Nordisk samarbeid om helseregisterforskning – muligheter og utfordringer

Kåre I. Birkeland
Professor, overlege

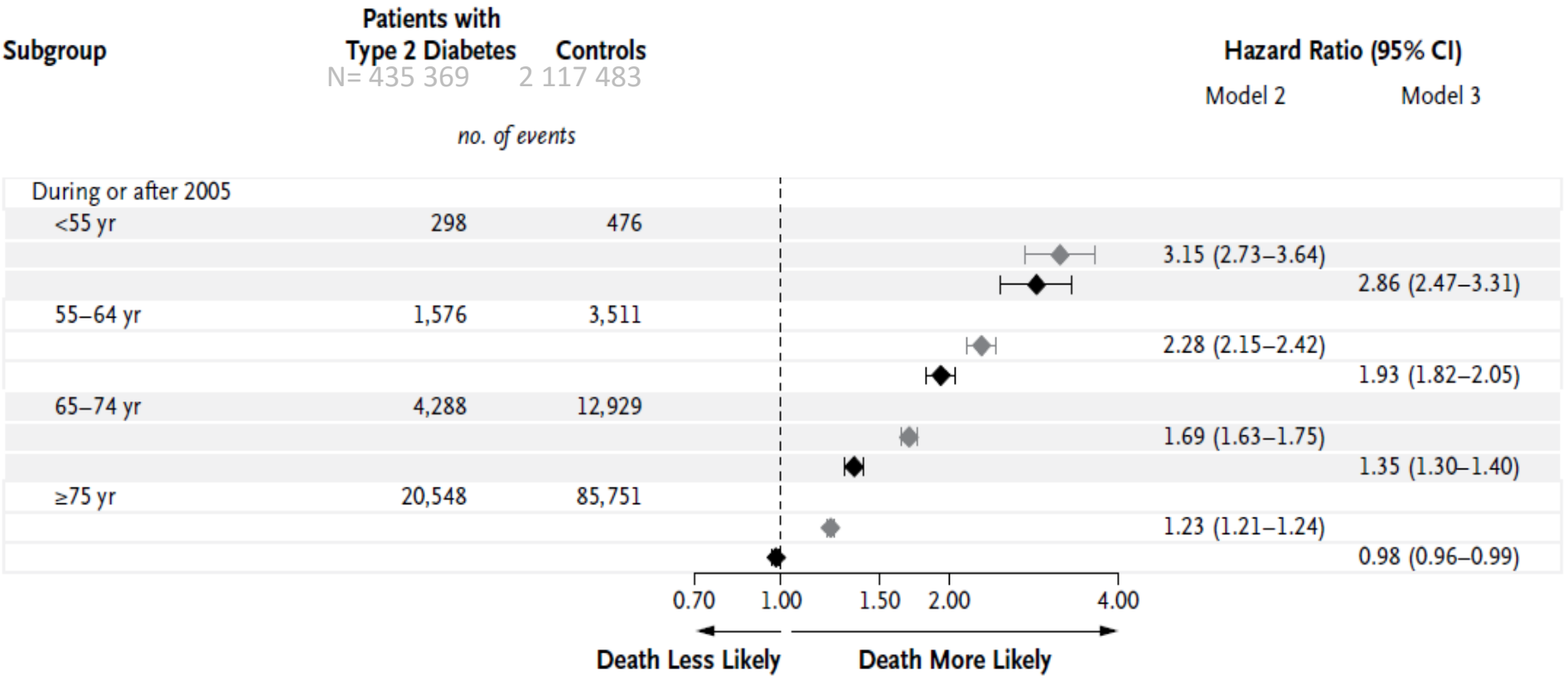
Nordisk samarbeid om helseregisterforskning – muligheter og utfordringer

- **Gode registre – hva kan de brukes til?**
  - **Eksempel fra diabetesforskning**
  - **CVD-REAL studiene**
- **Fremtidig bruk av registre i Norden?**

Registerforskning i Norge – fordeler og muligheter

- Personnummer og god dekningsgrad
- Høy kvalitet
  - Reseptregisteret
  - Dødsårsaksregisteret
  - Norsk pasientregister
- Ikke kostbart

Sverige: Et godt, nasjonalt diabetesregister med >400 000 pas. registrert
Dødelighet av hjerte-/karsykdommer ved type 2 diabetes



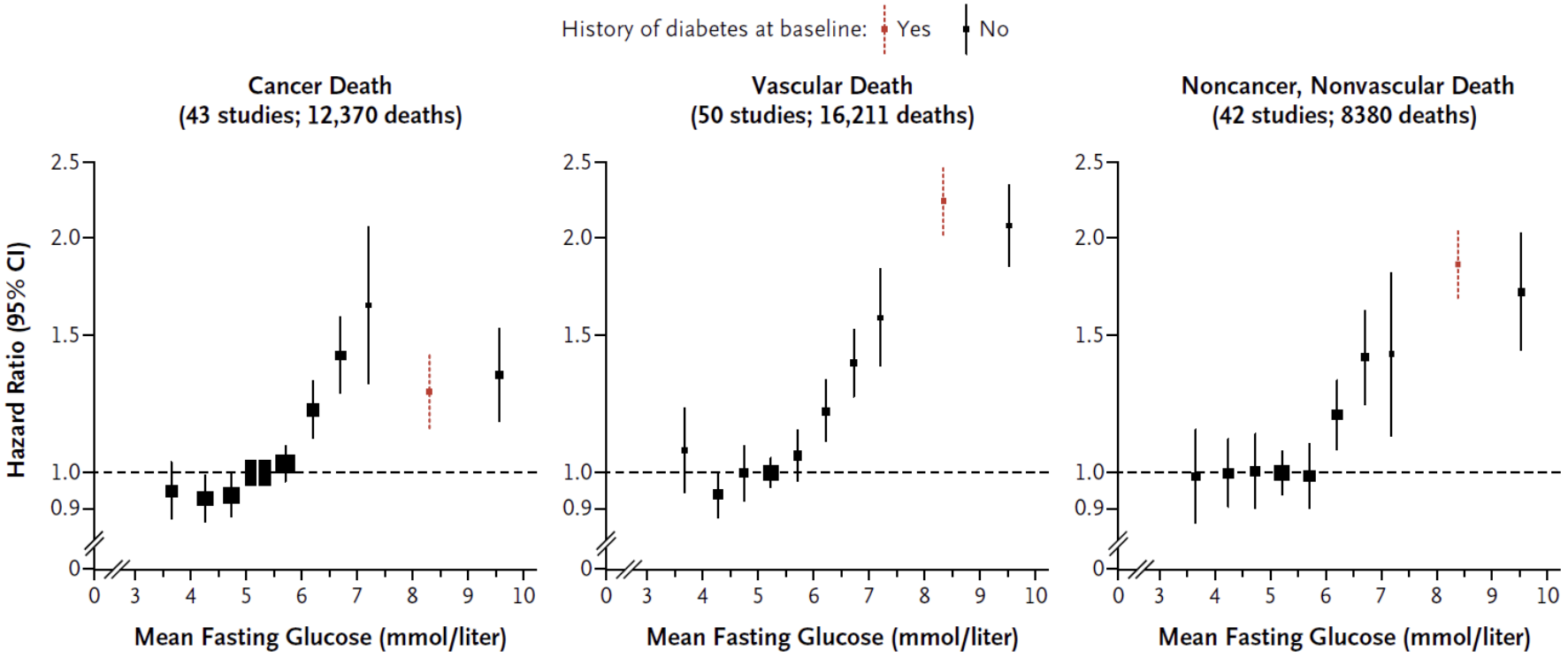
Norge: Et svært mangelfullt nasjonalt diabetesregister med ~ 40 000 pasienter registrert

The NEW ENGLAND JOURNAL of MEDICINE

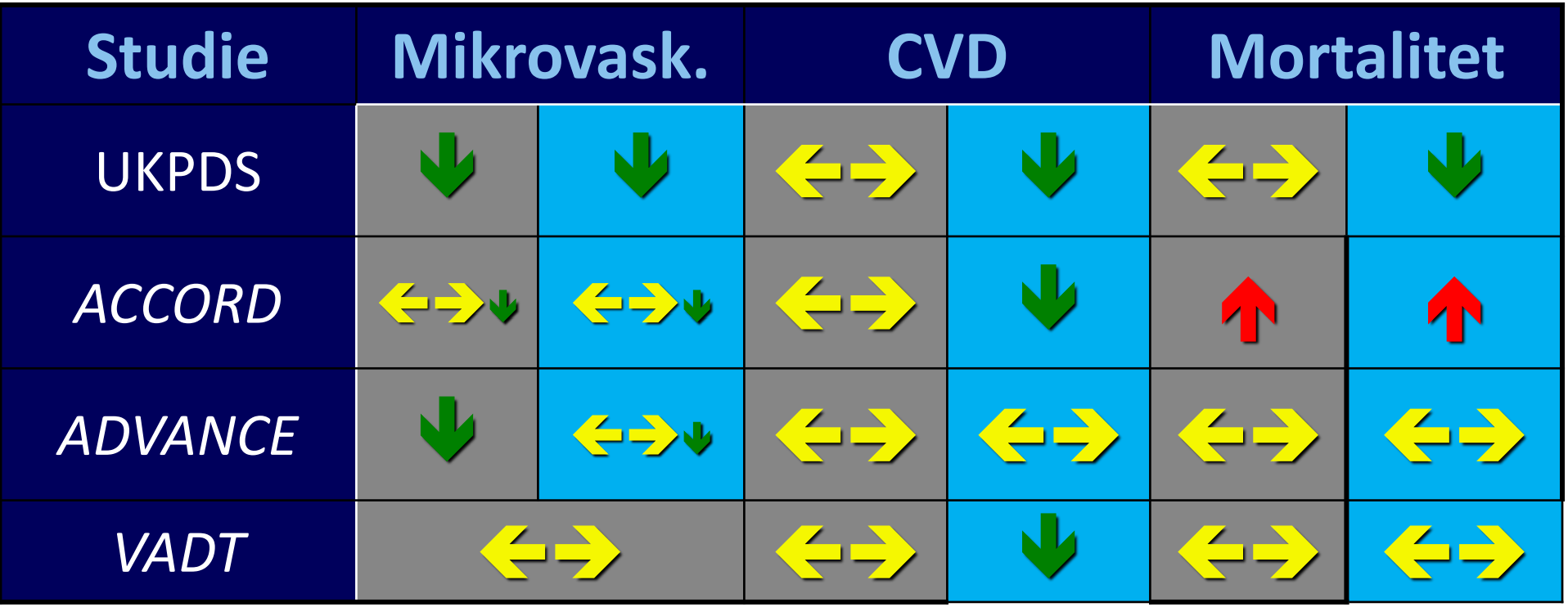
ORIGINAL ARTICLE

Diabetes Mellitus, Fasting Glucose, and Risk of Cause-Specific Death

The Emerging Risk Factors Collaboration*



Effekt av intensiv vs mindre intensiv blodsukkersenkende behandling ved T2D



Kendall DM, Bergenstal RM. © International Diabetes Center 2009

UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 1998;352:854.
Holman RR et al. *N Engl J Med*. 2008;359:1577. DCCT Research Group. N Engl J Med 1993;329;977.
Nathan DM et al. *N Engl J Med*. 2005;353:2643. Gerstein HC et al. *N Engl J Med*. 2008;358:2545.
Patel A et al. N Engl J Med 2008;358:2560. Duckworth W et al. N Engl J Med 2009;360:129. (erratum: Moritz T. *N Engl J Med* 2009;361:1024)

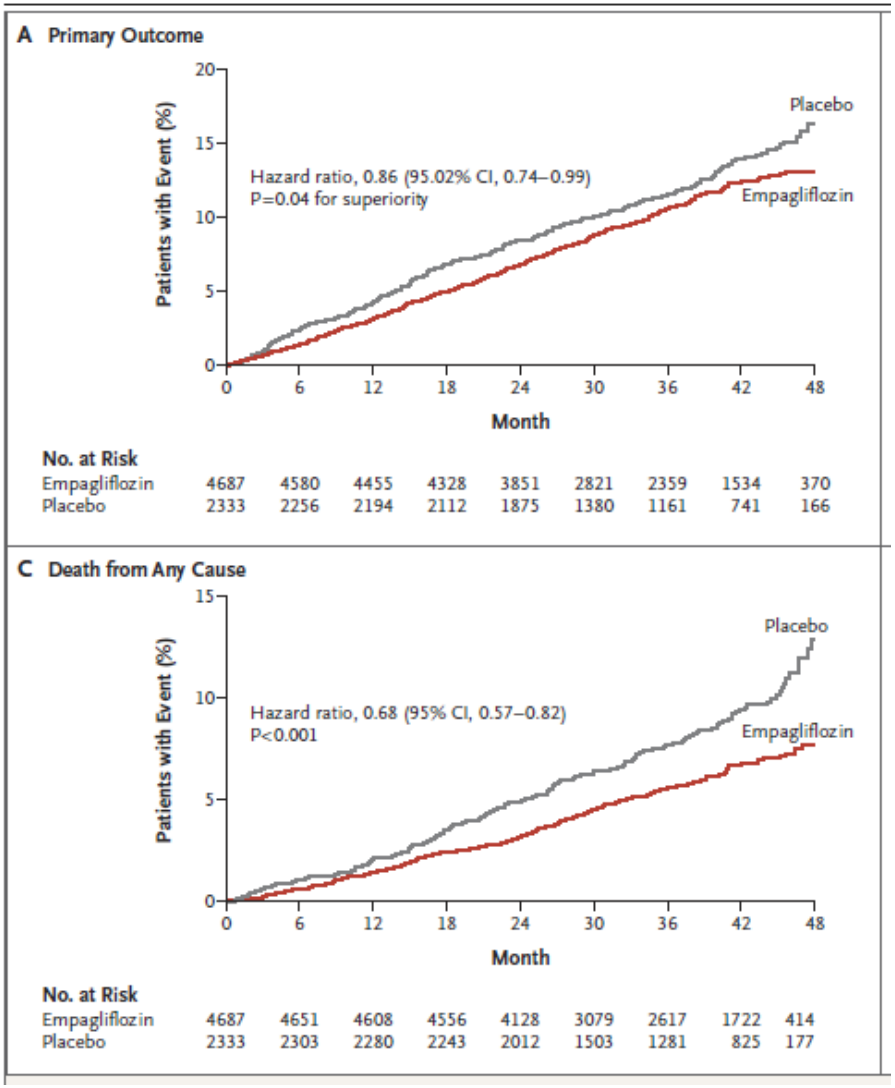
Initiale studie

Langtidsoppfølging

ORIGINAL ARTICLE

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for the EMPA-REG OUTCOME Investigators

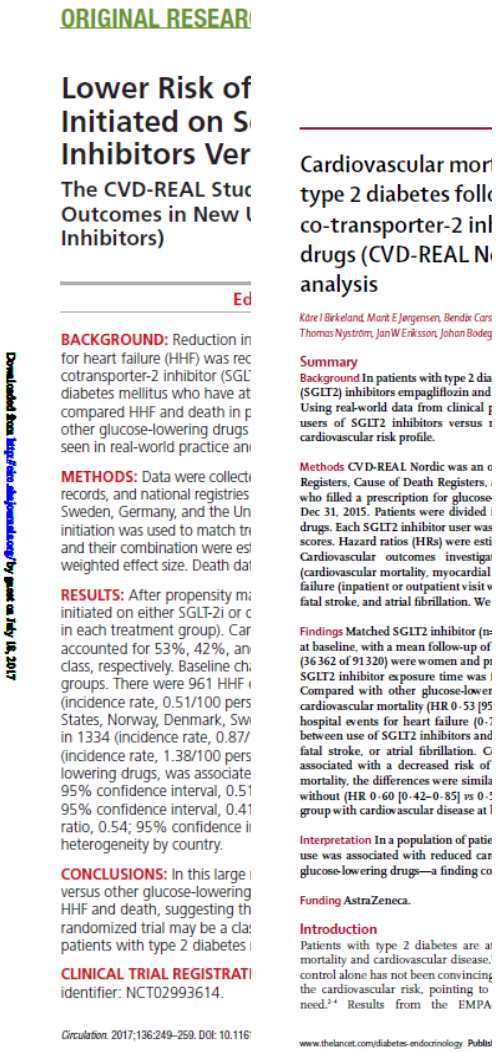


EMPA-REG: 7 020 T2D pas. & CVD
Rx to Empagliflozin eller placebo
Prim. Endepunkt: 3p MACE (major adverse cardiovascular events)

NEJM 2015

Etter EMPAREG:

- Er det en klasse-effekt?
- Gjelder det også for pas. uten hjerte-/karsykdom?



ORIGINAL RESEAR

Lower Risk of
Initiated on S
Inhibitors Ver

The CVD-REAL Stuc
Outcomes in New U
Inhibitors)

Ed

BACKGROUND: Reduction in
for heart failure (HHF) was rec
cotransporter-2 inhibitor (SGL
diabetes mellitus who have at
compared HHF and death in p
other glucose-lowering drugs
seen in real-world practice an

METHODS: Data were collect
records, and national registries
Sweden, Germany, and the Un
initiation was used to match tr
and their combination were es
weighted effect size. Death da

RESULTS: After propensity m
initiated on either SGLT-2i or c
in each treatment group). Car
accounted for 53%, 42%, an
class, respectively. Baseline ch
groups. There were 961 HHF
(incidence rate, 0.51/100 pers
States, Norway, Denmark, Sw
in 1334 (incidence rate, 0.87/
(incidence rate, 1.38/100 pers
lowering drugs, was associate
95% confidence interval, 0.5
95% confidence interval, 0.4
ratio, 0.54; 95% confidence i
heterogeneity by country.

CONCLUSIONS: In this large
versus other glucose-lowering
HHF and death, suggesting th
randomized trial may be a cla
patients with type 2 diabetes

CLINICAL TRIAL REGISTRAT
identifier: NCT02993614.

Circulation. 2017;136:249–259. DOI: 10.116

Cardiovascular mort
type 2 diabetes follo
co-transporter-2 inl
drugs (CVD-REAL N
analysis

Kåre I Birkeland, Marit E Jørgensen, Bendix Cars
Thomas Nyström, Jan W Eriksson, Johan Bodeg

Summary

Background In patients with type 2 dia
(SGLT2) inhibitors empagliflozin and
Using real-world data from clinical
users of SGLT2 inhibitors versus
cardiovascular risk profile.

Methods CVD-REAL Nordic was an
Registers, Cause of Death Registers,
who filled a prescription for glucose
Dec 31, 2015. Patients were divided
drugs. Each SGLT2 inhibitor user was
scores. Hazard ratios (HRs) were esti
Cardiovascular outcomes investiga
(cardiovascular mortality, myocardial
failure (inpatient or outpatient visit w
fatal stroke, and atrial fibrillation. We

Findings Matched SGLT2 inhibitor (n
at baseline, with a mean follow-up of
(36 362 of 91 320) were women and p
SGLT2 inhibitor exposure time was
Compared with other glucose-lower
cardiovascular mortality (HR 0·53 [95
hospital events for heart failure (0·
between use of SGLT2 inhibitors and
fatal stroke, or atrial fibrillation. C
associated with a decreased risk of
mortality, the differences were simila
without (HR 0·60 [0·42–0·85] *vs* 0·
group with cardiovascular disease at

Interpretation In a population of patie
use was associated with reduced car
glucose-lowering drugs—a finding co

Funding AstraZeneca.

Introduction

Patients with type 2 diabetes are a
mortality and cardiovascular disease.
control alone has not been convincing
the cardiovascular risk, pointing to
need.[2–4] Results from the EMPA

www.thelancet.com/diabetes-endocrinology Publis

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WILEY

ORIGINAL ARTICLE

Dapagliflozin is associated with lower risk of cardiovascular events and all-cause mortality in people with type 2 diabetes (CVD-REAL Nordic) when compared with dipeptidyl peptidase-4 inhibitor therapy: A multinational observational study

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[3]Oslo University Hospital, Oslo, Norway
[4]Statistikon AB, Uppsala, Sweden
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[6]Uppsala University, Uppsala, Sweden
[7]Karolinska Institutet, Stockholm, Sweden
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[9]AstraZeneca Nordic-Baltic, Oslo, Norway
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Funding information
This work was sponsored by AstraZeneca AB.

Aims: To compare the sodium-glucose-cotransporter-2 (SGLT-2) inhibitor dapagliflozin with dipeptidyl peptidase-4 (DPP-4) inhibitors with regard to risk associations with major adverse cardiovascular (CV) events (MACE; non-fatal myocardial infarction, non-fatal stroke or cardiovascular mortality), hospitalization for heart failure (HHF), atrial fibrillation and severe hypoglycaemia in patients with type 2 diabetes (T2D) in a real-world setting.

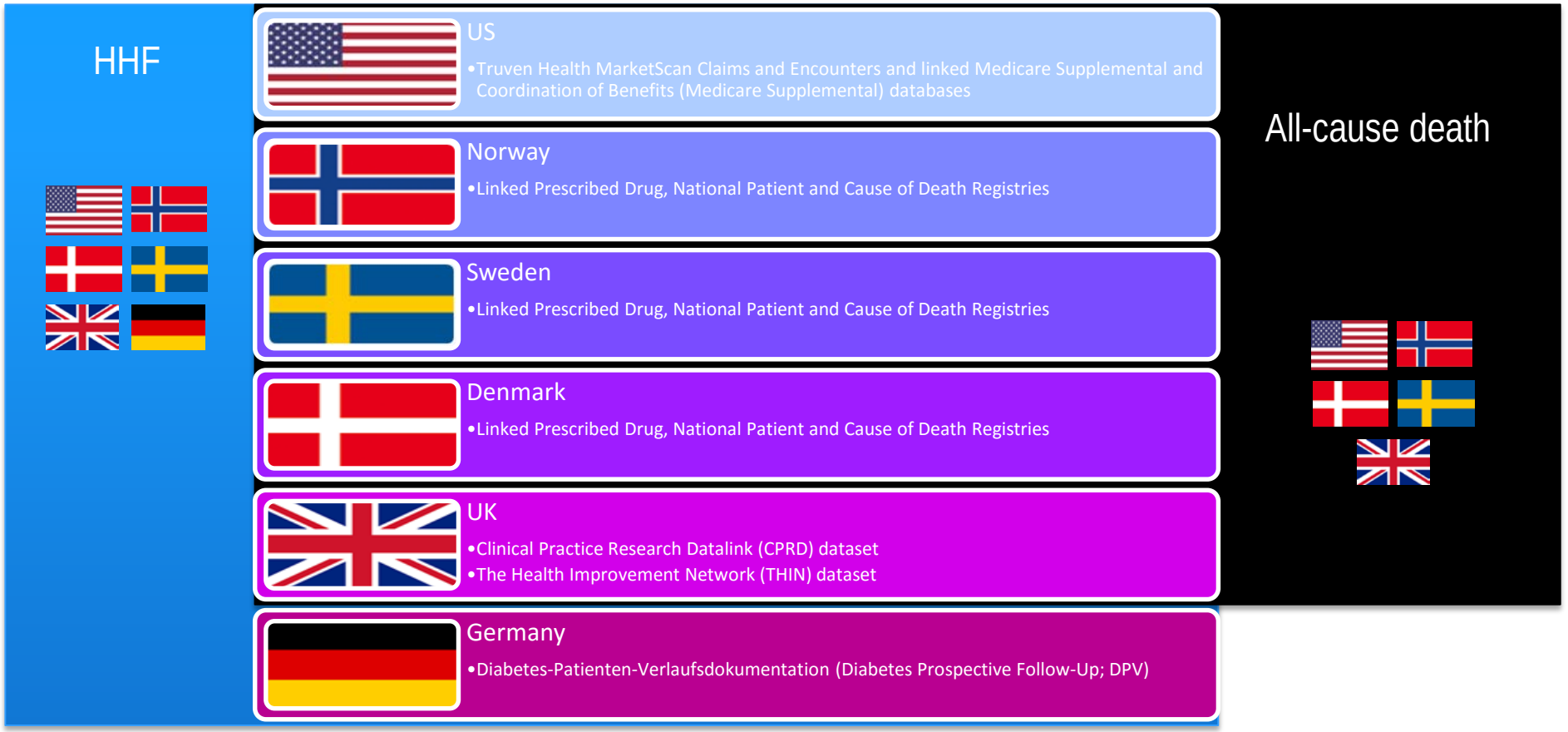
Methods: All patients with T2D prescribed glucose-lowering drugs (GLDs) during 2012 to 2015 were identified in nationwide registries in Denmark, Norway and Sweden. Patients were divided into two groups: new users of dapagliflozin and new users of DPP-4 inhibitors, matched 1:3 by propensity score, calculated by patient characteristics, comorbidities and drug treatment. Cox survival models were used to estimate hazard ratio (HR) per country separately, and a weighted average was calculated.

Results: After matching, a total of 40 908 patients with T2D were identified as new users of dapagliflozin (n = 10 227) or a DPP-4 inhibitor (n = 30 681). The groups were well balanced at baseline; their mean age was 61 years and 23% had CV disease. The mean follow-up time was 0.95 years, with a total of 38 760 patient-years. Dapagliflozin was associated with a lower risk of MACE, HHF and all-cause mortality compared with DPP-4 inhibitors: HRs 0.79 (95% confidence interval [CI] 0.67-0.94), 0.62 (95% CI 0.50-0.77), and 0.59 (95% CI 0.49-0.72), respectively. Numerically lower, but non-significant HRs were observed for myocardial infarction (0.91 [95% CI 0.72-1.16]), stroke (0.79 [95% CI 0.61-1.03]) and CV mortality (0.76 [95% CI 0.53-1.08]) Neutral associations with atrial fibrillation and severe hypoglycaemia were observed.

Conclusions: Dapagliflozin was associated with lower risks of CV events and all-cause mortality compared with DPP-4 inhibitors in a real-world clinical setting and a broad T2D population.

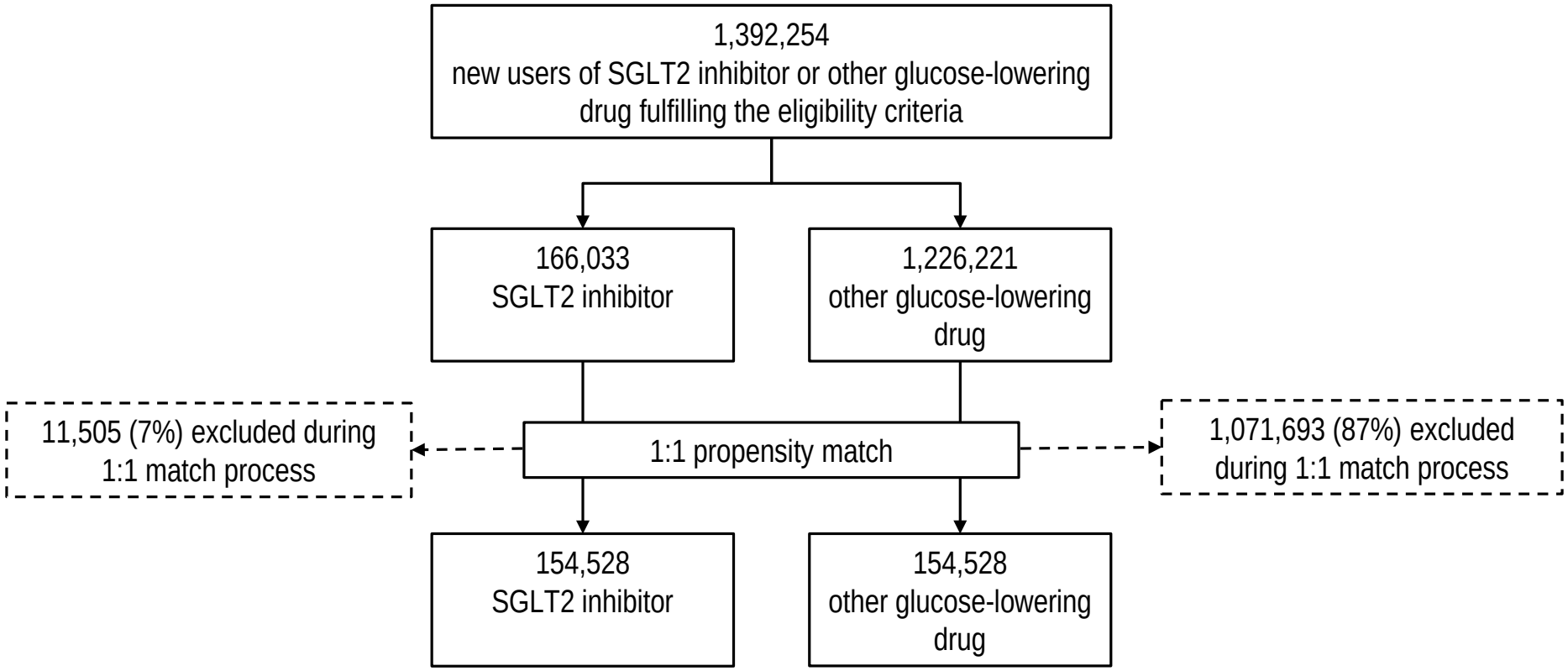
KEYWORDS
cardiovascular disease, dapagliflozin, diabetes complications, DPP-4 inhibitor, hypoglycaemia, type 2 diabetes

CVD-REAL Global: Data sources



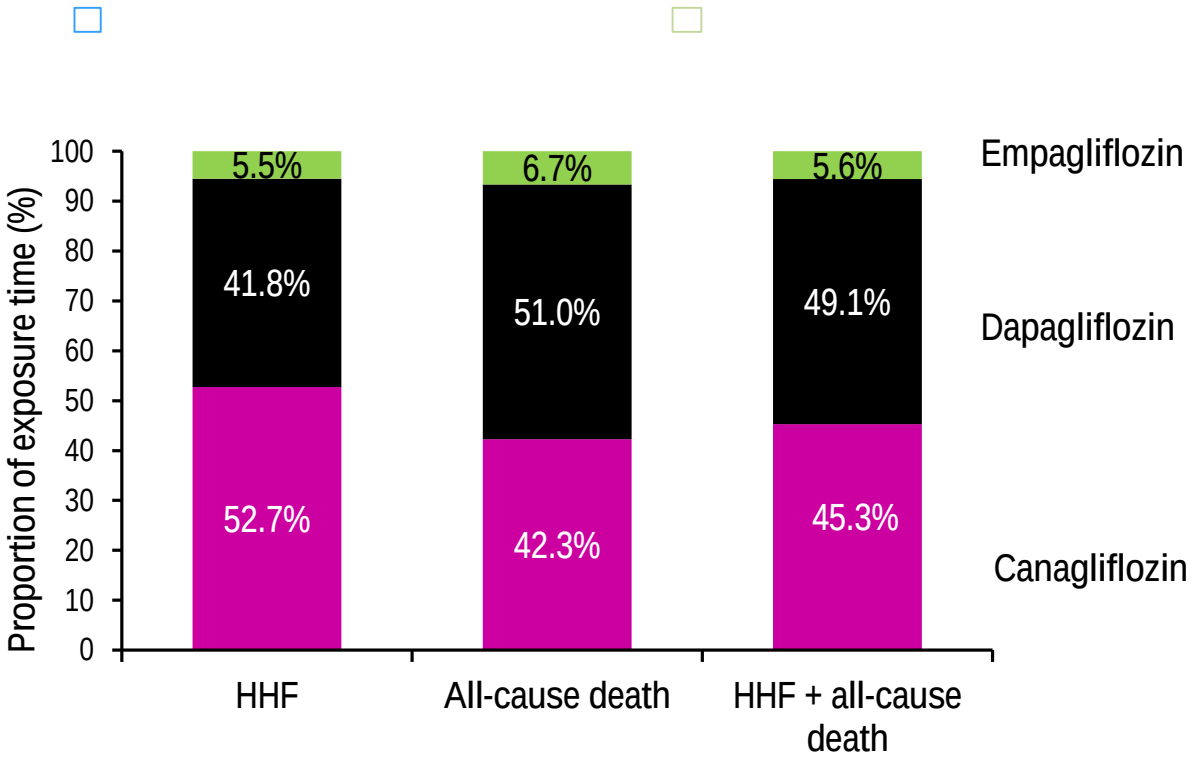
Kosiborod M et al, Circulation 2017; 136:249

CVD-REAL Global: Patient population for all countries/databases combined



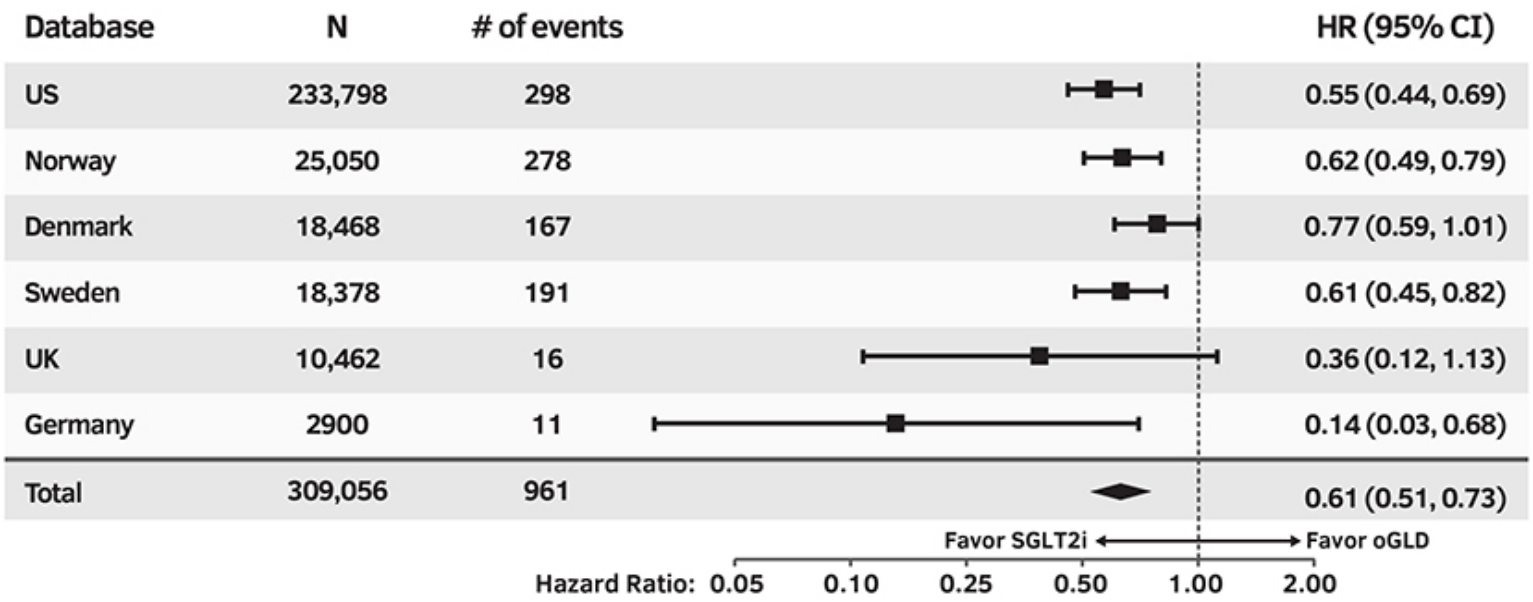
Kosiborod M et al, Circulation 2017; 136:249

Contribution of SGLT2 inhibitor: All countries combined



Kosiborod M et al, Circulation 2017; 136:249

CVD-REAL Global: Hospitalization for heart failure primary analysis



P-value for SGLT2 inhibitor vs other glucose-lowering drug: <0.001

Heterogeneity p-value: 0.169

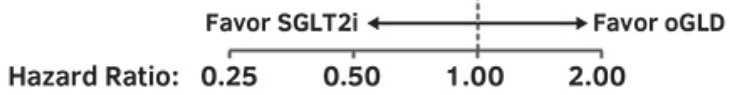
SENSITIVITY ANALYSES

Data are on treatment, unadjusted.

Kosiborod M et al, Circulation 2017; 136:249

CVD-REAL Global: All-cause death primary analysis

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 other glucose-lowering drug: <0.001

Heterogeneity p-value: 0.089

SENSITIVITY ANALYSES

Data are on treatment, unadjusted.

Circulation 2017

Hva med MACE, hjerteinfarkt, kardiovaskulær død?

CVD-REAL Nordic: Data sources and inclusion criteria

- **Data sources[1,2]**
  - Linked prescribed drug, national patient and cause of death registries

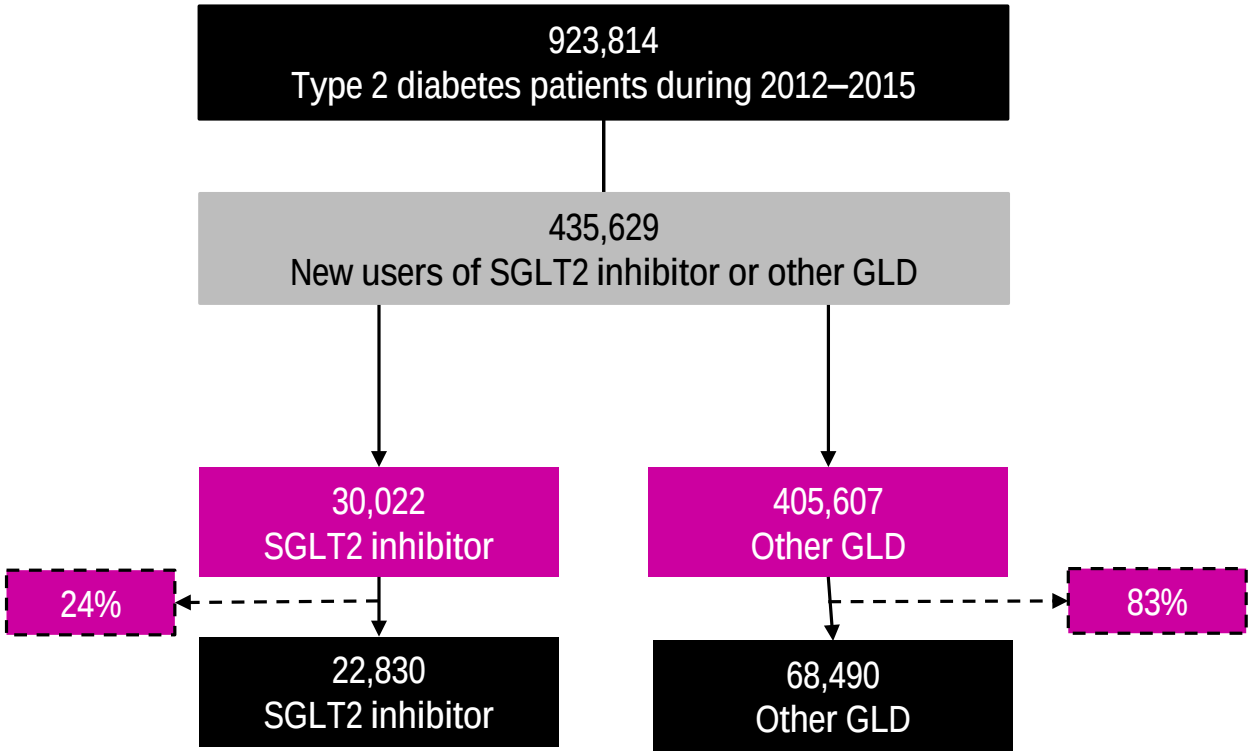
Inclusion criteria

- **All patients with Type 2 diabetes dispensed with glucose-lowering drugs between 2012–2015[1,2]**

Exclusion criteria

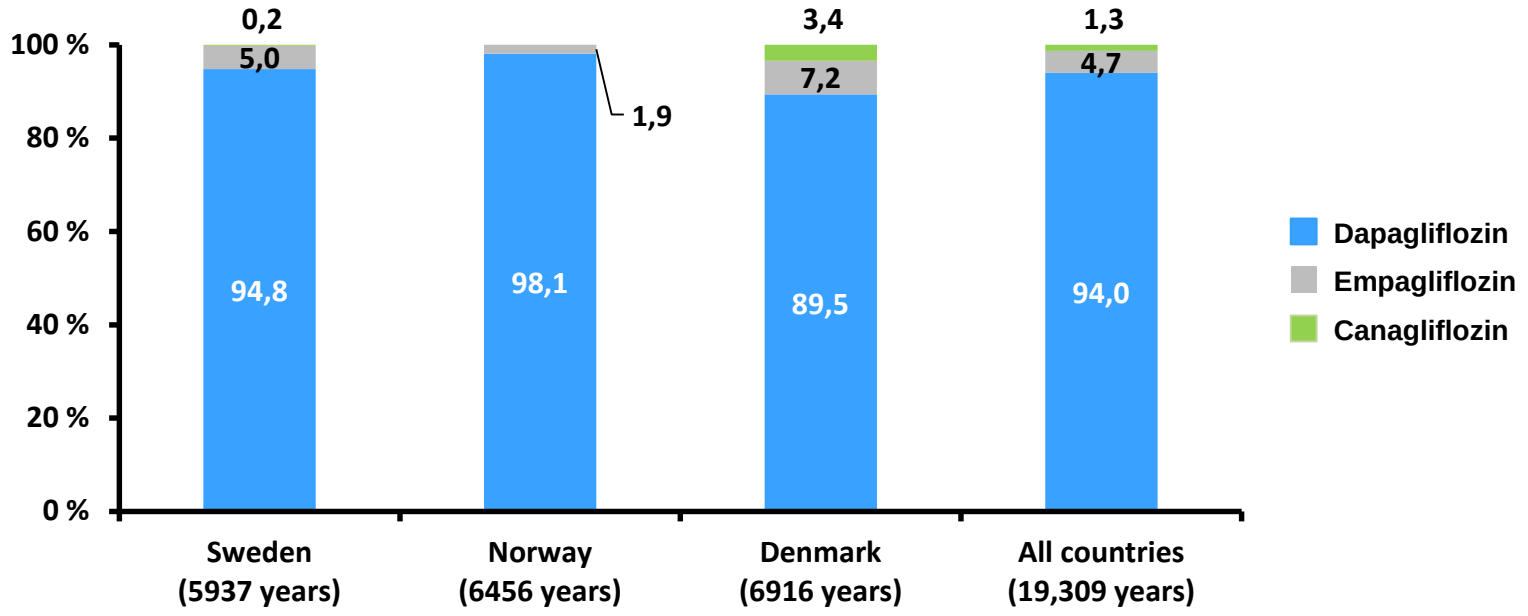
- **Type 1 diabetes, gestational diabetes, or polycystic ovarian syndrome[1,2]**

CVD-REAL Nordic: Patient flow chart

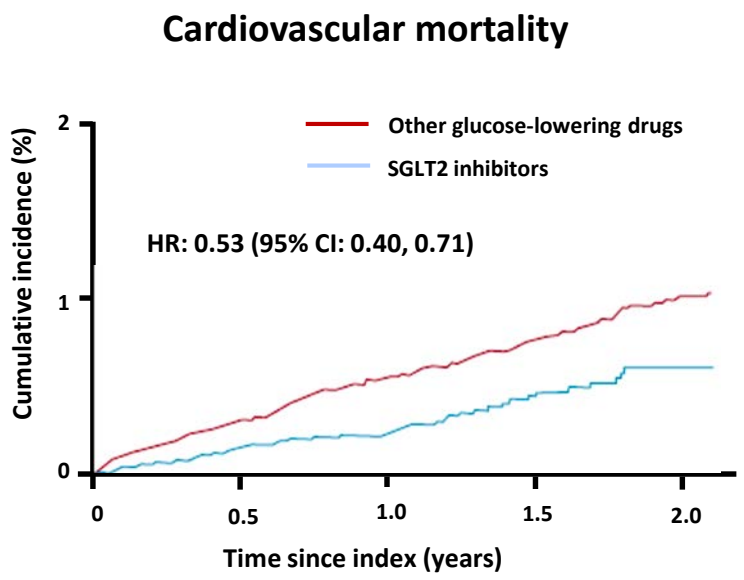


Contribution of SGLT2 inhibitors to exposure time

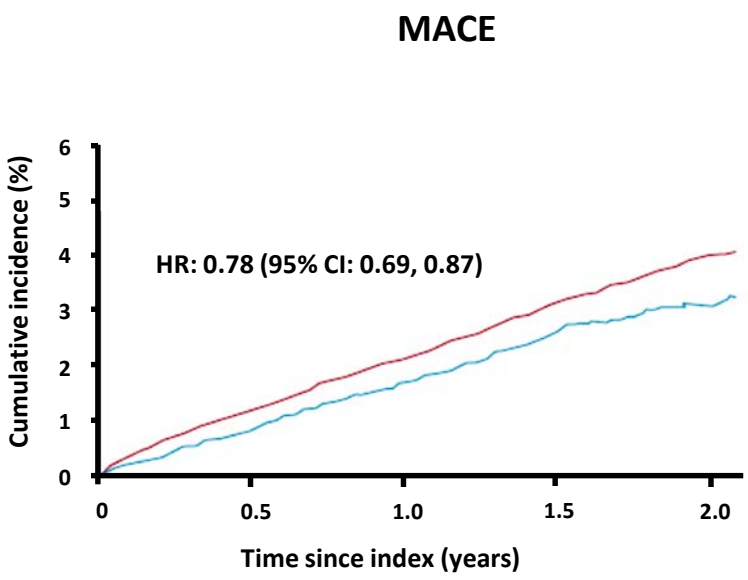
- Mean follow-up time was 0.9 years, with a total of 80,669 patient-years
- Exposure time for each SGLT2 inhibitor was 18,151 years (94%) for dapagliflozin, 915 years (5%) for empagliflozin and 243 years (1%) for canagliflozin



Kaplan–Meier curves for CV mortality and MACE



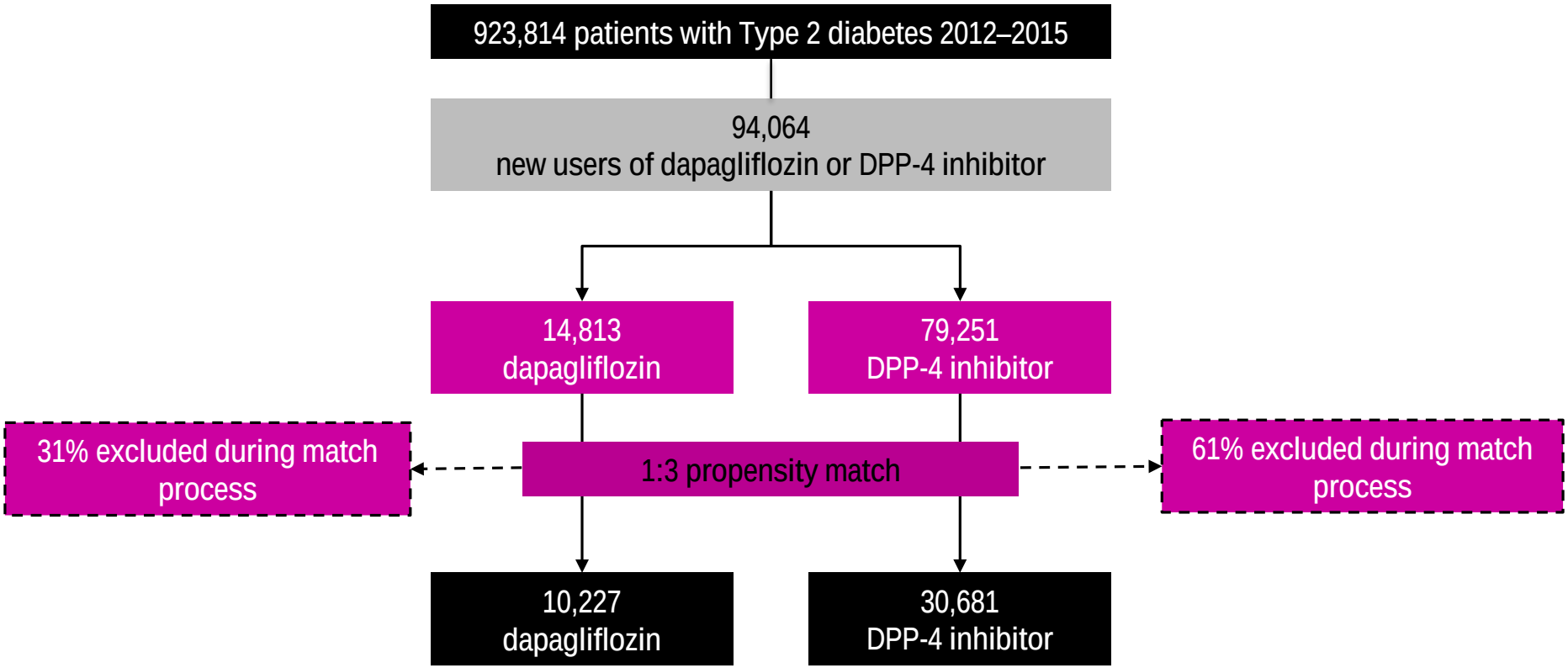
Numbers at risk					
Other glucose-lowering drugs	68490	48338	24586	15314	6434
SGLT2 inhibitors	22830	16051	7760	4687	1610



Numbers at risk					
Other glucose-lowering drugs	68490	48206	24633	14987	6553
SGLT2 inhibitors	22830	15982	8150	4792	2233

Gjelder det også når dapagliflozin sammenliknes direkte med andre nye medikamenter?

Dapagliflozin vs DPPIV-i: Patient flow chart



Persson F, et al. *Diabetes Obes Metab* 2017; doi: 10.1111/dom.13077

Results: Hazard ratios for dapagliflozin vs DPP-4 inhibitors

	Dapagliflozin N=10,227		DPP-4 inhibitor N=30,681		Weighted average estimates N=40,908		
	No. of events	Rate/ 100 P-Y	No. of events	Rate/ 100 P-Y	Hazard ratio	95% CI	P-value
MACE	177	1.86	695	2.34	0.79	0.67–0.94	0.006
Non-fatal myocardial infarction	87	0.91	304	1.02	0.91	0.72–1.16	0.445
Non-fatal stroke	69	0.72	270	0.90	0.79	0.61–1.03	0.086
CV mortality	38	0.40	160	0.53	0.76	0.53–1.08	0.122
HHF	95	0.99	467	1.57	0.62	0.50–0.77	<0.001
MACE +	202	2.12	779	2.63	0.81	0.69–0.94	0.007
Unstable angina	37	0.39	107	0.36	1.09	0.75–1.59	0.655
MACE ++	285	3.01	1164	3.96	0.75	0.66–0.86	<0.001
All-cause mortality	120	1.03	644	1.75	0.59	0.49–0.72	<0.001
Atrial fibrillation	140	1.47	469	1.58	0.92	0.76–1.12	0.414
Severe hypoglycaemia	91	0.95	300	1.01	0.94	0.74–1.19	0.618

Persson F, et al. *Diabetes Obes Metab* 2017; doi: 10.1111/dom.13077

Registerforskning i Norge – fordeler og muligheter

- - Deskriptive analyser
  - Insidens
  - Prevalens
  - Tapte leveår
  - Relative sykdomsrisiki
  - Behandling – tidstrender
- Sammenlikne behandlingsalternativer i forhold til ulike utfall

Registerforskning i Norge – fordeler og muligheter

- Kliniske multisenterstudier er redusert i Norge de siste årene
- Kan vi bruke registrene til pragmatiske, randomiserte klniniske studier?
- Samarbeid akademia, myndigheter og industri?

Registerforskning i Norge – noen utfordringer og mulige løsninger

- Lang behandlingstid
  - NPR
    - Økt betaling?
  - Datatilsynet
- Mangler biomarkør-data
  - Kobling mot offentlige/private laboratorier?
- Mangler gode registre fra allmennpraksis
  - KUHR, Nytt kommunalt register?