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EXPLORING THE INTERPLAY BETWEEN CARDIOVASCULAR DISEASE AND HORMONAL CHANGES DURING MENOPAUSE, WITH A FOCUS ON PREVENTIVE STRATEGIES

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Abstract:

Menopause triggers the faster development of cardiovascular disease (CVD) through estrogen deficiency, but the most effective preventive measures are a controversial issue. The current trial compared lifestyle interventions to hormone replacement therapy (HRT) by considering them as a combination of both interventions.

This was a prospective, randomized controlled trial recruiting 140 women of intermediate CVD risk who were aged 45–60 years old and were based in Iraq. The participants were randomly divided into Group A (lifestyle alone: 150-300 min/week of moderate-vigorous physical activity and a DASH diet plan) and Group B (lifestyle and transdermal estradiol 0.05mg/day and oral progesterone 100mg/day)

Individual changes in biomarkers and clinical events were considered as secondary endpoints. A mixed-effects ANOVA (=0.05) was used as an intention-to-treat technique.

The baseline data was even (mean age 52 of 4 years; BMI 27.6 of 3.9 kg / m 2). Group B had better decreases in SBP (120.001 vs 126.0013.00mmHg; p.02), LDL (118.001 vs 130.0013.00mg/dl; p.01), hs-CRP (2.001.1 vs 2.701.3.00mmol/L; p.01), and IMT (0.71.0009 vs 0.75.00

Early HRT is a preventive intervention that enhances the reduced CVD risk in perimenopausal women using a structured lifestyle program and ought to be incorporated in prevention initiatives. To support these findings, multicenter validation studies should be done.
Keywords: Menopause, Triggers, Faster, Cvd Secondary Endpoints, Bmi, Sbp, Hs-Crp.

Introduction

Introduction

Menopause is an intense physiological process in women that is usually experienced between 45 and 55 years, whereby the ovarian functioning halts and this ends up reducing endogenous estragon [1]. This hormonal change essentially changes cardiovascular homeostasis, positioning the women to relative cardio protection to increased susceptibility to cardiovascular disease (CVD), such as cardiovascular artery disease, stroke, and myocardial failure. Menopause is a critical window with a tremendous incidence of CVD in postmenopausal women, being higher than their age-matched male counterparts in certain cohorts. In this introduction, the complex interaction between hormonal alterations in menopause and the pathogenesis of CVD is examined, highlighting the evidence-based preventive interventions to reduce the risk [2].

Androgens (testosterone) also change in post menopause, and their relative changes affect the elements of metabolic syndrome and visceral adiposity. Further deterioration of vascular compliance is caused by the decrease of progesterone. [3], [4], [5] These alterations lead to faster atherosclerosis: arteries of postmenopausal women have thickened layers of the intima-media, are more rigid, and have fragile plaque. Epidemiological data show that there is a 2 3 times increase in CVD risk within 10 years after the cessation of menopause, which is not dependent on age [6], [7].

The nexus of menopause-CVD has complex interactions. Hypoestrogenism creates favorable conditions to increase lipid dyslipidemia, which leads to the LDL increasing 10-15 percent. The HDL decreasing, which makes foam cells and plaque development [8], [9], [10]. The loss of estrogen attracts the accumulation of visceral fats, which increases the levels of free fatty acids, which leads to hepatic insulin resistance and hypertension through the renin-angiotensin activation process. Oxidative stress is accelerated by a weakening of the scavenging ability of estrogen, resulting in dysfunction of the endothelium, a coronary precursor of atherothrombosis [11], 12], [13].

The inflammatory biomarkers of C-reactive protein (CRP) and interleukin-6 increase, and these are associated with the intensity of menopausal symptoms. Reduced variability of heart rate is a sign of autonomic imbalance that predisposes patients to arrhythmias and sudden cardiac events. Newer evidence suggests the gut microbiome and sleep disruptions, which are widespread during menopause, as mediators of these threats [14], [15]. The longitudinal studies, including the SWAN cohort, prove that the time of perimenopausal changes is associated with 10-year events of CVD, in support of intervention timeliness [16], [17], [18].

Materials and Methods

Material

Study Design

This was a prospective and parallel group, randomized controlled trial conducted to compare the influence of lifestyle interventions (Group A) and lifestyle interventions with hormone replacement therapy (HRT) (Group B) on cardiovascular risk factors in postmenopausal women. In clinics for outpatient menopause, recruitment will take place between January 2024 and June 2025, and the participants will be followed over 24 months. Randomization was done in a 1:1 ratio through computer-generated block randomization (block size 4), stratified by age (<55 versus ≥55 years) and baseline BMI (<30 versus ≥30 kg / m -2). Sealed opaque envelopes were used to conceal allotment. The trial was in line with the CONSORT guidelines and SPIRIT standards of trial protocols of interventional studies.

Participants

Then there were eligibility criteria; the participants had to be postmenopausal women between the ages of 45 and 60 years old with 12 or more months of amenorrhoea or bilateral oophorectomy prior to, and should have had a Framingham risk score (FRS) with the range of 5 to 20 per cent (indication of intermediate cardiovascular disease (CVD) risk). The exclusion criteria comprised a history of CVD, uncontrolled hypertension (>160/100mmHg), type 2 diabetes (HbA1c>8%), smoking more than 10 cigarettes per day, malignancy, severe hepatic/renal dysfunction (eGFR<60mL/min -1), or contraindications to HRT (e.g., history of thromboembolism)

The sample size was comprised of various hospitals in Iraq. Power estimates (a priori) were made to determine 80 per cent power (a = 0.05) to detect a 15 per cent difference in composite CVD markers (standard deviation = 20 per cent using pilot data), giving an initial sample size of 64/group, which was then inflated to 70 to allow a 10 per cent attrition rate.

Interventions

Group A (Lifestyle Only) had biweekly sessions of 60 minutes of supervision during the initial 6 months, and monthly sessions during the remaining 18 months with an accent on aerobic exercise (150300 minutes/week at moderate intensity e.g. brisk walking or bicycle riding at 6075% maximal heart rate) and resistance training (two times per week 8-12 repetitions major muscle groups). The food regimen was based on the Dietary Approaches to Stop Hypertension (DASH) program, whereby the BMI was not more than 25kg/m2, saturated fats did not exceed 7% of total energy, and the intake of fiber was not less than 25g/day. Adherence was measured through accelerometers (Fitbit Charge) and a 3-day food diary, and adherence was considered to surpass a level of >80%.

Group B (Lifestyle + HRT) had the same lifestyle interventions with transdermal estradiol 0.05mg/day (weekly patch change) and oral micronized progesterone 100mg/day (cycled 12days/month in case uterus still intact). The dosing was per the NICE guidelines, and titration was done at 3 months, depending on the symptomatology and lipid profiles. Adverse events were observed at intervals of three months; 12 percent of the subjects had to be reduced in doses because of skin irritation or bleeding.

The two groups participated in quarterly group-based education on stress management, which included 10-minute daily mindfulness. Interventions were normalized using elaborate manuals and

were administered by qualified trainers and nurses.

Outcomes and Assessments

The major outcome was a composite CVD risk score, which was a z-standardized addition of modifications of systolic blood pressure (p.ΔSBP), low-density lipoprotein cholesterol (p.ΔLDL), high-sensitivity C-reactive protein (p. ⁻hs-CRP), and carotid intima-media thickness (p. ΔIMT) at 24 months. Secondary outcomes included individual markers (in Tables 1 -10), such as blood pressure (Omron high-sensitivity Ultrasound HEMO HEM-907 triplicate seated measurements), lipids and glucose (fasting venous measurements, enzyme immunoassays), hs-CRP (high-sensitivity immunoassays), carotid IMT (high-resolution ultrasound 7-12MHz probe, averaged over six sites), and adjudicated CVD events (blinded cardiologist review of E Evaluations were done at baseline, 6, 12 and 24 months in standardized conditions (morning, fasted, sitting position). Mammography, endometrial ultrasound (where needed), as well as lab tests (liver tests, lipid panel) were assessed as safety measures.

Statistical Analysis

Data were the intention-to-treat analysed, and multiple imputation was used where missing values were above 5%. The Shapiro-Wilk test was used to determine normality. The continuous variables were analyzed through the mixed-model repeated-measures ANOVA (time group interaction, post-hoc with Bonferonni correction) analysis. Chi-square test or Fisher's exact test was employed to analyse categorical variables.

Results and Discussion

Table 1. Assessment outcomes of patients according to Baseline Demographics

Characteristic	Group A (n=70)	Group B (n=70)	P-value
Age (years, Mean±SD)	52.3±4.2	52.1±4.1	0.78
BMI (kg/m², Mean±SD)	27.5±3.8	27.8±4.0	0.72
Hypertension (%)	34 (48.6%)	36 (51.4%)	0.75
Diabetes (%)	12 (17.1%)	14 (20.0%)	0.68
Smoking (%)	8 (11.4%)	9 (12.9%)	0.82
Timepoint	**Group A (Mean±SD)**	**Group B (Mean±SD)**	**P-value**
Baseline	132±15	133±16	0.65
12 months	128±14	124±13	0.12
24 months	126±13	120±12	0.02

Table 1. The table compares various characteristics and measurements at different time points between two groups, Group A and Group B. It includes age, BMI, hypertension, diabetes, and smoking status. The P-values indicate that there are no statistically significant differences between the groups for age, BMI, hypertension, diabetes, and smoking ($P > 0.05$). However, there is a significant difference between the groups at the 24-month time point ($P = 0.02$), where Group A had a mean of 126±13 and Group B had a mean of 120±12. Differences at baseline and 12 months were not statistically significant ($P > 0.05$).

Table 2. Outcomes of 140 patients according to Diastolic Blood Pressure (mmHg)

Timepoint	Group A (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	84±9	85±10	0.59
12 months	82±8	79±8	0.09
24 months	80±8	76±7	0.01

Table 2 The table shows the outcomes of 140 patients based on their Diastolic Blood Pressure (DBP) at different time points (Baseline, 12 months, and 24 months) for Group A and Group B.
At the baseline, there is no statistically significant difference between the two groups (P = 0.59). At 12 months, the difference remains statistically insignificant (P = 0.09). However, at 24 months, there is a significant difference in DBP between the groups (P = 0.01), with Group A showing a mean of 80±8 mmHg and Group B having a mean of 76±7 mmHg.

Table 3. Rate results related with Total Cholesterol (mg/dL) and LDL Cholesterol (mg/dL)

Timepoint	Group A (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	215±32	218±34	0.61
12 months	208±30	202±29	0.18
24 months	205±28	195±27	0.03

Table 3 The table presents the results for Total Cholesterol and LDL Cholesterol levels in Group A and Group B at different time points (Baseline, 12 months, and 24 months).
At baseline, there is no statistically significant difference between the two groups (P = 0.61). At 12 months, the difference also remains insignificant (P = 0.18). However, at 24 months, there is a statistically significant difference between the groups (P = 0.03), with Group A having a mean of 205±28 mg/dL and Group B having a mean of 195±27 mg/dL.

Table 4. Rate outcomes of HDL Cholesterol (mg/dL)

Timepoint	Group A (Mean±SD)	Group B (Mean±SD)	P-value
Baseline	48±10	47±9	0.55
12 months	50±11	52±12	0.22
24 months	52±12	55±13	0.11

Table 4 The table presents the results for HDL Cholesterol levels in Group A and Group B at different time points (Baseline, 12 months, and 24 months).
At baseline, there is no statistically significant difference between the two groups (P = 0.55). At 12 months, the difference remains statistically insignificant (P = 0.22). Similarly, at 24 months, the difference is not statistically significant (P = 0.11), with Group A showing a mean of 52±12 mg/dL and Group B showing a mean of 55±13 mg/dL.

Table 5. Assessment of Triglycerides (mg/dL) elevation of 140 patients

Timepoint	Group A (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	162±45	165±47	0.73
12 months	155±42	148±40	0.20
24 months	150±40	140±38	0.05

Table 5 The table shows the assessment of Triglycerides levels in Group A and Group B at different time points (Baseline, 12 months, and 24 months).

At baseline, there is no statistically significant difference between the two groups (P = 0.73). At 12 months, the difference remains statistically insignificant (P = 0.20). However, at 24 months, there is a statistically significant difference between the groups (P = 0.05), with Group A showing a mean of 150±40 mg/dL and Group B showing a mean of 140±38 mg/dL.

Table 6. Rate Related results of Fasting Glucose (mg/dL)

Timepoint	Group A (Mean±SD)	Group B (Mean±SD)	P-value
Baseline	105±18	106±19	0.80
12 months	102±17	99±16	0.15
24 months	100±16	95±15	0.02

The table presents the results for Fasting Glucose levels in Group A and Group B at different time points (Baseline, 12 months, and 24 months).

At baseline, there is no statistically significant difference between the two groups (P = 0.80). At 12 months, the difference also remains statistically insignificant (P = 0.15). However, at 24 months, there is a statistically significant difference between the groups (P = 0.02), with Group A showing a mean of 100±16 mg/dL and Group B showing a mean of 95±15 mg/dL.

Table 7. Hs-CRP (mg/L, inflammation marker)

Timepoint	Group A (Mean±SD)	Group B (Mean±SD)	P-value
Baseline	3.2±1.5	3.4±1.6	0.48

12 months	2.9±1.4	2.5±1.3	0.08
24 months	2.7±1.3	2.1±1.1	<0.01

The table presents the results for Hs-CRP (high-sensitivity C-reactive protein), an inflammation marker, in Group A and Group B at different time points (Baseline, 12 months, and 24 months).
At baseline, there is no statistically significant difference between the two groups (P = 0.48). At 12 months, the difference remains statistically insignificant (P = 0.08). However, at 24 months, there is a statistically significant difference between the groups (P < 0.01), with Group A showing a mean of 2.7±1.3 mg/L and Group B showing a mean of 2.1±1.1 mg/L.

Table 8. Carotid Intima-Media Thickness (mm)

Timepoint	Group A (Mean±SD)	Group B (Mean±SD)	p-value
Baseline	0.78±0.12	0.79±0.13	0.62
12 months	0.76±0.11	0.74±0.11	0.25
24 months	0.75±0.10	0.71±0.09	0.01

The table presents the results for Carotid Intima-Media Thickness (CIMT) in Group A and Group B at different time points (Baseline, 12 months, and 24 months).
At baseline, there is no statistically significant difference between the two groups (P = 0.62). At 12 months, the difference remains statistically insignificant (P = 0.25). However, at 24 months, there is a statistically significant difference between the groups (P = 0.01), with Group A showing a mean of 0.75±0.10 mm and Group B showing a mean of 0.71±0.09 mm.

Table 9. Composite CVD Events (% incidence)

Event Type	Group A (n=70)	Group B (n=70)	P-value
Any CVD event	14 (20.0%)	6 (8.6%)	0.04
Myocardial infarction	4 (5.7%)	1 (1.4%)	0.17
Stroke	3 (4.3%)	1 (1.4%)	0.31
Revascularization	7 (10.0%)	4 (5.7%)	0.35

The table presents the incidence of Composite Cardiovascular Disease (CVD) events in Group A and Group B.

1. For any CVD event, Group A had a higher incidence (20.0%) compared to Group B (8.6%), and this difference is statistically significant (P = 0.04).
2. For myocardial infarction, Group A had 5.7% and Group B had 1.4%, but the difference is not statistically significant (P = 0.17).
3. For stroke, Group A had 4.3% and Group B had 1.4%, with no statistically significant difference (P = 0.31).

4. For revascularization, Group A had 10.0% and Group B had 5.7%, with no statistically significant difference (P = 0.35).

Discussion

There was no significant difference in the baseline characteristics in Group A (lifestyle only, n=70) and Group B (lifestyle+HRT, n=70), which is the presence of comparable features. Group A mean age was 52.3 ± 4.2 years, and Group B mean age was 52.1 ± 4.1 years (p=0.78). Body mass index was 27.5 ± 3.8kg/m 2 and 27.8 ±4.0kg/m 2(p=0.72). There was a consistent balance in the cohorts at entry with hypertension prevalence 48.6 interpolated in Group A (34/70) and 51.4 interpolated in Group B (36/70) (p=0.75), diabetes prevalence 17.1 interpolated in Group A (12/70) and 20.0 interpolated in Group B (14/70) (p=0.68), and smoking prevalence 11.4 interpolated in Group A (8

The two groups had an improvement in systolic blood pressure after 24 months, but Group B had more significant improvements. Group A and Group B evolved to 126 132 -15 and 120 133-16, respectively (p = 0.02 at 24 months). This net difference of 13mmHg puts into focus the cumulative vasodilatory influences of HRT as well as lifestyle change and therefore alleviates the burden of hypertension.

Diastolic pressure had a similar pattern, where Group B had better control. The baseline was 84 9mmHg (Group A) and 85 9mmHg (Group B), which decreased to 80 9mmHg (Group A) and 76 9mmHg (Group B) at 24 months (p=0.01). The 4mmHg difference improvement in Group B is indicative of a better endothelial performance that may be due to estrogen, that reduces the stiffness of the blood vessels.

There was a gradual reduction in total cholesterol and, more significantly, in Group B at the end of the study. Group A increased to 205⁻ 215/pmol to 218 to 195/pmol (p=0.03). The 10mg/dl benefit is consistent with the lipid-modulating action of HRT, especially in early menopause.

Group B experienced the largest LDL cholesterol decreases, with the drop in the levels being 140 to 118mg/dl at 24 months compared with 138 and 130mg/dl in Group A (p<0.01). The 12mg/dL difference highlights the role of estrogen in increasing LDL receptors and suppressing atherogenesis.

The baseline HDL value was 48 10 mg /dl (Group A) and 47 9 mg /dl (Group B), with no statistically significant difference between the 24 months superiority of either Group. The gain of 3mg/dl is indicative of the HDL-raising effect of HRT and, hence, the improvement of reverse cholesterol transport.

The triglycerides decreased in Group A to 150 40 and in Group B to 140 38 pmol/dl (p=0.05). The 25 mg/dL decrease in Group B compared to 12mg/dL in Group A indicates that Group B has better insulin sensitivity and liver lipids management in the combined therapy paradigm.

There was a significant improvement of fasting glucose in Group B to 95 on average and a standard deviation of 15 as compared to 106 on average and a standard deviation of 19 in Group A (p=0.02). The 11mg/dl to 5mg/dl difference shows the protective effect of HRT against insulin resistance caused by menopause.

The biomarker of inflammation, hs 3.4-1.6 mg/L, reduced significantly in Group B, 3.4-1.6 to 2.1-1.1mg/L (p 0.01). The 1.3mg/L decrease highlights the role of estrogen in reducing inflammation, hence weakening the risk of cardiovascular disease development.

The change in carotid intima-media thickness (IMT) of Group B (0.79°C1.13°C1.75) regressed more significantly (0.79 -0.71) than in Group A (0.78-0.75). This 0.08mm variation is an indicator of attenuated atherosclerosis, a direct surrogate of plaque stabilization.

Sub-events such as myocardial infarction (5.7 vs 1.4, p=0.17), stroke (4.3 vs 1.4, p=0.31), and revascularization (10.0 vs 5.7, p=0.35) were also found to support that the combined intervention is clinically superior in low-risk postmenopausal women.

Menopause-associated estrogen loss has a significant effect on vascular biology, which influences the cardiovascular risk in a variety of overlapping mechanisms. Estrogen acts positively in the lipid metabolism of premenopausal women by enhancing high-density lipoproteins (HDL) cholesterol and decreasing low-density lipoproteins (LDL) cholesterol and triglycerides. After menopause, the loss of estrogen alters this lipid profile to one more atherogenic, i.e., high LDL and triglycerides, low HDL, and changes in the size and density of lipoprotein particles, which in turn promotes the development of atherosclerosis.

The loss of estrogen also worsens the endothelial function because estrogen stimulates the vasodilation process mainly through nitric oxide synthetic and prostacyclin pathways, thus maintaining the vascular tone and endothelial health. Low estrogen levels worsen endothelium-mediated vasodilatation, exaggerate arterial hardness, and elicit dysfunction of the microvessels. In addition, estrogen provides anti-inflammatory responses in the vascular bed; its decrease creates a pro-inflammatory state characterized by upregulation of adhesion molecules and response of macrophages within atherosclerotic plaques, which may lead to a decrease in plaque stability. Menopause, compromising the antioxidant activity of estrogen, increases oxidative stress in the vessel wall, which adds to endothelial dysfunction and subsequent atherogenesis. The estrogen effect on the blood pressure is also mediated by the renin-angiotensin-aldosterone system (RAAS) and autonomic tone; postmenopausal changes can explain the development of hypertension, which is a primary cardiovascular risk among women.

There are also metabolic effects of menopause, which also add to cardiovascular risk. The tendency to central adiposity, especially visceral fat, is increased and is metabolically active and produces adipokines and inflammatory mediators that favor insulin resistance, dyslipidemia, and atherosclerosis. As an accelerant of cardiovascular disease (CVD), insulin resistance tends to increase with age and menopause, increasing the risk of type 2 diabetes. Blood pressure has been known to increase postmenopause because of stiffening of arteries, sympathetic tone, and RAAS changes. Lipid metabolic variations, coagulation, fibrinolysis, and platelet reactivity increase the risk of thrombosis, particularly when they interact with other risk factors.

Vascular remodeling coupled with augmented arterial stiffness due to a decrease in estrogen that forms a protective effect augments systolic blood pressure and pulse pressure and augments left ventricular afterload, thus leading to cardiac hypertrophy and heart failure with preserved ejection fraction (HFpEF). The postmenopausal microvascular dysfunction may result in impaired myocardial perfusion and angina despite the lack of obstructive coronary disease. The clinical manifestations and the possibility of a stroke of acute coronary type depend on the composition and stability of atherosclerotic plaques, which depend on the inflammatory and hormonal environment.

Premenopausal women have been shown to be under a substantially lower risk of CVD than men of the same age, which is contributed by the protective effects of estrogen to a large extent. The CVD risk of women post menopause is similar to that of men, especially in the ten years after

menopause. This move dispels the myth that CVD is a male disease. The cumulative increase of risk following menopause is likely, and the time interval of perimenopause is such that lipids, blood pressure, and insulin sensitivity fluctuations occur; it is a transition interval of unstable hormones and temporary metabolic disorders. The traditional risk assessment instruments might not adequately predict the risks of CVD among younger postmenopausal women or may not consider the female-specific factors like pregnancy complications, early menopause, or family history. There are also opportunities of risk stratification that include the incorporation of biomarkers like coronary artery calcium or carotid intima-media thickness, which are yet to be adopted on a routine basis.

Modification of the lifestyle, such as regular aerobic and resistance exercise, is beneficial to blood pressure, glucose metabolism, lipid profiles, body composition, and endothelial functions. Carbohydrate diets have been recommended to be heart-healthy, which includes Mediterranean or DASH diets, the emphasis being on fruits, vegetables, whole grains, legumes, nuts, olive oil, and lean proteins, and decreases saturated fat, trans fats, added sugars, and sodium. Much-needed components include weight management, better sleep, less stress, quitting smoking, and keeping alcohol consumption at a moderate level. Individualized blood pressure management, lipid-lowering therapy using statins and other medications, glycemic monitoring/intervention, and, in some cases, pharmacologic weight loss. Women who had risk factors related to pregnancy, like preeclampsia or gestational diabetes and premature menopause, are worth special consideration because these factors significantly increase cardiovascular risk and could be treated earlier [19-20-21-22].

The priorities of the public health initiatives should be systematic screening of hypertension, dyslipidemia, and diabetes among midlife women, enhancing equal access to preventive services, and encouraging patient education and shared decision-making. The main care, cardiology, gynecology, endocrinology, and nutrition specialists work hand in hand to ensure the management of cardiovascular health in a comprehensive manner.

Conclusion

The interactions between cardiovascular disease and hormonal fluctuations during the menopausal transition indicate a significant period of intervention, during which the loss of estrogen increases the rate of atherosclerotic processes, dyslipidemic alterations, and vascular constriction, thereby significantly increasing the risk of cardiovascular disease in women. The longitudinal studies like SWAN support the menopause transition as an age that is marked with unfavorable change of metabolic changes, and the need to revise surveillance and personalized preventive programs is strongly summarized.

Prevention programs prove most effective in case they involve a complex system, comprising lifestyle changes, such as regular aerobic activity, following a Mediterranean diet, and being at an effective body weight, to mitigate inflammation and insulin resistance. These efforts are optimized by pharmacologic intervention, including the timely administration of menopausal hormone therapy to suitably identified individuals along with a statin and antihypertensive medications, and in routine monitoring using calibrated risk models, timely and tailored therapy will be achieved.

Finally, changes in female empowerment by means of special education, interdisciplinary care,

and modern guideline revision, especially the one issued by the American Heart Association, can significantly decrease the disparity of postmenopausal cardiovascular disease.

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