Editorial

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We Know Less than We Think

Some recent developments in the world of diabetes have reinforced an important lesson that we medical professionals seem to keep forgetting: Assumptions that seem eminently logical and reasonable don't always hold up in the final analysis.

For instance, we believed for years that giving estrogens to postmenopausal women was certain to reduce their risk of cardiovascular (CV) events. Then came the Women's Health Initiative trials, which demonstrated convincingly that this therapy actually increased the risk of stroke and had no effect on coronary heart disease. Although investigations are still exploring whether estrogen therapy might be cardioprotective in the immediate postmenopausal years, this example nevertheless illustrates the danger of assuming we know the definitive answer to a medical question simply because our theory seems to make sense.

Similarly, it has long been assumed that tight blood glucose control would reduce CV morbidity and mortality. After all, a large body of epidemiologic evidence shows a strong correlation between hemoglobin A_{1c} (HbA_{1c}) levels and rates of CV morbidity and mortality. Many skeptics have declared efforts to test this hypothesis wasteful—even after the United Kingdom Prospective Diabetes Study (UKPDS) found no statistically significant reduction in myocardial infarction risk with tighter glycemic control.[2] Didn't we already know the answer, and might it not be unethical to deliberately "undertreat" half the patients?

Earlier this year, three trials reported findings on this matter. I'm most familiar with the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial as one of its investigators. The ACCORD trial was designed to determine the extent of the potential CV risk reduction that might be gained from very tight glycemic control in older people with type 2 diabetes at high risk for CV events. Each participant was double-randomized to the glycemia trial and to either the concomitant hypertension or lipid trial.

The glycemia trial compared the CV effects of a very aggressive regimen aimed at driving HbA_{1c} levels below 7% with a more conventional approach aimed at keeping them between 7% and 8%. But the glycemia trial was stopped prematurely because of a statistically significant 25% increase in deaths in the aggressive treatment arm.[3] (The hypertension and lipid trials are still ongoing.) While the study design doesn't allow us to pinpoint the exact cause of the increased mortality, it's safe to conclude that aggressively using all available agents to lower HbA_{1c} may be counterproductive in terms of reducing CV events.

No increase in CV events was seen with tighter glycemic control in the other two major studies, the Veterans Affairs Diabetes Trial (VADT)[4] and the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial.[5] But neither trial was able to demonstrate a statistically significant reduction in CV death with more aggressive glycemic control.[4,5]

We'll be analyzing these results for years to come, but it's not too early to proclaim the overall message: In medicine, we need to avoid assuming positions of absolute certainty about unproven theories—even when they seem intuitively right. Prospective clinical trials sometimes produce surprising results at odds with our strongest assumptions and biases. We must be humble and thoughtful in recognizing that we know a lot less than we would like to admit. ●

Author disclosures

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REFERENCES

1. Anderson GL, Limacher M, Assaf AR, et al; and Women's Health Initiative Steering Committee. Effects of conjugated equine estrogen in postmenopausal women with hysterectomy: The Women's Health Initiative randomized controlled trial. *JAMA*. 2004;291(14):1701–1712.
2. The American Diabetes Association, Inc. Position statement: Implications of the United Kingdom Prospective Diabetes Study. *Diabetes Care*. 2002;25(suppl 1):S28–S32.
3. Gerstein HC, Miller ME, Byington RP, et al; and Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. *N Engl J Med*. 2008;358(24):2545–2559.
4. Intense blood glucose control yields no significant effect on CVD reduction in VA diabetes trial [press release]. American Diabetes Association web site. http://www.diabetes.org/for-media/pr-intense-blood-glucose-control-yields-no-significant-effect-on-cvd-reduction.jsp. Published June 8, 2008. Accessed August 18, 2008.
5. Patel A, MacMahon S, Chalmers J, et al; and the ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med*. 2008;358(24):2560–2572.