

SHOULD STATINS BE STARTED IN ALL TYPE 2 DIABETICS IRRESPECTIVE OF LDL-CHOLESTEROL LEVEL?

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Case Scenario

Mr S is a 38 year old Indian man who has type 2 diabetes mellitus for 3 years. He is currently on metformin 500mg BD. His BMI is 24.9 kg/m² (weight 72 kg, height 170 cm). His blood glucose is well controlled (HbA_{1c} 6%). His fasting lipid levels are as follow: Total cholesterol 5.0 mmol/L, HDL-C 1.60 mmol/L, LDL-C 2.6 mmol/L and triglyceride 0.9 mmol/L. He has no family history of acute myocardial infarction. He is a smoker (14 sticks/day, 12 years) but non-hypertensive. He asks if he should take atorvastatin, a lipid-lowering drug that his father is taking.

Question

Should statins be started in type 2 diabetic patients without pre-existing coronary artery disease whose lipid level is not elevated?

Commentary

The use of statins in patients with type 2 diabetes mellitus and pre-existing coronary artery disease (CAD) is now generally accepted, for which guideline suggested the target LDL-cholesterol (LDL-C) should be <2.6 mmol/L.¹ Since diabetes mellitus is a CAD risk equivalent, it has been suggested that all patients with diabetes should receive statins even if they do not have CAD or raised LDL-C.² Three randomised controlled trials (RCTs) designed specifically to evaluate the benefit of statins in diabetic patients without overt CAD have so far been published;³⁻⁵ followed soon after by two meta-analyses^{6,7} (Table 1).

In the primary prevention component of the meta-analysis by Vijan *et al*⁶ five RCTs were included; they concluded that statins showed a 22% relative risk reduction (RRR). The meta-analysis by Thavendiranathan *et al*⁷ included seven trials (n=42,848, 90% of them did not have history of cardiovascular disease), statins showed a RRR of major coronary events and major cerebrovascular events by 29.2% (95%CI, 16.7-39.8%, p<0.001) and 14.4% (2.8-24.6%, p=0.02), respectively. However, statins did not show significant reduction in the CAD mortality and overall mortality. Interestingly, there is yet another RCT published

last year; in the ASPEN study⁵ there was no statistical difference in the major cardiovascular events after 4 years of follow up despite 29% reduction of LDL-cholesterol in the atorvastatin group.

Looking at the published RCTs and meta-analyses, what would be the appropriate response to Mr S? It appears that the evidence for statins in older diabetic patients without overt CAD is compelling enough. However, the RRR and NNT may change somewhat if CARDS and ASPEN studies were to be included in the meta-analysis. Moreover, published RCTs included diabetic patients >40 years of age and have multiple CAD risk factors (including LDL-C >2.6 mmol/L). For diabetic patients like Mr S who are <40 years and LDL-C <2.6 mmol/L, there is still insufficient evidence to recommend routine statins.

Reference

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Table 1: Summary of randomised controlled trials and meta-analyses evaluating the efficacy of statin therapy in preventing major cardiovascular events* in patients with diabetes but without overt coronary artery disease

Study (year)	Intervention	Control	RRR, % (95%CI)	ARR, % (95%CI)	NNT
Randomised controlled trials					
HPS ³ (2003)	13.8%	18.6%	35 (18-52)	4.8 (2.5 to 7.1)	21 (14-40)
CARDS ⁴ (2004)	5.8%	9.0%	51 (18-84)	3.0 (1.1 to 5.0)	33 (20-92)
ASPEN ⁵ (2006)	10.4%	10.8%	3 (-28 to 26)	Not applicable	Not applicable
Meta-analyses					
Vijan ⁶ (2004)			22 (11 to 33)	3 (1 to 4)	33 (25-100)
Thavendiranathan ⁷ (2006)			29 (17 to 40)	NA	NA

* Major cardiovascular events include any of the following: acute coronary syndrome, stroke, coronary revascularisation
 HPS: n=5963 type 2 diabetes (age 40-80 years, mean LDL-C 3.0 mmol/L), simvastatin 40 mg daily vs placebo for about 4.8 years.
 CARDS: n=2838 patients with type 2 diabetes (age 40-80 years, mean LDL-C 3.0 mmol/L) atorvastatin 10 mg daily vs placebo (this trial was terminated at 2 years because the prespecified early stopping rule for efficacy had been met).
 ASPEN: n=2410 patients with type 2 diabetes (mean age 60 years, mean LDL-C 3.0 mmol/L), atorvastatin 10 mg daily vs placebo for 4 years.
 NA, not available

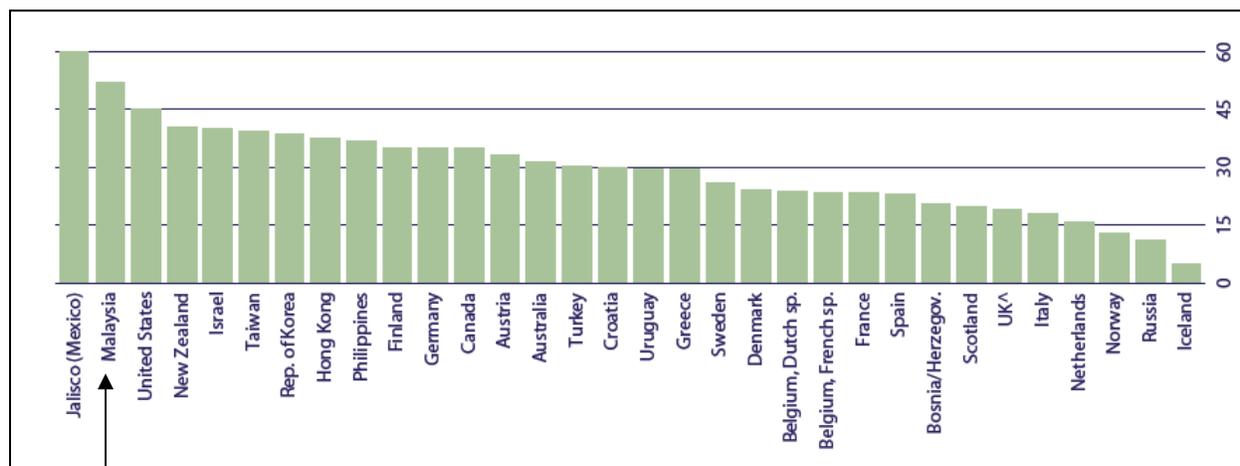
www.ClinicalTrials.gov

As of 13th September 2007, seventy-six trials in Malaysia have been registered in the clinical trials registry maintained by National Institutes of Health, USA. One of these trials is:

Community Based Multiple Risk Factors Intervention Strategy (CORFIS)

[NCT00490672]

Percentage of incident ESRD due to diabetes, 2005



Malaysia is almost right at the top where diabetes is a contributor of end-stage renal disease (in 2005, 52% of patients with end-stage renal disease have diabetes at the time of the diagnosis)

http://www.usrds.org/2007/pdf/12_intl.pdf