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.

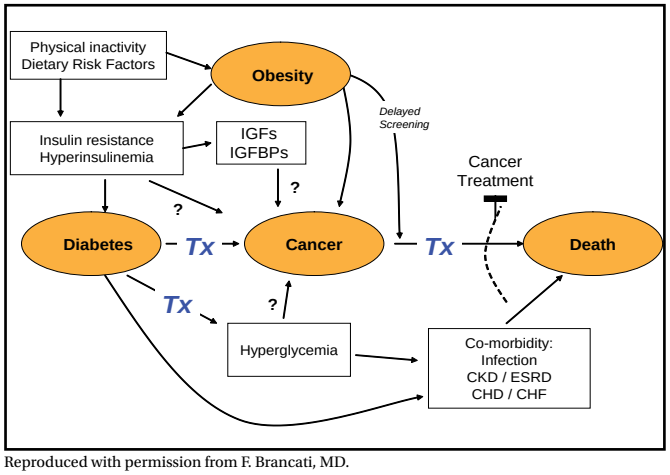
Diabetes and Cancer: ADA Consensus Statement

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

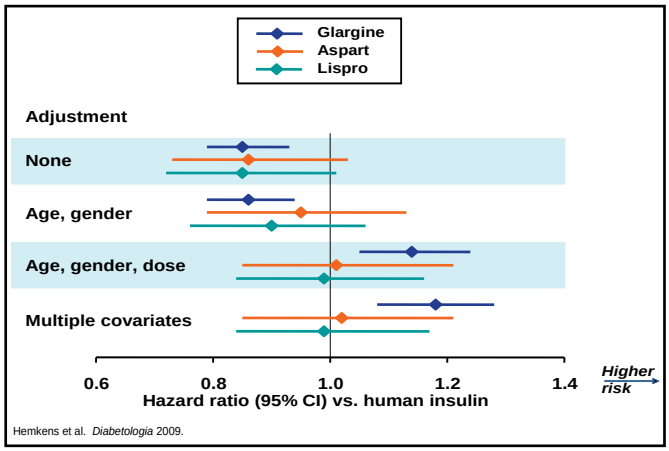
link. In a large cohort of women from New York City, the biological activity of elevated insulin-like growth factor-I levels was demonstrated to have only a modest negative impact on the incidence of colorectal cancer (Ma J et al. *JNCI* 2004).

Could Treatment Play a Role?

Turning to the recent controversy surrounding the use of insulin glargine as a driver of increased cancer incidence, Jay S. Skyler, MD, MACP, University of Miami, Miller School of Medicine, Miami, FL, explained the origin of and media reaction to the proposed theory that insulin glargine may be a carcinogen.

The controversy began in 2009 with an analysis of a German database that suggested that patients who were using higher doses of insulin glargine had an increased risk for cancers of all types but only when adjusted for dose (Figure 2).

Figure 2. Hazard Ratios for Risk of All Forms of Cancer.



This conclusion resulted in several high-profile news articles [Hemkens et al. *Diabetologia* 2009]. This finding prompted the *Diabetologia* editors to request a confirmatory analysis based on unrelated datasets from the United Kingdom, Scotland, and Sweden. The resultant submissions from these public health databases were in general agreement that the association between insulin glargine and cancer was unfounded.

As concluded by Dr. Skyler, "The press headline 'Glargine causes cancer' is unsubstantiated, unwarranted, and unproven."

For additional details and the ADA consensus statement regarding the controversy, see Giovannucci E et al. *Diabetes Care* 2010;33:1674-1685.

The Diabetic Foot Wound

David G. Armstrong, DPM, MD, PhD, University of Arizona College of Medicine, Tucson, AZ, presented the 2010 Roger Pecoraro Lecture at the American Diabetes Association 70th Annual Scientific Sessions, where he discussed management strategies for the treatment of the diabetic foot wound. Every 30 seconds, a lower limb is lost due to complications of diabetes [www.diabeticfootonline.com]. According to the Nord-Trondelag Health Study, foot ulcer history is associated with a 38% increased risk of death among diabetics after adjusting for lifestyle and demographic factors [Iverson MM et al. *Scandinavian J Public Health* 2008].

Dr. Armstrong recommends the team approach to diabetic foot wound management in order to reduce the incidence of amputation. In a study that evaluated 1708 procedures over a period of 32 months, patients who received the team approach to treatment were 61.0% less likely to undergo amputation versus 28.9% in the control group ($p<0.0001$) [Armstrong DG et al. ADA 2010]. An effective amputation prevention team should include the ability to perform certain tasks, such as site-appropriate culture techniques, vascular assessment and revascularization, neurological evaluation, wound assessment and infection staging/grading, site-specific bedside and intraoperative incision and debridement, culture- and patient-appropriate antibiotic therapy implementation, and postoperative monitoring with a focus on reulceration and infection risk reduction [Fitzgerald et al. *EPlasty* 2009; Armstrong DG et al. *JVS* 2010].

There are also many advances being made in the area of wound care that may optimize the management of diabetic foot ulcers. Among them is vacuum-assisted closure (VAC) therapy. This therapy provides several healing advantages, such as promotion of flap and graft survival, removal of interstitial fluid and infectious material, and uniform wound closure through the use of negative pressure [Saxena et al. *Plast Reconstr Surg* 2004]. VAC therapy resulted in fewer surgical procedures and dressing changes compared with standard moist wound therapy ($p<0.0001$ for both) [Apelqvist J et al. *Am J Surg* 2008].

Receptor activator of nuclear factor kappa B ligand (RANK-L), osteoprotegerin (OPG), and intranasal calcitonin may also facilitate healing in diabetic foot ulcers. RANK-L and OPG play a key role in bone remodeling and resorption. Dysregulation of RANK-L or OPG may result in bone loss. Upregulation of RANK-L may occur in the