New Research on Type 2 Diabetes

(One Size Does Not Fit All)

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Those of us who treat type 2 diabetes are aware that over the last year or so multiple studies have been published on the management of this devastating, complicated and expensive disease. The acronyms for the studies and what their research findings showed are presented herein with a summary of what might be considered a 2009 "bottom line" for the clinician and the patient.

1. UKPDS-33 (THE LANCET 1998 SEP 12;352:837.)

This United Kingdom Prospective Diabetes Study was, of course, a sentinel study on diabetes, and it is included here to form the basis for the newer studies. In essence, the authors concluded that intensive control with either sulfonylureas or insulin in the study's 3,867 patients with type 2 diabetes decreased the risk of microvascular complications (retinopathy, nephropathy, and neuropathy), but not macrovascular ones (MI, stroke, death from cardiovascular causes). Most of the microvascular improvement was manifest by reduced need for photocoagulation of the retina. None of the individual drugs had an adverse effect on cardiovascular (CV) outcomes. There was *no* decrease in diabetes-related mortality in the intensive group, and all intensive treatments increased the risk of hypoglycemia. The hemoglobin A_{1C} was 7.0 in the intensive treatment group and 7.9 in the conventional group. Weight gain was significantly higher in the intensive group as well as in patients assigned to receive insulin.

2. STENO-2 (NEJM 2008 FEB 7;358:580.)

This study from The Steno Diabetes Center of Denmark had only 160 patients with Type 2 diabetes and persistent microalbuminuria. They received either intensive or conventional therapy for a mean of 7.8 years, with an additional 5.8 years of follow-up. In the intensively treated patients, who received multiple drug combinations and behavior modification, there were sustained beneficial effects with respect to vascular complications, all-cause mortality, and death from cardiovascular causes. The main concern was the study's lack of generalizability because of its very small size.

3. ACCORD (NEJM 2008 JUN 12;358:2545.)

The Action to Control Cardiovascular Risk in Diabetes Study randomized 10,251 patients to conventional vs. intensive therapy (target $A_{1C} < 6.0\%$) for 3.5 years. In a major surprise, intensive therapy in this study increased mortality and did not significantly reduce major cardiovascular events, forcing early termination of the study. Hypoglycemia requiring assistance, and weight gain of more than 10 kg, were *again* found in the intensive group.

4. ADVANCE (NEJM 2008 JUN 12;358:2560.)

The Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation followed 11,140 randomized patients for a median of 5 years. The target A_{1C} in the intensive treatment group was 6.5% or less; the mean A_{1C} for the control standard treatment group was 7.3%. The intensive control group received gliclazide (modified release) and other drugs, if required. This regimen achieved a 10% relative reduction in the combined outcome of major macrovascular and microvascular events, primarily as a consequence of a 21% relative reduction in nephropathy, but there was no significant decrease in cardiovascular outcomes.

5. UKPDS (NEJM 2008 OCT 9;359:1577.)

This is the most recent United Kingdom Prospective Diabetes Study with a ten-year follow-up of intensive glucose control in 4,209 patients randomly assigned to either conventional therapy (dietary restriction) or intensive therapy (either sulfonylurea or insulin or, in overweight patients, metformin). There were no A_{1C} differences between groups after the first year. Despite this, continued reductions in microvascular risk and acute MI and death from any cause were observed. A continued benefit with metformin therapy was evident among overweight patients. Strategies for cardiovascular risk reduction in type 2 diabetes emphasized the importance of lipid-lowering therapy with statins and of targeted antihypertensive treatment. (A companion article in the same issue of the NEJM reports the ten year, post-interventional data on blood pressure control from the UKPDS.)

6. VADT (NEJM 2009(2);360:129.)

This Veterans Administration study of 1,700 randomized patients found that tight glucose control does not reduce the risk of macrovascular complications and may actually increase all-cause mortality in type 2 diabetes. The average A_{1C} in the intensive group was 6.9% versus 8.4% in the group that received usual treatment. The difference remained stable throughout the study but there was no difference in all-cause mortality, cardiovascular outcomes, progression of retinopathy, nephropathy, time to first cardiovascular event, or individual macrovascular outcomes.

7. HEART 2 D (DIABETES CARE 2009 MAR;32(3):521.)

This multinational randomized study of 1,115 patients was designed to compare the effects of prandial vs fasting glycemic control on the risks of cardiovascular outcomes in diabetics after an MI. The *Prandial* strategy targeted control of postprandial glycemia with administration of mealtime, thrice-daily insulin lispro (Humalog, Eli Lilly). The *Basal* strategy targeted fasting/interprandial glycemia with NPH insulin twice daily (Humulin, Eli Lilly), or insulin glargine once daily (Lantus, Sanofi-Aventis). Treatment of MI survivors with a prandial or basal strategy achieved similar levels of A_{1C} and no difference in risk of future cardiovascular events. The trial was stopped after a mean patient participation of 963 days (2.6 years) due to lack of efficacy.

8. NICE-SUGAR (NEJM 2009 MAR;360:1346.)

This study randomized over 6,000 critically ill patients (63% medical; 37% surgical) to either intensive glucose control (target 81–108 mg/dL) or conventional glucose control (144–180 mg/dL), using insulin infusions. The primary endpoint – death within 90 days after randomization – occurred significantly more often in the intensive group (number needed to harm, 38). Severe hypoglycemia was more common in the intensive group. The conclusion is that the aim of treatment should be "reasonable control" of blood sugar with a target in the mid 100's.

CONCLUSIONS

There are limits and deficiencies in all trials and studies, including those above. Though space does not allow us to go into the myriad intricacies of each study, where does this leave us in the treatment of our type 2 diabetic patients in 2009? As a result of the prior studies, a position statement was published jointly in the January 2009 issue of Diabetes Care by The American Diabetes Association (ADA), The American Heart Association (AHA), and The American College of Cardiology. (This can be viewed free at http://care.diabetesjournals.org.)

All groups advocate hypertension control, glycemic control, aspirin therapy, lowering lipids with statins, cessation of smoking, as well as other lifestyle changes to decrease cardiovascular disease (CVD) in diabetics. The lack of significant reduction in CVD with intensive therapy in the ACCORD, ADVANCE, and VADT randomized trials should not cause us to disregard the A_{1C} goal of less than 7.0% in most patients. There *is* a benefit for microvascular risks, especially retinopathy and perhaps nephropathy. For macrovascular risks, however, it appears that – as with microvascular complications - glycemic control plays a greater role before macrovascular disease is well developed.

However, the statement acknowledges that the goal of less than 7.0% A_{1C} may NOT be appropriate for some patients. Intensive glucose control may be more of a risk than a benefit in patients with long standing diabetes, a history of prolonged hypoglycemia, advanced microvascular or macrovascular disease, or any advanced disease that limits life expectancy. Indeed, a recent study (JAMA, 4/15/09) in over 16,000 Kaiser Permanente patients showed that severe hypoglycemic episodes (requiring admission or an ER visit) are associated with an increased risk of dementia among older (mean age 74) patients. Those with one episode were 26% more likely to develop dementia, with two episodes – 80%, and those with three episodes had a 94% greater risk of dementia. The results of an online review in the Annals of Internal Medicine (4/20/09) support the recommendation that tight glycemic control may not be in the best interest of all type 2 diabetics.

In the same issue of Diabetes Care mentioned above, a consensus statement from the ADA and The European Association For the Study of Diabetes provides a three-step algorithm for treatment:

- *Step 1* – Lifestyle changes and metformin (No metformin over age 85 or at any age if the creatinine ≥ 1.4 in women or ≥ 1.5 in men.)
- *Step 2* – If no control within 2–3 months, add insulin (especially if $A_{1C} > 8.5$) or a sulfonylurea
- *Step 3* – Start or intensify insulin and stop the sulfonylurea

Other oral agents should be used only in special clinical settings. This consensus group was against using

rosiglitazone (Avandia) due to potential cardiovascular risks. They also cautioned that both Avandia as well as pioglitazone (Actos) can increase the risk of fluid retention, congestive heart failure, and fractures in women and maybe men.

The bottom line is that type 2 diabetes in 2009 requires a comprehensive, thoughtful, multifactorial approach to treatment and that the goal of <7.0% A_{1C} in some (as previously described above) is not the "end all" number, just because the "auditors" expect us to attain it.

EDITORS NOTE

I have written previously to question the current popularity of acronyms for large, multi-institutional trials that not only give no indication of the studies' content, but are different from the concise original title of the published article.[1] *Since these constructed titles are developed to fit the acronym, they are almost always syntactically awkward, are often rather distorted, and – in the most egregious cases – can actually misstate a trial's design. Letters are often selected from arbitrary locations to fit the acronym by hopscotching through the artificial title.*

The ADVANCE trial's actual published title was Intensive Blood Glucose Control and Vascular Outcomes in Patients with Type 2 Diabetes. The acronym is derived from ***A****ction in* ***D****iabetes and* ***V****ascular Disease: Preterax* ***an****d Diamicron Modified Release* ***C****ontrolled* ***E****valuation.*

The HEART 2 D study was published as Effects of Prandial Versus Fasting Glycemia on Cardiovascular Outcomes in Type 2 Diabetes: The HEART2D trial. The acronym is derived from: ***H****yperglycemia and Its* ***E****ffect* ***A****fte****r*** *Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With* ***T****ype* ***2 D****iabetes.*

The NICE-SUGAR study was published as Intensive versus Conventional Glucose Control in Critically Ill Patients. The acronym is derived from ***N****ormoglycemic in* ***I****ntensive* ***C****are* ***E****valuation and* ***S****urvival* ***U****sing* ***G****lucose* ***A****lgorithm* ***R****egulation. Though the new title is more distorted than many, at least the word SUGAR in the acronym indicates that the study involves diabetes, and the acronym is derived from first letters, rather than from those selected by skipping along (see the ADVANCE Trial above).*

REFERENCES

1. Bonchek LI. What's in a Name? A Critique of Procrustean Acronyms. J Lanc Gen Hosp. 2008;3:82-83.

Neither Dr. Peterson nor any member of his immediate family have any relevant relationships with any corporate organizations associated with the manufacture, license, sale, distribution or promotion of a drug or device to disclose.

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