

Nasjonalt Diabetesforum 2017
**Hva kan vi lære av de siste års store
diabetesstudier?**

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Professor/overlege
Universitetet i Oslo/OUS

Hva kan vi lære av siste års store diabetesstudier?

- Kan god bl.s.kontroll bedre leveutsiktene ved T1D?
 - Langtidsoppfølging av DCCT
- Hjelper forebygging av T2D på lang sikt?
 - Langtidsoppfølging av DaQing
- Kan blodsukkersenkende medikamenter redusere dødelighet ved T2D?
 - EMPAREG-OUTCOME, LEADER, SUSTAIN-6

The New England Journal of Medicine

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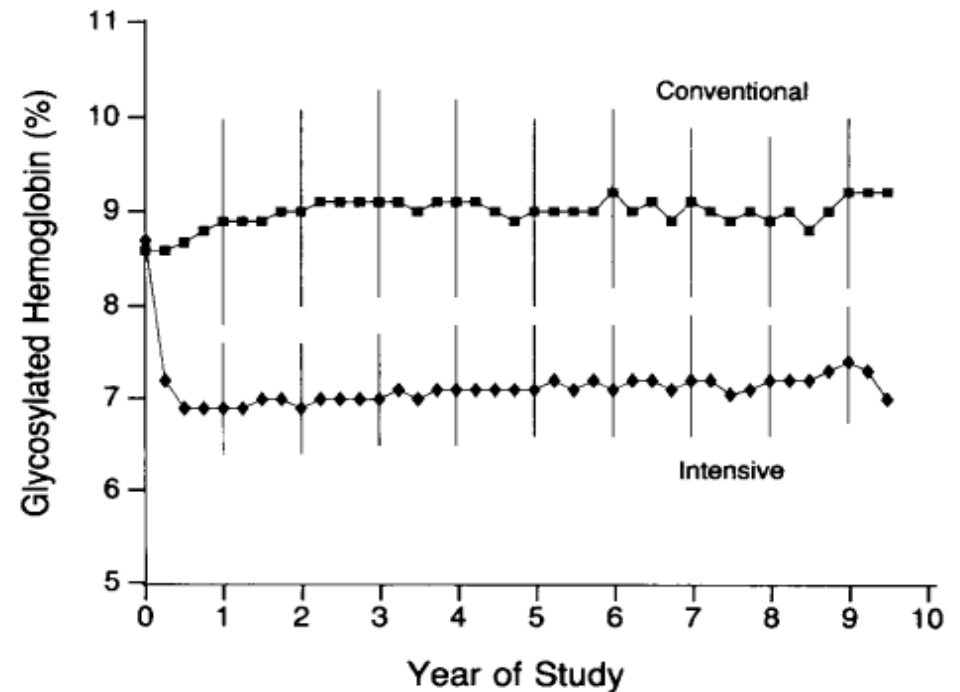
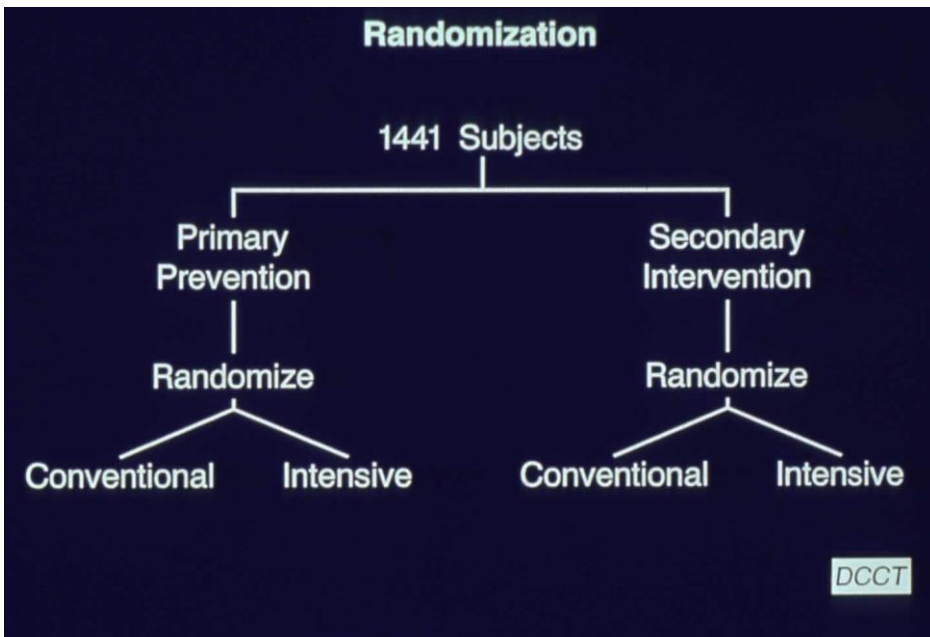
Volume 329

SEPTEMBER 30, 1993

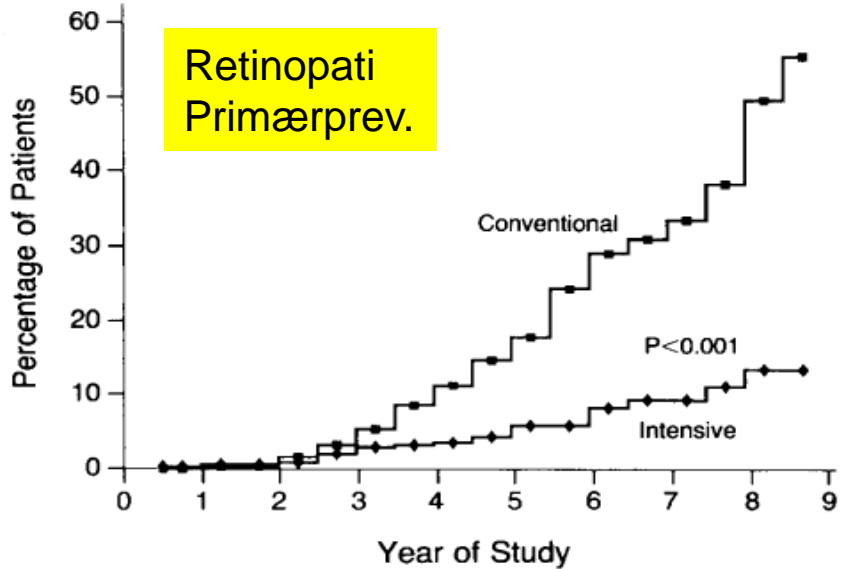
Number 14

THE EFFECT OF INTENSIVE TREATMENT OF DIABETES ON THE DEVELOPMENT AND PROGRESSION OF LONG-TERM COMPLICATIONS IN INSULIN-DEPENDENT DIABETES MELLITUS

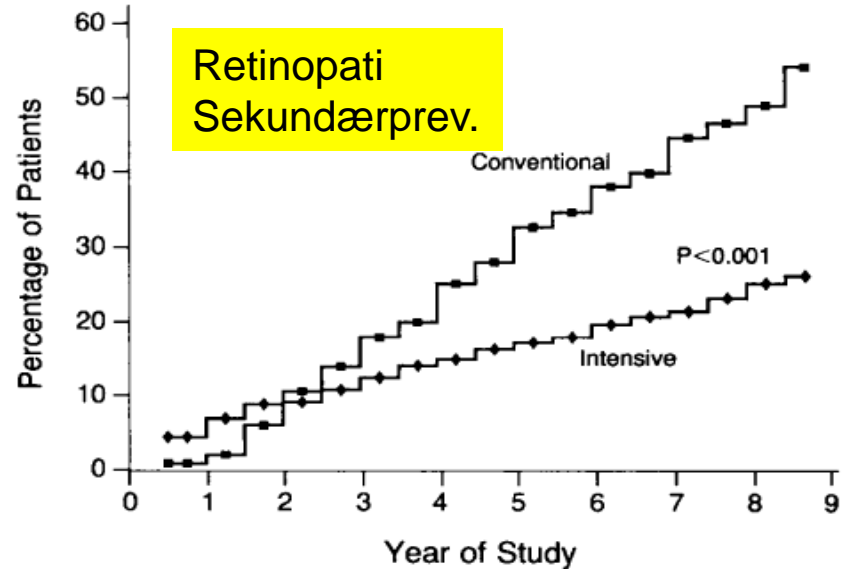
THE DIABETES CONTROL AND COMPLICATIONS TRIAL RESEARCH GROUP*



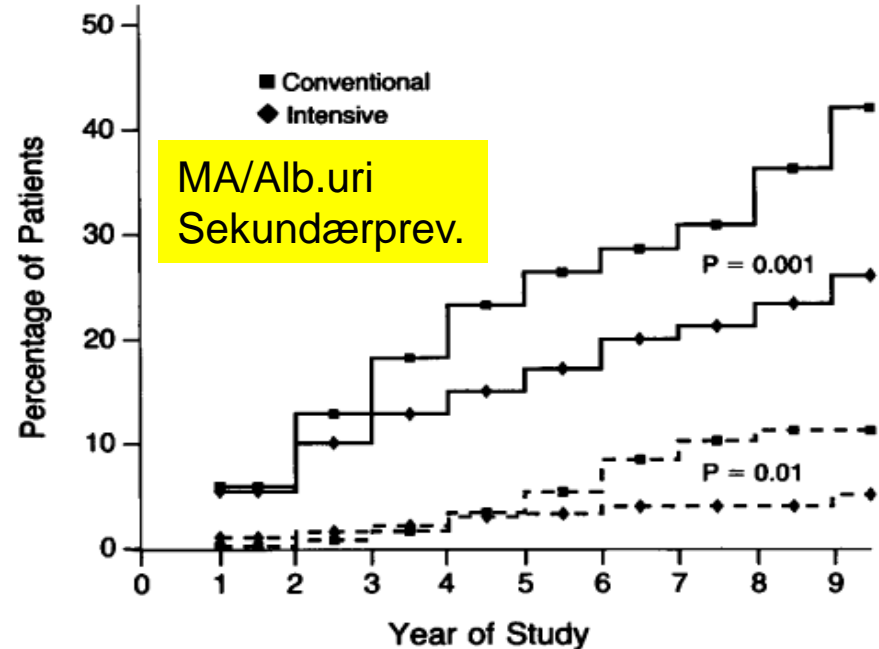
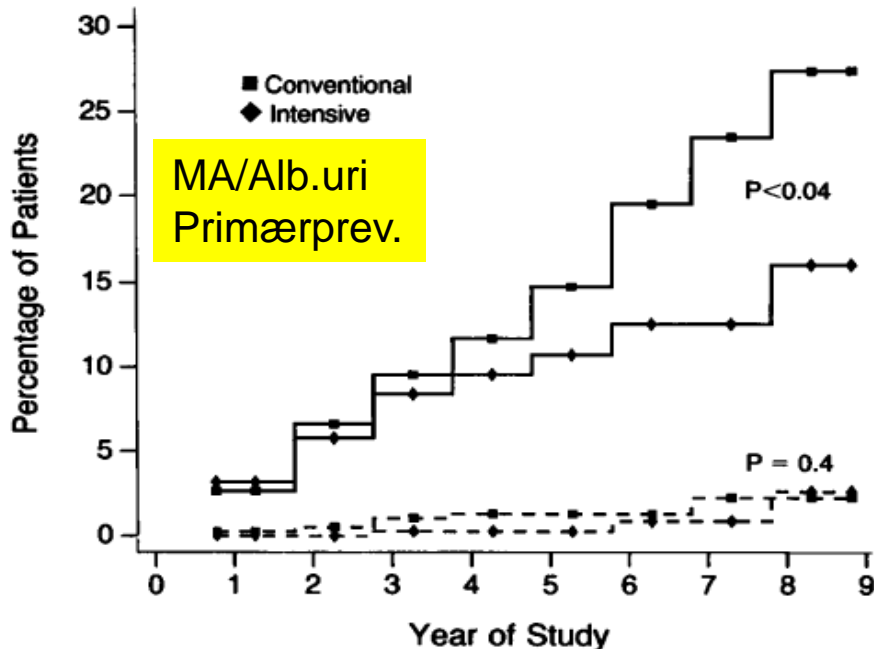
Øye- og nyrekomplikasjoner i DCCT



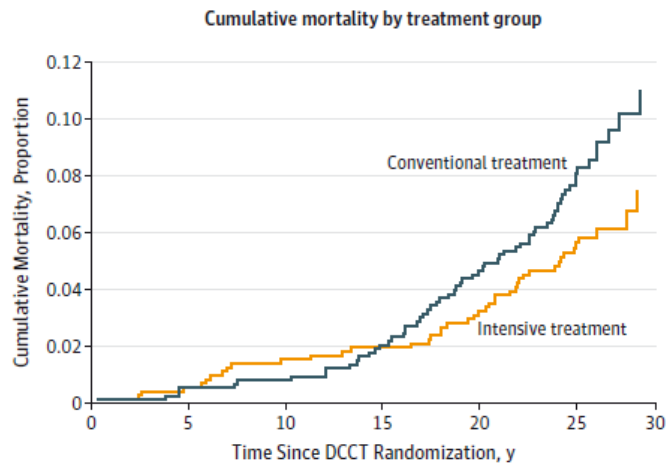
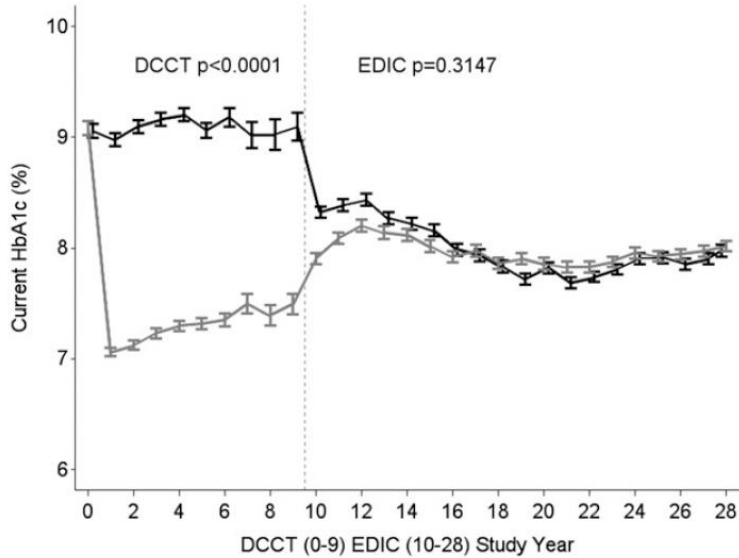
| | | | | |
|--------------|-----|-----|----|----|
| Conventional | 375 | 220 | 79 | 52 |
| Intensive | 342 | 202 | 78 | 49 |



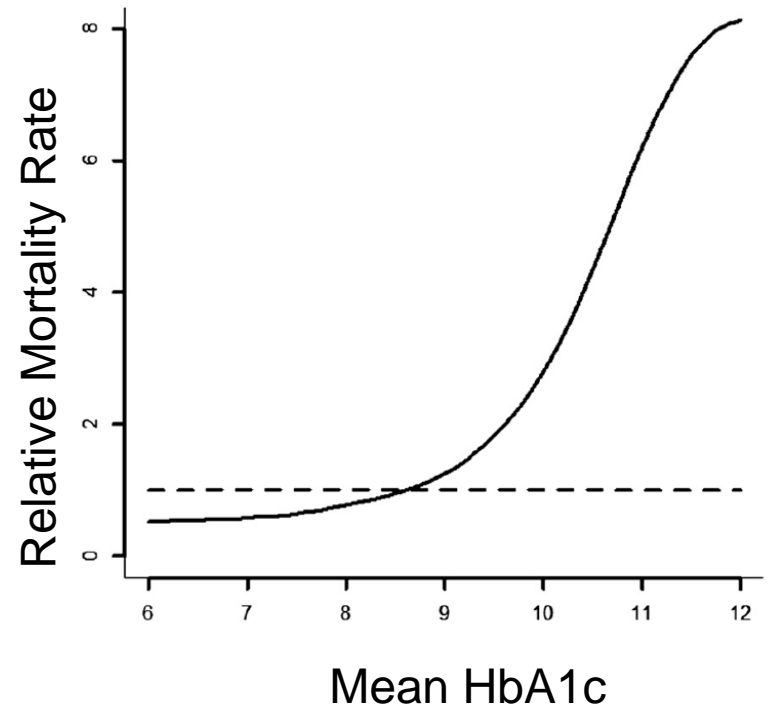
| | | | | |
|--------------|-----|-----|-----|----|
| Conventional | 348 | 324 | 128 | 79 |
| Intensive | 354 | 335 | 136 | 93 |



Langtidsoppfølging DCCT



| No. at risk | 730 | 726 | 721 | 712 | 693 | 476 |
|--------------|-----|-----|-----|-----|-----|-----|
| Conventional | 730 | 726 | 721 | 712 | 693 | 476 |
| Intensive | 711 | 706 | 697 | 694 | 685 | 501 |



Diabetes Care 2016;39:1621-30 and 686-93 and 1378-83
 JAMA 2015; 313:45

Hva kan vi lære av siste års store diabetesstudier?

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 - Ja!
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- Kan blodsukkersenkende medikamenter redusere dødelighet ved T2D?

Effects of Diet and Exercise in Preventing NIDDM in People With Impaired Glucose Tolerance

The Da Qing IGT and Diabetes Study

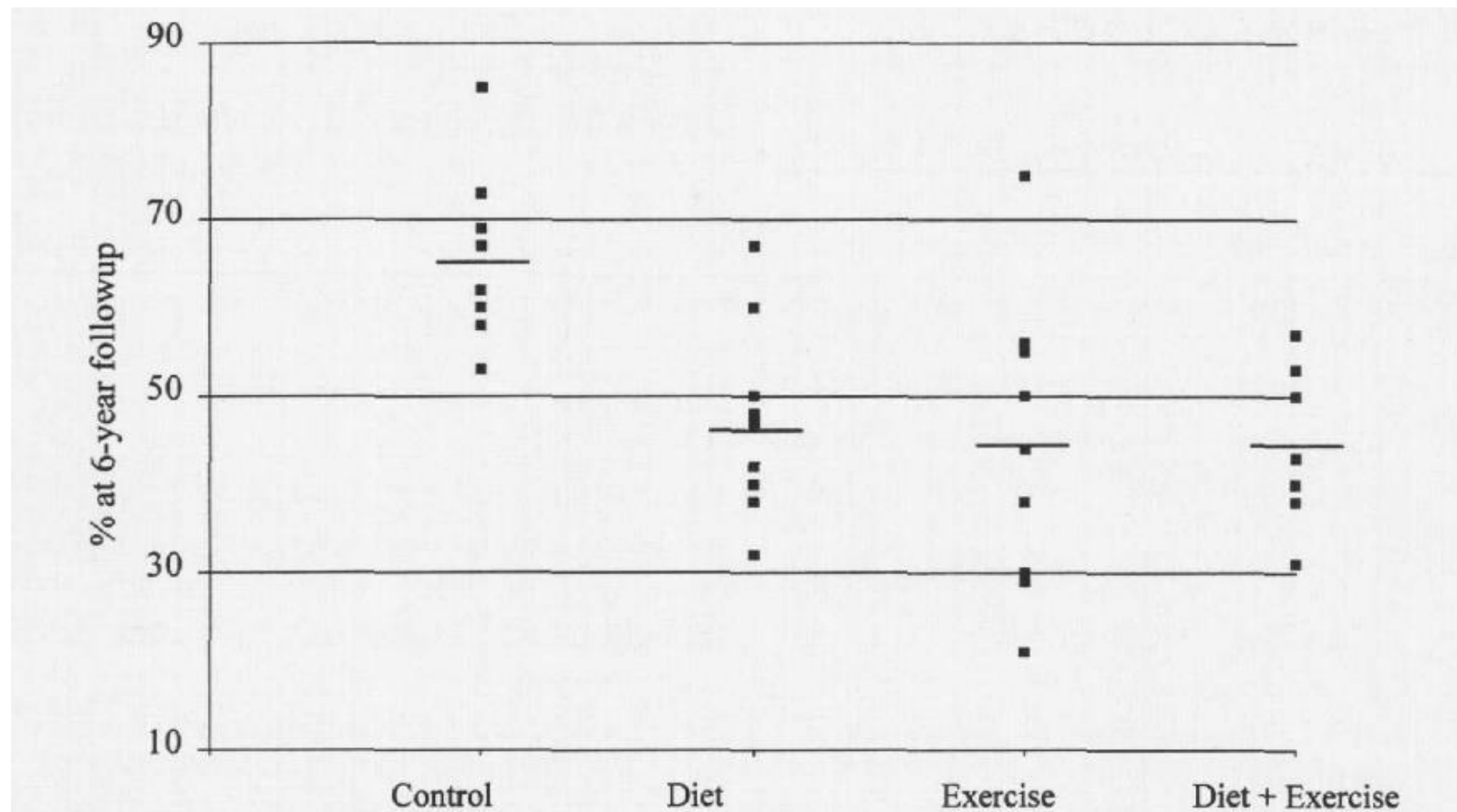
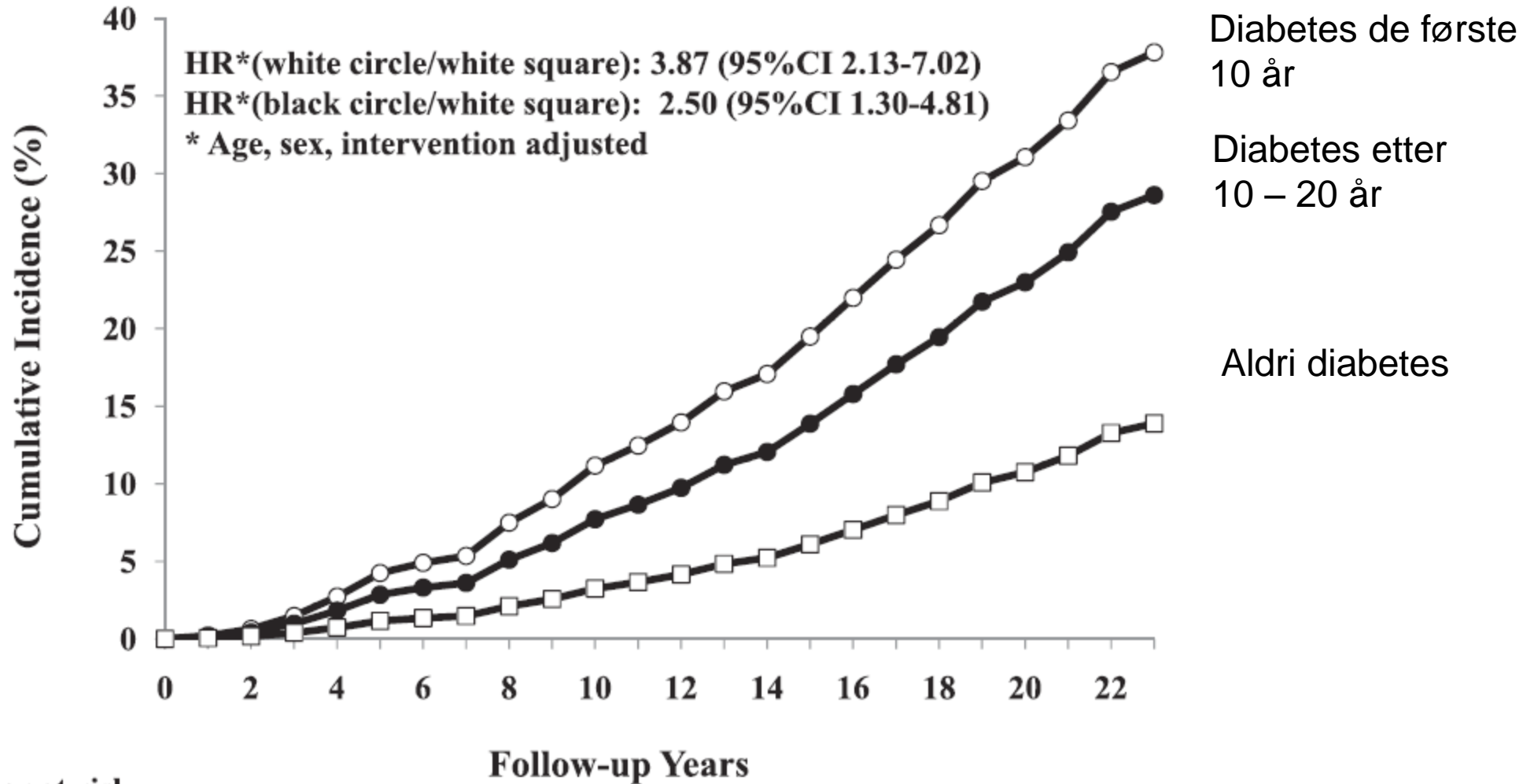


Figure 1—Mean rate of diabetes for each clinic at 6-year follow-up, by intervention group. Means (\pm SD) were control, 66 ± 10 ; diet, 47 ± 11 ; exercise, 45 ± 9 ; and diet plus exercise, 44 ± 17 .

DaQing – studien: Dødelighet etter 23 års oppfølging

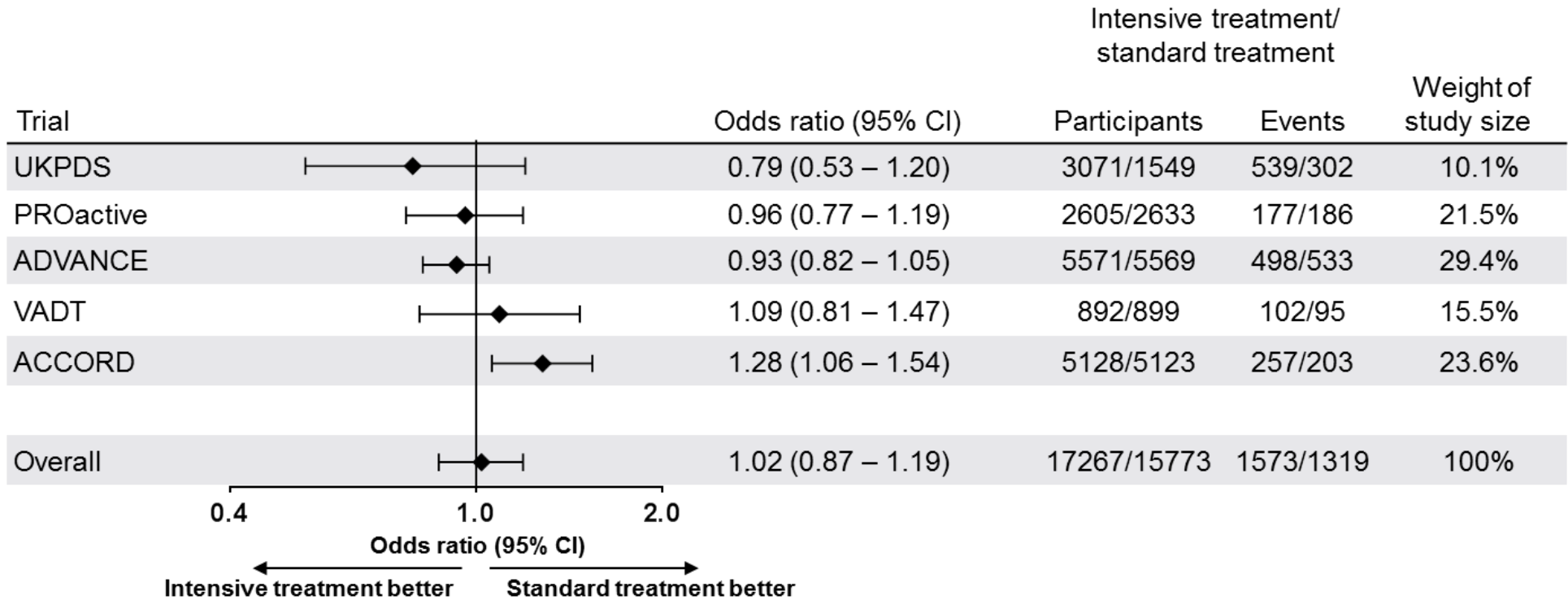


Hva kan vi lære av siste års store diabetesstudier?

- Kan god bl.s.kontroll bedre leveutsiktene ved T1D?
 - Ja!
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 - Ja!
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Dødelighet av alle årsaker

Intensive vs standard blodsukkersenkende behandling



CI: confidence interval; HR: hazard ratio.

Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

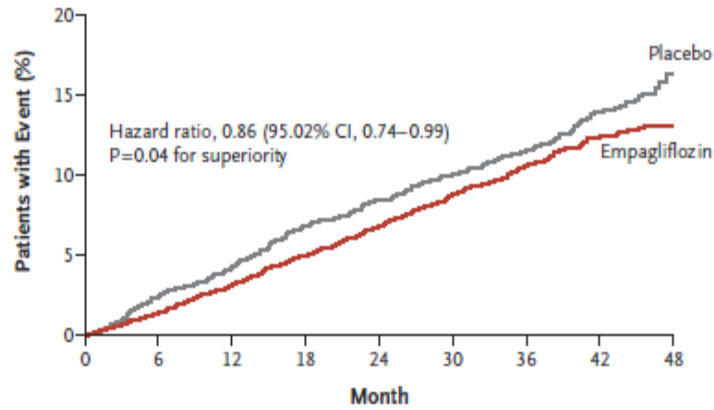
Bernard Zinman, M.D., Christoph Wanner, M.D., John M. Lachin, Sc.D., David Fitchett, M.D., Erich Bluhmki, Ph.D., Stefan Hantel, Ph.D., Michaela Mattheus, Dipl. Biomath., Theresa Devins, Dr.P.H., Odd Erik Johansen, M.D., Ph.D., Hans J. Woerle, M.D., Uli C. Broedl, M.D., and Silvio E. Inzucchi, M.D., for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

Table S2. Baseline characteristics

| Characteristic* | Placebo (N = 2333) | Empagliflozin 10 mg (N = 2345) | Empagliflozin 25 mg (N = 2342) | Pooled empagliflozin (N = 4687) |
|--|-----------------------|-----------------------------------|-----------------------------------|------------------------------------|
| Age – years | 63.2 ± 8.8 | 63.0 ± 8.6 | 63.2 ± 8.6 | 63.1 ± 8.6 |
| Male – no. (%) | 1680 (72.0) | 1653 (70.5) | 1683 (71.9) | 3336 (71.2) |
| Race – no. (%) | | | | |
| White | 1678 (71.9) | 1707 (72.8) | 1696 (72.4) | 3403 (72.6) |
| Asian | 511 (21.9) | 505 (21.5) | 501 (21.4) | 1006 (21.5) |
| Black/African-American | 120 (5.1) | 119 (5.1) | 118 (5.0) | 237 (5.1) |
| Other/Missing | 24 (1.0) | 14 (0.6) | 27 (1.2) | 41 (0.9) |
| Ethnicity – no. (%) | | | | |
| Not Hispanic or Latino | 1912 (82.0) | 1909 (81.4) | 1926 (82.2) | 3835 (81.8) |
| Hispanic or Latino | 418 (17.9) | 432 (18.4) | 415 (17.7) | 847 (18.1) |
| Missing | 3 (0.1) | 4 (0.2) | 1 (<0.1) | 5 (0.1) |
| CV risk factor – no. (%) | 2307 (98.9) | 2333 (99.5) | 2324 (99.2) | 4657 (99.4) |
| Coronary artery disease | 1763 (75.6) | 1782 (76.0) | 1763 (75.3) | 3545 (75.6) |
| Multi-vessel coronary artery disease | 1100 (47.1) | 1078 (46.0) | 1101 (47.0) | 2179 (46.5) |
| History of myocardial infarction | 1083 (46.4) | 1107 (47.2) | 1083 (46.2) | 2190 (46.7) |
| Coronary artery bypass graft | 563 (24.1) | 594 (25.3) | 581 (24.8) | 1175 (25.1) |
| History of stroke [†] | 553 (23.7) | 535 (22.8) | 549 (23.4) | 1084 (23.1) |
| Peripheral artery disease | 479 (20.5) | 465 (19.8) | 517 (22.1) | 982 (21.0) |
| Single vessel coronary artery disease [‡] | 238 (10.2) | 258 (11.0) | 240 (10.2) | 498 (10.6) |
| Cardiac failure [§] | 244 (10.5) | 240 (10.2) | 222 (9.5) | 462 (9.9) |
| Glycated hemoglobin – % | 8.08 ± 0.84 | 8.07 ± 0.86 | 8.06 ± 0.84 | 8.07 ± 0.85 |

EMPAREG-OUTCOME - Resultater

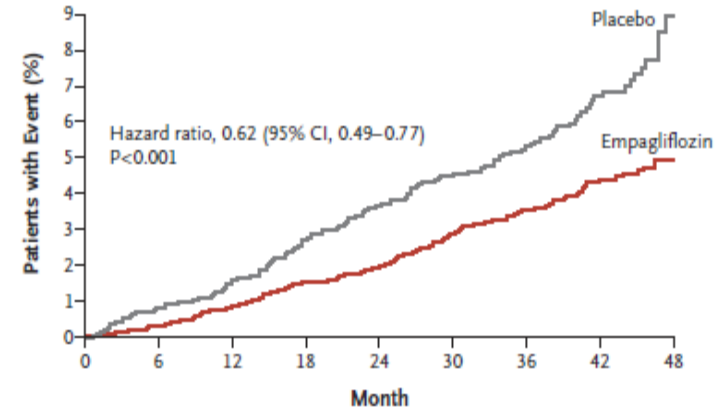
A Primary Outcome



No. at Risk

| | | | | | | | | | |
|---------------|------|------|------|------|------|------|------|------|-----|
| Empagliflozin | 4687 | 4580 | 4455 | 4328 | 3851 | 2821 | 2359 | 1534 | 370 |
| Placebo | 2333 | 2256 | 2194 | 2112 | 1875 | 1380 | 1161 | 741 | 166 |

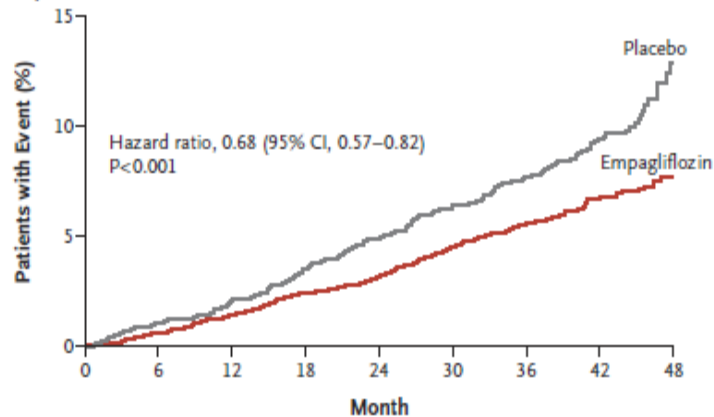
B Death from Cardiovascular Causes



No. at Risk

| | | | | | | | | | |
|---------------|------|------|------|------|------|------|------|------|-----|
| Empagliflozin | 4687 | 4651 | 4608 | 4556 | 4128 | 3079 | 2617 | 1722 | 414 |
| Placebo | 2333 | 2303 | 2280 | 2243 | 2012 | 1503 | 1281 | 825 | 177 |

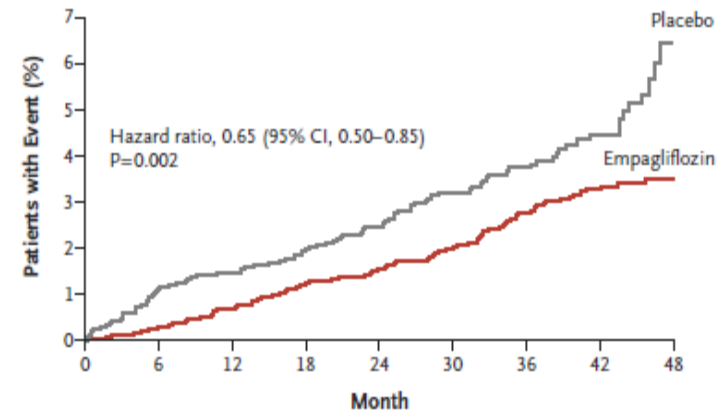
C Death from Any Cause



No. at Risk

| | | | | | | | | | |
|---------------|------|------|------|------|------|------|------|------|-----|
| Empagliflozin | 4687 | 4651 | 4608 | 4556 | 4128 | 3079 | 2617 | 1722 | 414 |
| Placebo | 2333 | 2303 | 2280 | 2243 | 2012 | 1503 | 1281 | 825 | 177 |

D Hospitalization for Heart Failure



No. at Risk

| | | | | | | | | | |
|---------------|------|------|------|------|------|------|------|------|-----|
| Empagliflozin | 4687 | 4614 | 4523 | 4427 | 3988 | 2950 | 2487 | 1634 | 395 |
| Placebo | 2333 | 2271 | 2226 | 2173 | 1932 | 1424 | 1202 | 775 | 168 |

SGLT2-hemmere og hjerte-/karsykdom: Klasseeffekt? Utenfor randomisert studie? Pas. uten hjerte-/karsykdom

- «DAPHNE»
 - Data fra Reseptregisteret, Dødsårsaksregisteret og NPR 2014-2016
 - 14 438 pas. begynte med SGLT2-hemmer
 - 96 947 pas. begynte med et annet blodsukkersenkende medikament

A. Norway National Registers

| Step | SGLT2i Patients | Other GLD Patients |
|--|-----------------|--------------------|
| New users of glucose-lowering drugs | 14,438 | 96,947 |
| ↓ | | |
| Excluded for not meeting the study eligibility criteria* | N/A | N/A |
| ↓ | | |
| Patients used in propensity score 1:1 matching | 14,438 | 96,947 |
| ↓ | | |
| Excluded because match was not available | 1913 | 84,422 |
| ↓ | | |
| Final cohort (after 1:1 match) | 12,525 | 12,525 |
| ↓ | | |
| For HHF analysis | 12,525 | 12,525 |
| ↓ | | |
| For all-cause death analysis; For HHF or all-cause death analysis | 12,525 | 12,525 |

*Inclusion/exclusion criteria were already applied prior to the first step

CVD-REAL studien: Datakilder, aidentifiserte registerdata fra fem land



Truven MarketScan Claims & Encounters and linked **Medicare**
>300 large, self-insured US employers and >25 US health plans



National full-population registries – DAPHNE



National full-population registries – DAFFODIL



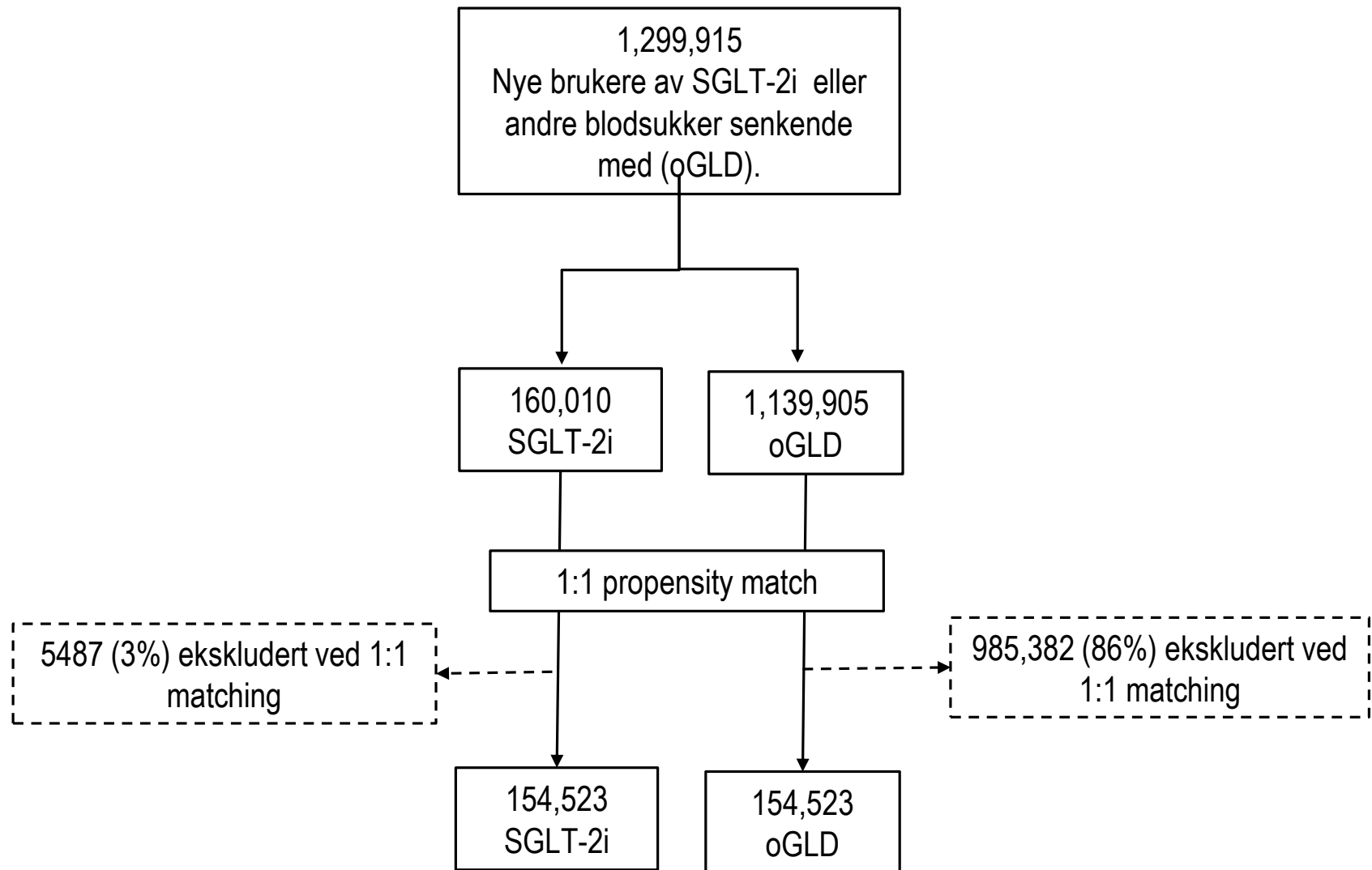
National full-population registries – DAISY



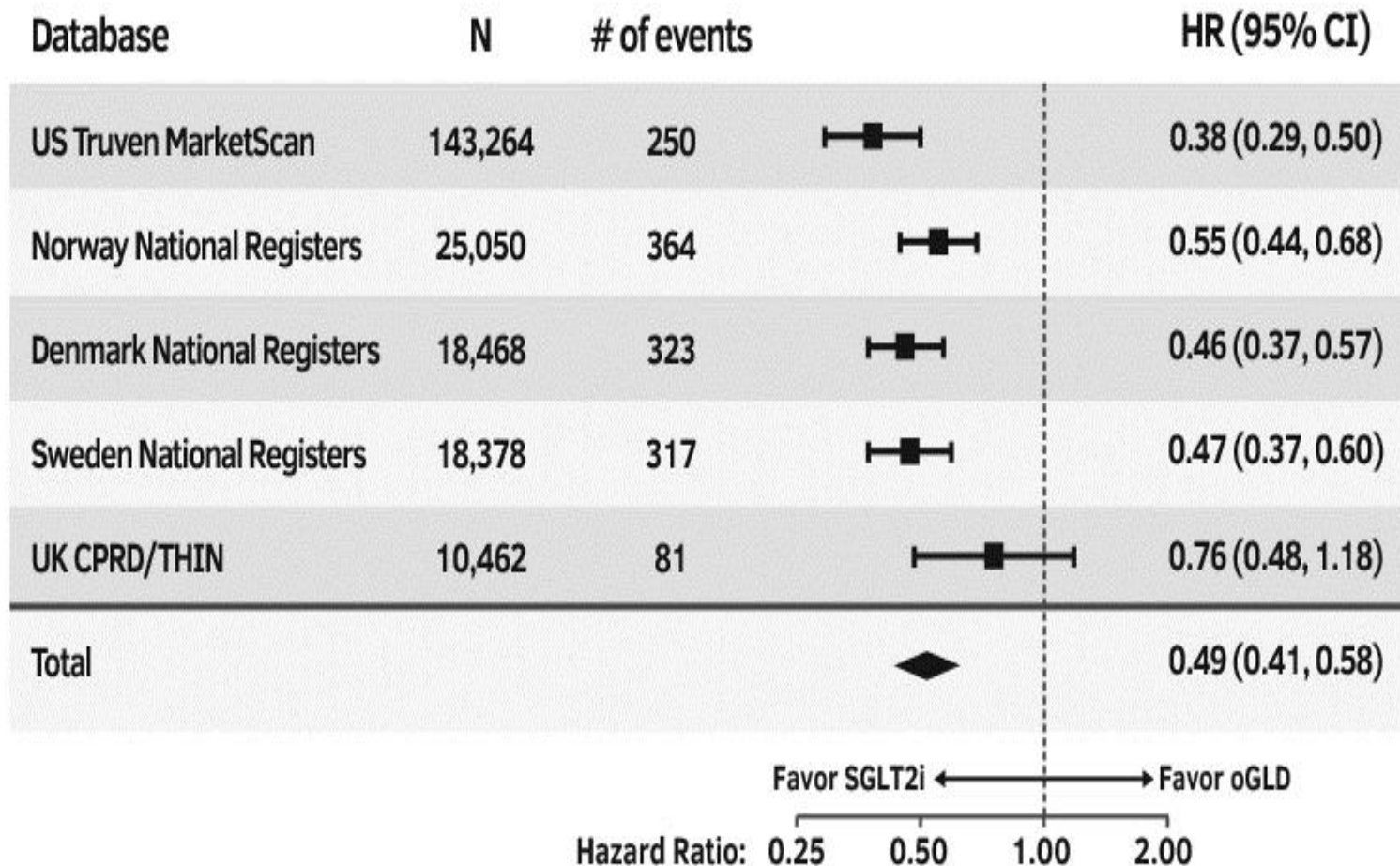
Clinical Practice Research Datalink (CPRD) and
The Health Improvement Network (THIN)
Primary care data from >670 practices

Dødelighet av alle årsaker

CVD-REAL pasientpopulasjon



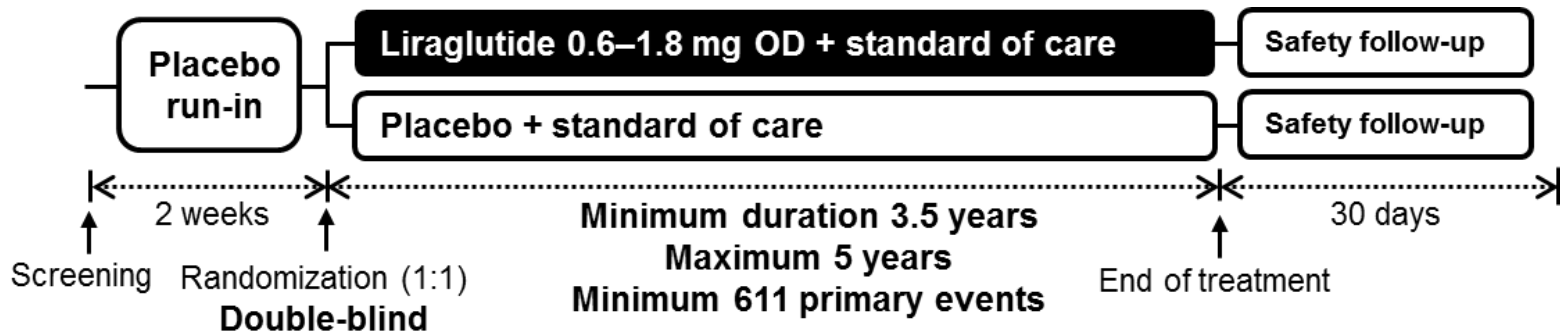
CVD-REAL: Død av alle årsaker



P-value for
SGLT2i vs oGLD:
<0.001

Heterogeneity p-value:
0.071

LEADER: Study design



Key inclusion criteria

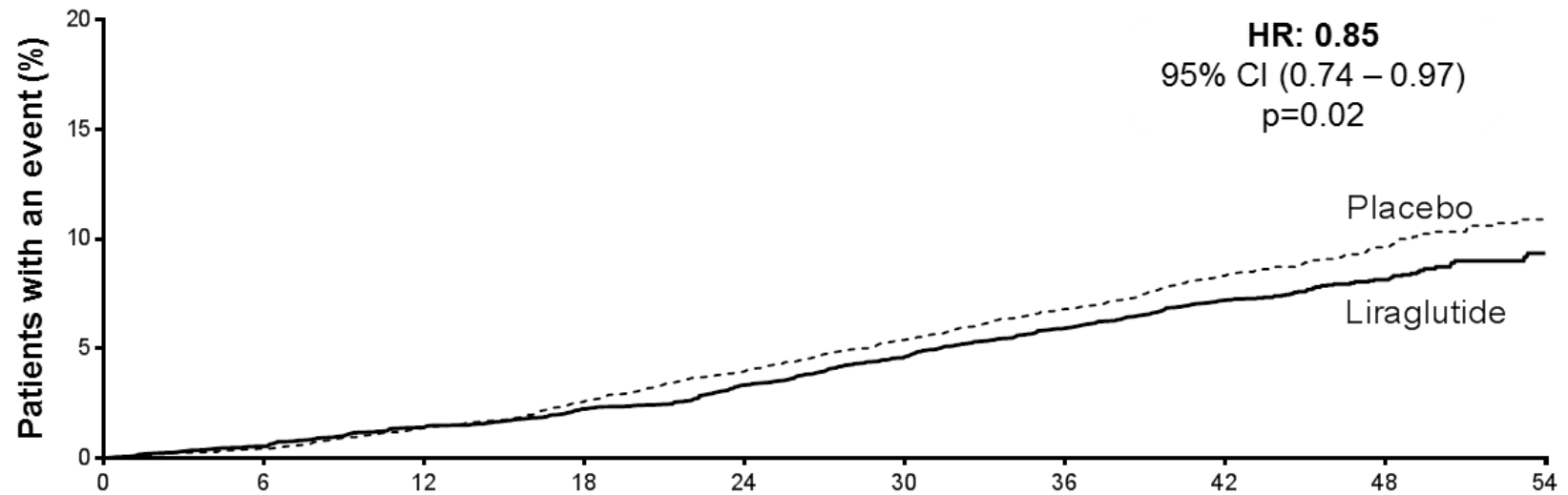
- T2DM, HbA_{1c} ≥7.0%
- Antidiabetic drug naïve; OADs and/or basal/premix insulin
- Age ≥50 years and established CV disease or chronic renal failure
- **or**
- Age ≥60 years and risk factors for CV disease

Key exclusion criteria

- T1DM
- Use of GLP-1RAs, DPP-4i, pramlintide, or rapid-acting insulin
- Familial or personal history of MEN-2 or MTC

CV: cardiovascular; DPP-4i, dipeptidyl peptidase-4 inhibitor; GLP-1RA: glucagon-like peptide-1 receptor agonist; HbA_{1c}: glycated hemoglobin; MEN-2: multiple endocrine neoplasia type 2; MTC: medullary thyroid cancer; OAD: oral antidiabetic drug; OD: once daily; T2DM: type 2 diabetes mellitus.

LEADER - All-cause death



| | Time from randomization (months) | | | | | | | | | |
|------------------|----------------------------------|------|------|------|------|------|------|------|------|-----|
| Patients at risk | 0 | 6 | 12 | 18 | 24 | 30 | 36 | 42 | 48 | 54 |
| Liraglutide | 4668 | 4641 | 4599 | 4558 | 4505 | 4445 | 4382 | 4322 | 1723 | 484 |
| Placebo | 4672 | 4648 | 4601 | 4546 | 4479 | 4407 | 4338 | 4268 | 1709 | 465 |

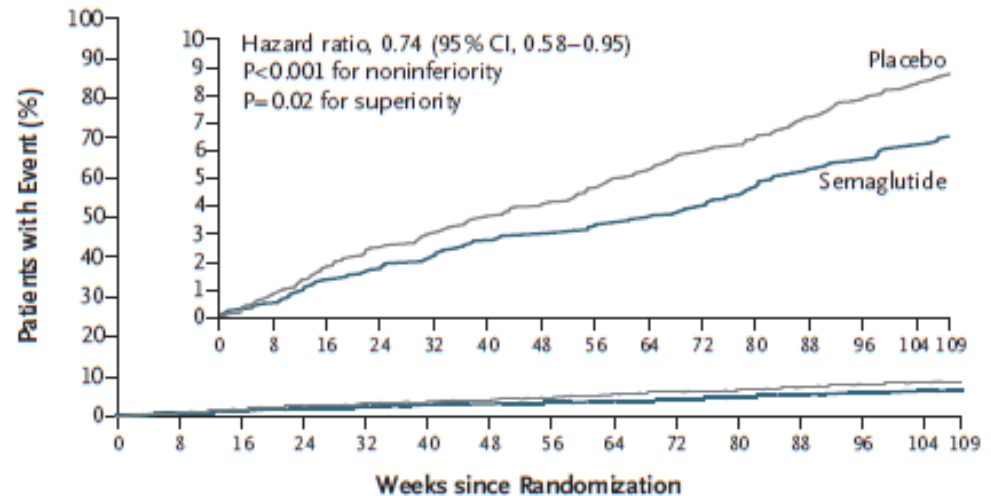
The cumulative incidences were estimated with the use of the Kaplan–Meier method, and the hazard ratios with the use of the Cox proportional-hazard regression model. The data analyses are truncated at 54 months, because less than 10% of the patients had an observation time beyond 54 months. CI: confidence interval; HR: hazard ratio.

ORIGINAL ARTICLE

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

Steven P. Marso, M.D., Stephen C. Bain, M.D., Agostino Consoli, M.D., Freddy G. Eliaschewitz, M.D., Esteban Jódar, M.D., Lawrence A. Leiter, M.D., Ildiko Lingvay, M.D., M.P.H., M.S.C.S., Julio Rosenstock, M.D., Jochen Seufert, M.D., Ph.D., Mark L. Warren, M.D., Vincent Woo, M.D., Oluf Hansen, M.Sc., Anders G. Holst, M.D., Ph.D., Jonas Pettersson, M.D., Ph.D., and Tina Vilsbøll, M.D., D.M.Sc., for the SUSTAIN-6 Investigators*

A Primary Outcome



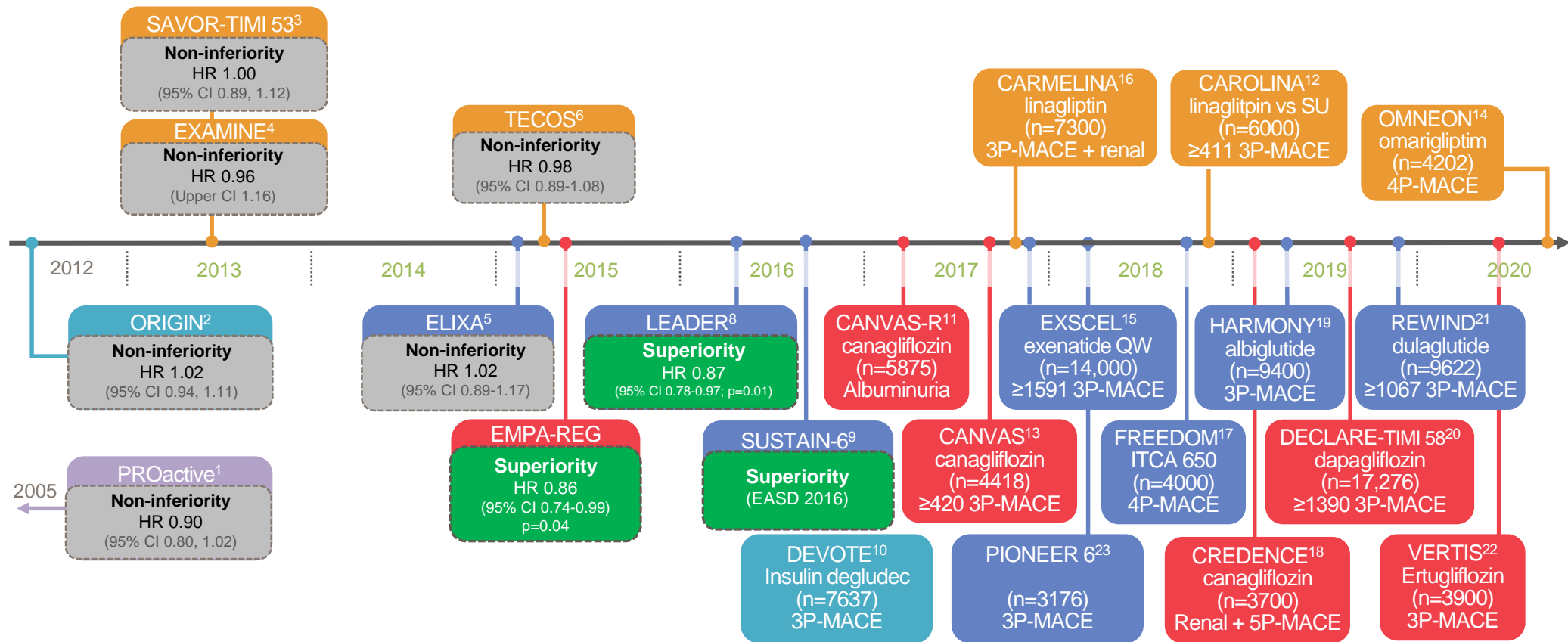
No. at Risk

| | | | | | | | |
|-------------|------|------|------|------|------|------|------|
| Placebo | 1649 | 1616 | 1586 | 1567 | 1534 | 1508 | 1479 |
| Semaglutide | 1648 | 1619 | 1601 | 1584 | 1568 | 1543 | 1524 |

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 - Ja!
- Kan blodsukkersenkende medikamenter redusere dødelighet ved T2D?
 - Ja!

Kardiovaskulære sikkerhetsstudier ved type 2-diabetes



Nøkkel

