What We Think and What We Know

This is an editorial that has found a voice only after a lot of struggle about what ought to be said and what ought not. In this issue, Crespo et al. (1) examined data from the Third National Health and Nutrition Examination Survey (NHANES III) and reported that postmenopausal women taking hormone replacement therapy (HRT) have better lipoprotein profiles as well as some improvement in components of the metabolic syndrome when compared with those not taking HRT.

Timing is everything. When the authors prepared the manuscript, when the reviewers and editors accepted it, and in fact when we were asked to prepare this editorial, studies like these were sufficient reason for health care providers to recommend that their postmenopausal diabetic patients consider HRT. In the absence of randomized controlled clinical-trial data, cross-sectional data suggesting benefits for intermediate measures of cardiovascular disease (CVD) risk might constitute "best evidence." In the HRT field, epidemiological studies inconsistently demonstrating an increased risk of breast cancer were the major limitation to wholesale adoption of HRT in our society.

Diabetic women suffer from four times the risk of CVD as nondiabetic women. Until a few weeks ago, the prevailing wisdom, based on such cross-sectional data, was to prescribe HRT for postmenopausal woman, with an aim to reduce CVD risk, prevent osteoporosis, and with exuberant hope, preserve memory, thwart dementia, keep skin supple, promote sexual well-being, as well as promote overall health and vitality. Many astute physicians were vexed by the results of the Heart and Estrogen/Progestin Replacement Study (HERS), a randomized controlled study published in 1998 that demonstrated that HRT had an early adverse effect in women with preexisting coronary disease (2). The authors suggested "given the favorable pattern of CHD events after several years of therapy, it could be appropriate for women already receiving this treatment to continue." More recently, Furberg and coworkers examined diabetes as a potential mitigator of CVD effects in HERS without finding any evidence of interaction (3). Many health professionals quieted the nagging voice and slid this information to the back burner for future reference, eagerly awaiting the Woman's Heath Initiative (WHI) trial scheduled for completion in 2005 to provide the confirmation of their biases.

That result has come 2 and a half years early. The WHI trial, which investigated the health risks and benefits of combined estrogen and progestin–replacement therapy in healthy postmenopausal women, was discontinued after some 5 years of follow-up because the evidence for harm from breast cancer as well as increases in the risk of coronary heart disease, stroke, and pulmonary embolism outweighed evidence for benefits in rates of fractures and possibly colon cancer (4). The arm of the trial that monitors the effects of unopposed estrogen continues because the balance of risks and benefits is as yet undetermined.

In the WHI, the incidence of coronary and stroke events increased by 29 and 41%, respectively, with a net increase of 15 events per 10,000 patient-years. This increase did reach nominal statistical significance for coronary disease. Evaluation of time trends suggested that the risk began to accrue early in the trial without much in the way of evidence of convergence of risk through 6 years of follow-up. These observations have set the world of HRT on its head.

How do the current publication and the WHI inform us regarding the treatment of postmenopausal women? We know that the average life expectancy of a woman reaching menopause is 30 years and that the leading cause of morbidity and mortality in this population is CVD. Unequivocally, the conclusion from the WHI is that we should not recommend combined HRT for primary prevention of CVD. There are many choices that should be employed to minimize CVD risk on the basis of randomized clinical trial data, including lipid management, blood pressure control, aspirin therapy, and modulation of the angiotensin system. There are epidemiological data to suggest a benefit from smoking cessation, which has not been formally tested in an interventional study.

It should be noted that the risks associated with combined HRT in the WHI were modest. There was no difference with regard to survival, and the absolute rates of adverse events were small. Strictly speaking, we must remember that the trial tested a particular form of HRT—conjugated equine estrogen 0.625 mg/day plus medroxyprogesterone acetate 2.5 mg/day (Prempro; Wyeth Ayerst, Philadelphia, PA)—and that the results may not apply to lower dosages of these agents, alternative preparations, skin patches, and vaginal creams. Also, the trial did not attempt to tease out estrogen's effects from progestin's; the unopposed estrogen trial in the WHI continues. In case we let the WHI "scare" our patients, or us, it is worth remembering that HRT may still be appropriate for short-term therapy for menopausal symptoms, including vasomotor instability with hot flushes, sleep disturbance, night sweats, and mood lability. These problems are often relieved by HRT and dissipate after 1–2 years of therapy.

There has also been fairly uniform adoption of the notion that HRT reduces fracture risk. In fact, this dogma is also largely derived from observational data. The WHI is the first trial to provide definitive data supporting the ability of HRT to prevent fracture rates; there was a 34% reduction in hip fractures and a 24% reduction in total fractures. However, there were more adverse events (CVD, cancers, etc.) than fractures avoided. Therefore, another conclusion from the WHI should be that combined HRT should not be used for primary prevention of fractures. Over half of all postmenopausal women will develop a spontaneous fracture as a result of bone loss. Fortunately, we now have other therapies indicated to address this problem. In postmenopausal women with osteoporosis or a history of osteoporotic fractures, raloxifene reduces fracture rates (5). There are prospective observational data in randomized studies to suggest that raloxifene reduces the incidence of breast cancer and CVD events (5,6).

Similarly, bisphosphonates provide for fracture reduction (7).

Are there specific implications for women with diabetes from the WHI? The study had nothing to say specifically except that there were "no noteworthy interactions" and to promise that data for this subset will be the subject of future publications.

How do the current publication and the WHI inform us regarding the larger issues of evidence based medical practice? We hope it serves as a reminder that there is actually very little that we "know" in medicine, whereas there is a great deal that we "think" that we know. As health care professionals, we are eating a bit of humble pie. Let us not mistake dogma for evidence. The former comes as a ready, authoritative opinion often delivered as fact. At its worst, it is arrogant. It is often promulgated by thought leaders promoting a pet theory, professional societies looking after their own interests, and the pharmaceutical industry's campaigns to create demand for a product. On the other hand, a discussion of evidence regarding a clinical issue generally comes with a number of stipulations regarding the details of the intervention, the population studied, and the limitations to the broad application of the conclusions. While randomized controlled clinical trials have their limits, cross-sectional studies are a first step in evaluating medical therapy and best used to generate hypotheses. As Crespo et al. (1) carefully point out, they are especially vulnerable to bias.

There are many areas of diabetes care where the evidence is wanting. The current paper and the WHI should make us consider carefully in every clinical interaction the costs and risks of the treatments we prescribe versus the uncertain benefits we hope will come as a result of interventions. Some of the currently fashionable dogma in diabetes include statements such as "postprandial glucose monitoring and treatment are essential to reduce cardiovascular events," "insulin sensitizers prevent cardiovascular disease and β-cell dysfunction," and "the systolic blood pressure should be <130 mmHg."

Time and time again in medicine, we are clubbed into submission with evidence. In fact, it is this progressive enlightenment that makes medicine dynamic and its practice fun. John Godfrey Saxe's version of an Indian parable provides us solace as we gradually move from what we think to what we know (8):

It was six men of Indostan
To learning much inclined,
Who went to see the Elephant
(Though all of them were blind),
That each by observation
Might satisfy his mind.

The First approached the Elephant,
And happening to fall
Against his broad and sturdy side,
At once began to bawl:
"God bless me! but the Elephant
Is very like a wall!"

The Second, feeling of the tusk
Cried, "Ho! what have we here,
So very round and smooth and sharp?
To me 'tis mighty clear
This wonder of an Elephant
Is very like a spear!"

The Third approached the animal,
And happening to take
The squirming trunk within his hands,
Thus boldly up he spake:
"I see," quoth he, "the Elephant
Is very like a snake!"

The Fourth reached out an eager hand,
And felt about the knee:
"What most this wondrous beast is like
Is mighty plain," quoth he;
"Tis clear enough the Elephant
Is very like a tree!"

The Fifth, who chanced to touch the ear,
Said: "E'en the blindest man
Can tell what this resembles most;
Deny the fact who can,
This marvel of an Elephant
Is very like a fan!"

The Sixth no sooner had begun
About the beast to grope,
Than, seizing on the swinging tail
That fell within his scope.
"I see," quoth he, "the Elephant
Is very like a rope!"

And so these men of Indostan
Disputed loud and long,
Each in his own opinion
Exceeding stiff and strong,
Though each was partly in the right,
And all were in the wrong!

Moral:

So oft in theologic wars,
The disputants, I ween,
Rail on in utter ignorance
Of what each other mean,
And prate about an Elephant
Not one of them has seen!

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