CV Safety Outcome Trials for New Diabetes Drugs

Occurrences since our Think Tank

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Views expressed are my mine.

Outline of Presentation

- **The need for biopharmaceuticals.**
- **Current regulatory landscapes and the effective need for CV safety outcome studies.**
- **Outcome trials: Results and ongoing studies.**
- **Alternative approaches discussed at our Think Tank, and also RMST**
- **Perspectives of two influential individuals at FDA.**
- **My perspective.**
- **Differing viewpoints in the Literature, and Conclusion: Much more multi-stakeholder discussion is needed on diabetes drug development (both safety and efficacy).**
- **FYI: The 13th Global CVCT Forum, December 1-3, Washington DC.**

The Need for Biopharmaceuticals: From the EMA's 2012 Guideline…

"Glucose control in type 2 diabetes deteriorates progressively over time, and, after failure of diet and exercise alone, needs on average a new intervention with glucose-lowering agents every 3-4 years in order to obtain/retain good control."

That is, a patient's drug regimen becomes insufficient over several years, meaning that an additional drug will be added.

When this happens, the drugs the patient is already taking are often kept as they still have a beneficial effect, but their effect alone is not great enough to counteract disease progression. Hence, a constant provision of new drugs is necessary.

Current Regulatory Landscapes in a Nutshell

Stimulus: Reported result from a single meta-analysis odds (relative) ratio for MI in rosiglitazone versus control group (*Nissen & Wolski, 2007*):

- 1.43 (95% CI: 1.03 to 1.98, p=0.03) [Absolute risk given minimal attention]

Guidelines arguably well intended:

- Life expectancy of a patient with type 2 diabetes is likely to be reduced by up to 10 years as a result of this condition (*Diabetes in the UK Report, 2010*), a dramatic statistic driven to a large extent by increased risk of heart disease, renal disease, and stroke.

FDA (2008: dedicated Guidance for Industry) and EMA (2012; incorporated in general Guideline for development of diabetes drugs) have a fundamental similarity: The prospective exclusion of an unacceptable cardiovascular risk, which essentially requires the conduct of a large, long, and expensive cardiovascular safety outcome study.

- Geiger et al (2015) discussed how best to meet requirements in a CSRC Expert Perspective paper.

This is a 'blanket requirement' for all new antidiabetic drugs for type 2 diabetes.

Outcome Trial Results: *Examples of Noninferiority*

Trial (Drug and class)	Main Result	Authors
EXAMINE (Alogliptin, DPP-4 inhibitor)	MACE: HR = 0.98 (upper bound ≤1.16)	White et al., 2013 (before Think Tank)
SAVOR-TIMI 53 (Saxagliptin, DPP-4 inhibitor)	MACE: HR = 1.00 (0.89, 1.12)	Scirica et al., 2013 (before Think Tank)
TECOS (Sitagliptin, DPP-4 inhibitor)	MACE+: HR = 0.98 (0.88, 1.09)	Green et al., 2015
ELIXA (Lixisenatide, GLP-1 receptor agonist)	MACE+: HR = 1.02 (0.89, 1.17)	Pfeffer et al., 2015

Outcome Trial Results: *Examples of Benefit (???)*

Trial (Drug and class)	Main Result	Authors
EMPA-REG (Empagliflozin, SGLT-2 inhibitor	MACE: HR = 0.86 (0.74-0.99)	Zinman et al., 2015
LEADER (Liraglutide, glucagon-like peptide 1 analogue)	MACE: HR = 0.87 (0.78-0.97)	Marso et al., 2016a
SUSTAIN-6 (Semaglutide, glucagon-like peptide 1 analogue)	MACE: HR = 0.74 (0.58-0.95)	Marso et al., 2016b

Examples of Ongoing Outcome Trials

Trial (Drug and class)	Expected Completion (Clinicaltrials.gov)
EXSCEL (Exenatide QW, GLP-1 Receptor Agonist)	April 2018 (NCT01144338)
REWIND (Dulaglutide, GLP-1 Receptor Agonist)	April 2019 (NCT01394952)
CARMELINA (Linagliptin, DPP-4 inhibitor)	January 2018 (NCT01897532)
DECLARE-TIMI 58 (Dapagliflozin, SLGT-2 inhibitor)	April 2019 (NCT01730534)
CREDENCE (Canagliflozin, SLGT-2 inhibitor)	January 2020 (NCT02065791)
VERTIS CV (Ertugliflozin, SLGT-2 inhibitor)	March 2021 (NCT01986881)

Alternative Approaches discussed at 2014 Think Tank

Discussions of alternative methodologies (see report published by *Sager et al., 2015*):

A *de novo* prospective registry/observational study

A prospective registry/ observational study built on an electronic health record platform

A prospective registry/ observational study built on an existing registry platform

A retrospective analysis built from data warehouses

- It was an excellent Think Tank that also led to an authoritative White Paper:
  - **However,** unlike the excellent regulatory science initiatives that will be discussed a little later today by Dr Darpo and Dr Gintant, there has been much less progress here.
  - **Therefore**, I'm very excited about tomorrow's Think Tank: "Cardiac Safety Assessment – Opportunities Beyond the Randomized Clinical Trial?"

Use of Hazard Ratio in a Noninferiority Trial
(4 slides courtesy of the CSRC RMST Working Group, not QuintilesIMS)

- The quantification of the treatment difference is routinely based on the hazard ratio (HR) estimate
- The precision of the HR estimate depends on the *number of observed events*, not directly on the exposure times or sample size of the study population
  - > *Event rates are often low in most safety studies* – therefore, a large number of events may be needed to ensure the prespecified criterion for the HR is attainable

- The HR is a model-based measure of differences between 2 groups and therefore assumes a relationship between the 2 distributions of the outcome variable – but what if this is not true?
- *How then is a HR interpreted clinically and in a meaningful way?*
- *What does this mean for an individual patient?*

Is there a Better Alternative?

Restricted Mean Survival Time (RMST)

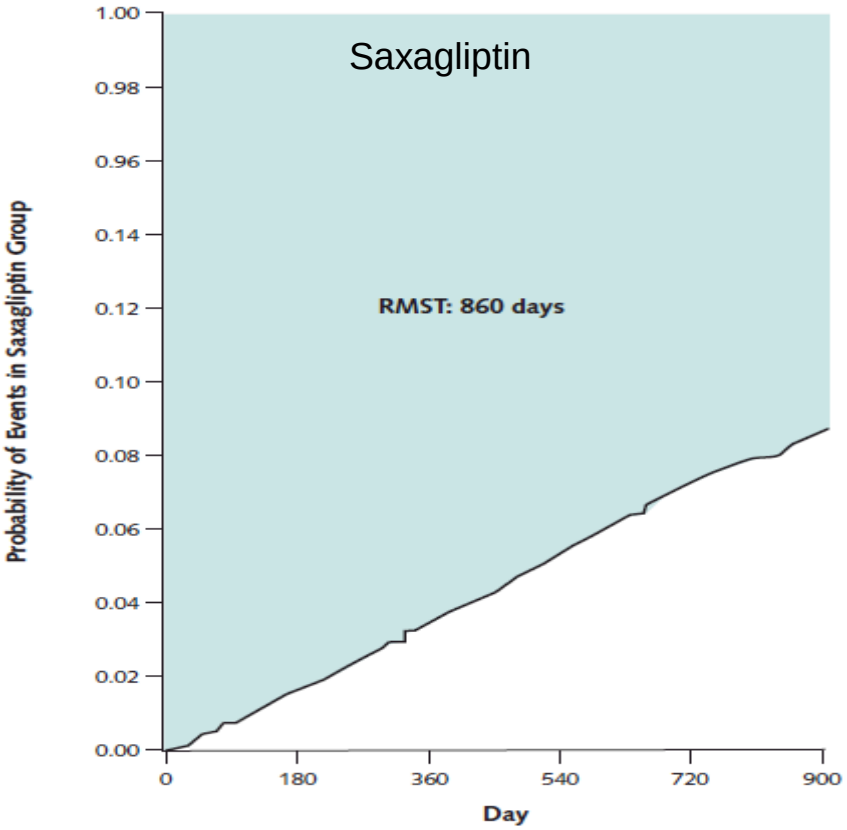
What is this?

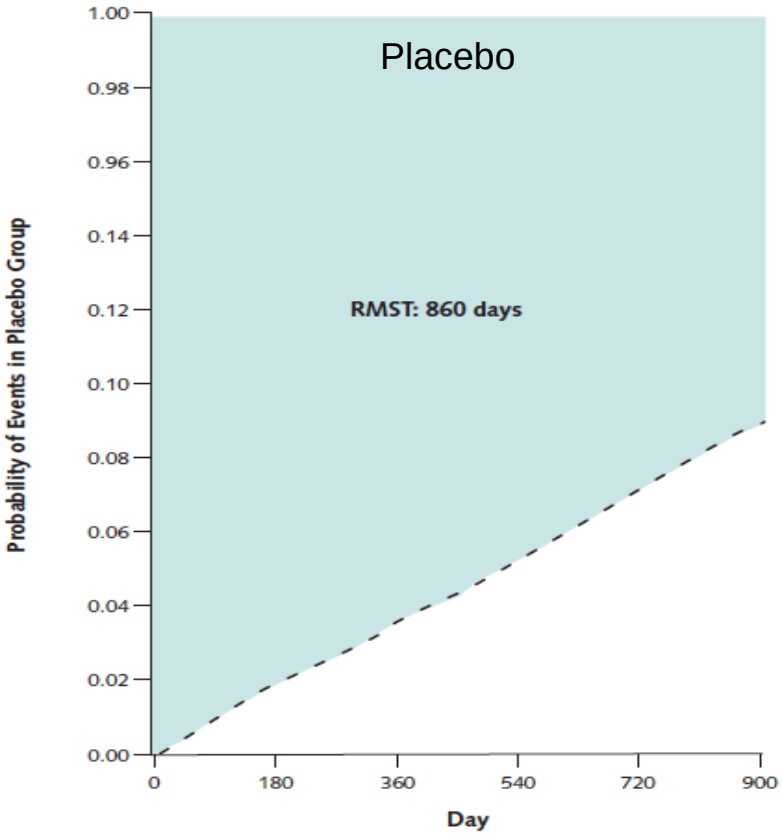
The expected time spent event-free for a future patient followed for a specified time

(the area above the empirical cumulative incidence curve)

RMST Example: SAVOR-TIMI 53
Observed Incidence Curves up to 900 days

RMST: The area above the curve is approximately 860 days in both groups





Interpretation: A patient treated & followed for 900 days, will be event free approximately 860 days for both groups. The observed difference between groups is 0 days!

RMST estimates incorporate the # of events and exposure times

Uno et al, Annals of Int Med 2015;163: 127-134

RMST vs Hazard Ratio

	Pros	Cons
RMST difference (model free)	May not need impractically large study to assess NI if the patients' exposure time is sufficiently large for safety evaluation	Need to pre-specify time point of interest
	Provides a more stable estimate than the median in survival time studies	
	Provides a clinically meaningful summary of the differences between groups	May selectively study a relatively healthy population with low event rates rather than the indicated patient population in order to obtain a NI claim
HR (model–based)	Valid summary for the difference between 2 cumulative incidence distributions (when the PH assumption is correct), with statistically efficient inference procedures	Lacks a clinically meaningful reference value for the hazard from the control group to assess the difference between groups
		Difficult to interpret if the PH model is incorrect
		May not have adequate power to detect a safety signal when the 2 hazard functions cross during the study follow-up
		May require an impractically large study because the precision of the estimated HR depends on the # of observed events and not directly on the # of patients and their exposure time
		May selectively study a higher-risk population than the indicated patient population for the new drug because many observed events are needed.

Uno et al, Annals of Int Med 2015;163: 127-134

Perspectives of Two Influential Individuals at FDA

Two spoke at a meeting at FDA on August 29th entitled “Diabetes Outcome Measures Beyond Hemoglobin A1c (HbA1c).” Focused on new potential efficacy measures

In the spirit of ‘benefit-risk assessment,’ yours truly took the opportunity to ask FDA and EMA representatives their views on CV outcome studies – specifically, would the ‘blanket’ requirement for all drugs likely be removed?

“FDA’s review of novel efficacy endpoints for diabetes therapies inevitably included discussion of the future of the cardiovascular outcomes study requirement for type 2 diabetes therapies; **comments by FDA and EMA officials sure make it sound like the requirement isn’t going away any time soon.”** (*Pink Sheet, 1st September, Executive Summary)*

November 2013: FDA Drug Safety Communication

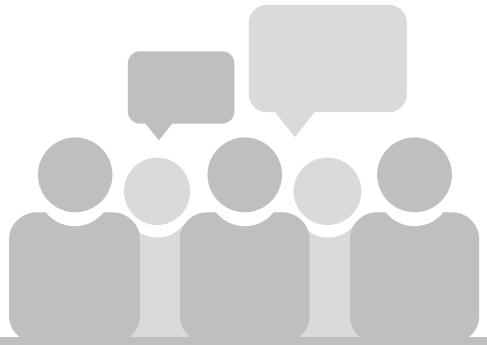
"The U.S. Food and Drug Administration (FDA) has determined that recent data for rosiglitazone-containing drugs, such as Avandia, Avandamet, Avandaryl, and generics, **do not show an increased risk of heart attack compared to the standard type 2 diabetes medicines metformin and sulfonylurea...** This decision is based on our review of data from a large, long-term clinical trial* and is supported by a comprehensive, outside, expert re-evaluation of the data conducted by the Duke Clinical Research Institute (DCRI)."

**Re-analysis of data from the RECORD trial, reported by Mahaffey et al., 2013*

December 2015: FDA Drug Safety Communication

"FDA is eliminating the Risk Evaluation and Mitigation Strategy (REMS) for rosiglitazone-containing type 2 diabetes medicines, which are approved as Avandia, Avandamet, Avandaryl, and generics…

[Since its December/November 2013 communication] **FDA has continued monitoring these medicines and identified no new pertinent safety information.** FDA will update the public if any new information becomes available."



My Perspective, therefore…

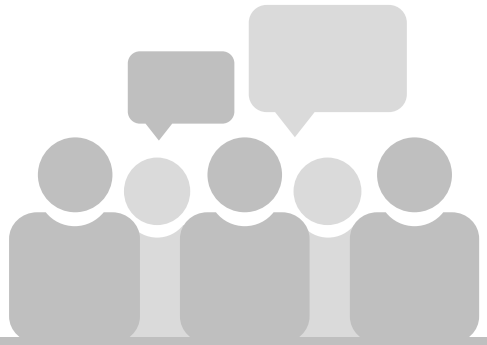
"It can reasonably be argued that there are currently burdensome regulatory landscapes in the US and Europe for all new antidiabetic drugs for type 2 diabetes that were driven by a purported increase in cardiovascular (myocardial infarction) risk that has subsequently been refuted by an influential regulatory agency."

Turner et al., © 2017

Differing Viewpoints in the Literature …

- The following perspective has been presented in the recent literature (*Lovre et al., 2016*):

"Despite criticism, these FDA-mandated trials have yielded a wealth of information about the side effects of these medications and have even shown benefits in specific clinical situations with some drugs."



Differing Viewpoints in the Literature *cntd*.

"A more specific approach might now be appropriate, where the need for CV outcome studies would be determined by regulators for each individual agent based on its mechanism of action and its preclinical and phase I to III development safety data. Requiring CV outcome safety trials seems reasonable when there is a cardiovascular signal from early development data…

"Given the difficult logistics of continuing CV safety trials for a long duration, it may be prudent to derive CV outcome data from observational studies, registries and ongoing surveillance through adverse event reporting systems."

Gupta and White, 2016

Conclusion: More multi-stakeholder discussion needed (*see next slide for info on an upcoming meeting….)*

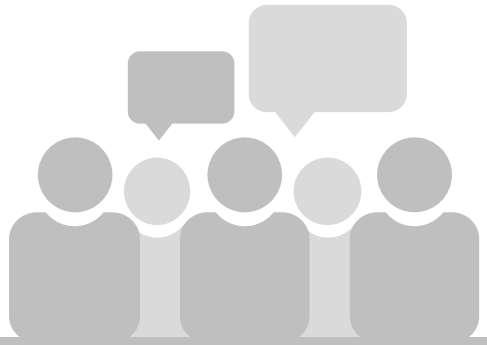
"It is critical to renew this debate so that stakeholders can collectively determine the optimal approach for developing new drugs to treat type 2 diabetes mellitus."

Zannad et al., 2016

"We endorse Zannad and colleagues' assertion that the requirements for cardiovascular safety outcome studies and the employment of cardiovascular efficacy outcome studies in this therapeutic area necessitate continued discussion in the scientific, clinical, and regulatory communities."

Turner et al., 2016

Paper and subsequent Editorial published recently in the *European Heart Journal-Cardiovascular Pharmacotherapy*



FYI: 13th Global CardioVascular Clinical Trialists Forum

The 13th Global CVCT Forum will be held on December 1-3, Washington DC
(*CVCT Forum, 2016*)

A session entitled “Diabetes Outcome Trials: Transitioning to Cardiovascular Efficacy Trials.”

LEADER and SUSTAIN-6 main results will be presented, along with further results from EMPA-REG.

Goal is to encourage discussion between diabetology, nephrology, and cardiology clinical trialists about the possibility that some of the new glucose lowering drugs might be CV (and perhaps also renal) disease-modifying drugs:

Industry, regulatory, and payers’ viewpoints will be presented.

Please join us…. (you can email Rick.Turner@quintilesims.com for details)

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