Cardiovascular Events in People With Type 2 Diabetes: Performance of Framingham, UKPDS, and ADVANCE Risk Equations

Elaheh Yaghoubvand[1], Rokhsareh Aghili[2], Alireza Khajavi[3], Mohammad Ebrahim Khamseh[2]

[1] *Imam Khomeini Hospital Complex, Tehran University of Medical Sciences, Tehran, Iran*

[2] *Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran*

[3] *Student Research Committee, Faculty of Paramedical Sciences, Shahid Beheshti University of Medical Sciences, Tehran, Iran*

Received: 19 Apr. 2021; Accepted: 28 Sep. 2021

Abstract- The aim of this study was to assess the performance of the Framingham, UK Prospective Diabetes Study (UKPDS), and the Action in Diabetes and Vascular disease: Preterax and Diamicron-MR Controlled Evaluation (ADVANCE) risk equations in the prediction of 4-year cardiovascular disease CVD) in Iranian people with type 2 diabetes. The 4-year risks of CVD were estimated using the three equations in a community of 557 patients with type 2 diabetes and free of CVD at baseline. A trained physician evaluated all of the participants regarding the occurrence of CVD events during follow-up. CVD was defined as major events including fatal/non-fatal myocardial infarction as well as fatal/non-fatal stroke, minor events including treated coronary heart disease (CHD), and established peripheral arterial disease (PAD). During four years of follow-up, 64 CVD events were observed (66% minor CVD events). Despite having a good calibration (estimated to observed ratio ranging from 91.37 to 98.2 percent, Hosmer–Lemeshow $\chi 2$ (HL$\chi 2$) values <15), both general (Framingham) and diabetes-specific (UKPDS and ADVANCE) equations did not have adequate discriminative ability (Area Under the Curve (AUC) ranging from 0.48 to 0.56). Framingham, UKPDS, and ADVANCE risk equations, regardless of being general or diabetes-specific, could not precisely predict 4-year risk of CVD in Iranian individuals with type 2 diabetes.

Acta Med Iran 2021;59(10):610-616.

Keywords: Cardiovascular disease (CVD); Risk; Event; Framingham

Introduction

Cardiovascular disease (CVD) is the major cause of death throughout the world, with obviously higher death rates in developing countries. Primary prevention and early detection are important strategies to reduce the cost and burden of CVD (1). Diabetes mellitus (DM), as a strong and independent risk factor, causes a significantly higher risk for CVD compared to patients without diabetes (2,3). DM is growing rapidly, so that its worldwide prevalence has more than doubled over the past three decades (4). Iran is a country in the Middle East and North Africa (MENA) region, with a high prevalence of diabetes. A national survey in 2011 estimated the prevalence of diabetes of 11.4% in the Iranian adult population, with a 35% increase from 2005 (5). Despite preventive and therapeutic strategies, the prevalence of diabetes in Iran has increased steadily (6). It is estimated that by the year 2030, 9.2 million Iranian adults will have diabetes (7).

Some recommendations consider DM equivalent to confirmed coronary heart disease (CHD), but others suggest using risk scores to predict the risk of CVD (8). Various multivariable risk models have been developed to estimate cardiovascular risk. Generally, these models purpose ranking patients according to their risk measure (9). Therefore, resources can be targeted at high-risk populations, and overtreatment can be avoided (10). First tools for cardiovascular risk prediction were developed based on data from the Framingham study (11). These first models did not consider DM or hyperglycemia as a risk factor. Although the presence of DM has been

Corresponding Author: M.E. Khamseh
Endocrine Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
Tel: +98 2188945172, Fax: +98 2188945173, E-mail address: khamseh.m@iums.ac.ir

considered in many recent Framingham models, their accuracy in diabetic populations is unclear (12). In addition to Framingham based models (13-16), some other risk scores have been developed from the general population, such as Prospective Cardiovascular Münster (PROCAM) (17), Systematic Coronary Risk Evaluation (SCORE) (18), and Diabetes Epidemiology: Collaborative Analysis of Diagnostic Criteria in Europe (DECODE) (19). These general models were also accounting DM as a qualitative variable, without considering any chronic hyperglycemia index. Therefore, diabetes specific risk scores were formed (9). These specific scores were derived mainly from United Kingdom Prospective Diabetes Study (UKPDS) (20-23). Numerous validation studies are available for existing models, either derived from general or diabetic populations (9). Studies that compare the utility of general and diabetes-specific models in diabetic populations show paradoxical results (24,25). Diabetes-specific models are expected to have better performance in patients with DM, but real pieces of evidence do not confirm the issue (9,26). Both Framingham and UKPDS equations had a poor function in a large multiethnic people with diabetes (8). Thus, based on the AVDANCE study, a new risk equation was developed for cardiovascular risk prediction in type 2 diabetes (12). Validation studies are needed for each model to examine its performance in communities different from the original population to see whether it can be generalized to other countries and ethnicities or not. There are scant validation studies on existing risk scores in the Iranian population (27). In this study, we aimed to evaluate and compare the performance of three models (Framingham, UKPDS & ADVANCE) in Iranian people with type 2 diabetes.

Materials and Methods

We included 823 individuals with type 2 diabetes, aged 22-70 years. They were obtained from one hospital clinic and one private diabetes clinic in Tehran between 2010 and 2013. The majority of participants were from the private clinic, therefore of a high socioeconomic level. Exclusion criteria were history of prior CVD or lack of necessary data for risk prediction models. Baseline data was achieved from patients' medical records, then 4-year expectancy to have CVD events was calculated using the three models:

1. Framingham model to predict 4-year CVD probability was derived using Framingham mathematical functions for predicting CVD risk (15,28). The equation makes it accessible to design CVD scores for a period of 1 to 10 years.

2. UKPDS risk equation version 2.0 to calculate 4-year expectancy to have CHD, fatal CHD, stroke, and fatal stroke, which were separately calculated.

3. Online ADVANCE risk equation to predict 4-year risk for major CVD, including fatal and non-fatal myocardial infarction (MI) plus fatal and non-fatal stroke.

We chose a 4-year duration for follow-up because two of the three mentioned risk engines were designed to predict a 4-year risk .At the end of the follow-up duration, a trained physician re-evaluated all of the participants regarding the occurrence of CVD events during follow-up. This step was done by phone call. When there was a history of suspected CVD events, medical records were obtained and reviewed in detail. All CVD events four years after enrollment were recorded. The outcomes are based on the definition of each model.

CVD was defined as:

Major events include fatal/non-fatal myocardial infarction, fatal/non-fatal stroke.

Minor events include treated CHD (angioplasty or medical) and established peripheral arterial disease (PAD).

Hypertension (HTN) is defined as systolic blood pressure ≥140 mmHg and/or diastolic blood pressure ≥90 mmHg in two separate outpatient measurements or previous diagnosis of HTN by a physician.

The methods of the study were in accordance with the latest revision of the Declaration of Helsinki 1964. The ethics committee of the local university approved the study protocol.

Statistical analysis

Discrimination defines the ability to correctly rank individuals based on cardiovascular risk. To measure the discrimination, the univariate logistic regression models were fitted, using the outcomes incidences as the response and risk scores obtained from the three mentioned equations as the covariate or predictor. After fitting the models, the Receiver-Operating Characteristic (ROC) curve was drawn, and the area under the ROC curve (AUC) was calculated as a measure for assessing the ability to predict the outcome. This measure is also known as the C statistic. It takes values between 0.5 and 1, and the higher its value, the better the covariate as a predictor. Generally, values more than 0.7 are considered favorable.

Calibration, which is the accuracy in risk estimation, was calculated by the ratio of expected to observed risk.

In other words, calibration shows the level of concordance between the predicted probabilities and the outcome observed values. Applying a cut-off on the predicted probabilities, they are categorized into two categories, similar to levels of the outcome. Finally, through a cross-tabulation of the observed and expected responses, the calibration is measured as the correctly specified observations percentage.

Hosmer-Lemeshow test was also utilized to assess the model fitness, which corresponds with the agreement between predicted and observed event rates. Values smaller than 15 indicate good calibration. The null hypothesis for this test is that the model provides a good fit for the response. Finally, the three risk engines' performance was compared on the basis of discrimination and calibration.

In addition, the gender effect on each of the outcomes was assessed through tabulation of gender and the outcomes and calculating the hazard ratios (HR), taking the men as the reference category.

The STATA version 10 was used as the analysis software. The error level of 0.05 was chosen as the significant level.

Results

From 823 individuals, 557 (68%) had documented profiles to fit in the models. Baseline characteristics of the participants are presented in Table 1.

Table 1. Baseline Characteristics of Study participants
N=557

Gender (women), n (%)		309 (55.5)
Age (years), mean±SD		55±8.3
Diabetes duration (years), mean±SD		7.5±6.8
Smoking, n (%)		57 (10.2)
Systolic BP (mmHg), mean±SD		126±17
Diastolic BP (mmHg), mean±SD		77±10
HbA1c (%), mean±SD		8.1±2.3
Total cholesterol (mg/dl), mean±SD		177±43
HDL-cholesterol (mg/dl), mean±SD		44±11
LDL-cholesterol (mg/dl), mean±SD		99±33
Treated hypertension, n (%)		172 (30.9)
Retinopathy, n (%)		167 (30.0)
Atrial Fibrillation, n (%)		1 (0.2)
Albuminuria, n (%)	**Micro Albuminuria**	129 (23.2)
	Macro Albuminuria	28 (5.0)
Lipid-Lowering Agents, n (%)		134 (24.1)

Total cardiovascular events observed during four years were 64 events (48 CHD presentations), from which 18 were major events, and six events were fatal. The number of participants who experienced CVD was 56 individuals (10%) (Some patients had two or more events). The all-cause mortality rate was 3%, and cardiovascular death occurred in 1%. There was no significant difference between men and women in CVD events except for CABG and PAD, which were more incidents in men (P=0.017 and P=0.025, respectively).

Table 2 shows the distribution of observed CVD and CHD events stratified by gender.

The mean expected risk in each model is shown in Figure 1.

Table 3 demonstrates observed events in the study population considering the risk equation based on defined outcomes for each model. Then discrimination and calibration were calculated. All of the three models had poor discrimination abilities, with AUC ranging from 0.48 to 0.56. Despite being ineffective at predicting individual risk, the models had acceptable calibration: E/O ratio was >95% and HLχ^2 <15 for all of the three models.

Discrimination (AUC) and Hosmer-Lemeshow calibration χ2 test (HLχ2) plus accompanying p-value are presented for each model equation in Table 4.

Table 2. Observed Events in the Study Population Considering Gender

Outcome		Women	Men	Frequency	HR	*P*
Fatal MI*		3	2	5	1.20	0.838
Non-fatal MI		2	3	5	0.54	0.484
Fatal stroke		1	0	1	--	--
Non-fatal stroke		3	4	7	0.60	0.499
Stable Angina (medical therapy)		3	3	6	0.80	0.786
Angioplasty	**PCI****	10	13	23	0.62	0.237
	CABG***	3	10	13	0.24	0.017
PAD****		0	4	4	0	0.025
Total		25 (39%)	39 (61%)	64	--	--

* Myocardial Infarction
** Percutaneous Coronary Intervention with balloon or stent
*** Coronary Artery Bypass Graft
**** Peripheral Arterial Disease

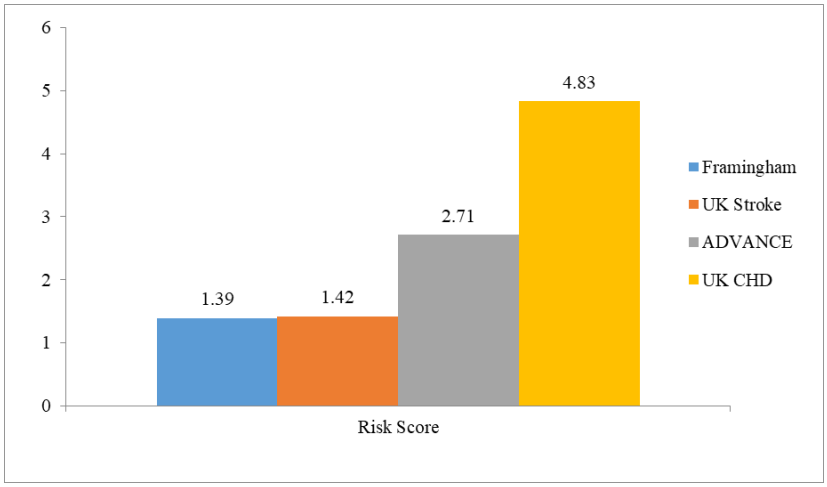

Figure 1. Mean expected (predicted) risk for each CVD risk equation

Table 3. Observed Events in Study Population Considering the Risk Engine

Risk Score	Defined Outcomes	Incidence, n (%)
UKPDS-CHD	Fatal/non-fatal MI*	10 (1.8 %)
UKPDS-Stroke	Fatal/non-fatal stroke	8 (1.4 %)
ADVANCE	Fatal/non-fatal MI or stroke	14 (2.5 %)
Framingham	Fatal/non-fatal MI or stroke or established PAD	18 (3.2 %)

*MI: Myocardial Infarction

Table 4. The ratio of 4-year expected (E) CVD, CHD, and cerebrovascular event rates was estimated by the Framingham, UKPDS, and ADVANCE equations, with 95% CI.

Risk model	AUC	E/O ratio*	HLχ^2 (*P*)
Framingham	0.57 (0.42-0.72)	0.97 (0.62-1)	3.6 (0.057)
UKPSD-CHD	0.48 (0.26-0.69)	0.98 (0.72-1)	12.2 (0.141)
UKPDS-Stroke	0.51 (0.31-0.70)	0.99 (0.76-1)	8.1 (0.427)
ADVANCE	0.49 (0.30-0.69)	0.97 (0.66-1)	9.0 (0.347)

*Expected/Observed ratio

Discussion

This is the first validation study on the performance of three different risk scores in an Iranian population with type 2 diabetes. Our results showed that Framingham, UKPDS, and ADVANCE risk equations properly estimate CVD occurrence in a population of Iranian patients with type 2 diabetes; however, they were not able

to precisely stratify high-risk and low-risk individuals. Both general and diabetes-specific models were similar in this respect, although Framingham had the best and UKPDS-CHD had the poorest discrimination ability in this study. Framingham as a general risk equation incorporated traditional cardiovascular risk factors such as age, lipid profile, BP, and smoking. UKPDS and ADVANCE models also incorporated diabetes-specific measures such as HbA1c and diabetes duration. ADVANCE score considered two additional risk factors: the presence of retinopathy and atrial fibrillation. In addition to the difference in risk factors, the models had some discrepancies on outcome definition, as were described in Table 3. Diabetes-specific models are usually expected to have better prediction ability in a population with diabetes; however, our results did not support this issue. Previous validation studies which compared the general and diabetes-specific models had shown such paradoxical results, as well (24,25). In the present study, we found that the three mentioned models, regardless of being general or diabetes-specific, are not reliable to use for individualized decision making in Iranian people with type 2 diabetes, as they had poor discrimination and were not able to reliably distinguish high-risk individuals. This was against the result of the previous validation study on cardiovascular risk scores in Iran, which was performed within the Tehran Lipid Glucose Study (TLGS) (27). In TLGS, the predictive ability of the Framingham risk equation for the prediction 5-year occurrence of CVD and CHD was good, with acceptable discrimination and calibration indices. However, TLGS just evaluated the performance of the Framingham general model in a general population of 3838 participants with only 15.55% diabetes prevalence. The absolute number of individuals with diabetes in TLGS was approximately similar to our study (593 versus 557), although TLGS did not specifically assess the performance of Framingham score in the diabetic participants. This substantial difference in baseline characteristics of populations may be responsible for the different results of the two Iranian validation studies.

Furthermore, the inappropriate performance of a model in a validation study may be the consequence of big differences between the new sample and the original or deficiencies in the development methods (29). Although several cardiovascular risk prediction scores are available today, they have major bugs to be widely used in clinical practice (30).

In this study, we precisely documented the observed CVD events and applied the three models to assess the accuracy of the prediction of CVD. Poor discrimination ability of the models might be due to considerable minor events in this population, such as angioplasty or medical treatment for CVD. Recent cardiovascular risk estimators, such as pooled cohort equations (PCE), lack this universality in predicted outcomes, as well (31). Today, minor CVD events might be more prevalent due to available diagnostic methods and have at least the same importance to prevent than major CVD events, as they are very costly to the health care system. This shows a considerable defect in both traditional and recent modelings for cardiovascular risk assessment.

We also noticed the contribution of risk factors to total CVD and CHD events (major+minor events) and Stroke. We found some predictable and unpredictable associations:

1. Systolic BP showed a significant positive association with total CVD and total CHD in men (*P* were 0.001 and 0.009 respectively), while it had a negative association with total CVD and total CHD in women (*P* were 0.04 and 0.014 respectively).

2. HbA1c level showed a negative association with total CVD in men (*P* was 0.03).

3. Diastolic BP and LDL-Cholesterol had a significant positive association with Stroke in men (both *P* were 0.007)

4. Treated HTN showed a significant negative association with Stroke in men (*P* was<0.0001).

Our findings showed a negative association between HbA1c and CVD in men. It may be because HbA1c level is believed as an independent predictor of diabetes microvascular but not macrovascular complications (32).

High BP has been demonstrated as a strong risk factor for CVD (33,34), thus established HTN is expected to increase the risk of CVD. While we found that systolic BP had a significant positive association with total CVD and total CHD in men, while it had a negative association with total CVD and total CHD in women. However, in a meta-analysis that was conducted by Wei *et al*., the pooled ES for increased risk of CVD per 10 mmHg increment in SBP was 25% for women and 15% for men (35). As a matter of fact, HTN affects men more than women. In addition, up to 65 years of age, the percentage of men with HTN is equal to or higher than age-matched women (35). While after age 65, women are affected more than men (36). Therefore, our findings may be justified by the age range of our study population. In addition, these conflict associations could demonstrate the necessity of risk factor assessment and risk prediction in a continuous manner rather than a single measurement, although different risk factors to CVD events therapeutic methods and diversity in patient's compliance and

response to treatment might be responsible for part of this inconsistency.

Some important limitations of this study are explained below:

First, our study was performed in a group of urban Tehranian adults that were predominantly from an expensive private clinic and had a high socioeconomic level. Second, the rate of smoking is prone to under-reporting due to cultural reasons. Third, to follow up with the participants, we screened them through a telephone interview with a physician, not via an appointment. This type of data gathering has the potential to miss some events. Finally, we detected a considerable trend in coronary perfusion study tools in asymptomatic or mildly symptomatic patients among cardiologists in Tehran, particularly at private health centers. This may lead to an unrealistic increase in minor CVD events, like a percutaneous coronary intervention. The strength of the present study remains in applying and comparing three well-known risk prediction tools in a relatively large population of Iranian type2 diabetic individuals.

In conclusion, Framingham, UKPDS, and ADVANCE risk equations could not precisely predict CVD in Iranian people with type 2 diabetes. More studies are needed to validate population specific risk score.

Acknowledgments

The authors wish to thank all people who participated in this study.

References

1. Pandya A, Weinstein MC, Gaziano TA. A comparative assessment of non-laboratory-based versus commonly used laboratory-based cardiovascular disease risk scores in the NHANES III population. PloS One 2011;6:e20416.
2. Association AD. 9. Cardiovascular disease and risk management: standards of medical care in diabetes—2018. Diabetes Care 2018;41:S86-104.
3. Liu L, Simon B, Shi J, Mallhi AK, Eisen HJ. Impact of diabetes mellitus on risk of cardiovascular disease and all-cause mortality: evidence on health outcomes and antidiabetic treatment in United States adults. World J Diabetes 2016;7:449-61.
4. Chen L, Magliano DJ, Zimmet PZ. The worldwide epidemiology of type 2 diabetes mellitus--present and future perspectives. Nat Rev Endocrinol 2012;8:228-36.
5. Esteghamati A, Larijani B, Aghajani MH, Ghaemi F, Kermanchi J, Shahrami A, et al. Diabetes in Iran: prospective analysis from first nationwide diabetes report of National Program for Prevention and Control of Diabetes (NPPCD-2016). Scientific Rep 2017;7:13461.
6. Noshad S, Afarideh M, Heidari B, Mechanick JI, Esteghamati A. Diabetes care in Iran: Where we stand and where we are headed. Ann Glob Health 2015;81:839-50.
7. Javanbakht M, Mashayekhi A, Baradaran HR, Haghdoost A, Afshin A. Projection of diabetes population size and associated economic burden through 2030 in Iran: evidence from micro-simulation Markov model and Bayesian meta-analysis. PloS one 2015;10:e0132505.
8. Kengne AP, Patel A, Colagiuri S, Heller S, Hamet P, Marre M, 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.
9. Chamnan P, Simmons RK, Sharp SJ, Griffin SJ, Wareham NJ. Cardiovascular risk assessment scores for people with diabetes: a systematic review. Diabetologia 2009;52:2001-14.
10. Beswick A, Brindle P. Risk scoring in the assessment of cardiovascular risk. Curr Opin Lipidol 2006;17:375-86.
11. Truett J, Cornfield J, Kannel W. A multivariate analysis of the risk of coronary heart disease in Framingham. J Chronic Dis 1967;20:511-24.
12. Kengne AP. The ADVANCE cardiovascular risk model and current strategies for cardiovascular disease risk evaluation in people with diabetes: review. Cardiovasc J Afr 2013;24:376-81.
13. Anderson KM, Odell PM, Wilson PWF, Kannel WB. Cardiovascular disease risk profiles. Am Heart J 1991;121:293-8.
14. D'Agostino RB, Wolf PA, Belanger AJ, Kannel WB. Stroke risk profile: adjustment for antihypertensive medication. The Framingham Study. Stroke 1994;25:40-3.
15. Wilson PWF, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of Coronary Heart Disease Using Risk Factor Categories. Circulation 1998;97:1837-47.
16. D'AgostinoSr 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;117:743-53.
17. Assmann G, Cullen P, Schulte H. Simple Scoring Scheme for Calculating the Risk of Acute Coronary Events Based on the 10-Year Follow-Up of the Prospective Cardiovascular Münster (PROCAM) Study. Circulation 2002;105:310-5.
18. Conroy RM, Pyörälä K, Fitzgerald AP, 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;24:987-1003.

19. Balkau B, Hu G, Qiao Q, Tuomilehto J, Borch-Johnsen K, Pyorala K, et al. Prediction of the risk of cardiovascular mortality using a score that includes glucose as a risk factor. The DECODE Study. Diabetologia 2004;47:2118-28.
20. Stevens RJ, Kothari V, Adler AI, Stratton IM, Holman RR. The UKPDS risk engine: a model for the risk of coronary heart disease in Type II diabetes (UKPDS 56). Clin Sci (Lond) 2001;101:671-9.
21. 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;33:1776-81.
22. Stevens RJ, Coleman RL, Adler AI, Stratton IM, Matthews DR, Holman RR. Risk factors for myocardial infarction case fatality and stroke case fatality in type 2 diabetes: UKPDS 66. Diabetes Care 2004;27:201-7.
23. Donnan PT, Donnelly L, New JP, Morris AD. Derivation and validation of a prediction score for major coronary heart disease events in a UK type 2 diabetic population. Diabetes Care 2006;29:1231-6.
24. Protopsaltis ID, Konstantinopoulos PA, Kamaratos AV, Melidonis AI. Comparative study of prognostic value for coronary disease risk between the UK prospective diabetes study and Framingham models. Diabetes Care 2004;27:277-8.
25. Guzder RN, Gatling W, Mullee MA, Mehta RL, Byrne CD. Prognostic value of the Framingham cardiovascular risk equation and the UKPDS risk engine for coronary heart disease in newly diagnosed type 2 diabetes: results from a United Kingdom study. Diabet Med 2005;22:554-62.
26. 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;39:389-96.
27. Bozorgmanesh M, Hadaegh F, Azizi F. Predictive accuracy of the 'Framingham's general CVD algorithm' in a Middle Eastern population: Tehran Lipid and Glucose Study. Int J Clin Pract 2011;65:264-73.
28. D'Agostino RB, Grundy S, Sullivan LM, Wilson P, CHD Risk Prediction Group. Validation of the Framingham coronary heart disease prediction scores: results of a multiple ethnic groups investigation. JAMA 2001;286:180-7.
29. Altman DG, Vergouwe Y, Royston P, Moons KG. Prognosis and prognostic research: validating a prognostic model. BMJ 2009;338:b605.
30. Weng SF, Reps J, Kai J, Garibaldi JM, Qureshi N. Can machine-learning improve cardiovascular risk prediction using routine clinical data? PloS one 2017;12:e0174944.
31. Muntner P, Colantonio LD, Cushman M, Goff DC, Howard G, Howard VJ, et al. Validation of the atherosclerotic cardiovascular disease Pooled Cohort risk equations. JAMA 2014;311:1406-15.
32. Yozgatli K, Lefrandt J, Noordzij M, Oomen P, Brouwer T, Jager J, et al. Accumulation of advanced glycation end products is associated with macrovascular events and glycaemic control with microvascular complications in Type 2 diabetes mellitus. Diabet Med 2018 (Online Ahead of Print).
33. Vasan RS, Larson MG, Leip EP, Evans JC, O'donnell CJ, Kannel WB, et al. Impact of high-normal blood pressure on the risk of cardiovascular disease. N Engl J Med 2001;345:1291-7.
34. Jackson R, Lawes CMM, Bennett DA, Milne RJ, Rodgers A. Treatment with drugs to lower blood pressure and blood cholesterol based on an individual's absolute cardiovascular risk. Lancet 2005;365:434-41.
35. Wei YC, George NI, Chang CW, Hicks KA. Assessing sex differences in the risk of cardiovascular disease and mortality per increment in systolic blood pressure: a systematic review and meta-analysis of follow-up studies in the United States. PLoS One 2017;12:e0170218.
36. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Executive summary: heart disease and stroke statistics—2015 update: a report from the American Heart Association. Circulation 2015;131:434-41.