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Guideline No. 422e: Menopause and Cardiovascular Disease

(En français : Directive clinique n° 422e : Ménopause et maladies cardiovasculaires)

The English document is the original version. In the event of any discrepancy between the English and French content, the English version prevails.

This clinical practice guideline was prepared by the authors and overseen by the Menopause Working Group. It was reviewed by the SOGC's Clinical Practice Gynaecology committee, SOGC's Family Physician Advisory Committee, and the SOGC's Urogynaecology committee and approved by the SOGC Guideline Management and Oversight Committee and SOGC Board of Directors.

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RECOMMENDED CHANGES IN PRACTICE

1. In appropriately selected, symptomatic women, short-term menopausal hormone therapy does not confer increased cardiovascular risk, according to long-term follow-up data.
2. There is a lack of high-quality data to inform a recommendation on the safety of routes of administration of estrogen for women at average risk.
3. Providing menopausal hormone therapy to women with premature or early-onset menopause until the average age of menopause appears to decrease the risk of adverse cardiovascular outcomes.

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This document reflects emerging clinical and scientific advances as of the publication date and is subject to change. The information is not meant to dictate an exclusive course of treatment or procedure. Institutions are free to amend the recommendations. The SOGC suggests, however, that they adequately document any such amendments.

Informed consent: Everyone has the right and responsibility to make informed decisions about their care together with their health care providers. In order to facilitate this, the SOGC recommends that health care providers provide patients with information and support that is evidence-based, culturally appropriate, and personalized.

Language and inclusivity: The SOGC recognizes the importance to be fully inclusive and when context is appropriate, gender-neutral language will be used. In other circumstances, we continue to use gendered language because of our mission to advance women's health. The SOGC recognizes and respects the rights of all people for whom the information in this document may apply, including but not limited to transgender, non-binary, and intersex people. The SOGC encourages health care providers to engage in respectful conversation with their patients about their gender identity and preferred gender pronouns and to apply these guidelines in a way that is sensitive to each person's needs.

KEY MESSAGES

1. Menopausal hormone therapy is indicated for relief of symptoms, but it is not indicated for primary or secondary prevention of cardiovascular disease.
2. Women who initiate menopausal hormone therapy 10 or more years after menopause are at increased risk for adverse cardiac events.
3. Women who initiate menopausal hormone therapy shortly after menopause are at low risk for cardiovascular events in subsequent years.
4. More data are needed to provide guidance on the impact of routes of estrogen administration on venous thromboembolism or cardiovascular disease risk.

ABSTRACT

Objective: Provide strategies for improving the care of perimenopausal and postmenopausal women based on the most recent published evidence.

Target Population: Perimenopausal and postmenopausal women.

Benefits, Harms, and Costs: Target population will benefit from the most recent published scientific evidence provided via the information from their health care provider. No harms or costs are involved with this information since women will have the opportunity to choose among the different therapeutic options for the management of the symptoms and morbidities associated with menopause, including the option to choose no treatment.

Evidence: Databases consulted were PubMed, MEDLINE, and the Cochrane Library for the years 2002–2020, and MeSH search terms were specific for each topic developed through the 7 chapters.

Validation Methods: The authors rated the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach. See online Appendix A (Tables A1 for definitions and A2 for interpretations of strong and weak recommendations).

Intended Audience: physicians, including gynaecologists, obstetricians, family physicians, internists, emergency medicine specialists; nurses, including registered nurses and nurse practitioners; pharmacists; medical trainees, including medical students, residents, fellows; and other providers of health care for the target population.

SUMMARY STATEMENTS:

1. Women who initiate menopausal hormone therapy shortly after menopause are, in general, at low risk for events in the next few years (*high*). Evidence supports aggressive identification and modification of risk factors as the most effective means of reducing cardiovascular risk (*high*).
2. Women who initiate menopausal hormone therapy 10 or more years after menopause are at increased risk for adverse cardiac events (*high*).
3. With respect to stroke, increased risk has been identified in all age groups using standard formulations of menopausal hormone therapy; however, the incidence in young women is extremely low (*low*).
4. Incidence of venous thrombotic events increase with age (> 60 y) and BMI, even in otherwise healthy women; menopausal hormone therapy increases the risk (*high*).
5. Menopausal hormone therapy is not indicated for primary or secondary prevention of cardiovascular disease (*moderate*).
6. Women with premature or early-onset menopause appear to be at an increased risk of adverse cardiovascular outcomes, and this risk may be prevented by the use of menopausal hormone therapy until the average age of menopause (*moderate*).
7. Menopausal hormone therapy increases the risk of venous thromboembolism; oral and combined hormone therapy preparations are more closely associated with risk of venous thromboembolism than either with transdermal preparations or estrogen alone (*moderate*).
8. There is a lack of high-quality data to provide guidance on the impact of routes of estrogen administration on the risk of venous thrombotic events or cardiovascular disease (*low*).

RECOMMENDATIONS:

1. Menopausal hormone therapy should be offered as the most effective treatment for the relief of menopausal symptoms (*strong, high*).
2. When prescribing menopausal hormone therapy, the lowest effective dose of estrogen, and, where indicated, estrogen-only therapy, should be offered to minimize the associated risk of venous thromboembolism (*conditional, low*).
3. The lowest effective dose of estrogen, either oral or transdermal, should be prescribed to minimize the risk of stroke (*conditional, low*).
4. When prescribing combined hormone therapy, choice of progestogen should favour those least likely to affect markers for cardiovascular disease. (*strong, moderate*).
5. A tissue selective estrogen complex may be used without a progestin to provide menopausal hormone therapy and uterine protection for relief of early menopausal symptoms (*conditional, moderate*). To date, these agents do not appear to be associated with cardiovascular risk.

INTRODUCTION

Cardiovascular disease (CVD) remains a leading cause of death and disability in women. The use of menopausal hormone therapy (MHT) and risk for CVD continue to be evaluated to help women make informed decisions concerning treatment. This guideline updates and expands the recommendations in the 2014 guideline to reflect newer data.

A Cochrane review found that MHT initiated within 10 years of menopause lowered coronary heart disease in postmenopausal women (relative risk [RR] 0.52; 95% CI 0.29−0.96). It also found a reduction in all-cause mortality (RR 0.70; 95% CI 0.52−0.95) and no increased risk of stroke, but an increased risk of venous thromboembolism (VTE; RR 1.74; 95% CI 1.11−2.73).[1]

SUMMARY STATEMENT 1

This review was heavily weighted by the Women's Health Initiative (WHI) dataset. In contrast, no evidence was found that MHT reduced or had an effect on coronary heart disease (RR 1.07; 95% CI 0.96−1.20) or all-cause mortality (RR 1.06; 95% CI 0.95−1.18) in women who initiated MHT more than 10 years after menopause or who were aged older than 60 years at initiation. Risks included an increased risk of stroke and VTE.[1]

SUMMARY STATEMENT 2

Across all ages combined, there was no evidence for primary or secondary prevention of all-cause mortality, CVD, non-fatal myocardial infarction, angina, or revascularization. Compared with placebo, MHT use was associated with 6 additional strokes, 8 additional cases of VTE, and 4 additional cases of pulmonary embolism per 1000 women. These event rates are higher than previously reported in population cohorts, possibly because higher doses of estrogen may have been used.[1]

SUMMARY STATEMENTS 3 AND 4

In 2017, Manson et al. assessed MHT and long-term mortality from the WHI randomized trials. In more than 18 years of follow-up, there was no difference in all-cause mortality (hazard ratio [HR] 0.99; 95% CI 0.94−1.03) or cardiovascular mortality (HR 1.00; 95% CI 0.92−1.08). Hormone therapy with conjugated estrogens plus medroxyprogesterone acetate for a median of 5.6 years or with conjugated estrogens alone for a median of 7.2 years was not associated with risk of all-cause or cardiovascular mortality over long-term follow-up.[2]

RECOMMENDATION 1

To assess the link between cardiovascular risk and MHT, several studies have looked at surrogate markers. While coronary calcium score and carotid intimal medial thickness are both markers for future cardiovascular risk, as end points, they should be interpreted with caution. These data should be used as hypothesis-generating for future studies looking at clinical end points.[3−6]

Given the lack of cardiovascular protection, the US Preventive Services Task Force recommends against the use MHT for the primary prevention of chronic conditions in postmenopausal women. However, when providing individualized care for women with symptoms requiring MHT, recent data suggest a lack of long-term harm.[7]

SUMMARY STATEMENT 5

AGE AT MENOPAUSE

Women with premature or early-onset menopause appear to be at an increased risk of adverse cardiovascular outcomes. A 2016 systematic review and meta-analysis compared women who experienced menopause at <45 years to those who had undergone menopause at a later age. After adjusting for age, smoking, lipid levels, hypertension, body mass index, and hormone therapy, the group with early menopause had a 50% increased risk of coronary heart disease events (RR 1.50; 95% CI 1.28−1.76), a 23% increased

ABBREVIATIONS

CVD	cardiovascular disease
DOPS	Danish Osteoporosis Prevention Study
ELITE	Early Versus Late Intervention Trial With Estradiol
KEEPS	Kronos Early Estrogen Prevention Study
MHT	menopausal hormone therapy
SERM	selective estrogen receptor modulator
SMART	Selective estrogens, Menopause and Response to Therapy
VTE	venous thromboembolism
WHI	Women's Health Initiative

risk of stroke (RR 1.23; 95% CI 0.98−1.53), a 19% increased risk of cardiovascular mortality (RR 1.19; 95% CI 1.08−1.31), and a 12% increased risk of all-cause mortality (RR 1.12; 95% CI 1.03−1.21).[8]

The risk of these adverse cardiovascular outcomes may be prevented by providing MHT until the average age of menopause.[9,10] However, there is limited epidemiologic evidence to support this. A prospective cohort study of 10 533 Danish women found that use of MHT at any time reduced the risk of ischemic heart disease in women who had undergone early surgical menopause, but not spontaneous premature or early menopause.[10]

SUMMARY STATEMENT 6

In addition, there is increasing evidence that women who develop hypertension or diabetes during pregnancy have increased CVD risk. These women may present with cardiovascular events even before menopause.[11,12]

IMPACT OF ROUTE OF ADMINISTRATION ON RISK OF VENOUS THROMBOEMBOLISM OR CARDIOVASCULAR DISEASE

There is a lack of high-quality data in the literature on the impact of routes of estrogen administration on the risk of VTE or CVD, especially in women at average risk. A Cochrane review has shown that in women >60 years, or those who initiate MHT more than 10 years after menopause, VTE risk is higher in general (RR 1.96; 95% CI 1.37−2.80).[1]

RECOMMENDATION 2

Lower-quality observational studies, often including older patients and those with increased baseline risk, have been used as evidence that transdermal estrogens have a lower risk of VTE than oral estrogens. These observational studies may have biases, and they do not control for dose of estrogen or concomitant effect of endometrial protective agents, both of which are implicated in VTE risk.

SUMMARY STATEMENTS 7 AND 8

Data from randomized controlled trials (RCTs) are limited by the smaller size of these trials. The Early Versus Late Intervention Trial With Estradiol (ELITE), which used 1 mg of oral 17 beta-estradiol and vaginal micronized progesterone, showed no increase in VTE prevalence in the early intervention group throughout the more than 6 years of the trial.[4] The Kronos Early Estrogen Prevention Study (KEEPS), which is the only head-to-head RCT using bioequivalent doses of oral and transdermal estrogen with micronized progesterone, did not demonstrate any difference in VTE prevalence in women at average risk who initiated MHT within 36 months of their final menstrual period.[3] Neither KEEPS nor ELITE was powered statistically for these outcomes to be meaningfully reported. The Selective estrogens, Menopause and Response to Therapy trials (SMART) of oral conjugated estrogens/bazedoxifene were RCTs in generally healthy women with hot flashes. There was no increase in VTE in the treatment group compared with placebo.[13] Again, this study was underpowered for this outcome. The Danish Osteoporosis Prevention Study (DOPS) was an open-label RCT in healthy recently postmenopausal women. This trial used higher doses of oral estradiol (2 mg) and a synthetic progestin (norethisterone acetate). Over the 11 years of the study, there was no excess of VTE events seen.[14] Again, this study was statistically underpowered to report this outcome.

Observational studies are prone to bias (lack of data on dosage or age of participants, lack of control for endometrial protective agent). These studies may include women at increased baseline risk (owing to age, obesity, prior VTE, or elevated cardiovascular risk). A recent database analysis demonstrating a safety advantage of transdermal estrogens included patients with an average age of 63.8 years, and many had cardiovascular comorbidities, where transdermals would have been preferred in any case. In women in the younger age group, the absolute increase in VTE seen with low-dose oral hormone therapy was 0.5 per 1000 woman years.[15]

For women of average VTE or CVD risk who are initiating MHT within 10 years of their final period or before age 60 years, there is insufficient evidence to advocate any route of administration over another for VTE safety. For women who are over age 60 years, or who have additional VTE or cardiovascular risk, use of lower-dose transdermal estrogen may have safety advantages.

STROKE

Because stroke is a rare outcome in women aged 50 to 59 (the most likely time for a woman to be on MHT), there is conflicting evidence from published data regarding actual increased stroke risk associated with MHT. It is difficult to

quantify stroke risk without ascertaining the underlying additional risk. A recent Cochrane review, heavily weighted by the WHI data, did not show an increased stroke risk when MHT was initiated within 10 years of the final menstrual period; however, the overall rate of stroke was higher in women over 60 years at MHT initiation or more than 10 years after menopause (RR 1.21; 95% CI 1.06−1.38).[11]

RECOMMENDATION 3

In DOPS, where participants were young at initiation and relatively free of CVD risk factors, there was no increased risk of stroke seen over the 11 years of the study, in spite of the fact that the study used higher-dose oral estrogens.[14]

Three recent RCTs of MHT (KEEPS, ELITE, and SMART) did not demonstrate an increased stroke risk in young, relatively healthy symptomatic women initiating MHT close to the time of their final menstrual period.[11]

There is insufficient evidence to support any route of estrogen administration over another in younger women of average CVD risk to reduce the risk of stroke.

NEWER THERAPIES

For women with moderate risk of CVD, use of micronized progesterone (or another progestogen that does not adversely modify metabolic parameters) may be advantageous, because these preparations have less untoward effect on blood pressure, triglycerides, and carbohydrate metabolism.[16]

RECOMMENDATION 4

Studies of conjugated estrogens/bazedoxifene have not demonstrated increased risk of CVD, VTE, or stroke when initiated in low-risk women close to the time of their final menstrual period.[13]

RECOMMENDATION 5

Although widely available internationally for many years, tibolone received Health Canada approval only recently, in 2019. Studies of tibolone have not demonstrated increased CVD or VTE risk. In women under the age of 65 years, there does not appear to be an increased risk of stroke.[17]

Although it is beyond the scope of this discussion, since the last review, there have been several studies informing women and health care on non-hormonal therapy for primary prevention of CVD. Statins may play a preventive role for some postmenopausal women at moderate future CVD risk.[18] Aspirin is no longer used in primary prevention of CVD for men or women.[19,20]

CONCLUSION

In summary, high-quality scientific data has recently emerged to help inform a women's decision regarding MHT and cardiovascular risk. Evidence to date suggests that, in appropriately selected, symptomatic women, short-term use of MHT does not appear to confer increased risk of CVD.

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APPENDIX A

Tables A.1 and A.2

Table A.1. Key to Grading of Recommendations, Assessment, Development and Evaluation Quality of Evidence

Grade	Definition
Strength of recommendation	
Strong	High level of confidence that the desirable effects outweigh the undesirable effects (strong recommendation for) or the undesirable effects outweigh the desirable effects (strong recommendation against)
Conditional [a]	Desirable effects probably outweigh the undesirable effects (weak recommendation for) or the undesirable effects probably outweigh the desirable effects (weak recommendation against)
Quality of evidence	
High	High level of confidence that the true effect lies close to that of the estimate of the effect
Moderate	Moderate confidence in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low	Limited confidence in the effect estimate: The true effect may be substantially different from the estimate of the effect
Very low	Very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

[a] Do not interpret conditional recommendations to mean weak evidence or uncertainty of the recommendation.

Adapted from GRADE Handbook (2013), Table 5.1.

Table A.2. Implications of Strong and Conditional recommendations, by guideline user

Perspective	Strong Recommendation • "We recommend that. . ." • "We recommend to not. . ."	Conditional (Weak) Recommendation • "We suggest. . ." • "We suggest to not. . ."
Authors	The net desirable effects of a course of action outweigh the effects of the alternative course of action.	It is less clear whether the net desirable consequences of a strategy outweigh the alternative strategy.
Patients	Most individuals in the situation would want the recommended course of action, while only a small proportion would not.	The majority of individuals in the situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the course of action. Adherence to this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Recognize that patient choices will vary by individual and that clinicians must help patients arrive at a care decision consistent with the patient's values and preferences.
Policymakers	The recommendation can be adapted as policy in most settings.	The recommendation can serve as a starting point for debate with the involvement of many stakeholders.

Adapted from GRADE Handbook (2013), Table 6.1.