New insights into Vascular disease in diabetes

Naveed Sattar

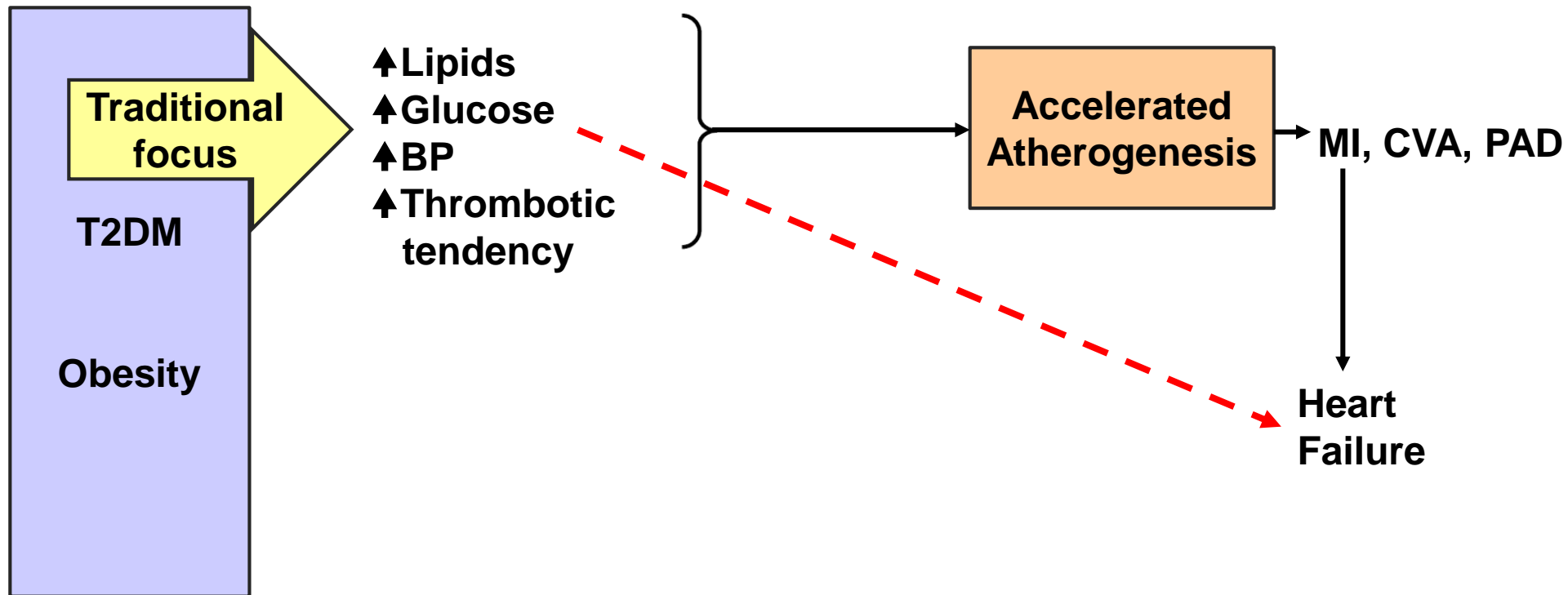## Professor of Metabolic Medicine

University of Glasgow | Institute of Cardiovascular & Medical Sciences

British Heart Foundation

Duality of Interest Declaration

Consultant or speaker for:
Eli Lilly, Boehringer Ingelheim, Janssen, AstraZeneca, Novo Nordisk, Sanofi
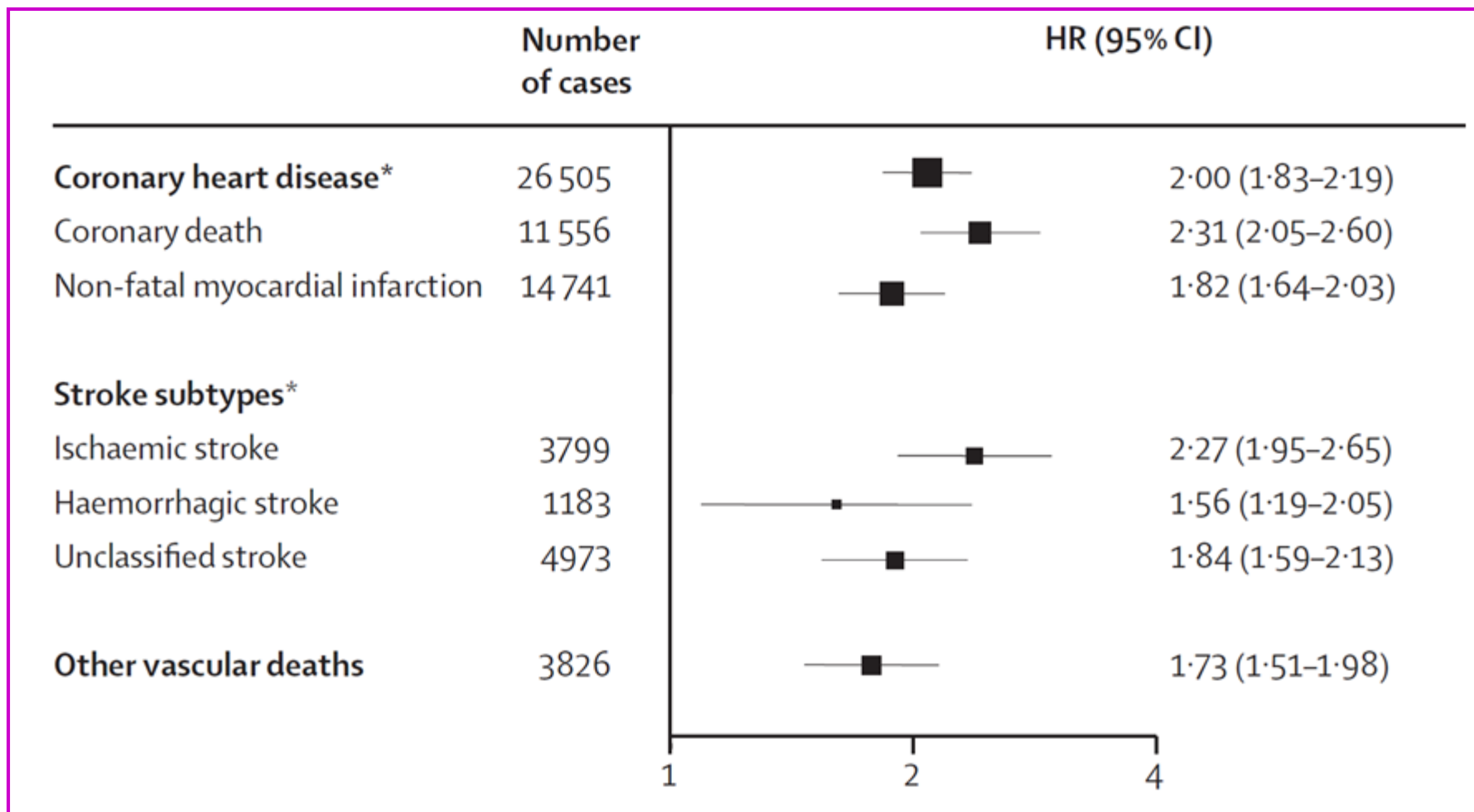
Grants: Boehringer Ingelheim

Diabetes research fixated on lowering HbA1c, atherogenesis for years

Traditional focus

T2DM

Obesity

↑**Lipids**
↑**Glucose**
↑**BP**
↑**Thrombotic tendency**

Accelerated Atherogenesis → **MI, CVA, PAD**

Heart Failure

Sattar N, McGuire D. Circulation (In press)

DM: double CVD risk on average
ERFC (2010) Lancet

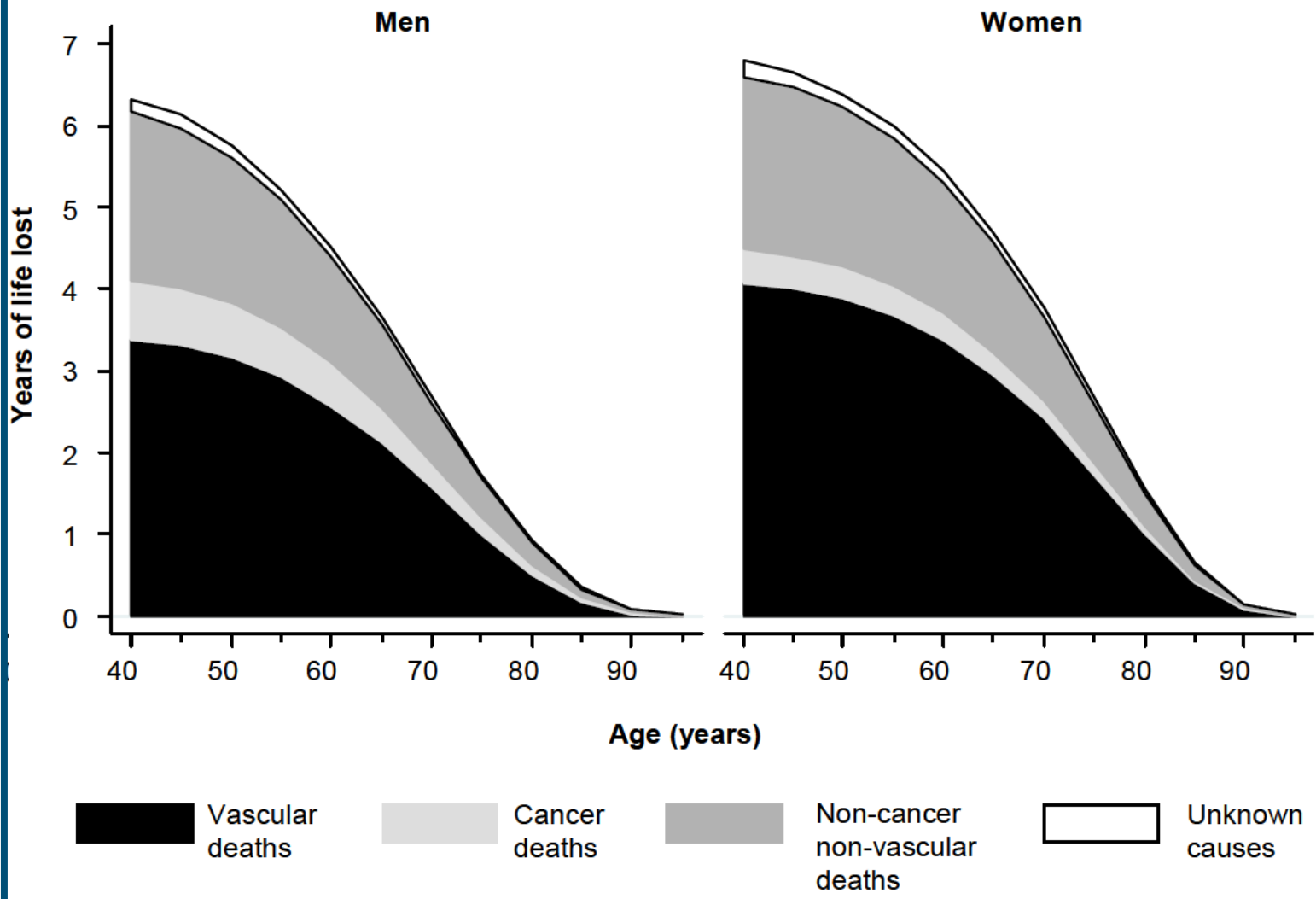|	Number of cases	HR (95% CI)
Coronary heart disease*	26 505	2·00 (1·83–2·19)
Coronary death	11 556	2·31 (2·05–2·60)
Non-fatal myocardial infarction	14 741	1·82 (1·64–2·03)
Stroke subtypes*		
Ischaemic stroke	3799	2·27 (1·95–2·65)
Haemorrhagic stroke	1183	1·56 (1·19–2·05)
Unclassified stroke	4973	1·84 (1·59–2·13)
Other vascular deaths	3826	1·73 (1·51–1·98)

Hazard ratios for vascular outcomes DM vs. no DM

Things that matter to vascular risk?

- Age of onset?

- Sex?

- Ethnicity?

- T1 vs T2DM?

Estimated future years of life lost due to diabetes by sex, age and cause

Men

Women

Years of life lost

Age (years)

Vascular deaths

Cancer deaths

Non-cancer non-vascular deaths

Unknown causes

ERFC (2011) NEJM

Trends in risk factors by Age of onset of diabetes Steinarsson et al (2018) Diabetologia

- **100,606 patients in NDR**
- **2.83 years average follow-up**
- **Max up to 10 years of follow-up**
- Andri Oddur Steinarsson, Araz Rawshani, Soffia Gudbjörnsdottir Stefan Franzén, Ann-Marie Svensson, Naveed Sattar
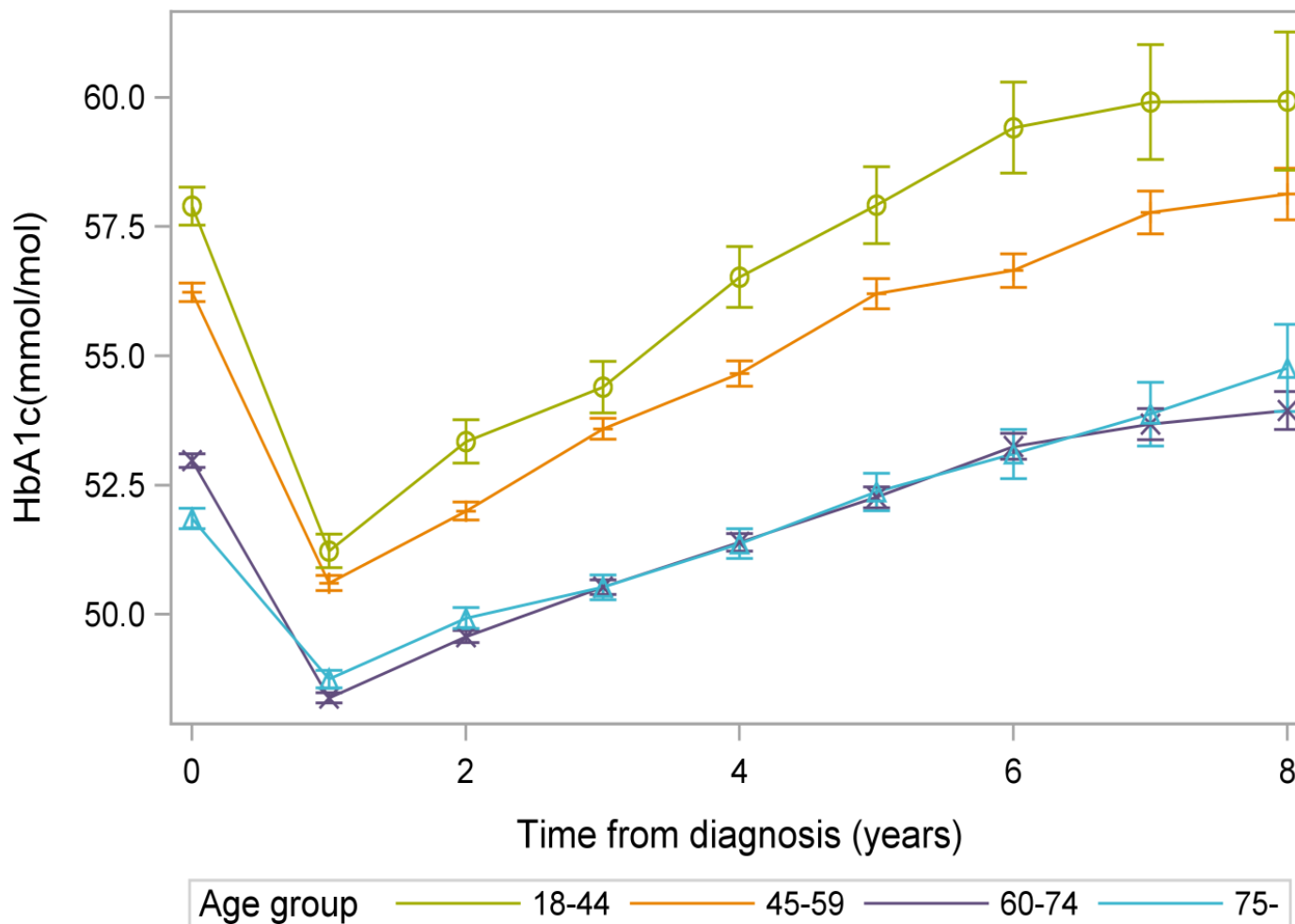
Higher BMI in young

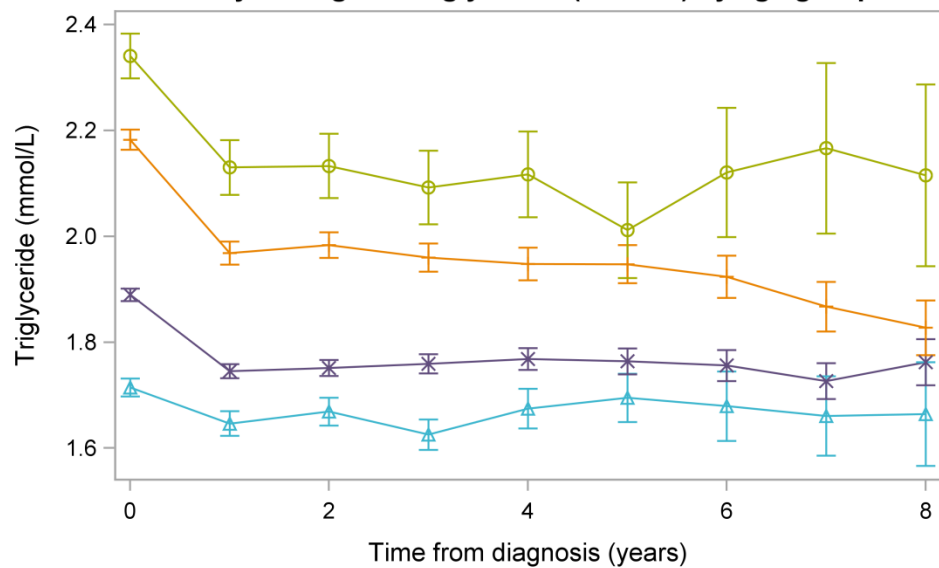Yearly average of BMI(kg/m2) by age groups
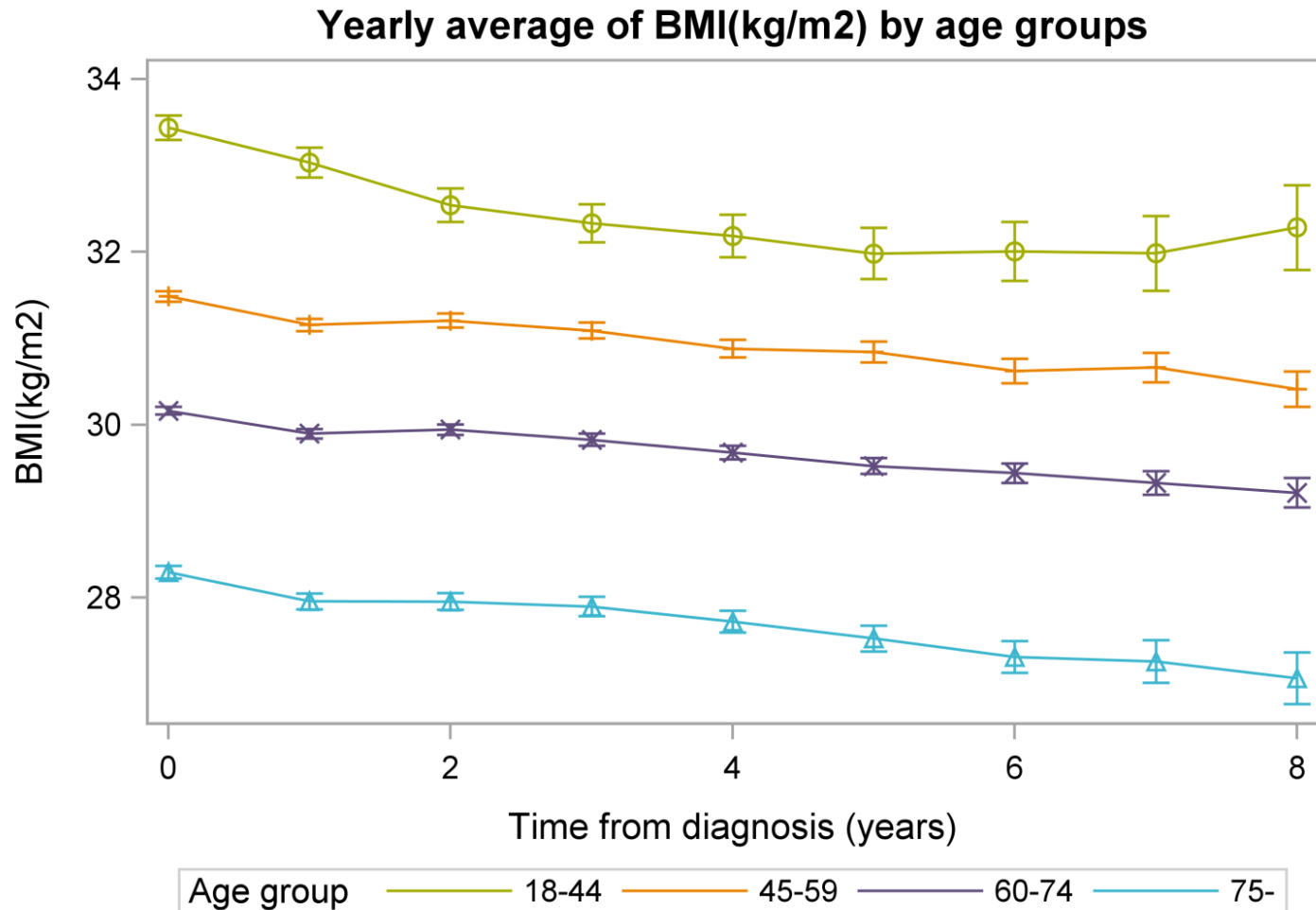
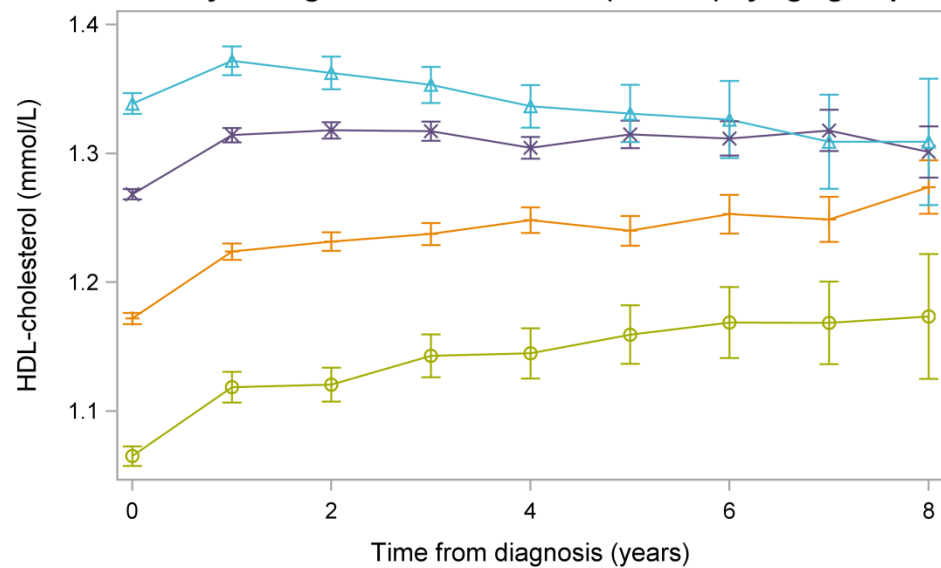# Younger T2DM higher HbA1c diagnosis and after treatment

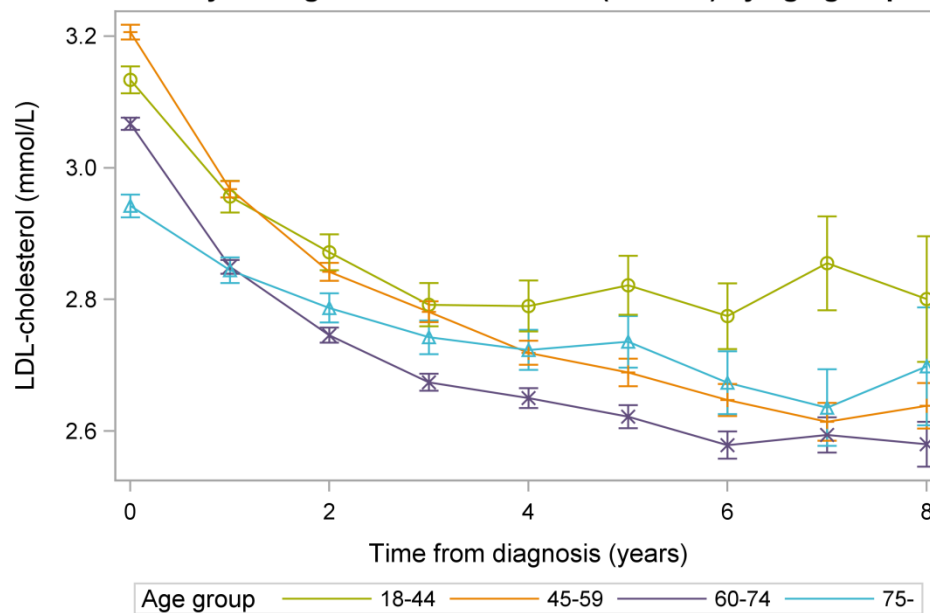Yearly average of HbA1c(mmol/mol) by age groups

Yearly average of Triglyceride (mmol/L) by age groups

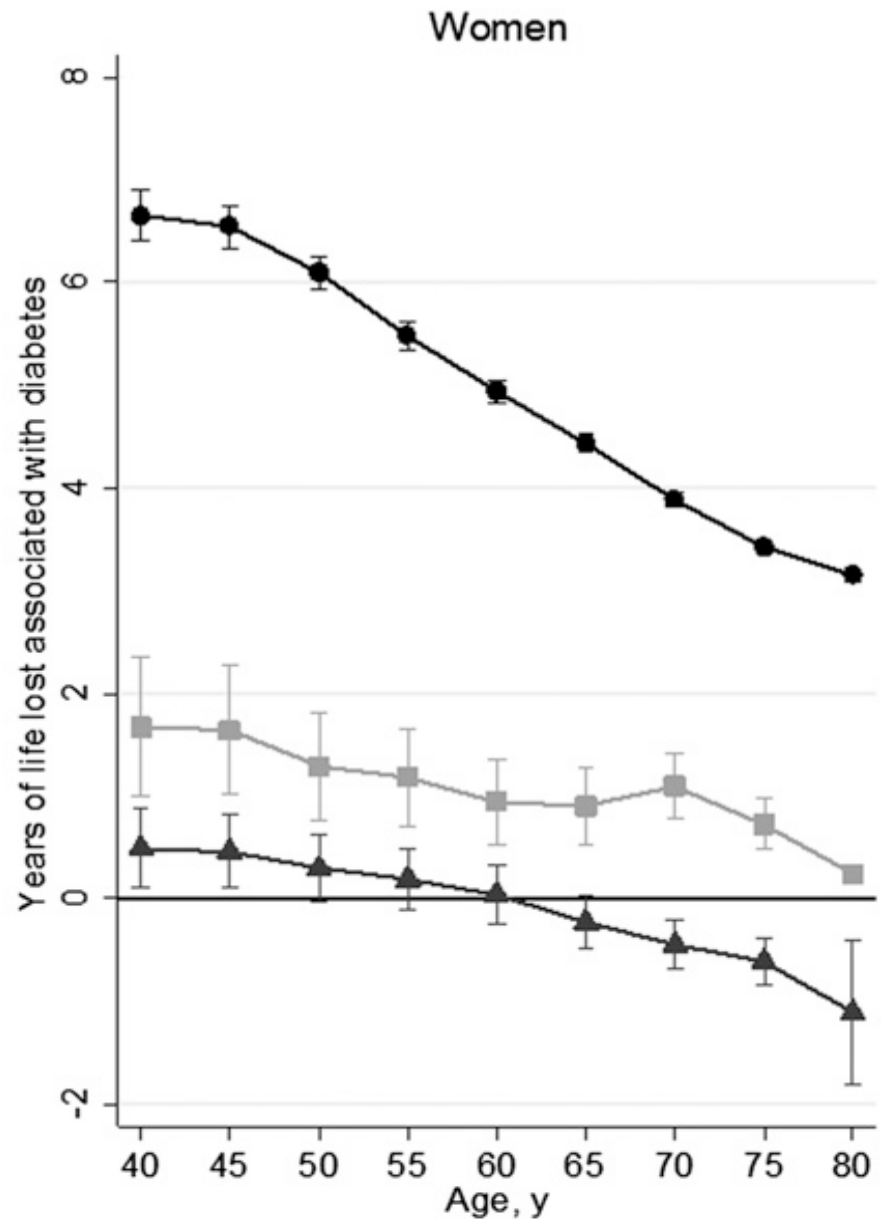**Yearly average of HDL-cholesterol (mmol/L) by age groups**

Yearly average of LDL-cholesterol (mmol/L) by age groups

Age group — 18-44 — 45-59 — 60-74 — 75-

Years lost due to diabetes by ethnicity – something surprising?

Wright et al 2017 Diabetes Care

Men

Women

Wright AK et al. Life Expectancy and Cause-Specific Mortality in Type 2 Diabetes… Diabetes Care. 2017 Mar;40(3):338-345
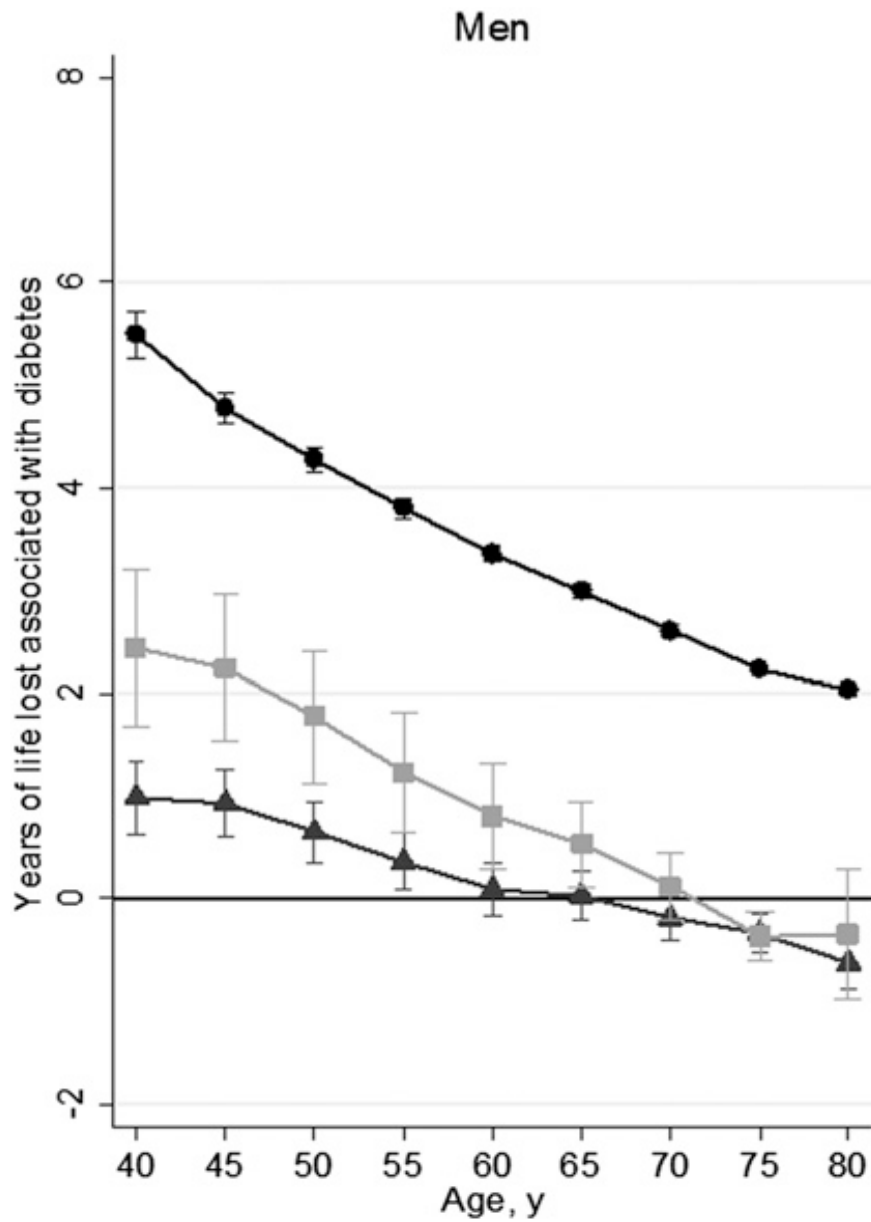
The good news

Magnitude of Improvement in Risk Factors and Control among the US Diabetic Population, 1970 – 2010
**(Large: 15+ % point; Moderate: 5-14 % point; Small/None: <5 % point)**

Gregg, Sattar, Ali (2016) Lancet D/E

|	1970s	1980s	1990s	2000s
Smoking	LARGE	Moderate	Small / none	Small / none
Glycemic control			Small / none	Moderate
Blood pressure	Small / none	LARGE	Moderate	Moderate
Lipids	Small / none	Moderate	Moderate	LARGE

Compared to Persons without Diabetes
- Lower smoking rates and higher smoking cessation/quit rates.
- Better (20+point) HTN control levels.
- Much Higher statin use and greater LDL improvement.
- Exception: Adults age 20-44

References: Ali et al., NEJM, 2014; Imperatore et al., Am J Epidemiol; Wang et al., Diabetes Care, 2010; Gu et al., Hypertension 2012; Fan et al., Prev Chronic Dis 2013; Ford et al., Cardiovascular Diabetol 2013; www.cdc.gov

Diabetes-related CV complications have declined with improved care, but substantial burden remains
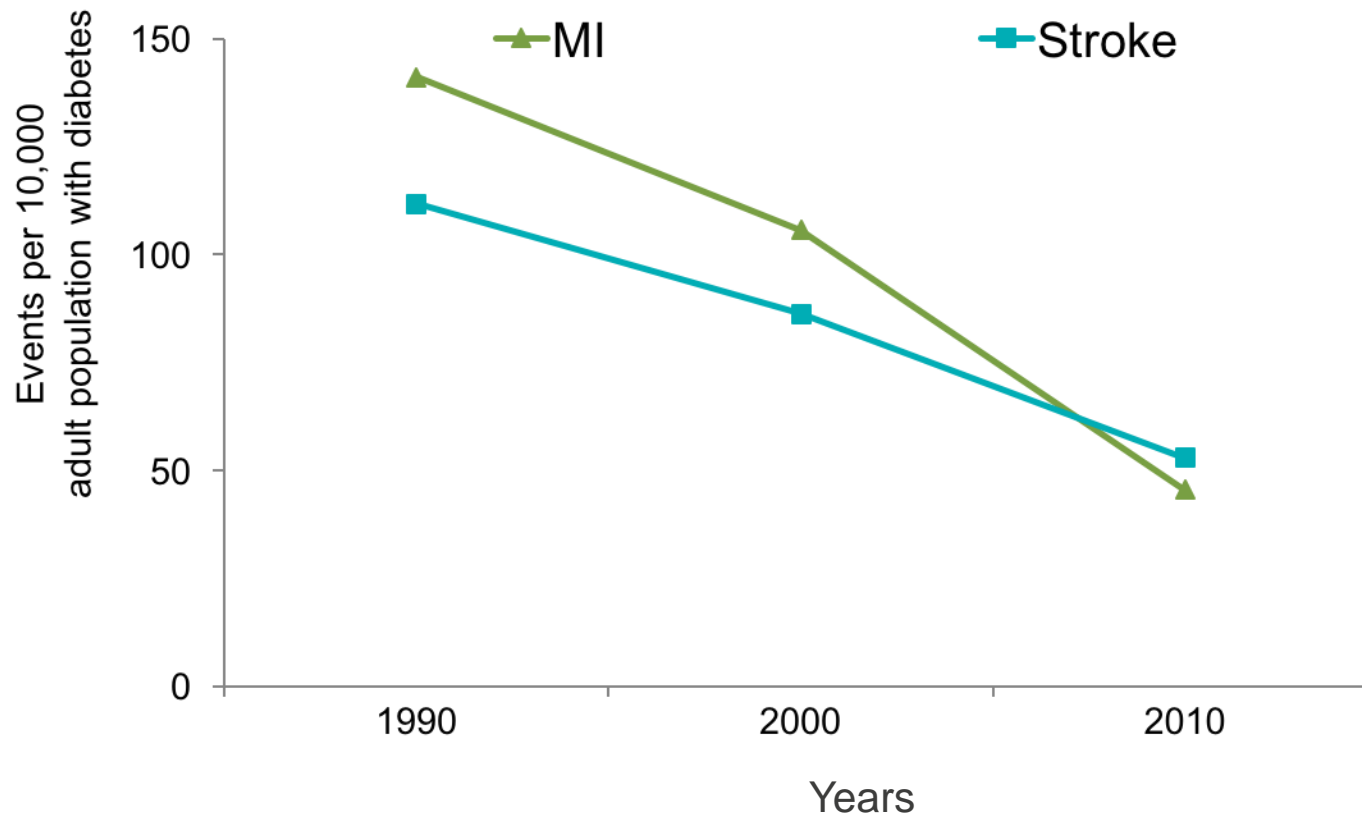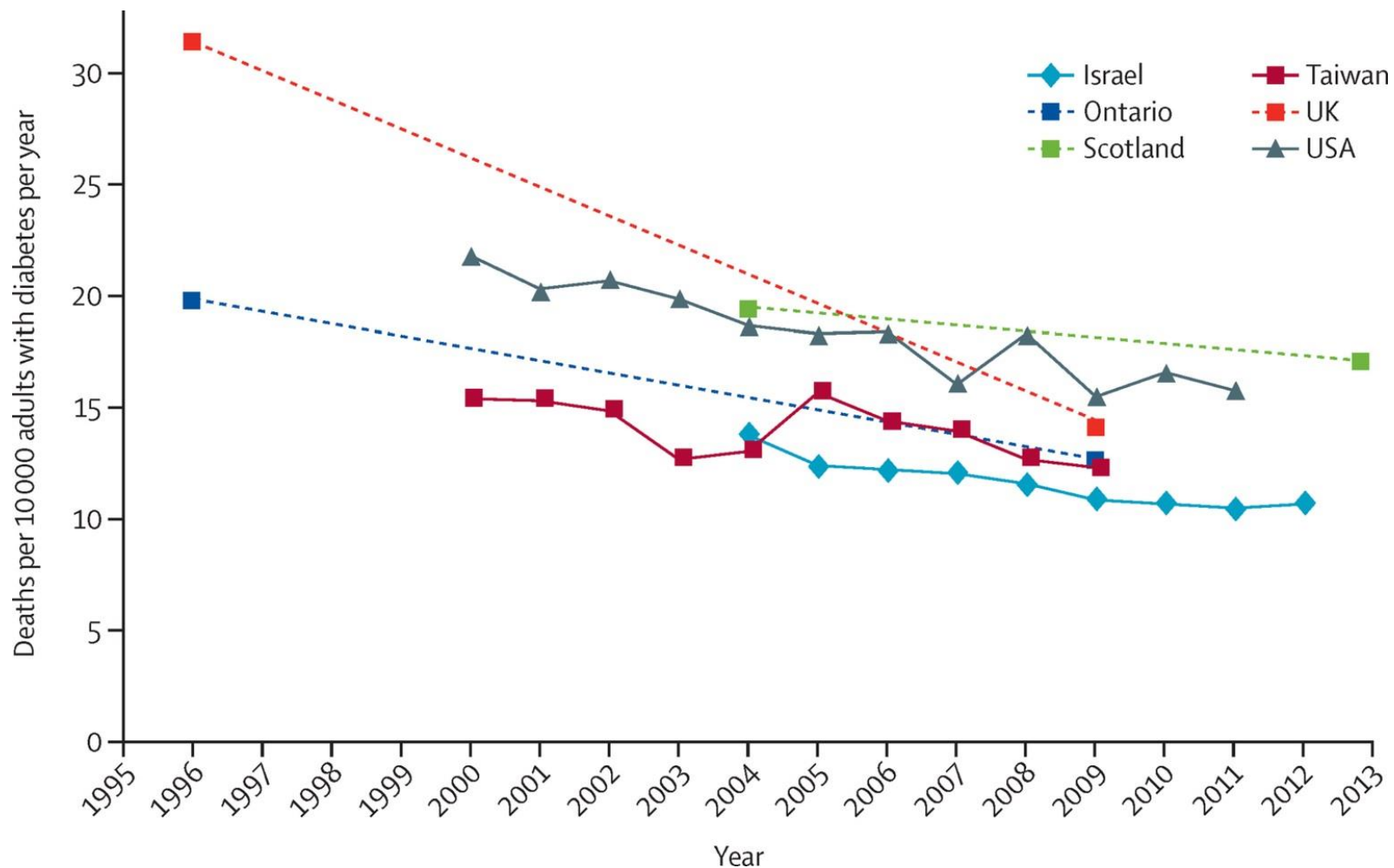
**Trends in rates of all-cause mortality
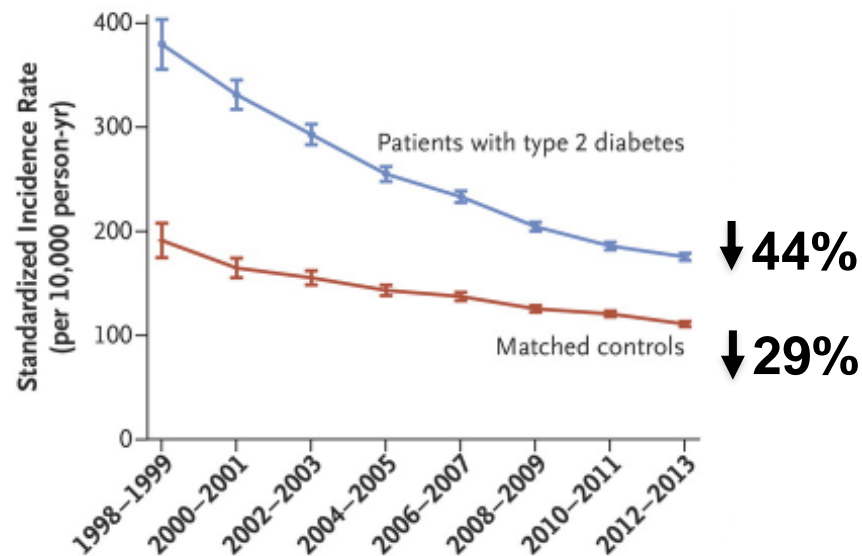in those with diagnosed type 2 DM**

B Death from Cardiovascular Disease

Standardized Incidence Rate (per 10,000 person-yr)

Patients with type 2 diabetes

Matched controls

1998–1999, 2000–2001, 2002–2003, 2004–2005, 2006–2007, 2008–2009, 2010–2011, 2012–2013
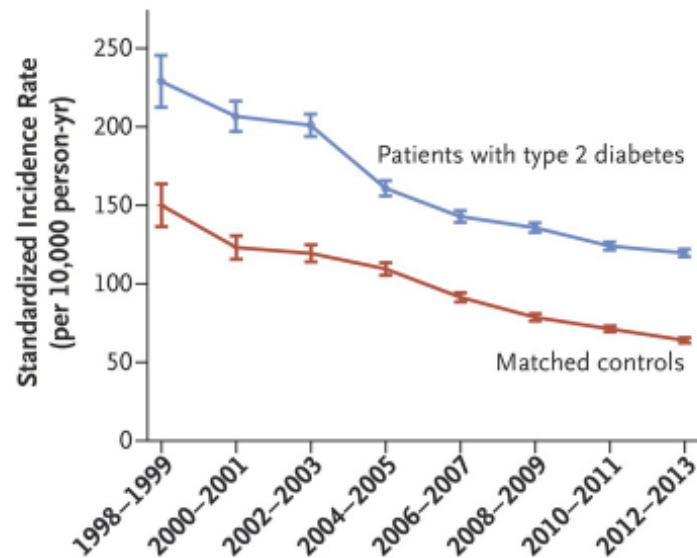
D Hospitalization for Cardiovascular Disease

Standardized Incidence Rate (per 10,000 person-yr)

Patients with type 2 diabetes

↓44%

Matched controls

↓29%

1998–1999, 2000–2001, 2002–2003, 2004–2005, 2006–2007, 2008–2009, 2010–2011, 2012–2013

Rashwani et al (2017) NEJM

NDR NATIONELLA DIABETESREGISTRET
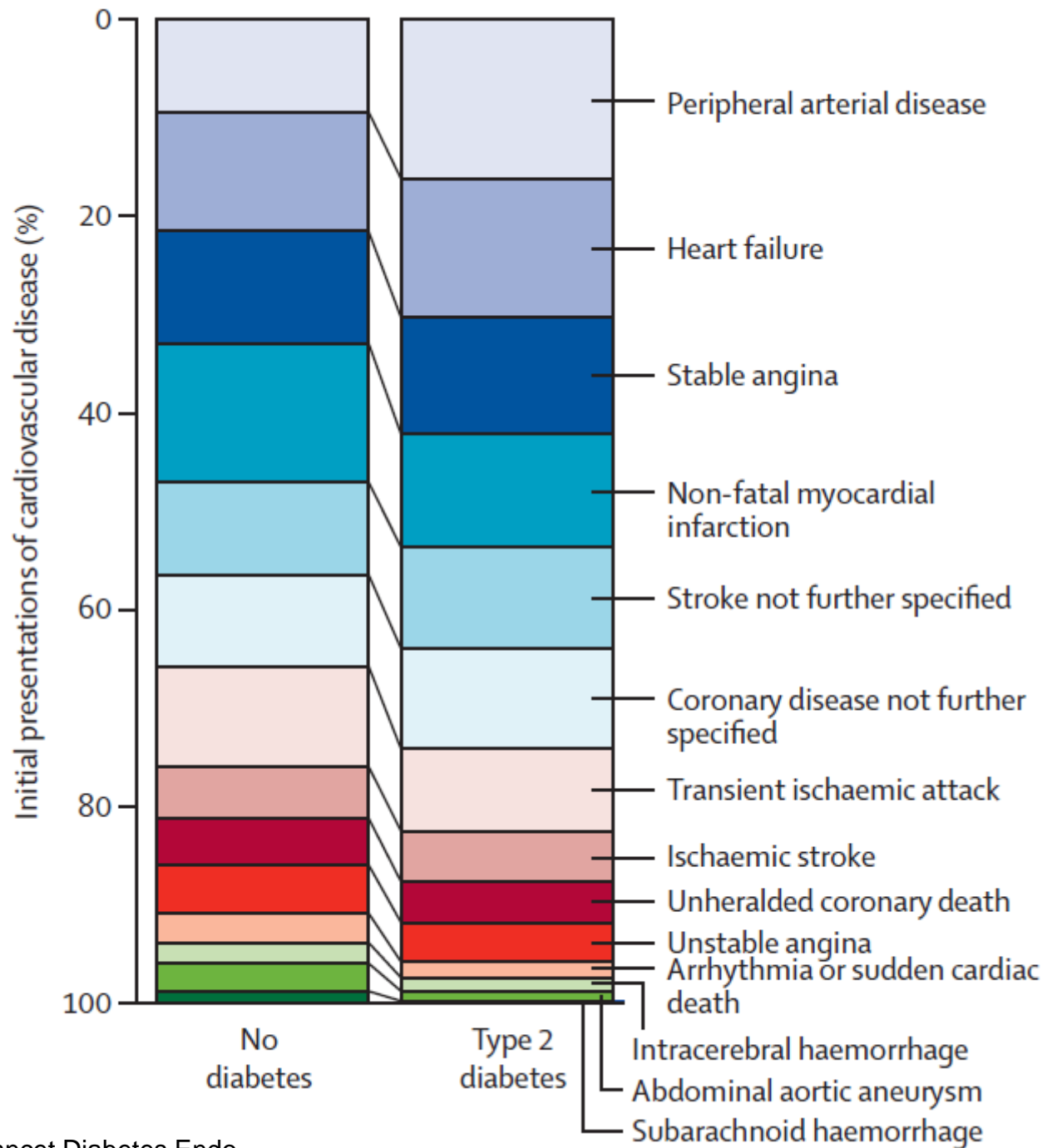SWEDISH NATIONAL DIABETES REGISTER

So what else do we need to tackle?

- **HF common first "CVD presentation" in T2DM (14%), second only to PAD (16%), >>MI**
  - Shah A et al (2015) Lancet Diabetes Endo

K **Peripheral arterial disease (10 514 events)**

Shah A et al (2015) Lancet Diabetes Endo
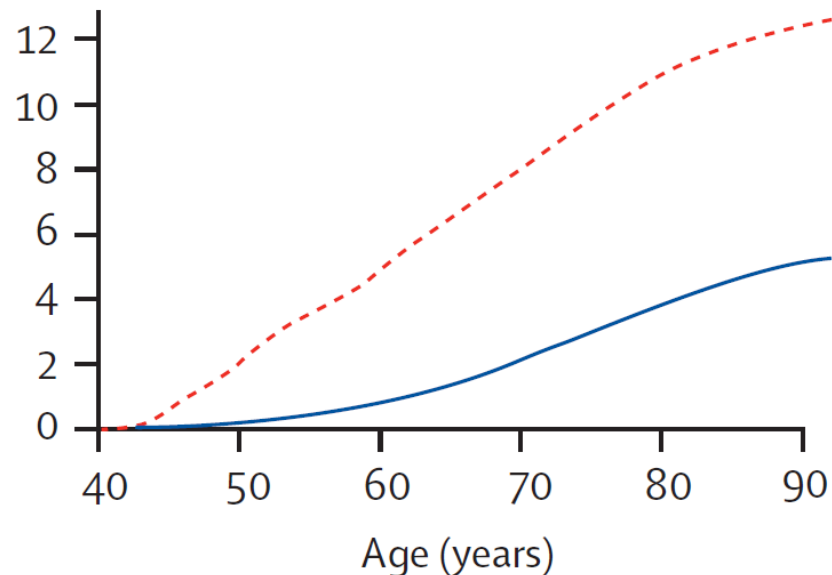
Unexpected HF benefits and CVD death (Empa) in SGLT2i trials

- **EMPAREG Outcomes - Empagliflozin**

- **CANVAS – Canagliflozin**

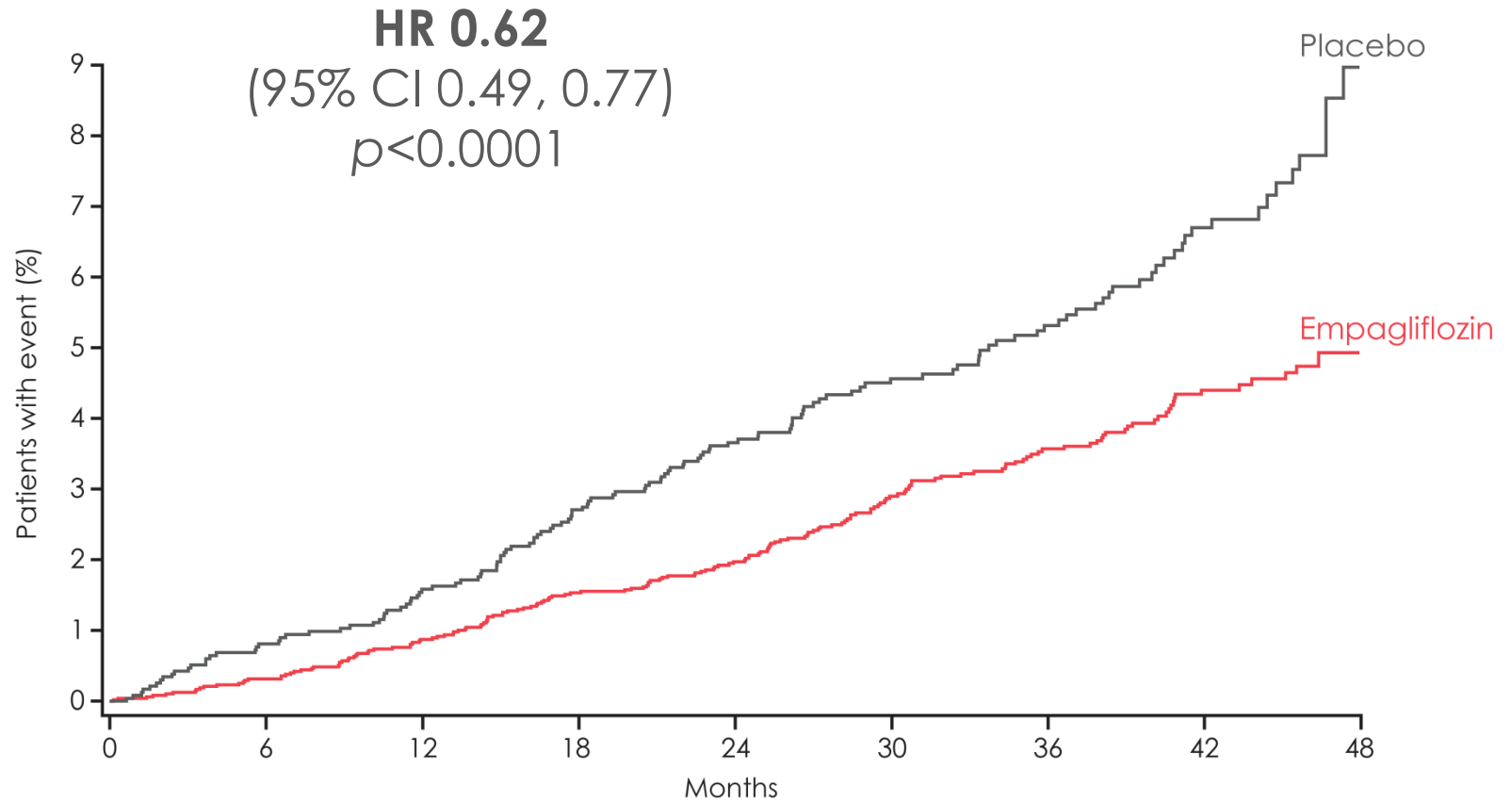Zinman B et al. *N Engl J Med* 2015
Neal B et al. N Engl J Med. 2017

CV Outcomes: Relative Risk Reductions
Blue Boxes Imply Significant Outcomes; This is Not a Head-to-Head Comparison

	EMPA-REG OUTCOME	Pooled CANVAS Program
3P-MACE	14% (HR 0.86, 95%CI 0.74-0.99)	14%* (HR 0.86, 95%CI 0.75-0.97)
4P-MACE	HR 0.89, p=0.08	N/a
CV Death	38% (HR 0.62, p <0.001)	13% (HR 0.87, 95%CI 0.72-1.06)
All-cause Death	32% (HR 0.68, p <0.001)	13% (HR 0.87, 95%CI 0.74-1.01)
Nonfatal MI	13% (HR 0.87, 95%CI 0.7-1.09)	15% (HR 0.85, 95%CI 0.69-1.05)
Nonfatal Stroke	HR 1.24 (95%CI 0.92-1.67)	HR 0.90 (95%CI 0.71-1.15)
HHF or CV Death	34% (HR 0.66, 95%CI 0.55-0.79)	22% (HR 0.78, 95%CI 0.67-0.91)

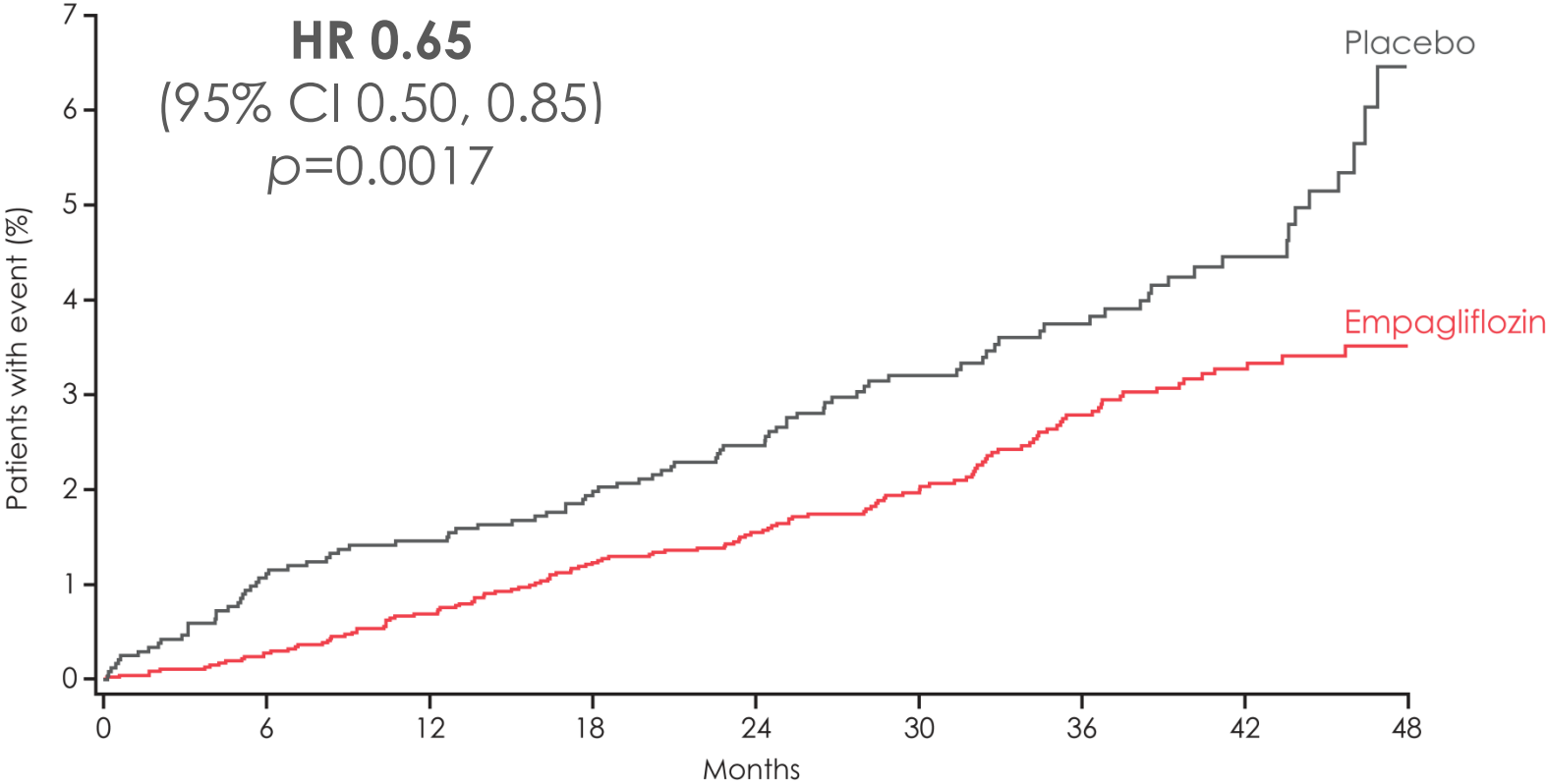* Analysis not powered to detect superiority for 3P MACE

Zinman B et al. *N Engl J Med* 2015;doi:10.1056/NEJMoa1504720
Neal B et al. N Engl J Med. 2017 Jun 12. doi: 10.1056/NEJMoa1611925.

CV death

HR 0.62
(95% CI 0.49, 0.77)
p<0.0001

Placebo

Empagliflozin

Patients with event (%)

Months

No. of patients									
Empagliflozin	4687	4651	4608	4556	4128	3079	2617	1722	414
Placebo	2333	2303	2280	2243	2012	1503	1281	825	177

Cumulative incidence function. HR, hazard ratio

EMPA-REG
OUTCOME®

Hospitalisation for heart failure

HR **0.65**
(95% CI 0.50, 0.85)
p=0.0017

Patients with event (%)

Placebo

Empagliflozin

Months

No. of patients

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

Cumulative incidence function. HR, hazard ratio

EMPA-REG
OUTCOME®

The cardio-renal axis: haemodynamic benefits appear important

SGLT2 inhibition
⇓ Glucose and sodium reabsorption in proximal tubule
⇓ Nephron hyperfiltration

⇑ Urinary glucose & sodium

Generalized decongestion

⇓ Cardiac afterload/pre-load
⇓ Systolic & diastolic dysfunction
⇓ Heart failure hospitalization
⇓ Fatal arrhythmias

Slow renal dysfunction
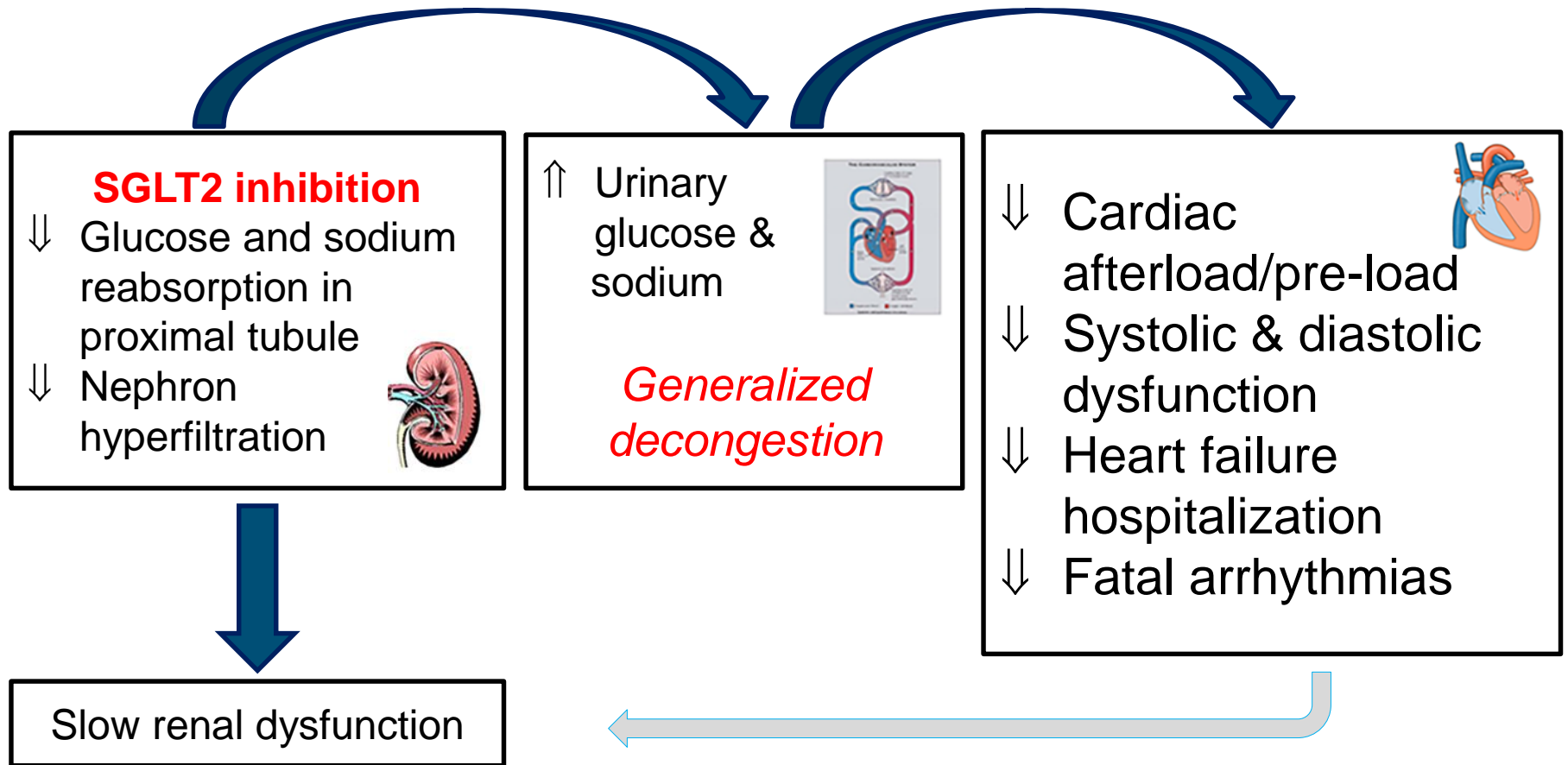
SGLT2i trial - a rethink on diabetes to CVD pathways

Sattar N, McGuire D. Circulation (In press)
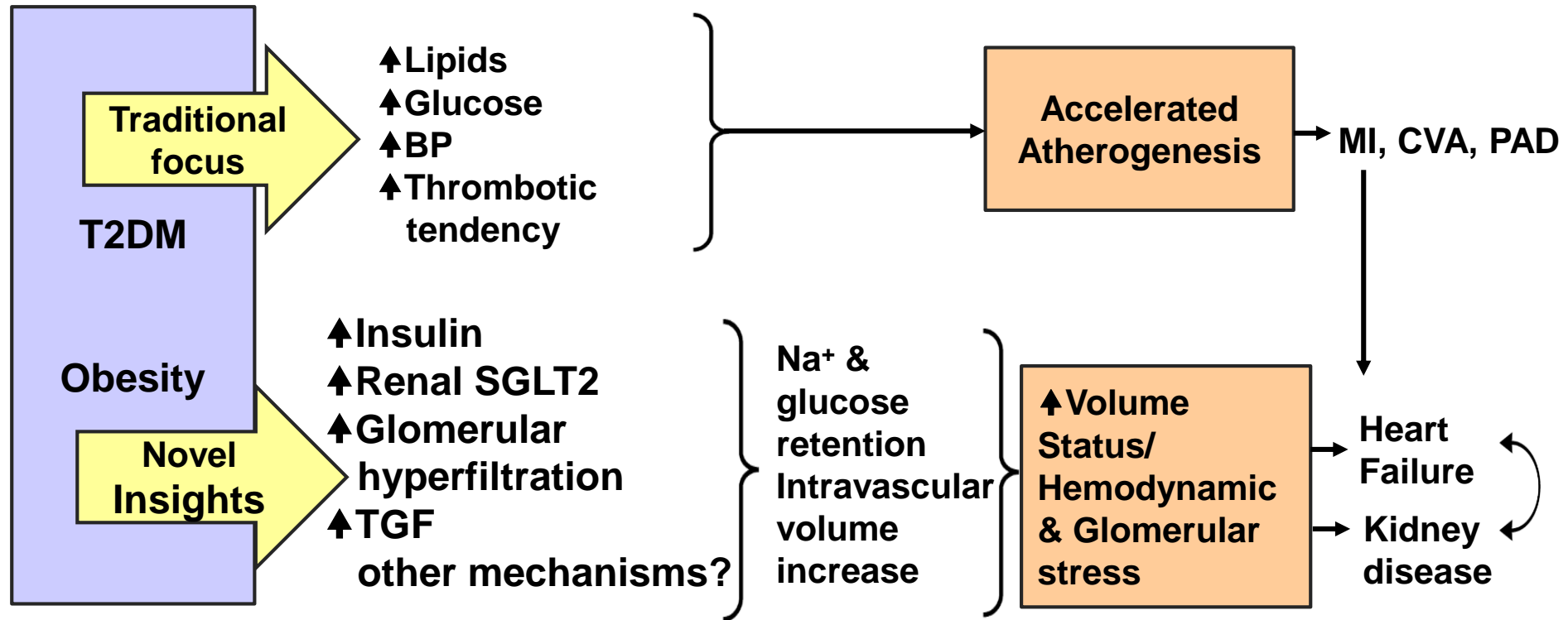
Summary

- **Vascular disease – lots of success**

- **Moving forwards: need to do better at**

  - **Younger ages, T1DM**

  - **Consider why some groups lower mortality?**

  - **PAD, CHF – how to screen, prevent**

  - **Rethink targets? LLT, HBP, etc**