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Commentary: Hormone replacement therapy and coronary heart disease: four lessons

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In 1991, Stampfer and Colditz,[1] reviewing epidemiological studies of the effect of postmenopausal oestrogen on coronary heart disease concluded that: '… the bulk of evidence strongly supports a protective effect of estrogens that is unlikely to be explained by confounding factors …'

Their best estimate of the relative risk of coronary heart disease (CHD) in postmenopausal oestrogen users was calculated using meta-analytical techniques applied to the epidemiological studies they deemed to be of high quality based on their designs—prospective studies with internal controls and angiographic studies. This estimate was 0.50. The CI was narrow −0.43 to 0.56.

The Stampfer and Colditz paper was cited widely. It became a shorthand citation for the contention that the 'epidemiologic evidence showing that hormone replacement therapy prevents coronary heart disease is overwhelming.'

In 1998, the results of the first large randomized, placebo-controlled trial of the effect of combined oestrogen/progestin hormone replacement therapy on coronary events—the Heart Progestin/Estrogen Replacement study (HERS)—reported no beneficial effect of combined therapy on morbidity or mortality from CHD in women with established coronary disease.[2] In 2002, the Women's Health Initiative (WHI) reported that combined oestrogen/progestin hormone replacement therapy did not prevent the development of CHD in women.[3] Further follow-up of women in HERS,[4] other randomized trials of the effect of oestrogen alone or combined oestrogen/progestin therapy on CHD endpoints or on measures of subclinical atherosclerosis,[5–10] and a meta-analysis of small randomized trials of hormone replacement that provided data on cardiovascular endpoints[11] all reported no overall benefit of either oestrogen alone or oestrogen plus progestin on any cardiovascular endpoint. In March 2004, the oestrogen only arm of the WHI was terminated early after showing no effect of oestrogen alone in increasing or decreasing the risk of CHD.[12]

What can epidemiologists learn by rereading Stampfer and Colditz in the harsh light of the experimental studies?

Lesson one: do not turn a blind eye to contradiction

The Coronary Drug Project was begun in the mid-1960s and completed in the early 1970s. It was a large multicentre randomized trial that evaluated the ability of various therapies to decrease morbidity and mortality from coronary heart disease in men who had a history of coronary disease. The Coronary Drug Project included two active treatment arms in which conjugated equine oestrogen was administered at two doses, 5.0 mg and 2.5 mg.

In the Coronary Drug Project, there was no benefit of either dose of conjugated equine oestrogen in preventing recurrent CHD events.[13,14] The relative risk of non-fatal myocardial infarction (MI) or CHD death was 1.47 in high oestrogen-dose group[14] and 1.00 in the low oestrogen-dose group.[15]

The oestrogen used in HERS and the Coronary Drug Project was the same. The eligibility criteria and endpoints in HERS and the Coronary Drug Project were virtually identical. In addition to differing in enrolment solely of men or solely of women, the two studies differed in the doses of oestrogen they used. The dose of oestrogen in HERS was lower (0.625 mg) than both doses of oestrogen used in the Coronary Drug Project.

If the epidemiological studies were true and oestrogen decreased the risk of CHD in women, it would mean that the effect of the oestrogen is 'crossed' by sex or by dose. That is, it would mean that oestrogen increases (or does not affect) the risk of CHD in men (Coronary Drug Project) but it decreases risk in women (epidemiological studies) or that oestrogen use increases (or does not affect the risk) of CHD at a high dose (Coronary Drug Project) but it decreases risk at a low dose (epidemiological studies).

There are no examples where the effects of either exogenous or endogenous factors on CHD are crossed—the factor increases the risk of CHD in people of one sex and decreases risk in those of the opposite sex. There are no examples where the effect of exogenous administration of a drug on CHD is different between high and low doses of the drug.

HERS but not the Coronary Drug Project involved administration of a progestin. That is, HERS was a study of combined oestrogen/progestin therapy. What else was known in 1991 about combined hormone therapy and coronary disease in women?

Soon after they were first marketed in the early 1960s, there were isolated case reports of 'coronary thrombosis' in young women using combination oestrogen/progestin oral contraceptives. By the mid-1970s, the increase in the risk of MI in young women using oral contraceptives was established.[16]

The oestrogen used in combination oestrogen/progestin oral contraceptives differs from that used for hormone replacement therapy. Combination oestrogen/progestin oral contraceptives contain the oestrogen, ethinyl oestradiol. The oestrogen administered as hormone replacement therapy is generally either conjugated equine oestrogen, 17-beta-oestradiol, or oestradiol valerate.

The progestins in combination oestrogen/progestin oral contraceptives and those used for combined oestrogen/

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progestin hormone replacement therapy also are generally different, although there is overlap. In the US, the progestin in most combined oestrogen/progestin hormone replacement regimens is medroxyprogesterone acetate; in Europe, norethindrone (norethisterone) is also widely used. There are at least 12 different progestins in currently marketed combination oestrogen/progestin oral contraceptives, but only some of these (e.g. norethindrone/norethisterone and norethindrone acetate/norethisterone acetate) are marketed for use as hormone replacement therapy.

However, the oestrogens and progestins are more similar than different. Oral contraceptives can be used to alleviate menopausal symptoms. An oestrogen/progestin oral contraceptive product containing medroxyprogesterone acetate was marketed in the past and was effective as a contraceptive. It is technically feasible to formulate a combination oestrogen/progestin oral contraceptive containing conjugated oestrogen or 17-beta-oestradiol.

If there truly were an effect of oestrogen/progestin combinations in decreasing the risk of CHD in postmenopausal women (as hormone replacement therapy), it would mean that the effect of administration of combinations of oestrogen and progestin in women is crossed by age. That is, the drugs are a hazard to the heart in younger women (oral contraception) and a benefit in older women (hormone replacement therapy).

There are no examples of where the effect of a drug on the risk of CHD at one age is the opposite of its effect at another.

Stampfer and Colditz do not discuss either the Coronary Drug Project or the oral contraceptive data but must have known of them.

Crossed effects are contradictions. Contradiction must be identified and explained. There is much to learn from contradiction.

Stampfer and Colditz teaches us not to turn a blind eye to contradiction.

Lesson two: do not be seduced by mechanism

There is a vast literature that documents a favourable effect of postmenopausal hormone replacement on levels of total cholesterol, low density lipoprotein cholesterol, and high density lipoprotein cholesterol. There is an equally vast literature that shows that some lipid-lowing drugs, in particular the statins, prevent primary and secondary CHD events. Stampfer and Colditz cite the effect of oestrogen on the lipid profile as the likely mechanism for the lowering of CHD risk.

Considering only lipid effects, oestrogen replacement therapy (ERT) and combined progestogen/oestrogen replacement therapy (PERT) increase serum triglyceride levels,[17] a lipid effect that would be considered 'negative.' This was known in 1991.

Besides affecting lipids and the interaction of platelets with the endothelium, ERT and PERT affect glucose metabolism, coagulation and fibrinolysis, homocysteine, measures of inflammation, and the renin-angiotensin-aldosterone system, which also play a role in the development of CHD and in recurrent events and atherosclerosis progression.[18–24] Some of these effects are individually in the 'negative' direction (would suggest an increase in CHD or coronary atherosclerosis risk). The fact that hormones have complex effects on a number of factors involved in coagulation and atherosclerosis was also known in 1991.

Even if all of the mechanistic data had pointed in the same direction either in 1991 or later, we never know all there is to know of mechanism. Mechanism is complex.

Stampfer and Colditz teaches us not to be seduced by mechanism.

Lesson three: suspend belief

In 1988, writing about causal inference, Weed[25] wrote: '… given that certainty is impossible, there are three alternatives to consider: belief, probability, and criticism.'

Weed goes on to describe the difficulties with belief: '… it may prevent us from making sincere attempts to test the cause as strenuously as possible' and 'it makes it somewhat easier to conceal error.'

In 2003, Humphrey, Chan, and Sox pointed out that a large majority of otherwise well-conducted epidemiological studies of coronary heart disease and postmenopausal hormone use did not take socioeconomic status into account.[26] Three epidemiological studies that reported CHD risk in current users of hormone replacement had been published up to the time of their review in 2003 and met their quality criteria. The relative risk estimates were 0.8 (95% CI: 0.4, 1.3),[27] 0.96 (95% CI: 0.66, 1.40),[28] and 1.05 (95% CI: 0.76, 1.46).[29]

Stampfer and Coldiz do not mention socioeconomic status as a potential uncontrolled confounder. But by 1991, social class, education, and socioeconomic status were well-studied and known to affect coronary heart disease risk.[30,31]

How can we understand this oversight? Was belief in the primacy of design—that prospective designs overcome confounding—too strong? These were the heady days of meta-analysis of epidemiological data. Was belief driven by the misleading narrowness of the confidence interval? Whatever the reason, there is no doubt rereading the 1991 paper that Stampfer and Colditz believed.

And, as Weed would have predicted, belief caused them to be unstrenuous in considering uncontrolled confounding as an explanation for the studies to that date. Worse, as Weed would have predicted, subsequent collective belief in the overwhelming nature of the epidemiological evidence made it easy to conceal the error.

Most of all, Stampfer and Colditz teaches us to suspend belief.

Lesson four: maintain scepticism

The story of hormone replacement and the heart will not end in 2004. Despite the 'overwhelmingness' of the evidence from experiments, there remain legitimate questions about whether oestrogens other than conjugated equine oestrogen, especially those that affect only certain receptors, or oestrogen delivered transdermally[32] or hormone therapy initiated near the menopause might have a beneficial effect on CHD.[33]

The possibility that some form of oestrogen, some way of administering it, or some group given oestrogen might have a benefit in terms of a reduction in CHD risk is a longshot. Science is full of longshots with big payoffs. Science doors that are closed have a way of reopening.

Stampfer and Coldizt teaches epidemiologists to maintain scepticism, even when there are experiments.

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