"721 – HIGH DOSES VERSUS LOW DOSES OF STATIN THERAPY "

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Apoio: CNPq Conselho Nacional de Desenvolvimento Científico e Tecnológico

Objective

Review the information about secondary prevention with statins in high dose versus low doses, within the precepts of evidence-based medicine, with results in absolute numbers, regarding morbidity and mortality rather than surrogate outcomes, such as laboratory tests, and composite endpoints.

Methods

We conducted a search of articles in the PubMed, EMBASE and Cochrane, with an end date in 31/12/10. The articles were criticaly appraised by the Jadad scale, and the adequacy to the items of the CONSORT statement.

Methods

We extracted data from articles by a spreadsheet developed based on SR_CRD York. Data were tabulated comparing statins in high and low doses, by absolute risk in the control group (RAC) the reduction in the intervention group (ARR), $CI^{95\%}$ and NNT.

Methods

Absolute risks were pooled using a fixed-effects model meta-analysis. Statistical heterogeneity across studies was quantified using the χ^2 (or Cochran Q statistic) and I^2 statistics, with P >.10 considered statistically nonsignificant. All P values were 2-sided and P < .05 considered statistically significant. Analyses were conducted using L. Bax. MIX 2.0. Professional software for meta-analysis in Excel. Version (2.0.1.0) BiostatXL, 2010.

Results

29.202 articles were retrieved, 2.997 selected with RCT as publication type, 2.925 excluded after title and resume evaluation and 30 after full evaluation. 42 articles were included and entirely extracted, 6 of them were comparing high doses versus low doses

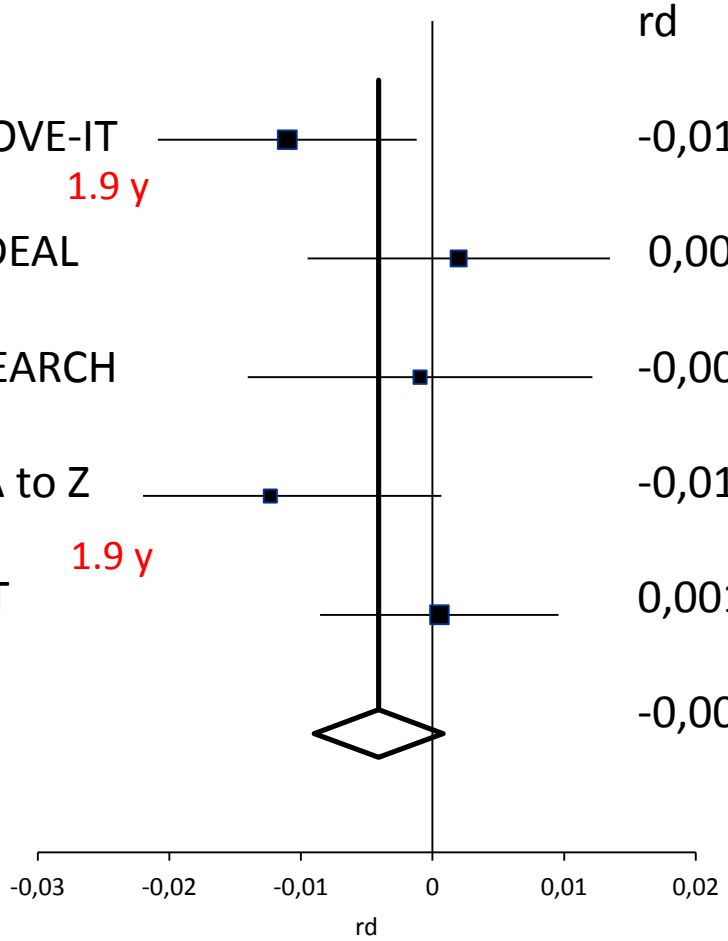
Results

Author	IG	CG	Age (y)	M:F	Num Rand	Follow-up (y)	Jadad	CONSORT %
Cannon, 2004 (PROVE-IT)	A80	P40	58	78-22	4162	1.9	4	81
de Lemos, 2004 (A-Z)	S80	S20	61	75-25	4497	1.9	5	85
LaRosa, 2005 (TNT)	A80	A10	61	80-20	10001	4.9	3	72
Pedersen, 2005 (IDEAL)	A80	S20	62	81-19	8888	4.8	3	48
Deedwania, 2007 (SAGE)	A80	P40	72	69-31	893	1.0	5	80
Armitage, 2010 (SEARCH)	S80	S20	64	83-17	12064	7.0	5	75

40.505 patients

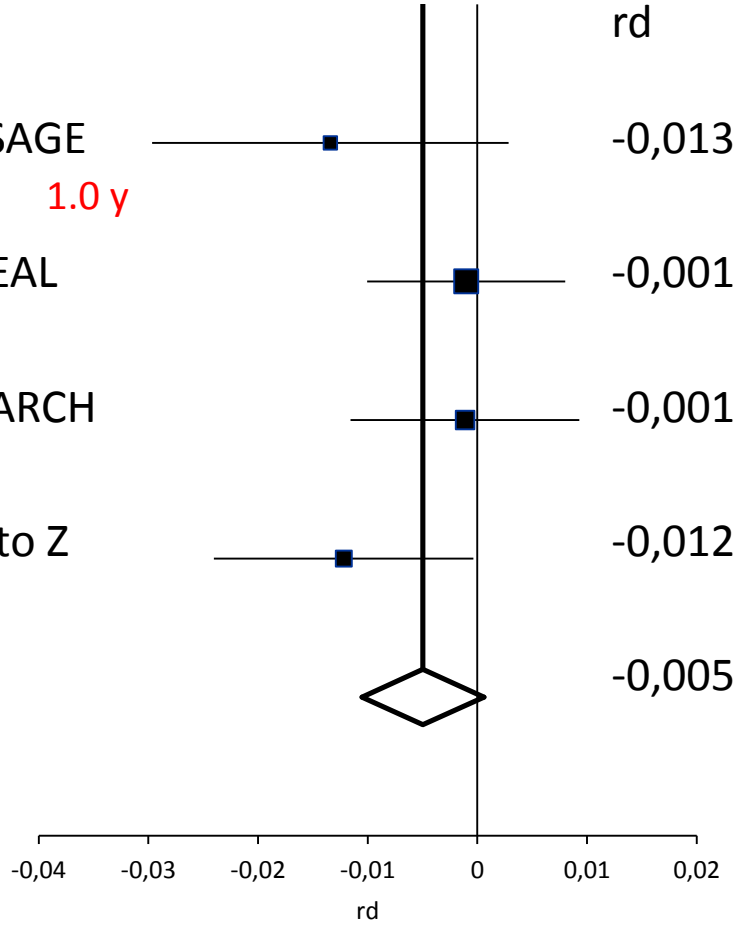
ALL CAUSE MORTALITY

Author	rd	95%CI	weight
Cannon, 2004 – PROVE-IT	-0,011	-0,021 a -0,001	24,66%
1.9 y			
Pedersen, 2005 – IDEAL	0,002	-0,009 a 0,013	18,11%
Armitage, 2010 – SEARCH	-0,001	-0,014 a 0,012	13,94%
De Lemos, 2004 – A to Z	-0,012	-0,025 a 0,001	14,16%
1.9 y			
La Rosa, 2005 – TNT	0,001	-0,009 a 0,010	29,13%
	-0,004	-0,009 a 0,001	100,00%



Heterogeneity: Q = 5,753 (p = 0,218) I^2 = 30,48 (95%CI = 0,00 a 85,54)

CARDIOVASCULAR MORTALITY

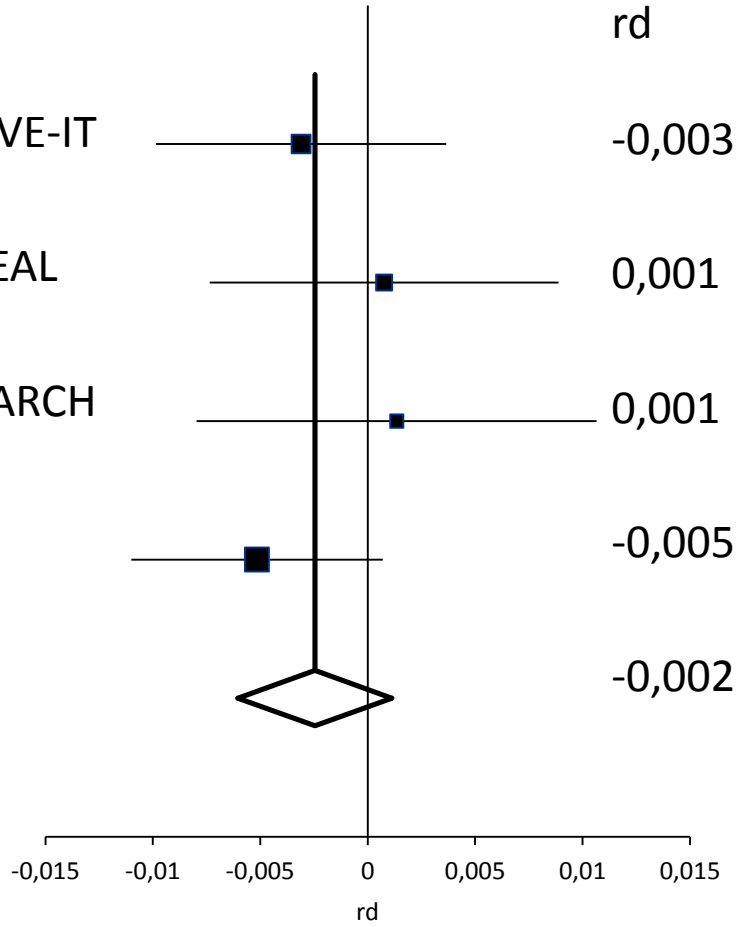


Author	rd	95%CI	weight
Deedwania, 2007 – SAGE (1.0 y)	-0,013	-0,030 a 0,003	11,67%
Pedersen, 2005 – IDEAL	-0,001	-0,010 a 0,008	37,86%
Armitage, 2010 – SEARCH	-0,001	-0,012 a 0,009	28,39%
De Lemos, 2004 – A to Z	-0,012	-0,024 a 0,000	22,08%
	-0,005	-0,011 a 0,001	100,00%

Heterogeneity: Q = 3,724 (p = 0,292) I^2 = 19,44 (95%CI = 0,00 a 87,66)

ACUTE MYOCARDIAL INFARCTION MORTALITY

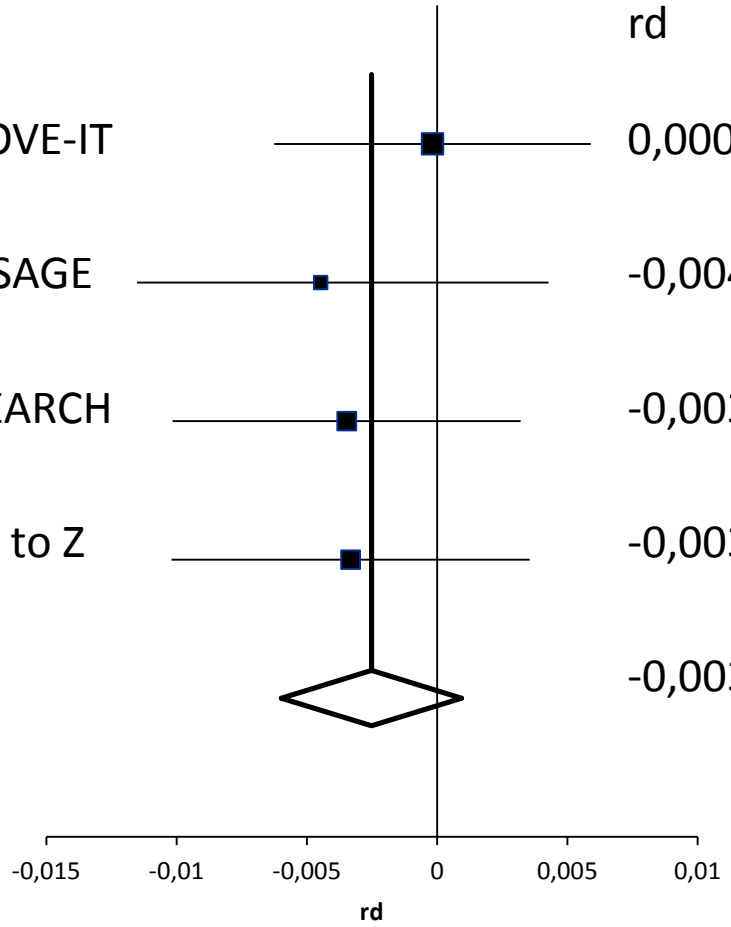
Author	rd	95%CI	weight
Cannon, 2004 – PROVE-IT	-0,003	-0,010 a 0,004	28,15%
Pedersen, 2005 – IDEAL	0,001	-0,007 a 0,009	19,48%
Armitage, 2010 – SEARCH	0,001	-0,008 a 0,011	14,82%
La Rosa, 2005 – TNT	-0,005	-0,011 a 0,001	37,55%
	-0,002	-0,006 a 0,001	100,00%



Heterogeneity: Q = 2,095 (p=0,552) I^2 = 0,00 ($^{95\%}$CI = 0,00 a 84,69)

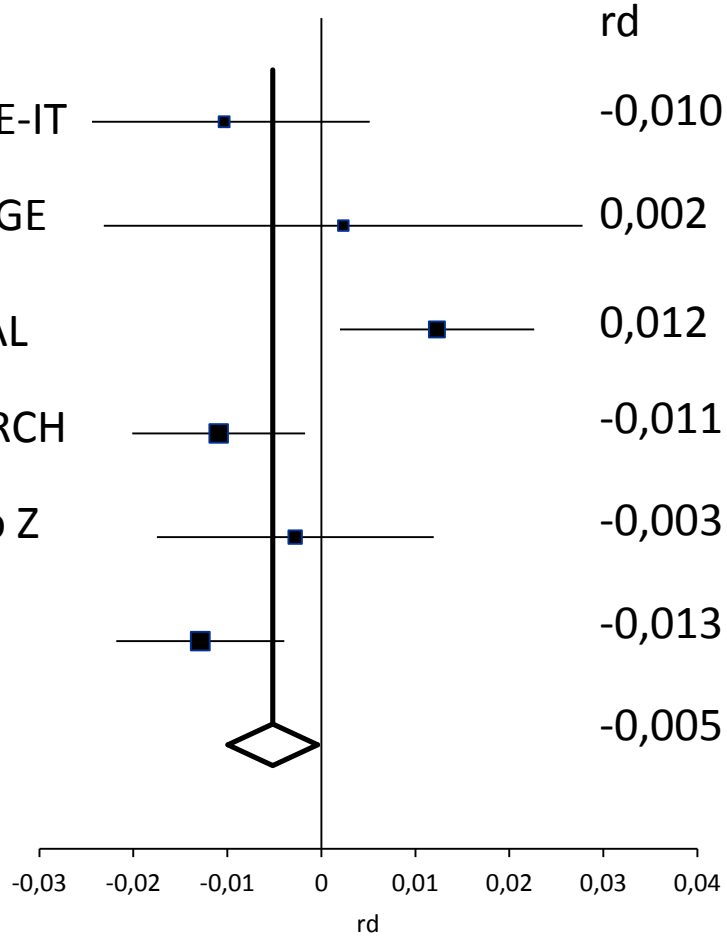
STROKE-NON FATAL

Author	rd	95%CI	weight
Cannon, 2004 – PROVE-IT	0,000	-0,006 a 0,006	32,38%
Deedwania, 2007 - SAGE	-0,004	-0,013 a 0,004	15,60%
Armitage, 2010 – SEARCH	-0,003	-0,010 a 0,003	26,75%
De Lemos, 2004 – A to Z	-0,003	-0,010 a 0,004	25,27%
	-0,003	-0,006 a 0,001	100,00%



Heterogeneity: Q = 0,893 (p=0,827) I^2 = 0,00 (95%CI = 0,00 a 84,69)

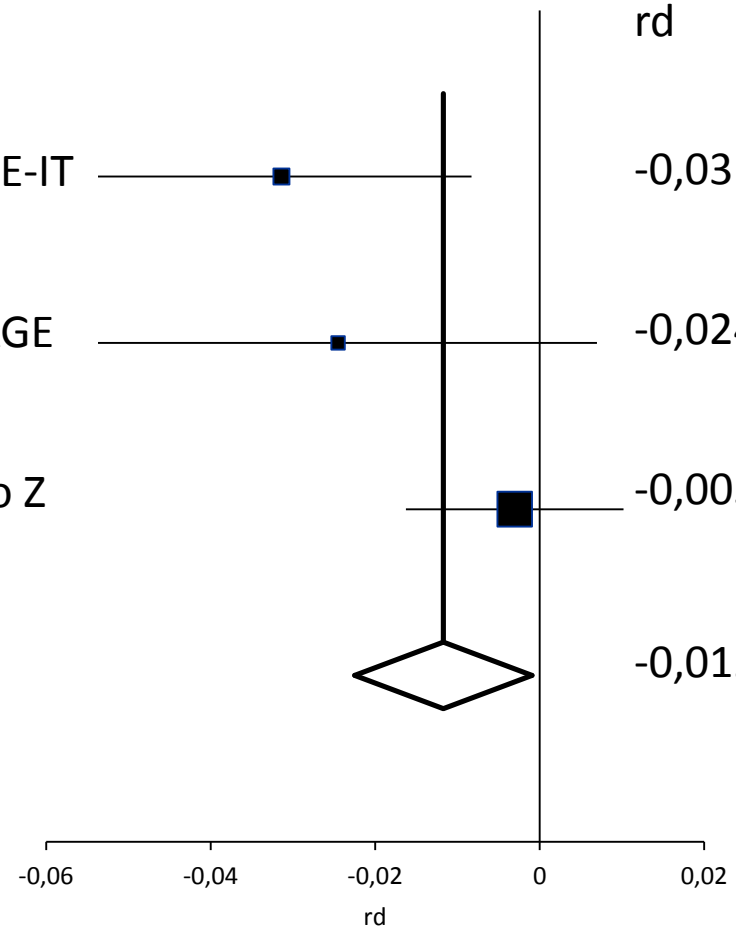
ACUTE MYOCARDIAL INFARCTION NON FATAL



Author	rd	95%CI	weight
Cannon, 2004 – PROVE-IT	-0,010	-0,026 a 0,005	9,44%
Deedwania, 2007 - SAGE	0,002	-0,023 a 0,028	3,50%
Pedersen, 2005 – IDEAL	0,012	0,002 a 0,023	21,26%
Armitage, 2010 – SEARCH	-0,011	-0,020 a -0,002	26,93%
De Lemos, 2004 – A to Z	-0,003	-0,018 a 0,012	10,47%
La Rosa, 2005 – TNT	-0,013	-0,022 a -0,004	28,40%
	-0,005	-0,010 a 0,000	100,00%

Heterogeneity: Q = 16,205 (p=0,006) I^2 = 69,15 (95%CI = 27,39 a 86,89)

CORONARY ARTERY BYPASS GRAFT



Author	rd	95%CI	weight
Cannon, 2004 – PROVE-IT	-0,031	-0,055 a -0,008	21,75%
Deedwania, 2007 - SAGE	-0,024	-0,056 a 0,007	11,72%
De Lemos, 2004 – A to Z	-0,003	-0,016 a 0,010	66,52%
	-0,012	-0,022 a -0,001	100,00%

Heterogeneity: Q = 5,080 (p = 0,078) I^2 = 60,63 ($^{95\%}$CI = 0,00 a 88,78)

Results

	ARC	ARR (95% CI)	NNT
Non fatal AMI	0,0674	0,0051 (0,0004 – 0,0099)	196
Non fatal stroke	0,0142	0,0025 (0,0009 – 0,0059)	400
CABG	0,0272	0,0117 (0,0009 – 0,0224)	85

in favor of high doses

Results

The only evidence available among the eight trials that tested atorvastatin (any dose) in terms of mortality from all causes was obtained with an average dose between 18.5 and 33.5 mg per day and average of 97 mg/dl in serum LDL–Cholesterol during the test (GREACE trial), unlike the 4 trials that used a fixed dose of 80 mg daily, wich show no difference in mortality from all causes between the groups.

Increased diabetes risk

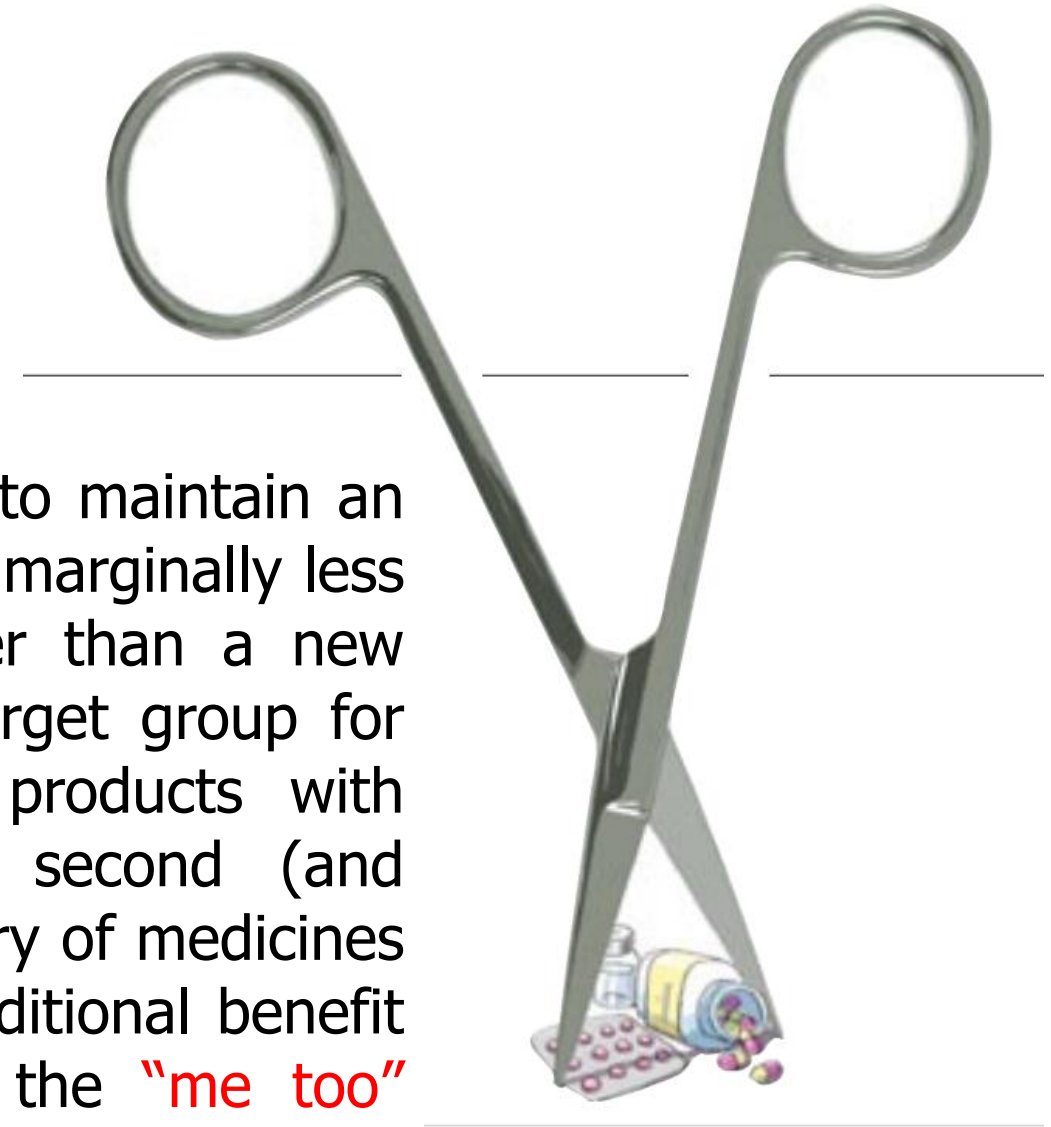
Five trials comparing high- versus moderate-dose statins in some 32.752 patients free of diabetes at baseline, 2749 developed DM (1449 intensive, 1300 moderate-dose). During a mean follow-up of almost 5 years. NNH 498 patients per year would need to take high-dose statins to cause one additional case of diabetes. To prevent one cardiovascular composite event, 155 patients would need to be treated.

JAMA. 2011 Jun 22;305(24):2556-64

Conclusion

There is no evidence based on randomized trials, with the clinical outcome of major relevance (hard endpoint), in favor of intensive treatment. High doses of statins demonstrated more relevant morbidity outcomes only related to non fatal AMI and CABG, however the effect size expressed in NNT are 196 ($^{95\%}$CI 101 to 2500) and 85 ($^{95\%}$CI 45 to 1111).

DISINVESTMENT



Sometimes it makes sense to maintain an older treatment that is only marginally less effective but much cheaper than a new drug. The most obvious target group for disinvestment is branded products with generic alternatives. The second (and perhaps the largest) category of medicines that produce little or no additional benefit but which cost more are the "me too" products—new entrants to an existing therapeutic class.

Dyfrig A Hughes BMJ 2010;340:c572

Implications of the review for practice

Guidelines should be drawn up with specific recommendations against intensive use of statin for the secondary prevention of atherosclerotic cardiovascular diseases.