HART
CENTRUM

Hypercholesterolemie: slikken of prikken?

Dr Mark Ronsyn

ZIEKENHUIS aan de STROOM

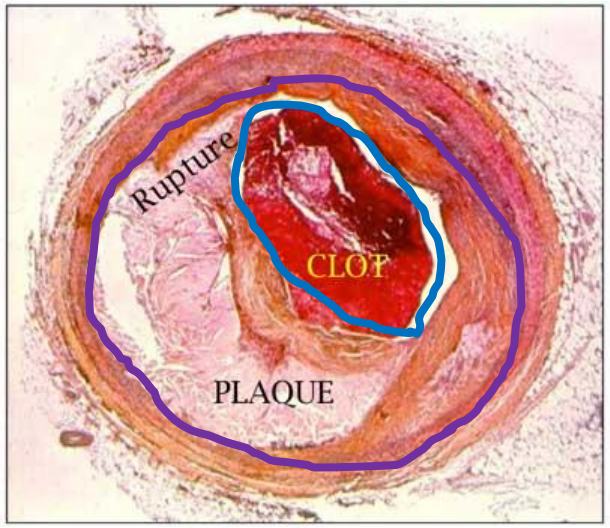
Besluit

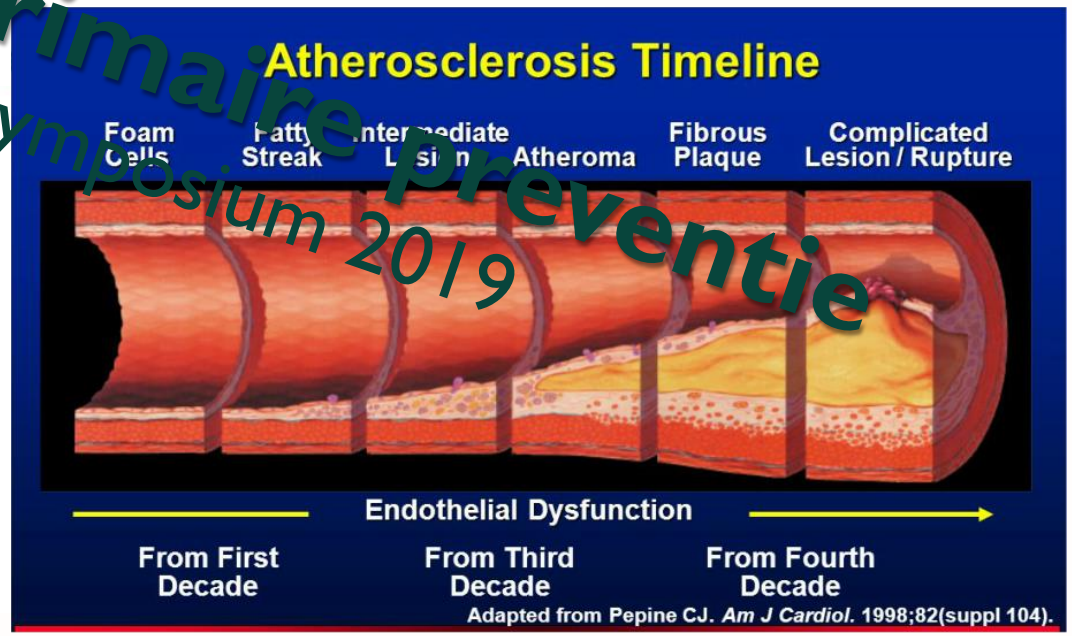
Aspirine biedt geen klinisch voordeel op MACE/overleving in primaire preventie bij "gezonde ouderen", wel bij diabeten (-12%)

Aspirine verhoogt de kans op bloedingen (+30%)

Aspirine in primaire preventie

Huisartensymposium 2019





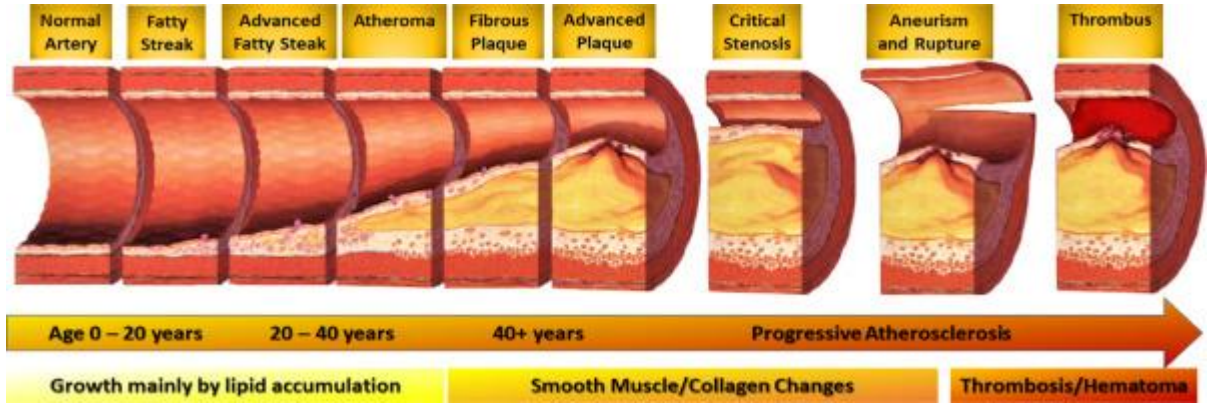
ZAS HART CENTRUM

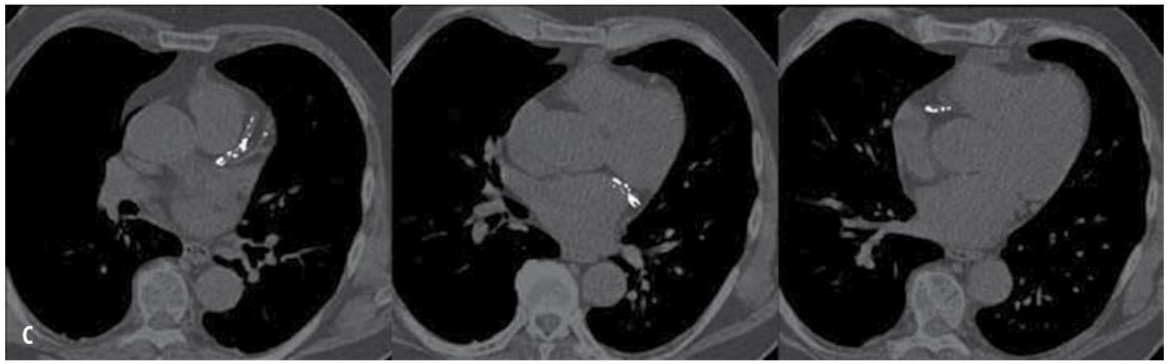
ZIEKENHUIS aan de STROOM

Secundaire preventie >> vasculair event

Het lipidenbeleid anno 2021

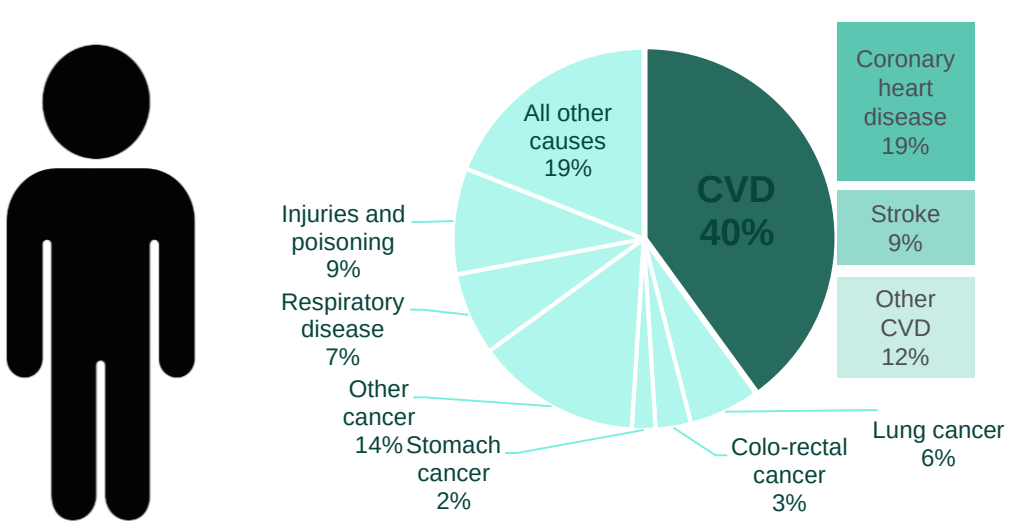
- Na een klinisch event: ACS, angor, PCI, CABG, CVA, TIA, perifeer vaatlijden
- Beeldvorming: significante plaques op duplex halsvaten, ileofemorale vaten of coronaire CT
- Morbiditeit: DM
- Ernstig nierlijden (eGFR < 30 ml/min)
- Familiale HyperCh
- Cardiovasculair RisicoScore >=10%

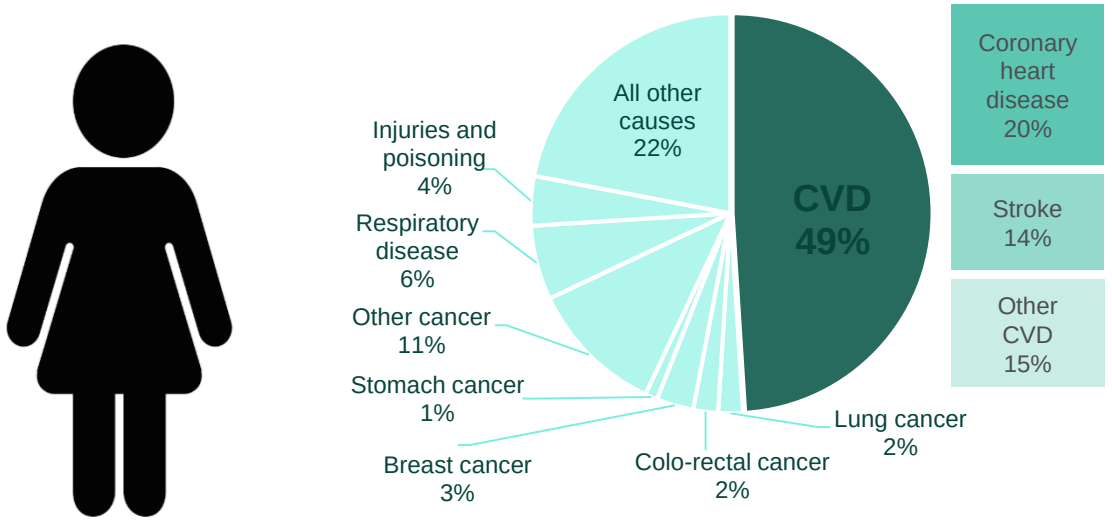




- CVZ: belangrijkste doodsoorzaak wereldwijd

- CVZ > 4 miljoen doden per jaar in Europa: 1,4 miljoen premature overlijdens < 75 jr
  - 45% overall mortaliteit/jaar
    - 49% bij vrouwen
    - 45% bij mannen

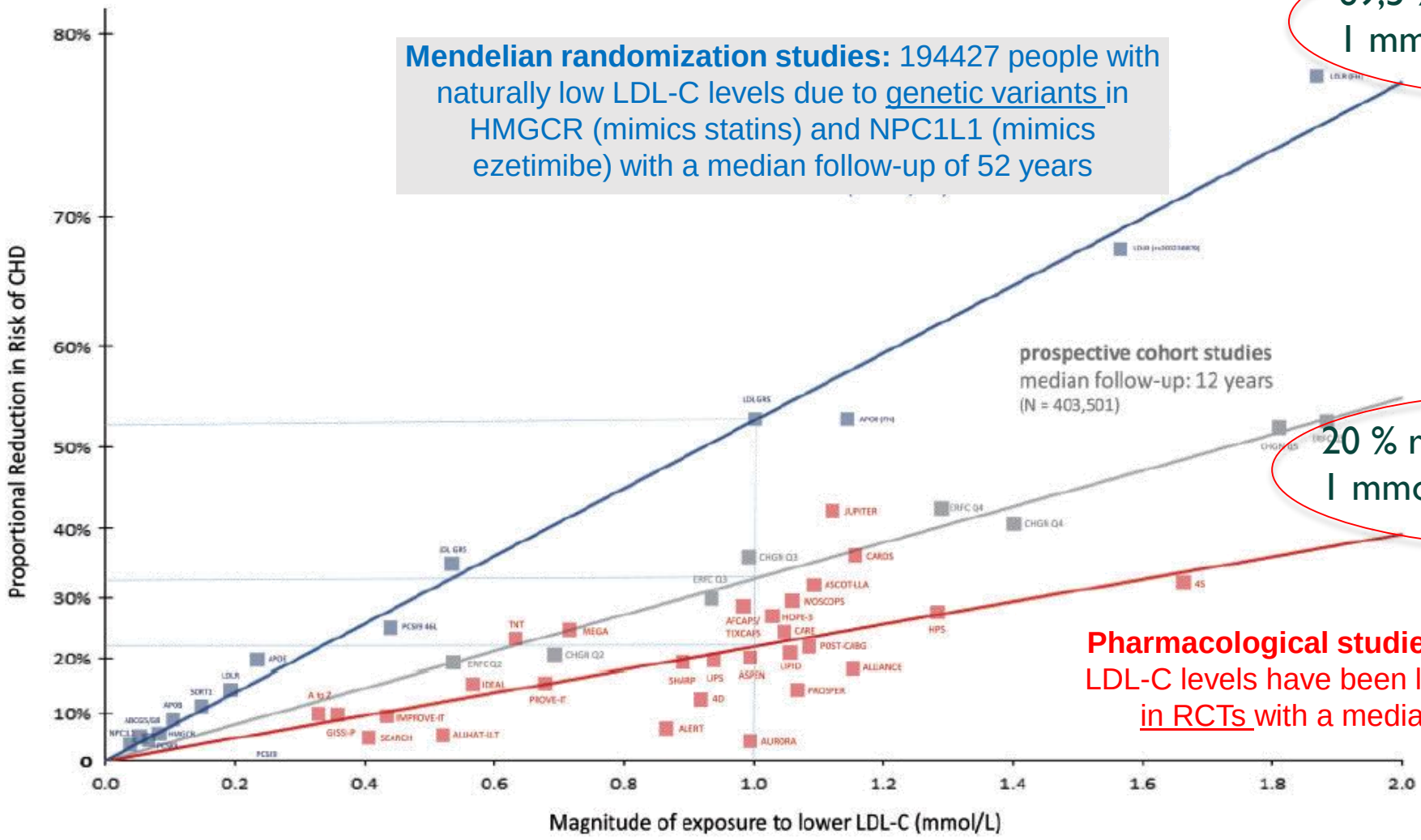




Cholesterol (LDL) >> cardiovasculaire events

69,5 % risicoreductie in CVZ per 1 mmol/l (38,6 mg/dl) LDL-daling

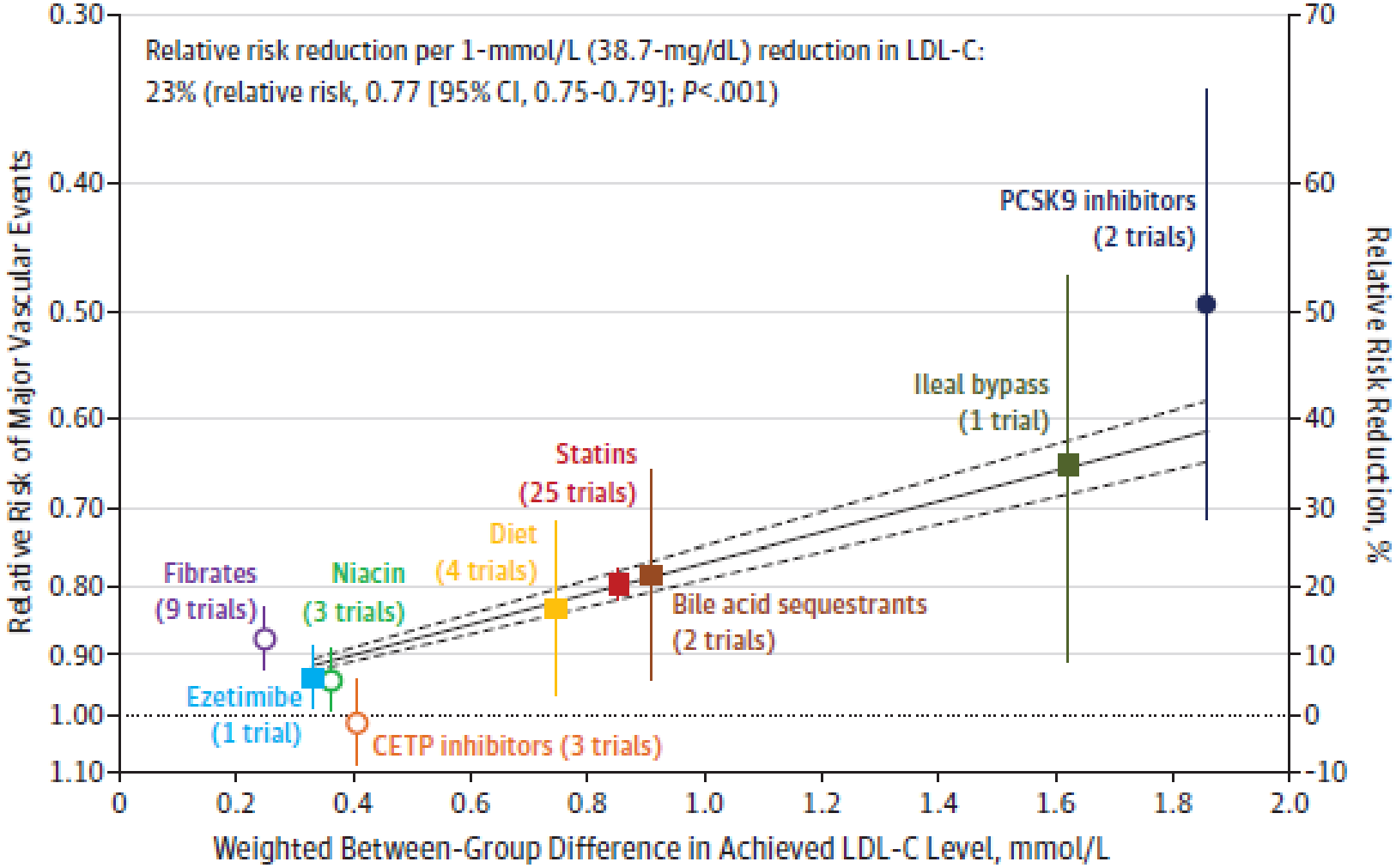
Mendelian randomization studies: 194427 people with naturally low LDL-C levels due to genetic variants in HMGCR (mimics statins) and NPC1L1 (mimics ezetimibe) with a median follow-up of 52 years



20 % risicoreductie in CVZ per 1 mmol/l (38,6 mg/dl) LDL-daling

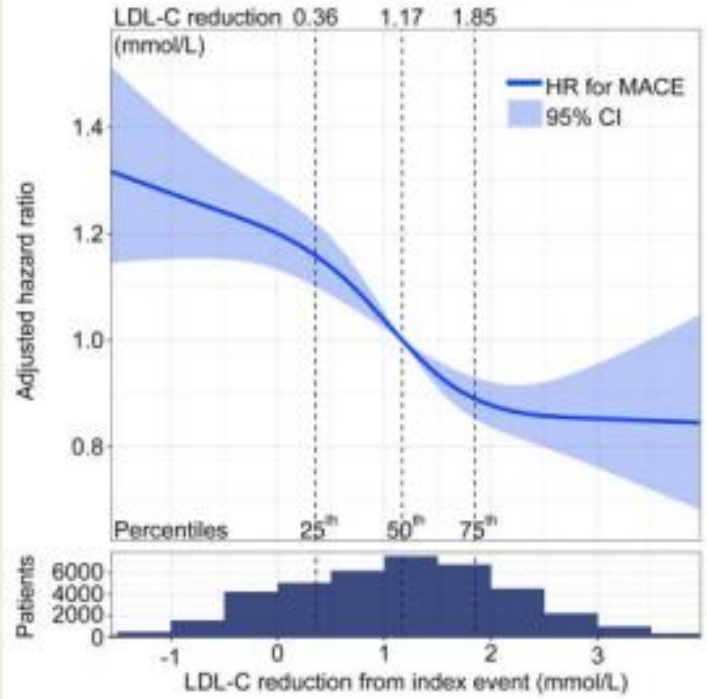
Pharmacological studies: 196 522 people whose LDL-C levels have been lowered by drug treatment in RCTs with a median follow-up of 5 years

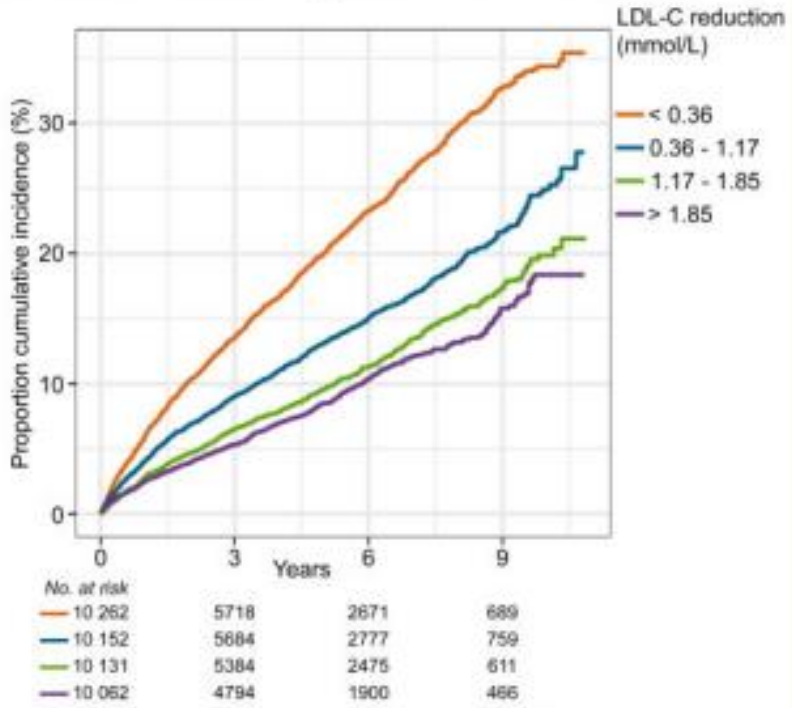
LDL-reductie is de driver van de relatieve risicoreductie, ongeacht de therapie



Silverman MG, et al., JAMA. 2016;316(12):1289–1297

Adjusted hazard ratio and incidence rates for major adverse cardiovascular events by change in LDL-C 6-10 weeks after myocardial infarction





HR for 1.85 vs 0.36 mmol/L LDL-C reduction: **0.77 (95% CI 0.70 - 0.84)**

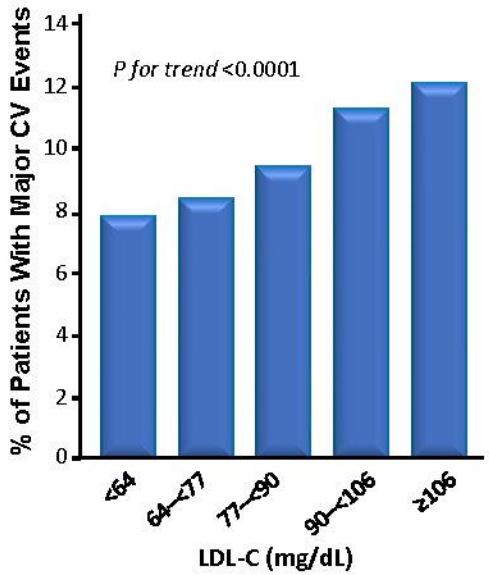
vords Myocardial infarction • Secondary prevention • LDL-C • Cardiovascular outcomes • Cardiovascular mortality • Statin

Swedeheart studie, Eur Heart J 2021

Hoe lager, hoe beter

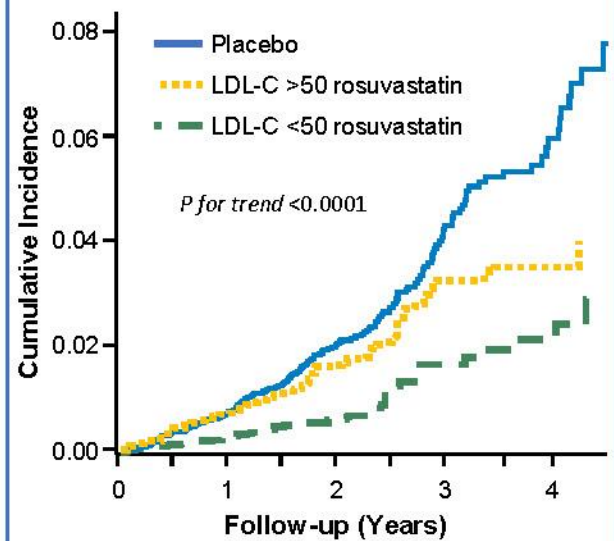
TNT[1,a]

Rate of major CV events



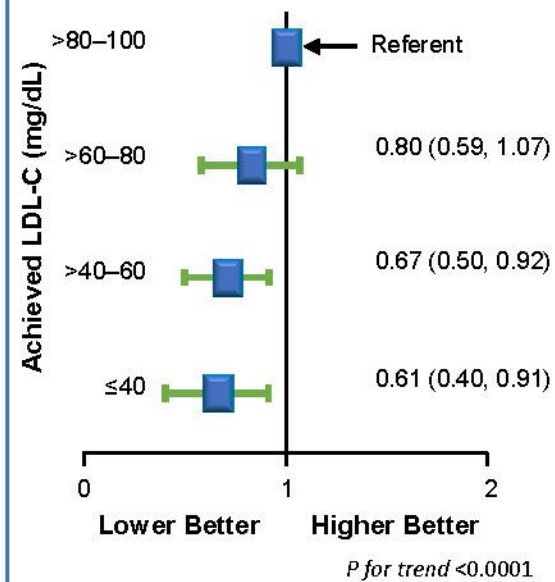
JUPITER[2,b]

Time to occurrence of major CV events



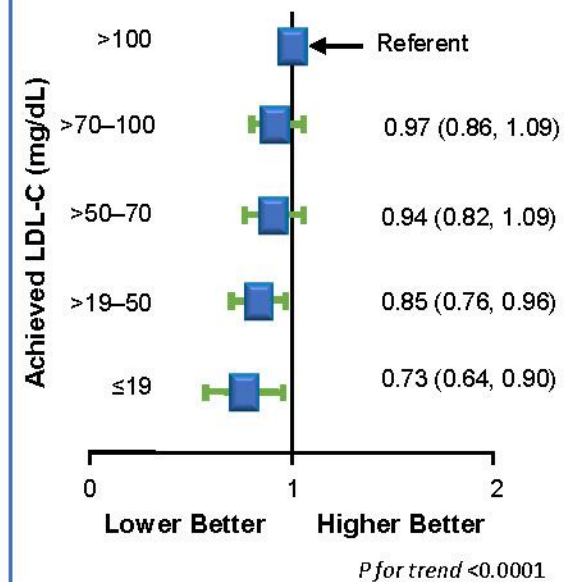
PROVE-IT[3,c]

Hazard ratio of primary endpoint



FOURIER[4,d]

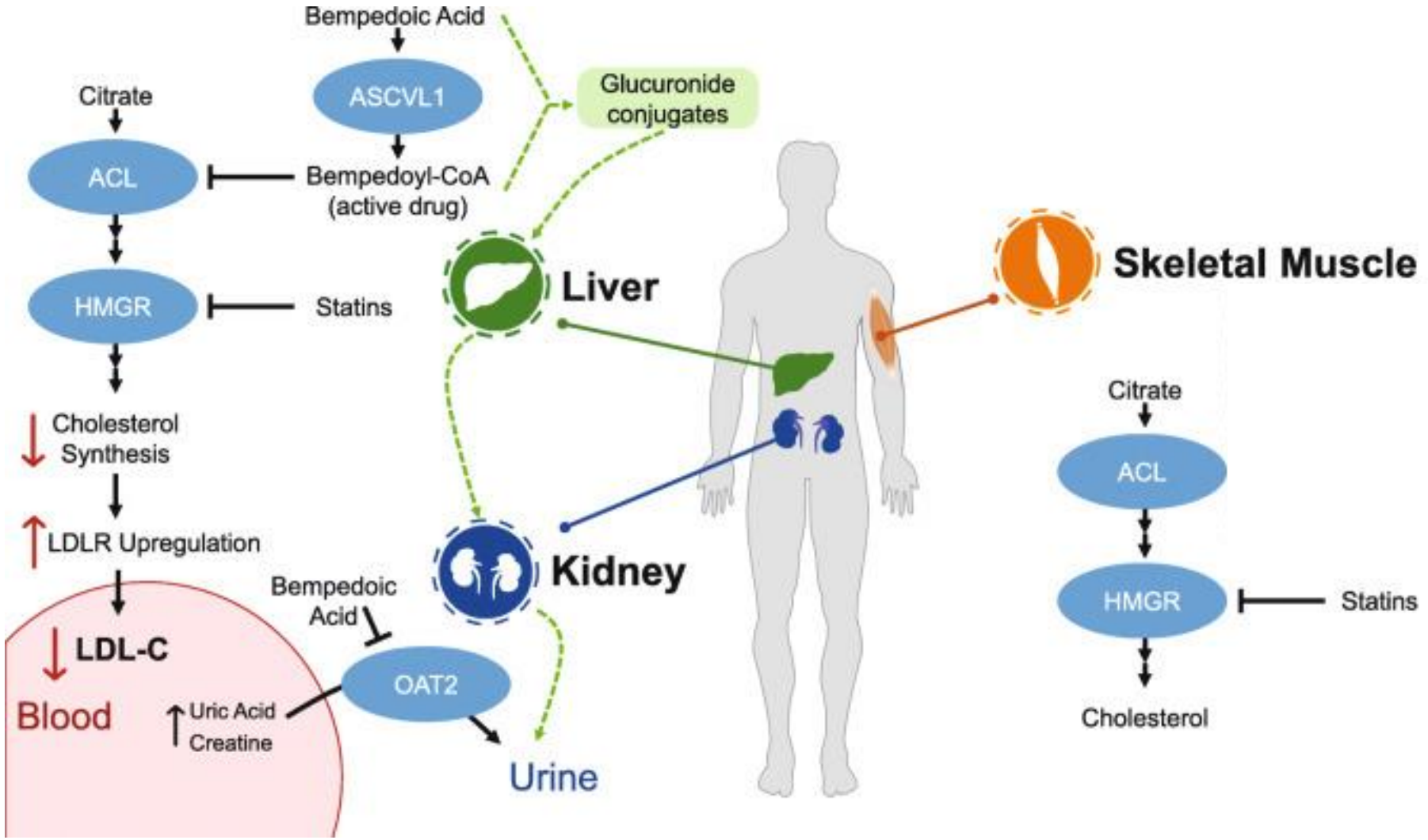
Hazard ratio of primary endpoint



[a]RCT in patients with stable coronary disease. Major CV Events = death from CHD, nonfatal non-procedure-related MI, resuscitation after cardiac arrest, or fatal or nonfatal stroke. [b]RCT of patients with LDL-C <130 mg/dL, high-sensitivity C-reactive protein ≥2.0 mg/L, and no history of CVD or diabetes mellitus. Major CV events = CV death, MI, stroke, arterial revascularization, or hospitalized UA. [c]post randomization LDL-C. [d]RCT in patients with stabilized ACS. Primary composite endpoint of death, MI, stroke, revascularization, and UA requiring hospitalization. [d]RCT in patients with stabilized ACS, stroke or PAD. Primary composite endpoint of cardiovascular death, MI, stroke, coronary revascularization or UA.

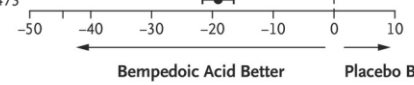
1. LaRosa JC, et al. J Am Coll Cardiol 2007. 2. Hsia J, et al. J Am Coll Cardiol 2011. 3. Wiviott SD, et al. J Am Coll Cardiol 2005. 4. Giugliano RP et al. Lancet 2017

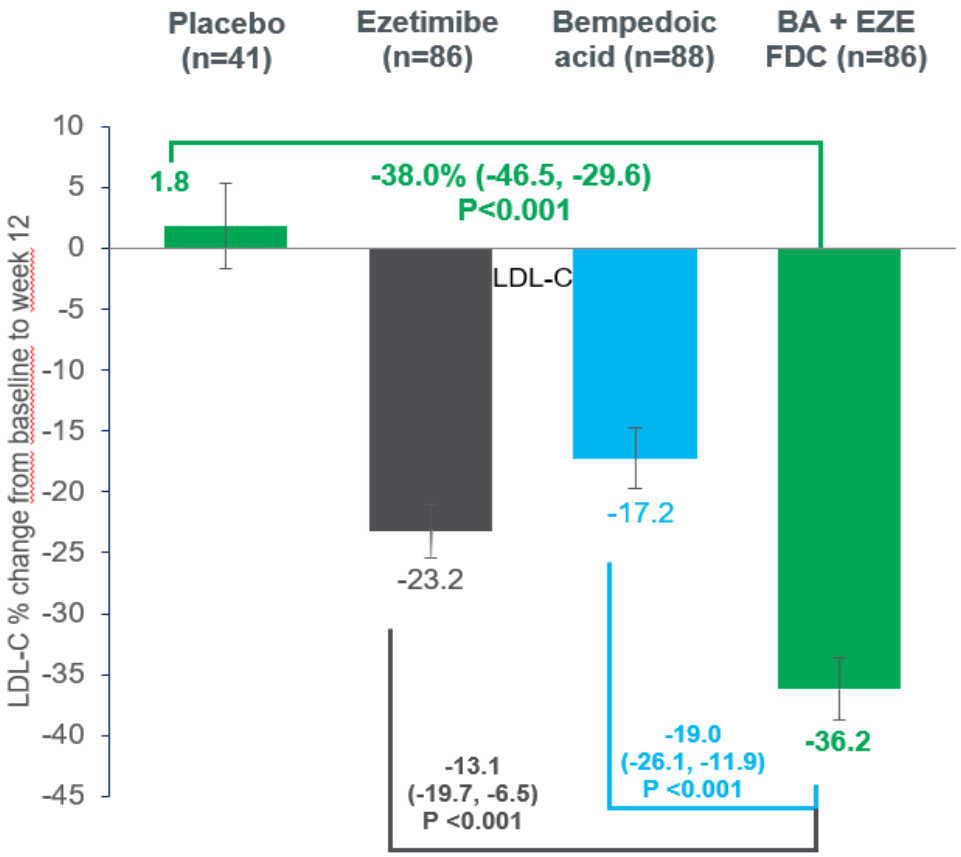
Bempedoïnezuur: Nilemdo 180 mg/d of Nustendi 180 mg/10 mg



Adapted from Ballantyne C. et al.; Cardiovasc Drugs Ther. 2021; 35(4): 853–864

Subgroup	Bempedoic Acid	Placebo	Least-Squares Mean Difference (95% CI)	P Value for Interaction
	no. of patients		*percentage points*	
Sex				0.03
Male	1058	519	−17.4 (−19.4 to −15.4)	
Female	336	206	−22.3 (−26.9 to −17.7)	
Race				0.82
White	1363	700	−18.7 (−20.7 to −16.8)	
Other	61	25	−20.0 (−34.0 to −6.1)	
Age <65 yr or ≥65 yr				0.71
<65 yr	576	260	−18.3 (−21.6 to −15.0)	
≥65 yr	848	465	−19.0 (−21.4 to −16.6)	
Age <75 yr or ≥75 yr				0.87
<75 yr	1182	590	−18.8 (−21.0 to −16.6)	
≥75 yr	242	135	−18.4 (−22.7 to −14.1)	
Cardiovascular disease risk category				
Atherosclerotic cardiovascular disease				0.43
Yes	1388	710	−18.6 (−20.6 to −16.7)	
No	36	15	−24.8 (−47.1 to −2.6)	
Heterozygous familial hypercholesterolemia				0.68
Yes	54	23	−20.6 (−35.7 to −5.4)	
No	1370	702	−18.7 (−20.6 to −16.7)	
Background lipid-lowering therapy				
Intensity of statin therapy				0.18
Low or moderate	706	362	−20.0 (−22.8 to −17.3)	
High	718	363	−17.5 (−20.2 to −14.7)	
Ezetimibe				0.57
Yes	112	53	−15.8 (−23.5 to −8.2)	
No	1312	672	−18.9 (−20.9 to −16.9)	
Fibrate				0.32
Yes	51	25	−23.8 (−34.1 to −13.5)	
No	1373	700	−18.5 (−20.5 to −16.6)	
Baseline LDL cholesterol				0.85
≥100 mg/dl	631	303	−18.8 (−21.5 to −16.1)	
<100 mg/dl	793	422	−18.5 (−21.3 to −15.7)	
History of diabetes				0.82
Yes	405	207	−19.1 (−22.7 to −15.5)	
No	1019	518	−18.6 (−20.9 to −16.3)	
Body–mass index				0.14
≥30	597	290	−20.1 (−24.9 to −15.2)	
25 to <30	624	320	−16.5 (−19.1 to −13.8)	
<25	201	114	−20.7 (−24.0 to −17.3)	
Geographic region				0.67
North America	480	252	−18.1 (−21.0 to −15.3)	
Europe	944	473	−19.1 (−21.6 to −16.5)	





Add –on: – 17,8%

Statine-naïef: - 24,5 %

Statineverdubbeling: -6%

Indicaties volgens de terugbetalingsvoorwaarden van bempedoïnezuur (Nilemdo®) in België

- Patiënten met een **gemengde dyslipidemie of een primaire hypercholesterolemie met een hoog en met een zeer hoog cardiovasculair risico** (Bf):

  - In combinatie met de maximaal verdraagbare dosis statine en ezetimibe, waarbij de streefwaarde van LDL-C < 70 mg/dl (hoog risico) of < 55 mg/dl (zeer hoog risico) niet kon bereikt worden.

- Patiënten met **familiale heterozygote hypercholesterolemie** (DLCN* > 8 punten) (Af):

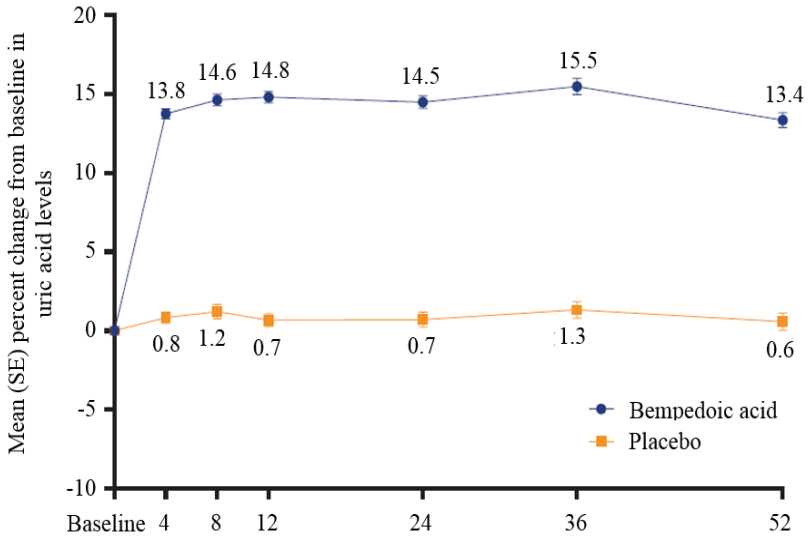
  - In combinatie met de maximaal verdraagbare dosis statine en ezetimibe, waarbij de streefwaarde van respectievelijk < 55 mg/dL (bij een coronaire/cerebrale/perifere aandoening gedocumenteerd door een technisch onderzoek en minstens 1 van de volgende risicofactoren: ≥65j, diabetes, hypertensie, roken en/of obesitas) of in alle andere gevallen < 70 mg/dL niet kon bereikt worden.

- **Intolerantie of contra-indicatie voor statines** (Bf et Af)

* DLCN: Dutch Lipid Clinical Network clinical criteria for diagnosis of HeFH (zie Descamps OS et al. Louvain Med 2011:140; 451-459)

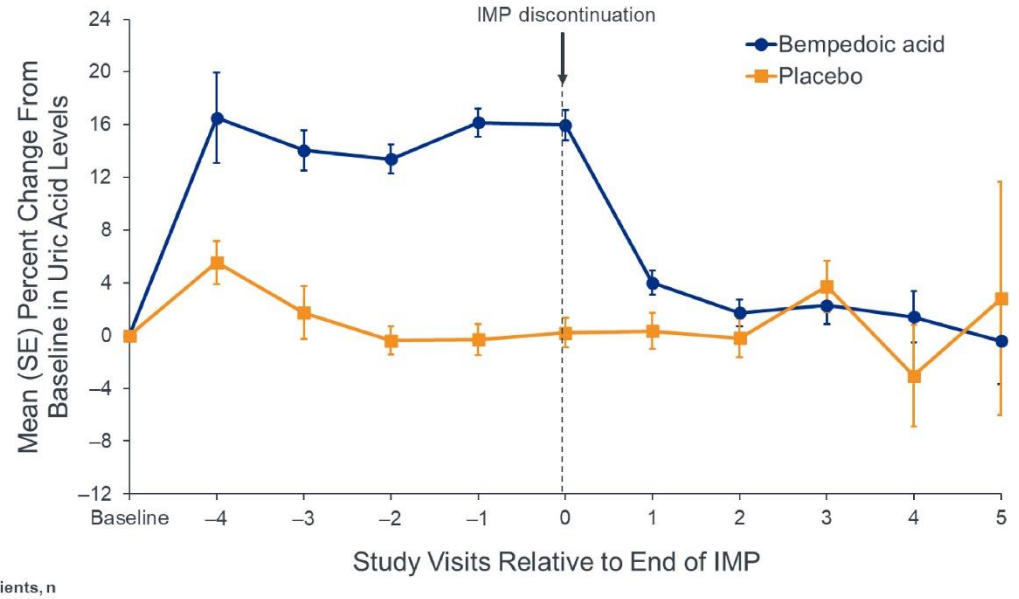
Adapted from [1] Mertens A. et al.; Louvain Med 2022; 141; p1-8, [2] Scheen A. et al.; Rev Med Liege 2022; 77 :2 :124-131

Hyperuricemie en jicht



Patients, n							
Bempedoic acid	2424	2357	1571	2321	2102	1373	1825
Placebo	1197	1173	801	1168	1060	693	918

Figure 1. Uric acid levels relative to baseline values, pooled safety analysis [1]



Patients, n											
Bempedoic acid	312	41	77	194	253	312	312	221	163	67	28
Placebo	123	17	38	96	110	123	123	69	51	12	5

Figure 2. Change in uric acid levels before, during, and after treatment in the ASCVD/HeFH on statins pool. [2]

Gemiddelde toename van **0.8 mg/dl** ten opzichte van baseline met bempedoïnezuur in week 12

ASCVD, atherosclerotic cardiovascular disease; HeFH, heterozygous familial hypercholesterolemia; IMP, investigational medicinal product ; OAT2 = Organic Anion Transporter 2 ; SE, standard error.

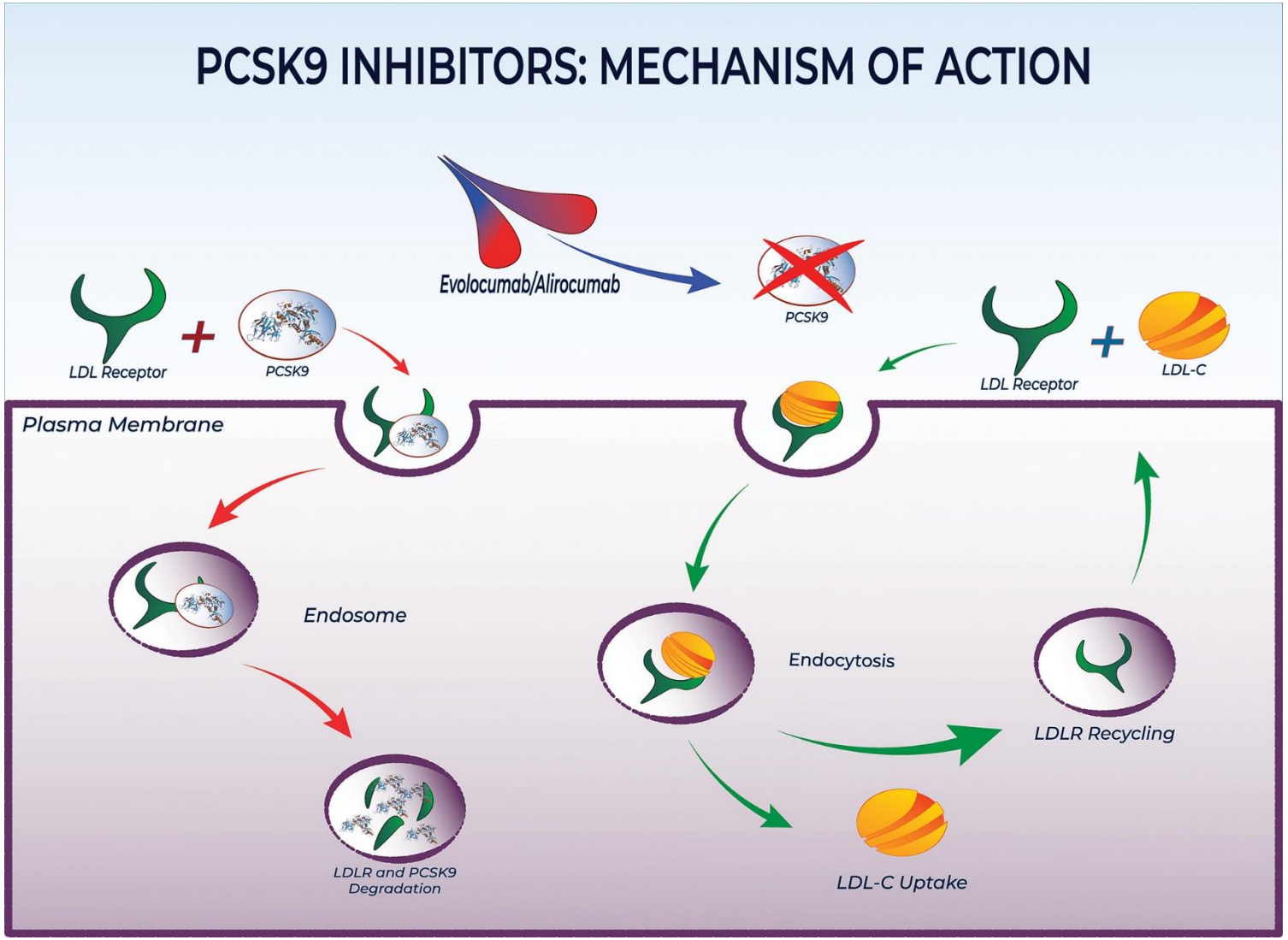
[1] Ray K et al. Effect of bempedoic acid on uric acid and gout in 3621 patients with hypercholesterolaemia: pooled analyses from phase 3 trials. ePoster presented virtually at the European Society of Cardiology Congress (August 29th – September 1st 2020). [2] Bays H et al., Journal of Clinical Lipidology (2020), 14, 649–659. [3] SmPc Nilemdo

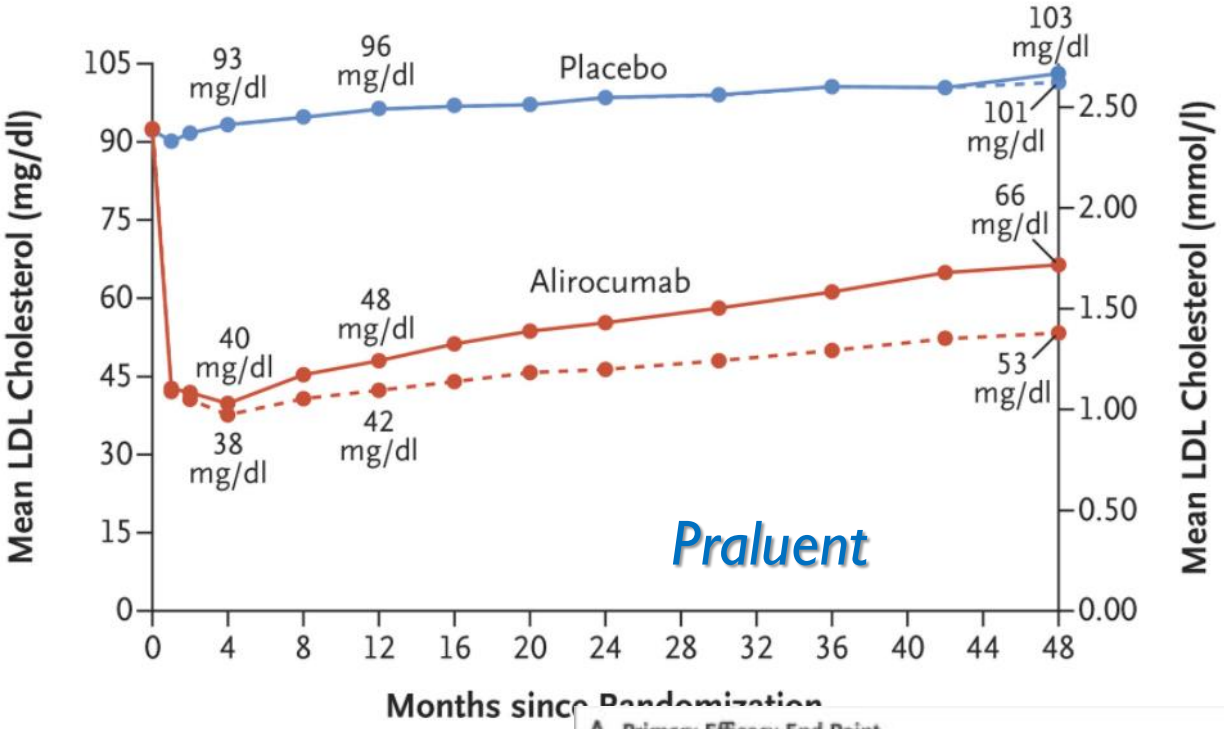
LDL reductie van 50% EN < 55 mg/dl

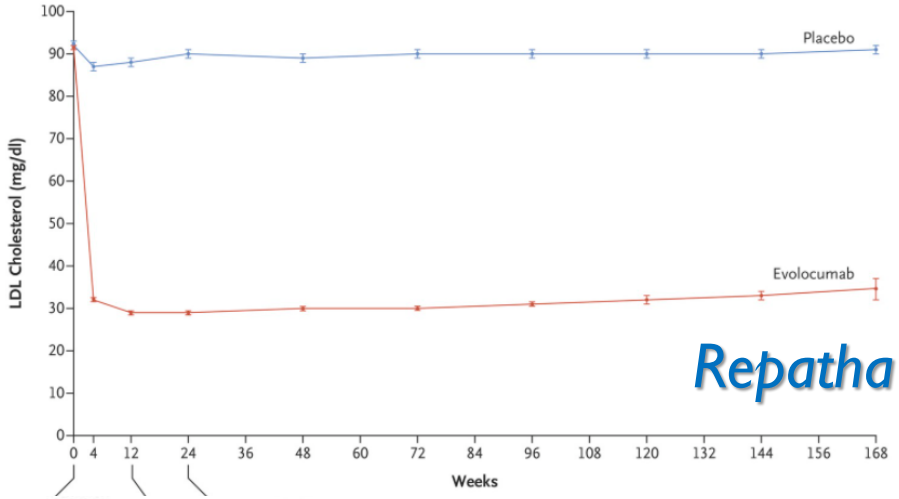
- Langetermijn
- Zo snel als mogelijk, zo laag als mogelijk

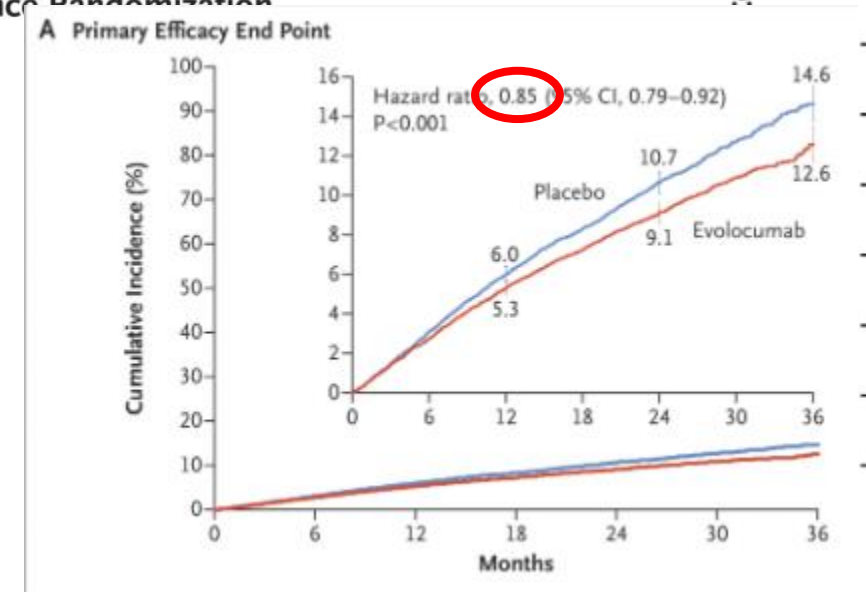
Matig-intens statine	>> -30%
Hoog-intens statine	>> -50%
Hoog-intens statine + Ezetimibe	>> -65%
Hoog-intens statine + Ezetimibe + Bempedoïnezuur	>> -70-75%

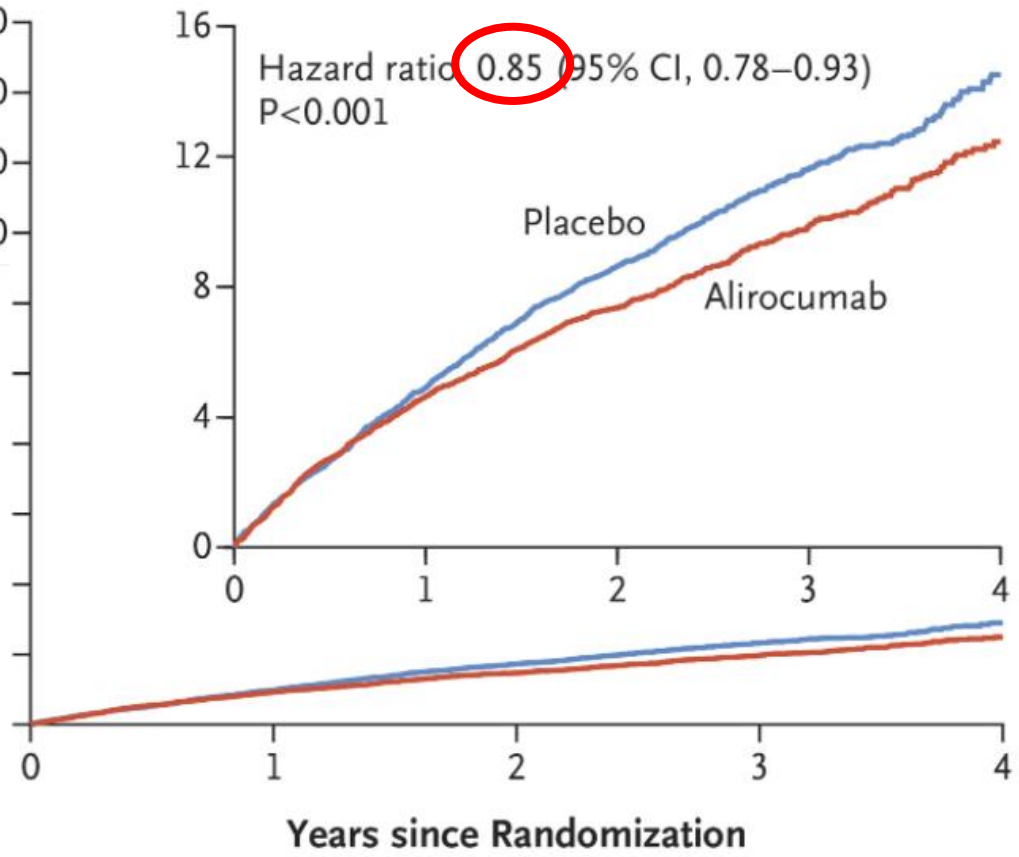
PCSK-9 inhibitoren











Schwartz, 2018, NEJM

Sabatine, 2017, NEJM

1. *Arnaud Suarez, Vascul Pharmacol. 2019;114:64-75;*
2. *Lam JKW, et al. Mol Ther Nucleic Acids. 2015;4:e252;*
3. *The Nobel Prize in Physiology or Medicine 2006.*

LDL reductie van 50% EN < 55 mg/dl

- Langetermijn
- Zo snel als mogelijk, zo laag als mogelijk

Matig-intens statine	>> -30%
Hoog-intens statine	>> -50%
Hoog-intens statine + Ezetimibe	>> -65%
Hoog-intens statine + Ezetimibe + Bempedoïnezuur	>> -70-75%
Hoog-intens statine + PCSK-9 inhibitor	>> -75%
Hoog-intens statine + Ezetimibe + PCSK-9 inhibitor	>> -85%

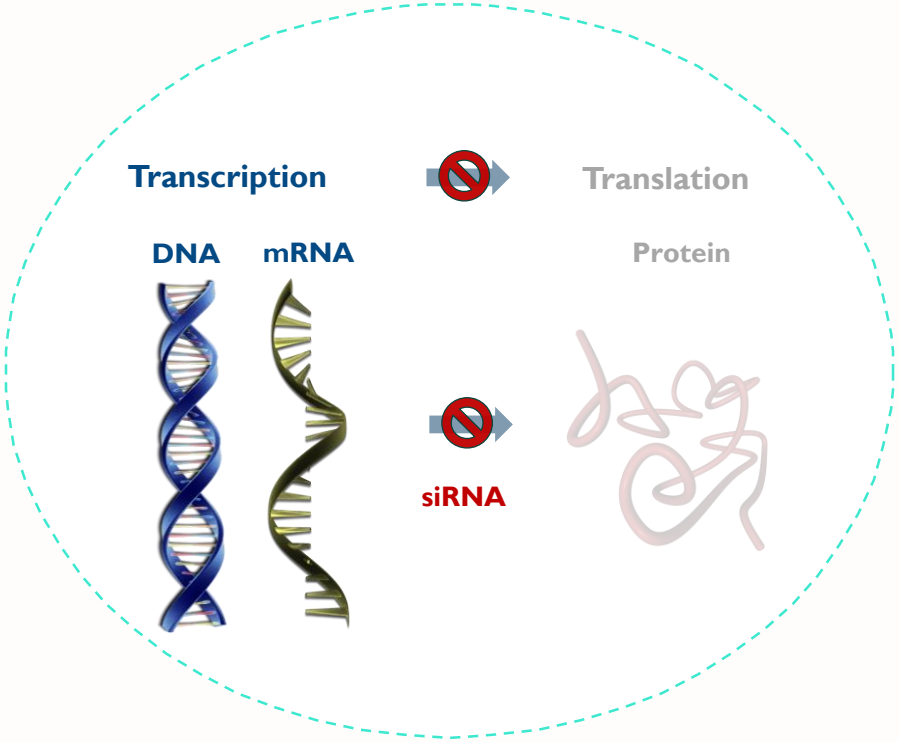
Repatha:

- Volwassenen met heterozygote FH (> 8 DLCN score of genmutatie) EN
  - LDL > 100 mg/dl + ACS
  - LDL > 130 mg/dl

Praluent:

- Volwassenen met heterozygote FH (> 8 DLCN score of genmutatie) EN
  - LDL > 100 mg/dl + ACS
  - LDL > 130 mg/dl

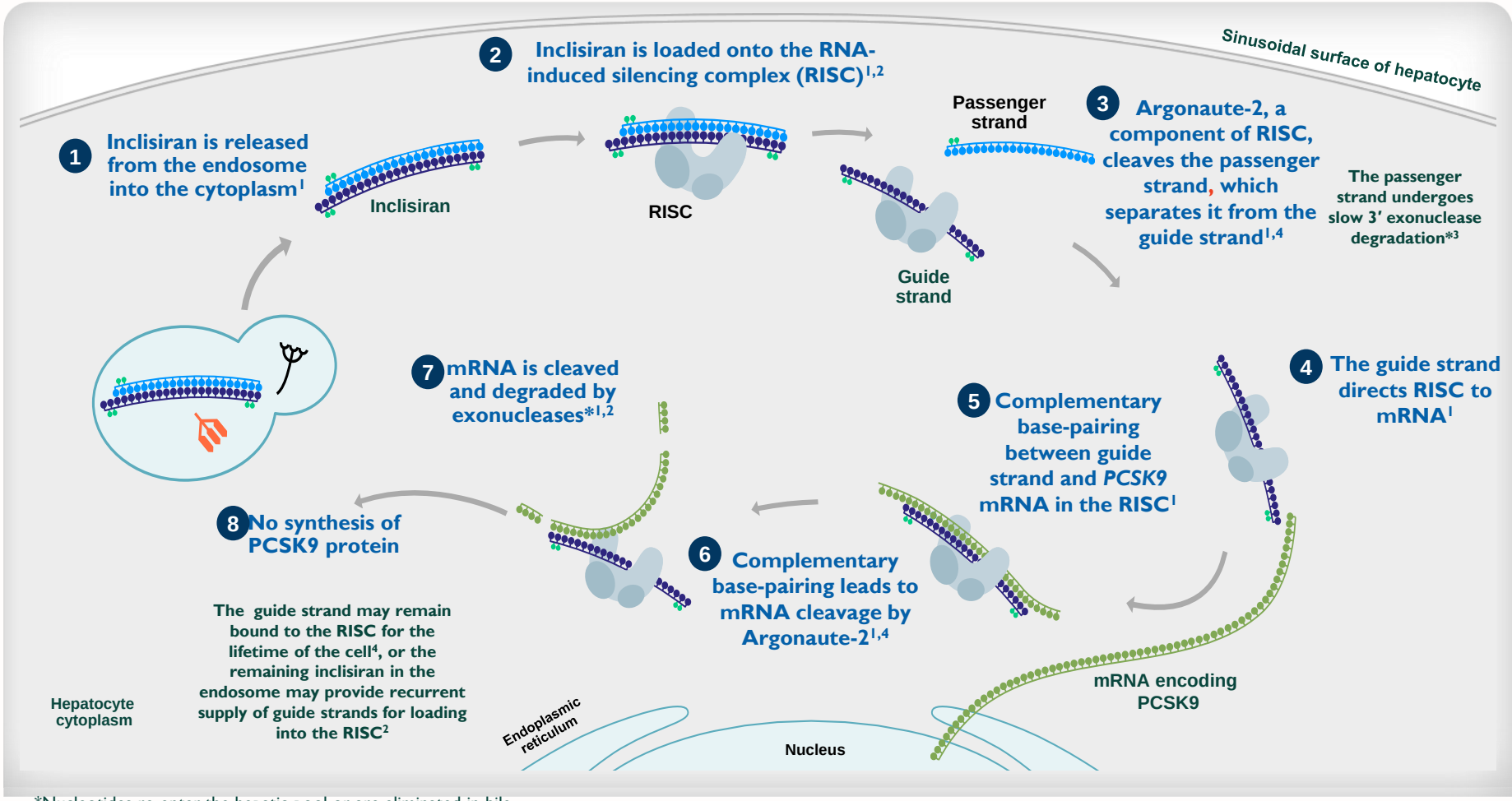
siRNA – natuurlijk mechanisme van gen-expressie silencing



Small interfering RNAs (siRNA) are short double-stranded non-coding RNAs that function in gene silencing[1,2]

siRNAs **prevent protein synthesis** by degrading unique target mRNA through a natural mechanism called RNA interference[1,2]

Werkingsmechanisme Inclisiran (Leqvio)

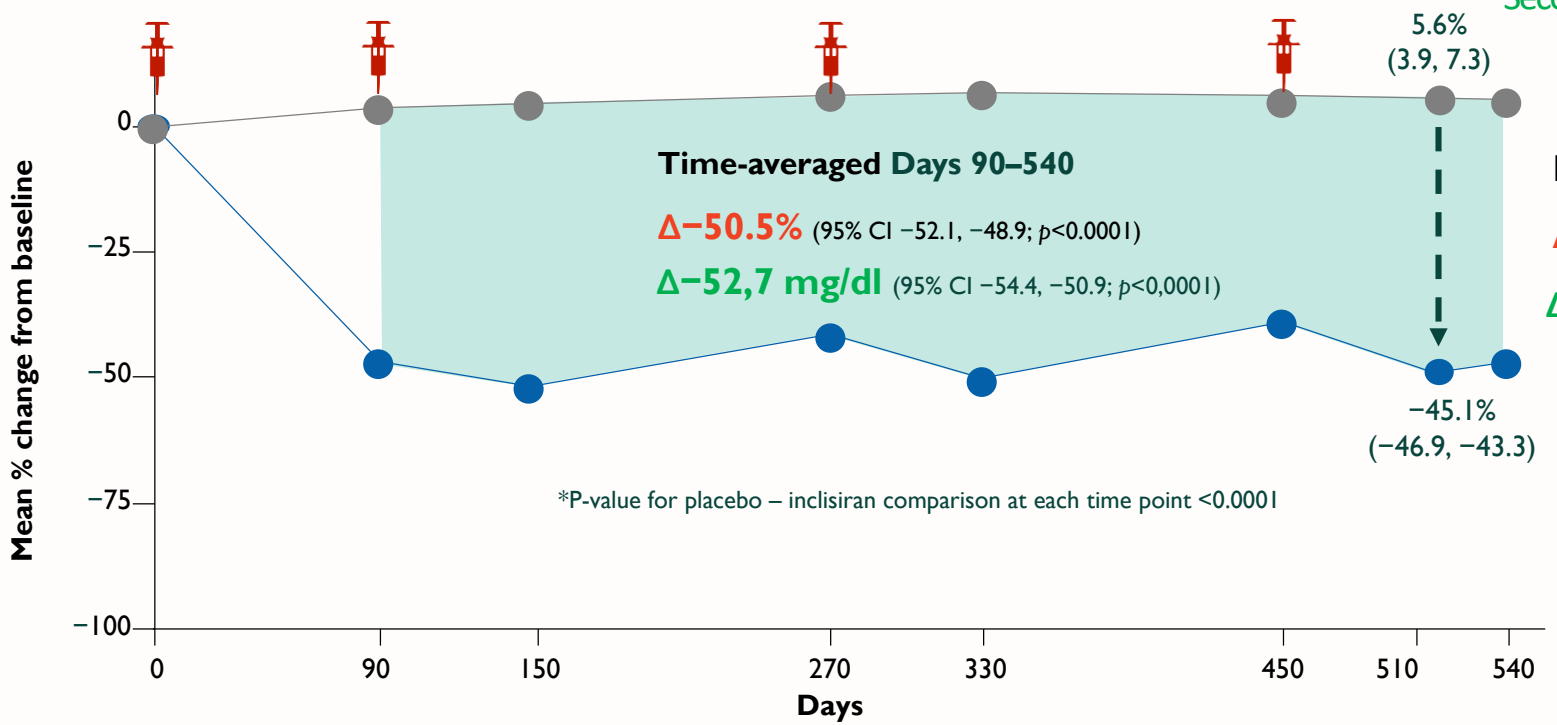


*Nucleotides re-enter the hepatic pool or are eliminated in bile

Duurzaam en krachtig effect van Inclisaran over 18 mnd

Primary endpoint – % LDL-C reduction

Secondary endpoint – absolute LDL-C reduction



Day 510

Δ−50.7% (95% CI −52.9, −48.4; p<0.0001)

Δ−55,1 mg/dl (95% CI −57,4; − 52,8; p<0.0001)

No. of patients	Day 0	Day 90	Day 150	Day 270	Day 330	Day 450	Day 510	Day 540
Inclisiran	1833	1788	1792	1755	1741	1726	1646	1679
Placebo	1827	1796	1768	1733	1721	1695	1634	1651

ZIEKENHUIS aan de STROOM

HART CENTRUM

Robuste LDL-daling

Subgroup	Inclisiran N	Placebo N	LS Mean Percent Difference in LDL-C
Overall			
Overall	1833	1827	-54.1
Sex			
Male	1226	1244	-53.8
Female	607	583	-54.8
Age <65 yr or ≥65 yr			
<65 yr	853	884	-54.3
≥65 yr	980	943	-53.7
Age <75 yr or ≥75 yr			
<75 yr	1593	1575	-54.0
≥75 yr	240	252	-55.0
Body mass index			
≤29.7	942	888	-51.6
>29.7	891	937	-56.8
Race			
White	1670	1708	-54.2
Black	130	102	-53.6
Other	33	17	-49.8
Baseline statin treatment			
On statin	1686	1675	-54.5
Not on statin	147	152	-48.8
Intensity of statin treatment			
High intensity statin	1356	1345	-54.6
Not on high intensity statin	477	482	-52.7
Lipid management treatment (LMT)			
Any statin	1686	1675	-54.5
Other LMT but no statin	75	62	-53.9
No LMT	72	90	-45.6
Metabolic disease			
Diabetes	687	631	-56.1
Metabolic syndrome	499	526	-56.2
Neither	647	670	-50.6

Inclisiran better **Placebo better**

Subgroup	Inclisiran N	Placebo N	LS Mean Percent Difference in LDL-C
Risk category			
ASCVD	1552	1555	-55.3
ASCVD equivalent	281	272	-47.1
Renal function (eGFR - Cockcroft Gault)			
Normal	996	1020	-54.1
Mild impairment	637	600	-53.3
Moderate impairment	196	202	-56.9
Baseline triglycerides in mg/dL			
≤130	918	914	-52.2
>130	915	913	-55.9
Baseline LDL-C in mg/dL			
≤100	927	925	-61.1
>100	906	902	-46.9
Baseline LDL-C quartiles in mg/dL			
≤82	455	482	-65.2
>82 - ≤100	472	443	-56.9
>100 - ≤129	434	465	-50.7
>129	472	437	-43.1
Ethnicity			
Hispanic or latino	120	116	-43.6
Not hispanic or latino	1713	1711	-54.8
Geographic region			
North America	826	823	-56.4
Europe	859	854	-51.1
South Africa	148	150	-57.6

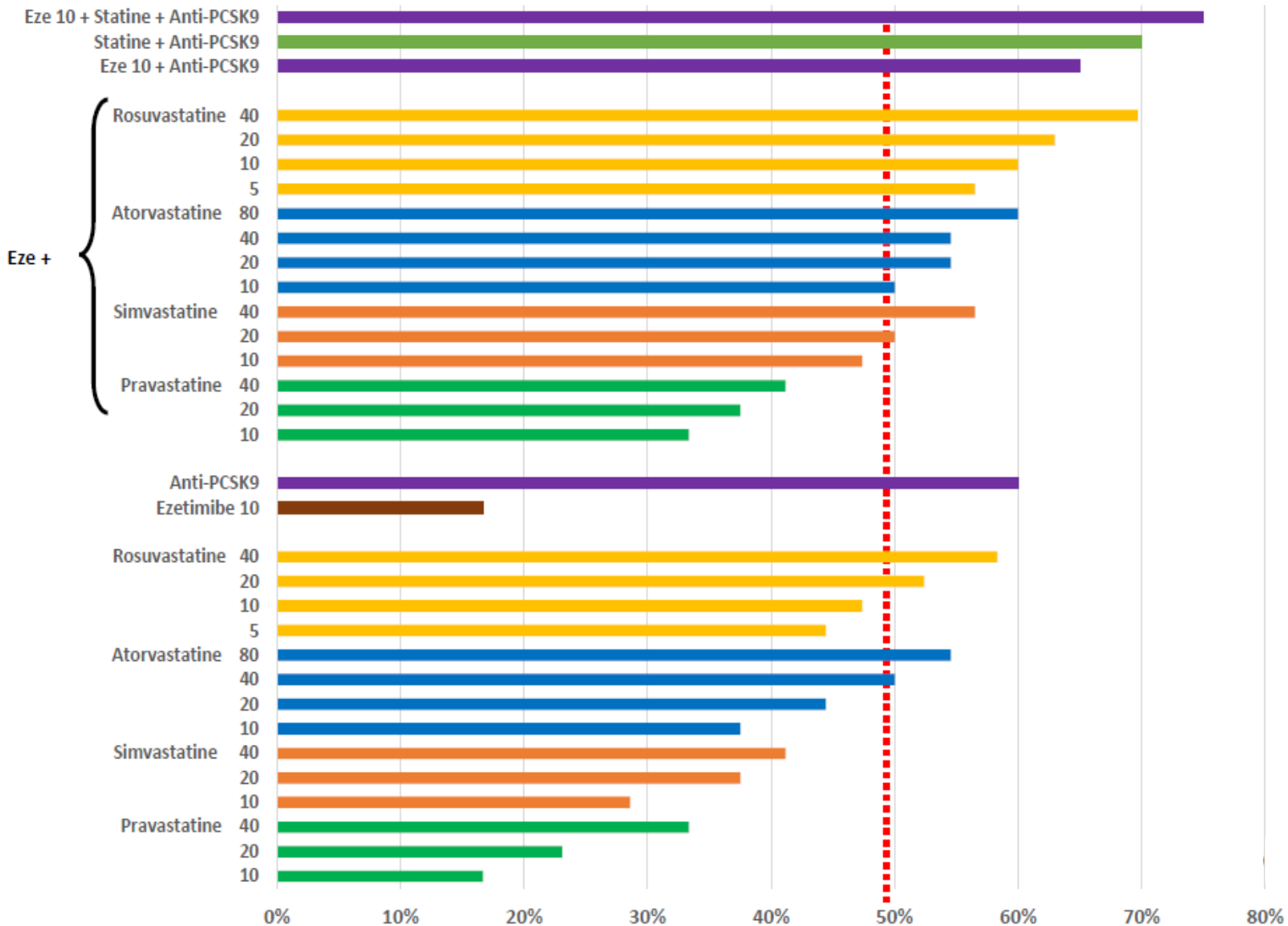
Inclisiran better **Placebo better**

Repatha en Praluent:

- Volwassenen met heterozygote FH (> 8 DLCN score of genmutatie) EN
- LDL > 100 mg/dl + ACS
- LDL > 130 mg/dl
- ½ wkn SC (zelf)

Leqvio:

- Volwassenen met heterozygote FH (> 8 DLCN score of genmutatie) en LDL > 100 mg/dl
- ACS en LDL >100 mg/dl
- 0-3 mnd, daarna 1/6 mnd (zorgverlener)

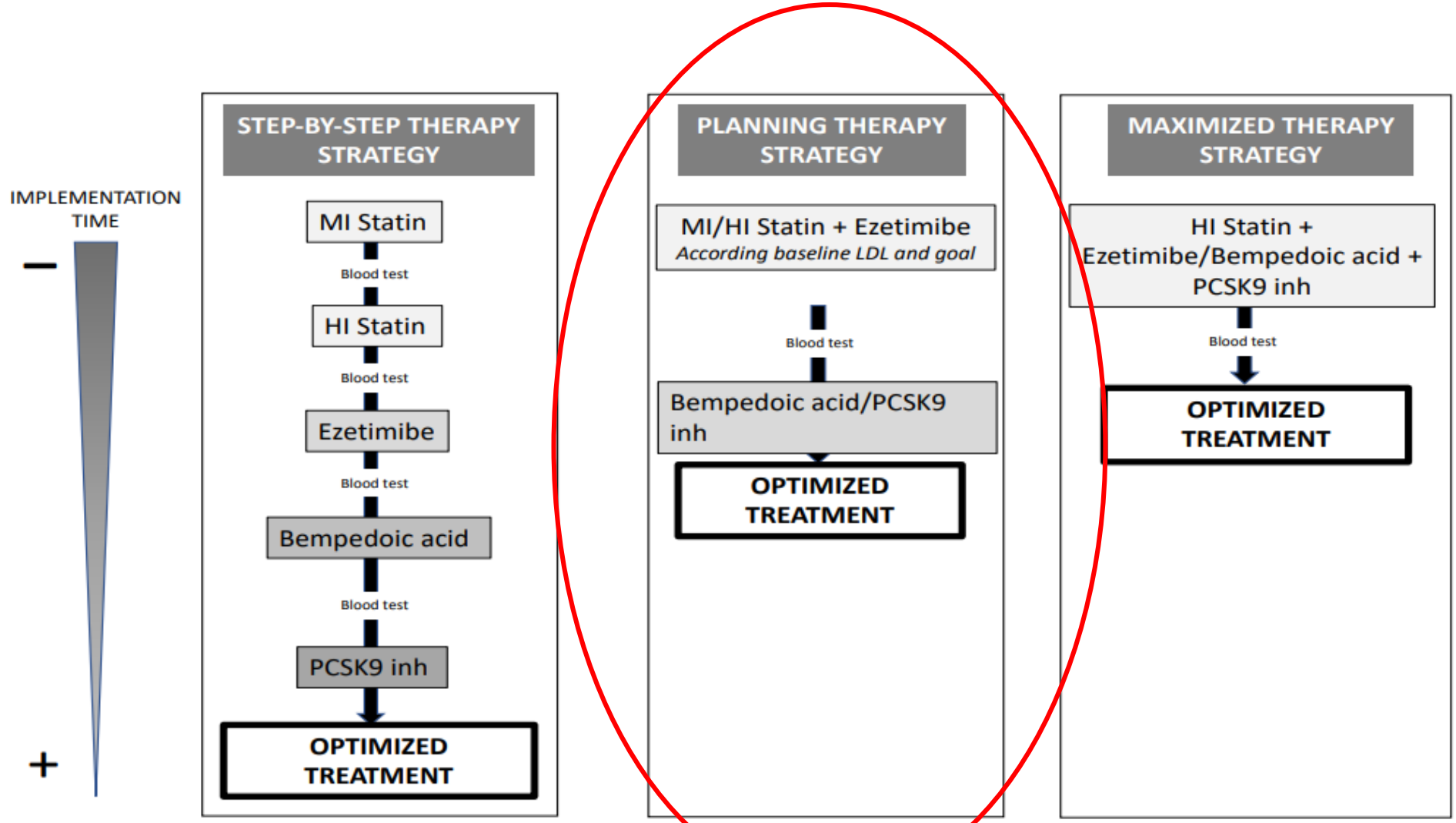

Eze 10 + Statine + Anti-PCSK9
Statine + Anti-PCSK9
Eze 10 + Anti-PCSK9
Eze +
Rosuvastatine 40
20
10
5
Atorvastatine 80
40
20
10
Simvastatine 40
20
10
Pravastatine 40
20
10
Anti-PCSK9
Ezetimibe 10
Rosuvastatine 40
20
10
5
Atorvastatine 80
40
20
10
Simvastatine 40
20
10
Pravastatine 40
20
10
0%
10%
20%
30%
40%
50%
60%
70%
80%

Recommendations for pharmacological low-density lipoprotein cholesterol lowering up to 70 years of age (recommendations for persons aged >70 years, see respective recommendations tables) (2)

Recommendations	Class	Level
In patients with established ASCVD, lipid-lowering treatment with an ultimate LDL-C goal of ≥50% reduction vs baseline and an LDL-C of <1.4 mmol/L (<55 mg/dL) is recommended.	I	A
If the goals are not achieved with the maximum tolerated dose of a statin, combination with ezetimibe is recommended.	I	B
For primary prevention patients at very high risk, but without FH, if the LDL-C goal is not achieved on a maximum tolerated dose of a statin and ezetimibe, combination therapy including a PCSK9 inhibitor may be considered.	IIb	C

2021 ESC Guidelines on cardiovascular disease prevention in clinical practice
(European Heart Journal 2021 – doi:10.1093/eurheartj/ehab484)

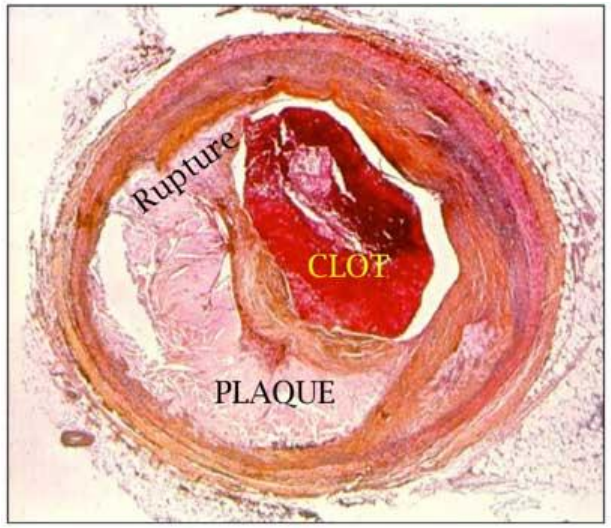
3 verschillende strategieën van lipidenverlagende therapie

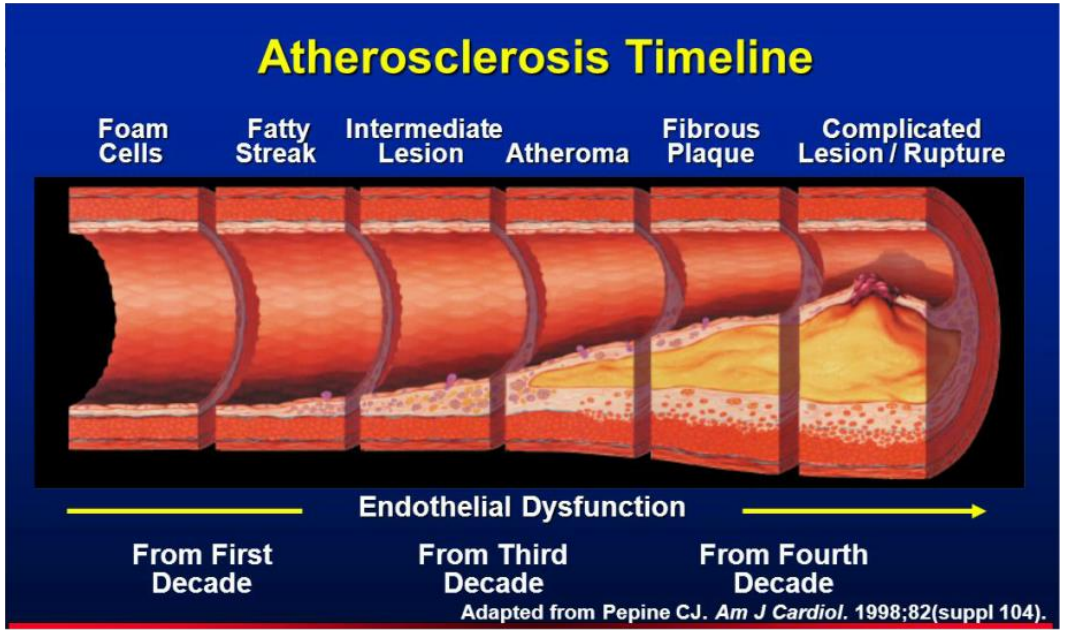


MI, moderate intensity; HI, high intensity; PCSK9 inh, proprotein convertase subtilisin/kexin type 9 inhibitor; LDL, low-density lipoprotein

Masana L. et al; EAJ 2022;1:25-29

Take home image





Ziekenhuis aan de Stroom
[ZAS] is het netwerk van
ZNA en GZA Ziekenhuizen

GZA
Ziekenhuizen
GasthuisZusters Antwerpen
Sint-Augustinus - Sint-Vincentius - Sint-Jozef

zna

ZIEKENHUIS aan de STROOM