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Critical Comments

1. Introduction to Critical Comments

The American Heart Association published a Statement for Healthcare Professionals on "Hormone Replacement Therapy and Cardiovascular Disease" in the July 24, 2001 issue of Circulation (2001;104:499–503).

After addressing the biological basis for a role of oestrogen replacement therapy in cardiovascular disease, this publication addresses several questions, such as

- should HRT be used in women with established cardiovascular disease (CVD)?
- should HRT be used for primary prevention of coronary heart disease (CHD)?
- are there adverse cardiovascular effects associated with oestrogen replacement (ERT) or combined hormone replacement therapy (HRT)?
- are there alternatives to HRT? and
- what are accepted preventive strategies for CHD in postmenopausal women?

The Summary Recommendations for HRT[1] and CVD are as follows:Secondary prevention

- HRT should not be initiated for the secondary prevention of CVD.
- The decision to continue or stop HRT in women with CVD who have been undergoing long-term HRT should be based on established non-coronary benefits and risks and patient preference.
- If a woman develops an acute CVD event or is immobilized while undergoing HRT, it is prudent to consider discontinuance of the HRT or to consider venous thromboembolic events (VTE) prophylaxis while she is hospitalized to minimize risk of VTE associated with immobilization. Reinstitution of HRT should be based on established non-coronary benefits and risks, as well as patient preference.

Primary prevention

- Firm clinical recommendations for primary prevention await the results of ongoing randomized clinical trials.
- There are insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention of CVD.
- Initiation and continuation of HRT should be based on established non-coronary benefits and risks, possible coronary benefits and risks, and patient preference.

These recommendations differ in some respect from other recent published recommendations, such as for instance the IMS Workshop Paper "Controversial issues in climacteric medicine (I), Cardiovascular disease and hormone replacement therapy", based on the International Menopause Society Expert Workshop, held in London, Octo-

[1] The majority of data available to make clinical recommendations are based on standard doses of oral CEE/MPA. Evidence is insufficient to determine whether different preparations, routes of delivery, doses or different progestins have a more favorable or more adverse effect on clinical CVD end points.

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ber 13-16, 2000 and published in Maturitas 2001;38:263–271 and in Climacteric 2000;3:233–240.

As some of the authors of the present AHA Science Advisory Statement also were present at this specially confined expert workshop in London and approved the final document, these differences are intriguing.

The Editor of Maturitas, the European Menopause Journal, invited some organisations and experts to give a reaction in this Critical Comment Section of Maturitas. Under these reactions obtained is the official reaction of the European Menopause and Andropause Society as approved by the full board of EMAS.

2. A critique of the criticism: points to consider when reading the AHA comment

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The American Heart Association recently published a statement on Hormone replacement therapy and cardiovascular disease (CVD) (1). In essence, the recommendations were as follows:

Use of HRT should be based on non-coronary benefits and risks and patient preference, and not initiated for the sole purpose of primary prevention of CVD.

HRT should not be initiated for the secondary prevention of CVD. If a woman develops an acute CVD or is immobilized while on HRT it is prudent to consider discontinuance of HRT.

In women with CVD, HRT continuance should be based on non-coronary benefits and risks.

The AHA interpretation of our present knowledge of CVD and HRT is also presented in the paper .The reader is given the impression that AHA considers the null results of two randomized clinical trials (HERS and ERA) to outweigh well over a 1000 clinical and experimental studies on surrogate CVD markers showing benefits as well as some 30 large scale observational studies of both cohort and case-control design also showing benefits both for primary and secondary CVD prevention. Only the HERS trial has hard clinical endpoints, and the study has been subjected to a number of valid criticisms. We would be surprised if the AHA thought it valid to make firm recommendations for clinical management using a database of just one study. The much smaller ERA trial used a surrogate clinical endpoint. Whilst the trial did not show any benefit of HRT, it also did not show any benefit of statins, or any detrimental effect of hypertension or smoking.

While shortcomings and interpretation problems with surrogate end point studies and observational data are well recognized the magnitude and diversity of these studies are such that the overall results should carry considerable weight in our understanding of the relationship between HRT and CVD. Randomized clinical trials (RCTs) are not problem free and are subject to bias, as exemplified by the following:

1. RCTs have inclusion and exclusion criteria much more rigid than observational studies many of which have implications for CVD such as hypertension, high BMI, lipid abnormalities and impaired hepatic or renal function, leading to recruitment of a lower than average risk population. Hence results are only valid for those who meet those inclusion and exclusion criteria.
2. According to the Helsinki declaration, information to RCT participants must be such that they understand the current scientific knowledge on which the hypothesis of the RCT is based, recognizing that there is a 50% chance to be on placebo for a considerable time. This is likely to recruit a population at lower than average risk into RCTs, which seems to be the case for both HERS and WHI.
3. Subjects are new starters, but whether they had never used HRT, or used HRT for a considerable time prior to the trial, is not without importance for the development of CVD. Of particular relevance for primary prevention, it is likely that women devoid of climacteric symptoms, and with previously higher endogenous estrogens, are recruited into RCTs.

4. RCTs use one preparation at one given dose and mode of administration. Interpretation of the results should be limited to this and to the target group of the RCT, and not generalized to include all populations and all HRT preparations regardless of their composition, dose and mode of administration. In addition, the composition of the target population regarding age and concomitant medication must be considered, as this may impact on steroid pharmacology.
5. RCTs are usually short term and are at present limited to 4 years observation time.

CVD are multi-factorial and can be influenced by lifestyle. For both primary and secondary prevention of CVD much could be gained by modifying life style factors i.e. stop smoking, using a well-balanced low fat diet and exercise regularly. These very important risk factors are non-controversial to modify and life style modifications should be emphasized to all patients.

Incidence and mortality can also be modified by use of pharmacological agents other than HRT. There is evidence that anti-fibrinolytic drugs, beta-blockers, ACE inhibitors and statins all may lower risk, both in primary, and especially in secondary, prevention settings. Despite their proven benefits, it should be remembered that all these agents are not natural compounds to humans. Widespread long-term use of such compounds may lead to other untoward effects, as exemplified by the recent withdrawal of a marketed a statin due to side effects. None of these drugs is mentioned under the heading 'Are there alternatives to HRT?' in the AHA paper. Instead, SERMS are mentioned and reference is made to the ongoing raloxifene use for the heart (RUTH) study. The reason for this is obscure, but as several of the authors of the AHA paper are heavily involved in the ongoing RUTH trial. Hence, they may have access to information that is not yet in the public domain.

AHA also highlights the meta-analysis on CVD events from clinical trials on HRT (2). There was no significant increase (but no benefit either) on CVD events. Although 22 trials were included in this meta-analysis, it should be remembered that none of the trials was designed to study CVD events. Each trial had a limited number of subjects. Of the trials, very few were longer than one year and none longer than 4 years. Consequently, the 95% confidence intervals (CI) are large, as exemplified by the CI for venous thromboembolism which was 0.34–24.8.

Time seems to be crucial in several studies, and in many observational studies a clear reduction cannot be seen until 4–5 years of HRT treatment. However, this time effect could well be influenced by dropouts.

AHA also puts weight on the results from the Coronary Drug Project (3). This is difficult to understand as doses of CEE used in this secondary prevention study in men exceeded by 4- to 10-fold the doses in clinical use for postmenopausal women.

Data based almost exclusively on conjugated equine estrogens suggest that HRT in doses used to treat climacteric symptoms increases the incidence of VTE, but only during the first 1–3 years of usage (ref Perez-Gutham BMJ 1997). The reason for this remains obscure. Our current insufficient understanding of HRT administration and surveillance should encourage further research especially on the effects of lower doses and non-oral approaches. It should not impact on the overall concept, which is that estrogens may well be beneficial for the heart.

Until we have further evidence, it seems prudent not to include CVD prevention as a sole indication for HRT. However, there is little evidence to support withdrawal of HRT in long-term users, should a CVD event occur. There is also no good evidence to deny HRT to women with increased CVD risk, including those with established CVD. The grey zone in between must be met on an individual basis. So far most studies have been performed with conjugated equine estrogens on its own or combined with medroxyprogesterone acetate. We cannot make firm recommendations until further studies on a variety of HRT preparations and regimens inclusive of different delivery systems, doses and construction have been performed, and these are obviously urgently required.

The view of EMAS is similar to the view of the International Menopause Society which, after an expert gathering published its views (5).

It is of interest to note that two authors appear on both the IMS and AHA list of contributors despite the fact that conclusions from the same database are so different. So we now have yet another example that so called expert group consensus statements are subject to bias. Today we have guidelines for how evidence based medicine should be executed. There is no reason not to follow these. Hence we believe that the statement from the AHA is both premature and not fully justified.

For The European Menopause and Andropause Society (EMAS). Unanimously approved by all board members.

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3. Imaginary women

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The American Heart Association (AHA) has approved the following recommendation for HRT and CVD :*There are insufficient data to suggest that HRT should be initiated for the sole purpose of primary prevention of CVD*

This statement needs reflection. I have difficulty to find asymptomatic postmenopausal women who, for some reason, will not need an hormonal treatment. Be it for the vasomotor symptoms, or for mood disorders, or for their libido problems, they will always benefit from a short to medium term hormonal treatment. If, later, the time comes to suggest its discontinuation they very often complain and insist to continue because they felt better on it. Therefore the above statement is not applicable to the daily clinical practice. A case where HRT was to be used for the *sole* purpose of primary prevention of CVD does not exist but in the minds of those who are inexperienced in clinical practice. Thus, one remains as before, and as the AHA concludes: *Initiation and continuation of HRT should be based on established noncoronary benefits and risks*, *possible coronary benefits and risks*, *and patient preference*.

It is regrettable that all previous large and important observational studies seem to have been considered irrelevant, although they may better reflect *good clinical practice* rather than the rigid unrealistic and unadapted high doses of CEE/MPA which were used in the HERS trial (1).

The AHA Statement is inspired by some principles of the *Evidence Based Medicine* philosophy, but it does not reflect the everyday *Medicine Based Evidence* …

It is likely that most readers will interprete these recommendations of the prestigious American Heart Association as strong guidelines, based on the firm convictions of the reporters. If that will be the case, may be serious doubts will arise after reading the bottom note of the said document: '**The majority of data available to make clinical recommendations are based on standard doses of oral CEE/MPA. Evidence is insufficient to determine whether different preparations, routes of delivery, doses, or different progestins have a more favorable or more adverse effect on clinical CVD end points*'…

In conclusion, recommendations such as these of the AHA, written as they are, may be less helpful than intended, both for clinicians and women.

Reference

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4. AHA Statement on HRT and Cardiovascular Disease: The Tone Makes the Music

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The American Heart Association (AHA) published in the July issue of Circulation a statement on the use of HRT for prevention of coronary artery disease (CAD) (1). In brief, the statement says that HRT should not be initiated for secondary prevention, while for primary prevention the decision on either its use or its discontinuation should be based on non-cardiac benefits and risks. Until the publication of the HERS study almost all data were derived from observational trials. The HERS study (2), as well as the recent trials on osteoporosis (investigating the effects of bisphosphonates and raloxifen), introduced the concept of evidence-based medicine into the field of menopause. Technically, this means that long-term studies, which included tens of thousands, or even more than a hundred thousand women, have been pushed aside because of shorter-term and smaller scale studies designed in a superior methodology by being double-blind, placebo-controlled and randomized. It is true that by mid 2001 there have been already several such studies showing that it is not advisable to start HRT for secondary cardio-prevention, because of early increase in the incidence of recurrent cardiovascular events (2–4). Also, according to recent data it seems that when significant vascular atherosclerosis is already evident, HRT does not change its natural progression (5–6). Nevertheless and although mentioned in the paper, the AHA statement did not emphasize enough the findings that HRT probably has a dual effect with early risk but late cardiovascular benefit (2–3,7). Additionally, women already using HRT at the time of the index coronary event did not have an increased risk for further events.

But the segment in the AHA statement referring to primary cardio-protection was summarized to my mind with too much caution. It was not based on hard evidence since there is yet no information from double-blind, placebo-controlled trials on healthy women. In several years from now we will have such results from the Women's Health Initiative in the USA and from the WISDOM trial in Europe.

Unlike the AHA opinion, which is focused on cardiac aspects only, those who are involved in menopause medicine must have a more holistic view. HRT should not be prescribed solely for cardioprotection, but prevention of CAD should be discussed with women who use hormones because of other indications. *It is the tone who makes the music:* the facts included in the AHA statement are correct, but the message delivered to the cardiologists is to avoid HRT. Why bother if there is an arsenal of other drugs (such as statins, ACE inhibitors and aspirin), all supported by solid evidence-based medicine, that may be used in the prevention of CAD?

But AHA statements are not merely for the cardiologist's eyes. Other health care providers and the general public have nowadays a quick access to such guidelines and related information, and therefore any statement should be phrased in a more balanced and sophisticated way. To my mind, and based on the same available data, our message should emphasize the positive aspects of HRT use. Indeed, HRT should not be recommended for the treatment of CAD, nor should it be prescribed only for

the purpose of prevention of future cardiovascular events. But HRT has many advantages, thus physicians and consumers alike should realize that on the long-run hormone users have better quality of life and a better prognosis, especially in regard with CAD morbidity and mortality. They should also realize that there are yet no high-degree evidence-based data on primary cardioprotection by HRT, whereas the results of large-scale population trials strongly favor its use. Healthy women, who enjoy the benefits of HRT given for other indications, should be told that at the same time they might gain important cardiovascular advantages.

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5. Overdue

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It was overdue to put into writing that primary prevention of cardiovascular disease at least at the moment is *not* an indication for hormone replacement therapy. However, it would have been helpful to provide health care providers with recent evidence about the usefulness of life style changes for the maintenance of cardiovascular health.

There is both abundant observational evidence and recent evidence from randomized controlled, prospective clinical trials that physical exercise helps prevent cardiovascular disease (1–3). The Nurses Health Study was able to simultaneously analyze how various risk factors modify the relative risks of cardiovascular disease. In this cohort study life style modifications such as abstinence from smoking and adherence to a diet with low amounts of saturated fats were shown to explain 13 and 16%, respectively, of the decline of the incidence of coronary heart disease while the use of ERT/HRT explained 9% (4). Thus, the effect of certain life style modifications appear to exceed the effect of postmenopausal estrogen (plus progestogen) use. In the Activity Counseling Trial it was demonstrated that a sustained increase of physical activity can be achieved in previously sedentary women (3).

The message at the moment should be *not* to look out for an exchange of pharmacological options, but to increase efforts of health care providers how cardiovascular disease can be targeted in the setting of both primary and secondary prevention. At present there is no sound body of clinical and epidemiological evidence for soy products (5) and SERMs, such as raloxifene, respectively, in the context of primary prevention of cardiovascular disease.

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6. Response of North American Menopause Society's executive director to the AHA science advisory regarding HRT and CVD

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Expressions of confusion and concern from healthcare providers and the general public regarding the science advisory statement (1) from the American Heart Association (AHA) on the relationship between hormone replacement therapy (HRT) in postmenopausal women and cardiovascular disease (CVD) have stimulated The North American Menopause Society (NAMS) to issue its response.

It should be noted that there is nothing substantially new in the AHA statement. This is the second official statement from scientific organizations in the past months on this issue. The first was from the International Menopause Society (IMS) (2). Previously, NAMS—in its *Menopause Core Curriculum Study Guide* (published June 2000)—had addressed this issue. All three organizations appear to have a concordant point of view. Nevertheless, there appears to be a need for clarification, particularly with regard to use of HRT for either secondary or primary prevention of CVD.

As for *Secondary Prevention*, the AHA statement includes a recommendation against prescribing HRT, either estrogen alone or estrogen plus a progestogen, to prevent another adverse cardiovascular event (eg, heart attacks, stroke) in women who already have CVD.

As stated in the NAMS study guide we have called this the 'don't start, don't stop' policy, which simply means, until there is more evidence, for women with CVD, it would be prudent to emphasize cardiovascular risk reduction with established evidence-based treatments rather than initiate HRT. Women who have been using HRT for several years without problems should be advised not to discontinue therapy until more definitive data are available.

The issue as to whether to prescribe HRT to women with no known pre-existing CVD to prevent a cardiovascular event is one of primary prevention. Both IMS and AHA confirm the lack of adequate data in the medical literature to make any conclusion regarding this issue. NAMS, in its study guide of June 2000, has briefly presented evidence that there may be a primary preventive role for HRT. However, in the absence of confirmatory, randomized, prospective trials, HRT should probably not be prescribed with the only indication being primary protection against CVD. Nonetheless, when HRT is prescribed for other indications (eg, relief of hot flashes, reducing the risk of osteoporosis), reducing the risk of CVD may turn out to be a benefit. The NAMS study guide mentions that for women with no history of cardiovascular disease, initiating HRT for other indications may eventually be shown to demonstrate CVD benefits.

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7. President's Comments on Recent HRT and Heart Disease Announcement

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The American Heart Association recently issued revised guidelines for the use of hormone replacement therapy (HRT) or estrogen replacement therapy (ERT) in the management of postmenopausal women related to cardiovascular protection. These were published in the July 24, 2001 issue of Circulation, the Journal of the American Heart Association.

Hormone replacement therapy refers to the use of combined estrogen and progestin, synthetic or natural forms of hormones secreted by the ovary in pre-menopausal women, while ERT refers to the use of estrogen alone for that purpose. ERT primarily is used in women who have had a hysterectomy (surgical removal of the uterus), as progestin use reduces the risk of uterine cancer in women who receive estrogen treatment.

Based upon recent prospective, placebo-controlled studies in women who had previous cardiovascular disease, such as heart attacks or strokes, no improvement in morbidity or mortality was noted in the women who received HRT compared to those who received a placebo (sugar pill). This type of study is called a secondary prevention study, as it is a study in women who had previous evidence of cardiovascular disease. The American Heart Association stated that women who had already had a cardiovascular event should not use HRT for the sole purpose of preventing another cardiovascular event.

The American Heart Association indicated that they no longer recommend the use of HRT or ERT solely for the purpose of preventing further cardiovascular disease in women who have a history of these diseases. They also recommend that physician and other caregivers no longer recommend HRT solely for the prevention of cardiovascular disease.

Two major primary prevention studies of HRT currently are underway. The results from these studies will not be known until approximately 2005. These studies, which also are prospective and placebo-controlled, are being carried out in healthy postmenopausal women, who have not had previous cardiovascular disease (heart disease or strokes).

Numerous observational, epidemiologic studies have indicated that use of HRT or ERT reduces the risk of cardiovascular disease by 40 to 50 percent. Like the secondary prevention studies, these epidemiologic studies have been performed by experienced well-recognized experts.

Hormone replacement therapy and ERT have been proven to be effective in the treatment of osteoporosis, a disorder that involves thinning of the bone and subsequent fractures. Osteoporosis is more common after the menopause, in large part because of the loss of ovarian estrogen, and is associated with extensive morbidity and mortality.

Hormone replacement therapy solely for the prevention or treatment of cardiovascular disease has not been approved by the U.S. Food and Drug Administration, and pharmaceutical manufacturers of estrogen and estrogen-progestin combinations have not listed cardiovascular disease in their indications for the medication's use. In addition, few clinicians prescribe HRT or ERT solely for the purpose of preventing heart disease, although many have felt that it was an added benefit of the medication. Whether or not it will be demonstrated to be of benefit as a primary prevention measure for cardiovascular disease awaits the outcomes of the large ongoing trials.

In addition to its benefits in the prevention and treatment of osteoporosis, estrogen is effective in

treating menopausal hot flashes (vasomotor instability) and vaginal dryness and irritation, which can result in increased vaginal infection and painful intercourse. In addition, there are suggestive, although not completely proven data indicating that postmenopausal estrogen use reduces the risk of colon cancer, Alzheimer's disease (dementia), memory and cognition.

Estrogen use in postmenopausal women also is associated with an increased risk of blood clots, particularly in the first year of use, as well as an increased risk of gallbladder and liver disease. Some, but not all, studies also indicate that its long-term use is associated with a slight increased risk of breast cancer.

In view of these and other studies, the Hormone Foundation feels that women should discuss the individual benefits and risks of HRT and ERT with their physicians, so that they might determine the appropriate decision in their particular situations.

8. Intriguing and confusing

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The American Heart Association (AHA) recently published in Circulation a Statement on Hormone Therapy and Cardiovascular Disease (1). The Authors of the AHA Statement report the biological basis of estrogen benefits on cardiovascular apparatus, and mention the epidemiological data showing a 35% reduction of cardiovascular events in normal women using hormones after menopause. However, in their conclusions and final messages they refer mainly to the secondary prevention trial named HERS. The term "HRT", as it is used in the article, includes treatment with estrogen alone or in combination with different progestins and using different schedules of administration. At the end of the article, the Authors say that their conclusions are based primarily on a fixed dose of oral conjugated estrogens/medroxyprogesterone acetate. In the past we used to recommend a "golden" standard dose for all women and all indications. Today we all recognize that even healthy menopausal women in their fifties need individualized therapies (in terms of substances, doses and schedules), given the heterogeneous nature of disorders related to menopause. In the HERS study, elderly and obese women, affected by heart disease, were treated with doses of hormones that were studied and intended for healthier women, at least 15 years younger. For this and other reasons the HERS cannot be seen as a landmark study, as reviewed by a European Expert Panel (2).

Two different medical Journals (3), Climacteric and Maturitas recently published a position paper from the Workshop on Controversial Issues in Climacteric Medicine: HRT and Cardiovascular Diseases, organized in October 2000 by the IMS. The Authors of the AHA Statement state that clinical recommendations for primary prevention await the results of ongoing randomized clinical trials. Since December 2000, when the IMS Position Paper was available, no other relevant information from Randomised clinical trials (RCT) has been published. Some of the Authors of the AHA Statement also were present at this specially IMS expert workshop in London. They approved the final document, and thus these differences are intriguing. On the contrary, recent publications from observational studies confirmed the protective effects of long term HRT on cardiovascular disease (4–6). A trend of decreasing risk for recurrent major CHD events with increasing duration of hormone use was observed in primary and secondary prevention (4–6). Primary prevention can be achieved even with lower estrogen doses than those considered as the gold standard (6). A barely significant increased risk seems to be confined to the first 60 days after HRT initiation after hospital discharge in postmenopausal women who survived to their first myocardial infarction (4,5). We can only emphasize that primary and secondary prevention differs, and ovarian hormones cannot be seen as the therapy for coronary heart disease in women.

New Position Papers need new data and new results. As "experts" we cannot assert different opinions at intervals of only a few months, based on the same set of data. These frequent "position papers" can generate confusing and contradictory outlooks, and affect the message that the lay press decodes to the population. The puzzling information on HRT can distract thousands of normal postmenopausal women from a treatment that gives them benefits and a substantial improvement in their quality of life.

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9. Hormone Replacement Therapy and Cardiovascular Disease—the AHA statement. Does it need revision already?

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The statement from the American Heart Association (AHA) Science Advisory Committee (1), includes an attempt to summarise the currently available data concerning potential cardiovascular benefits and risks associated with unopposed (ERT) and opposed (HRT) oestrogen replacement therapy, and to provide updated clinical recommendations regarding its use in the secondary and primary prevention of cardiovascular disease. It is, as such, a good example of the extremely difficult task these advisory boards, representing large medical associations as the AHA, have.

The authors of this only four-page counting statement have tried to cover decades of experience, reported in thousands of scientific papers that were published in internationally peer reviewed journals world-wide. Moreover, they conclude with recommendations based primarily on randomised controlled trials (RCT), of which there are only relatively few, regrettably. Nevertheless, it seems they have done a good job. At least, as long as one prefers to fully negate the recent data from the Nurses' Health Study (NHS), published in two very interesting papers published in December 2000 (2) and July 2001 (3).

The first of these NHS papers by Grodstein et al. (2) already was a strong argument for renewed confidence in the future of ERT/HRT as a tool for primary prevention of coronary artery disease (CAD) in postmenopausal women. In their observational cohort study including 70 533 postmenopausal women, in whom 1258 major coronary events and 767 strokes were identified between 1976 and 1996, the authors compared relative risks (RR) of women treated with 0.3 mg conjugated oestrogens (CE) with those treated with higher dosages (0.625 mg and ≥ 1.25 mg

CE). Lowering the oestrogen dosage did not attenuate the CAD risk reduction observed with conventional dosages (0.625 mg: RR 0.54; 95% CI, 0.44–0.67), and still resulted in a significantly reduced relative risk (RR 0.58; 95% CI, 0.37–0.92). Data on stroke also indicated a reduced risk by lower oestrogen dosage.

The second NHS paper (3) suggests that secondary prevention is not such a fiction as the results of the Heart and Estrogen/progestin Replacement Study (HERS) (4) indicate. Regrettably, this paper was published only 3 weeks earlier than the AHA statement and this probably is the reason that the statement did not mention these interesting data.

This paper by Grodstein et al. (3) reports a subset in the NHS of 2489 postmenopausal women with previous myocardial infarction or documented atherosclerosis, in which 213 cases of recurrent nonfatal myocardial infarction or coronary death were identified from 1976 through 1996. There was much similarity between this study population and the one in the HERS. As in the HERS, the authors found an increased risk for short-term HRT users (RR 1.25; 95% CI, 0.78–2.00). However, already after use of 2 years and more, the RR was 0.38 (95% CI, 0.22–0.66), a reduction in risk that persisted for up to 20 years (RR 0.65; 95% CI, 0.45–0.95). These observations justify a revision of the AHA statement, at least to some extent.

As suggested in another comment by this author (5), we should not limit ourselves to RCT's only, and negate so many excellent (observational) data, despite the biases that are inherent to their design. Even the so-called superior randomised controlled design of the HERS could not prevent some remarkable differences between the two intervention populations. The fact that secondary prevention in the NHS study also detected a short-term increase in risk is good reason to rely on the observed lower risk in the period of 2 and more years of HRT use, a trend that was also observed in the HERS!!

In this author's opinion, the NHS deserves the recognition it has had for many years before the HERS was published (5). The presently available data justify the AHA statement regarding the lack of evidence to initiate oral ERT/HRT only for secondary prevention of CAD, at least as long as we can not identify those women whose risk actually is going to be increased. Future research should therefore focus on factors that help to identify those women. However, continuation of ERT/HRT should not be limited to noncoronary benefits and risks only. The secondary prevention NHS paper (3) confirms the earlier trend observed in the HERS, and therefore justifies considering long-term coronary benefits as an indication to continue hormone treatment.

Last but not least, observations done with other preparations than those used in the HERS, e.g. with lower dosages and non-oral routes of administration, are promising and should urge researchers to study these preparations' cardiovascular impact.

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