Cardiovascular Outcomes Trials in Patients with Diabetes: Issues & Opportunities

EMDAC Public Advisory Committee Meeting
FDA
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Disclosures

Research Grant Support through BWH:

Amgen; AstraZeneca; Daiichi-Sankyo; Eisai; GlaxoSmithKline; Intarcia; Janssen Research Development; Medicines Company; MedImmune; Merck; Novartis; Pfizer; Poxel; Takeda

Scientific Advisory Boards & Consulting:

Amgen; AstraZeneca; Bristol-Myers Squibb; CVS Caremark; Dyrnamix, Esperion; Intarcia; Janssen Research Development; Medicines Company; MedImmune; Merck; Novartis
1. Work that goes into a randomized, controlled cardiovascular outcomes trial (CVOT)
2. Non-CVOT RCTs
3. Observational data
4. Streamlined or pragmatic CVOT
5. Equipoise as data emerge in a drug class
6. Optimal safety & efficacy endpoints
Outline

1. Work that goes into a randomized, controlled cardiovascular outcomes trial (CVOT)
2. Non-CVOT RCTs
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Trial Personnel & Cmtes

- Sponsor
- Academic Leadership
  - Principal Investigator
  - Executive and/or Steering Cmtes
- Clinical Events Cmte (for event adjudication)
- Independent Data Monitoring Cmte
- Contract Research Organization
- Other vendors (data management, labs, etc.)
Key Documents

- Protocol
- Informed Consent Form
- Event Reporting
  - Efficacy (Definitions & Clinical Events Cmte Charter)
  - Safety
- Statistical Analysis Plan
- Data Monitoring Cmte Charter
- Monitoring Plan
- SOPs
- Review of Key Documents by Regulators, Investigators, IRBs
Start-up

• Country selection
• Site selection & evaluation in each country
• Site contracts
• Regulatory & Ethics approval
• eCRF development & validation
• Site training & activation
• Study drug production & distribution
During Trial - Sites

- Screening & enrolling patients
- Dispensing study drug
- Bring back patients for follow-up visits
- Assessing for efficacy and safety outcomes
- Data entry
- Compiling efficacy outcome packets for CEC
- Expedited safety reporting
- Monitor visits
- Periodic IRB submissions
During Trial – ARO/Sponsor

• Tracking pace of enrollment
• Assessing characteristics of participants
• Tracking pace of efficacy event accrual
• Rates of safety outcomes (aggregate)
• Data cleaning
• Monitoring sites, both remote & on-site
• Event packet assembly and adjudication
• DMC reports & meetings
• Retention efforts
• **Assessing external events relevant to trial**
Close out

• Final participant visits
• Minimize missing data
  – Withdrawal of consent (WDC): find vital status (where permissible); WDC ideally <1%/yr, VS in majority
  – Lost to follow-up (LTFU): find them; ideally <0.1%/yr
• Data cleaning
• Complete adjudications
• PI signatures on eCRF
• Validation of analyses on blinded data
• Lock the database
Summary of CVOT

It is a huge amount of work!

• Many 1000s of subjects
• 1000s of researchers
• 1000+ sites in dozens of countries
• 1000s of staff at Sponsor & CRO
• $XXX millions of dollars
• Many years
Return on Investment?

• Trials are sponsored by for-profit companies
• Fiduciary responsibility to shareholders to maximize return on their investment
• An effective and safe new drug is a win for all (patients & the company)
• If the burden to get approval is too high, investment in new drugs will diminish
  – Pre- and post-marketing requirements with different burdens of evidence is an example of an attempt at a thoughtful balance
• If the burden is too low, patients could be exposed to ineffective or unsafe drugs
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Non-CVOT RCTs

- CV outcomes will occur in phase 2 and phase 3 trials
- #s small
- But, some programs have fairly extensive Ph2/3 programs (different types of patients, different background Rx)
- Could one aggregate such data and use to inform on safety? On efficacy?
Stepwise Approach to CV Safety Assessment of DM Drugs

Pre-marketing Analyses
Upper Bound 95% CI <1.8
At HR=1.0; 90% power; 122 events

Post-marketing Analyses
Upper Bound 95% CI <1.3
At HR=1.0; 90% power; 611 events
## DPP4i Meta-analysis of non-CVOTs

<table>
<thead>
<tr>
<th>Condition</th>
<th># trials (DPP4i)</th>
<th># trials (Comparator)</th>
<th># events (DPP4i)</th>
<th># events (Comparator)</th>
<th>MH-OR [95% CI]</th>
<th>p</th>
<th>Kendall’s tau [p]</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>70</td>
<td>63</td>
<td>263</td>
<td>232</td>
<td>0.71 [0.59; 0.86]</td>
<td>&lt;0.001</td>
<td>0.04</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>27</td>
<td>24</td>
<td>77</td>
<td>67</td>
<td>0.86 [0.60; 1.24]</td>
<td>0.430</td>
<td>0.04</td>
</tr>
<tr>
<td>Vildagliptin</td>
<td>16</td>
<td>15</td>
<td>75</td>
<td>74</td>
<td>0.61 [0.43; 0.88]</td>
<td>0.005</td>
<td>0.03</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>13</td>
<td>12</td>
<td>52</td>
<td>46</td>
<td>0.67 [0.45; 0.99]</td>
<td>0.047</td>
<td>0.36</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>9</td>
<td>8</td>
<td>37</td>
<td>41</td>
<td>0.72 [0.45; 1.16]</td>
<td>0.18</td>
<td>0.00</td>
</tr>
<tr>
<td>Alogliptin</td>
<td>5</td>
<td>4</td>
<td>12</td>
<td>4</td>
<td>0.86 [0.25; 2.93]</td>
<td>0.81</td>
<td>0.30</td>
</tr>
<tr>
<td>AMI</td>
<td>62</td>
<td>41</td>
<td>61</td>
<td>59</td>
<td>0.64 [0.44; 0.94]</td>
<td>0.023</td>
<td>-0.13</td>
</tr>
<tr>
<td>Stroke</td>
<td>63</td>
<td>29</td>
<td>41</td>
<td>33</td>
<td>0.77 [0.48; 1.24]</td>
<td>0.290</td>
<td>-0.24</td>
</tr>
<tr>
<td>Mortality</td>
<td>53</td>
<td>30</td>
<td>50</td>
<td>51</td>
<td>0.50 [0.41; 0.88]</td>
<td>0.008</td>
<td>0.13</td>
</tr>
<tr>
<td>CV Mortality</td>
<td>48</td>
<td>20</td>
<td>26</td>
<td>26</td>
<td>0.67 [0.39; 1.14]</td>
<td>0.140</td>
<td>0.05</td>
</tr>
</tbody>
</table>
Plethora of putative mechanisms for CV benefit ...

Overweight / Obesity and Physical Inactivity lead to Insulin Resistance

Neuroprotection
• ↑GLP-1 / ↓DPP-4
  • ↓ Stroke
  • ↓ MMP activity

Adipoprotection
- Anti-inflammatory Effects
- Immunomodulation
  • ↑ macrophage infiltration
  • ↓ Insulin sensitivity

Increased DPP-4 activity

DPP-4i secretion of DPP-4

Cardioprotection
• Improved diastolic function
• ↓ Infarct size and fibrosis
• ↑ SDF-1a, CD34, c-kit, CXCR-4
• Improved cardiac function and structure, ↓ BNP

Vasculoprotection
• ↑ endothelial function
• ↓ decreased BP
• ↑ Insulin sensitivity
• ↓ vascular inflammation
  ↓ oxidative stress, ↓ expression of inflammatory genes and ↓ infiltration of inflammatory cells (mediated by GLP-1(7-36) and split products GLP-1 (9-36) and GLP-1(28-37))

Renoprotection
• ↓ Microalbuminuria
• Suppression of TGF-β, fibronectin and AP-1 binding in PTC

Bone Marrow
• ↑ SDF-1α mediated EPC recruitment
DPP4 inhibitors CV Trials

- **SAVOR-TIMI 53** *(saxagliptin)*
  - 16,492 Pts w/ CV disease or mult risk factors; 1222 MACE

- **EXAMINE** *(alogliptin)*
  - 5380 Pts w/ ACS; 621 MACE

- **TECOS** *(sitagliptin)*
  - 14,671 Pts w/ CV disease; 1211 MACE

---

### SVORA-TIMI 53
- HR 1.00 (0.89-1.12)

### EXAMINE
- HR 0.96 (0.83-1.11)

### TECOS
- HR 0.99 (0.89-1.11)

---

**CV Death, MI, Stroke (% per yr)**

- **DPP4i**
- **Placebo**

### Comparison of non-CVOT & CVOT

#### Study name

<table>
<thead>
<tr>
<th>Study name</th>
<th>Hazard ratio</th>
<th>Lower limit</th>
<th>Upper limit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Non-CVOT RCTs</td>
<td>0.71</td>
<td>0.59</td>
<td>0.86</td>
</tr>
<tr>
<td></td>
<td>0.71</td>
<td>0.59</td>
<td>0.86</td>
</tr>
<tr>
<td>SAVOR-TIM 53</td>
<td>1.00</td>
<td>0.89</td>
<td>1.12</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>0.96</td>
<td>0.83</td>
<td>1.11</td>
</tr>
<tr>
<td>TECOS</td>
<td>0.99</td>
<td>0.89</td>
<td>1.11</td>
</tr>
<tr>
<td></td>
<td>0.99</td>
<td>0.92</td>
<td>1.06</td>
</tr>
</tbody>
</table>

#### Hazard ratio and 95% CI

- **P for heterogeneity by trial type 0.001**
Linagliptin

- Pre-specified patient-level pooled analysis of all available double-blind, randomized, controlled trials, ≥12 weeks’ duration
  - 19 trials, 9459 subjects
  - Linagliptin versus placebo/active treatment
  - 122 MACE events
  - MACE HR: 0.78 (0.55-1.11)

- CARMELINA
  - Dedicated CV outcomes trial
  - 6980 patients
  - Linagliptin vs. placebo
  - ≥611 MACE events
  - MACE HR: 1.02
# SGLT2i Dapagliflozin

## Meta-analysis of non-CVOTs

9339 patients from 21 trials

<table>
<thead>
<tr>
<th>Event</th>
<th>DAPA  n/N</th>
<th>Event rate/100 p-y</th>
<th>Control n/N</th>
<th>Event rate/100 p-y</th>
<th>HR (95% CI)</th>
<th>HR in dedicated CVOTs for other SGLT2i</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>20/3825</td>
<td>0.37</td>
<td>18/2200</td>
<td>0.59</td>
<td>0.704 (0.364, 1.359)</td>
<td>0.62-0.87</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>30/5244</td>
<td>0.48</td>
<td>33/3014</td>
<td>0.91</td>
<td>0.567 (0.339, 0.947)</td>
<td>0.85-0.87</td>
</tr>
<tr>
<td>Stroke</td>
<td>25/4227</td>
<td>0.45</td>
<td>18/2412</td>
<td>0.57</td>
<td>0.999 (0.536, 1.864)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina</td>
<td>26/4592</td>
<td>0.44</td>
<td>20/2697</td>
<td>0.58</td>
<td>0.870 (0.475, 1.593)</td>
<td></td>
</tr>
<tr>
<td>Unplanned coronary revascularisation</td>
<td>58/5525</td>
<td>0.90</td>
<td>55/3153</td>
<td>1.47</td>
<td>0.729 (0.497, 1.067)</td>
<td></td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>10/2576</td>
<td>0.15</td>
<td>16/1780</td>
<td>0.41</td>
<td>0.361 (0.156, 0.838)</td>
<td></td>
</tr>
</tbody>
</table>
Why can non-dedicated CVOTs be unreliable?

- Smaller # of events and hence wide confidence intervals? *but would not explain why point estimates almost always seem to be more favorable*
- “Development bias” to only take forward drugs that have promising phase 2/3 CV outcomes data? *but has been seen for multiple drugs in a class*
- Publication bias to only publish if meta-analysis shows favorable results? *but has been seen for multiple classes of drugs*
- Lower risk study population? *but no data to suggest such effect modification (greater benefit in less sick patients) in CVOTs; if anything, the contrary*
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Observational Data

• Convenient as much easier to obtain
• But lack of randomization raises concern that analyses, despite attempts at adjustment, are hopelessly confounded
Hormone Replacement Therapy

Nurses Health Study

- Prospective observational study
- 32,317 postmenopausal women
- Categorized based on HRT use

Table 3. Relative Risks of Coronary Heart Disease, According to Postmenopausal Hormone Use, after Simultaneous Adjustment for Potential Risk Factors in Proportional-Hazards Model.*

<table>
<thead>
<tr>
<th>Disease and Hormone Use</th>
<th>Coefficient</th>
<th>Relative Risk*</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total coronary disease</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current vs. never</td>
<td>-1.22</td>
<td>0.30 (0.14, 0.64)</td>
<td>0.002</td>
</tr>
<tr>
<td>Past vs. never</td>
<td>-0.52</td>
<td>0.59 (0.33, 1.06)</td>
<td>0.08</td>
</tr>
<tr>
<td>Nonfatal infarction only</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Current vs. never</td>
<td>-1.08</td>
<td>0.34 (0.14, 0.82)</td>
<td>0.02</td>
</tr>
<tr>
<td>Past vs. never</td>
<td>-0.43</td>
<td>0.65 (0.33, 1.28)</td>
<td>0.11</td>
</tr>
</tbody>
</table>

*The potential risk factors were a paternal history of infarction (none, at ≤60 yr, at >61 yr), a maternal history of infarction (none, at ≤60 yr, at >61 yr), type of menopause (natural or surgical), time period (1976-1978, 1978-1980), smoking status (current [at three levels of intensity], past, or never), hypertension (yes, no), diabetes (yes, no), past use of oral contraceptives (yes, no), high serum cholesterol level (yes, no), age (five categories), obesity (three categories), current hormone use (yes, no), and past hormone use only (yes, no).

†Figures in parentheses are 95% confidence limits.
Hormone Replacement Therapy

Nurses Health Study
• Prospective observational study
• 32,317 postmenopausal women
• Categorized based on HRT use

Women’s Health Initiative
• Randomized controlled trial
• 16,608 postmenopausal women
• Randomized to HRT vs placebo

Table 3. Relative Risks of Coronary Heart Disease, According to Postmenopausal Hormone Use, after Simultaneous Adjustment for Potential Risk Factors in Proportional-Hazards Model. *

<table>
<thead>
<tr>
<th></th>
<th>HR 1.29 (95% CI 1.02-1.63)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adjusted RR</td>
<td>0.30, P=0.002</td>
</tr>
</tbody>
</table>

*The potential risk factors were a paternal history of infarction (none, at ≤60 yr, at >61 yr), a maternal history of infarction (none, at ≤60 yr, at >61 yr), type of menopause (natural or surgical), time period (1976-1978, 1978-1980), smoking status (current [at three levels of intensity]. past, or never), hypertension (yes, no), diabetes (yes, no), past use of oral contraceptives (yes, no), high serum cholesterol level (yes, no), age (five categories), obesity (three categories), current hormone use (yes, no), and past hormone use only (yes, no).

Figures in parentheses are 95% confidence limits.
## Antiplatelet Therapy

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RANDOMIZED Controlled Trial Data (TRITON-TIMI 38, n=13,608)</th>
<th>OBSERVATIONAL Data (TRANSLATE-ACS, n=11,784)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Unadjusted</td>
<td>Inverse Probability of Treatment Weighting</td>
</tr>
<tr>
<td>MACE</td>
<td>0.81</td>
<td>0.76</td>
</tr>
<tr>
<td>Bleeding</td>
<td>1.32</td>
<td>0.71</td>
</tr>
</tbody>
</table>

“Conclusions regarding the safety and efficacy of antiplatelet therapy varied depending on analytic technique, and none were concordant with the results from randomized trials.”

*NEJM 2007;357:2001-15*

*JAMA Cardiol 2016;1:655-65*
# DPP4 Inhibitors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RANDOMIZED Controlled Trial Data</th>
<th>OBSERVATIONAL Data</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>SAVOR-TIMI 53 (n=16,492; saxagliptin)</td>
<td>US Claims Data (n=79,538)</td>
</tr>
<tr>
<td></td>
<td>EXAMINE (n=5380; alogliptin)</td>
<td>0.85 MI 0.88 CVA</td>
</tr>
<tr>
<td></td>
<td>TECOS (n=14,671; sitagliptin)</td>
<td>n/a</td>
</tr>
<tr>
<td></td>
<td>CARMELINA (n=6980; linagliptin)</td>
<td>0.81</td>
</tr>
<tr>
<td>MACE</td>
<td>1.00</td>
<td>0.99</td>
</tr>
<tr>
<td>HF</td>
<td>1.27</td>
<td>1.07</td>
</tr>
</tbody>
</table>

Comparator not placebo, but other glucose-lowering agents

# Incretin-Based Drugs and Heart Failure

<table>
<thead>
<tr>
<th>Class of Glucose-Lowering Agent</th>
<th>Hazard Ratio for Hospitalization for Heart Failure</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RANDOMIZED Controlled Trial Data (Meta-analysis)</strong></td>
<td><strong>OBSERVATIONAL Data (Adjusted)</strong></td>
</tr>
<tr>
<td><strong>80,375 patients</strong></td>
<td><strong>458,982 patients</strong></td>
</tr>
<tr>
<td>DPP4 inhibitor</td>
<td>~1.05 (0.90-1.24)</td>
</tr>
<tr>
<td>GLP-1 analogue</td>
<td>~0.90 (0.80-1.01)</td>
</tr>
</tbody>
</table>

Comparator not placebo, but other glucose-lowering agents

# SGLT2 Inhibitors

<table>
<thead>
<tr>
<th>Outcome</th>
<th>RANDOMIZED Controlled Trial Data</th>
<th>OBSERVATIONAL Data (Propensity Score Adjusted)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>EMPA-REG Outcomes (n=7020; empagliflozin)</td>
<td>CANVAS (n=10,142; canagliflozin)</td>
</tr>
<tr>
<td>Hosp HF</td>
<td>0.65</td>
<td>0.67</td>
</tr>
<tr>
<td>Death</td>
<td>0.68</td>
<td>0.87</td>
</tr>
</tbody>
</table>

~5% empagliflozin use. majority was canagliflozin

*NEJM 2015;373:2117-28 & 2017;377:644-57*  
*Circulation 2017;136:249-59; ACC 2018*
Why can observational data be unreliable?

• Confounding
• Confounding
• Confounding
• Magnitude of any plausible treatment effect is very likely to be outweighed by measured (but incompletely adjusted for) and unmeasured confounders related to patients and/or physicians more likely to:
  – be cognizant of
  – want
  – be prescribed / think to prescribe
  – be able to afford
  – receive
expensive new therapies.
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Streamlined RCTs (1)

• Critical to keep randomization
• Can make trial more efficient
• PROBE [prospective, randomized, open-label, blinded endpoint]

• Sites
  – Utilize very high-enrolling sites to allow for fewer sites, but more patients per site
  – Better quality and sites more experienced and focused
  – Monitoring resources not as scattered

• Patient contact through mobile devices
• Risk-based monitoring
• Or, embed in health care delivery system
Streamlined RCTs (2)

- **Data collection**
  - May be able to get key efficacy outcomes from medical records
  - But more detailed data (sometimes requested by FDA; e.g., MI type or size; modified Rankin for stroke) unlikely to be readily unavailable
  - AEs will not be uniformly captured; some SAEs might be captured; causality will not be reliably assessed
  - Safety laboratory testing would require dedicated visits
Streamlined RCTs (3)

- Claims / national database data
  - Depends on system
  - Questions regarding fidelity
  - Unable to do focused safety assessments

<table>
<thead>
<tr>
<th>Event</th>
<th>No. of Events by Type of Agreement</th>
<th>κ (95% CI)a</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Claims Yes, Physician Yes</td>
<td>Claims No, Physician Yes</td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>482</td>
<td>264</td>
</tr>
<tr>
<td>First diagnosis code</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First diagnosis code</td>
<td>101</td>
<td>28</td>
</tr>
<tr>
<td>All bleeding</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First diagnosis code</td>
<td>351</td>
<td>514</td>
</tr>
</tbody>
</table>
Streamlined RCTs (4)

• Monitoring
  – Large amounts of time and resources spent monitoring trials
  – Much of it spent on items that could not meaningfully impact internal validity of a large, randomized, double-blind, controlled trial
  – But done for fear that even minor errors would cast doubt on integrity of trial
  – Shifting more to centralized, risk-based monitoring and focusing on truly important issues would be a better use of resources
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Equipoise: Safety (1)

- Logical for initial trials for safety to be placebo-controlled
- Assume have shown safety (but not efficacy) with a drug in a class

*Is it ethical to continue to conduct placebo-controlled trials to study additional members of same drug class?* Yes

*Is it necessary to require such trials to study additional members of same class?* Probably. There can be drug-specific adverse reactions …
Primary Outcome

An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School

REVEAL Collaborative Group. *NEJM* 2017;377:1217-27

**Primary Outcome**

- **Participants with Event (%):**
  - Anacetrapib: 1640 (10.8%)
  - Placebo: 1803 (11.8%)

- **Rate ratio:** 0.91 (0.85 to 0.97)

- **P-value:** 0.004

---

**Graph: Years of Follow-up vs. Participants with Event (%)**

- **Anacetrapib (LDL-C 53 mg/dL):**
- **Placebo (LDL-C 63 mg/dL):**
• 15,067 patients with vascular disease
• Atorvastatin titrated to achieve LDL-C <100 mg/dL
• Intervention: torcetrapib 60 mg qd vs placebo

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Torcetrapib</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HDL-C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>2% ↑</td>
<td>72% ↑</td>
</tr>
<tr>
<td>Achieved (mg/dl)</td>
<td>49</td>
<td>83</td>
</tr>
<tr>
<td><strong>LDL-C</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>% Change</td>
<td>3% ↑</td>
<td>25% ↓</td>
</tr>
<tr>
<td>Achieved (mg/dl)</td>
<td>81</td>
<td>58</td>
</tr>
</tbody>
</table>

**All-cause mortality:**
HR 1.58 (95% CI 1.14-2.19), P=0.006

**Major cardiovascular events:**
HR 1.25 (95% CI 1.09-1.44), P=0.001

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Torcetrapib</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Δ SBP (mmHg)</td>
<td>+0.9</td>
<td>+5.4</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Δ DBP (mmHg)</td>
<td>-0.1</td>
<td>+2.0</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>
DPP4 inhibitors: MACE & HF

- SAVOR-TIMI 53 (saxagliptin): 16,492 patients w/ CV disease or multiple risk factors
- EXAMINE (alogliptin): 5380 patients w/ ACS
- TECOS (sitagliptin): 14,671 patients w/ CV disease

**SAVOR-TIMI 53**
- HR 1.00

**EXAMINE**
- HR 0.96

**TECOS**
- HR 0.99

**CV Death, MI, Stroke (% per yr)**

- SAVOR-TIMI 53
- EXAMINE
- TECOS

**Hosp for Heart Failure (% per year)**

- SAVOR-TIMI 53
- EXAMINE
- TECOS

**HR**
- SAVOR-TIMI 53: 1.27 (1.07-1.51)
- EXAMINE: 1.07 (0.79-1.46)
- TECOS: 1.00 (0.83-1.20)

*NEJM 2013;369:137 & 1327 & 2015;373:232*
Equipoise: Safety (2)

- Could consider different thresholds of data as information for the class evolves
- But need to be careful not to disincentivize company to be 1\textsuperscript{st} in class
- Consider different populations that would expand the overall knowledge base for the class while still providing robust data for the drug
Equipoise: Efficacy (1)

• Now assume drug has shown efficacy (↓ risk of some cardiovascular outcome)

• Is it ethical to continue to conduct placebo-controlled trials to study additional members of same drug class? Maybe …
Equipoise: Efficacy (2)

Equipoise depends on several factors:

1. **Magnitude of clinical benefit**
   - Type of event being prevented
   - Relative risk reduction
   - *Large* ↓ *mortality* vs. *small* ↓ *coronary revascularization*
Equipoise: Efficacy (3)

Equipoise depends on several factors:

2. Certainty of benefit
   – Is it plausible based on data to date?
   – Was outcome prespecified primary endpoint?
   – Consistency with data from other trials?
TAPAS Trial

Primary efficacy endpoint was post-procedural frequency of myocardial blush grade 0 or 1.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>TAPAS (n=1071)</th>
<th>TASTE (n=7244)</th>
<th>TOTAL (n=10,732)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death</td>
<td>0.60</td>
<td>0.94</td>
<td>0.95</td>
</tr>
<tr>
<td>Reinfarction</td>
<td>0.51</td>
<td>0.81</td>
<td>1.05</td>
</tr>
</tbody>
</table>
Equipoise: Efficacy (4)

Equipoise depends on several factors:

3. Generalizability to proposed study population
   - Different types of patients (w/ & w/o ASCVD)
   - Concomitant use of other medications that could be effect modifiers (ie, benefit has not been shown in patients also being treated with X)
Equipoise: Efficacy (5)

Equipoise depends on several factors:

4. Availability & acceptance of other Rx that showed efficacy
   – Announcement of primary results
   – Publication of primary results
   – Incorporation into guidelines
   – FDA review and approval of new indication
   – Availability of drug
   – Payor willingness to reimburse
   – Acceptance by practicing clinicians
If Lack of Equipoise

- **Active control**
  - Reasonable if think new drug should have efficacy profile similar to established drug
  - *What should the safety (non-inferiority) boundary be?*
  - Assume estab drug had HR 0.80 (95% CI 0.70-0.92) vs. placebo
  - Could apply standard boundary of <1.3
  - Could argue 1.3 too conservative, as comparing with established drug that is better than placebo
  - Could argue for 1.3 [expt/pbo] × 1.25 [pbo/estab] or <1.63
  - Or, more conservatively, use UL of obs HR, so 1.3 × 1.09 or <1.41
  - If want to test for similar *efficacy*, maintain ≥50% of benefit: UL <1.12 (necessitate a very large trial)
If Lack of Equipoise

• Different population
  – Primary ASCVD prevention vs. Secondary prevention
  – Prediabetes vs Diabetes
  – Patients with Heart failure or Renal disease ± diabetes

Analogous to statins, which started in patients with prior MI and high LDL-C, and then targeted patients with lower levels of LDL-C, and then shifted from secondary to primary prevention.
Outline

1. Work that goes into a randomized, controlled cardiovascular outcomes trial (CVOT)
2. Non-CVOT RCTs
3. Observational data
4. Streamlined or pragmatic CVOT
5. Equipoise as data emerge in a drug class
6. Optimal safety & efficacy endpoints
What is the right safety endpoint?

• CV Safety Trials stemmed from concern for possible ↑ risk of MI
• Composite safety outcome: CV death, MI, or stroke
• Is that necessarily correct CV safety concern for all diabetes drugs?
  – Hard, “irreversible damage” outcomes
  – But largely atherosclerosis-centered outcomes
  – Seen data for TZDs and some DPP4i for increased risk for heart failure
What is the right efficacy endpoint?

• Composite efficacy outcome of “CV death, MI, or stroke” natural extension of safety analysis
• Is that necessarily most logical efficacy outcome for all diabetes drugs?
  – Hard, “irreversible damage” outcomes
  – But largely atherosclerosis-centered outcomes
  – Seen data for SGLT2i for decreased risk for heart failure and renal disease
DECLARE-TIMI 58
Initial Analytic Plan

• Based on regulatory requirement, safety outcome MACE (CV death, MI, or stroke)
• Primary efficacy outcome MACE; hospitalization for heart failure secondary outcome
DECLARE-TIMI 58: New External Data

• Data from EMPA-REG Outcomes showed much greater efficacy of SGLT2 inhibition on CVD/HHF than on MACE

• While blinded and before 1st DMC meeting, elevated CVD/HHF so that now dual primary endpoints

• Press release:
  “[Dapagliflozin] met its primary safety endpoint of non-inferiority for MACE. [Dapagliflozin] achieved a statistically-significant reduction in [CVD/HHF] … fewer MACE events were observed with [dapagliflozin] however, this did not reach statistical significance.”
What is the right population?

- 100% of patients with diabetes?
- Pre-diabetes? Normoglycemia? Especially if safety data for other members of the class
- ASCVD? Necessary for MACE events
- Heart failure?
- Chronic kidney disease?
- Combine multiple populations in a single trial (or program with certain analyses pooled)
Prior to the FDA Guidance

"Your blood sugar is too high."
### 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure

<table>
<thead>
<tr>
<th>Recommendations</th>
<th>Class</th>
<th>Level</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Treatment of hypertension is recommended to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
<td>126, 129, 150, 151</td>
</tr>
<tr>
<td>Treatment with statins is recommended in patients with or at high-risk of CAD whether or not they have LV systolic dysfunction, in order to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
<td>137–140, 152</td>
</tr>
<tr>
<td>Counselling and treatment for smoking cessation and alcohol intake reduction is recommended for people who smoke or who consume excess alcohol in order to prevent or delay the onset of HF.</td>
<td>I</td>
<td>C</td>
<td>131–134</td>
</tr>
<tr>
<td>Treating other risk factors of HF (e.g. obesity, dysglycaemia) should be considered in order to prevent or delay the onset of HF.</td>
<td>IIA</td>
<td>C</td>
<td>130, 141, 153–155</td>
</tr>
<tr>
<td><strong>Empagliflozin should be considered in patients with type 2 diabetes in order to prevent or delay the onset of HF and prolong life.</strong></td>
<td>IIA</td>
<td>B</td>
<td>130</td>
</tr>
<tr>
<td>ACE-I is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction in order to prevent or delay the onset of HF and prolong life.</td>
<td>I</td>
<td>A</td>
<td>5, 144, 145</td>
</tr>
<tr>
<td>ACE-I is recommended in patients with asymptomatic LV systolic dysfunction without a history of myocardial infarction, in order to prevent or delay the onset of HF.</td>
<td>I</td>
<td>B</td>
<td>5</td>
</tr>
<tr>
<td>ACE-I should be considered in patients with stable CAD even if they do not have LV systolic dysfunction, in order to prevent or delay the onset of HF.</td>
<td>IIA</td>
<td>A</td>
<td>142</td>
</tr>
<tr>
<td>Beta-blocker is recommended in patients with asymptomatic LV systolic dysfunction and a history of myocardial infarction, in order to prevent or delay the onset of HF or prolong life.</td>
<td>I</td>
<td>B</td>
<td>146</td>
</tr>
</tbody>
</table>
| ICD is recommended in patients:  
a) with asymptomatic LV systolic dysfunction (LVEF ≤30%) of ischaemic origin, who are at least 40 days after acute myocardial infarction,  
b) with asymptomatic non-ischaemic dilated cardiomyopathy (LVEF ≤30%), who receive OMT therapy, | I     | B     | 149, 156–158 |
Antihyperglycemic Therapy in Adults with Type 2 Diabetes

At diagnosis, initiate lifestyle management, set A1C target, and initiate pharmacologic therapy based on A1C:

- **A1C is less than 9%, consider Monotherapy.**

- **A1C is greater than or equal to 9%, consider Dual Therapy.**

- **A1C is greater than or equal to 10%, blood glucose is greater than or equal to 300 mg/dL, or patient is markedly symptomatic, consider Combination Injectable Therapy** (See Figure 8.2).

### Monotherapy

**Lifestyle Management + Metformin**

Initiate metformin therapy if no contraindications* (See Table 8.1)

**A1C at target after 3 months of monotherapy?**

**Yes:**
- Monitor A1C every 3–6 months

**No:**
- Assess medication-taking behavior
- Consider Dual Therapy

### Dual Therapy

**Lifestyle Management + Metformin + Additional Agent**

**ASCVD?**

**Yes:**
- Add agent proven to reduce major adverse cardiovascular events and/or cardiovascular mortality (see recommendations with * on p.575 and Table 8.1)

**No:**
- Add second agent after consideration of drug-specific effects and patient factors (See Table 8.1)
<table>
<thead>
<tr>
<th>Drug</th>
<th>Efficacy*</th>
<th>Hypoglycemia</th>
<th>Weight Change</th>
<th>CV Effects</th>
<th>Cost</th>
<th>Oral/SQ</th>
<th>Renal Effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metformin</td>
<td>High</td>
<td>No</td>
<td>Neutral (Potential for Modest Loss)</td>
<td>Potential Benefit</td>
<td>Neutral</td>
<td>Low</td>
<td>Oral</td>
</tr>
</tbody>
</table>
| SGLT-2 Inhibitors             | Intermediate | No           | Loss | Benefit: canagliflozin, empagliflozin | Benefit: canagliflozin, empagliflozin | High | Oral | Benefit: canagliflozin, empagliflozin | ▪ Canagliflozin not recommended with eGFR <45  
▪ Dapagliflozin not recommended with eGFR <60; contraindicated with eGFR <30  
▪ Empagliflozin: contraindicated with eGFR <30 |
| GLP-1 RAs                     | High      | No           | Loss | Neutral | Lixisenatide, exenatide extended release | Neutral | High | SQ | Benefit: liraglutide | ▪ Exenatide: not indicated with eGFR <30  
▪ Lixisenatide: caution with eGFR <30  
▪ Increased risk of side effects in patients with renal impairment |
| DPP-4 Inhibitors              | Intermediate | No           | Neutral | Neutral | Potential Risk: saxagliptin, alogliptin | High | Oral | Neutral | ▪ Renal dose adjustment required: can be used in renal impairment |
| Thiazolidinediones            | High      | No           | Gain | Potential Benefit: pioglitazone | Increased Risk | Low | Oral | Neutral | ▪ No dose adjustment required  
▪ Generally not recommended in renal impairment due to potential for fluid retention |
Conclusions

1. CVOT for glucose-lowering agents are large affairs, requiring large investment of time & money

2. That burden may dissuade some companies to target resources for diabetes

3. However, the trials have led to a wealth of data that have advanced diabetes care
   a) Shift from focusing on HbA1c (which may be largely unrelated to macrovascular outcomes)
   b) To reducing cardiovascular risk
Conclusions

4. No substitute for dedicated CVOT to definitely answer these questions (although can be simpler)

5. As robust, validated treatment benefits consistently emerge for a class, equipoise for ongoing trials needs to be considered

6. When designing a new trial, careful attention needs to be paid to existing data to guide selection of:
   a) Patients to be studied
   b) Comparator
   c) Endpoints