International Journal of Cardiology Research
www.cardiologyjournal.in
E-ISSN: 2663-4112, P-ISSN: 2663-4104
Received Date: 18-12-2018 Accepted Date: 20-12-2018; Published: 20-01-2019
Volume 1; Issue 3; 2019 page No. 18-23

Risk assessment tools in hypertensive patients who are likely to develop target organ damage: A narrative mini-review

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DOI: https://doi.org/10.33545/26634104.2019.v1.i1a.5

Abstract

Background: Hypertension is a major detrimental event in the cardiovascular continuum. Inadequately controlled blood pressure is a driving event for Target Organ Damage (TOD), namely heart, arterial blood vessels, brain, and kidneys. However, vigilance of TOD among hypertensive is imperative. On the basis of this background, we aim to discuss different risk assessment tools in hypertensives who are likely to develop TOD.

Methods: We identified relevant full-length articles by electronic databases, namely Medline/PubMed and Google scholar. Studies were searched using key words such as ''Risk assessment", "Framingham Risk Score'' AND Cardiovascular Disease (CVD), Vascular Age, Stroke, Chronic Kidney Disease.

Results: The studies demonstrated that the Framingham Risk Score (FRS) has the potential to predict next 10-year risk of CVD, stroke, and vascular age. Kidney Failure Risk Equation (KFRE) predicts 5-year risk of developing kidney failure. The traditional factors such as increasing age, male gender, high blood pressure, diabetes mellitus, and smoking strongly increase the risk of Atherosclerotic Cardiovascular Disease (ASCVD), stroke, and higher vascular age. In contrast, risk of kidney failure is due to creatinine, eGFR, and Urine Albumin: Creatinine (UACR).

Conclusion: Traditional risk factor factors contribute to CVD among hypertensive patients. The Framingham-based assessment tools including 10-year CVD, stroke, and vascular age can stratify the level of risk. These are well-known, most useful, and easy to calculate and can estimate absolute risk of an individual hypertensive who is likely to develop TOD. The KFRE provides excellent discrimination of the risk of End-stage Renal Disease (ESRD). These further assist clinicians in counselling and guiding the patients for timely initiation of pharmacotherapy and thus improve compliance. For hypertension, being a cause for TOD, multiple risk assessment tools are required to maximize the organ protection and should be strongly encouraged in the routine clinical practice.

Keywords: risk assessment, framingham risk score, cardiovascular disease, vascular age, stroke, and chronic kidney disease

Introduction

Hypertension is one of the most prevalent non-communicable Cardiovascular Diseases (CVD). It is a major cause of morbidity and mortality in developing countries like India [1]. Globally, 1 billion people are existing with high Blood Pressure (BP) [2]. In India, the crude prevalence of hypertensionis about 25.3%; rural3.68 to 4.61 and in urban 2.38 to 3.65% [3].Hypertension is a major detrimental event in the Cardiovascular (CV) continuum along with others like diabetes mellitus and dyslipidemia [4]. These events cause atherosclerosis, Coronary Artery Disease (CAD) followed by Myocardial Infarction (MI), which eventually lead to end-stage cardiac disease [5]. The likelihood of CVD risk is increased by two times with each elevation of Systolic Blood Pressure/Diastolic Blood Pressure (SBP/DBP) of 20/10 mmHg or even with lower SBP/DBP of 115/75 mmHg in some of the age groups [6]. Type 2 Diabetes Mellitus (T2DM) increases the risk of CVD by two to fourtimes [7]. Chronic Kidney Disease (CKD) is an independent risk factor for CVD, and mortality of the patients due to CVD is more rather than

progressing to End-stage Renal Disease (ESRD) [8]. Therefore, it is essential to recognize these patient groups (hypertension, diabetes, and CKD) who are at high risk for developing CVevents [9]. In the current scenario, risk assessment is an imperative tool for primary prevention of Atherosclerotic Cardiovascular Disease (ASCVD) [10]. A significant reduction of individual's CVD risk can be achieved through CV risk assessment tools along with counseling, lifestyle changes, and therapeutic interventions [11]. Moreover, hypertension with inadequately controlled BP is a driving event for target organ damage, and the prime target organs are heart, brain, arterial blood vessels, and kidneys. Hence, watchfulness of target organ damage among hypertensive patients must be included during evaluation. The urgency and intensity of drug treatment is determined by the evidence of target organ damage presence, and it may also dictate which antihypertensive drug class needs to be started [12]. Taken together, these observations reinforce the need to protect target organs through a timely assessment and effective therapy. In the clinical practice, the evaluation of a patient's individual risk can be facilitated using several tools. On this background, we aim to discuss the risk assessment tools in the hypertensive who are likely to develop target organ damage.

Methods

We searched in PubMed and Google Scholar using the search words risk assessment, Framingham Risk Score AND cardiovascular disease AND stroke, Kidney failure for articles published in English. We also identified articles thorough the references accessed for Risk Assessment Studies.

Result

A total of8 studies met the inclusion criteria (Table 1) i.e., assessment of CVD risk (n=4), vascular age (n=1), stroke risk (n=2), and risk of kidney failure (n=2).

Cardiovascular disease risk

The Framingham Risk Score- Cardiovascular Diseases (FRS-CVD) is one of the most widely used 10-year CVD risk assessment tool among several scoring systems. The risk score is result from computing score points or different variables, namely age, gender, plasma total and HDL-cholesterol, SBP, medication to treat high BP, smoking, and diabetes mellitus status. The added scoring points are transformed to a 10-year absolute CVD risk and classified as low risk (<10%), intermediate risk (10–20%), and high risk (>20).[13]It offers global risk factor of developing general and individual absolute ASCVD events such as CVD, cerebrovascular and peripheral artery disease (PAD), and heart failure. The estimated CVD event rates predicted can be used to quantify risk and to guide preventive primary care.[13]ACC/AHA 2017 guideline recommends 10-year ASCVD risk scoring to guide therapy as no pharmacological or antihypertensive therapy based on levels of risk [14]. Table 1 lists the number of study characteristics and outcomes involved in the current review. The 4 studies reported the estimation of10-year risk of developing CVD with FRS score in patients with hypertension (n=2), diabetes (n=1) as well as CKD (n=1). All studies used variables and risk scoring points as per the FRS [13]. Tungdim, *et al*., reported that greater proportions of diabetic patients had high CVD risk (38.3%) followed by moderate (37.0%) and lower (24.7%) [15]. Dasgupta, *et al*., reported that the risk for developing CVD among patients was high in 3.9%, medium in 32.4%, and low in 63.7% patients. The author found that CVD risk is well associated with increasing age, male gender, diabetes, hypertension, dyslipidemia, and tobacco use [16]. The study led by Mora SC, *et al*., used FRS-CVD and ASCVD (AHA/ACC 2013) scores and their ability to predict atherosclerotic Cardiovascular Events (CVEs) among patients with CKD. The study found a high CV risk, 59% with FRS-CVD and 75% with ASCVD. The predication of CVEs for both score was about 79; 49 of which were atherosclerotic events (ischemic heart disease 27, strokes 10, peripheral vascular disease 12) and 30were non-atherosclerotic (all episodes of heart failure) during 40.3±6.6 months of follow-up [17]. The study by, Garg N and colleagues evaluated the accuracy of various 10-year CVD risk calculators for predication of CV risk in Indians. With considering 20% as cut-off for high-risk score, FRS-CVD score had stratified maximum number of patients (51.9%) with high CVD risk followed by QRISK2 (48.3%), FRS-CHD (43.2%), JBS3 (41.4%), ASCVD (28.3%), and WHO (16.2%).Study concluded that FRS-CVD represents to be most useful tool for reorganization of CV risk in high-risk CVD patients [18].

Vascular age

The vascular age is calculated from scoring points or different variables as mentioned for 10-year CVD risk [13]. However, CVD risk of an individual is transformed to the age of a person that is vascular age or heart age. The added scoring points are transformed to a 10-year vascular age and classified as low (<30 years), intermediate risk (30–80 years), and high risk (≥80 years) [13]. It predicts age of the vascular system of a person based on his or her CV risk factor profile. It is measurement of individual current heart age when compared to actual (ideal) age. When heart age is older than an individual's current age, it indicates the high risk of developing CVD in the next 10 years [13]. This approach transforms the absolute risk into another concept more easily understood bypatients [16]. Increasing age or older age is an independent risk factor for CVD when compared to the current age.[19] Table 1 describes study outcomes of vascular age risk also. One of the study reported that the estimation of vascular age with FRS score in patients with hypertension. Dasgupta A, *et al*., found that the mean vascular age was much higher than the actual mean biological age (46.5±6.1*vs*. 39.1±15.0 years) among participants. However, higher percentage of patients (64.3%) had higher vascular age than their actual biological age. Conversely, those having vascular age less than and equal to their biological age were 30.7% and 5%, respectively. For subjects with higher vascular age than biological age, 10-year CVD risk is high when compared to those having vascular age less than and equal to their biological age (8.1% *vs*. 2.0 and 3.2%). Moreover, study documented maximum vascular age of 86 years for the most of variables such as age, female gender, SBP (≥140), on antihypertensive therapy, history of diabetes and high total cholesterol (≥200). The author concluded that this tool can be utilized to generate awareness and to motivate people for the prevention of CVD [16].

10-year stroke risk tool

The Framingham Stroke Risk Score (FSRS) is used routinely to

estimate 10-year risk of stroke. The computed score is based on stroke risk factors such as age, gender, SBP, use of antihypertensives, prevalent CVD, current/previous atrial fibrillation, presence/absence of Left Ventricular Hypertrophy (LVH) on ECG, current status of diabetes and smoking [20]. The summated points are transformed to a 10-year probability stroke risk percentage, i.e., ≥20% is considered high, 10–20% moderate, and <10% low risk [20]. It may help to identify persons at substantially increased risk to develop stroke and to take the necessary protective measures. Two studies used FSRS to estimate next 10-year stroke risk in patients with hypertension. Bestehorn K, *et al*., found that mean 10-year stroke risk was in 26% of hypertensive patients (low risk in 50.6%, medium in 32.7%, and high in 16.7%). The author concluded that FSRS can be easily used in everyday care to calculate the absolute risk in hypertensive patients and is likely to be helpful to counsel patients and make decisions on treatment [21]. Another study by Choi CU, *et al*., documented an average 10-year probability of stroke risk in 24.27% (24.17% women, 24.39% men, p=0.825) of hypertensive patients with the use of FSR scoring system [22].

Kidney failure risk calculator

Kidney Failure Risk Equation (KFRE) classifies the risk of developing kidney failure. Tabulation is based on scoring points for the parameters such as age, gender, region, creatinine, eGFR, and ratio of urine albumin: creatinine [23, 24]. The added points are transformed to a 2-and 5-year probability of treated kidney failure as a percentage, so risk of 15% is considered high risk, 5–15% is an intermediate risk and 0–5% is low risk [23]. Whitlock RH, *et al*., used KFRE to determine its ability to discriminate which patients will progress to kidney failure in an un-referred population. At a3% threshold over 5 years, the KFRE had a sensitivity of 97% and a specificity of 62%. At 10% risk, sensitivity was 86% and specificity was 80%. The study author concluded that KFRE performs well at predicting the 5-year risk of dialysis in CKD patient's stages 3 to 5 [25]. Another study by Peeters MJ, *et al*., validated the KFRE in CKD patients. Study found that the development of kidney failure within 5-year among 114 participants. KFRE accurately predicted the progression to kidney failure in European CKD patients [26].

Table 1: Study characteristics and outcomes of risk assessment tools

Author/year	Study design	Study population	Risk assessment tools	Risk of CVD in % (n/N)
Tungdim, *et al*., 2014 [15]	Cross-sectional study	A total of 81 diabetic patients (age 36–74 years) with FBG ≥126 mg/dL. Males (n=39) and females (n=42).	FRS-CVD risk. Score stratified as low (<10%), medium (10-20%), high (>20%).	**10-year predicted CVD risk as** Low in 24.7%(n=20/81) Moderate in 37% (n=30/81) High in 38.3%(n=31/81)
Dasgupta, *et al*., 2018 [16]	Observational cross-sectional study	A total of 182 patients (age 30–49 years) with mean SBP of 125±19 mmHg.	Framingham heart study CVD risk. Risk score stratified as low (<0-6%), medium (>6-20%), high (>20%).	**10-year predicted CVD risk as** Low in 63.7% (116/182) Medium in 32.4% (59/182) High in 3.9% (7/182) **10-year predicted vascular age** Higher vascular age(86 years) than biological age among 64.3% (117/182) Lesser vascular age than biological age among 30.7% (56/182) Equal vascular age to biological age among 5% (9/182)
Mora, *et al*., 2017 [17]	A prospective observational study	A total of 400 patients with CKD (stages 1–4 as per KDOQI; not on dialysis). Mean age of 64.7±10.3 years.	FRS-CVD and ASCVD (AHA/ACC 2013) scores. Both scores were calculated at baseline and during mean follow-up of 40.3±6.6 months.	**FRS-CVD *vs*. ASCVD (AHA/ACC 2013) scores** High CV risk among both scores (59% *vs*. 75%) The sensitivity for predicting atherosclerotic CVEs were similar for both scores (81% *vs*. 91%) Both scores can estimate the probability of atherosclerotic CVEs in patients with CKD regardless of renal function, albuminuria, and previous CV events
Garg, *et al*., 2017 [18]	Comparative study	A total of 1110 patients (25–85 years) with a history of acute MI.	FRS-CHD, FRS-CVD, QRISK2, JBS3, ACC/AHA, ASCVD, and WHO risk charts. 20% as cut-off for high-risk score	**FRS-CVD *vs*. other risk scores** FRS-CVD score had stratified maximum number of patients (51.9%, n=576) with high CVD risk followed by QRISK2 (48.3%, n=536), FRS-CHD (43.2%, n=480), JBS3 (41.4%, n=460), ASCVD (28.3%, n=314), and WHO (16.2%, n=180).
Risk of stroke in %				
Bestehorn, *et al*., 2008 [21]	Cross-sectional prospective observational study	A total of 2482 hypertensive patients (mean age 66.5 years).	FSRS stratified as low (0–19%), medium (20–49%), and high (≥50%).	Mean 10-year stroke risk was in 26% of patients Low risk in 50.6% Medium in 32.7% High in 16.7%
Choi, *et al*., 2008 [22]	A multicenter study	A total of 1402 hypertensive patients (55-84 years) with mean SBP/DBP of 132 ± 17/ 79	FSRS	Average 10-year probability of stroke in hypertensive patients was 26.27% (26.9% women, 25.5% men)

		± 10 mmHg.		
Risk of kidney failure in % (n/N)				
Whitlock, *et al*., [25]	retrospective cohort study	A total of 1512 patients with CKD stages 3 to 5.	KFRE, thresholds of 3% and 10%.	Upon 5-year follow-up, - Kidney failure observed among10% (n=151/1512) patients; 146 had a risk greater than 3% at baseline - At a 3% threshold over 5 years, the KFRE had a sensitivity of 97% and a specificity of 62% - At 10% risk, sensitivity was 86% and specificity was 80%
Peeters, *et al*., [26]	Randomized controlled trial	A total of 595 non-transplanted CKD patients (60.8 years) with stages 3–5.	KFRE	- Kidney failure within 5-yearin 19.15% (n=114/595) participants

n = No. of patients developing CVD, N= Total no. of patients
FBS = Fasting Blood Sugar, MI= Myocardial Infarction, FRS-CHD= Framingham Risk Score-Coronary Heart Disease, FRS-CVD= Framingham Risk Score- Cardiovascular Disease, JBS3= Joint British Society Risk Calculator 3, ACC/AHA=American College of Cardiology/American Heart Association (ACC/AHA), WHO= World Health Organization

Discussion

This review has evidence of effective use of 4tools in the risk estimation among hypertensive individuals who are likely to develop target organ damage, namely, heart, blood vessels, brain, and kidneys. Thorough assessment of CV risk, including the presence and degree of target organ damage, is a prerequisite for devising effective therapeutic strategies and for tailoring treatment goals in hypertensive patients. Assessing the presence of target organ damage may also be helpful when choosing antihypertensive agents and in monitoring the effectiveness of treatment [27]. However, unquestionable evidence exists to support the statement that diagnostic assessment of organ damage allows better prediction of CV risk, with a more precise identification of high- risk individuals in whom a more strong treatment is required [28]. Based on the evidence, an individual having a high risk for developing CVD demonstrates the importance of controlling risk factors and consequently reducing the CVrisk [29].

The traditional risk factors have been found to explain between 75%–90% of CVD events [30, 31]. From the evidence presented, it appears that early detection and treatment of the risk factors that initiate the CV continuum could stop or greatly delay its further progression [32]. On the other hand, scores of the 10-year FRS CVD, vascular age as well as stroke risk are mainly computed by traditional risk factors. These factors included were age, cholesterol (total cholesterol and HDL), BP, and history of smoking [19]. Whereas, the risk of kidney failure computed creatinine, eGFR, and urine albumin creatinine ratio along with the traditional risk factors [23]. The descriptions of each risk factor which influences the scoring system have been discussed in detail. Additionally, these risk factors were correlated with studies included in the current review.

Age

An increasing age is considered as an independent risk factor for CVD and stroke [19]. this is consistent with risk scores. A greater proportion with an individual age of 40–49 years had medium-to-higher CVD risk (61.9%) followed by lower CVD risk (38.1%) [16]. Similarly, the stroke risk was higher in patient age group of ≥80 years (51.2%) followed by 70–79 years (25.9%), 60–69 years (8.5%), 50–59 years (1.8%), 20–29 years (1.2%), and 40–49 years (0.6%).[21]

Gender

Males are more at risk for MI than females [33]. Similarly, men are at greater risk of death due to stroke than women [34]. These agree with the risk score. The greater proportion of men had higher risk of developing CVD in the next 10years as compared to women (59% *vs*. 19%) [15]. in a similar manner, the study by Dasgupta, *et al*., documented that greater proportion of men had medium–to-high risk of CVD than women (44.4% *vs*. 26.5%) [16]. In case with stroke risk, men aged 60–69 years had a higher 10-year probability of stroke than women of similar age [21]. With respect to CKD, most of the evidence in the current literature suggests a higher progression rate and mortality risk of CKD in men compared with women, except in post-menopausal women and diabetic patients [35].

Lipid abnormality

The dyslipidemia is common in hypertension and diabetic patients and is strongly correlated with CVD [36]. Moreover, no significant difference in the development of medium-to-high CVD risk among individuals with high total cholesterol (≥200 mg/dL) or low total cholesterol [16].

High BP

Hypertension is the strongest risk factor for almost all different CVDs including stroke [37]. This is broadly consistent with the risk scores. A greater proportion of patients with SBP of ≥140 mmHg had medium CVD risk (73.7%) followed by low risk (26.3%) [16]. Stroke risk was higher in women compared to that of men with SBP/DBP of ≥160/100 mmHg. Conversely, no difference between men and women with SBP/DBP of <160/100 mmHg. Treatment for BP: The stroke risk was increased even among patients treated for high BP [22]. Moreover, patients with a higher stroke risk received a higher number of antihypertensive drugs [21].

Diabetes mellitus

Based on 10-year FRS-CVD score, a greater proportion of individuals with history of diabetes had medium-to-high CVD risk (80.7%) followed by low CVD risk (19.4%).[16]

Smoking

This is a risk factor for CAD in hypertension and diabetes patients. Current smokers (1–14 cigarettes/day) increase the risk of CAD by 1.66 times and stroke by 1.04 times [38]. As per the FRS-CVD risk score, the greater percentage of current smokers

had 10-year medium-to-high CVD risk (56.1%) followed by low risk (43.9%) [16].This is confirmed by Choi, *et al*. The average 10-year probability of stroke was higher in patients with metabolic syndrome than in patients without metabolic syndrome [22].

Atrial fibrillation

Higher proportion of patients have persistent/permanent atrial fibrillation representing a high stroke risk [39]. The Indian-based study demonstrated that 10% of stroke patients had AF [40].

LVH

The presence of LVH on ECG is a risk profile for ischemic stroke [41]. The risk of kidney failure is based on the factors like creatinine, eGFR, and ratio of urine albumin: creatinine (UACR). Creatinine predicts a greater risk of kidney failure and patient mortality [42]. With respect to eGFR, it is widely accepted as the best assessment mean of kidney function. As eGFR declines, patients experience higher rates of Acute Kidney Injury (AKI), CKD complications, CVD, and all-cause mortality [43]. On the other hand, UACR is found to be fundamentally important for both diagnosis and prognosis of CKD. It is now recommended that all patients with diabetes and/or hypertension be screened annually with this test. Effects of UACR along with eGFR are additive in causing mortality in patients with both CKD and AKI [43].

The knowledge of the CV risk of hypertensive patients helps in the development and implementation of strategies aimed at the control of risk factors and prevention of complications [29]. Numerous studies concluded that FRS-CVD scores have the potential to predict next 10-year CVD risk in patients with metabolic syndrome including CKD. Its risk profile appears to have its utility due to its broad outcome that includes ASCVD events as well as unstable angina/coronary insufficiency, transient ischemic attack, claudication, and heart failure [13]. Knowledge of the 10-year risk for ASCVD identifies patients in higher-risk groups who are likely to have greater net benefit and lower number needed to treat for both antihypertensive and statin therapy [10]. In contrast, vascular age is an intuitive and easily understood method for communicating about risk. It may facilitate lifestyle change. Indeed, the communication of a given vascular age would have a superior emotive impact improving observance of therapies and healthier lifestyles [44]. Framingham stroke risk scores appear satisfactory enough to attempt predicting stroke over 10 years [45]. Kidney failure risk tool is based on 4-variable KFRE. Evidence provided a valuable addition to the chain of evidence in support of the wider adoption of clinical prediction tools such as the KFRE as decision aids in ESRD planning for patients with CKD. These tools are easy to use, are widely available, and should continue to be evaluated in clinical settings to optimize CKD care [46].

Conclusion

Traditional risk factors contribute to CVD among patients with hypertension, diabetes, and CKD. The Framingham-based assessment tools including 10-year CVD, stroke and vascular age can stratify the levels of risk. These are well-known, most useful, and easy to calculate and can estimate absolute risk of an individual hypertensive who are likely to develop target organ damage. The KFRE provides excellent discrimination of the risk of ESRD. These further assist clinicians in counseling and guiding the patients for timely initiation of pharmacotherapy and improve compliance. Hypertensions being a cause for target organ damage, multiple risk assessment tools are required to maximize the organ protection and should be strongly encouraged in routine clinical practice.

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