Impact and Importance of the 2008 Guidance in Diabetes Care

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Disclosures

**Contracts and/or Grants:** Grants from the following pharmaceutical companies were paid to my institution (Duke University) for performance of research or research-related activities, and in part supported my salary:

<table>
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<th>Company</th>
<th>Role</th>
<th>Product</th>
<th>Significance</th>
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<tr>
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<td>Intarcia Therapeutics</td>
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<td>Janssen</td>
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**Scientific Advisor/Consulting Fees:**

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<td>NovoNordisk</td>
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Impact and Importance of the 2008 Guidance in Diabetes Care

- The good, the bad, the ugly, and the future
The Good

- **Completed CVOTs**
  - Provide reassurance that newer drugs for T2DM do not increase risk MACE
  - Have **established CV benefits** of several drugs
    - *In patients at high CV risk*
    - *As a complement to existing CV risk reduction strategies*

CV = cardiovascular
CVOT = cardiovascular outcomes trial
MACE = major adverse cardiovascular events
The Good

- Completed CVOTs
  - Highlighted HF as an important complication in T2DM
  - Suggest heterogeneity of CV, other effects of drugs both between and within classes
  - Identified unexpected other benefits of treatments
    - Heart failure
    - Renoprotection

CV = cardiovascular
CVOT = cardiovascular outcomes trial
HF = heart failure
The Good

- **Completed CVOTs**
  - Provide important data re: other safety outcomes
    - Addressed or identified issues of clinical interest
      - Thyroid malignancy, pancreatic safety, amputations, fractures, HHF
    - Frequency with which complications occur
    - Some safety data potentially not otherwise available

CV = cardiovascular
CVOT = cardiovascular outcomes trial
HHF = hospitalization for heart failure
The Good

- Benefits of enhanced safety expectations
  - Taspoglutide (~600 pt years) development discontinued due to emergence of rare allergic reactions, including anaphylaxis.
  - Aleglitazar (>14,000 patient years) development discontinued due to lack of CV efficacy and increases in fractures, kidney problems, GI bleeds, and heart failure.
  - Fasiglifam (~2000 patient years) clinical development program was terminated due to drug-associated liver injury (10-fold increase in elevated LFTs)

The Good

- Evidence generated by CVOTs meeting specifications of FDA guidance has contributed to a remarkable evolution and refinement of diabetes care guidelines for the highest risk patients
Diabetes Care Guidelines Circa 2006-2008

Emphasis upon intensive glycemic control to reduce risk complications

ADA Guidelines

Table 8—Summary of glycemic recommendations for adults with diabetes

<table>
<thead>
<tr>
<th>A1C</th>
<th>&lt;7.0%*</th>
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<tbody>
<tr>
<td>Preprandial capillary plasma glucose</td>
<td>70–130 mg/dl (3.9–7.2 mmol/l)</td>
</tr>
<tr>
<td>Peak postprandial capillary plasma glucose†</td>
<td>&lt;180 mg/dl (&lt;10.0 mmol/l)</td>
</tr>
</tbody>
</table>

Key concepts in setting glycemic goals:
- A1C is the primary target for glycemic control
- Goals should be individualized based on:
  - duration of diabetes
  - pregnancy status
  - age
  - comorbid conditions
  - hypoglycemia unawareness
  - individual patient considerations
- More stringent glycemic goals (i.e., a normal A1C, <6%) may further reduce complications at the cost of increased risk of hypoglycemia
- Postprandial glucose may be targeted if A1C goals are not met despite reaching preprandial glucose goals

2006 ACE/AACE targets for glycemic control

- A1C ≤6.5%
- Fasting/preprandial plasma glucose <110 mg/dL
- 2-hour postprandial plasma glucose <140 mg/dL

“Early use of insulin therapy is frequently needed for timely achievement of glycemic goals.”

Diabetes Care 2008 Jan; 31(Supplement 1): S12-S54
Endocrine Practice Vol 12 No. 1 January/February 2006
## 2012 Update to ADA Guidelines

### Individualization of glycemic targets...

<table>
<thead>
<tr>
<th>Approach to management of hyperglycemia:</th>
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<th>Less stringent</th>
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<td>Highly motivated, adherent, excellent self-care capacities</td>
<td>Less motivated, non-adherent, poor self-care capacities</td>
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<tr>
<td>Risks potentially associated with hypoglycemia, other adverse events</td>
<td>Low</td>
<td>High</td>
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<tr>
<td>Disease duration</td>
<td>Newly diagnosed</td>
<td>Long-standing</td>
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<tr>
<td>Life expectancy</td>
<td>Long</td>
<td>Short</td>
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<tr>
<td>Important comorbidities</td>
<td>Absent</td>
<td>Few / mild</td>
</tr>
<tr>
<td>Established vascular complications</td>
<td>Absent</td>
<td>Few / mild</td>
</tr>
<tr>
<td>Resources, support system</td>
<td>Readily available</td>
<td>Limited</td>
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</table>
2012 Update to ADA Guidelines

...but drug choices largely guided by type and risk of class side effects
**Current Guidelines Incorporate Evidence from CVOTs**

**ASCVD PREDOMINATES**
- GLP-1 RA with proven CVD benefit\(^1\)
- SGLT2i with proven CVD benefit\(^2\), if eGFR adequate\(^3\)

**HF OR CKD PREDOMINATES**
- PREFERABLY
  - SGLT2i with evidence of reducing HF and/or CKD progression in CVOTs if eGFR adequate\(^3\)
- OR
  - If SGLT2i not tolerated or contraindicated or if eGFR less than adequate\(^2\)
  - add GLP-1 RA with proven CVD benefit\(^1\)

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1. Proven CVD benefit means it has lower incidence of major adverse cardiovascular events, for GLP-1 RA, evidence of reduction in cardiovascular mortality. For SGLT2i evidence, major adverse cardiovascular events
2. OR means that GLP-1 RA may be used in individual agents with higher risk of CVD events with additional CV benefit
3. Both GLP-1 RA and SGLT2i have shown reduction in CV events in CVOTs
4. Regimens with GLP-1 RA have demonstrated CV safety
5. Use lower dose of GLP-1 RA (if tolerated) for GLP-1 RA
6. Choose prior generation SU with lower risk of hypoglycemia

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Duke Clinical Research Institute
The Bad

- Guidance requirements increase costs of drug development
  - Large CVOTs as traditionally conducted can cost >$500 million
- Costs conveyed to patients, increase total care expenditures
- May serve as a disincentive to diabetes drug development
**Impact on Diabetes Drug Development**

- **However** 15 CVOTs of agents in 3 new classes and one of insulin therapy completed; numerous ongoing

- **SAVOR-TIMI 53** (n=16,692)
  - DPP-4 inhibitor
- **EXAMINE** (n=5380)
  - SGLT-2 inhibitor
- **TECOS** (n=14,671)
  - GLP1 RA
- **ORIGIN** (n=12,537)
  - Insulin
- **Devote** (n=7637)
  - PPAR agonist
- **AleCardio** (n=7226)
  - TZD
- **DECLARE-TIMI 58** (n=18,692)
  - DPP-4 inhibitor
- **CAROLINA** (n=6041)
  - SGLT-2 inhibitor
- **CREDENCE** (n=4200)
  - GLP1 RA
- **CAROLINA®** (n=6041)
  - Insulin
- **TOCO IT25** (n=3371)
  - PPAR agonist
- **OMNEON** (n=4000)
  - TZD
- **Ertugliflozin CVOT** (n=3900)
  - GLP1 RA

*figure not a comprehensive list*
Impact on Diabetes Drug Development

- 14 new agents for T2DM approved in US since 2008
  - Not including insulins or combination therapies
- Market steadily increasing
- Potential multiple indications (HF, CKD) may serve as incentive
- Vibrant research space
  - Clinicaltrials.gov search 10/10/2018

820 Studies found for: Recruiting, Not yet recruiting, Active, not recruiting, Enrolling by invitation, Studies | Intervenational Studies | Diabetes | Investigational drug

Also searched for Experimental, Agent, Medications and more. See Search Details
## Impact on Diabetes Drug Development

<table>
<thead>
<tr>
<th>Therapeutic Area</th>
<th>Preclinical/Research Project</th>
<th>Phase I</th>
<th>Phase II</th>
<th>Phase III</th>
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<th>Total Projects</th>
<th>Total Products</th>
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<td>78</td>
<td>104</td>
<td>59</td>
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<td>537</td>
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<td>1,757</td>
<td>1,920</td>
<td>329</td>
<td>24</td>
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<td>434</td>
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<td>87</td>
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<td>Diabetes</td>
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<td>75</td>
<td>10</td>
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<td>298</td>
<td>182</td>
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Impact on Diabetes Drug Development

- **Additional Disincentives**
  - Saturation of classes with demonstrated safe and/or beneficial agents
    - Fewer “me too” drugs
  - Unclear path forward for drugs found safe but without CV benefit
    - **These agents remain clinically relevant**
      - Increased need for complex regimens over time
      - Safety of all agents used is important
    - **Current guidelines outline role in care**
      - Antihyperglycemic therapy in lower risk patients
      - As a component of antihyperglycemic care for higher risk patient
Impact on Diabetes Drug Development

Key Disincentive

*Underutilization of beneficial agents in clinical care*

Harmony Outcomes Example

- Contemporary trial *(July 2015-March 2018)*
- 100% patients had ASCVD
- Limited baseline and within-trial use of SGLT2i therapy

Hernandez A, et al. Lancet; online first October 2, 2018
The Ugly

- Devaluation of glycemic control in diabetes management
- A recent tweet:

  Does HgbA1c matter anymore...isn’t it ancillary?
# Benefits of Glycemic Control: A Reminder

<table>
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<th>Study</th>
<th>Microvascular</th>
<th>CV Disease</th>
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* in T1DM

Kendall DM, Bergenstal RM. © International Diabetes Center 2009
Glycemic Control

- Initial approval DM drugs based upon HbA1c lowering
  - Accepted surrogate for risk microvascular complications

- UKPDS suggests early glycemic control may affect long term CV risk
  - Unclear when it becomes less or unimportant to CV risk
    - Only true of older drugs?

- Glycemic contribution to CVOT findings
  - All trials have had between-group differences in glycemic control
  - Estimated contribution to results varies

- Competing risks
  - Will glycemia become more important as people live longer with diabetes?
Effects of Risk Reduction Strategies: Changing Rates of Complications Over Time

Rates of many serious complications have fallen: numbers of events have not
Multiple Overlapping Outcomes of Interest

- Cardiovascular
  - MACE
  - HF
- Glycemic
  - Microvascular
  - Neuropathic
- Patient Centered
- Clinical Practice Outcomes
Steno-2: Efficacy of Multiple Risk Factor Intervention in T2DM with Microalbuminuria

More intensive management of HbA1c, BP, lipids reduced risk of micro and macrovascular complications – using older drugs
The Future

- Adequately powered, randomized CV outcomes trials of individual antihyperglycemic agents should continue
  - Information allows patients and providers to understand effects of available drugs, and make informed decisions regarding care

- Work still needed
  - Implementation
  - More efficient but still robust trials methodology
Implementation Issues

- Barriers to Implementation in Clinical Practice
  - Unawareness
  - Confusion in application
  - Unanswered clinical questions
  - Assessment of actual risk vs. benefit
  - Cost and access issues
  - Time needed to learn, discuss, execute new care plans
  - Not currently an expectation of care for the high risk patient

- Not a justification!
Implementation Issues

- **Address Barriers**
  - Need relevant care expectations and quality measures
  - Guidelines should
    - Be readily understandable and applicable
    - Consider audience
      
      *only 15% of all diabetes care is provided by endocrinologists*
    - Avoid unnecessary complexity, cost if not evidence-based

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**2018 ADA Guidelines**

In patients with type 2 diabetes and established atherosclerotic cardiovascular disease, antihyperglycemic therapy should begin with lifestyle management and metformin and subsequently incorporate an agent proven to reduce major adverse cardiovascular events and cardiovascular mortality (currently empagliflozin and liraglutide), after considering drug-specific and patient factors.
Revise Traditional Roles

**Diabetologist**
- Focus on blood sugar
- Expert in wide range of diabetes drugs
- Expert in global care of diabetes, microvascular complications
- Often defers to cardiologist for CV protection

**Cardiologist**
- Focus on hypertension, lipids, diet
- Management of cardiovascular disease
- Defers to diabetologist on diabetes drugs
Novel Paradigm for Care of T2DM and CV Disease

Patient with established cardiovascular (CV) disease but no prior Type 2 diabetes mellitus (T2DM): Cardiologist to perform routine, systematic measurement of HbA1c to evaluate presence of T2DM

And/or

Eligible patients with CV disease and prior T2DM

Consider recommending treatments if no contraindication:

- **SGLT2 inhibitor: empagliflozin**
  - Decreased CV mortality and decreased heart failure hospitalizations
  - Decreased blood glucose
  - Promotes weight loss
  - Renal benefits

- **GLP-1 receptor agonist: liraglutide**
  - Decreased CV mortality
  - Decreased blood glucose
  - Promotes weight loss
  - Potential renal benefits

Refer to primary care physician or endocrinologist
Follow CV and T2DM progress in tandem
Address Barriers to Implementation

Start to fill in the missing pieces

- Effects in lower risk, underrepresented populations
- Better define high risk
- Trials with active comparators, drug combinations
- Assess longer term effects
- Best place in therapy

*First line; incorporation into existing regimens*

Engagement of other agencies, institutions, societies, and interested groups
Moving the Field Forward

- Previously used CVOT model should not be the only acceptable path forward
  - Explore novel approaches to trial design, operations, outcomes
    - Reduce time, costs
    - Maximize ability to identify benefits
  - Pragmatism must be more than a catch phrase

- Possible new paradigm for DM drug approval
  - Is HbA1c lowering required if benefit demonstrated in other meaningful outcomes?
Thank you