Impact of Regulatory Guidance on Evaluating Cardiovascular Risk of New Glucose-Lowering Therapies to Treat Type 2 Diabetes Mellitus:
Lessons Learned and Future Directions

Christopher Granger MD
Duke Clinical Research Institute
Abhinav Sharma MD, PhD
McGill University Health Centre

Disclosures – Christopher Granger

- Research contracts: Akros, Apple, AstraZeneca, Bayer, BMS, Boehringer Ingelheim, Daiichi Sankyo, Janssen, Novartis, GSK, Medtronic Foundation, Pfizer, FDA, NIH

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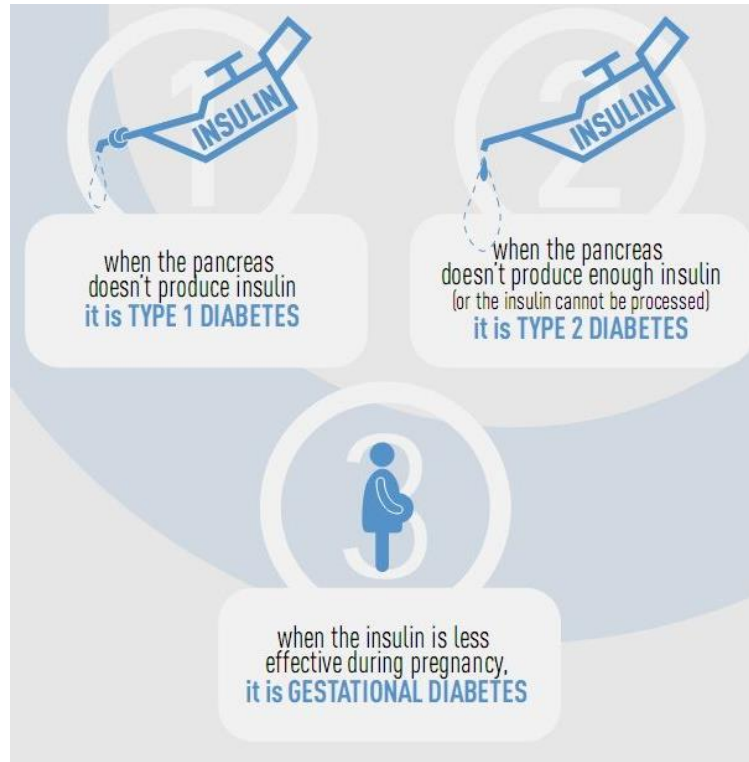- For full listing see www.dcri.duke.edu/research/coi.jsp

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- FRSQ-Junior 1 clinician scientist award

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Agenda

- Diabetes and the scope of the problem

- Outcomes among patients with diabetes

- The need for the 2008 Regulatory Guidance

- Impact of the 2008 Regulatory Guidance

- New updates: 2020 Draft Regulatory Guidance

- Future direction and discussion

Diabetes: An Introduction

when the pancreas doesn't produce insulin it is TYPE 1 DIABETES

when the pancreas doesn't produce enough insulin (or the insulin cannot be processed) it is TYPE 2 DIABETES

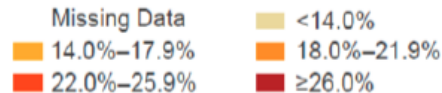when the insulin is less effective during pregnancy, it is GESTATIONAL DIABETES
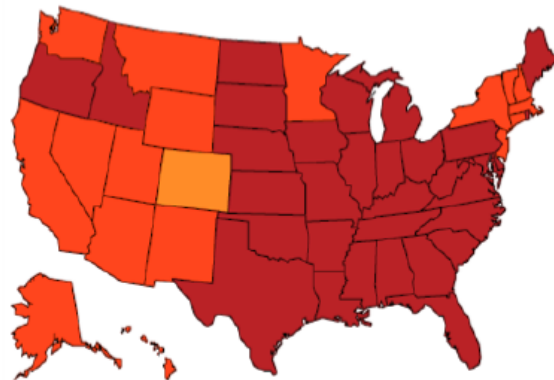
Type 2 Diabetes Mellitus

- **Type 2 diabetes** used to be called non-insulin dependent diabetes or adult-onset diabetes,

- 90% of all cases of diabetes.

- Hallmark is **insulin resistance** and relative insulin deficiency

- The diagnosis of type 2 diabetes can occur at any age

- Associated with overweight or obesity

- People with type 2 diabetes can often initially manage their condition through exercise and diet.

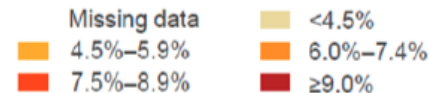- Over time most people will require oral drugs and or insulin.
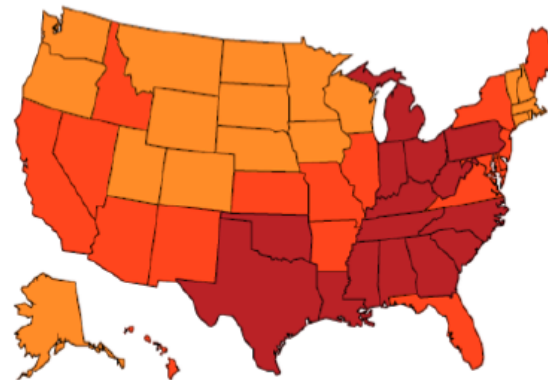
Age-Adjusted Prevalence of Obesity and Diagnosed Diabetes Among U.S. Adults

2010

Obesity (BMI≥30 kg/m²)

Diabetes

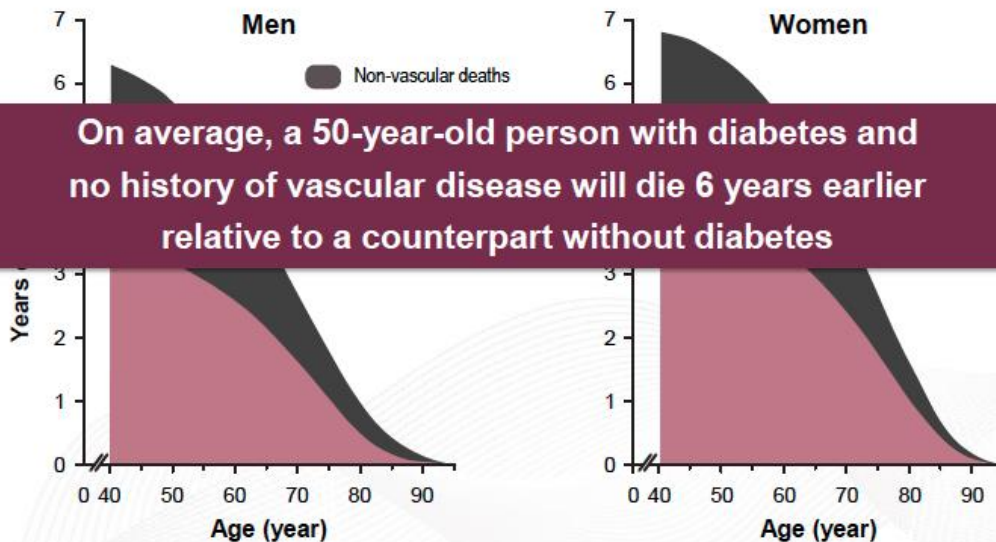Missing Data
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≥9.0%

CDC's Division of Diabetes Translation. National Diabetes Surveillance System
Available at http://www.cdc.gov/diabetes/statistics

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Diabetes* is Associated with Significant Loss of Life Years

12.3M patient years follow-up; Mean Age 55; 48% women

Men — Non-vascular deaths

Women

On average, a 50-year-old person with diabetes and no history of vascular disease will die 6 years earlier relative to a counterpart without diabetes
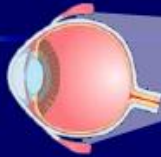
Years of...

Age (year)

*Type 1 or 2 diabetes mellitus
Emerging Risk Factors Collaboration. N Engl J Med. 2011;3;364:829-41.

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Complications of Diabetes

Diabetic Retinopathy
Leading cause of blindness in adults[1,2]

Diabetic Nephropathy
Leading cause of end-stage renal disease[3,4]

Stroke
2- to 4-fold increase in cardiovascular mortality and stroke[5]

Cardiovascular Disease
8/10 individuals with diabetes die from CV events[6]

Diabetic Neuropathy
Leading cause of non-traumatic lower extremity amputations

Scope of the problem

Hospitalization for acute myocardial infarction | Hospitalization for coronary heart disease | Hospitalization for stroke | Hospitalization for heart failure

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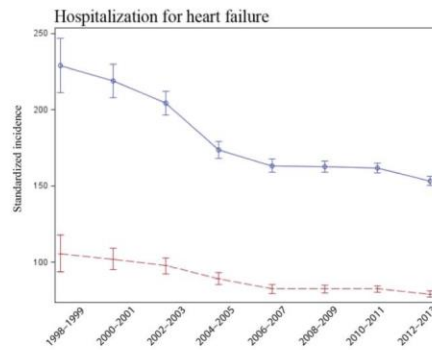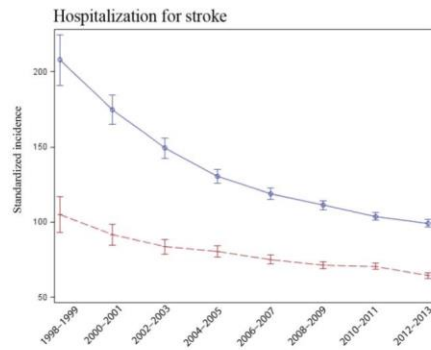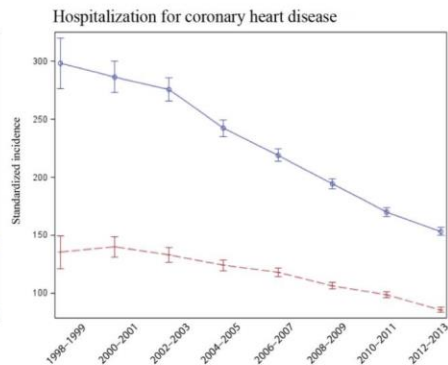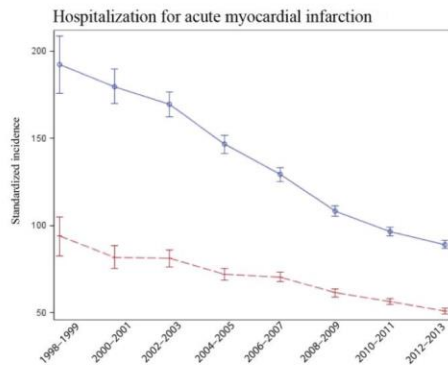
Heart Failure and Diabetes: Emerging Epidemic?

Individual non-CV comorbidities

Sharma A et al. Circulation Heart failure; 2018; 11(6)
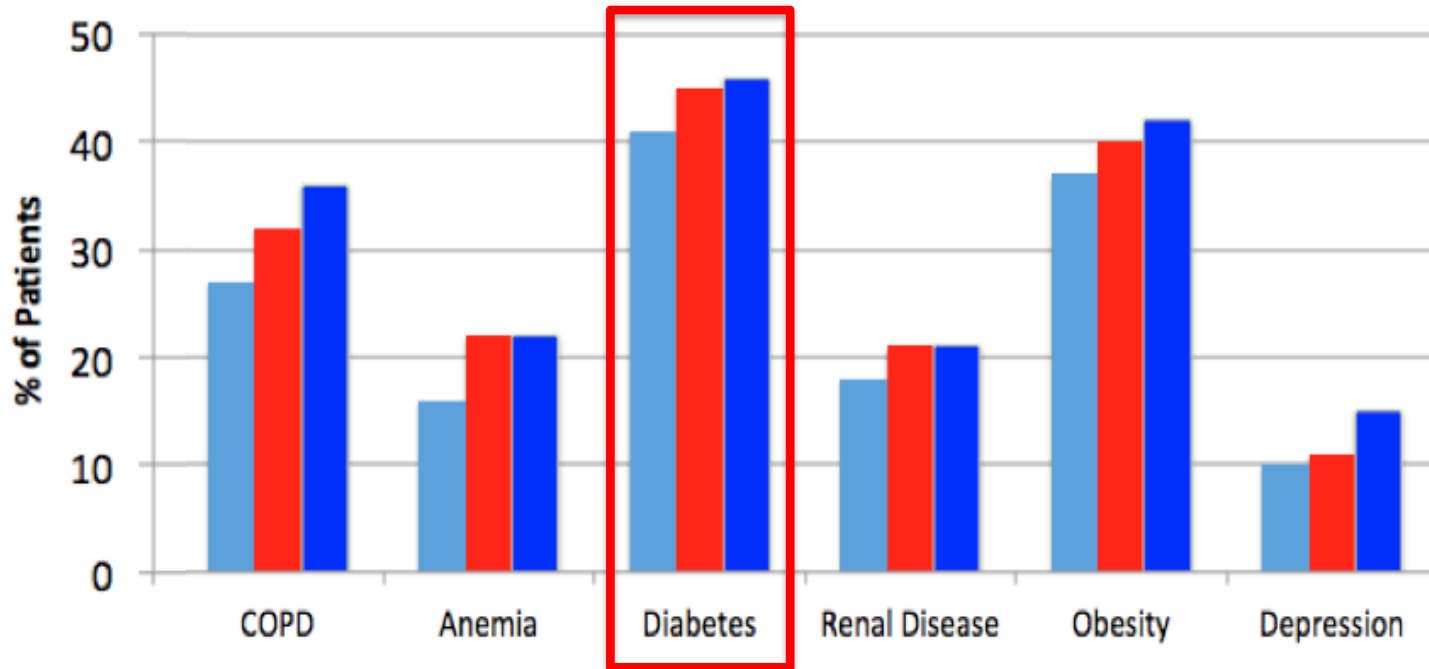
Scope of the problem
Take away message

- Among patients with diabetes, atherosclerotic disease is the largest driver of morbidity and mortality

- Heart failure is just as common (if not more) in patients with type 2 diabetes

- Diabetes is present in nearly half of patients with heart failure

- Strategies are needed reduce the burden of cardiovascular outcomes in patients with diabetes

Anti-hyperglycemic Therapies
In Patients with Diabetes

Trigger for the 2008 U.S. FDA Guidance

- Two controversial meta-analyses evaluating MACE risk of 2 classes of T2DM drugs spurred the development of guidance from the FDA and other regulatory agencies

- Guidance calling for the evaluation of the risk of CV outcomes with glucose-lowering therapies.

Anti-hyperglycemic Therapies and CV Risk

Effect of Rosiglitazone on the Risk of Myocardial Infarction and Death from Cardiovascular Causes

Steven E. Nissen, M.D., and Kathy Wolski, M.P.H.

Table 4. Rates of Myocardial Infarction and Death from Cardiovascular Causes.

Study	Rosiglitazone Group	Control Group	Odds Ratio (95% CI)	P Value
	no. of events/total no. (%)			
Myocardial infarction				
Small trials combined	44/10,285 (0.43)	22/6106 (0.36)	1.45 (0.88–2.39)	0.15
DREAM	15/2,635 (0.57)	9/2634 (0.34)	1.65 (0.74–3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2895 (1.42)	1.33 (0.80–2.21)	0.27
Overall			1.43 (1.03–1.98)	0.03
Death from cardiovascular causes				
Small trials combined	25/6,845 (0.36)	7/3980 (0.18)	2.40 (1.17–4.91)	0.02
DREAM	12/2,635 (0.46)	10/2634 (0.38)	1.20 (0.52–2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2895 (0.17)	0.80 (0.17–3.86)	0.78
Overall			1.64 (0.98–2.74)	0.06

Effect of Muraglitazar on Death and Major Adverse Cardiovascular Events in Patients With Type 2 Diabetes Mellitus

Steven E Nissen [1], Kathy Wolski, Eric J Topol

Affiliations + expand

	No. (%)			
	Muraglitazar (n = 2374)	Control (n = 1351)	Relative Risk (95% CI)	P Value
Composite End Points				
All-cause mortality plus nonfatal MI or stroke	35 (1.47)	9 (0.67)	2.23 (1.07-4.66)	.03
All-cause mortality plus nonfatal MI, stroke, CHF, or TIA	50 (2.11)	11 (0.81)	2.62 (1.36-5.05)	.004
Cardiovascular death plus nonfatal MI or stroke	27 (1.14)	7 (0.52)	2.21 (0.96-5.08)	.06
Cardiovascular death plus nonfatal MI, stroke, CHF, or TIA	42 (1.77)	9 (0.67)	2.69 (1.30-5.53)	.007
All-cause mortality or nonfatal MI	27 (1.14)	7 (0.52)	2.21 (0.96-5.08)	.06
Cardiovascular death or nonfatal MI	19 (0.80)	5 (0.37)	2.17 (0.81-5.83)	.12

U.S. FDA Response

- In 2008, the US Food and Drug Administration (FDA) put forth guidelines for sponsors to demonstrate that their anti-hyperglycemic medications do not increase the risk of cardiovascular disease

HISTORICAL CONSIDERATION OF THE 2008 US FDA GUIDANCE

- Approval for T2DM medications indicated to lower blood glucose was previously based primarily on demonstration of reductions in glucose or HbA1c.

- The duration of trials: typically 6 to 12 months or shorter

- Generally requiring only 300 to 600 patients exposed for 6 months and only 100 exposed for a year.

- Patients with existing cardiovascular disease, including HF, were often excluded

U.S. FDA Response

Table 1. Main Components of 2008 FDA Guidance for Sponsors on the Evaluation of Cardiovascular Risk of New Glucose-Lowering Drugs[13]

Outcome trial must exclude HR 1.8 (preapproval) and 1.3 (postapproval)
Patient selection should include high-risk population, including the elderly and those with advanced cardiovascular disease, and some degree of renal impairment
Duration must be at least 2 y
Required cardiovascular events: cardiovascular mortality, myocardial infarction, stroke
Optional cardiovascular events: hospitalization for acute coronary syndrome or urgent revascularization procedures
Cardiovascular events must be adjudicated in a blinded, independent process

FDA indicates US Food and Drug Administration; and HR, hazard ratio.

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Impact of the 2008 FDA Guidance
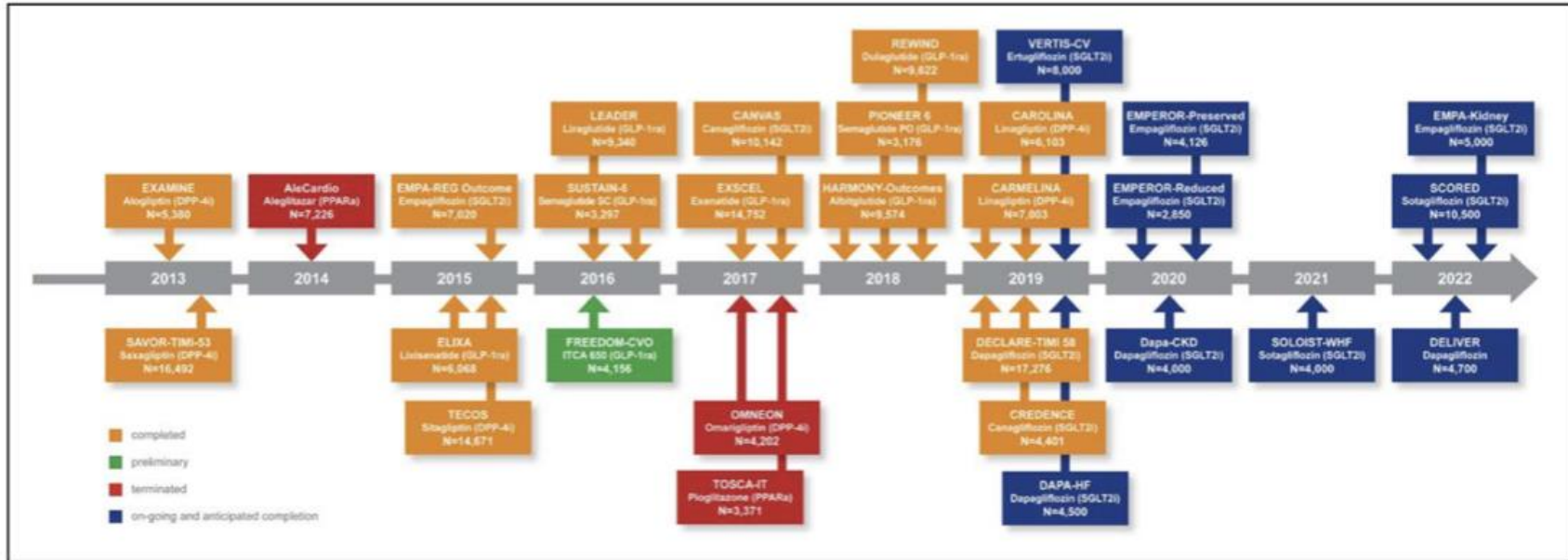
Figure 1. Timeline of cardiovascular outcome trials since the 2008 US Food and Drug Administration guidance.

Impact of the 2008 FDA Guidance

- Most studies conducted after the establishment of the guidelines were enriched for participants with CV disease or additional CV risk factors

- The recruitment of these patients satisfied the guidance requirement that the safety of studied drugs in the treatment of patients at high CV risk

- Helped in the accrual of adequate numbers of events to be able to rule out the upper bounds of risk.

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Characteristics of the CVOT

- Typically, trials were conducted to demonstrate cardiovascular safety with a noninferiority margin of <1.3

- Because no previous glucose-lowering drug has a claim or indication of CV efficacy, CVOTs used a placebo control arm as the comparator group

- An exception to the placebo control design is the recently completed CAROLINA trial (Cardiovascular Outcome Study of Linagliptin Versus Glimepiride in Patients With Type 2 Diabetes), which compared linagliptin with glimepiride

Characteristics of the CVOT

- Most of the CVOTs had the 3-point MACE outcome (CV death, nonfatal MI, or nonfatal stroke) as the primary outcome.

- Three trials added hospitalization for unstable angina to create a 4-point MACE outcome as the primary outcome

Results of the CVOT

- To date, the completed CVOTs have all demonstrated noninferiority

- i.e. no trial demonstrated an increase in the risk of 3-point or 4-point MACE associated with the antihyperglycemic agent compared to placebo

- Several trials have demonstrated superiority in 3-point MACE outcomes and other outcomes include HF and renal endpoints

Results of the CVOT

- Some molecules within two classes of anti-hyperglycemic therapies have demonstrated efficacy in reducing the risk of CV outcomes

- GLP-1 receptor agonists and SGLT-2 inhibitors

GLP-1 Receptor Agonists

	GLP-1 receptor agonist n/N (%)	Placebo n/N (%)		Hazard ratio (95% CI)	NNT (95% CI)	p value
Three-component MACE						
ELIXA	400/3034 (13%)	392/3034 (13%)		1·02 (0·89–1·17)		0·78
LEADER	608/4668 (13%)	694/4672 (15%)		0·87 (0·78–0·97)		0·015
SUSTAIN-6	108/1648 (7%)	146/1649 (9%)		0·74 (0·58–0·95)		0·016
EXSCEL	839/7356 (11%)	905/7396 (12%)		0·91 (0·83–1·00)		0·061
Harmony Outcomes	338/4731 (7%)	428/4732 (9%)		0·78 (0·68–0·90)		<0·001
REWIND	594/4949 (12%)	663/4952 (13%)		0·88 (0·79–0·99)		0·026
PIONEER 6	61/1591 (4%)	76/1592 (5%)		0·79 (0·57–1·11)		0·17
Overall (I^2=40·9%, p=0·118)	2948/27 977 (11%)	3304/28 027 (12%)		0·88 (0·82–0·94)	75 (50–151)	<0·001
Cardiovascular death						
ELIXA	156/3034 (5%)	158/3034 (5%)		0·98 (0·78–1·22)		0·85
LEADER	219/4668 (5%)	278/4672 (6%)		0·78 (0·66–0·93)		0·007
SUSTAIN-6	44/1648 (3%)	46/1649 (3%)		0·98 (0·65–1·48)		0·92
EXSCEL	340/7356 (5%)	383/7396 (5%)		0·88 (0·76–1·02)		0·096
Harmony Outcomes	122/4731 (3%)	130/4732 (3%)		0·93 (0·73–1·19)		0·58
REWIND	317/4949 (6%)	346/4952 (7%)		0·91 (0·78–1·06)		0·18
PIONEER 6	15/1591 (1%)	30/1592 (2%)		0·49 (0·27–0·92)		0·021
Overall (I^2=13·5%, p=0·327)	1213/27 977 (4%)	1371/28 027 (5%)		0·88 (0·81–0·96)	175 (110–524)	0·003

SGLT-2 Inhibitors

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with atherosclerotic cardiovascular disease								
EMPA-REG OUTCOME	4687	2333	772	37·4	43·9	29·4		0·86 (0·74–0·99)
CANVAS Program	3756	2900	796	34·1	41·3	32·4		0·82 (0·72–0·95)
DECLARE-TIMI 58	3474	3500	1020	36·8	41·0	38·2		0·90 (0·79–1·02)
Fixed effects model for atherosclerotic cardiovascular disease (p=0·0002)								0·86 (0·80–0·93)
Patients with multiple risk factors								
CANVAS Program	2039	1447	215	15·8	15·5	25·9		0·98 (0·74–1·30)
DECLARE-TIMI 58	5108	5078	539	13·4	13·3	74·1		1·01 (0·86–1·20)
Fixed effects model for multiple risk factors (p=0·98)								1·00 (0·87–1·16)

0·35   0·50   1·00   2·50

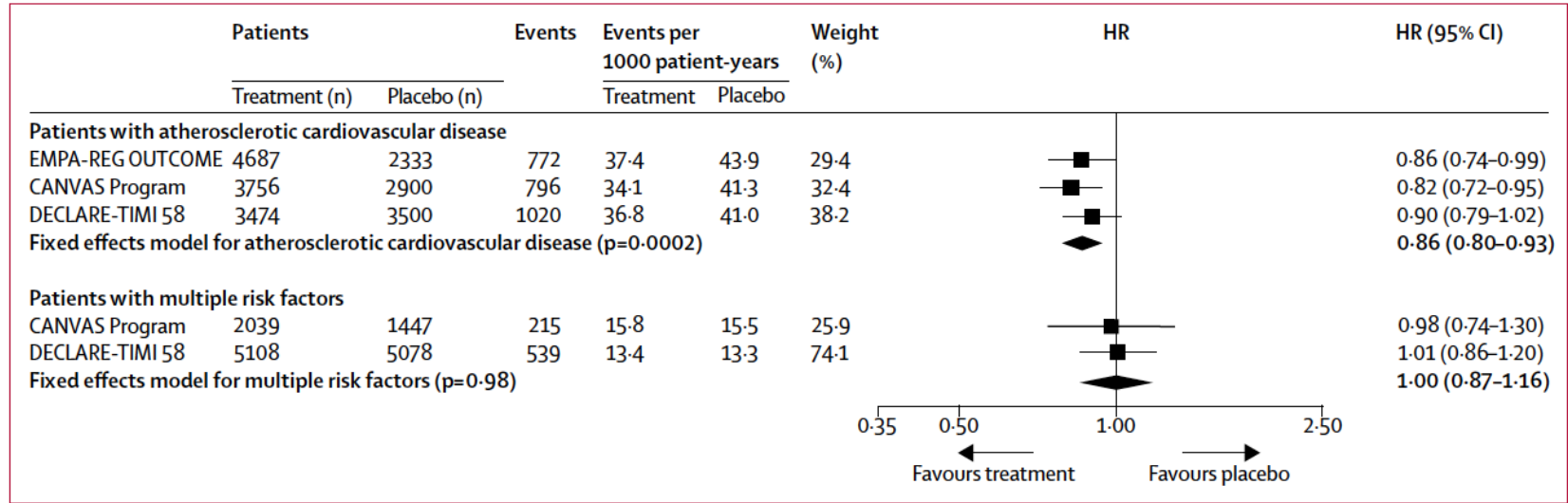← Favours treatment   Favours placebo →

Figure 1: Meta-analysis of SGLT2i trials on the composite of myocardial infarction, stroke, and cardiovascular death (major adverse cardiovascular events) stratified by the presence of established atherosclerotic cardiovascular disease

Lancet 2019; 393: 31–39

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SGLT-2 Inhibitors

	Patients		Events	Events per 1000 patient-years		Weight (%)	HR	HR (95% CI)
	Treatment (n)	Placebo (n)		Treatment	Placebo			
Patients with history of heart failure								
EMPA-REG OUTCOME	462	244	124	63·6	85·5	23·6		0·72 (0·50–1·04)
CANVAS Program	803	658	203	35·4	56·8	34·1		0·61 (0·46–0·80)
DECLARE-TIMI 58	852	872	314	45·1	55·5	42·4		0·79 (0·63–0·99)
Fixed effects model for history of heart failure (p<0·0001)								0·71 (0·61–0·84)
Patients with no history of heart failure								
EMPA-REG OUTCOME	4225	2089	339	15·5	24·9	30·0		0·63 (0·51–0·78)
CANVAS Program	4992	3689	449	13·6	15·2	32·4		0·87 (0·72–1·06)
DECLARE-TIMI 58	7730	7706	599	8·9	10·5	37·6		0·84 (0·72–0·99)
Fixed effects model for no history of heart failure (p<0·0001)								0·79 (0·71–0·88)

HR scale: 0·35   0·50   1·00   2·50

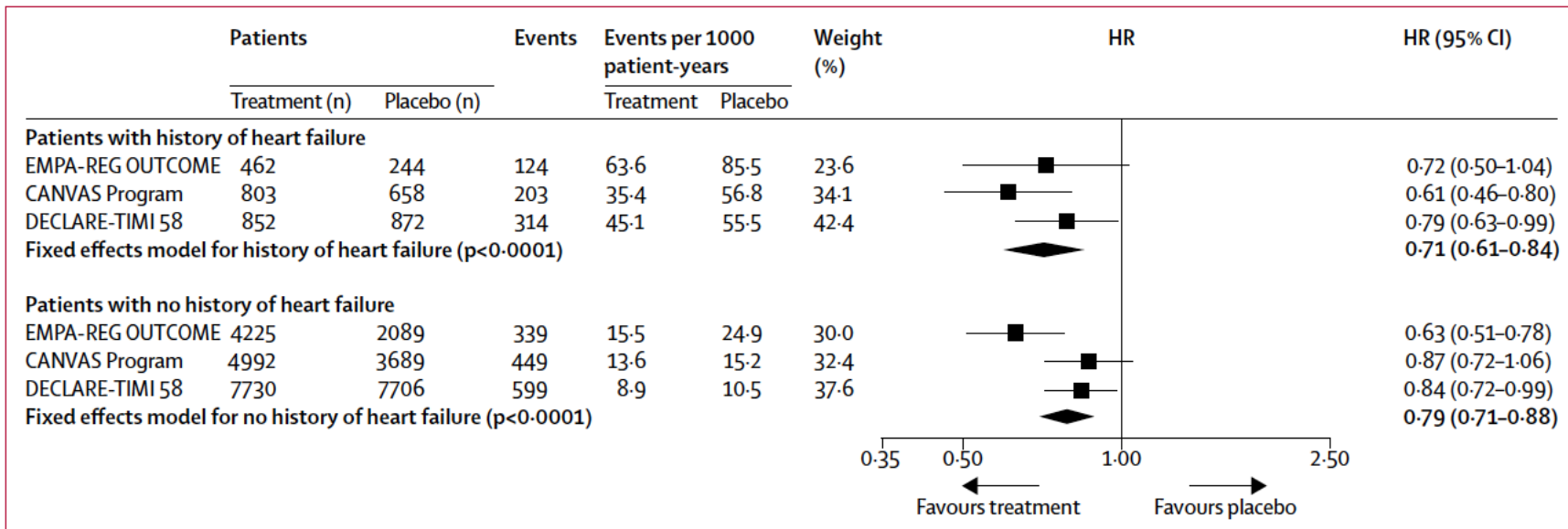← Favours treatment   Favours placebo →

Figure 3: Meta-analysis of SGLT2i trials on hospitalisation for heart failure and cardiovascular death stratified by history of heart failure

Adverse Safety Issues in CVOT

- In SAVOR-TIMI 53, saxagliptin was, compared to placebo was associated with an increased risk of HF (HR, 1.27; 95% CI 1.07–1.51)

- In EXAMINE, alogliptin was associated with a trend to increased HF risk (HR, 1.19 95% CI 0.90–1.58)

- There is now a black-box warning for the risk of HF among DPP-4 inhibitors due to data from the SAVOR-TIMI 53 trial and EXAMINE trial

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Adverse Safety Issues in CVOT

- In the CANVAS trials an unexpected finding was an increased risk of extremity amputation with canagliflozin (HR, 1.97 [95% CI, 1.41–2.75])

- liraglutide and semaglutide were was associated with a numerical increase in the risk of diabetic retinopathy complications compared with placebo

Overall Summary

- Explosion of CVOT since in the 2008 FDA guidance

- Significant costs to conducting these trials – estimated at $ 2 billion from discovery to FDA approval

- Affirmed the 3-point MACE safety of newer anti-hyperglycemic drugs

- Identified CV benefit with regards to CV death, HF and renal outcomes for various agents

- Identified safety issues with various agents

2018 FDA Advisory Committee

- In October 2018, the FDA's Endocrinologic and Metabolic Drugs Advisory Committee met to discuss the 2008 guidance

- The primary question: whether an unacceptable increase in CV risk needed to be excluded for all new antihyperglycemics in patients with T2DM, regardless of the presence or absence of a signal for CV risk in the development program

- The advisory committee narrowly voted 10 to 9 in favor of continuing to exclude unacceptable increases in CV risk for all new glucose-lowering therapies

2018 Diabetes Think Tank

- A think tank with representatives from academia, industry, government, private payers, and regulatory agencies convened to review the impact of the FDA guidance since 2008

- The aims of this meeting were to review the experience of CVOTs conducted since the guidance was issued and future directions

2018 Diabetes Think Tank

Circulation

WHITE PAPER

Impact of Regulatory Guidance on Evaluating Cardiovascular Risk of New Glucose-Lowering Therapies to Treat Type 2 Diabetes Mellitus

Lessons Learned and Future Directions

2020 Draft FDA Guidance

- FDA recently updated the 2008 FDA Guidance and released a new draft version

- Removed the recommendation for the demonstration of a 1:3 non-inferiority margin

- Instead, focused on three features:
  1. Size and exposure duration of the Safety Database
  2. Patient Characteristics in the Development Program
  3. Other Considerations

2020 Draft FDA Guidance

Size of the Safety Database:

- At least 4,000 patient-years of exposure to the new drug in phase 3 clinical trials. (This exposure includes all dosage strengths studied in the phase 3 clinical trials.)
- At least 1,500 patients exposed to the new drug for at least 1 year
- At least 500 patients exposed to the new drug for at least 2 years

2020 Draft FDA Guidance

**Patient Characteristics in the Development Program:**

- At least 500 patients with stage 3/4 chronic kidney disease exposed to the new drug.

- At least 600 patients with established CV disease (e.g., previous myocardial infarction, documented coronary artery disease, previous stroke, peripheral vascular disease) exposed to the new drug

- At least 600 patients older than 65 years of age exposed to the new drug

2020 Draft FDA Guidance

Other Considerations :

- Sponsors should use rigorous methods for the collection of adverse CV events and assess them by adjudication.

- In some cases, the evaluation of a premarket safety concern may require that a drug development program accrue a minimum number of relevant adverse events to exclude a meaningful degree of risk. Adjudication of these adverse events may also be needed. The Agency expects that situations where the collection of these additional safety data is necessary will be identified and discussed before phase 3 trials are initiated

- Sponsors should include DSMB or committees to provide independent oversight

Future Directions
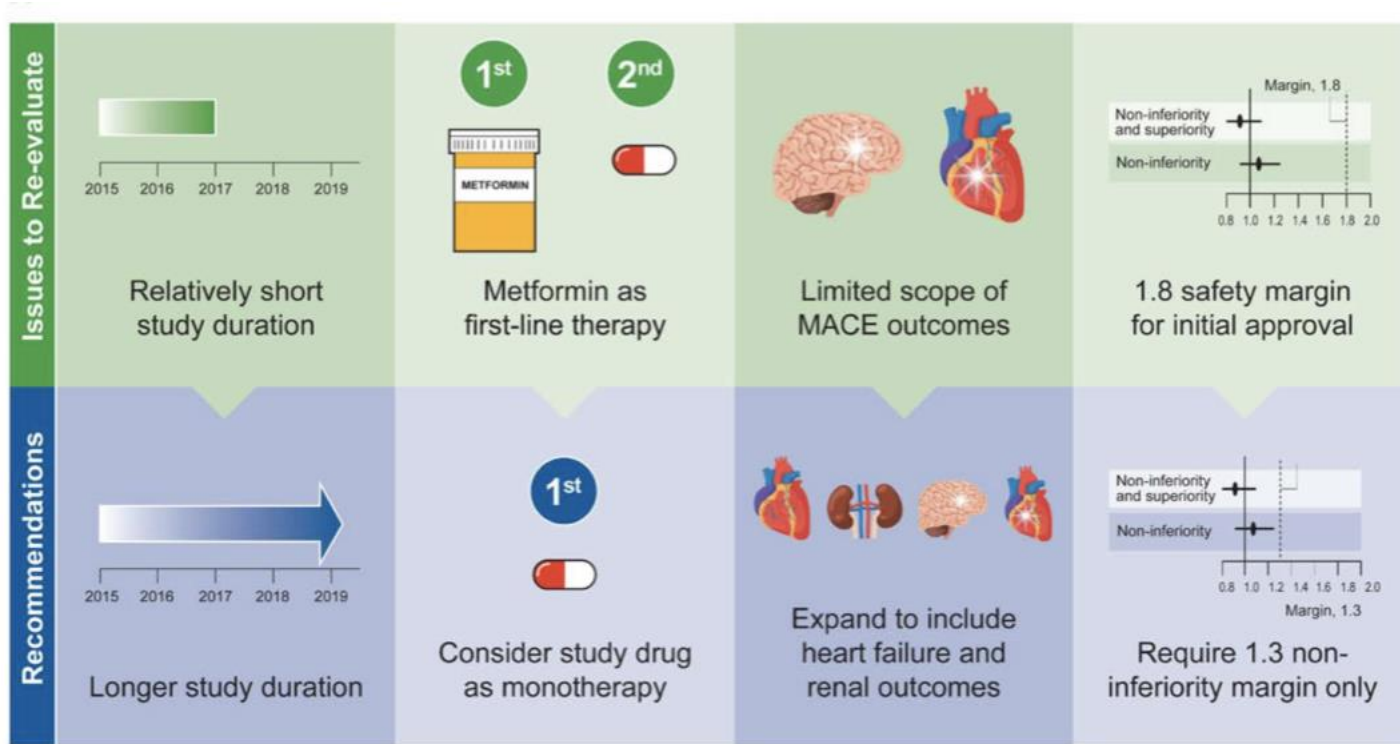
Future Directions
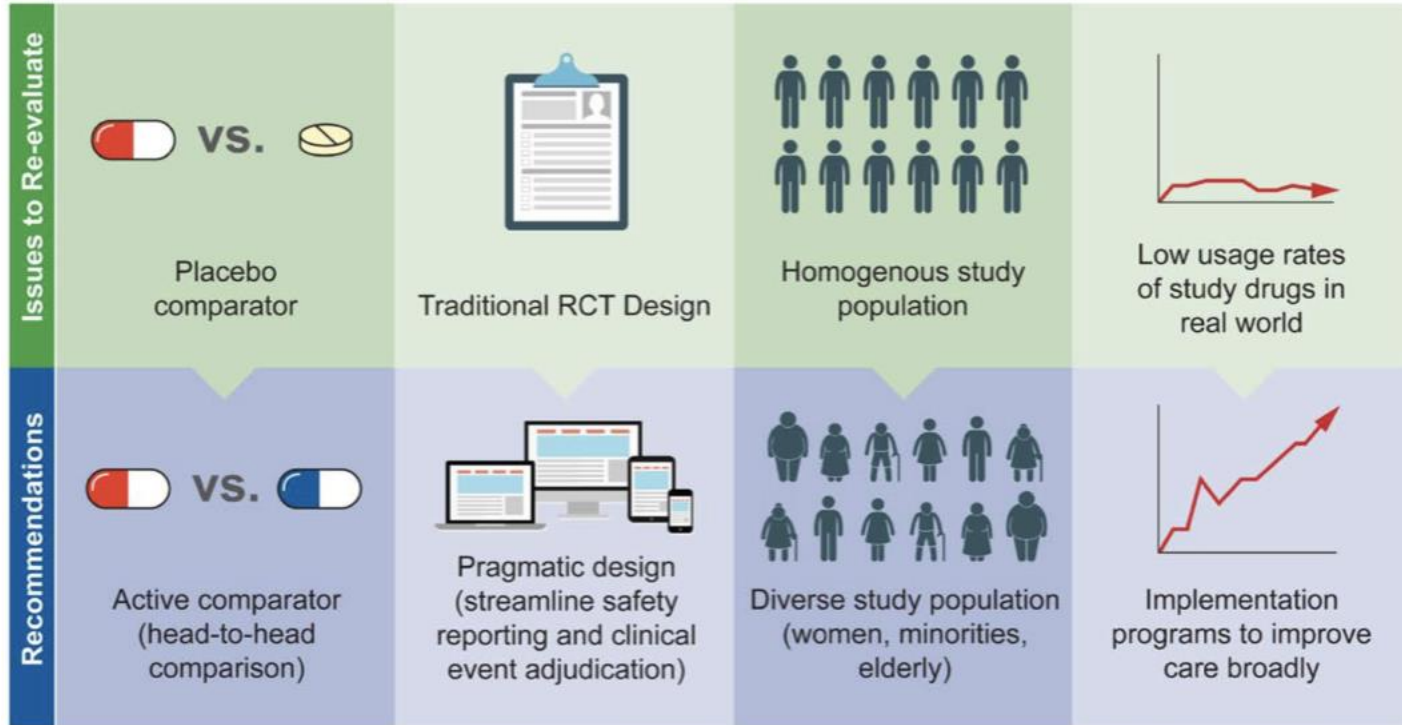
Questions

- When there is substantial evidence of efficacy and safety in a drug class, should the regulatory requirements for approval of a new drug be different?

- Is the cardiovascular protection of some of the antihyperglycemic drugs independent of effect on blood glucose?

- How should we consider varying effects on ischemic events, heart failure and kidney disease?

- How can regulators, industry, academia, payers, patient advocacy groups assure that evidence generation to improve care is incentivized without undue regulatory burdens?

Thank you for your time!