Review

Cardiovascular Risk Assessment among Postmenopausal Women: A Review

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Abstract: Cardiovascular diseases (CVD) are rising rapidly among the postmenopausal woman but they are less likely to identify their risk by an appropriate risk assessment tool. This review evaluates available literature on cardiovascular risk assessment among postmenopausal women to provide a concise view of risk factors and disease burden among them, present risk assessment systems including their drawbacks, emergence of new risk factors and their role in risk prediction, and finally use of hormone replacement therapy during menopause. Results demonstrate that menopause is a transition point for developing CVD not due to physiological changes only but psychosocial factors like depression and marital stress are also responsible. Both conventional and emerging risk factors burden are high among postmenopausal women. Though data regarding CVD risk assessment among postmenopausal population is lacking but existing evidences claimed underestimation or overestimation of risk among women. Moreover application of different tools on same population has revealed significant variation in result. In this regard, recalibration of conventional tools with local data and new risk factors has showed improvement of risk prediction. Hormone replacement therapy during early menopause has reported beneficial to prevent CVD but in secondary prevention it has no role. All of these findings demand further studies on cardiovascular risk assessment, especially in developing countries where women after menopause are not in consideration of health strategy makers.

Keywords: cardiovascular risk assessment; postmenopausal women; cardiovascular risk factors; emerging risk factors; hormone replacement therapy

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1. Introduction

Cardiovascular diseases (CVD) are the leading cause of mortality worldwide and its incidence is gradually rising among the women of postmenopausal age [1, 2]. In a developing country like Bangladesh the burden is also increasing as the life expectancy has already higher among women than men [3]. Globally the incidence of CVD is also high in women of postmenopausal age compared to men but the rate is equal in men who are 10 years younger [4]. This gender based differences in CVD are reduced during transition from pre to postmenopausal state but the precise causes need to be fully elucidated through in depth research [5].

A most recent community based case control study has reported that the cardiac risk ratio of women is usually increased after menopause and prone them to develop CVD with its complication in near future [6]. Though postmenopausal women are at high risk for CVD but they are less likely to identify their risk than men and to participate in screening program. Beside this most often they are under-represented in cardiovascular research. From 2006 to 2009 about 62 randomized clinical trials published in which only 33.5% were women compared to men and only half of the clinical trials published their analysis report based on gender category. This under-representation is mostly notable in the field of ischaemic heart disease, cholesterol lowering therapy and heart failure. Though different risk prediction tools developed to assess cardiovascular risk but most of the times they fail to assess accurately the CVD risk of healthy women aged 45 years and above [7]. Again, these risk prediction tools are not validated in all population of varying age, ethnicity, country context and different resource settings [8]. It has also evidenced that conventional risk factors most often associated with misinterpretation of CVD risk through available risk prediction tools and therefore consideration of emerging risk factors we cannot be ignored in CVD risk assessment, claimed by other study [9]. This review aims to evaluate the existing evidences on assessment of cardiovascular risk among postmenopausal population from different perspectives of their health and provide future plan of action according to findings.

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2. Menopause as a transitional landmark for CVD

2.1. Physiological Aspect

Menopause is a physiological age related phase of women's life in which their health transit from reproductive to non-reproductive stage [10]. During menopausal period women experience physical changes resulting from changes in vascular system, body fat distribution, blood pressure and lipid profile [11]. All of these are supposed to be due to oestrogen deficiency that directly increases CVD risk or favours development of intermediate risk factors of CVD such as dyslipidemia, overweight, diabetes or hypertension that has an indirect effect on the risk of CVD [12]. Again, increase of body weight and subsequent obesity is associated with increase in visceral fat that favours insulin resistance resulting high prevalence of diabetes [13]. This insulin resistance is also responsible for high level of circulating insulin that causes retention of sodium and fluid which subsequently give rise to high blood pressure. Both hypertension and diabetes are important risk factors for development of CVD with greater relative risk among postmenopausal women [14].

2.2. *Psychosocial Aspect*

Depression is a controversial issue among the postmenopausal women as evidence for associations between depression and menopausal status was poor or mixed [15]. According to Harvard Study of Moods and Cycles, postmenopausal women experience depression nearly twice than the premenopausal women (OR 1.8, 95 % CI: 1.0 – 3.2) [16]. Another series of studies in the Penn Ovarian Aging cohort (POAS) also revealed that depression is three times higher among postmenopausal women than the premenopausal [17]. These data are alarming because depression causes >70% excess CVD risk irrespective of sex, predicted by Center for Epidemiological Studies Depression (CES-D) Scale [18].

During postmenopausal period most of the women expect emotionally supportive relation with the family members and evidence suggested that high degrees of caring, sympathy and understanding are cardio-protective [19]. Again menopause induces marital stress that puts

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them at 3 fold greater risks of recurrent coronary events compared with women who has low or no marital stress [20].

Above discussion has revealed that menopause is a transitional landmark for developing CVD not due to physiological changes only but psychosocial factors like depression and marital stress are also responsible.

3. Burden of CVD among postmenopausal women

CVD is the number one cause of mortality in women of developed countries worldwide and the prevalence differs within the age range of 50 to 70 years, indicating the menopausal age during which a considerable part of life is passed by women. Since 1990 the position of CVD has remained within the top 5 causes of mortality among women for prevalence, Disability adjusted life years (DALY) and Years lived with disability (YLD), but just order has changed with time. It has documented that in developed world, 54 % of all deaths and 39 % of all disability among women are caused by CVD above the age of 70 years. But the percentages are 31% and 18% for the women of aged 50-69 years, respectively [21]. According to projection estimation, the mortality burden of heart diseases will increase by 120 % for women of all developing countries and for the next two decades it will triple. Among the South Asian countries, India and China will represent higher proportion of CVD deaths among women by the year 2040 and 54.6 % death will occur among the Chinese women [22]. Again, analysis of economic burden among postmenopausal women of employed population revealed higher direct and indirect cost due to CVD and this additional cost is contributed by greater utilization of health care and high prevalence of work loss [23].

4. Cardiovascular risk factors among postmenopausal women

Cardiovascular risk assessment is not possible without evaluation of the CVD risk factors. More than 300 risk factors were identified which are related to CVD risk but only major risk factors are included in risk assessment. In **Table 1**, available articles assessed CVD risk factors among postmenopausal women are listed.

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114 *4.1. Conventional CVD risk* factors

115 Among the conventional CVD risk factors, age is considered as a most powerful
116 independent predictor [24]. This is because age determine the exposure time to risk factors
117 and severity of atherosclerosis [25]. It has observed that cardiovascular risk gradually
118 increases among women after 50 years of age [25-31]. But premature or early onset of
119 menopause is also associated with higher risk of CVD, its mortality, and overall mortality
120 among women [32].

121 **Table 1: List of studies assessed CVD risk factors among postmenopausal women**

1st Author, Year of publication, Reference	Country of study	Subjects	Sample size	Socio-demographic risk factors	Behavioral risk factors	Intermediate risk factors	Emerging risk factors
Sekuri *et al* 2004 [38]	Turkey	Rural	207	Age, Education level, Unemployed spouse, Number of children, Living alone, Introverted, Nuclear family, Negative balance of expenditure & income, Living in an urban area	Smoking	Dyslipidemia, Hypertension, Diabetes, Obesity,	Not reported
Abedi *et al* 2009 [37]	Iran	Urban	147	Age, Age of menopause, Beliefs of Participants towards CVD	Smoking, Physical activity level	Hyperlipidemia Hypertension, Diabetes, Overweight, Obesity	CRP*
Pelletier *et al* 2009 [44]	USA	Not reported	109	Age	Smoking	Dyslipidemia, Hypertension,	hs-CRP**, apolipoprotein

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1st Author, Year of publication, Reference	Country of study	Subjects	Sample size	Socio-demographic risk factors	Behavioral risk factors	Intermediate risk factors	Emerging risk factors
						Diabetes, Obesity	B-100
Tandon *et al* 2010 [35]	India	Rural	500	Age at menopause, Duration of menopause, Menopausal symptoms, Education level, Family history of premature heart disease, Awareness of menopause	Smoking, Tobacco chewing, Physical activity, Alcohol, Dietary lifestyle	Hypertension, Diabetes, Dyslipidemia, Generalized obesity, truncal obesity & abdominal obesity, Metabolic syndrome	CRP, Uric acid,
Pandey *et al* 2012 [34]	India	Rural	600	Age at menopause, Menopausal symptoms, Family history of premature CAD, Duration of menopause	Tobacco chewing, Physical activity level	Dyslipidemia, Hypertension, Diabetes, Truncal and abdominal obesity, Metabolic syndrome	Not reported
Masson *et al* 2013 [41]	Argentina	Urban	334	Age, Family history of early CVD	Smoking	Dyslipidemia, Hypertension, Diabetes, Obesity	CAP

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123 **Table 1 (continued)**

1st Author, Year of publication, Reference	Country of study	Subjects	Sample size	Socio-demographic risk factors	Behavioral risk factors	Intermediate risk factors	Emerging risk factors
Nahas *et al* 2013 [32]	Brazil	Urban	497	Age, Age of menopause, Menopause length, Personal history of HTN & DM, Family history of HTN, DM & CHD,	Smoking, Physical activity level,	Overweight, Generalized & central obesity, Hypertension, Diabetes, Dyslipidemia, Metabolic syndrome,	CRP
Ozdemir *et al* 2014 [36]	Turkey	Urban	58	Age, Age of menopause, Years of menopause	Smoking	Hypertension, Diabetes, Dyslipidemia, Obesity	Fasting insulin, hs-CRP, Serum Prolactin
Awotidebe *et al* 2014 [40]	Nigeria	Semi-urban	120	Age, Onset time of menopause, Education level, Monthly income, Duration of menopause, Occupation, Personal history of diabetes, Family history of DM and CVD	Smoking, Type of diet, Stress, Exercise	Hypertension, Overweight,	Not reported
Ventura *et al* 2014 [33]	Brazil	Urban	215	Age, Education level, Age of menopause, Length of menopause	Physical activity level, Poor diet, Excess sodium	Hypertension, Dyslipidemia, Overweight, Obesity, Diabetes,	Not reported

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1st Author, Year of publication, Reference	Country of study	Subjects	Sample size	Socio-demographic risk factors	Behavioral risk factors	Intermediate risk factors	Emerging risk factors
Nahas *et al* 2013 [32]	Brazil	Urban	497	Age, Age of menopause, Menopause length, Personal history of HTN & DM, Family history of HTN, DM & CHD,	Smoking, Physical activity level,	Overweight, Generalized & central obesity, Hypertension, Diabetes, Dyslipidemia, Metabolic syndrome,	CRP
Ozdemir *et al* 2014 [36]	Turkey	Urban	58	Age, Age of menopause, Years of menopause	Smoking intake	Hypertension, Diabetes, Dyslipidemia, Obesity	Fasting insulin, hs-CRP, Serum Prolactin
Mitra, 2016 [43]	India	Not reported	64	Age, Years of menopause,	Not reported	Dyslipidemia, Diabetes, Hypertension, Metabolic syndrome, Overweight/ Obesity, Central obesity	Vitamin D
Nansseu *et al* 2016 [42]	Cameroon	Urban	108	Age, Family History of HTN, DM & other related diseases,	Smoking, Physical activity, Alcohol,	Hypertension, Dyslipidemia, Obesity, Diabetes,	

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Nahas *et al* 2013 [32]	Brazil	Urban	497	Age, Age of menopause, Menopause length, Personal history of HTN & DM, Family history of HTN, DM & CHD,	Smoking, Physical activity level,	Overweight, Generalized & central obesity, Hypertension, Diabetes, Dyslipidemia, Metabolic syndrome,	CRP
Ozdemir *et al* 2014 [36]	Turkey	Urban	58	Age, Age of menopause, Years of menopause	Smoking Fruits & vegetables intake,	Hypertension, Diabetes, Dyslipidemia, Obesity	Fasting insulin, hs-CRP, Serum Prolactin

*CRP=C-reactive protein, **hs-CRP=high sensitivity C-reactive protein

Cigarette smoking is highly prevalent among postmenopausal women of American & European region [29, 31, 33, 34] but less prevalent in South Asian countries. Most of the women of South Asia are habituated to use smokeless tobacco rather than cigarette and they use it in the form of chewing [27, 28]. Based on the status of tobacco use it has evidenced that CVD risk is also higher among postmenopausal women of those countries where cigarette smoking is prevalent.

Current review has identified most of the postmenopausal women as physically inactive [27, 28, 33, 35]. Their dietary practice is also unfavorable for reduction of CVD risk as they

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used to take inadequate fruits (<3 servings) and vegetables [26, 28, 35]. Both physical inactivity and unhealthy dietary practice are contributed for high prevalence of overweight, central obesity, dyslipidaemia, hypertension and diabetes among them [25-31, 33, 34, 36, 37]. Again high prevalence of these parameters is also responsible for high prevalence of metabolic syndrome [38] that subsequently increases the CVD risk among them.

Data related to CVD risk factors among Bangladeshi postmenopausal women is very limited. According to a literature based on Noncommunicable Disease (NCD) risk factors survey Bangladesh 2010, more than one third of the Bangladeshi women are habituated to smokeless tobacco use and the prevalence is higher in rural area compared to urban. Again significant percentages of them are also detected with overweight [39]. The only representative data on countrywide physical activity level of Bangladesh detected more than half of the adult women as physically inactive [40], similar to above mentioned findings. Two other literatures also reported nearly half of the postmenopausal women of Bangladesh have the features of metabolic syndrome [41, 42].

4.2. Emerging CVD risk factors

To improve CVD risk assessment more than 100 new risk factors have discovered globally [43] which are termed as “emerging risk factors”. Among them high sensitivity C reactive protein (hs-CRP), carotid artery plaque (CAP), Apolipoprotein (apo) B-100 and serum uric acid are evaluated in current review for postmenopausal population. Evidence suggested high rise of hs-CRP [44] and Apolipoprotein (apo) B100 [37] are associated with menopause. Evaluation of hs-CRP among postmenopausal women has detected significant association with obesity, fasting insulin, hypertension and metabolic syndrome [25, 28-30, 37]. On the other hand Apolipoprotein B is the direct measurement of atherogenic particle in circulation and closely related to vascular diseases than LDL-C. Again, recent risk estimation has showed that Apo-B is the best, HDL-C is intermediate and LDL-C is the worst predictor of CVD risk [45]. Another promising emerging risk factor is carotid artery plaque (CAP) to diagnose subclinical atherosclerosis and showed relationship with other conventional risk factors. Studies under review have showed one third of the

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postmenopausal had CAP who was categorized as low risk according to FRS & score of WHO [34]. It has claimed that prevalence of subclinical atherosclerosis may be significant even analyze in low risk population and hence it needs to be recalibrated [46]. Evaluation of serum uric acid among postmenopausal women has demonstrated significant correlation with atherogenic index of plasma [25].

5. Current CVD risk assessment tools

Recently available CVD risk prediction tools should have the ability to assist a busy health professional to apply them in minimal resource setting. Current CVD risk assessment tools are listed below:

- Framingham risk score (FRS)
- World Health Organization (WHO) / ISH risk charts
- SCORE (Systematic Coronary Risk Evaluation)
- ASSIGN score (Scotland only)
- Reynolds risk score
- PROCAM
- QRISK2 risk calculator
- QRISK Lifetime cardiovascular risk calculator
- Pooled Cohort Equations
- The INTERHEART modifiable risk score
- CUORE risk score
- NHANES Follow-Up Study Cohort (NHEFS) non laboratory-based score
- Globo risk score

Above mentioned risk prediction tools are calibrated to estimate total CVD risk that is considered better than the individual risk factor approach and recommended for cost-effective prevention. The total CVD risk approach involves assessment of an individual's risk of developing CVD based on synergistic effect of multiple risk factors rather than estimating traditional method of single risk factor [47]. This total CVD risk is estimated for the period of 10 years usually and the cause behind this time limit is that 10

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years risk identifies most of the individuals likely to benefit from drug treatment in the near terms and thereby ensuring the cost-effectiveness and safety [48].

Framingham risk score is the pioneer of CVD risk assessment and based on its success other risk tools have derived. But one major critique about this tool is that it estimated risk in late 1960's and early 1970's among the high risk Caucasian population when most of the patients were not treated for their risk factors. Hence risk of this Framingham study population mismatched with the other population risk level through either underestimation or overestimation. For example, it has found that Framingham risk score based tools overestimate the CVD risk at least 30% among some European population [49]. Among the listed tools, few are suitable for the policy makers of developing countries like Bangladesh and only WHO/ISH without cholesterol version risk chart and NHEFS risk score can be applied in low resource setting where laboratory facilities are limited. Recently another risk tool has developed namely 'Globo risk score' which can be applied for most of the countries and its office based version is suitable to apply in low resource setting [50]. Though most of the tools are applicable for both men and women other than PROCAM and CUORE, only Reynolds risk score is based on the data of Women's Health Study and study included women of age 45 years and older. Again, though Framingham, SCORE and PROCAM risk score have been tested in various settings but all showed overestimation in external setting beyond their original study population. Among the risk tools, Framingham risk score has been evaluated in a developing country (China) where recalibration with local data improved accuracy [51]. Recently 'with' and 'without' versions of WHO/ISH risk tools have been applied in another developing country (Bangladesh) among remote rural population and findings revealed that 'without' cholesterol version has the capability to estimate CVD risk accurately in low resource setting where laboratory test is not possible [52].

It is believed that ideal CVD risk assessment tool is one that is developed from the population in which it is to be applied to predict the risk. In this context, Bangladesh has no such kind of risk prediction tools and hence needs to be developed one. This scenario also

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demands application of existing CVD risk assessment tools in low resource settings to test and compare their validity.

6. Cardiovascular risk in postmenopausal women

In this review we have found that four CVD risk prediction tools have been used more commonly to measure CVD risk among postmenopausal women of different countries of various socio-demographic & cultural background **(Table 2).**

Table 2: List of studies assessed CVD risk levels among postmenopausal women

1st Author, Year of publication, Reference	Country of study	Subjects	Sampling Procedure	Age group	Sample size	Risk tool(s) applied	Risk level
Abedi *et al* 2009 [37]	Iran	Urban	Not reported	Not reported	147	FRS*	Low
							FRS: Low (99%) Moderate (1%)
Pelletier *et al* 2009 [44]	USA	Not reported	Not reported	49-68 years	109	FRS WHS** model hs-CRP	WHS: Low (91%) Moderate (16%) High (2%)
							hs-CRP: Low (41%) Moderate (37%) High (31%)

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							FRS: low (96%) moderate (4%)
Masson *et al* 2013 [41]	Argentina	Urban	Consecutive sampling	≤ 65years	334	FRS WHO	WHO- low (91%) moderate (8%) High (1%)
Nahas *et al* 2013 [32]	Brazil	Urban	Non-probability sampling	≥45 years	497	FRS	Low (72.4%) Moderate 16.5%) High (11.1%)
Ozdemir *et al* 2014 [36]	Turkey	Urban	Not reported	Not reported	58	FRS	Low (67.24%) High (32.76%)
Awotidebe *et al* 2014 [40]	Nigeria	Semi-urban	Multi-stage sampling	≥ 55years	120	FRS	Low (60.8%) Moderate (28.4%) High (10.8%)
Nansseu *et al* 2016 [42]	Cameroon	Urban	Convenient sampling	Not reported	108	FRS	Low (39.8%), Moderate (36.1%), High (24.1%)

*FRS=Framingham risk score, **WHS=Women's Health Study

Among them, Framingham risk score has been used randomly with or without other risk tools and predominantly low CVD risk has detected [25, 29, 30, 33, 34, 35, 37]. Low risk in the postmenopausal women with FRS is not surprising as previously it was noted that FRS underestimates CVD risk among the women and those with family history of premature heart diseases [48]. Inverse scenario also observed with FRS in the Sub-Sahara region where no 'low risk' has identified. This finding has also observed in another study where the author mentioned that FRS may lack to accurately measure the risk of CVD among the African population as the pattern of CVD may differ from country to country [53]. Current review has identified that high sensitivity C reactive protein (hs-CRP) based risk estimation detected more postmenopausal women as moderate or high risk group, even some of those who were classified as low risk by FRS [37]. This is because hs-CRP level is influenced by

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central obesity which is highly prevalent among postmenopausal women. Among the available studies, postmenopausal women with high CVD risk is prevalent in USA [29] and Turkey [37] where in South Asian country Iran, no moderate or high risk group has detected [30].

7. Hormone replacement therapy (HRT) and CVD risk

Ground breaking findings of Women's Health Initiative has ensured that HRT never be initiated or continued for primary prevention of CVD [67]. To justify the use of ERT/HRT for secondary prevention among women with established CHD, the Estrogen Replacement and Atherosclerosis (ERA) Trial reported no significant progression of CHD [55]. Different observational studies reported that use of HRT during early stage of menopause is beneficial for cardiovascular health compared to use after 5-20 years after onset of menopause [56]. Finally it has been hypothesized that initiation of HRT during early stage of onset of menopause might be possible to provide benefit against CVD than to prevent its progression once established.

8. Conclusion

Postmenopausal women are at high risk for developing CVD but still no appropriate CVD risk assessment tool has developed for them. Hence this review demands further study to develop a cost-effective tool considering their risk factors for reducing the burden of CVD among them.

9. Recommendations

We have identified seven areas that we believe are promising in the field of cardiovascular research among postmenopausal women:

- Conducting large scale cohort studies to identify traditional and emerging CVD risk factors among postmenopausal women of developing countries
- Application and validation of available CVD risk tools among postmenopausal women in both rural and urban setting

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- Determining the level of physical activity among postmenopausal women and examining its association with CVD risk
- Applying physical activity interventions and justifying its efficacy in reduction of CVD risk among postmenopausal women
- CVD risk prediction following addition of local risk factors into the conventional risk tools and justify its accuracy among postmenopausal women
- Investigating the impacts of psychosocial factors on CVD risk in postmenopausal women
- Exploring the relationship between hormone replacement therapy and CVD risk among postmenopausal women of developing countries

Authors Contributions

L.B., M.F., P.C.B; and L.A. contributed to the conception and design of the work. L.B., and M.F contributed to the acquisition of data for the work. L.B; and P.C.B. contributed to the analysis of data for the work. L.B; M.F; and L.A. contributed to the interpretation of data for the work. L.B; and P.C.B. drafted the manuscript. M.F; P.C.B; and L.A. critically revised the manuscript. All authors gave final approval and agreed to be accountable for all aspects of work ensuring integrity and accuracy

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Conflict of interest

The authors declare that they have no conflict of interest.

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