#FSHP2018

Endocrine Update
Diabetes and Cardiovascular Outcomes

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Disclosure

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Objectives

- Compare cardiovascular (CV) outcomes with both older and newer treatment options for type 2 diabetes
- Discuss the implications of the cardiovascular outcome trials (CVOTs) of antidiabetic agents
- Use clinical reasoning skills to identify the ideal patient for newer therapies in management of type 2 diabetes
- Create a patient-specific treatment plan based on targeting CV outcomes

Type 2 Diabetes – Drug Therapy Selection

- Patient Factors
  - Magnitude of glucose or A1C lowering needed
  - Current weight, body mass index
  - History of hypoglycemia
  - Concomitant diseases and medications
  - Insurance coverage/access to therapies
  - Willingness to inject

Type 2 Diabetes – Drug Therapy Selection

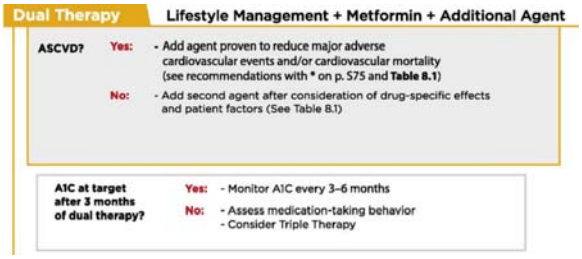
- Prescriber Factors
  - Comfort level with drug classes
- Drug Factors
  - Efficacy
  - Adverse reactions
  - Drug and disease state interactions
  - Cost
  - Rout and frequency of administration
  - **Cardiovascular effects**

Type 2 Diabetes and CVD

- CVD is the most prevalent cause of morbidity and mortality
  - Mortality rate is 2-4 time higher than patients without diabetes
- Evidence that glucose control reduces CV events is conflicted
- Pleotropic effects of certain drug classes or individual agents may be the key to reducing CV events

Matheus AS, et al. *International Journal of Hypertension*. 2013;2013:653789.

ADA Standards of Care



Diabetes Care 2018;41:S73-S85

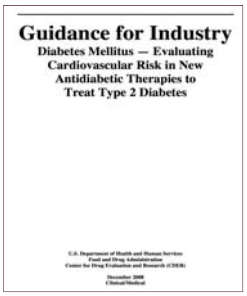
Rosiglitazone

- Jun 2007 Meta-analysis of 42 trials found increased CV risk with rosiglitazone vs control
  - Myocardial infarction (MI): 1.43 (95% CI, 1.03-1.98; P=0.03)
  - Cardiovascular (CV) death: 1.64 (95% CI, 0.98-2.74; P=0.06)
- Resulted in boxed warning for increase MI risk
- May 2011 Updated Risk Evaluation and Mitigation Strategy (REMS) to restrict access and distribution

Nissen, et al. *N Engl J Med.* 2007;356(24):2457.
FDA Drug Safety Communication. www.fda.gov/Drugs/DrugSafety/ucm241411.htm
FDA Drug Safety Communication. www.fda.gov/Drugs/DrugSafety/ucm255005.htm

FDA Guidance

- **Ensure new drugs will not cause unacceptable increase in CV risk**
  - Meta-analysis of Phase 2 and 3 clinical trials
  - Dedicated Phase 4 clinical trial
- Minimum duration of 2 years
- Include high risk patients
  - Advanced disease, elderly, renal impairment

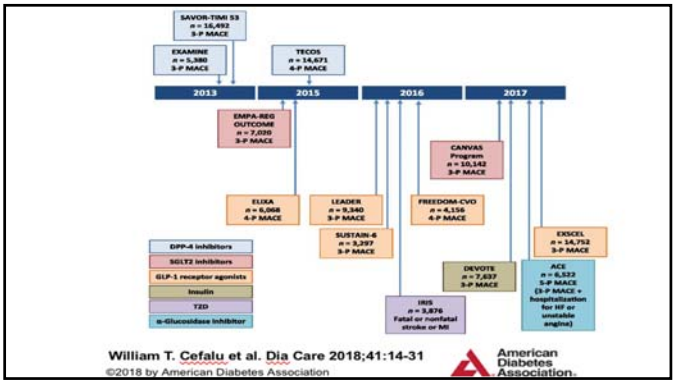

Guidance for Industry
Diabetes Mellitus — Evaluating Cardiovascular Risk in New Antidiabetic Therapies to Treat Type 2 Diabetes

FDA Guidance for Industry. www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf

FDA Guidance

- **3-point MACE**
  - Cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke
- **4-point or 5-point MACE**
  - 3-point MACE *plus* hospitalization for acute coronary syndrome, heart failure hospitalization and/or urgent revascularization
- Acceptable Results
  - Confidence interval (CI) for estimated risk ratio must be less than 1.3

FDA Guidance for Industry. www.fda.gov/downloads/Drugs/Guidances/ucm071627.pdf



Thiazolidinediones (TZDs)

RECORD Reevaluation

End Point	Rosiglitazone (N=309)	Met/SU (N=279)	HR (95% CI)
	no. (%)		
3pt MACE	**186 (8.4%)**	**191 (8.6%)**	**0.97 (0.79-1.18)**
CV Death	88 (4.0)	96 (4.3)	0.90 (0.68-1.21)
MI	72 (3.2)	62 (2.8)	1.15 (0.82-1.62)
Stroke	53 (2.4)	64 (2.9)	0.82 (0.57-1.18)

Mahaffey et al. *Am Heart J.* 2013 Aug;166(2):240.

IRIS

End Point	Placebo (N=1937)	Pioglitazone (N=1939)	HR (95% CI)	P Value
	no. (%)			
Primary-MI or stroke	**228 (11.8)**	**175 (9.0)**	**0.76 (0.62– 0.93)**	**0.007**

Kernan et al. *N Engl J Med* 2016;374:1321-31.

PROACTIVE

End Point	Placebo (N=2633)	Pioglitazone (N=2605)	HR (95% CI)	P Value
Primary Composite	**572 (21.8)**	**514 (19.7)**	**0.90 (0.80-1.02)**	**0.095**

Dormandy et al. *Lancet* 2005;366:1279–89.

DPP-4 Inhibitors

DPP-4 Inhibitors

	SAVOR-TIMI 53	EXAMINE	TECOS
Intervention	Saxagliptin vs placebo	Alogliptin vs placebo	Sitagliptin vs placebo
Inclusion	CVD or multiple risk factors	Recent ACS	CVD
Age (y)	65.1	61.0	65.4
DM Duration (y)	10.3	7.1	11.6
Follow Up (y)	2.1	1.5	3.0

Diabetes Care 2018;41(Suppl. 1):S97.

DPP-4 Inhibitors

	SAVOR-TIMI 53	EXAMINE	TECOS
Baseline A1C (%)	8.0	8.0	7.2
End of study difference in A1C between groups (%)	-0.3	-0.3	-0.3
Prior CVD/HF (%)	78/13	100/28	74/18
Statin Use (%)	78	91	80

Diabetes Care 2018;41(Suppl. 1):S97.

EXAMINE

End Point	Placebo (N=2679)	Alogliptin (N=2701)	HR (95% CI)	P Value
	no. (%)			
Primary 3pt MACE	**316 (11.8)**	**305 (11.3)**	**0.96 (UL≤1.16)**	**0.32**
CV Death	111 (4.1)	89 (3.3)	0.76 (0.60-1.04)	0.10
Nonfatal MI	173 (6.5)	187 (6.9)	1.08 (0.88-1.33)	0.47
Nonfatal Stroke	32 (1.2)	29 (1.1)	0.91 (0.55-1.50)	0.71

White et al. *N Engl J Med* 2013;369:1327-35.

SAVOR-TIMI 53

End Point	Placebo (N=8212)	Saxagliptin (N=8280)	HR (95% CI)	P Value
	no. (%)			
Primary 3pt MACE	**609 (7.2)**	**613 (7.3)**	**1.0 (0.89-1.12)**	**0.99**
CV Death	260 (2.9)	269 (3.2)	1.03 (0.87-1.22)	0.72
Nonfatal MI	265 (3.2)	278 (3.4)	0.95 (0.8-1.12)	0.52
Nonfatal Stroke	157 (1.9)	141 (1.7)	1.11 (0.88-1.39)	0.38

Scirica et al. *N Engl J Med* 2013;369:1317-26.

TECOS

End Point	Placebo (N=7266)	Sitagliptin (N=7257)	HR (95% CI)	P Value
	no. (%)			
Primary 4pt MACE	**851 (11.6)**	**839 (11.4)**	**0.98 (0.89-1.09)**	**0.65**
CV Death	291 (4.0)	311 (3.2)		
Nonfatal MI	286 (3.2)	278 (3.4)		
Nonfatal Stroke	157 (2.1)	145 (2.0)		
Unstable Angina	117 (1.6)	108 (1.5)		

Green et al. *N Engl J Med* 2015;373:232-42.

DPP-4 Inhibitors

Secondary End Point	Saxagliptin	Alogliptin	Sitagliptin
HF hosp. no. (%)	**1.27 (1.07-1.51)**	1.19 (0.90-1.58)	1.00 (0.83-1.20)

Scirica et al. *N Engl J Med* 2013;369:1317-26.
White et al. *N Engl J Med* 2013;369:1327-35.
Green et al. *N Engl J Med* 2015;373:232-42.

GLP-1 Receptor Agonists

GLP-1 Receptor Agonists

	ELIXA	LEADER	SUSTAIN-6	EXSCEL
Intervention	Lixisenatide vs placebo	Liraglutide vs placebo	Semaglutide vs placebo	Exenatide ER vs placebo
Inclusion	Recent ACS	CVD or high risk	CVD or high risk	70% CVD/ 30% no CVD
Age (y)	60.3	64.3	64.6	62
DM Duration	9.3	12.8	13.9	12
Follow Up	2.1	3.8	2.1	3.2

Diabetes Care 2018;41(Suppl. 1):S97.

	ELIXA	LEADER	SUSTAIN-6	EXSCEL
Baseline A1C (%)	7.7	8.7	8.7	8.0
End of study difference in A1C between groups (%)	-0.3	-0.4	-0.7/-1.0	-0.53
Prior CVD/HF (%)	100/22	81/18	60/24	73.1/16.2
Statin Use (%)	93	72	73	74

Diabetes Care 2018;41(Suppl. 1):S97.

ELIXA

End Point	Placebo (N=3034)	Lixisenatide (N=3034)	HR (95% CI)	P Value
	no. (%)			
Primary 4pt MACE	**399 (13.2)**	**406 (13.4)**	**1.02 (0.89-1.17)**	**0.81**
CV Death	93 (23.3)	88 (21.7)		
Nonfatal MI	247 (61.9)	255 (62.8)		
Nonfatal Stroke	49 (12.3)	54 (13.3)		
Unstable Angina	10 (2.5)	9 (2.2)		

Pfeffer et al. *N Engl J Med* 2015;373:2247-57.

LEADER

End Point	Placebo (N=4668)	Liraglutide (N=4672)	HR (95% CI)	P Value
	no. (%)			
Primary 3pt MACE	**694 (149)**	**608 (13.0)**	**0.87 (0.78-0.97)**	**0.01**
CV Death	278 (6.0)	219 (4.7)	0.78 (0.66-0.93)	0.007
Nonfatal MI	317 (6.8)	281 (6.0)	0.88 (0.75-1.03)	0.11
Nonfatal Stroke	177 (3.8)	159 (3.4)	0.89 (0.72-1.11)	0.30

Marso et al. *N Engl J Med* 2016;375:311-22.

LEADER

End Point	Placebo (N=4668)	Liraglutide (N=4672)	HR (95% CI)	P Value
	no. (%)			
Expanded Primary	1062 (22.7)	948 (20.3)	0.88 (0.81-0.96)	0.005
Revascular-ization	441 (9.4)	405 (8.7)	0.91 (0.80-1.04)	0.18
Nephropathy	337 (7.2)	268 (5.7)	0.78 (0.67-0.92)	0.003
Retinopathy	92 (2.0)	106 (2.3)	1.15 (0.87-1.52)	0.33

Marso et al. *N Engl J Med* 2016;375:311-22.

SUSTAIN-6

End Point	Placebo (N=2679)	Semaglutide (N=2701)	HR (95% CI)	P Value
	no. (%)			
Primary 3pt MACE	**146 (8.9)**	**108 (6.6)**	**0.74 (0.58-0.95)**	**0.02**
CV Death	46 (2.8)	44 (2.7)	0.98 (0.65-1.48)	0.92
Nonfatal MI	64 (3.9)	47 (2.9)	0.74 (0.51-1.08)	0.12
Nonfatal Stroke	44 (2.7)	27 (1.6)	0.61 (0.38-0.99)	0.04

Marso et al. *N Engl J Med* 2016;375:1834-44.

SUSTAIN-6

End Point	Placebo (N=2679)	Semaglutide (N=2701)	HR (95% CI)	P Value
	no. (%)			
Expanded Primary	264 (16.0)	199 (12.1)	0.74 (0.58-0.95)	<0.001/ 0.02
Revascular-ization	126 (7.6)	83 (5.0)	0.65 (0.50-0.86)	0.003
Nephropathy	100 (6.1)	62 (3.8)	0.64 (0.46-0.88)	0.005
Retinopathy	29 (1.8)	50 (3.0)	1.76 (1.11-2.78)	0.02

Marso et al. *N Engl J Med* 2016;375:1834-44.

EXSCEL

End Point	Placebo (N=2679)	Exenatide ER (N=2701)	HR (95% CI)
	no. (%)		
Primary 3pt MACE	**905 (12.2)**	**839 (11.4)**	**0.91 (0.83-1.00)**
CV Death	383 (5.2)	340 (4.6)	0.88 (0.76-1.02)
MI	493 (6.7)	483 (6.6)	0.97 (0.85-1.10)
Stroke	218 (2.9)	187 (2.5)	0.85 (0.70-1.03)
All Mortality	584 (7.9)	507 (6.9)	0.86 (0.77-0.97)

Holman et al. *N Engl J Med* 2017;377:1228-39.

SGLT2 Inhibitors

SGLT2 Inhibitors

	EMPA-REG OUTCOME	CANVAS PROGRAM
Intervention	Empagliflozin vs placebo	Canagliflozin vs placebo
Inclusion	CVD	CVD or no CVD
Age (y)	63.1	63.3
DM Duration	57% >10 y	13.5 y
Follow Up (y)	3.1	5.7 / 2.1

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SGLT2 Inhibitors

	EMPA-REG OUTCOME	CANVAS PROGRAM
Baseline A1C (%)	8.1	8.2
End of study A1C (%) difference between groups	-0.3	-0.58
Prior CVD/HF (%)	99/10	65.6/14.4
Statin Use (%)	77	75

Diabetes Care 2018;41(Suppl. 1):S97.

Zinman et al. *N Engl J Med* 2015;373:2117-28.
Inzucchi et al. *Diabetes Care* 2018;41:e4-e5.

EMPA-REG OUTCOME

End Point	Placebo (N=2333)	Empagliflozin (N=4687)	HR (95% CI)	P value
	no. (%)			
Primary 3pt MACE	**282 (12.1)**	**490 (10.5)**	**0.86 (0.74-0.99)**	**0.04**
CV Death	137 (5.9)	172 (3.7)	0.62 (0.49-0.77)	<0.001
All Mortality	194 (8.3)	269 (5.7)	0.68 (0.57-0.82)	<0.001
HF Hosp.	95 (4.1)	126 (2.7)	0.65 (0.50-0.85)	0.002
AKI	37 (1.6)	45 (1.0)		<0.05
Amputations	43 (1.8)	88 (1.9)	1.00 (0.70-1.44)	

CANVAS Program

End Point	Placebo (N=5795)	Canagliflozin (N=4347)	HR (95% CI)
	no. per 1000 patient-year		
Primary 3pt MACE	**31.5**	**26.9**	**0.86 (0.75-0.97)**
CV Death	12.8	11.6	0.87 (0.72-1.06)
All Mortality	19.5	17.3	0.87 (0.74-1.01)
HF Hosp.	20.8	5.5	0.67 (0.52-0.87)
Nephropathy	5.5	9.0	0.60 (0.47-0.77)
Amputations	3.4	6.3	1.97 (1.41-2.75)

Neal et al. *N Engl J Med* 2017;377:644-57.

Alpha-Glucosidase Inhibitors

ACE

End Point	Placebo (N=3250)	Acarbose (N=3272)	HR (95% CI)	P Value
Primary 5pt MACE	*no. (%)* **479 (14.7)**	**470 (14.4)**	**0.98 (0.86-1.11)**	**0.73**
3pt MACE	299 (9.2)	285 (8.7)	0.95 (0.81-1.11)	0.51
CV Death	163 (5.0)	145 (4.4)	0.89 (0.71-1.11)	0.29
MI	108 (3.3)	122 (3.7)	1.12 (0.87-1.46)	0.38
Stroke	77 (2.4)	75 (2.3)	0.97 (0.70-1.33)	0.83

Holman et al. *Lancet Diabetes Endocrinol.* 2017;5(11):877-886.

Basal Insulin

DEVOTE

End Point	Degludec (N=3818)	Glargine (N=3819)	HR (95% CI)	P Value
Primary 3pt MACE	*no. (%)* **325 (8.5)**	**356 (9.3)**	**0.91 (0.78–1.06)**	**<0.001**
CV Death	136 (3.6)	142 (3.7)	0.96 (0.76–1.21)	0.71
Nonfatal MI	144 (3.8)	169 (4.4)	0.85 (0.68-1.06)	0.15
Nonfatal Stroke	71 (1.9)	74 (1.9)	0.90 (0.65-1.23)	0.50

Marso et al. *N Engl J Med* 2017;377:723-32.

Summary of CV Effects

Drug Class	ASCVD	HF
SGLT-2 Inhibitors	• **Benefit** (canagliflozin, empagliflozin*)	• **Benefit** (canagliflozin, empagliflozin)
GLP-1 RAs	• **Benefit** (liraglutide*, semaglutide) • Neutral (lixisenatide, exenatide ER)	• Neutral
Metformin	• Potential benefit	• Neutral

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Summary of CV Effects

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Drug Class	ASCVD	HF
DPP-4 Inhibitors	• Neutral	• Potential risk (saxagliptin, alogliptin)
TZDs	• Potential benefit (pioglitazone)	• Increased risk
AG inhibitors	• Neutral	• Neutral
Sulfonylureas	• Neutral	• Neutral
Insulin	• Neutral	• Neutral

ADA Standards of Medical Care in Diabetes Table 9.4

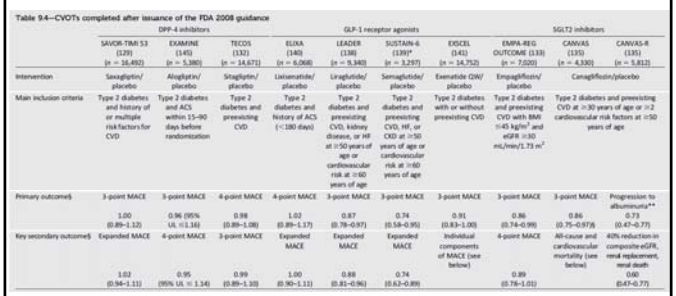

Table 9.4—CVOTs completed after issuance of the FDA 2008 guidance

	DPP-4 inhibitors			GLP-1 receptor agonists					SGLT2 inhibitors		
	SAVOR-TIMI 53 (129) (n = 16,492)	EXAMINE (145) (n = 5,380)	TECOS (132) (n = 14,671)	ELIXA (140) (n = 6,068)	LEADER (138) (n = 9,340)	SUSTAIN-6 (139)* (n = 3,297)	EXSCEL (141) (n = 14,752)	EMPA-REG OUTCOME (133) (n = 7,020)	CANVAS (135) (n = 4,330)	CANVAS-R (135) (n = 5,812)
Intervention	Saxagliptin/ placebo	Alogliptin/ placebo	Sitagliptin/ placebo	Lixisenatide/ placebo	Liraglutide/ placebo	Semaglutide/ placebo	Exenatide QW/ placebo	Empagliflozin/ placebo	Canagliflozin/placebo	
Main inclusion criteria	Type 2 diabetes and history of or multiple risk factors for CVD	Type 2 diabetes and ACS within 15–90 days before randomization	Type 2 diabetes and preexisting CVD	Type 2 diabetes and history of ACS (<180 days)	Type 2 diabetes and preexisting CVD, kidney disease, or HF at ≥50 years of age or cardiovascular risk at ≥60 years of age	Type 2 diabetes and preexisting CVD, HF, or CKD at ≥50 years of age or cardiovascular risk at ≥60 years of age	Type 2 diabetes with or without preexisting CVD	Type 2 diabetes and preexisting CVD with BMI ≤45 kg/m² and eGFR ≥30 mL/min/1.73 m²	Type 2 diabetes and preexisting CVD at ≥30 years of age or ≥2 cardiovascular risk factors at ≥50 years of age	
Primary outcome§	3-point MACE	3-point MACE	4-point MACE	4-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	3-point MACE	Progression to albuminuria**
	1.00 (0.89–1.12)	0.96 (95% UL ≤1.16)	0.98 (0.89–1.08)	1.02 (0.89–1.17)	0.87 (0.78–0.97)	0.74 (0.58–0.95)	0.91 (0.83–1.00)	0.86 (0.74–0.99)	0.86 (0.75–0.97)‖	0.73 (0.67–0.77)
Key secondary outcome§	Expanded MACE	4-point MACE	3-point MACE	Expanded MACE	Expanded MACE	Expanded MACE	Individual components of MACE (see below)	4-point MACE	All-cause and cardiovascular mortality (see below)	40% reduction in composite eGFR, renal replacement, renal death
	1.02 (0.94–1.11)	0.95 (95% UL ≤ 1.14)	0.99 (0.89–1.10)	1.00 (0.90–1.11)	0.88 (0.81–0.96)	0.74 (0.62–0.89)		0.89 (0.78–1.01)		0.60 (0.47–0.77)

http://care.diabetesjournals.org/content/41/Supplement_1/S86.full-text.pdf

Implications of CVOTs

Advantages
- Prevent harm
- Reduced CV events/mortality
- Identify other drug effects

Disadvantages
- Required resources
  - Time
  - Financial
  - Clinical
  - Professional
- Delay in drug approvals
- Study design limitations

Cefalu et al. *Diabetes Care* 2018;41:14–31

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