Multiple Small Feedings of the Mind
Update in Diabetes

CVD and Glycemic Pharmacotherapies: from UGDP to SUSTAIN-6

SIU School of Medicine

Michael Jakoby, MD/MA, FACP

Associate Professor of Medicine

Chief, Division of Endocrinology

University Group Diabetes Program

- Primary objective was to evaluate the efficacy of different hypoglycemic treatments in prevention of vascular complications.
- Patient enrollment started 1961 and follow up ended in 1975 (N=1,027)
- Two insulin arms, tolbutamide, phenformin, and placebo
- Tolbutamide (1969) and phenformin (1971) arms terminated early
- No micro- or macrovascular benefits of any pharmacotherapy

Mortality	Placebo	Tolbutamide	Phenformin	ISTD†	IVAR‡
CV (%)	3.1	12.7	12.7	8.8	4.2
All-cause (%)	9.4	14.7	15.2	8.8	6.2

†ISTD – standard (fixed dose) insulin
‡IVAR – variable insulin dosing regimen

Curtis L. Meinert. The Trials and Tribulations of the University Group Diabetes Program. 2015

SIU

Rosiglitazone and CVD

Cleveland Clinic Meta-analysis (Nissen SE NEJM 2007 356:2457)

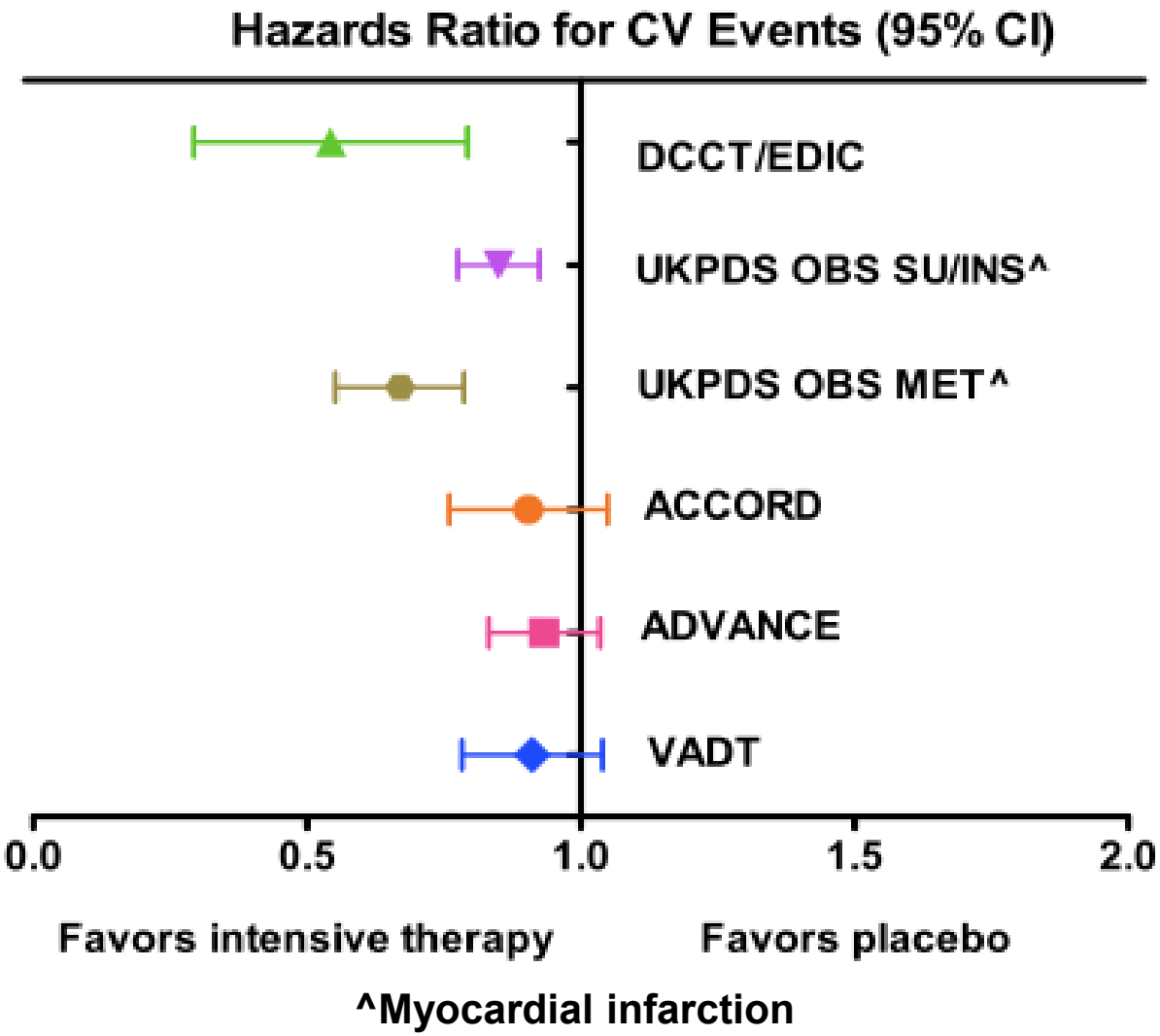
Study	Rosiglitazone	Control	OR (95% CI)	P-value
MI				
Small trials	44/10,285 (0.43)	22/6,106 (0.36)	1.45 (0.88-2.39)	0.15
DREAM	15/2,635 (0.57)	9/2,634 (0.34)	1.65 (0.74-3.68)	0.22
ADOPT	27/1,456 (1.85)	41/2,895 (1.42)	1.33 (0.80-2.21)	0.27
Overall			1.43 (1.03-1.98)	0.03
CVD death				
Small trials	25/6,845 (0.36)	7/3,980 (0.18)	2.40 (1.17-4.91)	0.02
DREAM	12/2,635 (0.46)	10/2,634 (0.38)	1.20 (0.52-2.78)	0.67
ADOPT	2/1,456 (0.14)	5/2,895 (0.17)	0.80 (0.17-3.86)	0.78
Overall			1.64 (0.98-2.74)	0.06

RECORD (Home PD et al. Lancet 2009 373:2125)

Outcome	Rosiglitazone	Control	OR (95% CI)	P-value
CV death	60/2,220 (2.7)	71/2,227 (3.2)	0.84 (0.59-1.18)	0.32
MI	64/2,220 (2.9)	56/2,227 (2.5)	1.14 (0.80-1.63)	0.47
Heart failure	61/2,220 (2.7)	29/2,227 (1.3)	2.10 (1.35-3.27)	0.001

SIU

Glycemic Control and CV Events



^Myocardial infarction

FDA Responses to CVD Results

2007: Rosiglitazone boxed warning of increased myocardial ischemia

2008: Guidance to Industry statement that all new type 2 diabetes drug development programs r/o unacceptable CV risk by demonstrating an upper bound of the two-sided 95% CI < 1.8 for the composite endpoint major adverse cardiac events in preapproval studies

2010: Access to rosiglitazone restricted and TIDE trial put on "partial clinical hold"

2013: Duke Clinical Research Institute readjudication of RECORD data indicates rosiglitazone meets FDA standards of acceptable CV risk

2015: Endocrinologic and Metabolic Drugs Advisory Committee votes alogliptin and saxogliptin have acceptable CV risk profiles

SIU

FDA Evaluation of New Type 2 Diabetes Medications

- Efficacy lowering blood glucose

- Cardiovascular safety
  - Upper bound of two-sided 95% CI for risk of major adverse cardiovascular events (MACE) – cardiovascular death, nonfatal MI, and nonfatal stroke -- < 1.8 for preapproval studies

  - Upper bound of two-sided 95% CI for risk of MACE < 1.3 in postapproval studies

- Overall safety

SIU

DPP-4 Inhibitor CV Outcome Trials

Drug	Trial	N	Hazard ratios (95% CI) MACE^	HF†	All-cause mortality
Saxagliptin	SAVOR-TIMI 53	16,492	1.00 (0.89-1.12)	1.27 (1.07-1.51)	1.11 (0.96-1.27)
Alogliptin	EXAMINE	5,380	0.96 (0.80-1.16)	1.19 (0.90-1.58)	0.88 (0.71-1.09)
Sitagliptin	TECOS	14,671	0.98 (0.88-1.09)	1.00 (0.83-1.20)	1.01 (0.90-1.14)

^CV death, nonfatal MI, nonfatal CVA (SAVOR-TIMI 53 and EXAMINE; CV death, nonfatal MI, nonfatal CVA, and hospitalization for unstable angina (TECOS)

†Hospitalization for heart failure

- Meta-analysis of trials reporting admission for heart failure showed higher risk for DPP-4 inhibitor treated patients than controls (OR 1.13, 1.00-1.26)[1]
- Meta-analysis of larger pool of trials showed similar risk of HF in treated and control patients (OR 0.97, 0.61-1.56)[1]
- Retrospective cohort study failed to show increased hospitalization for HF among users of saxagliptin or sitagliptin compared to pioglitazone, sulfonylureas, or insulin in the FDA Mini-Sentinel program[2]

[1]Li L et al. BMJ 2016 352:610
[2]Toh S et al. Ann Intern Med 2016:164:705

SIU

GLP-1 Receptor Agonist CV Outcome Trials

			Hazard ratios (95% CI)		
Drug	**Trial**	**N**	**MACE^**	**HF†**	**All-cause mortality**
Lixisenatide	ELIXA	6,068	1.02 (0.89-1.17)	0.96 (0.82-1.16)	0.94 (0.78-1.13)
Liraglutide	LEADER	9,340	0.87 (0.78-0.97)	0.87 (0.73-1.05)	0.85 (0.74-0.97)
Semaglutide	SUSTAIN 6	3,297	0.74 (0.58-0.95)	1.11 (0.77-1.61)	1.05 (0.74-1.50)

^CV death, nonfatal MI, nonfatal CVA; †Hospitalization for heart failure

- MACE was reduced in LEADER due to a significant reduction in CV death (HR 0.78, 0.66-0.93)
- MACE was reduced in SUSTAIN 6 due to a significant reduction in nonfatal CVA (HR 0.61, 0.38-0.99)
- Retinopathy complications (vitreous hemorrhage, blindness, retinal photocoagulation or other treatment for proliferative retinopathy) were significantly increased in SUSTAIN 6 (HR 1.76, 1.11-2.78) and a nonsignificant increase in LEADER (HR 1.15, 0.87-1.52)
- New or worsening nephropathy was decreased in both LEADER (HR 0.78, 0.67-0.92) and SUSTAIN 6 (HR 0.64, 0.46-0.88)

SIU

SGLT2 Inhibitor CV Outcome Trials

			Hazard ratios (95% CI)		
Drug	**Trial**	**N**	**MACE^**	**HF**	**All-cause mortality**
Empagliflozin	EMPA-REG	7,020	0.86 (0.74-0.99)	0.65 (0.50-0.80)	0.68 (0.57-0.82)

^CV death, nonfatal MI, nonfatal CVA; †Hospitalization for heart failure

- MACE was reduced by a significant reduction in CV death (HR 0.62, 0.49-0.77)
- High dose (25 mg) empagliflozin improved HbA1c ~ 0.4% compared to placebo
- Weight, waist circumference, systolic and diastolic blood pressures, and uric acid level improved in empagliflozin treated patients
- Modest increase in LDL cholesterol level occurred early in the empagliflozin group and then waned over the course of the study
- HDL cholesterol increased 2-3 mg/dL in the first 6 months among empagliflozin treated patients and then remained stable

SIU

CV Outcome Trials In Progress

Drug	Class	Trial	Enrollment	Completion date
Canagliflozin	SGLT2 inhibitor	CANVAS	4,407	June 2017
Linagliptin	DPP-4 inhibitor	CARMELINA	8,300	January 2018
Exenatide	GLP-1 RA	EXSCEL	14,000	January 2018
Linagliptin	DPP-4 inhibitor	CAROLINA	6,000	September 2018
Dapagliflozin	SGLT2 inhibitor	DECLARE-TIMI 58	17,150	April 2019
Dulaglutide	GLP-1 RA	REWIND	9,622	April 2019
Albiglutide	GLP-1 RA	HARMONY	9,400	May 2019
Ertugliflozin	SGLT2 inhibitor	NCT01986881	3,900	October 2020
Omarigliptin	DPP-4 inhibitor	NCT01703208	4,202	December 2020

SIU

Limitations of CV Outcome Trials

- Designed and powered for primary endpoint of CV safety, not CV benefit
- Use and dose adjustment of other agents that might influence outcomes (e.g. BP and lipid lowering agents, other blood glucose lowering drugs) permitted
- Unable to determine what role glucose lowering effects play in CV outcomes
- Short term trials of patients with established CVD or advanced atherosclerosis with results that may not be applicable to patients w/o CVD

SIU

Summary

- The importance of glycemic control to preventing CV events in type 2 diabetes remains unclear

- Three new classes of glucose lowering drugs have been prospectively evaluated for CV safety:

Class	Outcomes
DPP-4 inhibitors	• No increased risk of ischemic HD • May be increased risk of HF
GLP-1 RA	• Decreased MACE (but different components) in LEADER and SUSTAIN 6 • Decreased nephropathy • Increased retinopathy (SUSTAIN 6)
SLGT2 inhibitors	• Decreased MACE due to reduction in CV death (EMPA-REG) • Decreased hospitalization for HF

- Applicability of CV outcomes trial results to patients without known CVD is uncertain

SIU