Physicians' Corner

In Search of the Holy Grail? The Quest to Reduce Macrovascular Disease in Type 2 Diabetes Mellitus

Commentary provided by Charles F. Shaefer, Jr., MD, FACP, FCCP
University Primary Care Physicians, Augusta, Georgia

Those of us who raised children, or who were children, during the era of the Indiana Jones series of movies surely recall the elusive quest for the Holy Grail in "Indiana Jones and the Last Crusade." Despite well-planned strategies and superhuman commitment, Indy, like centuries of knights before him, just couldn't obtain the grail. Diabetes practitioners must feel something like Indiana Jones these days. Intensive diabetes control based on low glycosylated hemoglobin (A1C) levels seems to promise the achievement of reduced macrovascular complications—our Holy Grail, but somehow this accomplishment stays just beyond our grasp. In the last year, with the impact of the ACCORD (Action to Control Cardiovascular Risk in Diabetes) study,[1] the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study,[2] and the VADT (Veterans Administration Diabetes Trial)[3] sinking in, it seems that straightforward reduction of cardiovascular events in our diabetic patients remains surprisingly elusive.

GOOD GLYCEMIC CONTROL VERSUS MACROVASCULAR RISK

Exciting studies such as the DCCT (Diabetes Control and Complications Trial)[4] in type 1 diabetes mellitus (DM) and the UKPDS (United Kingdom Prospective Diabetes Study)[5] in type 2 DM showed us over a decade ago that tight glycemic control as measured by A1C can significantly reduce microvascular disease. Both of these studies aimed to lower A1C to <7%. This standard has become widely accepted by authoritative groups,[6,7] as well as practitioners. In my practice life, I have personally appreciated the impact of intensive control on microvascular disease, as I now see much less need for dialysis and fewer eye complications in diabetic patients compared with 2 decades ago.

With the UKPDS study, it appeared that tight glycemic control might also reduce macrovascular complications. In this study, every 1% reduction in A1C seemed to reduce macrovascular complications by 16%,[5] a very appealing prospect! This reduction in macrovascular disease resulting from intensive control of glucose levels appeared to parallel epidemiologic data, which clearly suggest that any increase in blood glucose contributes to increased cardiovascular events. For example, the East Anglican component of the European Prospective Investigation into Cancer (NORFOLK-EPIC) study showed that increasing A1C, even across the range regarded as normal, is associated with a steady rise in cardiovascular events and death.[8] People with diabetes are known to have a 3- to 4-fold increased risk for heart disease.[9] And when we recall that 80% of our patients with type 2 DM will experience a stroke or heart attack and that 66% of this group will die from the first event,[10] it seems extremely important to try aggressively to reduce this risk.

OOPS!

The ACCORD,[1] ADVANCE,[2] and VADT[3] studies all set out to show that, as anticipated, intensive control of A1C would do exactly what was needed—reduce cardiovascular events and death. Each study varied in the methods used and outcomes studied, but they were all centrally aimed at aggressively lowering A1C levels by using a variety of oral therapies and intensive insulin therapy, wherever needed, to lower A1C to intensive target levels. To our surprise and disappointment, in none of these studies was it clear that lowering A1C alone resulted in blanket improvement in the incidence of cardiovascular events or death! The ACCORD study[1] was even stopped early because there was an unexpected increase in cardiovascular deaths in the tightly controlled arm. In fact, the group aiming to lower A1C values to <6% experienced a 20% increase in mortality; but the data did not suggest that an A1C of <7% alone is a sole predictor of mortality risk. What seemed to be so intuitive, that lowering A1C levels would lower cardiovascular events, is actually proving to be as elusive as the Holy Grail.

The ADVANCE study[2] was encouraging in that it showed an overall benefit for the tightly controlled group; but that benefit came in the form of improvements in renal complications, not in reductions in cardiovascular events. The VADT[3] showed that intensified diabetes control reduced the risk of cardiovascular events provided that the therapy was initiated in the first 15 years after diagnosis. Interestingly, if such intensive therapy was started 16 to 20 years after diagnosis, there was no benefit regarding cardiovascular event reduction. In a VADT update,[11] it was shown that beyond

20 years after diagnosis, initiation of intensive therapy was associated with an increased risk of cardiovascular events. Obviously, these studies did not crystallize a clearly proven strategy to reduce macrovascular complications in type 2 DM.

In the wake of these 3 large studies, some practitioners have become uncertain of how to proceed. Some have interpreted the data to suggest that lower A1C levels are not desirable. Some have extrapolated that certain drugs or combinations of therapy are potentially problematic. There have been questions about the possible impact of hypoglycemia or weight gain on cardiovascular events. Unfortunately, further analyses[12] have not provided clear answers to these questions.

IT'S COMPLICATED

Based on the results of the ACCORD study, the impact of A1C control on cardiovascular outcomes is somewhat complicated. In the ACCORD study,[12] the more the A1C level fell in the first year of therapy, regardless of end point, the lower the risk of death. But, interestingly, the increased risk of cardiovascular death observed in the intensively treated group was seen in those subjects with an A1C >7% rather than in those achieving the intensive goal of <7%. It seems that those who respond readily to intensive therapy, as measured by a swift reduction in A1C, do well, whereas those who are refractory to intensive therapy, as indicated by an A1C level that does not reduce rapidly, seem to do more poorly. It is, therefore, the responsiveness of the individual to therapy that seems to matter more than does an intensive reduction of the A1C level itself.

The authors of the ACCORD and ADVANCE studies were quick to point out that these studies were not aimed at evaluating the benefit of one therapy over another. Similarly, these studies were not designed to assess the impact of hypoglycemia or weight on cardiovascular outcome. The ACCORD investigators have reported that studies looking at the impact of hypoglycemia and weight gain on treatment strategies are ongoing.[12]

IS HYPOGLYCEMIA AN OMINOUS PREDICTOR?

The issue of hypoglycemia has received a great deal of attention in the wake of these studies, and it needs the attention of health care practitioners. Hypoglycemia was clearly seen to affect outcomes in the VADT.[3] In that study, individuals who had a hypoglycemic event severe enough to cause a change in consciousness had an 88% increase in cardiovascular events and a 3-fold increase in cardiovascular death. This impact was seen in the standard-care and the intensive-care groups alike. The ACCORD study[1] showed surprisingly similar results. Severe hypoglycemia was associated with a higher risk of death with both standard and intensive treatment, but the impact was greater in the standard-care group. When it comes to cardiovascular risk, hypoglycemia seems to be an ominous predictor no matter what the treatment regimen.

HOW DO WE REDUCE MACROVASCULAR RISK?

So what does all this mean to the practicing clinician? How are we to go about reducing the risk of the very complication—macrovascular disease—that is most likely to afflict and even kill our type 2 DM patients? Let's try to glean some guidance from the studies we have just reviewed and then synthesize a treatment strategy from this information (**Table**),[1–3,12] although the information may seem initially confusing.

First, while there are few specific clinical outcomes data supporting reduction of A1C levels toward normal (ie, <6%) to achieve reduction of adverse cardiovascular events, there are also no convincing data to abandon the currently held

Table. Lessons in cardioprotective benefit gleaned from recent trials.[1–3,12]

- Control A1C: Target goals are <7% (ADA) or <6.5% (AACE).
- Individualize therapy: Duration and initial severity of disease matters.
- Initiate intensive therapy early on.
- Treat comorbid conditions: Blood pressure and lipid levels also need to be controlled.
- Avoid hypoglycemia: It is an ominous predictor of adverse cardiovascular events.
- Avoid weight gain: Studies are ongoing to clarify the impact of treatment-related weight gain, but it may be associated with adverse cardiovascular events.

A1C = glycosylated hemoglobin; ADA = American Diabetes Association; AACE = American Association of Clinical Endocrinologists.