PRIMARY HEALTHCARE ESSENTIAL MEDICINES LIST
CHAPTER 4 & 9: CARDIOVASCULAR CONDITIONS & ENDOCRINE SYSTEM
MEDICINE REVIEW: STATIN DOSE

Date: June 2013

A: STATIN DOSE

NEMLC had recommended that the PHC Expert Review Committee investigate the optimal simvastatin dose that produces a clinical benefit for secondary prevention.

Discussion: Clinical benefit was described as prevention of major cardiovascular events or death. The SEARCH[1] study showed that there was no difference (statistically not significant) in clinical outcomes between participants allocated the 20mg *vs.* 80mg simvastatin dose. More myopathy was associated with the 80 mg compared to the 20 mg dose (0.9% vs. 0.03%).

Clinical outcome	**Simvastatin 80 mg *vs*. 20 mg**	**p-value**
Major vascular events	Risk ratio= 0·94, 95% CI 0·88 to1·01	p=0·10

However, it was mentioned that the questions that should be answered are:

1. "What is the relationship between the reduction in LDL by statins and the reduction in the risk of cardiovascular events – i.e. how much of a reduction in LDL translates into a clinical benefit?"
2. "Which statin and at what dose would be the most cost-effective to accomplish this clinical benefit?"

1. HOW MUCH OF A REDUCTION IN LDL TRANSLATES INTO A CLINICAL BENEFIT?

A number of trials[2] suggested that there was an approximately linear relationship between the LDL cholesterol achieved and coronary mortality. However, evidence is lacking that directly answers the question of optimal LDL targets, as studies do not provide a breakdown of the incremental clinical benefits achieved by different LDL targets.

Delahoy *et al* (2009)[3]: A metaregression (25 RCTs, n= 155 613 with 23 791 major vascular events) reported a significant reduction in the risk of major vascular events associated with a reduction in LDL. For every 25 mg/dL (0.65 mmol/L) reduction in LDL, the proportional reduction, RR (95% CI and r^2 statistic), for various cardiovascular events were as follows:

- vascular mortality, 11% (0.89 [0.87-0.92], r^2 =0.75);
- major coronary events, 16% (0.84 [0.820.86], r^2 =0.87);
- major vascular events,14% (0.86 [0.84-0.88], r^2 =0.84); and
- fatal and nonfatal stroke, 10% (0.90 [0.86-0.94], r^2=0.47).

Thus, for every 1.0 mmol/L reduction in LDL, there was an equivalent proportional reduction of vascular mortality - 16%, major coronary events -20%, major vascular events - 23%, and fatal and nonfatal stroke - 15%.

These results support the linear relationship between reduction in LDL and reductions in clinical events.

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[1] Study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine (SEARCH) Collaborative Group, Armitage J, Bowman L, Wallendszus K, Bulbulia R, Rahimi K, Haynes R, Parish S, Peto R, Collins R. Intensive lowering of LDL cholesterol with 80 mg versus 20 mg simvastatin daily in 12,064 survivors of myocardial infarction: a double-blind randomised trial. *Lancet.* 2010 Nov 13;376(9753):1658-69. doi: 10.1016/S0140-6736(10)60310-8. Epub 2010 Nov 8. Erratum in: *Lancet.* 2011 Jan 8;377(9760):126.

[2] i. Verschuren WM, Jacobs DR, Bloemberg BP, et al. Serum total cholesterol and long-term coronary heart disease mortality in different cultures. Twenty-five year follow-up of the seven countries study. *JAMA.*1995;274:131–6.

ii. Padwal R, Straus SE, McAlister FA. Cardiovascular risk factors and their impact on the decision to treat hypertension: an evidence-based review. *BMJ.*2001;322:977–80.

iii. Baigent C, Keech A, Kearney PM, Blackwell L, Buck G, Pollicino C, Kirby A,Sourjina T, Peto R, Collins R, Simes R; Cholesterol Treatment Trialists' (CTT)Collaborators. Efficacy and safety of cholesterol-lowering treatment: prospective meta-analysis of data from 90,056 participants in 14 randomised trials of statins. *Lancet.* 2005 Oct 8;366(9493):1267-78.

[3] Delahoy PJ, Magliano DJ, Webb K, Grobler M, Liew D. The relationship between reduction in low-density lipoprotein cholesterol by statins and reduction in risk of cardiovascular outcomes: an updated meta-analysis. *ClinTher*. 2009 Feb;31(2):236-44.

Takagi *et al* (2013)[4]: To analyse if there is a threshold for the benefit of LDL reduction, achieved with statins; or whether greater reductions in LDL would bring greater reductions in vascular events, a more sophisticated model was used by Takagi *et al* (2013) compared to the linear model utilised by Delahoy *et al* (2009). The quadratic flexible metaregression model better fitted the data than the linear model, representing an almost horizontal line when the reduction in LDL level is more than approximately 40 mg/dL (1.03 mmol/L).
The data showed that there was almost no additional benefit in the use of statins beyond a 40 mg/dL (1.03 mmol/L) decrease in LDL level in preventing major vascular events.

2. WHICH STATIN AND AT WHAT DOSE WOULD BE THE MOST COST-EFFECTIVE TO ACCOMPLISH THIS CLINICAL BENEFIT?

Statin dose:
1. Naci *et al* (2013)[5] performed a meta-analysis (n=256,827; 181 RCTs) that analysed the dose-comparative effects of different statins on serum lipid levels, reported that the mean reduction of LDL from baseline of simvastatin 10 mg was 26%.

2. Law *et al's* (2003)[6] meta-analysis showed that simvastatin 10 mg reduced serum concentration of LDL by 27 % ; an absolute LDL reduction of 1.31 mmol/L (95% CI 1.22 to 1.40).

The Committee was of the opinion that simvastatin 10 mg reduces LDL by more than 1.03 mmol/L.

Cost:
Simvastatin is the cheapest statin currently available on tender.

Product (tablets)	ISN	Tender Price[7]
Atorvastatin 10 mg, 28	181798132	R13.90
Atorvastatin 20mg, 30	181798133	R19.38
Atorvastatin 40 mg, 30	181859938	R28.8511
Atorvastatin 80 mg, 30	181859939	R53.47
Pravastatin 10mg, 30	180230821	R15.99
Pravastatin 20 mg, 30	180230824	R17.38
Simvastatin 10 mg, 28	189762856	R3.645 (3.48 to 3.81)
Simvastatin 20 mg, 28	189762970	R5.42 (5.43 to 5.41)

Recommendation: The Committee recommended that the STGs retain simvastatin at a dose of 10 mg, orally, daily.
Rationale: Reducing LDL by more than 1.03 mmol/L showed no additional benefit in the risk reduction of major vascular events. Simvastatin 10 mg reduces LDL by 1.31 mmol/L, and simvastatin is currently the cheapest statin on tender.
Level of evidence: III Expert opinion

B: CALCIFICATION ASSOCIATED WITH STATINS
NEMLC had recommended that the safety data pertaining to calcification of arteries associated with statins be investigated.

[4] Takagi H, Umemoto T; for the ALICE (All-Literature Investigation ofCardiovascular Evidence) Group. Limit to Benefits of Large Reductions in Low-Density Lipoprotein Cholesterol Levels: Use of Fractional Polynomials to Assess the Effect of Low-Density Lipoprotein Cholesterol Level Reduction in Metaregression of Large Statin Randomized Trials. *JAMA Intern Med.* 2013 Apr 29:1-2. doi: 10.1001/jamainternmed.2013.659.
[5] Naci H, Brugts JJ, Fleurence R, Ades A. Dose-comparative effects of different statins on serum lipid levels: a network meta-analysis of 256,827 individuals in 181 randomized controlled trials. Eur J Prev Cardiol. 2013 Mar 25. [Epub ahead of print] PubMed PMID: 23529608.
[6] Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. *BMJ.* 2003 Jun 28;326(7404):1423.
[7] Contract circular HP09-2012SD, 1Aug2012 to 31July2014

A review of the published literature produced an underpowered, observational, cohort study[8] (n=167) that showed frequent use of statins *vs.* less frequent use is associated with accelerated coronary artery calcification (mean ± SE, 8.2 ± 0.5 mm^3 vs. 4.2 ± 1.1 mm^3, $p < 0.01$) in type 2 diabetics.

Conversely, an observational study[9] (n=245) in asymptomatic type 2 Hispanic diabetics demonstrated a reduction in coronary artery calcification associated with statin use.

The evidence provided is conflicting and not adequately robust to change policy.

Recommendation: The Committee recommended that statins be retained in the PHC STG for primary and secondary prevention of cardiovascular events.

[8] Saremi A, Bahn G, Reaven PD; VADT Investigators. Progression of vascular calcification is increased with statin use in the Veterans Affairs Diabetes Trial(VADT). *Diabetes Care.* 2012 Nov;35(11):2390-2.

[9] Reaven PD, Sacks J; Investigators for the Veterans Affairs Cooperative Study of Glycemic Control and Complications in Diabetes Mellitus Type 2. Reduced coronary artery and abdominal aortic calcification in Hispanics with type 2 diabetes. *Diabetes Care.* 2004 May;27(5):1115-20.