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ORIGINAL RESEARCH

Association of Kidney Function With 10-Year Risk of Atherosclerotic Cardiovascular Disease, Cardiovascular Disease and Its Risk Factors Among Women With Type 2 Diabetes Mellitus

Khalid Siddiqui[1,2], Teena P George[1], Muhammad Mujammami[1,3,4], Assim A Alfadda[1,4,5], Shaik Sarfaraz Nawaz[1], Mohamed Rafiullah[1]

[1]Strategic Center for Diabetes Research, College of Medicine, King Saud University, Riyadh, Saudi Arabia; [2]Department of Biochemistry, Faculty of Medicine, Kuwait University, Jabriya, 24923, Kuwait; [3]University Diabetes Center, King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia; [4]Department of Medicine, College of Medicine, and King Saud University Medical City, King Saud University, Riyadh, Saudi Arabia; [5]Obesity Research Center, College of Medicine, King Saud University, Riyadh, Saudi Arabia

Correspondence: Mohamed Rafiullah, Strategic Center for Diabetes Research, College of Medicine, King Saud University, P.O. Box 245, Riyadh, 11411, Saudi Arabia, Tel +966 530077087; +966 114724179 ext.1340, Email mrafiullah@ksu.edu.sa

Purpose: Women are at increased risk of developing kidney disease and cardiovascular disease (CVD) in their middle and older ages due to the impact of aging and hormonal variation associated with menopause transition. Women with diabetes are at greater risk of reduced kidney function. Reduced or even mildly reduced kidney function enhances the risk of developing atherosclerotic cardiovascular disease (ASCVD) among women with type 2 diabetes (T2D). Thus, the objective of this study is to determine the association of reduced or mildly reduced kidney function with an estimated 10-year risk of ASCVD, CVD, and cardiovascular risk factors among T2D women.

Patients and Methods: This cross-sectional study is conducted among 393 T2D women, aged between 40–70 years, subdivided into three groups according to the level of estimated glomerular filtration rate (eGFR) (eGFR ≥90 mL/min/1.73m^2(normal), eGFR 60–89 mL/min/1.73m^2 (mildly reduced) and eGFR <60 mL/min/1.73m^2 (reduced)). Association of kidney function with an estimated 10-year risk of ASCVD as well as cardiovascular disease was determined.

Results: Based on the current study findings, the presence of cardiovascular disease was found to be associated with mildly reduced (p=0.014) and reduced eGFR (p=0.004) among T2D participants with previous CVD. No association was found between mildly reduced or reduced eGFR with an estimated 10-year intermediate/high risk for ASCVD among T2D women without CVD. Even though the level of eGFR was significantly varied between pre and post-menopause T2D women, no association of kidney function with estimated 10-year ASCVD risk was observed. Among cardiovascular risk factors, the presence of hypertension was associated with mildly reduced/reduced eGFR among T2D women.

Conclusion: This study's findings highlight the graded, independent association of kidney function with cardiovascular disease among middle-aged and elderly T2D women with previous CVD, while no association with estimated 10-year risk for ASCVD among women without CVD.

Keywords: eGFR, cardiovascular disease, T2D women, cardiovascular risk factors

Introduction

Diabetes mellitus is a metabolic disease and the leading cause of chronic kidney disease (CKD), an emerging public health problem worldwide. As estimated by International Diabetes Federation (IDF), 537 million adults aged between 20–70 years were living with diabetes in 2021, with an expected increase to 783 million by 2045. The dramatic rise in the incidence and prevalence of diabetes mellitus is mainly due to the increase in type 2 diabetes mellitus and it is driven by population aging, economic development, and increasing urbanization leading to a sedentary lifestyle linked with obesity.[1] Diabetes mellitus increases the risk of developing kidney disease and approximately 20–40% of people with

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diabetes develop CKD.[2,3] People with diabetes mellitus and CKD are at higher risk of renal failure, atherosclerotic cardiovascular disease (ASCVD), and mortality.

Middle-aged and elderly women are at significant risk of having multiple chronic diseases which affects the quality of their life. The impact of aging and hormonal variation associated with menopause transition also plays an important role.[4,5] Risk of co-morbidities such as hypertension, hyperlipidaemia, obesity, cardiovascular disease (CVD), kidney disease, metabolic syndrome, osteoporosis, and dementia are also inevitable.[6,7] In addition to this, the increasing prevalence of type 2 diabetes (T2D) among women of reproductive age causes potential adverse effects on their health and well-being.[8] Diabetes mellitus is the leading cause of CKD and end-stage renal disease worldwide.[9,10] Recently, a longitudinal study reported a greater decline in renal function among T2D females compared to males.[11] Even though kidney function declines gradually with aging, it is considered an independent risk factor for cardiovascular mortality in the elderly.[12] It is important to recognise the risk of developing vascular disease among women, especially those with diabetes mellitus.[13–16] Patients with T2D mellitus have two 2–4 fold increased risk of cardiovascular morbidity and mortality.[17] Furthermore, in a meta-analysis, the relative risk of fatal coronary heart disease was reported higher among women with T2D.[18] Higher mortality rates in females with T2D further highlighted the necessity of cardioprotective measures.[19] So, it is highly important to assess the risk of CVD among T2D women. The risk of cardiovascular events and all-cause of mortality reported to be increase with a decrease in the estimated glomerular filtration rate (eGFR).[20] Recently, few studies reported the greater risk of CVD among Saudi women.[21,22] However, the association of mildly reduced (60–89 mL/min/1.73m^2) or reduced (<60 mL/min/1.73m^2) eGFR with 10-year ASCVD risk is unclear among middle-aged and elderly Saudi women with diabetes. Furthermore, the association of reduced kidney function with CVD risk among post and pre-menopause women with diabetes was not studied in this population. Currently, there are CVD risk calculators that could predict the 10-year risk of ASCVD among the diabetic population.[23,24] Predicting the risk of developing CVD based on present health status will help clinicians start early treatment strategies and lifestyle modification to improve the health condition.[25] Prevention strategies may help to improve the quality of life and enhance longevity.

This study aims to examine the effect of kidney function as estimated by eGFR on a 10-year risk of ASCVD. We hypothesize a graded, independent association between eGFR and 10-year risk of ASCVD. The purpose of this study is to investigate the association between reduced or mildly reduced kidney function and the estimated 10-year risk of ASCVD. This study hypothesizes that; (1) degree of kidney function is associated with risk of developing ASCVD. (2) Menopausal transition among middle-aged or elderly women is related to mildly reduced/reduced kidney function. (3) cardiovascular risk factors are associated with mildly reduced kidney function.

Materials and Methods

This is a cross-sectional study conducted among Saudi T2D women. Study participants were selected from previously published studies.[26,27] T2D women were randomly selected, and the age of eligible participants was between 40–70 years. Women with a history of breast cancer, uterine and ovarian cancer, or current receipt of hormonal therapy, women with polycystic ovary syndrome, and pregnant women were excluded from the study. The studies (E-14-1319 and E-13-1010) were approved by the Institutional Review Board (IRB) of the College of Medicine, King Saud University, Kingdom of Saudi Arabia, in accordance with the Declaration of Helsinki. Study participants with T2D were recruited from the University Diabetes Centre, King Saud Medical City, King Saud University, Saudi Arabia. Informed consent was obtained from all study participants.

Demographic and clinical data such as age, duration of diabetes mellitus, systolic blood pressure (SBP), diastolic blood pressure (DBP), and body mass index (BMI) were collected from previous records. Medical history includes the history of hypertension, hyperlipidemia, obesity, cardiovascular disease, and other conditions were collected from the medical records and recorded previously. Diagnosis of T2D was based on American Diabetes Association (ADA) criteria.[28] Participants were using oral hypoglycaemic drugs and/or insulin to manage diabetes mellitus.

Renal function was defined based on estimated GFR calculated using the Chronic Kidney Disease-Epidemiology Collaboration (CKD-EPI) equation.[29] Participants were divided into three groups according to the level of eGFR: ≥90, 60–89, and <60 mL/min/1.73m^2. "Reduced" renal function was diagnosed with eGFR <60 mL/min/1.73m^2. and eGFR 60–89 mL/min/1.73m^2 is categorized into "mildly reduced" renal function. Participants with eGFR ≥90 mL/min/1.73m^2

are grouped into "normal". The American College of Cardiology/American Heart Association ASCVD risk calculator (Risk Estimator Plus) was used to estimate the 10-year risk of the first ASCVD event.[30] The 10-year ASCVD risk is stratified as low (<5%), borderline (5–7.4%), intermediate (7.5–19.9%), and high (≥20%).

Biochemical parameters such as fasting blood glucose, HbA1c, total cholesterol, high-density lipoprotein (HDL) cholesterol, low-density lipoprotein (LDL) cholesterol, and creatinine were measured using RX Daytona clinical chemistry analyzer, Randox, UK.

Statistical Analysis

Statistical analysis was performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA). Participants were categorized into 3 groups according to eGFR levels of ≥90, 60–89, and <60 mL /min/1.73m^2. Analysis of variance (ANOVA) was applied to compare the general characteristics of participants across different eGFR groups. Multivariate nominal logistic regression analysis was used to determine the association of kidney function with cardiovascular risk factors, the presence of CVD, and the estimated 10-year ASCVD risk. Association of kidney function with estimated 10-year ASCVD risk among pre- and post-menopause T2D women was also assessed. Two sets of models were used: model 1, age-adjusted; model 2, adjusted for age, BMI, current smoking status, HbA1c, SBP, DBP, and hyperlipidaemia (yes/no), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) use (yes/no), statin use (yes/no), and insulin use (yes/no). Results of logistic regression analysis are reported as odds ratios (OR) and 95% confidence intervals. A p-value less than 0.05 was considered statistically significant.

Results

From the randomly selected 393 women with T2D, 239 (60.8%) had an eGFR of ≥90 mL/min/1.73m^2 (normal), 103 (26.2%) had an eGFR of 60–89 mL/min/1.73m^2 (mildly reduced), and 51 (13%) had <60 mL/min/1.73m^2 (reduced) eGFR and 9.6% had a previous history of cardiovascular disease. The median (range) age of the participants was 55 (40–70) years. Table 1 shows the baseline characteristics of study participants among different eGFR categories. Women with reduced eGFR (<60 mL/min/1.73m^2) were older with longer diabetes duration, had higher total cholesterol,

Table 1 The Demographic and Clinical Characteristics of Study Participants (n=393)

Kidney Function (eGFR (mL/min/1.73m^2)				
Parameters	**Normal ≥90 (n=239)**	**Mildly Reduced 60–89 (n=103)**	**Reduced <60 (n=51)**	**p-value**
Age (years)	53.31±5.01	56.53±4.50	57.84±5.74	<0.001
DM duration (years)	15.65±7.96	18.51±6.15	19.37±6.33	<0.001
SBP (mm Hg)	128.15±15.68	136.17±19.01	149.37±21.96	<0.001
DBP (mm Hg)	72.37±9.94	72.69±11.29	74.90±13.55	0.31
Hypertension n (%)	117 (49.0)	77 (74.8)	45 (88.2)	<0.001
Hyperlipidaemia n (%)	183 (76.6)	85 (82.5)	40 (78.4)	0.47
BMI (kg/m^2)	33.40±5.75	34.26±5.73	33.29±5.90	0.41
FBS (mmol/l)	9.14±3.40	10.80±4.64	11.91±5.32	<0.001
HbA1c (%)	8.93±1.79	10.31±1.78	10.58±1.77	<0.001
Total cholesterol (mmol/l)	4.56±0.95	4.71±1.04	5.26±1.31	<0.001
Triglyceride (mmol/l)	1.61±0.86	1.81±0.94	2.08±1.03	0.002
HDL cholesterol (mmol/l)	1.31±0.32	1.22±0.27	1.29±0.35	0.06
LDL cholesterol (mmol/l)	2.64±0.87	3.28±1.11	3.54±1.23	<0.001
Creatinine (mg/dl)	0.62±0.089	0.91±0.09	1.36±0.40	<0.001

Notes: Data represents in mean ± standard deviation. DM duration, diabetes mellitus duration; BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; FBS, fasting blood sugar; HDL cholesterol, high density lipoprotein cholesterol; LDL cholesterol, low density lipoprotein cholesterol; eGFR, estimated glomerular filtration rate. P value <0.05 is statistically significant.

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Table 2 The Association Between Kidney Function and Cardiovascular Risk Factors Among Women With Type 2 Diabetes

Kidney Function (eGFR (mL/min/1.73m^2)						p-value
Parameters	**Normal ≥90**	**Mildly Reduced 60–89**	**p-value**	**Reduced <60**	**p-value**	
Obesity						
N (%)	165 (69.0)	75 (72.8)	0.484	36 (70.6)	0.827	0.781
Model 1 (Age adjusted OR (95% CI))	Ref.	1.35 (0.79–2.31)	0.270	1.28(0.64–2.56)	0.489	0.499
Model 2 (Multivariable adjusted, OR (95% CI))*	Ref.	1.20 (0.68–2.12)	0.531	1.20 (0.55–2.62)	0.645	0.794
Hypertension						
N (%)	117(49.0)	77 (74.8)	<0.001	45 (88.2)	<0.001	<0.001
Model 1 (Age adjusted OR (95% CI))	Ref.	2.44 (1.44–4.16)	0.001	5.56(2.24–13.82)	<0.001	<0.001
Model 2 (Multivariable adjusted, OR (95% CI))**	Ref.	2.16 (1.22–3.80)	0.008	5.49(2.11–14.27)	<0.001	<0.001
Hyperlipidaemia						
N (%)	183(76.6)	85 (82.5)	0.221	40 (78.4)	0.775	0.471
Model 1 (Age adjusted OR (95% CI))	Ref.	1.25 (0.68–2.31)	0.473	0.92 (0.43–1.99)	0.840	0.705
Model 2 (Multivariable adjusted, OR (95% CI))#	Ref.	1.35 (0.70–2.61)	0.366	0.99 (0.42–2.34)	0.982	0.618

Notes: Model 1 adjust for age. *Model 2 (multivariable model adjusted for age, current smoking status, HbA1c, SBP, systolic blood pressure; DBP, diastolic blood pressure; and hyperlipidaemia(yes/no). ** Model 2 (multivariable model adjusted for age, BMI, body mass index; current smoking status, HbA1c, hyperlipidaemia (yes/no)). #Model 2 (multivariable model adjusted for age, BMI, current smoking status, HbA1c, SBP, DBP).

triglyceride, LDL cholesterol, and creatinine values, and were more likely to be hypertensive. The median BMI (kg/m^2) of the participants was 33.5 (16.2–54.5) and the median HbA1c (%) was 9.3 (5.7–15.0).

Table 2 shows the association between kidney function and cardiovascular risk factors. The multivariate nominal logistic regression model showed a significant odd of having mildly reduced (OR=2.16; 95% CI (1.22–3.80), p=0.008) and reduced eGFR (OR=5.49; 95% CI (2.11–14.27), p=<0.001) with the presence of hypertension. Risk factors such as obesity and hyperlipidaemia were not associated with either mildly reduced or reduced eGFR.

In a multivariable-adjusted model, the presence of cardiovascular disease was found to be associated with both mildly reduced (OR=3.26; 95% CI (1.26–8.41), p=0.014) and reduced eGFR (OR=4.90; 95% CI (1.66–14.49), p=0.004) among participants with previous CVD. Overall significant association of cardiovascular disease was found with eGFR level. When the analysis was done among participants without CVD, the logistic regression model adjusted for age showed significant odds of having mildly reduced/reduced eGFR with estimated 10-year intermediate/high risk for ASCVD (mildly reduced: OR=2.24; 95% CI (1.13–4.44), p=0.02), reduced eGFR: OR= 8.01; 95% CI (3.14–20.47), p=<0.001)), while the multivariable-adjusted model showed an insignificant association with both mildly reduced and reduced eGFR (Table 3).

Table 4 shows the association of kidney function with estimated 10-year cardiovascular risk among pre and post-menopause women with T2D. The level of eGFR was found to be significantly varied between pre and post-menopause T2D women without CVD (Table S1). Among post-menopausal women, the logistic regression model adjusted for age showed a significant odds (OR=3.54; 95% CI (1.82–6.86), p=<0.001) of having estimated 10-year intermediate/high risk for ASCVD with presence of reduced eGFR (<90 mL/min/1.73m^2 eGFR) while the multivariable-adjusted model found insignificant (OR=2.19; 95% CI (0.78–6.14), p=0.13).

Discussion

In the current study, the presence of cardiovascular disease was found to be associated with mildly reduced and reduced eGFR among T2D women with previous CVD. No association was found between mildly reduced/reduced eGFR and the presence of an estimated 10-year intermediate/high risk for ASCVD among T2D women without CVD. Even though the level of eGFR was significantly varied between pre and post-menopause women, no association of kidney function with estimated 10-year ASCVD risk was observed. Among cardiovascular risk factors, the presence of hypertension was associated with mildly reduced/reduced eGFR among middle-aged/elderly T2D women.

Table 3 The Association Between Kidney Function and Cardiovascular Diseases Among T2D Women

Kidney Function (eGFR (mL/min/1.73m^2)						p-value
Parameters	**Normal ≥90**	**Mildly Reduced 60–89**	**p-value**	**Reduced <60**	**p-value**	
Cardiovascular diseases*						
N (%)	9 (3.8)	17 (16.5)	<0.001	12 (23.5)	<0.001	<0.001
Model 1 (age adjusted OR (95% CI))	Ref.	4.12 (1.73–9.85)	0.001	5.90 (2.23–15.62)	<0.001	<0.001
Model 2 (adjust for CV risk factors, OR (95% CI))	Ref.	3.26 (1.26–8.41)	0.014	4.90 (1.66–14.49)	0.004	0.007
10-year intermediate /high risk for ASCVD**						
N (%)	33 (14.3)	33 (38.4)	<0.001	26 (66.7)	<0.001	<0.001
Model 1 (age adjusted OR (95% CI))	Ref.	2.24 (1.13–4.44)	0.021	8.01 (3.14–20.47)	<0.001	<0.001
Model 2 (adjust for CV risk factors, OR (95% CI))	Ref.	1.56 (0.67–3.66)	0.306	2.89 (0.87–9.61)	0.083	0.191

Notes: *Individuals with CVD. **Individuals without CVD and estimated ASCVD score ≥7.5% is identified as intermediate/ high risk for 10-year ASCVD. Model 1 adjust for age. Model 2 (multivariable model adjusted for age, BMI, current smoking status, HbA1c, SBP, systolic blood pressure; DBP, diastolic blood pressure; and hyperlipidaemia (yes/no), angiotensin-converting enzyme inhibitor/ angiotensin receptor blocker (ACEI/ARB) use (yes/no), statin use (yes/no), and insulin use (yes/no).

Table 4 The Association of Kidney Function With 10-year Cardiovascular Risk Among Pre and Post Menopause T2D Women

	10-Year Intermediate /High Risk for ASCVD*			
	Model 1		Model 2	
	OR (95% CI)	p-value	OR (95% CI)	p-value
Pre-menopause women				
≥90 eGFR <90 eGFR	1.29 (0.05–32.88)	0.879	285.3 (0.00 - NA)	0.999
Post-menopause women				
≥90 eGFR <90 eGFR	3.54 (1.82–6.86)	<0.001	2.19 (0.78–6.14)	0.136

Notes: Model 1 adjust for age; Model 2 (multivariable model adjusted for age, BMI, current smoking status, HbA1c, SBP, systolic blood pressure; DBP, diastolic blood pressure; and hyperlipidemia (yes/no), angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB) use (yes/no), statin use (yes/no), and insulin use (yes/no). *Individuals without CVD and estimated ASCVD score ≥ 7.5% is identified as intermediate/ high risk for 10-year ASCVD.

Diabetes mellitus is the leading cause and risk factor for the development of renal impairment and end-stage renal disease, which affects approximately 50% of patients with T2D.[31] Impaired renal function among T2D patients indicates an increased risk of cardiovascular mortality.[32] Women with T2D show greater risk of CVD and menopausal transition further increases the cardiometabolic risk profile.[11,33] The complex relationship between kidney disease and CVD involves a combination of cardiovascular risk factors including advanced age, diabetes mellitus, hypertension, hyperlipidaemia, and factors specific to kidney disease including anaemia, volume overload, proteinuria, oxidative stress, and inflammation.[34] CKD causes a systemic proinflammatory state leading to vascular and myocardial remodelling resulting in vascular calcification, atherosclerotic lesions, and myocardial fibrosis. CVD risk assessment tools are extensively used to identify high-risk individuals and perform appropriate interventions as a primary prevention strategy.[35]

It is well established that kidney function is related to ASCVD risk.[36] Although kidney function declines with age, the level of eGFR is one of the independent risk factors for ASCVD. The relation between mildly reduced (60–89 mL/min/1.73m^2) or reduced (<60 mL/min/1.73m^2) levels of eGFR with ASCVD risk was evaluated previously.[37–39] However,

this study evaluates the level of eGFR and its association with ASCVD risk exclusively among middle-aged/elderly T2D women. Based on the current study findings, the presence of CVD is associated with both mildly reduced and reduced eGFR, while the analysis was done among participants without CVD, the risk of estimated 10-year intermediate/high risk for ASCVD was not associated with mildly reduced/reduced eGFR level among T2D women. Even though obesity was prevalent among both groups, participants without CVD showed better glycemia and were less likely to be hypertensive comparatively. Reduced or mildly reduced eGFR was reported to be associated with the risk for CVD among patients with T2D.[40,41] Recently, a study reported a negative correlation between eGFR and 10-year ASCVD risk in patients with diabetic kidney disease.[41] Furthermore, as shown in Figure S1, some of the participants with mildly reduced or reduced eGFR were categorized under estimated 10-year low risk for ASCVD highlighting the importance of incorporating kidney function parameters into cardiovascular risk prediction models.[42] Based on this, prospective studies with large sample sizes are required to explore and determine the interrelation between ASCVD risk and renal dysfunction.[43]

This study also evaluated the association of kidney function with different cardiovascular risk factors. Based on the current knowledge, many studies reported that hypertension, obesity, and hyperlipidaemia are the most prevalent modifiable cardiovascular risk factors.[44,45] Hypertension is a highly prevalent risk factor for CKD as well as a powerful CVD risk factor found higher in women than men.[46] Transition to menopause increases the risk of developing hypertension, hyperlipidaemia, and weight gain.[47] In the present study, hypertension was found to be associated with reduced as well as mildly reduced eGFR. Recently, a meta-analysis of 16 cohort studies reported that hypertension is an independent predictor of decreased estimated GFR.[48] Individuals with poorly controlled blood pressure are at high risk of developing kidney disease and cardiovascular complications.[49,50] Adequate knowledge about CVD risk factors and population awareness about modifiable risk factors may help to reduce the incidence rate.

Although CVD is the leading cause of death among women, very few studies evaluated the risk of developing CVD among women with diabetes.[51,52] It has been reported that diabetes mellitus increases the risk of CVD three to four times in women.[53] Accumulating evidence demonstrated that diabetes mellitus alters estrogen-related protective mechanisms and leads to enhanced atherogenesis in females.[54,55] Protective effects of estrogen on the kidney may reduce the incidence of decreased eGFR.[56] In this study, the level of eGFR is found to be reduced among post-menopause women than pre-menopause women while no association of eGFR with estimated 10-year risk for ASCVD was observed. A previous study also observed no significant interaction between renal function and menopausal status.[57]

The strength of this study is the inclusion of middle-aged and elderly T2D women which allowed us to explore the association of kidney function with estimated 10-year cardiovascular risk among pre- and post-menopause women. The primary limitation of this study is the cross-sectional study design which limits assessing temporal relation and causality. Furthermore, the level of female sex hormones and gynaecological history was not available for all selected participants which limited us to assess the involvement of sex-related factors which may affect kidney function and CVD risk.

Conclusion

In conclusion, the presence of cardiovascular disease was found to be associated with reduced/mildly reduced kidney function among T2D women with previous CVD. No association of kidney function with the presence of an estimated 10-year intermediate/high risk for ASCVD was observed among T2D women without CVD. Among cardiovascular risk factors, the presence of hypertension was associated with mildly reduced/reduced eGFR among middle-aged/elderly T2D women. In order to reduce CVD-associated morbidity and mortality, it is imperative to identify CVD risk factors earlier, promote a healthy lifestyle, and implement pharmacologic treatment expeditiously when indicated.

Focus on primary prevention of CVD is necessary to reduce cardiovascular mortality among high-risk populations. Educational programs to promote awareness of risk factors, prevention strategies, lifestyle modification, and healthy dietary habits are needed. Moreover, incorporating female-specific risk factors (history of gestational diabetes, hypertensive pregnancy disorders, and menopausal transition) may help to improve the risk assessment among women with diabetes.

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Disclosure

The authors report no conflicts of interest in this work.

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