(För?) Tidig statinbeh till T1DM – pro/con

- Tyngden av befintlig evidens
- Hälsoekonomi/Kostnader?
- Biverkningar av långtidsanvändning?
- Compliance?

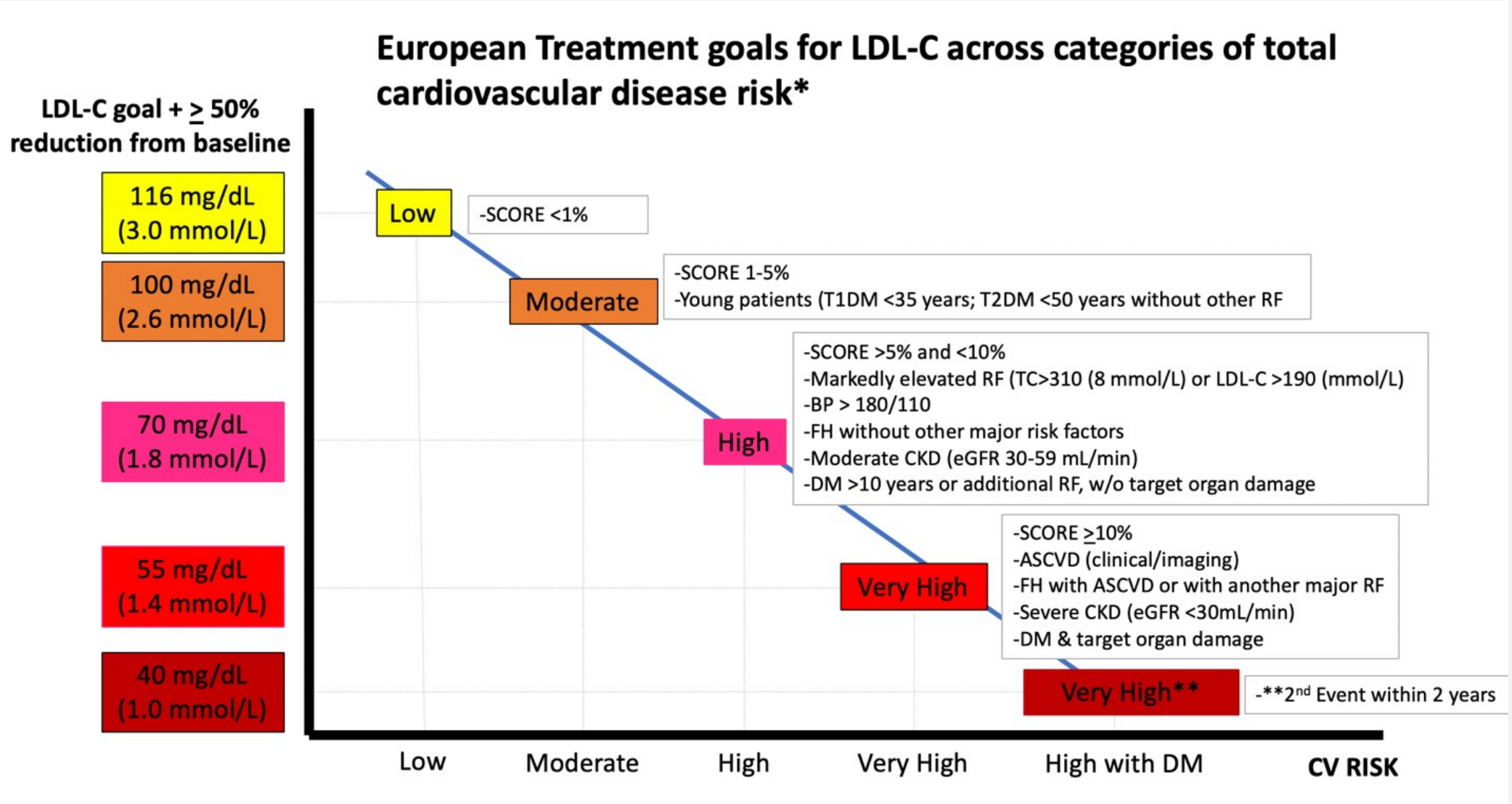
Guidelines & Evidens

100tals guidelines…”Mer till alla”…”Allt till alla”…eller ”Oskuret är bäst”?

ὠφελέειν ή μὴ βλάπτειν (1)

1. Hippocratic treatise on Epidemics, 1;2;5, Corpus Hippocraticum, *Hippocrates school of Medicine, Kos, c:a 397 fKr*

ESC/EAS riktlinjer



*Adapted from slideset available on www.escardio.org/guidelines which is from 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk

ESC/EAS - 2019 Guidelines on Dyslipidaemias

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High-risk	People with: Markedly elevated single risk factors, in particular TC >8 mmol/L (>310 mg/dL), LDL-C >4.9 mmol/L (>190 mg/dL), or BP ≥180/110 mmHg. Patients with FH without other major risk factors. Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor. Moderate CKD (eGFR 30–59 mL/min/1.73 m^2). A calculated SCORE ≥5% and <10% for 10-year risk of fatal CVD.

→ LDL <1,8

↓

Patients with DM without target organ damage,[a] with DM duration ≥10 years or another additional risk factor.

[a]Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

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T1DM med 10 års duration och LDL <1,8 (med eller utan beh)

År	Antal patienter
2025	11310
2024	44260
2023	44450
2022	43140
2021	41950
2020	39900

Alltså 26% når målet 1,8

33.000 som behöver skärpt behandling

Very-high-risk

People with any of the following:

Documented ASCVD, either clinical or unequivocal on imaging. Documented ASCVD includes previous ACS (MI or unstable angina), stable angina, coronary revascularization (PCI, CABG, and other arterial revascularization procedures), stroke and TIA, and peripheral arterial disease. Unequivocally documented ASCVD on imaging includes those findings that are known to be predictive of clinical events, such as significant plaque on coronary angiography or CT scan (multivessel coronary disease with two major epicardial arteries having >50% stenosis), or on carotid ultrasound.

DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years).

Severe CKD (eGFR <30 mL/min/1.73 m^2).

A calculated SCORE ≥10% for 10-year risk of fatal CVD.

FH with ASCVD or with another major risk factor.

LDL <1,4

DM with target organ damage,[a] or at least three major risk factors, or early onset of T1DM of long duration (>20 years).

[a]Target organ damage is defined as microalbuminuria, retinopathy, or neuropathy.

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T1DM med 20 års duration och LDL <1,8 (med eller utan beh)

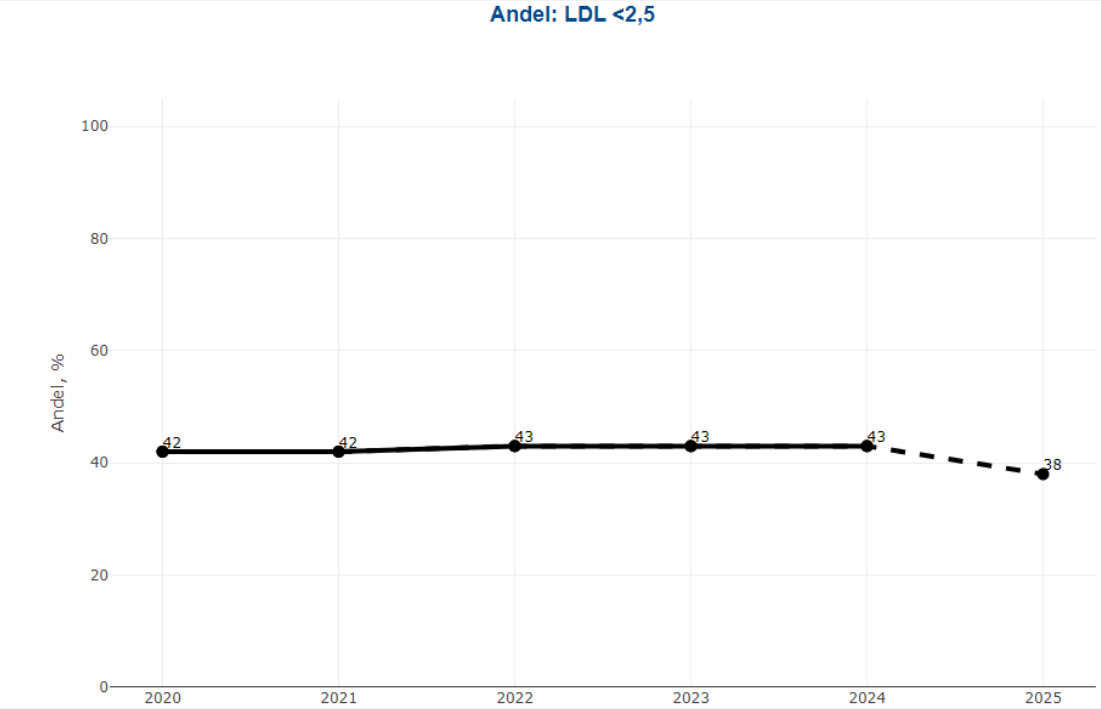
Namn	År	Antal patienter
Riket	2025	7500
Riket	2024	30890
Riket	2023	30860
Riket	2022	29740
Riket	2021	28750
Riket	2020	27130

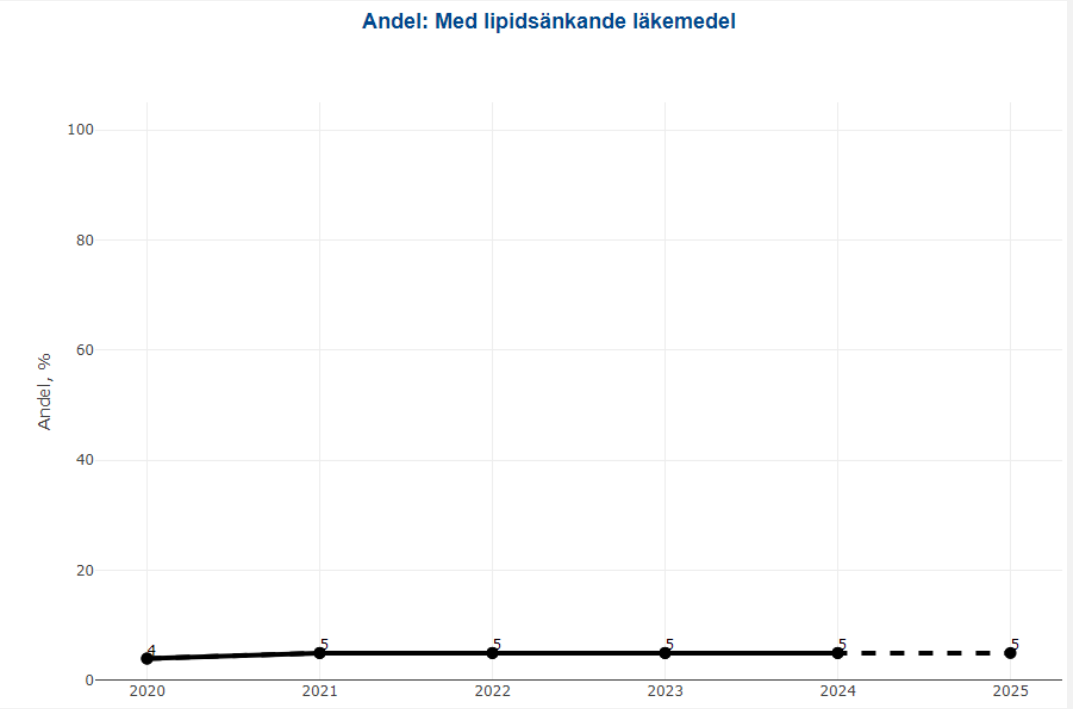
Alltså 30% når målet 1,8 (eg 1,4)

21.000 som behöver skärpt behandling

Moderate-risk Young patients (T1DM <35 years; T2DM <50 years) with DM duration <10 years, without other risk factors. Calculated SCORE ≥1 % and <5% for 10-year risk of fatal CVD.

LDL <2,6





ESC/EAS - 2019 Guidelines on Dyslipidaemias, resp NDR

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

Table 7 Cardiovascular risk categories in type 2 diabetes

Very high CV risk	Patients with T2DM with: • Clinically established ASCVD or • Severe TOD or • 10-year CVD risk ≥20% using SCORE2-Diabetes
High CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 10 to <20% using SCORE2-Diabetes
Moderate CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk 5 to <10% using SCORE2-Diabetes
Low CV risk	Patients with T2DM not fulfilling the very high-risk criteria and a: • 10-year CVD risk <5% using SCORE2-Diabetes

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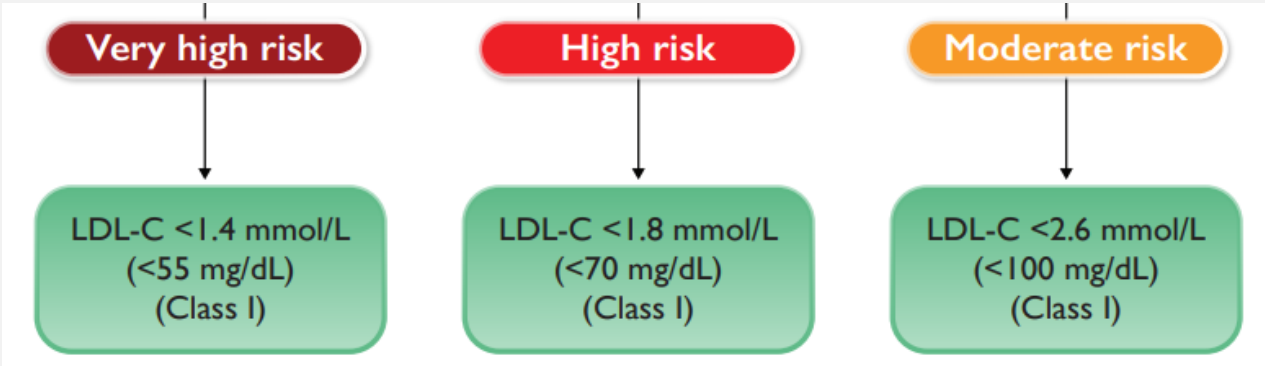
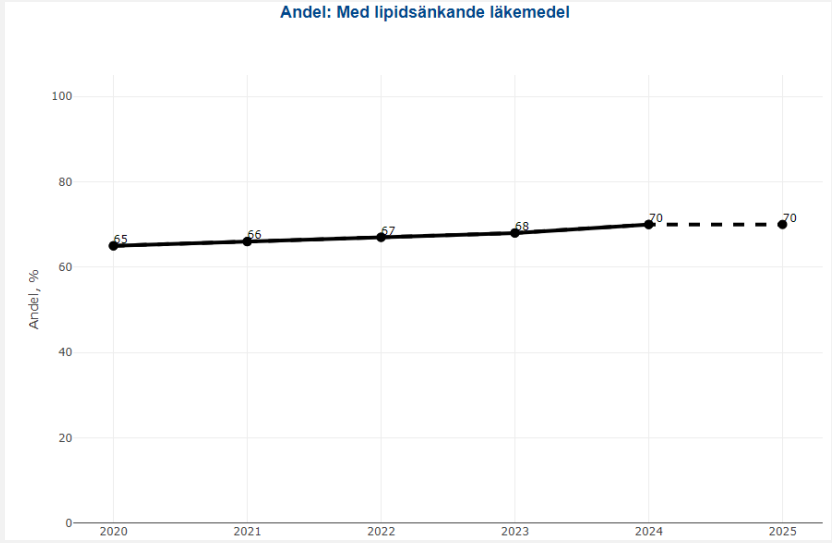
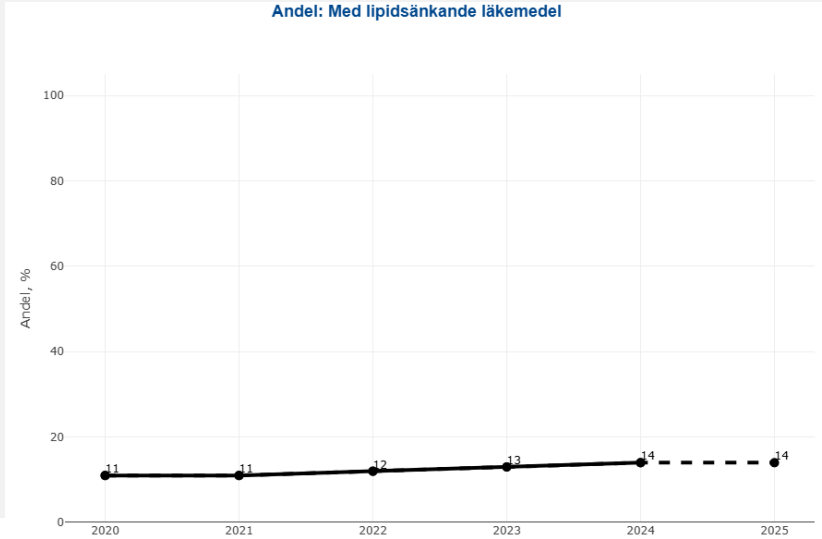


2023 ESC Guidelines for the management of cardiovascular disease in patients with diabetes *EHJ 2023*

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

Type 1 diabetes and cardiovascular disease—*Section 11*		
In patients with T1DM, it is recommended that adjustment of glucose-lowering medication follows principles of patient self-management under the guidance of the diabetes healthcare multidisciplinary team.	I	C
Avoiding hypoglycaemic episodes is recommended, particularly in those with established CVD.	I	C
Statins should be considered for LDL-C lowering in adults older than 40 years with T1DM without a history of CVD to reduce CV risk.	IIa	B
Statins should be considered for use in adults younger than 40 years with T1DM and other risk factors of CVD or microvascular end-organ damage or 10-year CVD risk ≥10% to reduce CVD risk.	IIa	B
The use of the Scottish/Swedish risk prediction model may be considered to estimate 10-year CVD risk in patients with T1DM.	IIb	B





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

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Målen satta utifrån resultat från studier med PCSK-9-behandling

The targeted approach to lipid management is primarily aimed at reducing atherosclerotic risk by substantially lowering LDL-C to levels that have been achieved in recent large-scale trials of PCSK-9 inhibitors. Therefore, for patients at very high CV risk, whether in

ESC/EAS - 2019 Guidelines on Dyslipidaemias

Vilken evidens anges som bakgrund till rek?…

Recommendations	Class[a]	Level[b]
Statins are recommended in patients with T1DM who are at high or very-high risk.[c] [427]	I	A
Statin therapy may be considered in both T1DM and T2DM patients aged ≤30 years with evidence of end organ damage and/or an LDL-C level >2.5 mmol/L, as long as pregnancy is not being planned.	IIb	C

	Definition	Wording to use
Class I	Evidence and/or general agreement that a given treatment or procedure is beneficial, useful, effective.	Is recommended or is indicated

Level of evidence A	Data derived from multiple randomized clinical trials or meta-analyses.
Level of evidence B	Data derived from a single randomized clinical trial or large non-randomized studies.
Level of evidence C	Consensus of opinion of the experts and/or small studies, retrospective studies, registries.

"Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes"
Laing et al, Diabetologia 2003

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Ref 427 - “Mortality from heart disease in a cohort of 23,000 patients with insulin-treated diabetes”

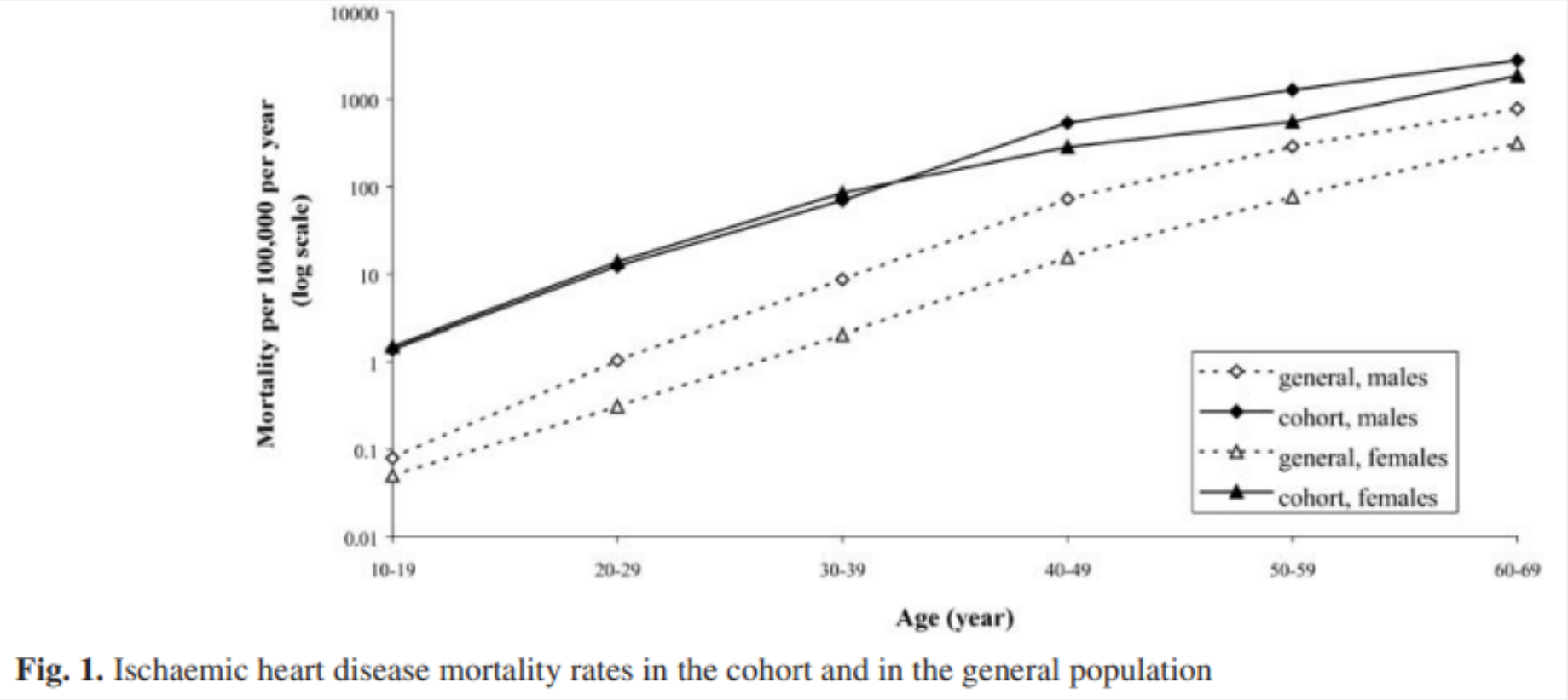

Fig. 1. Ischaemic heart disease mortality rates in the cohort and in the general population

Är en riskpopulation…men beror det på lipiderna?

AHA/ADA SCIENTIFIC STATEMENT

Type 1 Diabetes Mellitus and Cardiovascular Disease

A Scientific Statement From the American Heart Association and American Diabetes Association

- **"Very little clinical trial evidence exists for people with type 2 diabetes under the age of 40 years or for people with type 1 diabetes of any age" (1)**

  - 1. HPS
  - 2. CCT

1.Cardiovascular Disease and Risk Management: *Standards of Care in Diabetes—2024 American Diabetes Association Professional Practice Committee, Diabetes Care 2024*

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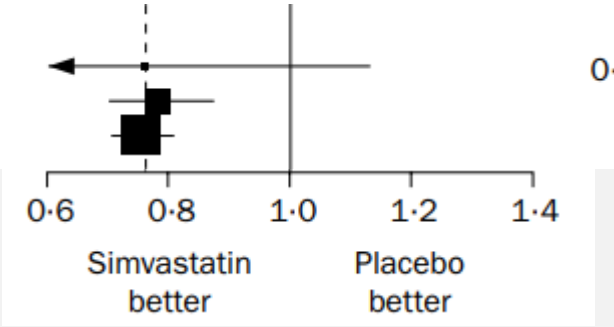
AHA/ADA SCIENTIFIC STATEMENT

Type 1 Diabetes Mellitus and Cardiovascular Disease

A Scientific Statement From the American Heart Association and American Diabetes Association

- In the Heart Protection Study (lower age limit 40 years), the subgroup of ~600 people with type 1 diabetes had a reduction in risk proportionately similar, although not statistically significant, to that in people with type 2 diabetes (96).

Baseline diabetes and other features	Simvastatin-allocated	Placebo-allocated	Event rate ratio (95% CI)	P-value for heterogeneity
Type of diabetes				
Type 1	43/313 (13·7%)	53/302 (17·5%)		0·9
Type 2	558/2665 (20·9%)	695/2683 (25·9%)		
No diabetes	1432/7291 (19·6%)	1837/7282 (25·2%)		



1. Heart Protection Study of cholesterol-lowering with simvastatin in 5963 people with diabetes: a randomised placebocontrolled trial. *Lancet 2003*

CTT (Cholesterol Treatment Trialists') Collaboration

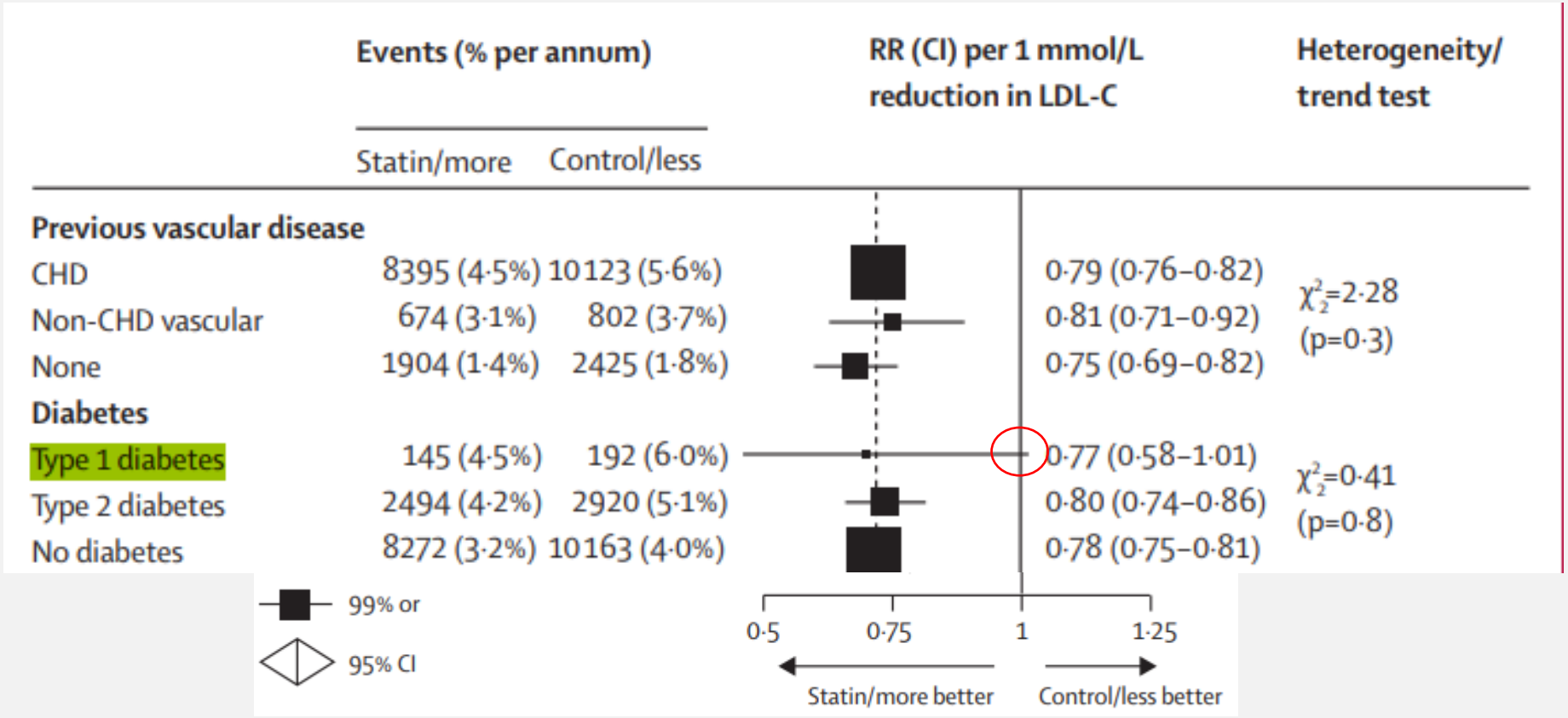


Figure 3: **Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, by baseline prognostic factors**
Rate ratios (RRs) are plotted for each comparison of first event rates between treatment groups, and are weighted per 1·0 mmol/L LDL cholesterol (LDL-C) difference at 1 year. Missing data are not plotted. RRs are shown with horizontal lines denoting 99% CIs or with open diamonds showing 95% CIs. CHD=coronary heart disease. GFR=glomerular filtration rate.

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170 000 participants in 26 randomised trials, *CTT, Lancet 2010*

AHA/ADA (American Heart Association and American Diabetes Association)

Type 1 Diabetes Mellitus and Cardiovascular Disease

- *Most studies show that as is true for the general population, dyslipidemia is a risk factor for CVD in T1DM…*

- *Conventionally, pharmacotherapy is used more aggressively for patients with T1DM and lipid disorders than for nondiabetic patients; however, recommendations for treatment are mostly extrapolated from interventional trials in adults with T2DM, in which rates of CVD events are equivalent to those in secondary prevention populations.*

- *For people who are <40 years of age and/or have type 1 diabetes with other ASCVD risk factors, it is recommended that the individual and health care professional discuss the relative benefits and risks and consider the use of moderate-intensity statin therapy.*

Evidensen…

Evidence for Lipid-Lowering Therapy People with T1DM

The evidence supporting aggressive lipid-lowering therapy for cardiovascular risk reduction and prevention is compelling. A meta-analysis pooling data from 4 major trials comparing high-dose versus standard statin therapy [illegible] a 16% reduction in coronary death or [illegible] infarction with intensive lipid-lowering [56]. A much larger subsequent meta-analysis of 170,000 participants in 26 [illegible] trials supported this early finding [illegible] more intensive regimen produced a [illegible] 15% reduction in CVD events [57], highlighting a significant protective [illegible] intensive statin dosing [58]. [illegible] evidence to support aggressive lipid lowering was provided from the recent IMPROVE-IT study and from PCSK-9 inhibitor trials. In patients with diabetes, ezetimibe and statin combination therapy [illegible] adverse cardiovascular events by 5.5% [59]. [illegible] recover, in the FOURIER study, evolocumab use in patients with diabetes reduced LDL-C by 57% and led to a significant reduction in CVD risk [60]. Additionally, in the ODYSSEY outcomes study, alirocumab treatment to a target LDL-C of 25–50 g/dl after an acute coronary syndrome led to a twice-absolute reduction in CVD events in patients with diabetes [61].

However, there is a paucity of randomized clinical trials in patients with T1D treated with lipid-lowering therapy. Therefore, current treatment guidelines are similar for patients with T1DM and T2DM, and we can extrapolate data from patients with T2DM to those with T1DM [62]. The Heart Protection Study, a 2003 trial of simvastatin in more than 5000 patients with diabetes, including 10% of patients with T1DM, showed that simvastatin significantly reduced cardiovascular event rates, including major coronary

56. Post-infarkt-patienter

57. Tydligt för T2DM. Ej sign för subgruppen T1DM.

58. Metaanalys, postinfarkt, tittade ej på diabetes

59. T2DM

60. T2DM (3% T1DM, analyserades ihop)

61. T2DM (0,007% T1DM, analyserades ihop)

62. ADAs uttalande

63. T2DM, ej sign för subgruppen T1DM

64. T2DM, ej sign för subgruppen T1DM

65. Arterial stiffness/endotelfunktion 12v, T1DM

66. T1DM, observ NDR

events, [illegible] revascularization. However, due to the small number of patients included with T1DM, there was no significant event reduction in this subgroup alone [63]. A similar finding was demonstrated in a 2008 meta-analysis of 14 randomized statin trials among patients with diabetes. In the subgroup of patients with T1DM, the hazard ratio for cardiovascular events was 0.79, which did not reach statistical significance [64]. In 2009, the Pediatric Atorvastatin in Diabetes Trial evaluated atorvastatin specifically in T1DM adolescents. Although the study was unable to achieve its primary endpoint of reduced arterial stiffness at a 12-week follow-up, likely as it was underpowered and included only a few subjects, it did demonstrate a statistically significant reduction in LDL accompanied by an excellent safety profile [65]. Hero et al. studied 25,000 people with T1DM without a history of CVD and demonstrated that lipid-lowering therapy was associated with a significantly reduced total death, CVD death, and both fatal and non-fatal stroke and myocardial infarction by 22–[illegible] [66]. Collectively, these studies support intensive statin therapy in patients with diabetes for cardiovascular event reduction. While no prospective studies have been performed in patients with T1DM, there is no evidence that the benefit of major cardiovascular events differs in patients with T1DM from those with T2DM.

Hyperlipidemia and Cardiovascular Disease in People with Type 1 Diabetes: Review of Current Guidelines and Evidence. *Curr Card Rep 2023. Cleveland Clinic*

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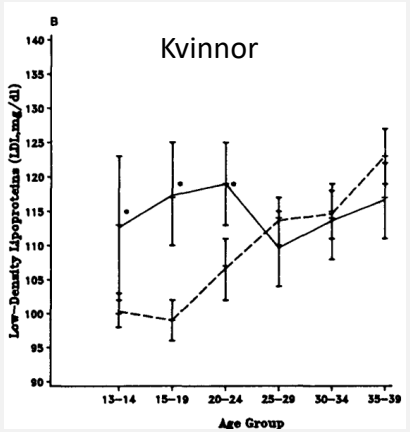
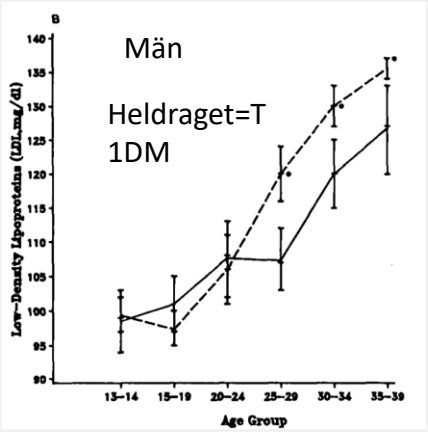
In general, the lipid levels of adults with well-controlled T1DM are similar to those of individuals without DM…(1)



(2)



- Många spännande prekliniska studier rörande bla insulinbehandlings påverkan på LPL/Hepatiskt lipas aktivitet, VLDLomsättning, påverkan på LDL, TG och HDL. I T1DM förändrade LDL och HDL-partiklar med ökad aterogenicitet.

1. Type 1 Diabetes Mellitus and Cardiovascular Disease AHA/ADA, Circulation 2014
2. Lipid and Lipoprotein Levels in Patients With IDDM, DCCTgroup, Diabetes Care 1992
3. ESC/EAS - 2019 Guidelines on Dyslipidaemias

Glykemisk kontroll/Exogent insulin spelar stor roll

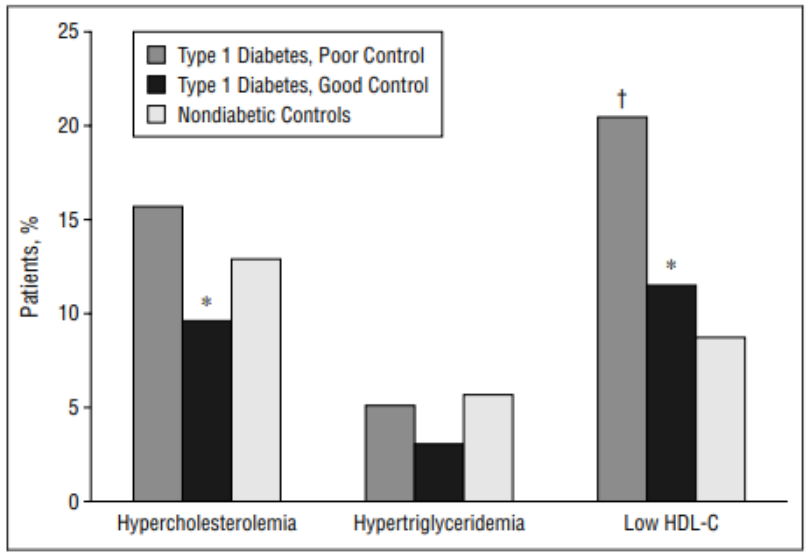
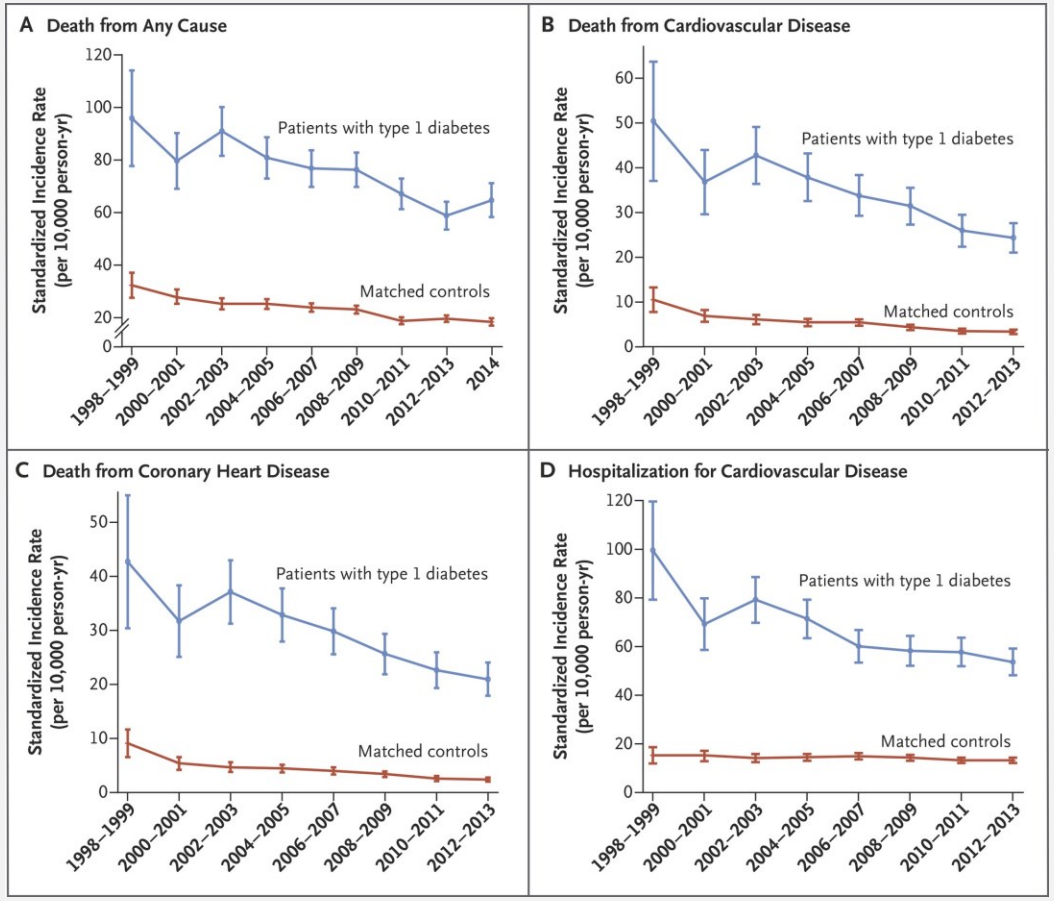


Figure 2. *Prevalence of dyslipidemic disorders in patients with type 1 diabetes mellitus before and after glycemic optimization and in nondiabetic controls. Asterisk indicates P = .01 vs patients with poorly controlled type 1 diabetes; dagger, P < .001 vs nondiabetic controls. See the "Definition of Dyslipidemia, Dyslipidemic Phenotypes, and Recommended LDL-C Concentrations" subsection of the "Patients and Methods" section for definitions of the dyslipidemic disorders.*

- Poor Control; medelHbA1c 70
- Good Control; medelHbA1c 45

Prevalence and Phenotypic distribution of dyslipidemia in T1DM, *Arch Int Med 2000*

Mortalitet förbättrats hos T1DM ”ändå” 1998-2014…bättre glykemisk kontroll(?)



Mortality and Cardiovascular Disease in Type 1 and Type 2 Diabetes, *N Engl J Med 2017*

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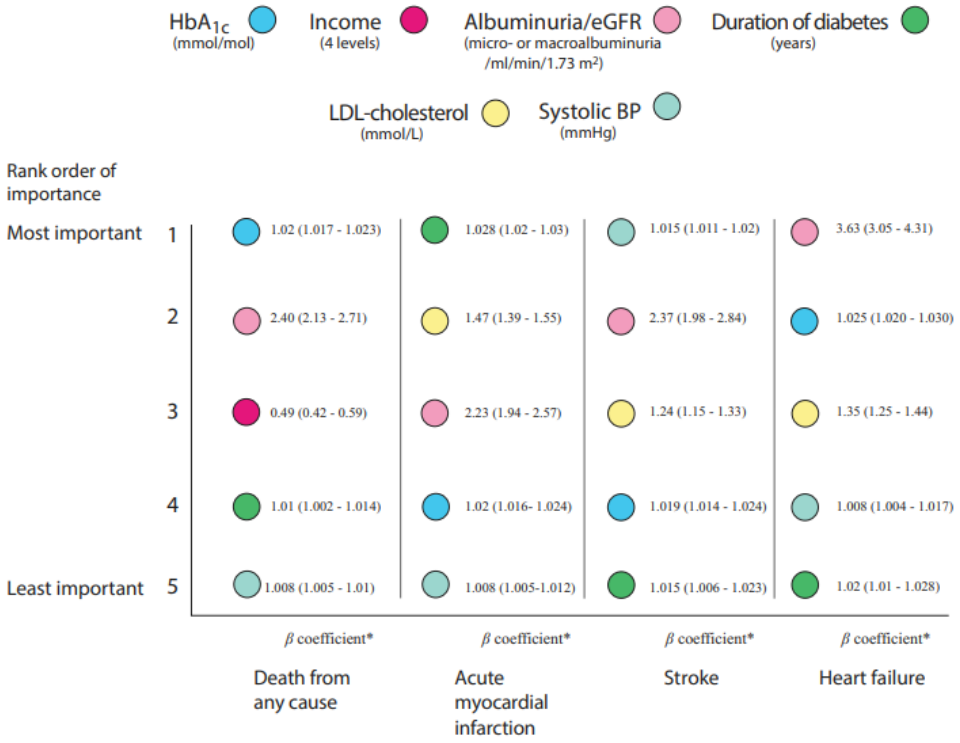
Flera viktiga riskfaktorer, LDL en av flera…

Predictors for mortality & cardiovascular complications

RISK FACTOR	RANK
Albuminuria/eGFR	1
HbA_{1c}	2
Duration of diabetes	3
Systolic BP	4
LDL-cholesterol	5

Different model building for the relative importance analyses showed that all these risk factors interacted significantly with age and duration of diabetes

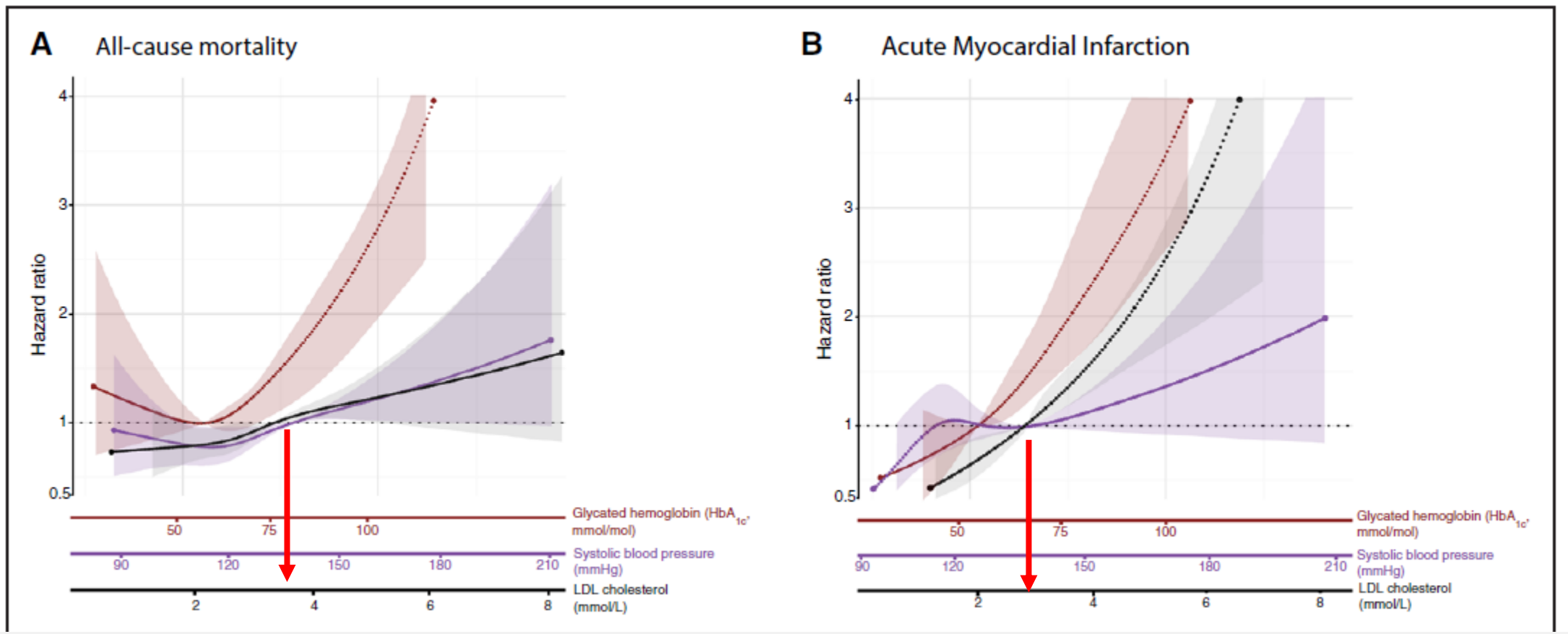


"Glycated hemoglobin and albuminuria were the 2 most important predictors for mortality and cardiovascular disease in patients with type 1 diabetes mellitus"

Relative Prognostic Importance and Optimal Levels of Risk Factors for Mortality and Cardiovascular Outcomes in Type 1 Diabetes Mellitus, *Circulation 2019*

-NDR-data

För att få hazard ratio till 1,0….vilken LDLnivå krävs?



Relative Prognostic Importance and Optimal Levels of Risk Factors for Mortality and Cardiovascular Outcomes in Type 1 Diabetes Mellitus, *Circulation 2019*

-NDR-data

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För att få hazard ratio till 1,0….vilken LDLnivå krävs?

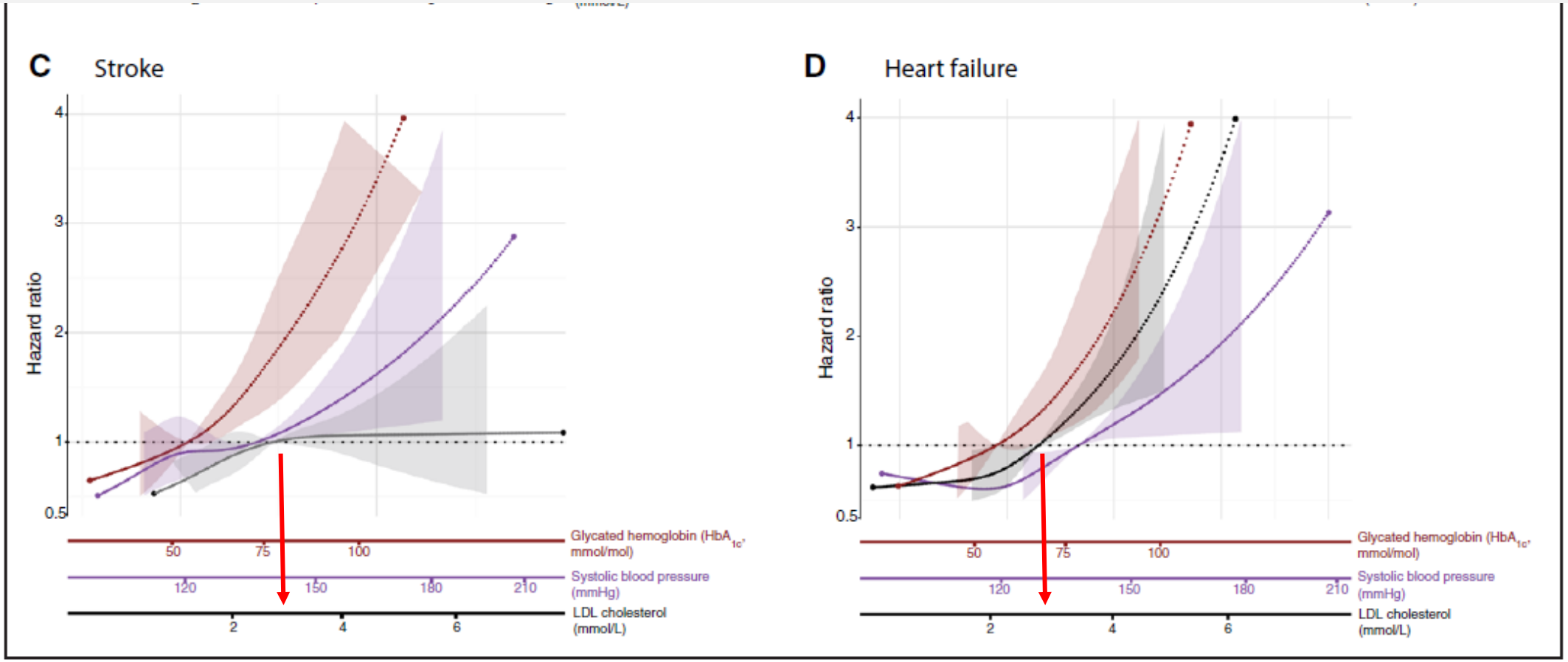


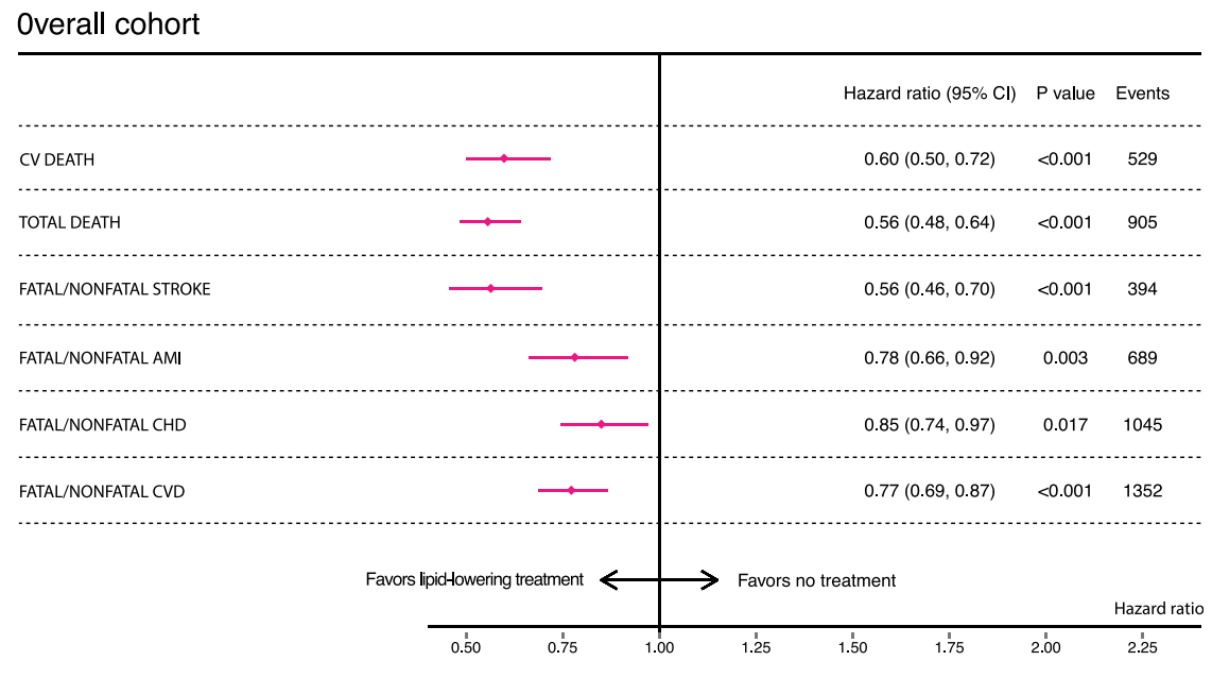
Figure 4. Association between glycohemoglobin (HbA_{1c}), systolic blood pressure (SBP), and low-density lipoprotein (LDL) cholesterol (LDL-C) and all-cause mortality, acute myocardial infarction (AMI), stroke, and hospitalization for heart failure.

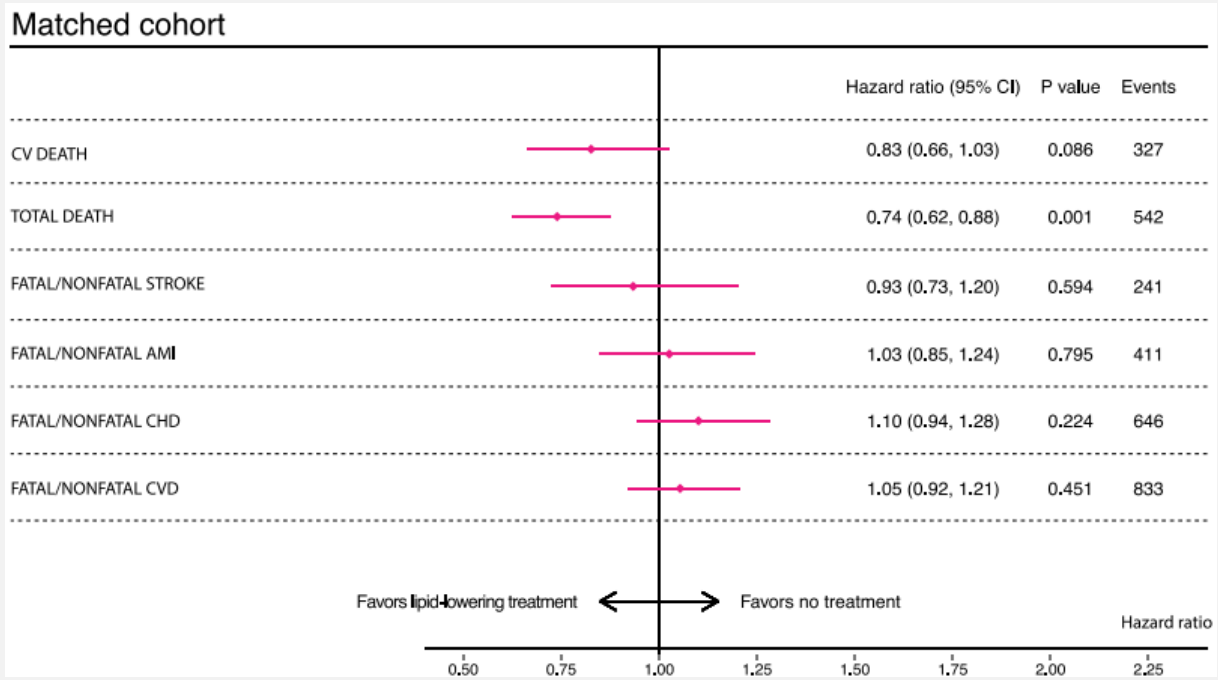
Aktivera Windows

Relative Prognostic Importance and Optimal Levels of Risk Factors for Mortality and Cardiovascular Outcomes in Type 1 Diabetes Mellitus, *Circulation 2019*

-NDR-data

NDR – Observationella data





"In the overall cohort, 18,843 did not have LLT, while 5,387 were treated with such medication. People with LLT were

- older,
- had longer diabetes duration,
- more often used antihypertension medication,
- and had a slightly higher HbA1c. "

Association Between Use of Lipid-Lowering Therapy and Cardiovascular Diseases and Death in Individuals With Type 1 Diabetes, *Diabetes Care 2016*

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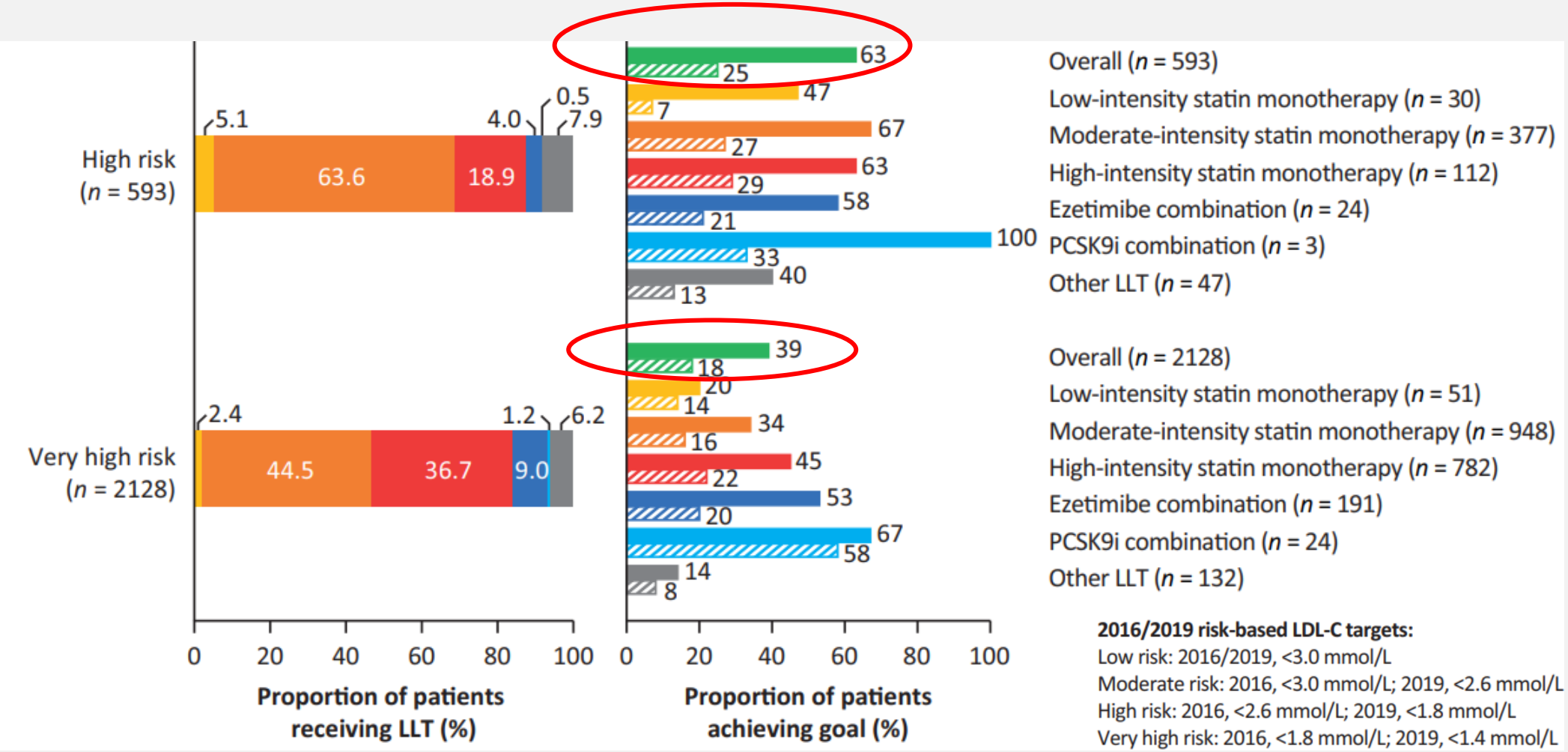
Hur ser det ut i verkligheten?

Och vad kostar det?

The targeted approach to lipid management is primarily aimed at reducing atherosclerotic risk by substantially lowering LDL-C to levels that have been achieved in recent large-scale trials of PCSK-9 inhibitors. Therefore, for patients at very high CV risk, whether in

Real life data (Da Vinci studien)



25%

18%

EU-Wide Cross-Sectional Observational Study of Lipid-Modifying Therapy Use in Secondary and Primary Care: the DA VINCI study *European Journal of Preventive Cardiology (2021)*

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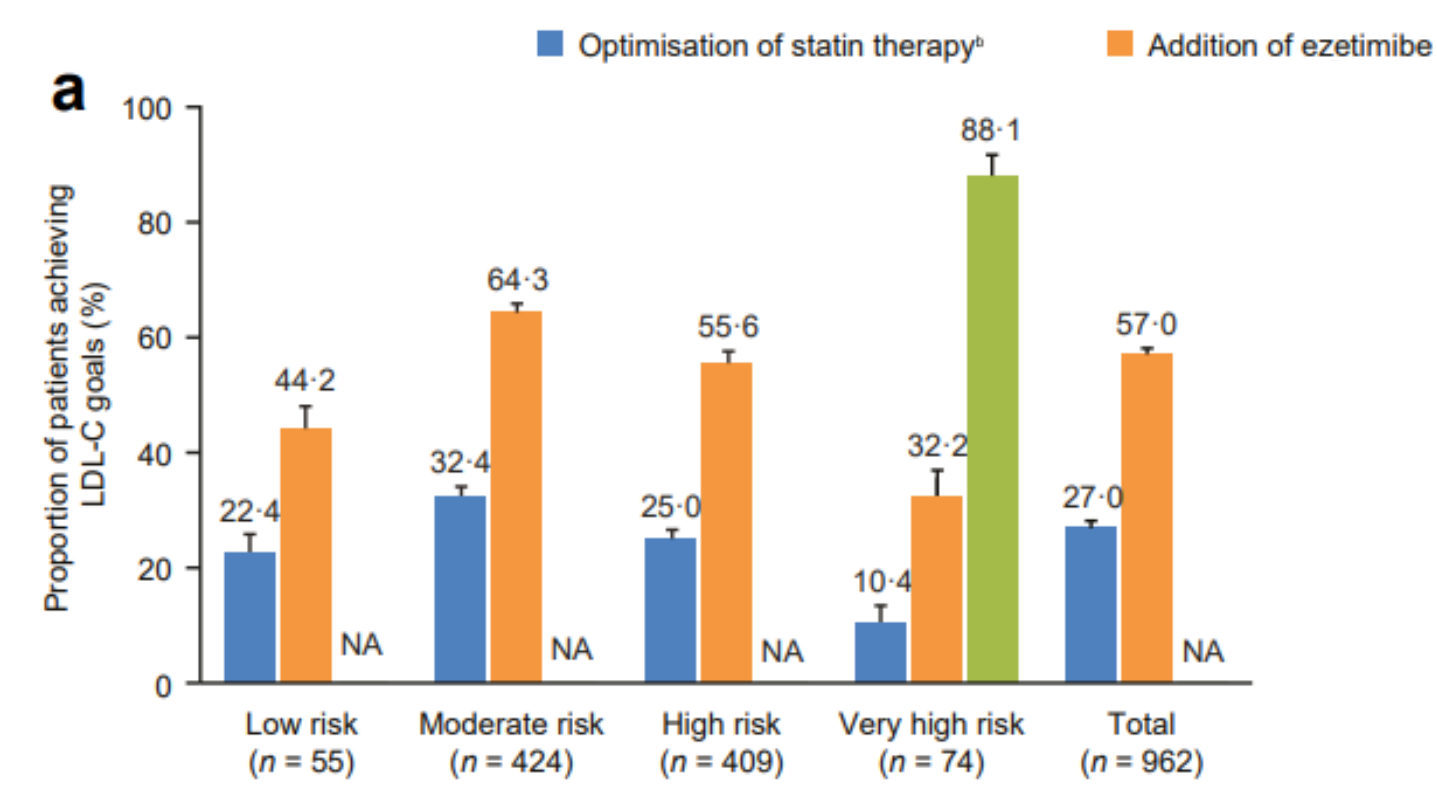
Simulering… hur många behöver PCSK9?



- 45% uppnår ej i high risk gruppen
- 68% uppnår ej i very high risk gruppen

- High n45.000
- Very High n30.000

- High 15.000 (överlapp)*0,45=6750
- Very high 30.000*0,68=20400

- Totalt 27.000 patienter på PCSK-9

  =1,35 miljarder

Guidelines förespråkade ej PCSK9 i high risk Gruppen här, därav ej utfört.

Optimal implementation of the 2019 ESC/EAS dyslipidaemia guidelines in patients with and without atherosclerotic cardiovascular disease across Europe: a simulation based on the DA VINCI study, Lancet 2023

Biverkningar & Compliance

Compliance till livslång statinbehandling hos diabetiker?

Mätt som uthämtade recept (västeuropeisk population, n6462):

- 60% efter 1 år
- Långvarig (13år) compliance < 50%

- **Negativa prediktorer:**
  - Yngre patienter
  - Högre HbA1c
  - Icke rökare
  - Ingen kardiovaskulär sjuklighet
  - Kardiovaskulär händelse efter start av statinbehandling

Long-term adherence to statin treatment in diabetes, *Diabet Med 2008*

PCSK-9-hämmare nästan biverkningsfria… eller?

- **Real-life data från 3 holländska register, bägge PCSK9:orna:**

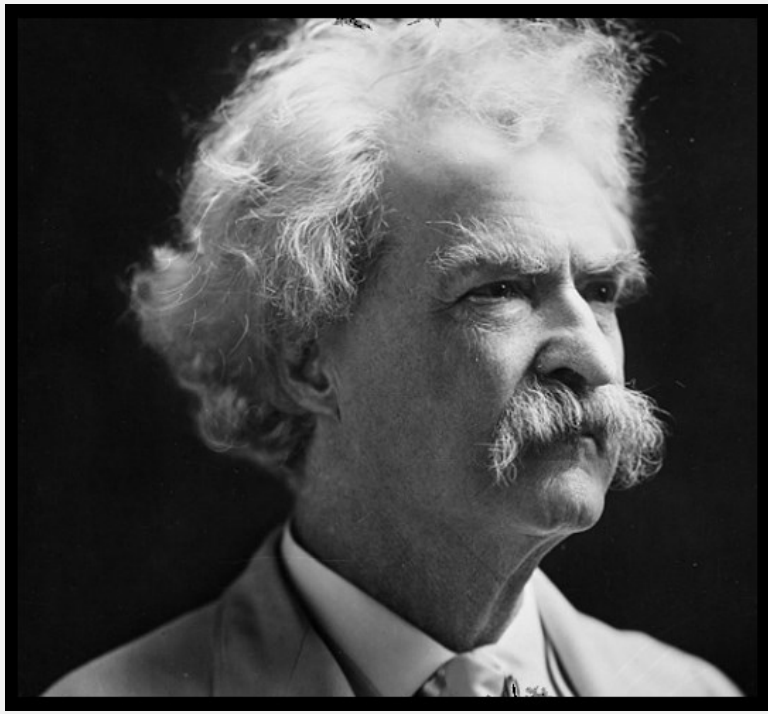
- 41,5% någon biverkan
- 33,8% injektionsplatsreaktion
- 27,9% Influensaliknande symtom
- 8,3-12,8% myalgi

- 7% avslutade medicineringen

- 71,1% av biverkningarna försvann när behandling sattes ut
- Ingen skillnad i kön, preparat, eller annan ”subgroup”

Adverse Events Associated With PCSK9 Inhibitors: A Real-World Experience. *Clinical Pharmacology & Therapeutics 2019*

- **Tveksamt tung evidens – Observationsdata & Extrapolering. Mer rimligt att diskutera tidig statinbehandling för hela befolkningen?**
- **Påtaglig kostnad då många kommer behöva PCSK-9**
- **Biverkningar & Compliance av ett halvt livs behandling?**
- **Extrapolering…**



"There are three kinds of lies: lies, damned lies and Extrapolering

[Mark Twain's]

There are three kinds of lies:
lies, damned lies, and Extrapolering

– Benjamin Disraeli

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