What are we expecting from incoming CVOTs?

Professor Guntram Schernthaner

Medical University of Vienna

em Head of the Department of Medicine I, Rudolfstiftung Hospital, Vienna, Austria

XXI AMD National Congress (Associazone Medici Diabetologi), Naples (Italy) , May 17-20, 2017

Professor Guntram Schernthaner: disclosure

- Grants for scientific or clinical research
- Honoraria for advisory board meetings
- Honoraria for lectures

Abbot	DeveloGen	Novo Nordisk
Amgen	Eli Lilly	Pfizer
Andromeda	GlaxoSmithKline	Roche
AstraZeneca	Janssen	Sanofi-Aventis
Bayer	Merck Serono	Sankyo
Boehringer Ingelheim	MSD	Servier
Bristol-Myers Squibb	Novartis	Takeda

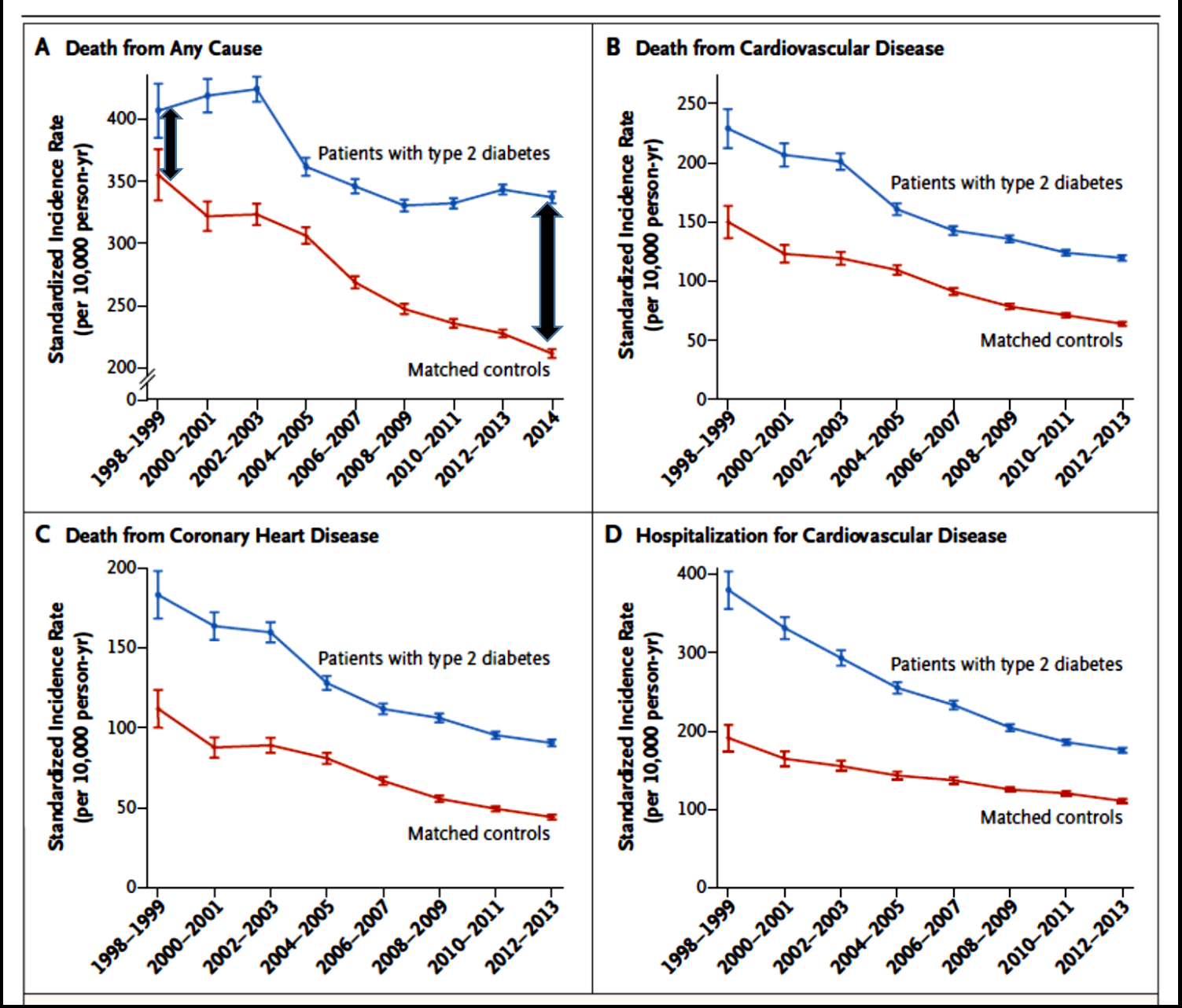
Principal investigator in more than 40 studies, e.g. Canadian-Cyclosporin trial, Diapep277 study, ACTION LADA, IDNT, IRMA2, QUARTET, PROactive, GUIDE, ORIGIN, LEAD-6, DIRECT, EUREXA, DURATION 6, and GENERATION

Involved in 3 FDA CV outcome studies with new antidiabetes drugs

Involved in many Guideline Committees

Total Impact 2.500, h-Factor 58 Citation 15.000

Major Cardiovascular Outcomes in Patients with Type 2 Diabetes and Matched Controls



1998 - 2014

- HbA1c: **7.7%** - **7.2%**
- LDL: **3.1** mmol/L– **2.7** mmol/l
- Statins: **12%** - **60%**
- RRsyst: **148mmHg**- **136**mm Hg
- Antihypertensive: **50** - **75%**

Rawshani et al. N Engl J Med 2017;376:1407-18.

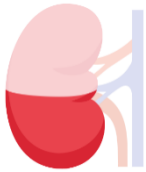
EMPA-REG OUTCOME®, LEADER® and SUSTAIN-6™
Key CV and renal outcomes[1–4]


↓ 3P-MACE


↓ CV death


↓ All-cause mortality


↓ HHF


↓ Composite renal outcomes

↓Doubling of serum creatinine

EMPA-REG OUTCOME®						
RRR	14%	38%	32%	35%	39%	44%
p-Value	0.04†‡	<0.001	<0.001	0.002	<0.001	<0.001

LEADER®						
RRR	13%	22%	15%	13%	22%	12%
p-Value	0.01†	0.007	0.02	NS	0.003	NS

SUSTAIN-6						
RRR	26%	2%	+5%	+11%	+28% (doubling of S-Kreatinine	+28%
p-Value	p=0.02	NS	NS	NS	-9% (need for replacement)	NS

Please note that this is not a head-to-head comparison SUSTAIN-6 was a non-inferiority study, and testing for superiority was not a pre-specified endpoint

1Zinman et al. NEJM 2015;373:2117. 2. Wanner et al. NEJM 2016;375:323 3. Marso et al. NEJM 2016;375:311–22. 4. Marso et al. NEJM 2016;375:1834–1844.

Schernthaner G. Invited lecture at the American Heart Association (AHA), New Orleans, November 13, 2016

Effect of Glucose Lowering Drugs on the Combined Endpointof CV Mortality, Nonfatal Myocardial Infarction and Stroke

	Antidiabetic Drug	HR	P-value
• PROactive	Pioglitazone	0.84 (CI 0·72 - 0.98)	0.02
• ORIGIN	Insulin Glargine	1.02 (CI 0.94 -1.11)	NS
• SAVOR	Saxagliptin	1.00 (CI 0.89 -1.12)	NS
• EXAMINE	Alogliptin	0.96 (CI 0.80-1.15)	NS
• ELIXA	Lixisenatide	1.02 (CI 0.89, 1.17)	NS
• TECOS	Sitagliptin	0.98 (CI 0.89, 1.08)	NS
• EMPA-REG	Empagliflozin	0.86 (CI 0.74-0.99)	0.038
• LEADER	Liraglutide	0.87 (CI 0.78-0.97)	0.01
• SUSTAIN-6	Semiglutide	0.78 (CI 0.66-0.93)	0.001

Schernthaner G and Sattar N. Journal of Diabetes and Its Complications 2014; 28: 430–433
Schernthaner G et al. Clin Ther. 2016; 38: 1288-1298

CV Outcome Trials

	PRO-active	EMPA-REG	LEADER	SUSTAIN-6
MACE	0.82 [0.70-0.97]	0.86 [0.74-0.99]	0.87 [0.78-0.97]	0.74 [0.58-0.95]
Nonfatal MI	0.83 [0.65-1.06]	0.87 [0.70-1.09]	0.88 [0.75-1.03]	0.74 [0.51-1.08]
Nonfatal stroke	0.81 [0.61-1.07]	1.24 [0.92-1.67]	0.89 [0.72-1.11]	0.61 [0.38-0.99]
CV death	0.94 [0.74-1.20]	0.62 [0.49-0.77]	0.78 [0.66-0.93]	0.98 [0.65-1.48]
All deaths	0.96 [0.78-1.18]	0.68 [0.57-0.82]	0.85 [0.74-0.97]	1.05 [0.74-1.50]
Heart failure	1.41 [1.10-1.80]	0.65 [0.50-0.85]	0.87 [0.73-1.05]	1.11 [0.77-1.61]
Nephropathy	–	0.61 [0.53-0.70]	0.64 [0.46-0.88]	–

Schernthaner G. International PACE meeting, Seoul/Korea Nov 5, 2016

Effect of Glucose Lowering Drugs on the Combined Endpoint of CV Mortality, Nonfatal Myocardial Infarction and Stroke

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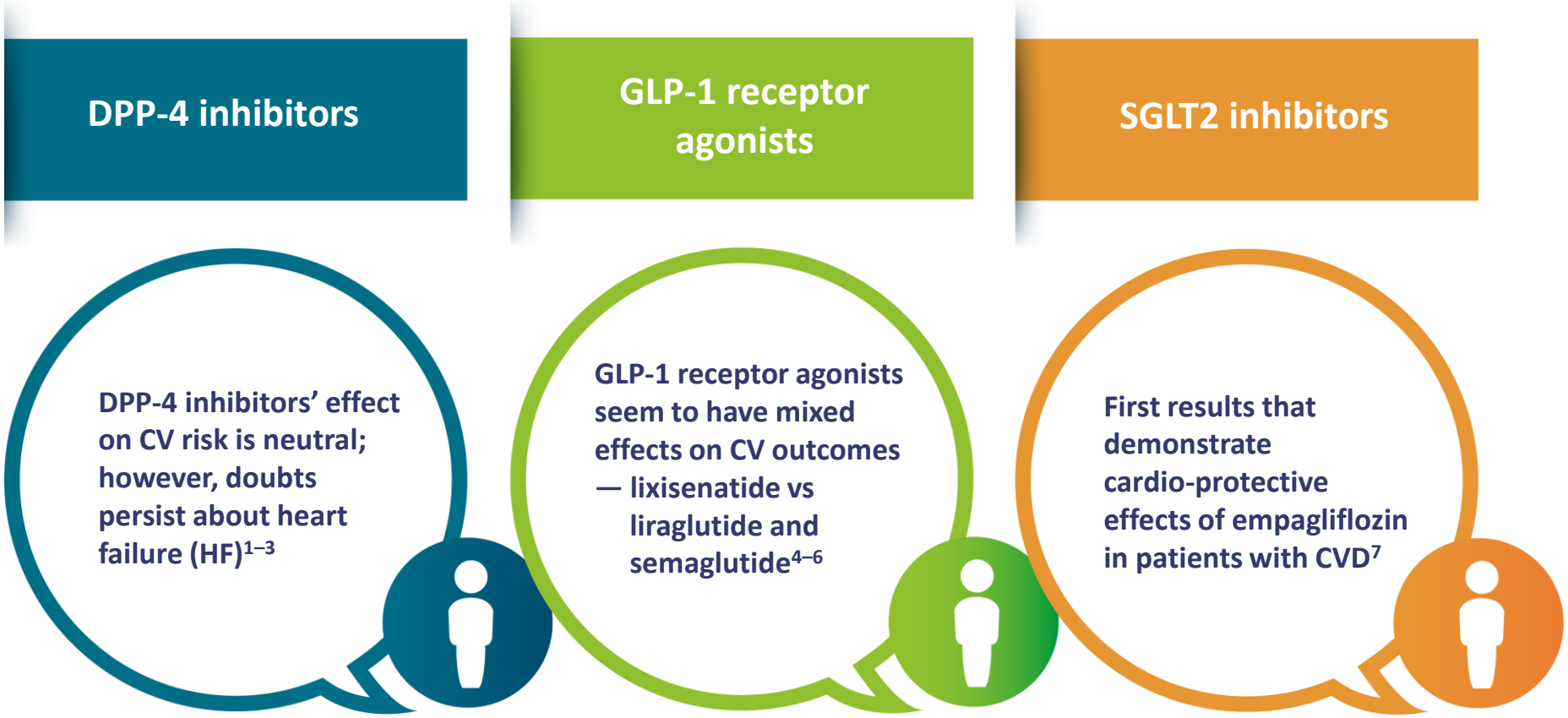
Schernthaner G and Sattar N. Journal of Diabetes and Its Complications 2014; 28: 430–433
Schernthaner G et al. Clin Ther. 2016; 38: 1288-1298

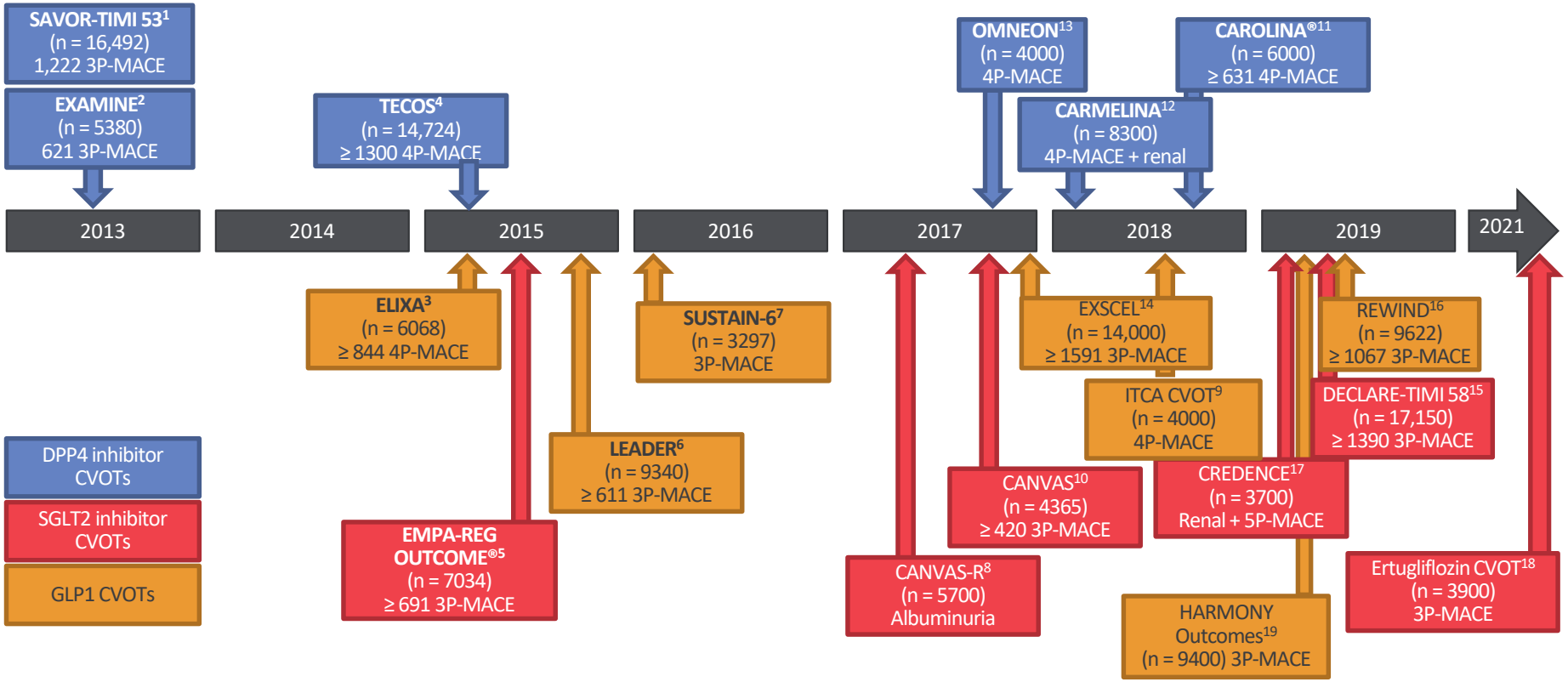
CVOT results are coming in[1–7]



'Class effects' cannot be assumed from the results of drug-specific trials

1. Scirica et al. N Engl J Med 2013;369:1317–1326. 2. White et al. N Engl J Med 2013;369:1327–1335. 3. Green et al. N Engl J Med 2015;373:232–242.
4. Pfeffer et al. N Engl J Med 2015;373:2247–2257. 5. Marso et al. N Engl J Med 2016; 375:311–322 6. Marso et al. N Engl J Med. 2016;375:1834–1844.
7. Zinman et al. N Engl J Med 2015;373:2117–2128.c

CV safety trials are being conducted for each compound within the newer classes



Timings represent estimated completion dates as per ClinicalTrials.gov.

Adapted from Johansen. World J Diabetes 2015;6:1092–96. (references 1–19 expanded in slide notes)

CANVAS Program
CREDENCE

Optimising the analysis strategy for the CANVAS Program – a pre-specified plan for the integrated analyses of the CANVAS and CANVAS-R trials

Bruce Neal,1-4; Vlado Perkovic,1,5; Kenneth W. Mahaffey, 6; Greg Fulcher, 5; Ngozi Erondu, D7; Mehul Desai,7; Wayne Shaw, 7; Gordon Law 7; Marc K. Walton,7 ; Norm Rosenthal, 7; Dick de Zeeuw, 8; David R. Matthews,9; on behalf of the CANVAS program collaborative group

Institutions
1 The George Institute for Global Health, Sydney, Australia;
2 The Charles Perkins Centre, University of Sydney, Australia;
3 Royal Prince Alfred Hospital, Sydney, Australia;
4 Imperial College London, London, UK;
5 The Royal North Shore Hospital and University of Sydney, Australia;
6 Stanford Center for Clinical Research,Stanford University, Department of Medicine, USA;
7Janssen Research & Development, LLC, Raritan, NJ, USA;
8 University of Groningen, University Medical Center Groningen, The Netherlands;
9 University of Oxford, Oxford, UK

Neal B et al. Diab Obes Metab 2017 (online)

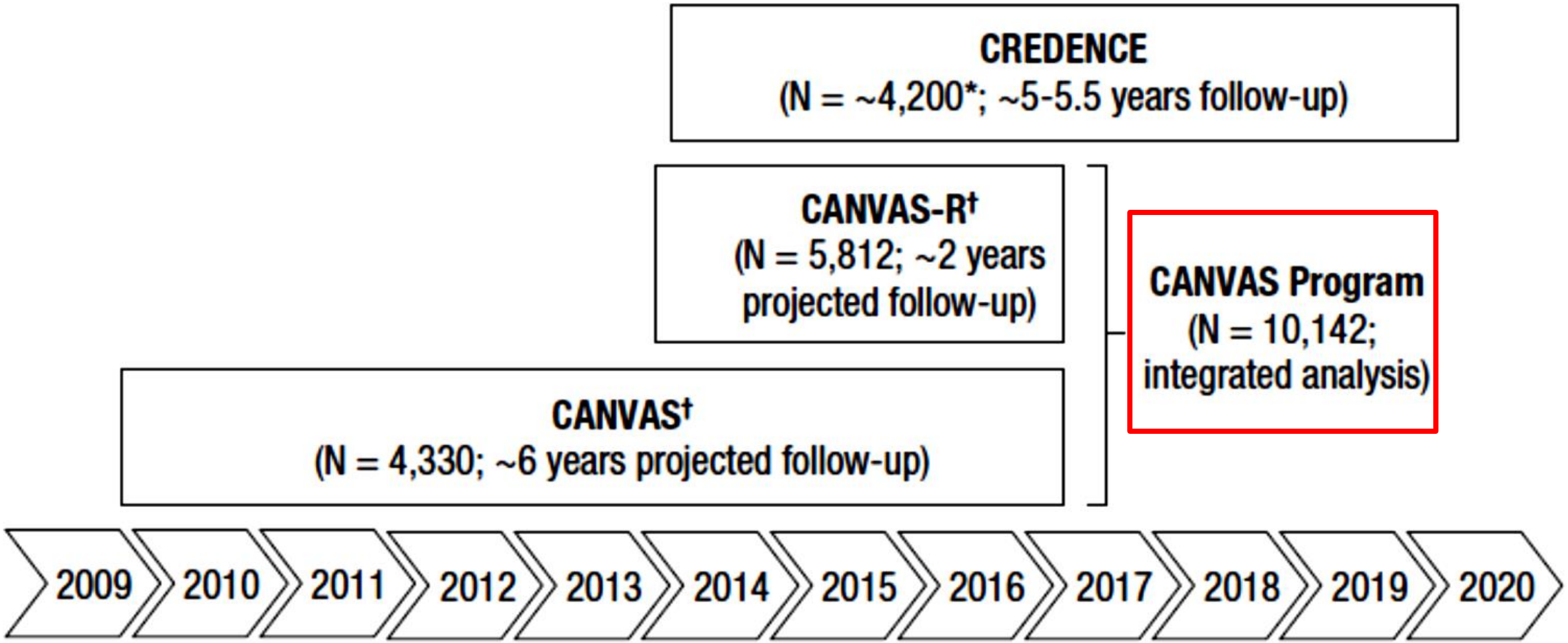
The CANVAS Program comprises two trials, CANVAS and CANVAS-R, and includes a pre-specified integrated analysis of the two.

The **interim unblinding of the CANVAS** data done in 2012. The decision not to expand CANVAS recruitment for the planned second stage meant that the capacity for CANVAS alone to address the primary objective of CV protection was severely impacted, because the failure to recruit the additional 14,000 individuals greatly reduced statistical power.

CANagliflozin cardioVascular Assessment Study – Renal (CANVAS-R)
The CANVAS-R study is a second large prospective, randomized, double-blind, placebo-controlled clinical trial of patients with T2DM with a history or at high risk of CV events. CANVAS-R patients have nearly identical inclusion criteria to CANVAS patients and have been assigned to once-daily placebo or canagliflozin 100 mg (with optional up-titration to 300 mg) for a planned average of 2 years of follow-up. CANVAS-R completed randomization of 5,812 individuals between January 2014 and May 2015 and median follow-up is currently 1.7 years.

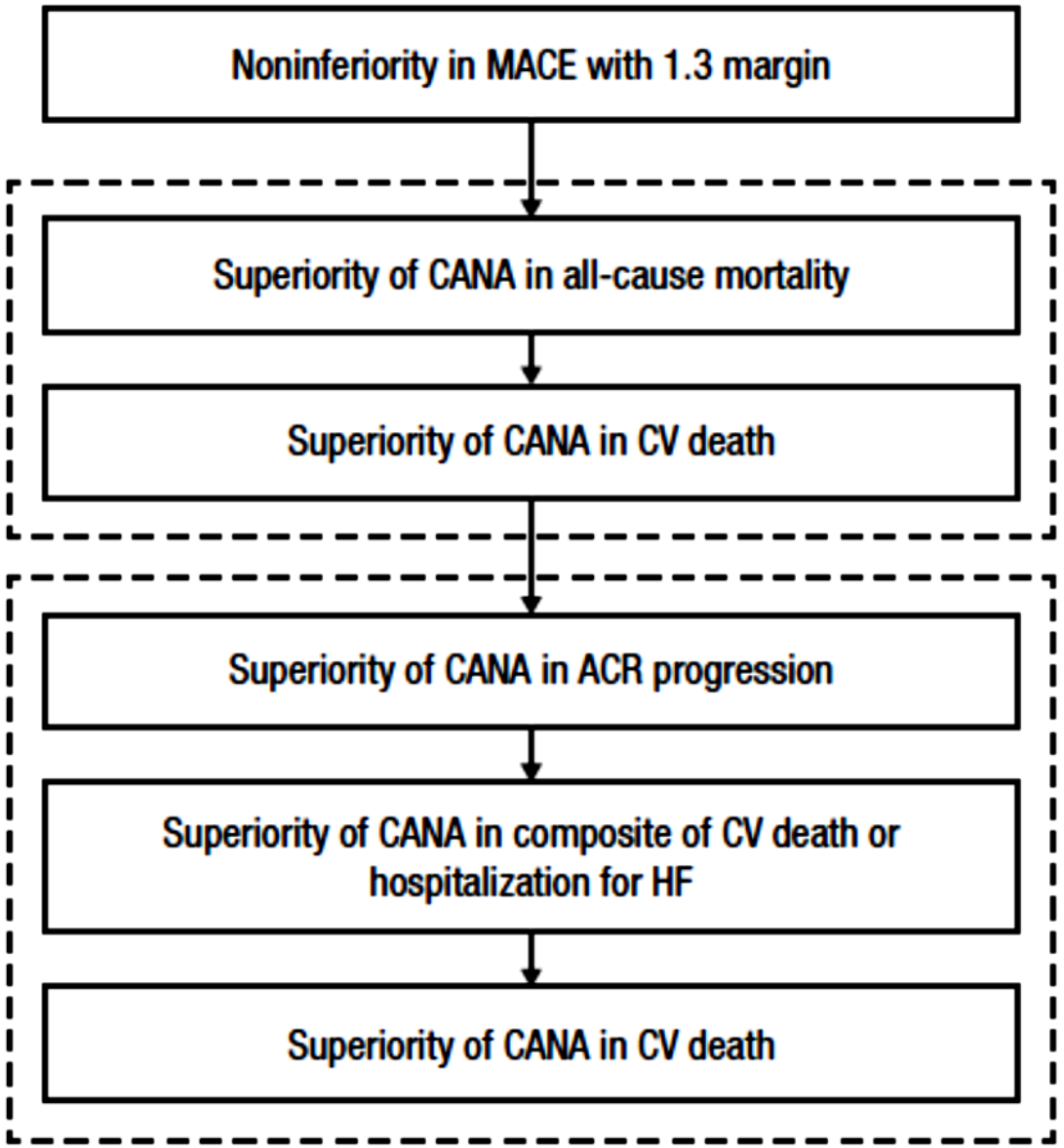
The primary objective of **CANVAS-R** is attenuation of **kidney disease progression**, as evidenced by fewer transitions from normo-as evidenced by fewer transitions from normo- to micro- or macro-, or micro- to macroalbuminuria. Secondary objectives: regression of albuminuria, on estimated glomerular filtration rate and on albumin creatinine ratio.

Overview of Canagliflozin trial timelines



CREDENCE: Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation;
CANVAS: CANagliflozin cardioVascular Assessment Study;
CANVAS-R: CANagliflozin cardioVascular Assessment Study–Renal.

Sequential hypothesis testing plan for the CANVAS program



Based on the integrated database of CANVAS-R and CANVAS ($\alpha = 5\%$)

Based on the integrated CANVAS and CANVAS-R database, but with the removal of all study time and mortality events accrued prior to 20 November 2012 ($\alpha = 5\%$)

Based on CANVAS-R ($\alpha = 5\%$)

Table 2. Participant Characteristics for CANVAS, CANVAS-R and the CANVAS Program

	CANVAS Program N=10,142	CANVAS N=4,330	CANVAS-R N=5,812
Age, years (mean, SD)	63.3 (8.3)	62.4 (8.0)	64.0 (8.4)
Female, n (%)	3633 (35.8)	1469 (33.9)	2164 (37.2)
Race, n (%)			
White	7944 (78.3)	3179 (73.4)	4765 (82.0)
Asian	336 (3.3)	105 (2.4)	231 (4.0)
Black or African American	1284 (12.7)	795 (18.4)	489 (8.4)
Other	578 (5.7)	251 (5.8)	327 (5.6)
Current smoker (%)	1806 (17.8)	776 (17.9)	1030 (17.7)
History of hypertension (%)	9121 (89.9)	3795 (87.6)	5326 (91.6)
History of heart failure (%)	1461 (14.4)	515 (11.9)	946 (16.3)
Duration of diabetes, years (mean, SD)	13.5 (7.8)	13.4 (7.5)	13.7 (7.9)

Table 2. Participant Characteristics for CANVAS, CANVAS-R and the CANVAS Program

	CANVAS Program N=10,142	CANVAS N=4,330	CANVAS-R N=5,812
Drug therapy, n (%)			
Insulin	5093 (50.2)	2174 (50.2)	2919 (50.2)
Sulphonylurea	4356 (43.0)	2029 (46.9)	2327 (40.0)
Metformin	7821 (77.1)	3166 (73.1)	4655 (80.1)
GLP-1 receptor agonist	407 (4.0)	96 (2.2)	311 (5.4)
Statin	7592 (74.9)	3131 (72.3)	4461 (76.8)
Antithrombotic	7455 (73.5)	3098 (71.5)	4357 (75.0)
RAAS inhibitor	8095 (79.8)	3487 (80.5)	4608 (79.3)
Microvascular disease history, n (%)			
Retinopathy	2130 (21.0)	865 (20.0)	1265 (21.8)
Nephropathy	1774 (17.5)	660 (15.2)	1114 (19.2)
Neuropathy	3111 (30.7)	1346 (31.1)	1764 (30.4)

Table 2. Participant Characteristics for CANVAS, CANVAS-R and the CANVAS Program

	CANVAS Program N=10,142	CANVAS N=4,330	CANVAS-R N=5,812
Atherosclerotic vascular disease history, n (%)*			
Coronary	5349 (52.7)	2212 (51.1)	3137 (54.0)
Cerebrovascular	1845 (18.2)	683 (15.8)	1162 (20.0)
Peripheral	2043 (20.1)	705 (16.3)	1338 (23.0)
Any	6933 (68.4)	2748 (63.5)	4185 (72.0)
CV disease history, n (%)†	6572 (64.8)	2471 (57.1)	4101 (70.6)
Body mass index, kg/m^2 (mean, SD)	32.0 (5.9)	32.1 (6.2)	31.9 (5.7)
Systolic BP, mmHg (mean, SD)	136.6 (15.8)	136.3 (15.7)	136.9 (15.8)
Diastolic BP, mmHg (mean, SD)	77.7 (9.7)	77.8 (9.7)	77.6 (9.6)
HbA1c, % (mean, SD)	8.2 (0.9)	8.2 (0.9)	8.3 (1.0)
Total cholesterol, mmol/L (mean, SD)	4.4 (1.2)	4.4 (1.2)	4.4 (1.2)
Triglycerides, mmol/L (mean, SD)	2.0 (1.4)	2.0 (1.4)	2.1 (1.5)
HDL-C, mmol/L (mean, SD)	1.2 (0.3)	1.2 (0.3)	1.2 (0.3)
LDL-C, mmol/L (mean, SD)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)
LDL-C:HDL-C ratio (mean, SD)	2.0 (0.9)	2.0 (0.9)	2.1 (0.9)

Table 2. Participant Characteristics for CANVAS, CANVAS-R and the CANVAS Program

	CANVAS Program N=10,142	CANVAS N=4,330	CANVAS-R N=5,812
eGFR, mL/min/1.73 m^2 (mean, SD)[‡]	76.5 (20.5)	77.2 (18.9)	75.9 (21.7)
eGFR ≥90 ml/min/1.73 m^2, n (%)	2474 (24.4)	1036 (24.0)	1438 (24.7)
eGFR ≥60 to <90 mL/min/1.73 m^2, n (%)	5620 (55.5)	2573 (59.6)	3047 (52.4)
eGFR ≥45 to <60 mL/min/1.73 m^2, n (%)	1484 (14.6)	544 (12.6)	940 (16.2)
eGFR ≥30 to <45 mL/min/1.73 m^2, n (%)	526 (5.2)	163 (3.8)	363 (6.2)
eGFR ≥15 to <30 mL/min/1.73 m^2, n (%)	26 (0.3)	3 (0.1)	23 (0.4)
eGFR <15 mL/min/1.73 m^2, n (%)	2 (<0.1)	1 (<0.1)	1 (<0.1)
Albumin:creatinine ratio (mean, mg/mmol)[§]	13.0 (49.9)	10.1 (39.7)	15.2 (56.3)
Normoalbuminuria, n (%)	7002 (69.8)	3085 (71.7)	3917 (68.4)
Microalbuminuria, n (%)	2263 (22.6)	966 (22.5)	1297 (22.7)
Non-nephrotic range macroalbuminuria, n (%)	703 (7.0)	236 (5.5)	467 (8.2)

Table 4. All Primary, Secondary and Exploratory Outcomes Planned for CANVAS, CANVAS-R and the Integrated CANVAS Program Data*

	CANVAS	CANVAS-R	CANVAS Program
Primary	MACE	Albuminuria progression	MACE (safety)
Secondary	Beta-cell function (HOMA-B, proinsulin/insulin ratio)[†]	Cardiovascular mortality or hospitalised heart failure	Total mortality[‡]
	Albuminuria progression		
	Albumin:creatinine ratio	Cardiovascular mortality	Cardiovascular mortality[‡]
	eGFR		
	HbA1c		
	FPG[§]		
	Body weight[§]		
	HbA1c <7%[§]		
	Systolic and diastolic BP[§]		
	Fasting plasma lipids		

Table 5. Anticipated Statistical Power for Hypothesis Testing

Hypothesis	Outcome	Dataset	Anticipated events		Assumed Hazard Ratio	Statistical power	
			Active	Placebo		Individual Test	Hierarchal Test
Primary: Non inferior to placebo*	Major adverse cardiovascular events	Integrated	515/5808	362/4333	0.91	99.9%	99.9%
Secondary: Superiority over placebo	Total mortality	Integrated **	254/5669	224/4249	0.72	92.3%	92.2%
	Cardiovascular death	Integrated **	139/5669	133/4249	0.68	85.1%	78.5%

Table 5. Anticipated Statistical Power for Hypothesis Testing

Hypothesis	Outcome	Dataset	Anticipated events		Assumed Hazard Ratio	Statistical power	
			Active	Placebo		Individual Test	Hierarchal Test
Albuminuria progression	CANVAS-R	430/2615	581/2615	0.74	99.8%	78.3%
Cardiovascular mortality or hospitalised heart failure	CANVAS-R	61/2906	93/2905	0.66	73.2%	57.3%
Cardiovascular death	CANVAS-R	40/2906	60/2905	0.68	48.7%	27.9%

Conclusion

The updates to the analysis strategy for **CANVAS, CANVAS-R and the CANVAS Program** proposed here will ensure that the completion of these trials results in the maximum possible likelihood of advances in scientific knowledge and patient care. They take a deliberately conservative approach to minimise the likelihood of spurious findings and to maximise the likelihood that any observed effects are real.

The specification of these **changes prior to knowledge of the trial results**, their careful planning by the independent scientific trial Steering Committee, the detailed ***a priori* definition** of the statistical analysis plans and **input provided by the US FDA**, all provide for efficient and robust utilisation of the data.

The new data from the **CANVAS program** should significantly advance our understanding of the effects of canagliflozin, and the **broader SGLT2 inhibitor class,** on a range of **efficacy and safety outcomes of key importance to patients with diabetes.**

ADA Congress , San Diego, June 12th, 2017, 3:15- 4:15

- **The Integrated Results of the CANVAS Program**

Background to the Design of the Trials
Gregory R. Fulcher, MBBS, MD

Methods for the Trials and the Integrated Analyses
Kenneth W. Mahaffey, BS, MD

Effects on Cardiovascular Outcomes
Bruce Neal, MB, ChB, PhD

Effects on Renal Outcomes
Dick de Zeeuw, MD, PhD

Effects on Safety Outcomes
Vlado Perkovic, MBBS, PhD

Implications for Clinical Practice
David R. Matthews, BM, BCh, DPhil

Independent Commentary
Clifford J. Bailey, PhD, FRCP Edin, FRCPath

FDA Drug Safety Communication (May 18th, 2017):
FDA confirms increased risk of leg and foot amputations with the diabetes medicine canagliflozin (Invokana, Invokamet, Invokamet

The **CANVAS trial** showed that over a year's time, the risk of amputation for patients in the trial were equivalent to:

- 5.9 out of every 1,000 patients treated with canagliflozin
- 2.8 out of every 1,000 patients treated with placebo

The **CANVAS-R trial** showed that over a year's time, the risk of amputation for patients in the trial were equivalent to:

- 7.5 out of every 1,000 patients treated with canagliflozin
- 4.2 out of every 1,000 patients treated with placebo

Canagliflozin CREDENCE Study (Ongoing)

CREDENCE – Canagliflozin and Renal Events in Diabetes with Established Nephropathy Clinical Evaluation

Study design

- **Aim: Assess whether CANA has a renal and vascular protective effect in reducing the progression of renal impairment relative to placebo in T2DM patients with stage 2 or 3 CKD and macroalbuminuria, who are receiving standard of care including a maximum-tolerated labelled daily dose of an ACE inhibitor or angiotensin receptor blocker**
- **1:1 randomization to Cana 100 mg or matching placebo**
- **Due to report in 2019**

Patient population

- **3627 T2D patients with diabetic nephropathy**
- **Stage 2 or 3 CKD and macroalbuminuria**
- **Receiving standard of care therapy plus ACE inhibitors or ARBs**

Study endpoints

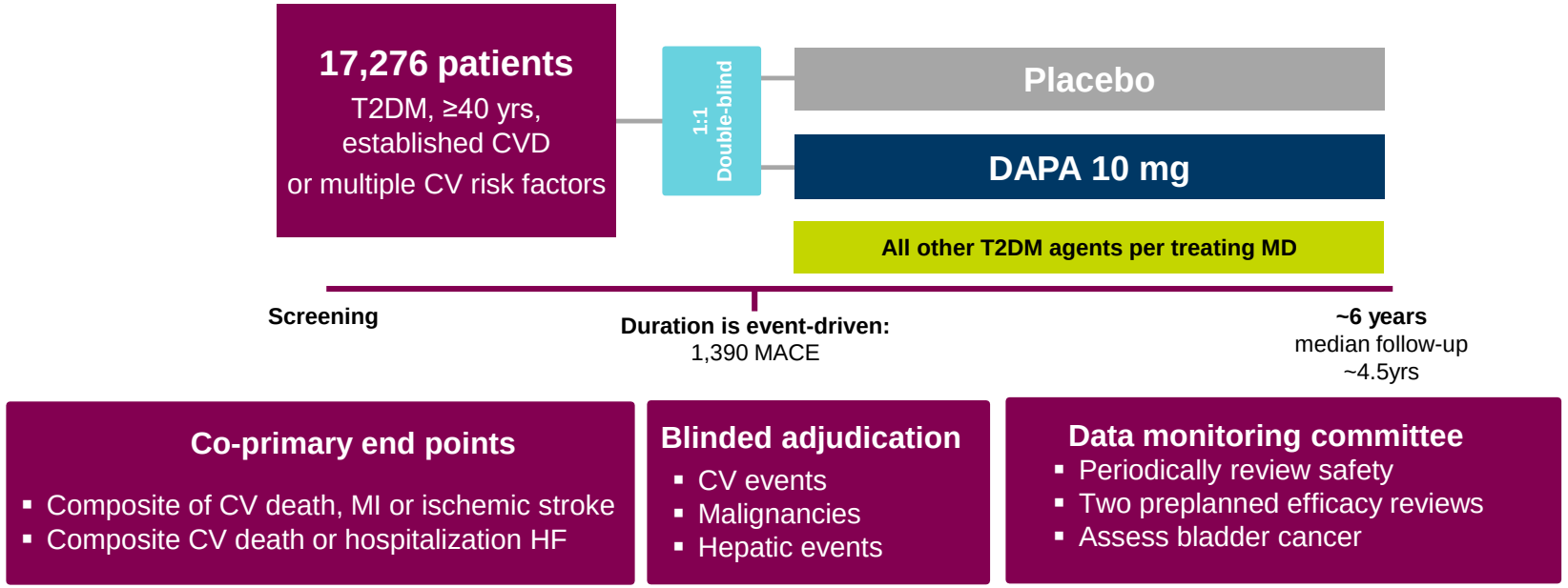
- **Primary: Time to first occurrence of event in primary composite endpoint – ESKD, doubling of serum creatinine, renal or CV death**
- **Secondary: Time to first occurrence of an event in the CV composite endpoint – CV death, non-fatal MI, non-fatal stroke, hospitalized congestive heart failure and hospitalized unstable angina, Time to first occurrence of an event in the renal composite endpoint including ESKD, doubling of serum creatinine and renal death**

CREDENCE is a renal outcomes trial in T2DM designed to show whether treatment with Canagliflozin can slow progression of nephropathy and reduce the risk of death due to renal insufficiency in patients with pre-existing nephropathy

1. Janssen Research & Development LLC. (2014). Janssen Initiates CREDENCE Study in Patients with Type 2 Diabetes and Diabetic Nephropathy. Press Release. February 21, 2014.
2. Clinicaltrials.gov. http://clinicaltrials.gov/show/NCT02065791. accessed 4.11.14

DECLARE

DECLARE: Dapagliflozin effects on cardiovascular events



Estimated Completion: April 2019

CV, cardiovascular; CVD, cardiovascular disease; DAPA, dapagliflozin; T2DM, type 2 diabetes mellitus.

DECLARE-TIMI58 trial, AstraZeneca. https://clinicaltrials.gov/ct2/show/NCT01730534. Accessed December 2016.
DECLARE-TIMI58 study group website http://www.timi.org/index.php?page=declare-timi-58 December 2016

DECLARE: Primary and secondary outcomes

Primary outcome

- **Step 1: Non-inferiority with respect to MACE (CV death, MI, or ischaemic stroke)**
- **Step 2 (if Step 1 met): Co-primary CV composite endpoints (MACE and composite of hospitalisation for HF or CV death)**

Secondary outcomes

- ***Renal composite endpoint (sustained ≥40% decrease in eGFR to eGFR <60 ml/min/1.73m^2 and/or ESRD and/or renal or CV death)***
- ***All-cause mortality***

DECLARE-TIMI58 trial, AstraZeneca. https://clinicaltrials.gov/ct2/show/NCT01730534. Accessed December 2016.
DECLARE-TIMI58 study group website http://www.timi.org/index.php?page=declare-timi-58 December 2016

DEVOTE

ADA Congress , San Diego, June 12th, 2017, 2:15-3:15

- **Cardiovascular Safety of Insulin Degludec vs. Insulin Glargine in Patients with Type 2 Diabetes at High Risk of Cardiovascular Events (DEVOTE) Trial Results**

Introduction and Trial Design
Steven P. Marso, MD

Cardiovascular Outcomes
Darren K. McGuire, MD, MHSc

Glycemic Efficacy and Hypoglycemia
Bernard Zinman, CM, MD, FRCPC, FACP

Safety
Richard E. Pratley, MD

Conclusion and Clinical Implications
John B. Buse, MD, PhD

Independent Commentary
Elizabeth R. Seaquist, MD

- **DEVOTE** was designed to evaluate the CV safety of **insulin degludec (IDeg)** vs **insulin glargine U100 (IGlar)** in patients with T2D at high risk of CV events
- **DEVOTE** is an event driven trial that would continue until **633** positively adjudicated primary events were accrued
- Primary end point: composite outcome consisting of the first occurrence of CV death, nonfatal myocardial infarction, or nonfatal stroke
- Patients with T2D at high risk of CV complications were randomized 1:1 to receive either **IDeg** or **IGlar,** each added to background therapies.
- This trial was designed to demonstrate statistical noninferiority of IDeg vs IGlar for the primary end point
- **DEVOTE** enrolled 7,637 patients, 6,506 had prior CV or CKD and the remainder had multiple CV risk factors.

EXSCEL (EASD Congress, Lisbon, Sept 2017)

- **EXSCEL: randomized, double-blind, placebo-controlled trial examining the effect of exenatide once weekly (EQW) versus placebo on the primary composite outcome (CV death, nonfatal M or nonfatal stroke) in T2DM patients with a wide range of CV risk**
- **In total 14,752 patients were randomized (6/2010-9/2015); 46.0% of patients were from Europe; 25.1% North America; 18.5% Latin America; and 10.4% from Asia Pacific**
- **73% had at least one prior CV event (70% CAD, 24% PAD and 22% CBVD, 16% CHF)**
- **Median age was 63 years, 38% were female, median baseline HbA1c was 8.0%**
- **Patients without a prior CV event were younger, had a shorter duration of diabetes and a better renal function than those with at least one prior CV event.**
- **Compared with prior GLP-1RA trials, EXSCEL has a larger percentage of patients without a prior CV event and a 15% who were taking a DPP-4 inhibitors at baseline**
- **EXSCEL is one of the largest global GLP-1RA trials, evaluating the safety and efficacy of EQW with a broad patient population that may extend generalizability compared to priorGLP-1RA trials**

ClinicalTrials.gov number,NCT01144338).

Mentz RJ et al. Am Heart J 2017;187:1-9

CAROLINA - CARMELINA

CAROLINA study has a truly unique trial design and is very different from the published CVOTs with DPP-4 Inhibitors

	CAROLINA[1]	TECOS[2]	SAVOR-TIMI53[3]	EXAMINE[4]
DPP-4 inhibitor	Linagliptin	Sitagliptin	Saxagliptin	Alogliptin
Comparator	Sulfonylurea (active)	Placebo	Placebo	Placebo
No. of patients	6,000	14,000	16,500	5,400
Trial initiation	Oct 2010	Nov 2008	May 2010	Sept 2009
Background diabetes therapy per protocol	Predominantly on metformin background	Any	Any	Any
Expected diabetes stage focus	Early	Advanced	Advanced	All but limited to acute CV events

1,2,4. Primary endpoint: CV death, non-fatal MI, non-fatal stroke, hospitalization due to unstable angina pectoris.
3. Primary endpoint: Major adverse cardiovascular events (CV death, non-fatal MI, non-fatal stroke).

Source: 1. NCT01243424, 2. NCT00790205, 3. NCT01107886, 4. NCT00968708 .

CAROLINA will evaluate CV safety of linagliptin in patients with T2DM at high CV risk

Inclusion if at least 1 of the following is fulfilled

1. **Previous vascular complications**
2. **Evidence of end organ damage such as e.g., albuminuria**
3. **Aged > 70 years**
4. **Two or more specified traditional CV risk factors**

With or without metformin background therapy (including patients with contraindication to Metformin use in renal impairment)

Linagliptin 5 mg vs **Glimepiride 1-4 mg[1]**

n= 6,000; approx. 6-7 year follow up

Primary endpoint: Time to the first occurrence of the primary composite endpoint:

1. **CV death (including fatal stroke and fatal MI)**
2. **Non-fatal MI**
3. **Non-fatal stroke**
4. **Hospitalization for unstable angina pectoris**

1. 16 weeks titration phase of glimepiride up to 4 mg/day.

Source: Rosenstock et al. American Diabetes Association 71st Scientific Sessions, San Diego, CA, June 24-28, 2011; 1103-P; NCT01243424.

CV Safety of Linagliptin vs Glimepiride in Type 2 DM at High CV Risk

CAROLINA Baseline Demographic Characteristics

Variable Characteristics	Total (n = 6046)
Age, years, mean ± SD	64 ± 10
Male / Female, %	59.9 / 40.1
HbA1c, %, mean ± SD	7.2 ± 0.6
HbA1c <7.0%, %	41.3
BMI, kg/m^2, mean ± SD	30.1 ± 5.3
SBP / DBP, mmHg, mean ± SD	138 ± 17 / 80 ± 10
eGFR (MDRD), mL/min/1.73m^2, mean ± SD	77 ± 20
Diabetes Duration, %	
≤5 years	40.8
>5 years	58.9
Geographical Region, %	
Europe	45.4
North America	19.2

Between2010 -2012, 581 clinical sites randomized 6103 patients

CAROLINA

Marx N et al. Diab Vasc Dis Res. 2015;12:164-74

CV Safety of Linagliptin vs Glimepiride in Type 2 DM at High CV Ris

CAROLINA Baseline Clinical Characteristics

Variable Characteristics	Total (n = 6046)
CV Severity Risk Category, %	
Previous CV Complications	35
Microvascular Complications	9
Age ≥70 years	19
Multiple CV Risk Factors	37
Glucose-Lowering Treatment, %	
No Therapy	9
Monotherapy	66
Dual Therapy	24
Insulin Therapy	0
Other therapies, %	
ASA	50
Statins	62
Antihypertensive	87

CAROLINA

Marx N et al. Diab Vasc Dis Res. 2015;12:164-74

CAROLINA Baseline Characteristics According to CV Risk

Variable Characteristics	Total (n = 6046)	Previous CV Events (n = 2105)	Retinopathy/ Albuminuria (n = 515)	Age >70 years (n = 1163)	≥2 CV Risk Factors (n = 2235)
Age, years, mean ± SD	64 ± 10	65 ± 9	66 ± 10	74 ± 3	58 ± 7
Male / Female, %	60 / 40	72 / 28	55 / 45	51 / 49	54 / 46
HbA1c, %, mean ± SD	7.2 ± 0.6	7.2 ± 0.6	7.1 ± 0.6	7.1 ± 0.5	7.2 ± 0.6
HbA1c <7.0%, %	41.3	42.0	43.5	44.2	38.9
BMI, kg/m^2, mean ± SD	30.1 ± 5.3	29.8 ± 5.2	30.1 ± 5.3	28.9 ± 4.8	31.1 ± 5.4
eGFR (MDRD), mL/min/1.73m^2, mean ± SD	77 ± 20	75 ± 19	63 ± 23	73 ± 17	84 ± 18
Diabetes Duration, %					
≤5 years	40.8	43.7	37.1	30.9	44.2
>5 years	58.9	56.3	62.9	69.1	55.8
CV Therapy, %					
ASA	49.8	78.9	39.2	39.5	30.7
Statins	61.8	70.8	49.1	51.9	62.0
Antihypertensive	86.5	91.7	86.6	80.1	85.5

Marx N et al. Diab Vasc Dis Res. 2015;12:164-74

Contrasting CAROLINA vs Completed DPP-4 CV Outcome Trials

Baseline Variables	SAVOR (Saxagliptin)	EXAMINE (Alogliptin)	CAROLINA (Linagliptin)
Participants (n)	16,500	5,400	6,103
Age (y)	65	61	64
Diabetes Duration (y)	12	7.2	~6
BMI (kg/m^2)	31	29	30
A1C (%)	8.0	8.0	7.2
Prior CVD (%)	78	~100	34
Hypertension (%)	81	83	84
Prior Insulin Use (%)	41	30	0
Comparator	Placebo	Placebo	Glimepiride

CAROLINA

Scirica BM, et al. New Engl J Med 2013 White WB, et al. N Engl J Med 2013 Marx N et al. Diab Vasc Dis Res. 2015;12:164-74

CARMELINA

CARdiovascular safety & clinical outcoME with LINAgliptin

- **CARMELINA will compare the CV and renal safety of linagliptin versus placebo, when added to standard care in ~8,000 patients with T2DM at high CV risk**

- **CARMELINA is a phase IIIb, multicenter, multinational, randomised, double-blind, placebo controlled, parallel group study to compare the treatment with linagliptin (5 mg once daily) to treatment with placebo (5 mg matching tablets once daily as add-on therapy to standard glucose-lowering treatment**

CARMELINA: Study design for CV & renal outcome*

Study focus on patients with high risk for cardiovascular disease and high risk of renal disease

Inclusion criteria

Documented diagnosis of T2DM and concurrently insufficient glycaemic control and a increased CV risk prior to informed consent with either:

a) **A history of cardiovascular disease (i.e. myocardial infarction, stroke, peripheral artery disease)**

or

b) **Documented kidney end-organ damage at least one of the following: eGFR 15-45 (with any UACR) or eGFR ≥45-75 and UACR >200 mg/g crea**

Screening

Screening-phase

Randomization 1:1

Placebo | **Linagliptin**

Target for glycemic control

HbA1c <7.5 | **HbA1c <7.5**

Optimizing glycemic control

If **HbA1c >7.5%: If already on insulin: treat to target recommendation (without insulin, apply insulin)**

Expected annual event rate

CV: 3.5%; Renal: 2.0%

* Planned analyses (draft – FDA approval pending): Interim analyses after ~3-4 years: final analysis after 4-5 years
Study initiation Q1 2013

Summary of future CVOTs

- In total, almost 300.000 patients with type 2 diabetes have been included in CVOTs
- Since the baseline characteristics of the patients included in the CVOts are very different, even studies using molecules from the same classes (e.g. dapagliflozin, canagliflozin or empagliflozin) could finally arrive at different results, positive or only neutral
- Thus, in 2021/2022 it could be very difficult to make simple recommendations for individualisation of treatment for patients with type 2 diabetes