

EDITORIAL

Managing Thrombosis in Diabetes

We have an unsatisfactory state of affairs regarding thrombotic management in diabetes patients. We know that there's a strong relationship between inflammation and thrombosis, and as diabetes progresses, that risk is enhanced, leading to increased risk of obstructive coronary artery disease and stroke. The treatments that we have don't seem to be working, and there doesn't seem to be a one-size-fits-all medication.

Options for the treatment of thrombotic risk in diabetes are limited. There are three ways that we can look at this.

The first is by taking a general view of how we can improve glycemic control, and a variety of pleiotropic things that might benefit thrombosis. There's evidence that lipid-lowering agents and some specific diabetes treatments have beneficial effects on inflammatory and thrombotic processes. If we improve glycemic control, that benefits elements of all these processes.

Second, we can try to generate drugs that are specifically designed to treat these problems. The peroxisome proliferator-activated receptor (PPAR)-gamma agonists (such as rosiglitazone) are a model of this process. They have several effects, all of which should be beneficial in relation to both thrombosis and heart disease in general.

Third, we can target the specific pathways that are involved in thrombosis. Antiplatelet therapies are one example. Let's look at aspirin.



BY PETER J. GRANT, M.D.

A meta-analysis by the Antithrombotic Trialists' Collaboration (Lancet 2009; 373:1849-60) examined 6 primary prevention trials (95,000 subjects at low average risk who were treated for 660,000 person-years) and 16 secondary prevention trials (17,000 people at high average risk who were treated for 43,000 person-years). In primary prevention, aspirin did not seem to have any effect on mortality but it did significantly increase major gastrointestinal and extracranial bleeds. Most people would now say we shouldn't be giving aspirin to healthy people with uncomplicated diabetes for primary prevention because of the increase in major bleeds.

But for secondary prevention, aspirin in this huge analysis provided a 23% reduction in total events and nearly a 20% reduction in stroke—a major statistical advantage.

My associates and I looked at the effects of aspirin in a separate study of 2,499 patients with acute coronary syndrome, 425 of whom had diabetes (Diabetes Care 2008;31:363-5). We found a major reduction in mortality in nondiabetic subjects and no mortality effect in diabetic subjects, leading us to wonder about the precise role of aspirin in diabetes.

The results of a separate study of aspirin use in 58,465 Swedish patients with diabetes are especially worrisome, particularly when you consider it alongside the Antithrombotic Trialists' Collaboration data set. In the Swedish study, aspirin use increased mortality in diabetes

patients without cardiovascular disease by 17% at age 50 and by up to 29% at age 85 years (Pharmacoepidemiol. Drug Saf. 2009;18:1143-9). Aspirin increased the risk of serious bleeding in patients without cardiovascular disease by 46%. In contrast, aspirin tended to decrease mortality and the risk of serious bleeds in elderly diabetes patients with cardiovascular disease.

In Europe, the view is developing that aspirin should be used with caution in primary prevention in type 2 diabetes.

Clopidogrel, another antiplatelet drug that acts differently from aspirin, was shown to be beneficial in the Clopidogrel Versus Aspirin in Patients at Risk of Ischemic Events (CAPRIE) study (Lancet 1996;348:1329-

39). A substudy of the 3,866 patients in this cohort who had diabetes confirmed that clopidogrel was better than aspirin for secondary prevention.

In diabetes patients, clopidogrel probably should be used as primary prevention only in those with a very high risk for ischemic events.

Dual antiplatelet therapy in primary prevention is not recommended. The combination of aspirin and clopidogrel is widely used, however, in patients with unstable angina or non-ST-elevation myocardial infarction.

The Food and Drug Administration, the American College of Cardiology, and the American Heart Association all recommend clopidogrel in patients with

ST-elevation myocardial infarction as well. The recommendations are that it should be used in acute coronary syndrome and continued for 1 year.

For the new kid on the block—prasugrel—there has been one study that included patients with diabetes and acute coronary syndrome (N. Engl. J. Med. 2007;357:2001-15). In the overall cohort of 13,608 patients, prasugrel lowered the rate of ischemic events, increased major bleeding, and made no difference in mortality. In the diabetes subgroup, however, prasugrel was associated with a 30% reduction in ischemic events, but it still didn't bring risk down to that of the nondiabetic population.

Novel anticoagulants and antiplatelet therapies are being developed. And an area that is open to investigation in diabetes is inflammation therapeutics, which is aimed at linking our understanding of inflammation with the treatment of thrombotic risk and vascular disease progression. ■

Most people would now say we shouldn't be giving aspirin to healthy people with uncomplicated diabetes for primary prevention because of the increase in major bleeds.

DR. GRANT is a professor of medicine and head of the division of cardiovascular and diabetes research at the University of Leeds, England, and a consultant diabetologist in the Leeds Acute Trust. He has given lectures for, and been an adviser to, GlaxoSmithKline (which markets rosiglitazone), Eli Lilly & Co. (which markets prasugrel), Takeda, and AstraZeneca.

LETTERS

Working Toward Antitobacco Stamp

In a recent letter, Dr. Alan Blum discussed Dr. James Lutschg's remarkable postage stamp collection related to smoking ("No Rubber Stamp for Tobacco," Feb. 15, 2010, p. 14).

I would like to update a statistic in his letter and let readers know that 65 countries have issued antitobacco postage stamps or other postal items such as postcards. It is ironic that Jan. 11, 2014, will be the 50th anniversary of the release of Surgeon General Luther Terry's landmark report on smoking and health, and yet the United States is not among the many countries that have issued an antitobacco postage stamp.

I plan to introduce a resolution at this month's annual meeting of the Medical Association of the State of Alabama (Dr. Luther Terry's home state) and subsequently to the American Medical Association asking them to urge the U.S. Postal Service's Citizens' Stamp Advisory Committee to recommend that such a postage stamp be issued. The resolution also will urge the AMA to en-

courage other national medical specialty societies and state medical associations to add their voices of support to this effort.

I am hopeful that physicians will take up this cause.

W. Jeff Terry, M.D.
Mobile, Ala.

Dr. Terry reports that he is the cousin of Dr. Luther Terry and that he is chair of Alabama's delegation to the AMA.

LETTERS

Letters in response to articles in INTERNAL MEDICINE NEWS and its supplements should include your name and address, affiliation, and conflicts of interest in regard to the topic discussed. Letters may be edited for space and clarity.

Mail: Letters, INTERNAL MEDICINE NEWS, 5635 Fishers Lane, Suite 6000, Rockville, MD 20852

Fax: 240-221-2541

E-mail: imnews@elsevier.com

EDITORIAL ADVISORY BOARD

JON O. EBBERT, M.D., Mayo Clinic, Rochester, Minn.

FAITH T. FITZGERALD, M.D., University of California, Davis

PETER D. FRIEDMANN, M.D., M.P.H., Brown University, Providence, R.I.

WILLIAM E. GOLDEN, M.D., University of Arkansas, Little Rock

ROBERT H. HOPKINS, M.D., University of Arkansas, Little Rock

J. LEONARD LICHTENFELD, M.D., American Cancer Society, Atlanta

DIANE E. MEIER, M.D., Mount Sinai School of Medicine, New York

FRANKLIN A. MICHOTA, M.D., Cleveland Clinic, Cleveland

ALAN R. NELSON, M.D., special adviser to the CEO, American College of Physicians, Fairfax, Va.

VICTOR L. ROBERTS, M.D., University of Florida, Gainesville

BARBARA L. SCHUSTER, M.D., Medical College of Georgia, Athens

ANITA SCHWANDT, M.D., Case Western Reserve University, Cleveland

DONNA E. SWEET, M.D., University of Kansas, Wichita

ERIC G. TANGALOS, M.D., Mayo Clinic, Rochester, Minn.

MATTHEW R.G. TAYLOR, M.D., PH.D., University of Colorado, Denver

ROWEN K. ZETTERMAN, M.D., Creighton University, Omaha, Neb.