DIABETES AND CARDIOVASCULAR DISEASE (ND WONG, SECTION EDITOR)

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The Evolving Cardiovascular Disease Risk Scores for Persons with Diabetes Mellitus

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Abstract

Purpose of Review We briefly introduce the concept and use of cardiovascular disease (CVD) risk scores and review the methodology for CVD risk score development and validation in patients with diabetes. We also discuss CVD risk scores for diabetic patients that have been developed in different countries.

Recent Findings Patients with diabetes have a gradient of CVD risk that needs to be accurately assessed. Numerous CVD risk scores for diabetic patients have been created in various settings. The methods to develop risk scores are highly diverse and each choice has its own pros and cons. A well-constructed risk score for diabetic patients may be advocated by guidelines and adopted by healthcare providers to help determine preventive strategies. New risk factors are being investigated in order to improve the predictive accuracy of current risk scores.

Summary A suitable CVD risk score for the diabetes population should be accurate, low-cost, and beneficial to outcome. While the performance (accuracy) has all been internally validated, validation on external populations is still needed. Cost-effectiveness and clinical trials demonstrating improvement in outcomes are limited and should be the target of future research.

Keywords Cardiovascular disease · Disease risk score · Diabetes

Introduction

Diabetes mellitus (DM) is a well-established independent risk factor for cardiovascular disease (CVD) [1–3]. To reduce CVD morbidity and mortality among DM patients, multifactorial preventive strategies should be adopted according to one's specific risk profile. These facts yield a need for reliable and accurate CVD risk assessment to inform patients about their risk status and guide effective and cost-saving preventive interventions. The "coronary heart disease (CHD) risk equivalent" approach

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[4], or the idea of taking DM as a universally high-risk group as those who already have CHD, is the most simplistic way to classify CVD risk for patients with DM. Today, contradictory evidence suggests an overall lower CHD risk among patients with DM compared to those without DM but with a prior CHD [5]. Even within the diabetic population, heterogeneous CVD risk exists due to comorbidities or severity of the DM itself [6]. This has made the risk scoring tools an appropriate approach in CVD risk assessment in persons with DM.

Over the past decades, various CVD risk scoring systems have been developed to help CVD risk assessment for persons with DM [7]. In this review, we briefly introduce the concept of CVD risk and its use in the clinic and in research. We then thoroughly review the methodological advances in the development and validation of CVD risk scores for persons with DM. We also present the latest CVD risk scores specifically for the DM population from different countries and regions.

Cardiovascular Disease Risk Scores

CVD risk scores, sometimes called CVD risk engines or CVD risk calculators, are continuous scores that integrate CVD-

related risk factors with different weights and are used to estimate the risk of CVD. The Framingham risk score (FRS) was the first developed CVD risk score, and since then, many other CVD risk scores have been developed to predict CVD risk for different populations [8–11]. The Reynolds Risk Score was originally designed for CVD-free women [12] and the UK Prospective Diabetes Study (UKPDS) risk engine was specifically created for the diabetic population [13]. Other scores were developed for those with prior CVD [14]. Some countries usually use their own population to develop a CVD risk score instead of borrowing an outside calculator [15, 16].

A well-constructed CVD risk score may be referenced in CVD management guidelines. In the clinic, CVD risk scores are often used by health care providers to help identify the high-risk population and further guide the preventive treatment [17]. For instance, the 2013 ACC/AHA cholesterol management guideline recommends initiation of statin treatment among those 10-year atherosclerotic CVD risk $\geq 7.5\%$ [18]. Most recently, these risk scores have been made as online risk calculators or mobile apps that allow non-professional individuals to evaluate risk. Such self-awareness of disease risk may be a good impetus to promote risk-reduction behaviors. In research, existing risk scores are usually used as the reference model to be compared when new CVD risk model is being developed. Another important use of CVD risk scores is similar to exposure-based propensity scores to reduce the dimension of individual covariates to control confounding [19].

Development and Validation of CVD Risk Score for DM Patients

There are important components and criteria for developing CVD risk scores [20, 21]. D'Agostino et al. summarized the complete process of development and validation for a CVD risk score into the following 10 steps: (1) endpoint (event/outcome), (2) at-risk population, (3) follow-up time, (4) risk factors, (5) mathematical model, (6) estimation (relative and absolute risks), (7) performance (discrimination, calibration), (7) internal validation, (8) external validation (performance and recalibration), (9) new markers, and (10) long-term prediction [21]. With regard to CVD risk scores for DM patients, we often observe variable methods when carrying out these steps and the choice of selection often involves different considerations.

Outcome

For current risk scoring systems, various endpoints have been used such as total CVD, hard CHD, and hard atherosclerotic CVD. It seems that there is no best choice on whether we should include soft events in CVD endpoints among DM patients. DM patients are featured with longer asymptomatic or preclinical period for CVD and suffer more silent coronary heart events than their non-diabetic counterparts. Therefore, only counting the hard events may not catch all the true events and lead to the underestimation of the risk score and thus bad calibration. On the other hand, the softer endpoints such as percutaneous coronary interventions, bypass surgery, and coronary revascularization are more prone to be misclassified and lead to poor discrimination, and the time of occurrence of certain endpoints such as angina, angiographic disease, or coronary calcium can be quite uncertain. The FRS/UKPDS validation study in the ADVANCE cohort did find that when any CVD event was used as endpoint instead of hard CVD event, calibration was better while c-statistics (discrimination) were poorer [22]. In addition to these commonly seen endpoints, CVD mortality, CHF, and even microvascular complications have been used in risk models for diabetes patients.

At Risk Population

It seems that the choice of target population is obvious here, which should be patients with diabetes. However, the most commonly used CVD risk scores in clinic are usually those designed for the general population that includes both those with and without DM. Such risk scores usually include DM as a binary factor, ignoring its heterogeneity in risks and interaction with other risk factors. In contrast, CVD risk scores specifically developed for DM patients include more DM-related variables such as HbA1c and DM duration. A study that directly compared the performance of general population vs diabetes-specific CVD risk models in DM patients showed discriminatory advantage of diabetes-specific over general population-based models for CVD risk stratification in diabetes [23].

The type of DM also matters. In fact, there are many more CVD risk scores for T2DM patients than for all DM patients or T1DM patients. One reason is that many of these risk scores were developed using large sample-sized clinical trial cohorts, which specifically targets T2DM [13, 24••, 25]. Such clinical trial data includes information on many cardiometabolic variables, thus providing great pool of candidate predictors when developing a risk score. Although observational studies include different types of DM patients, the small proportion of DM patients, missing information on DM type, and fewer DM-related variables limits the use of such data to develop risk scores for all DM patients. Given that T1DM are much fewer than T2DM in the population, CVD risk scores for T1DM usually use data from medical record, or national health registry [26, 27].

Candidate Risk Factors

In addition to traditional risk factors seen in general population, DM severity indicators, i.e., HbA1c, retinopathy, and kidney

functions, i.e., urinary albumin creatinine ratio (UACR) are commonly found in CVD risk scores for DM patients. Such measures may be relatively normal among non-DM subjects and do not have as strong a predictive value as in DM patients. On the contrary, various measures that indicate the severity and complications of DM may play important role in CVD risk assessment for those with DM.

Novel risk predictors include biomarkers and subclinical atherosclerosis measures. We previously reviewed the advances of these novel risk factors in risk assessment, including C-reactive protein (inflammatory biomarker), lipoprotein (a), low density lipoprotein and high density lipoprotein particles, lipoprotein-associated phospholipase A2 (lipid biomarkers), coronary artery calcium, carotid intima media thickness (subclinical atherosclerosis measures), etc. [7]. Biomarkers representing pathophysiological processes of atherosclerosis, such as growth differentiation factor 15, N-terminal pro B-type natriuretic peptide, and high-sensitive troponin T, were also found to enhance CVD risk prediction among diabetics [28]. All these potential new risk factors were independently associated with future CVD risk; however, whether or not they can improve a risk model needs further examination. Yeboah et al. investigated the additional predictive ability of six novel risk factors in the general population using C statistics and found CAC to be the single strongest predictors for CVD events in addition to traditional risk factors [29]. Fewer studies attempted to develop CVD risk scores to formally include these novel risk factors. The MESA-HNR Diabetes CHD Risk Score explored multiple subclinical atherosclerosis measures and CAC measure was added in the final risk score [30].

Unlike certain types of cancer, CVD may have multiple genetic predispositions. Therefore, single gene is unlikely to have predictive ability for CVD events. However, other forms of genetic information may be included. With the help of genome-wide association studies (GWAS), different single-nucleotide polymorphisms (SNPs) can be identified and then summarized into a weighted genetic risk score (GRS) [31]. Such GRS are found to be correlated with CVD independent of traditional risk factors in various studies. When incorporated with traditional risk factors, prediction (assessed by c-statistics) was found to be improved [32].

Risk Estimation

Risk estimation involves the selection of risk factors and calculation of risk scores. A wide variety of methods have been used to select the risk factors to be included. The purpose of risk factor selection is not only to include the risk factors that are associated with CVD events and can improve the accuracy of risk scores, but also to control the total number of risk factors to avoid over-complex equation or high cost related to the tests. The most commonly used selection method is a stepwise selection based on a prespecified p value. More

recently, machine learning methods have gained popularity and were increasingly used to select risk factors. The Pooled Cohort Equation adopted by current AHA/ACC guidelines used random survival forest method to determine the "importance" parameter of potential risk factors [17].

Once the risk factors are selected, they need to be integrated into a single-risk score using certain mathematical models. The early Framingham Risk Score for CHD events used logistic regression model to generate the score [33]. Logistic regression model treated event as binary outcome and neglects the timing of event. Poisson regression models have also been used alternatively to estimate incidence rates assuming homogenous risk over time. Currently, the most widely used model is the Cox proportional hazard regression model, which makes no assumption about baseline risk and time. In the Cox model, a baseline survival at the target time frame, i.e., 10 years, is needed. Other models involving event time such as Poisson model, Weibull model, and accelerated failure time model are sometimes used instead of the Cox model.

Evaluation of Risk Score Performance

Binary outcome and time-to-event outcome have a number of evaluation methods regarding prediction performance such as R^2, goodness of fit test, mean squared error, C-statistics, etc. C-statistics are routinely reported in almost all risk scores' performance evaluation stage. The Harrell's C-statistic is specially designed for time-to-event outcome and is similar to area under the ROC curve for binary outcome which lies between the value of 0.5–1. The C-statistic enables the quantification of predictive ability of risk scores but is also found to be conservative in pair-wise comparison when the two compared models have large overlap of covariates or when the old model is already good enough [34]. The net reclassification index (NRI) has been frequently used since its introduction in 2008. Compared to C-statistics, the categorical NRI has greater clinical relevance and importance when two risk scores are compared. However, NRI, especially category-free NRI, sometimes suffers a false positive problem in reporting significant results [35].

Before a CVD risk score can be used in diabetic patients, the score also needs to be tested in other external DM cohorts. Performance of a risk score is more heterogeneous and generally poorer in external validation. Since many of the CVD risk scores for the general population can also be used in DM patients, they usually serve as a reference model in head-to-head comparisons with the DM-specific CVD risk models. More importantly, all these risk scores were derived from older cohorts dated back years ago during which the baseline risk factors, disease incidence and preventive management were notably different from the contemporary population. This temporal disparity may also have a negative impact on the performance of risk scores.

An Update: New CVD Risk Scores for DM Patients in Different Countries

In 2012, Van Dieren et al. systematically reviewed 45 CVD risk scores that can be used for T2DM population, among which 12 were T2DM-specific CVD risk scores [36]. Here, we summarize the newly emerged risk scores for both T1DM and T2DM as well as updates of the old DM-specific CVD risk scores (see Table 1). These new CVD risk scores have used new types of endpoints, new dataset from contemporary cohorts, or elongated follow-up from original derivation cohort.

United Kingdom

The UKPDS risk engine is the earliest and the most well-known CVD risk scoring system for patients with diabetes. The first UKPDS risk engine was dated back to 2001 and was developed to separately predict 10-year CHD and stroke instead of composite CVD events [13, 45]. Post-trial follow-up of UKPDS cohort continues contributing to a new set of CVD risk scores called UKPDS Outcomes Model (UKPDS-OM). The current version of OM is OM2, which has significant distinction from the old UKPDS risk engine [37]. The OM2 predicts lifetime risk of seven primary complications of myocardial infarction, ischemic heart disease, stroke, congestive heart failure, amputation, blindness, and renal failure. Additional models were also developed for total mortality, diabetic ulcer, and some second events. OM2 does not provide estimate of risk for composite CVD events. The study directly compared observed vs. predicted event for internal validation. External validation showed tendency of underestimation of risk [46].

England researchers developed a risk score as part of QDiabetes risk score for 10-year heart failure risk from 437,806 diabetic patients in general practice [38]. Unlike the OM2 for heart failure, the model can be used in both T1DM and T2DM and in both with or without prior CVD. The risk score included common risk predictors of age, BMI, SBP, cholesterol/HDL ratio, HbA1c, material deprivation, ethnicity, smoking, duration and type of DM, atrial fibrillation, cardiovascular disease, and chronic renal disease. External validation on two large cohorts from England showed satisfactory AUC (ranged 0.76–0.78) and excellent calibration.

United States and Canada

To date, only two CVD risk scores were developed for DM populations in the USA and both have used the Atherosclerosis Risk in Communities Study (ARIC) cohort. The old one predicted CHD risk with a basic model of 8 predictors and a full model of 17 predictors [39]. The new ARIC CVD risk score for DM estimated 10-year CVD risk and successively explored four clusters of predictors with four models [47]. Model 1 with 13 self-reported risk factors had C-

statistics of 0.667 and model 4 with self-report risk factors, clinical measured risk factors, HbA1c and 12 novel biomarkers reached a C-statistic of 0.714. Each inclusion of an additional set of predictors significantly improved C-statistics.

Basu et al. developed a comprehensive risk scoring system named RECODe (Risk Equations for Complications Of type 2 Diabetes) for microvascular and macrovascular complications using the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial cohort recruited from USA and Canada [24••]. Multiple risk scores were developed to predict 10-year risk of each microvascular complications including nephropathy, retinopathy and neuropathy, and macrovascular endpoints of myocardial infarction, stroke, congestive heart failure, and cardiovascular mortality as well as composite endpoints of ASCVD and total mortality. Internal and external validation achieved moderate discrimination and good calibration. When compared with UKPDS and PCE, statistically significant improvement in NRI was observed [48]. The RECODe risk score for ASCVD events includes CVD history as one significant predictor, therefore may be applicable to those with past history of CVD.

Another set of risk assessment models for DM was developed using the Diabetes Control and Complications Trial and the Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) cohort from 29 clinic centers in the USA and Canada [40]. Although the developers claimed the models for all DM patients, the whole derivation cohort is only composed of T1DM. The risk models predict micro- and macrovascular complications as well as adverse events of hypoglycemia and ketoacidosis that are commonly seen in T1DM. External validation showed general better performance in T1DM than T2DM with the exception of predicting long-term CVD events.

Sweden

Two CVD risk scores for T2DM and T1DM were developed in Sweden [27, 49]. The Swedish National Diabetes Registry (NDR) risk score for T2DM was featured with the wide age range from 18 to 70 years old and simple achievable risk profiles, with HbA1c as the only lab test [49] to predict first-time CVD in 5 years. An important difference of the T1DM NDR risk score is that it is applicable to T1DM patients both with and without prior CVD. In this model, CVD history was identified as an independent predictor with seven common predictors including DM onset age, diabetes duration total cholesterol/HDL-C ratio, HbA1c, SBP, smoker, and macroalbuminuria. External validation showed excellent discrimination and calibration [27].

Germany

In Germany, a CVD mortality risk score for DM patients, called VILDIA risk score, investigated 135 potential risk factors (mostly biomarkers) and eventually selected NT-proBNP, age,

Table 1 Cardiovascular risk prediction scores in diabetes

Author and year	Name of score	Country	Derivation cohort	Outcome(s) assessed[a]	# of Predictors[b]	Features
Hayes et al. 2013 [37]	UKPDS-OM2	United Kingdom	5102 T2DM participants in UKPDS trial	Life-time risk of 7 primary endpoints, total mortality, diabetic ulcer and some repeated events	11	• 30 years of follow-up • Inclusion of time varying risk factors • Estimation of life expectancy and quality-adjusted life years
Hippisley-Cox et al. 2015 [38]	QDiabetes (Heart Failure)[c]	England	437,806 DM subjects in general practice	10-year HF risk	13	• Large derivation and validation cohorts • Online risk calculator • Easy-to-get predictors
Parrinello et al. 2016 [39]	New ARIC risk score for DM	US	654 subjects with DM in ARIC study	10-year CVD risk	13–30	• Successive examination of risk factors based on accessibility
Basu et al. 2017 [24••]	RECODe[c]	US and Canada	9635 T2DM subjects from ACCORD study	10-year risk for CVD and its components, microvascular event, total mortality	14	• Contemporary and large derivation cohort • Composite and individual complication events
Lagani et al. 2015 [40]	DCCT/EDIC risk score	US and Canada	1441 T1DM subjects in DCCT/EDIC cohort	Micro- and macrovascular complications, hypoglycemia, ketoacidosis	7	• Prediction for adverse events of hypoglycemia and ketoacidosis
Cederholm et al. 2011 [27]	NDR risk score for T1DM[c]	Sweden	3661 T1DM with and without CVD	5-year CVD risk	8	• Excellent performance in external validation
Goliasch et al. 2017 [41]	VILDIA score[c]	Germany	864 DM patients from German LURIC study	10-year CVD mortality	7	• Prediction of CVD mortality • Large selection pool of potential predictors, including multiple novel biomarker
Vistisen et al. 2016 [42]	The Steno Type 1 Risk Engine	Denmark	4306 T1DM in STENO cohort	5-year CVD risk	10	• Excellent performance in external validation • Contemporary and large derivation cohort
Wan et al. 2018 [43•]	Chinese CVD risk score for T2DM	China	137,935 T2DM patients In Hong Kong	5-year CVD risk	6–12	• Contemporary and large derivation cohort • A web calculator and color-coded chart
Woodward et al. 2016 [44]	AD-on score	20 Countries	6951 T2DM subjects from ADVANCE-On trial	10-year CVD risk 10-year renal disease risk	13	• Region-specific calibration of risk scores • Potential to be applied to various countries

[a] Some risk scores include several separate algorithms for different endpoints

[b] Mean or range of the number of predictors is reported if multiple models were developed

[c] Applicable to those with and without prior CVD

male sex, renin, diabetes duration, Lp-PLA2, and 25-OH vitamin D3 using bootstrapping stepwise selection [41]. The VILDIA CVD mortality risk score showed better discrimination for CVD mortality in an external German cohort than UKPDS risk engine. Since the UKPDS risk engine and the VILDIA risk score predicted different endpoints, it is usually not recommended to make such direct comparison.

Denmark

The Steno Type 1 Risk Engine, a 5-year CVD risk score for T1DM in Denmark, was developed with outpatient clinic data

and has shown excellent performance [26]. It is so far the largest CVD-free T1DM cohort used to develop CVD risk score. The risk engine includes age, sex, diabetes duration, SBP, LDL-C, HbA1c, albuminuria, glomerular filtration rate, smoking, and exercise.

China

Three independent 5-year risk scores for CHD, HF, and stroke were previously developed for T2DM patients using population-based data in Hong Kong [36]. Recently, Hong Kong researchers developed new 5-year CVD risk scores for

T2DM patients [43•]. The baseline derivation cohort was in 2010 and therefore is the most recent derivation cohort among all CVD risk scores. The set of risk scores had two versions with one using fewer risk factors. In both models, age, smoking, HbA1c, SBP, TC/HDL-C ratio, and eGFR were identified as predictors. The complete model additionally included diabetes duration, usage of anti-hypertensive drug and insulin, BMI, DBP, and UACR. The new model showed superior discrimination and calibration ability to other CVD risk scores for DM patients. The risk scores still need to be validated among DM patients in mainland China before being applied in the whole country.

ADVANCE Risk Score and AD-On Risk Score

The Action in Diabetes and Vascular Disease (ADVANCE) clinical trial enrolled high CVD risk participants with DM from across 20 countries in Asia, Australasia, Europe, and Canada. Despite the short follow-up of main trial, ADVANCE researchers managed to develop a 4-year CVD risk score from ADVANCE participants that may be applicable to T2DM in diverse countries [25]. Retinopathy was identified as one of the DM-related predictors in the final model. In external validation, the ADVANCE CVD risk score showed barely modest discrimination and a tendency to underestimate risk regarding calibration, partially due to the BP and glycemic intervention [50]. ADVANCE researchers also developed 5-year risk scores for early and late stage of renal disease [51]. C-statistics were 0.847 for major kidney-related events and 0.647 for new-onset albuminuria.

With the longer post-trial follow-up, ADVANCE-On Project further developed 10-year risk scores for CVD and major renal disease [44]. In the new risk score, age, sex, SBP, antihypertensive medication, duration of diabetes, HbA1c, UCAR, eGFR, age at completion of formal education, exercise, history of diabetic retinopathy, and atrial fibrillation were included. Discrimination of the 4-year and 10-year risk scores were similar for both 4-year and 10-year events. The risk scores for renal events performed better with C-statistics around 0.8 mainly due to the highly predictive renal function measures like eGFR and UACR.

Conclusion

In the era of personalized health care and evidence-based medicine, discussion of future CVD risk with DM patients with a quantitative, easy-to-understand risk score based on the patient's own risk profile is important for informing much appreciated. Popularity of a risk score generally depends on the cost and convenience of those tests used in the risk score. For risk scores based on routine tests, calculation of the risk score brings no additional medical expenditure and is usually

favored. When specific tests such as CAC scanning or genetic tests are needed for the purpose risk assessment, a clinical trial and cost-effectiveness assessment should be carried out, specifically for the DM population, to demonstrate the net benefit on outcome before the advocation of the risk score.

Compliance with Ethical Standards

References

Papers of particular interest, published recently, have been highlighted as:
• Of importance
•• Of major importance

1. Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the US population, 1971–1993. Diabetes Care. 1998;21(7):1138–45.
2. Diabetes Drafting Group. Prevalence of small vessel and large vessel disease in diabetic patients from 14 centres: the World Health Organisation multinational study of vascular disease in diabetics. Diabetologia. 1985;28:615–40.
3. Gail MH, Brinton LA, Byar DP, Corle DK, Green SB, Shairer C, et al. Projecting individualized probabilities of developing breast cancer for white females who are being examined annually. J Natl Cancer Inst. 1989;81(24):1879–86.
4. Haffner SM, Lehto S, Rönnemaa T, Pyörälä K, Laakso M. Mortality from coronary heart disease in subjects with type 2 diabetes and in nondiabetic subjects with and without prior myocardial infarction. N Engl J Med. 1998;339:229–34.
5. Bulugahapitiya U, Siyambalapitiya S, Sithole J, Idris I. Is diabetes a coronary risk equivalent? Systematic review and meta-analysis. Diabet Med. 2009;26:142–8.
6. Howard BV, Best LG, Galloway JM, Howard WJ, Jones K, Lee ET, et al. Coronary heart disease risk equivalence in diabetes depends on concomitant risk factors. Diabetes Care. 2006;29:391–7.
7. Zhao Y. Cardiovascular risk assessment and screening in diabetes. Cardiovasc Endocrinol Metab. 2017;6(1):17–22.
8. Kannel WB, McGee D, Gordon T. A general cardiovascular risk profile: the Framingham study. Am J Cardiol. 1976;38(1):46–51.
9. D'Agostino RB, Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, et al. General cardiovascular risk profile for use in primary care the Framingham heart study. Circulation. 2008;117(6):743–53.
10. Conroy RM, Pyörälä K, Fitzgerald AE, Sans S, Menotti A, De Backer G, et al. Estimation of ten-year risk of fatal cardiovascular disease in Europe: the SCORE project. Eur Heart J. 2003;24(11):987–1003.
11. World Health Organization. WHO/ISH cardiovascular risk prediction charts. Prevention of cardiovascular disease: guideline for

assessment and management of cardiovascular risk [cited 2018 Aug 12]. Geneva: WHO; 2007.

12. Ridker PM, Buring JE, Rifai N, Cook NR. Development and validation of improved algorithms for the assessment of global cardiovascular risk in women: the Reynolds risk score. JAMA. 2007;297(6):611–9.

13. Stevens RJ, Kothari V, Adler AI, Stratton IM. United Kingdom prospective diabetes study (UKPDS) group. The UKPDS risk engine: a model for the risk of coronary heart disease in type II diabetes (UKPDS 56). Clin Sci (Lond). 2001;101(6):671–9.

14. Poppe KK, Doughty RN, Wells S, Gentles D, Hemingway H, Jackson R, Kerr AJ. Developing and validating a cardiovascular risk score for patients in the community with prior cardiovascular disease. Heart. 2017;103(12):891–892.

15. Yang X, Li J, Hu D, Chen J, Li Y, Huang J, et al. Predicting the 10-year risks of atherosclerotic cardiovascular disease in Chinese PopulationClinical perspective: the China-PAR project (prediction for ASCVD risk in China). Circulation. 2016;134(19):1430–40.

16. Jee SH, Jang Y, Oh DJ, Oh BH, Lee SH, Park SW, et al. A coronary heart disease prediction model: the Korean heart study. BMJ Open. 2014;4(5):e005025.

17. Goff DC Jr, Lloyd-Jones DM, Bennett G, Coady S, D'Agostino RB Sr, Gibbons R, et al. American College of Cardiology/American Heart Association Task Force on Practice Guidelines. 2013 ACC/AHA guideline on the assessment of cardiovascular risk: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(25 Pt B):2935–59.

18. Stone NJ, Robinson JG, Lichtenstein AH, Merz CN, Blum CB, Eckel RH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association task force on practice guidelines. J Am Coll Cardiol. 2014;63(25 part B):2889–934.

19. Arbogast PG, Ray WA. Performance of disease risk scores, propensity scores, and traditional multivariable outcome regression in the presence of multiple confounders. Am J Epidemiol. 2011;174(5):613–20.

20. Kengne AP, Masconi K, Mbanya VN, Lekoubou A, Echouffo-Tcheugui JB, Matsha TE. Risk predictive modelling for diabetes and cardiovascular disease. Crit Rev Clin Lab Sci. 2014;51(1):1–2.

21. D'Agostino RB Sr, Pencina MJ, Massaro JM, Coady S. Cardiovascular disease risk assessment: insights from Framingham. Glob Heart. 2013;8(1):11–23.

22. Kengne AP, Patel A, Colagiuri S, et al. The Framingham and UK prospective diabetes study (UKPDS) risk equations do not reliably estimate the probability of cardiovascular events in a large ethnically diverse sample of patients with diabetes: the action in diabetes and vascular disease: Preterax and Diamicron-MR controlled evaluation (ADVANCE) study. Diabetologia. 2010;53:821–31.

23. Echouffo-Tcheugui JB, Kengne AP. Comparative performance of diabetes-specific and general population-based cardiovascular risk assessment models in people with diabetes mellitus. Diabetes Metab. 2013;39(5):389–96.

24.•• Basu S, Sussman JB, Berkowitz SA, Hayward RA, Yudkin JS. Development and valudation of Risk Equations for Complications Of type 2 Diabetes (RECODe) using individual participant data from randomised trials. Lancet Diabetes Endocrinol. 2017;5:788–98 **The RECODe risk scoring system predicts risk for the whole spectrum of diabetes macrovascular and microvascular complications and may better help pick out the high-risk for a specific type of complications among type 2 diabetes patients.**

25. Kengne AP, Patel A, Marre M, Travert F, Lievre M, Zoungas S, et al. Contemporary model for cardiovascular risk prediction in people with type 2 diabetes. Eur J Cardiovasc Prev Rehabil. 2011;18(3):393–8.

26. Vistisen D, Andersen GS, Hansen CS, Hulman A, Henriksen JE, Bech-Nielsen H, et al. Prediction of first cardiovascular disease event in type 1 diabetes mellitus. Circulation. 2016;133(11):1058–66.

27. Cederholm J, Eeg-Olofsson K, Eliasson B, Zethelius B, Gudbjörnsdottir S. Swedish National Diabetes Register. A new model for 5-year risk of cardiovascular disease in type 1 diabetes; from the Swedish National Diabetes Register (NDR). Diabet Med. 2011;28(10):1213–20.

28. Resl M, Clodi M, Vila G, Luger A, Neuhold S, Wurm R, Adlbrecht C, Strunk G, Fritzer-Szekeres M, Prager R, Pacher R. Targeted multiple biomarker approach in predicting cardiovascular events in patients with diabetes. Heart. 2016;102(24):1963–1968.

29. Yeboah J, McClelland RL, Polonsky TS, et al. Comparison of novel risk markers for improvement in cardiovascular risk assessment in intermediate-risk individuals. JAMA. 2012;308:788–95.

30. Yeboah J, Erbel R, Delaney JC, Nance R, Guo M, Bertoni AG, et al. Development of a new diabetes risk prediction tool for incident coronary heart disease events: the multi-ethnic study of atherosclerosis and the Heinz Nixdorf recall study. Atherosclerosis. 2014;236(2):411–7.

31. Knowles JW, Ashley EA. Cardiovascular disease: the rise of the genetic risk score. PLoS Med. 2018;15(3):e1002546.

32. Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, et al. Genomic risk prediction of coronary artery disease in nearly 500,000 adults: implications for early screening and primary prevention. BioRxiv. 2018;1:250712.

33. Wilson PW, D' Agostino RB, Belanger AM, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998;97(18):1837–47.

34. Pepe MS, Kerr KF, Longton G, Wang Z. Testing for improvement in prediction model performance. Stat Med. 2013;32(9):1467–82.

35. Pepe MS, Fan J, Feng Z, Gerds T, Hilden J. The net reclassification index (NRI): a misleading measure of prediction improvement even with independent test data sets. Stat Biosci. 2015;7(2):282–95.

36. Van Dieren S, Beulens JW, Kengne AP, Peelen LM, Rutten GE, Woodward M, et al. Prediction models for the risk of cardiovascular disease in patients with type 2 diabetes: a systematic review. Heart. 2012;98:360–9.

37. Hayes AJ, Leal J, Gray AM, Holman RR, Clarke PM. UKPDS outcomes model 2: a new version of a model to simulate lifetime health outcomes of patients with type 2 diabetes mellitus using data from the 30 year United Kingdom prospective diabetes study: UKPDS 82. Diabetologia. 2013;56(9):1925–33.

38. Hippisley-Cox J, Coupland C. Development and validation of risk prediction equations to estimate future risk of heart failure in patients with diabetes: a prospective cohort study. BMJ Open. 2015 Sep 1;5(9):e008503.

39. Folsom AR, Chambless LE, Duncan BB, Gilbert AC, Pankow JS. Atherosclerosis risk in communities study investigators. Prediction of coronary heart disease in middle-aged adults with diabetes. Diabetes Care. 2003;26(10):2777–84.

40. Lagani V, Chiarugi F, Thomson S, Fursse J, Lakasing E, Jones RW, et al. Development and validation of risk assessment models for diabetes-related complications based on the DCCT/EDIC data. J Diabetes Complicat. 2015;29(4):479–87.

41. Goliasch G, Silbernagel G, Kleber ME, Grammer TB, Pilz S, Tomaschitz A, et al. Refining long-term prediction of cardiovascular risk in diabetes–the VILDIA score. Sci Rep. 2017;7(1):4700.

42. Vistisen D, Andersen GS, Hansen CS, Hulman A, Henriksen JE, Bech-Nielsen H, et al. Prediction of first cardiovascular disease event in type 1 diabetes mellitus: the steno type 1 risk engine. Circulation. 2016;133(11):1058–66.

43.• Wan EYF, Fong DYT, Fung CSC, Yu EYT, Chin WY, Chan AKC, et al. Development of a cardiovascular diseases risk prediction model and tools for Chinese patients with type 2 diabetes mellitus:

A population-based retrospective cohort study. Diabetes Obes Metab. 2018;(2):309–318. https://doi.org/10.1111/dom.13066. **This CVD risk score for Chinese diabetic population is the latest DM-specific risk score with the most contemporary cohort**.

44.   Woodward M, Hirakawa Y, Kengne AP, Matthews DR, Zoungas S, Patel A, et al. Prediction of 10-year vascular risk in patients with diabetes: the AD-ON risk score. Diabetes Obes Metab. 2016;18(3): 289–94.

45.   Kothari V, Stevens RJ, Adler AI, Stratton IM, Manley SE, Neil HA, et al. UKPDS 60: risk of stroke in type 2 diabetes estimated by the UK prospective diabetes study risk engine. Stroke. 2002;33(7): 1776–81.

46.   Lundqvist A, Carlsson KS, Johansen P, Andersson E, Willis M. Validation of the IHE cohort model of type 2 diabetes and the impact of choice of macrovascular risk equations. PLoS One. 2014;9(10):e110235.

47.   Parrinello CM, Matsushita K, Woodward M, Wagenknecht LE, Coresh J, Selvin E. Risk prediction of major complications in individuals with diabetes: the atherosclerosis Risk in Communities Study. Diabetes Obes Metab. 2016;18(9):899–906.

48.   Basu S, Sussman JB, Berkowitz SA, Hayward RA, Bertoni AG, Correa A, Mwasongwe S, Yudkin JS. Validation of risk equations for complications of type 2 diabetes (RECODe) using individual participant data from diverse longitudinal cohorts in the US. Diabetes care. 2017:dc172002.

49.   Zethelius B, Eliasson B, Eeg-Olofsson K, Svensson AM, Gudbjörnsdottir S, Cederholm J. A new model for 5-year risk of cardiovascular disease in type 2 diabetes, from the Swedish National Diabetes Register (NDR). Diabetes Res Clin Pract. 2011;93(2):276–84. https://doi.org/10.1016/j.diabres.2011.05.037.

50.   Read SH, van Diepen M, Colhoun HM, Halbesma N, Lindsay RS, McKnight JA, McAllister DA, Pearson ER, Petrie JR, Philip S, Sattar N. Performance of cardiovascular disease risk scores in people diagnosed with type 2 diabetes: external validation using data from the national Scottish diabetes register. Diabetes care. 2018: dc180578.

51.   Jardine MJ, Hata J, Woodward M, Perkovic V, Ninomiya T, Arima H, et al. Prediction of kidney-related outcomes in patients with type 2 diabetes. Am J Kidney Dis. 2012;60(5):770–8.