

Il rischio cardiovascolare nel diabete tipo 1

Nuove opportunità terapeutiche e
impatto sugli **ENDPOINT EPATICI,**
CARDIOVASCOLARI e RENALI

Sandro Inchiostro

***Direzione Percorso Aziendale
di Cura del Diabete***

4 OTTOBRE 2017
APSS – Trento

TRENTO, Grand Hotel Trento

DICHIARAZIONE CONFLITTO DI INTERESSI

Il sottoscritto_____Inchostro Sandro_____

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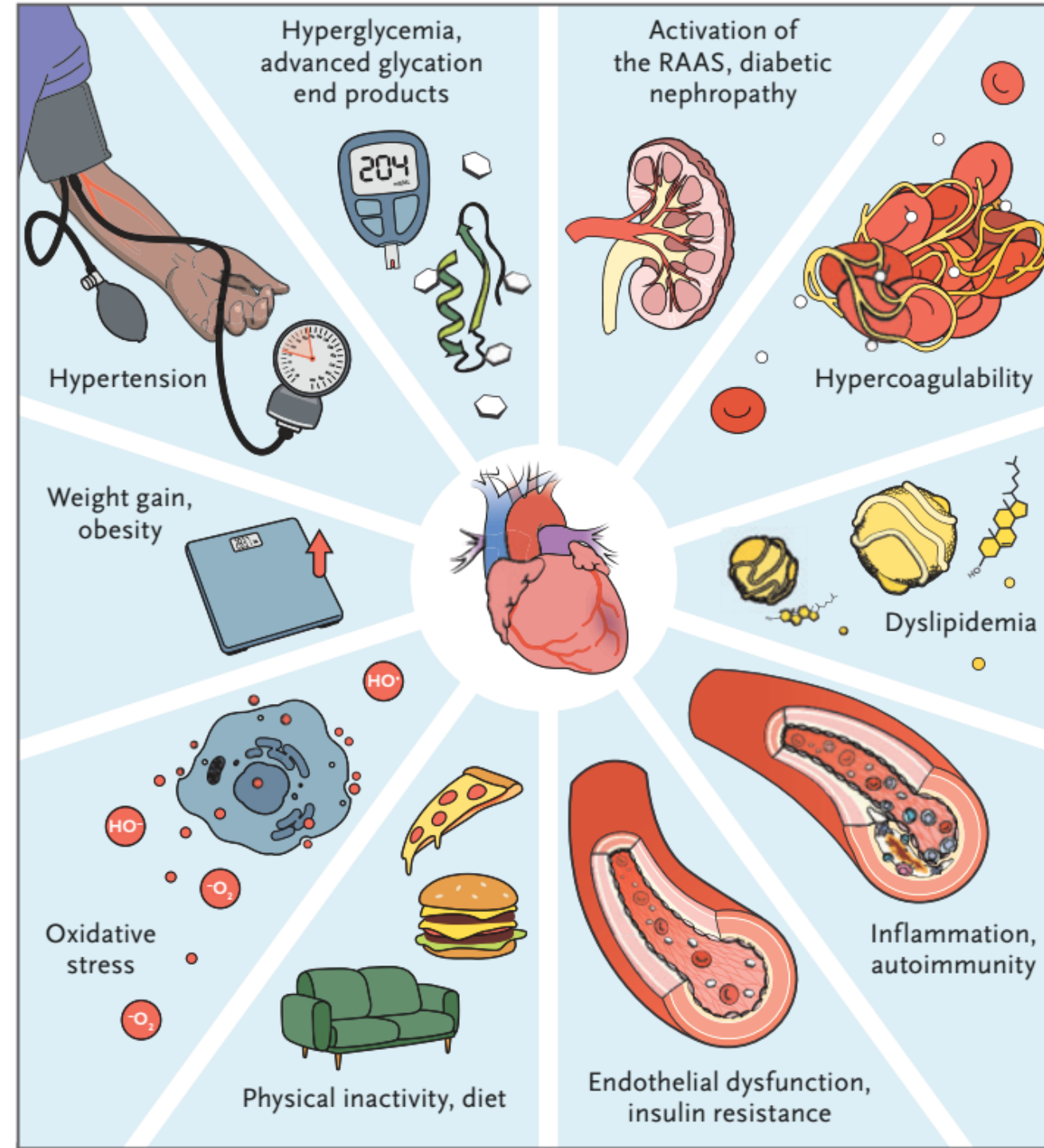
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Pathophysiology of Cardiovascular Disease in Patients with Type 1 Diabetes.



Time course of vascular complications in diabetes

The New England Journal of Medicine

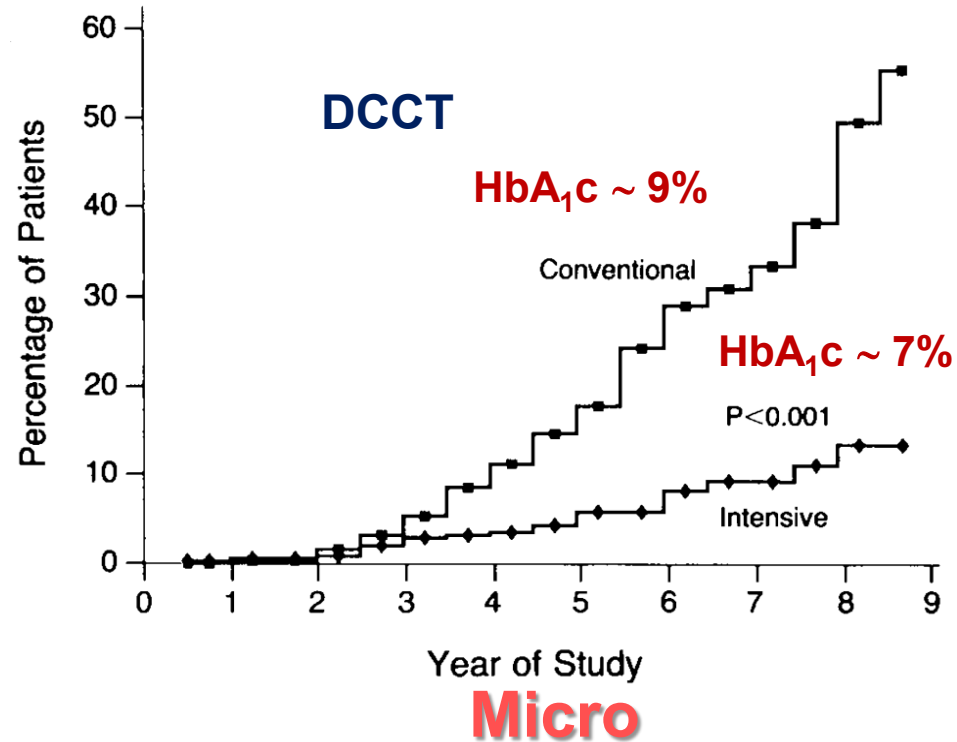
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Volume 329

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Number 14

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



The NEW ENGLAND JOURNAL of MEDICINE

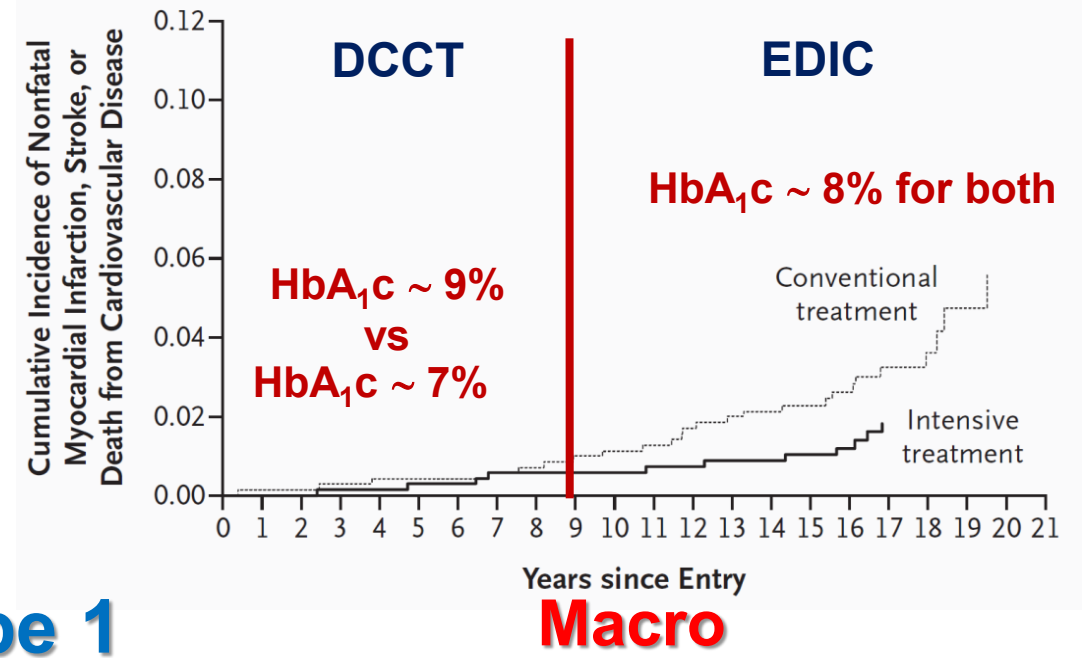
ESTABLISHED IN 1812

DECEMBER 22, 2005

VOL. 353 NO. 25

Intensive Diabetes Treatment and Cardiovascular Disease in Patients with Type 1 Diabetes

The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group*



The NEW ENGLAND JOURNAL *of* MEDICINE

ESTABLISHED IN 1812

APRIL 13, 2017

VOL. 376 NO. 15

Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes

Aidin Rawshani, M.D., Araz Rawshani, M.D., Ph.D., Stefan Franzén, Ph.D., Björn Eliasson, M.D., Ph.D.,
Ann-Marie Svensson, Ph.D., Mervete Miftaraj, M.Sc., Darren K. McGuire, M.D., M.H.Sc.,
Naveed Sattar, M.D., Ph.D., Annika Rosengren, M.D., Ph.D., and Soffia Gudbjörnsdottir, M.D., Ph.D.

We included patients registered in the Swedish National Diabetes Register from 1998 through 2012 and followed them through 2014.

Trends in deaths and cardiovascular events were estimated with Cox regression and standardized incidence rates.

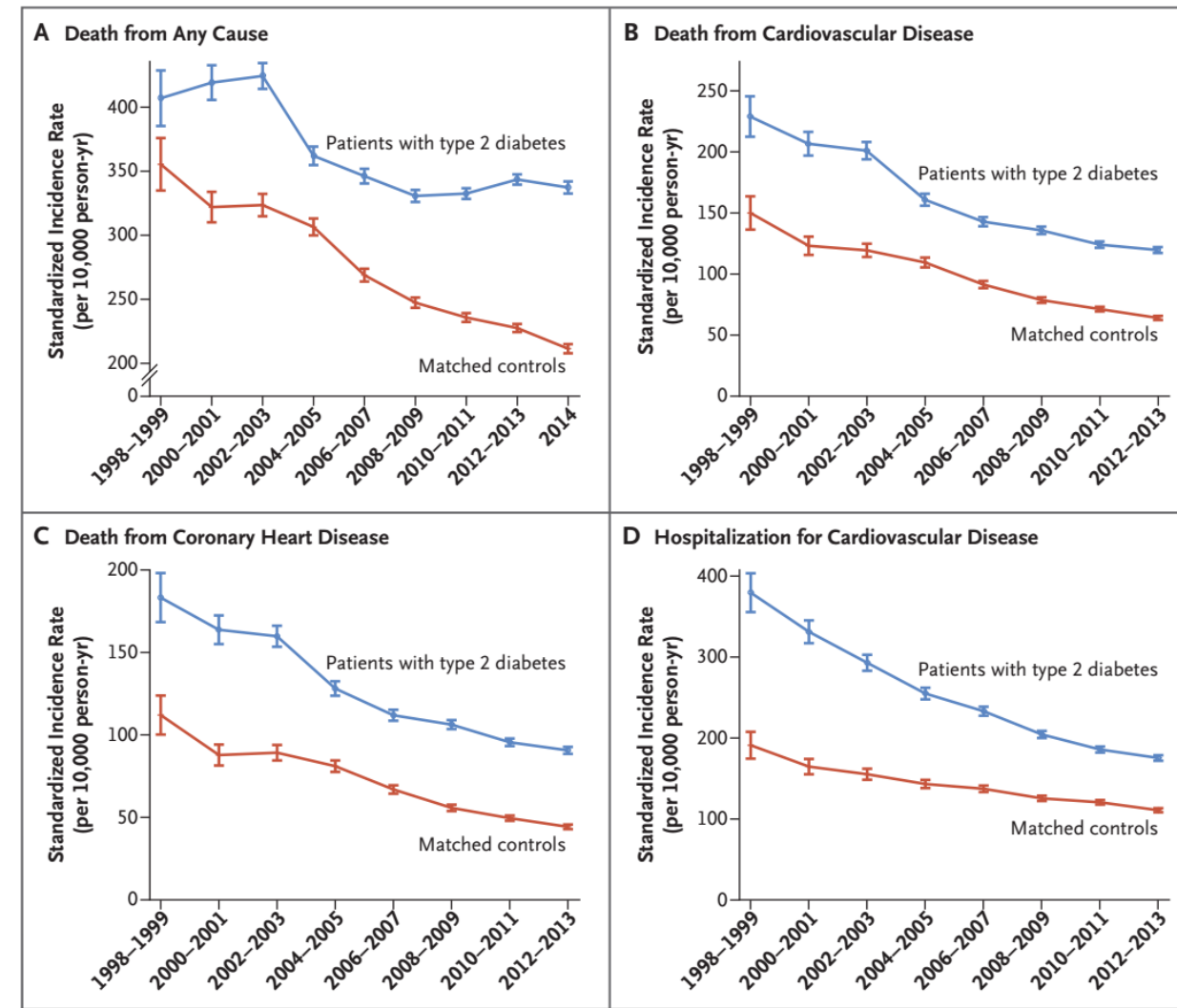
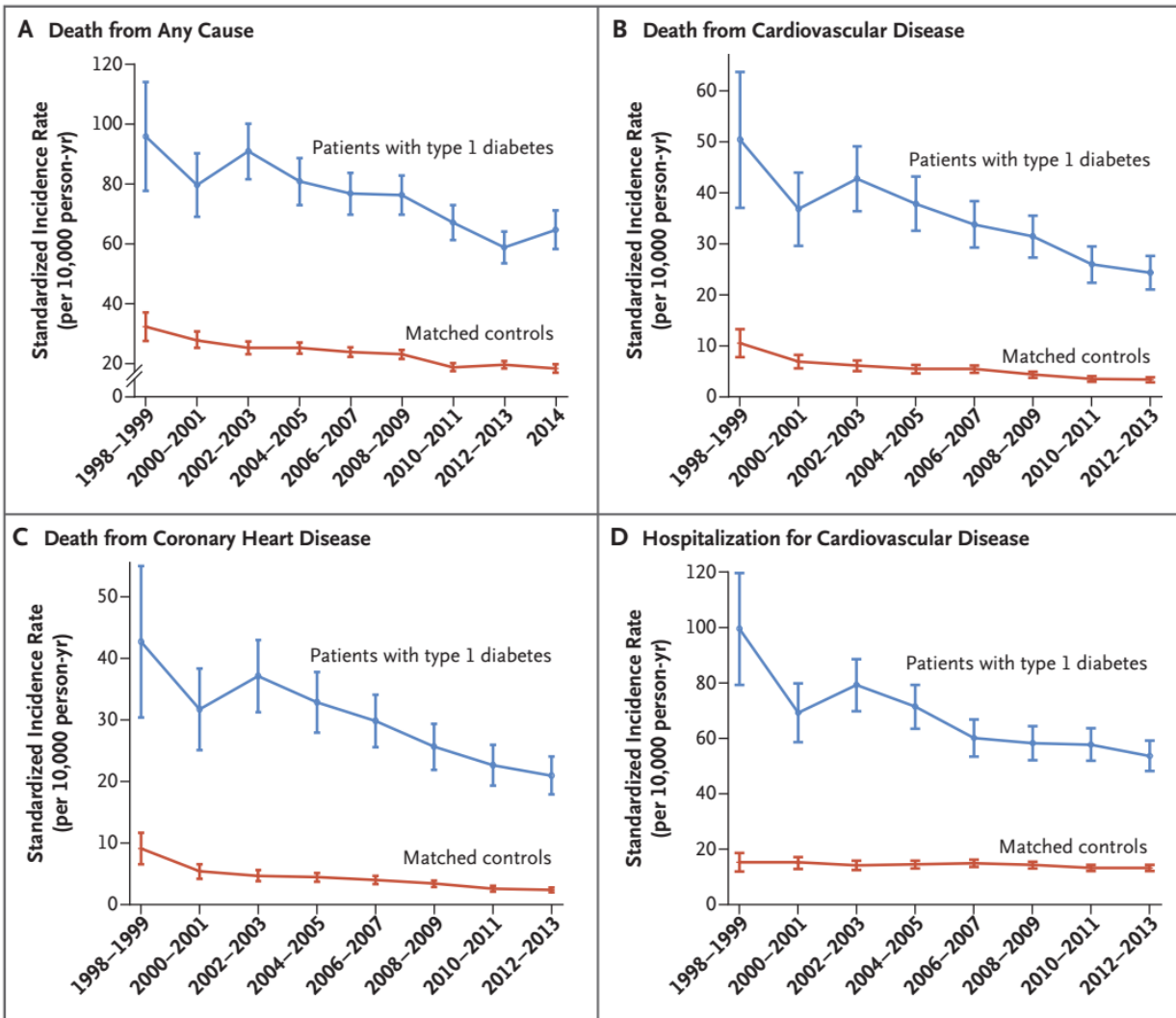
For each patient, controls who were matched for age, sex, and county were randomly selected from the general population.

Follow-up: median of 15 years.

Major Cardiovascular Outcomes in Patients with Type 1 and Type 2 Diabetes and Matched Controls

Type 1 Diabetes

Type 2 Diabetes



Cardiovascular and Renal Disease Burden in Type 1 Compared With Type 2 Diabetes: A Two-Country Nationwide Observational Study

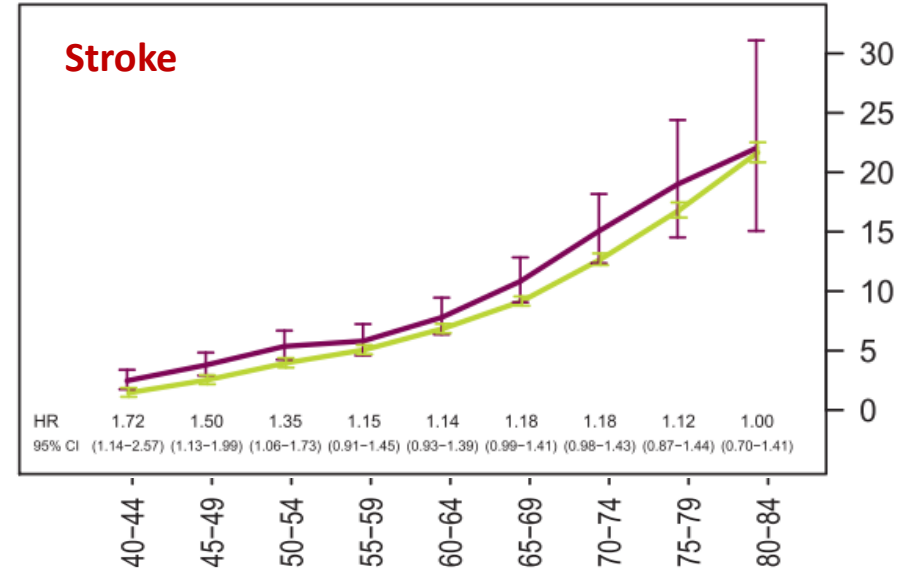
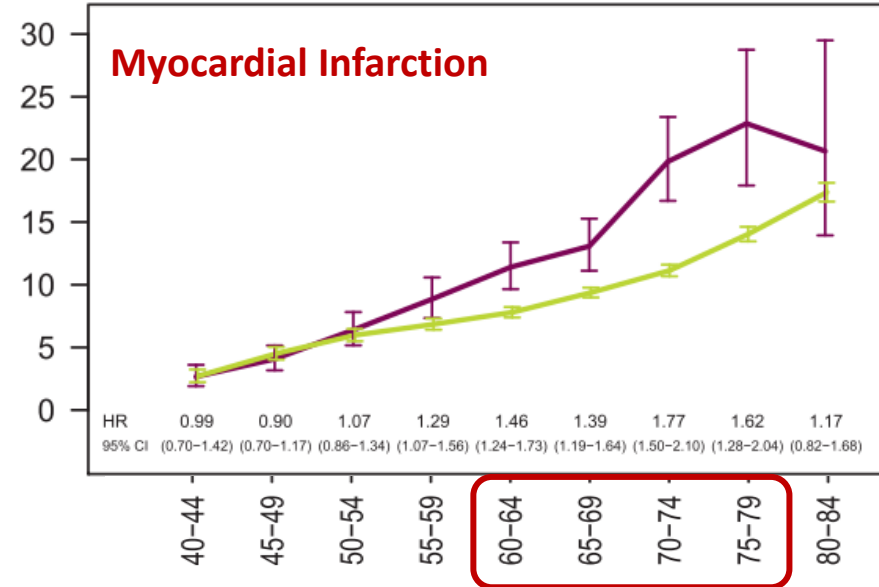
*Robin Kristófi,¹ Johan Bodegard,²
Anna Norhammar,^{3,4} Marcus Thuresson,⁵
David Nathanson,⁶ Thomas Nyström,⁷
Kåre I. Birkeland,⁸ Jan W. Eriksson¹*

Diabetes Care 2021;44:1211–1218 | <https://doi.org/10.2337/dc20-2839>

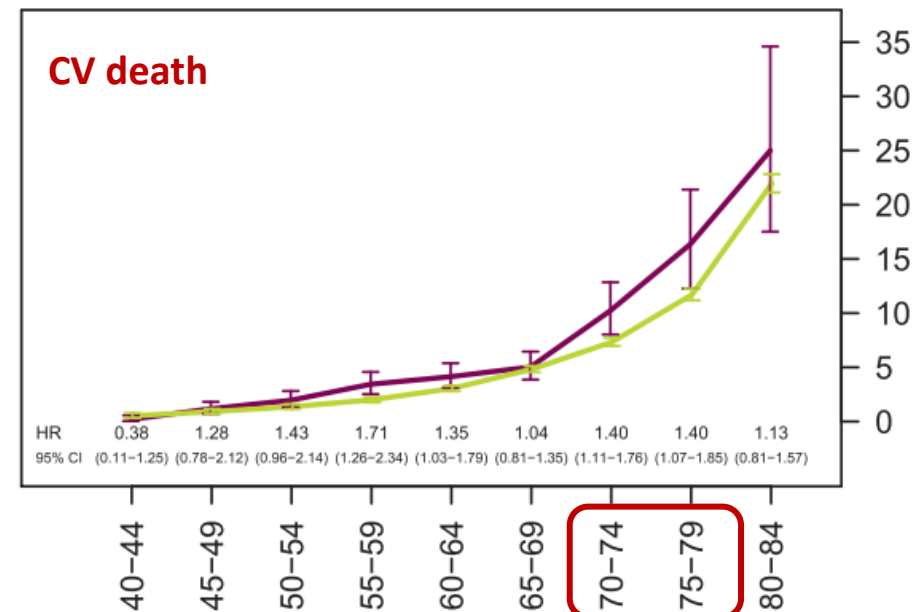
A total of 59,331 patients with T1D and 484,241 patients with T2D, aged 18–84 years, were followed over a mean period of 2.6 years from 31 December 2013.

Patients were identified in nationwide prescribed drug and hospital registries in Norway and Sweden.

Age-stratified incidence of any CVRD events (including MI, stroke, HF, CKD, or CV death), cardiorenal disease (HF or CKD), HF, CKD, MI,stroke, all-cause death, and CV death.



— Type 1 diabetes
— Type 2 diabetes



Risk differences and underlying factors of cardiovascular events and mortality in patients with type 2 diabetes versus type 1 diabetes: a longitudinal cohort study of Swedish nationwide register data

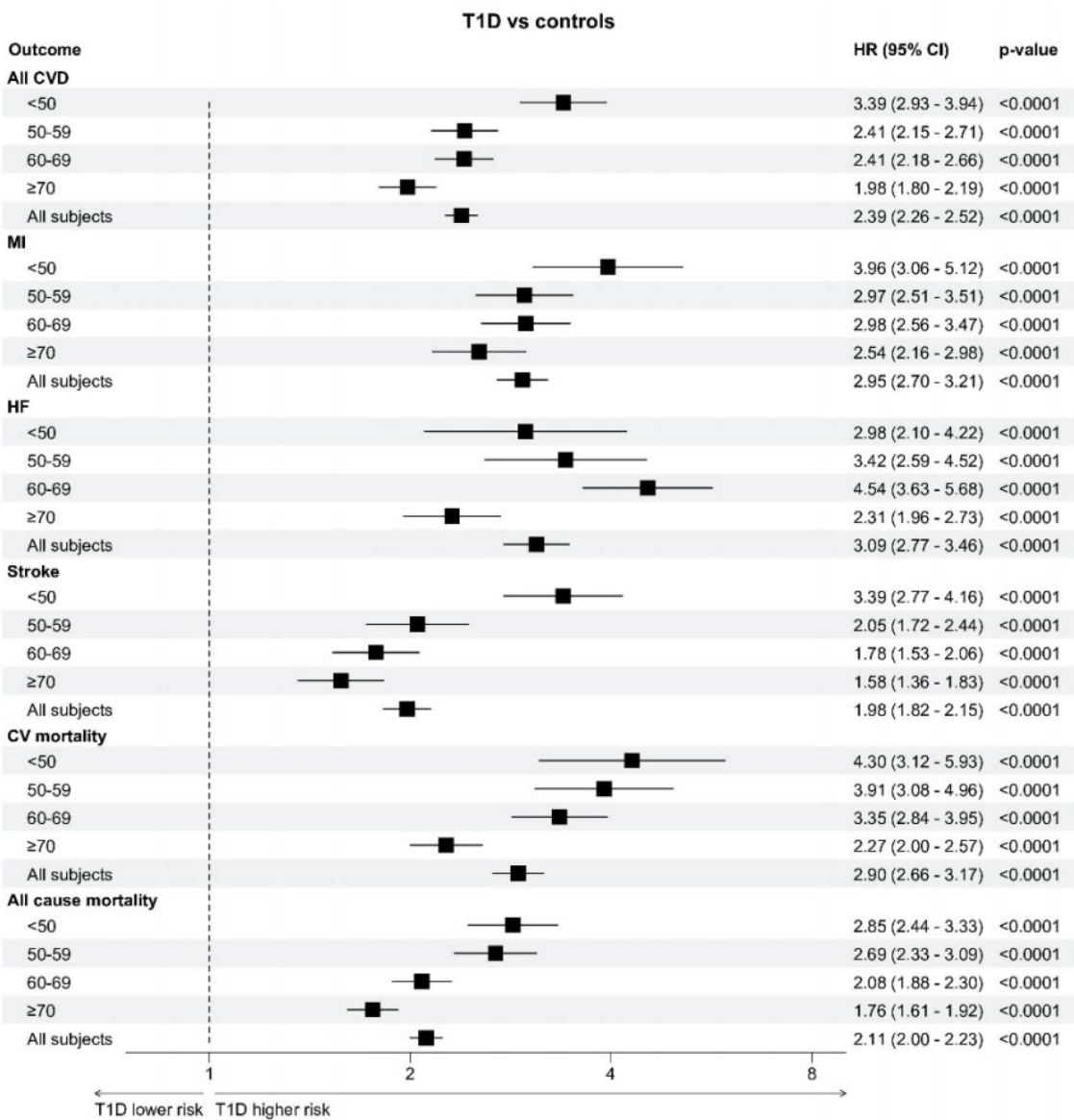
Vagia Patsoukaki, Lars Lind, Erik Lampa, Sadiq Radhi, Katarina Eeg-Olofsson, Björn Eliasson, Jan W Eriksson

This study aimed **to compare the risk of cardiovascular disease and mortality**, as well as the contribution of underlying risk factors, **between type 1 and type 2 diabetes**.

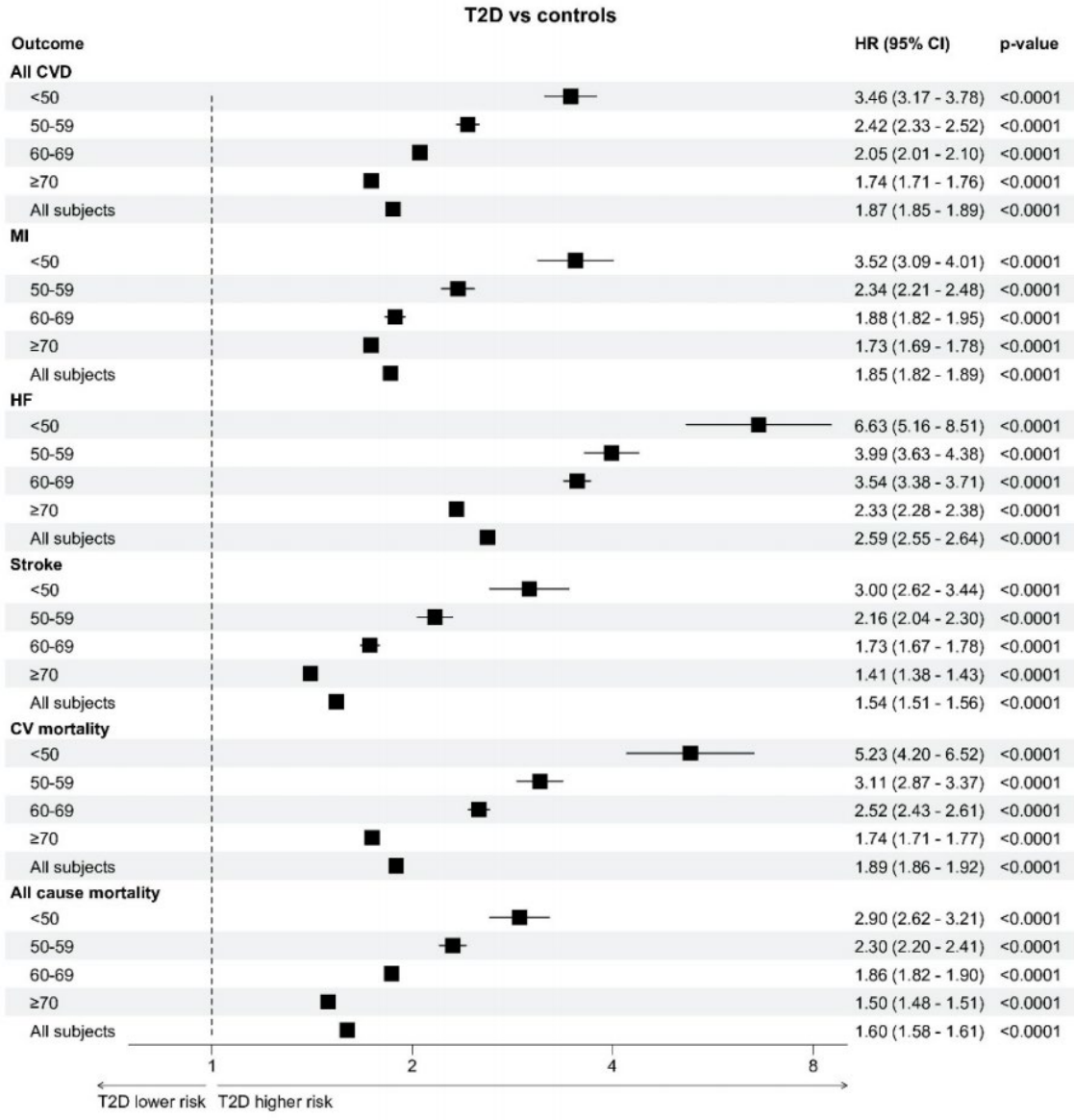
In this nationwide, population-based cohort study, all living people with diabetes aged 18–84 years reported in the **Swedish National Diabetes Register (NDR)** by Jan 1, 2016, were **followed-up over a period of 5 years** until Dec 31, 2020.

In addition, the type 1 diabetes and type 2 diabetes **cohorts were compared with matched control groups with no diabetes**.

Comparison of risk for events in T1D vs matched control group in the whole study population



Comparison of risk for events in T2D vs matched control group in the whole study population



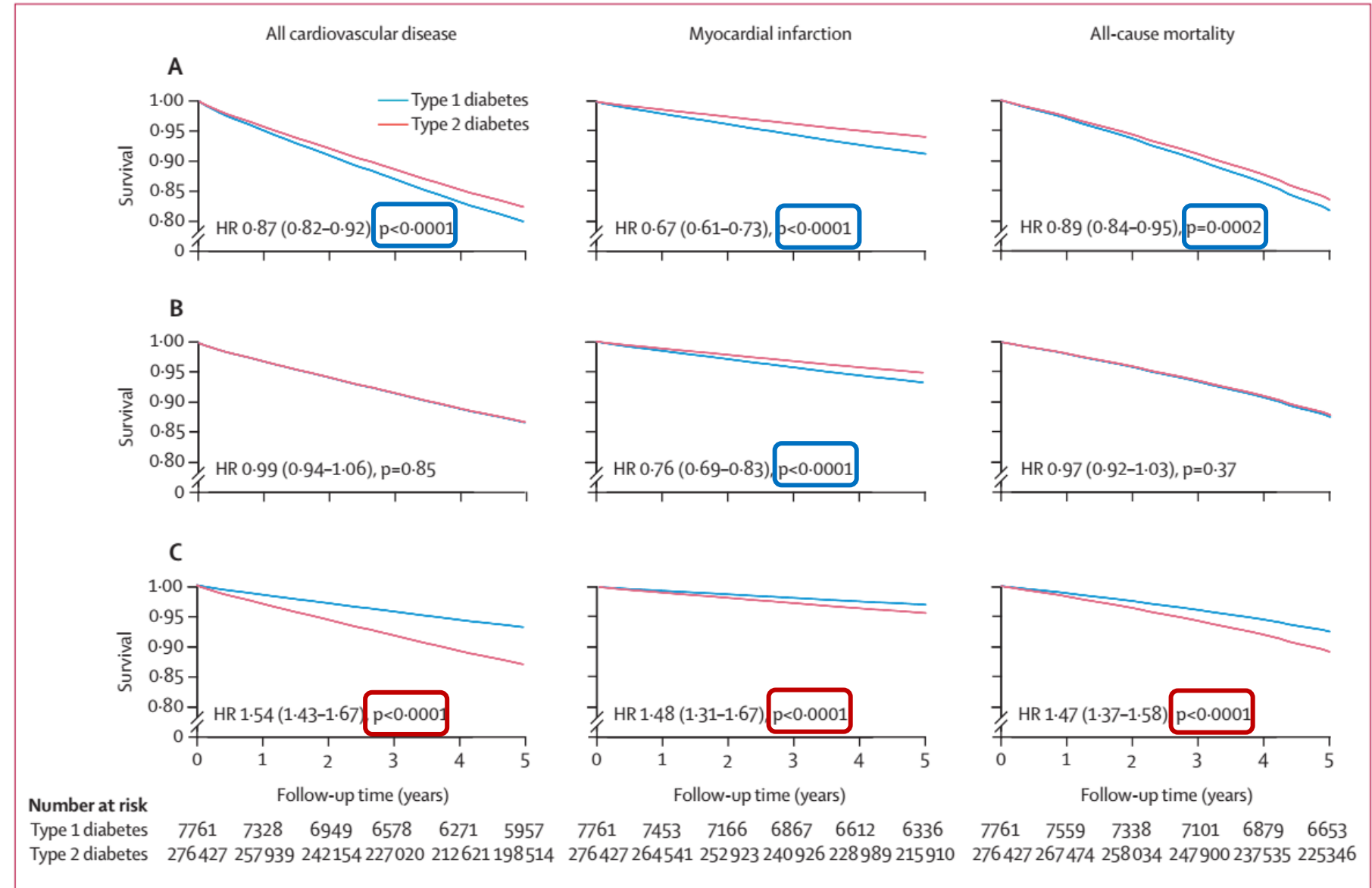
HR 2-4 ↑ both in T1D and T2D vs control *Lancet Diabetes Endocrinol 2025; 13: 848–62*

All CV disease, myocardial infarction, and all-cause mortality during follow-up: event-free survival in the type 2 diabetes compared with type 1 diabetes populations older than 60 years

A) age and sex-adjusted

B) A+ HbA1c, LDL, systolic blood pressure, and smoking

C) A+ B + diabetes duration

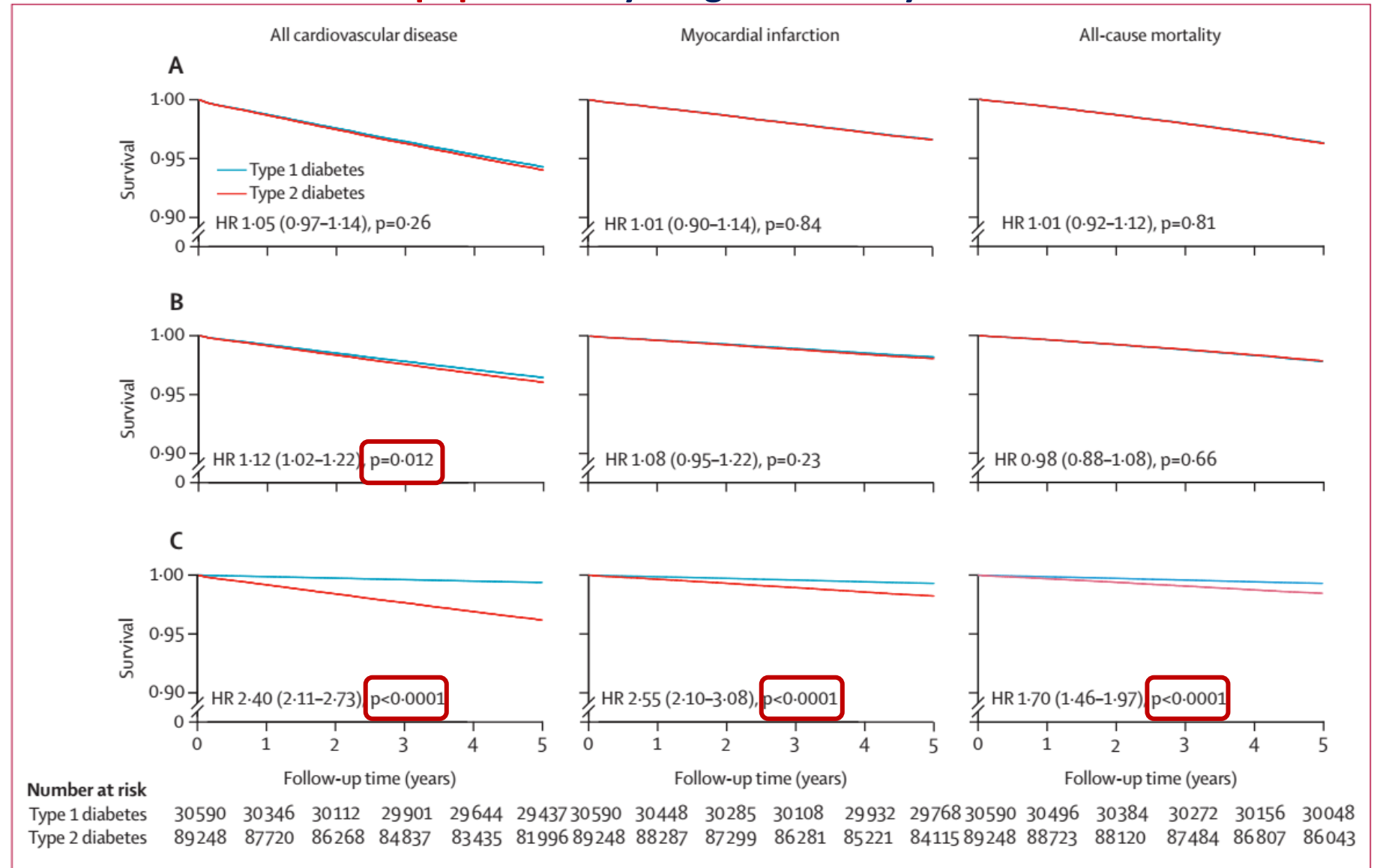


All CV disease, myocardial infarction, and all-cause mortality during follow-up: event-free survival in the type 2 diabetes compared with type 1 diabetes populations younger than 60 years

A) age and sex-adjusted

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Risk differences and underlying factors of cardiovascular events and mortality in patients with type 2 diabetes versus type 1 diabetes: a longitudinal cohort study of Swedish nationwide register data

Vagia Patsoukaki, Lars Lind, Erik Lampa, Sadiq Radhi, Katarina Eeg-Olofsson, Björn Eliasson, Jan W Eriksson

In this study, type 1 diabetes was associated with higher overall risk for cardiovascular disease events and all-cause mortality than type 2 diabetes, particularly at ages older than 60 years for the studied outcomes.

Longer diabetes duration seems to be a main contributing factor for higher risk found in people with type 1 diabetes versus those with type 2 diabetes in this age group.



Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study

Araz Rawshani, Naveed Sattar*, Stefan Franzén, Aidin Rawshani, Andrew T Hattersley, Ann-Marie Svensson, Björn Eliasson, Soffia Gudbjörnsdottir*

Individuals with type 1 diabetes in the **Swedish National Diabetes Register** and matched controls from the general population.

We included patients with at least one registration between Jan 1, 1998, and Dec 31, 2012, **mean age 29 years**

Using Cox regression, and **with adjustment for diabetes duration**, we estimated the excess risk ofcardiovascular mortality, non-cardiovascular mortality, acute myocardial infarction, stroke, cardiovascular disease (a composite of acute myocardial infarction and stroke), coronary heart disease,

Individuals with type 1 diabetes were categorised into five groups, according to age at diagnosis: **0–10 years, 11–15 years, 16–20 years, 21–25 years, and 26–30 years**

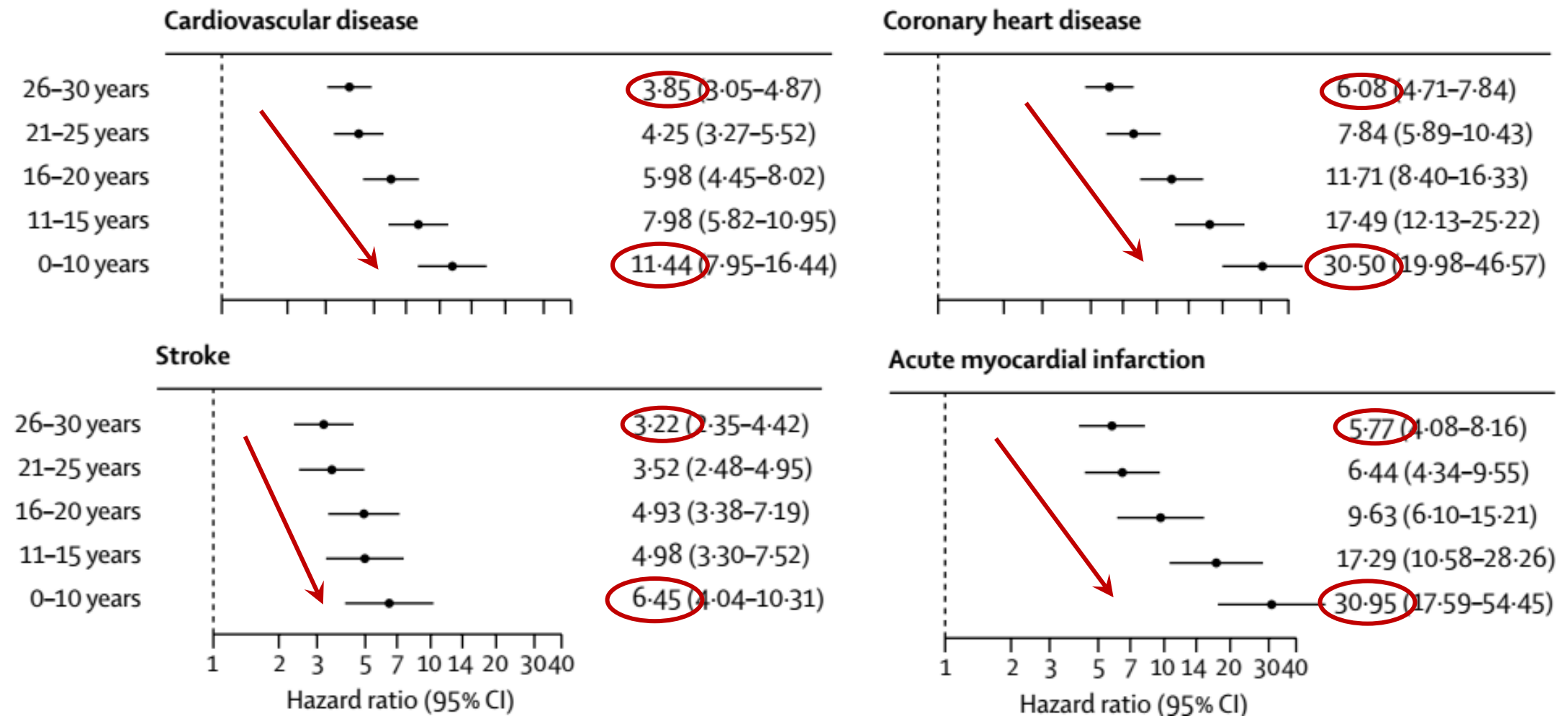
27195 individuals with type 1 diabetes and 135178 matched controls were selected for this study. **Median follow-up ~ 10 years**

Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study



Araz Rawshani*, Naveed Sattar*, Stefan Franzén, Aidin Rawshani, Andrew T Hattersley, Ann-Marie Svensson, Björn Eliasson, Soffia Gudbjörnsdóttir

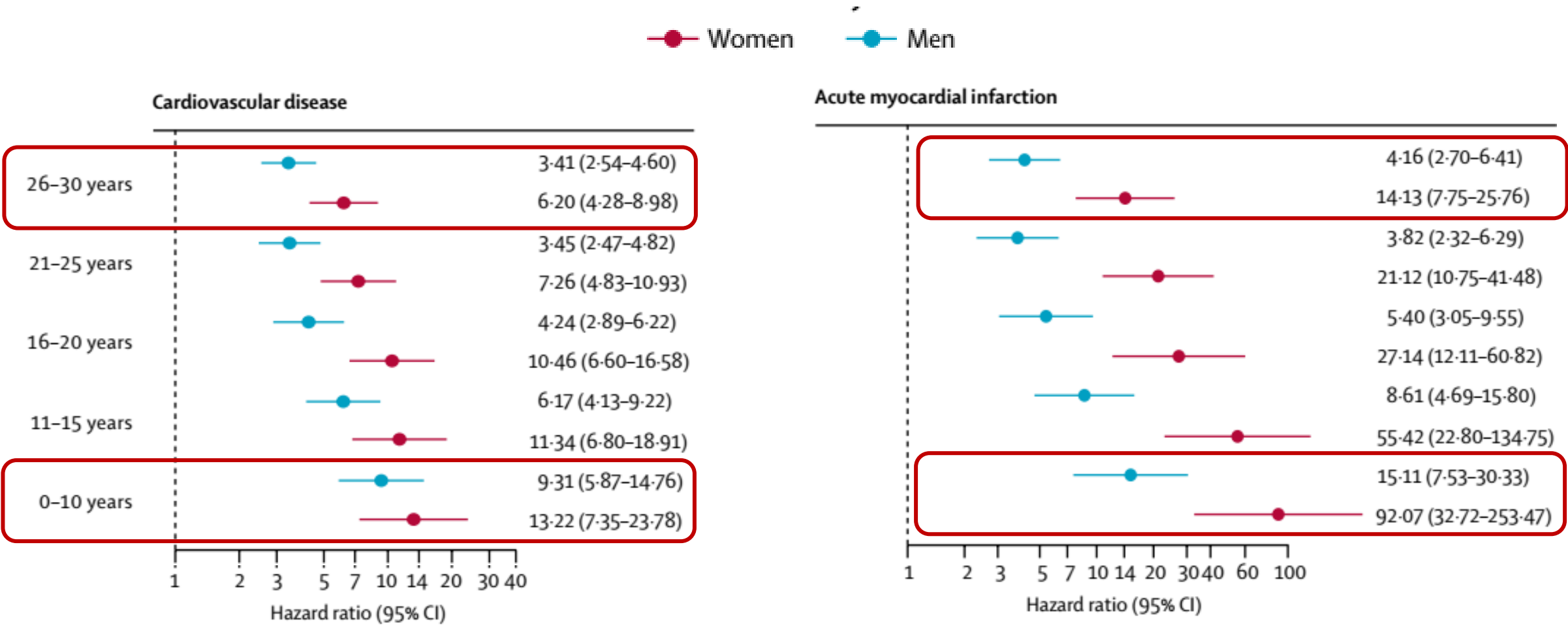
Adjusted hazard ratios for CV disease according to age at type 1 diabetes diagnosis



Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study

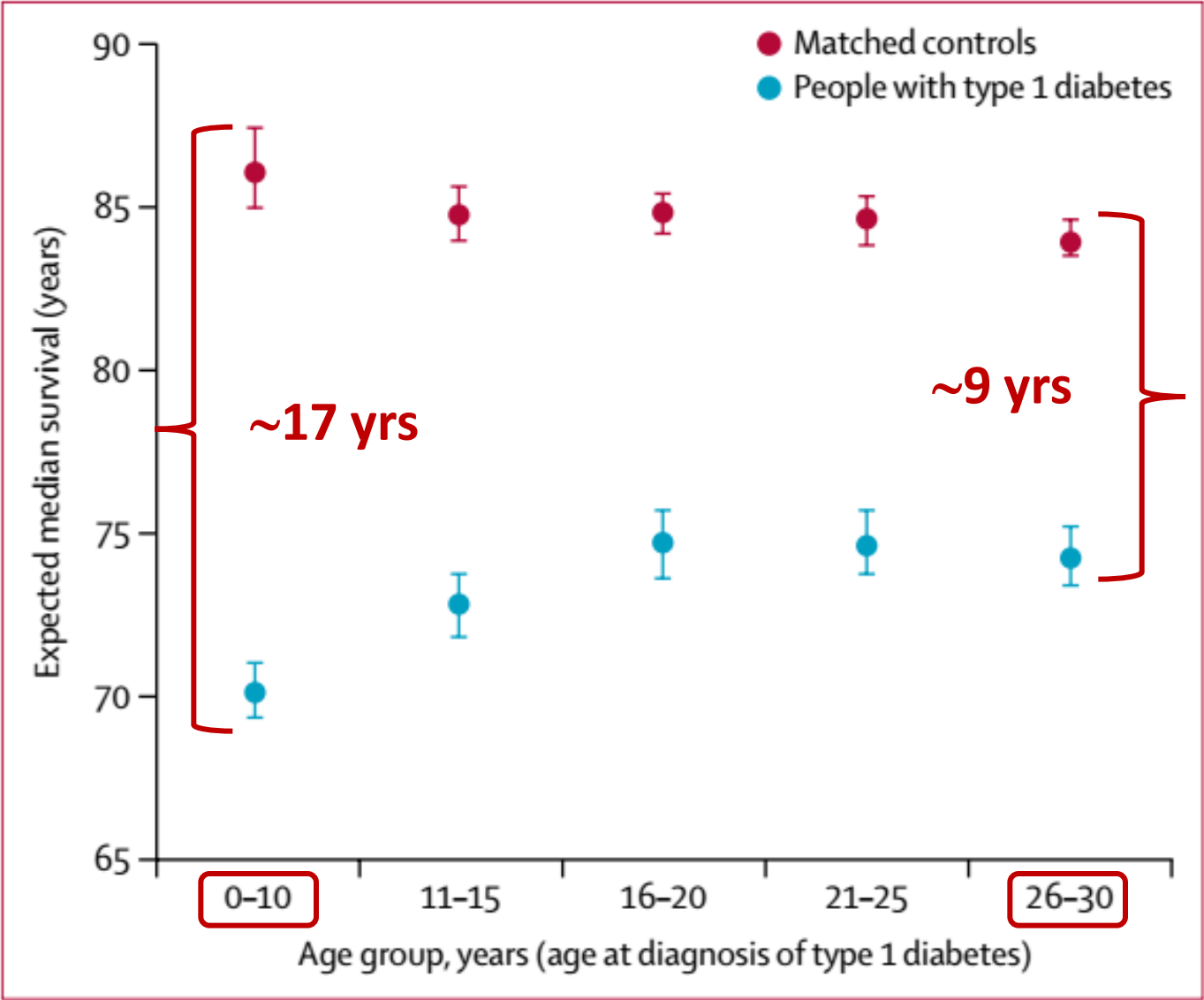
Araz Rawshani*, Naveed Sattar*, Stefan Franzén, Aidin Rawshani, Andrew T Hattersley, Ann-Marie Svensson, Björn Eliasson, Sofia Gudbjörnsdóttir

Adjusted hazard ratios for CV disease and Acute myocardial infarction, according to age at type 1 diabetes diagnosis and sex



Excess mortality and cardiovascular disease in young adults with type 1 diabetes in relation to age at onset: a nationwide, register-based cohort study

Araz Rawshani*, Naveed Sattar*, Stefan Franzén, Aidin Rawshani, Andrew T Hattersley, Ann-Marie Svensson, Björn Eliasson, Sofia Gudbjörnsdóttir



Although the explanations for our findings are likely to be multifaceted, **diabetes duration is likely to have a key role**; even though we adjusted for duration more robustly than other studies, **complete adjustment is impossible**.

ORIGINAL RESEARCH ARTICLE



Relative Prognostic Importance and Optimal Levels of Risk Factors for Mortality and Cardiovascular Outcomes in Type 1 Diabetes Mellitus

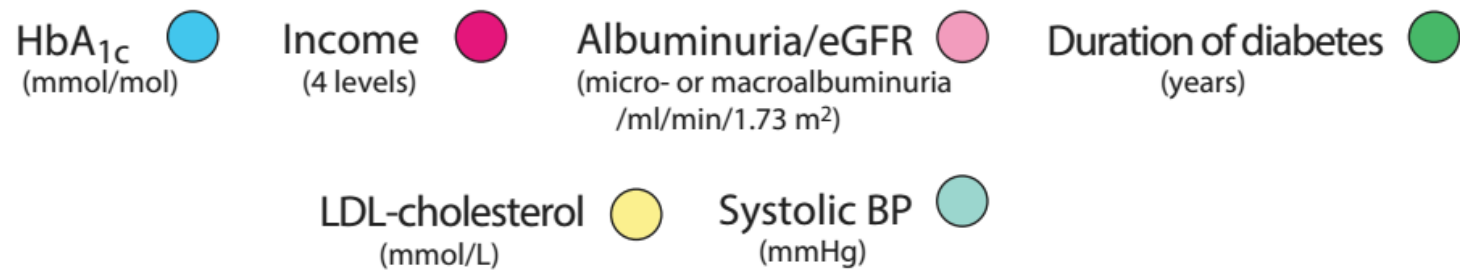
Swedish National Diabetes Register from 1998 to 2014

Relative prognostic importance of **17 risk factors** for death and cardiovascular outcomes

Analysis: Cox regression and machine learning analyses.

32611 patients with type 1 diabetes mellitus

Follow-up of **10.4 years**.



Rank order of importance

Most important

1



1.02 (1.017 - 1.023)



1.028 (1.02 - 1.03)



1.015 (1.011 - 1.02)



3.63 (3.05 - 4.31)

Duration of diabetes

2



2.40 (2.13 - 2.71)



1.47 (1.39 - 1.55)



2.37 (1.98 - 2.84)



1.025 (1.020 - 1.030)

LDL Cholesterol

3



0.49 (0.42 - 0.59)



2.23 (1.94 - 2.57)



1.24 (1.15 - 1.33)



1.35 (1.25 - 1.44)

Albuminuria/eGFR

4



1.01 (1.002 - 1.014)



1.02 (1.016 - 1.024)



1.019 (1.014 - 1.024)



1.008 (1.004 - 1.017)

HbA1c

Least important

5



1.008 (1.005 - 1.01)



1.008 (1.005 - 1.012)



1.015 (1.006 - 1.023)



1.02 (1.01 - 1.028)

Systolic BP

β coefficient*

β coefficient*

β coefficient*

β coefficient*

Death from any cause

Acute myocardial infarction

Stroke

Heart failure

HbA_{1c} (mmol/mol) ●
 Income (4 levels) ●
 Albuminuria/eGFR (micro- or macroalbuminuria /ml/min/1.73 m²) ●
 Duration of diabetes (years) ●

LDL-cholesterol (mmol/L) ●
 Systolic BP (mmHg) ●

Rank order of importance

Most important

1

● 1.02 (1.017 - 1.023)

● 1.028 (1.02 - 1.03)

● 1.015 (1.011 - 1.02)

● 3.63 (3.05 - 4.31)

Systolic BP

2

● 2.40 (2.13 - 2.71)

● 1.47 (1.39 - 1.55)

● 2.37 (1.98 - 2.84)

● 1.025 (1.020 - 1.030)

Albuminuria/eGFR

3

● 0.49 (0.42 - 0.59)

● 2.23 (1.94 - 2.57)

● 1.24 (1.15 - 1.33)

● 1.35 (1.25 - 1.44)

LDL Cholesterol

4

● 1.01 (1.002 - 1.014)

● 1.02 (1.016 - 1.024)

● 1.019 (1.014 - 1.024)

● 1.008 (1.004 - 1.017)

HbA1c

Least important

5

● 1.008 (1.005 - 1.01)

● 1.008 (1.005 - 1.012)

● 1.015 (1.006 - 1.023)

● 1.02 (1.01 - 1.028)

Duration of diabetes

β coefficient*

β coefficient*

β coefficient*

β coefficient*

Death from any cause

Acute myocardial infarction

Stroke

Heart failure

Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study

Diabetes Care 2020;43:867–874 | <https://doi.org/10.2337/dc19-2292>

*Ionut Bebu,¹ David Schade,²
Barbara Braffett,¹ Mikhail Kosiborod,^{3,4}
Maria Lopes-Virella,⁵ Elsayed Z. Soliman,⁶
William H. Herman,⁷ David A. Bluemke,⁸
Amisha Wallia,⁹ Trevor Orchard,¹⁰ and
John M. Lachin,¹ on behalf of the DCCT/EDIC
Research Group**

The Diabetes Control and Complications Trial (DCCT) and its observational follow-up Epidemiology of Diabetes Interventions and Complications (EDIC) **demonstrated the dominant role of glycemia, second only to age, as a risk factor for a first cardiovascular event in type 1 diabetes (T1D).**

We now investigate the association between established risk factors and the **total cardiovascular disease (CVD) burden, including subsequent (i.e., recurrent) events.**

1,441 DCCT/EDIC participants, mean age at baseline 27 years.

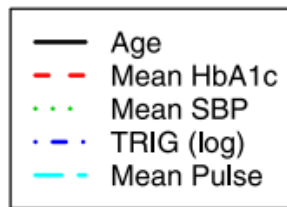
Over a median **follow-up of 29 years**, 239 participants had **421 CVD events**, and 120 individuals had **149 MACE**.



Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study

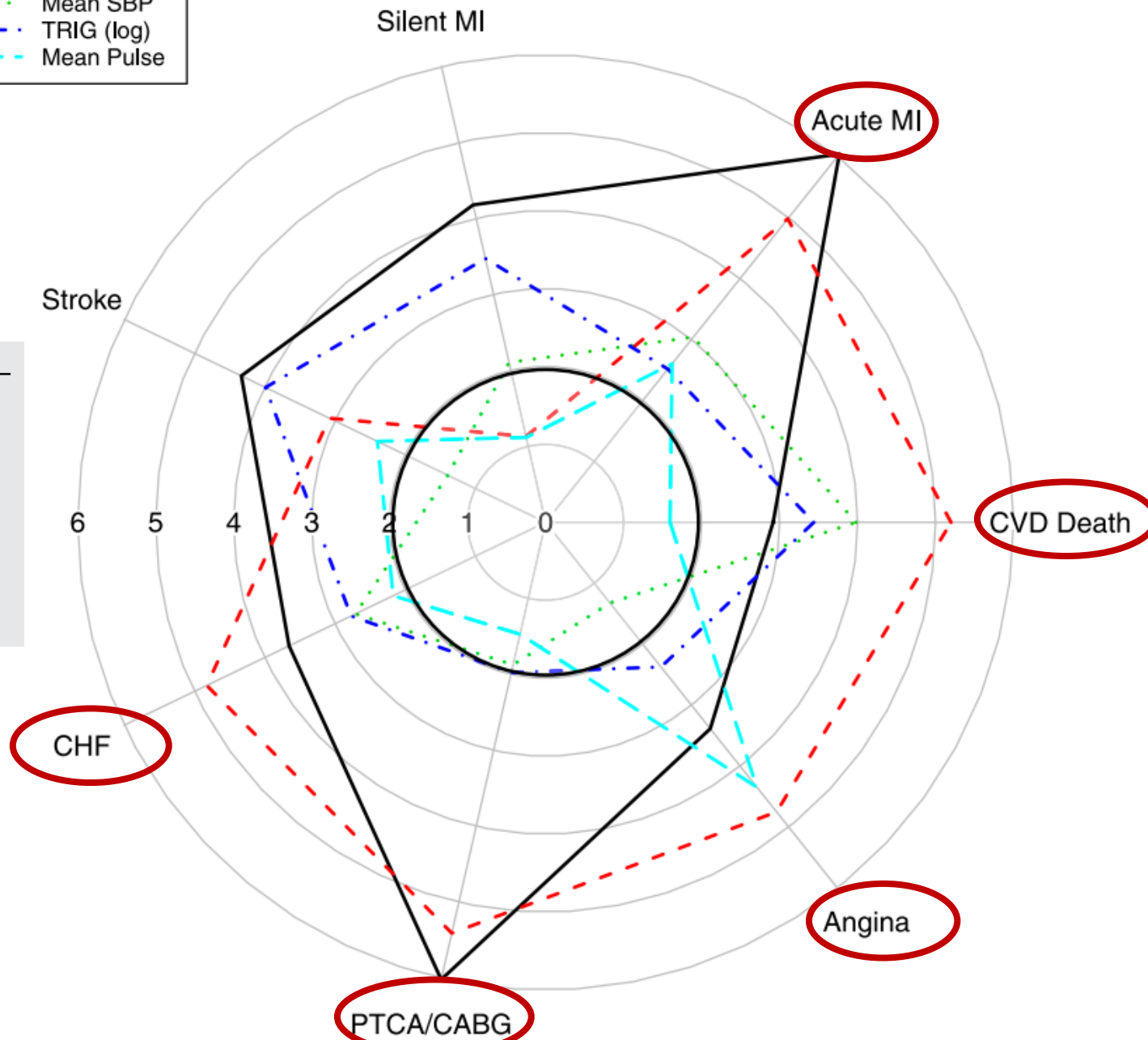
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Multivariable proportional rate models for all (including recurrent) CVD events

	Type*	IR (95% CI)	z score	P value
CVD				
Age (per 5 years)	C	1.51 (1.35, 1.68)	7.325	<0.001
Mean HbA _{1c} (per 1% or 11 mmol/mol)	M	1.53 (1.30, 1.80)	5.165	<0.001
Mean SBP (per 10 mmHg)	M	1.28 (1.07, 1.53)	2.736	0.006
Triglycerides (log) (per 10 mg/dL)	C	1.47 (1.13, 1.92)	2.883	0.004
Mean pulse (per 10 bpm)	M	1.41 (1.08, 1.85)	2.530	0.011
Duration of T1D (per 5 years)	C	1.25 (1.04, 1.50)	2.388	0.017
ACE inhibitor (yes vs. no)	C	0.67 (0.51, 0.88)	−2.821	0.005
Family history of MI (yes vs. no)	B	1.48 (1.08, 2.04)	2.449	0.014
Mean LDLc (per 10 mg/dL)	M	1.03 (0.96, 1.11)	1.018	0.309



Adult-onset type 1 diabetes: predictors of major cardiovascular events and mortality

Yuxia Wei ^{1,*}, Tomas Andersson ¹, Tiinamaija Tuomi ^{2,3,4,5},
Thomas Nyström ⁶, and Sofia Carlsson ^{1,*}

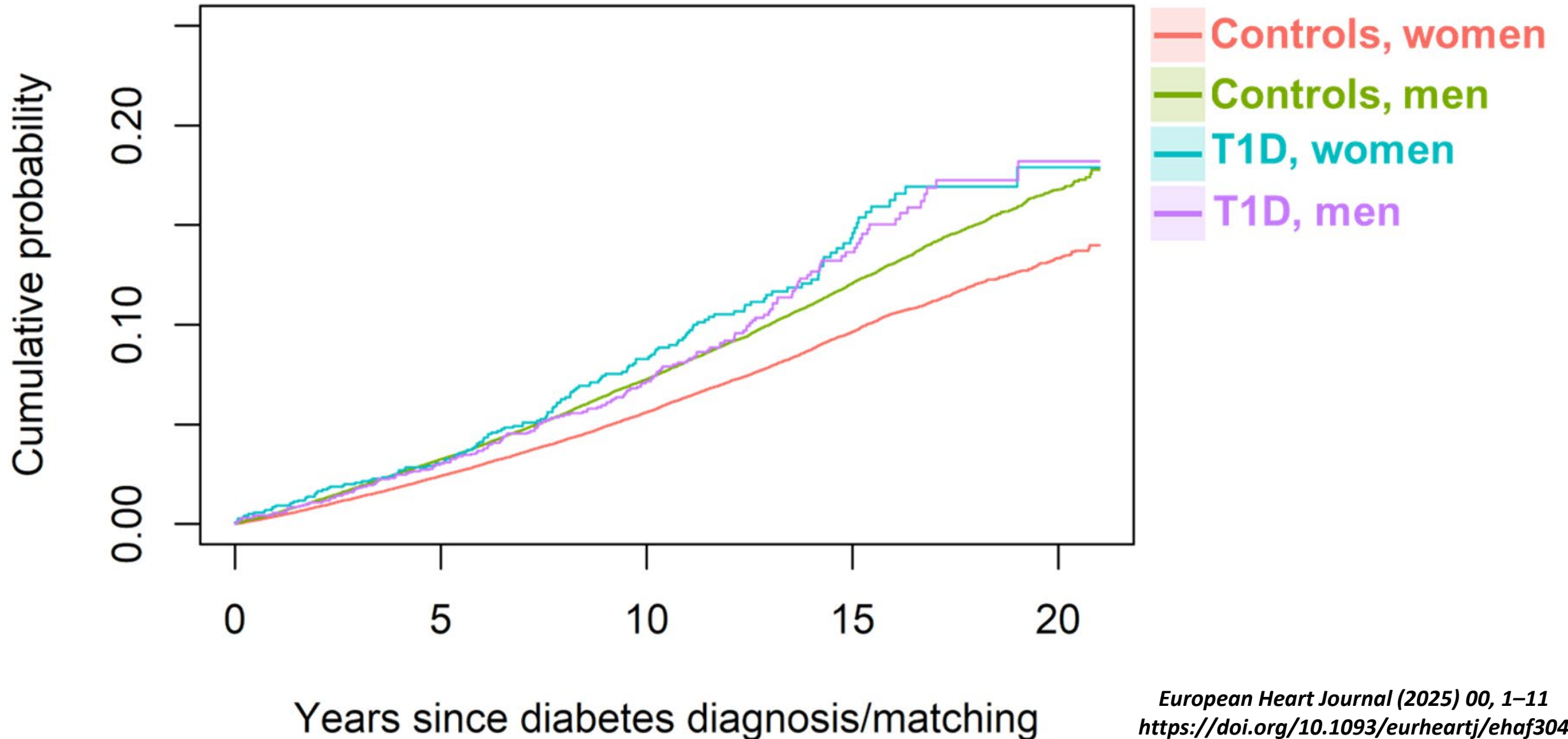
The prognosis of adult-onset type 1 diabetes (T1D) and prognostic factors are sparsely investigated. This study assessed **mortality, major adverse cardiovascular events (MACE)**, and prognostic factors in adult-onset T1D, **particularly focusing on those diagnosed at age ≥ 40 .**

Participants were people diagnosed with adult-onset T1D (n = 10 184) or type 2 diabetes (T2D, n = 375 523) in 2001–2020 from the Swedish National Diabetes Register and 509 172 population controls from the Total Population Register, followed until 2022.

Hazard ratios (HR) and **population attributable risk fraction (PAR%)** were estimated.

Median follow-up of 10.2 years.

Cumulative probability of MACE in T1D diagnosed after age 40 years and matched controls by sex



Hazard ratios for all-cause mortality and MACE in adult-onset type 1 diabetes by baseline prognostic factors

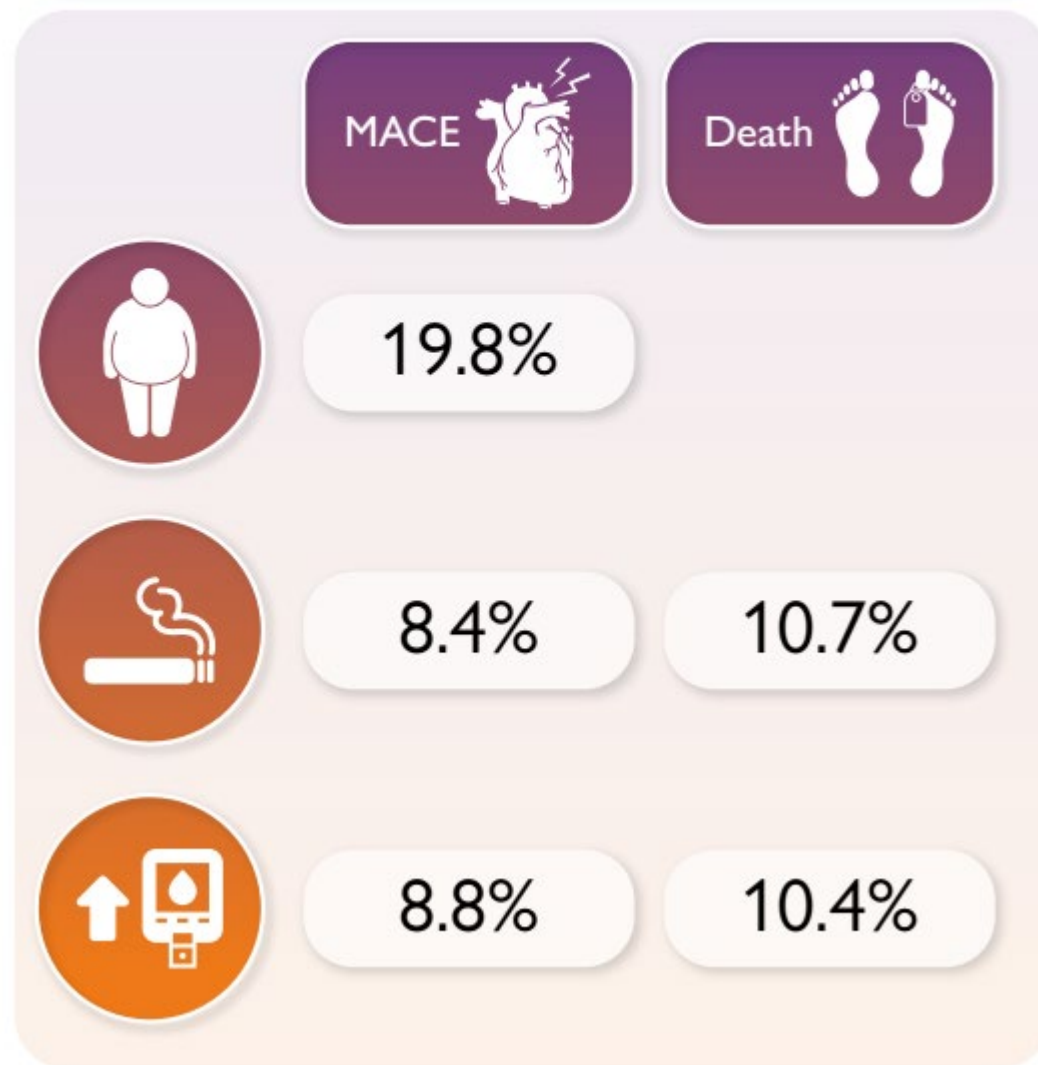
Table 2 Hazard ratios for all-cause mortality and MACE in adult-onset type 1 diabetes by baseline prognostic factors

Lifestyle and clinical characteristics	Overall				T1D diagnosed at age ≥ 40 years			
	Proportion, %	Main model	Mutually adjusted model	PAR %	Proportion, %	Main model	Mutually adjusted model	PAR %
MACE								
Smoking vs. non-smoking	15.4	1.60 (1.12, 2.28)	1.62 (1.12, 2.32)	8.4	18.8	1.50 (1.01, 2.23)	1.52 (1.01, 2.28)	8.9
Being physically inactive vs. active	5.6	1.42 (0.88, 2.29)	1.24 (0.76, 2.01)	1.2	5.5	1.54 (0.99, 2.39)	1.34 (0.86, 2.08)	1.8
BMI								
Underweight	2.6	1.71 (0.73, 3.99)	1.86 (0.80, 4.33)	2.3	1.9	1.53 (0.63, 3.72)	1.71 (0.70, 4.17)	1.3
Overweight	31.3	1.56 (1.16, 2.10)	1.47 (1.06, 2.03)	12.1	35.4	1.50 (1.10, 2.05)	1.41 (0.99, 1.99)	12.2
Obesity	10.2	2.15 (1.50, 3.09)	1.82 (1.18, 2.82)	7.7	12.5	2.09 (1.44, 3.04)	1.76 (1.10, 2.81)	8.6
HbA1c out of target	49.5	1.33 (1.04, 1.69)	1.19 (0.91, 1.54)	8.8	52.4	1.26 (0.98, 1.63)	1.13 (0.86, 1.49)	7.3
Blood pressure out of target	39.4	1.30 (1.01, 1.68)	1.16 (0.89, 1.51)	5.6	54.1	1.20 (0.91, 1.58)	1.07 (0.81, 1.42)	4.0
Triglycerides out of target	13.5	1.72 (1.26, 2.35)	1.31 (0.91, 1.90)	4.2	18.3	1.73 (1.20, 2.49)	1.33 (0.86, 2.06)	5.7
eGFR out of target	2.2	1.46 (1.00, 2.14)	1.39 (0.95, 2.02)	0.7	5.3	1.46 (1.00, 2.15)	1.39 (0.95, 2.03)	1.8
Albuminuria	5.2	1.40 (0.98, 2.00)	1.17 (0.83, 1.65)	0.9	8.8	1.43 (0.99, 2.05)	1.20 (0.85, 1.71)	0.7

Adult-onset type 1 diabetes: predictors of major cardiovascular events and mortality

Yuxia Wei ^{1,*}, Tomas Andersson ¹, Tiinamaija Tuomi ^{2,3,4,5},
Thomas Nyström ⁶, and Sofia Carlsson ^{1,*}

Proportions of events attributed to key prognostic factors in T1D



Original Investigation | Diabetes and Endocrinology

Cardiometabolic Risk Factors and Incident Cardiovascular Disease Events in Women vs Men With Type 1 Diabetes

Barbara H. Braffett, PhD; Ionut Bebu, PhD; Laure El ghormli, MS; Catherine C. Cowie, PhD; William I. Sivitz, MD; Rodica Pop-Busui, MD, PhD; Mary E. Larkin, MS, RN; Rose A. Gubitosi-Klug, MD, PhD; David M. Nathan, MD; John M. Lachin, ScD; Samuel Dagogo-Jack, MD, DSc; for the DCCT/EDIC Research Group

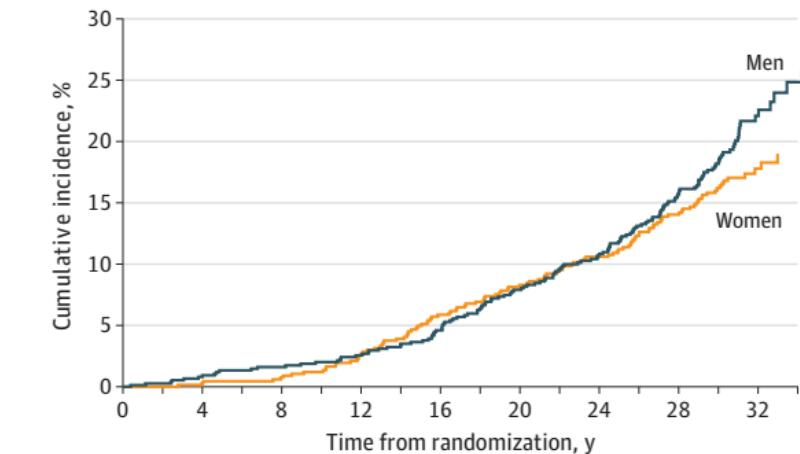
To evaluate cardiometabolic risk factors and their management in association with CVD events in **women vs men with type 1 diabetes enrolled in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study**

Original Investigation | Diabetes and Endocrinology

Cardiometabolic Risk Factors and Incident Cardiovascular Disease Events in Women vs Men With Type 1 Diabetes

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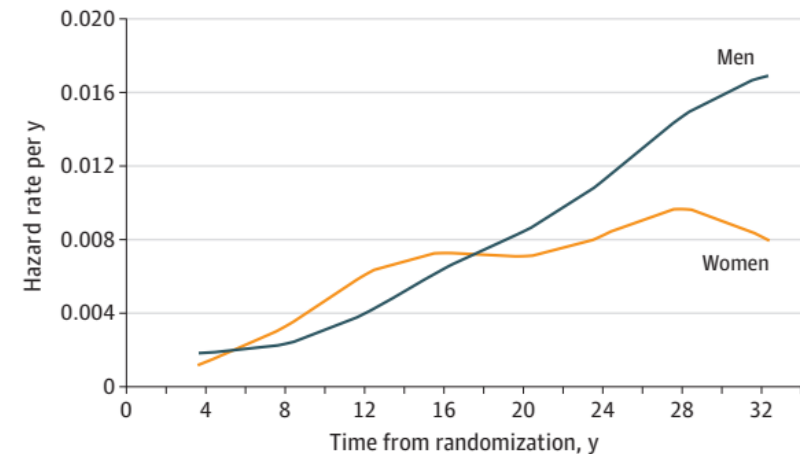
A Incidence of any CVD



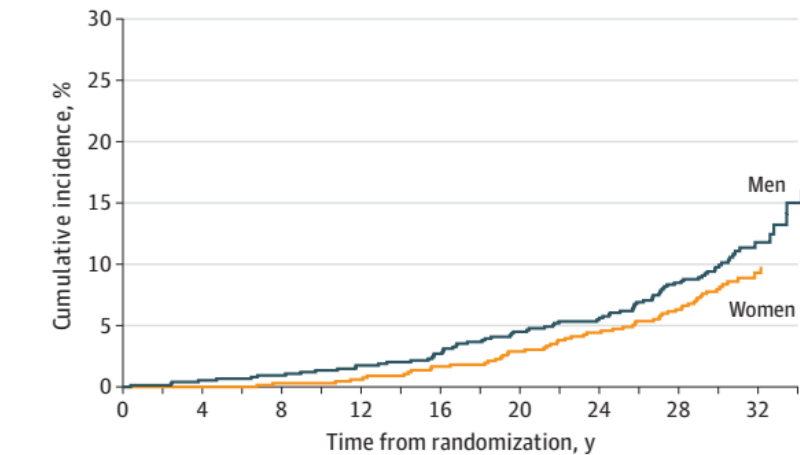
No. at risk

Women	667	666	664	651	626	601	578	544	198
Men	751	743	726	719	702	670	636	588	186

B Hazard rate of any CVD



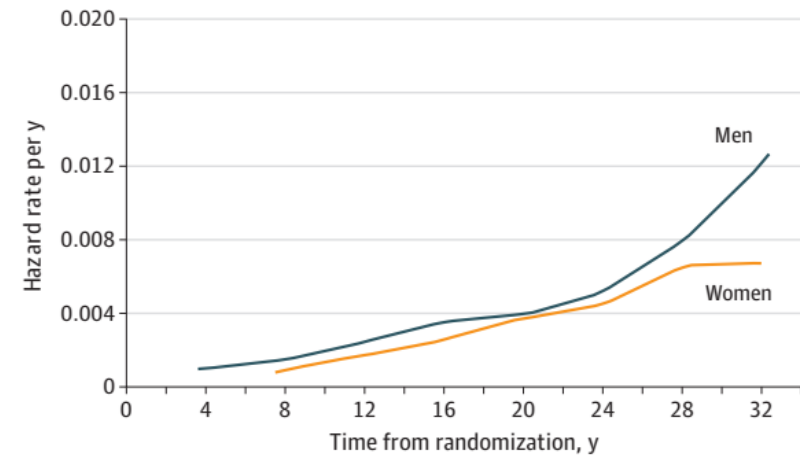
C Incidence of MACE



No. at risk

Women	665	665	664	659	650	632	617	592	214
Men	750	744	730	725	713	693	668	633	204

D Hazard rate of MACE



Original Investigation | Diabetes and Endocrinology

Cardiometabolic Risk Factors and Incident Cardiovascular Disease Events in Women vs Men With Type 1 Diabetes

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Table 2. Mean Differences in Longitudinal Cardiometabolic Risk Factors and HbA_{1c} Between Women and Men During Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications

Measure	Mean (SD)		Women vs men comparison ^a		
	Women (n = 680)	Men (n = 761)	β (SE)	t value/z value ^b	P value
BMI	25.1 (3.0)	25.6 (3.0)	−0.43 (0.16)	−2.75	.006
Waist circumference, cm	82.5 (10.0)	93.1 (10.1)	−10.56 (0.52)	−20.43	<.001
Blood pressure, mm Hg					
Systolic	113.1 (6.9)	118.9 (6.9)	−5.77 (0.35)	−16.55	<.001
Diastolic	72.3 (5.1)	75.5 (5.2)	−3.23 (0.26)	−12.41	<.001
Pulse pressure	40.9 (5.1)	43.5 (5.2)	−2.58 (0.26)	−9.94	<.001
Pulse rate, bpm	75.2 (6.8)	71.8 (6.9)	3.41 (0.35)	9.85	<.001
Any hypertension, % (95% CI) ^c	90.5 (88.2-92.4)	95.3 (93.8-96.4)	−0.75 (0.16)	−4.62	<.001
Lipids, mg/dL					
Total cholesterol	186.0 (26.0)	179.4 (26.0)	6.63 (1.37)	4.83	<.001
HDL cholesterol	58.8 (11.1)	49.4 (11.2)	9.36 (0.57)	16.35	<.001
LDL cholesterol	111.4 (23.1)	112.2 (23.2)	−0.76 (1.22)	−0.62	.53
Triglycerides ^d	79.4 (39.4)	89.5 (39.7)	−10.10 (1.98)	−5.11	<.001
Any hyperlipidemia, % (95% CI) ^c	58.9 (55.2-62.5)	57.1 (53.8-60.2)	0.07 (0.11)	0.70	.49
Medications, % (95% CI)					
ACEIs or ARBs	29.6 (25.7-33.9)	40.0 (36.1-44.0)	−0.46 (0.14)	−3.20	.001
β-blockers	4.4 (3.5-5.6)	5.1 (4.1-6.3)	−0.14 (0.16)	−0.86	.39
Calcium channel blockers	5.2 (4.1-6.6)	5.9 (4.7-7.5)	−0.14 (0.19)	−0.74	.46
Lipid-lowering	25.3 (22.1-28.7)	39.6 (36.1-43.2)	−0.66 (0.12)	−5.75	<.001
Kidney disease, % (95% CI) ^c					
Any sustained eGFR<60 mL/min/1.73 m ²	2.4 (1.7-3.5)	2.9 (2.1-4.1)	−0.19 (0.20)	−0.93	.35
Any sustained AER ≥30 mg/24 h	16.2 (12.8-20.4)	23.8 (20.3-27.8)	−0.48 (0.20)	−2.40	.02
Any AER ≥300 mg/24 h	6.0 (4.6-7.8)	12.5 (10.5-14.9)	−0.80 (0.17)	−4.71	<.001
Glycemic control					
HbA _{1c} , %	8.3 (1.0)	8.1 (1.0)	0.13 (0.05)	2.46	.01
HbA _{1c} , mmol/mol	66.7 (10.8)	65.3 (10.9)	1.41 (0.57)	2.46	.01

Original Investigation | Diabetes and Endocrinology

Cardiometabolic Risk Factors and Incident Cardiovascular Disease Events in Women vs Men With Type 1 Diabetes

Barbara H. Braffett, PhD; Ionut Bebu, PhD; Laure El ghormli, MS; Catherine C. Cowie, PhD; William I. Sivitz, MD; Rodica Pop-Busui, MD, PhD; Mary E. Larkin, MS, RN; Rose A. Gubitosi-Klug, MD, PhD; David M. Nathan, MD; John M. Lachin, ScD; Samuel Dagogo-Jack, MD, DSc; for the DCCT/EDIC Research Group

Compared with men with type 1 diabetes, women with type 1 diabetes

- ✓ **may have a lower burden of cardiometabolic risk factors,**
- ✓ **receive less aggressive cardioprotective medications (despite current guidelines),**
- ✓ **have no advantage associated with sex in CVD outcomes**

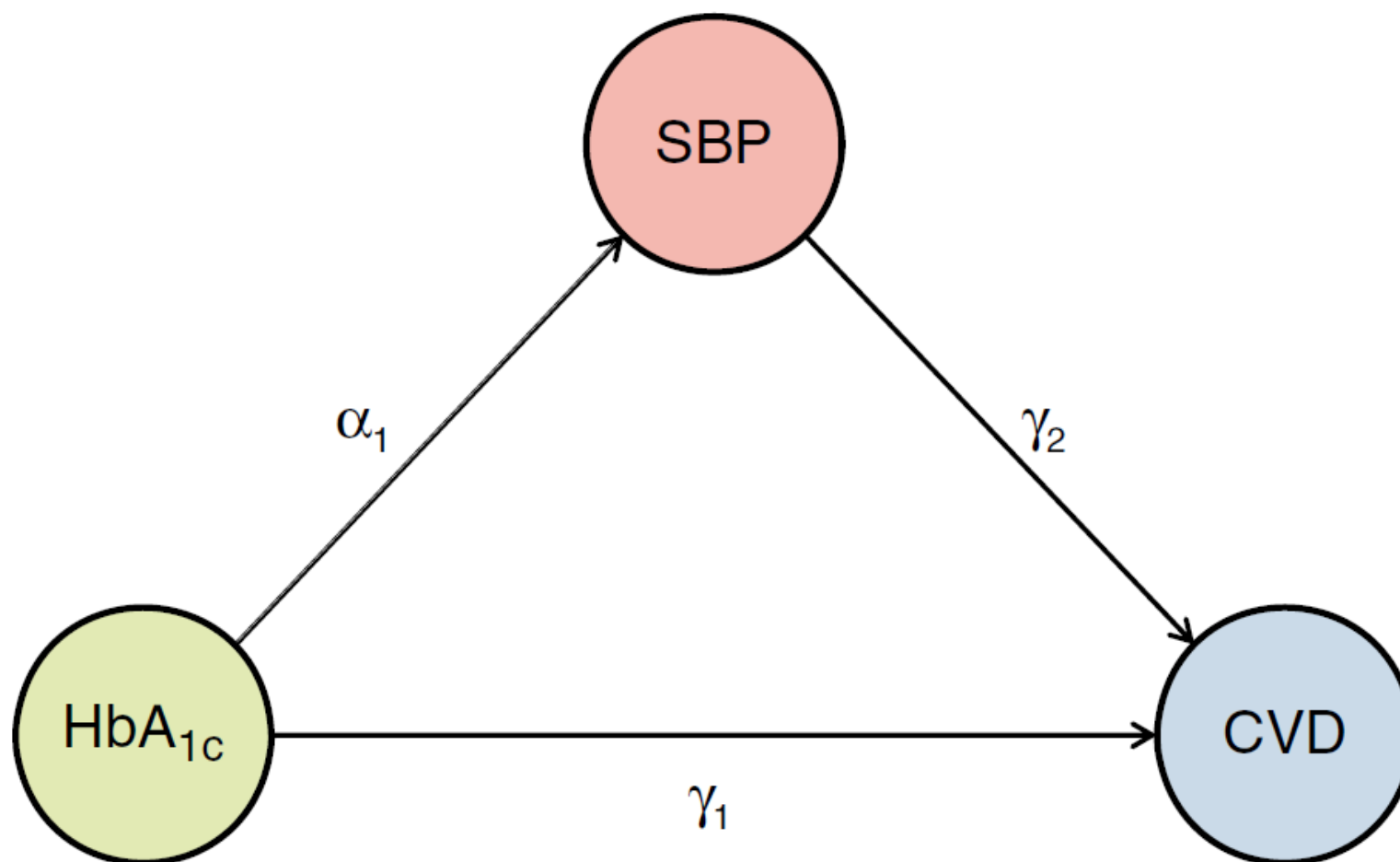
The relationship of blood glucose with cardiovascular disease is mediated over time by traditional risk factors in type 1 diabetes: the DCCT/EDIC study

Ionut Bebu¹ · Barbara H. Braffett¹ · Rodica Pop-Busui² · Trevor J. Orchard³ · David M. Nathan⁴ · John M. Lachin¹ · the DCCT/EDIC Research Group

Our aim was to describe the degree to which the effect of HbA1c on the risk of CVD is mediated by its effect on traditional risk factors over time, and how these mediation pathways change over time

The relationship of blood glucose with cardiovascular disease is mediated over time by traditional risk factors in type 1 diabetes: the DCCT/EDIC study

Ionut Bebu¹ · Barbara H. Braffett¹ · Rodica Pop-Busui² · Trevor J. Orchard³ · David M. Nathan⁴ · John M. Lachin¹ · the DCCT/EDIC Research Group



**The relationship of blood glucose with cardiovascular disease
is mediated over time by traditional risk factors in type 1 diabetes:
the DCCT/EDIC study**

Ionut Bebu¹ · Barbara H. Braffett¹ · Rodica Pop-Busui² · Trevor J. Orchard³ ·
David M. Nathan⁴ · John M. Lachin¹ · the DCCT/EDIC Research Group

**Decomposition of the total effect of HbA1c on CVD
risk into the direct and indirect effects**



Associations of Microvascular Complications With the Risk of Cardiovascular Disease in Type 1 Diabetes

*Rose Gubitosi-Klug,¹ Xiaoyu Gao,² Rodica Pop-Busui,³ Ian H. de Boer,⁴ Neill White,⁵ Lloyd P. Aiello,⁶ Ryan Miller,⁷ Jerry Palmer,⁸ William Tamborlane,⁹ Amisha Wallia,¹⁰ Mikhail Kosiborod,¹¹ John M. Lachin,² Ionut Bebu,² and the DCCT/EDIC Research Group**

Diabetes Care 2021;44:1499–1505 | <https://doi.org/10.2337/dc20-3104>

We examined whether the presence of microvascular complications was associated with increased subsequent risk of cardiovascular disease (CVD) among participants with type 1 diabetes in the Diabetes Control and Complications Trial and Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) study followed for >35 years.

Table 3—Associations (HRs, 95% CIs, and P values) of prior microvascular complications with new-onset CVD events (A) and MACE (B)

	Unadjusted models		Minimally adjusted models*		Fully adjusted models^	
	HR (95% CI)	P value	HR (95% CI)	P value	HR (95% CI)	P value
A. CVD						
PDR and/or CSME	1.98 (1.51, 2.58)	<0.0001	1.47 (1.11, 1.94)	0.0069	1.13 (0.84, 1.53)	0.4033
PDR	1.91 (1.44, 2.55)	<0.0001	1.44 (1.06, 1.95)	0.0187	1.09 (0.79, 1.51)	0.5852
CSME	1.86 (1.40, 2.46)	<0.0001	1.33 (0.99, 1.77)	0.0562	1.03 (0.77, 1.40)	0.8244
Three-step progression	1.18 (0.90, 1.55)	0.2391	0.89 (0.66, 1.19)	0.4329	0.76 (0.56, 1.03)	0.0816
Sustained AER ≥30 mg/24 h and/or eGFR <60 mL/min/1.73 m ²	2.36 (1.82, 3.05)	<0.0001	1.99 (1.51, 2.61)	<0.0001	1.54 (1.15, 2.07)	0.0038
AER ≥300 mg/24 h	2.13 (1.51, 3.01)	<0.0001	1.67 (1.16, 2.41)	0.0059	1.15 (0.78, 1.70)	0.4884
Sustained AER ≥30 mg/24 h	2.22 (1.71, 2.87)	<0.0001	1.91 (1.45, 2.52)	<0.0001	1.47 (1.09, 1.97)	0.0119
eGFR <60 mL/min/1.73 m ²	3.18 (2.15, 4.69)	<0.0001	2.12 (1.43, 3.15)	0.0002	1.48 (0.97, 2.23)	0.0658
CAN	1.91 (1.45, 2.51)	<0.0001	1.36 (1.03, 1.80)	0.0313	1.11 (0.83, 1.49)	0.4767
Presence of retinal and kidney disease+	1.81 (1.54, 2.12)	<0.0001	1.55 (1.30, 1.85)	<0.0001	1.28 (1.05, 1.56)	0.0127
B. MACE						
PDR and/or CSME	2.45 (1.69, 3.56)	<0.0001	1.61 (1.09, 2.40)	0.0178	1.29 (0.85, 1.95)	0.2342
PDR	2.09 (1.41, 3.11)	0.0002	1.34 (0.88, 2.04)	0.1735	1.00 (0.64, 1.56)	0.9877
CSME	2.22 (1.52, 3.25)	<0.0001	1.39 (0.93, 2.07)	0.1087	1.16 (0.77, 1.75)	0.4695
Three-step progression	1.49 (0.99, 2.23)	0.0541	1.00 (0.65, 1.54)	0.9866	0.88 (0.56, 1.36)	0.5561
Sustained AER ≥30 mg/24 h and/or eGFR <60 mL/min/1.73 m ²	2.59 (1.80, 3.72)	<0.0001	1.93 (1.31, 2.85)	0.0009	1.43 (0.94, 2.18)	0.0913
AER ≥300 mg/24 h	2.99 (1.94, 4.61)	<0.0001	2.12 (1.33, 3.38)	0.0015	1.56 (0.94, 2.59)	0.0878
Sustained AER ≥30 mg/24 h	2.51 (1.74, 3.61)	<0.0001	1.93 (1.30, 2.85)	0.0010	1.41 (0.92, 2.14)	0.1134
eGFR <60	3.63 (2.20, 5.97)	<0.0001	2.06 (1.23, 3.44)	0.0058	1.54 (0.90, 2.65)	0.1182
CAN	2.23 (1.52, 3.26)	<0.0001	1.49 (1.01, 2.20)	0.0471	1.14 (0.76, 1.73)	0.5195
Presence of retinal and kidney disease+	2.03 (1.62, 2.54)	<0.0001	1.59 (1.24, 2.04)	0.0003	1.31 (0.99, 1.73)	0.0572

ORIGINAL INVESTIGATION

Open Access



Microvascular complications burden (nephropathy, retinopathy and peripheral polyneuropathy) affects risk of major vascular events and all-cause mortality in type 1 diabetes: a 10-year follow-up study

Monia Garofolo¹, Elisa Gualdani², Rosa Giannarelli¹, Michele Aragona¹, Fabrizio Campi¹, Daniela Lucchesi¹, Giuseppe Daniele¹, Roberto Miccoli¹, Paolo Francesconi², Stefano Del Prato^{1*}  and Giuseppe Penno¹

We evaluated the relationship between microvascular complications burden and incidence of major cardiovascular events and all-cause mortality in subjects with type 1 diabetes.

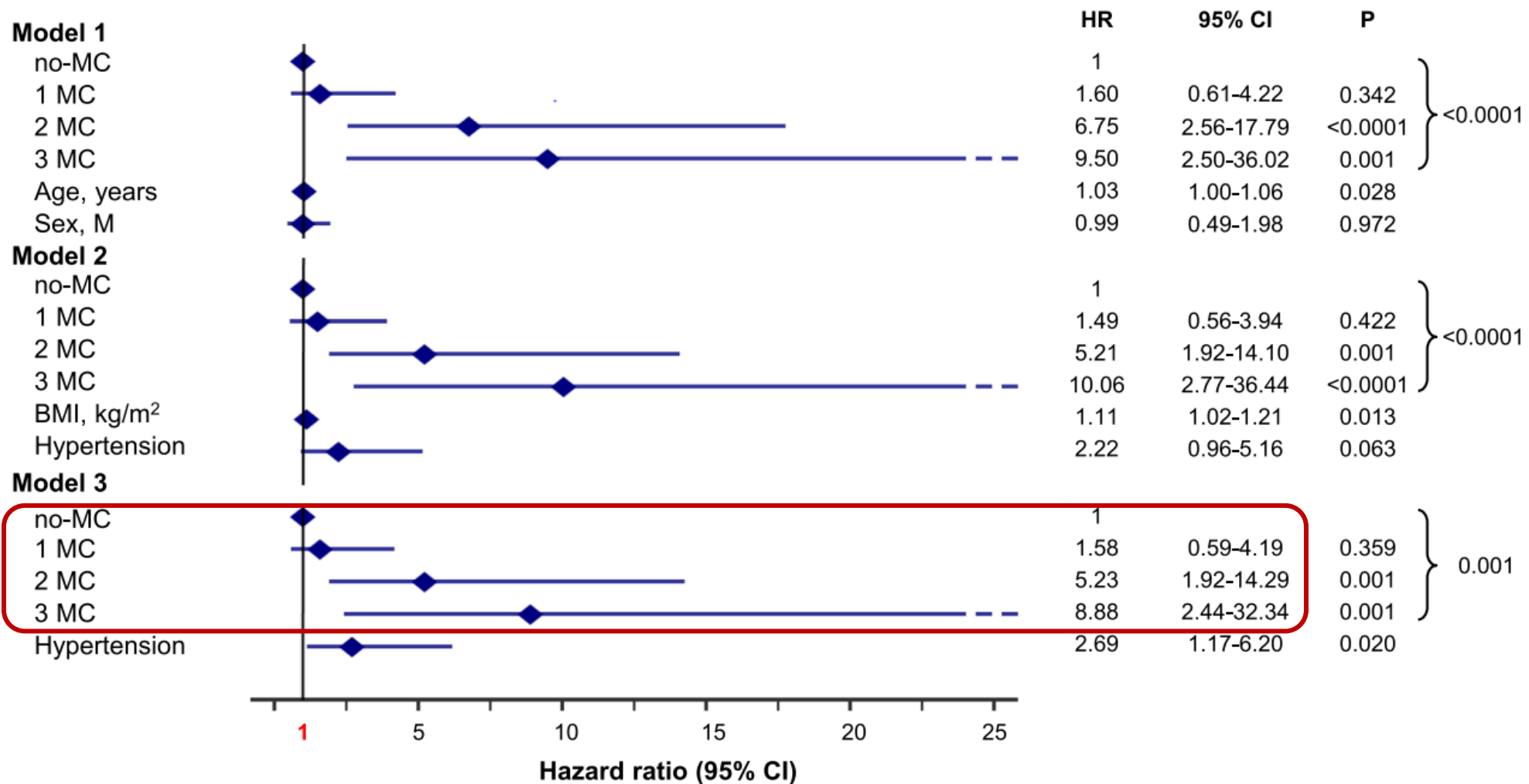
We recruited 774 participants with type 1 diabetes in a single-center observational study over a follow-up of 10.8±2.5 years.



Microvascular complications burden (nephropathy, retinopathy and peripheral polyneuropathy) affects risk of major vascular events and all-cause mortality in type 1 diabetes: a 10-year follow-up study

Monia Garofolo¹, Elisa Gualdani², Rosa Giannarelli¹, Michele Aragona¹, Fabrizio Campi¹, Daniela Lucchesi¹, Giuseppe Daniele¹, Roberto Miccoli¹, Paolo Francesconi², Stefano Del Prato¹ and Giuseppe Penno¹

Adjusted HR for major vascular events by microvascular complications in CVD-



Genetic Risk Factors for CVD in Type 1 Diabetes: The DCCT/EDIC Study

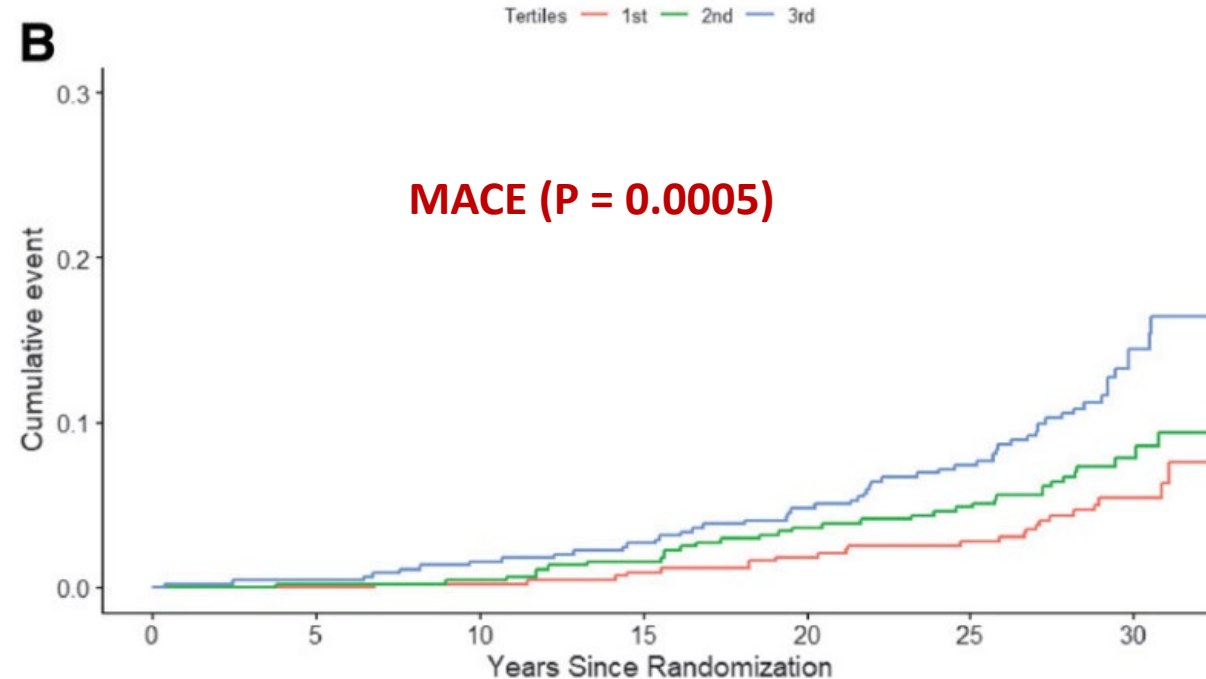
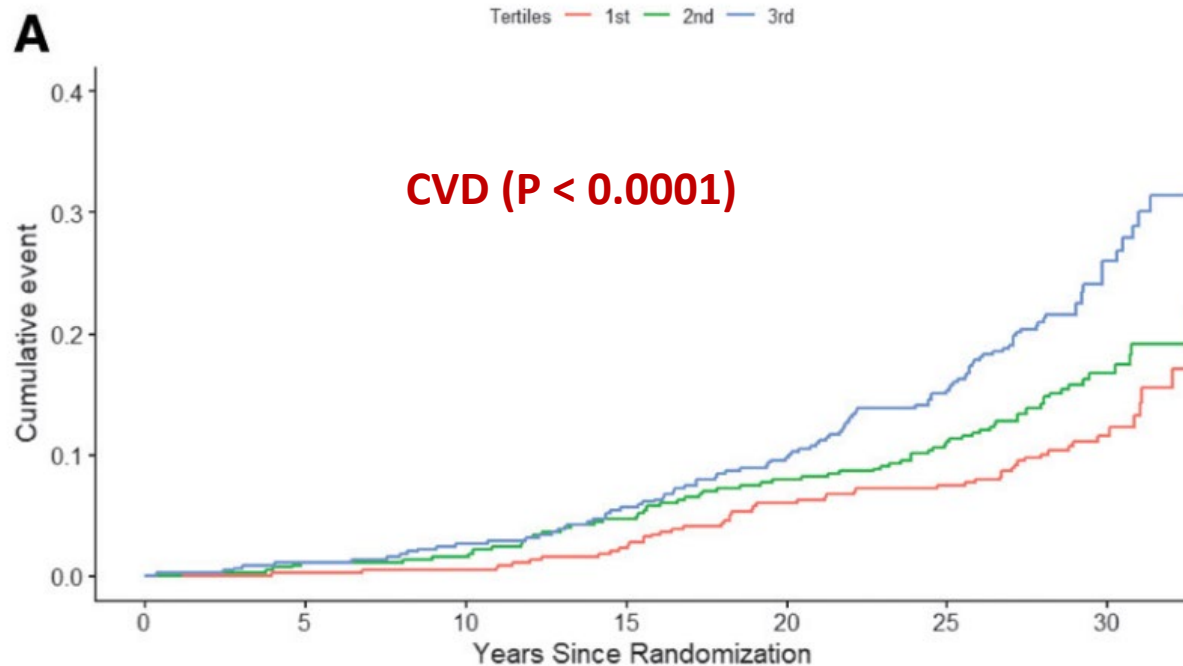
Diabetes Care 2021;44:1309–1316 | <https://doi.org/10.2337/dc20-2388>

We examined whether previously identified genetic factors for coronary artery disease (CAD) are associated with the risk of CVD above and beyond established demographic and clinical factors in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) study.

Genetic Risk Factors for CVD in Type 1 Diabetes: The DCCT/EDIC Study

Diabetes Care 2021;44:1309–1316 | <https://doi.org/10.2337/dc20-2388>

Cumulative incidence of CVD and MACE differed by CAD PRS tertile



Genetic Risk Factors for CVD in Type 1 Diabetes: The DCCT/EDIC Study

Diabetes Care 2021;44:1309–1316 | <https://doi.org/10.2337/dc20-2388>

Table 2—Cox proportional hazards models assessing association between CAD PRS and risk of CVD and MACE

	Unadjusted			Adjusted for age and HbA _{1c}			Fully adjusted*		
	HR (95% CI)	z score	P	HR (95% CI)	z score	P	HR (95% CI)	z score	P
CVD									
Highest 33%†	1.83 (1.41, 2.37)	4.52	6.1E−6	1.80(1.38, 2.34)	4.40	1.1E−5	1.75 (1.34, 2.28)	4.10	4.1E−5
Per SD increase	1.42 (1.25, 1.62)	5.26	1.4E−7	1.42 (1.25, 1.62)	5.34	9.2E−8	1.38 (1.21, 1.58)	4.81	1.5E−6
MACE									
Highest 33%†	1.96 (1.36, 2.85)	3.57	3.6E−4	1.89 (1.31, 2.74)	3.37	7.4E−4	1.80 (1.24, 2.62)	3.07	2.1E−3
Per SD increase	1.50 (1.25, 1.80)	4.31	1.7E−5	1.47 (1.23, 1.76)	4.23	2.3E−5	1.40 (1.17, 1.67)	3.73	1.9E−4



ESC

European Society
of Cardiology

European Heart Journal (2024) 45, 3912–4018

<https://doi.org/10.1093/eurheartj/ehae178>

ESC GUIDELINES

2024 ESC Guidelines for the management of elevated blood pressure and hypertension

Developed by the task force on the management of elevated blood pressure and hypertension of the European Society of Cardiology (ESC) and endorsed by the European Society of Endocrinology (ESE) and the European Stroke Organisation (ESO)

BP < 130/80 mmHg

ESH Guidelines

2023 ESH Guidelines for the management of arterial hypertension

The Task Force for the management of arterial hypertension of the European Society of Hypertension

Endorsed by the International Society of Hypertension (ISH) and the European Renal Association (ERA)

American Diabetes Association
Professional Practice Committee*

10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2025

Diabetes Care 2025;48(Suppl. 1):S207–S238 | <https://doi.org/10.2337/dc25-S010>

2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes

Developed by the task force on the management of cardiovascular disease in patients with diabetes of the European Society of Cardiology (ESC)

Recommendation Table 12 — Recommendations for patients with diabetes without a history of symptomatic atherosclerotic cardiovascular disease or revascularization

Recommendation	Class ^a	Level ^b
In adults with T2DM <u>without a history of symptomatic ASCVD or revascularization</u> , ASA (75–100 mg o.d.) may be considered to prevent the first severe vascular event, in the absence of clear contraindications. ^{c,292,293}	IIb	A

© ESC 2023

ASA, acetylsalicylic acid; ASCVD, atherosclerotic cardiovascular disease; o.d., once daily; T2DM, type 2 diabetes mellitus.

^aClass of recommendation.

^bLevel of evidence.

^cHigh risk of bleeding due to gastrointestinal haemorrhage or peptic ulcer within the previous 6 months, active hepatic disease (such as cirrhosis, active hepatitis), or history of ASA allergy.

American Diabetes Association
Professional Practice Committee*

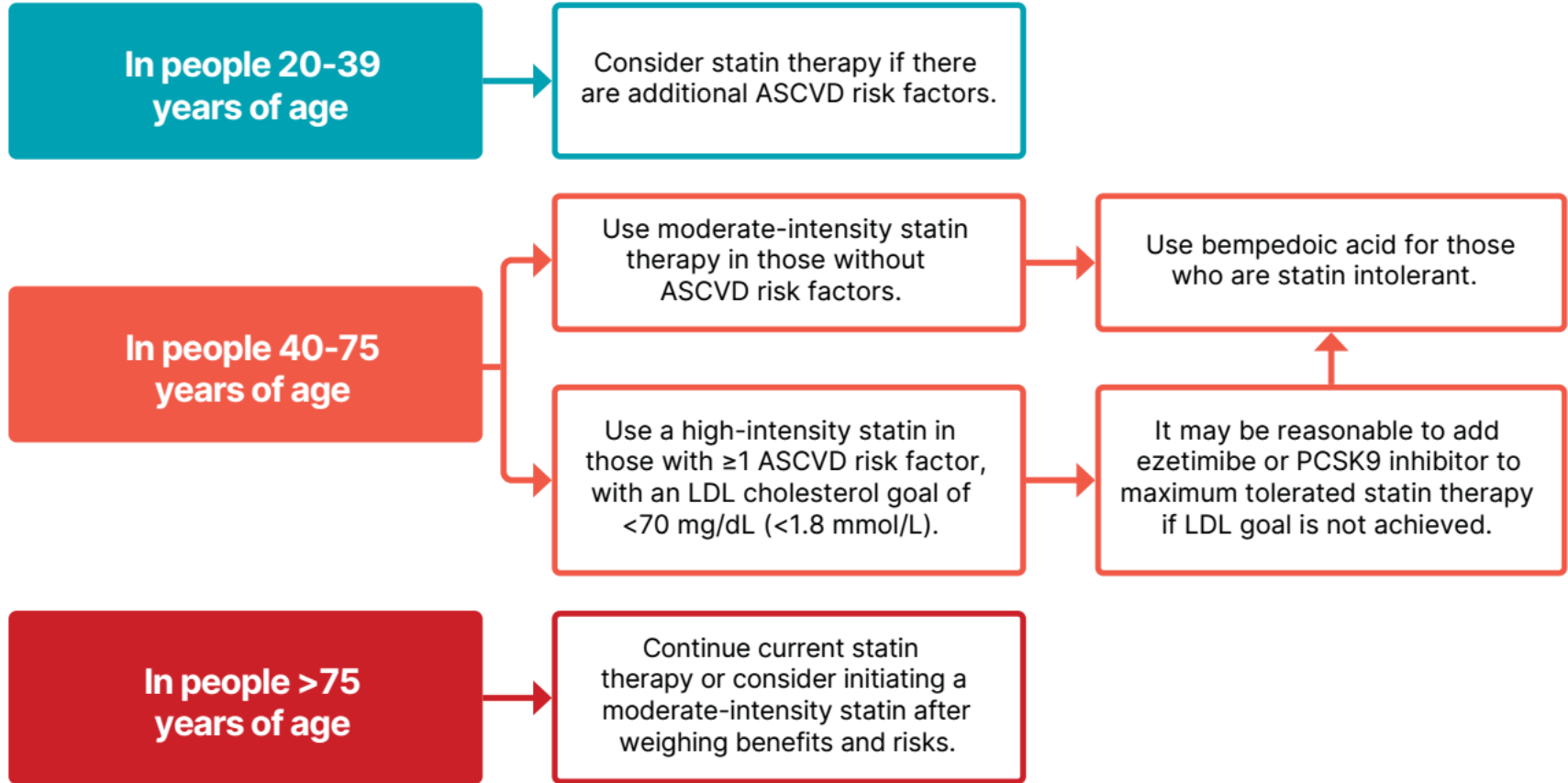
10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2025

Diabetes Care 2025;48(Suppl. 1):S207–S238 | <https://doi.org/10.2337/dc25-S010>

10. Cardiovascular Disease and Risk Management: Standards of Care in Diabetes—2025

Diabetes Care 2025;48(Suppl. 1):S207–S238 | <https://doi.org/10.2337/dc25-S010>

Lipid Management for Primary Prevention of Atherosclerotic Cardiovascular Disease Events in People With Diabetes in Addition to Healthy Behavior Modification



CV Risk Score/Engine for Type 1 Diabetes

Pittsburgh CHD in T1DM risk model

Swedish T1D Risk Score

Steno Type 1 Risk Score

EURODIAB risk engine (EURO-RE)

.....

High discriminative performance → pooled C-statistic of 0.81

RIASSUNTO 1

- ✓ **Nel T1D il rischio relativo di andare incontro ad malattia cardiovascolare è:**
 - ✓ **due-quattro volte superiore rispetto alla popolazione generale,**
 - ✓ **tanto più elevato quanto più precoce è l'insorgenza del diabete,**
 - ✓ **Il rischio assoluto è simile a quello riscontrato nel T2D, e tende ad essere superiore nell'età più avanzata.**
- ✓ **Il rischio assoluto nelle donne con T1D tende a essere simile a quello del sesso maschile.**

RIASSUNTO 2

- ✓ Accanto all'età, il maggior fattore clinico associato alla malattia cardiovascolare nel T1D è rappresentato dal «carico glicemico», espresso dal livello dell'iperglicemia e dalla sua durata nel tempo (durata del diabete).
- ✓ I classici fattori di rischio cardiovascolare contribuiscono ad aumentare il rischio di CVD nel T1D.
- ✓ Il continuum di danno micro/macrovascolare è espresso pienamente anche nel T1D.

TAKE HOME MESSAGE

La malattia cardiovascolare è una complicanza molto frequente e invalidante nel diabete tipo 1.

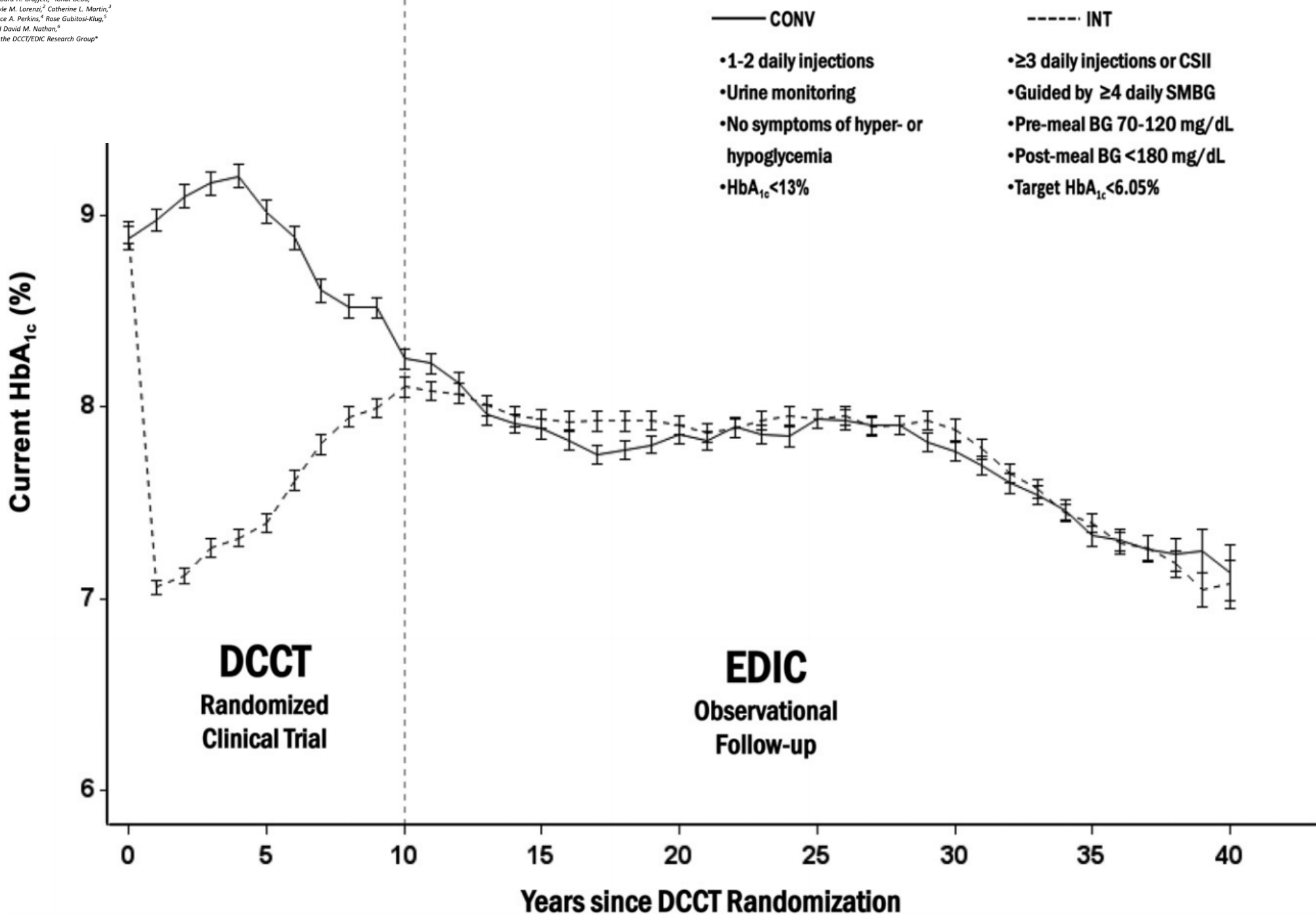
**La prevenzione della malattia cardiovascolare deve essere estremamente precoce
attraverso il controllo di tutti i fattori di rischio che possono portare al danno
micro e macroangiopatico, presupposti fisiopatologici
della malattia cardiovascolare nel diabete di tipo 1.**

Grazie per l'attenzione!

The NIDDK Takes on the Complications of Type 1 Diabetes: The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study

*Barbara H. Braffett,¹ Ionut Bebu,¹
Gayle M. Lorenzi,² Catherine L. Martin,³
Bruce A. Perkins,⁴ Rose Gubitosi-Klug,⁵
and David M. Nathan,⁶
for the DCCT/EDIC Research Group**

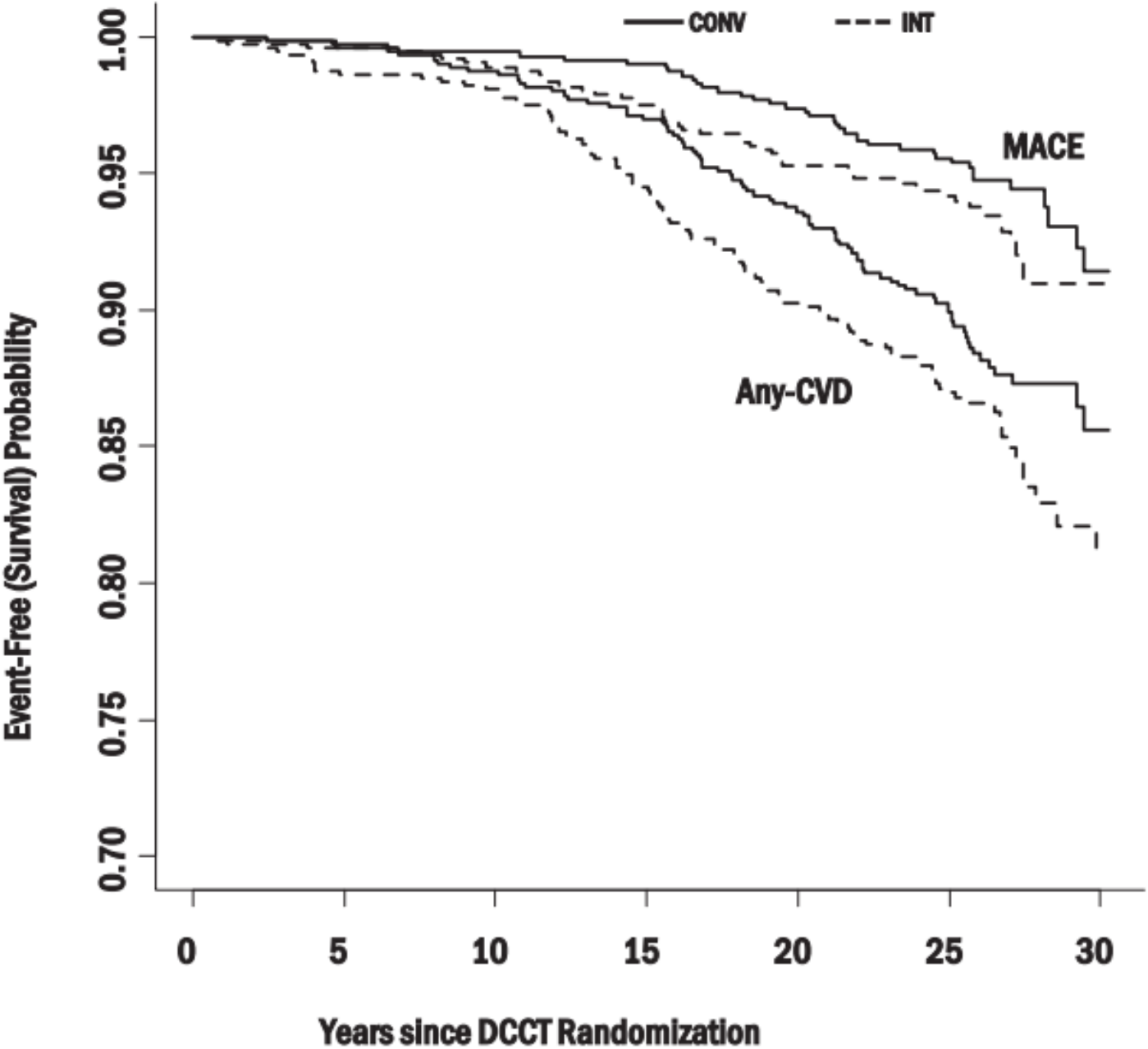
Diabetes Care 2025;48:1089–1100 | <https://doi.org/10.2337/dc24-2885>



The NIDDK Takes on the
Complications of Type 1
Diabetes: The Diabetes Control
and Complications Trial/
Epidemiology of Diabetes
Interventions and Complications
(DCCT/EDIC) Study

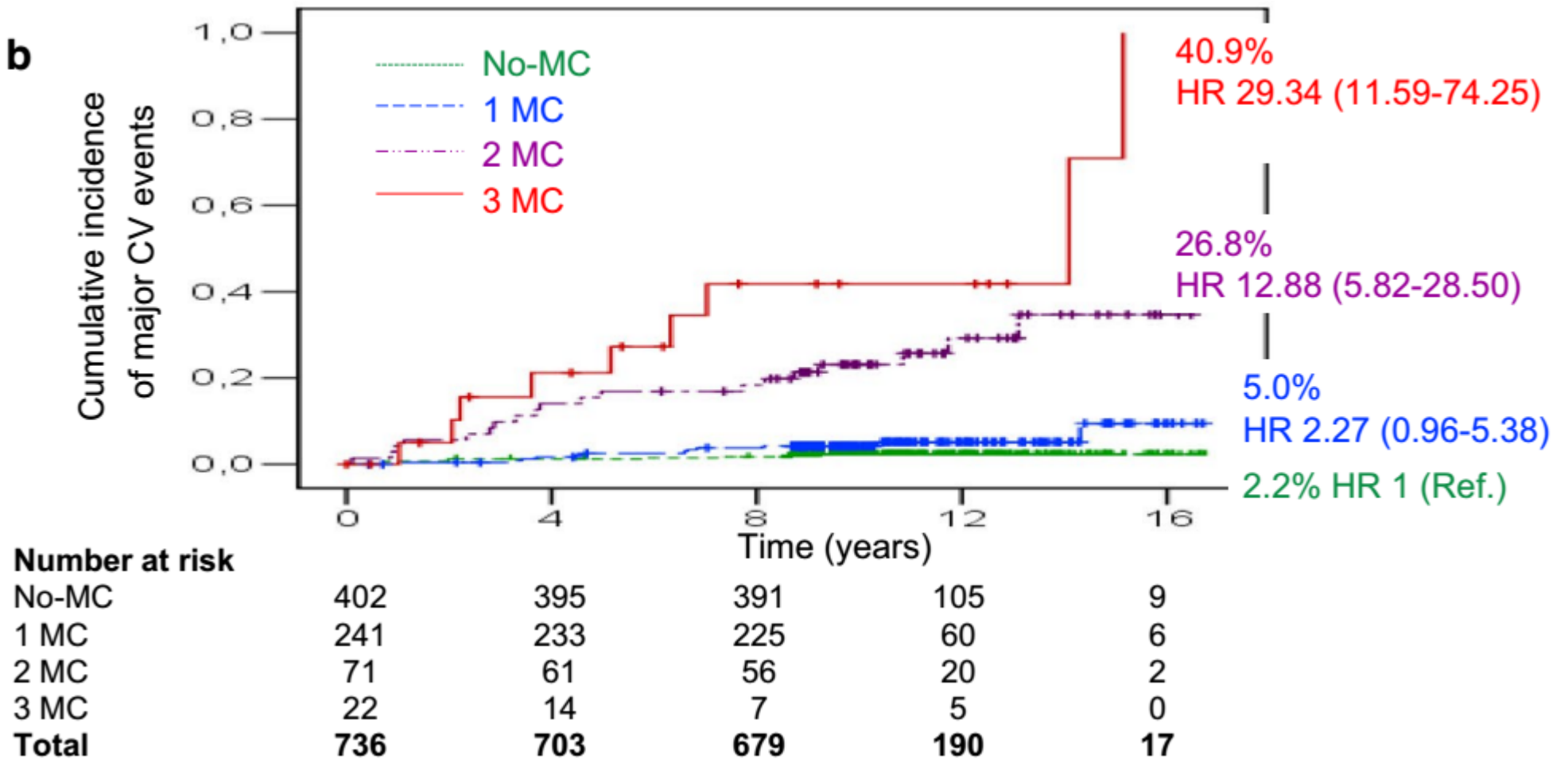
Diabetes Care 2025;48:1089–1100 | <https://doi.org/10.2337/dc24-2885>

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Microvascular complications burden
(nephropathy, retinopathy and peripheral
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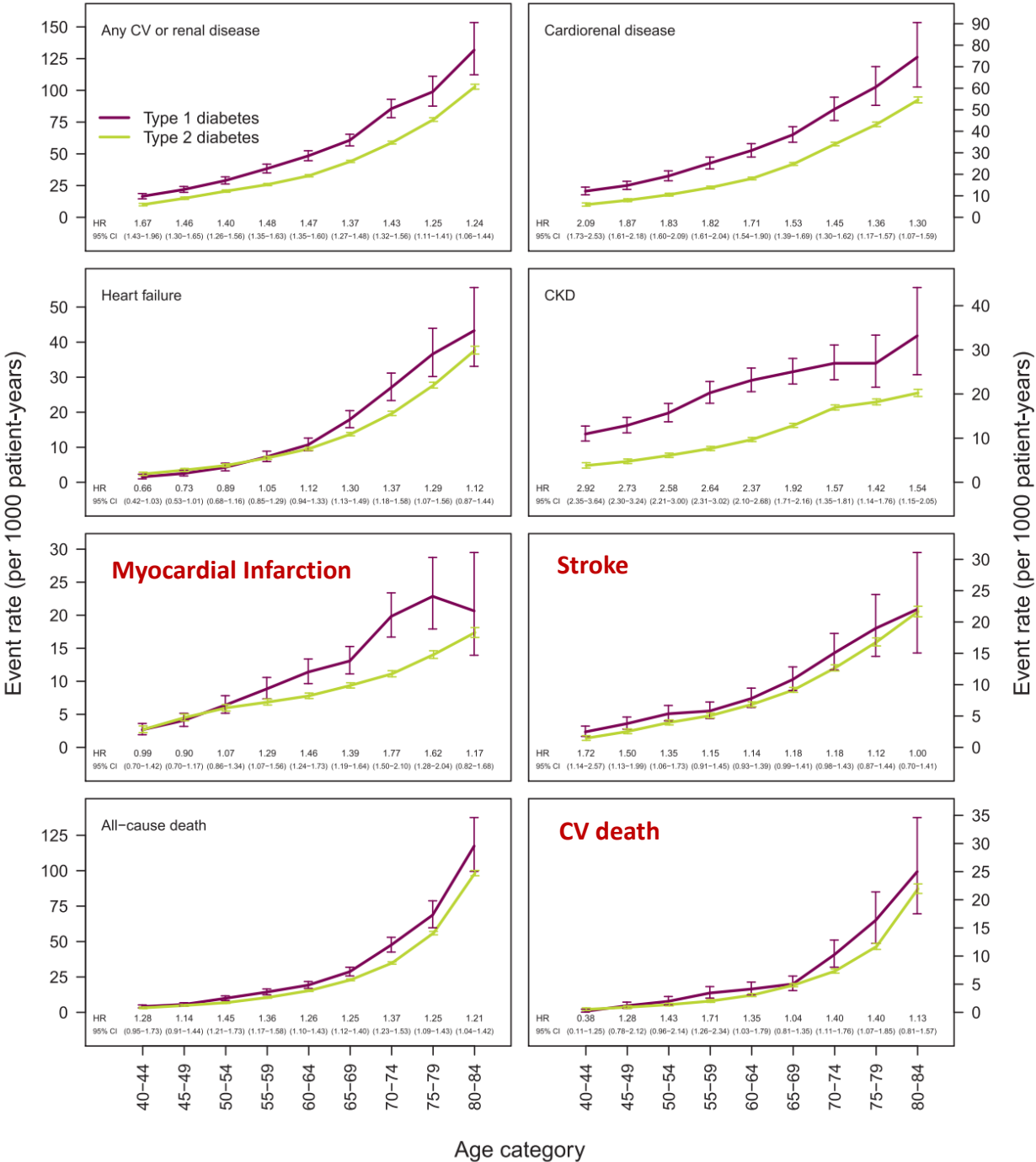


Cardiovascular and Renal Disease Burden in Type 1 Compared With Type 2 Diabetes: A Two-Country Nationwide Observational Study

Diabetes Care 2021;44:1211–1218 | <https://doi.org/10.2337/dc20-2839>

Robin Kristófi,¹ Johan Bodegard,²
Anna Norhammar,^{3,4} Marcus Thuresson,⁵
David Nathanson,⁶ Thomas Nyström,⁷
Kåre I. Birkeland,⁸ Jan W. Eriksson¹

Age-stratified incidence of any CVRD events (including MI, stroke, HF, CKD, or CV death), cardiorenal disease (HF or CKD), HF, CKD, MI,stroke, all-cause death, and CV death.





Risk Factors for First and Subsequent CVD Events in Type 1 Diabetes: The DCCT/EDIC Study

Diabetes Care 2020;43:867–874 | <https://doi.org/10.2337/dc19-2292>

*Ionut Bebu,¹ David Schade,²
Barbara Braffett,¹ Mikhail Kosiborod,^{3,4}
Maria Lopes-Virella,⁵ Elsayed Z. Soliman,⁶
William H. Herman,⁷ David A. Bluemke,⁸
Amisha Wallia,⁹ Trevor Orchard,¹⁰ and
John M. Lachin,¹ on behalf of the DCCT/EDIC
Research Group**

1,441 DCCT/EDIC participants, mean age at baseline 27 years
Median follow-up of 29 years
17 participants had 22 episodes of CHF

The Diabetes Control and Complications Trial/Epidemiology of Diabetes
Interventions and Complications (DCCT/EDIC) Research Group*

Risk Factors for Cardiovascular Disease in Type 1 Diabetes

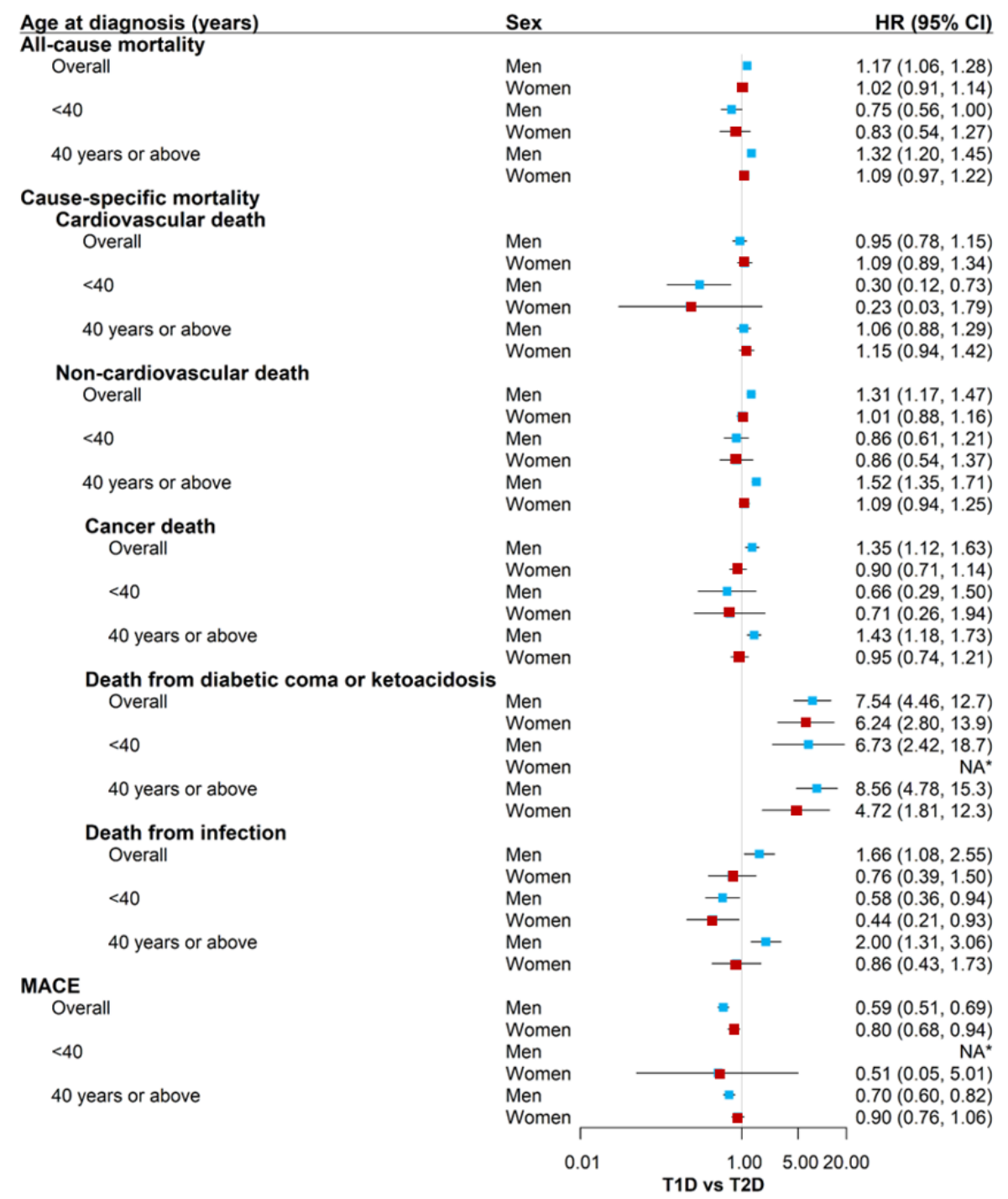
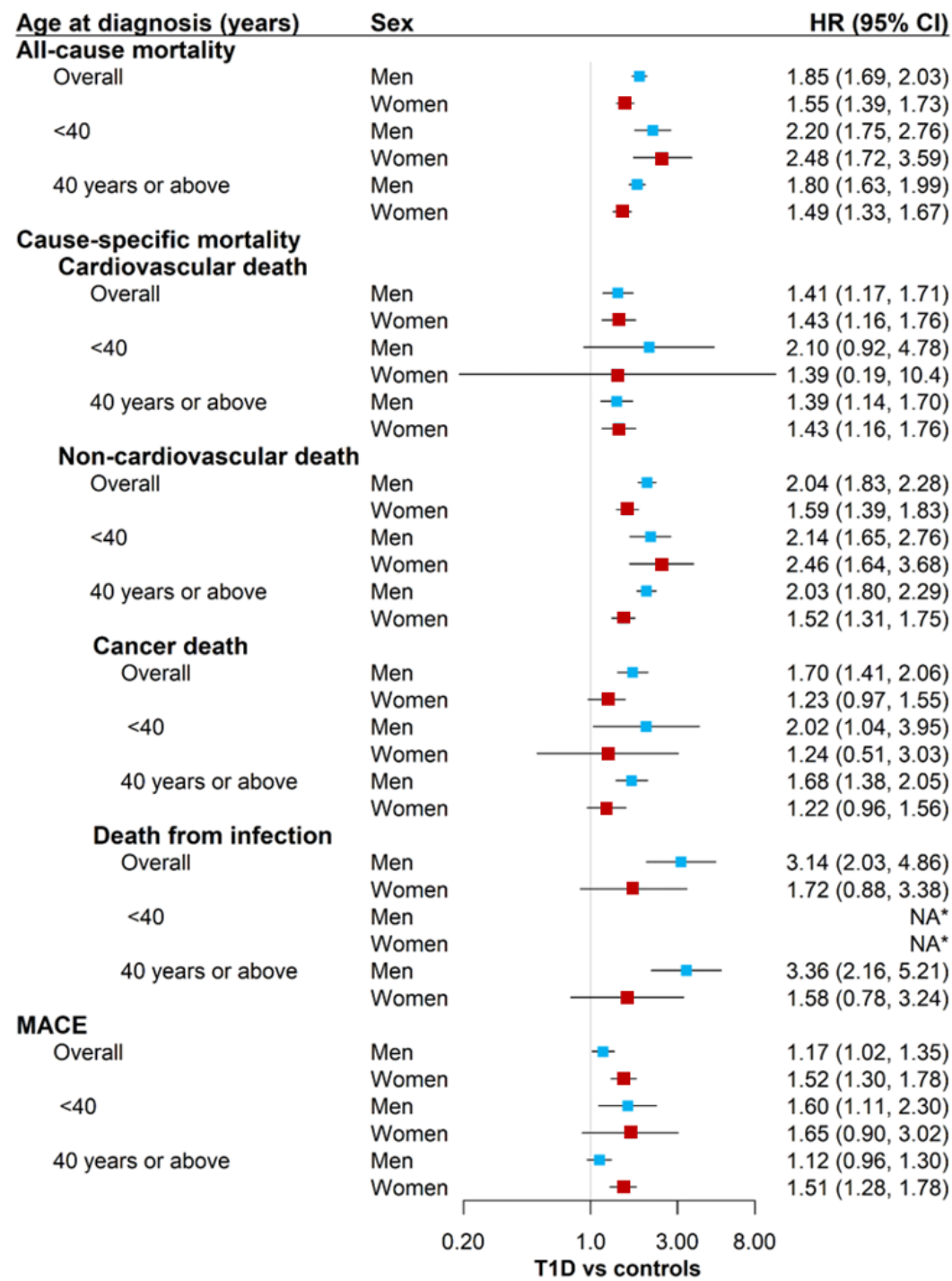
Diabetes 2016;65:1370–1379 | DOI: 10.2337/db15-1517

We assessed risk factors in the **long-term (mean 27 years)**
follow-up of the Diabetes Control and Complications Trial
(DCCT) cohort with T1DM.

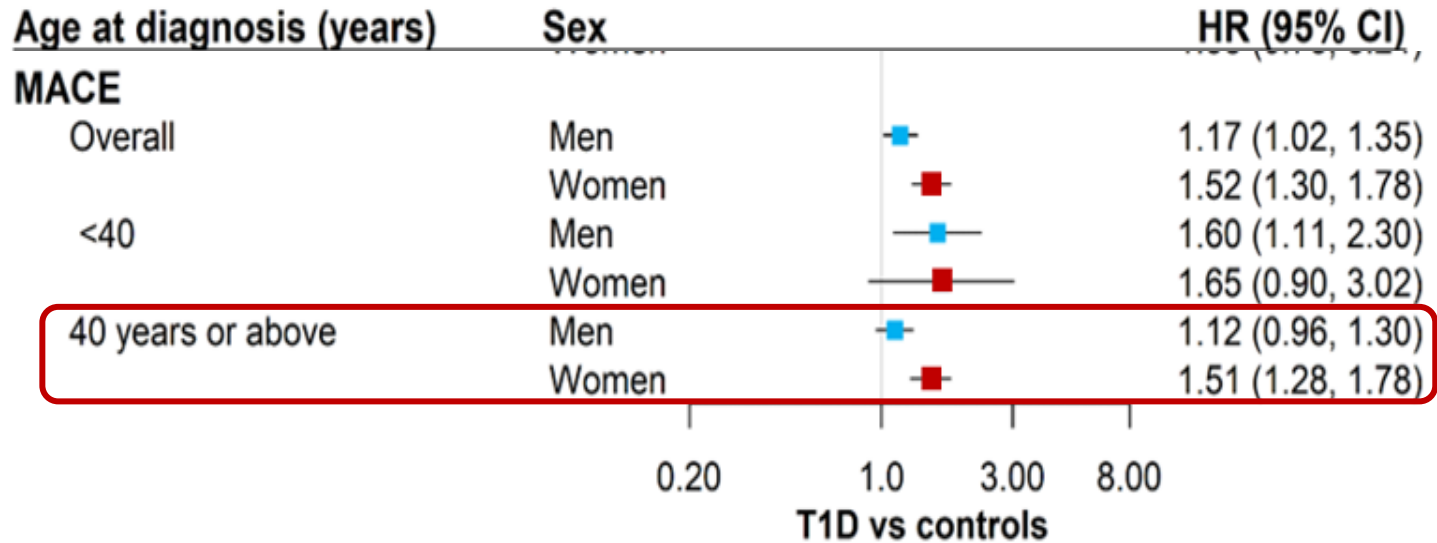
Risk Factors for Cardiovascular
Disease in Type 1 Diabetes

Diabetes 2016;65:1370–1379 | DOI: 10.2337/db15-1517

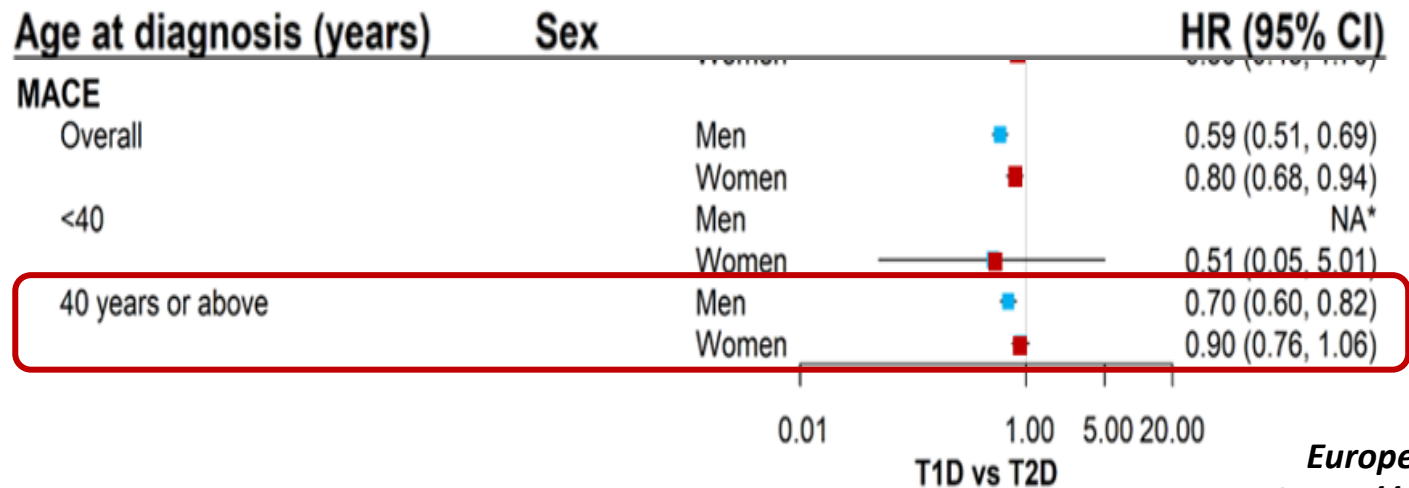
	HR (95% CI)*	Z-test value	P value
Any-CVD model			
covariate			
Baseline age (per 5 years)	1.5366 (1.3641, 1.731)	7.0711	<0.001
Mean HbA _{1c} (per 1%)	1.3115 (1.1488, 1.4972)	4.0133	<0.001
Mean systolic blood pressure (per 10 mmHg)	1.3186 (1.1096, 1.567)	3.1419	0.002
Current triglycerides (log)	1.5536 (1.1688, 2.065)	3.0346	0.003
Mean pulse rate (per 10 bpm)	1.3855 (1.1051, 1.737)	2.8267	0.005
Baseline duration of diabetes (per 5 years)	1.247 (1.0514, 1.4789)	2.5364	0.02
Current use of ACE inhibitor (yes vs. no)	0.6732 (0.4777, 0.9486)	−2.2611	0.03
Baseline family history of MI (yes vs. no)	1.3866 (1.0294, 1.8678)	2.1507	0.04
Mean LDLc (per 10 mg/dL)	1.0721 (1.0037, 1.1451)	2.0697	0.04
MACE model			
covariate			
Baseline age (per 5 years)	1.7748 (1.4872, 2.1179)	6.3613	<0.001
Mean HbA _{1c} (per 1%)	1.4186 (1.1785, 1.7077)	3.6965	<0.001
Mean pulse rate (per 10 bpm)	1.5975 (1.1576, 2.2046)	2.8509	0.005
Current triglycerides (log)	1.7844 (1.1909, 2.6737)	2.8071	0.005
Mean systolic blood pressure (per 10 mmHg)	1.3863 (1.0929, 1.7583)	2.6931	0.007
Current smoking (yes vs. no)	1.8686 (1.1647, 2.9978)	2.5924	0.01
Baseline duration of diabetes (per 5 years)	1.3334 (1.0399, 1.7098)	2.2685	0.03
Current use of ACE inhibitor (yes vs. no)	0.5819 (0.3553, 0.9529)	−2.1515	0.04
Current LDLc (per 10 mg/dL)	1.0692 (1.0035, 1.1392)	2.0685	0.04



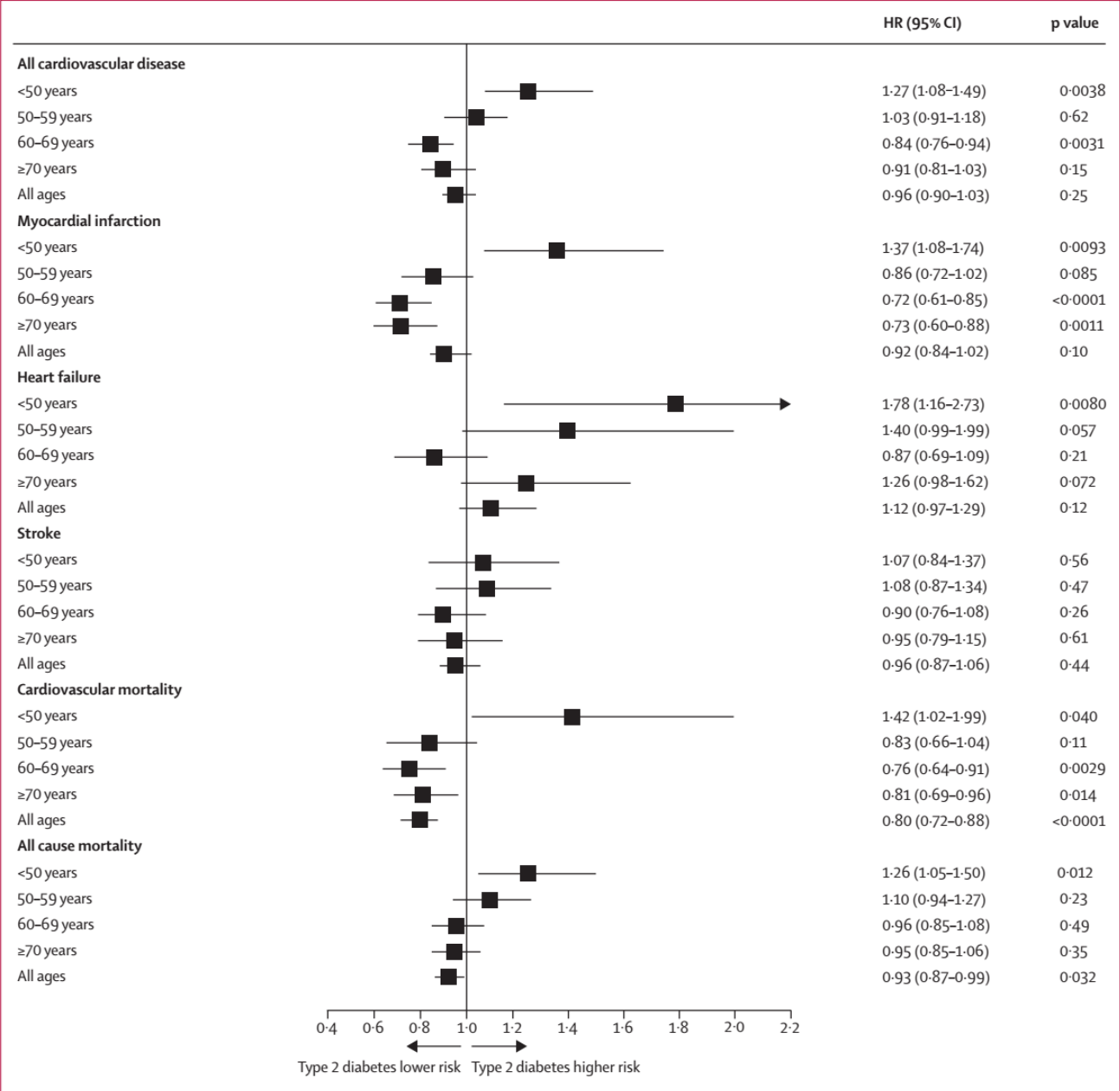
T1D vs controls

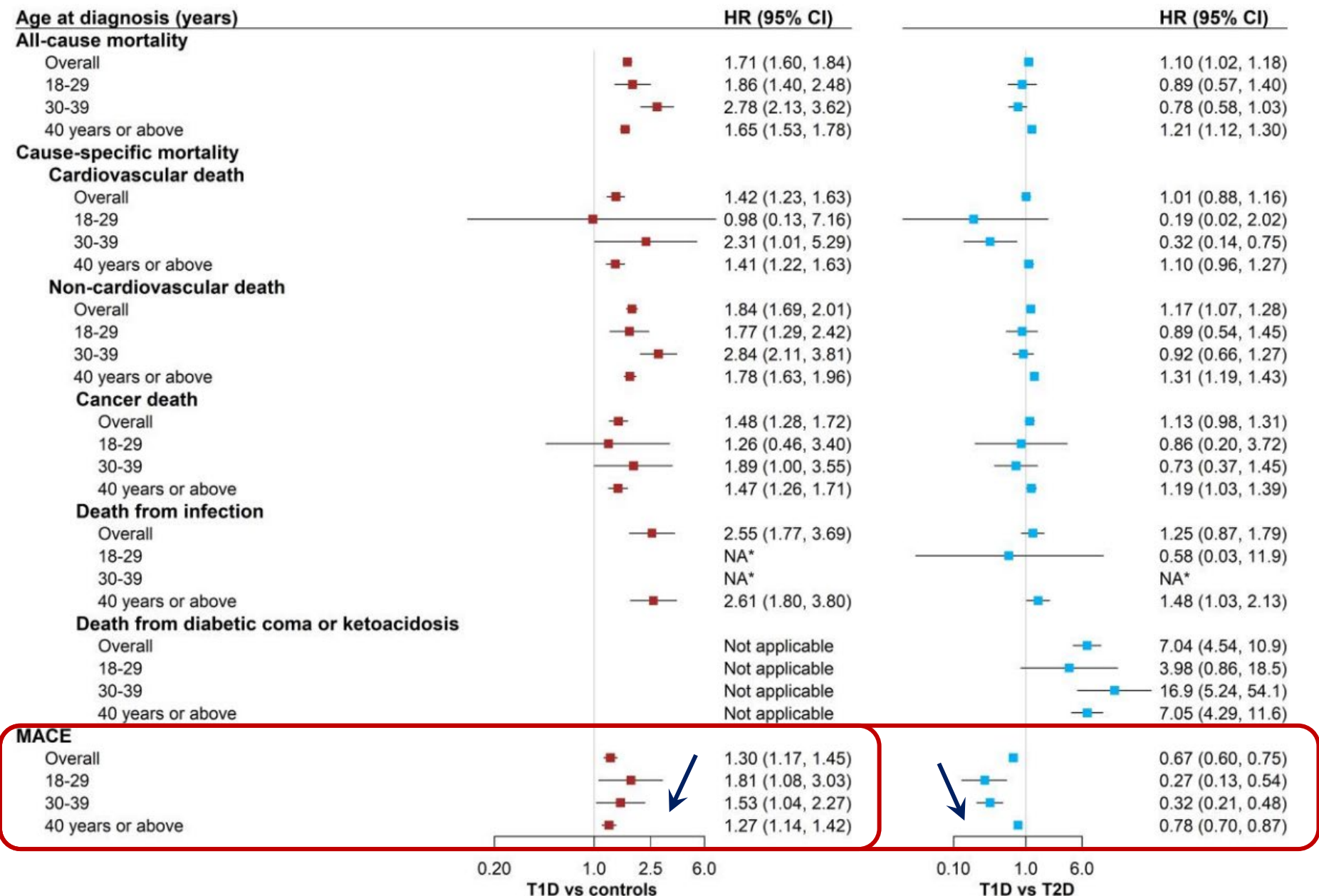


T1D vs T2D



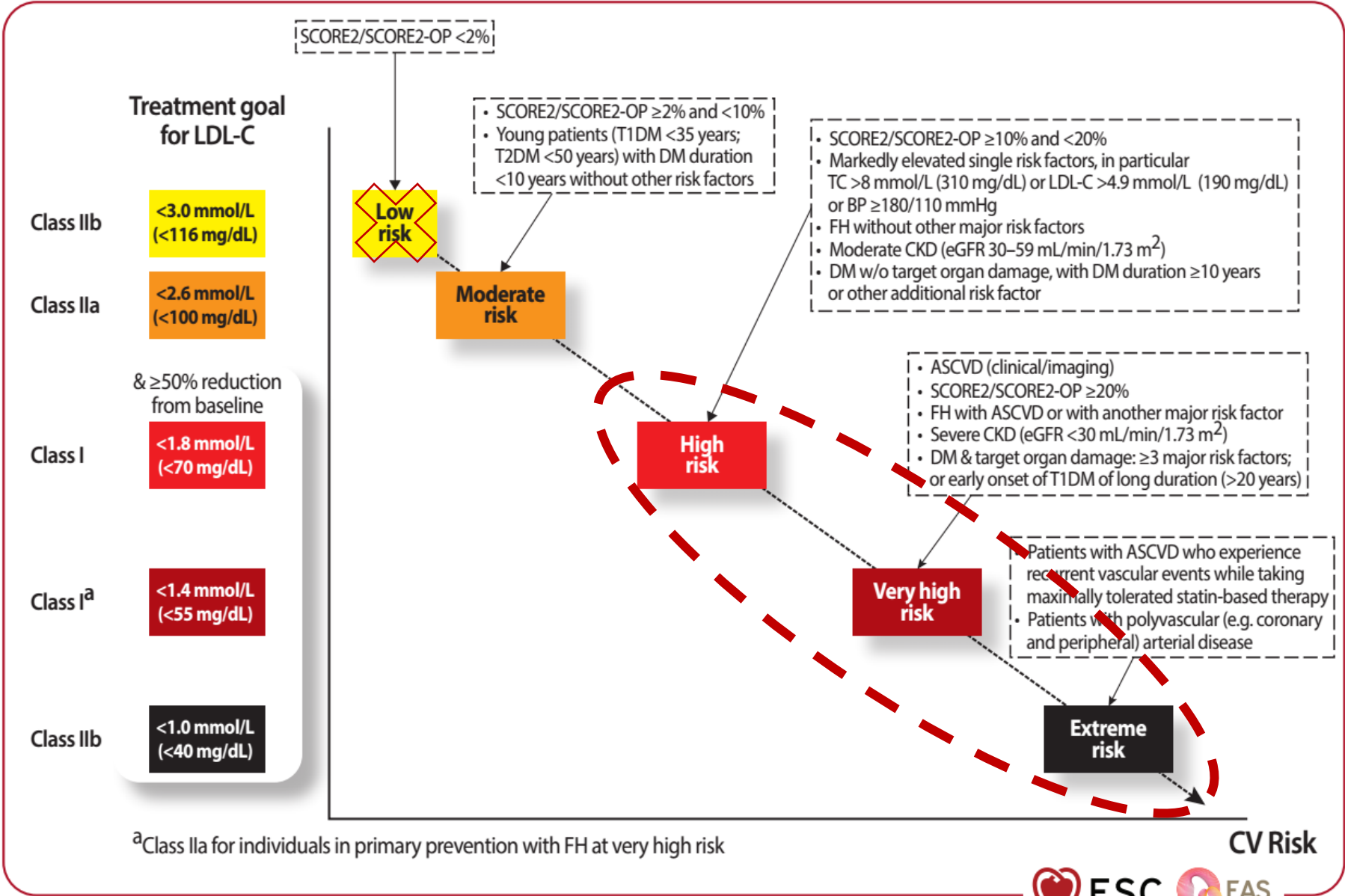
Comparison of risk for events in type 2 diabetes versus type 1 diabetes in the study population with no previous cardiovascular disease events





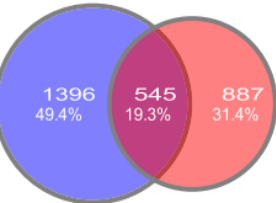
**2025 Focused Update of the 2019 ESC/EAS
Guidelines for the management of
dyslipidaemias**

Developed by the task force for the management of dyslipidaemias
of the European Society of Cardiology (ESC) and the European
Atherosclerosis Society (EAS)



Persons with T1D ≥45 years with cardiorenal complications

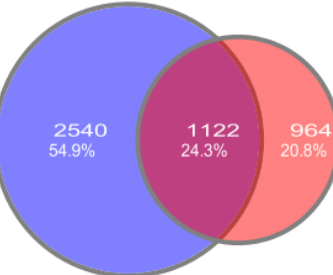
2002-2004



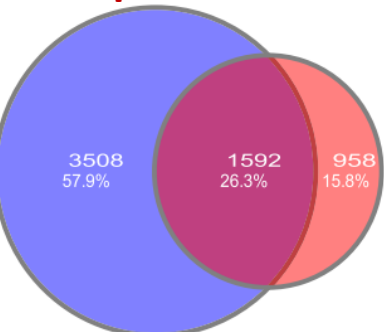
Renal

Cardiovascular

2005-2007



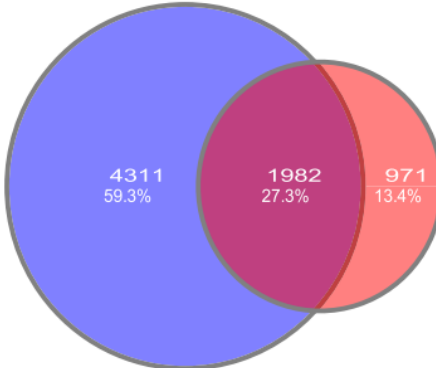
2008-2010



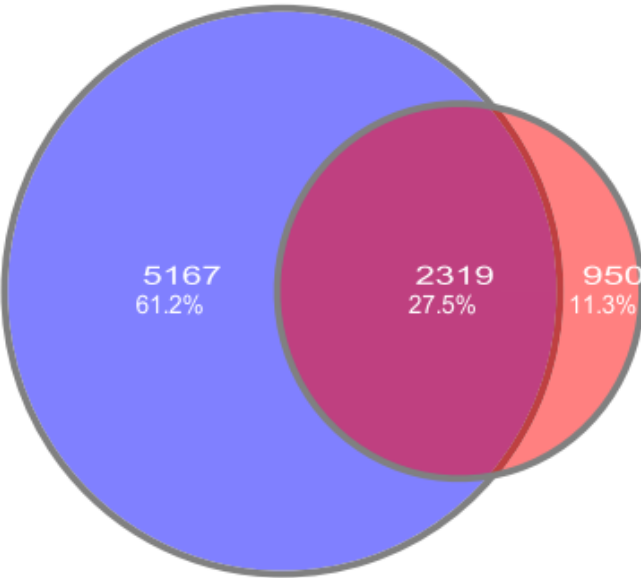
Renal

Cardiovascular

2011-2013



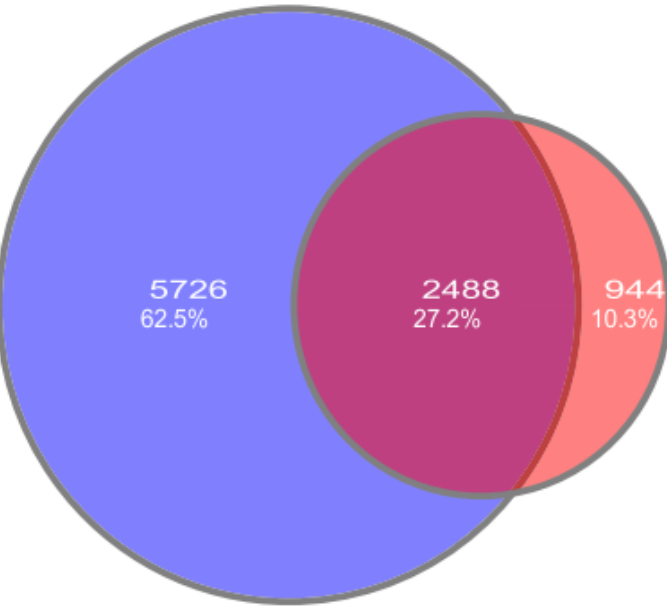
2014-2016



Renal

Cardiovascular

2017-2019



72,5% of T1D with CVD have Renal Disease

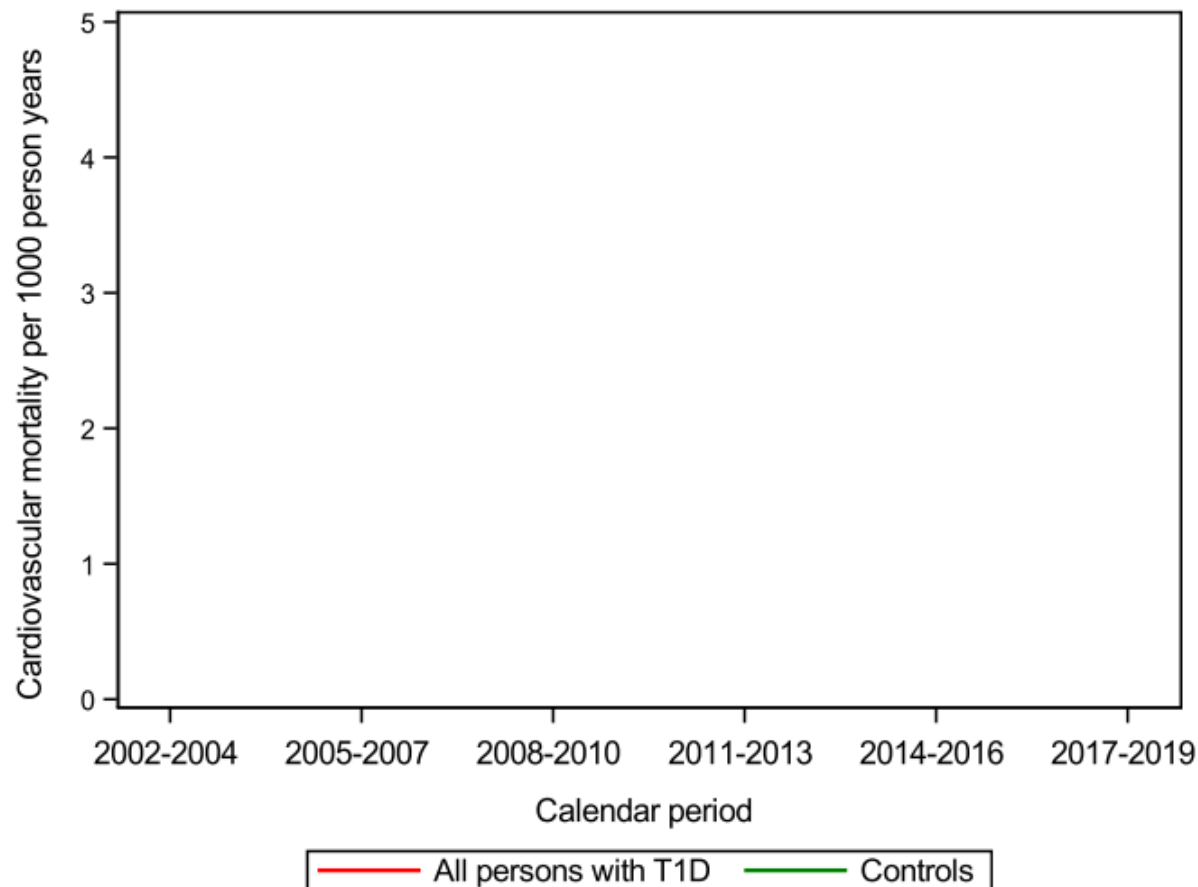
30% of T1D with Renal Disease have CVD

Risk factors, mortality trends, and cardiovascular diseases in people with Type 1 diabetes and controls in Sweden: An observational cohort study

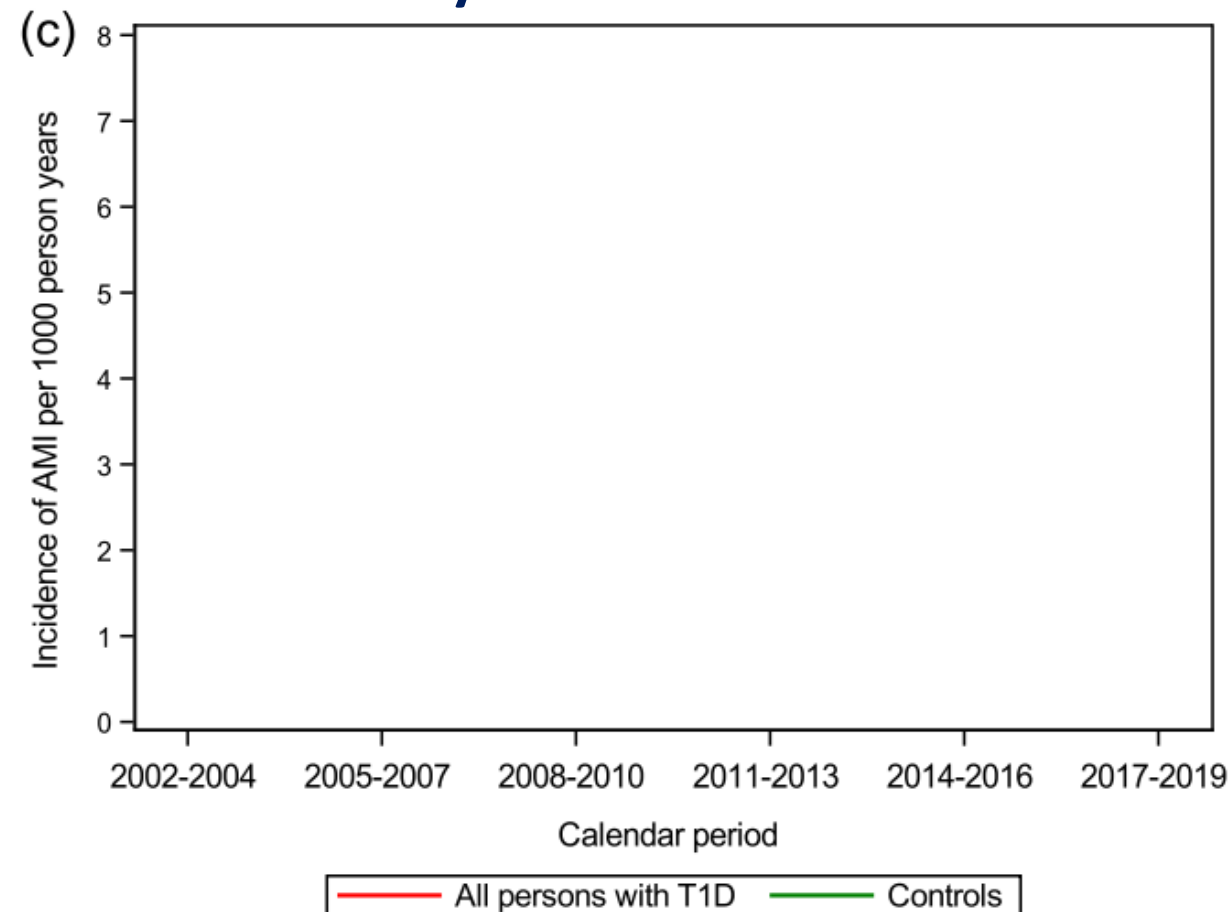
Sara Hallström,^{a,b,} Magnus Olof Wijkman,^c Johnny Ludvigsson,^d Per Ekman,^e Marc Alan Pfeffer,^f Hans Wedel,^g Annika Rosengren,^b and Marcus Lind^{a,b,h}*

Standardized incidence rates per 1000 person years of CV mortality and AMI. All T1D and Controls

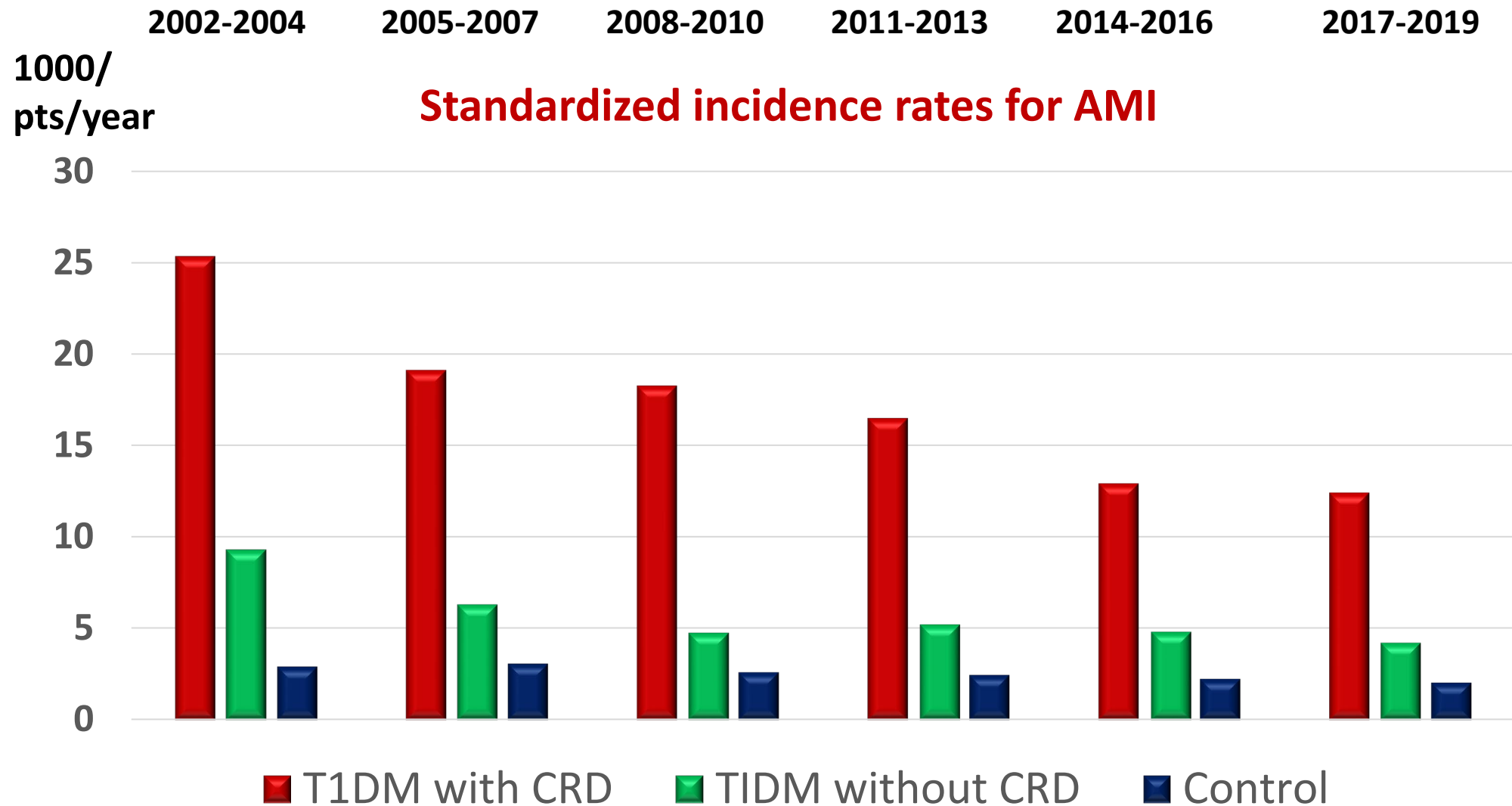
Cardiovascular mortality



Acute myocardial infarction



IMPACT OF CARDIORENAL DISEASE ON INCIDENCE OF AMI



Cardiac autonomic neuropathy and risk of cardiovascular disease and mortality in type 1 and type 2 diabetes: a meta-analysis

Mahin Chowdhury ¹, Sarah Nevitt,² Aikaterini Eleftheriadou,¹
Prathap Kanagala,^{1,3} Hani Esa,^{1,3} Daniel J Cuthbertson,^{1,3} Abd Tahrani,^{4,5,6}
Uazman Alam^{1,3,7,8}

Relative risk of cardiovascular disease in DMT1 with cardiac autonomic neuropathy

Study or Subgroup	CAN		Control		Weight	Risk Ratio		Year	Risk Ratio	
	Events	Total	Events	Total		M-H, Random, 95% CI			M-H, Random, 95% CI	
1.1.1 Type 1 diabetes										
Sampson et al 1990	4	73	0	38	0.8%	4.74 [0.26, 85.85]	1990			
O'Brien et al 1991	8	84	7	422	5.1%	5.74 [2.14, 15.41]	1991			
Astrup et al 2006	91	281	6	107	6.9%	5.78 [2.61, 12.80]	2006			
Lykke et al 2008	14	34	1	100	1.6%	41.18 [5.62, 301.56]	2008			
Pop-Busui et al 2017	49	131	191	1262	15.8%	2.47 [1.91, 3.20]	2017			
Subtotal (95% CI)		603		1929	30.2%	5.54 [2.28, 13.45]				
Total events	166		205							
Heterogeneity: Tau ² = 0.63; Chi ² = 16.77, df = 4 (P = 0.002); I ² = 76%										
Test for overall effect: Z = 3.78 (P = 0.0002)										

Scaletta

Meccanismi di azione

Epidemiologia con età insorgenza, durata confronto con tipo 2 fattori di rischio e loro peso, microangiopatia neuropatia autonoma, nefropatia, genetica, durata diabete
amnesia metabolica come rene in fioretto dcct

Linee guida EAS e ESC e ADA

Score di rischio