Discordances among different tools used to estimate cardiovascular risk in postmenopausal women

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BACKGROUND: New cardiovascular disease (CVD) risk factors are being recognized and suggested to be included in CVD risk stratification. High-sensitivity C-reactive protein (hs-CRP) and the metabolic syndrome (MetS) are among these risk factors. However, CVD risk classification may be divergent when using different approaches.

OBJECTIVES: To compare differences in CVD risk estimation using the Framingham risk score (FRS), hs-CRP and the presence of the MetS in a group of 109 postmenopausal women in primary CVD prevention.

METHODS: The FRS and presence of the MetS were determined. CVD risk was evaluated with a cardiovascular point scoring system based on Framingham covariables and hs-CRP values (Women's Health Study [WHS] model). The estimated CVD risks based on hs-CRP levels and the WHS model were compared with the FRS.

RESULTS: Using the FRS, 99% of women (n=108) were determined to have a low CVD risk. The MetS was identified in 39.4% (n=43) of the women. When hs-CRP was used alone to estimate CVD risk, 37.6% (n=41) of women were classified as being at low, 33.9% (n=37) at moderate and 28.4% (n=31) at high CVD risk. With the WHS model, 83.5% (n=91), 14.7% (n=16) and 1.8% (n=2) of women were classified as being at low, moderate and high CVD risk, respectively.

CONCLUSIONS: A substantial number of postmenopausal women showing evidence of the MetS were not identified by the FRS, even though women with the MetS are at higher risk of CVD. Estimation of risk by hs-CRP is significantly divergent when using conventional hs-CRP cut-off values compared with an integrated use in the WHS model.

Key Words: CVD risk assessment; Framingham risk score; hs-CRP; Metabolic syndrome; Women's health

Les discordances entre les différents outils utilisés pour évaluer le risque cardiovasculaire chez les femmes ménopausées

HISTORIQUE: De nouveaux facteurs de risque de maladie cardiovasculaire (MCV) sont décelés. Il est proposé de les inclure dans la stratification du risque de MCV. La protéine C-réactive de haute sensibilité (PCR-hs) et le syndrome métabolique (Smét) en font partie. Toutefois, la classification du risque de MCV pourrait diverger selon les approches.

OBJECTIFS : Comparer les différences d'estimation du risque de MCV au moyen de l'indice de risque de Framingham (IRF), de la PCR-hs et de la présence de Smét dans un groupe de 109 femmes ménopausées pour la prévention primaire de MCV.

MÉTHODOLOGIE : Les auteurs ont déterminé l'IRF et la présence de Smét. Ils ont évalué le risque de MCV au moyen du système de pointage cardiovasculaire fondé sur les covariables de Framingham et les valeurs de PCR-hs (modèle WHS de l'étude de la santé chez les femmes). Ils ont comparé les risques estimatifs de MCV selon les taux de PCR-hs et le modèle WHS par rapport à l'IRF.

RÉSULTATS : Selon l'IRF, les auteurs ont déterminé que 99 % des femmes (n=108) présentaient un faible risque de MCV. Ils ont dépisté un Smét chez 39,4 % (n=43) des femmes. Lorsqu'ils utilisaient la PCR-hs seule pour évaluer le risque de MCV, 37,6 % (n=41) des femmes étaient classées à faible risque, 33,9 % (n=37) à risque modéré et 28,4 % (n=31) à haut risque de MCV. Selon le modèle WHS, 83,5 % (n=91), 14,7 % (n=16) et 1,8 % (n=2) des femmes se classaient à risque faible, modéré et élevé de MCV, respectivement.

CONCLUSION : Un nombre important de femmes ménopausées présentant des signes de Smét n'étaient pas dépistées par l'IRF, même si elles sont plus vulnérables à la MCV. L'évaluation du risque par PCR-hs diverge considérablement lorsqu'on utilise les valeurs seuils classiques de PCR-hs plutôt que le modèle WHS intégré.

Primary prevention of cardiovascular diseases (CVDs) requires identification of high-risk patients. Emerging risk factors are being suggested to more accurately identify high-risk patients. One of these – high-sensitivity C-reactive protein (hs-CRP) – has received substantial attention in recent years. Moreover, a cardiovascular point scoring system for women, combining Framingham covariables and hs-CRP, was developed using the Women's Health Study (WHS) model (1). The metabolic syndrome (MetS) was also found to be associated with a greater risk of CVD and this issue has been reviewed (2). However, the estimated CVD risk may be divergent when using these different approaches. Thus, the aim of our study was to compare CVD risk estimation differences using the Framingham risk score (FRS) (3), hs-CRP, the WHS model and presence of the MetS in a group of postmenopausal women not taking hormone therapy.

METHODS

A previously described sample of 109 Caucasian postmenopausal women 49 to 68 years of age was used (4). Participants were in primary CVD prevention and none had been diagnosed with or were being treated for heart disease, diabetes, glucose intolerance or hypertension. Five women were smokers and none were taking hormone therapy, although one started hormone supplementation during the testing period. The present research was approved by the Centre Hospitalier de l'Université Laval (Quebec City, Quebec) and the Laval University Research Ethics committees. All participants signed an informed consent form.

Blood samples were collected after a 12 h overnight fast. Cholesterol and triglycerides concentrations were determined enzymatically in plasma with a Technicon RA-500 analyzer (Bayer Corp, USA). Plasma lipoprotein fractions were isolated by sequential

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TABLE 1
Characteristics of postmenopausal women in the study

Variables	All (n=109)	MetS ⁺ (n=43)	MetS ⁻ (n=66)	P*
Age, years	57.0±4.3	57.7±3.8	56.6±4.5	NS
Body mass index, kg/m ²	29.0±5.9	32.2±7.1	26.9±3.8	<0.001
LDL cholesterol, mmol/L	3.60±0.81	3.59±0.83	3.61±0.80	NS
Total cholesterol/HDL cholesterol	4.11±1.13	4.85±1.17	3.62±0.81	<0.001
HDL cholesterol, mmol/L	1.41±0.35	1.16±0.21	1.57±0.33	<0.001
Triglycerides, mmol/L	1.29±0.64	1.70±0.73	1.02±0.38	<0.001
Systolic blood pressure, mmHg	131±16	138±15	126±14	<0.001
Diastolic blood pressure, mmHg	82±8	86±7	80±7	<0.001
Waist circumference, cm	92±13	102±12	86±9	<0.001
Fasting glycemia, mmol/L	5.60±0.80	6.12±0.95	5.27±0.43	<0.001
Apolipoprotein B-100, g/L	1.02±0.21	1.08±0.23	0.98±0.19	<0.001
High-sensitivity CRP, mg/L	2.84±3.58	4.22±4.16	1.94±2.84	<0.001
Geometric mean, mg/L	1.61	2.79	1.12	<0.001

Data are presented as mean ± SD. *Critical P-value for a statistically significant difference between women with the metabolic syndrome (MetS⁺) and women without the metabolic syndrome (MetS⁻) was set at 0.05. CRP C-reactive protein; HDL High-density lipoprotein; LDL Low-density lipoprotein; NS Nonsignificant

ultracentrifugations that have been described elsewhere (5). hs-CRP and apolipoprotein (apo) B-100 were measured by nephelometry (BN ProSpec, Siemens Healthcare Diagnostics, USA).

The MetS (defined as the presence of three or more of the following traits: waist circumference 88 cm or larger, triglycerides 1.7 mmol/L or greater, high-density lipoprotein [HDL] less than 1.3 mmol/L, blood pressure 130/85 mmHg or greater, and glucose 5.7 mmol/L or greater) status was determined (6,7). Classification according to conventional hs-CRP cut-off values was performed. Low hs-CRP was defined as less than 1.0 mg/L, moderate hs-CRP as 1.0 mg/L to 3.0 mg/L and high hs-CRP as greater than 3.0 mg/L. Finally, CVD risk was determined through an experimental CVD point scoring system for women based on Framingham covariables and hs-CRP (WHS model) (1).

RESULTS

The baseline characteristics of subjects are listed in Table 1. The MetS was found in 39.4% (n=43) of women. Women with the MetS had lower HDL cholesterol, higher triglycerides and higher apoB-100 levels, representing a more atherogenic lipid profile. hs-CRP levels were also higher in these women. Figure 1 shows the CVD risk classifications among the women. Using the FRS, all women except one (n=108) were classified as low risk (less than 10% risk). When hs-CRP was used alone or in the WHS model, more women were determined to have a moderate to high estimated CVD risk. Figure 2 shows that women with moderate to high hs-CRP (1 mg/L or greater) had significantly greater waist circumferences than women with low hs-CRP.

DISCUSSION

The present study showed that the FRS was unable to identify a substantial number of women at higher risk of CVD. Using only the FRS, we would have concluded that all but one woman had a low CVD risk. However, a significant number of subjects fulfilled the MetS definition, putting them at higher risk. Estimation of risk by hs-CRP was divergent when using conventional hs-CRP cut-off values (less than 1 mg/L, 1 mg/L to 3 mg/L, and greater than 3 mg/L) compared with an integrated use within the WHS model.

Explanations

Moderate to high elevation of hs-CRP in women with a low FRS may initially seem somewhat unexpected. A substantial number of these women (62.3%) had an hs-CRP level of 1 mg/L or greater, potentially

Figure 1 Cardiovascular disease (CVD) risk estimation according to different approaches. *Number of patients. FRS Framingham risk score (low <10%, moderate 10% to 20%, high >20%); hs-CRP High-sensitivity C-reactive protein (low <1 mg/L, moderate 1 mg/L to 3 mg/L, high >3 mg/L); WHS model Model derived from the Women's Health Study combining Framingham covariables and hs-CRP (low <10%, moderate 10% to 20%, high >20%)

Figure 2 Average waist circumference according to high-sensitivity C-reactive protein (hs-CRP) values (low <1 mg/L, moderate 1 mg/L to 3 mg/L, high >3 mg/L). Bars with different superscript letters (a versus b) denote a statistically significant difference

putting them at higher CVD risk than anticipated by their FRS. However, hs-CRP levels are influenced by abdominal adiposity and many studies have shown that elevated hs-CRP levels are associated with higher abdominal adiposity (8-15). This association is even stronger in women (8,16). Consequently, our findings could at least be partially attributed to an elevated abdominal adiposity: women with moderate to high hs-CRP (1 mg/L or greater) had significantly greater waist circumferences than women with low hs-CRP (Figure 2). Furthermore, sex differences in hs-CRP levels have been demonstrated in the past – the average hs-CRP level seems to be higher in women (17-19). Thus, the use of a single hs-CRP cut-off value to estimate high risk in both men and women may not be appropriate.

Clinical practice guidelines integrating the potential use of hs-CRP in CVD risk assessment recommend determining the FRS, then using hs-CRP values to enhance CVD risk stratification in some patients (6). This approach may seem similar to the use of a cardiovascular point scoring system that uses Framingham covariables and integrates hs-CRP (WHS model) (1). However, these two strategies produced different results in our study, possibly in part because the Framingham covariables and hs-CRP are not weighted equally.

Whether hs-CRP should be used in CVD risk estimation is a subject of debate and the question has been reviewed (20). There is plenty of evidence on the epidemiological relationship between elevated hs-CRP and a higher risk of CVD. However, test characteristics (sensitivity, specificity, positive predictive value and negative predictive value) must be considered when trying to implement day-to-day use (21). For instance, hs-CRP shows a very large biological variability that could limit its usefulness (22-26). As a result, some patients showing fluctuating hs-CRP levels could have different CVD risk estimates from one visit to another. Averaging the results of repeated samples is used to limit variability. This would require multiple samples and could be impractical in a real-life clinical setting.

The greater CVD risk associated with the MetS should warrant its identification. Studies have shown that older patients with the MetS have an increase in RR for CVD (2,27-31). Moreover, MetS patients also have an approximate fivefold increase in RR for diabetes (29). We demonstrated that many women can have a low FRS, even though they should be considered at higher risk because of the presence of the MetS. This is not surprising because abdominal obesity and elevated triglyceride and glucose levels, which characterize the MetS, are not included in the FRS. Furthermore, atherogenic dyslipidemia, characterized by elevated triglycerides, low HDL cholesterol and increased apoB-100 levels, is common in the MetS, and our findings were consistent with this feature.

Limitations

The present study had limitations. First, the sample studied consisted entirely of Caucasian women. Second, information regarding the

familial history of premature heart diseases was unavailable. However, only eight patients (data not shown) would have changed from low to moderate FRS, assuming they had a positive family history. Third, we used a single hs-CRP measurement, contrary to what is proposed in guidelines to limit biological variability (32). On the other hand, even multiple samples can be insufficient to limit variability. Fourth, the WHS model was proposed by its authors in the original publication as an illustration and is not yet recommended for clinical use. Finally, the present study is not a prospective observational cohort study. Thus, it was not designed to establish which tool has the best ability to predict future CVD.

CONCLUSIONS

Different methods to assess CVD risk stratification can lead to significant differences in risk level. A great number of postmenopausal women showing evidence of the MetS are unidentified by the FRS, even though they may be at higher risk of CVD. Consequently, searching for evidence of the MetS, especially abdominal obesity, should be part of risk determination. Moreover, many components of the MetS are potentially reversible, emphasizing the need for appropriate identification.

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