Oral hypoglycemic agents의 심혈관계 질환에 대한 위험(DPP4s를 중심으로)

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From UKPDS to SAVOR :
the Evolving Landscape of
CV Outcome Studies in T2DM

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- Data regarding the CV risk associated with T2DM
- The effect of intensive glycemic control on CV events : Hypoglycemia & Weight gain
- FDA guidance for evaluating CV risk in new anti-diabetic therapies to treat T2DM
- Background data from SAVOR Study

Data regarding the CV risk associated with T2DM

Introduction: T2DM and CV Risk

- T2DM remains a formidable public health issue and is associated with decreased survival predominantly due to CV disease (CVD)[1-3]
- Evidence suggests T2DM and CVD are integrally related with regard to pathophysiologic processes and clinical outcomes[1-3]
  - Diabetes is associated with a 2- to 4-fold increase in the risk of CVD compared with risk in non-diabetic subjects[1]
  - Approximately 80% of patients with T2DM will develop and die of macrovascular disease[2]
  - Heart disease and stroke are the top causes of death and disability in diabetes[1]
  - Many diabetics possess other CVD risk factors, such as obesity, hypertension, and dyslipidemia[3]
- Evidence regarding the effect of intensive glycemic control in T2DM on CVD risk is contradictory[4,5]

1. American Heart Association. http://www.heart.org/HEARTORG/Conditions/Diabetes/WhyDiabetesMatters/Cardiovascular-Disease-Diabetes_UCM_313865_Article.jsp. Updated Sep 8, 2010. Accessed Nov 18, 2011; 2. Buse JB, et al. *Circulation*. 2007;115:114-126; 3. Eckel RH, et al. *Diabetes Care*. 2006;29: 1697-1699; 4. Home PD, et al. *Lancet*. 2009;373:2125-2135; 5. Dormandy JA, et al. *Lancet*. 2005; 366:1279-1289.

UKPDS: Reducing levels of HbA_{1c} reduces micro and macro vascular risk

- Risk reductions for every 1% reduction in HbA_{1c}

	Relative Risk*	95% CI
Microvascular complications	↓ 37%	33-41
Any diabetes-related endpoint	↓ 21%	17-24
Diabetes-related death	↓ 21%	15-27
All-cause mortality	↓ 14%	9-19
Fatal and non-fatal MI	↓ 14%	8-21

*All P<0.0001
Newly diagnosed type 2 diabetes at baseline; 7.5-12.5 years' follow-up (median = 10.0 years)

Stratton IM, et al. BMJ. 2000;321:405-12.

UKPDS post-trial monitoring: Early intensive glycaemic control reduces the risk of MI and all-cause mortality

- Results after a median of 8.5 years' post-trial follow-up[1]

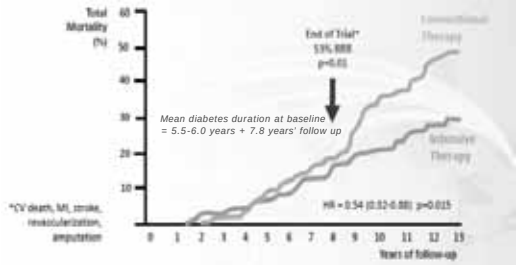
Aggregate endpoint		1997[2]	2007[1]
Anti diabetes-related endpoint	RRR: P:	12% 0.029	9% 0.04
Microvascular Disease	RRR: P:	25% 0.0099	24% 0.001
Myocardial infarction	RRR: P:	16% 0.052	15% 0.01
All-Cause Mortality	RRR: P:	6% 0.44	13% 0.007

RRR: Relative Risk Reduction with intensive glycaemia control (sulphonylurea-insulin) vs conventional therapy; P: Log Rank
Median diabetes duration at baseline = 10.0 years + 8.5 years' follow up

1. Holman R. N Engl J Med. 2008;359:1577-89. 2. UKPDS 33. Lancet. 1998;352:837-53.

STENO-2 : Multifactorial management significantly reduces risk of cardiovascular events

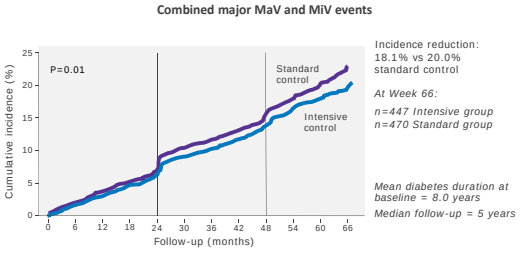
- Multiple risk-factor intervention study comparing conventional vs intensive treatment of risk factors in a high-risk population with type 2 diabetes



Primary composite endpoint: conventional therapy (44%) and intensive therapy (24%).
*Death from CV causes, non-fatal MI, CABG, PCI, non-fatal stroke, amputation, or surgery for peripheral atherosclerotic artery disease

Gaede P, et al. N Engl J Med. 2003;348:383-93.

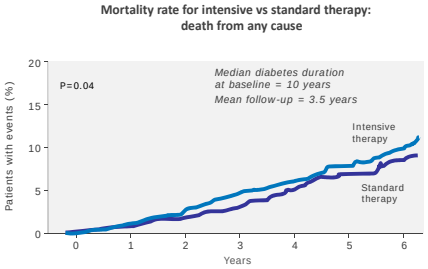
ADVANCE: Intensive glycaemic control significantly reduces combined macro- and microvascular events



IGC: intensive glucose control; MaV: non-fatal stroke, non-fatal myocardial infarction or CV death; MiV: new or worsening nephropathy or diabetic eye disease

ADVANCE Study Group. N Engl J Med. 2008;358:2560-72.

ACCORD: Intensive glycaemic control leads to a significant increase in mortality



No. At Risk							
Intensive ther.	5128	4972	4803	3250	1748	523	506
Standard ther.	5123	4971	4700	3180	1642	499	480

ACCORD Study Group. N Engl J Med. 2008;358:2545-59.

ACCORD: Risk of primary outcome in prespecified subgroups

- Better outcomes were observed with intensive treatment in subjects with no previous history of CV disease

Median diabetes duration at baseline = 10 years

Subgroup	No. of subjects	No. of events	Hazard ratio	P value
Total	10,251	723		
Previous cardiovascular event				0.04
No	6643	330		
Yes	3608	393		
Sex				0.74
Female	3952	212		
Male	6299	511		
Age at baseline				0.65
<65 yr	6779	383		
≥65 yr	3472	340		
Glycated haemoglobin at baseline				0.03
≤8.0%	4868	284		
>8.0%	5360	438		
Race				0.29
Non-white	3647	222		
White	6604	501		

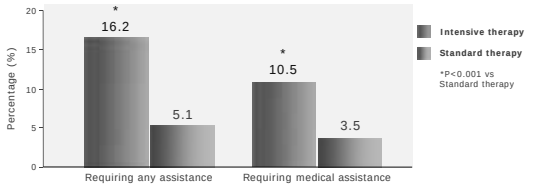
0.6 1.0 1.4
Intensive therapy better | Standard therapy better

ACCORD Study Group. N Engl J Med. 2008;358:2545-59.

ACCORD: Significantly greater risk of hypoglycemia with intensive glycemic control

- Proportion of participants with hypoglycaemia
  - Annualised rate of hypoglycaemic episodes requiring medical assistance was 3.1% in the intensive-therapy group and 1.0% in the standard-therapy group

Proportion of patients (%) with hypoglycaemia requiring assistance during the study period



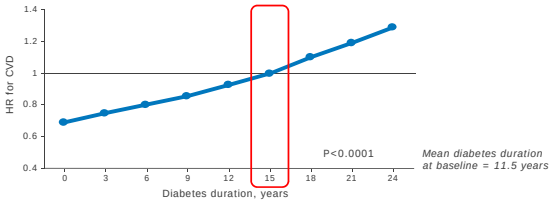
Median diabetes duration at baseline = 10 years

ACCORD Study Group. N Engl J Med 2008;358:2545-9.

VADT: Duration of diabetes and risk of CVD

- Duration of type 2 diabetes and risk of CVD with intensive therapy
  - Hazard ratios for CVD owing to IGC was found to increase with the duration of diabetes[1,2]

Relationship between diabetes duration and hazard ratio for CVD events with intensive vs standard therapy[2]

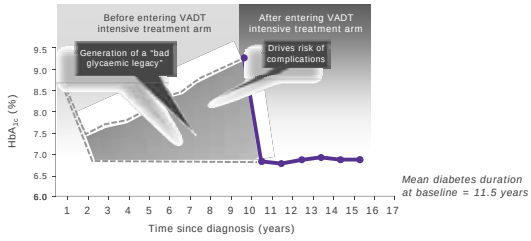


CVD: cardiovascular disease; IGC: intensive glucose control

1. Del Prato S. Diabetologia. 2009;52:1219-2. 2. Duckworth W, ADA Scientific Sessions 2008. Available at: http://webcasts.prous.com/netadmin/webcast_viewer/Preview.aspx?type=0&id=3853. Accessed: 5 Oct, 2009.

VADT: Time course of glycemic control: "bad glycemic legacy"

Hypothetical representation of the natural history of diabetes patients recruited in VADT



The upper dotted line represents the time course of HbA_{1c} estimated on the basis of the average glucose profile described by the UKPDS. The lower dotted line represents the ideal time course of glycaemic control. The solid line represents the time course of HbA_{1c} in the VADT

Del Prato S. Diabetologia. 2009;52:1219-26.

Recent trial outcomes for intensive glycemic control: ADVANCE, ACCORD, VADT

Summary of study key features and results

	ADVANCE (11,140)	ACCORD (10,251)	VADT (1791)
Achieved HbA_{1c} (%)[a]	**7.3 vs 6.5**	**7.5 vs 6.4**	**8.4 vs 6.9**
Primary outcome	**Non-fatal MI, non-fatal stroke, CVD death**	**Non-fatal MI, non-fatal stroke, CVD death**	**MI, stroke, death from CV causes, new or worsening CHF, revascularisation and inoperable CAD, amputation for ischaemic gangrene**
HR (95% CI) for primary outcome	**0.94 (0.84-1.06)**	**0.90 (0.78-1.04)**	**0.87 (0.730-1.04)**
HR (95% CI) for mortality	**0.93 (0.83-1.06)**	**1.22 (1.01-1.46)[b]**	**1.065 (0.801-1.416)**

[a] Conventional vs intensive therapy
[b] P=0.04
CAD: coronary artery disease; CHF: congestive heart failure; CVD: cardiovascular disease; MI: myocardial infarction

Del Prato, S. Diabetologia. 2009;52:1219-26.

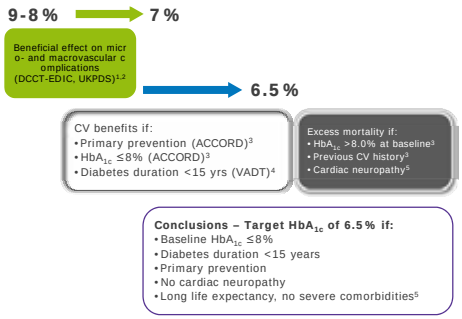
Recent trial data: conflicting evidence for MaV risk reduction

- Effects of intensive vs conventional/standard therapy

– UKPDS (10y follow-up)[1]:	↓ MI and all-cause mortality
– STENO-2[2]:	↓ Vascular complications and all-cause mortality
– ADVANCE[3]:	No significant effect on macrovascular events
– ACCORD[4]:	Mortality (leading to premature termination of study at 3.5 years)
– VADT[5]:	No significant effect on CV events or death

1. Holman RR, et al. N Engl J Med. 2008;359:1577-89. 2. Gaede P, et al. N Eng J Med. 2008;358:580-91. 3. ADVANCE Study Group. N Engl J Med. 2008;358:2560-72. 4. ACCORD Study Group. N Engl J Med. 2008;358:2545-59. 5. Duckworth W, et al. N Engl J Med. 2009;360:129-39.

Which HbA_{1c} target?



1. DCCT/EDIC. N Engl J Med. 2005;353:2643-53. 2. UKPDS 33. Lancet. 1998;352:837-53. 3. ACCORD Study Group. N Engl J Med. 2008;358:2545-59. 4. Duckworth W. ADA Scientific Sessions, 2008. 5. Skyler JS, et al. Diabetes Care. 2009;32:187-92.

Current goals and the importance of individualisation

Current guidelines generally recommend:[1-4]

HbA_{1c} level ≤7.0% (53 mmol/mol) to lower the risk of micro and macrovascular complications
OR
HbA_{1c} level ≤6.5% (48 mmol/mol) to achieve near normoglycemic control

- Episodes of hypoglycemia should be carefully titrated against this

- Individuals with hypoglycaemia unawareness or severe hypoglycemia should raise their glycemic targets to avoid further episodes of hypoglycemia

Selecting the **most appropriate therapy** and **individualising treatme nt** are key to reducing the prevalence of hypoglycemia

Education and **motivation** are important to avoid hypoglycemia

1. Canadian Diabetes Association. Can J Diabetes. 2008;32(Supp1):S1-S201. 2. American Diabetes Association. Diabetes Care. 2009;32(Suppl 1):S13-61. 3. Matthaei S, et al. Exp Clin Endocrinol Diabetes. 2009;117:522-57. 4. Ryden L, et al. Eur Heart J. 2007;28:88-136.

Personalized Treatment Goals to Minimize Adverse CV outcomes

- The ADA and EASD recommendations identify CV risk as an important factor to consider when setting treatment goals
  - Avoid severe hypoglycemia in patients with advanced CVD
  - Modify HbA1c level criteria for patients with significant CVD

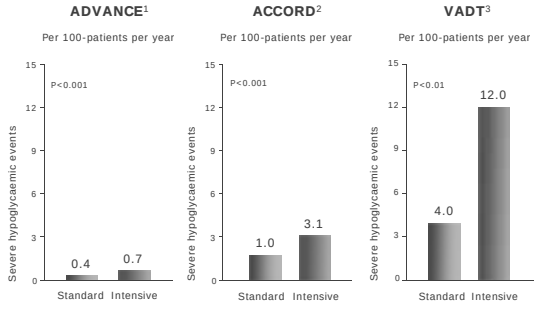
More stringent HbA1c goals **(<6.5%)** for selected patients, including those with short duration of diabetes, long life expectancy, and **no significant CVD**

Less stringent HbA1c goals **(<8%)** may be appropriate for patients with a history of severe hypoglycemia, limited life expectancy, advanced microvascular or **macrovascular complications**, or **extensive comorbid conditions**

Inzucchi SE, et al. *Diabetes Care.* 2012;35:1364-1379; American Diabetes Association. *Diabetes Care.* 2013;36 (suppl 1): S11-S66.

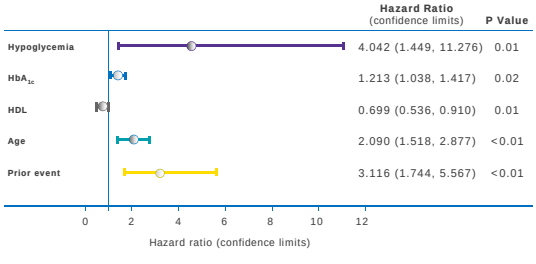
The effect of intensive glycemic control on CV events : Hypoglycemia & Weight gain

Intensive glucose-lowering contributes to an increased risk of hypoglycemia by 2- to 3-fold



1. ADVANCE Collaborative Group. N Engl J Med. 2008;358:2545-59. 2. ACCORD Study Group. N Engl J Med. 2008;358:2545-59. 3. Duckworth W, et al. N Engl J Med. 2009;360:129-39.

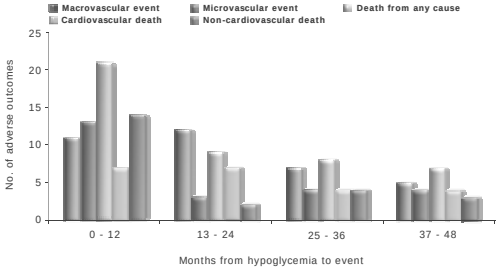
Hypoglycemia was a major predictor of cardiovascular death in the VADT study



Duckworth W. Presented at the ADA 68th Scientific Sessions, 2008. Available at: http://professional.diabetes.org/presentations_details.aspx?session=3167. Accessed: 12 Nov, 2010.

Severe hypoglycemia in ADVANCE

- In the ADVANCE study, severe hypoglycemia was clearly associated with an increased risk of macrovascular and microvascular events and death (both cardiovascular and non-cardiovascular causes)



Zoungas S, et al. N Engl J Med. 2010;363(15):1410-8.

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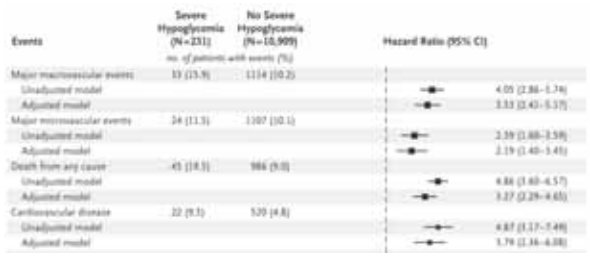


Zoungas S, et al. N Engl J Med. 2010;363(15):1410-8.

Risk factors and Causes of hypoglycemia

Behavioural

- Missed or irregular meals
- Alcohol or drug use Exercise
- Incorrect use of glucose-lowering medication

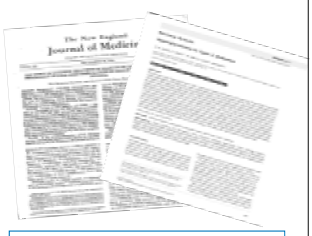
Physiological

- Advancing age
- Longer diabetes duration
- Presence of comorbidity
- Deterioration of renal and hepatic function
- Loss of awareness of hypoglycaemia

Therapeutic

- Glucose-lowering therapy
- Concurrent medication (e.g. aspirin, warfarin, NSAIDs)

Amiel SA, et al. Diabetic Med. 2008;25:245-54.



The main cause of hypoglycemia in people with type 2 diabetes is their diabetes medication

Amiel SA, et al. Diabet Med. 2008;25:245-54.

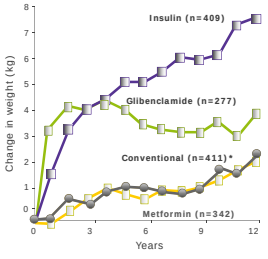
Glucose-lowering agents classified by risk of hypoglycemia

High risk[1,2]	Low risk[1,2]
Insulin	Metformin
Sulphonylureas	α-glucosidase inhibitors
Glinides	Pioglitazone
	GLP-1 receptor agonists
	DPP-4 inhibitors

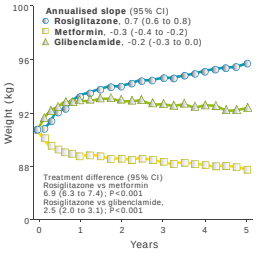
1. Nathan DM, et al. Diabetologia. 2009;52:17-306. 2. Cefalu WT. Nature. 2007;81:636-49.

Most current therapies result in weight gain over time

UKPDS: up to 8 kg in 12 years[1]



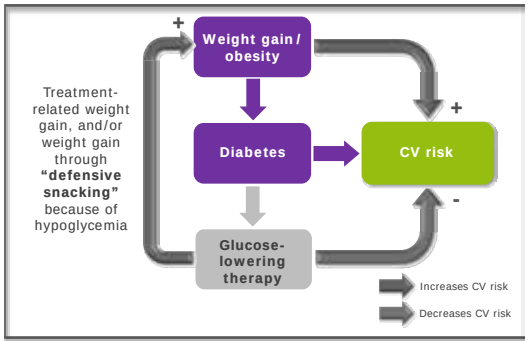
ADOPT: up to 4.8 kg in 5 years[2]



* Conventional treatment; diet initially then sulphonylureas, insulin and/or metformin if FPG >15 mmol/L (>270 mg/dL)
n= at baseline

1. UK Prospective Diabetes Study (UKPDS) Group. Lancet. 1998;352:854-65. 2. Kahn SE, et al (ADOPT). N Engl J Med. 2006;355:2427-43.

Inter-relationship between overweight/obesity, diabetes and CV risk: potential impact of treatment-related weight gain



FDA Guidance and CV Safety Studies in new anti-diabetes to treat T2DM

Why CV Safety Is Important?

FDA requirements for regulatory approval – CV safety

FDA Issues Safety Alert on Avandia, 21st May 2007

*"The U.S. Food and Drug Administration (FDA) is aware of a **potential safety issue** related to Avandia (rosiglitazone), a drug approved to treat type 2 diabetes. Safety data from controlled clinical trials have shown that there is a **potentially significant increase in the risk of heart attack and heart-related deaths** in patients taking Avandia…"*

Accessed 1st July: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2007/ucm108917.htm

FDA Criteria Assessing CV Safety

- Sponsor should compare the incidence of important CV events with the investigational agent to incidence with the control group and calculate a 2-sided 95% confidence interval (95% CI) for the estimated risk ratio.
- Pre-marketing data showing:
  - Upper bound of 95% CI between 1.3 and 1.8 would support approval; *post-marketing trial needed to show upper bound is <1.3*
  - Upper bound of 95% CI <1.3 would support approval; post-marketing CV trial may not be necessary
  - Point estimate of 1.5 would not be reassuring, even if upper bound of 95% CI is <1.8

Frederich R, et al. Postgrad Med. 2010;122(3):16-27.

FDA Now Requires CVOTs With New Submissions

- Owing to the potential for CV risk with drugs for T2DM, in December 2008, the FDA issued new guidance for all diabetes drugs in development: **Manufacturers of diabetes drugs and biologics need to provide evidence that therapy will not increase the risk of CV events**

More robust and adequate design and data collection are required for Phase 2/3 clinical trials:
- ✓ **New diabetes therapies should not increase CV risk compared with current therapies, especially when used by older patients and in those with advanced diabetes or renal impairment**
- ✓ **Trials should include patients at higher risk of CV events**

CV events occurring during clinical trials should be analyzed by independent committees
- ✓ **This includes major events (CV mortality, MI, and stroke) and can also include hospitalization for ACS, urgent revascularization procedures, and other end points**

FDA. December 2008. http://www.fda.gov/downloads/Drugs/Guidance Compliance Regulatory Information/Guidances/ucm071627.p. Accessed Aug 12, 2013.

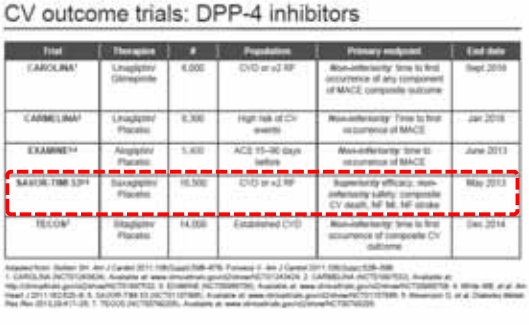
Time to Onset of First Primary MACE in Prior Pooled Analysis

Numerous Studies Assessing CV Outcomes in T2DM Drugs Are Either Recently Completed or Ongoing

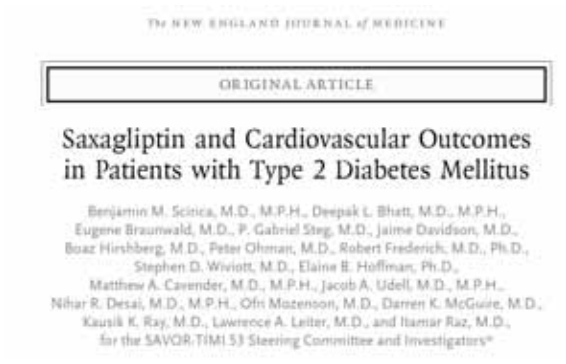
Trial Name	Drug	Target Enrollment	Timing*
DPP-4 Inhibitors			
SAVOR	Saxagliptin	N=16,492	Began 2010; Complete
EXAMINE	Alogliptin	N=5384	Began 2009; Complete
TECOS	Sitagliptin	N=14,000	Began 2008; Ending 2014
CAROLINA	Linagliptin	N=6000	Began 2010; Ending 2018
CARMELINA	Linagliptin	N=8300	Began 2013; Ending 2018
GLP-1 Agonists			
ELIXA	Lixisenatide	N=6000	Began 2010; Ending 2014
EXSCEL	Exenatide	N=9500	Began 2010; Ending 2017
LEADER	Liraglutide	N=9340	Began 2010; Ending 2016
REWIND	Dulaglutide	N=9622	Began 2011; Ending 2019
SUSTAIN 6	Semaglutide	N=3260	Began 2013; Ending 2016
SGLT-2 Inhibitors			
CANVAS	Canagliflozin	N=4410	Began 2009; Ending 2018
C-SCADE 8	Empagliflozin	N=7000	Began 2010; Ending 2018
DECLARE	Dapagliflozin	N=17,150	Began 2013; Ending 2019

*Trial ending dates are anticipated based on publicly available information.
Clinicaltrials.gov; Accessed on Aug 12, 2013.

DPP4 : CV Outcome Trials



CV Outcome Trials : SAVOR



The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Saxagliptin and Cardiovascular Outcomes in Patients with Type 2 Diabetes Mellitus

Benjamin M. Scirica, M.D., M.P.H., Deepak L. Bhatt, M.D., M.P.H., Eugene Braunwald, M.D., P. Gabriel Steg, M.D., Jaime Davidson, M.D., Boaz Hirshberg, M.D., Peter Ohman, M.D., Robert Frederich, M.D., Ph.D., Stephen D. Wiviott, M.D., Elaine B. Hoffman, Ph.D., Matthew A. Cavender, M.D., M.P.H., Jacob A. Udell, M.D., M.P.H., Nihar R. Desai, M.D., M.P.H., Ofri Mosenzon, M.D., Darren K. McGuire, M.D., Kausik K. Ray, M.D., Lawrence A. Leiter, M.D., and Itamar Raz, M.D., for the SAVOR-TIMI 53 Steering Committee and Investigators*

Scirica BM, et al. *N Engl J Med*. 2013.10.1056/NEJMoa1307684

Comparison of Meta-analysis and SAVOR Trial

	Saxagliptin Post Hoc Meta-analysis[1] N = 4607	SAVOR[2] N = 16,492
Study Design	Meta-analysis of 8 studies from the saxagliptin Phase 2/3 registrational trials	• Double-blind, RCT • The primary **safety** objective was assessed by testing for **non-inferiority** to placebo • The primary **efficacy** objective was assessed by testing for **superiority** to placebo
CV Assessment	Occurrence of CV event (death, MI, stroke, revascularization procedures, cardiac ischemia)	• Time to confirmed CV event (composite of death, nonfatal MI, nonfatal ischemic stroke) • Time to the first occurrence plus hospitalization for heart failure, unstable angina or coronary revascularization
Patient Characteristics	• Patients with inadequately controlled T2DM • Average age: 54 years • Prior history of CVD: 12% • ≥1 CV risk factor (in addition to T2DM): 81%	• Patients with T2DM at risk of cardiovascular events • Average age: 65 years • History of established CVD or multiple risk factors for vascular disease: 100%
Results	No increased risk of CV death, MI, or stroke	• Non-inferiority for CV outcomes compared with placebo, with no excess in the risk of the primary endpoint • Increased the risk for hospitalization for HF and the risk for hypoglycemic events

1. Frederich R, et al. *Postgrad Med*. 2010;122:16-27; 2. Scirica BM, et al. *N Engl J Med*. 2013.10.1056/NEJMoa1307684.

Conclusions

- **Early achievement** and maintenance of glycemic control reduces the number of long-term microvascular outcomes, myocardial infarction and death
- **Individualised treatment** is key in order to avoid hypoglycemia and weight gain and glucose-lowering medication must be adapted to each person's needs and lifestyle.
- **Hypoglycemic episodes and weight gain** may be associated with cardiovascular death, MI, cardiac arrhythmias, nervous system abnormalities and cardiac ischaemia

DPP-IV Outcome Trials

	SAVOR (Saxagliptin) N = 16,492	EXAMINE (Alogliptin) N = 5400	TECOS (Sitagliptin) N = 14,000	ELIXA (Lixisenatide) N = 6000
Timing	Began 2010 Complete	Began 2009 Complete	Began 2008 Ending 2014*	Began 2010 Ending 2014*
Planned Duration	Event-driven until the occurrence of 1040 primary events	Event driven with multiple interim analyses after 80, 100, 125, 150, 550, 600, and 650 events (~5 years)	>4 years or until the occurrence of 1300 primary events	Event-driven until the occurrence of ~844 primary events
Statistical Analysis	Superiority	Non-inferiority	Non-inferiority	Superiority
1° or 2° Prevention	Both	Secondary	Secondary	Secondary

*Trial ending dates are anticipated based on publicly available information.
Clinicaltrials.gov; Accessed on Aug 12, 2013.

Comparison of SAVOR with Other Ongoing Trials (cont'd)

	SAVOR (Saxagliptin) N = 16,492	EXAMINE (Alogliptin) N = 5400	TECOS (Sitagliptin) N = 14,000	ELIXA (Lixisenatide) N = 6000
Primary Outcomes	• Efficacy AND safety: Time to confirmed CV event (composite of death, nonfatal MI, nonfatal ischemic stroke)	• Time to CV event (composite of CV death, nonfatal MI, nonfatal stroke)	• Time to confirmed CV event (composite of death, nonfatal MI, nonfatal stroke, unstable chest pain requiring hospitalization)	• Time to first occurrence of the primary CV event: CV death, nonfatal MI, nonfatal stroke, hospitalization for unstable angina
Secondary Outcomes	• Time to the first occurrence of primary outcome plus hospitalization for heart failure, unstable angina or coronary revascularization • All-cause mortality	• Time to the occurrence of any event in the secondary MACE composite of CV death, nonfatal MI, nonfatal stroke, and urgent revascularization for unstable angina	• Time to CV event composite of CV-related death, nonfatal MI, nonfatal stroke • Time to all-cause mortality • Time to CHF • Change in renal function over time	• Time to any event in the primary composite plus hospitalization for heart failure • Time to primary composite plus hospitalization for heart failure or coronary revascularization procedure • Percent change in urinary / albumin creatinine ratio

Clinicaltrials.gov; Accessed on Aug 12, 2013.

Comparison of SAVOR with Other Ongoing Trials *(cont'd)*

	SAVOR (Saxagliptin) N = 16,492	EXAMINE (Alogliptin) N = 5400	TECOS* (Sitagliptin) N = 14,000	ELIXA (Lixisenatide) N = 6000
Key Inclusion	• ≥40 yrs • HbA1c ≥6.5% and ≤12.0% within 6 months • Preexisting CV disease OR high risk for CV or multiple CV risk factors	≥18 yrs HbA1c 6.5% to 11.0% while receiving monotherapy or combination antihyperglycemic therapy or from 7.0% to 11.0% if the regimen includes insulin Diagnosis of ACS within 15 to 90 days prior to randomization	• ≥50 yrs • HbA1c 6.5% to 8% on stable doses of OADs (M, S, and/or P with or without insulin • Preexisting CV disease defined as documented vascular disease in the coronary, cerebral, or peripheral arteries	• ≥30 years • If newly diagnosed with T2DM, fasting glucose ≥7.0 mmol/L or 2-hour post glucose load ≥11.1 mmol/L • No HbA1c <5.5% or >11% at screening • Spontaneous recent ACS events (STEMI, NSTEMI, unstable angina with elevated troponin or CK-MB)
Key Exclusion	• Acute vascular event <2 months prior to randomization • Treatment with DPP-4 inhibitors or GLP-1 agonists within 6 months	Type 1 diabetes Treatment with GLP-1 agonist at screening Treatment with DPP-4 inhibitor within 3 months of screening or more than 14 days total	• Type 1 diabetes • Unable to take sitagliptin	• Type 1 diabetes • CABG surgery following qualifying event • PCI within 15 days of screening • Planned PCI or CABG or coronary angiogram within 90 days after screening

CABG, coronary artery bypass grafting
Clinical trials.gov; Accessed May 20, 2013; *http://www.dtu.ox.ac.uk/tecos/protocol.php. Accessed Jun 14, 2013.