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POSITION STATEMENTS AND GUIDELINES

Is postmenopausal hormone replacement therapy suitable after a cardio- or cerebrovascular event?

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Abstract
Purpose Vascular disease is the leading cause of death in women. One-third of acute events affect women below age 60, when the prevalence of menopausal symptoms is high. This raises the question if hormone replacement therapy (HRT) may be an appropriate treatment for individual women although vascular disease is generally considered a contraindication.
Methods Selective literature search was used for this study.
Results In healthy women, HRT increases risks for venous thromboembolism and ischemic stroke, but for cardiovascular disease apparently only beyond 10 years after menopause or 60 years of age. Limited data in women with cardio or cerebrovascular disease have not demonstrated an increased risk for a vascular recurrent event, but for the first year after initiation. In HRT users affected by a cardiovascular event continuation of HRT has not been found to be associated with adverse outcome. Low dose estradiol—preferentially as transdermal patches, if necessary combined with metabolically neutral progestins—appears to convey lower risk.
Conclusions Safety data on HRT in survivors of cardiovascular events or ischemic stroke are limited, but exceptionally increased risk appears to be excluded. If off-label use of HRT is considered to be initiated or continued in women with cardio- or cerebrovascular disease, extensive counseling on the pros and cons of HRT is mandatory.

Keywords Menopause · Hormone replacement therapy · Coronary heart disease · Stroke

Introduction

The randomized arms of the Women's Health Initiative (WHI) have demonstrated that early in the postmenopause women may benefit from HRT in respect to cardiovascular risk, but independently the risk for thromboembolism and stroke rises with age [1, 10, 11, 19]. The Women's Health Initiative Observational Study (WHI-OS) has also shown that the risk of HRT for vascular events is low when HRT is initiated within the first 5 years of the postmenopause, however, is strongly increasing with time, up to tenfold when HRT is started 20 years after menopause [23]. Thus, the vascular risk of HRT is particularly high at an age at which the question of HRT after a vascular event becomes most often relevant. Thus, HRT initiation in postmenopausal women aged 60 or older should be an exception, and individual risks and benefits should be strictly weighted [13]. In this context the question arises if it is suitable at all to initiate HRT for vasomotor symptom relief after a

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vascular event although prior cardiovascular events are considered as a contraindication for HRT.

Is HRT after a vascular event a relevant problem?

Mortality statistics reveal cardiovascular events as the main cause of death among women. Yet, for the most part this pertains to women above the age of 70. This raises the question if cardiovascular risk is an issue at all for an early postmenopausal woman choosing HRT for vasomotor symptom control. Yet, about one-third of all incident non-fatal cardiovascular events until age 80 occur in women below age 60, i.e. in a stage of life prone to menopausal symptoms [32]. The prevalence of severe vasomotor symptoms is maximal during the first year after menopause, however, remains elevated for another 10 years. By then, one in two women still suffers from moderate hot flushes [8, 15]. Thus, the question whether to use or to avoid HRT for menopausal symptom relief in postmenopausal women with prevalent cardiovascular disease is of considerable practical relevance.

The impact of HRT on the cardiovascular event rate in women with cardiovascular disease has been studied in at least eight randomized controlled trials (Table 1) [9]. Neither estrogen alone nor estrogen combined with progestins had an impact on the incidence of non-fatal cardiovascular events. Similarly, cardiovascular and total mortality were not significantly altered, respectively.

Table 1 Meta-analysis of relative risks of hormone replacement therapy in cardiovascular secondary prevention [9]

	Number HRT vs. placebo	Relative risk	95 % confidence interval
Estrogen monotherapy			
Non-fatal myocardial infarction	990 vs. 927	1.20	0.84–1.72
Stroke	950 vs. 884	1.01	0.73–1.40
Thromboembolism	437 vs. 380	1.20	0.37–3.84
Cardiovascular mortality	990 vs. 927	0.73	0.48–1.11
Total mortality	950 vs. 884	1.00	0.75–1.33
Combined hormone therapy			
Non-fatal myocardial infarction	1,765 vs. 1,718	0.89	0.71–1.12
Stroke	1,690 vs. 1,649	1.14	0.89–1.47
Thromboembolism	1,765 vs. 1,718	2.59	1.51–4.42
Cardiovascular mortality	1,714 vs. 1,669	1.16	0.85–1.59
Total mortality	1,694 vs. 1,649	1.09	0.87–1.36

However, the sample sizes were relatively small and the trials' duration did not exceed 5 years (Table 1). Still, based on randomized trials, there is no definite proof of a particular cardiovascular risk in women with manifest cardiovascular disease.

However, given the limited data basis for HRT use in women with cardiovascular disease it appears appropriate to consider data from cardiovascular healthy women as well to draw more reliable conclusions. Despite all limitations the WHI provides most of the evidence. If HRT was initiated within 10 years after menopause or in women aged less than 60 years HRT did not raise the risk for coronary heart disease [1, 11]. In contrast, the risk may be appreciably elevated if HRT is initiated more than 20 years after menopause, i.e. in woman of advanced age.

A meta-analysis of 39 studies in more than 39,000 women came to a similar conclusion [21]. Estrogen appears to display differential effects in early and later stages of atherosclerotic disease [2, 12, 20, 23, 24]. According to these data, it appears advisable to be cautious when starting HRT in women at advanced age until there are more trials involving women with cardiovascular disease.

Is HRT initiation too risky in women after a cardiovascular event at all?

The first year of HRT appears to be the most problematic period. HRT initiation is associated with an increased cardiovascular risk especially within the first year of use as has been observed in the Nurses' Health Study (NHS) [5]. This finding is supported by randomized trials as the WHI [11] and even more pronounced in HERS, a secondary prevention trial, in which HRT did not increase the risk for coronary events on average of 4.1 years, but the risk was temporarily increased by the factor of 2.5 in the first year after starting HRT [7, 11]. Even though the absolute risk is low and ranges within one in 1,000 women, the effect should be taken serious and be part of the physician's advice. Based on HERS it has been recommended not to start HRT within the first year after a cardiovascular event [4]. However, there is no evidence that HRT initiation is less risky in the second than in the first year after a cardiac event.

Thus, it appears crucial to reduce the risk for cardiovascular recurrence by all available medical means before starting HRT. This involves the treatment of risk factors and drugs indicated after a vascular event such as beta-blockers, aspirin and additional anticoagulants after stent implantation. However, the efficacy of these interventions in reducing the increase of risk when starting HRT has not been proven so far. Yet, a post hoc analysis of HERS has shown that women using statins when initiating HRT were not at an increased cardiovascular risk [6]. However, that does not

mean that the total risk can be eliminated by statin therapy. More likely, women who could afford statins in the USA at the time of HERS were also willing to engage in additional strategies to decrease cardiovascular risk. This would also explain why women using statins generally had less vascular events, not only cardiovascular, but also less cerebrovascular and thromboembolic events, and even a lower total mortality. Possibly the initial cardiovascular risk in women starting on HRT is lower in countries like Germany due to a general obligation to obtain health insurance and hence a general high standard of health care. For example, during a 3-year period, no woman presented at the University Hospital Hamburg because of an incident cardiovascular event who had started HRT within the preceding year [31].

Should HRT be discontinued after the onset of a cardiovascular event?

There is no clear evidence that a cardiovascular event takes a more serious course in HRT users than in non-users [17]. Quite in contrast, there is some indication from observational studies that HRT users have a lower mortality rate after myocardial infarction than non-users [22, 27]. In detail, after a cardiovascular event the hospital mortality rate of 7,353 HRT users was by 25 % lower independent of age, compared to HRT non-users [22]. Similarly, the hospital mortality rate and mortality rate within 30 days after the cardiovascular event were even 50 % lower in 379 HRT users compared to HRT non-users [27].

These two studies differ principally from HERS, in which HRT was started after a cardiovascular event. However, since both studies were observational, it remains unclear if the lower mortality rate is partly or completely due to HRT use. Continuation of HRT may simply be a surrogate of a better treatment request, also reflected in a better adherence to medication and a healthy lifestyle. Indeed, the 30-day mortality after a cardiovascular event appears primarily determined by conventional risk factors and the degree of cardiac impairment [27]. This is in line with a recent analysis of the WHI, which identified increased cardiovascular risk only in women on HRT characterized by a metabolic syndrome [30]. Still, since HRT is labeled as contraindicated in women after myocardial infarction extensive counseling is compulsory if HRT is continued or started anew in such cases.

Is HRT initiation after a cerebrovascular event permissible?

Patients with cardiovascular disease are at increased risk of a cerebrovascular event and vice versa after an ischemic stroke cardiac mortality is regarded as the most frequent cause of death. Thromboembolism is the common pathomechanism of ischemic strokes. Since estrogen has procoagulatory activity the question arises if HRT is suitable after an ischemic stroke or a transitory ischemic attack (TIA). In accord with previous studies, in the WHI oral HRT was associated with an increased risk of ischemic stroke in healthy women [29]. The risk for stroke increased with the duration of use ranging from 1:10,000 within the first 5 years to 1:1,000 per year after 10 years of use.

HERS, a secondary prevention trial, indicated a similar trend that, however, did not reach significance [25]. This may be due to the general low incidence of strokes and small sample size possibly reducing statistical power to detect significant differences. This limitation should also be considered when interpreting meta-analyses of predominantly smaller trials including women with cardiovascular disease [9]. Neither for estrogen alone nor for combined HRT a significantly elevated risk for stroke has been found (Table 1).

The randomized Women's Estrogen for Stroke Trial (WEST) revealed similar results for the risk of recurrent stroke after an initial stroke [28]. There was a non-significant trend towards more fatal strokes in women using estrogens who had had experienced a stroke before. Again, the cardiovascular risk was not notably increased compared to that of women without HRT. However, this WEST comprising $n = 337$ vs. $n = 327$ women was too small for a definite conclusion.

On the other hand, all these trials taken together exclude a dramatic increase in risk for a recurrent event in women with vascular disease using HRT. Still, despite the low incidence of ischemic stroke, women with and likewise without vascular disease need to be informed about the increased risk when choosing HRT. For younger women within the first 10 years after menopause the overall risk of stroke is quite low, yet, stroke can undoubtedly cause severe and particularly at young age long-lasting disability.

Which estrogen dosage and route of administration should be preferred?

It takes large cohorts to sufficiently compare various estrogen dosages and routes of administration. In particular, the question of cerebrovascular risk has been addressed in a large population-based nested case–control study comparing 15,710 women that had experienced a stroke with 59,958 controls [18]. Transdermal estrogen up to a dosage of 50 μg/day—mostly combined with micronized progesterone—was not associated with an increased risk of stroke (rate ratio 0.81, 95 % CI 0.62–1.05). In contrast, in women on oral low and standard dose estrogen therapy the risk of stroke was appreciably elevated (rate ratio 1.28, 95 % CI 1.15–1.42), even

after thorough adjustment for known risk factors for stroke. Still, this is the result of an observational study and not a randomized trial. However, selection bias through allocation of transdermal estrogen to women at risk for stroke would rather mitigate any result in favor of the transdermal route.

Currently, the Women's Health Initiative Observational Study (WHI-OS) is the largest trial directly comparing the risk profile of various HRT types [23]. Despite the magnitude of the study ($n = 93{,}679$) and the long period of observation no significant differences as to cardiovascular or cerebrovascular events were found. However, with respect to cardio- and cerebrovascular risk at least a trend in favor of transdermal estrogen application was found, which is the preferred treatment for women with a thrombogenic predisposition, anyway. In addition, oral low dose estradiol alone or in combination with progestins appeared to be superior to standard dose estradiol or conjugated equine estrogens.

The WHI-OS has also shown that the vascular risk for vascular events is low when HRT is initiated within the first 5 years of the postmenopause, however, is strongly increasing with time, up to tenfold when HRT is started 20 years after menopause [23]. Thus, the vascular risk is particularly high at an age at which the question of HRT after a vascular event becomes most often relevant.

Conclusion

This overview focuses on HRT in women who experienced a cardio- or cerebrovascular event. Although an increased risk for recurrence by HRT has not been unequivocally shown due to limited data, it cannot be excluded with certainty. However, derived from data of various sources transdermal low dose estradiol combined with metabolically neutral progestogens may be the HRT of choice. In any event, when considering HRT informed consent needs to include any benefits and risks of HRT including vascular, cancer and osteoporosis, and time since menopause as a strong confounder. The German S3 guideline, the North American Menopause Society position statement, the recommendations of the International Menopause Society, and the recent global consensus statement on HRT provide detailed information [3, 14, 16, 26].

Conflict of interests EW has received honoraria for lectures sponsored by Bayer Healthcare Pharmaceuticals, Dr. Kade Pharma, Gedeon Richter, manufacturers of hormone replacement drugs.

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