Role of Oral Agents in Improving Cardiovascular Prognosis in Diabetes Mellitus

To the Editor: In their otherwise excellent review entitled "Primary and Secondary Prevention of Cardiovascular Diseases: A Practical Evidence-Based Approach," O'Keefe et al[1] highlight the increased risk associated with diabetes mellitus (DM). They state that optimization of the dismal cardiovascular prognosis associated with DM requires aggressive risk factor treatment. The first risk factor they address is glycemic control. To support their contention, they cite the UK Prospective Diabetes Study, indicating that the trial showed sustained reductions in retinopathy, nephropathy, and neuropathy. Notably absent from that list is macrovascular cardiovascular disease. The authors then recommend use of oral agents that have a limited risk of hypoglycemia, such as metformin, dipeptidyl peptidase-4 inhibitors, glucosidase inhibitors, and thiazolidinediones. They do not include sulfonylureas, apparently because of the propensity to cause hypoglycemia, but then state that insulin, the leading culprit in hypoglycemia, is often needed to achieve adequate control.

What the authors fail to do is to present evidence, as the title of the article suggests, to support this recommendation. We have recently seen in the Veterans Affairs Diabetes Study that tighter control of DM with oral agents and insulin does not lower the rate of cardiovascular events in high-risk patients.[2] Many of the agents cited have been approved by the Food and Drug Administration on the basis of their ability to lower hemoglobin A_{1c} levels, a surrogate marker for DM; no data exist that they prevent any important patient-oriented outcomes, including cardiovascular disease.

In contrast, the authors did provide studies that support control of lipids and blood pressure, and data are clear that better control leads to better cardiovascular outcomes.

Evidence-based cardiovascular prevention recommendations should be based on evidence. Until there is evidence that each of the agents mentioned by O'Keefe et al is effective in reducing cardiovascular disease, such agents should not be included in an authoritative review. Adding cost, drug interactions, and adverse effects to a patient's regimen is not good medicine. Physicians need to be guided by data, not conventional wisdom, no matter how much intuitive sense it may make.

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In reply: We appreciate Dr Hirsch's kind comments regarding our recent article and are delighted to respond to his opinion that glucose-lowering drugs should not be included among the evidence-based strategies that have been shown to reduce the incidence of adverse cardiovascular (CV) events. His assertion highlights one of the most important unresolved dilemmas in modern medicine: If elevated glucose levels powerfully increase the risk of CV disease, why have we been unable to prove that lowering glucose back toward normal improves CV prognosis?

There is no doubt that an abnormally elevated blood glucose level is a pernicious CV risk factor.[1] The EPIC-Norfolk (European Prospective Investigation Into Cancer in Norfolk) study showed that, during 6 years of follow-up, glycated hemoglobin (HbA_{1c}) levels were highly correlated in a direct fashion with risk of all-cause mortality.[2] In that study, for every 0.5% increase in HbA_{1c} levels greater than 5% for men and 6% for women, the relative risk of adverse CV events increased by approximately 25%.[2] Similarly, the observational UKPDS (United Kingdom Prospective Diabetes Study)[35] found a 14% change in the risk of myocardial infarction (MI) for each 1% change in mean HbA_{1c} level.[3] Despite the fact that approximately 70% of patients with diabetes mellitus (DM) die of CV disease,[4] glucose-lowering therapy has not been conclusively shown to improve CV outcomes. This missing evidence is not due to a lack of prospective DM studies; during the 9 decades that have elapsed since Dr Frederick Banting discovered insulin, scores of randomized trials of glucose-lowering therapies have repeatedly failed to firmly establish a cardioprotective role for these drugs.

The University Group Diabetes Project, a widely publicized early failure, reported that the sulfonylurea tolbutamide significantly increased CV death compared with placebo.[5] Subsequently, UKPDS randomized patients to either intensive treatment (with either a sulfonylurea or insulin) or conventional therapy (predominantly diet alone) and found HbA_{1c} values of 7% and 7.9%, respectively, while receiving treatment.[6] Intensive insulin therapy yielded a statistically insignificant trend toward reduction in the risk of MI in type 2 DM after 10 years of follow-up. More recently, 3 large randomized trials that tested the "lower is better" approach to treating hyperglycemia also failed to prove that an intensive glucose-lowering strategy is superior to a less aggressive glycemic control for reducing CV events.[7-9] The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial actually showed a higher CV mortality in patients with type 2 DM randomized to intensive glycemic control after 3.5 years of follow-up. Subgroup analysis suggested that intensive glycemic control may have reduced the risk of fatal and nonfatal CV events in patients with no documented coronary heart disease (CHD) at baseline.[7] The VADT (Veterans Affairs Diabetes Trial) compared intensive and standard treatment strategies in patients with type 2 DM and found no significant difference in the incidence of a major CV event after a median follow-up of 5.6 years.[8] ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) showed no difference between intensive control and standard control groups in macrovascular outcomes but showed a lower risk of nephropathy with intensive control after a median

follow-up of 5 years.[9] Therefore, the cumulative findings from ACCORD, ADVANCE, and VADT suggest that an intensive glycemic control strategy does not significantly reduce macrovascular events and may even be harmful to older patients with long-standing DM and/or established CHD at baseline. In contrast, younger patients with shorter duration of DM and no documented CV disease appear to benefit from a more intensive glucose-lowering strategy.[7-9]

Importantly, hypoglycemia was more common in the intensive therapy arms of all 3 of these recent trials[7-9] and also in the UKPDS.[6] Possibly, CV toxicity caused by recurrent hypoglycemia induced by an aggressive glycemic control strategy (especially one that uses insulin and/or a sulfonylurea) overwhelms the potential CV benefits of a more normal HbA_{1c}. This would be particularly true for patients with conditions that predispose to adverse CV events, such as CHD and other structural heart disease. Thus, it is not surprising that individuals with long-standing DM and/or existing CV disease appear to be particularly susceptible to the cardiotoxicity associated with aggressive glycemic control and hypoglycemia.

Besides hypoglycemia, another possible reason for the recurring failure of glucose-lowering strategies to improve CV prognosis is the use of fasting glucose or HbA_{1c} as the primary target of treatment. Postprandial hyperglycemia is associated with increased risk of CV events in patients with and without type 2 DM.[10,11] Even in the setting of controlled fasting glucose levels, postprandial spikes in glucose will powerfully increase risk of CV events.[10,11]

Taken together, these data suggest that the most logical and effective approaches to improve CV prognosis of type 2 DM would use therapies that (1) improve glycemic control without leading to hypoglycemia and (2) effectively lower postprandial glucose excursions. In fact, outcome data suggest that these 2 features are the common denominators of the therapeutic strategies that have been shown in prospective trials to reduce CV events. A lower all-cause mortality was reported in the metformin arm of the UKPDS 34 trial that randomized overweight or obese patients with type 2 DM to metformin or conventional therapy (primarily diet).[12] Metformin, as compared with a sulfonylurea or insulin, was associated with a greater risk reduction in all-cause mortality and stroke, but not MI, and a lower risk of hypoglycemia.[12] Proactive (PROspective pioglitAzone Clinical Trial In macroVascular Events) randomized patients with type 2 DM to receive pioglitazone or placebo in addition to standard of care during a 3-year period. A statistically significant improvement in the secondary end point of the composite of all-cause mortality, nonfatal MI, and stroke was noted in the pioglitazone arm.[13] The pioglitazone arm also showed a nonsignificant favorable trend in the primary end point of composite adverse CV and peripheral artery disease events.[13] The NIDDM (STOP-Noninsulin-Dependent Diabetes Mellitus) trial is a large randomized, placebo-controlled trial that assesses acarbose for preventing DM in patients with pre-DM.[14] Acarbose, a nonsystemic medication that decreases postprandial hyperglycemia by blocking α-glucosidase, was associated with a 49% lower risk of CV events during the 3.3-year randomized trial. Recent evidence provides promise for bile acid sequestrants, especially colesevelam, and bariatric surgery to safely improve glucose control and reduce clinical events in patients with DM.[15-17]

In conclusion, we agree with Dr Hirsh that the foremost treatment of DM is strict control of the associated CV risk factors, particularly hypertension and dyslipidemia. Glycemic control is important for preventing microvascular complications, such as retinopathy, nephropathy, and neuropathy, and may confer macrovascular CV benefits when optimal treatments are used in appropriate patients. However, controversy remains regarding the optimal targets for glucose control and whether specific agents are superior to others. The American Dietetic Association/American College of Cardiology/American Heart Association recommendations for HbA_{1c} target are less than 7%.[18] Available data suggest that aggressive control beyond this goal does not provide benefit and might be harmful, particularly in elderly patients with a long duration (>10 years) of DM and those with established CHD. In contrast, younger patients with relatively recently diagnosed DM and no known CHD might benefit from a more aggressive approach. Finally, a therapeutic strategy that targets postprandial hyperglycemia, while avoiding agents that cause hypoglycemia, seems to offer the best chance of improving long-term CV health in patients with type 2 DM.

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Optimal Medical Management of Acute Attacks of Acquired Angioedema

To the Editor: I read with great interest the article by Vanderschueren et al[1] in the September 2009 issue of *Mayo Clinic Proceedings* regarding monoclonal gammopathy of undetermined significance. The first case provided an excellent overview of the acquired form of angioedema. However, the authors were incorrect in their discussion of the treatment of this disease. It is correct that the first goal is to treat the underlying disorder. The second goal is long-term prophylaxis of acute attacks. This is most commonly achieved with antifibrinolytic agents such as tranexamic acid.

I disagree with their discourse on the medical management of acute attacks. Although the US Food and Drug Administration (FDA) has not approved medications for the indication of acute attacks of acquired angioedema, treatments are available. The preferred treatment is replacement of C1 inhibitor (C1-INH). This can be accomplished by giving either fresh frozen plasma or C1-INH concentrate. There has been a theoretical concern that fresh frozen plasma contains some of the substances, such as C4, that could potentially worsen the clinical course. However, this concern has not been substantiated clinically.[2] Cinryze (ViroPharma, Exton, PA), a C1-INH concentrate, was recently approved by the FDA for use in prophylactic treatment of hereditary angioedema (HAE).[3] Berinert P (CSL Behring, Marburg, Germany) is another form of C1-INH concentrate that has been available in some European countries for many years. It has an excellent track record for both prophylaxis and treatment of acute attacks.[4] Because acquired angioedema is often the result of hypercatabolism of C1-INH, one can assume that the dosing required for treatment of hypercatabolism would be higher than that for HAE.

Other, much-needed therapeutic options are on the horizon. DX-88 (Ecallantide, Dyax, Cambridge, MA) is a plasma kallikrein inhibitor, and full FDA approval is pending. The mechanism of this medication is to prevent the formation of bradykinin via the kallikrein-kinin system, which is normally inhibited by C1-INH.[3] Icatibant (Jerini, Berlin, Germany) is a synthetic decapeptide structurally similar to bradykinin that functions as a specific inhibitor to the bradykinin B_2 receptor, thus preventing the clinical picture of angioedema. Despite excellent initial study results, the medication was rejected by the FDA for acute attacks of HAE and is currently undergoing additional investigation.

Angioedema in all its forms is a complex disease process. The clinician must have a detailed understanding of its pathophysiology to appreciate the treatment options.

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In reply: I thank Dr Wilkerson for his valuable comments. The treatment of acquired angioedema is shaped after that of hereditary angioedema. However, the acquired form is even less prevalent than the hereditary form, precluding large-scale studies. Thus, current experience is mainly based on case reports and case series. It should be kept in mind that acquired angioedema or C1 inhibitor deficiency is immune-mediated. Thus, in contrast to patients with the hereditary form, patients with acquired angioedema may be partially resistant to C1 inhibitor substitution (given as a concentrate or as fresh frozen plasma) because of hypercatabolism. Theoretically, the problem of C1-inhibitor catabolism can be bypassed by products that inhibit the bradykinin pathway. However, to my knowledge, studies on these new agents in acquired C1-inhibitor deficiency are currently nonexistent.

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CORRECTIONS

Inaccurate statements: The Commentary by Hirsch entitled "Conflicts of Interest, Authorship, and Disclosures in Industry-Related Scientific Publications: The Tort Bar and Editorial Oversight of Medical Journals" published in the September 2009 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2009;84(9):811-821) contained the following inaccuracies.

1. Dr Egilman's income from serving as a medical expert in tort litigation, etc, was incorrectly reported as $20-$25 million during a 20-year period. Dr Egilman actually testified in court that it was $2-$2.5 million during that time. The source for the original statement in the Commentary was an online newspaper article dated July 31, 2005. The newspaper revised its report of the court testimony by Dr Egilman in a correction that was published *only* in the local, printed edition on August 2, 2005 (Michael Morris, oral communication, September 11, 2009).

2. Dr Egilman was not fined by a judge for leaking court-sealed documents concerning the Lilly-Zyprexa litigation. Rather, Dr Egilman and Lilly entered into an (Stipulated) agreement by US District Judge Jack Weinstein, filed September 9, 2007, in which Dr Egilman agreed to pay Lilly $100,000 and to dismiss his appeal of the Court's Final Judgment, Order and Injunction from February and March, 2007 (http://lawprofessors.typepad.com/tortsprof/files/EgilmanSettlement.pdf).

3. Dr Egilman has not testified in court in breast implant and connective tissue disease, or in antidepressant or antipsychotic drug cases. Dr Egilman did provide a sworn affidavit in one case involving local effects of leakage of silicone from breast implants (Vassallo F vs Baxter Healthcare Corporation. Decisions of the Supreme Judicial Court of Massachusetts. May 5-July 16, 1998, p. 7). In the Lilly-Zyprexa (antipsychotic) litigation, the Lanier law firm represented certain plaintiffs and retained Dr Egilman as an expert medical consultant. When the Lanier law firm learned that Dr Egilman had leaked court-sealed documents (as described in the Commentary), the firm terminated its consultancy with Dr Egilman (http://library.findlaw.com/2007/Mar/1/247065.html and http://technology.findlaw.com/resources/images/weinsteinzyprexainjunction.pdf, p. 27).

I regret these inaccuracies in my Commentary.

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Incorrect dosage: In the article by Merli and Litin entitled "Clinical Pearls in Thrombosis and Anticoagulation," published in the December 2009 issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2009:84(12):1120-1124), the dosage of enoxaparin was incorrect. The sentence on page 1121, left-hand column, under the heading "Clinical Pearl," should read as follows: For patients receiving once-daily therapeutic LMWH (200 IU/kg of dalteparin subcutaneously every 24 hours; **1.5 mg/kg of enoxaparin subcutaneously every 24 hours**; 175 IU/kg of tinzaparin subcutaneously every 24 hours), the dose 24 hours before surgery should be reduced by 50%.

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Incorrect headings in tables: In the article by Yawn et al entitled "Health Care Utilization and Cost Burden of Herpes Zoster in a Community Population," published in the September issue of *Mayo Clinic Proceedings* (*Mayo Clin Proc*. 2009:84(9):787-794)**,** some of the column headings in Tables 2 and 3 were incorrect. The headings in Tables 2 and 3 on pages 790 and 792, respectively, should read as follows: No. of patients, **Cost of hospital admissions ($)**, **Cost of ED visits ($)**, **Cost of outpatient visits ($)**, **Cost of prescribed medications ($)**, **Cost of procedures ($)**, Total health care cost ($) ± SE.

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