Farmacologische aanpak van cardiovasculaire risicofactoren bij 80-plussers: start en stop

Hyperlipidemie

Tine De Backer

Symposium Geriatrie, Alumni Geneeskunde UGent

28 april 2021

UZ GENT

New recommendations (2)

EAS ESC
European Society of Cardiology

Drug treatments of patients with hypertriglyceridaemia
In high-risk (or above) patients with TG between 1.5 and 5.6 mmol/L (135 - 499 mg/dL) despite statin treatment, n-3 PUFAs (icosapent ethyl 2 x 2g/day) should be considered in combination with statins.

Treatment of patients with heterozygous FH
In primary prevention, for individuals with FH at very-high risk, an LDL-C reduction of ≥50% from baseline and an LDL-C goal of <1.4 mmol/L (<55 mg/dL) should be considered.

Treatment of dyslipidaemias in older people
Treatment with statins is recommended for primary prevention, according to the level of risk, in older people aged ≤75.

Treatment of dyslipidaemias in older people
Initiation of statin treatment for primary prevention in older people aged >75 may be considered, if at high risk or above.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Changes in recommendations (7)

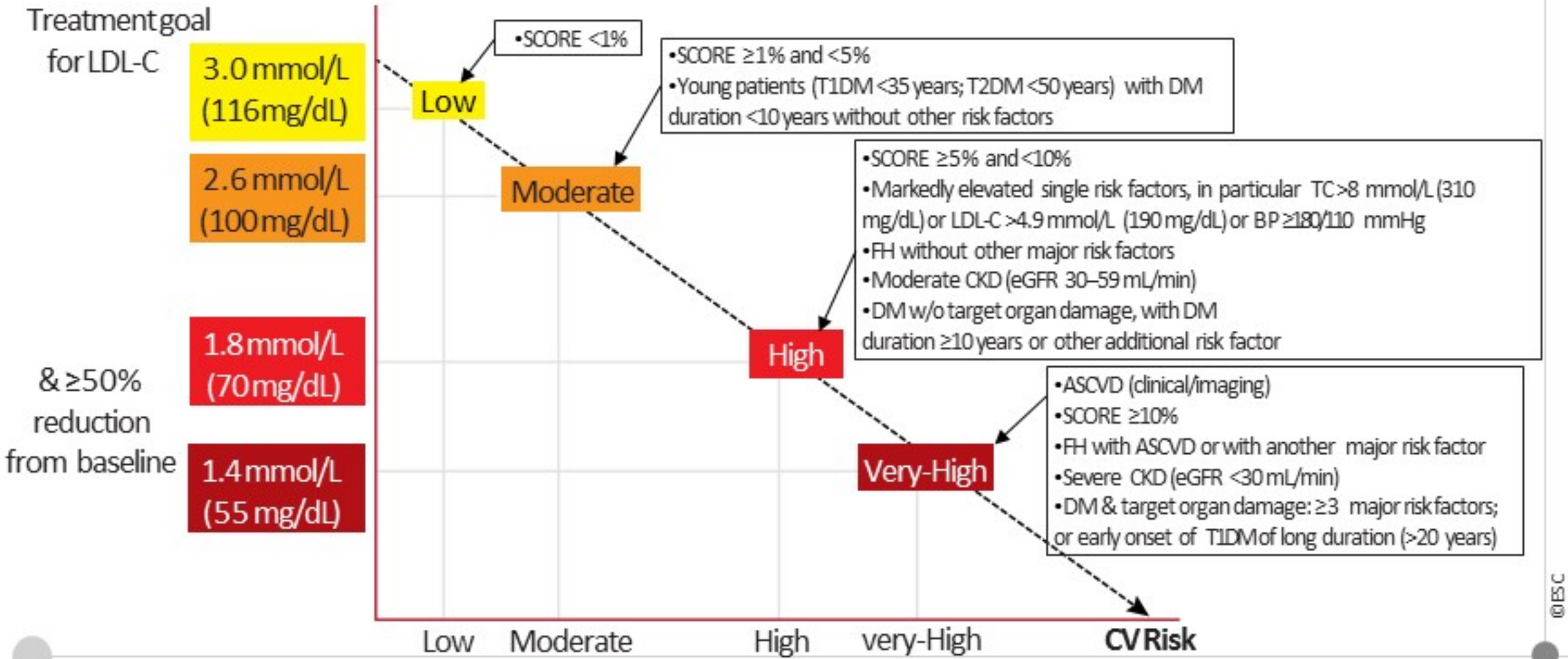
EAS ESC European Society of Cardiology

2016	2019
Treatment of dyslipidaemias in older adults	**Treatment of dyslipidaemias in older adults**
Since older people often have comorbidities and have altered pharmacokinetics, lipid-lowering medication should be started at a lower dose and then titrated with caution to achieve target lipid levels that are the same as in younger people.	It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Central Illustration Upper panel Treatment goals for low-density lipoprotein cholesterol (LDL-C) across categories of total cardiovascular disease risk

EAS ESC European Society of Cardiology



www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
NEW Treatment with statins is recommended for primary prevention, according to level of risk, in older people aged ≤ 75.	I	A
Initiation of statin treatment for primary prevention in older people aged > 75 may be considered, if at high risk or above.	IIb	B
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Summary of recommendations for monitoring lipids and enzymes in patients before and on lipid-lowering therapy (5)

EAS ESC European Society of Cardiology

Monitoring liver and muscle enzymes

How often should creatine kinase (CK) be measured in patients taking lipid- lowering drugs?

Pre-treatment:

- Before starting therapy.
- If baseline CK is >4x ULN, do not start drug therapy; recheck.

Monitoring:

- Routine monitoring of CK is not necessary.
- Check CK if patient develops myalgia.

Be alert regarding myopathy and CK elevation in patients at risk such as: elderly patients, concomitant interfering therapy, multiple medications, liver or renal disease, or athletes.

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

The Evidence (based medicine)

RCTS

- In primary prevention **RCTs** few elderly are included

- Post-hoc analyses show heterogeneous results due to different inclusion criteria, study designs, outcome parameters, small numbers, ..

- **MA** (Ridker, Circulation 2017) of the primary prevention **trials**

JUPITER and **HOPE-3**:

→in the subgroup of ≥70y

(32% and 24%)

incidence of non-fatal MI, non-fatal stroke, and CV death:

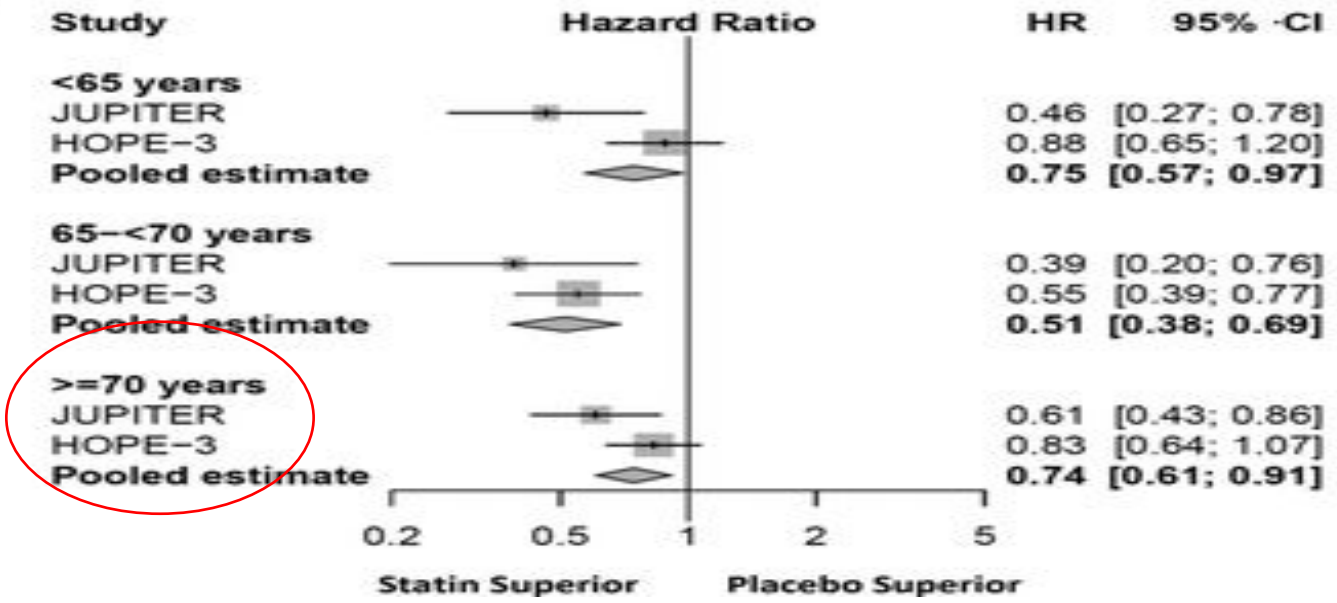
26% lower for rosuvastatin vs placebo

A **Effects of rosuvastatin on the composite endpoint of nonfatal myocardial infarction, nonfatal stroke, or cardiovascular death in the JUPITER and HOPE-3 primary prevention trials, stratified by age.**

Age Group	Trial	N	Rosuvastatin N (IR*)	Placebo N (IR*)
< 65 years	JUPITER	7,458	20 (0.27)	45 (0.59)
	HOPE-3	6,059	78 (0.46)	88 (0.53)
65-< 70 years	JUPITER	4,649	12 (0.24)	30 (0.61)
	HOPE-3	3,559	50 (0.50)	91 (0.91)
≥ 70 years	JUPITER	5,695	51 (0.82)	82 (1.36)
	HOPE-3	3,086	107 (1.25)	125 (1.50)

*rates are per 100 person-years. The test for heterogeneity by age for the effects of statin therapy on clinical outcomes was non-significant (P=0.10).

B



Paul M Ridker. Circulation. Primary Prevention With Statin Therapy in the Elderly, Volume: 135, Issue: 20, Pages: 1979-1981, DOI: (10.1161/CIRCULATIONAHA.117.028271)

The Evidence (based medicine)

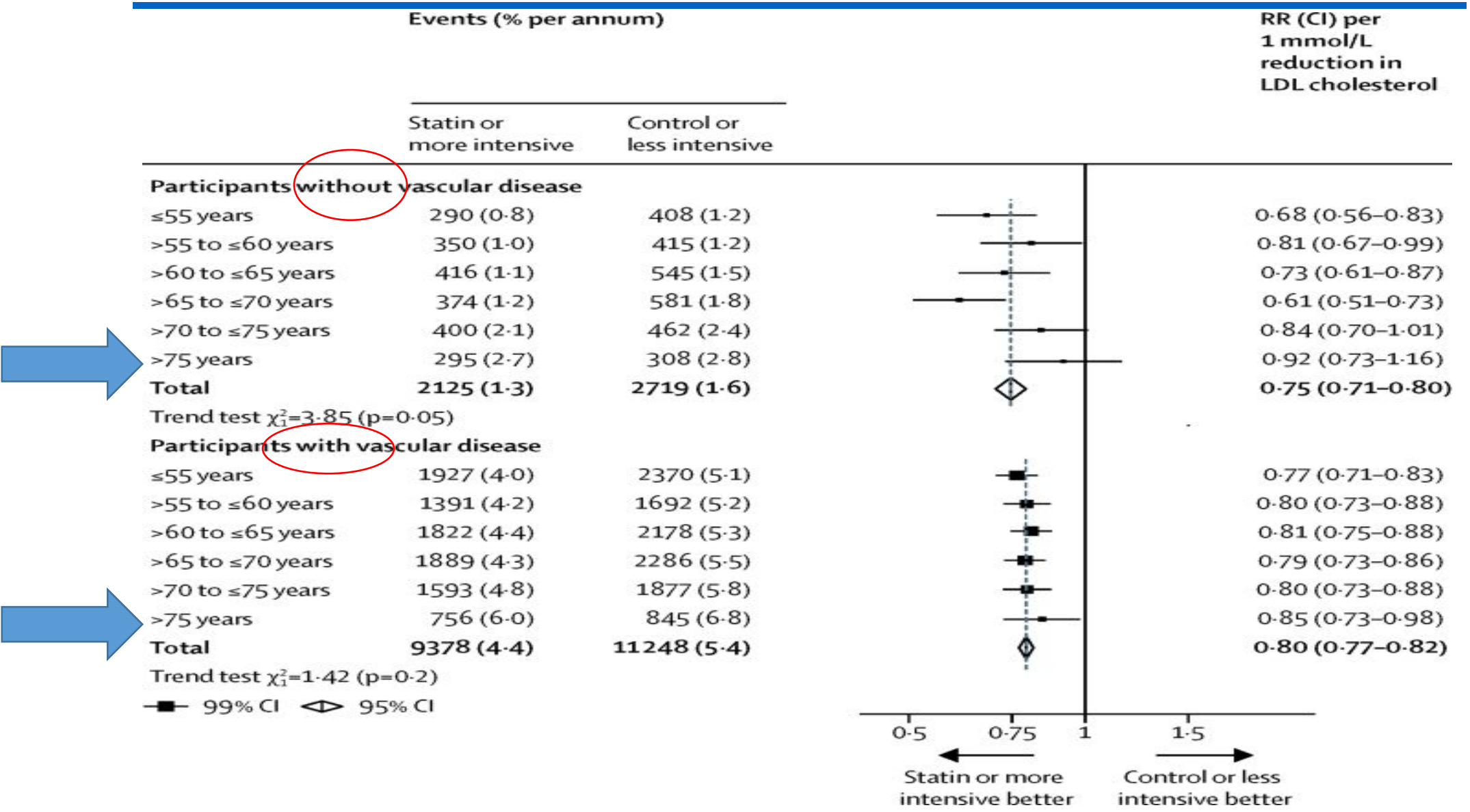
- **CTTC analysis** (Lancet 2019) Efficacy and safety of statin therapy in older people (28 RCT's with statins(IPD), 186 854 participants): *only 8 % was > 75y.*

→Statins prevent CVD in the elderly as well as in the young, mainly in patients with known CVD.

→In patients without CVD risk reduction in the statin group ↓ with age,

efficacy of primary prevention of CVD in pts >75 y less clear (only 6449 persons >75y…)

Cholesterol Treatment Trialists' Collaboration



Lancet 2019 Feb 2;393(10170):407-415. doi: 10.1016/S0140-6736(18)31942-

→ Heterogeneous results of RCT's with statins in the primary prevention of CVD in the elderly

→→ **???**

-►Do not give or stop statins in elderly

-►2019 Lipid Guidelines: less firm

Recommendations for the treatment of dyslipidaemias in older people (aged >65 years)

EAS ESC European Society of Cardiology

Recommendations	Class	Level
Treatment with statins is recommended for older people with ASCVD in the same way as for younger patients.	I	A
Treatment with statins is recommended for primary prevention, according to level of risk, in older people aged ≤ 75.	I	A
Initiation of statin treatment for primary prevention in older people aged > 75 may be considered, if at high risk or above.	IIb	B
It is recommended that the statin is started at a low dose if there is significant renal impairment and/or the potential for drug interactions, and then titrated upwards to achieve LDL-C treatment goals.	I	C

www.escardio.org/guidelines

2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk (European Heart Journal 2019 -doi: 10.1093/eurheartj/ehz455)

Primary Prevention in Other Age Groups (Older Adults)

Recommendations for Older Adults		
COR	LOE	Recommendations
IIb	B-R	In adults 75 years of age or older with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), initiating a moderate-intensity statin may be reasonable.
IIb	B-R	In adults 75 years of age or older, it may be reasonable to stop statin therapy when functional decline (physical or cognitive), multimorbidity, frailty, or reduced life-expectancy limits the potential benefits of statin therapy.
IIb	B-R	In adults 76 to 80 years of age with an LDL-C level of 70 to 189 mg/dL (1.7 to 4.8 mmol/L), it may be reasonable to measure CAC to reclassify those with a CAC score of zero to avoid statin therapy.

AMERICAN COLLEGE of CARDIOLOGY

American Heart Association.

Total CV Risk, co-morbidities, polypharmacy, life expectancy, shared decision patient-doctor

RCT patients ≠ daily life patients ..Added value of

Observational studies

-**Retrospective study Spain** in 46 864 persons ≥75 y:

-Subgroup of DM **75-84 y** without CVD:

incidence of CVD – 24%

total mortality - 16% in statin treated compared to non-statin group

-In the **> 85y** with or without DM: no ≠

-**Population based cohort study France**: in subgroup of 752 people **>75y** without CVD and without risk factors:

no ≠ in incidence of ACS &total mortality in statin treated vs non-statin group

Ramos et al., BMJ 2018; 362; Bezin et al. Am J Med 2019; 132(6)

Observational studies

-

Longitudinal follow up study in 326 981 **US veterans ≥75 y** without CVD → total (–19.5%) & CV mortality (-3,1%) at 6.8 y follow-up significantly lower in statin treated veterans in all age groups **up to > 90 y**

-**SCOPE-75 study Korea**: 1278 persons **≥ 75y** without CVD but ≥ 1 CV risk factor: -41% CV events & - 44% total mortality in statin treated group

Orkaby et al, JAMA 2020; 324(1); Kyu et al, Atherosclerosis 2019 May;284:31-36. doi: 10.1016/j.atherosclerosis.2019.02.026

The Evidence (based medicine)

- There remains clinical uncertainty regarding the benefits and harms of prescribing statins in healthy subjects ≥70 years of age.

- In an older population the patient's overall life expectancy and priorities has to be taken into account

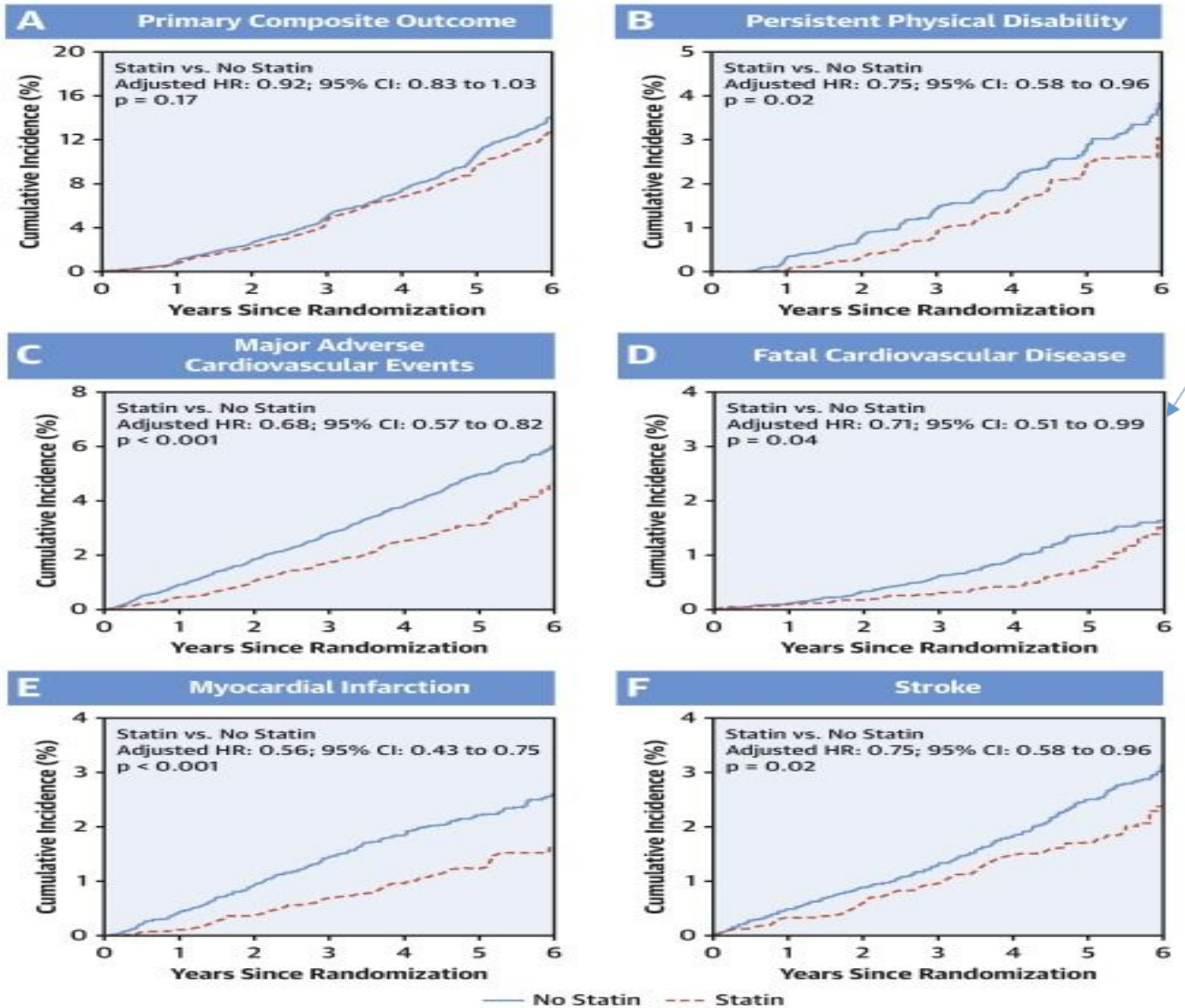
Association of Statin Use With Disability–Free Survival and Cardiovascular Disease Among Healthy Older Adults

Objectives: Association among statins, dementia-free and disability-free survival, and cardiovascular disease (CVD) in healthy older adults using data from the **ASPREE** (Aspirin in Reducing Events in the Elderly) trial.
Methods: RT of 19,114 community-dwelling persons in Australia and the United States
≥65 years and free of documented CVD, dementia, and disability.
Data were collected for those **≥70 years** of age. Participants on statins at baseline compared with those not.
***Primary* outcome"disability-free survival“:** composite of all-cause mortality, dementia, persistent physical disability.
Secondary outcomes: the individual components of the composite outcome, major adverse CV events, fatal CVD, myocardial infarction, and stroke.
Results: 18,096 participants (median age 74.2 years, 56.0% women)
5,629 took statins at baseline.
Median follow-up period of 4.7 years
Baseline **statin**: **Not associated with disability-free survival or with the risk for all-cause mortality or dementia**.
However, associated with **lower risks for physical disability and all cardiovascular outcomes**.

Conclusions: Among healthy community-dwelling adults ≥70 years of age, **statin use may be beneficial for preventing physical disability and CVD but not beneficial for prolonging disability-free survival or avoiding death or dementia**. Future clinical trials are needed to confirm these findings.

Zhou et al. JACC 2020

CENTRAL ILLUSTRATION: Cumulative Incidence of Primary and Selected Secondary Outcomes Stratified by Baseline Statin Use



Zhou, Z. et al. J Am Coll Cardiol. 2020;76(1):17–27.

Despite the reduction in major adverse cardiovascular events observed in ASPREE,
it is not a randomized controlled trial.
While the researchers adjusted for confounding variables, it is nearly impossible to account for the myriad of reasons why some patients are started on statin therapy and others are not.

Future trials will take the selection bias out of the equation.

STAREE and **PREVENTABLE** will look not just at cardiovascular outcomes with statin therapy, but also at important endpoints such as cognitive decline, disability, and quality of life.

J Am Coll Cardiol. 2020 Jul 7; 76(1): 28–30.
Published online 2020 Jun 29. doi: 10.1016/j.jacc.2020.05.024

Elevated LDL cholesterol and increased risk of myocardial infarction and atherosclerotic cardiovascular disease in individuals aged 70–100 years: a contemporary primary prevention cohort

- Data on 91,131 people living in Copenhagen, Denmark, who did not have atherosclerotic CVD or diabetes at baseline and were not taking statins.
  -10,592 were aged 70 to 79 years
  -3188 participants were aged 80 to 100 years.

- Average follow-up period of 7.7 years
  1515 participants had a first myocardial infarction
  3389 developed atherosclerotic cardiovascular disease.

- **Higher levels of LDL** cholesterol even in the elderly were associated with a **higher risk** of MI and ASCVD.

- In the entire cohort 20 to 100 years old, **each 1-mmol/L increase in LDL** cholesterol was associated with a **34% increased risk of MI** and a **16% increased risk of ASCVD.** These risks were observed across all age groups.

- For the **older patients**, specifically those aged **70-79 and 80-100** years, each 1-mmol/L increase in LDL cholesterol was associated with a significant **25% and 28% increased risk of MI**, respectively, **12% and 16%** increased risk of **ASCVD**

Martin Bødtker Mortensen, PhD, Prof Børge Grønne Nordestgaard, MD; The Lancet; Volume 396 Issue 10263 Pages 1644-1652 (November 2020) DOI: 10.1016/S0140-6736(20)32233-9

The risk of having a **heart attack** per 1.0 mmol/L increase in LDL cholesterol was increased **overall hazard ratio [HR] 1.34**

The increased risk was observed for all age groups,

80 to 100 (HR, 1.28)

70 to 79 (HR, 1.25)

60 to 69 (HR, 1.29)

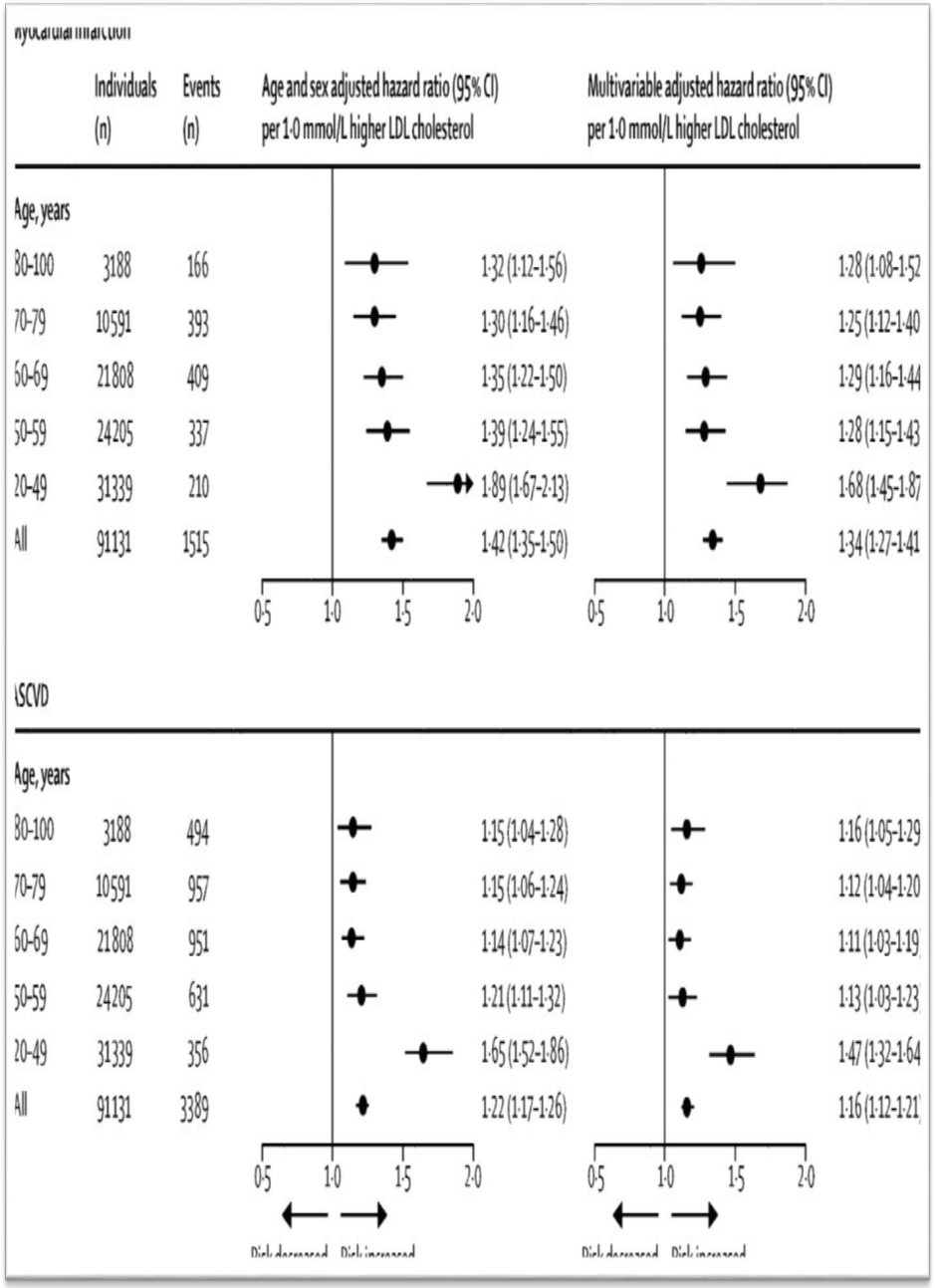
50 to 59 (HR, 1.28)

20 to 49 (HR, 1.68)

Risk for **atherosclerotic cardiovascular disease** was also raised **per 1.0 mmol/L** increase in LDL chol.

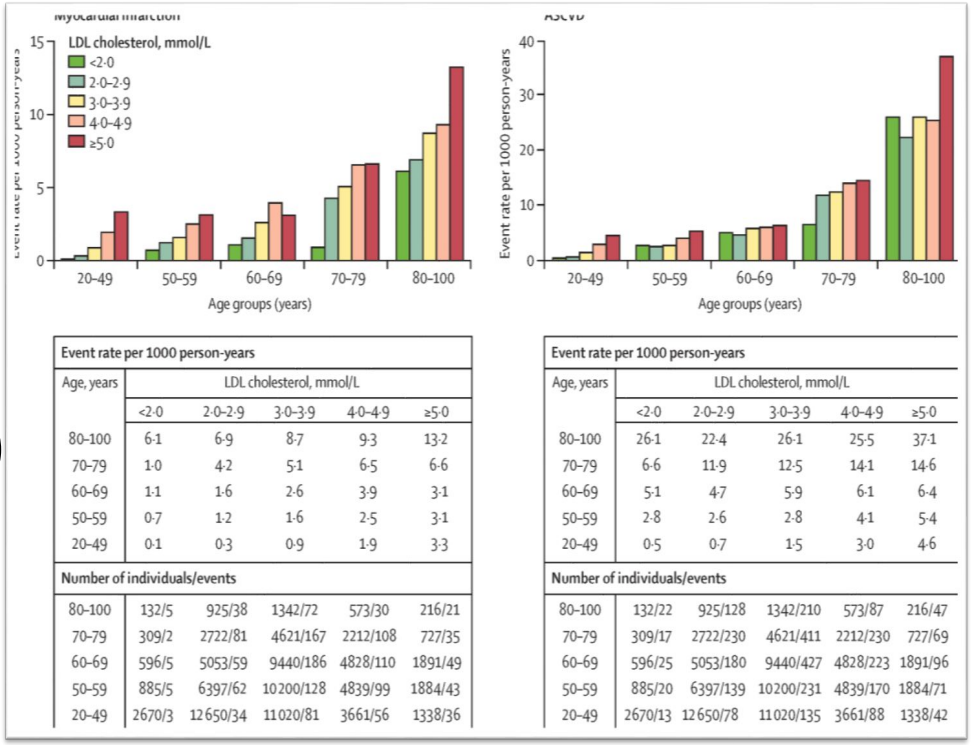
overall HR, 1.16 and in **all** age groups

1mmol= 38,67 mg/dl



The Lancet 2020; 396; 1644-1652DOI: (10.1016/S0140-6736(20)32233-9

Greater elevations in **LDL cholesterol (≥5.0 mmol/L)** (>190mg/dl)
associated with a notably higher risk for heart attack after multivariate adjustment
in people aged **80 to 100 (HR, 2.99).**
Risk was also higher among those aged **70 to 79 (HR, 1.82)**



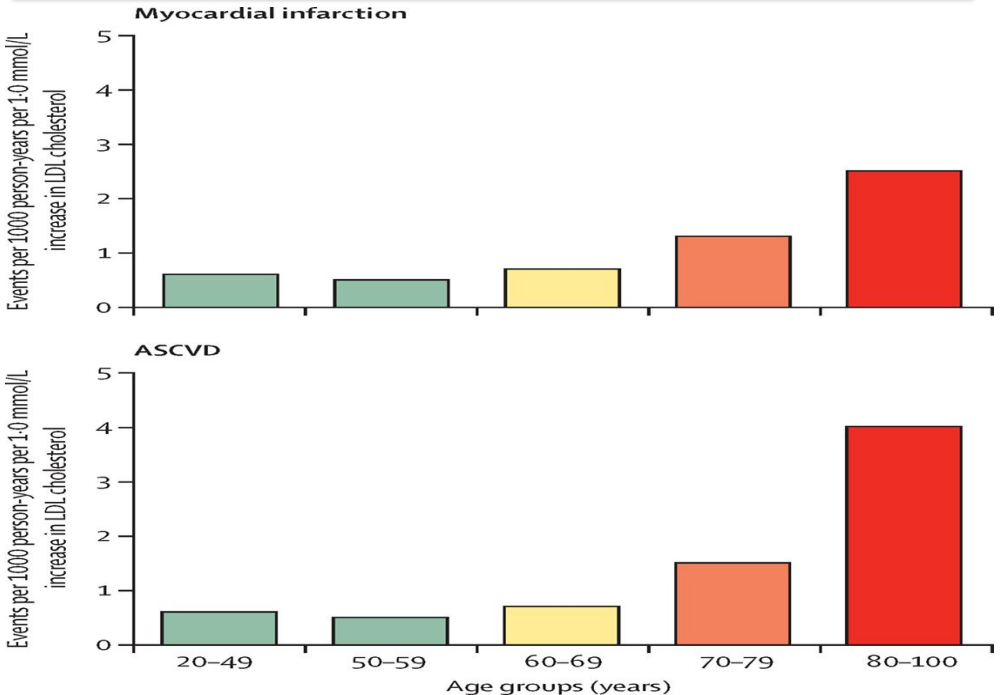
Event rate per 1000 person-years

Age, years	LDL cholesterol, mmol/L				
	<2·0	2·0–2·9	3·0–3·9	4·0–4·9	≥5·0
80–100	6·1	6·9	8·7	9·3	13·2
70–79	1·0	4·2	5·1	6·5	6·6
60–69	1·1	1·6	2·6	3·9	3·1
50–59	0·7	1·2	1·6	2·5	3·1
20–49	0·1	0·3	0·9	1·9	3·3
Number of individuals/events					
80–100	132/5	925/38	1342/72	573/30	216/21
70–79	309/2	2722/81	4621/167	2212/108	727/35
60–69	596/5	5053/59	9440/186	4828/110	1891/49
50–59	885/5	6397/62	10200/128	4839/99	1884/43
20–49	2670/3	12650/34	11020/81	3661/56	1338/36

Event rate per 1000 person-years

Age, years	LDL cholesterol, mmol/L				
	<2·0	2·0–2·9	3·0–3·9	4·0–4·9	≥5·0
80–100	26·1	22·4	26·1	25·5	37·1
70–79	6·6	11·9	12·5	14·1	14·6
60–69	5·1	4·7	5·9	6·1	6·4
50–59	2·8	2·6	2·8	4·1	5·4
20–49	0·5	0·7	1·5	3·0	4·6
Number of individuals/events					
80–100	132/22	925/128	1342/210	573/87	216/47
70–79	309/17	2722/230	4621/411	2212/230	727/69
60–69	596/25	5053/180	9440/427	4828/223	1891/96
50–59	885/20	6397/139	10200/231	4839/170	1884/71
20–49	2670/13	12650/78	11020/135	3661/88	1338/42

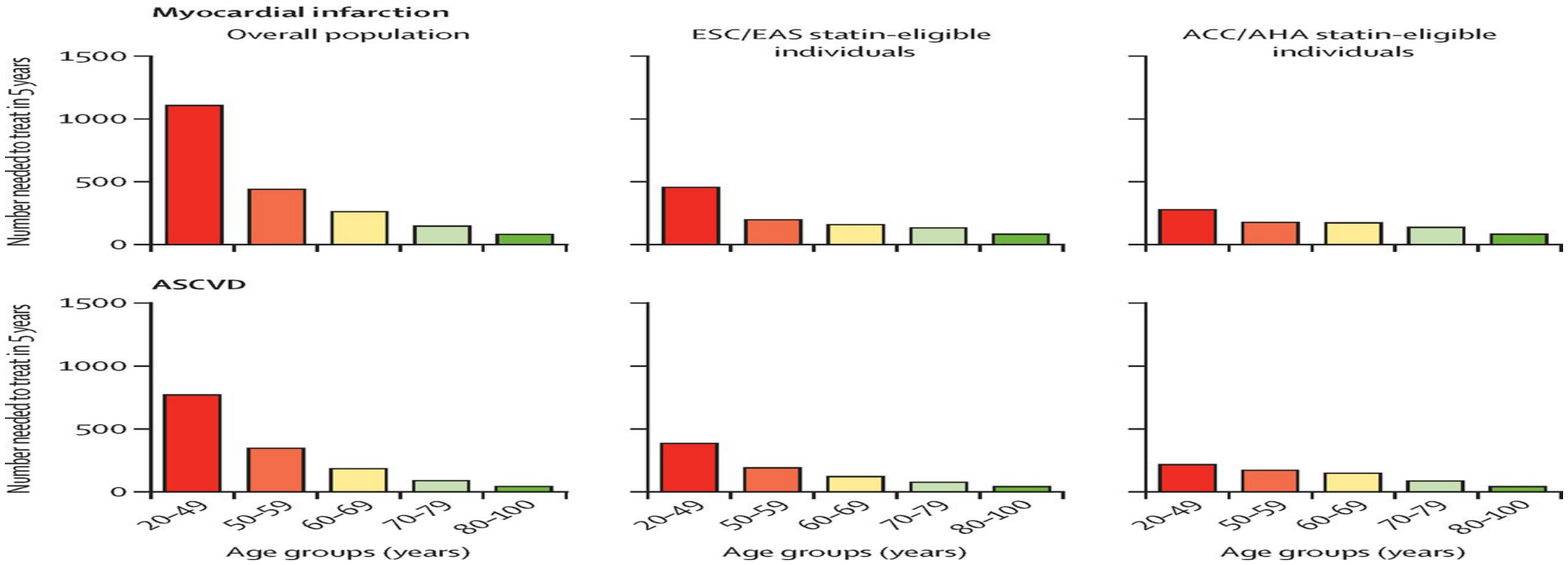
8.5 heart attacks per 1000 people/y aged 80 to 100
5.2 heart attacks per 1000/y aged 70 to 79
2.5 per 1000/y aged 60 to 69
1.8 per 1000/y aged 50 to 59
0.8 per 1000/y aged 20 to 49.



The Lancet 2020 3961644-1652DOI: (10.1016/S0140-6736(20)32233-9)

"The absolute risk [of cardiovascular events] is of course much higher in the elderly than those under the age of 75, but what was a surprise was **how clear our results were on a relative risk scale, that the risk associated with elevated LDL was as high in people aged 80 to 100 as the younger patients**"

With regard to the benefits of cholesterol-lowering drugs, the study showed that the **number needed to prevent one heart attack over 5 years** was **80 among those aged 80 to 100**; the number was **439 for people aged 50 to 59**. With regard to stronger statins, when moderate-intensity statins were used, the number needed to treat to prevent one cardiovascular disease event of any type dropped to 42 for patients aged 80 to 100. It was 88 for those aged 70 to 79, 164 for those aged 60 to 69, 345 for those aged 50 to 59, and 769 for those aged 20 to 49.



Martin Bødtker Mortensen, PhD, Prof Børge Grønne Nordestgaard, MD; The Lancet; Volume 396 Issue 10263 Pages 1644-1652 (November 2020)
DOI: 10.1016/S0140-6736(20)32233-9

-**LDL cholesterol is an important risk factor** for myocardial infarction and atherosclerotic cardiovascular disease in a contemporary primary prevention cohort of individuals aged **70 to 100 years**

-By lowering LDL cholesterol in healthy individuals aged 70 to 100 years, **the potential for preventing myocardial infarctions and atherosclerotic cardiovascular disease is huge,** and at a substantially lower number needed to treat when compared with those aged 20 to 69 years

Martin Bødtker Mortensen, PhD, Prof Børge Grønne Nordestgaard, MD; The Lancet; Volume 396 Issue 10263 Pages 1644-1652 (November 2020)
DOI: 10.1016/S0140-6736(20)32233-9

“The clinical significance of this is that it appears those in older age groups indeed benefit from cholesterol-lowering therapy“
"I think many people have this idea that LDL is not important over the age of about 70 to 75, but that's not the case."
"These robust findings are novel"

“Despite these observational findings, **whether lipid-lowering therapy should be initiated for primary prevention in people aged 75 years or older is unclear, owing to the host of risks and benefits that need to be balanced.**
The findings of an ongoing randomized, placebo-controlled trial (STAREE) may answer this question”

F. Raal , F. Mohamed; Lancet 2020; https://doi.org/10.1016/ S0140-6736(20)32333-3

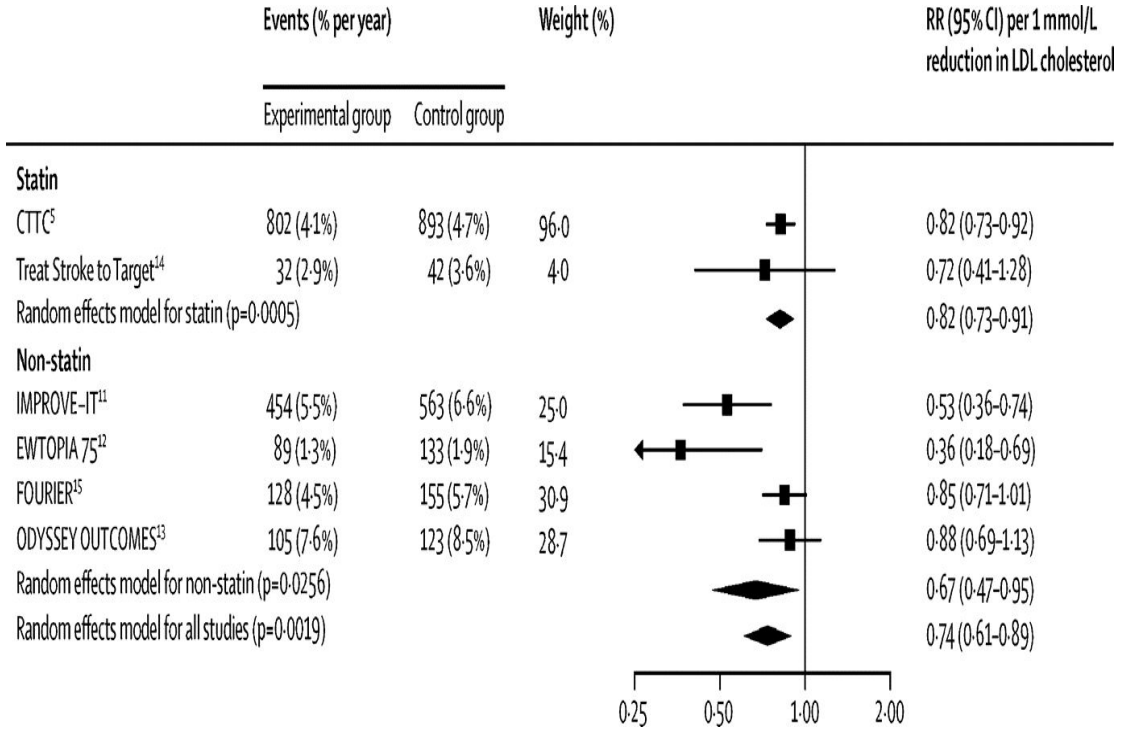
Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials

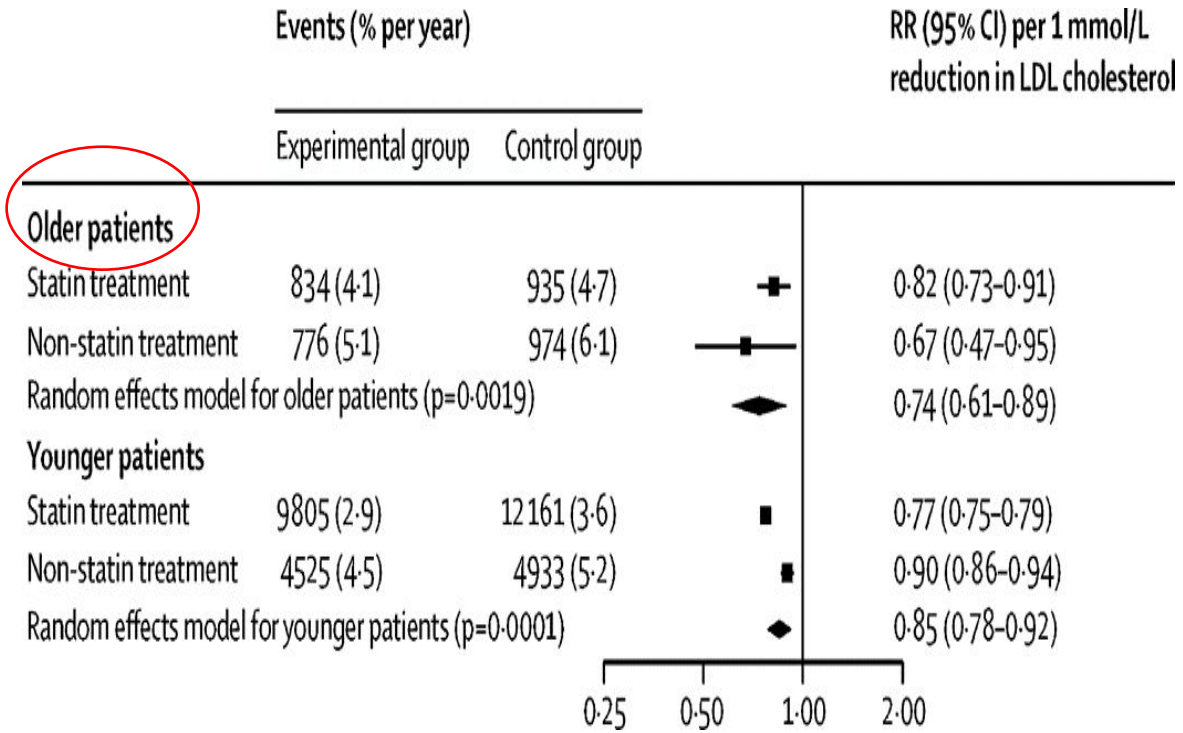
- Data from 29 primary and secondary prevention trials
  - 24 of those studies included as part of the Cholesterol Treatment Trialists' Collaboration (CTTC) meta-analysis published in 2019.
  - The 5 additional trials included the large cardiovascular outcomes studies testing the PCSK9 inhibitors in FOURIER and ODYSSEY OUTCOMES,
  - Ezetimibe IMPROVE-IT, EWTOPIA
  - Treat Stroke to Target study.
- Of the 244,090 patients, 21,492 were at least 75 years old.

Baris Gencer et al. The Lancet 2020Volume 396 Issue 10263 Pages 1637-1643 (November 2020)
DOI: 10.1016/S0140-6736(20)32332-1

Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials

- The use of lipid-lowering therapy cut the risk of major vascular events by 26% for each 1-mmol/L (roughly 39 mg/dL) reduction in LDL cholesterol, not statistically different in the older versus younger.

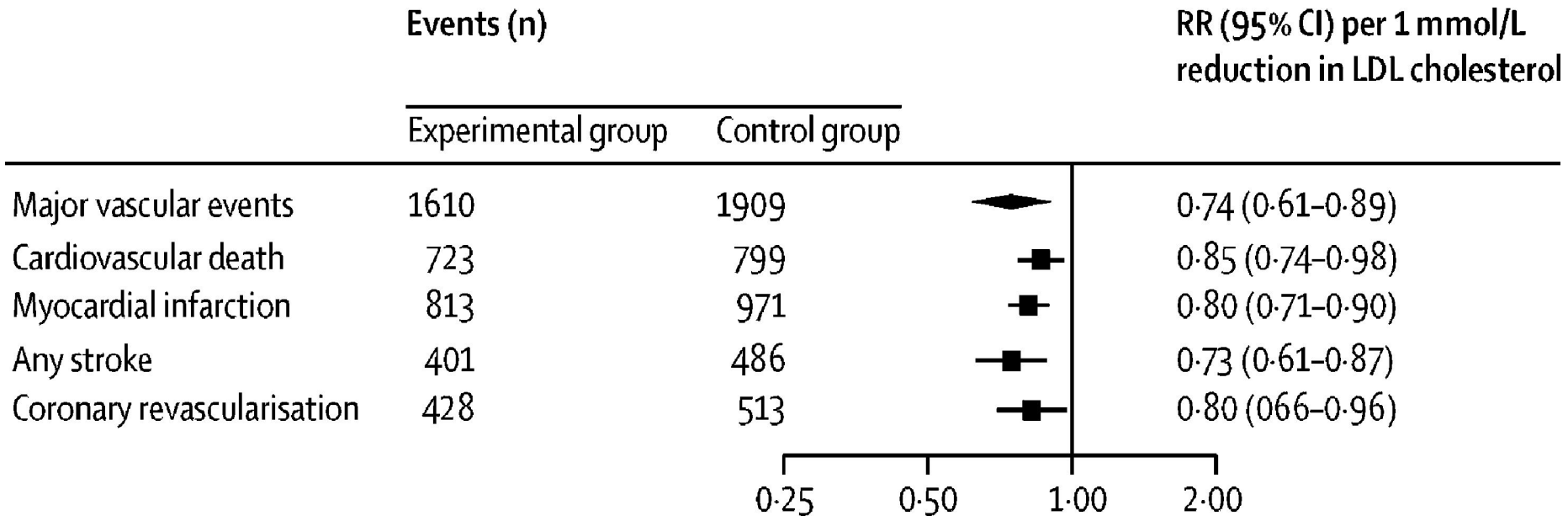




Baris Gencer et al. The Lancet 2020Volume 396 Issue 10263 Pages 1637-1643 (November 2020)
DOI: 10.1016/S0140-6736(20)32332-1

Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials

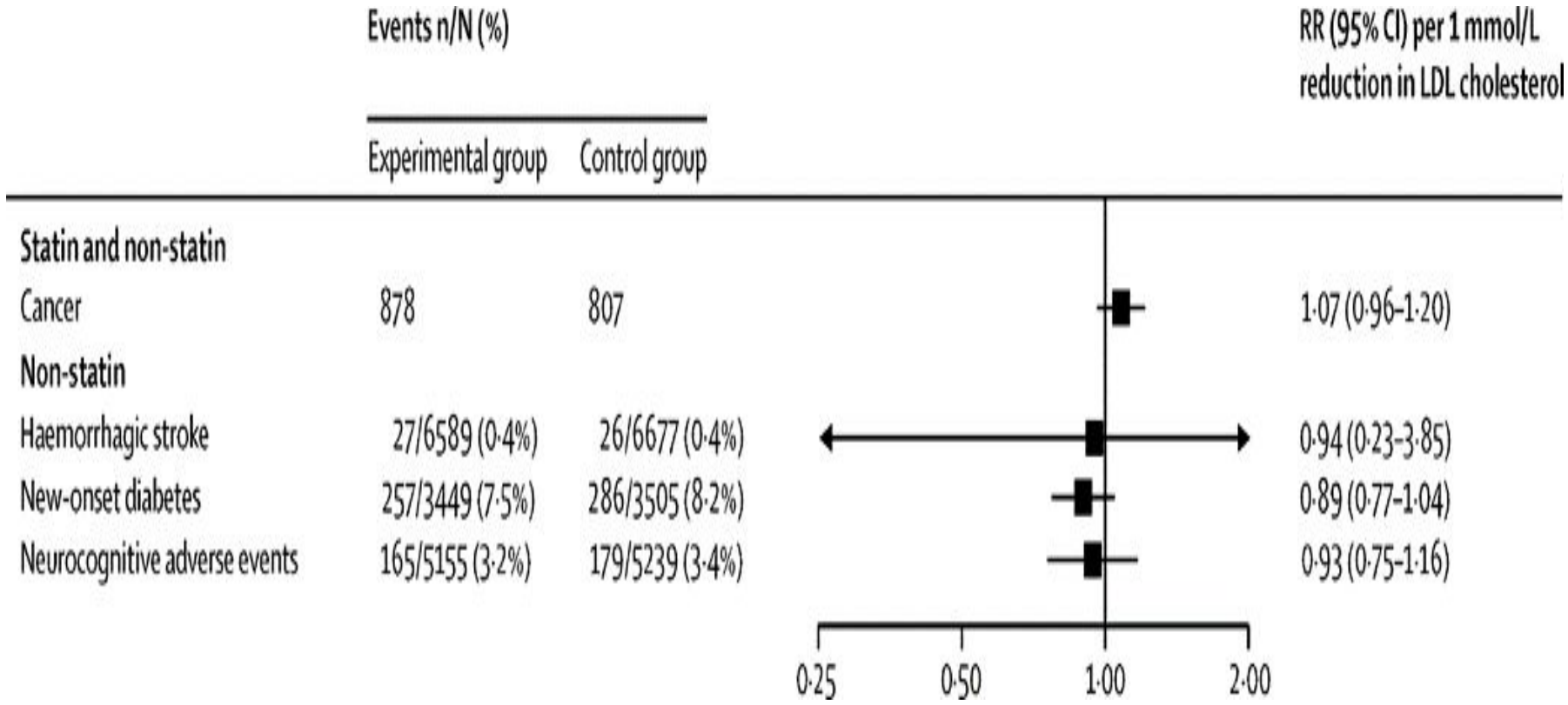
- The risk of cardiovascular death was reduced 15%, myocardial infarction by 20%, stroke by 27%, coronary revascularization by 20% for each 1-mmol/L reduction in LDL cholesterol among patients **75 y or older**.



Baris Gencer et al. The Lancet 2020Volume 396 Issue 10263 Pages 1637-1643 (November 2020)
DOI: 10.1016/S0140-6736(20)32332-1

Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials

No offsetting safety concerns



Baris Gencer et al. The Lancet 2020Volume 396 Issue 10263 Pages 1637-1643 (November 2020)
DOI: 10.1016/S0140-6736(20)32332-1

Efficacy and safety of lowering LDL cholesterol in older patients: a systematic review and meta-analysis of randomised controlled trials

"More than 80% of fatal cardiovascular events occur in individuals older than 65 years, and the incidence of cardiovascular events is increasing in those older than 80 years; therefore, the findings of Gencer and colleagues' study should encourage the use of lipid-lowering therapy in older patients."

F. Raal , F. Mohamed; Lancet 2020; https://doi.org/10.1016/ S0140-6736(20)32333-3

Aim of statins in the Elderly?

Frailty

A physiological syndrome characterized by diminished reserves and reduced resistance to stressors as a result of
the cumulative decline of multiple physiological systems that increase vulnerability to adverse health outcomes, among which are:
risk of acute diseases, falls and their consequences (injuries, fractures), hospitalization, institutionalization (nursing home), disability, dependency and death.

The prevalence of frailty in patients with CVD varies from 10 to 60% depending upon the definition and measurement methods. (Afilalo et al. JACC 2014; 63).

Are statins efficacious and safe in frail elderly?

-RCT's: ?? No answer: Frail patients = exclusion criterion
-**Observational data:..**

Statin treatment reduces the risk of death among elderly frail patients: evidence from a large population-based cohort

Aim: To assess the protective effect of statins in a large and unselected cohort of **frail elderly subjects**.

Methods:

460 460 Lombardy residents, ≥65 years, ≥3 consecutive prescriptions of a statin during 2011–2012.

Case–control study, the cases being the cohort members who died during 2011–2018.

Adherence to drug therapy measured by the proportion of the follow-up covered by prescriptions.

Analysis stratified according to 4 clinical categories:
good, medium, poor, and very poor clinical status
based on different life expectancies conditions.

Federico Rea, Giuseppe Mancia, Giovanni Corrao; *European Journal of Preventive Cardiology*, zwaa126, https://doi.org/10.1093/eurjpc/zwaa126

Statin treatment reduces the risk of death among elderly frail patients: evidence from a large population-based cohort

Results

The 7-year death probability increased from 11% (good) to 52% (very poor clinical status).

In each clinical status, there was a **significant reduction** of **all-cause mortality** as adherence to statin treatment increased.

The reduction in the adjusted risk of mortality from the lowest to the highest adherence level was greatest among patients with a good clinical status (−56%) and progressively less among other cohort members, i.e. −48%, −44% and −47% in medium, poor, and very poor groups, respectively.

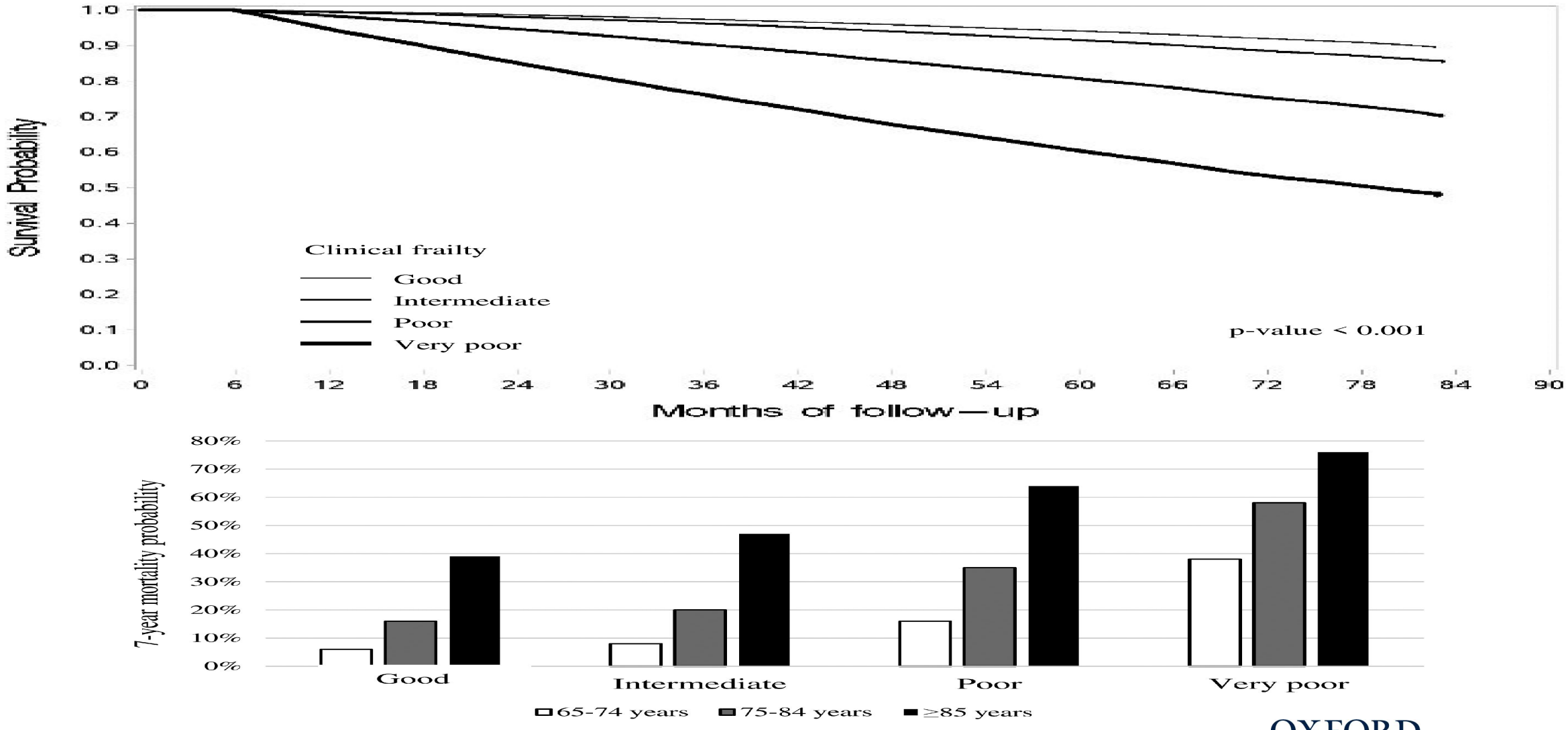
Similar findings were obtained for the risk of **cardiovascular mortality.**

Conclusion

In a real-life setting, **adherence to statin treatment reduced the death risk also in frail elderly**. However, in these patients, **the benefit of statin treatment may be lower** than in those in good clinical conditions.

Federico Rea, Giuseppe Mancia, Giovanni Corrao; *European Journal of Preventive Cardiology*, zwaa126, https://doi.org/10.1093/eurjpc/zwaa126

Kaplan–Meier survival curves for all-cause death according to the clinical frailty as determined by Multisource Comorbidity Score (MCS) and
7-year mortality probabilities according to the clinical frailty and age strata.

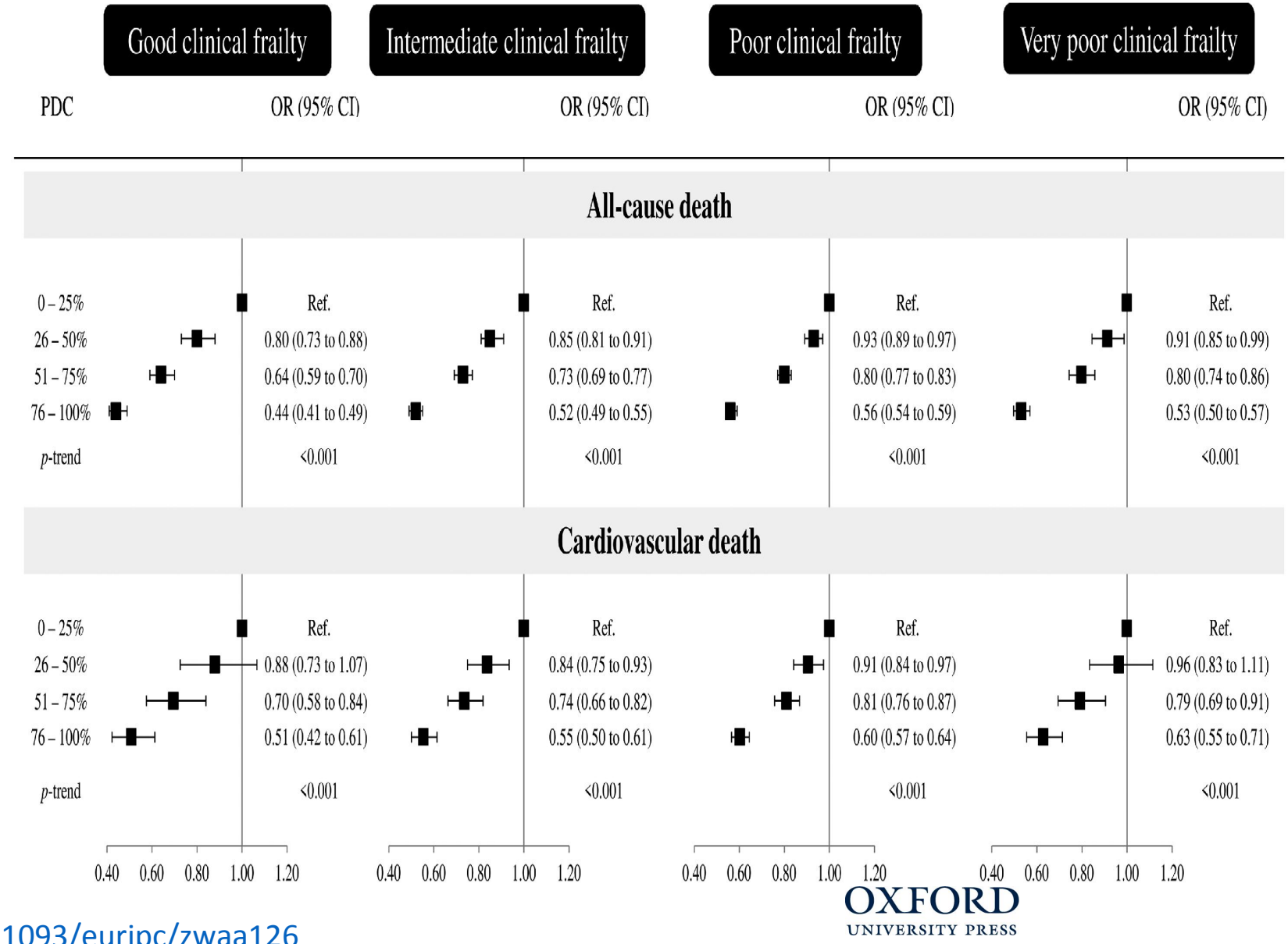


Eur. J. Prev. Cardiol., zwaa126, https://doi.org/10.1093/eurjpc/zwaa126

Effect of adherence with statins on the odds ratio (OR) of all-cause and cardiovascular death according to the clinical frailty as measured by Multisource Comorbidity Score (MCS) OR

Total as well as CV death in the elderly was lower if adherence to statins was better in all age groups and independently from frailty status. Also in people >85y.
Elderly in poor health did less well than elderly at the same age in good health,
still the outcome was better when statin adherence was better.

Given the potential for bias, and the conflicting results from the existing literature on this issue,
additional high-quality studies are needed.



Eur. J. Prev. Cardiol., zwaa126, https://doi.org/10.1093/eurjpc/zwaa126

Statin therapy in the elderly: less or more?

Guy G De Backer

European Journal of Preventive Cardiology 2021, zwaa164, https://doi.org/10.1093/eurjpc/zwaa164

Aim of statins in the Elderly?

Immortality? ∞ Not really…

Life in good health

→ prevention of diseases causing disability, dependence, decreased quality of life (e.g. after ACS, Stroke)

→Good health is more than absence of cardiovascular disease

Statin therapy in the elderly: less or more?

European Journal of Preventive Cardiology 2021, zwaa164, https://doi.org/10.1093/eurjpc/zwaa164

The results of this observational study emphasize
importance of adherence to therapy in all age groups and all categories of frailty.

Good compliance is associated with better survival.

More studies are needed to investigate whether this better survival corresponds to life prolongation in good physical and mental health.

From all this, it seems that **age by itself is not a good or sufficient indicator** to initiate, sustain or deprescribe statin therapy.

Statin therapy in the elderly: less or more?
Guy G De Backer
European Journal of Preventive Cardiology 2021, zwaa164, https://doi.org/10.1093/eurjpc/zwaa164

Based on the scientific evidence that is available today including results from observational studies such as the one reported in this issue of the *EJPC* and from RCT's, **the use of statin therapy in elderly persons should be considered taking into account other conditions such as frailty.**

But **frailty in itself should not be used as a measure to determine the eligibility for statin use in the elderly**; it can serve to the development of more personalized preventive strategies.

If statin use is recommended, special attention should go into adherence to therapy.

In patients with established ASCVD, the benefits of statins are well documented at all ages; all patients should receive them if no contra-indication and if tolerated.

Statin therapy in the elderly: less or more?
Guy G De Backer
European Journal of Preventive Cardiology 2021, zwaa164, https://doi.org/10.1093/eurjpc/zwaa164

Although there is less direct evidence of benefits in the primary prevention setting among patients older than 75 years, results from RCT's support the use of statins in older patients at high or very high risk of ASCVD.

The results from the STAREE and from the SITE/SAGA trials will be of help to elucidate some of the questions that remain unanswered at a moment where shared decision making on statin therapy in 75+ primary prevention subjects should be based on good **clinical judgement, patient preferences, co-morbidities, frailty, and life expectancy**.

Statin therapy in the elderly: less or more?
Guy G De Backer
European Journal of Preventive Cardiology 2021, zwaa164, https://doi.org/10.1093/eurjpc/zwaa164

Deprescribing
Round One Ranking: Drug/drug classes identified by ≥ 70% of participants as probably or definitely useful.

Drug/Drug class	Number and percent of participants identifying that a deprescribing guideline would be probably or definitely useful	Mean rating	Standard Deviation
1. Benzodiazepines	59/64 (92%)	4.63	0.96
2. Atypical antipsychotics	59/64 (92%)	4.55	0.77
3. Proton-pump inhibitors	56/64 (88%)	4.44	0.75
4. Typical antipsychotics	56/64 (88%)	4.38	0.86
5. Zopiclone	55/64 (86%)	4.41	0.86
6. Opioids	53/64 (83%)	4.22	0.80
7. Statins	52/64 (81%)	4.25	0.94
8. Urinary anticholinergics	52/64 (81%)	4.19	0.88
9. Tricyclic antidepressants	49/64 (77%)	4.17	0.94
10. Beta blockers	49/64 (77%)	4.11	0.95
11. Cholinesterase inhibitors	47/64 (73%)	4.16	0.88
12. Antiplatelets	47/64 (73%)	3.94	1.04
13. Selective serotonin reuptake inhibitors	46/64 (72%)	3.98	0.93
14. Trazodone	46/64 (72%)	4.09	0.84

doi:10.1371/journal.pone.0122246.t002

Farrell B, Tsang C, Raman-Wilms L, Irving H, Conklin J, et al. (2015) What Are Priorities for Deprescribing for Elderly Patients? Capturing the Voice of Practitioners: A Modified Delphi Process. PLOS ONE 10(4): e0122246. https://doi.org/10.1371/journal.pone.0122246
https://journals.plos.org/plosone/article?id=10.1371/journal.pone.0122246

Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: nationwide population-based cohort study France

- The role of statin therapy in primary prevention of cardiovascular disease in persons older than 75 years remains a subject of debate with little evidence to support or exclude the benefit of this treatment.

- **Aim** The effect of **statin discontinuation** on cardiovascular outcomes in previously adherent **75-year-olds treated for primary prevention**.

- **Methods**

A population-based cohort study using French national healthcare databases, studying all subjects who turned 75 in 2012–14, with no history of cardiovascular disease and with a statin medication possession ratio ≥80% in each of the previous 2 years.

Statin discontinuation was defined as three consecutive months without exposure.

The outcome was hospital admission for cardiovascular event.

The hazard ratio comparing statin discontinuation with continuation was estimated using a marginal structural model adjusting for both baseline and time-varying covariates (cardiovascular drug use, comorbidities, and frailty indicators).

Philippe Giral, Anke Neumann, Alain Weill, Joël Coste
European Heart Journal, Volume 40, Issue 43, November 2019, 3516–3525, https://doi.org/10.1093/eurheartj/ehz458

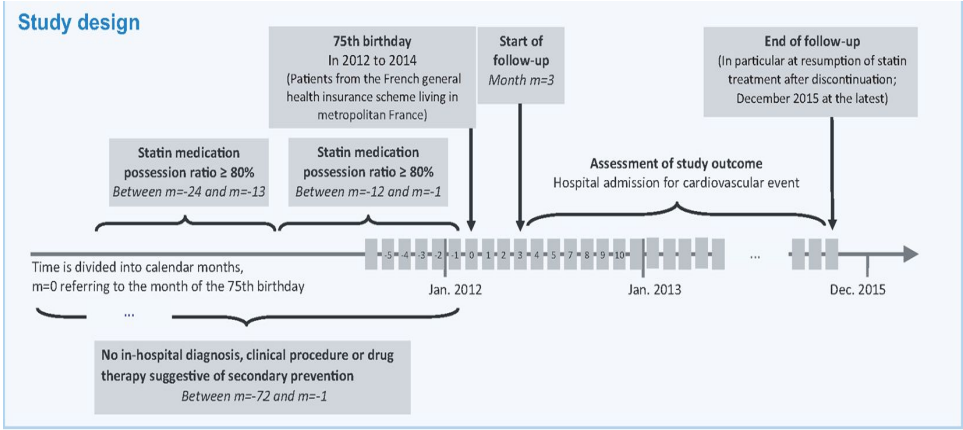
Cardiovascular effect of discontinuing statins for primary prevention at the age of 75 years: nationwide population-based cohort study France

- **Results**

120 173 subjects followed for an average of 2.4 years

17 204 (14.3%) discontinued statins

5396 (4.5%) admitted for a cardiovascular event.



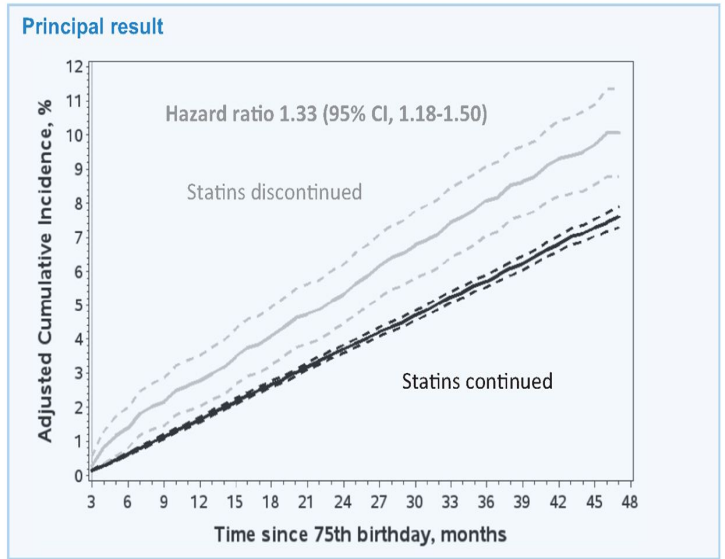
Adjusted hazard ratios for statin discontinuation

1.33 [95% confidence interval (CI) 1.18–1.50] (any cardiovascular event)

1.46 (95% CI 1.21–1.75) (coronary event)

1.26 (95% CI 1.05–1.51) (cerebrovascular event)

1.02 (95% CI 0.74–1.40) (other vascular event).



- **Conclusion**

Statin discontinuation was associated with **a 33% increased risk of admission for cardiovascular event** in 75y old primary prevention patients. Future studies, including randomized studies, are needed to confirm these findings and support updating and clarification of guidelines on the use of statins for primary prevention in the elderly.

Philippe Giral et al.; European Heart Journal, Volume 40, Issue 43, November 2019, 3516–3525, https://doi.org/10.1093/eurheartj/ehz458

Lipidlowering therapy & Elderly
Future studies

- **STAREE** Statin Therapy for Reducing Events in the Elderly; NCT02099123

- Australian **randomized, placebo-controlled trial atorvastatin 40 mg/d or placebo**

- **Will atorvastatin 40 mg daily in primary prevention improve disability-free survival in 18,000 community-dwelling patients age ≥70 years.**
- Primary outcome measures: time from randomization to death or development of dementia (as measured by cognitive function tests), development of disability, and time to a major fatal or nonfatal cardiovascular event.
- Length of a disability-free life assessed on the basis of survival outside permanent residential care.

- Results are expected in 2022–2023.

Lipidlowering therapy & Elderly
Future studies

- **PREVENTABLE** Pragmatic Evaluation of Events and Benefits of Lipid-Lowering in Older Adults; NCT04262206

- 20,000 community-dwelling patients age ≥75 years without clinical evidence of cardiovascular disease at 100 U.S. sites.
- Participants will be **randomized to atorvastatin 40 mg daily, or placebo.**
- The trial will use a pragmatic design to identify **outcomes (including dementia and physical disability as primary outcomes)** over 5 years via electronic health records.
- Additional specific outcome measures include a cognitive function screen and assessments of physical function performed by telephone calls

Lipidlowering therapy & Elderly
Future studies

- **Statins In The Elderly (SITE)** NCT02547883

Mortality and Economic Impact of Stopping Statins in People Aged of 75 and Over: a Pragmatic Clinical Trial

- In patients ≥ 75 years, there is no evidence that statins in primary prevention are associated with a decreased mortality and recent US recommendations consider statins in people only between 40 and 75 years.
- Moreover, statins are associated with numerous side effects impacting quality of life of those people and represent a high cost for the French healthcare system.

- Aim: evaluate **cost/effectiveness ratio, in real life, of statin cessation in people ≥ 75 years treated in primary prevention**.
- In patients ≥ 75 years treated with statins in primary prevention, the studied strategy will be to stop statin therapy. (n 1230)

Comparison: patients who will continue their statin at the same dose.

- Follow up every three months, during 36 months. Clinical events will be prospectively registered

Statins In The Elderly (SITE)

Primary Outcome Measures

1. **Incremental Cost per QALY gained** [Time Frame: 36 month after inclusion]
   Ratio between QALYs (quality-adjusted life years) gained estimated by the EQ-5D scale and cost for the French healthcare system

2. **Overall mortality** [Time Frame: 36 month after inclusion]

Secondary Outcome Measures

1. Quality of life [Time Frame: 3, 12, 24 and 36 moth after inclusion]
   Quality of life as measured by the SF12

   Clinical events [Time Frame: 3, 12, 24 and 36 moth after inclusion]
   Clinical events: cardiovascular events, diabetes, cognitive disorders

Results expected by December 2022

We treat people, not risk factors

Risk factors- Risk qualifiers

Blood Pressure, Diabetes Mellitus, Lipids, Obesity, Smoking

Co-morbidities, Ethnicity, Environment, Family history, Frailty, Genetics, Life expectancy, Polypharmacy, Psychosocial & Socioeconomic factors, …

co-house in a certain person

Who will benefit (the most) from the treatment?

Benefit-Risk balance

We treat people, not risk factors

From an overall Standard approach to a **Tailored** approach

Precision medicine also & especially for the elderly

Thank you for your attention