density lipoprotein cholesterol, HR: hazard ratio, MAP: mean arterial pressure, SBP: systolic blood pressure, SD: standard deviation

Table 27 Dos-gradient Association of Time-weighted BPs and CAD (Adjustment for Age but not Diabetes Duration)

	Model 1		Model 2	
	HR (95% CI)	p value	HR (95% CI)	p value
SBP, mmHg				
<110	0.9 (0.6, 1.3)	0.498	1.1 (0.7, 1.6)	0.763
110 to <120	ref		ref	
120 to <130	1.6 (1.1, 2.4)	0.020	1.5 (1.02, 2.3)	0.039
130 to <140	2.3 (1.4, 3.7)	<0.001	1.9 (1.2, 3.0)	0.011
140+	3.2 (1.9, 5.4)	<0.001	2.6 (1.5, 4.5)	<0.001
DBP, mmHg				
<60	1.1 (0.6, 2.0)	0.689	1.0 (0.6, 1.8)	0.985
60 to <70	ref		ref	
70 to <80	1.9 (1.3, 2.7)	<0.001	1.8 (1.2, 2.6)	0.004
80 to <90	5.9 (3.9, 8.9)	<0.001	4.5 (2.9, 6.9)	<0.001
90+	9.3 (5.3, 16.3)	<0.001	5.6 (3.1, 10.2)	<0.001
MAP, mmHg				
<80	0.9 (0.6, 1.4)	0.780	1.0 (0.7, 1.5)	0.999
80 to <90	ref		ref	
90 to <100	2.8 (2.0, 4.0)	<0.001	2.4 (1.7, 3.5)	<0.001
100 to <110	4.3 (2.7, 6.9)	<0.001	3.1 (1.9,5.2)	<0.001
110+	13.6 (7.0, 2)	<0.001	8.3 (4.2, 16.4)	<0.001

Model 1: Adjusted for age, sex, and current use of antihypertensive medications
Model 2: Model 1+ time-weighted HbA1c, ever smoking, updated mean BMI, HDL and non-HDL cholesterol, and raised albuminuria
BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CI: confidence interval, DBP: diastolic blood pressure, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, HR: hazard ratio, MAP: mean arterial pressure

Table 28 Risk Stratification by Time-weighted BPs and Time-weighted HbA1c for CAD Risk Prediction (Adjustment for Age but not Diabetes Duration)

	Model 1		Model 2	
	HR (95% CI)	p value	HR (95% CI)	p value
SBP/DBP				
BP≥120/80 vs. <120/80	2.4 (1.8, 3.3)	<0.001	1.9 (1.4, 2.6)	<0.001
BP<120/80, and HbA1c<8	ref		Ref	
BP≥120/80, and HbA1c<8	2.4 (1.3, 4.3)	0.004	2.1 (1.1, 4.0)	0.028
BP<120/80, and HbA1c≥8	2.3 (1.4, 3.7)	0.001	1.7 (0.99, 2.9)	0.055
BP≥120/80, and HbA1c≥8	5.8 (3.5, 9.8)	<0.001	3.4 (1.9, 6.0)	<0.001
MAP				
MAP≥90 vs. <90	3.4 (2.5, 4.6)	<0.001	2.5 (1.8, 3.5)	<0.001
MAP<90, and HbA1c<8	ref		ref	
MAP≥90, and HbA1c<8	4.4 (2.4, 8.0)	<0.001	3.2 (1.7, 6.1)	<0.001
MAP<90, and HbA1c≥8	2.6 (1.6, 4.2)	<0.001	1.9 (1.1, 3.2)	0.017
MAP≥90, and HbA1c≥8	8.4 (5.1, 14.1)	<0.001	4.9 (2.7, 8.7)	<0.001

Model 1: Adjusted for age, sex, and current use of antihypertensive medications
Model 2: Model 1+ ever smoking, updated mean BMI, HDL and non-HDL cholesterol, and raised albuminuria
BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CI: confidence interval, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, HR: hazard ratio, MAP: mean arterial pressure

Table 29 Stratified Analysis of Time-weighted BPs and CAD by Antihypertensive Use Status (Adjustment for Age but not Diabetes Duration)

	Subgroup of **never** treated by antihypertensives (n=223, events=89)		Subgroup of **ever** treated by antihypertensives (n=382, events=130)	
	HR (95% CI)	p value	HR (95% CI)	p value
BP ≥ 120/80 vs. <120/80	2.1 (1.2, 3.7)	0.006	2.5 (1.6, 3.9)	<0.001
MAP ≥ 90 vs. <90	2.4 (1.4, 4.2)	0.001	3.8 (2.4, 5.9)	<0.001

Adjusted for age, sex, ever smoking, time-weighted HbA1c, and updated mean BMI, HDL and non-HDL cholesterol, and raised albuminuria

BMI: body mass index, BP: blood pressure, CAD: coronary artery disease, CI: confidence interval, HbA1c: hemoglobin A1c, HDL: high density lipoprotein, HR: hazard ratio, MAP: mean arterial pressure

Appendix B Supplemental Materials of Paper III: Sensitivity Analysis with Different Model Specifications

Table 30 Associations of Covariates with RAS Inhibition Exposure and with CAD Outcome

variables	p value		Covariates for Model 1	Covariates for Model 2	Covariates for Model 3	Covariates for Model 4
	Model A: Prediction of RAS inhibition exposure	Model B: Prediction of CAD outcomes	p value <0.25 in both RAS inhibition and CAD models	p value <0.25 in both models or only the CAD model	p value <0.25 in both models or only RAS inhibition model	p value <0.25 in either of the two models
Age	0.15	0.00	v	v	v	v
Diabetes duration	0.28	0.15		v		v
Female	0.10	0.75			v	v
MI family history	0.05	0.15	v	v	v	v
College education	0.30	0.12		v		v
Diabetes diagnosis year < vs ≥ 1965	0.08	0.60			v	v
Haptoglobin allele	0.44	0.25		v		v
Ever smoked at baseline	0.21	0.31			v	v
Race	0.49	0.71				
HbA1c	0.05	0.00	v	v	v	v
Current smoker	0.28	0.20		v		v
BMI	0.43	0.43				
High WHR	0.35	0.61				

Table 30 Continued

SBP	0.91	0.14		v		v
Hypertension	0.00	0.30			v	v
DBP	0.90	0.48				
eGFR	0.19	0.05	v	v	v	v
Urine AER	0.00	0.02	v	v	v	v
non-HDL	0.03	0.96			v	v
HDL	0.33	0.01		v		v
Triglycerides	0.80	0.65				
WBC	0.15	0.62			v	v

Table 31 Association of Time-varying RAS Inhibition and CAD outcomes by Different Model Specifications

Covariates	Model 1	Model 2	Model 3	Model 4	Model 5 (More parsimonious)
Age	v	v	v	v	v
Diabetes duration		v		v	
Female			v	v	v
MI family history	v	v	v	v	v
College education		v		v	v
Diabetes diagnosis year $<$ vs $\geq$ 1965			v	v	
Haptoglobin allele		v		v	v
Ever smoked at baseline			v	v	
Race					
HbA1c	v	v	v	v	v
Current smoker		v		v	
BMI					
High WHR					
SBP		v		v	v
Hypertension			v	v	
DBP					
eGFR	v	v	v	v	v
Urine AER	v	v	v	v	v
non-HDL			v	v	v
HDL		v		v	v
Triglycerides					
WBC			v	v	
No.of Covariates	5	11	11	17	11
HR (95%CI)	0.77 (0.27, 2.23)	0.72 (0.24, 2.15)	0.74 (0.25, 2.18)	0.62 (0.23, 1.77)	0.58 (0.19, 1.77)
HR (95%CI) *	0.64 (0.22, 1.85)	0.51 (0.16, 1.62)	0.62 (0.20, 1.87)	0.52 (0.18, 1.53)	0.41 (0.13, 1.33)

* Other than SBP and AER, the other variables are time-invariant updated mean

Appendix C Supplemental Materials of Paper III: Causal Mediation Analysis with Time-varying SBP and Albuminuria

Table 32 Mediaiton Analysis with Time-varying Covariates Using Controlled Direct Models

RAS inhibition effect	Total effect (from MSM [a])	Controlled direct effect	Mediation proportion (extrapolated)
Mediated by SBP (per 10 mmHg)			
HR (95%CI)	0.62 (0.23, 1.77)	0.73 (0.20, 2.59)	
	(100%)	(66%)	34%
Mediated by albuminuria (per 1-log unit of AER)			
HR (95%CI)	0.62 (0.23, 1.77)	0.74 (0.16, 3.35)	
	(100%)	(63%)	37%

AER: urinary albumin excretion ration, MSM: marginal structural model

[a]: results from the Model 4 in the Table 30 (Appendix B)

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