What is the target for low-density lipoprotein cholesterol in patients with heart disease?

EVIDENCE-BASED ANSWER Large published randomized controlled trials (RCTs) show that pravastatin and simvastatin are well-tolerated and reduce major coronary events such as death, myocardial infarction, and revascularization by about 25%. The Heart Protection Study suggested this benefit is noted even among individuals with pretreatment low-density lipoprotein (LDL) cholesterol of less than 100 mg/dL. Fluvastatin reduces major coronary events, but current studies are too small to prove reduced overall mortality. The best evidence to date suggests that most patients at significant risk for major coronary events should be given pravastatin or simvastatin 40 mg daily, without concern for the initial or follow-up LDL levels. (Grade of recommendation: A, based on large randomized trials.)

TABLE

LDL levels and relative risk of major coronary events after treatment

Study, year	N	Intervention medication	LDL level, mg/dL		Relative risk of major coronary events
			Control group	Intervention group	
4S,[1] 1994	4444	Simvastatin 20 mg/d*	190	122	0.66 (0.59–0.85)
CARE,[3] 1996	4159	Pravastatin 40 mg/d	139	97	0.76 (0.64–0.91)
LIPID,[2] 1998	9014	Pravastatin 40 mg/d	150	113	0.76 (0.68–0.85)
LIPS,[4] 2002	1677	Fluvastatin 80 mg/d	132	100	0.78 (0.64–0.95)
HPS,[5] 2002	20,536	Simvastatin 40 mg/d	127	89	0.76 (0.72–0.81)

*Increased to 40 mg/d if total cholesterol did not drop to less than 200 mg/dL.
4S, Scandinavian Simvastatin Survival Study; CARE, Cholesterol and Recurrent Events trial; HPS, Heart Protection Study; LDL, low-density lipoprotein; LIPID, Long-Term Intervention with Pravastatin in Ischaemic Disease study; LIPS, Lescol Intervention Prevention Study.

EVIDENCE SUMMARY The evidence is solid to support the use of HMG–CoA reductase inhibitors (statins) for patients with coronary artery disease (CAD). The Scandinavian Simvastatin Survival study used simvastatin 20 mg daily unless total cholesterol levels did not decrease to less than 200 mg/dL.[1] The Long-Term Intervention with Pravastatin in Ischaemic Disease study randomized patients to pravastatin 40 mg daily or placebo, without titration.[2] The intervention arm in the Cholesterol and Recurrent Events trial was also pravastatin 40 mg daily, with cholestyramine added if the LDL level remained higher than 175 mg/dL.[3] The Lescol Intervention Prevention study randomized patients after angioplasty to fluvastatin 40 mg twice daily or placebo.[4] The Heart Protection Study used simvastatin 40 mg daily, without titration.[5] No RCTs have evaluated the clinical benefit of adding medications to adequate doses of statins to lower LDL to less than 175 mg/dL. See Table of major RCTs with clinical outcomes.

Subgroup analyses of earlier major RCTs had suggested that patients with CAD and low initial LDL levels (< 125 mg/dL) have little to gain from pravastatin.[2,3] However, the Heart Protection Study enrolled 20,000 people with CAD or equivalent (diabetes, peripheral vascular disease, stroke, etc).[5] The study demonstrated a reduction of major coronary events with simvastatin, with numbers needed to treat (NNT) of 19 ($P < .0001$); the NNT for reduction in all-cause mortality was 55 ($P = .0003$). The benefit of simvastatin was noted in virtually every predefined subgroup, including individuals older than 70 years, women, and patients without known CAD (but with CAD equivalents).

Notably, no difference in benefit was found between patients with different pretreatment LDL levels. A significant reduction in major vascular events was noted even for the 3400 subjects with pretreatment LDL levels of less than 100 mg/dL (NNT = 22, $P = .0006$). A greater percentage reduction in LDL with medication did not predict better clinical outcomes.[5]

RECOMMENDATIONS FROM OTHERS The National Cholesterol Education Project (NCEP) recommends that patients with CAD and an LDL of more than 130 mg/dL adopt therapeutic lifestyle changes and start LDL-lowering medication, usually a statin. For patients with LDL between 100 and 130 mg/dL, the NCEP recommends therapeutic lifestyle changes, with the option of adding a statin. For patients with LDL less than 100 mg/dL, maintenance of LDL control is recommended with therapeutic lifestyle changes. For patients with high initial LDL levels that stay above 100 mg/dL on statin therapy, the NCEP recommends that additional medications, such as nicotinic acid or fibrates, as well as intensive therapeutic lifestyle changes, be considered.[6]

James J. Stevermer, MD, MSPH
Susan E. Meadows, MLS
Department of Family and Community Medicine
University of Missouri–Columbia

Clinical Commentary by William Chavey, MD, at http://www.fpin.org.

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