1:30 – 2:45 pm

Examining the Evidence: What Recent Cardiovascular Safety Trials Mean to the Treatment of High-Risk Patients with Diabetes

SPEAKERS

Darren K. McGuire, MD, MHSc

Richard E. Pratley, MD

Presenter Disclosure Information

The following relationships exist related to this presentation:

- Darren K. McGuire, MD, MHSc: Consultant for Ardea Biosciences; Boehringer Ingelheim Pharmaceuticals, Inc.; Ferring Pharmaceuticals Inc.; Merck & Co., Inc.; Novo Nordisk Inc.; Regeneron Pharmaceuticals Inc.; sanofi-aventis U.S.; Shire; and The Medicines Company. Trial Leadership Committees for AstraZeneca; Bristol-Myers Squibb Company; Cubist Pharmaceuticals; Eisai Co.; Eli Lilly and Company; GlaxoSmithKline; Janssen Pharmaceuticals Inc.; Lexicon Pharmaceuticals Inc.; Merck & Co., Inc.; Novo Nordisk Inc.; Orexigen Therapeutics, Inc.; and Takeda Pharmaceutical Company.
- Richard E. Pratley, MD: No financial relationships to disclose.

Presenter Disclosure Information

Off-Label/Investigational Discussion

- In accordance with pmiCME policy, faculty have been asked to disclose discussion of unlabeled or unapproved use(s) of drugs or devices during the course of their presentations.

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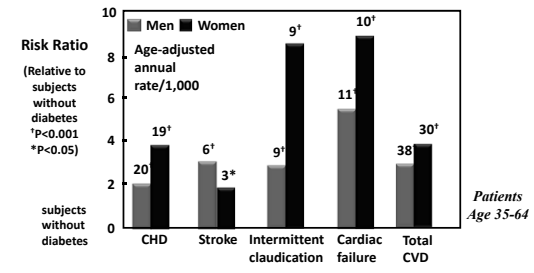
Vascular Disease Events in Patients with Diabetes: Framingham Heart Study, 30-year Follow-up



Diabetes is a Vascular Disease

Adapted from Wilson PWF, Kannel WB. In: *Hyperglycemia, Diabetes and Vascular Disease.* Ruderman N et al, eds. Oxford; 1992.

Impact of Intensive Therapy for Diabetes Mellitus: Summary of Major Clinical Trials

Study	Microvascular		CVD		Mortality	
UKPDS 33 (7.0 vs. 7.9%)	↓	↓	↔	↓	↔	↓
DCCT / EDIC* (7.2 vs. 9.1%)	↓	↓	↔	↓	↔	↓
ACCORD (6.4% vs. 7.5%)	↓		↔		↑	
ADVANCE (6.3% vs. 7.0%)	↓		↔		↔	
VADT (6.9% vs. 8.4%)	↓		↔	↓	↔	

Initial trial
Long-term follow-up

UKPDS = UK Prospective Diabetes Study; DCCT/EDIC = Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications; ACCORD = Action to Control Cardiovascular Risk in Diabetes; ADVANCE = Action in Diabetes and Vascular Disease; VADT = Veterans Affairs Diabetes Trial.

Bergenstal RM et al. *Am J Med.* 2010;123:374e9-e18. UK Prospective Diabetes Study (UKPDS) Group. *Lancet.* 1998;352:854-865. Holman RR. *N Engl J Med.* 2008;359(15):1577-1589. DCCT Research Group. *N Engl J Med.* 1993;329;977-986. Nathan DM, et al. *N Engl J Med.* 2005;353:2643-2653. Gerstein HC, et al. *N Engl J Med.* 2008;358:2545-2559. Patel A, et al. *N Engl J Med.* 2008;358:2560-2572. Duckworth W, et al. *N Engl J Med.* 2009;360:129-139. Hayward RA, et al. *N Engl J Med.* 2015;372:2197-2206.

ADA-EASD Position Statement: Management of Hyperglycemia in T2DM

Glycemic targets

- HbA_{1c} <7.0% (mean PG ~150-160 mg/dL [8.3-8.9 mmol/L])
  - Pre-prandial PG <130 mg/dL (7.2 mmol/L)
  - Post-prandial PG <180 mg/dL (10.0 mmol/L)
- Individualization is key
  - Tighter targets (6.0% - 6.5%) - younger, healthier
  - Looser targets (7.5% - 8.0%+) - older, comorbidities, hypoglycemia prone, etc
- Avoidance of hypoglycemia

ADA = American Diabetes Association; EASD = European Association for the Study of Diabetes; PG = plasma glucose; HbA_{1c} = glycated hemoglobin A_{1c}; *Diabetes Care.* 2012;35:1364-1379; *Diabetologia.* 2012 Jun;55(6):1577-1596.

Clinical Case

- A 65 year old man with a history of HTN, COPD, and obesity has been hospitalized following presentation to the ED with chest pain
- Cardiac catheterization revealed MVCAD and he subsequently underwent 3 vessel CABG
- He required an insulin drip for several days peri- and post-operatively to manage hyperglycemia

Clinical Case

- The patient is alert, well-appearing and eating a NCS diet consistently
- He is afebrile and vital signs are stable
  - Weight 213 lbs
  - Height 70.5 inches
  - BMI = 30.19

Laboratory Data:

HbA1c = 8.2%
Sodium = 144
Potassium = 3.5
Chloride = 107
Bicarb = 30
BUN = 23
Creatinine = 1.8
Glucose = 115
eGFR = 38

Pre-meal BG values range from 110-140 mg/dL on a scheduled SC insulin regimen totaling 24 units daily

Clinical Case

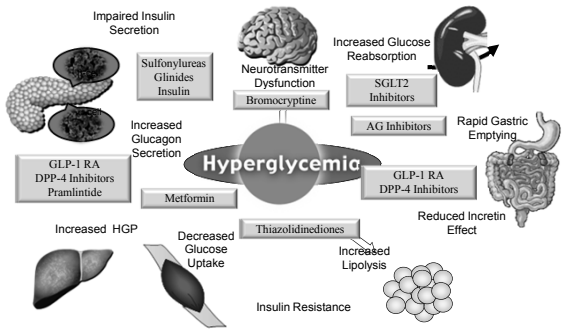
- You are considering a transition from scheduled insulin to other therapy to manage his newly-diagnosed type 2 diabetes mellitus
- What particular clinical issues affect decision making in in this patient?
- What do we know about diabetes drug safety in patients at high risk for CV even**ts?**

12 Classes of Antihyperglycemic Agents for T2DM

Class	A_{1c} Reduction	Hypo-glycemia	Weight Change	Dosing (times/day)	Other Safety Issues
Metformin	1.5	No	Neutral	2	GI, lactic acidosis, B12 deficiency
Basal insulin analog	1.5–2.5	Yes	Gain	1, injected	Hypoglycemia
Rapid-acting insulin	1.5–2.5	Yes	Gain	1-4,injected	
Sulfonylureas	1.5	Yes	Gain	1	Allergies, secondary failure
Thiazolidinediones	0.5–1.4	No	Gain	1	Edema, CHF, bone fractures
Short-acting GLP-1 RAs	0.5–1.0	No	Loss	2, injected	GI, ? pancreatitis, ARF
Long-acting GLP-1 RAs	~1.5	No	Loss	1, injected	GI, ? pancreatitis, ?MTC, ?ARF
Repaglinide	1–1.5	Yes	Gain	3	
Nateglinide	0.5–0.8	Rare	Gain	3	
Alpha-glucosidase inhibitors	0.5–0.8	No	Neutral	3	GI
Amylin mimetics	0.5–1.0	No	Loss	3, injected	GI
DPP-4 inhibitors	0.6–0.8	No	Neutral	1	Pancreatitis
Bile acid sequestrant	0.5	No	Neutral	1 or 2	GI
Bromocriptine quick release	0.7	No	Neutral	1	GI
SGLT2 inhibitors	0.8-1.0	No	Loss	1	Genital mycotic infections

GI = gastrointestinal; GLP-1 = glucagon-like peptide-1; RA = receptor agonist; CHF = congestive heart failure; ARF = acute renal failure; MTC = medullary thyroid carcinoma; DPP-4 = dipeptidyl peptidase-4; SGLT2 = sodium-dependent glucose cotransporter -2.
Adapted from: Nathan DM, et al. *Diabetes Care.* 2007;30(3):753-759. Nathan DM, et al. *Diabetes Care.* 2006;29(8):1963-1972. Nathan DM, et al. *Diabetes Care.* 2009;32(1):193-203. ADA. *Diabetes Care.* 2008;31:S12-S54. Buse J, et al. *Lancet.* 2009;374(9683):39-47.

Complementary Mechanisms of Action of Anti-Hyperglycemic Agents in T2DM



Adapted from DeFronzo RA. *Diabetes.* 2009;58(4):773-795.

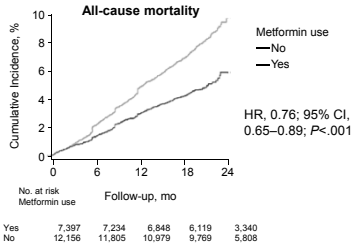
Other Considerations for Selecting Therapies

- Current HbA_{1c} and magnitude of reduction needed to reach goal
- Potential effects on body weight and BMI
- Potential for hypoglycemia – age, lack of awareness of hypoglycemia, disordered eating habits
- Effects on CVD risk factors – blood pressure and blood lipids
- Comorbidities – coronary artery disease, heart failure, chronic kidney disease, liver dysfunction
- Patient factors – adherence to medications and lifestyle changes, preference for oral vs injected therapy, economic considerations

Inzucchi SE, et al. *Diabetes Care.* 2012;35(6):1364-1379.

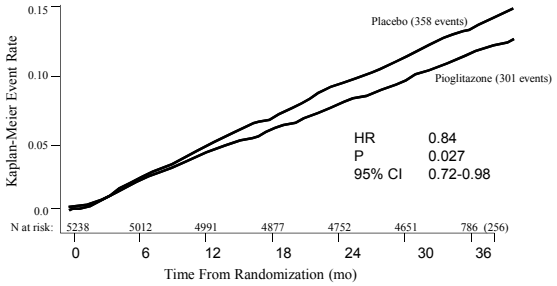
Metformin Use Among Patients With T2DM and Atherothrombosis

Prospective evaluation of 19, 691 patients with T2DM and established atherothrombosis participating in the REACH Registry, treated with or without metformin as part of a secondary CVD prevention strategy



REACH=Reduction of Atherothrombosis for Continued Health
Roussel R et al. *Arch Intern Med.* 2010;170:1892

PROactive Prioritized
Secondary Endpoint



Death, MI, CVA

Dormandy JA, et al. Lancet 2005; 366: 1279

Pioglitazone and Risk of Cardiovascular Events in Patients With Type 2 Diabetes Mellitus: Meta-analysis of Randomized Trials

Conclusions:

- Pioglitazone is associated with a significantly lower risk of death, myocardial infarction, or stroke among a diverse population of patients with diabetes.
- Serious heart failure is increased by pioglitazone, although without an associated increase in mortality.

JAMA. 2007;298(10):1180-1188.

Diabetes and CV Outcome Trials: Selected Lessons Learned

Darren K. McGuire, MD, MHSc

Professor of Medicine

University of Texas Southwestern Medical Center

Guidance for Diabetes Drug Development 1990-2008

- ICH Guidelines:
  - 1500 patients exposed
  - 300-600 x 6 months
  - 100 x 1 year
- Approval based on as little as **200 patient-years** of exposure

Paradigm Shift

- Increasing incidence/prevalence of T2DM
  - >10% of US adult population
- Growing awareness of CV impact of T2DM
- Proliferation of medications available
- Numerous examples of adverse drug effects
  - On target
  - Off target

Present FDA Regulatory Guidance for Drugs for Type 2 Diabetes

FDA NEWS RELEASE

FOR IMMEDIATE RELEASE
December 17, 2008

Media Inquiries:
Karen Riley, 301-796-4674
Consumer Inquiries:
888-INFO-FDA

FDA Announces New Recommendations on Evaluating Cardiovascular Risk in Drugs Intended to Treat Type 2 Diabetes

The U.S. Food and Drug Administration recommended today that manufacturers developing new drugs and biologics for type 2 diabetes provide evidence that the therapy will not increase the risk of such cardiovascular events as a heart attack. The recommendation is part of a new guidance for industry that applies to all diabetes drugs currently under development.

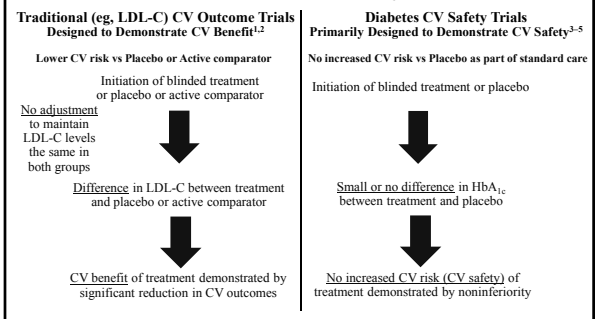
"We need to better understand the safety of new antidiabetic drugs. Therefore, companies should conduct a more thorough examination of their drugs' cardiovascular risks during the product's development stage," said Mary Parks, M.D., director, Division of Metabolism and Endocrinology Products, Center for Drug Evaluation and Research (CDER), FDA. "FDA's guidance outlines the agency's recommendations for doing such an assessment."

"…sponsors should demonstrate that the therapy will not result in an unacceptable increase in cardiovascular risk."

Requires ~15,000 pt-yrs of exposure

http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116994.htm

Traditional CV Outcome Trials vs Diabetes CV Safety Trials



CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4; LDL-C = low density lipoprotein cholesterol.
1.Heart Protection Study Collaborative Group. *Lancet.* 2002;360:7–22. **2.** Heart Protection Study Collaborative Group. *Lancet.* 2003;361:2005–2016. **3.** White WB et al. *N Engl J Med.* 2013;369:1327–1335. **4.** Scirica BM et al. *N Engl J Med.* 2013;369:1317–1326. **5.** Green JB et al. *Am Heart J.* 2013;166:983–989.e7.

Purpose of Cardiovascular Safety Trials with Diabetes Drugs

- CV safety trials for diabetes drugs are designed to demonstrate no increased CV risk vs placebo when used as part of usual care[1–3,a]
- CV safety trials for diabetes drugs are not primarily designed to test the hypothesis of a CV benefit of HbA_{1c} reduction[3–5]
- Glucose control as measured by HbA_{1c} is intended to be similar between the two groups through adjustment of antihyperglycemic medications according to local treatment guidelines[3–5]
  - CV safety and CV benefit can be evaluated independently of HbA_{1c}

CV = cardiovascular; DPP-4 = dipeptidyl peptidase-4
[A] Patients enrolled in CV safety trials with DPP-4 inhibitors have a high risk of CV events (ie, established CV disease or multiple CV risk factors).
1. White WB et al. *Am Heart J.* 2011;162:620–626.e7. **2.** Scirica BM *Am Heart J.* 2011;162:818–825.e6. **3.** Green JB et al. *Am Heart J.* 2013;166:983–989.e7. **4.** White WB et al. *N Engl J Med.* 2013;369:1327–1335. **5.** Scirica BM et al. *N Engl J Med.* 2013;369:1317–1326.

Incretin Modulators on US Market

	Generic	Trade Names
GLP1-Receptor Agonists	exenatide	Byetta
	liraglutide	Victoza
	albiglutide	Tanzeum
	exenatide ER	Bydureon
DPP4 inhibitors	sitagliptin	Januvia
	saxagliptin	Onglyza
	alogliptin	Nesina
	linagliptin	Tradjenta

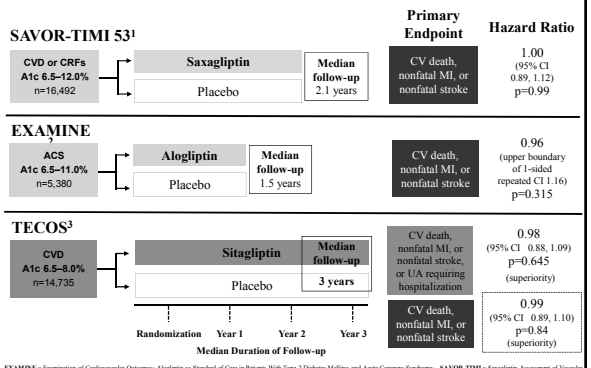
CV Outcomes Trials with Incretin-Based Therapies

Trial Name	Comparators	Population	Estimated Primary Completion Date
SAVOR-TIMI 53[1]	Saxagliptin vs placebo	T2DM with history of CVD or CV risk	Completed
EXAMINE[2]	Alogliptin vs placebo	T2DM with recent ACS	Completed
TECOS[3]	Sitagliptin vs placebo	T2DM with pre-existing CVD	Completed
ELIXA[4]	Lixisenatide vs placebo	T2DM with ACS	Completed
LEADER[5]	Liraglutide vs placebo	T2DM with CV risk	Oct 2015
EXSCEL[6]	Exenatide ER vs placebo	T2DM	Dec 2017
CARMELINA[7]	Linagliptin vs placebo	T2DM with CV risk	Jan 2018
CAROLINA[8]	Linagliptin vs glimepiride	T2DM with CV risk	Sep 2018

ACS = acute coronary syndrome; CV = cardiovascular; CVD = cardiovascular disease.

1. http://www.clinicaltrials.gov/ct2/show/NCT01107886. 2. http://www.clinicaltrials.gov/ct2/show/NCT00968708.
3. http://www.clinicaltrials.gov/ct2/show/NCT00790205. 4. http://www.clinicaltrials.gov/ct2/show/NCT01147250.
5. http://www.clinicaltrials.gov/ct2/show/NCT01179048. 6. http://www.clinicaltrials.gov/ct2/show/NCT01144338.
7. http://www.clinicaltrials.gov/ct2/show/NCT01897532. 8. http://www.clinicaltrials.gov/ct2/show/NCT01243424

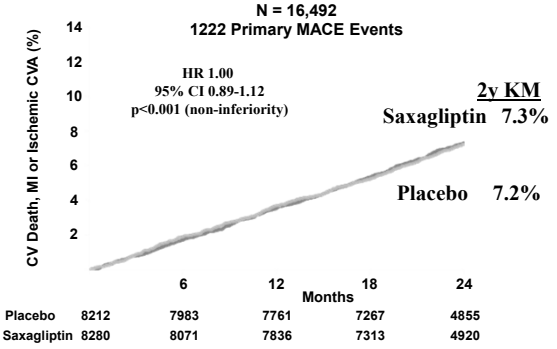
Cardiovascular Outcomes for DPP-4 Inhibitors



EXAMINE = Examination of Cardiovascular Outcomes: Alogliptin vs Standard of Care in Patients With Type 2 Diabetes Mellitus and Acute Coronary Syndrome; **SAVOR-TIMI** = Saxagliptin Assessment of Vascular Outcomes Recorded in Patients With Diabetes Mellitus Trial-Thrombolysis in Myocardial Infarction; **TECOS** = Trial to Evaluate Cardiovascular Outcomes after Treatment with Sitagliptin

1. Scirica BM, et a. NEJM. 2013;369:1317-1326; 2. White W, et al. NEJM. 2013;369:1327-1335; 3. Green JB, et al. NEJM, 2015 *in press*

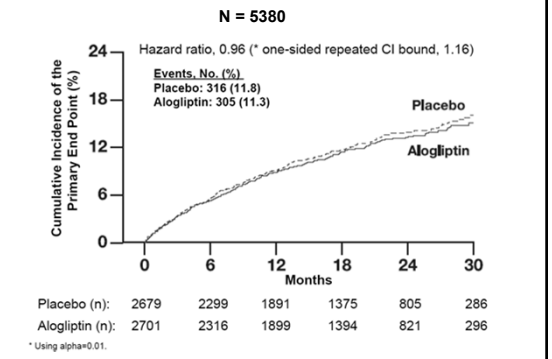
SAVOR TIMI 53-Primary Endpoint



Placebo	8212	7983	7761	7267	4855
Saxagliptin	8280	8071	7836	7313	4920

Scirica BM, et al. N Engl J Med 369: 1317-1326.

EXAMINE Primary end point



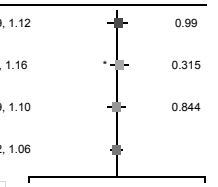
Placebo (n):	2679	2299	1891	1375	805	286
Alogliptin (n):	2701	2316	1899	1394	821	296

* Using alpha=0.01.

White WB, et. al. N Engl J Med. 2013; 369:1327

SAVOR-TIMI 53, EXAMINE, and TECOS: MACE Outcomes

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	p-Value
SAVOR-TIMI (saxagliptin vs placebo)	613/8280 (7.4%)	609/8212 (7.4%)	1.00	0.89, 1.12	0.99
EXAMINE (alogliptin vs placebo)	305/2701 (11.3%)	316/2679 (11.8%)	0.96	NA, 1.16	0.315
TECOS (sitagliptin vs placebo)	745/7332 (10.2%)	746/7339 (10.2%)	0.99	0.89, 1.10	0.844
SAVOR + EXAMINE + TECOS	1663/18313 (9.1%)	1671/18230 (9.2%)	0.99	0.92, 1.06	



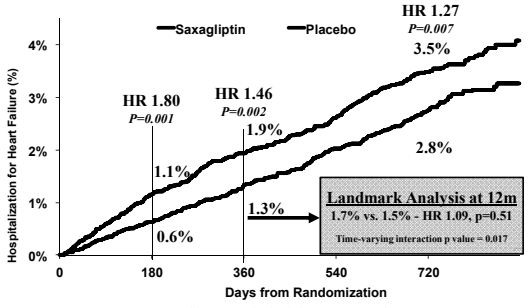
Test for heterogeneity for 3 trials: p=0.877, I^2=0%

***Lower Confidence Limit not given for EXAMINE trial;* MACE = major adverse cardiac events.**

1. Scirica BM, et al. *N Engl J Med*. 2013;369:1317–1326. 2. White WB, et al. *N Engl J Med*. 2013;369:1327–1335.
3. Green JB, et al. *N Engl J Med*. 2015;373(3):232–242.

SAVOR TIMI 53-Hospitalization for Heart Failure

Time to the 1st occurrence of any hospitalization for heart failure; 517 events



Scirica BM, et al. Circulation 2014; 10.1161/CIRCULATIONAHA.114.010389

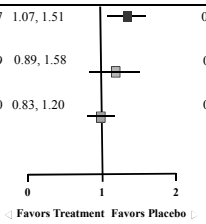
Heart Failure in SAVOR-TIMI / EXAMINE / TECOS

TRIAL			Hazzard Ratio (95% CI)	P-value
SAVOR – TIMI 53	Saxagliptin (n=8280)	Placebo (n=8212)		
Hospitalization for heart failure, No (%)[1]	290 (3.5)	230 (2.8)	1.27 (1.07 – 1.51)	.007
EXAMINE	Alogliptin (n=2701)	Placebo (n=2679)		
Hospitalization for heart failure, No (%)[2]	106 (3.9)	89 (3.3)	1.19 (0.90 – 1.58)	.22
TECOS	Sitagliptin (n=7332)	Placebo (n=7339)		
Hospitalization for heart failure, No (%)[3]	228 (3.1)	229 (3.1)	1.00 (0.83 – 1.20)	.98

1. Scirica BM, et al. *N Engl J Med*. 2013;369:1317-1326. 2. Zannnad F, et al. *Lancet* 2015;385(9982):2067-76. 3. Holman et al. ADA, 2015.

SAVOR-TIMI 53, EXAMINE, and TECOS: Hospitalization for Heart Failure

	Study Drug n/N (%)	Placebo n/N (%)	Hazard Ratio	95% CI	*p*-Value
SAVOR-TIMI (saxagliptin vs placebo)	289/8280 (3.5%)	228/8212 (2.8%)	1.27	1.07, 1.51	0.009*
EXAMINE (alogliptin vs placebo)	106/2701 (3.9%)	89/2679 (3.3%)	1.19	0.89, 1.58	0.238
TECOS (sitagliptin vs placebo)	228/7332 (3.1%)	229/7339 (3.1%)	1.00	0.83, 1.20	0.983



***Statistically significant increase in hospitalizations for heart failure associated with saxagliptin use in SAVOR-TIMI.**

1. Scirica BM, et al. *N Engl J Med*. 2013;369:1317–1326. 2. White WB, et al. *N Engl J Med*. 2013;369:1327–1335.
3. Green JB, et al. *N Engl J Med*. 2015;373(3):232–242.

Why Did HF Findings Differ Among the DPP-4 Trials?

Potential reasons may include:

- Differences in patients enrolled
- Differences in background care provided
- Variation in acquisition/definition of HF events among trials
- Intrinsic pharmacologic differences among the DPP-4 inhibitors

FDA decisions pending regarding changes to prescribing information for DPP-4 inhibitors (saxagliptin & alogliptin) based upon HF findings.

1. Scirica BM, et al. *N Engl J Med*. 2013;369:1317–1326. 2. White WB, et al. *N Engl J Med*. 2013;369:1327–1335.
3. Green JB, et al. *N Engl J Med*. 2015;373(3):232–242.

ELIXA Study

First trial to present CV outcomes data for an agent in the GLP-1 RA class

- Lixisenatide is not yet approved in the U.S.
- 6,068 subjects with T2DM and recent ACS event randomized to lixisenatide vs placebo

Outcome	Lixisenatide n=3034	Placebo n=3034	HR (95% CI)
Primary outcome (CV death, nonfatal MI, nonfatal stroke, or hospitalization for UA)	**13.4%**	**13.2%**	**1.02 (0.89–1.17)**
Primary outcome plus hospitalization for HF	**15%**	**15.5%**	**0.97 (0.85–1.10)**
Hospitalization for HF	**4.0%**	**4.2%**	**0.96 (0.75–1.23)**
All-cause mortality	–	–	**0.94 (0.78–1.13)**

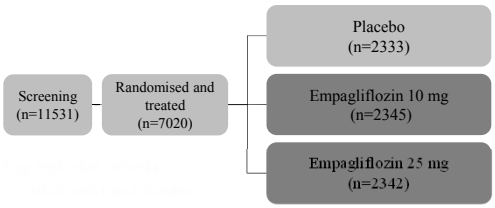
ELIXA = Evaluation of Lixisenatide in Acute Coronary Syndrome;
ACS = acute coronary syndrome; UA = unstable angina; HF = heart failure.

Trial data presented by Pfeffer, MA et al, ADA Scientific Sessions, June 8 2015, Boston *Patients followed for a mean of 2.1 years*

SGLT-2 Inhibitors on US Market

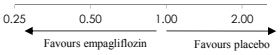
Generic	Trade Name
canagliflozin	**Invokana**
dapagliflozin	**Farxiga**
empagliflozin	**Jardiance**

EMPA-REG: CV Outcomes Trial of the SGLT-2 Inhibitor Empagliflozin



CV death, MI and stroke

	Patients with event/analysed Empagliflozin	Placebo	HR	(95% CI)	*p*-value
3-point MACE	490/4687	282/2333	0.86	(0.74, 0.99)*	0.0382
CV death	172/4687	137/2333	0.62	(0.49, 0.77)	<0.0001
Non-fatal MI	213/4687	121/2333	0.87	(0.70, 1.09)	0.2189
Non-fatal stroke	150/4687	60/2333	1.24	(0.92, 1.67)	0.1638



Cox regression analysis. MACE, Major Adverse Cardiovascular Event; HR, hazard ratio; CV, cardiovascular; MI, myocardial infarction
*95.02% CI

EMPA-REG OUTCOME: Summary

Empagliflozin:

- reduced risk for 3-point MACE by 14%
- was associated with a reduction in HbA1c without an increase in hypoglycaemia, reductions in weight and blood pressure, and small increases in LDL and HDL cholesterol
- was associated with an increase in genital infections but was otherwise well tolerated
- reduced hospitalization for heart failure by 35%
- reduced CV death by 38%
- improved survival by reducing all-cause mortality by 32%

MACE, Major Adverse Cardiovascular Event; HDL, high density lipoprotein; LDL, low density lipoprotein

Richard Pratley, MD

Medical Director
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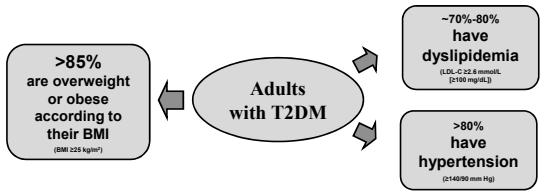
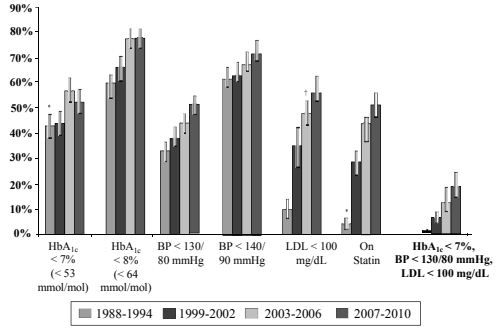
Most Adults with T2DM Have Multiple Risk Factors for CVD



CVD = cardiovascular disease; BMI = body-mass index; LDL-C = low-density lipoprotein cholesterol.

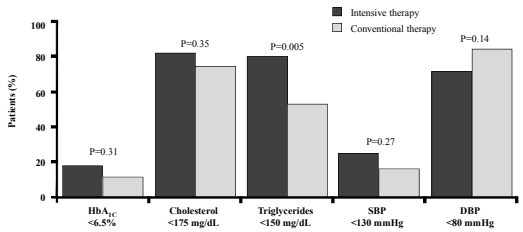
Daousi C, et al. *Postgrad Med J.* 2006 Apr;82(966):280-284. Jacobs MJ, et al. *Diabetes Res Clin Pract.* 2005 Dec;70(3):263-269. Tarnow L, et al. *Diabetes Care.* 1994 Nov;17(11):1247-1251.

Prevalence of U.S. Adults with Diabetes Achieving A1C, Blood Pressure, and LDL-C Goals 1998 - 2010: NHANES



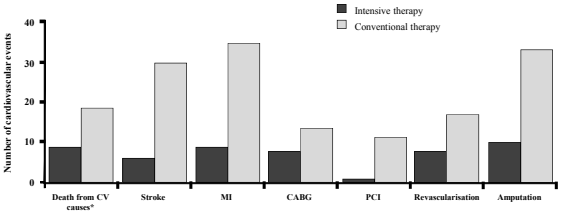
Casagrande SS, Fradkin JE, Saydah SH, Rust KF, Cowie CC. Diabetes Care 2013;36:2271-2279

Multifactorial intervention may improve CV risk factors in patients with Type 2 diabetes



Gaede P, *et al. N Engl J Med* 2008;358:580–91.

Multifactorial intervention may reduce CV events in patients with Type 2 diabetes



*P=0.03. P values not reported for other outcomes. CABG, coronary artery bypass grafting; MI, myocardial infarction; PCI, percutaneous coronary intervention.

Gaede P, *et al. N Engl J Med* 2008;358:580–91.

Treating the ABCs Reduces Diabetic Complications

Strategy	Complication	Reduction of complication
Lipid control	• Coronary heart disease mortality	↓35%[1]
	• Major coronary heart disease event	↓55%[2]
	• Any atherosclerotic event	↓37%[2]
	• Cerebrovascular disease event	↓53%[1]
Blood pressure control	• Cardiovascular disease	↓ 51%[3]
	• Heart failure	↓ 56%[4]
	• Stroke	↓ 44%[4]
	• Diabetes-related deaths	↓ 32%[4]
Blood glucose control	• Heart attack	↓ 37%[5]

[1]Grover SA, et al. *Circulation*. 2000;102:722-727.
[2]Pyörälä K, et al. *Diabetes Care*. 1997;20:614-620.
[3]Hansson L, et al. *Lancet*. 1998;351:1755-1762.
[4]UKPDS Study Group (UKPDS 38). *BMJ*. 1998;317:703-713.
[5]UKPDS Study Group (UKPDS 33). *Lancet*. 1998;352:837-853.

Clinical Case

- A 65 year old man with a history of HTN, COPD, and obesity has been hospitalized following presentation to the ED with chest pain
- Cardiac catheterization revealed MVCAD and he subsequently underwent 3 vessel CABG
- He required an insulin drip for several days peri- and post-operatively to manage hyperglycemia

Clinical Case

- The patient is alert, well-appearing and eating a NCS diet consistently
- He is afebrile and vital signs are stable
  - Weight 213 lbs
  - Height 70.5 inches
  - BMI = 30.19

Laboratory Data:

HbA1c = 8.2%
Sodium = 144
Potassium = 3.5
Chloride = 107
Bicarb = 30
BUN = 23
Creatinine = 1.8
Glucose = 115
eGFR = 38

Pre-meal BG values range from 110-140 mg/dL on a scheduled SC insulin regimen totaling 24 units daily

Take Home Messages

- Type 2 diabetes increases the risk for micro- and macro-vascular complications
  - Treatment of glucose, BP and lipids have dramatically decreased complications of diabetes over the past 20 years.
  - Glucose lowering, by itself, does reduce CVD risk, but the reduction is modest and takes time to be appreciated.
- Several newer drugs in the DPP-4 inhibitor, GLP-1 RA, and SGLT2 classes have been found safe for the treatment of diabetes and do not increase CVD risk.
- Heart failure remains a common and clinically important complication of DM that should always be considered and needs further study
- Treatment guidelines will likely change in response to new outcomes data &may include consideration of patient comorbidities