Current State of Diabetes Drug Development Challenges and Opportunities

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Overview

- **Introduction**
- **Diabetes Drug Development: Past, Present, Future**
- **Challenges**
- **Opportunities**
- **Efforts of Today's Meeting**

Overview of T2DM

- **Affects > 20 million in the U.S.**
- **Leading cause of kidney failure, blindness, non-traumatic amputations**
- **2 to 4-fold increase in CV death**
- **Chronic disease with need for multiple drug therapy over time**
- **Multiple co-morbid conditions (obesity, renal disease, HTN, heart disease)**
- **Rising prevalence includes a wide spectrum of age**

Past, Present and Future

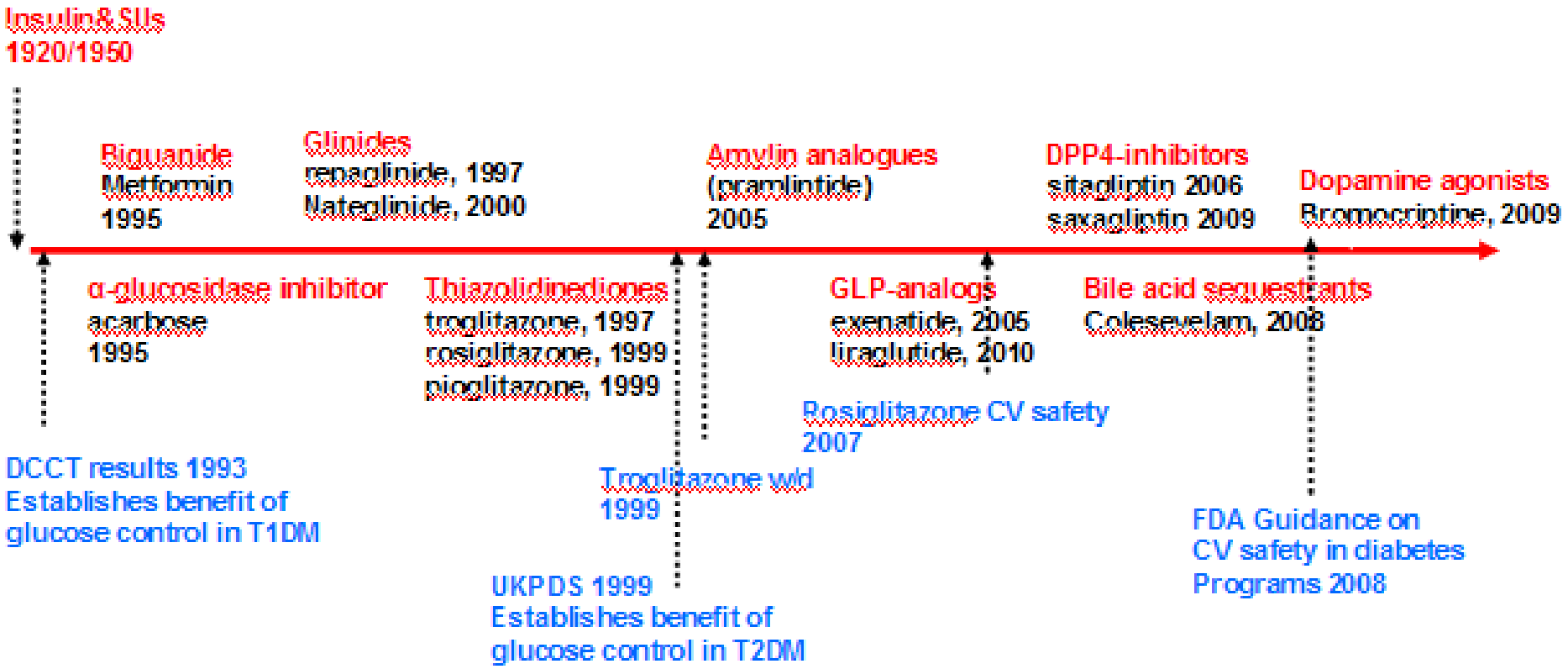
Pre-2000

- Insulin
- Sulfonylureas
- Metformin
- Alpha-glucosidase inhibitors
- Glinides
- TZDs

Post-2000

- Amylin analogues
- GLP-1 analogues/receptor agonists
- DPP4-inhibitors
- Bile-acid sequestrants
- Dopamine agonists

Past, Present, and Future



Diabetes Cardiovascular Guidance: Specific Recommendations

- **For new clinical studies in the planning stage:**
  - **Establish an independent CV endpoints committee for prospective adjudication of all Phase 2 and 3 trials**
  - **Events of interest should include CV death, MI, and stroke**
  - **Can include hospitalization for acute coronary syndrome, urgent revascularization procedures, and possibly other endpoints**
  - **Patient population should include those at higher risk for a CV event (longer duration of DM, elderly, renal impairment)**
  - **Studies are designed and conducted such that a MA can be performed**
  - **Protocol describing statistical methods for the proposed MA should be submitted**

Diabetes Cardiovascular Guidance: Specific Recommendations

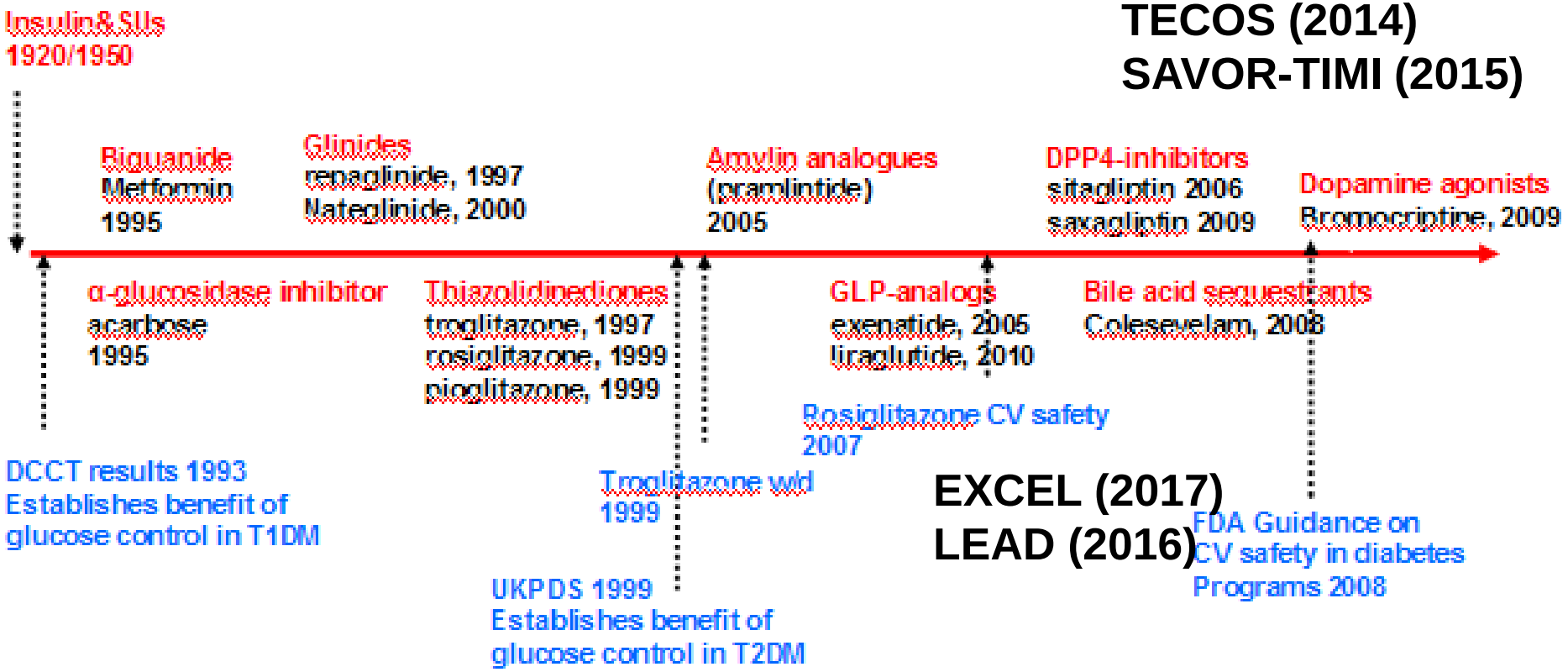
- **<u>For completed studies, before submission of the NDA/BLA:</u>**
  - **Compare incidence of CV events with investigational agent to incidence in control group obtained through**
    - **A meta-analysis of phase 2 and 3 trials**
    - **A single, large safety trial**

Diabetes Cardiovascular Guidance: Specific Recommendations

UPPER BOUND OF 95% CI FOR RISK RATIO	CONCLUSION
>1.8	Inadequate to support approval
>1.3 but <1.8*	Postmarketing trial(s) needed to show definitively <1.3
<1.3*	Postmarketing cardiovascular trial(s) generally not necessary

CI=confidence interval
*with a reassuring point estimate

Past, Present, and Future



Future……

2011 →

- **Larger pre-marketing programs, including prospective CV outcomes data**
  - **Programs currently underway have planned CV outcomes trials, some with objectives of showing CV benefit**
- **More data in diverse T2DM population**
- **More comparative efficacy and safety data**

Challenges in Trial Design

- Choice of comparator (active control, add-on to pbo control)
- Worsening glycemic control in long-term CV safety trial
- Controlling other CV risk factors
- Choice of CV endpoint
  - Primary endpoint – MACE or MACE plus hospitalization for unstable angina
- Individual contribution of a component to the overall composite endpoint
- Maintaining trial integrity with interim analyses

Report from HHS's Agency for Healthcare Research and Quality

Gaps in Knowledge with Current Diabetes Therapies

- **Limited enrollment of high risk patients (elderly, multiple co-morbid medical conditions)**
- **Sparse information on comparative effectiveness of many multi-drug regimens**
- **Insufficient data on long-term clinical outcomes (CVD, nephropathy, neuropathy)**
- **Duration of trials – "few studies on harms lasted longer than 2 yrs"**

Report from HHS's Agency for Healthcare Research and Quality

Opportunities in Diabetes Development Programs

- Assurance of CV safety for diabetes therapies
- Longer duration of evaluation to better assess safety of chronic therapy
- Comparative E/S data ---- which drug to choose when and for whom
- Other benefits of diabetes therapy?

CSRC Thinktank: Today's Agenda

- **Effort #1: Phase 3 and 4 trials in T2DM**
- **Effort #2: How best to utilize database coming from Phase 3 and 4 trials**
- **Effort #3: What else should we be asking from these large CV trials**