



UMC Utrecht



ZonMw

Identifying the right patient to treat

Estimating absolute treatment effect for prevention of vascular
disease in individual patients

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Disclosures

- None
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 - George Institute Sydney, Australia



Topics – prevention of vascular disease

- **Part 1: current practice: 10-year risk prediction**
- Part 2: individual treatment effect estimation
- Part 3: example “Statins in the elderly”



ZonMw meeting “Diversity”



Diversity in clinical practice



Randomised trials: “average” patient

30%



R. van Petersen



Randomised trials: “average” patient

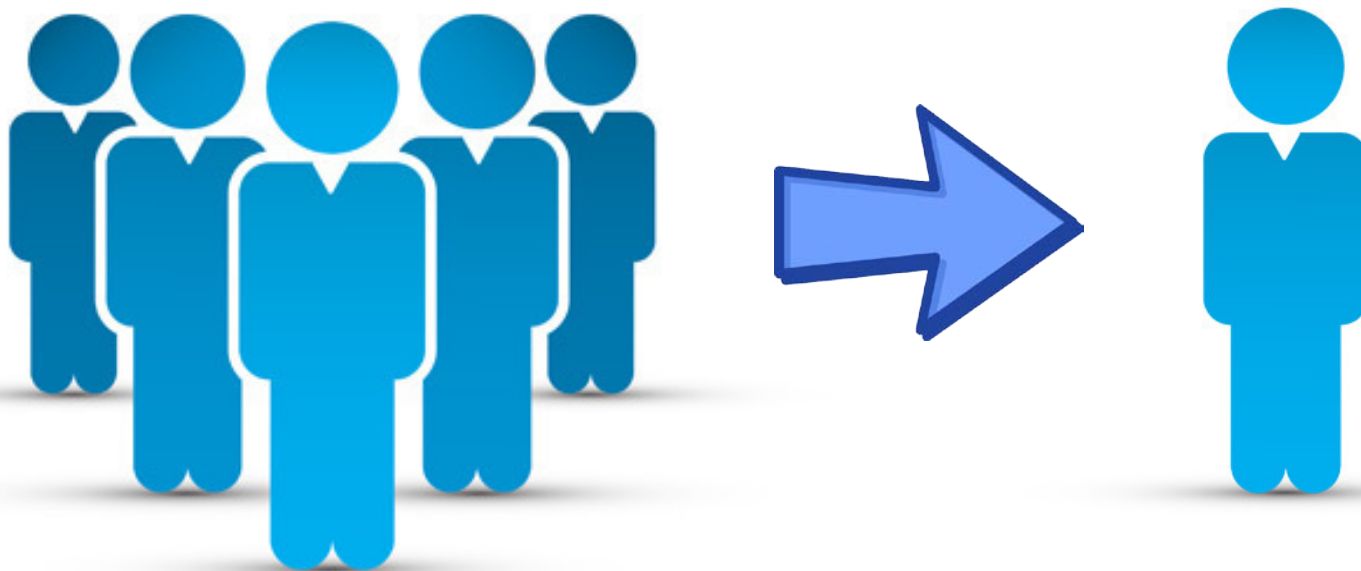
20 years



R. van Petersen



From RCT to individual



Individual 10-year CVD risk

SBD	Vrouwen					Leeftijd	Mannen								
	Niet-rookster		Rookster				Niet-roker		Roker						
180	35	38	41	43	44	70	>50	>50	>50	>50	>50	>50	>50	>50	
160	28	31	33	35	36		45	48	>50	>50	>50	>50	>50	>50	>50
140	22	24	26	28	29		37	40	42	44	46	49	>50	>50	>50
120	18	19	21	22	23		30	32	34	36	38	40	43	45	48
180	14	17	20	24	30	65	25	30	36	44	>50	43	>50	>50	
160	10	12	14	17	21		18	21	26	32	40	33	39	47	>50
140	7	8	10	12	15		12	15	18	23	29	23	28	34	42
120	5	6	7	9	11		9	11	13	16	21	17	20	24	30
180	10	12	15	18	23	60	22	26	32	40	50	40	48	>50	
160	7	8	11	13	16		15	19	23	29	36	29	35	42	>50
140	5	6	7	9	12		11	13	16	20	26	20	25	30	38
120	4	4	5	7	8		8	9	12	15	19	14	18	22	27
180	5	6	8	10	12	55	13	16	20	26	32	25	31	38	
160	4	4	5	7	9		10	12	15	23	25	18	22	27	34
140	3	3	4	5	6		7	8	10	13	17	13	16	19	24
120	2	2	3	3	4		5	6	7	9	12	9	11	14	17
180	2	3	4	5	6	50	8	10	12	15	20	15	18	23	
160	2	3	3	3	4		6	7	9	11	14	11	13	16	
140	1	1	2	2	3		4	5	6	8	10	7	9	12	
120	1	1	1	2	2		3	3	4	6	7	5	7	8	
180	1	1	1	1	1	40	3	3	4	6	7	5	6	8	
160	<1	<1	1	1	1		2	2	3	4	5	4	4	6	
140	<1	<1	<1	1	1		1	1	2	2	3	3	3	4	
120	<1	<1	<1	<1	<1		1	1	2	2	3	2	2	3	
	4	5	6	7	8		4	5	6	7	8	4	5	6	
	Ratio totaal cholesterol/HDL						Ratio totaal cholesterol/HDL								

Mr. C. 55 years
 Smoking: no
 Diabetes: no
 CVD-history: negative
 RR 160/90 mmHg
 TC 6 mmol/L
 HDLc 1.00 mmol/L



Individual 10-year CVD risk

SBD	Vrouwen					Leeftijd	Mannen								
	Niet-rookster		Rookster				Niet-roker		Roker						
180	35	38	41	43	44	70	>50	>50	>50	>50	>50	>50	>50	>50	
160	28	31	33	35	36		45	48	>50	>50	>50	>50	>50	>50	>50
140	22	24	26	28	29		37	40	42	44	46	49	>50	>50	>50
120	18	19	21	22	23		30	32	34	36	38	40	43	45	48
180	14	17	20	24	30	65	25	30	36	44	>50	43	>50	>50	
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140	7	8	10	12	15		12	15	18	23	29	23	28	34	42
120	5	6	7	9	11		9	11	13	16	21	17	20	24	30
180	10	12	15	18	23	60	22	26	32	40	50	40	48	>50	
160	7	8	11	13	16		15	19	23	29	36	29	35	42	>50
140	5	6	7	9	12		11	13	16	20	26	20	25	30	38
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160	4	4	5	7	9		10	12	15	23	25	18	22	27	34
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160	2	3	3	3	4		6	7	9	11	14	11	13	16	
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120	1	1	1	2	2		3	3	4	6	7	5	7	8	
180	1	1	1	1	1	40	3	3	4	6	7	5	6	8	
160	<1	<1	1	1	1		2	2	3	4	5	4	4	6	
140	<1	<1	<1	1	1		1	1	2	2	3	3	3	4	
120	<1	<1	<1	<1	<1		1	1	2	2	3	2	2	3	
	4	5	6	7	8		4	5	6	7	8	4	5	6	

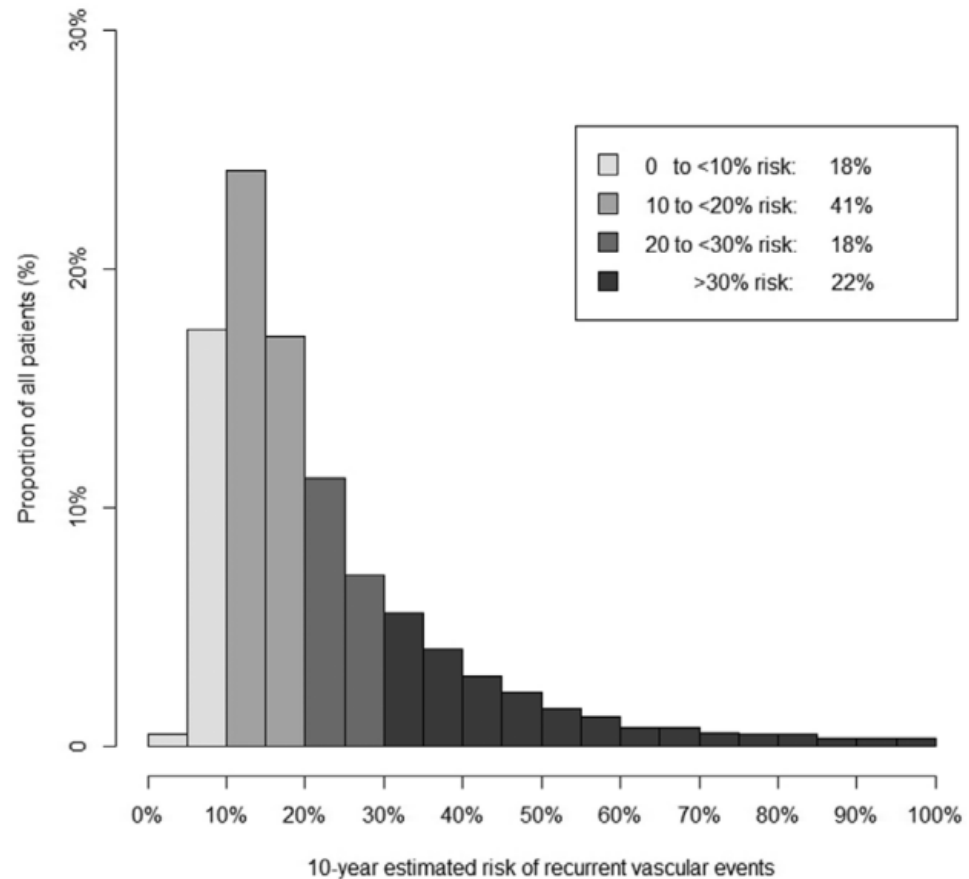
Ratio totaal cholesterol/HDL

Ratio totaal cholesterol/HDL

Mrs. A. 65 years
 Smoking: yes
 Diabetes: no
 CVD-history: negative
 RR 140/90 mmHg
 TC 4 mmol/L
 HDLc 1.00 mmol/L



SMART risk score



Heart. 2013 Jun;99(12):866-72
Circulation. 2016 Nov 8;134(19):1419-1429



Topics – prevention of vascular disease

- Part 1: current practice: 10-year risk prediction
- **Part 2: individual treatment effect estimation**
- Part 3: example “Statins in the elderly”



Individual treatment effect

$$\begin{aligned} &\text{Individual Absolute Risk Reduction} \\ &= \\ &\text{Individual Absolute Risk} \\ &\times \\ &\text{Relative Risk Reduction} \end{aligned}$$



Individual treatment effect

$$\begin{aligned} &\text{Individual Number Needed to Treat (iNNT)} \\ &= \\ &1 / \text{Individual Absolute Risk Reduction (iARR)} \end{aligned}$$



Case discussion

10-yr CVD risk = 13%
 LDL-cholesterol = 4.2 mmol/L
 Relative risk reduction = 31%

10-yr iARR = $13\% * 0.31 = 4.0\%$
 10-yr iNNT = $1 / 0.04 = 25$

10-yr CVD risk = 14%
 LDL-cholesterol = 2.2 mmol/L
 Relative risk reduction = 17%

10-yr iARR = $14\% * 0.17 = 2.4\%$
 10-yr iNNT = $1 / 0.024 = 42$



Articles

The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials

Cholesterol Treatment Trialists' (CTT) Collaborators*

Summary
 Background Statins reduce LDL cholesterol and prevent vascular events, but their net effects in people at low risk of vascular events remain uncertain.

Methods This meta-analysis included individual participant data from 22 trials of statin versus control (n=134 537; mean LDL cholesterol difference 1.08 mmol/L; median follow-up 4.8 years) and five trials of more versus less statin (n=39 612; difference 0.51 mmol/L; 5.1 years). Major vascular events were major coronary events (ie, non-fatal myocardial infarction or coronary death), strokes, or coronary revascularisations. Participants were separated into five categories of baseline 5-year major vascular event risk on control therapy (no statin or low-intensity statin) (<5%, ≥5% to <10%, ≥10% to <20%, ≥20% to <30%, ≥30%); in each, the rate ratio (RR) per 1.0 mmol/L LDL cholesterol reduction was estimated.

Findings Reduction of LDL cholesterol with a statin reduced the risk of major vascular events (RR 0.79, 95% CI 0.77-0.81 per 1.0 mmol/L reduction), largely irrespective of age, sex, baseline LDL cholesterol or previous vascular disease, and of vascular and all-cause mortality. The proportional reduction in major vascular events was at least as big in the two lowest risk categories as in the higher risk categories (RR per 1.0 mmol/L reduction from lowest to highest risk: 0.62 [99% CI 0.47-0.81], 0.69 [99% CI 0.60-0.79], 0.79 [99% CI 0.74-0.85], 0.81 [99% CI 0.77-0.86], and 0.79 [99% CI 0.74-0.84]; trend p=0.04), which reflected significant reductions in these two lowest risk categories in major coronary events (RR 0.57, 99% CI 0.36-0.89, p=0.0012, and 0.61, 99% CI 0.50-0.74, p<0.0001) and in coronary revascularisations (RR 0.52, 99% CI 0.35-0.75, and 0.63, 99% CI 0.51-0.79; both

Lancet 2012; 380: 583-90
 Published Online
 May 17, 2012
[http://dx.doi.org/10.1016/S0140-6736\(12\)60567-5](http://dx.doi.org/10.1016/S0140-6736(12)60567-5)
 See Comment page 541 and 545
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Overview ZonMw project

	Intermediate vascular risk (10-20%)	Type 2 diabetes	Clinically manifest vascular disease	Elderly patients
Lipid-lowering treatment	JUPITER	CARDS ALLHAT-LLT ASCOT-LLA	TNT IDEAL	PROSPER ASCOT-LLA SMART cohort study
	BMJ 2011. 3;343:d5888	Circ Cardiovasc Qual Outc 2016. 9(3):213-21.	Circulation 2013. 25;127:2485-93	Clin Res Cardiol 2017. Jan;106(1):58-68
			J Am Heart Assoc 2017. Feb 18;6(2)	
Blood pressure- lowering treatment	SAVE TRACE SOLVD studies	ADVANCE	EUROPA HOPE	
	In revision (BMJ)	Hypertension 2015. 65(1):115-21	Int J Cardiol 2015. 1;182:194-9	
Antiplatelet / antithrombotic treatment	WHS		RELY	
	Eur Heart J. 2011. 32:2962-9		Manuscript in preparation	



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Topics – prevention of vascular disease

- Part 1: current practice: 10-year risk prediction
- Part 2: individual treatment effect estimation
- **Part 3: example “Statins in the elderly”**





ORIGINAL PAPER

Personalized absolute benefit of statin treatment for primary or secondary prevention of vascular disease in individual elderly patients

Manon C. Stam-Slob¹ · Frank L. J. Visseren^{1,8} · J. Wouter Jukema² · Yolanda van der Graaf³ · Neil R. Poulter⁴ · Ajay Gupta⁴ · Naveed Sattar⁵ · Peter W. Macfarlane⁵ · Patricia M. Kearney⁶ · Anton J. M. de Craen⁷ · Stella Trompet^{2,7}

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Abstract

Objective To estimate the absolute treatment effect of statin therapy on major adverse cardiovascular events (MACE; myocardial infarction, stroke and vascular death) for the individual patient aged ≥ 70 years.

Methods Prediction models for MACE were derived in patients aged ≥ 70 years with ($n = 2550$) and without ($n = 3253$) vascular disease from the “PROspective Study of Pravastatin in Elderly at Risk” (PROSPER) trial and validated in the “Secondary Manifestations of ARterial disease” (SMART) cohort study ($n = 1442$) and the “Anglo-Scandinavian Cardiac Outcomes Trial-Lipid Lowering Arm” (ASCOT-LLA) trial ($n = 1893$), respec-

MACE in 5 and 10 years were estimated by subtracting on-treatment from off-treatment risk.

Results Individual ARR were higher in elderly patients with vascular disease [5-year ARRs: median 5.1 %, interquartile range (IQR) 4.0–6.2 %, 10-year ARRs: median 7.8 %, IQR 6.8–8.6 %] than in patients without vascular disease (5-year ARRs: median 1.7 %, IQR 1.3–2.1 %, 10-year ARRs: 2.9 %, IQR 2.3–3.6 %). Ninety-eight percent of patients with vascular disease had a 5-year ARR ≥ 2.0 %, compared to 31 % of patients without vascular disease.

Conclusions With a multivariable prediction model the absolute treatment effect of a statin on MACE for indi-



What is the absolute benefit of statin therapy in individuals ≥ 70 years of age?

	PROSPER (n=5804)	ASCOT-LLA (n=2415)	SMART (n=1603)
Age (years)	70-82	70-79	70-82
Origin	Scotland, Ireland, the Netherlands	United Kingdom, Scandinavia	the Netherlands
Intervention	Pravastatin 40 mg	Atorvastatin 10 mg	Observational
Control	Placebo	Placebo	Observational
Mean follow-up (years)	3.2	3.3	5.6
Statin treatment effect (HR [95%CI])	With CVD: 0.78 [0.66-0.93] Without CVD*: 0.87 [0.73-1.03]	Without CVD*: 0.87 [0.73-1.03]	NA



Model development and validation

- Two models:
 - Patients WITH vascular disease
 - Patients WITHOUT vascular disease
- Predictors:
 - Classical risk factors
 - Polyvascular disease
 - Number of medications
- Competing risk analysis



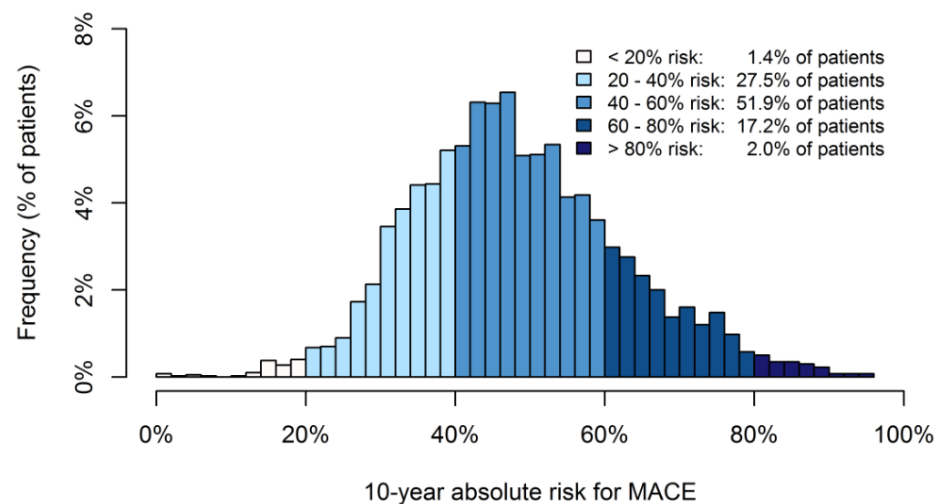
Risk estimation example

- Individual 10-year CVD risk = $(1 - 0.801^{\wedge \exp(\mathbf{A} - 1.968)}) * 100\%$
- $\mathbf{A} = 0.283$ (if male) + $0.037 * (\text{age in years}) + 0.290$ (if current smoker) + 0.210 (if diabetes) + $0.090 * (\text{number of medications}) + 0.0060 * (\text{systolic blood pressure in mmHg}) + 0.0070 * (\text{LDL-cholesterol in mmol/L}) - 0.359 * (\text{HDL-cholesterol in mmol/L}) - 0.061 * (\text{MDRD in ml/min/1.73}) + 0.00048 * (\text{MDRD in ml/min/1.73})^2$
- Relative risk reduction with a statin 15%

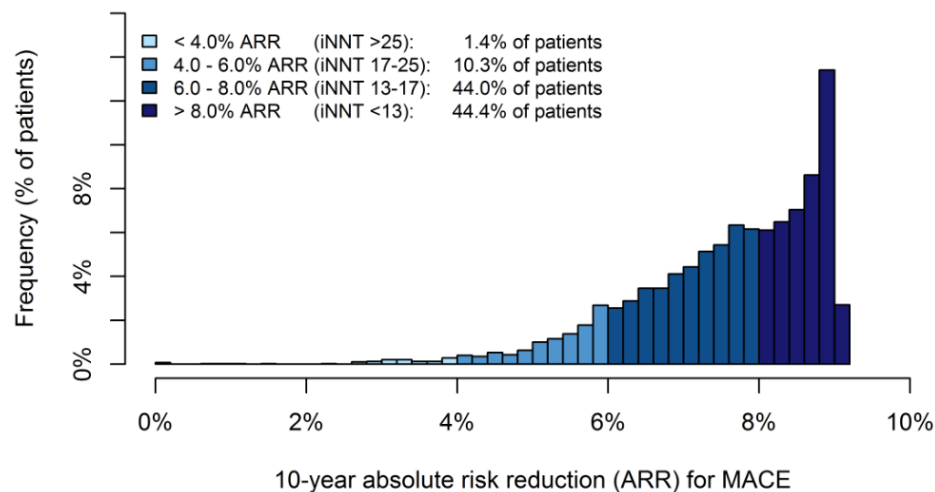


Elderly patients with vascular disease

Absolute risk for MACE in 10 years

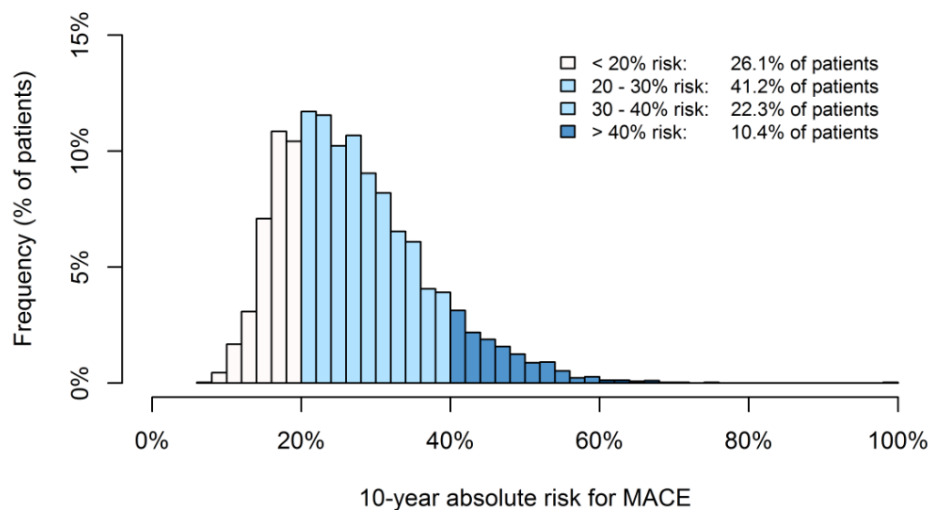


Absolute risk reduction for MACE in 10 years

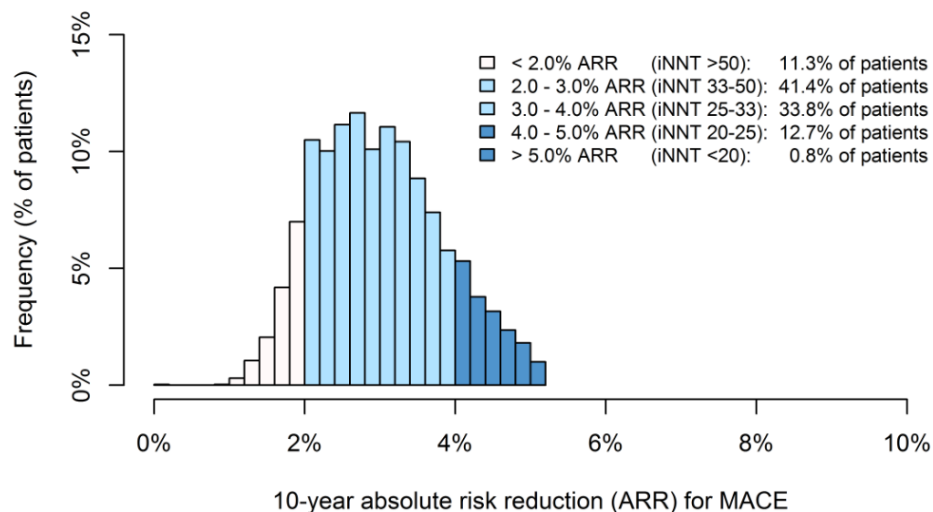


Elderly patients without vascular disease

Absolute risk for MACE in 10 years



Absolute risk reduction for MACE in 10 years



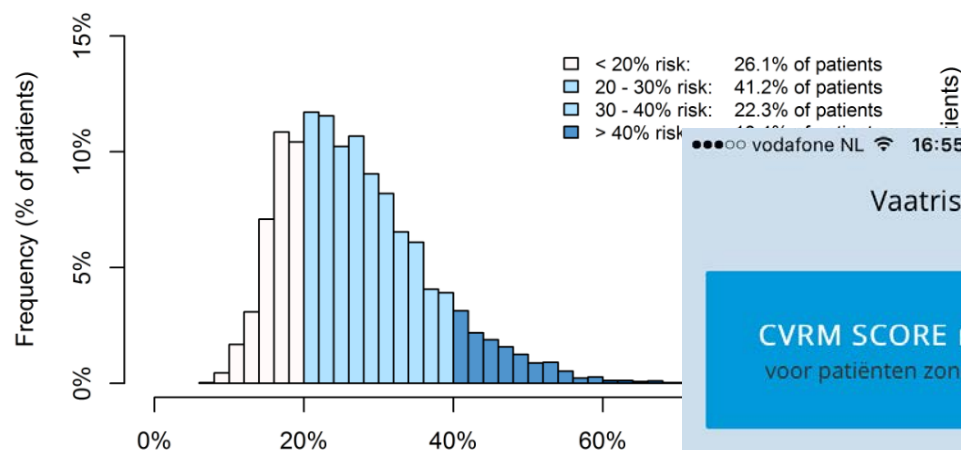
Conclusions

- Patients with vascular disease:
 - Statin treatment is beneficial for most
- Patients without vascular disease:
 - The prediction model identifies those who benefit (most) from statin therapy
 - $ARR \geq 3.0\%$ ($NNT \geq 33$): 47% of patients

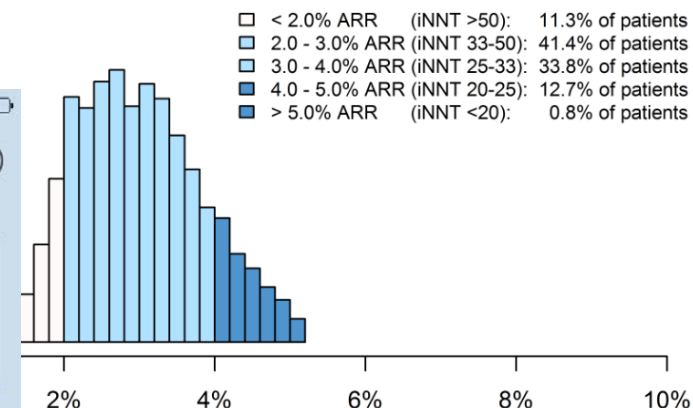


Implications

Absolute risk for MACE in 10 years



Absolute risk reduction for MACE in 10 years



10-year absolute risk for MACE

120	4	4	5	7
180	5	6	8	10
160	4	4	5	7
140	3	3	4	5
120	2	2	3	3
180	2	3	4	5
160	2	3	3	3
140	1	1	2	2
120	1	1	1	2
180	1	1	1	1
160	<1	<1	1	1
140	<1	<1	<1	1
120	<1	<1	<1	<1
	4	5	6	7
				Ratio to

Vaatrisico

CVRM SCORE risicotabel
voor patiënten zonder vaatziekte

ADVANCE risicoscore
voor patiënten met diabetes mellitus type 2 zonder vaatziekte

SMART risicoscore
voor patiënten met vaatziekte

Ouderen risicoscore

UMC Utrecht
Hart- en vaatcentrum

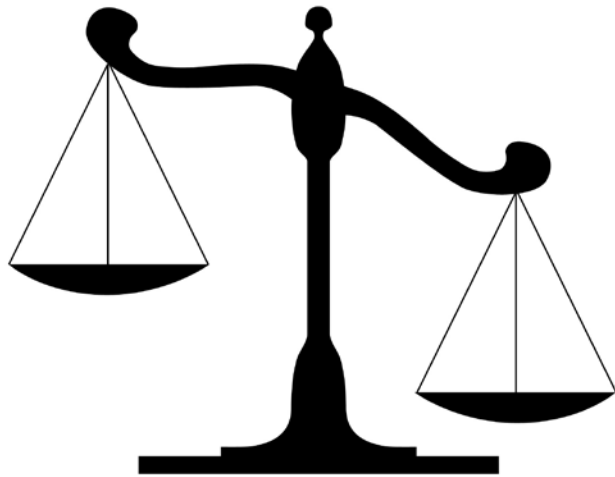
Ratio totaal cholesterol/HDL

10-year absolute risk reduction (ARR) for MACE

14	18	22	27	34
25	31	38	47	>50
18	22	27	34	43
13	16	19	24	31
9	11	14	17	22
15	18	23	28	36
11	13	16	20	26
7	9	12	15	19
5	7	8	10	13
5	6	8	10	13
4	4	6	7	9
3	3	4	5	7
2	2	3	4	5
4	5	6	7	8
cholesterol/HDL				



Discussion



Treatment harm:

- Adverse events (NNH)
- Financial costs
- Daily pill burden



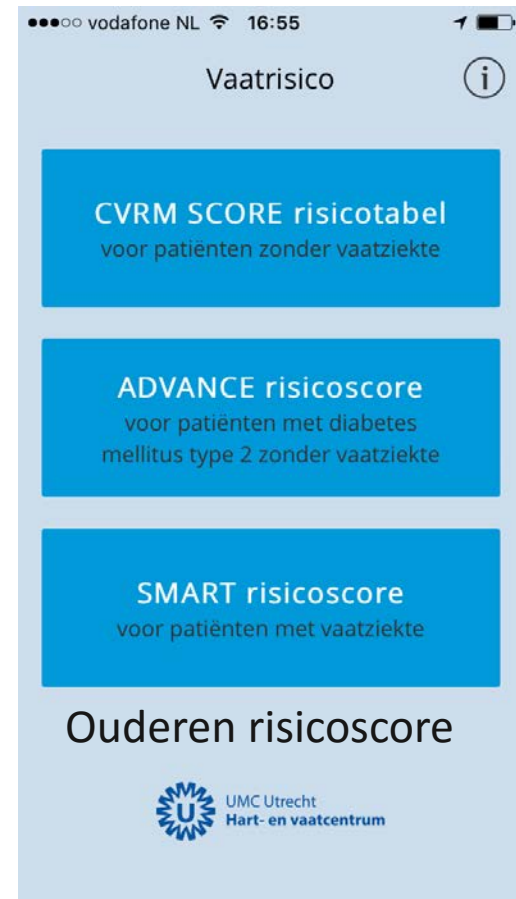
Advantages of individualized medicine

- Identifying the right patient to treat
- Lower number needed to treat
- Shared decision-making
- Saves costs for expensive treatment strategies



Future directions

- Lifetime benefit
 - Gain in disease-free life-expectancy
 - Quality of life
- Cost-effectiveness
- Implementation
 - Guidelines
 - Vaatrisico app





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