DIABETES AND CARDIAC SAFETY: KNOWLEDGE GAPS

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TYPE 2 DIABETES MELLITUS (T2DM) IS TWO DISTINCT DISEASES

Chronic Hyperglycemia

T2DM

Hypertension
Dyslipidemia
Obesity
Endothelial dysfn
Insulin Resistance
Inflammation

MICROVASCULATURE

MACROVASCULATURE
2007 ECONOMIC COST ($175 billion) OF DIABETES IN U.S. BY CATEGORY

ADA, Diabetes Care 31:596-615, 2008

<table>
<thead>
<tr>
<th>Category</th>
<th>Expenditure (%)</th>
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<tbody>
<tr>
<td>CVD/PVD</td>
<td>33.7%</td>
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<tr>
<td>EYE, KIDNEY, NERVE</td>
<td>38.9%</td>
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<tr>
<td>OTHER</td>
<td>27.4%</td>
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There is no cost that can be assigned to the morbidity and suffering associated with blindness, dialysis, and neuropathy.
UKPDS: Effect of SU & Metformin Rx on HbA$_{1c}$

ETIOLOGY OF T2DM

- Decreased Glucose Uptake
- Impaired Insulin Secretion
- Increased Lipolysis
- Increased HGP
- Decreased Incretin Effect
- Decreased Insulin Secretion
- Increased Glucagon Secretion
- Increased Glucose Reabsorption
- Neurotransmitter Dysfunction
- Increased Lipolysis
- Decreased Glucose Uptake

OMINOUS OCTET
We need novel and more efficacious medications that correct known pathophysiologic disturbances present in T2DM.

Multiple medications used in combination will be required to reverse the multiple and diverse pathogenic abnormalities present in T2DM.
63% of patients with type 2 diabetes have A1C > 7.0%

7. AACE, State of Diabetes in America, 2006
10. NCQA, www.neca.com

12.4% have A1C > 10%
20.2% have A1C > 9%
37.2% have A1C > 8%

ADA target (< 7%)
AACE /EASD target (≤ 6.5%)
Upper limit of normal (6.0%)
POOR DIABETES CONTROL (HbA1c > 9.0%) is present in 29 - 45% of T2DM patients in COMMERCIAL, MEDICAID, and MEDICARE HEALTH PLANS based upon 2009 HEDIS
Upper bound of 2-sided 95% CI for cardiovascular HR <1.8

IMPACT – Requires data on >120 events

REALITY: Using MACE (CV mortality, MI, stroke) with annual incidence of 1.5% (traditional population), this would require ~8,000 patient years
FDA GUIDELINES, DECEMBER 2008

**PHASE 3**
Upper bound of 2-sided 95% CI for cardiovascular HR <1.3

**IMPACT** – Requires data on 600-700 events

**REALITY:**
Using MACE (other endpoints uncertain) with annual incidence of 2-3% (high risk population), this would require ~20,000 patient years
CV outcome trials may be relevant to elderly patients with type 2 diabetes, but they do not address therapy in the growing number of younger patients, who are less likely to experience CV events and in whom a lifetime of exposure to hyperglycemia is likely to increase the risk for microvascular complications.
DRUG DISCOVERY SHOULD NOT BE ABANDONED JUST BECAUSE MEDICATIONS HAVE A NEUTRAL EFFECT ON CV OUTCOMES OR CVRFs

- The concentration on risks of heart attack/stroke may miss important benefits in prevention of blindness or renal failure.

- The recruitment into trials of individuals with pre-existing heart disease (or high risk of developing it) may obscure other benefits or problems. It also raises ethical concerns.
Recent discussions by the FDA have focused on cardiovascular safety, and for new antidiabetic agents a cardiovascular outcome trial is required.

However, the only absolutely safe drug policy would be not to prescribe any medications whatsoever.

Then, there would be no drug safety problems, and patients simply would die from their diabetes and associated complications.
RISK OF REGULATIONS

- By mandating CV outcome trials, the cost of drug development will increase by ~300 million per drug, and only very large pharmaceutical companies will be able to afford this.

- The increased cost of drug development will, of necessity, be passed onto the patient, making the medication(s) unaffordable.

- Some pharmaceutical companies already have decreased their metabolic pipeline and/or are getting out of the diabetes business. This will reduce discovery efforts for novel antidiabetic medications.

- The recruitment into trials of individuals with pre-existing heart disease (or high risk of developing it) may obscure other benefits or problems. It also raises ethical concerns.
CONCERNS ABOUT THE CURRENT FDA GUIDELINES FOR CARDIOVASCULAR SAFETY

- When should the cardiovascular outcome trials be performed? Before approval? After approval? During the approval process?
- What is an appropriate CV signal for a CV outcome trial?
- What is the appropriate population for a CV outcome trial? Elderly? Prior CV event? Renal disease?
- Requirements for CV safety trial can change without sufficient time for pharmaceutical companies to respond.
- Much of the information from these CV outcome trials can not be included in the label.
(1) Combine Phase 3 with Phase 4 study

(2) Graded approval based upon surrogate CVRFs with subsequent removal of restrictions
   (i) biomarkers, i.e. A1c, lipids, BP, other
   (ii) carotid IMT, plaque volume (or equivalent)
   (iii) large CV safety trial

(3) Real life CV safety trial using national electronic record data base