Is there other RCT evidence available?

An extensive literature search found 6 additional RCTs, which reported some outcome data and lasted at least 1 year. These trials, 1 in men\(^3\), and 5 in women\(^4\) - \(^8\), are smaller and except for the one in men were not designed to measure clinically relevant outcomes. However, the limited data from these trials corroborates the evidence from the HER\(S\) trial.

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**Case**

Mrs. AG is new to your practice. You are seeing her for the second time and she wants to know whether she should be taking hormone therapy as she read an article that stated that she should. She is a 67-year-old married Caucasian retired teacher, who was well until 2 years ago, when she suffered an acute inferior myocardial infarction. She recovered completely from that episode and is asymptomatic. She has been taking 80 mg of ASA and 40 mg of nadolol daily since her infarct. She has had no surgery. Her last menstrual period occurred at age 52 and she experienced only mild hot flashes for a year. She is a non-drinker. She has a negative family history for cardiovascular disease and osteoporosis. When you first saw her you did a complete physical exam and found no significant abnormal findings. She is 5ft 2in. and weighs 60 kg., BP 136/74 mm Hg., Pulse 66/min. Total cholesterol 4.8 mmol/L, LDL 2.9 mmol/L, HDL 1.5 mmol/L, Triglycerides 2.0 mmol/L.

**Is there evidence available to assist us in this case?**

Up until August 1998, there was no Level I evidence to answer this patient’s question. In August 1998 the first randomised controlled trial (RCT) relating to this question was published: the Heart and Estrogen/ progestin Replacement Study, or (HER\(S\)) trial\(^1\),\(^2\).

**HER\(S\) TRIAL**

**Objective:** To determine if estrogen plus progestin therapy alters the risk for coronary heart disease events in postmenopausal women with established coronary disease.

**Design:** Randomised, double-blinded, placebo controlled secondary prevention trial in 20 US outpatient centers.

**Intervention:** Conjugated equine estrogens, 0.625 mg, plus medroxyprogesterone acetate, 2.5 mg, Hormone Therapy (HT) in 1 tablet daily (n =1380) or an identical appearing placebo (n = 1383).

**Participants:** Menopausal women (mean age 67 yrs), intact uterus, average follow-up 4.1 years.

**Outcome measures:** Primary: non-fatal myocardial infarction or CHD death. Secondary: total mortality, coronary revascularization, unstable angina, congestive heart failure, stroke, etc.

**Results:** No statistically significant difference between groups in primary outcome: 12.5% HT, 12.7% placebo, or any predefined secondary outcome (total mortality 9.5% HT, 8.9% placebo), was seen. The only statistically significant finding was more frequent adverse outcomes in the HT group: venous thromboembolic events HT 2.5%, placebo 0.9%; and gall bladder disease HT 6.1%, placebo 4.5%. There were no statistically significant differences in any cancer or any fracture categories. Interestingly, there was a statistically significant 11% net reduction in LDL and 10% net increase in HDL associated with the HT, yet there was no cardiovascular benefit. The sum of all adverse events in both groups (includes individuals with more than one event) was: HT=1298 events and placebo=1274 events.

**Authors’ Conclusion:** “We do not recommend starting this treatment for the purpose of secondary prevention of CHD.”

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What should we advise her?

Based on this well designed large RCT with clinically relevant outcomes (Level I evidence), and the fact that she meets the inclusion criteria of this trial, we can advise her that HT is unlikely to prevent further CHD or other cardiovascular events. In addition HT is associated with a small increased risk of thromboembolic events and gallbladder disease. There is also no Level I evidence that attempting to lower her LDL cholesterol by other means would be beneficial.

What can be learned from this example?

Before the HERS trial the available evidence was from observational studies and RCTs looking at surrogate markers. Controversy was present, but many clinicians and guidelines were recommending HT for primary and secondary prevention of CHD and osteoporosis. The observational evidence (Therapeutics Letters #14 &16) suggested a consistent reduction in risk of coronary heart disease with estrogens and combined HT (pooled relative risk 0.65 [0.59-0.71]). This magnitude of reduced risk (Level III evidence) is inconsistent with the HERS trial evidence and is likely due to 2 types of bias that can occur with observational studies: 1. Selection bias—women who choose HT are healthier at baseline than those who do not or 2. Compliance bias—people who comply with placebo have better outcomes than those who do not. There was also RCT evidence that various regimens of HT had beneficial effects on lipid levels (possible surrogate markers for cardiovascular events, Level II evidence). The HERS trial has demonstrated that reduction in lipid levels with HT is not a valid surrogate for CHD outcomes.

What if our patient was merely at risk for CHD (primary prevention)?

In this case the risk of CHD events would be less and therefore the opportunity for benefit would be less. On the other hand the chance of adverse outcomes would most likely remain the same. It is unlikely that a drug would be beneficial in primary prevention if there is no demonstrable benefit for secondary prevention.

What if our patient had a previous osteoporotic fracture instead of an MI?

At the present time the evidence for the use of HT (or estrogen or progesterone alone) for osteoporosis is based on the same levels of evidence for CHD before the HERS trial, i.e. observational data and RCT evidence using bone mineral density as the surrogate. The same observational data also suggests a small increased risk of breast cancer for women taking HT for 8 or more years (Letter #14). Fortunately, further large RCTs studying HT are in progress.

Dosing and cost data on the drugs available for Menopausal Hormone Therapy can be found on our web site in the updated Table 1, Therapeutics Letter #14: http://www.b.ubc.ca/pages/letter14.html

Conclusion

Is the controversy over prescribing HT resolved by the HERS trial? Probably not. Recent publications, while including the HERS trial in their list of references, are still advising doctors to encourage use of HT for prevention of CHD and osteoporosis. It will likely take some time for the full implications of the Level I evidence from the HERS trial to be reflected in the literature and practice.

This Letter contains an assessment and synthesis of published (and whenever possible peer-reviewed) publications up to July 1999. We attempt to maintain the accuracy of the information in the Therapeutics Letter by extensive literature searches and verification by both the authors and the editorial board. In addition, this Therapeutics Letter was submitted for review to 75 experts and primary care physicians in order to correct any identified shortcomings or inaccuracies and to ensure that the information is concise and relevant to clinicians.

References: