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Assessing Cardiovascular Risk and Testing in Type 2 Diabetes

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Abstract
Purpose of review Type 2 diabetes confers approximately twofold-increased risk for cardiovascular disease. Early risk stratification of these patients may help reduce cardiovascular events. This review discusses the state of the art of risk factors, biomarkers, and subclinical disease parameters potentially useful in cardiovascular risk assessment in type 2 diabetes.
Recent findings Scientific progress in the past decade has identified a spectrum of risk in diabetic individuals rather than categorizing diabetes as a coronary heart disease equivalent as previously done. Recent data on emerging biomarkers and diagnostic imaging, along with traditional risk factors, provide evidence to help inform individualized cardiovascular risk assessment.
Summary Comprehensive assessment of traditional risk factors, biomarkers, complications of diabetes, and subclinical atherosclerosis may help classify diabetic individuals as low, intermediate, or high risk for determining the intensity of lifestyle modification and pharmacotherapy. Further research may lead to a comprehensive pathway for cardiovascular disease risk assessment in diabetic patients.

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Introduction

Type 2 diabetes mellitus, a state of relative insulin deficiency with underlying insulin resistance, accounts for majority of cases of hyperglycemia worldwide. An estimated 422 million people worldwide have diabetes [1•], and this number is expected to reach 592 million by the year 2035 [2]. Almost 30 million Americans (9% of the population) have diabetes, with estimated total health care costs of $245 billion due to extensive complications, primarily micro- and macrovascular pathology.

Atherosclerotic cardiovascular disease (ASCVD) is the leading cause of death among individuals with type 2 diabetes, in whom adverse cardiovascular outcomes occur, on average, 14.6 years earlier [3] and with increased severity compared to individuals without diabetes mellitus. People with type 2 diabetes have twofold-increased risk of developing ASCVD [4]. The increment in the diabetic population with cardiovascular events reflects the steady increase in the number of older individuals in the USA and the improved survival of individuals with diabetes. Prevalence of obesity, which is related to risk for ASCVD and diabetes, is also on an upsurge in the USA as well as globally.

Guidelines from the American Heart Association (AHA)/American Diabetes Association (ADA) [5•] and the European Society of Cardiology [6] present different recommendations for individuals with diabetes depending on an individual's risk profile. To identify patients who will benefit most from treatment or to determine the intensity of treatment, accurate cardiovascular risk stratification is important. Reducing ASCVD burden in diabetes is a major clinical imperative that should be

prioritized to reduce myocardial infarctions, strokes, heart failure hospitalizations, and premature deaths; improve quality of life; and lessen individual and economic burdens of decreased productivity and high cost of medical care.

This review article describes traditional risk factors, emerging biomarkers, and subclinical disease parameters that may be helpful in the assessment of cardiovascular risk in patients with type 2 diabetes.

Traditional Risk Factors

Blood Pressure

Uncontrolled blood pressure in diabetes is a well-known risk factor for worse cardiovascular outcomes [7]. Unregulated blood pressure in diabetes accelerates the risk for myocardial infarction, stroke, heart failure, and all-cause mortality.

Optimal blood pressure in patients with diabetes has been a topic of debate over the past several years [8]. The Joint National Commission (JNC) 8 guidelines of 2013 liberalized the recommendation for patients with diabetes from <130/80 mmHg in the previous guidelines [9] to <140/90 mmHg [10]. A systematic review published after JNC 8 concluded that blood pressure–lowering treatment in people with diabetes and systolic blood pressure already <140 mmHg was associated with reduced risk of stroke and albuminuria, and therefore challenged the relaxation of guidelines by JNC 8 [11]. However, a more recent meta-analysis that included unpublished data in patients with diabetes supported a more liberal blood pressure range up to 140/80 mmHg and concluded that if systolic blood pressure was <140 mmHg, further treatment was associated with increased risk of cardiovascular death [12]. However, the Systolic Blood Pressure Intervention Trial (SPRINT), which showed benefits of lower blood pressures to 120/80 mmHg in patients with cardiovascular risk factors but excluded all patients with diabetes mellitus [13], has renewed the controversy regarding the optimum range of blood pressure.

Consistent with JNC 8 [10], the AHA/ADA guidelines recommend blood pressure of <140/90 mmHg for most individuals with diabetes [5•], although the optimal blood pressure for individuals with diabetes in conjunction with other cardiovascular risk factors remains controversial.

Lipids

Low-Density Lipoprotein Cholesterol Low-density lipoprotein cholesterol (LDL-C) has been the cornerstone of cardiovascular risk assessment for the past three decades. LDL is a major atherogenic lipoprotein in the bloodstream, and LDL-C is associated with the genesis and progression of ASCVD. Numerous clinical trials, epidemiologic studies, and animal models have clearly demonstrated the role of LDL-C elevation in adverse cardiovascular outcomes.

The 2013 ACC/AHA cholesterol guidelines recommend that individuals with diabetes, aged 40–75 years, without clinical ASCVD be on moderate-intensity statin therapy if their baseline LDL-C is 70–189 mg/dL, with consideration of high-intensity statin in those with 10-year ASCVD risk ≥7.5%; high-intensity statin therapy is recommended as first-line therapy in patients aged ≤75 years who have clinical ASCVD [14]. In the Collaborative Atorvastatin Diabetes Study (CARDS), treatment with atorvastatin 10 mg (moderate intensity) resulted in significant reduction in major cardiovascular events irrespective of pretreatment LDL-C levels [15]. The 2016 ACC Expert Consensus Decision Pathway on nonstatin therapy identified individuals with diabetes who have concomitant ASCVD risk factors, 10-year ASCVD risk ≥7.5%, chronic kidney disease (CKD), albuminuria, retinopathy, evidence of subclinical atherosclerosis, elevated lipoprotein (a), or elevated high-sensitivity C-reactive protein (hs-CRP) as higher risk and therefore potential candidates for high-intensity statin therapy, with the addition of ezetimibe (or colesevelam) as needed [16••].

Low-Density Lipoprotein Particle Concentration In diabetes, LDL-C concentration may not be a true representation of the atherogenic potential in an individual [5•], as the LDL particles are small and dense. Studies suggest that small, dense LDL particles may be more atherogenic and more readily oxidized and glycated [17]. However, the benefit of measuring LDL particle concentration (LDL-P) for ASCVD risk assessment is uncertain, and LDL-P was not included in the 2013 AHA/ACC guidelines for cholesterol [14] or cardiovascular risk assessment [18], nor in the 2016 European guidelines [19, 20].

Non-High-Density Lipoprotein Cholesterol Non-high-density lipoprotein cholesterol (non-HDL-C) is the sum of cholesterol in LDL, triglyceride-rich lipoproteins such as very-low-density lipoprotein (VLDL), chylomicrons, and their remnants, and lipoprotein (a) [21], therefore including the cholesterol content of all the atherogenic lipoproteins. Literature published in the last decade has shown that non-HDL-C level is a strong marker for ASCVD and may have a stronger association with ASCVD risk than LDL-C concentration [22, 23]. Several meta-analyses have shown that apolipoprotein B-100 (apoB) and non-HDL-C are better markers for ASCVD risk in statin-treated individuals [24, 25]. Non-HDL-C may be useful in patients with high triglycerides, as commonly seen in patients with diabetes, in whom the calculation of LDL-C is problematic, and can be calculated from a nonfasting sample.

The 2016 European Society of Cardiology (ESC)/ European Atherosclerosis Society (EAS) lipid guidelines recommend calculating non-HDL-C for risk assessment, especially in patients with hypertriglyceridemia, and defined desirable non-HDL-C in individuals with diabetes or metablic syndrome as <130 mg/dL in high-risk patients and <100 mg/dL in very-high-risk patients [19]. The International Atherosclerosis Society defined optimal non-HDL-C as <130 mg/dL for primary prevention (particularly in high-risk patients, including those with diabetes with other risk factors) and <100 mg/dL for secondary prevention [26].

In patients with diabetes, non-HDL-C may remain elevated despite near-normal levels of LDL-C; therefore, non-HDL-C thresholds are included in the 2016 ACC Expert Consensus Decision Pathway on nonstatin therapy, in which non-HDL-C levels ≥130 mg/dL are considered higher risk in patients in diabetes [16••].

Apolipoprotein B Measurement of apoB signifies the total burden of atherogenic particles; each chylomicron, VLDL, intermediate-density lipoprotein (IDL), LDL, and lipoprotein (a) particle has one molecule of apoB [21]. In several studies and post hoc analyses, apoB was a better predictor of ASCVD than LDL-C [27, 28]. ApoB and LDL-P also appear to be more closely associated with diabetes [29–31]. In a recently published retrospective analysis of 851 patients, with a subset of 419 individuals with diabetes or metabolic syndrome, the correlation between apoB and non-HDL-C was lower in individuals with diabetes or metabolic syndrome [32]. This study and others [21] concluded that apoB is likely a better marker to assess ASCVD risk in diabetic patients with elevated triglycerides. However, in an analysis of 9026 participants with obesity and insulin resistance syndromes, including diabetes, in the Atherosclerosis Risk in Communities (ARIC) study, apoB was not a superior prognostic marker of incident coronary heart disease (CHD) risk to non-HDL-C [33].

The 2016 European Guidelines on Cardiovascular Disease Prevention found no evidence that apoB was better than LDL-C for ASCVD risk prediction [20], and in the 2013 ACC/AHA cholesterol guidelines, apoB measurement for assessment of ASCVD risk was considered of uncertain value [14]. However, for individuals with diabetes or metabolic syndrome, the 2016 ESC/EAS lipid guidelines defined desirable apoB concentration as <100 mg/dL in high-risk patients and <80 mg/dL in very-high-risk patients [19].

Triglycerides The role of triglycerides as a direct measure of ASCVD risk is elusive. In a meta-analysis of prospective studies including 300,000 men and women, triglyceride was correlated with ASCVD; however, this association was significantly lowered after adjustment for non-HDL-C and HDL-C levels [34]. In the Pravastatin or Atorvastatin Evaluation and Infection Therapy (PROVE-IT) study, lower on-treatment triglyceride level (<150 mg/dL) was associated with reduced ASCVD risk, compared with higher triglyceride level, independent of the level of LDL-C [35]. A recent review of the literature and genome-wide association studies suggested that triglycerides and triglyceride-rich lipoproteins are in the causal pathway of ASCVD [36].

The AHA scientific statement on triglycerides and ASCVD classified fasting triglyceride levels <100 mg/dL as optimal and <150 mg/dL as normal [37]. In the 2016 ADA guidelines, triglyceride levels ≥150 mg/dL are considered elevated [38]. The presence of hypertriglyceridemia is a marker for elevated triglyceride-rich lipoproteins, which, because of their atherogenic potential, should be included in ASCVD risk assessment especially in patients with diabetes, who often have increased production and impaired clearance of triglyceride-rich lipoproteins [39].

High-Density Lipoprotein Cholesterol Low HDL-C, typically in conjunction with elevated triglycerides, is the most common diabetic dyslipidemia [38]. Although low HDL-C is a marker of ASCVD risk, it has not been established as a risk factor in clinical trials of HDL-C–raising therapies. The Atherothrombosis Intervention in Metabolic Syndrome With Low HDL/High Triglycerides: Impact on Global Health Outcomes (AIM-HIGH) trial evaluated 3414 patients (34% of whom had diabetes) who were randomly assigned to receive niacin or placebo in addition to simvastatin ± ezetimibe. The trial was stopped prematurely for lack of benefit on the composite endpoint of ASCVD events, despite the rise in the HDL-C with niacin combination therapy [40]. Similarly, in the Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) in 25,673 patients (32% with diabetes), adding extended-release niacin–laropiprant to statin did not reduce ASCVD event risk and increased risk for serious adverse events [41]. Increasing HDL-C with cholesteryl ester transfer protein (CETP) inhibition has also failed to reduce ASCVD event rates in clinical trials [42, 43]. Genetic studies also have not shown the expected ASCVD benefit of polymorphisms that increase HDL-C levels [44].

The 2016 ADA guidelines define low HDL-C levels as <40 mg/dL in men and <50 mg/dL in women [38].

Hemoglobin A1c

Glycosylated hemoglobin (HbA1c) reflects the glycemic index of the hemoglobin for the past 8–12 weeks. It is the most commonly used test in diabetes assessment along with fasting glucose. Mounting evidence supports the association of elevated HbA1c, even below the threshold for diagnosis of diabetes, with adverse cardiovascular outcomes after adjustment for traditional cardiovascular risk factors [45–47]. However, as with HDL-C, clinical trials of interventions to improve

HbA1c have failed to demonstrate ASCVD benefit with intensive verus standard glycemic control [48–50], and the Action to Control Cardiovascular Risk in Diabetes (ACCORD) study was stopped early as a result of increased total and cardiovasular mortality in the intensive–glucose lowering group [48]; the cause for the excess mortality has not been determined [48]. On the basis of these trials, the ADA, ACC, and AHA issued a joint statement emphasizing an individualized approach to HbA1c evaluation [51].

Biomarkers

High-Sensitivity C-Reactive Protein

Hs-CRP is a marker of inflammation that has been associated with the development of diabetes [52] and atherosclerosis [53]. Several large studies have reported an association between hs-CRP concentration and ASCVD outcomes [54–56]. In the Women's Health Study, the addition of hs-CRP to traditional risk factors improved ASCVD risk prediction [57, 58]. In the ARIC cohort, comparison of 6-year change in hs-CRP with incident diabetes and ASCVD indicated that individuals with increased hs-CRP or sustained hs-CRP elevation had increased risk for incident diabetes compared with individuals whose hs-CRP remained low/moderate; individuals with sustained hs-CRP elevations also had increased risk for CHD, ischemic stroke, heart failure, and mortality [59•].

The 2013 ACC/AHA guidelines did not include hs-CRP as a routine measurement but recommended selective use by clinicians [14]. The Centers for Disease Control and Prevention and AHA recommend using the mean of two hs-CRP measurements performed 2 weeks apart to minimize within-person variability and defined hs-CRP >3.0 mg/L as a high relative risk level [60]. Two large trials of anti-inflammatory therapies, Cardiovascular Inflammation Reduction Trial (CIRT) [61] and Canakinumab Anti-inflammatory Thrombosis Outcomes Study (CANTOS) [62], are ongoing.

N-terminal Pro–B-Type Natriuretic Peptide

N-terminal pro–B-type natriuretic peptide (NT-proBNP) is a hormone with natriuretic and vasodilatory properties that is secreted by cardiac ventricular myocytes in response to elevated ventricular filling pressures and increased wall stress [63]. NT-proBNP has a powerful association with ASCVD in both high-risk patients with established ASCVD and the general population [64].

Natriuretic peptides are inversely correlated with obesity. Patients with higher body mass index tend to have lower NT-proBNP levels [65], which may be secondary to increased NT-proBNP clearance receptors in adipose tissue [65], whereas higher NT-proBNP levels are associated with enhanced lipolysis and metabolism [66]. In the ARIC study, higher NT-proBNP levels were associated with increased risk of heart failure even among individuals with obesity [67].

The predictive value of NT-proBNP for ASCVD events has also been shown in individuals with diabetes [68, 69]. Normal NT-proBNP (<125 pg/mL) was a strong negative predictor of short-term ASCVD events and of higher predictive value than traditional ASCVD risk markers in 631 consecutive diabetic outpatients [68], and among elderly individuals with diabetes in the population-based Cassale Monferrato study, NT-proBNP was predictive of ASCVD events and of additive value to the albumin excretion rate for ASCVD risk prediction [69]. A clinic-based prospective study in diabetic patients also established the superiority of NT-proBNP to albuminuria for prediction of cardiac events [70]. This finding was successfully translated into clinical practice, using NT-proBNP to identify patients with diabetes warranting intensive work-up and primary preventive cardiovascular therapy in the NT-proBNP Selected Prevention of Cardiac Events in a Population of Diabetic Patients without a History of Cardiac Disease (PONTIAC) trial [71].

High-Sensitivity Cardiac Troponins

The development of high-sensitivity assays for cardiac troponins T (hs-cTnT) and I (hs-cTnI) enables earlier and more-sensitive detection, which facilitates the diagnosis of myocardial infarction [72–74] and the evaluation of these biomarkers for ASCVD risk prediction. Community-based studies have established strong associations between hs-cTnT and incident CHD, stroke, heart failure, and all-cause mortality. In the ARIC study, adding hs-cTnT and NT-proBNP to clinical characteristics significantly improved heart failure prediction [75], and among ARIC participants without clinical ASCVD, detectable hs-cTnT levels (≥3–13.9 ng/L) were more frequent in individuals with diabetes [76]. Elevated hs-cTnT (≥14 ng/L) also occurred more frequently in ARIC participants with diabetes and was associated with substantially increased risks for heart failure, mortality, and CHD [77], and combined assessment of hs-cTnT and NT-proBNP elevation in ARIC participants with diabetes identified a subgroup with twofold-increased risk for incident ASCVD after adjustment for traditional risk factors [78–80]. In the observational Zwolle Outpatient Diabetes Project Integrating Available Care (ZODIAC-37) in stable outpatients with diabetes, hs-cTnT levels were related to mortality; at 11-year follow-up of 1133 patients, 84% of those with elevated hs-cTnT (≥14 ng/L) had died, compared with 58% of those with low-detectable hs-cTnT (3–14 ng/L) and only 23% of those with undetectable hs-cTnT levels (<3 ng/L), suggesting the potential use of hs-cTnT as a marker for mortality in individuals with diabetes [81].

Hs-cTnI was evaluated for ASCVD risk prediction in a cohort study among asymptomatic adults and shown to improve prediction of incident CHD events beyond traditional risk factors combined with hs-CRP and estimated glomerular filtration rate (GFR) [79]. In a secondary-prevention study of pravastatin, both baseline hs-cTnI and 1-year change in hs-cTnI improved CHD risk prediction in models that included traditional risk factors and other biomarkers [82]. Among individuals with diabetes, a case–control study found significantly higher hs-cTnI levels in those with CHD than in those without CHD [80], and in the Cleveland Clinic GeneBank study, detectable hs-cTnI below the diagnostic threshold for myocardial infarction (9–29 ng/L) was strongly associated with 3-year incident ASCVD events in individuals with diabetes even after adjustment for traditional and other risk factors [83], suggesting a role for this biomarker in ASCVD risk assessment in diabetic patients.

Microalbuminuria and Chronic Kidney Disease

Microalbuminuria predicts increased risk for vascular disease complications [84, 85] as well as for the progression to overt nephropathy in patients with diabetes. Microalbuminuria was also a predictor of inducible ischemia in asymptomatic diabetes patients [86].

Diabetic nephropathy leads to overt CKD. Diabetic kidney disease (DKD), present in 34.5% of US adults with diabetes [87], is associated with substantially increased ASCVD morbidity and mortality [88]. Even mild albuminuria and slightly decreased GFR are strongly linked to elevated ASCVD and death risks [89]. It is important to note that while diabetes is the major contributor to CKD in patients with diabetes, other causes of CKD also need to be evaluated.

The ADA [90] and National Kidney Foundation [91] recommend measuring both urine albumin excretion and GFR annually to screen for DKD in all patients with type 2 diabetes.

Cardiac and Subclinical Atherosclerosis Evaluation

Electrocardiography

Asymptomatic patients with diabetes may have signs of previously unrecognized myocardial infarction on resting electrocardiography (ECG). In the United Kingdom Prospective Diabetes Study (UKPDS), one in every six newly diagnosed diabetic patients had ECG evidence of silent myocardial infarction [92]. Typical ECG abnormalities include abnormal Q-waves, deep T-wave inversions, left bundle branch block, and nonspecific ST-T wave changes, and warrant evaluation for ASCVD and inducible ischemia.

The AHA/ADA guidelines concluded that obtaining a resting ECG for cardiovascular risk stratification in asymptomatic adults with diabetes was reasonable [5•].

Coronary Calcium Score

Coronary artery calcium (CAC) screening can enhance risk prediction in asymptomatic individuals and increase the predictive value of the Framingham Risk Score [93]. In the Multi-Ethnic Study of Atherosclerosis (MESA), the adjusted risk for coronary events among participants without ASCVD at baseline was ~7 times higher for CAC score >300 compared with CAC score of 0 [94]. The role of CAC scoring has also been well established in ASCVD risk stratification in diabetes; nearly 20% of asymptomatic patients with diabetes had markedly elevated CAC scores in several well-powered studies, and the absence of CAC indicated low risk of mortality among this high-risk population [95–97], suggesting that the use of CAC may help improve risk assessment in individuals with diabetes [98].

In the 2013 AHA/ACC guidelines, CAC scoring was recommended for further risk assessment in intermediate-risk patients [14]. Commonly used CAC score categories for plaque burden estimation are 0 (no identifiable disease), 1–99 (mild disease), 100–399 (moderate disease), and ≥400 (severe disease).

Carotid Intima–Media Thickness

Carotid intima–media thickness (CIMT) assessment is noninvasive and uses nonionizing-radiation ultrasound to measure the combined thickness of the intima and media of the carotid artery wall. In numerous studies, CIMT was shown to be a surrogate marker of atherosclerosis and was associated with incident CHD and improved CHD risk prediction [99–102]. In the ARIC study, the addition of CIMT and ultrasound-assessed presence or absence of plaque to traditional risk factors improved CHD risk prediction, with a net reclassification index of 9.9% overall [103]. However, a meta-analysis of 14 population-based studies including 45,828 individuals found little improvement in prediction of first myocardial infarction or stroke with the addition of common CIMT to Framingham Risk Score [104]. Another meta-analysis, which included 16 population-based studies and 36,984 individuals without known ASCVD, showed that the mean of CIMT measurements at baseline and follow-up, but not change in CIMT, was predictive of ASCVD events [105].

The role of CIMT in ASCVD risk assessment in diabetes is also unclear. In an analysis from MESA, CIMT in individuals with diabetes, metabolic syndrome, or neither was not associated with CHD or ASCVD after adjustment for traditional risk factors [106]. However, in a Japanese study in 287 diabetic patients with carotid plaque but without any known ASCVD, ultrasound assessment of plaque thickness and, using gray-

scale median, plaque echogenicity to determine presence of lipid-rich plaque showed that carotid plaque thickness was an independent predictor of ASCVD events after adjustment for traditional risk factors, and that inclusion of plaque echogenicity further improved risk prediction [107].

The 2010 ACCF/AHA Guideline for Assessment of Cardiovascular Risk in Asymptomatic Adults recommended CIMT for further cardiovascular risk assessment in asymptomatic adults at intermediate risk, based on clinical judgment [93]. However, the 2013 ACC/AHA Guideline on the Assessment of Cardiovascular Risk [18] and 2016 European Guidelines on Cardiovascular Disease Prevention in Clinical Practice [20] do not recommend routine CIMT testing for ASCVD risk assessment.

Myocardial Perfusion Scintigraphy and Other Imaging Modalities

Numerous studies have screened asymptomatic diabetes patients for ASCVD risk with nuclear scintigraphy [108]. The Detection of Ischemia in Asymptomatic Diabetics (DIAD) trial, a large randomized controlled study, showed that screening asymptomatic patients with diabetes with myocardial perfusion scintigraphy (MPS) was predictive of ASCVD events but did not lead to improved clinical outcomes [109]. Similarly, another large trial, Do You Need to Assess Myocardial Ischemia in Type 2 Diabetes (DYNAMIT), did not show improved clinical outcomes with screening for silent ischemia and was ended prematurely [110]. Current evidence does not support routine screening of patients with MPS.

Table 1 Potential parameters for atherosclerotic cardiovascular disease risk assessment in individuals with type 2 diabetes

Marker/test	Potential use in risk assessment
Blood pressure	<140/90 mmHg recommended [5•, 10]
LDL-C	Any level: high-intensity statin recommended in patients with clinical ASCVD aged ≤75 years [14]
	70–189 mg/dL at baseline without clinical ASCVD in ages 40–75 years: moderate-intensity statin, consider high-intensity statin if 10-year ASCVD risk ≥7.5% [14]; concomitant ASCVD risk factors, 10-year ASCVD risk ≥7.5%, CKD, albuminuria, retinopathy, evidence of subclinical atherosclerosis, elevated lipoprotein (a), or elevated hs-CRP indicate higher risk and warrant high-intensity statin therapy ± ezetimibe (or colesevelam) [16••]
Non-HDL-C	<130 mg/dL desirable in high-risk patients, <100 mg/dL desirable in very-high-risk patients [20]
	≥130 mg/dL higher risk in patients in diabetes [16••]
ApoB	<100 mg/dL desirable in high-risk patients, <80 mg/dL desirable in very-high-risk patients [20]
Triglycerides	<100 mg/dL optimal, <150 mg/dL normal [37];
	≥150 mg/dL elevated [38]
HDL-C	<40 mg/dL low in men, <50 mg/dL low in women [42]
Hs-CRP	>3.0 mg/L high relative risk [60]
NT-proBNP	<125 pg/mL normal
Hs-cTnT	3–13.9 ng/L low-detectable, ≥14 ng/L elevated
Hs-cTnI	9–29 ng/L low-detectable, below diagnostic threshold for myocardial infarction
GFR and urine albumin excretion	Measure annually to screen for DKD [90]
ECG	Obtain resting in asymptomatic adults [5•].
CAC scoring	0: no identifiable disease; 1–99: mild disease; 100–399: moderate disease; ≥400 severe disease
	Recommended for risk refinement in intermediate-risk patients [14]
CIMT	Not recommended for routine ASCVD risk assessment [18, 20]
Retinopathy	Screen for at time of diabetes diagnosis and reexamine annually or biannually depending on findings [90]
Neuropathy	Screen for autonomic and peripheral, beginning at time of diabetes diagnosis [90]

apoB apolipoprotein B, *ASCVD* atherosclerotic cardiovascular disease, *CAC* coronary artery calcium, *CIMT* carotid intima–media thickness, *CKD* chronic kidney disease, *DKD* diabetic kidney disease, *ECG* electrocardiography, *GFR* glomerular filtration rate, *HDL-C* high-density lipoprotein cholesterol, *hs-CRP* high-sensitivity C-reactive protein, *hs-cTnI* high-sensitivity cardiac troponin I, *hs-cTnT* high-sensitivity cardiac troponin T, *LDL-C*, low-density lipoprotein cholesterol, *NT-proBNP* N-terminal pro–B-type natriuretic peptide

Other imaging modalities used for ASCVD risk assessment in patients with diabetes include cardiac computed tomography angiography (CCTA) and cardiac magnetic resonance imaging; however, the risk–benefit profiles of these tests have not been established [5•]. The Screening for Asymptomatic Obstructive Coronary Artery Disease among High-Risk Diabetic Patients Using CT Angiography, Following Core 64 (FACTOR-64) trial, in which 900 asymptomatic patients with type 1 or type 2 diabetes were randomized to CCTA (and CCTA-directed standard or aggressive therapy) or standard care, showed no difference in the primary outcome of fatal or nonfatal cardiovascular events at 4-year follow-up [111]. Although some small studies had promising results in detection of occult CHD with CCTA [112], the current technology limits the utility of CCTA for general screening [113].

Testing for Other Diabetic Complications

Retinal Examination

Diabetic retinopathy is a sign of macrovascular disease and an indicator of ASCVD risk both type 1 and type 2 diabetes [114]. In a study in which 557 asymptomatic patients with type 2 diabetes were assessed for CHD by CCTA, retinopathy was an independent clinical predictor of significant CHD [115]. In ACCORD, severe retinopathy more than doubled the risk for ASCVD events, and each categorical increase in retinopathy increased ASCVD risk by 38% [116]. Retinopathy has also been linked to inducible ischemia [117].

The ADA recommends screening for diabetic retinopathy at the time of diagnosis, with reexaminations every 1–2 years depending on presence, progression, or severity of retinopathy [90].

Neuropathy

Cardiovascular neuropathy is divided into autonomic and peripheral neuropathies. Cardiovascular autonomic neuropathy has been studied more widely in diabetes and has been associated with poor prognosis [118] and elevated incidence of additional microvascular complications, including peripheral neuropathy [119]. Cardiovascular autonomic neuropathy is an independent risk factor for cardiovascular death and silent myocardial ischemia [120]. Peripheral neuropathy has also been associated with increased cardiovascular risk in individuals with diabetes and no prior history of ASCVD, and improved risk prediction when added to a model based on standard ASCVD risk factors [121].

The ADA recommends screening for diabetic neuropathy, including autonomic and peripheral, beginning at diagnosis of type 2 diabetes [90].

Conclusion

In summary, although type 2 diabetes was previously considered a CHD risk equivalent, more recent scientific and clinical data have revealed that individuals with diabetes have a spectrum of risk dependent on other risk factors [5•], therefore warranting an individualized approach to risk assessment. Enormous progress has been made in the prevention of ASCVD in diabetes, as reflected in reduced mortality from ASCVD causes among individuals with diabetes in the past two decades [122], but the increased risk in individuals with diabetes still lingers. Individuals with diabetes are 1.7 times more likely to suffer from ASCVD-related death and 1.8 times more likely to have a myocardial infarction than their nondiabetic counterparts [123]. Evaluation of concurrent traditional risk factors, other biomarkers, and imaging parameters may help provide more-comprehensive risk assessment in patients with diabetes (Table 1), although limited evidence on emerging markers warrants clinician judgment and individualized case-based selection of appropriate measures. Continuing research in this field will enable further progress toward a comprehensive risk assessment algorithm for ASCVD in diabetes.

Compliance with Ethical Standards

Conflicts of Interest Anum Saeed declares that she has no conflict of interest.

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Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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