WHAT'S HOT IN... MEDICINE , May/Jun 2009

2008/09 Trials Ignite Debate about Regimen for Type 2 Diabetes

by David W. Sharp

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Citations processed in the last two months of 2008 are dominated by diabetes and insulin. At #4, #5, and #9 we have the genetics of this disease; at #6 lies the antidiabetic drug rosiglitazone; still outside the Top Ten but rising at #15 is the *New England Journal of Medicine* paper by Brunkhorst *et al.* discussed in the March/April issue (20[2]: 5, 2009); and now we have two newcomers, related trials with differing results but very similar citation records. The study called ADVANCE, an acronym of astonishing clumsiness even for this genre, is at #11 (A. Patel, *et al.*, *New Engl. J. Med.*, 358 [24]: 256-72, 2008; total cites 67, latest count 45), while at #8 is ACCORD (Action to Control Cardiovascular Risk in Diabetes). At the time of counting these papers had been in print for only six months.

Insulin

Before looking at the above two newcomers let us tidy up something from the previous *Science Watch*. Studies of intensive blood-glucose control in intensive-care settings had indicated that there could be problems with this approach. A clearer picture was expected from the results of a large international trial, not then published. It is now. The NICE-SUGAR investigators (S. Finfer, *et al.*, *New Engl. J. Med.*, 360[13]: 1283-97, 2009)

Medicine Top Ten Papers

Rank	Papers	Cites This Period Nov-Dec 08	Rank Last Period Sep-Oct 08
1	J. Yu, *et al.*, "Induced pluripotent stem cell lines derived from human somatic cells," *Science*, 318(5858): 1917-20, 21 December 2007. [Genome Ctr. Wisconsin, Madison; U. Wisconsin, Madison] *243HE	87	5
2	R.J. Motzer, *et al.*, "Sunitinib versus interferon alfa in metastatic renal-cell carcinoma," *New Engl. J. Med.*, 356(2): 115-24, 11 January 2007. [10 institutions worldwide] *124NE	65	1
3	B. Escudier, *et al.*, "Sorafenib in advanced clear-cell renal-cell carcinoma," *New Engl. J. Med.*, 356(2): 125-34, 11 January 2007. [15 institutions worldwide] *124NE	63	2
4	L.J. Scott, *et al.*, "A genome-wide association study of type 2 diabetes in Finns detects multiple susceptibility variants," *Science*, 316(5829): 1341-5, 1 June 2007. [12 U.S. and Finland institutions] *173PS	63	8
5	E. Zeggini, *et al.*, "Replication of genome-wide association signals in UK samples reveals risk loci for type 2 diabetes," *Science*, 316(5829): 1336-41, 1 June 2007. [10 U.K. institutions] *173PS	56	9

compared glucose targets of 4.5-6.0 mmol/L (intensive control) and 10.0 mmol/L or less (conventional) and found that mortality was significantly higher in the intensive group; so was the frequency of severe hypoglycemia. This trial increases by about a half the number of patients available for a meta-analysis, and that too has been re-done (D.E. Griesdale, *et al.*, *Can. Med. Assoc. J.*, e-pub March 24, 2009). In 26 trials mortality was not significantly different for intensive-care patients put on intensive or conventional insulin regimens for glucose control. The latest meta-analysis suggests a benefit for intensive insulin in surgical intensive care while NICE-SUGAR found no difference here.

The American Diabetes Association and the American Association of Clinical Endocrinologists, in a joint statement in March 2009, expressed worry lest NICE-SUGAR "swing[s] the pendulum of glucose control too far in the other direction" so that hospital staff become "complacent" about uncontrolled hyperglycemia with its attendant risks of dehydration and infection. A similar concern accompanies publication of the ADVANCE and ACCORD studies (#11 and #8) of more stringent targets for blood glucose in patients with type 2 diabetes. ACCORD compared targets of below 6.0% and 7.0-7.9% for glycated hemoglobin but the trial was stopped when a significant increase in mortality in the intensive group emerged. Such a mortality difference was not found in ADVANCE, and rates of major macrovascular events such as fatal and non-fatal myocardial infarctions did not differ between the two treatment groups. In ADVANCE the primary endpoint was a combination of the microvascular and the macrovascular, but it is the effect of glucose lowering on the latter that physicians need the answer to.

6	S.E. Nissen, K. Wolski, "Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes," *New Engl. J. Med.*, 356(24): 2457-71, 14 June 2007. [Cleveland Clinic, OH] *178DR	55	3
7	T.M. Frayling, *et al.*, "A common variant in the *FTO* gene is associated with body mass index and predisposes to childhood and adult obesity," *Science*, 316(5826): 889-94, 11 May 2007. [19 institutions worldwide] *166HM	53	7
8	The ACCORD Study Group (H. C. Gerstein, *et al.*), "Effects of intensive glucose lowering in type 2 diabetes," *New Engl. J. Med.*, 358(23): 2545-59, 12 June 2008. [Writing Group: 10 U.S. and Canadian institutions] *311IJ	49	†
9	R. Sladek, *et al.*, "A genome-wide association study identifies novel risk loci for type 2 diabetes," *Nature*, 445(7130): 881-5, 22 February 2007. [14 institutions worldwide] *138CR	48	6
10	G. Hudes, *et al.*, "Temsirolimus, interferon alpha, or both for advanced renal-cell carcinoma," *New Engl. J. Med.*, 356(22): 2271-81, 31 May 2007. [17 institutions worldwide] *172PO	45	4

SOURCE: Thomson Reuters Hot Papers Database. Read the Legend.

In recent years there has been much pressure to produce guidelines for good practice in the management of patients with specific diseases. The ACCORD study group set the scene for their trial with the argument that although there are plenty of hints that lowering glycated hemoglobin levels (a standard measure of disease severity in diabetes) should reduce the risk of cardiovascular events, guidelines recommending near-normal levels as a target for therapy have lacked the support of large randomized trials. ACCORD is such a trial and so is ADVANCE, with more than 10,000 patients taking part in each. There are many differences between the two studies, conveniently tabulated in the first of two accompanying editorials (R.G. Dluhy, G.T. McMahon, *New Engl. J. Med.*, 358[24]: 2630-3, 2008) and providing fuel for much further discussion. The rapid rise in the citation listings is hardly surprising. The results will be seen by many as negative, but guidelines have not changed overnight and commentators on ACCORD and ADVANCE have been stressing the need for judgement in individual cases; that glucose targets should not be abandoned; and that more could be done about cholesterol and blood-pressure levels in the battle against cardiovascular disease in people with type 2 diabetes.

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