

Physicians' Corner

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

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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 super-human 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 Diamicon 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 Anglian 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 VADT³ 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 study¹ 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 study² 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 VADT³ 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 analyses¹² 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 study¹ 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.

American Diabetes Association (ADA) A1C goal of <7%.¹² Clearly, subjects in the ACCORD study¹ who were able to lower their A1C levels toward normal with ease in the first year of treatment did have a lower risk of death. Conversely, the risk of death was greater for subjects in the intensive treatment arm of the study whose A1C levels were >8.5%. All things considered, A1C <7% remains a viable goal.

Second, while no specific therapy used in the ACCORD study¹ or the VADT³ was found to be uniquely beneficial in reducing adverse cardiovascular events (remember, these studies were done before clinical use of incretin therapies), hypoglycemia was found to be an adverse predictor whether an individual was undergoing standard or intensive forms of therapy. Certainly, these findings should lead us to carefully craft therapeutic strategies that are aimed at avoiding hypoglycemia in any patient.

Third, it appears that cardiovascular outcomes in type 2 DM depend more on the duration of the disease than on whether one is given intensive therapy or standard treatment. The VADT³ particularly points out how important early detection of and intervention for type 2 DM is to successfully affect cardiovascular risk. To put the VADT diagnostic timelines in perspective, one must consider 2 interesting observations: (1) elevated blood glucose levels may exist as prediabetes for 5 to 10 years before diagnosis¹³; and (2) once diagnosed, the average American with type 2 DM remains at an A1C level >8.5% for >9 years.¹⁴ The results of the VADT seem to indicate that the ability to reduce cardiovascular events is lost ~15 years after diagnosis. Therefore, early detection of type 2 DM and timely control of A1C may be significantly beneficial to reduce cardiovascular events.

Finally, while these studies did not address specific therapies as being particularly beneficial or harmful with regard to cardiovascular outcomes, studies investigating these issues are ongoing.¹² We may learn which of our established therapies are best suited to reducing cardiovascular events. Furthermore, we now have 2 other types of therapy—the dipeptidyl peptidase (DPP)-4 inhibitors¹⁵ and the incretin mimetics.¹⁶ These agents were not included widely in the ACCORD or ADVANCE studies, or in the VADT. Although there is not yet a wealth of clinical outcomes trials, it is possible that wise selection of therapy may have substantial benefit for cardiovascular protection.

DOES THERAPEUTIC CHOICE MATTER?

Several years ago, the DIGAMI (Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction) study¹⁷ pointed to a cardioprotective benefit for an intensive insulin regimen after acute myocardial infarction. The PROACTIVE (PROspective pioglitAzone Clinical Trial In macroVascular Events) study¹⁸ showed a cardiovascular protective benefit with pioglitazone, although this benefit fell short of statistical significance owing to some surprisingly poor peripheral arterial outcomes. The CHICAGO (Carotid Intima-Media Thickness in Atherosclerosis Using Pioglitazone)¹⁹ and PERISCOPE (Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation)²⁰ trials also showed some benefit with pioglitazone compared with glimepiride to improve surrogate markers of coronary occlusion in otherwise well-treated type 2 DM patients. In the UKPDS,⁵ metformin was shown to reduce cardiovascular events. It seems obvious, therefore, that careful selection of therapies might have an impact on cardiovascular event risk.

Treatment strategies for type 2 DM involving a combination of metformin, possibly an additional oral agent, and early insulin use are now widely recommended.²¹ With the newly appreciated concerns about hypoglycemia,¹² selection of an insulin product is quite critical. Basal or rapid-acting analogue insulins clearly are associated with less hypoglycemia than are neutral protamine Hagedorn (NPH) insulin, recombinant human insulin (RHI), or premixed derivatives.^{22–24} The ORIGIN (Outcome Reduction with Initial Glargine INtervention) trial²⁵ is currently in progress and should shed tremendous light on whether early insulin therapy is beneficial for cardiovascular event reduction.

NEW HORIZONS

It is also possible that new therapeutic agents may reduce macrovascular risk. In my opinion, an ideal diabetic treatment strategy might conceivably be an agent or combination of agents that: (1) would be readily accepted by the patient soon after diagnosis; (2) could drop the A1C level to <7%; (3) would have little or no likelihood of hypoglycemia; and (4) would have evidence-based data about cardiovascular event protection. Ideally, the agent or combination of agents would also be weight neutral or weight reducing, in light of the ADA standard of care with regard to weight.²⁶ The newer agents that are currently on the market, the DPP-4 inhibitors sitagliptin and saxagliptin¹⁵ and the incretin mimetic exenatide,¹⁶ come close to fulfilling these ideal properties, especially when these agents are combined with metformin.

Recent studies^{27,28} have shown promising data with regard to the impact of exenatide on cardiovascular protection. In a study by Klonoff et al,²⁷ exenatide was shown to significantly lower systolic blood pressure, diastolic blood pressure, total cholesterol, triglycerides, low-density lipoprotein cholesterol, and weight. It was also associated with an increase in high-density lipoprotein (HDL) cholesterol. Another study by Bergenstal et al²⁸ has shown that use of exena-

tide improves an array of cardiovascular risk markers, including plasminogen activator inhibitor-1, high-sensitivity C-reactive protein, albumin-creatinine ratio, and B-type natriuretic peptide (BNP). Animal data²⁹ have suggested that exenatide can limit ischemic infarct size.

One of the currently available DPP-4 inhibitors, sitagliptin, was approved several years ago, before the US Food and Drug Administration started requiring stringent cardiovascular outcomes data for approval, so there are not a great deal of cardiovascular data available for this agent. However, some very interesting cardiovascular data have been gathered on the more recently approved DPP-4 inhibitor, saxagliptin. In a late-breaking poster displayed at the 69th Scientific Sessions of the ADA,³⁰ saxagliptin was shown to reduce cardiovascular events by ~50% in almost every category of at-risk patient. Although many details are not yet known about this study, at first pass the data seem quite intriguing.

While the quest to significantly reduce cardiovascular disease currently seems as elusive as the Holy Grail, there may be new hope on the horizon. Just blindly forcing A1C to a lower level clearly does not seem to be the answer. More effective strategies will be those that are individualized for each patient. The successful provider will have to consider the duration of disease, the initial elevation of A1C, and how quickly the patient's A1C level is lowered. The VADT also showed that a major factor in decreasing mortality risk was the HDL cholesterol level,³ a reminder of the excellent cardiovascular risk reduction demonstrated in type 2 DM patients in the Steno-II study,³¹ which focused on control of A1C (<6.5%), cholesterol, and blood pressure levels. The provider will need to track response to treatment carefully and adapt treatment strategies to the patient's progress. Newer agents like the DPP-4 inhibitors and incretin mimetics may contribute an additional layer of cardiovascular protection.

CONCLUSIONS

Much like the knights of medieval times who pursued the Holy Grail, true enlightenment in the successful treatment of type 2 DM will come from asking the right questions while seeking the elusive perfect therapy. Providers should question who they are treating (the individual patient), how they are treating that patient, what else is going on with the patient's health parallel to the diabetes treatment, and how the patient is progressing. While we may one day uncover the Holy Grail of diabetes treatment and thereby find the key to eliminating macrovascular risks for our patients, for the time being, we need to find joy in the prosecution of the journey, as we discover more about reducing risks and introduce promising new therapies. Like the Indiana Jones saga, I'm pretty sure there will be a sequel.

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