HORMONE THERAPY AND CARDIOVASCULAR DISEASE

To the Editor:

I read the review article by Dr Chen [1] with grave concern. First, in the section of "Difference between observational studies and RCTs on cardiovascular effects", under the title "Observational trials of HT", "Meta-analysis of epidemiological data from several observational trials [3–10]..." was quoted. Epidemiologic studies are traditionally classified as either observational or experimental. In an observational study, the investigator measures but does not intervene. Therefore, observational studies should better not be quoted as observational trials. Epidemiologic studies are primarily descriptive or analytic. Analytic studies may be subdivided into nonexperimental (observational) and experimental studies. Nonexperimental analytic studies include cohort and case-control studies, and take advantage of "natural experiments" in which individuals do not involve in any kind of trial. Experimental studies include clinical trials. Randomization of the treatment assignment is the cornerstone of a good clinical trial. Field and community intervention trials are considered as experimental studies [2]. The major difference between clinical trials and observational studies is that, in clinical trials, the investigators manipulate the administration of a new intervention and measure the effect of that manipulation, whereas observational studies only observe associations (correlations) between the treatments experienced by participants and their health status or diseases. These are fundamental distinctions in evidence-based medicine [3]. For example, level I evidence is the evidence obtained from at least one properly designed randomized controlled trial; by the way, RCTs are now considered the "gold standard" in the field of clinical research.

Second, I found that all the reference numbers quoted in both Table 1 and Table 2 are incorrect. Please amend.

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References

1. Chen FP. Hormone therapy and cardiovascular disease. *Taiwanese J Obstet Gynecol* 2006;45:287–93.
2. Cramer DW. Epidemiology for the gynecologist. In: Berek JS, ed. *Novak' Gynecology*, 13th edition. Philadelphia: Lippincott Williams & Wilkins, 2002:49–65.
3. Clinical trial. Wikipedia, the free encyclopedia. Available at: http://en.wikipedia.org/wiki/Clinical_trial [Date accessed: January 5, 2007]

Reply:

Dear Dr Tsai Horng-Jyh,

Thank you for your comments on the review article "Hormone therapy and cardiovascular disease". I completely agree with your opinion that RCTs are now considered as the "gold standard" in the area of clinical research. Therefore, the WHI as an RCT study had a tremendous impact on both the public and the clinicians. Although these RCTs have contributed to our understanding of the benefit:risk relation associated with HT, they have not answered questions regarding the effect of such a therapy on cardiovascular risk. As per your comments, as an example of evidence-based medicine, their results do deserve consideration. However, if we are to adhere to the principles of evidence-based medicine, these results cannot be extrapolated to **a different population** from the one studied in the trial, not to **a different HT regimen**. Thus, as per your comments "...in clinical trials, the investigators manipulate the administration of **a new intervention** and measure the effect of that manipulation, whereas observational studies only observe associations (correlations) between the treatments experienced by participants and their health status or disease", RCTs may reveal the effects from only one kind of regimen in HT, as well as the effects in advanced-age population. The significance of observational trials (you may prefer observational studies) is that they did not restrict to one type of HT and they evaluated a younger population. That is why I have to mention the difference between observational

Table 1. Summary of randomized clinical trials of hormone therapy by evaluating intermediate coronary artery disease outcomes

Study	Age of subjects, yr	Regimens	Effect
ERA [42]	65.8	CEE/CEE + MPA	↔
PHOREA [43]		17β-E2 + gestodene	↔
EPAT [44]	62.2	17β-E2	+
HERS B-Mode substudy [45]	67	CEE + MPA	↔
WAVE [46]	65	CEE/CEE + MPA	↔
WELL-HART [47]	63.5	17β-E2/17β-E2 + MPA	↔

CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate; 17β-E2 = 17β-estradiol.

Table 2. Summary of randomized clinical trials of hormone therapy on cardiovascular disease outcomes

	Age, yr	Regimen	Effect	Early events
Primary prevention studies				
WHI [11]	63.3	CEE + MPA	↑	↑
WHI update [13]	63.3	CEE + MPA	↔	↑
WHI [12]	63.6	CEE	↔	↔
Secondary prevention studies				↑
HERS [14,48]	66.7	CEE + MPA	↔	
PHASE [49]	66.5	Transdermal E2 + NETA	↔	
ESPRIT [50]	62.6	E2	↔	
WHISP [51]	> 55	17β-E2 + NETA	?	↔

CEE = conjugated equine estrogen; MPA = medroxyprogesterone acetate; E2 = estradiol; NETA = norethisterone acetate.

and RCT studies. Therefore, serious questions remain regarding the choice of HT preparations, different estrogen and progestin combinations and doses, and more importantly, the age and physical conditions, at which women are exposed to these agents.

Epidemiologic approaches used to study the association between HT and cardiovascular risk include case-control, cross-sectional, prospective, and cohort with internal controls studies. Most cited observational papers in this manuscript are from prospective observational studies. Thus, they actually involve some kind of trials (HT). The description "observational trials of HT" has also been noted in many international papers and presentations. However, using "observational study" may be better than "observational trials".

Thank you for your correction. The reference numbers quoted in both Tables 1 and 2 are incorrect, but they were correct in the manuscript. I have amended them above.

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