ASSESSING THE CARDIOVASCULAR RISK OF ANTI-DIABETIC THERAPIES IN PATIENTS WITH TYPE 2 DIABETES MELLITUS

UNC-Chapel Hill Biostatistics Seminar

Richard C. Zink, Ph.D.
Principal Research Statistician Developer
JMP Life Sciences
SAS Institute, Inc.

03 Sep 2015

INTRODUCTION

- Work of the ASA Biopharm Section Safety Working Group
  - Aloka Chakravarty (FDA/CDER)
  - Christy Chuang-Stein (Chuang-Stein Consulting)
  - Qi Jiang (Amgen)
  - Chunlei Ke (Amgen)
  - Haijun Ma (Amgen)
  - Jeff Maca (Quintiles)
  - Olga Marchenko (Quintiles)
  - Estelle Russek-Cohen (FDA/CBER)
  - Matilde Sanchez-Kam (Arena Pharmaceuticals)
  - Richard C. Zink (JMP Life Sciences, SAS Institute)

OUTLINE

- Define diabetes mellitus
- Safety concerns of medications
- Regulatory guidance
- Review of drug submissions
  - Discuss implications
- Development Strategies
  - Discuss implications
- Emerging Questions
- Conclusions

INTRODUCTION

- What is diabetes? (1)
  - Type I
    - Immune system destroys insulin producing cells in pancreas, eliminating production altogether
    - 5-10% of all diabetes cases
    - Formerly juvenile-onset or insulin-dependent diabetes
  - Type II
    - Insulin resistance and/or insulin deficiency
    - 90-95% of all diabetes cases
    - Formerly adult-onset or non-insulin-dependent diabetes

INTRODUCTION

- What is insulin?
  - Hormone produced by the pancreas
  - Allows your body to convert sugar (glucose) in the bloodstream to be used by cells for energy
  - Regulates blood sugar
    - Hyperglycemia (too high)
    - Hypoglycemia (too low)

INTRODUCTION

- Diabetic patients are at risk for
  - Hyperglycemia
    - Damage and dysfunction to kidneys, eyes, nerves, heart and blood vessels, limbs
  - Hypoglycemia
    - Seizures, unconsciousness, or death
  - Other
    - High blood pressure
    - High LDL cholesterol
    - Higher risk of stroke and heart disease

INTRODUCTION

- 7th leading cause of death in 2010
- Medical costs in 2012
  - Direct: $176 billion
  - Indirect: $69 billion (disability, work loss, premature death)
  - Total: $245 billion

INTRODUCTION

- Treatments
  - Type I: insulin from injections or pump (no generic form available [2])
  - Type II
    - Insulin
    - Oral meds (most common, and often multiple)
    - Both insulin and oral meds
    - Neither
  - Healthy eating and physical activity
  - Medications for blood pressure and cholesterol

INTRODUCTION

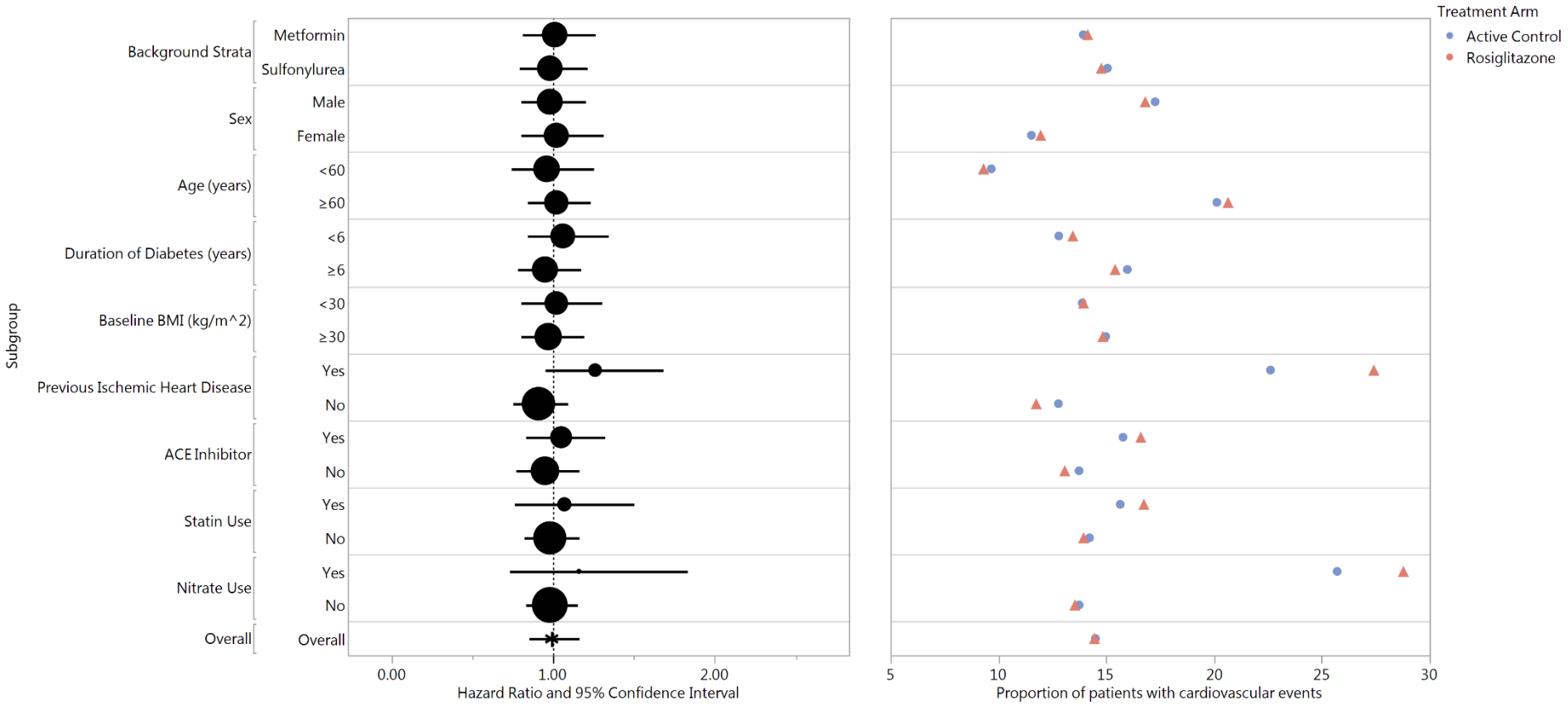
- Trials
  - Glycated haemoglobin (A1c) typically the primary endpoint
  - Change from baseline in A1c at Week 26
  - Parallel-group trials against placebo

ROSIGLITAZONE

- Meta-analysis in *New England Journal of Medicine* [3]
  - Analysis of 42 clinical trials of rosiglitazone (Avandia)
  - Elevated risk of myocardial infarction (p = 0.03)
  - Elevated risk of death from cardiovascular causes (p = 0.06)
- However
  - 6 clinical trials were excluded with no events in either arm
- Advisory committee where FDA presented a meta-analysis including the 48 trials above
  - Need better event adjudication and to assess CV risk
- Thorough summary of rosiglitazone in [5]
- 2008 FDA guidance on cardiovascular risk in T2DM [6]

CARDIOVASCULAR RISK OF TYPE 2 DIABETES MELLITUS

META-ANALYSIS



Data from [4]

FDA GUIDANCE

- Risk of major adverse cardiovascular events (MACE) assessed in two Stages
- MACE includes CV death, non-fatal myocardial infarction, and non-fatal stroke events
- Stage 1 (Pre-market)
  - $H_{10}: \frac{\lambda_t}{\lambda_c} \geq 1.8$ versus $H_{11}: \frac{\lambda_t}{\lambda_c} < 1.8$
- Stage 2 (Post-market)
  - $H_{20}: \frac{\lambda_t}{\lambda_c} \geq 1.3$ versus $H_{21}: \frac{\lambda_t}{\lambda_c} < 1.3$
- Each hypothesis tested at $\alpha = 0.05$
- EMA guidance (2012) [7]

FDA GUIDANCE

- Stage 1
  - Rewrite H_{10}: $\frac{\lambda_t}{\lambda_c} \geq 1.8$ as H_{10}: $-\log\left(\frac{\lambda_t}{\lambda_c}\right) + 0.5878 \leq 0$

```
proc seqdesign; [8]
    Stage1_Fixed: design nstages=1 alt=twosided alpha=0.05;
    samplesize model=twosamplesurv(nullhazard=1.8 1.0 hazard=1.0);
run;
```

  - 122 events for a fixed trial

- Stage 2
  - With 1.3 and 0.2624 get 611 events

FDA GUIDANCE

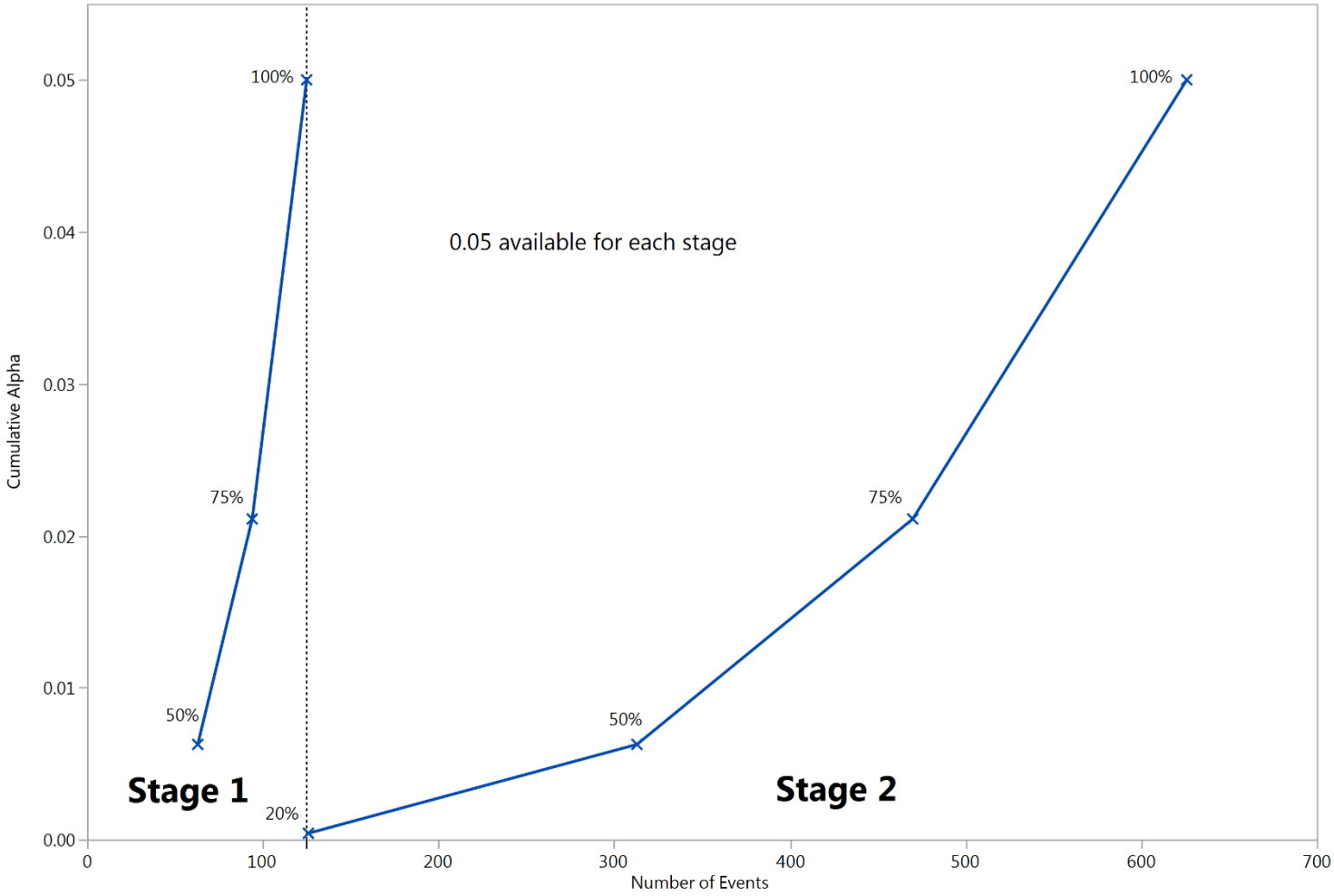
```
proc seqdesign errspend pss stopprob boundaryscale=mle plots=all; [8]
   stage1power: design nstages=3 method=errfuncpow(rho=3) alt=twosided
   alpha=0.05 info=cum(0.5 0.75 1);
   samplesize model=twosamplesurv(nullhazard=1.8 1.0 hazard=1.0);
   ods output Boundary=test_interim1;
run;
ods graphics off;

/* Analysis of Stage 1 data */
proc phreg data=T2DM;
   model weeks*event(0)=treatment;
   ods output ParameterEstimates=parms_interim1;
run;

data parms_interim1;
   set parms_interim1;
   where parameter='Treatment';
   parameter=-parameter+0.5878;
   _scale_='MLE';
   _stage_=1;
   keep _scale_ _stage_ parameter estimate stderr;
run;

proc seqtest boundary=test_interim1 parms(testvar=treatment)=parms_interim1
   infoadj=none boundaryscale=mle;
   ods output Test=test_interim2;
run;
```

FDA GUIDANCE



α-spending functions for a hypothetical sequential trial using OBF-like boundaries

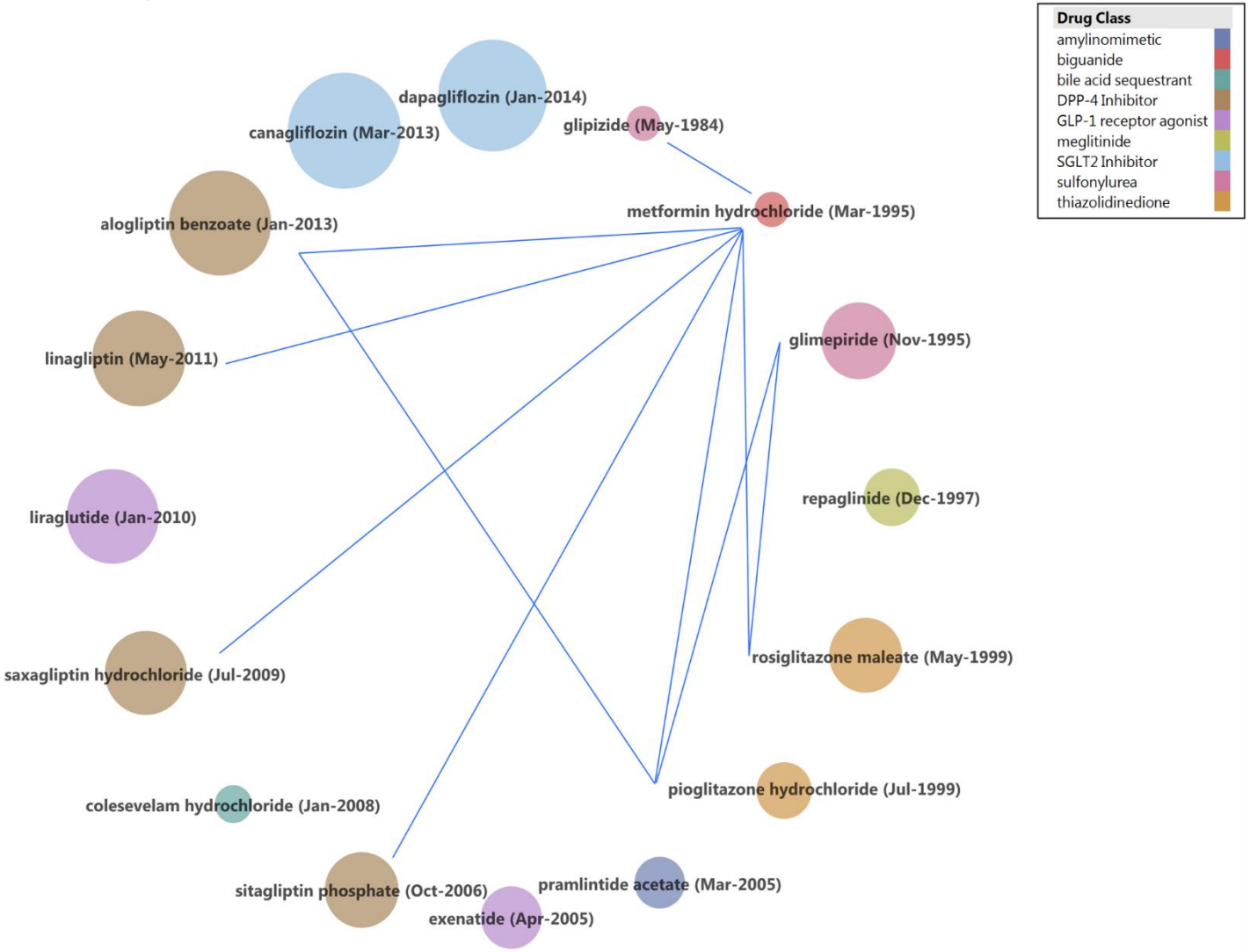
METHODS TO ASSESS CV RISK

- Information taken from www.clinicaltrials.gov, advisory committee materials, and Drugs@FDA: FDA Approved Drug Products [9]
- Details on pre-marketing meta-analysis
- Details from CV outcome trial (CVOT)
- Three eras
  - 2002 – 2008 (Pre-guidance)
  - 2009 – 2012
  - 2013 – Jan 2014

RESULTS

- Meglitinides and sulfonylureas lower blood glucose by increasing the secretion of insulin from the pancreas
- Biguanides and thiazolidinediones simultaneously decrease the production of glucose in the liver while increasing the glucose utilization of muscle cells.
- Amylinomimetics are synthetic versions of the hormone amylin. Amylin slows the movement of food through the stomach and the subsequent glucose into the bloodstream. These effects also help to decrease appetite to better allow patients to maintain a healthy weight.
- GLP-1 receptor agonists mimic the effect of the hormone incretin which stimulates the release of insulin. Further, these agonists reduce the hormone glucagon which in turn slows the movement of food through the stomach, decreasing appetite.
- DPP-4 inhibitors allow the available incretin to stay in the bloodstream longer, triggering additional insulin to be released to lower glucose levels.
- SGLT2 inhibitors lower glucose levels in the blood by increasing the renal excretion of glucose.
- The bile acid sequestrant colesevelam hydrochloride, originally approved as a lipid-lowering agent, has been shown to lower glucose levels, though the exact mechanism for this glycemic control is unknown

RESULTS



Includes earlier-released monotherapies.
Connections indicate availability of at least one combination therapy.

POST-HOC PERIOD

- No pre-specified outcome
- No adjudication
- Two endpoints
  - SMQ MACE –composite endpoint of CV death and all preferred terms in the Standardized MedDRA Queries (SMQs) for "Myocardial Infarction" and "Central Nervous System Haemorrhages and Cerebrovascular Accidents";
  - Custom MACE – subset of the above
- Post-marketing CV requirement for a CVOT

RESULTS

- CV risk assessment population typically consists of all randomized patients who received at least one dose of double-blind study therapy
- For NME, CVOT usually required. Many sponsors started studies during late phase III
- Stage 1
  - CV meta-analysis including completed phase II-III studies.
  - Prospectively adjudicate CV events
  - Some cases (canagliflozin, alogliptin), meta-analysis included interim CVOT data

RESULTS

- Cox proportional hazard models stratified by study often the primary analysis method for meta-analysis
- CMH methods treating endpoints as binary often used as sensitivity analyses
- Extensive subgroup analyses, pre-planned and ad hoc
- Stage 2
  - Second meta-analysis plus CVOT
  - Analyzing CVOT as stand-alone study if planned with enough events
- CVOT large, randomized, double-blinded, placebo-controlled in T2DM patients with high CV risk

RESULTS

- No substantial delay between submission and approval due to potential CV risk
- All completed CVOTs ruled out HR > 1.3
- Development programs have gotten larger and more expensive
- CVOT populations have worse cardiovascular disease than general T2DM population

STRATEGIES

- Strategy 1 (10)
  - Stage 1: Meta-analysis of CV events of phase II/III trials
  - Stage 2: CVOT
- Strategy 2
  - Stage 1: CVOT
  - Stage 2: Meta-analysis of CVOT and a new CVOT
- Strategy 3
  - Stage 1: Interim analysis of ongoing CVOT
  - Stage 2: Analysis of completed CVOT
- Strategy 4
  - Stage 1: Meta-analysis of CV events of phase II/III trials and interim CVOT
  - Stage 2: Analysis of completed CVOT

POINTS TO CONSIDER

- Conduct and integrity of an ongoing study with dissemination of interim results
- DMC considerations and firewall of selected project personnel [11]
- Starting CVOT early
  - Dose selection
  - Monitoring other safety signals
- Use of all available events and timeframe
- Cardio-protective?

EMERGING QUESTIONS

- Can we stop a CVOT early?
  - Interim results meets < 1.3 threshold
  - No animal data indicating CV risk?

- Are there occasions when CVOT not needed?
  - What if CVOTs in certain classes rule out risk, CVOT for new drug in class be warranted?

EMERGING QUESTIONS

- Active-control CVOT?
  - Ethical, fewer discontinuations?
  - Head-to-head info could be useful for prescribing
  - Risk against these drugs informative, but doesn't really address guidance

- Indirect treatment comparisons have a role?
  - A – C and B – C
  - (A – C) – (B – C) = A – B
  - Comparable populations, time effects?

ACCESS TO INTERIM DATA

- Who has access to interim data? (12)
  - Ethical not to release?
  - DMC, but who at the sponsor? Need to know when to file
    - Could bias study if sponsor personnel have role in the trial
    - How to firewall from rest of team?
  - Should regulatory agencies have access?
  - Need to prevent results being leaked to public
    - May make it impossible to carry out trial
- Minimize number with access to data
- Data access plan

ACCESS TO INTERIM DATA

- Global trials will require buy-in from other regulatory agencies to maintain confidentiality
- Despite firewalls, integrity issues remain
  - Availability of data in real time
  - Enrollment, event or adherence rates
  - Drop out or cross-in rates may signal issues

CONCLUSIONS

- Trials are not designed for safety
- Balance between evidence on CV safety and excessive delay of novel therapies
- Lot of similarities in approaches taken and subsequent analyses for T2DM programs thus far
- Access to interim data critical for CV assessment strategies
- CVOTs have shown no elevated risk, but fail to show superiority
- Is it worth the cost? (13,14)
- Biosimilars may help reduce cost of diabetes treatments (15)

ASA SECTION ACTIVITIES

- http://www.amstat.org/sections/sectionlist.cfm
- Subset of available sections
  - Bayesian Statistical Science
  - Biometrics
  - Biopharmaceutical
  - Health Policy Statistics
  - Medical Devices and Diagnostics
  - Mental Health Statistics
  - Nonparametric
  - Statistics in Epidemiology
  - Statistics in Genomics and Genetics
  - Survey Research Methods
  - Teaching of Statistics in the Health Sciences

REFERENCES

1. Centers for Disease Control and Prevention. (2014). National diabetes statistics report: Estimates of diabetes and its burden in the United States, 2014. Atlanta, GA: U.S. Department of Health and Human Services.
2. Green JA & Riggs KR. (2015). Why Is there no generic Insulin? Historical origins of a modern problem. *New England Journal of Medicine* 372: 1171-1175.
3. Nissen SE & Wolski K. (2007). Effect of rosiglitazone on the risk of myocardial infarction and death from cardiovascular causes. *New England Journal of Medicine* 356: 2457-2471.
4. Home PD, Pocock SJ, Beck-Nielsen H, Curtis PS, Gomis R, Hanefeld M, Jones NP, Komajda M & JJV McMurray. (2009). Rosiglitazone evaluated for cardiovascular outcomes in oral agent combination therapy for type 2 diabetes (RECORD): A multicentre, randomised, open-label trial. *Lancet* 373: 2125–2135.
5. Turner JR & Durham TA. (2008). *Integrated Cardiac Safety: Assessment Methodologies for Noncardiac Drugs in Discovery, Development, and Postmarketing Surveillance*. Hoboken, New Jersey: John Wiley & Sons.
6. U.S. Food and Drug Administration. (2008). Guidance to industry: Diabetes mellitus - Evaluating cardiovascular risk in new antidiabetic therapies to treat type 2 Diabetes.
7. Committee for Medicinal Products for Human Use. European Medicines Agency. (2012). Guideline on clinical investigation of medicinal products in the treatment or prevention of diabetes mellitus.
8. Wu J, Menon S, Zink RC & Perevozskaya I. (2015, in press). Designing and monitoring group sequential clinical trials. In Menon S & Zink RC, eds. *Clinical Trials Using SAS: Classical, Adaptive and Bayesian Methods*. Cary, North Carolina: SAS Institute Inc.

REFERENCES

9. Marchenko O, Jiang Q, Chakravarty A, Ke C, Ma H, Maca J, Russek-Cohen E, Sanchez-Kam M, Zink RC & Chuang-Stein C. (2015). Evaluation and review of strategies to assess cardiovascular risk in clinical trials in patients with type 2 diabetes mellitus. *Statistics in Biopharmaceutical Research* (in press).
10. Geiger MJ, Mehta C, Turner JR, Arbet-Engels C, Hirshberg B, Koglin J, Mendzelevski B, Sager PT, Shapiro D, Stewart M, Todaro TG & Gaydos B. (2015). Clinical development approaches and statistical methodologies to prospectively assess the cardiovascular risk of new antidiabetic therapies for type 2 diabetes. *Therapeutic Innovation and Regulatory Science* 49: 50-64.
11. U.S. Food and Drug Administration. (2015). Guidance for clinical trial sponsors: Establishment and operation of clinical trial data monitoring committees.
12. U.S. Food and Drug Administration. (2014). Confidentiality of Interim Results in Cardiovascular (CV) Outcomes Safety Trials.
13. Andrews M. (2015, Aug 8). Cost of diabetes drugs often overlooked, but it shouldn't be. *Kaiser Health News*.
14. Brown P. (2015, Jun 11). Are diabetes CV trials worth It? Some say no - Debate heats up over need for expensive diabetes drug trials. *MedPage Today*.
15. U.S. Food and Drug Administration. (2015). Guidance to industry: Scientific considerations in demonstrating biosimilarity to a reference product.