

Can We Win the Battle Against Diabetes?



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In 1927, E.P. Joslin (*Ann Clin Med* 1927; 5:1061-1080) made a profound comment that has since been proven correct. Joslin stated, “With an excess of fat, diabetes begins and from an excess of fat, diabetics die; formerly of coma, recently of arteriosclerosis.” The most fascinating point in this quote was that, the year in which it was written, Joslin did not know of antidiabetic therapy or that its administration could reduce mortality and arteriosclerosis. The standard of care was to focus on hyperglycemia. Today, the United Kingdom Prospective Diabetes Study (UKPDS) has shown that antihyperglycemic therapy yields no statistically significant, positive effect on macrovascular events such as stroke and MI (please refer to the article by David Lau starting on page 4). In fact, though not all diabetics have elevated LDL, the treatment of diabetics with an antidiabetic therapy has been shown to reduce mortality in the recent CARDS study. This effect goes beyond that of lipid lowering and is thought to be attributable to the pleiotropic (action that is unrelated to that of the original indication) effect of the medication.

Alternatively, by administering antihypertensive agents such as ACE inhibitors or ARBs, these agents have shown benefits that many of the glycemic-control agents have not been able to produce. In fact, when a patient has diabetes but does not have hypertension (as in the patients of the HOPE study) the use of an ACE inhibitor can reduce CV events. The dramatic reduction (23%) in new onset diabetes in studies such as VALUE opens up a new concept: that diabetes can possibly be prevented. Similar findings utilizing ARBs were seen in CHARM and LIFE, supporting the concept that the induction/progression of diabetes is multifactorial, with an angiotensin/angiotensin receptor component. As mentioned by Dr. Lau, CRP also plays a role in diabetes, mediating its effect in part through the AT1 receptor; adding further understanding to how these agents are able to achieve their benefit. As a result, studies still in progress, such as NAVIGATOR and DREAM, are powered to define if an ARB, an ACE inhibitor, glitazone, or oral insulin secretagogue are able to reduce or delay the onset of diabetes and CV disease in an impaired-glucose-tolerant population.

Not all CV treatment agents have positive pleiotropic effects. Agents such as diuretics were shown to increase the incidence of developing diabetes (30% to 43%) in the ALLHAT study, confirming the concept that the pleiotropic positive effects of all antihypertensives are not a class effect. This is important as Verdecchia (*Hypertension* 2004) demonstrated that patients with new or prior diabetes have a three-fold higher likelihood to have a CV event compared to those without diabetes. Dose also plays a role, as a recent British study was unable to reproduce the benefits of the HOPE study. The conclusion made by the authors was that, although hypertension was controlled at the lower dose, the pleiotropic effects seen in HOPE require the full dose of ACE inhibitors.

With the increasing concern of high pharmaceutical costs, there is a heightened need to define which treatments (and at what dose) are able to provide mortality benefits. Put another way, the concept of “two birds with one stone” applies to the treatment of diabetes, as this concept has marked pharmacoeconomic implications. By implementing evidence-based medicine, as reflected in CARDS, VALUE, HOPE, etc., we are now able to utilize therapeutic agents that not only achieve their primary indication, but are also able to provide multiple unrelated benefits (through their pleiotropic effects) that can reduce healthcare costs and utilization in the long term. ☺

A handwritten signature in black ink that reads "Peter Wozniak". The signature is stylized and written in cursive.

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