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Cardiovascular Risk in Children and Adolescents with Type 1 and Type 2 Diabetes Mellitus

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Abstract

Rising rates of both type 1 and type 2 diabetes mellitus in children have led to increased concern regarding cardiovascular disease (CVD) risk during childhood. Diabetic children face prolonged exposure to hyperglycemia, and have increased risk of both microvascular and macrovascular disease. These circumstances may result in a generation of young adults presenting with cardiovascular outcomes, a tremendous personal and public health toll. In this article, we review CVD risk in type 1 and type 2 diabetes, discuss aspects of pathophysiology, and review current methods of CVD risk assessment. We also identify crucial areas in need of future research in order to devise effective prevention and treatment of CVD risk in children.

Keywords

type 1 diabetes mellitus; type 2 diabetes mellitus; lipoprotein subclass particle analysis; adipokines; adiponectin; inflammation; cardiovascular risk; body mass index; pediatrics; lipids; obesity; carotid intimal medial thickness; flow mediated dilation of the brachial artery; pulse wave velocity; pulse wave analysis; echocardiography; left ventricular mass; coronary artery calcification

Introduction

Cardiovascular risk assessment in diabetic children has become critically important in pediatric preventative medicine. Though the pathophysiology differs, both type 1 (T1DM) and type 2 diabetes (T2DM) confer increased cardiovascular disease (CVD) risk. Moreover, rates of both types of diabetes are rising. T1DM incidence is increasing worldwide[1,2], particularly in children less than 5 years of age[3]. The rise in pediatric obesity[4] has led to increased insulin resistance and T2DM in children[5,6]. T2DM has risen from affecting less than 4% of newly diagnosed diabetic children before the 1990's, to current estimates of 15% in 10–19 year olds[7]. This is significant because both obesity and diabetes are risk factors for CVD[8]. In fact, in adults T2DM is considered a coronary heart disease equivalent[9]. Increases in both types of diabetes and their comorbidities during childhood may result in society being faced with a generation presenting with CVD decades younger than previously experienced.

Atherosclerosis begins in youth. The Pathobiological Determinants of Atherosclerosis in Youth Study[10], an autopsy study of subjects who died of external causes, revealed that intimal lesions were seen among 15 –19 year-olds in the aortas and in more than half of right

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coronary arteries. In young adult men, atherosclerosis severity increased with obesity[11]. The relationship between CVD risk factors and atherosclerosis was also investigated in subjects aged 2 to 39 years, as part of the Bogalusa Heart Study[12]. Body mass index (BMI), systolic and diastolic blood pressure, total cholesterol, triglycerides, low density lipoprotein cholesterol (LDL-C), and high density lipoprotein cholesterol (HDL-C) measured before death, were associated with arterial fatty streaks and fibrous plaques at autopsy. Furthermore, childhood obesity that persisted into adulthood was associated with elevated carotid intimal medial thickness (CIMT) at age 35 years. However, thin children who became overweight adults did not have elevated CIMT [13]. The Muscatine study found that increased BMI, decreased HDL-C, and increased blood pressure measured at average ages of 15 and 27 years, were associated with coronary artery calcification at a mean age of 33 years[14]. In the Young Finns Study, childhood LDL-C, systolic blood pressure, BMI, and smoking were associated with CIMT in adulthood [15]. Thus, CVD risk factors during childhood track into adulthood and cause morbidity and mortality.

Type 1 Diabetes

Research shows that 35% of individuals with T1DM will die of coronary artery disease by age 55yrs, compared to 4% of women and 8% of men without diabetes. Mortality rates increase rapidly after 30years of age, and are worse in those with renal disease[16]. T1DM confers an increased risk of both microvascular and macrovascular disease. The landmark Diabetes Control and Complications Trial (DCCT) established that intensive glucose control in T1DM decreased retinopathy, nephropathy, and neuropathy associated with the disease[17]. Follow up of this patient cohort longitudinally in the Epidemiology of Diabetes Interventions and Complications (EDIC) study demonstrated a relationship between tighter glycemic control and decreased CVD[18] and atherosclerosis[19] in T1DM. Hyperglycemia causes glycation of proteins, resulting in the formation of advanced glycation end products, which contribute to atherogenesis[20,21]. Other studies have also confirmed the importance of glycemic control. In adults with T1DM, having an HbA1c >7.5% was strongly associated with increased progression of coronary artery calcification measured by CT scan, compared to those with an HbA1c < 7.5%[22]. Studies in children are limited, but Shamir et al found that among a group of adolescents with T1DM, tighter glycemic control was associated with decreased oxidative stress and improved lipids[23]. Among the 195 adolescents who participated in the DCCT, those with tighter glycemic control had decreased retinopathy and nephropathy, although they also had increased hypoglycemia [17].

In addition to hyperglycemia, other contributors to CVD risk in T1DM include mitochondrial dysfunction and oxidative stress,[24] as well as insulin resistance[25], the latter traditionally considered more relevant to T2DM. In a subset of the CACTI study, insulin resistance was increased in T1DM compared to nondiabetic controls both with respect to glucose utilization and suppression of non-esterified fatty acids. In addition, insulin resistance was associated with the extent of coronary artery calcification in both type 1 diabetics and controls[25]. In children, Nadeau et al[26] used hyperinsulinemic clamp studies to show increased insulin resistance in nonobese type 1 diabetic adolescents compared to nondiabetic controls. The adolescents with T1DM also had decreased functional exercise capacity and cardiovascular dysfunction. Female youth with T1DM compared to nondiabetic controls showed evidence of delayed myocardial relaxation, unrelated to HbA1c and duration of diabetes, although findings were not as strong in male type 1 diabetics[27]. In addition, with increased childhood obesity in society[4], more children with T1DM may also be obese, potentially increasing the pathologic role for insulin resistance.

Type 2 Diabetes

CVD is a leading cause of death among individuals with T2DM[28,29]. Both obesity and insulin resistance are risk factors for T2DM, and are components of the "metabolic syndrome," a constellation of risk factors which also includes dyslipidemia and hypertension, and is predictive of CVD in adults[30]. Dyslipidemia is prevalent among obese children, with 17% to 43% having low HDL-C (depending on the cut-offs used) [31–33]. T2DM is caused by a combination of insulin resistance and defective insulin secretion. Insulin resistance is an important part of T2DM, but many feel that pancreatic beta cell function determines when those genetically at risk will develop T2DM[34], beginning with defective first phase insulin secretion [35]. T2DM also involves a decrease in beta cell mass, due to factors such as glucose toxicity on the beta cell and lipotoxicity. The United Kingdom Prospective Diabetes Study (UKPDS) established that a decrease in HbA1c in T2DM decreases the incidence of microvascular complications[36]. Follow-up studies of this cohort showed that the same is true for macrovascular complications as well [37,38]. As in T1DM, hyperglycemia can cause increased oxidative stress, glycosylation of proteins such as LDL-C (making them more atherogenic), decreased nitric oxide production, and increased coagulability, leading to endothelial injury and increased atherogenic risk [34]. In a meta-analysis of studies investigating the effect of improved glycemic control on macrovascular disease in both T1DM and T2DM, Stettler et al[39] found that overall, improved glycemia decreased the incidence of macrovascular disease in T1DM and T2DM. In T2DM the effect was more modest, and stronger in younger individuals with shorter disease duration. In another study comparing complications prevalence in youth with T1DM to those with T2DM, the authors found that those with T2DM had increased prevalence of microalbuminuria and hypertension than those with T1DM, even though the youth with T2DM had shorter disease duration and lower HbA1c[40].

Pathophysiology

The metabolic consequences of obesity and insulin resistance in T2DM also lead to a specific atherogenic lipid profile, *metabolic dyslipidemia* [41]. Increased liver free fatty acid levels lead to increased triglyceride production, decreased LDL-C breakdown, decreased apolipoprotein B degradation, and increased very low density lipoprotein (VLDL) secretion [42]. Through the transfer of cholesterol esters and the action of hepatic lipase, increased VLDL results in increased triglycerides, decreased HDL-C, and the production of small, dense LDL particles. Increased free fatty acids may result from insulin resistance impairing the suppression of lipolysis, or from an adipocyte defect in the incorporation of free fatty acids into triglycerides. Increased free fatty acids also suppresses glucose uptake in muscle cells, further increasing insulin resistance[42]. In both type 1 and type 2 diabetics, poor glycemic control is associated with increased total cholesterol, LDL-C and triglycerides[43].

The most recent pediatric CVD risk guidelines from the National Institutes of Health (NIH) National Heart, Lung, and Blood Institute (NHLBI) Expert Panel recommend universal lipid screening as well as more stringent cut-offs for normal triglyceride levels[44]. Moreover, it revised a previous scientific statement by the American Heart Association for children at high risk for CVD, which categorized T1DM as a high-risk condition and T2DM as moderate risk[45]. The new NHLBI guidelines state that based on increasing evidence of vascular disease in children with T2DM, both T1DM and T2DM should be included in the high risk category for risk stratification and management[44].

Inflammation is also a key factor causing atherosclerosis[46]. Factors such as elevated and modified LDL-C cause endothelial injury, triggering an inflammatory response. The endothelium becomes more adhesive for leukocytes and platelets, increasing permeability and pro-coagulant properties. Cytokines, cellular adhesion molecules, and growth factors

increase. Monocytes move to the endothelium, adhere to the surface, migrate into the subendothelium, and transform into macrophages. They take up lipoproteins, become foam cells, and initiate the fatty streak[46], the beginning of the atherosclerotic lesion. Further injury continues to attract macrophages, mast cells, and activated T cells, and the lesion grows [46–48]. Insulin resistance is also felt to be involved in atherogenesis. Markers of insulin resistance are related to coronary atherosclerosis, independent of traditional risk factors [49].

Traditional and Novel Risk Factors for CVD in Youth

The National Cholesterol Education Program (NCEP) identified the risk factors for early onset coronary heart disease in children and adolescents as elevated LDL-C, family history of early coronary heart disease, CVD or peripheral vascular disease, smoking, hypertension, HDL-C < 35 mg/dl, obesity, physical inactivity, and diabetes[50] As part of the SEARCH for Diabetes in Youth Study, Rodriguez et al compared the prevalence of CVD risk factors in children with T1DM and T2DM[51], defining CVD risk factors according to the NCEP ATP III modified for age[52]. These authors defined CVD risk factors as HDL-C< 40mg/dl, age- and sex- specific waist circumference >90%ile, systolic or diastolic blood pressure >90%ile for age, sex, and height (or taking hypertension medication), and triglycerides >110mg/dl. They found that 21% of diabetic children had at least two CVD risk factors- specifically 92% of children with T2DM and 14% of youth with T1DM[51]. Thus risk factors for CVD are clearly already present in youth with diabetes.

In a longitudinal study of fasting lipids in youth with T1DM, authors found that the prevalence of elevated LDL-C (>100mg/dl in diabetics compared to >110 mg/dl in nondiabetics[53]) increased from 50% to 58% after a minimum of 3 years follow up. Furthermore, the changes in LDL-C, non-HDL-C, total cholesterol, and triglycerides were significantly related to changes in HbA1c. Changes in BMI-z score over time were significantly associated with changes in LDL-C and total cholesterol[54]. Non-HDL cholesterol has more recently been used to assess CVD risk, and is calculated as total cholesterol less HDL-C. It includes LDL-C, VLDL-C, and atherogenic apo-B containing lipoproteins. The Bogalusa Heart Study found non-HDL-C predicted carotid intimal-medial thickness in young adults[55]. The Pathological Determinants of Atherosclerosis in Youth study found non-HDL-C was strongly related to asymptomatic early subclinical coronary atherosclerosis[56]. In teens, non-HDL-C was strongly associated with the metabolic syndrome, with a non-HDL-C of 120mg/dl and 145 mg/dl indicated high and very high risk of metabolic syndrome, respectively[57].

Optimal blood pressure for diabetic children is < 90%ile for age, sex, and height, or < 130/80 (whichever is lower), with ≥ 95%ile considered hypertension[53]. The SEARCH for Diabetes in Youth Study found that 73% of those with T2DM had elevated (≥ 90%ile) systolic or diastolic blood pressure, compared to 22% in T1DM[51]. These results were consistent with those of Eppens et al, who found that 36% of adolescents with T2DM had hypertension, compared to 16% of those with T1DM[40]. Hypertension plays an important role in the development of atherosclerosis. Among children with T1DM followed over 4 years, investigators found that systolic blood pressure at baseline was a significant predictor of CIMT increase over time[58]. In youth with T2DM, Shah et al found that systolic blood pressure z-score was significantly associated with increased common carotid IMT[59]. Wadwa et al compared arterial stiffness measures in youth with T1DM and T2DM. They found significantly worse arterial stiffness in those with T2DM, and that this difference was largely determined by higher blood pressures and increased central adiposity in T2DM[60]. Prospective studies will be needed to determine whether hypertension plays a larger role in increasing CVD risk in childhood T2DM compared to its effects in T1DM.

There are also several non-traditional CVD risk factors currently being used in research settings. Lipoprotein subclass particle analysis by NMR spectroscopy can yield important information about CVD risk, not evident from traditional lipid analysis[61]. Obesity and insulin resistance can lead to a highly atherogenic dyslipidemia pattern characterized by decreased HDL-C, increased TG, and increased small subspecies of LDL-particles[41]. In adults, small LDL[62], large VLDL, and small HDL[63] are associated with increased CVD risk. Smaller HDL[64], larger VLDL and small LDL[65] particles correlate with obesity and insulin resistance in children. Although small subspecies of LDL-particles not measured in routine pediatric clinical care, a recent study found that in white overweight youth, TG/HDL-C ≥ 3 and a non-HDL-C of ≥ 120mg/dl each predicted increased small atherogenic LDL-particles. In black overweight youth, these cut-offs were ≥ 2.5 for TG/HDL and ≥ 145 mg/dl for non-HDL-C[66]. These calculated measures based on a standard lipid panel hold great promise to identify children at increased CVD risk in clinical practice.

Inflammatory markers are also being measured by investigators. The liver produces high-sensitivity C-reactive protein (hs-CRP), which in adults is an independent predictor of CVD events [67], and is related to insulin sensitivity in the metabolic syndrome [68]. In children, hs-CRP is significantly elevated in obese compared to nonobese adolescents, but its association with insulin resistance is unclear [69,70]. Adipose tissue, now recognized as an endocrine organ, produces interleukin-6 (IL-6), which has also been associated with CVD in adults [67] and with obesity in children [70]. Both CRP and IL-6 were predictive of T2DM development in adult women of the Women's Health Study [71], suggesting that inflammation may play a role in diabetes development. Macrophages produce cytokines such as tumor necrosis factor alpha (TNF-α, also produced by adipose tissue), which act as mediators of T cell activation and foam cell formation [46], and of the acute phase response [72]. In adults [73,74] and children [75], TNF-α receptor II (TNFR2) has been found to be higher in obese subjects with impaired glucose tolerance, IR, and diabetes. Finally, the endothelium is also involved in inflammation, and produces cellular adhesion molecules such as intercellular adhesion molecule 1 (ICAM-1), which provide evidence of endothelial cell activation and dysfunction [76,77]. Endothelial dysfunction, as measured by ICAM-1, was found to be predictive of T2DM in women, independent of obesity or CRP [76], and was elevated in obese compared to nonobese children [78]. Plasminogen activator inhibitor-1 (PAI-1) is an inhibitor of fibrinolysis, and is secreted by several sources, including adipose tissue and vascular endothelium. It is increased in the inflammatory state, and associated with increased CVD risk.[79] These markers may provide incremental information in assessing CVD risk in obese children, but have been limited thus far to the research setting.

Adipocytes also produce adipokines which have inflammatory and/or atherogenic effects. Adiponectin and leptin have been implicated in the physiology of obesity and have receptors present throughout the cardiovascular system[80]. Adiponectin has anti-inflammatory and anti-atherogenic effects.[81,82] In adults, hypoadiponectinemia has been associated with insulin resistance, the progression of T2DM [83], and coronary artery disease [84], including among type 2 diabetics [85]. In children, adiponectin is decreased with obesity [70], insulin resistance [86], and T2DM [87]. The mechanism of adiponectin's seemingly protective effect is unknown. Our group showed lower adiponectin levels and a more atherogenic lipoprotein profile, both associated with increased insulin resistance, in obese compared to lean adolescents. Adiponectin was associated inversely with small LDL-P and small HDL-P, and positively with HDL-P size in obese adolescents, even after adjusting for BMI and insulin resistance.[88] In a study of obese children, Beauloye et al found that adiponectin, more than conventional CVD risk factors, was an independent determinant of CIMT[89]. Leptin acts at the hypothalamus to suppress appetite and regulate weight,[90] and has proinflammatory and proatherogenic effects[91]. It is positively associated with percent body fat, and obese individuals may have a degree of leptin resistance[92]. In a prospective treatment trial to

prevent ischemic heart disease, elevated plasma leptin levels predicted acute CVD events[93]. Leptin is also associated with intimal-medial thickness of the common carotid artery in normal weight and obese individuals[94].

Vitamin D deficiency (VDD) may be another non-traditional risk factor for CVD among youth with diabetes. Adults with T2DM have a higher prevalence of VDD than controls, and those with VDD had increased CIMT[95]. Among adult diabetics, VDD was associated with the presence of nephropathy as well[96]. In a recent study of adolescents with T1DM, VDD was associated with diabetic retinopathy, independent of diabetes duration and HbA1c[97]. Further research is needed to establish causation.

Vascular Imaging Studies

One of the obvious limitations to studying CVD risk in children is that the final outcome has not yet occurred. Therefore, valid surrogate endpoints are crucial. Noninvasive vascular imaging techniques, developed to investigate CVD risk in adults, are particularly suited to a pediatric population, given that they can detect early disease and that they are non-invasive. One of these techniques is carotid intimal medial thickness (CIMT), measured by Doppler ultrasound to evaluate subclinical atherosclerosis[98]. CIMT is established as an independent predictor of CVD risk in adults[99,100], and increased CIMT is a structural marker of early atherosclerosis. CIMT is higher in type 2 diabetic adults than healthy controls [101], and CIMT has been found to respond to treatment of T2DM [102,103]. Several studies have found that obese children have significantly increased CIMT than controls [104–106]. In a study of 129 adolescents and young adults with T2DM, Shah et al found that higher HbA1c and longer diabetes duration was associated with increased CIMT. For each 1% increase in HbA1c or 1 year in diabetes duration, there was a 30% increased odds of thicker CIMT. Moreover, among the T2DM cohort, males had worse CIMT[59] than females.

CIMT studies in youth with T1DM have had conflicting results, with some showing increased CIMT in children with T1DM[107–109], and others showing no difference[110–112]. Krantz et al not only found that children with T1DM had increased CIMT compared to controls, but also that CIMT was higher in those with T1DM and a complication such as retinopathy, hypertension, and/or microalbuminuria[109]. In a large study of more than 300 children with T1DM in Norway, investigators found that boys with T1DM, but not girls, had a statistically significant increase in CIMT[113]. In a study of 270 German children with T1DM, boys had significantly higher bilateral mean CIMT compared to females, and the authors developed sex-specific CIMT percentiles. CIMT was related to diabetes duration and pulse pressure in males, and with LDL-C, HbA1c, and diabetes duration in females[114]. However, longitudinal studies of CIMT in youth with diabetes are very limited. In children with T1DM, Dalla Pozza et al found that CIMT increased significantly over 4 years, and that the increase was predicted by baseline BMI z-score, diabetes duration, and systolic blood pressure[58].

Another vascular technique, flow-mediated dilation (FMD) of the brachial artery, is also measured by Doppler ultrasound[115–117]. FMD is measured after transient vascular occlusion, and is thought to be a measure of nitric oxide bioavailability, and thus endothelial function. FMD has been used to show that severely obese children have reduced endothelial function, compared to nonobese controls [118], which normalized after an exercise therapy intervention [119]. Several studies have found that obese children have significantly worse FMD [104,105,119]. Children with T1DM have impaired endothelial function compared to controls, within the first decade of diagnosis[110,120], and even in prepubertal children[112]. A recent study by Battelino et al found that 33% of children and adolescents with T1DM had endothelial dysfunction, as defined by endothelium dependent dilation of 3.3% or less[121], based on FMD measurements in healthy children by Jarvisalo et al[116]. This endothelial

dysfunction was independently negatively associated with HbA1c. Interestingly, it was also independently associated with the presence of a polymorphism of the endothelial nitric oxide synthase gene[121].

Arterial stiffness can be assessed using aortic PWV and pulse wave analysis (PWA) to obtain central pulse pressure (CPP). PWV measures arterial stiffness--a stiffer aorta conducts the pulse wave more quickly. It is a marker of CVD[122] and is increased in obesity[123]. Higher mean arterial BP increases PWV, but other factors are also operative. As the aorta stiffens, its ability to cushion stroke volume is diminished and the pulsatile energy of left ventricular contraction passes onto peripheral tissues. Increased pulsatile forces at smaller vessels contribute to vascular remodeling and hypertrophy, and target organ damage. PWA estimates reflected wave effects on central circulation. Increasing reflected wave magnitude affects ventricular systole and contributes to LV hypertrophy and coronary ischemia.

Arterial stiffness measures have been used in children to identify evidence of early CVD. In a pilot study, Gungor et al[124] found no difference in CIMT between 20 T2DM adolescents, 20 obese nondiabetics, and 22 lean controls, but did find differences in arterial stiffness. In "The Search for Diabetes in Youth" study[60] PWV was higher in T2DM (6.4± 1.3 m/s) vs T1DM (5.3±0.8 m/s), $p<0.0001$, suggestive of increased CVD risk in T2DM. Another group used T1DM data from the same study, and found that children with T1DM had increased PWV compared to controls, which was especially true in males. Also, traditional CVD risk factors such as blood pressure, BMI, and cholesterol correlated with PWV[125]. Collins et al found differences in arterial compliance already present in normotensive adolescent subjects[126]. Age-, height- and sex- specific reference values for PWV in children have been published as well[127]. Recent findings by Shah et al show racial differences in PWV. These investigators found that African American adolescents and young adults with T2DM had increased arterial stiffness compared to Caucasians with T2DM, and that this stiffness was mediated by different CVD risk factors in the two races[128].

Coronary artery calcification (CAC) measurement by electron beam computed tomography (CT) is another surrogate measure used to identify coronary atherosclerosis[98]. Studies measuring CAC in adolescents and young adults with T1DM, have had variable results, possibly due to the age of the youth studied as CAC develops late in the atherosclerotic process. Gunczler et al studied Hispanic children 3–16 years old with T1DM, and found no evidence of CAC in either diabetics or controls[129]. However, Starkman et al studied youth 17–28 years old with T1DM, and found that 10.9% had CAC[130]. Use of this technique in the pediatric population should be limited because of the radiation exposure involved and low likelihood of positive studies.

Left ventricular (LV) mass, measured by echocardiography, is associated with pediatric obesity[131], and is a predictor of cardiovascular events in adults[132,133]. Childhood obesity is associated with increased cardiac mass as an adult[134], and increased childhood weight may increase adult LV mass beyond expected based on growth alone[135]. Recently, Crowley et al showed that LV mass indexed for height was higher in this generation of children (not limited to obese) compared to a generation ago, due in part to increased BMI over time[136]. Furthermore, age-specific reference intervals for LV mass index in children have been published[137]. However, in adolescents with T1DM, Parikh et al did not find an increase in LV mass[111].

In recent novel studies, retinal photography has been used to measure retinal vascular geometry among adolescents with T1DM to predict microvascular complications. Benitez-Aguirre et al performed prospective studies in adolescents and young adults with T1DM,

and found that measures of retinal vascular geometry independently predicted diabetic retinopathy[138] and nephropathy[139] among type 1 diabetics 12 to 20 years old. Further studies will be needed to confirm these results.

Conclusion

With rates of T1DM and T2DM in children rising, it is crucial that physicians identify children at the greatest CVD risk and implement prevention and treatment measures during childhood. Many have been reluctant to put children going through the growth and puberty associated with adolescence on pharmacologic therapy. However, the alternative may not be very reassuring. Knowing that atherosclerosis begins in youth, and with copious research illustrating increased prevalence of CVD risk factors (both traditional and nontraditional) during childhood, these findings need to be translated into clinical practice. Research is rapidly moving forward, trying to identify which biomarkers and/or vascular imaging techniques are the best surrogate markers for CVD risk. Longitudinal clinical intervention trials using these surrogate markers are sorely needed in pediatrics to establish the best ways to slow the progression of atherosclerosis in children with diabetes. In order to prevent a generation of youth from developing cardiovascular events during their 30's and 40's, pediatricians will need to be able to identify those diabetic children at the highest CVD risk, and initiate aggressive prevention and treatment.

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