Diabetes, Glycemia and Cardiovascular Disease: Is it Time to Rethink the Regulatory Approach?

Reducing complications of diabetes mellitus (DM) such as cardiovascular disease (CVD) is a multifaceted dilemma. Several CVD factors are associated with DM, and often, the data that concern these factors conflict. Current US Food and Drug Administration (FDA) regulations handle new diabetes drugs in a similar manner to other drugs that are submitted for approval. While there are potential concerns about the current approach to drug approval for diabetes medications, there are also valid arguments for retaining the regulatory status quo.

Reducing blood glucose levels in diabetes may not be the answer to overall risk reduction. In fact, the use of "surrogate" endpoints such as glucose and lipid lowering may result in premature approval of drugs that may actually increase risk. In the case of the dual peroxisome proliferators-activated receptor, muraglitazar, the FDA advisory committee voted 8 to 1 in favor of approval of the drug as monotherapy (7:1 approval for use with metformin and 7:2 against approval for use with sulfonylureas) based on laboratory endpoints. However, these endpoints did not predict CV outcomes and further evaluation brought to light an excess incidence of major adverse CV events that were associated with muraglitazar treatment. The approval process for muraglitazar was subsequently halted. As seen in this example, glucose-lowering medications may increase macrovascular risk in some instances [Nissen SE et al. *JAMA* 2005].

Additionally, the method in which blood glucose levels are lowered may play a role in CV risk. Similar drugs (even within the same class) may have diverse effects on CV outcomes. In the ACCORD trial, the rate of all-cause death and death from CV causes was significantly higher in the intensive-therapy group compared with the standard-therapy group (p=0.04 for all-cause and p=0.02 for CV-related death) [The ACCORD Study Group. *N Engl J Med* 2008]. Of note, more patients in the intensive-therapy group received repaglinide, rosiglitazone, insulin and/or an alpha glucosidase inhibitor than in the standard-therapy group. The source of this excess in mortality remains unclear, as there were too many therapies involved to determine individual effects with accuracy.

Randomized trials that were designed to evaluate CV outcomes may provide necessary data for the approval process. Meta-analyses and *post hoc* data may not be robust enough to establish CV risk in diabetes drugs. Current regulatory policy remains focused on the glucose-lowering aspect of diabetes drugs that await approval but there is an absence of hard data that are related to CV outcomes.

A new regulatory approach that may fulfill the need for more robust clinical outcome data without delaying the approval of new diabetes therapies may be in order. A pre-approval set of clinical trials that are designed to rule out a high level of CV risk (ie, HR>18) with larger outcome trials following approval that may rule out a lower level of CV risk (ie, HR>1.3) may ameliorate the regulatory gap. This method may encourage trialists to include higher-risk patients in their pre-approval studies and provide more reliable data with regards to CV events for pooled trials. Though this method may initially delay approval by 6 to 12 months, it has the potential to drastically reduce CV morbidity and mortality by providing comprehensive data that concern medication-associated CV risk profiles.

While the concept of "safe is better than sorry" is certainly a legitimate edict, there is another perspective with regard to CV risk in the setting of diabetes management and the regulatory debate.

First, there is currently no evidence that establishes that glucose dysregulation is intrinsically harmful to CV health. Much of the data that are available imply risk, but this is not consistently the case. While the exception may disprove the rule in certain instances, the issue is not quite so black and white and some ambiguity remains about CV outcomes that are related to diabetes drug treatment.

It is also important to be aware of the FDA regulations as they currently stand so as not to misinterpret the regulatory mission. According to regulatory guidelines, CV risk should not be substantially *increased* as a result of drug therapy. However, there is nothing in the current guidelines about *decreasing* CV risk. The current focus remains on significant risk exclusion rather than risk reduction and this aim may be the more reasonable approach. Unacceptable risk assessment as it applies to clinical trial design is handled differently than CV benefit assessment and most trials are not powered to evaluate both. Evaluation of CV benefit requires considerably more power and resources than risk assessment.

Ultimately, diabetes is a multi-factorial disease that warrants an integrated management approach. Obligatory focus on any one aspect of diabetes would be costly and may misdirect care. Therapeutic stability should remain a priority and the various associated comorbidities should all be considered when treating diabetes.

The FDA is charged with ensuring efficacy, safety, and reliability of new therapies while facilitating advances in public health. This is a delicate balance. Altering current regulatory strategies to accommodate one aspect of a given disease without equal consideration for other associated complications does not seem prudent and may unnecessarily exaggerate priorities. Adequate resources and cost-effectiveness are also part of the regulatory protocol and the addition of new criteria that concern CV measures in diabetes drug approval does not appear to be conducive to the regulatory objective.

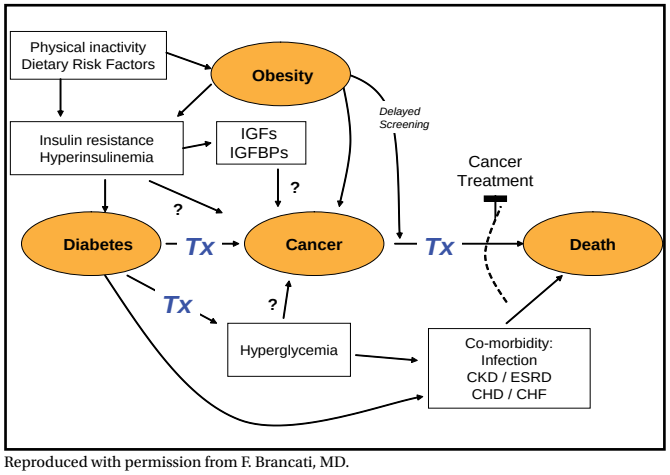
Diabetes and Cancer: ADA Consensus Statement

The association between diabetes and elevated cancer risk is of increasing concern. Some investigators suggest that in addition to the pathology of type 2 diabetes mellitus (T2DM), the diabetes treatments themselves may play a malignant role. These issues, as highlighted in recent journal and mass media articles as well as in conjunction with the release of a related consensus statement from the American Diabetes Association (ADA), were addressed at a symposium at the 70th Scientific Session of the ADA.

Jeffrey Johnson, PhD, University of Alberta, Edmonton, Canada, presented an epidemiological overview that reviewed the mortality statistics. Cancer is the second leading cause of death in patients with T2DM (27%), with cardiovascular disease being the first (43%; Lin et al. *Ann Fam Med* 2009). For specific cancer types, meta-analyses suggest that increased risk of incidence ranges from 1.2 times for breast cancer to as high as 2.5 times the normative risk for liver cancer in patients with T2DM.

That individuals with diabetes are at elevated risk for certain cancers seems clear. Explaining the specific mechanism(s) by which this association occurs is not as straightforward (Figure 1). As pointed out by Dr. Johnson, the two disease states share certain risk factors, the most prominent being obesity, which studies have consistently demonstrated increases cancer incidence and worsens treatment outcomes [Renehan et al. *Lancet* 2008].

Figure 1. Conceptual Framework for Obesity, Diabetes, Cancer, and Mortality.



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Hyperglycemia has also been considered. An analysis from a 10-year prospective study of over 1.23 million individuals in Korea demonstrated that fasting blood glucose values in excess of 90 mg/dL for men or 125 mg/dL for women were associated with increased cancer risk ($p<0.003$ and $p<0.03$, respectively; Jee et al. *JAMA* 2005). Conversely, a recent meta-analysis of over half a million individuals in the United States and the United Kingdom failed to show any relationship between elevated cancer risk and hyperglycemia or, for that matter, glycemic control [Johnson et al. submitted].

The accumulating evidence suggests, however, that hyperinsulinemia is likely a more important biological