Treating Diabetes To Lower Cardiovascular Disease Risk

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Consultantship
Abbott Diabetes Care
Amgen
BD, Biodel
Janssen, Lexicon, Lilly
Medscape, Merck
Medtronic Minimed
NovoNordisk
Sanofi, Takeda
FDA

Speakers Bureau
NovoNordisk
Janssen

Research Funding
Janssen
Medtronic Foundation

LDL Cholesterol Targets in Diabetes

UKPDS: “Legacy Effect” of Insulin/Sulfonylurea Therapy

<table>
<thead>
<tr>
<th>Aggregate Endpoint</th>
<th>1997</th>
<th>2007</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any diabetes related endpoint</td>
<td>12%</td>
<td>9%</td>
</tr>
<tr>
<td></td>
<td>P: 0.029</td>
<td>0.040</td>
</tr>
<tr>
<td>Microvascular disease</td>
<td>25%</td>
<td>24%</td>
</tr>
<tr>
<td></td>
<td>P: 0.009</td>
<td>0.001</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>16%</td>
<td>15%</td>
</tr>
<tr>
<td></td>
<td>P: 0.005</td>
<td>0.001</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>6%</td>
<td>6%</td>
</tr>
<tr>
<td></td>
<td>P: 0.44</td>
<td>0.007</td>
</tr>
</tbody>
</table>

After median 8.8 years post-trial followup

RRA = Relative Risk Reduction
P = Log Rank


UKPDS: “Legacy Effect” of Insulin/Sulfonylurea vs. Metformin Therapy
Meta-Analysis of Glycemic Control Trials and Coronary Heart Disease

<table>
<thead>
<tr>
<th>Intensive treatment/ standard treatment</th>
<th>Weight of study size (Odds ratio (95% CI))</th>
<th>Odds ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS&lt;sup&gt;17&lt;/sup&gt;</td>
<td>3571/3459</td>
<td>0.64 (0.54-0.75)</td>
</tr>
<tr>
<td>PPAS&lt;sup&gt;20&lt;/sup&gt;</td>
<td>2650/2652</td>
<td>0.80 (0.64-1.00)</td>
</tr>
<tr>
<td>ADVANCE&lt;sup&gt;19&lt;/sup&gt;</td>
<td>2471/2067</td>
<td>0.65 (0.56-0.77)</td>
</tr>
<tr>
<td>ADVANCE&lt;sup&gt;20&lt;/sup&gt;</td>
<td>528/512</td>
<td>0.81 (0.68-0.99)</td>
</tr>
<tr>
<td>Overall</td>
<td>12760/11577</td>
<td>0.85 (0.77-0.93)</td>
</tr>
</tbody>
</table>


Hyperglycemia and Coronary Heart Disease (CHD)

- Possible reasons that individual trials failed to show a beneficial effect on CHD
  - Event rates were lower than expected
  - Differences in glycemic control were not large enough
  - The intervention or observation period was too short
  - Need to start intervention earlier in natural history of the disease


Hyperglycemia and CHD (cont’d)

- Conclusions
  - Do not discount the benefits of managing hyperglycemia
    - Reduced microvascular disease well established
    - Premature to conclude that glucose control plays no part in CHD residual risk
    - Benefits of glucose control will be less than BP and lipid control
  - Additional studies needed to evaluate the effects of controlling hyperglycemia on CHD risk


Management of Hyperglycemia in Type 2 Diabetes: A Patient-Centered Approach

Position Statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD)

The ADA/EASD Position Statement on Management of Hyperglycemia in Type 2 Diabetes

ADA
- Richard M. Bergenstal MD
  - 1 Diabetes Center, Minneapolis, MN
- John B. Buse MD, PhD
  - University of North Carolina, Chapel Hill, NC
- Anne L. Peters MD
  - Univ. of Southern California, Los Angeles, CA
- Richard Wender MD
  - Thomas Jefferson University, Philadelphia, PA
- Silvio E. Inzucchi MD (co-chair)
  - Yale University, New Haven, CT

EASD
- Michaela Diamant MD, PhD
  - VU University, Amsterdam, The Netherlands
- Ele Ferrannini MD
  - University of Pisa, Pisa, Italy
- Michael Nauck MD
  - Diabetesszentrum, Bad Lauterberg, Germany
- Apostolos Tsapas MD, PhD
  - Aristotle University, Thessaloniki, Greece
- David R. Matthews MD, Dphil
  - Oxford University, Oxford, UK

Impact of Intensive Therapy for Diabetes: Summary of Major Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>Microvasc</th>
<th>CVD</th>
<th>Mortality</th>
</tr>
</thead>
<tbody>
<tr>
<td>UKPDS</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>DCCT / EDIC&lt;sup&gt;*&lt;/sup&gt;</td>
<td>▼</td>
<td>▼</td>
<td>▼</td>
</tr>
<tr>
<td>ACCORD</td>
<td></td>
<td>▼</td>
<td></td>
</tr>
<tr>
<td>ADVANCE</td>
<td>▼</td>
<td>▼</td>
<td></td>
</tr>
<tr>
<td>VADT</td>
<td>▼</td>
<td>▼</td>
<td></td>
</tr>
</tbody>
</table>

<sup>*</sup> in T1DM

Diabetes Care 2012;35:1364-1379
Diabetologia 2012;55:1577-1596
**Patients with type 2 diabetes who experience symptomatic, severe hypoglycaemia are at increased risk of death, regardless of the intensity of glucose control.**

**The increased risk of death seen in the ACCORD trial among participants in the intensive glycaemia control arm cannot be attributed to the increased rate of severe hypoglycaemia in intensive arm participants.**

* Bonds et al. BMJ 2010;340:c4909
Results: Weight Loss


Mean F/U 9.6 years

1-yr wt loss:
8.6% ILI
0.7% control group

Study end:
6.0% ILI
3.5% control group

Results: Primary Outcome


Events/100 person-yrs:
1.83 ILI
1.32 Control

Hazard ratio 0.95
(95% CI 0.83-1.09, P=0.51)

4-Yr Wt Loss Trajectories of 887 ILI Participants Who Lost ≥ 10% Initial Weight at Yr 1 (~35%)

Mean Annual Number of Meal Replacements Used in Years 2-4

Mean Weekly Kcal Expenditure at Year 4 (as Determined by Paffenbarger)

Metformin: The Only Choice in Type 2 DM?

- Most commonly used therapy for T2 DM (2/3rds of patients)
- Clinical effects
  - Lowers A1C 1-2% (especially at high baseline A1C), no weight gain
  - Maximal clinical effect at 1500-2000 mg/day
- Possible side effects and precautions
  - GI side effects common – less well tolerated by up to 10%
  - Not advised if significant renal or liver disease, heart failure (~20%)
- Other features
  - Lower CV risk in obese patients (UKPDS)
  - Extensive clinical experience and lower cost
  - ? Favorable impact on cancer risk and mortality
Sulfonylureas and the Secretagogues
How Do We Use Them Now?

• Most common (traditional) 2nd agent in T2 DM
  - Stimulate insulin release – during hyperglycemia and post-meal

Clinical Use
  - Inexpensive and commonly used, rapid glucose lowering
  - Limited dose effect and limited “durability” of effect

Side effects
  - Associated with weight gain and risk of hypoglycemia

Precautions and contraindications
  - Associated with risk of severe hypoglycemia (elderly, renal disease)
  - Highest risk of hypoglycemia with GLYBURIDE
  - May not be good for those at CVD risk (longstanding discussion)

Thiazolidinediones (TZDs)
Do We Target Insulin Resistance?

Clinical application
  - Targeted patients with clinical markers of insulin resistance
    - Dyslipidemia, HTN, established CVD, central obesity
  - May limit CVD risk and alter progression of diabetes

Adverse effects and considerations
  - Significant weight gain and increase risk of edema and HF
  - Increased risk of long-bone fractures
  - Macular edema

Patient selection
  - Higher CVD risk – particularly with dyslipidemia, est. CVD
  - Those at lower risk for fracture and with central obesity, NASH

Summary Of Pioglitazone Clinical Trials
Center for Drug Evaluation & Research, July 30, 2007

<table>
<thead>
<tr>
<th>PIO Meta-analysis</th>
<th>PIO Meta-Analysis plus PROactive</th>
<th>#CV Events</th>
<th># of Subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75</td>
<td>0.83</td>
<td>375</td>
<td>8554</td>
</tr>
<tr>
<td>PROactive</td>
<td></td>
<td>450</td>
<td>7836</td>
</tr>
</tbody>
</table>

DPP-4 Inhibitors: Sitagliptin (Januvia), Saxagliptin (Onglyza), Linagliptin (Tradjenta) and Alogliptin (Nesina)

Clinical Use
  - Moderate effectiveness (A1C reduction ~0.5-0.8%)
  - Use in both combo and mono therapy

Unique Features
  - Limited side effect profile, very well tolerated, pancreatitis?
  - Weight neutral, no significant weight loss, no hypoglycemia
  - Variable clinical response (A1C reduction 0.2-1.1%)
  - Reduced dosing in chronic kidney disease (except for linagliptin)
  - Saxagliptin increased risk of CHF in high risk population

GLP-1 RA’s: Exenatide (Byetta, Bydureon), liraglutide (Victoza), albiglutide (Tanzuem), dulaglutide (Trulicity)

Clinical Use
  - Lowers A1C 1 – 1.5%
  - Often associated with weight loss

Side Effects/Features
  - Injected once or twice daily or once weekly
  - GI side effects common, rare hypoglycemia
  - Warnings: pancreatitis, MCT
  - Drug-specific features
  - Potential CVD benefits

Potential Cardiovascular Effects of GLP-1-Based Therapies

- Improved weight, SBP, lipids
- Improved endothelial function
- Increased vasorelaxation
- Increased peripheral and coronary flow
- Increased ventricular function
- Decreased microvascular permeability
- Reduced inflammation

Okerson T, Chilton R. Cardiovasc Ther 30:e146-55, 2012
### Incretin Cardiovascular Outcome Trials

<table>
<thead>
<tr>
<th>Risk Factors</th>
<th>Stable CAD/CVD/PAD</th>
<th>ACS patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR TIMI 53 - Saxagliptin</td>
<td>n=16,092</td>
<td>September 2013</td>
</tr>
<tr>
<td>LEADER - Linagliptin</td>
<td>n=14,000</td>
<td>September 2013</td>
</tr>
<tr>
<td>CARMETINA (vs pbo) - Linagliptin</td>
<td>n=8,300</td>
<td>December 2014</td>
</tr>
<tr>
<td>SUSTAIN 6 - Semaglutide</td>
<td>n=3,297</td>
<td>January 2018</td>
</tr>
<tr>
<td>EXAMINE - Alogliptin</td>
<td>n=5,400</td>
<td>April 2018</td>
</tr>
<tr>
<td>CAROLINA (vs SU) - Linagliptin</td>
<td>n=6,000</td>
<td>January 2015</td>
</tr>
<tr>
<td>EXCEL - Exenatide LAR</td>
<td>n=14,000</td>
<td>October 2015</td>
</tr>
<tr>
<td>REWIND - Dipeptidyl peptidase-IV</td>
<td>n=9,622</td>
<td>April 2019</td>
</tr>
</tbody>
</table>

### SGLT-2 Inhibitors—Canagliflozin, Dapagliflozin, Empagliflozin

**Clinical Effects**
- Novel mechanism of action/oral agent
- Most will respond—action independent of beta-cell function
- A1C reduction ~1% with 2-3 kg weight loss

**Possible Side Effects and Precautions**
- Mycotic genital infections
- Findings due to volume depletion
- Don't use if eGFR <45%

**Other Features**
- Lowers BP slightly
- Raises LDL cholesterol

### Reducing CVD Risk Treating T2DM
- Use statins, control BP, give aspirin
- Use diabetes drugs that don’t cause hypoglycemia or minimize hypos in drugs that do
- Improve control early and maintain it
- Never forget importance of lifestyle

### Thank You