PCSK9i: Expanding benefits across the spectrum of cardiovascular disease

Fabrice Martens, MD, PhD
Amsterdam UMC
Amsterdam, The Netherlands

The LDL-c challenge in high cardiovascular risk - Integrating innovative therapies in clinical management

PHYSICIANS' ACADEMY FOR CARDIOVASCULAR EDUCATION
PACE-CME

Disclosures

Prof. dr. FMAC Martens MD, PhD, FESC
Cardiologist and professor of Preventive Cardiology

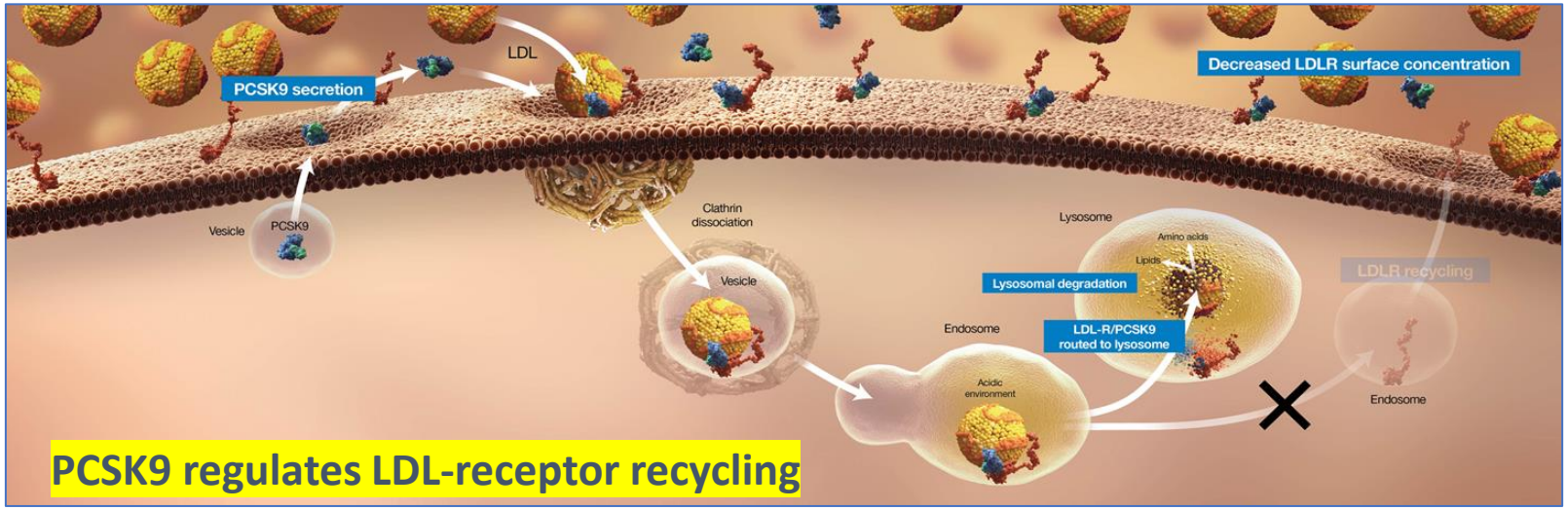
- **Presentation fees CVRM (lipids, antitrombotics and antidiabetics) without conflicts of interest because via intermediates or multisponsors**
  (*Amarin, Amgen, Astra Zeneca, Bayer, BMS, Boehringer, Daiichi, Sankyo, GSK, MSD, NewAmsterdam, Novartis, NovoNordisk, Pfizer, Sanofi, Viatris*)

- **Past President WCN and as such research grants via DCVA (Dutch CardioVascular Alliance (eg Hartstichting, ZonMW, Health Holland)) and previous announced farmaceutical companies**

- **On behalf of the NVVC (Dutch Society of Cardiology):**
  Member Steering committee Dutch Guideline CVRM and Vascular Surgery
  Member workinggroup implementation ESC-guidelines
  Chair workinggroup medication
  Advisor CVRM and medication

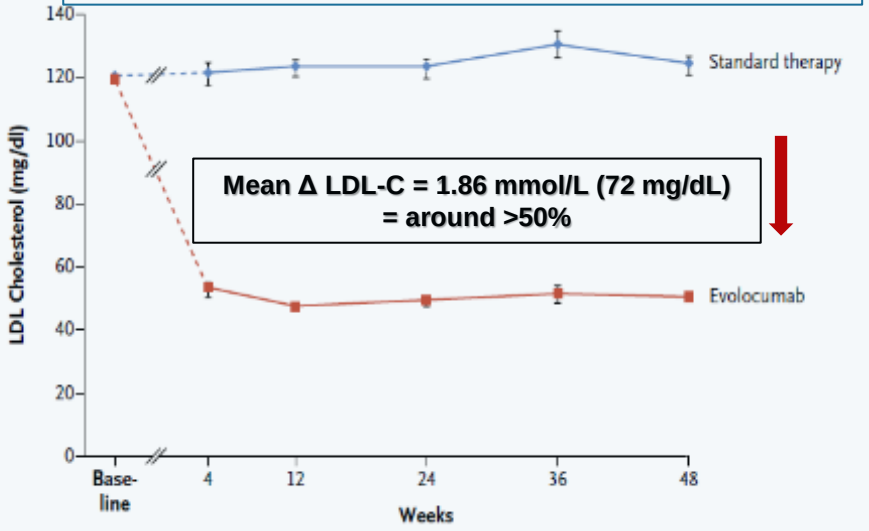
Proproteine convertase subtilisine/kexine type 9 monoclonal antibodies

eg evolocumab and alirocumab



PCSK9i and LDL-reduction

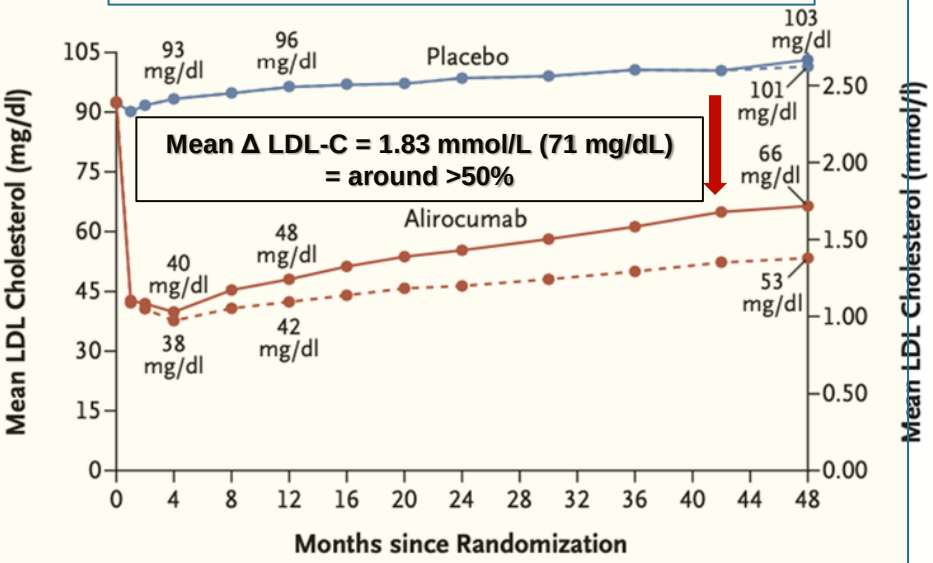
OSLER-1 (fase II) and OSLER-2 (fase III)
Evolocumab 420 mg every 4 weeks



Evolocumab:
140 mg every 2 weeks
or 420 mg monthly

Sabatine, NEJM 2015

ODYSSEY LONG TERM (fase III)
Alirocumab 150 mg every 2 weeks

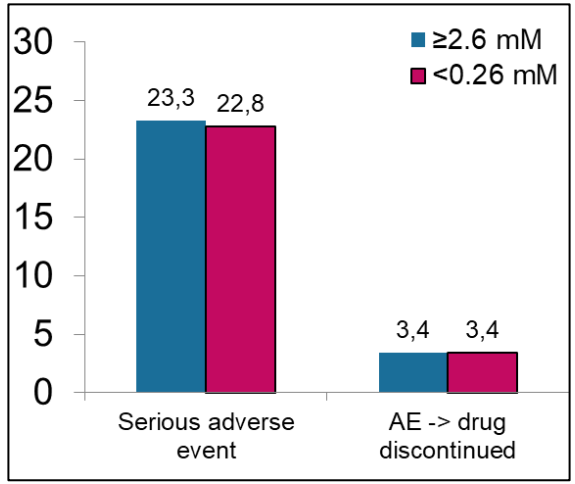


Alirocumab:
75 mg every 2 weeks
or 150 mg every 2 weeks
or 300 mg monthly

Robinson, NEJM 2015

PCSK9i and very low LDL-c-levels without more adverse events

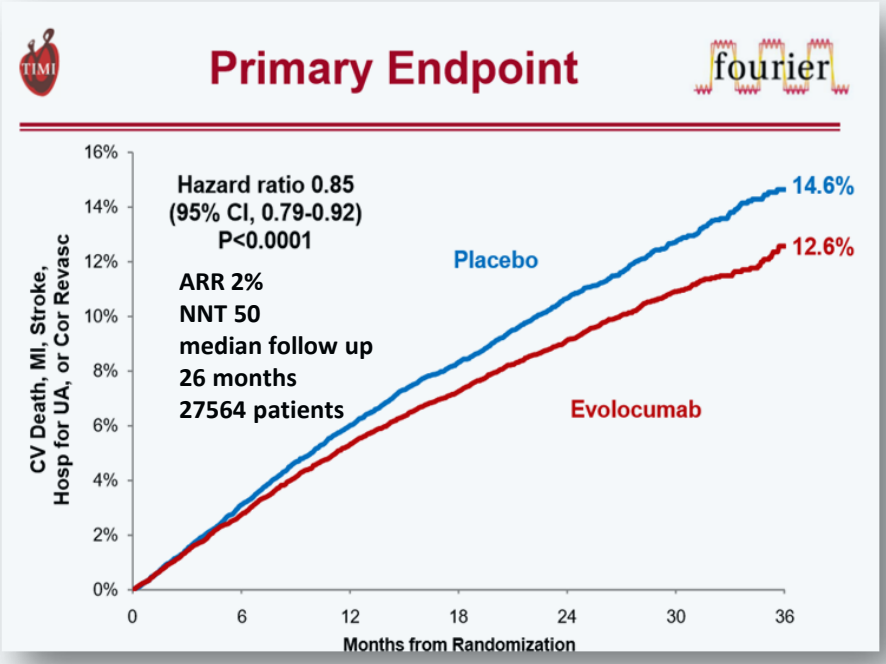
	Evolocumab subjects stratified by minimum achieved LDL-C				All EvoMab (n=2976)	SOC alone (n=1489)
	<0.65 mmol/L (n=773)	0.65 to <1.0 mmol/L (n=759)	<1.0 mmol/L (n=1532)	≥1.0 mmol/L (n=1426)		
Adverse events (%)						
Any	70.0	68.1	69.1	70.1	69.2	64.8
Serious	7.6	6.9	7.2	7.8	7.5	7.5
Muscle-related	4.9	7.1	6.0	6.9	6.4	6.0
Neurocognitive	0.5	1.2	0.8	1.0	0.9	0.3
Laboratory results (%)						
ALT/AST >3 × ULN	0.9	0.8	0.8	1.3	1.0	1.2
CK >5 × ULN	0.4	0.9	0.7	0.5	0.6	1.1



OSLER-studies, Sabatine, NEJM 2015

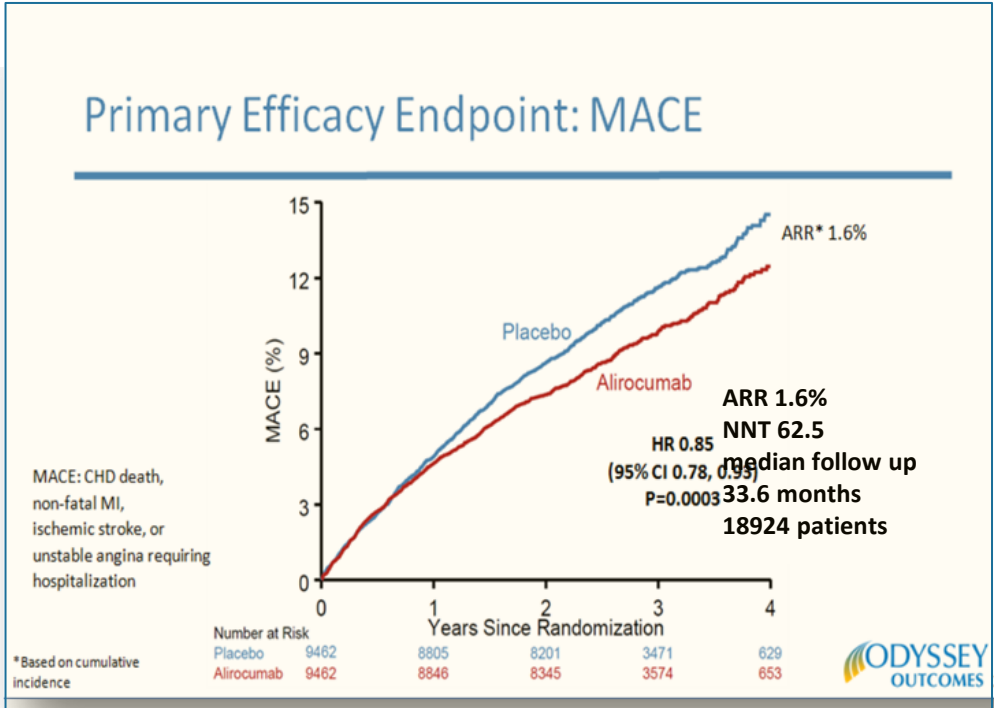
FOURIER/EBBINGHAUS, Giugliano, Lancet 2017

PCSK9i leading to significant CV-risk reduction



Evolocumab:
140 mg every 2 weeks
or 420 mg monthly

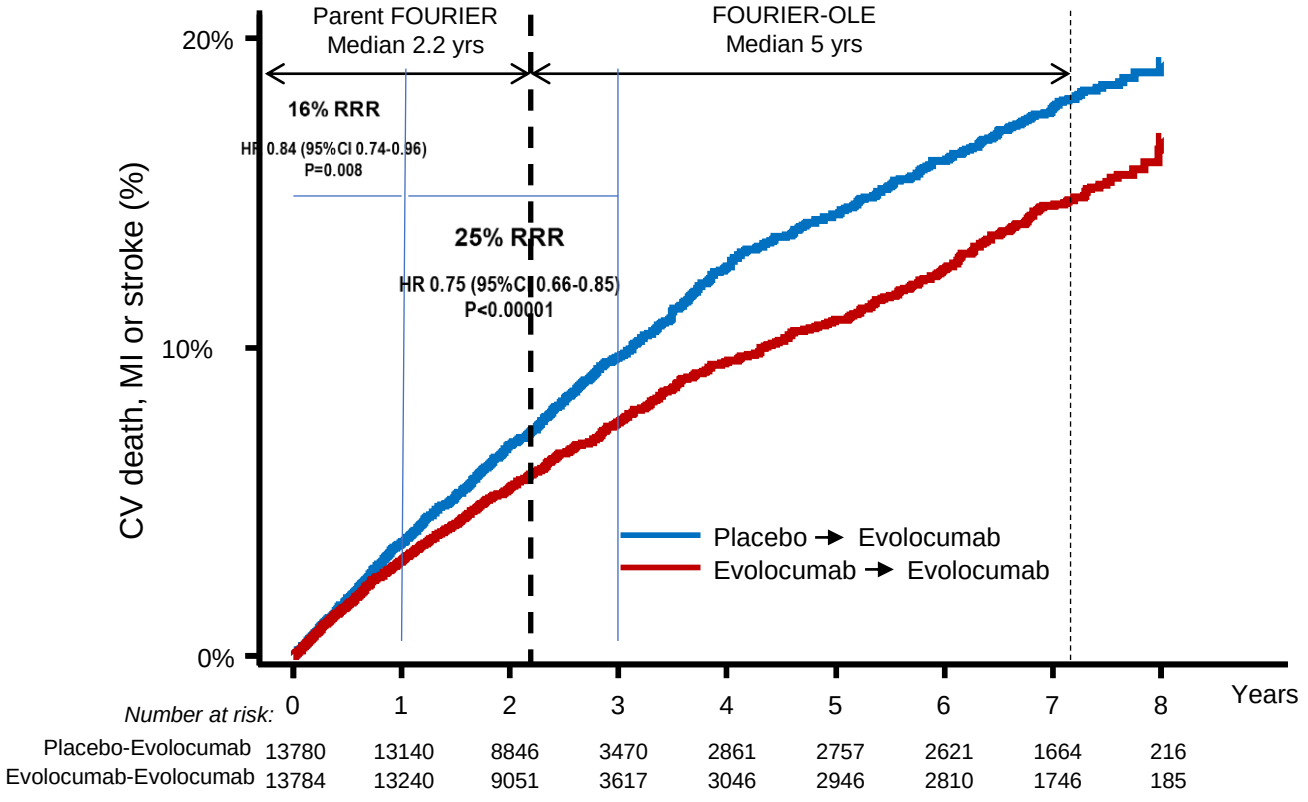
FOURIER, Sabatine, NEJM 2017



Alirocumab:
75 mg every 2 weeks
or 150 mg every 2 weeks
or 300 mg monthly

ODYSSEY OUTCOMES, Schwartz, NEJM 2018

“The lower LDL for longer (the earlier you start), the better it is” for CV-risk reduction



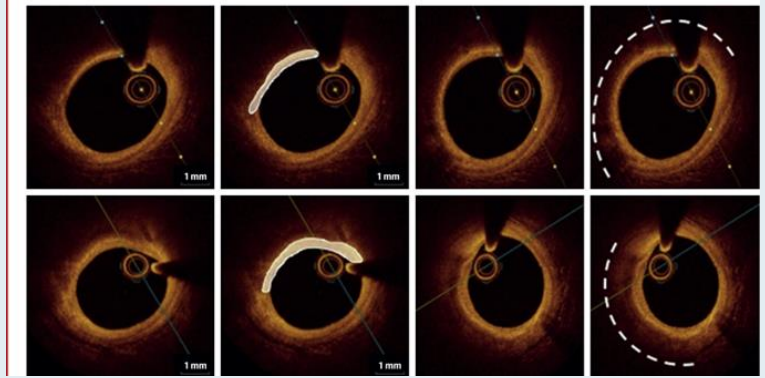
FOURIER-OLE, O’Donoghue, Circulation 2022

“The earlier you start to lower LDL aggressively, the better it is” for atheroma-volume regression

HUYGENS

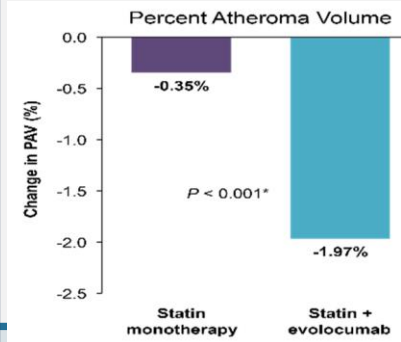
150 patients
420 mg evolocumab monthly
<24h after PCI for ACS
on top of HIST
52w follow up

CENTRAL ILLUSTRATION: Effects of Intensive Lipid Lowering on Plaque



HUYGENS, Nicholls, JACC 2022

GLAGOV

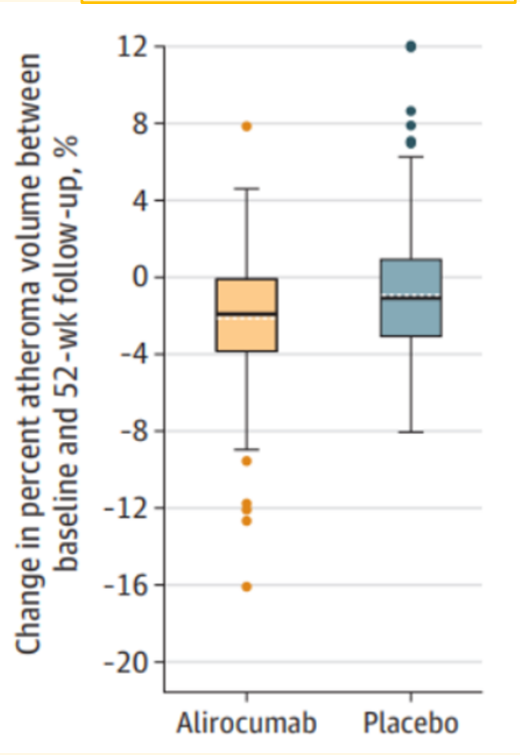


968 patients
with angiographic coronary disease
420 mg evolocumab monthly
on top of HIST
76w follow up

GLAGOV, Nicholls, JAMA 2016

PACMAN

300 patients
150 mg alirocumab every 2 weeks
<24h after PCI for ACS
on top of rosuvastatin 1dd 20 mg
52w follow up



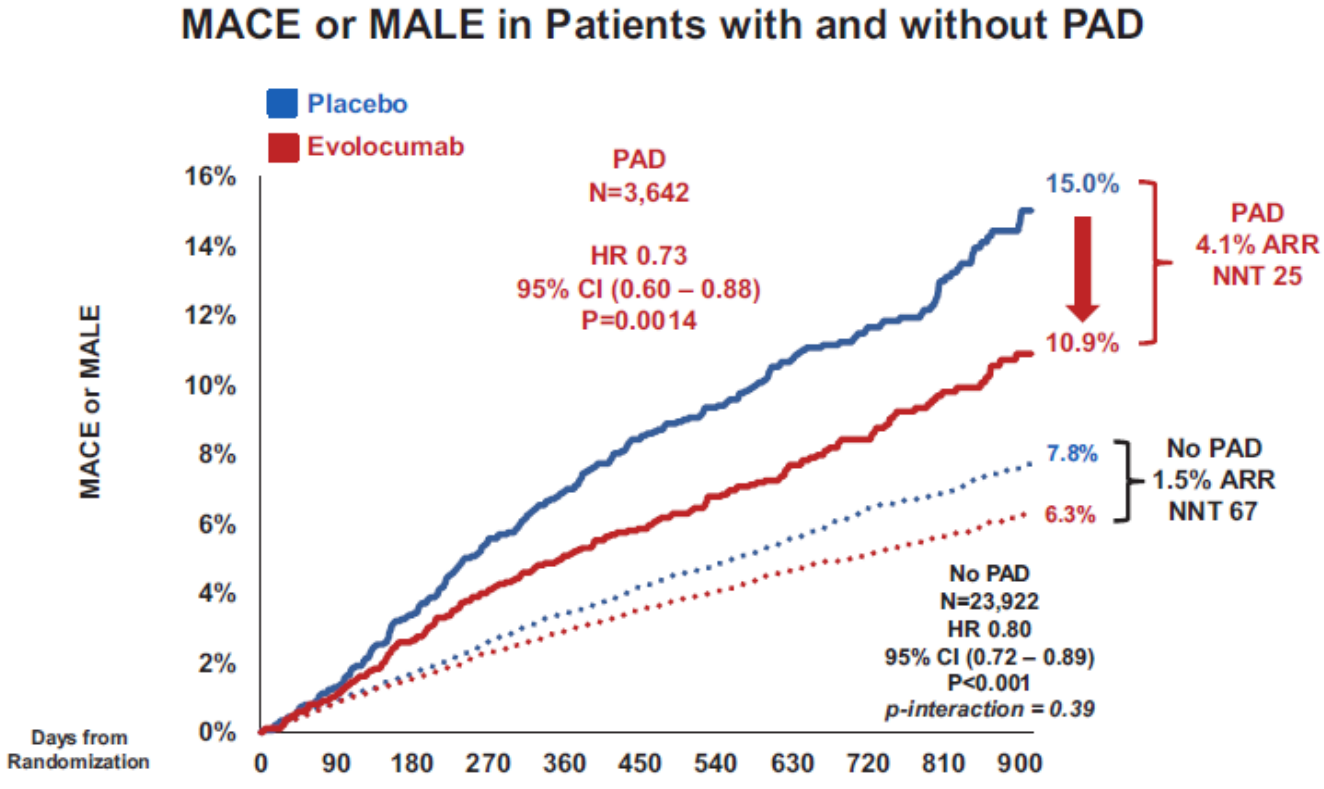
PACMAN, Raber, JAMA 2022

”The higher the CV-risk, the more benefit”

	N	Cumulative incidence of CV death, MI, or stroke	RRR	ARR	NNT
Overall patients with prior MI	N= 22,351	--	18%	--	--
Time from Qualifying MI	**< 2 y ago** N=8,402	10.8%	24%	2.9%	**35**
	≥ 2 y ago N=13,918	9.3%	13%	1.0%	101
Number of Prior MIs	**≥ 2** N=5,285	15.0%	21%	2.6%	**38**
	1 N=17,047	8.2%	16%	1.7%	60
Residual Multivessel CAD	**MVD** N=5,618	12.6%	30%	3.4%	**29**
	No MVD N=16,715	8.9%	11%	1.3%	78

FOURIER-analysis, Sabatine, Circulation 2018

”The higher the CV-risk, the more benefit”



Number at risk

Placebo PAD	1784	1753	1711	1665	1630	1601	1555	1305	994	712	438
Evolocumab PAD	1858	1832	1798	1764	1741	1721	1671	1412	1078	765	471
Placebo no PAD	11996	11859	11727	11600	11486	11367	10758	9089	7160	5424	3630
Evolocumab no PAD	11926	11802	11698	11582	11488	11394	10825	9133	7254	5471	3647

FOURIER-analysis, Bonaca, Circulation 2017

PCSK9i versus other LDL-lowering therapies efficacy and costs

HRs of non LDL-C lowering therapies

	3-Component MACE	Nonfatal MI
Ezetimibe	0.90	0.87
Evolocumab	0.80	0.73†
Alirocumab	0.86*	0.86
Bempedoic Acid	0.85	0.73

*Trial used all-cause mortality rather than CV death †Fatal and nonfatal MI

in NL

Statins around $50/year

Ezetimibe around $50/year

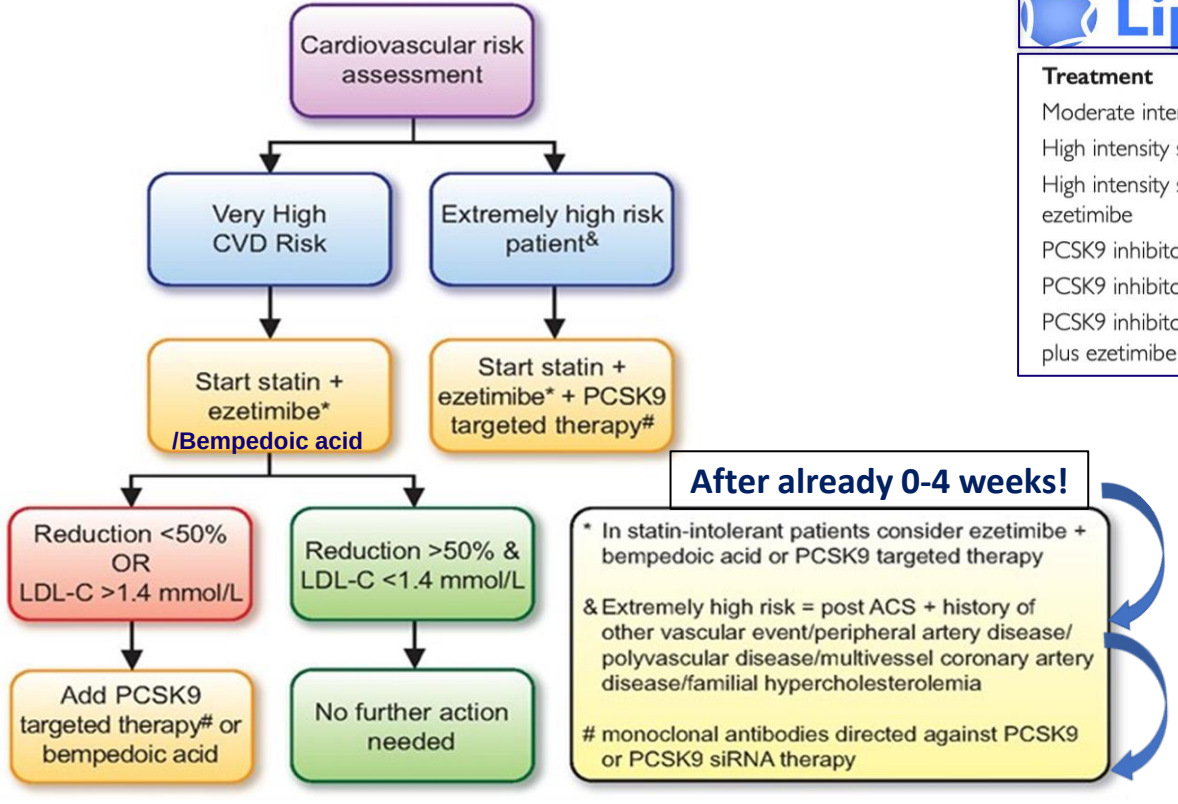
PCSK9i around $5000/year

Bempedoic acid around $800/year

Dutch Farmacotherapeutisch Kompas 2023

“Fast first time right”

Optimal guideline-directed medical therapy (GDMT) for LDL-lowering



Lipid Tools www.lipidtools.com

Treatment	Average LDL-C reduction
Moderate intensity statin	≈ 30%
High intensity statin	≈ 50%
High intensity statin plus ezetimibe	≈ 65%
PCSK9 inhibitor	≈ 60%
PCSK9 inhibitor plus high intensity statin	≈ 75%
PCSK9 inhibitor plus high intensity statin plus ezetimibe	≈ 85%

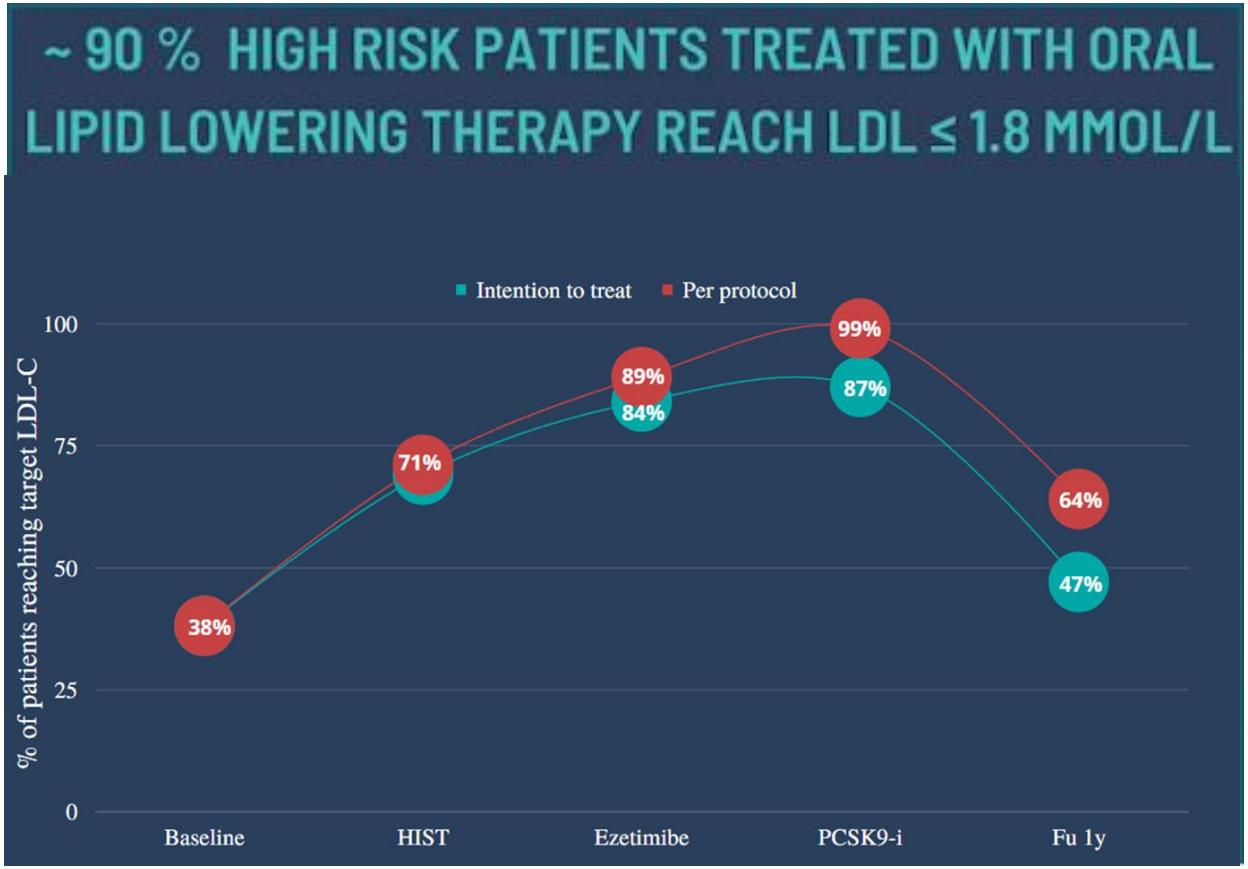
PCSK9i reimbursement in NL

if LDL > 1,8mmol/l despite optimal oral LDL-lowering (with ezetimibe as obligation) and:

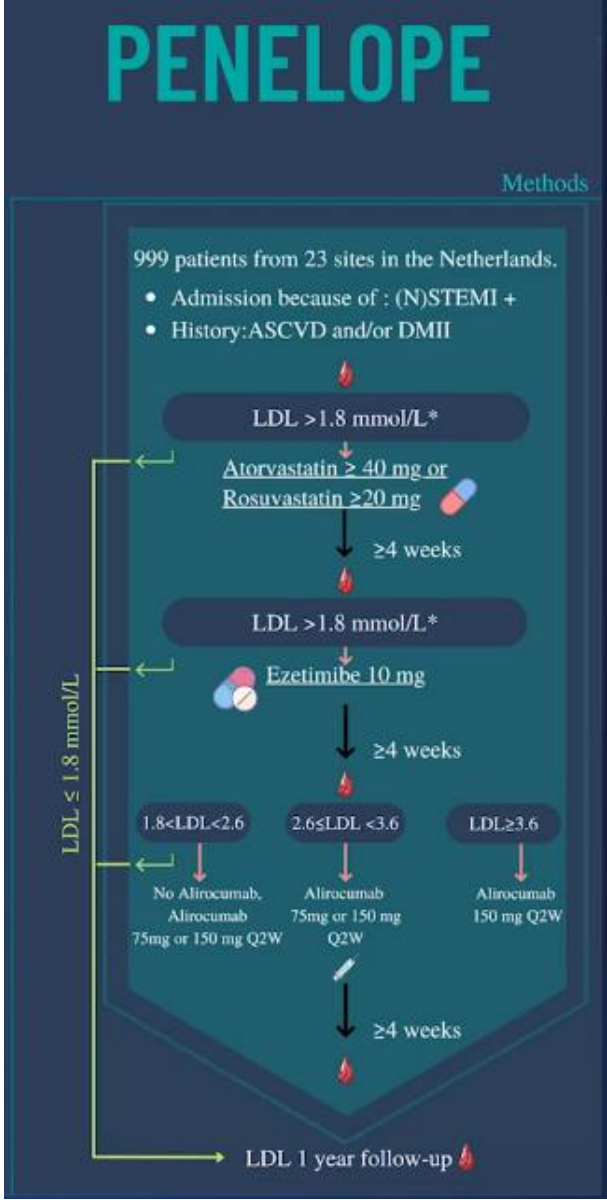
1) **FH**
2) **Re-CV-event**
3) **DM2 + CV-event**
4) **CV-event and statin-intolerant**

oa Ray, Stroes, Kastelein, EHJ 2022

Guideline-directed medical therapy (GDMT) although need for continuation…

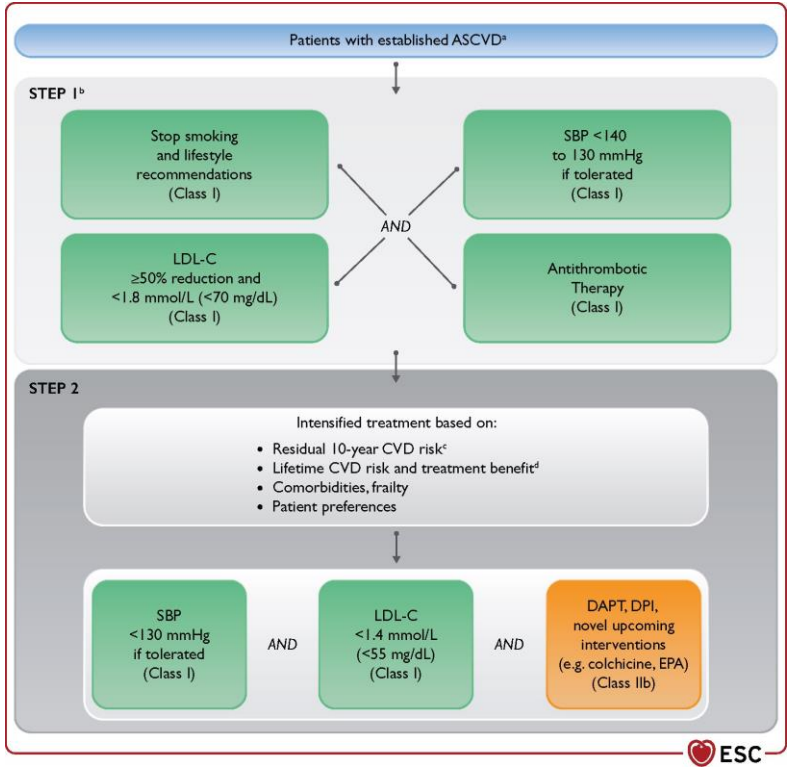


PENELOPE, submitted to Neth Heart Journal 2023



Conclusions and Take home messages I of III

- **Start with a good CV-risk-stratification with eg U-Prevent calculator based on CV-lifetime-risk, treatment benefits and patient preferences and estimate LDL-levels by certain LDL-lowering therapy with eg Lipid Tools**



U-Prevent

Lipid Tools www.lipidtools.com

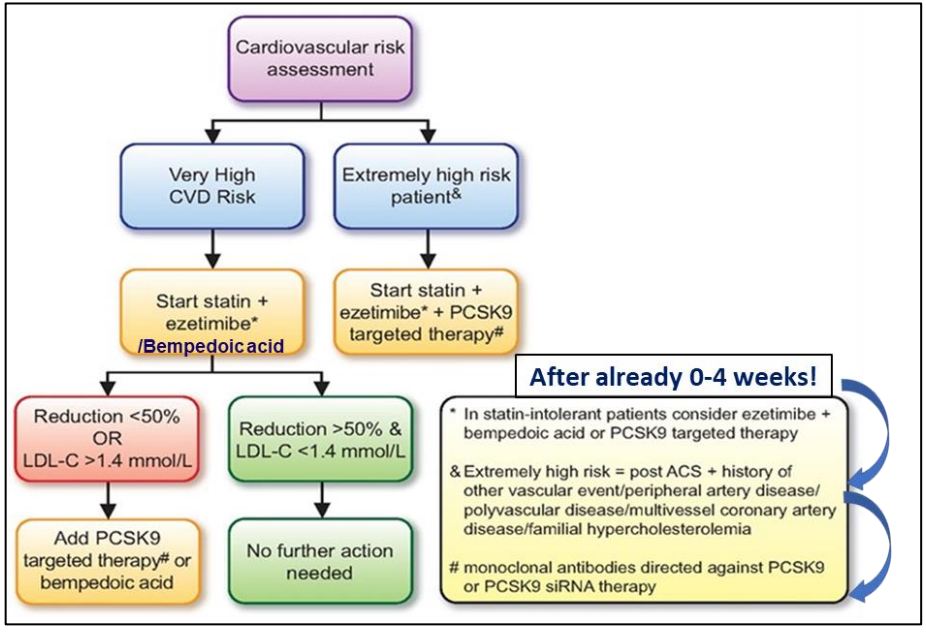
Conclusions and Take home messages II of III

- **Start *optimal* LDL-lowering therapy immediately after a CV-event keeping in mind that**

  “The lower LDL for longer (the earlier you start), the better it is”

  and

  “The higher the CV-risk, the more benefit”



GOLDEN
Guided Optimisation of Long-term Disease rEduction in secoNdary prevention of CVD

WCN

“Fast first time right”
(= quote for GOLDEN study)
Optimal guideline-directed medical therapy (GDMT) after ACS or revascularisation

Conclusions and Take home messages III of III

- Expanding benefits across the spectrum of cardiovascular disease
  also for the use of PCSK9i if necessary

Since 2016

PCSK9i reimbursement in NL
if LDL > 1,8mmol/l despite optimal oral LDL-lowering (with ezetimibe as obligation) and:

1) **FH**
2) **Re-CV-event**
3) **DM2 + CV-event**
4) **CV-event and statin-intolerant**

In the near future

PCSK9-antibodies reimbursement in NL
if LDL > 1,8mmol/l despite optimal oral LDL-lowering (without ezetimibe as obligation) and:

1) **Very high CV-risk according to the guideline**
2) **FH**

Glimpse into the future

- **Do not forget possible PCSK9i in the future like siRNA inclisiran or maybe oral…**