DECLARAÇÃO DE POTENCIAL CONFLITO DE INTERESSES

Dr. Freddy Goldberg Eliaschewitz

cpclin | centro de pesquisas clínicas

De acordo com a Norma 1595/2000 do Conselho Federal de Medicina e a Resolução RDC 96/2008 da Agência de Vigilância Sanitária, declaro que recebo patrocínio das seguintes empresas e instituições para atividades de pesquisas clínicas, congressos e palestras:

- Astra Zeneca
- Sanofi-Aventis
- Bayer
- Bristol Meyer Squibb
- Roche
- Boehringuer Inguelheim
- FAPESP
- FINEP
- IEP-HIAE
- Kowa Ind.
- Lilly
- Merck Sharp Dohme
- Novartis
- Novo Nordisk
- Pfizer

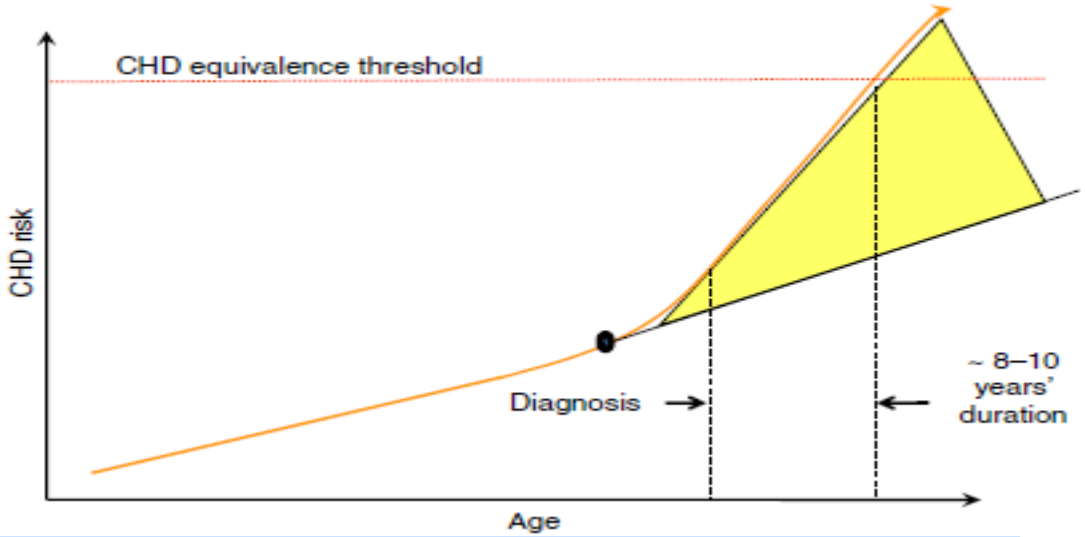
CVOT com iSGLT2 : Causas e consequências

Dr. Freddy Goldberg Eliaschewitz

Diretor clínico do CPCLIN – Centro de Pesquisas Clínicas
Membro Titular do Conselho Intersetorial de Ciência e Tecnologia do Conselho Nacional de Saúde.
Presidente da Comissão de Pesquisa Clínica da SBEM

Revisiting the links between glycaemia, diabetes and cardiovascular disease

N. Sattar

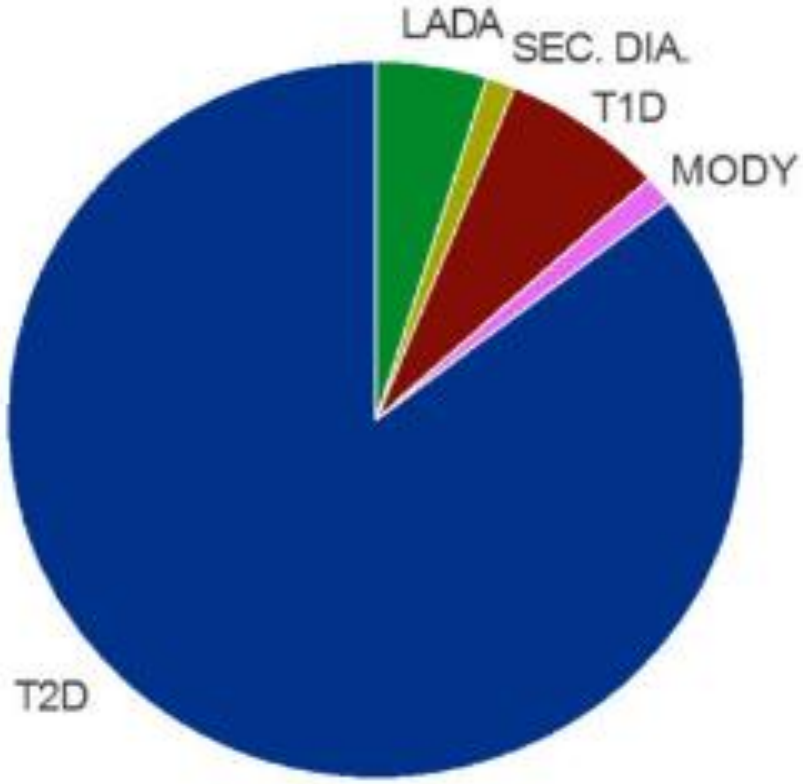


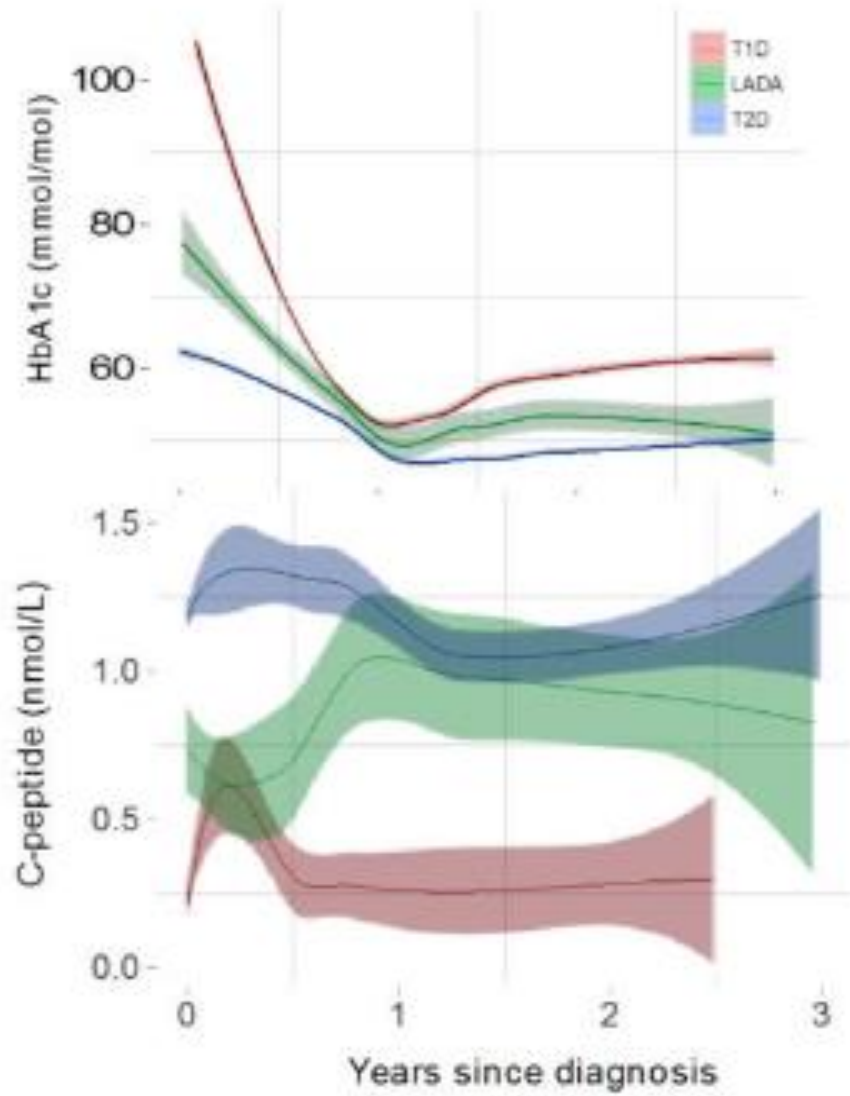
- Diabetes is not a CHD risk equivalent state at diagnosis or in those with short duration of disease (less than about a decade)
- Risk levels approach CHD risk equivalence after a diabetes duration of about a decade or in those with proteinuria or low eGFR
- Diabetic patients with existing CHD have a vascular risk well in excess of those with CHD but without diabetes

This review was invited based on the Minkowski lecture at the EASD, September 2011.

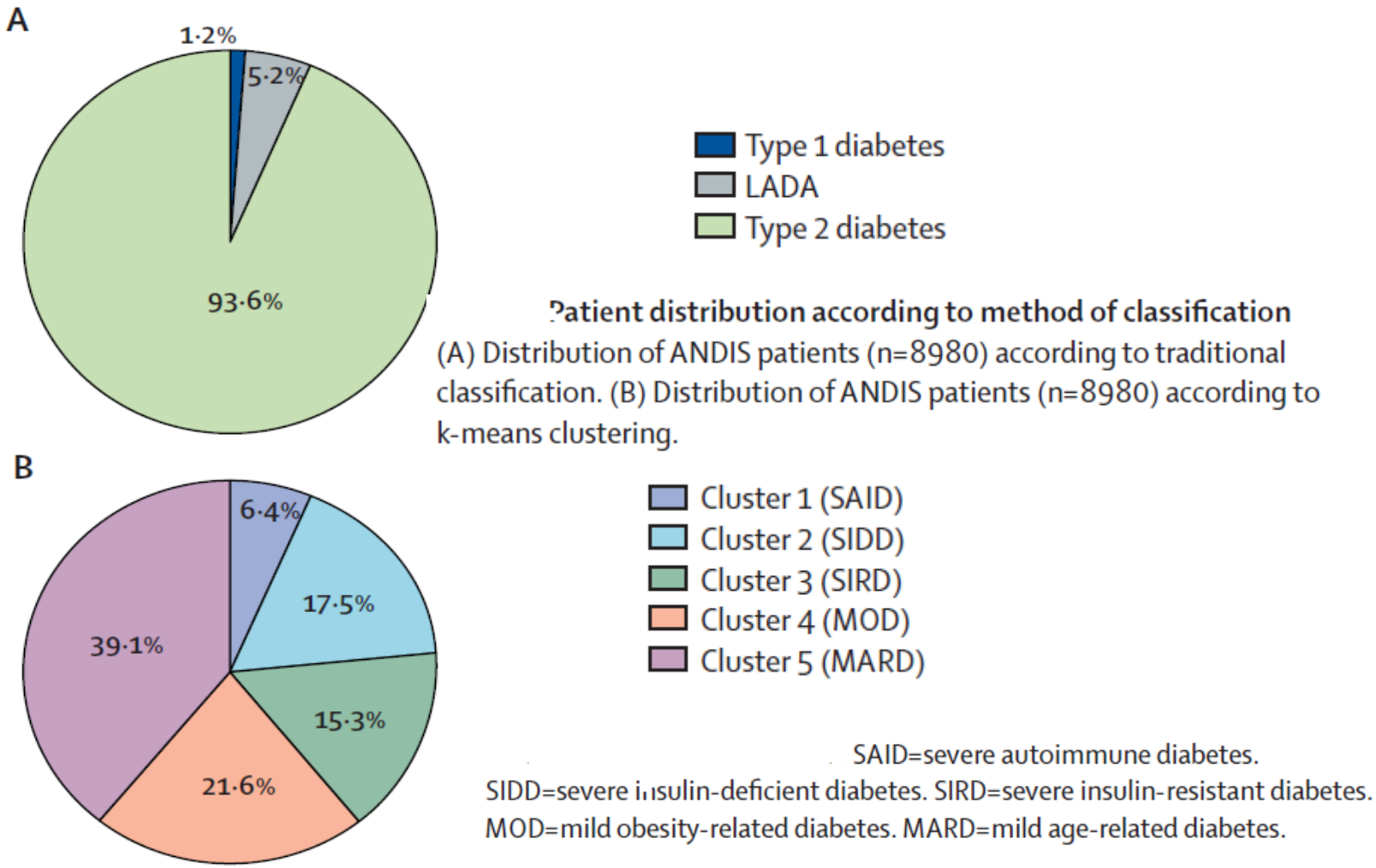
Diabetologia (2013) 56:686–695
DOI 10.1007/s00125-012-2817-5

ANDIS: traditional classification





Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables



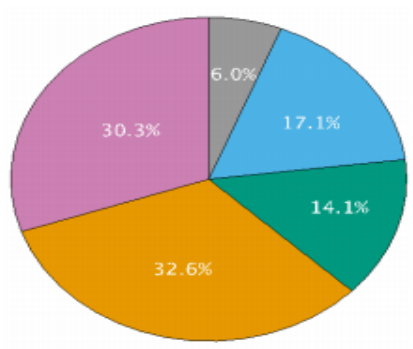
Patient distribution according to method of classification

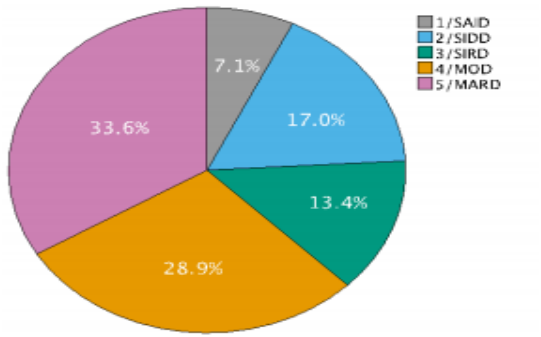
(A) Distribution of ANDIS patients (n=8980) according to traditional classification. (B) Distribution of ANDIS patients (n=8980) according to k-means clustering.

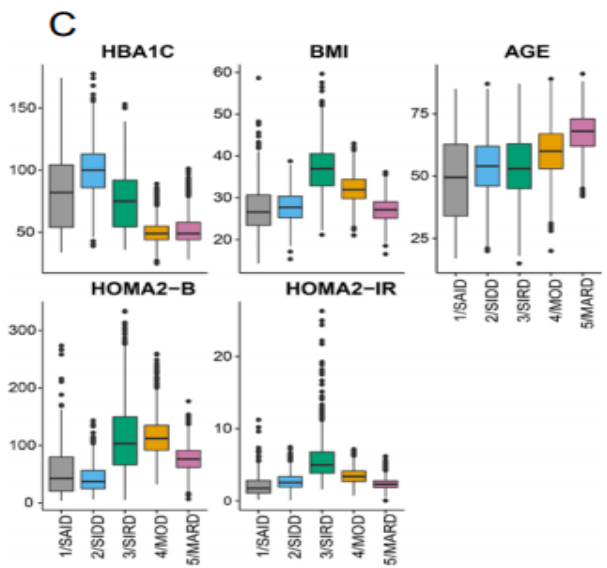
SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes.

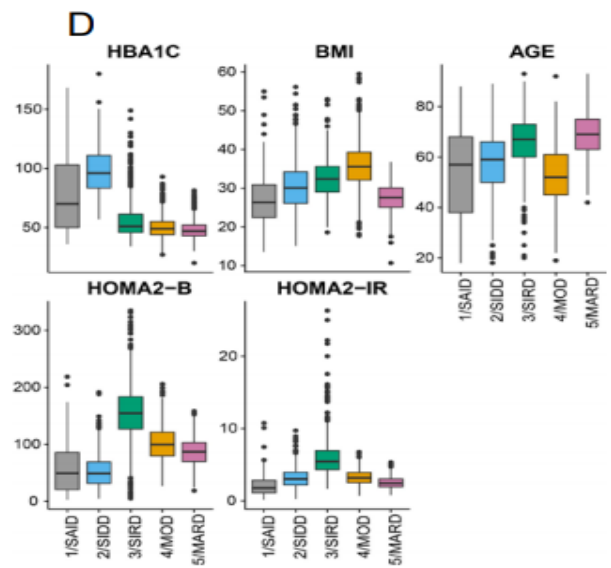
www.thelancet.com/diabetes-endocrinology **Published online March 1, 2018** **http://dx.doi.org/10.1016/S2213-8587(18)30051-2**

Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables









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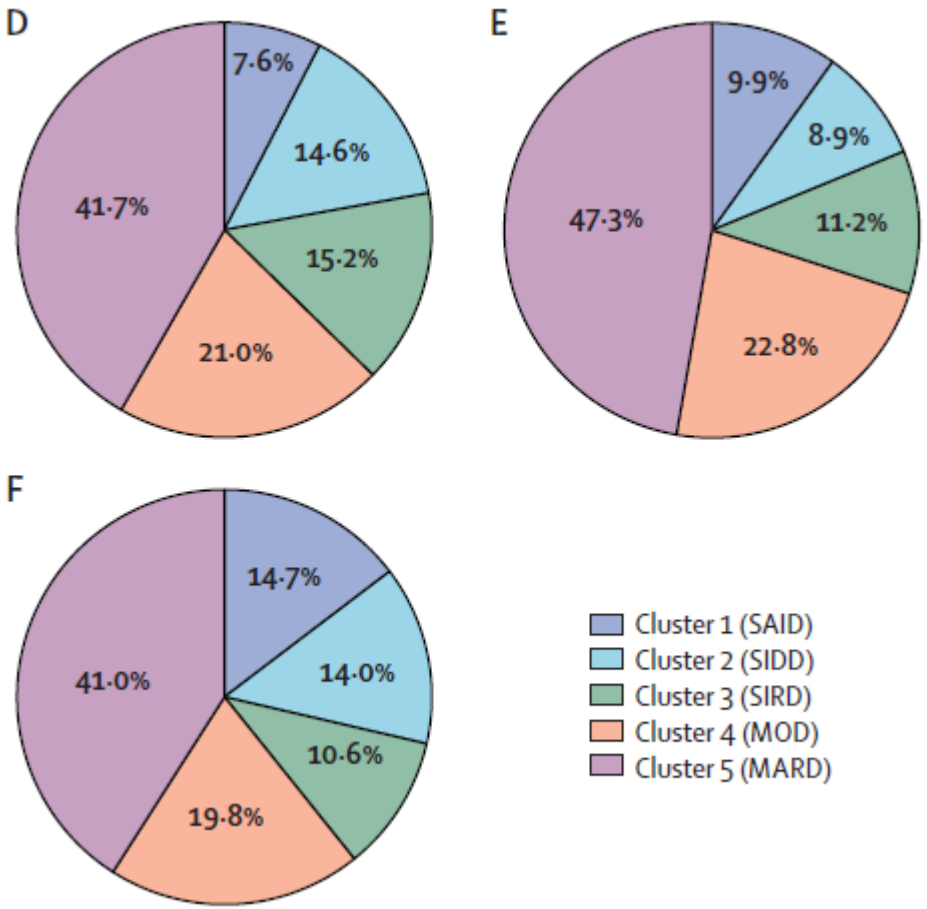

(D) Distribution of patients in the All New Diabetics in Uppsala cohort (n=844) according to k-means clustering. (E) Distribution of DIREVA patients with newly diagnosed diabetes (n=878) according to k-means clustering. (F) Distribution of DIREVA patients with longer-term diabetes (n=2607) according to k-means clustering

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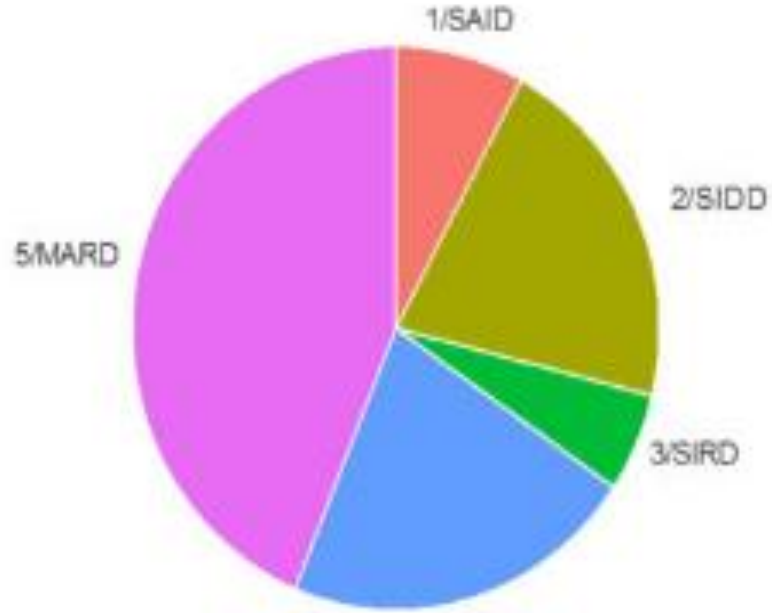
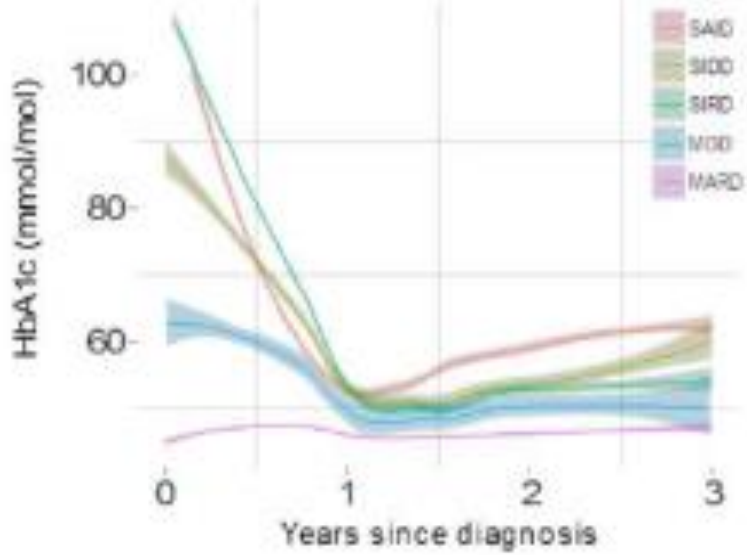
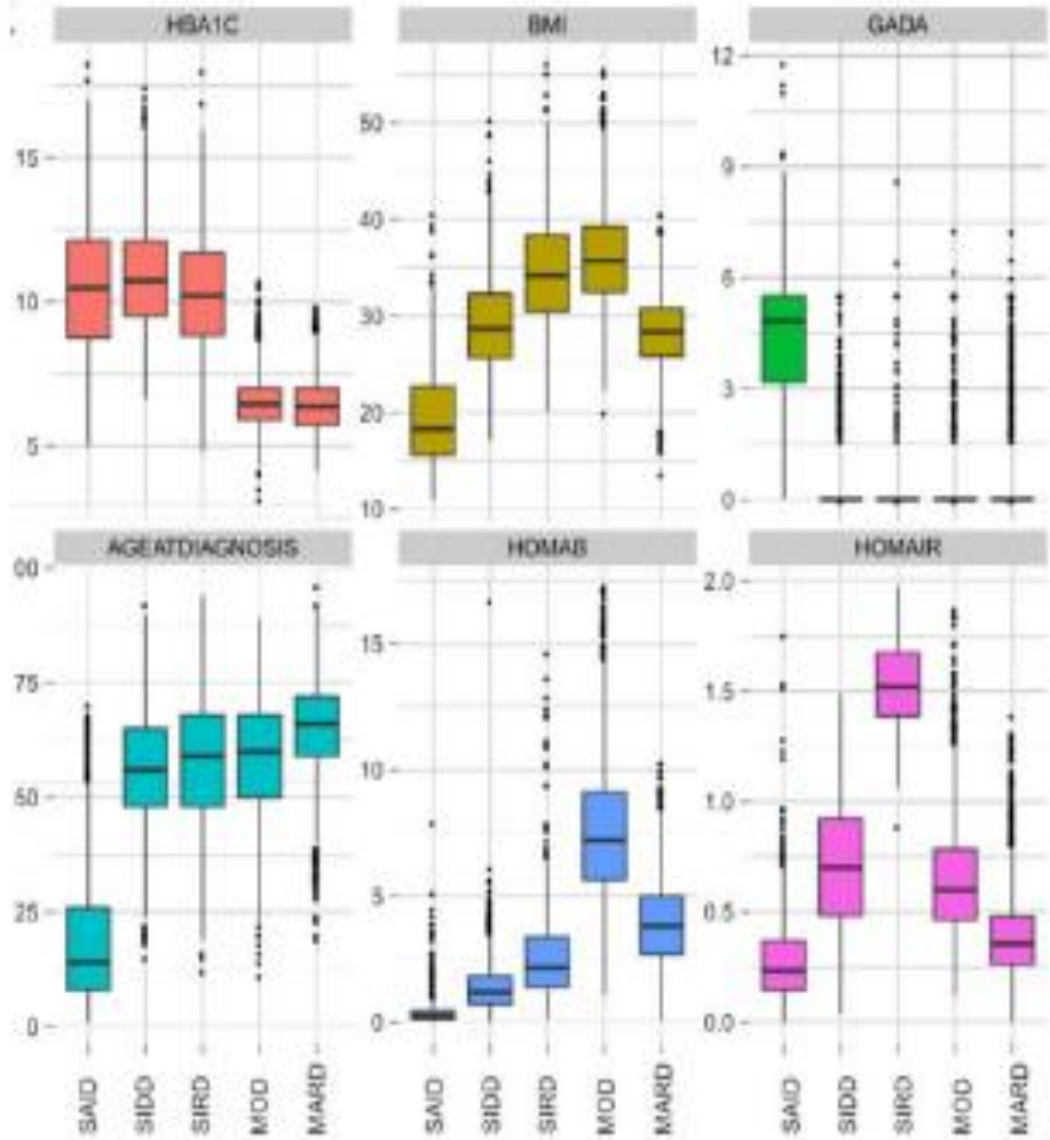
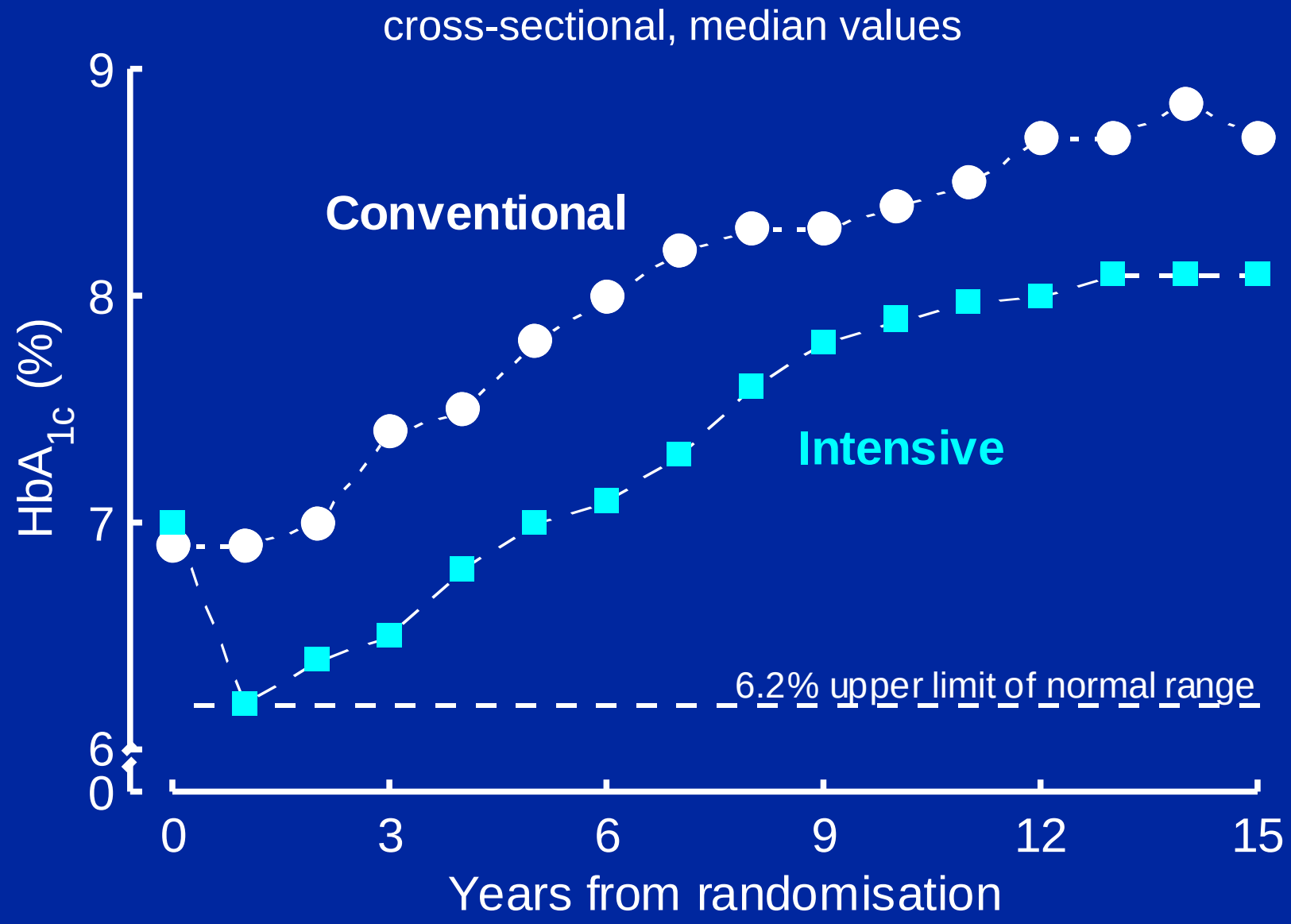
Data driven classification of diabetes







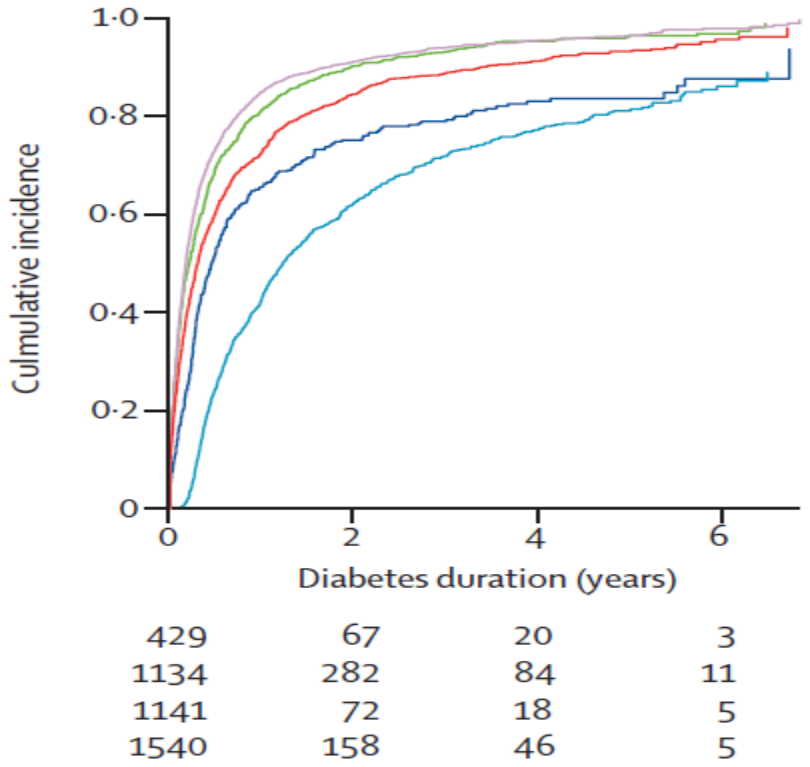
HbA_{1c}


cross-sectional, median values
9
8
7
6
0
HbA1c (%)
Conventional
Intensive
6.2% upper limit of normal range
0
3
6
9
12
15
Years from randomisation

ukpds

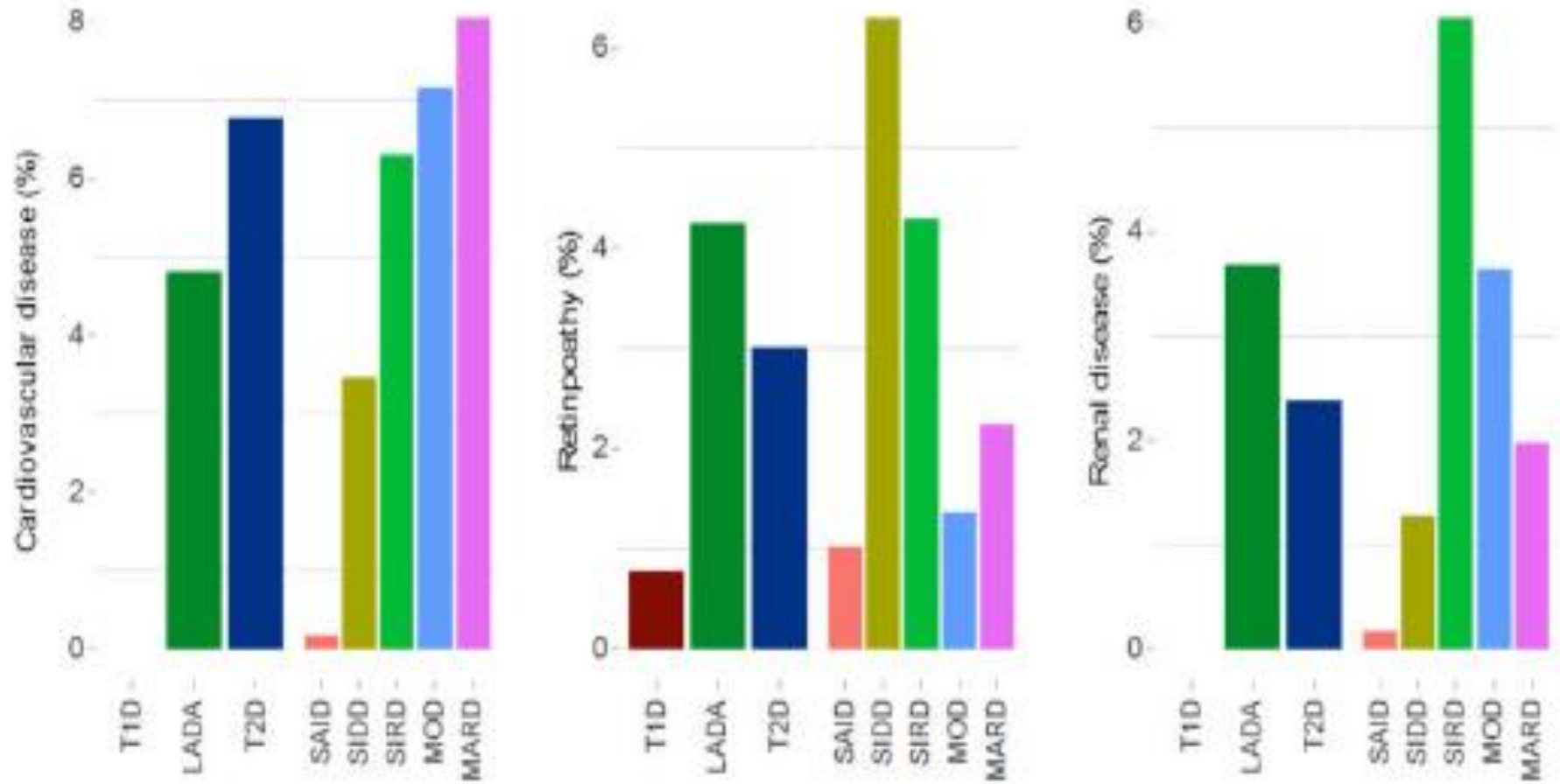
Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

Time to reach treatment goal (HbA1c<6·9% [52 mmol/mol])

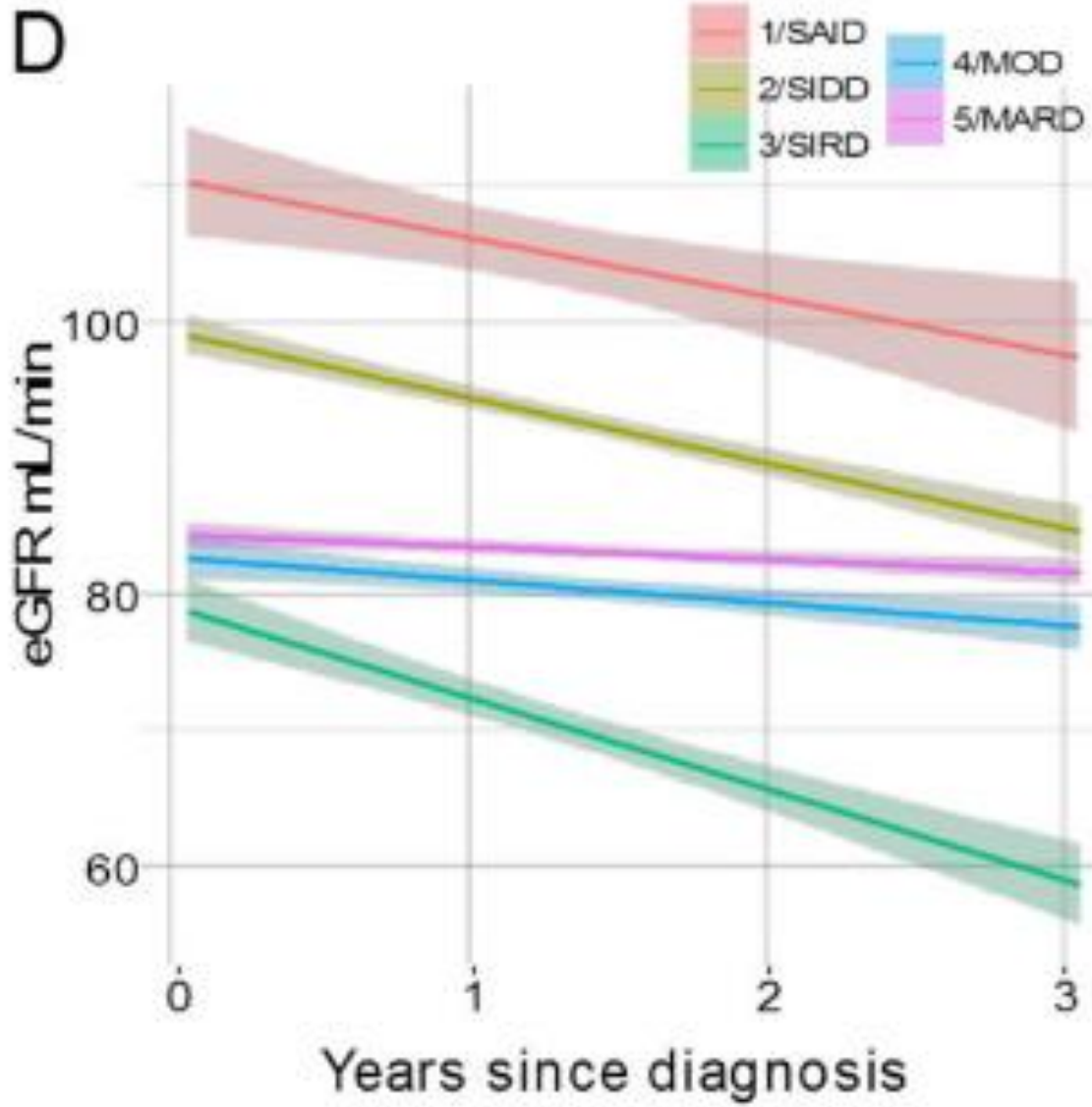


www.thelancet.com/diabetes-endocrinology **Published online March 1, 2018** **http://dx.doi.org/10.1016/S2213-8587(18)30051-2**

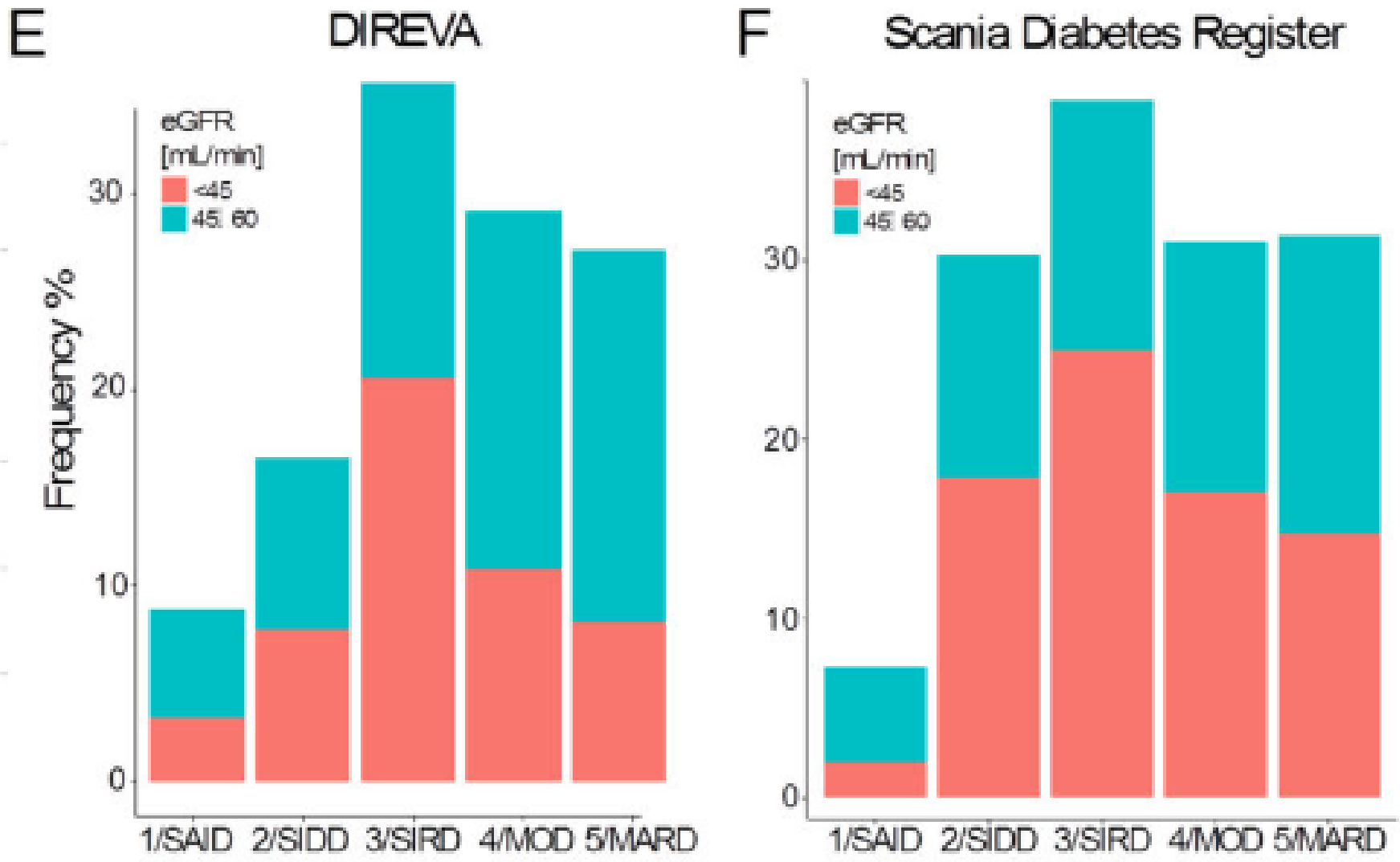
Highest risk of diabetic kidney disease in Severe Insulin Resistant Diabetes (SIRD)



eGFR declines rapidly in SIRD

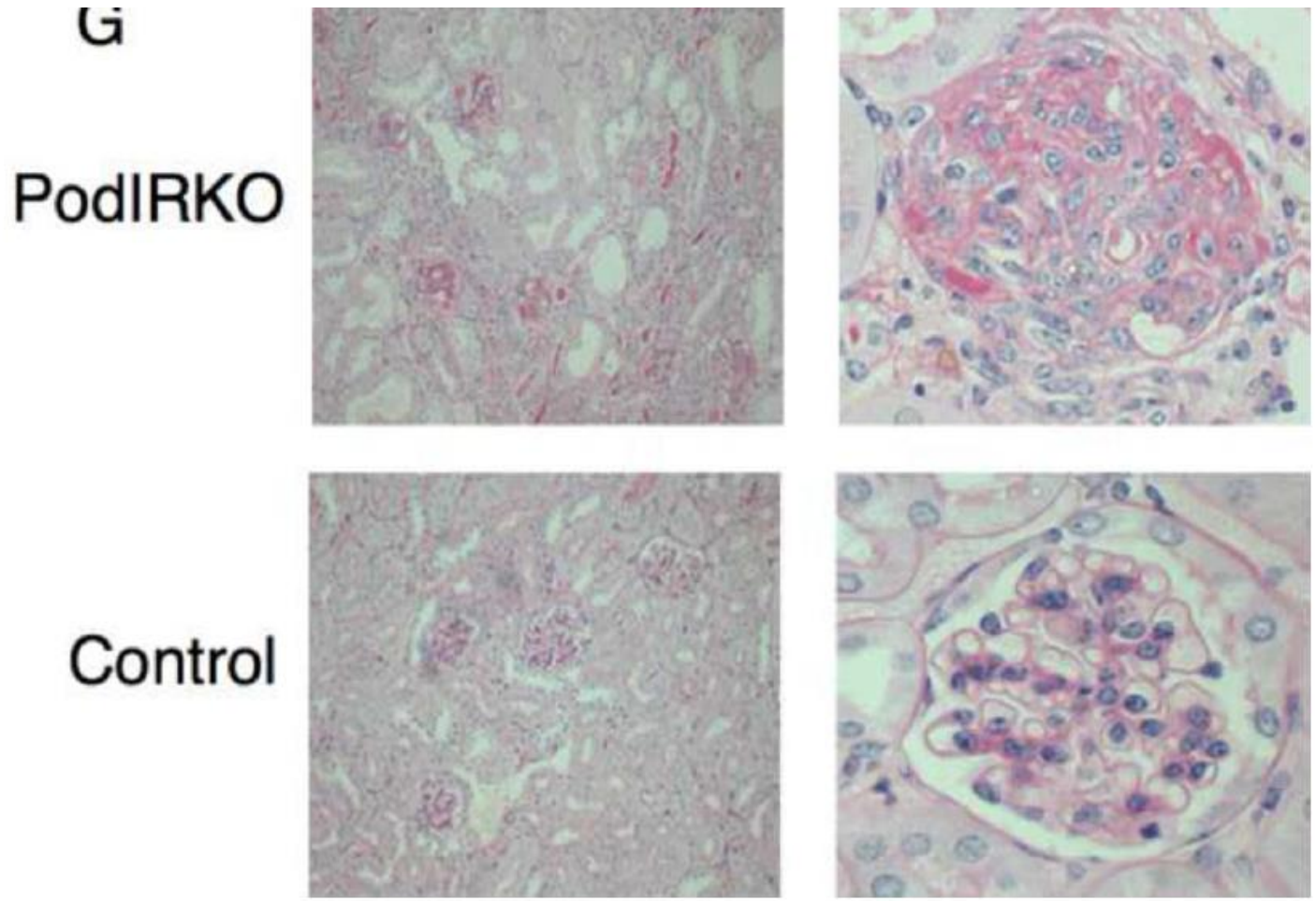


Highest risk of DKD in SIRD in two other cohorts with longer follow-up



Insulin Signaling to the Glomerular Podocyte is Critical for Normal Kidney Function

Cell Metab. 2010 October 6; 12(4): 329–340. doi:10.1016/j.cmet.2010.08.015.



Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables

	EA/NEA	MAF	Cluster 1 (SAID; n=313)	Cluster 2 (SIDD; n=676)	Cluster 3 (SIRD; n=603)	Cluster 4 (MOD; n=727)	Cluster 5 (MARD; n=1646)	p value of difference among clusters 2–5
TCF7L2 (rs7903146)	T/C	0·26	1·17 (0·97–1·40); p=0·077	1·51 (1·33–1·71); p<0·0001	1·00 (0·87–1·15); p=0·86	1·38 (1·21–1·56); p<0·0001	1·41 (1·28–1·55); p<0·0001	<0·0001*
KCNQ1 (rs2237895)	C/T	0·41	1·08 (0·91–1·28); p=0·31	1·13 (1·00–1·28); p=0·052	0·85 (0·74–0·97); p=0·0272	0·98 (0·86–1·10); p=0·88	1·13 (1·03–1·23); p=0·0196	0·0008
HHEX/IDE (rs1111875)	G/A	0·41	1·16 (0·98–1·38); p=0·10	1·21 (1·07–1·37); p=0·0045	1·05 (0·92–1·19); p=0·51	0·94 (0·84–1·06); p=0·31	1·11 (1·02–1·22); p=0·0228	0·0106
IGF2BP2 (rs4402960)	T/G	0·29	1·04 (0·87–1·24); p=0·50	1·23 (1·08–1·40); p=0·0002	1·01 (0·88–1·16); p=0·53	1·04 (0·92–1·18); p=0·31	1·22 (1·11–1·33); p<0·0001	0·0117
CDKN2B (rs10811661)	T/C	0·16	0·87 (0·70–1·08); p=0·24	1·33 (1·11–1·59); p=0·0014	0·98 (0·83–1·17); p=0·85	0·99 (0·84–1·16); p=0·92	1·18 (1·04–1·33); p=0·0054	0·0149
MTNR1B (rs10830963)	G/C	0·29	0·84 (0·70–1·01); p=0·05	0·93 (0·82–1·07); p=0·26	0·89 (0·77–1·02); p=0·056	1·13 (1·00–1·28); p=0·067	1·05 (0·96–1·15); p=0·29	0·0151
SLC30A8 (rs13266634)	T/C	0·31	0·98 (0·82–1·17); p=0·78	0·93 (0·82–1·06); p=0·23	1·11 (0·97–1·27); p=0·11	1·07 (0·94–1·21); p=0·30	0·92 (0·83–1·01); p=0·0457	0·0160
MC4R (rs12970134)	G/A	0·27	0·95 (0·79–1·14); p=0·52	0·97 (0·85–1·11); p=0·55	0·99 (0·86–1·13); p=0·59	0·87 (0·77–0·99); p=0·0229	1·07 (0·97–1·18); p=0·18	0·0230
TM6SF2 (rs10401969)	T/C	0·10	0·75 (0·58–0·97); p=0·038	0·69 (0·58–0·83); p=0·0002	0·62 (0·52–0·75); p<0·0001	0·89 (0·73–1·07); p=0·26	0·77 (0·67–0·89); p=0·0005	0·0233
ADAMTS9-AS2 (rs4607103)	T/C	0·24	1·05 (0·87–1·27); p=0·54	0·89 (0·77–1·03); p=0·15	0·93 (0·80–1·08); p=0·42	1·12 (0·98–1·27); p=0·064	0·92 (0·83–1·01); p=0·13	0·0278
VPS13C (rs17271305)	G/A	0·40	1·00 (0·84–1·19); p=0·93	0·97 (0·86–1·10); p=0·84	1·11 (0·98–1·26); p=0·092	0·88 (0·78–0·99); p=0·0491	0·93 (0·85–1·02); p=0·17	0·0281
SLC2A2 (rs11920090)	T/A	0·13	0·94 (0·74–1·20); p=0·54	0·83 (0·70–0·99); p=0·0162	0·91 (0·76–1·09); p=0·23	0·97 (0·82–1·16); p=0·63	1·08 (0·95–1·24); p=0·44	0·0368
KCNJ11 (rs5219)	T/C	0·38	1·05 (0·88–1·25); p=0·61	1·18 (1·04–1·34); p=0·0121	1·03 (0·90–1·18); p=0·67	1·28 (1·13–1·44); p=0·0001	1·10 (1·01–1·21); p=0·0324	0·0453
TSPAN8 (rs7961581)	T/C	0·26	0·97 (0·80–1·17); p=0·69	1·05 (0·92–1·21); p=0·55	1·13 (0·98–1·31); p=0·11	0·99 (0·87–1·13); p=0·80	0·92 (0·84–1·02); p=0·11	0·0464

Maximum likelihood estimation using geographically matched individuals without diabetes as controls (n=2754). EA=effect allele. NEA=non-effect allele. MAF=minor allele frequency. SAID=severe autoimmune diabetes. SIDD=severe insulin-deficient diabetes. SIRD=severe insulin-resistant diabetes. MOD=mild obesity-related diabetes. MARD=mild age-related diabetes. ANDIS=All New Diabetics in Scania. *Significant after correction for multiple testing (77 tests).

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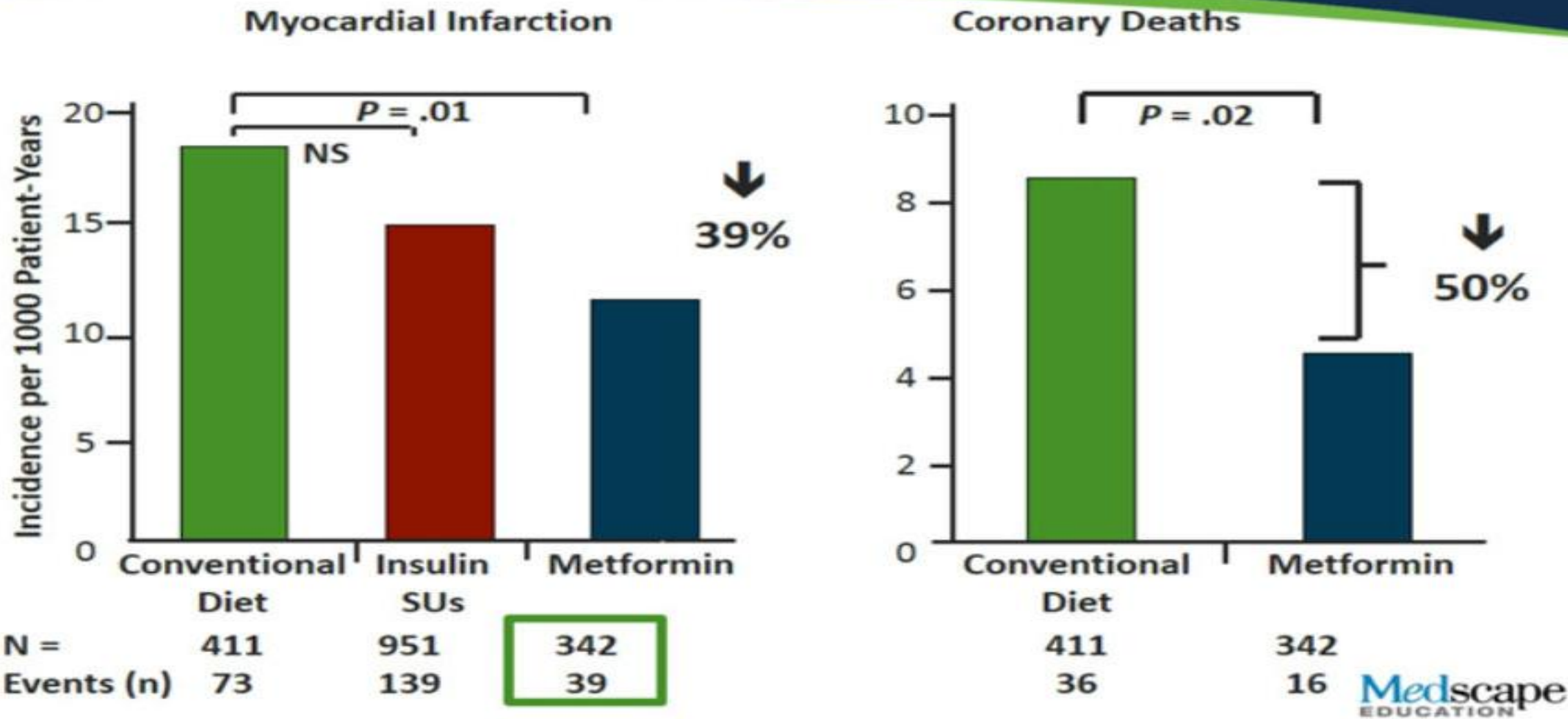
Pre-2008: Working Hypothesis on Diabetes and Outcomes

- Diabetes → ↑micro- and macrovascular complications[a]
- ↑ glucose is a major physiologic complication of diabetes
- ***Therefore, ↓glucose will improve diabetes and ↓micro- and macrovascular risk***
- Thus, a primary goal of diabetes therapy is to ↓ glucose
- True for microvascular complications and supported by type 1 diabetes data[b]

a. Kannel WB, et al. *Circulation*. 1979;59:8-13[1]
b. Nathan D, et al. *N Engl J Med*. 2005;353:2643-2653.[2]

UKPDS Metformin Substudy



UK Prospective Diabetes Study Group. *Lancet*. 1998;352:854-865.[3]

Guidance for Diabetes Drug Development 1990-2008

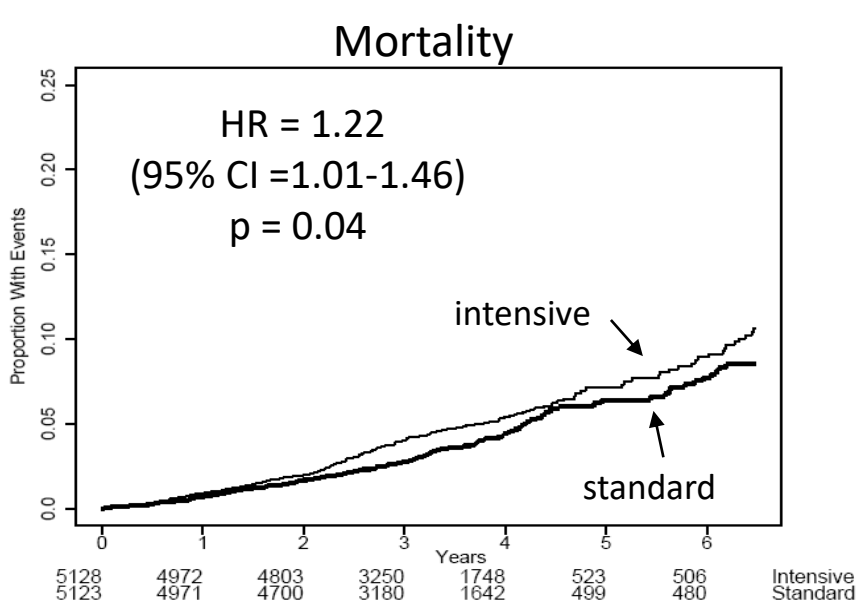
- ICH Guidelines:
  - 1500 patients exposed
  - 300-600 x 6 months
  - 100 x 1 year

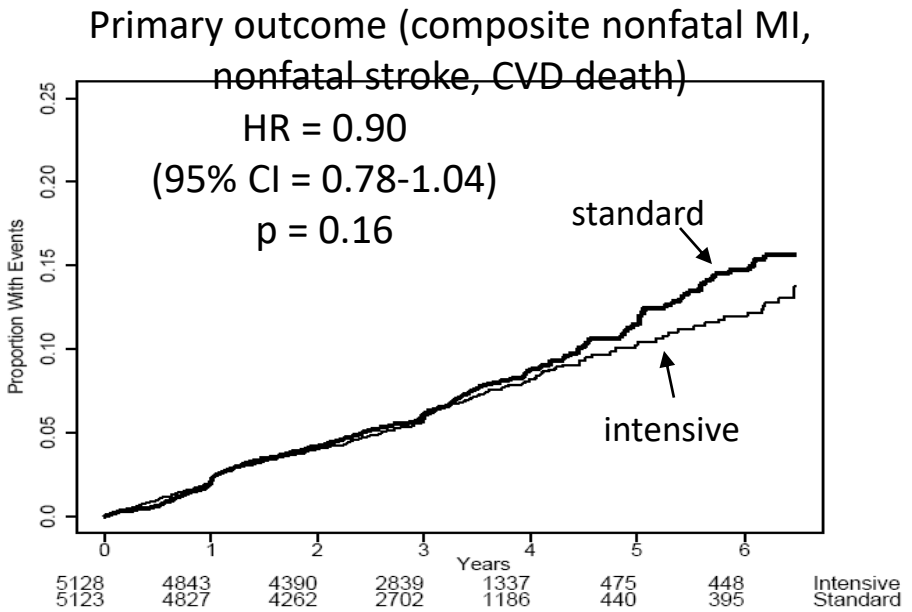
- Approval based on as little as **200 patient-years** of exposure

Rare but serious adverse drug reactions require large exposure…

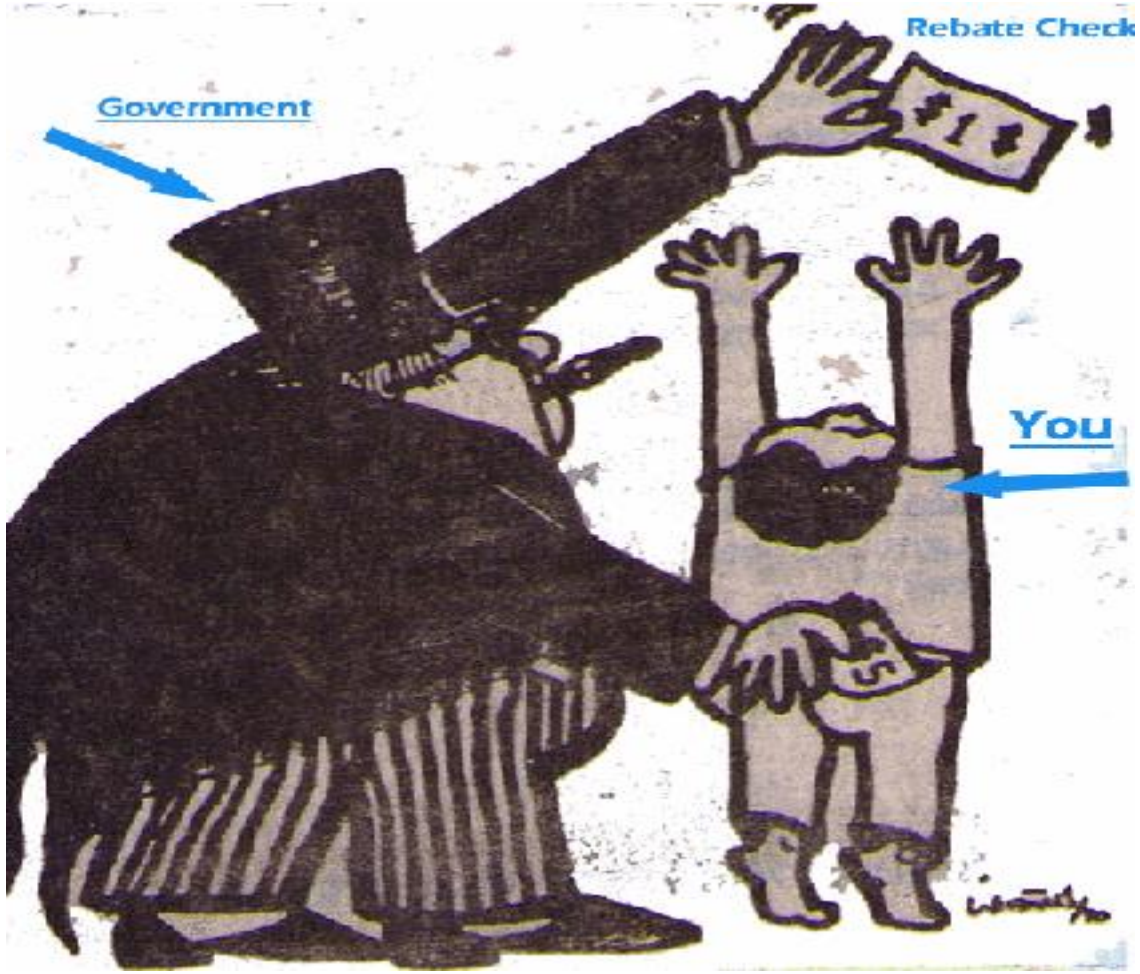
Courtesy of Ben Scirica, MD, TIMI Study Group

ACCORD All-Cause Mortality and Primary Outcome Event Curves





Dando com uma mão mas tirando com a outra....



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

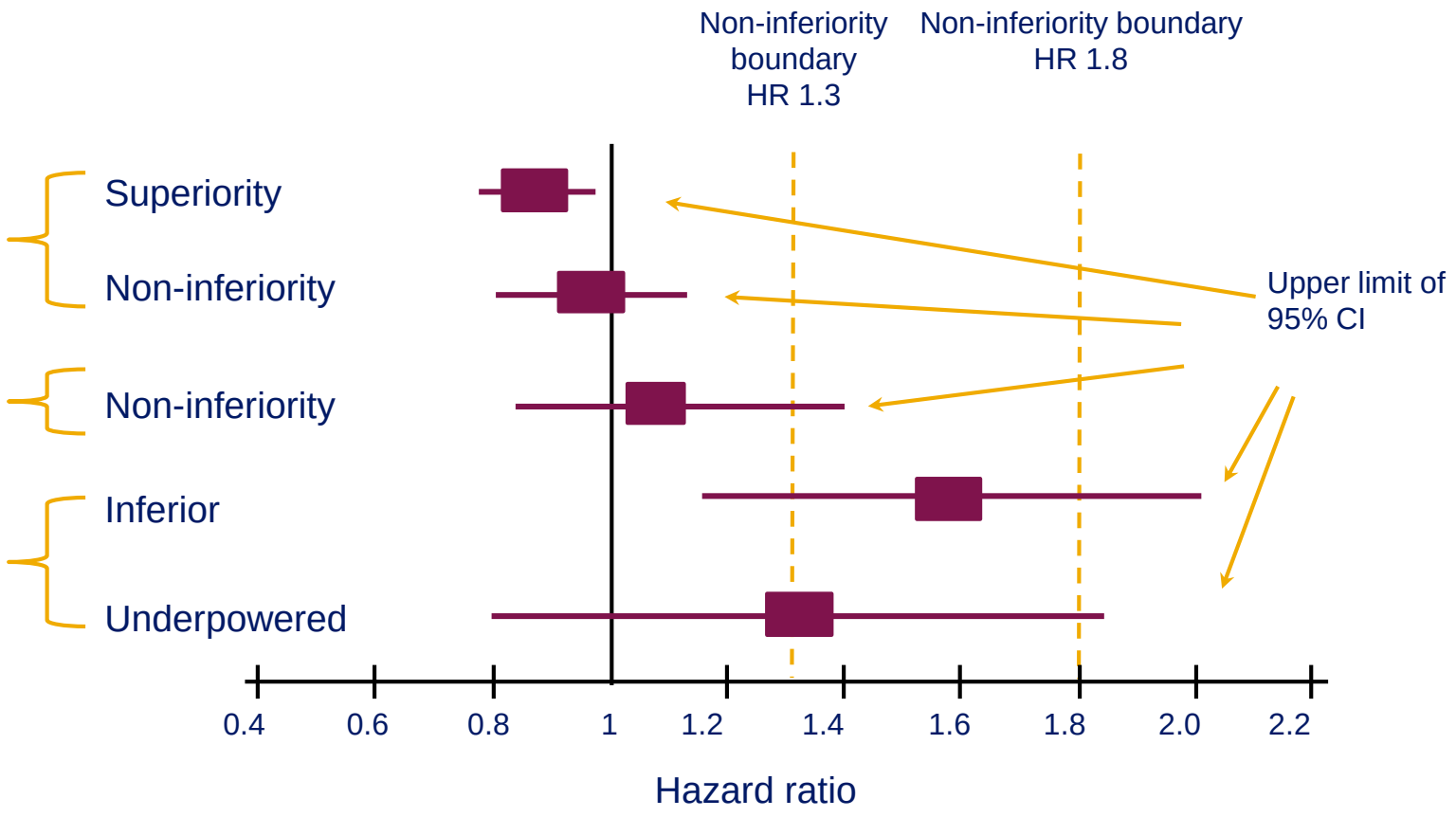
http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/2008/ucm116994.htm

FDA criteria for requirement of a postmarketing CV outcomes trial

Approvable: no need for postmarketing study

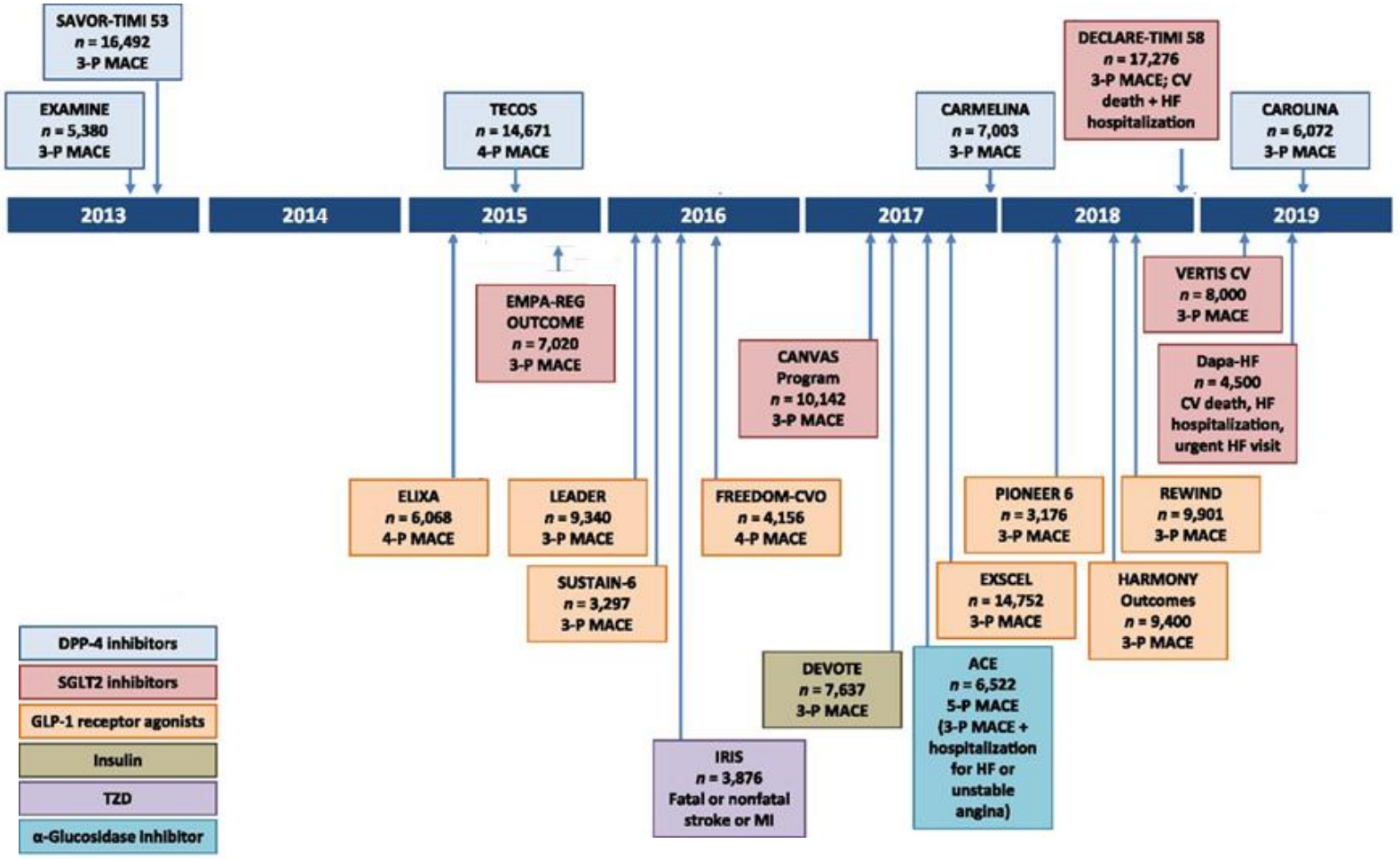
Approvable: need for postmarketing study

Not approvable



Hirshberg B, Raz I. *Diabetes Obes Metab* 2011;34(Suppl. 2):S101–6

Completed and ongoing CVOTs (6–14,39,44–58). 3-P, 3-point; 4-P, 4-point; 5-P, 5-point.

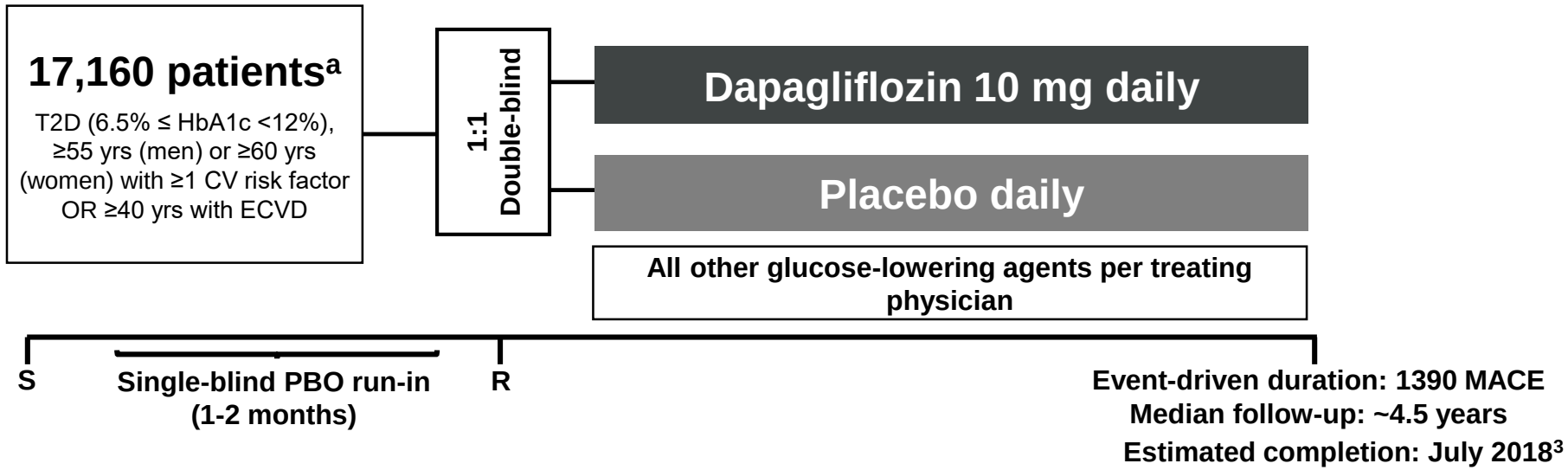


William T. Cefalu et al. Dia Care 2018;41:14-31

American Diabetes Association.

A Multinational, Randomized, Double-blind, Placebo-controlled, Phase IIIb Cardiovascular Outcomes Trial

Study Design[1,2]



Primary endpoint

- **Composite of CV death, nonfatal MI, or nonfatal ischemic stroke (MACE) Non inferiority vs placebo HR < 1,3 CI 95%**
- **Powered for superiority HR=0,85 with 80% P< 0,023**

Secondary endpoints

- Renal composite endpoint (sustained ≥40% **decrease CrCl <60 mL/min/1.73 m^2** and/or ESRD and/or renal or CV death)
- All-cause mortality
  - ETC…..

Blinded adjudication

- CV events
- Malignancies
- Liver events

Data monitoring committee

- Periodically review safety
- Two preplanned efficacy reviews
- Assess bladder cancer every 8 events

[a]A total of 17,190 patients were randomized; however, 30 patients were excluded from all analyses because of significant good clinical practice violations at a single site for a different dapagliflozin trial.
CV, cardiovascular; DKA, diabetic ketoacidosis; ECVD, established atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD = end-stage renal disease; HbA1c, glycated hemoglobin; MACE, major adverse cardiovascular events; MI, myocardial infarction; PBO, placebo; R, randomization; S, screening; T2D, type 2 diabetes; yrs, years.
1. Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110; 2. Wiviott SD et al. *Am Heart J*. 2018;200:83-89; 3. Study NCT01730534. ClinicalTrials.gov website. Accessed January 18, 2018.

Key Inclusion/Exclusion Criteria

Inclusion criteria:

1. Female or male; age ≥40 years
2. Diagnosis of T2D
3. Increased CV risk according to 2 categories: multiple risk factors for CV disease or established atherosclerotic CV disease

Exclusion criteria:

1. HbA1c ≥12% or <6.5%, with the proportion of patients with HbA1c of 6.5% to <7% capped at ~5%
2. **Creatinine clearance <60 mL/min based on the Cockcroft-Gault equation**
3. Unexplained hematuria
4. Lifetime history of bladder cancer or history of malignancy (other than nonmelanoma skin cancer) within the past 5 years
5. Recurrent urinary tract infections
6. Acute CV or cerebrovascular event within the past 8 weeks
7. Use of an SGLT2 inhibitor, pioglitazone, or rosiglitazone

.

CV, cardiovascular; HbA1c, glycated hemoglobin; SGLT2 , sodium-glucose cotransporter 2; T2D, type 2 diabetes.

Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

CV Risk Categories

Multiple Risk Factors for CV Disease (MRF)

Age ≥55 years (men), ≥60 years (women)

AND ≥1 additional risk factors:

- Dyslipidemia (≥1 of following)
  - LDL-C >130 mg/dL (>3.36 mmol/L)
  - On lipid-lowering therapy
- Hypertension (≥1 of following)
  - BP >140/90 mm Hg at enrollment
  - On antihypertensive therapy
- Current smoking
  - ≥5 cigarettes/day for ≥1 year

Established Atherosclerotic CV Disease (ECVD)

Age ≥40 years

AND ≥1 additional diagnoses:

- Ischemic heart disease (any of following)
  - MI
  - PCI
  - CABG
  - ≥50% coronary stenosis in ≥2 coronary arteries
- Cerebrovascular disease (any of following)
  - Ischemic stroke
  - Carotid stenting or endarterectomy
- Peripheral artery disease (any of following)
  - Peripheral arterial stenting or surgical revascularization
  - Lower extremity amputation as a result of PAD
  - Symptomatic IC and ABI <0.90 in last 12 mo.

ABI, ankle-brachial index; BP, blood pressure; CABG, coronary artery bypass grafting; CV, cardiovascular; IC, intermittent claudication; LDL-C, low-density lipoprotein cholesterol; MI, myocardial infarction; mo., month; PAD, peripheral artery disease; PCI, percutaneous coronary intervention.

Wiviott SD et al. Supplemental materials. *Am Heart J*. 2018;200:83-89.

Safety Assessments

Events of Special Interest

- Genital and urinary tract infections
- Liver events
- Renal events
- Fractures
- Malignancies (especially bladder cancer)
- Hypersensitivity
- Volume depletion events
- Major hypoglycemia events

Adjudicated Events

- Liver events
- Malignancies

Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

EMPA-REG OUTCOME®: BENEFÍCIOS CV INDEPENDENTES DO CONTROLE GLICÊMICO

Empagliflozina associada a terapia gold standard mostrou melhora da sobrevida total em adultos com DM2 e alto risco CV*

14%

↓ 3P-MACE

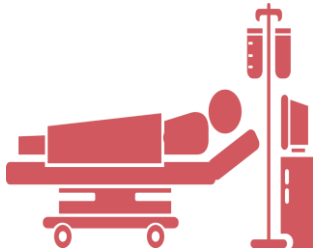
38%

↓ morte CV

32%

↓ morte por todas as causas

35%

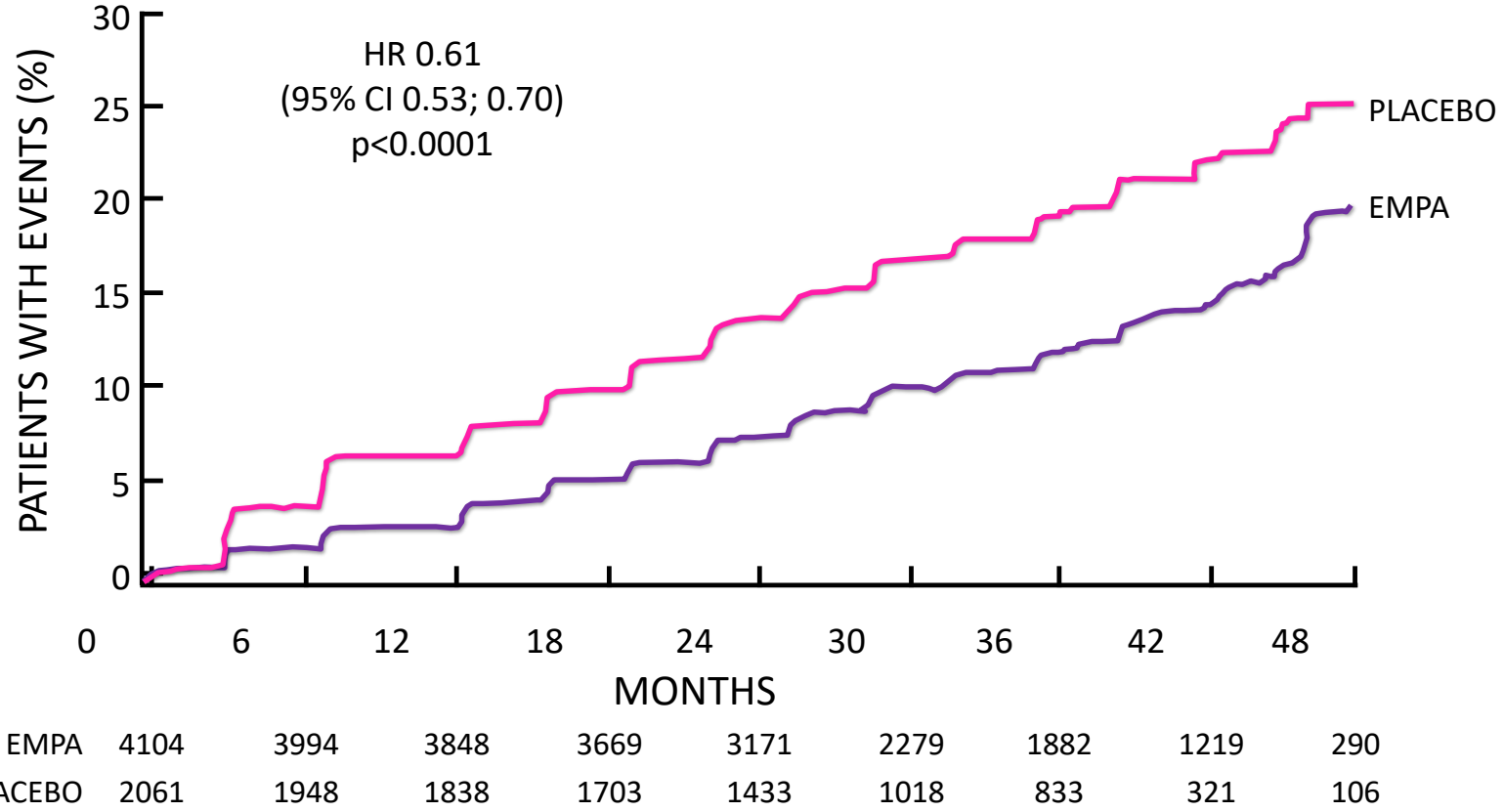


↓ Hospitalização por insuficiência cardíaca

*~80% iECA/BRA, ~40% diuréticos, ~77% estatinas, ~89% com anticoagulantes/antiplaquetários, ~73% metformina, ~42% sulfonilureias, ~48% insulina

3P-MACE= eventos cardiovasculares maiores: CV,

New onset or worsening of nephropathy



Zinman B et al. *N Engl J Med* 2015;373:2117-2128;

ACC.17

66th Annual Scientific Session & Expo

LOWER RATES OF HOSPITALIZATION FOR HEART FAILURE AND ALL-CAUSE DEATH IN NEW USERS OF SGLT-2 INHIBITORS VERSUS OTHER GLUCOSE LOWERING DRUGS – REAL WORLD DATA FROM SIX COUNTRIES AND MORE THAN 300,000 PATIENTS: THE CVD-REAL STUDY

Mikhail Kosiborod, MD on behalf of the CVD-REAL Investigators and Study Team

WASHINGTON, DC

FRI • SAT • SUN

CVDREAL

ACC.17

Baseline Characteristics for Propensity Match Cohort

	SGLT-2 inhibitor* N=154,523	Other GLD* N=154,523
Age, years, mean (SD)	57.0 (9.9)	57.0 (10.1)
Women	68,419 (44.3)	68,770 (44.5)
Established cardiovascular disease†	20,043 (13.0)	20,302 (13.1)
Acute myocardial infarction	3792 (2.5)	3882 (2.5)
Unstable angina	2529 (1.6)	2568 (1.7)
Heart failure	4714 (3.1)	4759 (3.1)
Atrial fibrillation	5632 (3.6)	5698 (3.7)
Stroke	6347 (4.1)	6394 (4.1)
Peripheral arterial disease	5239 (3.4)	5229 (3.4)
Microvascular disease	42,214 (27.3)	42,221 (27.3)
Chronic kidney disease	3920 (2.5)	4170 (2.7)

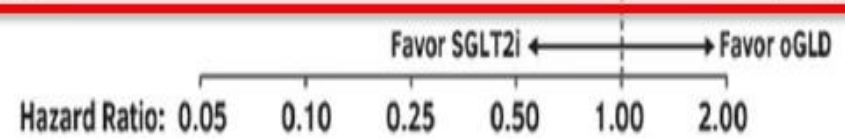
*Data are n (%) unless otherwise stated; †Myocardial infarction, unstable angina, stroke, heart failure, transient ischemic attack, coronary revascularization or occlusive peripheral artery disease

CVDREAL

ACC.17

HHF Primary Analysis

Database	N	# of events	HR (95% CI)
US	233,798	298	0.55 (0.44, 0.69)
Norway	25,050	278	0.62 (0.49, 0.79)
Denmark	18,468	167	0.77 (0.59, 1.01)
Sweden	18,378	191	0.61 (0.45, 0.82)
UK	10,462	16	0.36 (0.12, 1.13)
Germany	2900	11	0.14 (0.03, 0.68)
Total	309,056	961	0.61 (0.51, 0.73)



P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.169

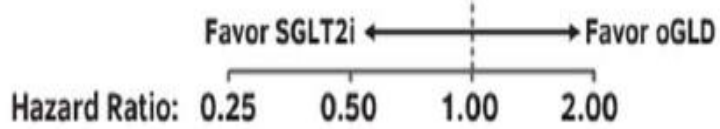
Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

CVDREAL

All-Cause Death Primary Analysis

ACC.17

Database	N	# of events	HR (95% CI)
US	143,264	250	0.38 (0.29, 0.50)
Norway	25,050	364	0.55 (0.44, 0.68)
Denmark	18,468	323	0.46 (0.37, 0.57)
Sweden	18,378	317	0.47 (0.37, 0.60)
UK	10,462	80	0.73 (0.47, 1.15)
Total	215,622	1334	0.49 (0.41, 0.57)

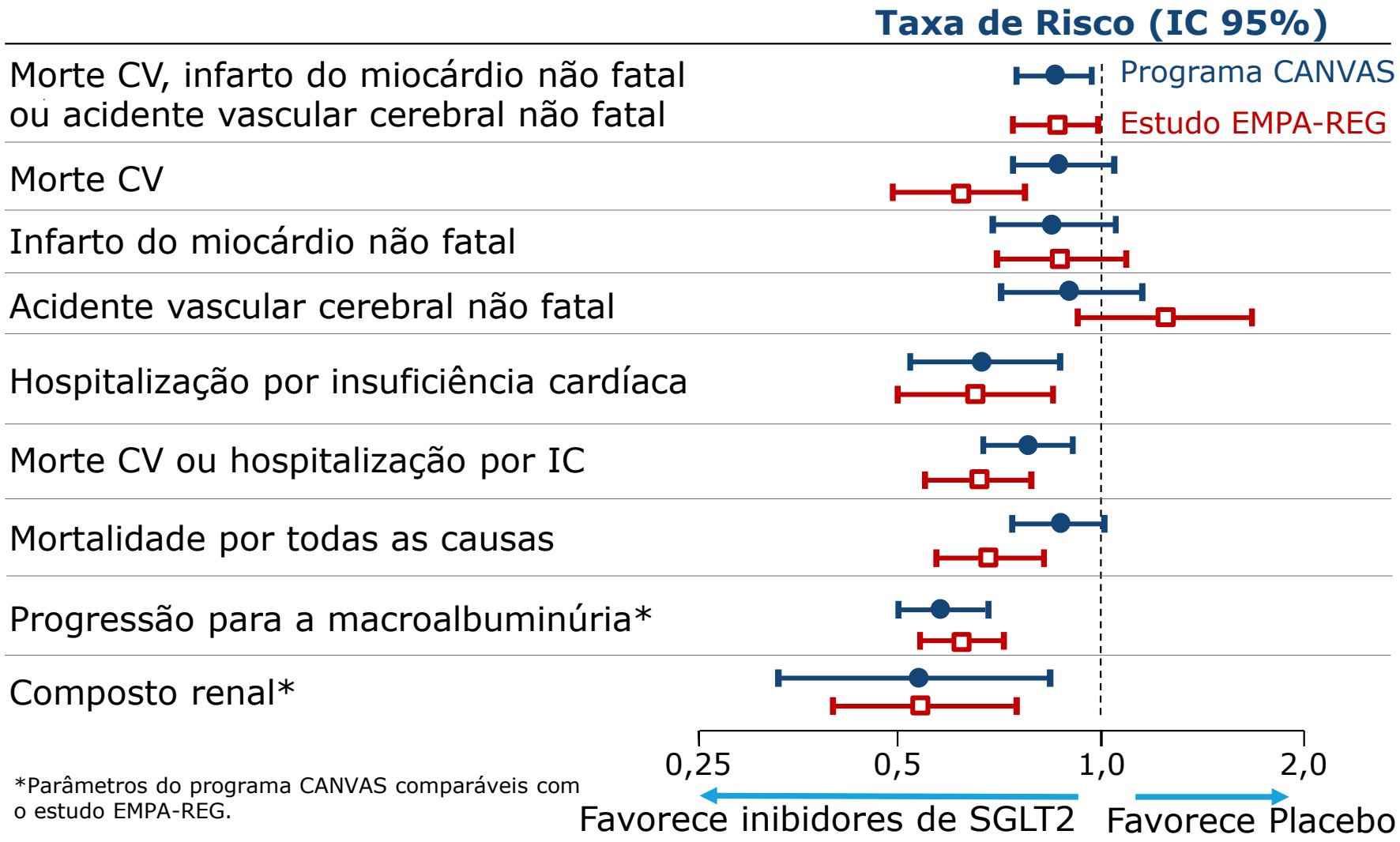


P-value for SGLT2i vs oGLD: <0.001

Heterogeneity p-value: 0.089

Data are on treatment, unadjusted; oGLD=other glucose-lowering drug; HR=hazard ratio

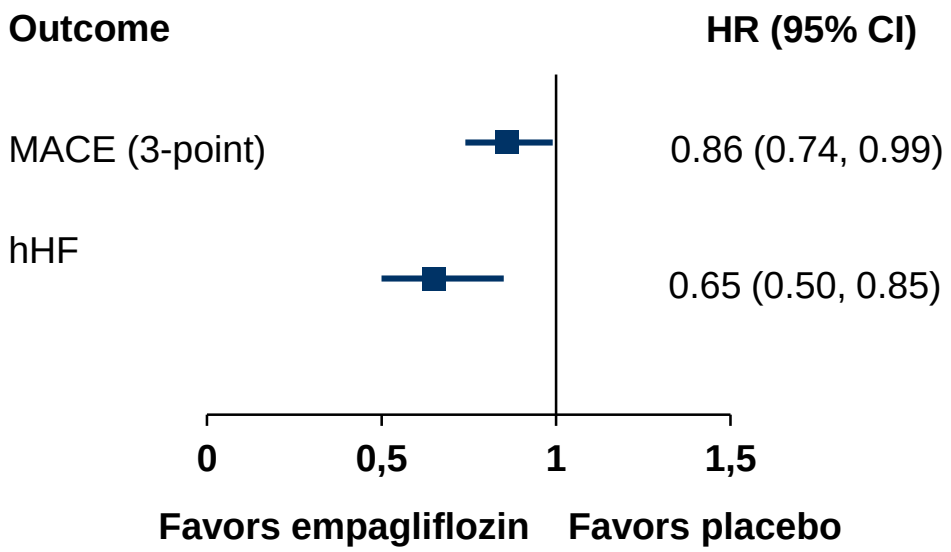
Principais Resultados no Programa CANVAS e no EMPA-REG



*Parâmetros do programa CANVAS comparáveis com o estudo EMPA-REG.

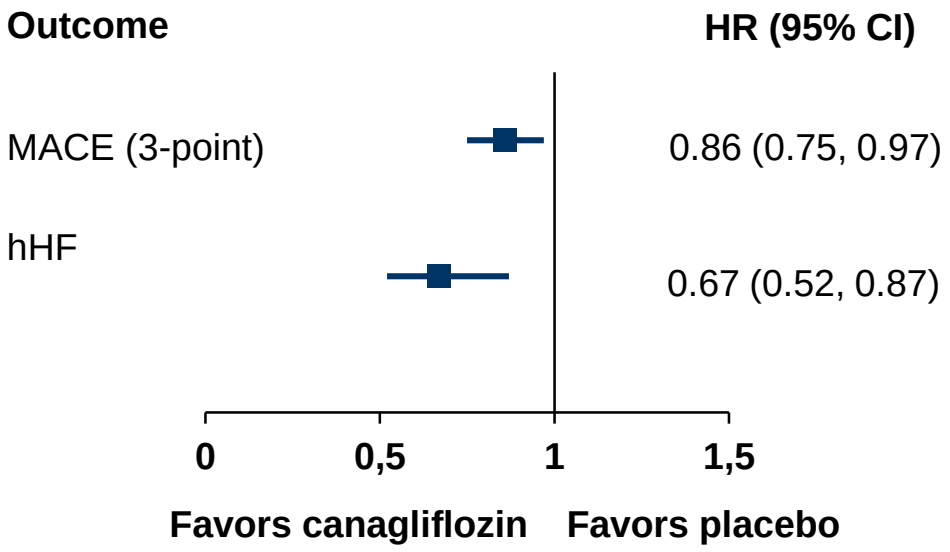
Two SGLT2 studies demonstrate a reduction in both MACE and heart failure endpoints

EMPA-REG OUTCOME demonstrated a significant reduction in CV events in patients receiving empagliflozin



Established CVD: 99%

CANVAS demonstrated a significant reduction in CV events in patients receiving canagliflozin

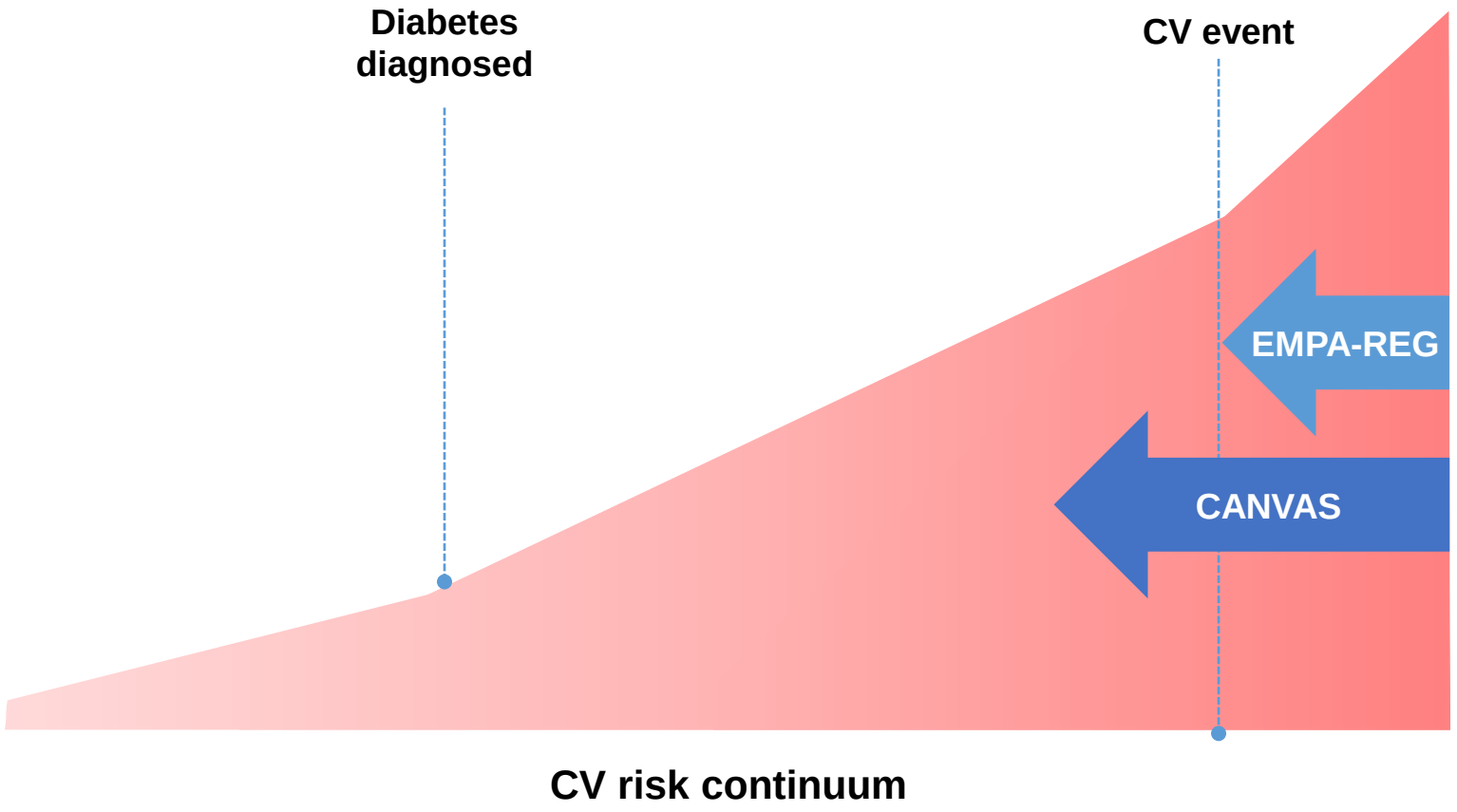


Established CVD: 66%

MACE, major adverse cardiovascular event (CV death, nonfatal MI and nonfatal stroke); MI, myocardial infarction; hHF hospitalization for heart failure.

Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; Neal B, et al. *N Engl J Med* 2017 377:644-57

CV outcomes data for SGLT2 inhibitors are building across the spectrum of CV risk



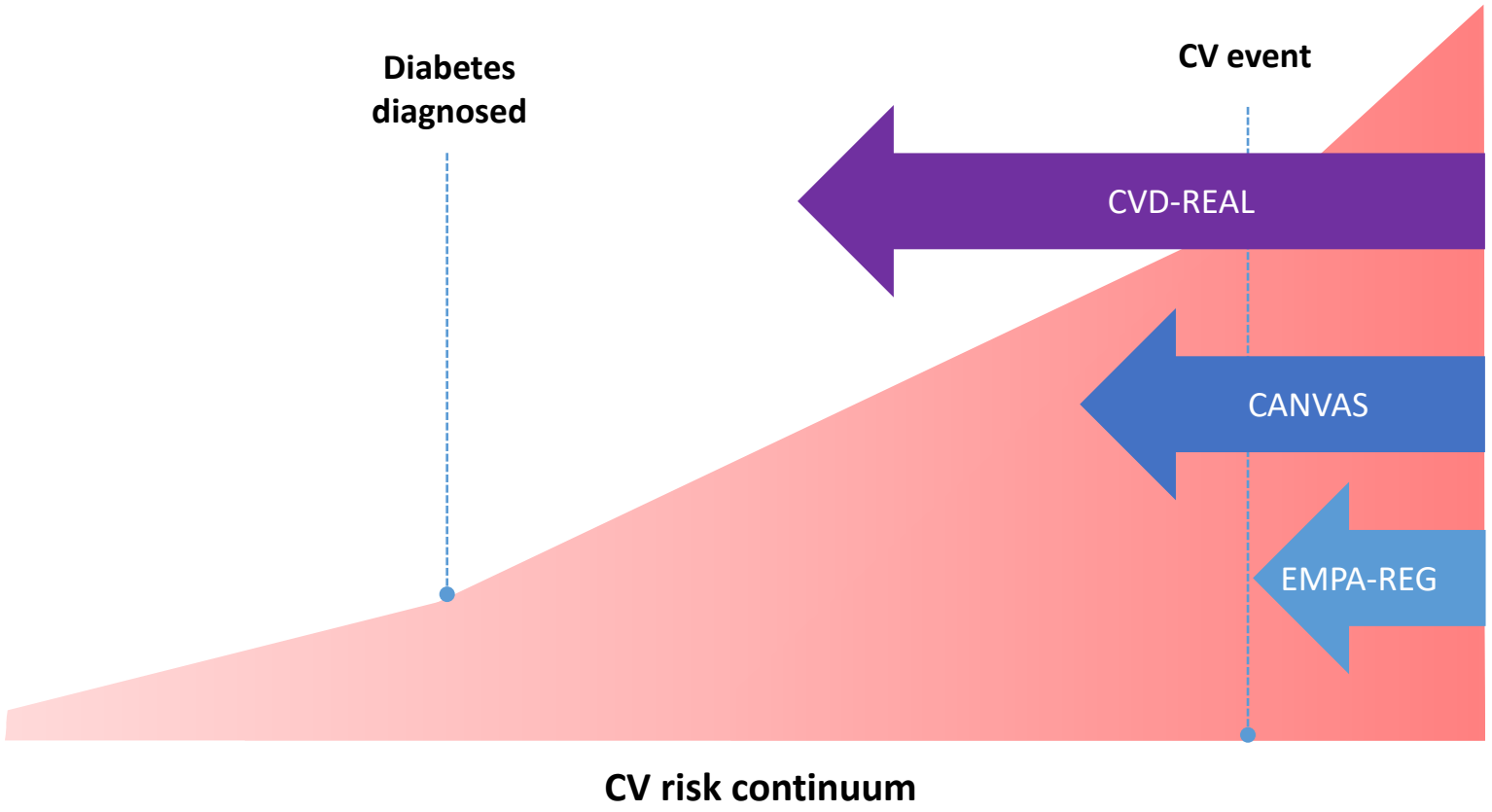
EMPA-REG: Patients with established CV disease (n=7,020)

CANVAS: Majority of patients have established CV disease (n=10,142)

CV, cardiovascular; SGLT2, sodium–glucose co-transporter inhibitor 2

1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 2. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925; 3. Sattar Diabetologia (2013) 56:686–695

CVD-REAL suggests that intervening early in the CV risk continuum can provide benefit



Real-world setting where majority of patients did not have established CV disease (n=309,056)

Majority of patients have established CV disease (n=10,142)

Patients with established CV disease (n=7,020)

CV, cardiovascular; SGLT2, sodium–glucose co-transporter inhibitor 2

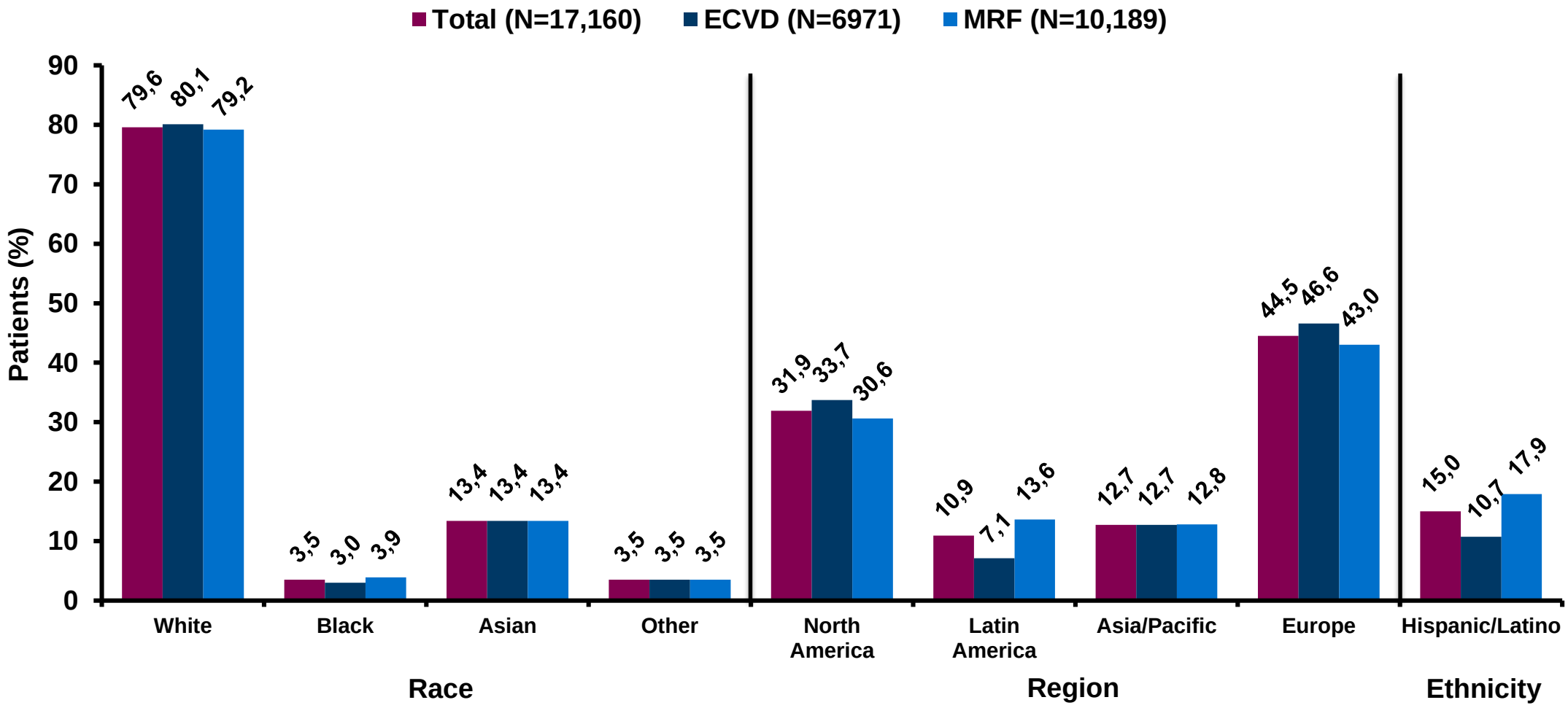
1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128; 2. Kosiborod M., et al. *Circulation* 2017;136:249–259; 3. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925; 4. Sattar Diabetologia (2013) 56:686–695

Baseline Characteristics

	Total (N=17,160)[a]	MRF (N=10,189)	ECVD (N=6971)
Gender, Male, n (%)	10,738 (62.6)	5715 (56.1)	5023 (72.1)
Age, years, mean (SD)	63.8 (6.8)	64.7 (5.6)	62.5 (8.1)
BMI, kg/m^2, mean (SD)	32.1 (6.0)	32.0 (6.0)	32.1 (6.0)
HbA1c, mmol/mol, mean (SD)	67 (9.7)	67 (9.7)	68 (9.7)
Cardiovascular risk factors, n (%)			
LDL-C >130 mg/dL	3174 (18.5)	2064 (20.3)	1110 (15.9)
On therapy for hypertension	15,343 (89.4)	9227 (90.6)	6116 (87.7)
Tobacco use	2488 (14.5)	1457 (14.3)	1031 (14.8)
Cardiac history, n (%)			
Angina pectoris	2802 (16.3)	681 (6.7)	2121 (30.4)
Heart failure	1698 (9.9)	565 (5.5)	1133 (16.3)
Atrial fibrillation/flutter	1110 (6.5)	511 (5.0)	599 (8.6)
Myocardial infarction	3580 (20.9)	NA	3580 (51.4)
Percutaneous coronary intervention	3655 (21.3)	NA	3655 (52.4)
Coronary artery bypass grafting	1678 (9.8)	NA	1678 (24.1)
History of microvascular complications,[b] n (%)			
Retinopathy	2131 (12.4)	1209 (11.9)	922 (13.2)
Retinal laser treatment	587 (3.4)	308 (3.0)	279 (4.0)
Nephropathy	1393 (8.1)	773 (7.6)	620 (8.9)

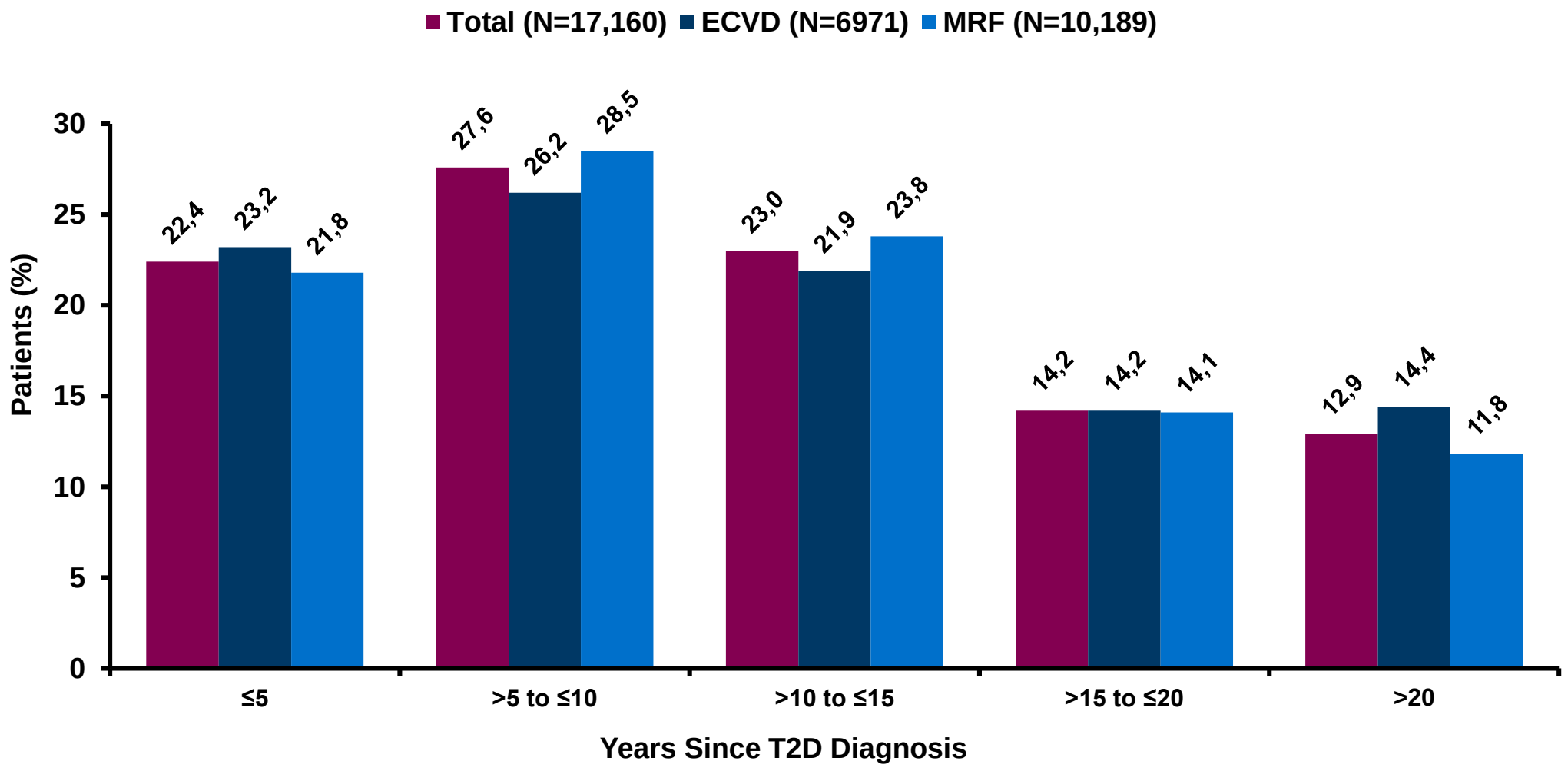
Note: Based on data as of April 2, 2017.
[a]A total of 17,190 patients were randomized; however, 30 patients were excluded from all analyses because of significant good clinical practice violations at a single site for a different dapagliflozin trial; [b]Investigator-reported.
BMI, body mass index; ECVD, established atherosclerotic cardiovascular disease; HbA1c, glycated hemoglobin; LDL-C, low-density lipoprotein cholesterol; MRF, multiple risk factors for cardiovascular disease; NA, not applicable: SD, standard deviation.
Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

Race, Region, and Ethnicity



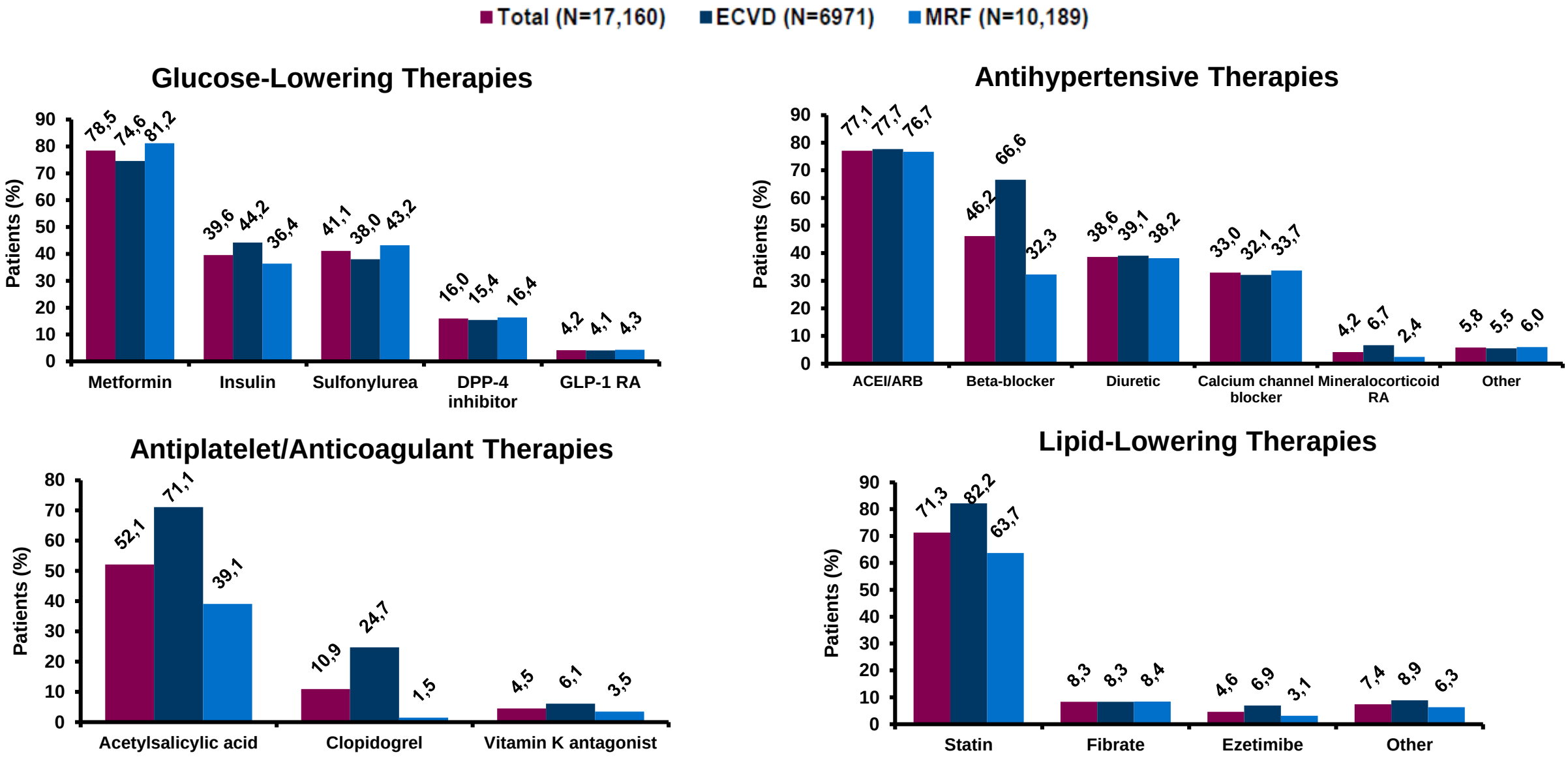
Note: Based on data as of April 2, 2017.
ECVD, established atherosclerotic cardiovascular disease; MRF, multiple risk factors for cardiovascular disease.
Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

Diabetes Duration



Note: Based on data as of April 2, 2017.
ECVD, established atherosclerotic cardiovascular disease; MRF, multiple risk factors for cardiovascular disease; T2D, type 2 diabetes.
Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

Baseline Use of Therapies



Note: Based on data as of April 2, 2017. ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DPP-4, dipeptidyl peptidase-4; ECVD, established atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MRF, multiple risk factors for cardiovascular disease; RA, receptor agonist.

Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

Atherosclerotic CV Disease History in ECVD Group

	Number of Patients With History	Percent of Total (N=17,160)	Percent of ECVD (N=6971)
Cardiovascular disease history			
Myocardial infarction	3580	20.9	51.4
PCI	3655	21.3	52.4
Coronary artery bypass grafting	1678	9.8	24.1
Coronary stenosis ≥50% in ≥2 coronary arteries, by PCI	2119	12.3	30.4
Cerebrovascular and carotid disease history			
Ischemic stroke	1107	6.5	15.9
Carotid stenting	120	0.7	1.7
Carotid endarterectomy	136	0.8	2.0
Peripheral artery disease history			
Obstructive peripheral artery disease	1025	6.0	14.7
Peripheral artery stenting	271	1.6	3.9
Peripheral surgical revascularization	215	1.3	3.1
Nontraumatic lower extremity amputation	105	0.6	1.5
Current symptoms of intermittent claudication	933	5.4	13.4

Note: Based on data as of April 2, 2017.
CV , cardiovascular; ECVD, established atherosclerotic cardiovascular disease; PCI, percutaneous coronary intervention.
Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

Vital Signs and Laboratory Measurements at Screening

	Total (N=17,160)	MRF (N=10,189)	ECVD (N=6971)
Systolic BP, mmHg, mean (SD)	135.0 (15.5)	135.6 (15.1)	134.0 (15.9)
Diastolic BP, mmHg, mean (SD)	78.0 (9.1)	78.4 (8.9)	77.4 (9.35)
Pulse, beats/min, mean (SD)	73.0 (10.6)	74.1 (10.5)	71.5 (10.6)
Total cholesterol, mmol/L, mean (SD)	4.4 (1.2)	4.5 (1.1)	4.2 (1.2)
LDL-C, mmol/L, mean (SD)	2.3 (0.9)	2.4 (0.9)	2.1 (0.9)
HDL-C, mmol/L, mean (SD)	1.2 (0.3)	1.3 (0.3)	1.2 (0.3)
Triglycerides, mmol/L, mean (SD)	2.0 (1.5)	2.0 (1.4)	2.1 (1.7)
eGFR,[a] mL/min/1.73m^2, mean (SD) [median (Q1, Q3)]	86.1 (21.8) [84.0 (71.0, 99.0)]	87.0 (21.4) [85.0 (72.0, 100.0)]	84.9 (22.3) [83.0 (69.0, 98.0)]
eGFR,[a] n (%)			
<60 mL/min/1.73m^2	1565 (9.1)	804 (7.9)	761 (10.9)
≥60 to <90 mL/min/1.73m^2	8739 (50.9)	5155 (50.6)	3584 (51.4)
≥90 mL/min/1.73m^2	6855 (39.9)	4229 (41.5)	2626 (37.7)
Urinary albumin:creatinine ratio, median (Q1, Q3)	13.1 (6.0, 43.6)	12.1 (5.9, 36.3)	15.0 (6.3, 55.1)
Urinary albumin:creatinine ratio, n (%)			
<30 mg/g	11,652 (67.9)	7200 (70.7)	4452 (63.9)
30 to ≤300 mg/g	4023 (23.4)	2239 (22.0)	1784 (25.6)
>300 mg/g	1169 (6.8)	593 (5.8)	576 (8.3)

Note: Based on data as of April 2, 2017.
[a]eGFR calculated with the Modification of Diet in Renal Disease formula. BP, blood pressure; ECVD, established atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; MRF, multiple risk factors for cardiovascular disease; SD, standard deviation.
Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

Similarities and Differences Between SGLT2 Inhibitor CVOTs

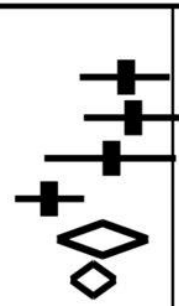
	DECLARE-TIMI 58[1,2]	CANVAS Program[3]	EMPA-REG OUTCOME[4]
Number of patients	17,160	10,142 (CANVAS: 4330; CANVAS-R: 5812)	7020
Key inclusion criteria	• HbA1c ≥6.5% and <12%[a] • CrCl[b] ≥60 mL/min	• HbA1c ≥7% and ≤10.5% • eGFR[c] >30 mL/min/1.73m^2	• HbA1c ≥7% and ≤10% • eGFR[c] ≥30 mL/min/1.73m^2
Study population	Not capped (MRF: 59.4%; ECVD: 40.6%)	Capped[d] (MRF: 34.4%; ECVD: 65.6%)	ECVD: >99%
Interventions (randomization ratio)	DAPA 10 mg or PBO (1:1)	CANVAS: CANA 100 mg, CANA 300 mg, or PBO (1:1:1) CANVAS-R: CANA 100 mg with optional increase to 300 mg or PBO (1:1)	EMPA 10 mg, EMPA 25 mg, or PBO (1:1:1)
Number of events	1390 (Target)	CANVAS: 658; CANVAS-R: 353 (Actual)	772 (Actual)
Median follow-up	~4.5 years	2.4 years (CANVAS: 5.7 years; CANVAS-R: 2.1 years)	3.1 years
Primary endpoint	Primary safety endpoint: MACE (composite of CV death, nonfatal MI, or nonfatal ischemic stroke). Coprimary efficacy endpoints: MACE and composite of CV death or hHF	Pooled MACE (composite of CV death, nonfatal MI, or nonfatal stroke) from CANVAS & CANVAS-R	Pooled MACE (composite of CV death, nonfatal MI,or nonfatal stroke) from 2 doses
Important secondary endpoints	Renal composite endpoint (sustained ≥40% decrease in eGFR to eGFR <60 mL/min/1.73 m^2 and/or ESRD and/or renal or CV death), all-cause mortality	All-cause mortality, CV death, albuminuria progression (>30% increase in albuminuria and change in category), composite of CV mortality or hHF	Composite of MACE or hospitalization for UA, silent MI, hHF, microvascular composite, new onset microalbuminuria, new onset macroalbuminuria

[a]Proportion of patients with HbA1c of 6.5% to <7% capped at ~5%; [b]Based on Cockcroft-Gault equation; [c]Based on Modification of Diet in Renal Disease criteria; [d]Overall 70%:30% target ratio for ECVD:MRF, with maximum of ~40% in MRF group.
CANA, canagliflozin; CrCl, creatinine clearance; CV, cardiovascular; CVOTs, cardiovascular outcome trials; DAPA, dapagliflozin; ECVD, established atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; ESRD, end-stage renal disease; HbA1c, glycated hemoglobin; hHF, hospitalization for heart failure; MACE, major adverse cardiovascular event; MI, myocardial infarction; MRF, multiple risk factors for cardiovascular disease; PBO, placebo, SGLT2, sodium-glucose cotransporter 2; UA, unstable angina.

1. Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110; 2. Wiviott SD et al. *Am Heart J*. 2018;200:83-89; 3. Neal B et al. Article, online protocol, and supplementary appendix. *N Engl J Med* 2017;377:644–657;
4. Zinman B et al. Article, online protocol, and supplementary appendix. *N Engl J Med* 2015;373:2117–2128.

Effects of SGLT2 inhibitors on MACE. CI indicates confidence interval; CANVAS, Canagliflozin Cardiovascular Assessment Study trial; EASEL, the evidence for cardiovascular outcomes with sodium glucose co-transporter 2 inhibitors in the real world s...

Outcome/Trial (year)	Events/Total SGLT2 inhibitor	Events/Total Control	HR (95% CI)	% Weight
MACE				
EMPA-REG OUTCOME (2015)[11]	490/4687	282/2333	0.86 (0.74, 0.99)	25.99
CANVAS (2017)[12]	425/2888	233/1442	0.88 (0.75, 1.03)	24.81
CANVAS-R (2017)[12]	160/2907	193/2905	0.82 (0.66, 1.01)	20.16
EASEL (2017)[24]	483/12629	714/12629	0.67 (0.60, 0.75)	29.04
Random-effects (DerSimonian-Laird)	1558/23111	1422/19309	0.80 (0.69, 0.92)	100.00
Fixed-effects (Mantel-Haenszel)			0.77 (0.72, 0.83)	
(I-squared = 73.3%, p = 0.011)				



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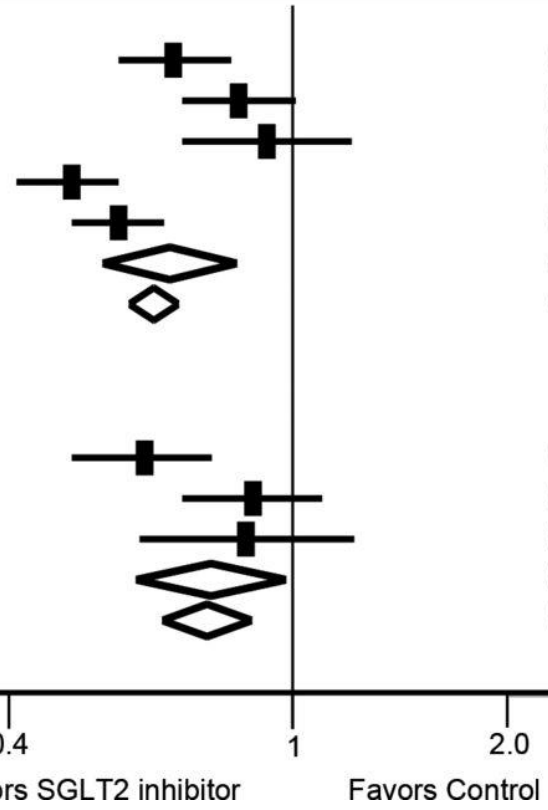
Favors SGLT2 inhibitor Favors Control

Xin-Lin Zhang et al. J Am Heart Assoc 2018;7:e007165

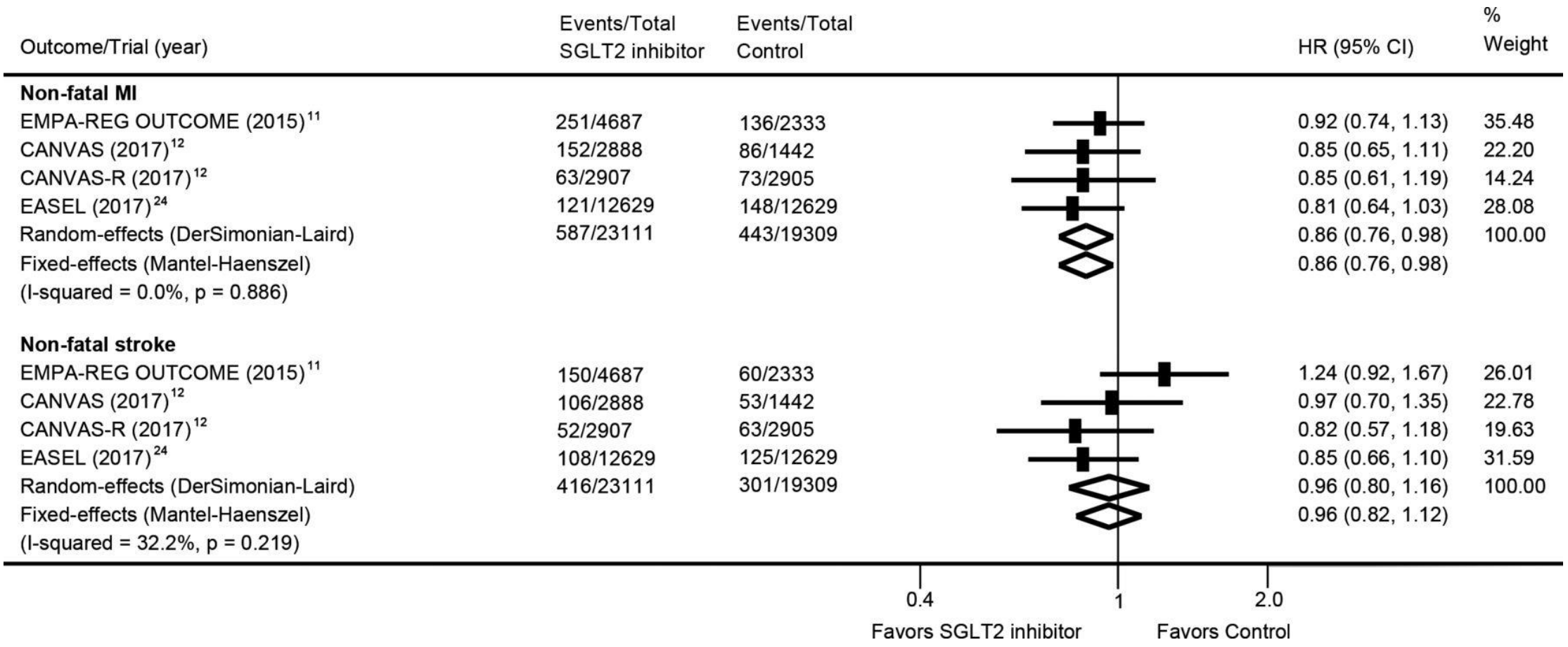
Effects of SGLT2 inhibitors on all-cause death (top) and cardiovascular death (bottom)

Outcome/Trial (year)	Events/Total SGLT2 inhibitor	Events/Total Control	HR (95% CI)	% Weight
All-cause death				
EMPA-REG OUTCOME (2015)[11]	269/4687	194/2333	0.68 (0.57, 0.82)	20.32
CANVAS (2017)[12]	301/2888	175/1442	0.84 (0.70, 1.01)	20.28
CANVAS-R (2017)[12]	99/2907	106/2905	0.92 (0.70, 1.21)	17.22
CVD-REAL (2017)[23]	412/107811	922/107811	0.49 (0.41, 0.57)	20.86
EASEL (2017)[24]	272/12629	475/12629	0.57 (0.49, 0.66)	21.32
Random-effects (DerSimonian-Laird)	1353/130922	1872/127120	0.67 (0.54, 0.84)	100.00
Fixed-effects (Mantel-Haenszel)			0.64 (0.59, 0.69)	
(I-squared = 85.7%, p < 0.001)				
Cardiovascular death				
EMPA-REG OUTCOME (2015)[11]	172/4687	137/2333	0.62 (0.49, 0.77)	37.08
CANVAS (2017)[12]	207/2888	115/1442	0.88 (0.70, 1.10)	37.08
CANVAS-R (2017)[12]	61/2907	70/2905	0.86 (0.61, 1.22)	25.85
Random-effects (DerSimonian-Laird)	440/10482	322/6680	0.77 (0.60, 0.98)	100.00
Fixed-effects (Mantel-Haenszel)			0.76 (0.66, 0.88)	
(I-squared = 61.7%, p = 0.073)				



Xin-Lin Zhang et al. J Am Heart Assoc 2018;7:e007165

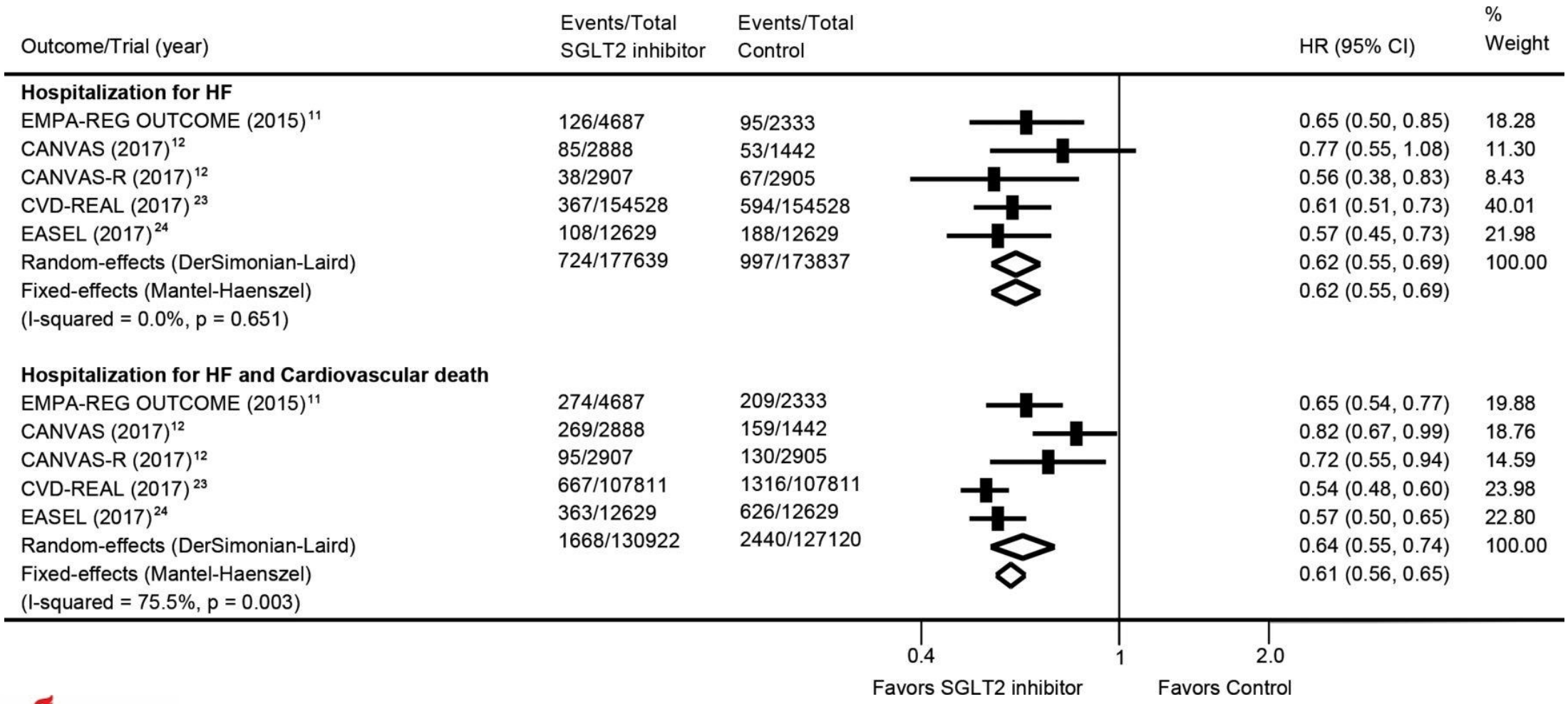
Effects of SGLT2 inhibitors on nonfatal MI (top) and nonfatal stroke (bottom)



American Heart Association | American Stroke Association

Xin-Lin Zhang et al. J Am Heart Assoc 2018;7:e007165

Effects of SGLT2 inhibitors on hospitalization for HF (top) and the composite of hospitalization for HF and cardiovascular death (bottom)

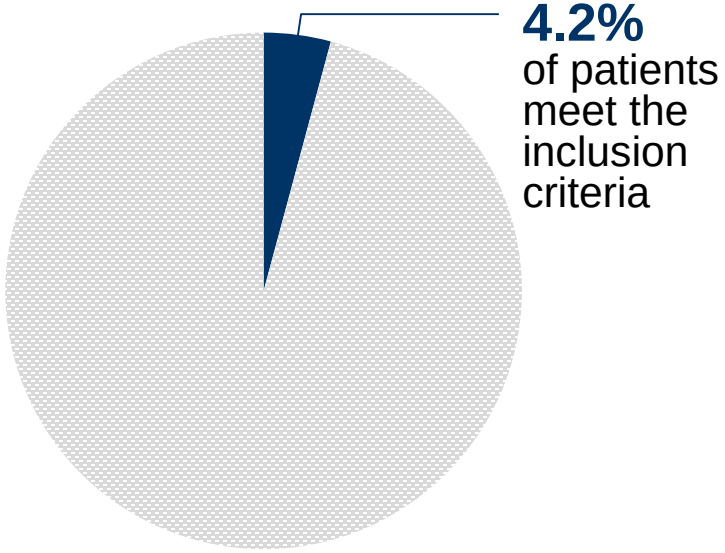


Xin-Lin Zhang et al. J Am Heart Assoc 2018;7:e007165

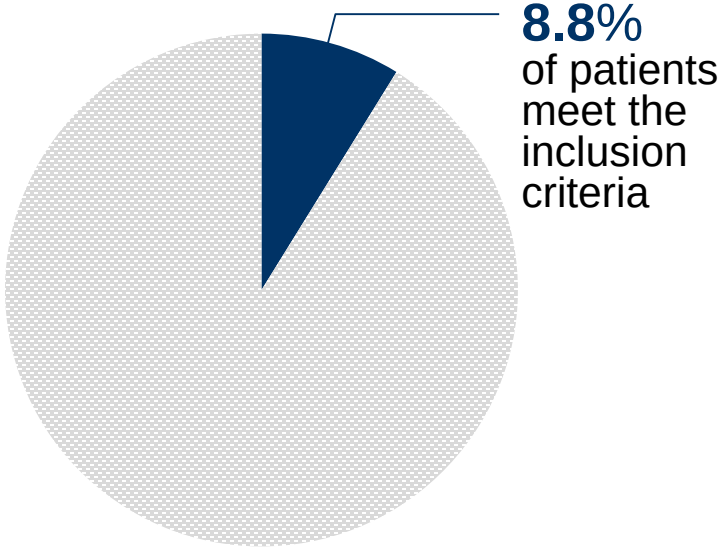

2004

However, while EMPA-REG and CANVAS suggest CV risk can be reduced, these results apply to a small proportion of the population with diabetes

EMPA-REG OUTCOME



CANVAS



The generalizability of the eligibility criteria of these 2 SGLT2 inhibitor CV outcome studies was assessed in the 2009−2010 and 2011−2012 National Health and Nutrition Examination Survey (NHANES) databases

CV, cardiovascular; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes.

Witbrodt. Presented at the 15th Annual World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease 2017.

Baseline Characteristics – Comparison of DECLARE-TIMI 58 and CANVAS Program (Both Include ECVD and MRF Patients)

	DECLARE-TIMI 58[1a] (N=17,160)	CANVAS Program[2] (N=10,142)
Gender, Male, %	62.6	64.2
Age, years, mean (SD)	63.8 (6.8)	63.3 (8.3)
BMI, kg/m^2, mean (SD)	32.1 (6.0)	32.0 (5.9)
HbA1c, %, mean (SD)	8.3 (1.2)	8.2 (0.9)
Race, %		
White	79.6	78.3
Asian	13.4	12.7
Black	3.5	3.3
Other	3.5	5.7
ECVD, n (%)	6971 (40.6)	6656 (65.6)
MRF, n (%)	10,189 (59.4)	3486 (34.4)
eGFR, mL/min/1.73 m^2, mean (SD)	86.1 (21.8)	76.5 (20.5)
Urinary ACR, %		
Normoalbuminuria (<30 mg/g)	67.9	69.8
Microalbuminuria (30 to ≤300 mg/g)	23.4	22.6
Macroalbuminuria (>300 mg/g)	6.8	7.6

[a]Based on data as of April 2, 2017.

ACR, albumin:creatinine ratio; BMI, body mass index; ECVD, established atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; HbA1c, glycated hemoglobin; MRF, multiple risk factors for cardiovascular disease;; SD, standard deviation.

1. Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110; 2. Neal B et al. Article and online protocol. *N Engl J Med* 2017;377:644–657.

Baseline Drug Use – Comparison of DECLARE-TIMI 58 and CANVAS Program (Both Include ECVD and MRF Patients)

	DECLARE-TIMI 58[1a] (N=17,160)	CANVAS Program[2] (N=10,142)
Lipid lowering therapy, %		
Statin	71.3	74.9
Anti-hypertensive therapy, %		
Beta blockers	46.2	53.5
ACEI/ARB	77.1	80.0[b]
Glucose lowering therapy, %		
Metformin	78.5	77.2
Sulfonylurea	41.1	43.0
Insulin	39.6	50.2
GLP-1 RA	4.2	4.0
DPP-4 inhibitors	16.0	12.4

[a]Based on data as of April 2, 2017; [b]Reported as renin angiotensin aldosterone system (RAAS) inhibitor

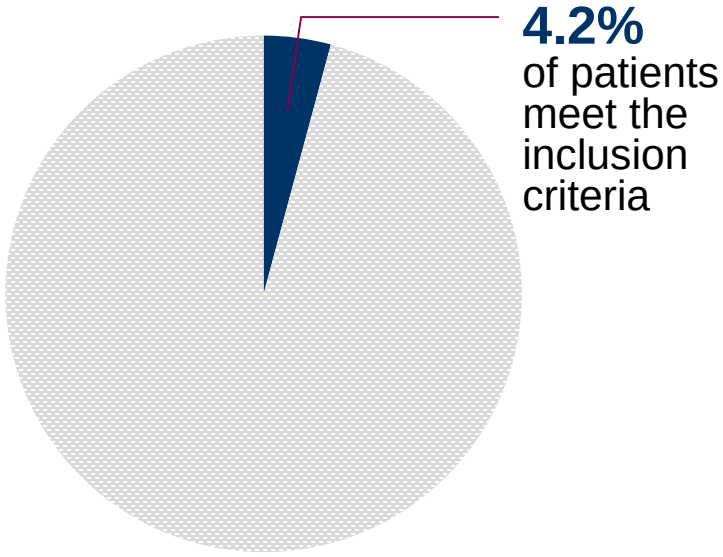
ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; DPP-4, dipeptidyl peptidase-4; ECVD, established atherosclerotic cardiovascular disease; GLP-1 RA, glucagon-like peptide-1 receptor agonist; MRF, multiple risk factors for cardiovascular disease.

1. Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110; 2. Neal B et al. Supplementary appendix. *N Engl J Med* 2017;377:644–657.

DECLARE is the most inclusive SGLT2i CV outcomes trial to date

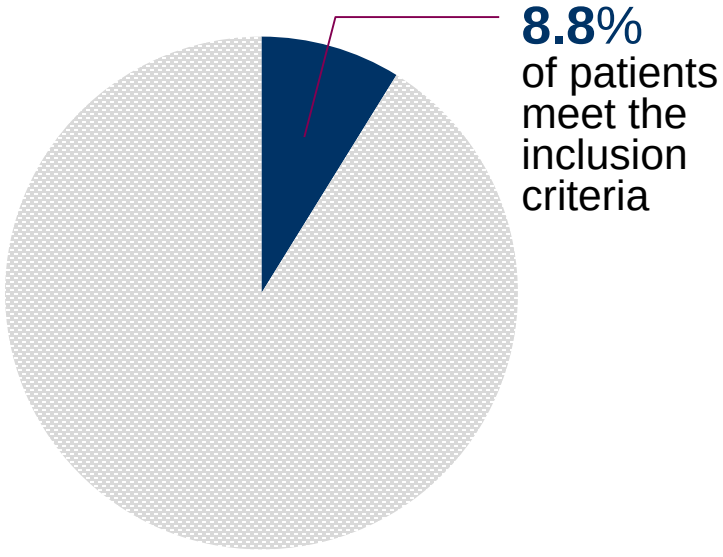
- The generalizability of the eligibility criteria of the 3 SGLT2 inhibitor CV outcome studies was assessed in the 2009−2010 and 2011−2012 National Health and Nutrition Examination Survey (NHANES) databases
- As the most inclusive study, DECLARE is poised to provide guidance on how to reduce risk in a population of patients with type 2 diabetes and a broader CV risk profile

EMPA-REG OUTCOME



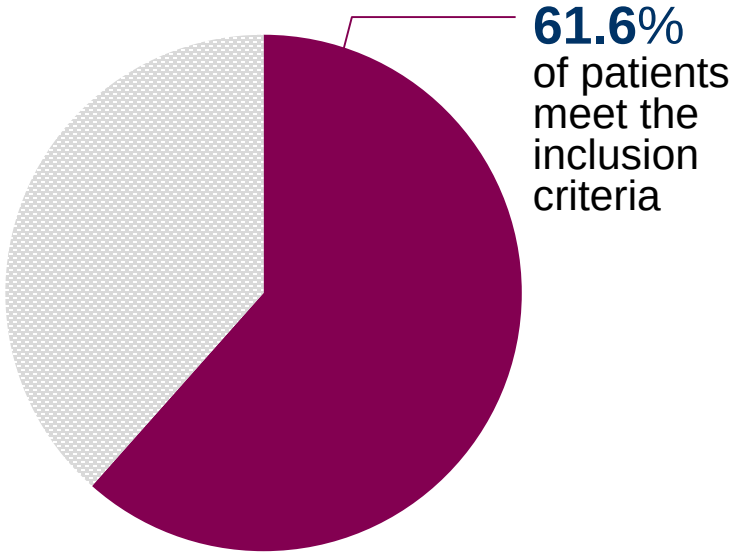
4.2% of patients meet the inclusion criteria

CANVAS



8.8% of patients meet the inclusion criteria

DECLARE



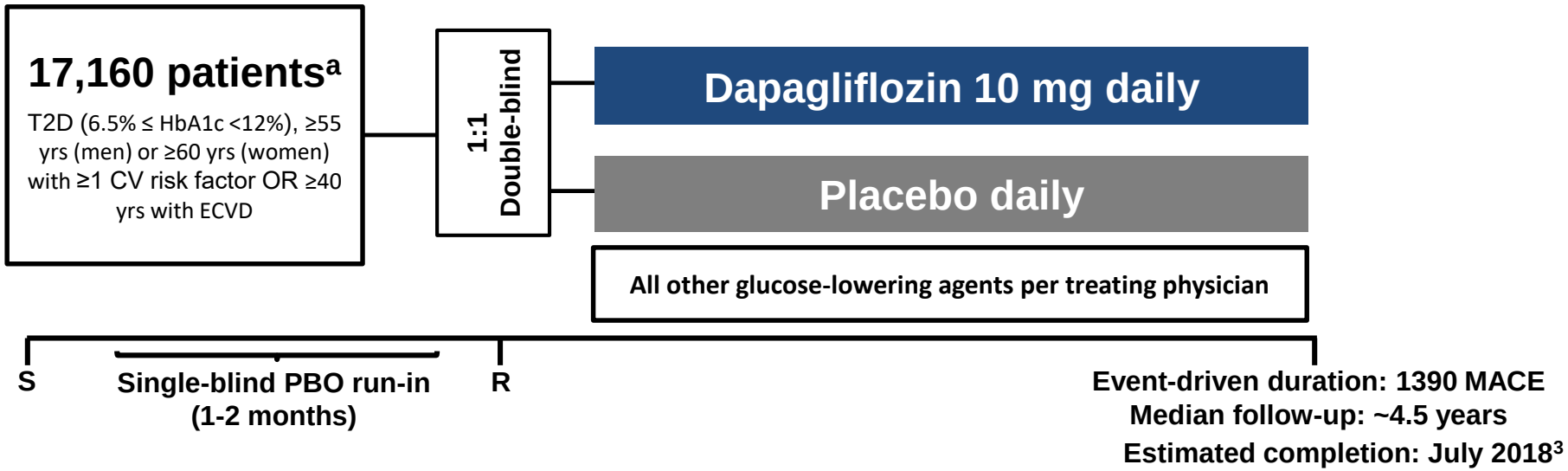
61.6% of patients meet the inclusion criteria

CV, cardiovascular; SGLT2, sodium glucose co-transporter 2; T2D, type 2 diabetes.

Witbrodt. Presented at the 15th Annual World Congress on Insulin Resistance, Diabetes & Cardiovascular Disease 2017.

A Multinational, Randomized, Double-blind, Placebo-controlled, Phase IIIb Cardiovascular Outcomes Trial

Study Design[1,2]



Primary safety endpoint

- Composite of CV death, nonfatal MI, or nonfatal ischemic stroke (MACE)

Primary efficacy endpoints

- MACE
- **Composite of CV death or hospitalization for heart failure**

Secondary endpoints

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

Blinded adjudication

- CV events
- Malignancies
- Liver events
- DKA events

Data monitoring committee

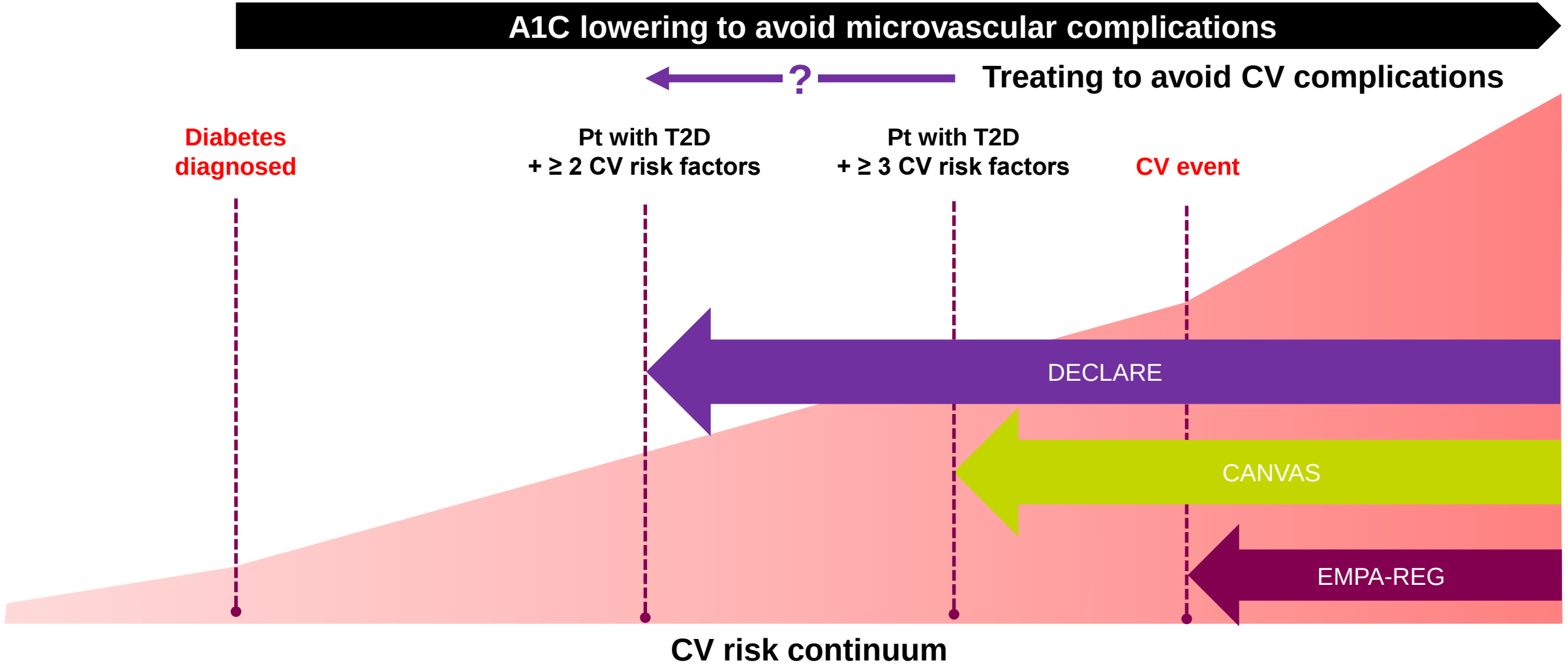
- Periodically review safety
- Two preplanned efficacy reviews
- Assess bladder cancer every 8 events

[a]A total of 17,190 patients were randomized; however, 30 patients were excluded from all analyses because of significant good clinical practice violations at a single site for a different dapagliflozin trial.

CV, cardiovascular; DKA, diabetic ketoacidosis; ECVD, established atherosclerotic cardiovascular disease; eGFR, estimated glomerular filtration rate; ESRD = end-stage renal disease; HbA1c, glycated hemoglobin; MACE, major adverse cardiovascular events; MI, myocardial infarction; PBO, placebo; R, randomization; S, screening; T2D, type 2 diabetes; yrs, years.

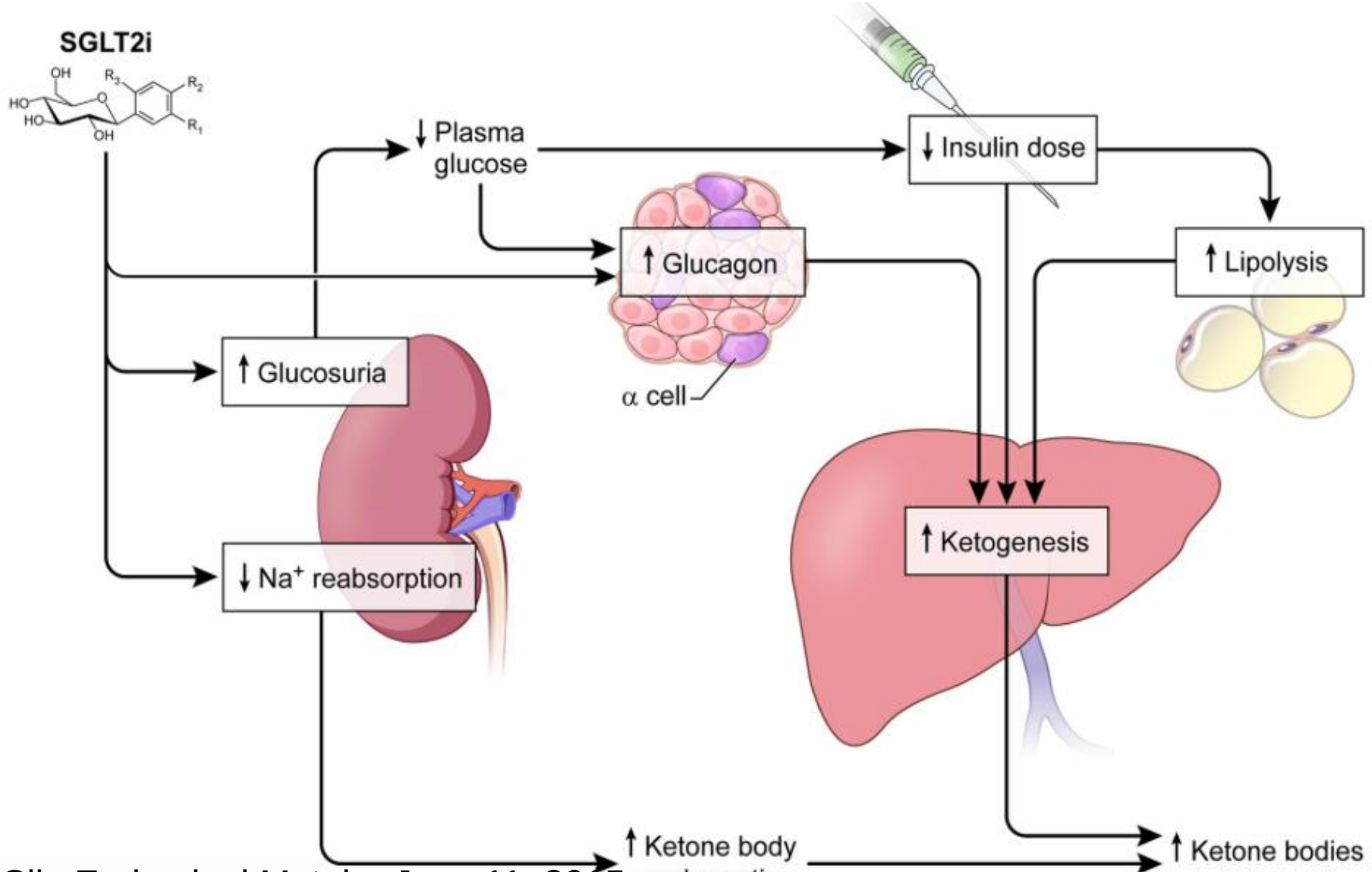
1. Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110; 2. Wiviott SD et al. *Am Heart J*. 2018;200:83-89; 3. Study NCT01730534. ClinicalTrials.gov website. Accessed January 18, 2018.

DECLARE can also provide guidance on when CV-protective therapy should be initiated



1. Zinman B, et al. *N Engl J Med* 2015;373:2117–2128;; 2. Neal B, et al. *N Engl J Med* 2017; DOI: 10.1056/NEJMoa1611925;3. Sattar Diabetologia (2013) 56:686–695 4. Raz I. et al. Presented at the 77th Scientific Session of the American Diabetes Association 9th–13th June 2017; San Diego, CA, USA; 1245–P

Potential mechanisms whereby adjunctive therapy with SGLT2 inhibitors may promote ketosis and increase the risk of ketoacidosis in type 1 diabetic (T1D) patients.



J Clin Endocrinol Metab June 11, 2015

Safety Assessments

Events of Special Interest

- Genital and urinary tract infections
- Liver events
- Renal events
- Fractures
- Malignancies (especially bladder cancer)
- Hypersensitivity
- Volume depletion events
- Major hypoglycemia events

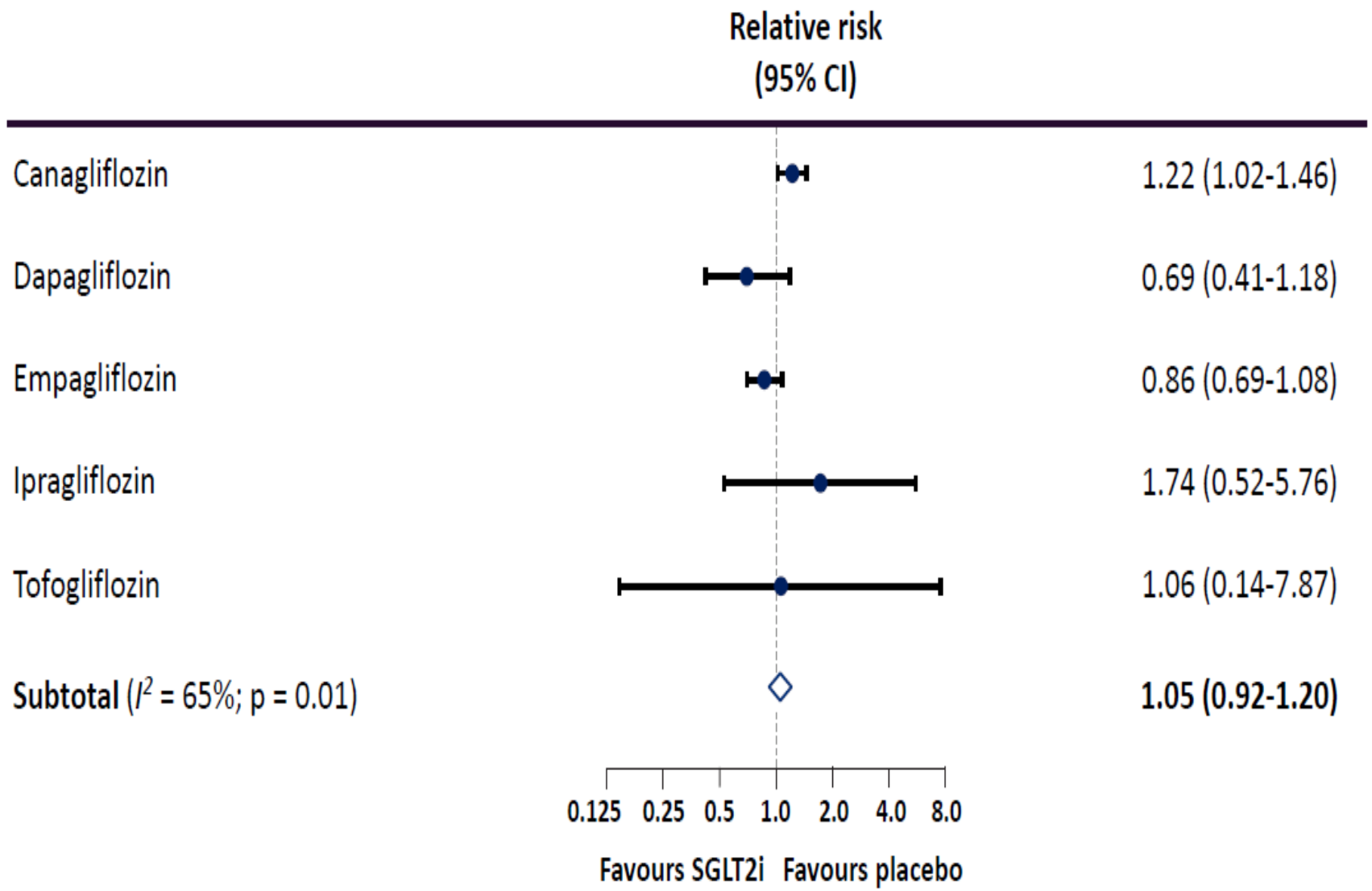
Adjudicated Events

- Liver events
- Malignancies
- **Diabetic ketoacidosis**

diabetic ketoacidosis assessed at each study visit

Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

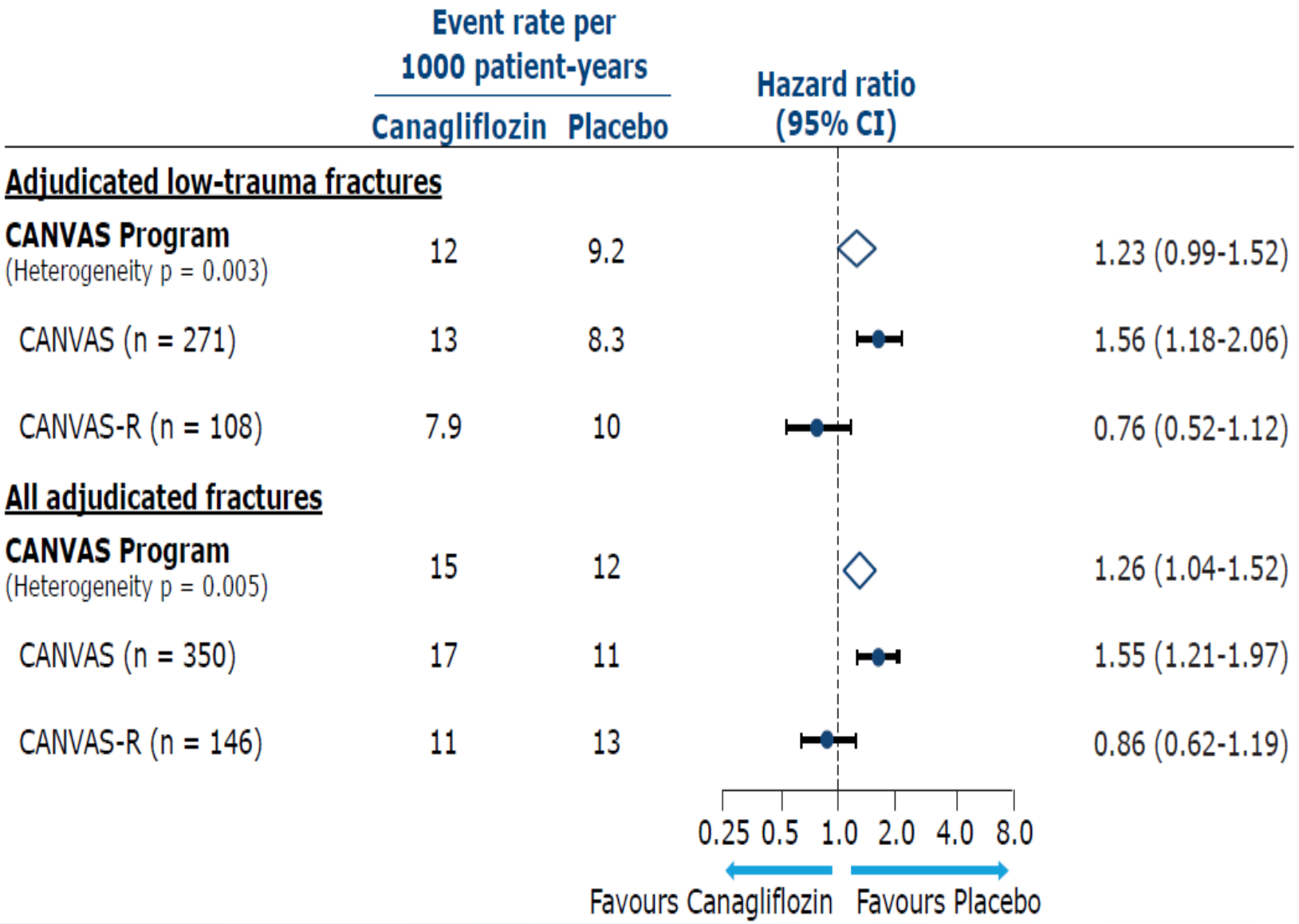
Fracture



Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes; 15 September 2017; Lisbon, Portugal.

Rådholm K, et al. 2017, submitted for publication

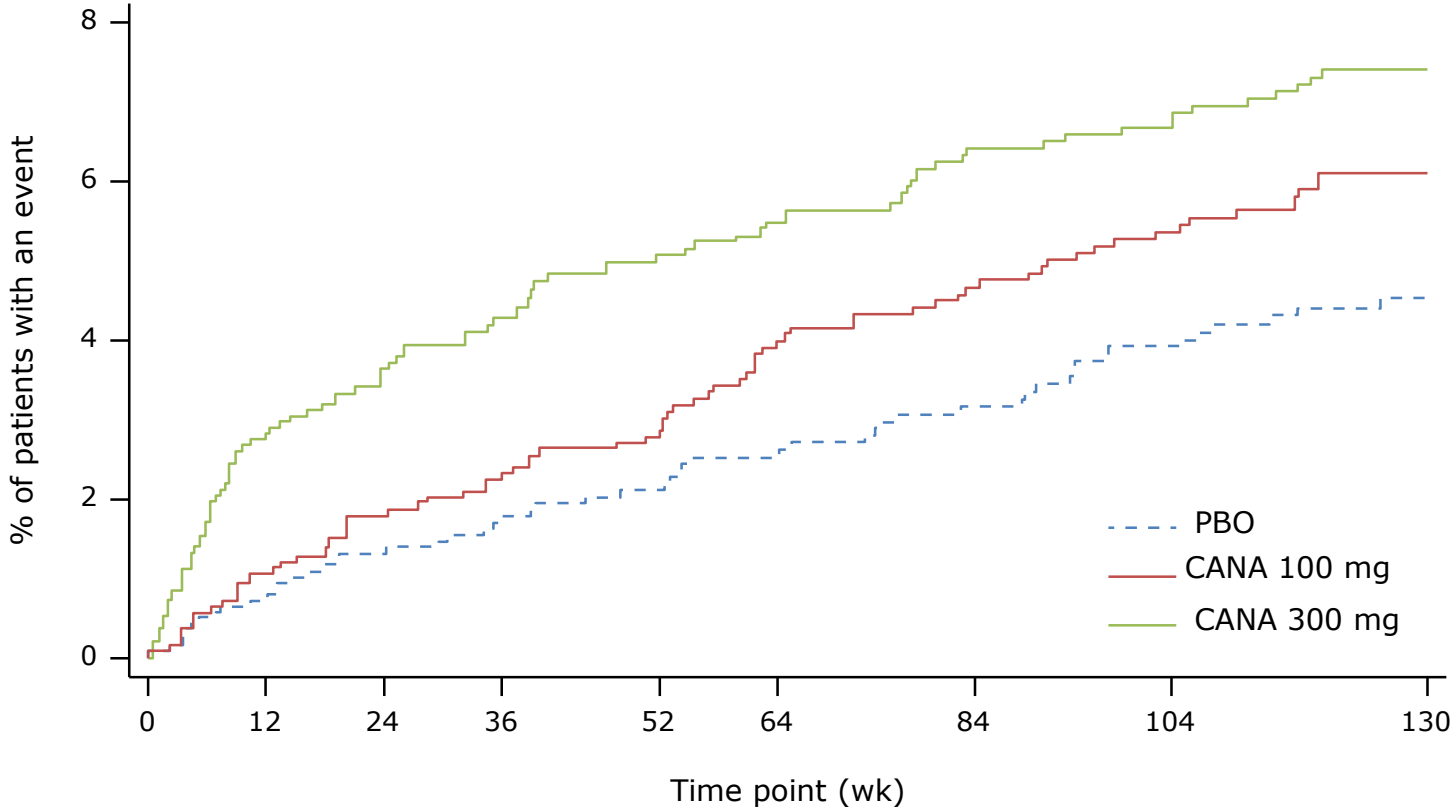
Fractures



Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes; 15 September 2017; Lisbon, Portugal.

CANVAS Program

Kaplan-Meier Plot of Time to First Volume-Depletion AE (CANVAS)

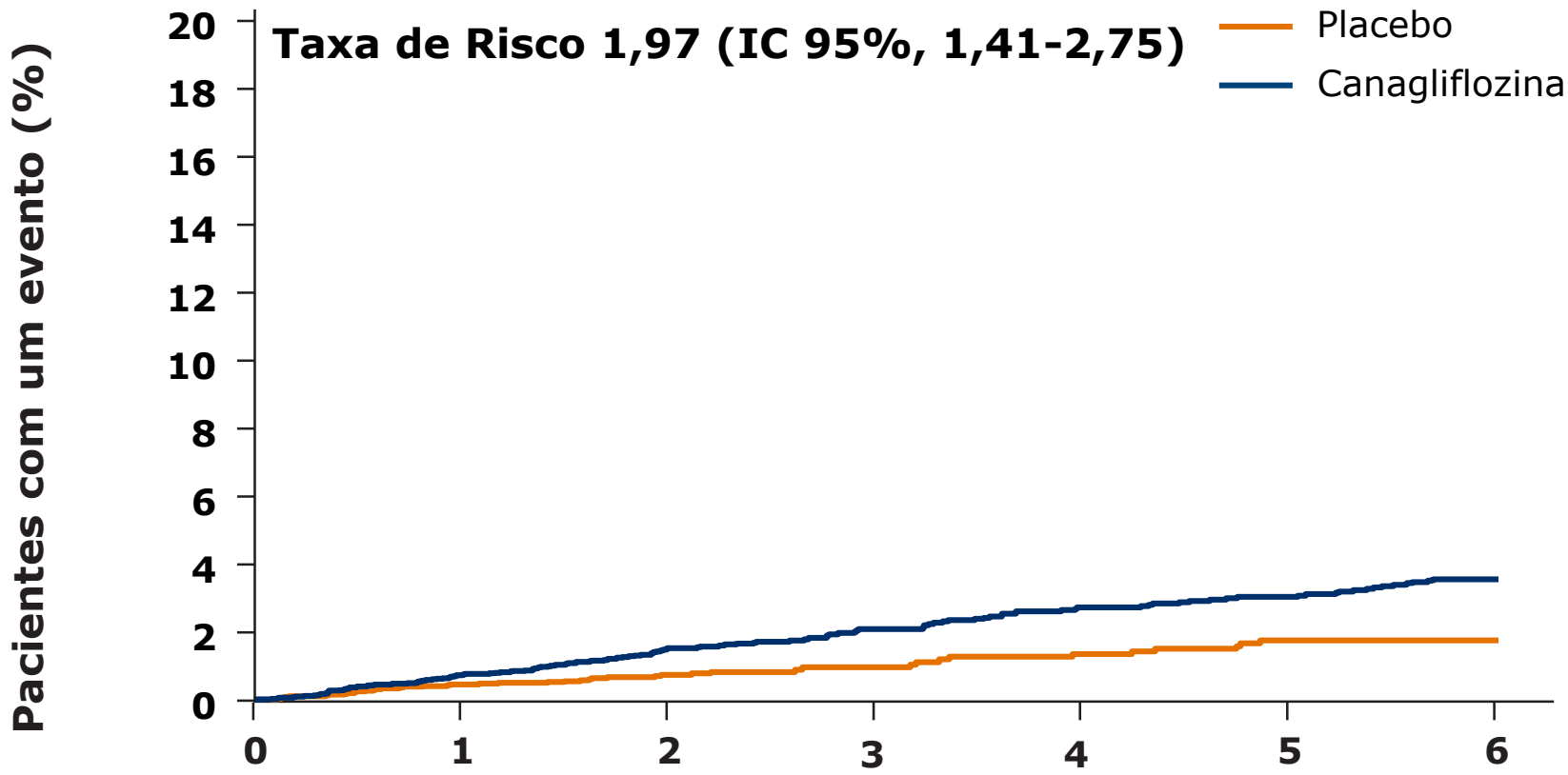


Patients, n									
PBO	1441	1369	1285	1221	1161	1104	1045	991	622
CANA 100 mg	1445	1389	1332	1278	1219	1171	1104	1067	661
CANA 300 mg	1441	1332	1262	1206	1158	1127	1084	1051	653

AE, adverse event; CANA, canagliflozin; CANVAS, CANagliflozin cardioVascular Assessment Study; PBO, placebo.

Watts NB, et al. *J Clin Endocrinol Metab.* 2015; In press.

Amputações de Membros inferiores



Nº em risco							
Placebo	4344	4217	3037	1289	1247	1194	844
Canagliflozina	5790	5634	4420	2618	2536	2460	1765

Neal et al. N Engl J Med. 2017 Aug 17;377(7):644-657

Amputation Risk Factors - Univariate Analysis

Risk Factor at Baseline	Hazard Ratio	95% CI
Amputation history	21.42*	(15.49-29.61)
Peripheral vascular disease (excludes amputation history)	2.52*	(1.86-3.42)
Neuropathy	3.38*	(2.52-4.52)
CV disease	2.87*	(1.97-4.18)
Nephropathy	2.20*	(1.61-3.00)
Baseline insulin use	2.37*	(1.73-3.24)
Gender (male vs female)	2.62*	(1.79-3.83)
Baseline HbA1c (>8% vs ≤8%)	1.95*	(1.44-2.64)
Retinopathy	2.28*	(1.70-3.07)
Use of loop diuretic	2.12*	(1.50-3.00)
HbA1c at baseline (%)	1.37*	(1.19-1.58)
Diabetic duration (y)	1.04*	(1.03-1.06)
Haemoglobin at baseline (g/L)	1.00	(0.99-1.01)
Age at baseline (y)	0.99	(0.97-1.00)
Baseline eGFR (<45 vs ≥45 mL/min/1.73 m^2)	1.82*	(1.07-3.09)
Use of any diuretic	1.26	(0.95-1.68)
Diabetes duration (≥10 vs <10 y)	1.55*	(1.16-2.19)
Baseline systolic BP (>140 vs ≤140 mmHg)	1.09	(0.82-1.46)
Baseline eGFR (<60 vs ≥60 mL/min/1.73 m^2)	1.66*	(1.20-2.29)
Use of non-loop diuretic	0.81	(0.59-1.11)
Smoking	1.11	(0.77-1.59)
Baseline systolic BP (>120 vs ≤120 mmHg)	1.02	(0.68-1.52)
Baseline systolic BP (mmHg)	1.01*	(1.00-1.01)
Baseline eGFR (mL/min/1.73 m^2)	0.99	(0.98-1.00)

*HR excludes 1.

Presented at the 53rd Annual Meeting of the European Association for the Study of Diabetes; 15 September 2017; Lisbon, Portugal.

Unpublished data

CANVAS Program

Safety Assessments

Events of Special Interest

- Genital and urinary tract infections
- Liver events
- Renal events
- **Fractures**
- Malignancies (especially bladder cancer)
- Hypersensitivity
- **Volume depletion events**
- Major hypoglycemia events

Adjudicated Events

- Liver events
- Malignancies
- Diabetic ketoacidosis

Amputation and diabetic ketoacidosis assessed at each study visit

Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.

Conclusions: Design and Baseline Characteristics

- The DECLARE-TIMI 58 trial population is broad and includes patients with MRF or ECVD
  - The diversity and size of the trial population, which includes a large number of patients with MRF, will strengthen the applicability of the trial results
- The extended follow-up of the DECLARE-TIMI 58 trial, compared to other CVOTs with SGLT2 inhibitors, will help to determine the impact of prolonged treatment with dapagliflozin on CV outcomes in a T2D population with broad CV risk
  - The trial examines 2 coprimary composite CV efficacy endpoints encompassing a broad range of commonly occurring CV complications in patients with T2D
  - The trial also evaluates the safety of dapagliflozin with respect to bladder cancer, amputation, and diabetic ketoacidosis
- The DECLARE-TIMI 58 trial is expected to provide conclusive data on the effect of dapagliflozin versus placebo, each in addition to standard of care, on CV outcomes in a T2D population with broad CV risk

CV, cardiovascular; CVOT, cardiovascular outcome trial; ECVD, established atherosclerotic cardiovascular disease; MRF, multiple risk factors for cardiovascular disease; SGLT2, sodium-glucose cotransporter 2; T2D, type 2 diabetes.

Raz I et al. *Diabetes Obes Metab*. 2018;20:1102-1110.