

OPTIMAL LDL CHOLESTEROL < 70 MG/DL, SCIENTIFIC UPDATE 3/30/09, CHARLES J. GLUECK MD, DIRECTOR ALLIANCE CHOLESTEROL CENTER. Phone 513-585-7800, Fax 513-585-7950, address 3200 Burnet Avenue, Cincinnati OH, 45229, email glueckch@healthall.com

How low should cholesterol go

The primary and secondary prevention and atherosclerosis regression studies below in aggregate suggest that for optimal effects, LDL cholesterol should be lowered well below 100 mg/dl, to levels <70 mg/dl.

IS THERE AN ASYMPTOTIC LIMIT FOR LDL AT WHICH CARDIOVASCULAR EVENT RATES APPROXIMATE ZERO?

The LDL level at which cardiovascular event rate may approach ZERO is estimated to be ~ 60 mg/dl for primary prevention (no previous clinical coronary disease), and 30 mg/dl for secondary prevention (previous clinical coronary disease).

“Primitive” hunter-gatherer populations: total cholesterol 100-150 mg/dl, (estimated) LDL 50-75 mg/dl.

Neonates’ LDL 30-70 mg/dl.

Familial hypobetalipoproteinemia: LDL cholesterol 30-40 mg/dl, associated with longevity, and life expectancy 15 years longer than their birth cohort. Atherosclerotic coronary and cerebrovascular disease almost never occurs in this common inherited disorder.

Threshold for progression of atherosclerosis estimated to be approximately 70 mg/dl

REVERSAL STUDY: 654 cases with symptomatic coronary disease and baseline stenosis \geq 20%, randomized to Lipitor 80 mg or Pravachol 40 mg. Coronary atherosclerosis (by IVUS) halted in Lipitor group where 48% reduction in LDL led to mean LDL on treatment of 79 mg/dl. Pravachol group had 28% decline in LDL to a mean of 110 mg/dl. There was a 0.4% regression of atheroma volume in the Lipitor group vs 2.7% mean progression in the Pravachol group over 18 months. High specificity CRP was reduced by 36% in the Lipitor group vs 5% decrease in the Pravachol group.

ASAP STUDY: Lipitor 80 mg vs Zocor 40 mg, 325 cases with familial hypercholesterolemia. Carotid intimal-medial thickness (IMT) regressed 0.031 mm over 2 years in the Lipitor group vs 0.036 mm progression in Zocor group.

ARBITER STUDY: Lipitor 80 mg vs 40 mg Pravachol, 161 cases with baseline LDL = 150 mg/dl. Lipitor reduced LDL by 50% to 76 mg/dl vs 110 mg/dl on Pravachol. Carotid IMT regressed 0.038 mm in Lipitor group vs mean progression of 0.026 mm in Pravachol group.

HEART PROTECTION STUDY: 3500 cases with LDL <100 mg/dl before treatment, with mean LDL of 97 mg/dl reduced to 65 mg/dl on Zocor 40 mg. This was associated with 25% reduction in CHD events.

PROVE-IT-TIMI: 4162 acute coronary symptom cases with pre-treatment total cholesterol \leq 200 mg/dl to Lipitor 80 mg or Pravachol 40 mg. On Lipitor, 51% fall in LDL to 62 mg/dl, vs 95 mg/dl (22%) decrease on Pravachol. After 2 years, 16% reduction in adverse CHD events, 28% reduction in CHD death in Lipitor group. In a retrospective analysis, there were lower clinical coronary heart disease events in patients who achieved LDL <60 or <40 mg/dl compared with those in the 80-100 mg/dl range. LDL <60 or < 40, well below current guidelines, were not associated with adverse safety outcomes. Hence, **do not reduce statin dose if LDL levels fall below the 70 mg/dl goal.**

TNT: 10,001 cases with stable coronary heart disease, all started on Lipitor 10 mg, and after run in period, half to 80 mg, half remained on 10 mg. LDL remained at 101 mg/dl in the case on 10 mg, and fell

to 77 mg/dl on the Lipitor 80 mg. The reduction in CHD events 22% ($p < .01$), 27% reduction in stroke ($p < .01$).

An increasing amount of data from primary prevention, secondary prevention, and atherosclerosis regression studies suggest that to provide optimal results in terms of lowering coronary heart disease events and /or stopping the progression of or reversing atherosclerotic lesions, LDL cholesterol should be lowered to well under 100 mg/dl, and optimally to < 80 mg/dl.

Prove-it (Cannon P, et al, New Eng J Med 2004;350:15)

In patients hospitalized for acute coronary syndrome ($n=4162$), half randomized to Lipitor 80 mg/day, half to Pravachol 40 mg/day. Primary endpoint was composite of death from any cause, MI, unstable angina, revascularization, and stroke. Mean followup 24 months.

Median cholesterol on Pravachol 95 mg/d, and 62 mg/dl on Lipitor. There was a 16% reduction in the hazard ratio in favor of Lipitor ($p = .005$), 95% CI 5% to 26%. Conclusion: Patients with acute coronary syndrome benefit from early and continued lowering of LDL cholesterol levels to $<$ than the current target of 100 mg/dl, and probably to < 80 mg/dl.

Heart Protection Study (HPS) ¹

Lower LDL cholesterol is associated with a lower risk of cardiovascular disease. The purpose of the Heart Protection Study (HPS) was to investigate whether lowering LDL cholesterol with simvastatin (brand name Zocor®) reduced the development of vascular disease irrespective of initial LDL concentrations. The researchers studied 20,536 patients in the United Kingdom with coronary disease, other occlusive arterial disease, or diabetes. Patients were randomly assigned to receive either 40mg of simvastatin per day or a placebo. The average compliance was 85%, and 17% of the patients were already taking statins not related to the study.

Among the findings was that patients taking simvastatin showed in a first non-fatal or fatal stroke compared to the placebo group (444 [4.3%] vs 585 [5.7%]; $p < 0.0001$). Additionally, patients taking simvastatin showed a lower frequency of first non-fatal or fatal heart attack (8.7% vs 11.8%, $p < 0.0001$). Overall, patients taking simvastatin had a 24% reduction in the first occurrence of any of the studied major vascular events. Importantly, patients who entered the study with LDL cholesterol < 100 mg/dl before receiving Zocor had a reduction in cardiovascular events which was essentially as great as patients whose baseline LDL cholesterol was 130 or 160 mg/dl. This focused attention on lowering LDL cholesterol to ~ 80 mg/dl (as in this group) for optimal prevention of cardiovascular events.

This reduction in major vascular events was not significant in the first year of the study, but it was significant in each of the following four years. Furthermore, this reduction was seen in each subcategory (based on the type of vascular disease in their history) of patients studied.

There are several important messages from this study. Adding simvastatin to an existing treatment (17% were already on statins) safely produces large additional benefits over a wide range of cholesterol ranges. Taking 40 mg of simvastatin daily reduced the rates of heart attack, stroke, and revascularization by roughly 25%. Because of 15% non-compliance in this study, the true reduction could be as large as 33%. Although treatment with simvastatin produced significant benefits, the size of the five-year benefit depends on the overall risk for vascular disease rather than only cholesterol concentrations. That is, lowering cholesterol is likely to decrease the risk of a vascular event but the amount of reduction depends largely on other factors such as smoking, obesity, and genetic predisposition, rather than cholesterol concentrations alone.

MIRACL Study ²

During the early time after an acute coronary syndrome—unstable angina (chest pain due to a blockage in the heart) or sudden heart attack—patients have the highest rate of death or recurrent ischemic (blockage) events. This study investigated whether 80 mg daily of atorvastatin (brand name Lipitor®), started 1-4 days after an acute coronary event, reduced the risk of death or non-fatal ischemic events. Patients at 122 clinical centers in Europe, North America, South Africa, and Australasia (n =3086) were randomly divided into two groups, receiving either 80 mg of atorvastatin per day or a placebo. Patients were followed for 16 weeks after the occurrence of an acute coronary syndrome. The significant finding was that patients in the atorvastatin group had a lower occurrence of recurrent ischemic events in the first 16 weeks after the appearance of acute coronary syndrome.

Anglo-Scandinavian Clinical Outcomes Trial (ASCOT) ³

Hypertension (high blood pressure) and elevated cholesterol are two of the most common risk factors for heart disease and stroke, which are major causes of death worldwide. Lowering blood pressure and cholesterol are important in controlling these conditions. The ASCOT study included 19,342 patients randomized into one of two antihypertensive regimens. A total of 10,305 patients were randomly selected from these groups and placed in a lipid-lowering group which consisted of 10 mg of atorvastatin daily or placebo. The atorvastatin and placebo groups of the lipid-lowering arm had identical *initial* cholesterol levels and blood pressure. Patients were followed for a median of 3.3 years. The atorvastatin group had a 35% relative reduction in the LDL compared to the placebo group. Fatal heart attack and fatal coronary heart disease were 36% lower in the atorvastatin group. There were also significant (29%) reductions in total coronary events and a 27% reduction in fatal and non-fatal strokes. In the atorvastatin group, LDL cholesterol levels were about 80 mg/dl on therapy, again providing emphasis on lowering LDL to well below 100 mg/dl.

Reversing Atherosclerosis with Aggressive Lipid Lowering (REVERSAL) ⁴

This recent study compared the effectiveness of atorvastatin and pravastatin in the reversal in atherosclerosis. Five hundred and two patients diagnosed with coronary heart disease and with LDL cholesterol around 150 mg/dl were treated with either atorvastatin or pravastatin (brand name Pravachol®). Intravascular ultrasound was used to assess atherosclerotic plaque status at pre-treatment baseline and after 18 months on therapy. The group treated with atorvastatin showed a median 0.4% reduction in plaque volume (the total plaque in a given section of an artery) while the pravastatin group had a median 2.7% increase in total plaque volume. Additionally, 97% of the patients taking atorvastatin reached the recommended LDL levels (≤ 100 mg/dL) while 67% of pravastatin patients reached this level. On atorvastatin, LDL cholesterol was lowered to around 80 mg/dl, while on pravastatin, to 110 mg/dl.

Regression Growth Evaluation Statin Study (REGRESS) ⁵

Restenosis (re-narrowing) after a type of angioplasty called percutaneous transluminal coronary angioplasty (PTCA) is one limitation of the long-term success of this procedure. In previous studies statins have failed to prevent restenosis. However their lack of success in the past may have been due in part to the fact that the studies did not allow a long enough follow-up time. Also, a better understanding of restenosis has led to a better evaluation of it. The REGRESS study investigated the efficacy of pravastatin in reducing restenosis after PTCA. The study considered 221 patients who had undergone PTCA. Patients were randomly selected to receive pravastatin or placebo. The pravastatin group showed a lower percentage of the artery blocked—based on the ratio of blockage to artery diameter (32% vs 45%). In addition, pravastatin provided a 7% reduction in clinical restenosis over placebo. Pravastatin, therefore, is an effective treatment to prevent restenosis after PTCA.

Effect of aggressive lipid lowering on progression of atherosclerosis after coronary artery bypass graft (CABG) ⁶

This follow-up study investigated the difference between moderate LDL lowering therapy and aggressive LDL therapy on the progression of atherosclerosis. Four hundred and two patients were randomly assigned into the two treatment groups (aggressive and moderate). The aggressive group received 75-80 mg of lovastatin daily and the moderate group received 2.5-5 mg of lovastatin. Patients in the aggressive group showed average LDL levels of 92-97 mg/dL (a 40% decrease from baseline) while patients in the moderate group had levels of 131-135 (a 12% decrease). More significantly, patients treated with the aggressive treatment had less atherosclerosis than the moderately treated group. Atherosclerosis was measured by minimum lumen diameter or by the average change in maximum arterial stenosis. This study, like the Heart Protection Study and the Reversal study demonstrates that in patients with CABG there are clear benefits to receiving aggressive LDL lowering therapy with a goal of lowering LDL cholesterol to below 100 mg/dl.

Arterial Biology for the Investigation of the Treatment of Effects of Reducing Cholesterol (ARBITER)⁷

This study further assessed the question of whether lowering LDL cholesterol to well under 100 mg/dl will have benefits above and beyond lowering levels to 100 mg/dl. This study compared pravastatin and atorvastatin, at different doses, on carotid intima-media thickness (CIMT) which is a measure commonly used as a surrogate for vascular atherosclerosis. One hundred and sixty one patients with known cardiovascular disease were randomly divided into a pravastatin (40mg/d) group (n=82) and an atorvastatin (80 mg/d) group (n=79). After one year the average LDL in the pravastatin group was 110 mg/dL and was 76 mg/dL in the atorvastatin group. The CIMT was stable in the pravastatin group while the atorvastatin group showed a regression in CIMT over 12 months. An aggressive reduction in LDL is an efficient way to induce the regression of atherosclerosis which may in turn lead to fewer coronary events.

Pravastatin in the secondary prevention of cardiovascular events in patients with kidney insufficiency⁸

Since statins have been overwhelmingly shown to reduce cardiovascular disease in the general population, this study investigated the ability of statins to reduce cardiovascular events in patients with renal insufficiency (when the kidneys lose their ability to remove waste from the body). There were 1711 participants in this study who were identified as having chronic kidney insufficiency by having a creatinine clearance of ≤ 75 mL/min. Patients were given either pravastatin or placebo. Pravastatin was associated with a lower occurrence of major coronary events but there was not a difference in total mortality between the two groups. The incidence of side effects was similar in patients receiving pravastatin to those receiving placebo. A significant finding is that patients will see the observed benefits whether or not they have kidney insufficiency and regardless of its severity. Pravastatin is therefore a safe and effective method of secondary prevention for patients who have mild chronic kidney insufficiency.

Fluvastatin and prevention of cardiac events after a successful, first percutaneous coronary intervention⁹ (LIPS study)

Percutaneous coronary intervention (PCI) is effective for short-term improvement in ischemic symptoms but has less long-term efficacy. Sixty percent of patients are free of a major adverse cardiac event (MACE) 5 years after PCI and only 33% after 10 years. The goal of this study was to assess whether fluvastatin reduces major cardiac events. A total of 1677 patients at 77 centers in Europe, Canada, and Brazil were studied. Eight hundred and forty four patients with unstable angina or silent ischemia after their first PCI were randomly assigned to receive 80 mg/d of fluvastatin and 833 a placebo. After a median follow-up time of 3.9 years 21.4% of the patients in the fluvastatin group had a MACE, compared to 26.7% in the placebo group. Also, there was a longer time before a MACE in the fluvistatin group. This study suggests that patients with average cholesterol levels will benefit from fluvistatin treatment after the first successful PCI. The LIPS study has also shown that patients treated with a stent and fluvistatin show a 28% reduction in MACE.

Atorvastatin versus simvastatin on atherosclerosis progression (ASAP) study^{10,11}

The purpose of the ASAP study was to assess the difference of aggressive versus traditional cholesterol treatment on the progression of atherosclerosis in patients with familial high cholesterol. Three hundred and twenty five patients with a family history of high cholesterol were randomly divided into an aggressive group (atorvastatin) and a traditional treatment group (simvastatin). After two years of treatment, the progression of atherosclerosis was compared between the two groups. In one test, the levels of hs-CRP were lower in patients taking atorvastatin compared to simvastatin. hs-CRP is a good marker of inflammation in atherosclerotic vascular disease. In another test—a measurement of the carotid intima media thickness—the atorvastatin group showed a regression of atherosclerosis, whereas the simvastatin group did not. These results show that aggressive lowering of LDL was accompanied by a regression of atherosclerosis in the carotid artery but conventional LDL lowering by simvastatin did not show any benefit.

The Benefit of Aggressive Lipid Lowering¹² (AVERT study)

This study examined 341 patients with stable coronary heart disease (CHD). They were randomly assigned to receive atorvastatin (80 mg/d) and conventional treatment or angioplasty followed by usual care. The differences in LDL and subsequent ischemic events were compared between the two groups. The atorvastatin/conventional treatment group showed a 48% decrease in LDL compared to an 18% decrease following angioplasty. The atorvastatin group had fewer ischemic events (13% vs 21%, $p=.048$) and a longer time before the first ischemic event ($p=.027$) when compared with the angioplasty group. Therefore aggressive lipid lowering is beneficial in patients with existing CHD.

Aggressive LDL lowering provides the greatest reduction in carotid atherosclerosis¹³

The purpose of this study was to investigate the effects on atherosclerosis of lowering LDL well below the current recommended level of 100 mg/dL. The investigators used the carotid intima media thickness (CIMT) as an indicator of atherosclerosis progression. The study compared the effects of pravastatin (40 mg/d) and atorvastatin (80mg/d) among 161 patients. The final LDL level was directly correlated with the amount of CIMT regression. Sixty-one percent of subjects with final LDL levels of < 70 mg/dL showed a regression whereas only 29% of those with final LDL of ≥ 114 mg/dL. The amount of atherosclerotic regression is directly related to absolute LDL level. The investigators recommend a lower National Cholesterol Education Program guideline.

The relation between atherosclerotic progression and cholesterol levels¹⁴

This study assessed the long-term (average of 18.3 months) progression or regression of atherosclerotic plaque in the left main coronary artery (LMCA) by intravascular ultrasound (IVUS). IVUS studies were performed on the LMCA of 60 patients. LDL and plaque progression were positively correlated (i.e. the more LDL, the more plaque). The researchers calculated that LDL levels below 75 mg/dL would not predict any progression of atherosclerosis (i.e. it would be essentially stopped, but not necessarily regress). Also, there was a negative correlation between HDL and plaque (i.e. more HDL less plaque). Therefore lower LDL (at least below 75 mg/dL) and higher HDL slows or halts progression of atherosclerosis. This study is particularly useful because unlike other similar studies it examined the effects of HDL cholesterol on atherosclerotic plaque.

TNT. Intensive lipid lowering with Atorvastatin in patients with stable coronary disease¹⁵

10,001 cases with stable coronary heart disease, all started on Lipitor 10 mg, and after run in period, half to 80 mg, half remained on 10 mg. LDL remained at 101 mg/dl in the half on 10 mg, fell to 77 on the 80 mg. Reduction in CHD events 22% ($p<.01$), 27% reduction in stroke ($p<.01$).

ASTEROID: Effect of very high-intensity statin therapy on regression of coronary atherosclerosis.¹⁶

507 cases had baseline IVUS and received Crestor, 40 mg/day. After 24 months, 349 patients had evaluable serial IVUS examinations. Mean \pm SD baseline LDL of 130 ± 34 fell to 61 ± 20 mg/dl, a mean reduction of 53.2% ($p < .0001$). HDL increased by 14.7%. This resulted in significant regression of atherosclerosis for all 3 prespecified IVUS measures of disease burden.

West of Scotland: Long term follow-up of the West of Scotland Coronary Prevention Study.¹⁷
Ford I, Murray H, Packard CJ, NEJM 2007;357:1477-86.

BACKGROUND: The West of Scotland Coronary Prevention Study was a randomized clinical trial comparing pravastatin with placebo in men with hypercholesterolemia who did not have a history of myocardial infarction, with an average follow-up of approximately 5 years. The combined outcome of death from definite coronary heart disease or definite nonfatal myocardial infarction was reduced from 7.9 to 5.5% ($P < 0.001$) in the treatment group. Extended follow-up data were obtained for approximately 10 years after completion of the trial. **METHODS:** For the survivors of the trial, all deaths, hospitalizations and deaths due to coronary events and stroke, and incident cancers and deaths from cancer were tracked with the use of a national computerized record-linkage system. The results were analyzed with time-to-event analyses and use of Cox proportional-hazards models. **RESULTS:** Five years after the trial ended, 38.7% of the original statin group and 35.2% of the original placebo group were being treated with a statin. In the period approximately 10 years after completion of the trial, the risk of death from coronary heart disease or nonfatal myocardial infarction was 10.3% in the placebo group and 8.6% in the pravastatin group ($P = 0.02$); over the entire follow-up period, the rate was 15.5% in the placebo group and 11.8% in the pravastatin group ($P < 0.001$). Similar percentage reductions were seen in the combined rate of death from coronary heart disease and hospitalization for coronary events for both periods. The rate of death from cardiovascular causes was reduced ($P = 0.01$), as was the rate of death from any cause ($P = 0.03$), over the entire follow-up period. There were no excess deaths from noncardiovascular causes or excess fatal or incident cancers. **CONCLUSIONS:** In this analysis, 5 years of treatment with pravastatin was associated with a significant reduction in coronary events for a subsequent 10 years in men with hypercholesterolemia who did not have a history of myocardial infarction. Copyright 2007 Massachusetts Medical Society.

PMID: 17928595 [PubMed - in process]

Related Links

[Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia. West of Scotland Coronary Prevention Study Group. \[N Engl J Med. 1995\]](#)

[The anatomy of a clinical trial. The West of Scotland Coronary Prevention Study. \[Med Princ Pract. 2002\]](#)

[Prevention of cardiovascular events and death with pravastatin in patients with coronary heart disease and a broad range of initial cholesterol levels. The Long-Term Intervention with Pravastatin in Ischaemic Disease \(LIPID\) Study Group. \[N Engl J Med. 1998\]](#)

[MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. \[Lancet. 2002\]](#)

[Baseline risk factors and their association with outcome in the West of Scotland Coronary Prevention Study. The West of Scotland Coronary Prevention Study Group. \[Am J Cardiol. 1997\]](#)

Crouse JR, Raichlen JS, Riley WA et al. **Effect of Rosuvastatin on progression of carotid intima-media thickness in low-risk individuals with subclinical atherosclerosis: The Meteor Trial. JAMA 2007;1344-53, 2007.**¹⁸

CONTEXT: Atherosclerosis is often advanced before symptoms appear and it is not clear whether treatment is beneficial in middle-aged individuals with a low Framingham risk score (FRS) and mild to moderate subclinical atherosclerosis. **OBJECTIVE:** To assess whether statin therapy could slow progression and/or cause regression of carotid intima-media thickness (CIMT) over 2 years. **DESIGN, SETTING, AND PARTICIPANTS:** Randomized, double-blind, placebo-controlled study (Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin [METEOR]) of 984 individuals, with either age (mean, 57 years) as the only coronary heart disease risk factor or a 10-year FRS of less than 10%, modest CIMT thickening ($1.2 < 3.5$ mm), and elevated LDL cholesterol (mean, 154 mg/dL);

conducted at 61 primary care centers in the United States and Europe between August 2002 and May 2006. INTERVENTION: Participants received either a 40-mg dose of rosuvastatin or placebo. MAIN OUTCOME MEASURES: Rate of change in maximum CIMT (assessed with B-mode ultrasound) for 12 carotid sites; changes in maximum CIMT of the common carotid artery, carotid bulb, and internal carotid artery sites and in mean CIMT of the common carotid artery sites. CIMT regression was assessed in the rosuvastatin group only. RESULTS: Among participants in the rosuvastatin group, the mean (SD) baseline LDL cholesterol level of 155 (24.1) mg/dL declined to 78 (27.5) mg/dL, a mean reduction of 49% ($P < .001$ vs placebo group). The change in maximum CIMT for the 12 carotid sites was -0.0014 (95% CI, -0.0041 to 0.0014) mm/y for the rosuvastatin group vs 0.0131 (95% CI, 0.0087 - 0.0174) mm/y for the placebo group ($P < .001$). The change in maximum CIMT for the rosuvastatin group was -0.0038 (95% CI, -0.0064 to -0.0013) mm/y for the common carotid artery sites ($P < .001$), -0.0040 (95% CI, -0.0090 to 0.0010) mm/y for the carotid bulb sites ($P < .001$), and 0.0039 (95% CI, -0.0009 to 0.0088) mm/y for the internal carotid artery sites ($P = .02$). The change in mean CIMT for the rosuvastatin group for the common carotid artery sites was 0.0004 (95% CI, -0.0011 to 0.0019) mm/y ($P < .001$). All P values are vs placebo group. Overall, rosuvastatin was well tolerated with infrequent serious adverse cardiovascular events (6 participants [0.86%] had 8 events [1.1%] over 2 years). CONCLUSIONS: In middle-aged adults with an FRS of less than 10% and evidence of subclinical atherosclerosis, rosuvastatin resulted in statistically significant reductions in the rate of progression of maximum CIMT over 2 years vs placebo. Rosuvastatin did not induce disease regression. Larger, longer-term trials are needed to determine the clinical implications of these findings.

Glueck CJ, Aregawi D, Agloria M, et al. **Rosuvastatin 5 and 10 mg/d: a pilot study of the effects in hypercholesterolemic adults unable to tolerate other statins and reach LDL cholesterol goals with nonstatin lipid lowering therapies.** Clin Therapeutics 2006;28: 933-942.¹⁹

BACKGROUND: Patients with high levels of low-density lipoprotein cholesterol (LDL-C) might not tolerate 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors ("statins") because of adverse effects (AEs) and might not respond well enough to nonstatin lipid-lowering therapies (LLTs) to meet LDL-C goals. OBJECTIVE: The purpose of this study was to assess the acceptability, effectiveness, and safety profile of rosuvastatin 5 and 10 mg/d in consecutively referred patients with primary high LDL-C who were unable to tolerate other statins because of myalgia and, subsequently in some cases, unable to reach LDL-C goals with nonstatin LLT. METHODS: This prospective, open-label pilot study was conducted in consecutively referred male and female patients aged 38 to 80 years with primary high LDL-C (mean, 177 mg/dL) at The Cholesterol Center, Jewish Hospital, Cincinnati, Ohio. Patients were instructed in the National Cholesterol Education Program Adult Treatment Panel III (NCEP ATP III) therapeutic lifestyle changes diet. Rosuvastatin 5 mg/d was administered to patients categorized by NCEP ATP III risk stratification as moderately high risk, and rosuvastatin 10 mg/d was administered to patients categorized as high or very high risk. End points included acceptability (assessed using patient-initiated discontinuation of rosuvastatin), effectiveness (absolute and percentage reductions in LDL-C and triglycerides), and safety profile (aspartate and alanine aminotransferases [AST and ALT, respectively] >3 times the laboratory upper limit of normal [\times ULN] or elevations in creatine kinase [CK] $>10\times$ ULN). RESULTS: A total of 61 patients were enrolled (41 women, 20 men; mean [SD] age, 60 [10] years; 5-mg/d dose, 25 patients; 10-mg/d dose, 36 patients). Myalgia, a predominant AE, had caused 50 patients to previously discontinue treatment with atorvastatin; 30, simvastatin; 19, pravastatin; 5, fluvastatin; 2, ezetimibe/simvastatin; and 1, lovastatin. Eighteen patients subsequently failed to reach LDL-C goals with nonstatin LLT(s) alone (colesevelam, 10 patients; ezetimibe, 8; niacin extended release, 2; and fenofibrate, 1). After a median treatment duration of 16 weeks, rosuvastatin 5 mg/d+diet was associated with a mean (SD) decrease from baseline in LDL-C of 75 (34) mg/dL (mean [SD] %Delta, -42% [18%]) ($P < 0.001$ vs baseline). After a median treatment duration of 44 weeks, rosuvastatin 10 mg/d+diet was associated with a mean (SD) decrease from baseline in LDL-C of 79 (49) mg/dL (mean [SD] %Delta, -42% [24%]) ($P < 0.001$ vs baseline). Of the 61 patients, 1 receiving the 10-mg/d dose discontinued rosuvastatin treatment because of unilateral muscular pain after 4 weeks; no AST or ALT levels were $>3\times$ ULN, and no CK levels were $>10\times$ ULN. CONCLUSION: In these 61 hypercholesterolemic patients unable to tolerate other statins and, subsequently in some cases, unable to meet LDL-C goals while receiving nonstatin LIT monotherapy, these preliminary observations suggest

that rosuvastatin at doses of 5 and 10 mg/d+diet was well tolerated, effective, and had a good safety profile.

] Related Links

Twelve-week, multicenter, randomized, open-label comparison of the effects of rosuvastatin 10 mg/d and atorvastatin 10 mg/d in high-risk adults: a DISCOVERY study. [Clin Ther. 2004]

The DISCOVERY PENTA study: a Direct Statin Comparison of LDL-C Value--an Evaluation of Rosuvastatin therapy compared with atorvastatin. [Curr Med Res Opin. 2005]

Effects of rosuvastatin versus atorvastatin, simvastatin, and pravastatin on non-high-density lipoprotein cholesterol, apolipoproteins, and lipid ratios in patients with hypercholesterolemia: additional results from the STELLAR trial. [Clin Ther. 2004]

Effect of rosuvastatin compared with other statins on lipid levels and National Cholesterol Education Program goal attainment for low-density lipoprotein cholesterol in a usual care setting. [Pharmacotherapy. 2006]

Lipid-altering efficacy of the ezetimibe/simvastatin single tablet versus rosuvastatin in hypercholesterolemic patients. [Curr Med Res Opin. 2006]

Mendelian Randomisation study²⁰

Rare mutations of the low-density lipoprotein receptor gene (LDLR) cause familial hypercholesterolemia, which increases the risk for coronary artery disease (CAD). Less is known about the implications of common genetic variation in the LDLR gene regarding the variability of cholesterol levels and risk of CAD. Single nucleotide polymorphism (SNP) within the LDLR gene in three European samples comprising 6 642 adults and 533 children and its association with CAD and High LDL-C was examined in six case-control studies involving more than 15 000 individuals. This association with LDL-C was uniformly found in children, men, and women of all samples studied. The study showed a functional link between the genetic variant at the LDLR gene locus, change in LDL-C and risk of CAD. So lowering LDL-C in these patients can benefit them by reducing their chances of fatal complications of CAD.

Jordan Hyperlipidaemia and Related Targets Study (JoHARTS-1)²¹

The study measured fasting serum total cholesterol (TC), triglycerides (TG), and low- and high-density lipoprotein cholesterol (LDL-C and HDL-C) levels in 5000 individuals. Coronary artery disease (CAD) was present in 31%. Compared with women, men had lower mean TC, LDL-C and HDL-C and higher mean TG. Optimal TC level was observed in only 46% of men and 41% of women, and optimal TG in 42% of men and 50% of women. Only 3% of men and 12% of women had HDL-C > 60 mg/dL. In all age groups, low HDL-C was more prevalent among men and women who had CAD.

Lipid profile and intensity of atherosclerosis disease in acute coronary syndrome²²

To evaluate the association between lipid profile and severity of CAD in patients with acute coronary syndrome without ST-segment elevation. In this retrospective study, the authors reviewed medical records of 107 consecutive patients diagnosed with acute coronary syndrome (ACS) without ST-segment elevation admitted within a one-year period and who had undergone coronary angiography during hospitalization. In the association between lipid profile and CAD, higher TC/HDL ratio was observed in the multivessel and two-vessel groups in comparison with the one-vessel group.

ENHANCE Trial.

This was a 2-year study comparing daily therapy with 80 mg of simvastatin plus either a placebo or 10 mg of ezetimibe on the average change in carotid intima-media thickness in patients with familial hypercholesterolemia. The study, called the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) trial, showed no significance between-group differences in any of several end points with respect to intima-media thickness. This seemingly rigorous and well-executed study of a combination therapy that has been approved by the Food and Drug Administration dramatically contradicts our expectations. "Lower is better". During a period of 3 to 6 years, most controlled trials of statins, resins, or partial ileal bypass have shown clinical or imaging

benefits that correlated with the concurrent reduction in LDL cholesterol.²³ The measurement of intima-media thickness has been the focus of at least 15 lipid-therapy trials. Among seven studies comparing various statins with placebo or with lower-dose statins, the progression of intima-media thickness has consistently been slowed or has even regressed with higher doses of statins. However, no study with 2 years or less of follow-up has shown a significant reduction in such events. This result is probably because 1 to 2 years are required for lipid depletion to stabilize plaque before clinical benefits emerge.^{24,25,26} If long-term therapy before entering a trial favorably alters the plaque, the potential for showing a benefit of treatment would be diminished in such patients. This finding supports the hypothesis that previous plaque lipid depletion is an explanation for the results of the ENHANCE study. The argument against this hypothesis is that, among the 19% of patients who were not receiving statins at the time of study enrollment, those who were treated with the combined regimen of simvastatin plus ezetimibe did not have a better response than did those receiving simvastatin alone. More detailed pretreatment history is needed for such patients. Finally, does the ENHANCE study prove that ezetimibe provides no benefit when added to statin therapy or, for that matter, as monotherapy? Answers to these questions, as well as results of trials that are under way,^{27,28} will clarify the findings of the ENHANCE study. The lack of benefit in the reduction of carotid plaque may be explained by the above-mentioned mechanisms, particularly by previous plaque lipid depletion, in which case a similar but longer trial in patients who have not undergone previous therapy could well show the anticipated clinical benefit of ezetimibe.

Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial

Atorvastatin versus Simvastatin on Atherosclerosis Progression (ASAP) trial,²⁹ compared daily therapy with 80 mg of atorvastatin with therapy with 40mg. The patients in this study were virtually identical in age, baseline levels of both LDL and high-density lipoprotein (HDL) when compared to patients in the ENHANCE trial. The two studies also used nearly identical methods for measuring carotid-artery intima-media thickness. In the control groups of the two trials, the in-treatment level of LDL cholesterol was 193 mg per deciliter among patients receiving 80 mg of simvastatin in the ENHANCE trial and 186 mg per deciliter among those receiving 40 mg of simvastatin in the ASAP trial. At 2 years, the increases in carotid-artery intima-media thickness were 0.0058 mm in the ENHANCE trial and 0.036 mm in the ASAP study. However, the intensive-therapy groups in the two studies differed in their responses. Among patients in the ENHANCE study who had an LDL cholesterol level of 178 mg per deciliter while receiving combination therapy with simvastatin plus ezetimibe, the carotid intima-media thickness progressed by 0.0111 mm. With a similar level of LDL cholesterol (167 mg per deciliter) during therapy with 80 mg of atorvastatin in the ASAP study, intima-media thickness regressed substantially, by 0.031 mm. Three differences between the two trials might explain this substantial discrepancy: First, the baseline intima-media thickness was 0.695 mm in the ENHANCE study, as compared with 0.925 mm in the ASAP study. Second, patients in the ENHANCE study almost certainly had a longer and more intensive history of statin therapy than did those entering the ASAP study 6 years earlier. And third, the intensive-therapy group in the ENHANCE study received ezetimibe, whereas the corresponding group in the ASAP study did not. These findings further question the validity of the ENHANCE trial and need for further studies.

Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial

The Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) study evaluated the effects of combination ezetimibe and simvastatin on clinical outcomes in patients with aortic stenosis. It was a randomized, double-blind trial involving 1873 patients with mild-to-moderate, asymptomatic aortic stenosis. The patients received either 40 mg of simvastatin plus 10 mg of ezetimibe or placebo daily. The primary outcome was a composite of major cardiovascular events, including death from cardiovascular causes, aortic-valve replacement, nonfatal myocardial infarction, hospitalization for unstable angina

pectoris, heart failure, coronary-artery bypass grafting, percutaneous coronary intervention, and nonhemorrhagic stroke. Secondary outcomes were events related to aortic-valve stenosis and ischemic cardiovascular events. The study showed that the cholesterol-lowering combination was no better than placebo in reducing the primary composite end point of aortic valve and cardiovascular events. Simvastatin and ezetimibe did not reduce the composite outcome of combined aortic-valve events and ischemic events in patients with aortic stenosis. Such therapy reduced the incidence of ischemic cardiovascular events by 22% but not events related to aortic-valve stenosis.

Rosuvastatin with atorvastatin for achieving lipid goals in Asian patients at high risk of cardiovascular disease (DISCOVERY-Asia study)

This study focused on evaluating the lipid-lowering effects of rosuvastatin and atorvastatin in Asian patients. Evaluation of Rosuvastatin therapy (DISCOVERY-Asia study) is one of nine independently powered studies assessing the efficacy of starting doses of statins in achieving target lipid levels in different countries worldwide. DISCOVERY-Asia was a 12-week, randomized, open-label, parallel-group study conducted in China, Hong Kong, Korea, Malaysia, Taiwan, and Thailand. A total of 1482 adults with primary hypercholesterolaemia and high cardiovascular risk (> 20%/10 years, type 2 diabetes, or a history of coronary heart disease) were randomized in a 2 : 1 ratio to receive rosuvastatin 10 mg or atorvastatin 10 mg once daily. This 12-week study showed that the starting dose of rosuvastatin 10 mg. was significantly more effective than the starting dose of atorvastatin 10 mg. at enabling patients with primary hypercholesterolaemia to achieve European goals for LDL-C and TC in a largely Asian population in real-life clinical practice. The safety profile of rosuvastatin 10 mg is similar to that of atorvastatin 10 mg in the Asian population studied here, and is consistent with the known safety profile of rosuvastatin in the white population.

Ref: Zhu, J. R., B. Tomlinson, et al. (2007). "A randomized study comparing the efficacy and safety of rosuvastatin with atorvastatin for achieving lipid goals in clinical practice in Asian patients at high risk of cardiovascular disease (DISCOVERY-Asia study)." *Curr Med Res Opin* **23**(12): 3055-68.

Lipid trial protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial

The Action to Control Cardiovascular Risk in Diabetes (ACCORD) lipid trial aimed to test whether statin plus a fibrate is more efficacious in reducing cardiovascular events than a statin plus placebo in patients with type 2 diabetes mellitus with defined glycemic control. This was a blinded component in a 5,518-patient subset of the ACCORD cohort. Participants were randomized to either be (1) treated with simvastatin (titrated to 40 mg/day if necessary to achieve a goal low-density lipoprotein [LDL] of 100 mg/dL) plus placebo or (2) treated to the same goal LDL cholesterol level with the statin plus active fenofibrate 160 mg/day.

Recruitment for ACCORD began in January 2001, and follow-up is scheduled to end in June 2009. The protocol is designed to provide an ethically justifiable test of combined statin plus fibrate treatment consistent with the highest level of safety and lipid treatment standards of care.

Ref: Ginsberg, H. N., D. E. Bonds, et al. (2007). "Evolution of the lipid trial protocol of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial." *Am J Cardiol* **99**(12A): 56i-67i.

Ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels.

The lowering effects of ezetimibe/simvastatin combination therapy on low-density lipoprotein (LDL) cholesterol and high-sensitivity C-reactive protein (CRP) were compared with those of simvastatin or

atorvastatin monotherapy in a large cohort of patients with primary hypercholesterolemia. Data were combined from 3 identical, prospective 12-week trials in which patients were randomized to receive placebo; ezetimibe 10 mg; ezetimibe 10 mg added to simvastatin 10, 20, 40, or 80 mg; or simvastatin 10, 20, 40, or 80 mg. At each individual simvastatin dose, co-administration with ezetimibe produced significant further CRP reductions versus simvastatin alone. Ezetimibe/simvastatin was significantly more effective at lowering LDL cholesterol than atorvastatin. The lipid-modulating and anti-inflammatory effects of ezetimibe/simvastatin provide additional benefits not realized by statin monotherapy alone.

Ref: Pearson, T., C. Ballantyne, et al. (2007). "Comparison of effects of ezetimibe/simvastatin versus simvastatin versus atorvastatin in reducing C-reactive protein and low-density lipoprotein cholesterol levels." Am J Cardiol **99**(12): 1706-1713

Impact of Triglyceride Levels After Acute Coronary Syndrome.

"Impact of Triglycerides beyond low density lipoprotein cholesterol after acute coronary syndrome in the PROVE IT-TIMI 22 trial" was a study done to assess the impact of triglycerides (TG) levels on coronary heart disease (CHD) risk after an acute coronary syndrome (ACS). The PROVE IT-TIMI (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction) 22 trial demonstrated that low-density lipoprotein cholesterol (LDL-C) <70 mg/dl was associated with greater CHD event reduction than LDL-C <100 mg/dl after ACS. However, the impact of low TG on CHD risk beyond LDL-C <70 mg/dl was not explored. On-treatment TG <150 mg/dl was independently associated with a lower risk of recurrent CHD events, lending support to the concept that achieving low TG may be an additional consideration beyond low LDL-C in patients after ACS.

JUPITER trial

The primary objective of the JUPITER trial (Justification for the use of statins in the Primary prevention: an intervention trial Evaluating rosuvastatin) was to determine whether long-term treatment with rosuvastatin (20 mg orally per day) will reduce the rate of first major cardiovascular events such as stroke, myocardial infarction, hospitalization for unstable angina, or arterial revascularization among individuals with LDL-C levels <130 mg/dL who are at high vascular risk because of an enhanced inflammatory response as indicated by hsCRP levels ≥ 2 mg/L. Secondary objectives of JUPITER were to evaluate the safety of long-term treatment with rosuvastatin in terms of total mortality, noncardiovascular mortality, and adverse events and to determine whether rosuvastatin reduces the incidence of type 2 diabetes. This latter objective reflects the fact that hsCRP levels also predict the onset of diabetes³⁰ and that inflammation appears to be a critical link between diabetes and atherothrombosis. On March 31st 2008 the pharmaceutical company who was supporting the study announced that they they were stopping the JUPITAR clinical trial because early findings showed that the drug reduced deaths and risk of heart problems in patients compared to placebo. The trial was taking place at over 1200 locations in 26 countries with over 15000 men over age 55 and women over 65 years or older 31.

Comparing impact and cost-effectiveness of primary prevention strategies for lipid-lowering³²

BACKGROUND: Lipid-lowering therapy is costly but effective at reducing coronary heart disease (CHD) risk. OBJECTIVE: To assess the cost-effectiveness and public health impact of Adult Treatment Panel III (ATP III) guidelines and compare with a range of risk- and age-based alternative strategies. DESIGN: The CHD Policy Model, a Markov-type cost-effectiveness model. DATA SOURCES: National surveys (1999 to 2004), vital statistics (2000), the Framingham Heart Study (1948 to 2000), other published data, and a direct survey of statin costs (2008). TARGET POPULATION: U.S. population age 35 to 85 years. Time Horizon: 2010 to 2040. PERSPECTIVE: Health care system. INTERVENTION: Lowering of low-density lipoprotein cholesterol with HMG-CoA reductase inhibitors (statins). OUTCOME MEASURE: Incremental cost-effectiveness. RESULTS OF BASE-CASE ANALYSIS: Full adherence to ATP III primary prevention guidelines would require starting (9.7 million) or intensifying (1.4 million) statin therapy for 11.1 million adults and would prevent 20,000 myocardial infarctions and 10,000 CHD deaths

per year at an annual net cost of \$3.6 billion (\$42,000/QALY) if low-intensity statins cost \$2.11 per pill. The ATP III guidelines would be preferred over alternative strategies if society is willing to pay \$50,000/QALY and statins cost \$1.54 to \$2.21 per pill. At higher statin costs, ATP III is not cost-effective; at lower costs, more liberal statin-prescribing strategies would be preferred; and at costs less than \$0.10 per pill, treating all persons with low-density lipoprotein cholesterol levels greater than 3.4 mmol/L (>130 mg/dL) would yield net cost savings. RESULTS OF SENSITIVITY ANALYSIS: Results are sensitive to the assumptions that LDL cholesterol becomes less important as a risk factor with increasing age and that little disutility results from taking a pill every day. LIMITATION: Randomized trial evidence for statin effectiveness is not available for all subgroups. CONCLUSION: The ATP III guidelines are relatively cost-effective and would have a large public health impact if implemented fully in the United States. Alternate strategies may be preferred, however, depending on the cost of statins and how much society is willing to pay for better health outcomes. FUNDING: Flight Attendants' Medical Research Institute and the Swanson Family Fund. The Framingham Heart Study and Framingham Offspring Study are conducted and supported by the National Heart, Lung, and Blood Institute.

Statin therapy in the elderly: A review³³

Cardiovascular morbidity is the leading cause of mortality in the developed nations. Elevated serum cholesterol is a major risk factor for ischemic heart disease, one of the common cardiovascular morbidity in older adults, statins have been shown to be effective in reducing serum cholesterol and improving outcomes. Hypercholesterolemia is common in older adults and is one of the major modifiable risk factors. Yet, these patients have often been excluded from major clinical trials of statins and evidence suggests of their underuse. Data from recent clinical trials of statins indicate that the elderly patients with the highest cardiovascular risk are likely to derive the most benefits from cholesterol lowering. With the aging of the population, the prevalence of hypercholesterolemia and cardiovascular morbidity is likely to increase. In this review we evaluate the evidence for the use of statins in older adults.

Meta-analysis of the relationship between non-high-density lipoprotein cholesterol reduction and coronary heart disease risk³⁴

OBJECTIVES: To determine the relationship between non-high-density lipoprotein cholesterol (HDL-C) lowering and coronary heart disease (CHD) risk reduction for various lipid-modifying therapies. BACKGROUND: Non-HDL-C is the second lipid target of therapy after low-density lipoprotein cholesterol (LDL-C). METHODS: Randomized placebo or active-controlled trials were evaluated. The effect of mean non-HDL-C reduction on the relative risk of nonfatal myocardial infarction and CHD death was estimated using Bayesian random-effects meta-analysis models adjusted for study duration. Cochrane's Q was used to test for heterogeneity. RESULTS: Inclusion criteria were met by 14 statin (n = 100,827), 7 fibrate (n = 21,647), and 6 niacin (n = 4,445) trials, and 1 trial each of a bile acid sequestrant (n = 3,806), diet (n = 458), and ileal bypass surgery (n = 838). For statins, each 1% decrease in non-HDL-C resulted in an estimated 4.5-year CHD relative risk of 0.99 (95% Bayesian confidence interval: 0.98 to 1.00). The fibrate model did not differ from the statin model (Bayes factor K = 0.49) with no evidence of heterogeneity. The niacin model was moderately different from the statin model (K = 7.43), with heterogeneity among the trials (Q = 11.8, 5 df; p = 0.038). The only niacin monotherapy trial (n = 3,908) had a 1:1 relationship between non-HDL-C and risk reduction. No consistent relationships were apparent for the 5 small trials of niacin in combination. The 95% confidence intervals for the single trials of diet, bile acid sequestrants, and surgery also included the 1:1 relationship. CONCLUSIONS: Non-HDL-C is an important target of therapy for CHD prevention. Most lipid-modifying drugs used as monotherapy have an approximately 1:1 relationship between percent non-HDL-C lowering and CHD reduction.

Lipoprotein predictors of cardiovascular events in statin-treated patients with coronary heart disease. Insights from the Incremental Decrease In End-points Through Aggressive Lipid-lowering Trial (IDEAL)³⁵

BACKGROUND: Few studies have looked into the ability of measurements of apolipoprotein B (apoB) and apolipoprotein A-1 (apoA-1) or apoB/apoA-1 to predict new coronary heart disease (CHD) events in patients with CHD on statin treatment. AIMS: In the IDEAL trial, to compare lipoprotein components to predict CHD events and to what degree differences in those parameters could explain the observed

outcome. METHODS: We compared the ability of treatment with atorvastatin 80 mg/day to that of simvastatin 20-40 mg/day to prevent CHD events in patients with CHD and used Cox regression models to study the relationships between on-treatment levels of lipoprotein components to subsequent major coronary events (MCE). FINDINGS: Variables related to low-density lipoprotein cholesterol (LDL-C) carried more predictive information than those related to high-density lipoprotein cholesterol (HDL-C), but LDL-C was less predictive than both non-HDL-C and apoB. The ratio of apoB to apoA-1 was most strongly related to MCE. However, for estimating differences in relative risk reduction between the treatment groups, apoB and non-HDL-C were the strongest predictors. INTERPRETATION: The on-treatment level of apoB/apoA-1 was the strongest predictor of MCE in the pooled patient population, whereas apoB and non-HDL-C were best able to explain the difference in outcome between treatment groups. Measurements of apoB and apoA-1 should be more widely available for routine clinical assessments.

Pravastatin for cardiovascular event primary prevention in patients with mild-to-moderate hypertension in the Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) Study³⁶

Lipid-lowering therapy in individuals with high risk of cardiovascular disease reduces the incidence of coronary heart disease. However, few studies have assessed the benefits of cholesterol lowering for primary prevention of coronary heart disease in hypertensive patients with mild dyslipidemia or without conventional dyslipidemia. The large, randomized Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese Study showed a 33% reduction in coronary heart disease incidence with pravastatin as the primary prevention in Japanese patients. We conducted an exploratory analysis of the effect of diet plus pravastatin therapy on the primary prevention of cardiovascular events (coronary heart disease, coronary heart disease plus cerebral infarction, and cardiovascular disease) in the 3277 patients with hypertension during the 5-year follow-up. There were no significant differences in mean baseline total cholesterol, blood pressure levels, or variation in blood pressure during the 5-year period between the diet (n=1664) and diet plus pravastatin (n=1613) groups. In the diet plus pravastatin group, the relative risk of coronary heart disease plus cerebral infarction was reduced by 35% (hazard ratio: 0.65; CI: 0.46 to 0.93; P=0.02), cerebral infarction by 46% (hazard ratio: 0.54; CI: 0.29 to 0.98; P=0.04), and cardiovascular disease by 33% (hazard ratio: 0.67; CI: 0.49 to 0.91; P=0.01). In patients without a history of cardiovascular disease who have hypertension and mildly elevated cholesterol, pravastatin was effective in reducing the incidence of cardiovascular disease, particularly cerebral infarction. Hence, in patients with hypertension with mildly elevated cholesterol levels, treatment with a statin is advisable to reduce the burden of cardiovascular disease.

Lipid levels in patients hospitalized with coronary artery disease: an analysis of 136,905 hospitalizations in Get With The Guidelines³⁷

BACKGROUND: Lipid levels among contemporary patients hospitalized with coronary artery disease (CAD) have not been well studied. This study aimed to analyze admission lipid levels in a broad contemporary population of patients hospitalized with CAD. METHODS: The Get With The Guidelines database was analyzed for CAD hospitalizations from 2000 to 2006 with documented lipid levels in the first 24 hours of admission. Patients were divided into low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), and triglyceride categories. Factors associated with LDL and HDL levels were assessed along with temporal trends. RESULTS: Of 231,986 hospitalizations from 541 hospitals, admission lipid levels were documented in 136,905 (59.0%). Mean lipid levels were LDL 104.9 +/- 39.8, HDL 39.7 +/- 13.2, and triglyceride 161 +/- 128 mg/dL. Low-density lipoprotein cholesterol <70 mg/dL was observed in 17.6% and ideal levels (LDL <70 with HDL > or =60 mg/dL) in only 1.4%. High-density lipoprotein cholesterol was <40 mg/dL in 54.6% of patients. Before admission, only 28,944 (21.1%) patients were receiving lipid-lowering medications. Predictors for higher LDL included female gender, no diabetes, history of hyperlipidemia, no prior lipid-lowering medications, and presenting with acute coronary syndrome. Both LDL and HDL levels declined over time (P < .0001). CONCLUSIONS: In a large cohort of patients hospitalized with CAD, almost half have admission LDL levels <100 mg/dL. More than half the patients have admission HDL levels <40 mg/dL, whereas <10% have HDL > or =60 mg/dL. These findings may provide further support for recent guideline revisions with even lower LDL goals and for developing effective treatments to raise HDL.

Further LDL cholesterol lowering through targeting PCSK9 for coronary artery disease ³⁸

Proprotein convertase subtilisin/kexin type 9 (PCSK9) is a serine protease that belongs to the proprotein convertase family. PCSK9 is synthesized as a zymogen and its prodomain is cleaved by its own catalytic activity. The cleaved prodomain forms a protein complex with the rest of the PCSK9 carboxyl terminus within the endoplasmic reticulum and is secreted. Secreted PCSK9 has been shown to be able to reduce low-density lipoprotein receptor (LDLR) levels in vitro and in vivo. Thus PCSK9 has emerged as an important player modulating LDLR levels and plasma LDL cholesterol. Furthermore, PCSK9 deficiency leads to significantly lowered LDL cholesterol levels in humans and provides dramatic protection against coronary heart disease. We review here the current understanding of PCSK9 and its potential as a therapeutic target through which to reduce LDL cholesterol for prevention and treatment of coronary heart disease.

Rationale and design of IMPROVE-IT (IMProved Reduction of Outcomes: Vytorin Efficacy International Trial): comparison of ezetimibe/simvastatin versus simvastatin monotherapy on cardiovascular outcomes in patients with acute coronary syndromes ³⁹

BACKGROUND: Reduction in low-density lipoprotein cholesterol (LDL-C) improves clinical outcomes in patients with chronic coronary artery disease and acute coronary syndromes (ACSs). The combination of ezetimibe/simvastatin produces greater reductions in LDL-C compared to simvastatin monotherapy. The IMProved Reduction of Outcomes: Vytorin Efficacy International Trial (IMPROVE-IT) is a multicenter, randomized, double-blind, active-control trial designed to test the hypothesis that the addition of ezetimibe to statin therapy, using ezetimibe/simvastatin, will translate into increased clinical benefit on cardiovascular outcomes relative to simvastatin monotherapy in patients with ACS. **STUDY DESIGN:** The study will recruit up to 18,000 moderate- to high-risk patients stabilized after ACS. Patients are randomized in a 1:1 ratio to once-daily doses of either ezetimibe/simvastatin 10/40 mg or simvastatin monotherapy 40 mg. Follow-up visits are at 1 and 4 months, and every 4 months thereafter. If consecutive measures of LDL-C are >79 mg/dL at follow-up visits, the simvastatin dose will be increased to 80 mg in a double-blind manner. The primary end point is the first occurrence of cardiovascular death, nonfatal myocardial infarction, rehospitalization for unstable angina, coronary revascularization (occurring at least 30 days after randomization), or stroke. Patients will be followed for a minimum of 2.5 years and until at least 5,250 patients experience a primary end point. **SUMMARY:** IMPROVE-IT will determine whether the addition of ezetimibe to statin therapy, using ezetimibe/simvastatin, improves cardiovascular outcomes compared with simvastatin monotherapy in patients after ACS. In addition, the difference in achieved LDL-C levels between the groups will provide data on whether the target for LDL-C lowering should be reduced further.

Cholesterol levels and in-hospital mortality in patients with acute decompensated heart failure ⁴⁰

BACKGROUND: In chronic heart failure (HF), lower total cholesterol (TC) levels have been associated with increased mortality. However, the relationship between lipid levels and outcomes in acute HF has not been studied. This study investigates the relationship between cholesterol levels and in-hospital mortality in patients hospitalized with acute HF. **METHODS:** The Get With the Guidelines-Heart Failure registry prospectively collects data on patients hospitalized with HF. We analyzed data on 17,791 patients admitted between January 2005 and June 2007 at 236 participating hospitals who had TC levels recorded. Baseline patient characteristics, treatment regimens, and in-hospital mortality were examined by TC level (mg/dL) quartiles (Q) as follows: Q1 (TC < or =118), Q2 (TC 119-145), Q3 (TC 146-179), and Q4 (TC > or =180). **RESULTS:** Mean TC level was 150 +/- 47 mg/dL. Patients with lower TC were older and had higher prevalence of ischemic heart disease. Of the patients, 46% were on a lipid-lowering drug, including 58%, 50%, 43%, and 34% of patients in TC Q1 to Q4, respectively. In-hospital mortality in TC Q1 to Q4 was 3.3%, 2.5%, 2.0%, and 1.3%, respectively (P < .0001). On multivariable adjusted analyses, each 10-mg/dL increase in TC level was associated with 4% decreased risk of in-hospital mortality (odds ratio 0.96, 95% CI 0.93-0.98). **CONCLUSIONS:** In patients hospitalized with HF, lower TC levels independently predict increased in-hospital mortality risk. Further evaluation of optimal cholesterol levels and influence of lipid-lowering medication use on outcomes in this population is warranted.

Efficacy and safety of ezetimibe added on to atorvastatin (40 mg) compared with uptitration of atorvastatin (to 80 mg) in hypercholesterolemic patients at high risk of coronary heart disease⁴¹.

The percentage of change from baseline in low-density lipoprotein (LDL) cholesterol after the addition of ezetimibe 10 mg to atorvastatin 40 mg was compared with uptitration to atorvastatin 80 mg. In this multicenter, double-blind, parallel-group study, adult hypercholesterolemic patients using atorvastatin 40 mg/day were randomly assigned to atorvastatin 40 mg plus ezetimibe 10 mg or uptitration to atorvastatin 80 mg. After 6 weeks of treatment, compared with atorvastatin 80 mg, atorvastatin 40 mg plus ezetimibe significantly reduced the primary end point of LDL cholesterol by -27% versus atorvastatin 80 mg by -11% ($p < 0.001$), as well as significantly reduced non-high-density lipoprotein cholesterol, apolipoprotein B, total cholesterol, and triglycerides significantly more than atorvastatin 80 mg (all $p < 0.001$). Percentages of change in high-sensitivity C-reactive protein, high-density lipoprotein cholesterol, and apolipoprotein A-I were similar between groups. Significantly more patients treated with atorvastatin 40 mg plus ezetimibe reached LDL cholesterol < 70 mg/dl versus patients treated with atorvastatin 80 mg (74% vs 32%; $p < 0.001$). Safety and tolerability profiles and incidence of liver and muscle adverse experiences were generally similar between groups. In conclusion, these results showed that adding ezetimibe to atorvastatin 40 mg was significantly more effective than uptitrating to atorvastatin 80 mg at lowering LDL cholesterol and other lipid parameters. Both treatments were generally well tolerated (clinical trial no.

Efficacy and safety of ezetimibe added on to atorvastatin (20 mg) versus uptitration of atorvastatin (to 40 mg) in hypercholesterolemic patients at moderately high risk for coronary heart disease⁴².

The aim of this study was to evaluate the efficacy and safety of ezetimibe 10 mg added to atorvastatin 20 mg compared with doubling atorvastatin to 40 mg in patients with hypercholesterolemia at moderately high risk for coronary heart disease who did not reach low-density lipoprotein (LDL) cholesterol levels < 100 mg/dl with atorvastatin 20 mg. In this 6-week, multicenter, double-blind, randomized, parallel-group study, 196 patients treated with atorvastatin 20 mg received atorvastatin 20 mg plus ezetimibe 10 mg or atorvastatin 40 mg for 6 weeks. Adding ezetimibe 10 mg to atorvastatin 20 mg produced significantly greater reductions in LDL cholesterol than increasing atorvastatin to 40 mg (-31% vs -11%, $p < 0.001$). Significantly greater reductions were also seen in non-high-density lipoprotein cholesterol, total cholesterol, and apolipoprotein B ($p < 0.001$). Significantly more patients reached LDL cholesterol levels < 100 mg/dl with atorvastatin 20 mg plus ezetimibe compared with atorvastatin 40 mg (84% vs 49%, $p < 0.001$). The 2 treatment groups had comparable results for high-density lipoprotein cholesterol, triglycerides, apolipoprotein A-I, and high-sensitivity C-reactive protein. The incidences of clinical and laboratory adverse experiences were generally similar between groups. In conclusion, the addition of ezetimibe 10 mg to atorvastatin 20 mg was generally well tolerated and resulted in significantly greater lipid-lowering efficacy compared with doubling atorvastatin to 40 mg in patients with hypercholesterolemia at moderately high risk for coronary heart disease.

Comparison of effectiveness of atorvastatin 10 mg versus 80 mg in reducing major cardiovascular events and repeat revascularization in patients with previous percutaneous coronary intervention (post hoc analysis of the Treating to New Targets [TNT] Study)⁴³.

The Treating to New Targets (TNT) study demonstrated that intensive atorvastatin therapy to achieve low-density lipoprotein cholesterol concentrations well below recommended target levels provides an incremental clinical benefit in patients with stable coronary artery disease. This post hoc analysis of the TNT study was conducted to investigate whether this benefit extends to patients with previous percutaneous coronary intervention (PCI). A total of 10,001 patients with clinically evident coronary artery disease, including 5,407 patients with previous PCI, were randomized to atorvastatin 10 or 80 mg/day and followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event. Revascularization, a component of a secondary end point, was also examined. In patients with previous PCI, mean low-density lipoprotein cholesterol levels at study end were 79.5 mg/dl in the 80-mg arm and 100.8 mg/dl in the 10-mg arm. First major cardiovascular events occurred in 230 patients (8.6%) receiving high-dose atorvastatin and 289 patients (10.6%) receiving low-dose atorvastatin (hazard ratio 0.79, 95% confidence interval 0.67 to 0.94, $p = 0.008$). Repeat revascularization during follow-up (PCI or coronary artery bypass grafting) was performed in 466

patients (17.3%) in the 80-mg arm and 624 patients (22.9%) in the 10-mg arm (hazard ratio 0.73, 95% confidence interval 0.65 to 0.82, $p < 0.0001$). In conclusion, intensive lipid lowering to a mean low-density lipoprotein cholesterol level of 79.5 mg/dl (2.1 mmol/L) with atorvastatin 80 mg/day in patients with previous PCI reduces major cardiovascular events by 21% and repeat revascularizations by 27% compared with a less intensive lipid-lowering regimen.

[Comparative assessment of antiinflammatory action of atorvastatin in ischemic heart disease and rheumatoid arthritis]⁴⁴

AIM: To assess dynamics of marker of inflammation (C-reactive protein - CRP) and parameters of lipid metabolism at the background of 3-months course application of 2 standard variants of therapy with atorvastatin (40 and 10 mg/day) in patients with rheumatoid arthritis (RA) compared with patients with ischemic heart disease (IHD) with moderate hyperlipidemia. MATERIAL AND METHODS: Patients of both sexes ($n=64$, 40 with IHD, 24 with RA, age from 45 to 60 years) with moderate hyperlipidemia and positive reaction to CRP were included into the study. Measures of efficacy of therapy with atorvastatin were percent changes of CRP, total (T) cholesterol (CH), and low density lipoprotein (LDL) CH compared with initial values. RESULTS: Portions of patients with IHD and RA who achieved target LDLCH level < 2.6 mmol/l were 84 and 67% on atorvastatin 40 mg/day, 44 and 50% on atorvastatin 10 mg/day, respectively. Changes of blood serum concentrations of triglycerides and high density lipoprotein CH were insignificant in all groups. Most pronounced lowering of CRP took place in a subgroups of IHD patients with initially high CRP level (-20%) and patients with RA (-65%) to whom atorvastatin was prescribed in a dose of 40 mg/day. Changes in patients in other subgroups were not significant. CONCLUSION: HMG-CoA-reductase inhibitor atorvastatin more effectively lowers concentration of CRP in blood plasma of patients with PA than with IHD what possibly is explained by higher initial level of this marker of inflammatory processes.

Small LDL-cholesterol is superior to LDL-cholesterol for determining severe coronary atherosclerosis⁴⁵

AIM: Recent evidence suggests that small dense low-density lipoprotein (sd-LDL) particles are more atherogenic than large-LDL in spite of their lower cholesterol content. This study aimed to determine whether sd-LDL-cholesterol (sd-LDL-C) is superior to LDL-C as a biomarker of coronary heart disease (CHD). METHODS: LDL particle size determined by gradient gel electrophoresis and sd-LDL-C concentrations quantified by heparin-magnesium precipitation were compared between 482 stable CHD patients and 389 non-diabetic subjects without CHD who were not receiving any lipid-lowering drugs. RESULTS: Both male and female CHD patients had significantly smaller LDL particles and lower large-LDL-C concentrations (estimated by subtracting the sd-LDL-C concentration from the LDL-C concentration), and significantly higher sd-LDL-C concentrations than the control subjects. LDL-C concentrations were modestly higher and sd-LDL-C concentrations were significantly higher in 258 patients with angiographically documented severe CHD than in the patients with mild CHD irrespective of treatment by LDL-lowering drugs and history of myocardial infarction and/or coronary revascularization. Large-LDL-C concentrations, in contrast, were similar between the two groups. Multivariate logistic regression analysis revealed that sd-LDL-C levels were significantly associated with severe CHD independently of LDL-C. CONCLUSION: sd-LDL-C levels are more powerful than LDL-C levels for the determination of severe stable CHD.

Relation between previous lipid-lowering therapy and infarct size (creatin kinase-MB level) in patients presenting with acute myocardial infarction⁴⁶

Animal experimental data have shown that lipid-lowering agents reduce myocardial infarct size. This association has not been well studied in humans. We compared infarct size in 10,548 patients in the GUSTO IIb and PURSUIT trials who were ($n = 1,028$) or were not ($n = 9,520$) on lipid-lowering therapy before an enrolling myocardial infarction (MI). Patients using lipid-lowering agents before their index MI had smaller infarcts than those who were not using these agents (median peak creatine kinase [CK]-MB 4.2 vs 5.2 times the upper limit of normal [ULN]; $p < 0.0001$). Similarly, in an unadjusted model, patients on previous lipid-lowering therapy were less likely to have a peak CK-MB > 3 times the ULN (620 of 1,028 [60.3%] vs 6,486 of 9,520 patients [68.1%]; $p < 0.001$; relative risk 0.88, 95% confidence interval 0.84 to 0.93, $p < 0.0001$). In a covariate- and propensity-adjusted multivariable model, the association

between pretreatment with lipid-lowering agents and smaller infarct size persisted (relative risk for CK-MB >3 times the ULN 0.94, 95% confidence interval 0.88 to 0.99, $p = 0.04$). In conclusion, patients on lipid-lowering agents before an MI had significantly smaller infarcts. These findings suggest that lipid-lowering therapy may exert additional salutary effects in the setting of acute coronary syndromes.

Pleiotropic effect of lovastatin, with and without cholestyramine, in the post coronary artery bypass graft (Post CABG) trial⁴⁷.

This study evaluated patients in the Post Coronary Artery Bypass Graft (Post CABG) trial for evidence of statin pleiotropic effects in preventing atherosclerotic progression in saphenous vein grafts (SVGs). We studied 1,116 of the 1,351 patients in the Post CABG trial who were randomized to aggressive (low-density lipoprotein [LDL] cholesterol target <85 mg/dl) or moderate (target LDL cholesterol <140 mg/dl) lovastatin treatment and who had sufficient data available. The generalized estimating equation models, adjusting for important covariates, were applied to estimate the odds ratios (ORs) and probability of substantial atherosclerotic SVG progression (decrease in lumen diameter ≥ 0.6 mm) and the difference in minimum lumen diameter change between treatment groups. Aggressive lovastatin treatment compared with moderate treatment was associated with a significant decrease in risk of significant SVG atherosclerotic progression after adjustment for baseline cholesterol level, LDL cholesterol on treatment, high-density lipoprotein cholesterol, and triglyceride changes on treatment and other independent predictors (OR 0.68, 95% confidence interval 0.49 to 0.94, $p = 0.019$). Results were similar when the change or percent change from baseline of LDL cholesterol level on treatment was adjusted for rather than on-treatment LDL cholesterol and in the subset achieving a year-1 LDL cholesterol level from 90 to 135 mg/dl (OR 0.64, 95% confidence interval 0.42 to 0.98, $p = 0.042$). Mean decrease in minimum lumen diameter was also significantly smaller in the aggressive than the moderate treatment arm (-0.256 vs -0.343 mm, $p = 0.042$). In conclusion, aggressive versus moderate lovastatin treatment appeared therapeutic in slowing the atherosclerotic process in SVGs from Post CABG patients, independent of its greater LDL cholesterol-lowering effect.

Pharmacogenetics of apolipoprotein E gene during lipid-lowering therapy: lipid levels and prevention of coronary heart disease⁴⁸.

A non-optimal plasma concentration of lipids is among the major modifiable risk factors of atherosclerosis. Therefore, the prevention of cardiovascular disease by means of lipid-lowering therapy with statins and other agents is of great importance for patient groups where a lifestyle change, for example, diet modification, does not lead to adequately reduced lipid levels. The response of low-density-lipoprotein cholesterol (LDL-C) levels to statin therapy is highly variable. This is partly attributed to hereditary variation in genes involved in pharmacokinetics, pharmacodynamics and lipid metabolism. The pharmacogenetics of lipid-lowering therapy have been investigated for more than 40 different genes. The gene for apolipoprotein E (APOE) has been the most frequently studied, particularly regarding the epsilon2/epsilon3/epsilon4 polymorphism. Those with the epsilon4 allele seem to have the poorest and those with the epsilon2 allele the strongest response to statins with regards to LDL-C levels. In addition, the epsilon2 carriers may reach the LDL-C treatment goals more frequently than epsilon4 carriers. Few studies have investigated the interaction of the APOE epsilon2/epsilon3/epsilon4 polymorphism and lipid-lowering therapy in relation to the course of coronary heart disease; the results are contradictory and so far inconclusive. This review summarizes the pharmacogenetic findings related to the influence of APOE gene variation on lipid responses and the prevention of coronary heart disease during lipid-lowering therapy.

Reclassification of patients for aggressive cholesterol treatment: additive value of multislice coronary angiography to the National Cholesterol Education Program guidelines⁴⁹.

BACKGROUND: National Cholesterol Education Program (NCEP) guidelines have been used to define treatment goals in patients with hypercholesterolemia. However, epidemiology-based guidelines are unable to identify all subjects with coronary artery disease for aggressive lipid intervention. **OBJECTIVE:** We sought to evaluate the additive value of multislice computed tomography (MSCT) angiography to the NCEP guideline classification for lipid treatment. **METHODS:** Multislice computed tomography was performed in 114 consecutive patients (mean age 57 \pm 14 y; 59% male) without known coronary artery disease. Subjects were classified into 3 categories (low-, intermediate-, and high-risk) according to their

Framingham risk scores (FRS). RESULTS: Traditional cardiac risk factors were common: hypertension 59%, diabetes 13%, and smoking 22%. On the basis of the FRS, 11% (n=12/114) of the patients met high-risk criteria requiring aggressive cholesterol reduction. Of those in the low- and intermediate-risk groups, MSCT found coronary plaque in 76% (n=77/102), with moderate or severe plaque in 38% (n=39/102), thus reclassifying them in the high-risk category. Use of statin drugs increased from 32% at baseline to 53% (p=0.002) based on MSCT results; statin dose was increased in 31% of the patients who were already on a statin. The mean low-density lipoprotein cholesterol (LDL-c) decreased from 114 mg/dL to 91 mg/dL after MSCT (p<0.001). CONCLUSION: Multislice computed tomography reclassifies a high percentage of patients considered to be low- to intermediate-risk into the high-risk category based on their coronary artery lesions. Thus, the rise in MSCT use at present may have a large impact on clinician practice patterns in lipid-lowering therapy. Copyright (c) 2008 Wiley Periodicals, Inc.

Baseline low-density lipoprotein cholesterol is an important predictor of the benefit of intensive lipid-lowering therapy: a PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) analysis⁵⁰

OBJECTIVES: This study sought to determine whether the benefit of intensive lipid-lowering therapy (LLT) is dependent on baseline low-density lipoprotein cholesterol (LDL-C). BACKGROUND: Aggressive LDL-C reduction with statins improves cardiovascular outcomes in acute and chronic coronary heart disease (CHD). The importance of baseline LDL-C is unclear. METHODS: We compared 2-year composites of death, myocardial infarction (MI), unstable angina, revascularization >30 days, and stroke (primary end point), and CHD death, MI, and revascularization >30 days (secondary end point) in 2,986 statin-naïve patients with recent acute coronary syndrome (ACS) randomized to atorvastatin 80 mg versus pravastatin 40 mg in the PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis In Myocardial Infarction 22) study stratified by quartiles of baseline LDL-C. Multivariable models assessed whether the treatment benefit was dependent on baseline LDL-C. RESULTS: A significant reduction in the hazards of the primary (hazard ratio [HR]: 0.63, 95% confidence interval [CI]: 0.47 to 0.85, p = 0.002) and secondary (HR: 0.57, 95% CI: 0.42 to 0.79, p = 0.001) end points occurred in patients within the highest quartile (>132 mg/dl) of baseline LDL-C treated with atorvastatin 80 mg. The benefit of intensive therapy progressively declined as baseline LDL-C decreased. The lowest quartile (LDL-C < or =92 mg/dl) experienced similar rates of the primary (HR: 0.93, 95% CI: 0.69 to 1.25, p = 0.63) and secondary (HR: 0.98, 95% CI: 0.71 to 1.35, p = 0.89) end points. Adjusted interaction tests between treatment and highest versus lowest baseline LDL-C quartile were significant for the primary and secondary end points (p = 0.03 and p = 0.007, respectively). Analyzing baseline LDL-C as a continuous variable, atorvastatin 80 mg was associated with improved outcomes provided the baseline LDL-C was >66 mg/dl. CONCLUSIONS: A progressive reduction in the benefit of intensive LLT with atorvastatin 80 mg over pravastatin 40 mg occurred in statin-naïve ACS patients as baseline LDL-C declined. (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction 22 [PROVE IT-TIMI 22]; NCT00382460).

Assessment of regional systolic and diastolic functions affected by atorvastatin in coronary artery disease using tissue Doppler imaging⁵¹

BACKGROUND: Several studies have shown regional left ventricular (LV) systolic and diastolic changes associated with coronary artery disease (CAD). Statins may have beneficial pleiotropic effects in addition to their lipid-lowering properties. HYPOTHESIS: We hypothesized that atorvastatin can improve regional LV systolic and diastolic functions in CAD patients using tissue Doppler imaging (TDI). METHODS: A total of 63 patients with hyperlipemia and CAD were studied. Forty-three patients were given 10 mg daily of atorvastatin and 20 patients were assigned only a low-fat diet. Tissue Doppler imaging was applied to evaluate LV peak systolic velocity (VS), early diastolic velocity (VE), and late diastolic velocity (VA) in 18 segments. The mean value of LV peak systolic velocity (VS(')), the mean value of early diastolic velocity (VE(')), and the mean value of late diastolic velocity (VA(')), in 18 segments were calculated. RESULTS: Compared with the baseline, VS('), and VE('), increased significantly after the therapy in the atorvastatin group (p < 0.05), while there was no change in the control group (p > 0.05). At 6 mo of therapy, a significant reduction in total cholesterol, triglyceride, and low-density lipoprotein (LDL) cholesterol was observed in the 2 groups (p < 0.05). CONCLUSIONS:

These findings demonstrate that atorvastatin can improve regional LV systolic and diastolic functions in CAD patients independent of its lipid-lowering properties. Copyright 2008 Wiley Periodicals, Inc.

Statin therapy alters the relationship between apolipoprotein B and low-density lipoprotein cholesterol and non-high-density lipoprotein cholesterol targets in high-risk patients: the MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin) trial⁵².

OBJECTIVES: The purpose of this analysis was to compare concentrations of low-density lipoprotein cholesterol (LDL-C), non-high-density lipoprotein cholesterol (HDL-C), and apolipoprotein B (apoB) before and during statin therapy. BACKGROUND: Reducing LDL-C to a pre-determined goal may still leave an excess of atherogenic lipoproteins, as reflected in apoB levels. METHODS: The MERCURY II (Measuring Effective Reductions in Cholesterol Using Rosuvastatin therapy II) trial examined the effects of statin treatment in patients with high coronary heart disease (CHD) risk, LDL-C $>$ or $=$ 130 and $<$ 250 mg/dl, and triglycerides $<$ 400 mg/dl. Therapy consisted of rosuvastatin (10 or 20 mg), atorvastatin (10 or 20 mg), or simvastatin (20 or 40 mg). The apoB and LDL-C or non-HDL-C at baseline and after 16 weeks of therapy were compared using linear regression. RESULTS: In untreated patients, the apoB target of $<$ 90 mg/dl was roughly equivalent to an LDL-C level $<$ 100 mg/dl and a non-HDL-C level $<$ 130 mg/dl, which is consistent with existing apoB and lipoprotein guidelines. However, during statin therapy, to reach an apoB target of $<$ 90 mg/dl it was necessary to reduce non-HDL-C to $<$ 100 mg/dl or to reduce LDL-C to $<$ 70 mg/dl (in high-triglyceride patients) or $<$ 80 mg/dl (in lower-triglyceride patients). The tight correlation seen for non-HDL-C with apoB while on statin therapy ($R^2 = 0.92$) implies that non-HDL-C may be an acceptable surrogate for direct apoB measurement. CONCLUSIONS: These data are consistent with the more aggressive cholesterol goals suggested for CHD patients, because achieving such targets also reduced apoB to the recommended level. (Mercury II-Compare the Efficacy and Safety of Lipid Lowering Agents Atorvastatin and Simvastatin With Rosuvastatin in High Risk Subjects With Type IIa and IIb Hypercholesterolemia; NCT00654407).

The relationship between obesity and atherosclerotic progression and prognosis among patients with coronary artery bypass grafts the effect of aggressive statin therapy⁵³.

OBJECTIVES: This study examines whether obesity accelerates atherogenic progression or adverse outcomes after coronary artery bypass graft (CABG) surgery. BACKGROUND: Obesity is a major risk factor for developing coronary heart disease. Whether obesity accelerates disease progression after CABG is unclear. METHODS: We examined how body mass index (BMI) related to atherosclerotic graft progression and a clinical composite outcome of death, nonfatal myocardial infarction, stroke, CABG surgery, or angioplasty among 1,314 participants in the Post CABG trial. Participants who had undergone CABG surgery were randomly assigned in a 2 x 2 factorial design to warfarin versus placebo and aggressive low-density lipoprotein cholesterol (LDL-C) lowering with lovastatin 40 to 80 mg/day (to achieve LDL-C of 60 to 85 mg/dl) versus moderate LDL-C lowering with lovastatin 2.5 to 5 mg/day (to achieve LDL-C of 130 to 140 mg/dl). Angiographic progression was assessed by coronary angiography at 4 to 5 years. RESULTS: Higher BMI was associated with a higher likelihood of angiographic progression (p trend = 0.003) after adjustment for demographic factors, treatment assignment, smoking status, and years since CABG surgery, but not with clinical events (p trend = 0.81). In stratified analyses, higher BMI was associated with angiographic progression in the low-dose lovastatin group (p trend $<$ 0.001) but not in the high-dose group ($p = 0.03$ for test for interaction of BMI and statin treatment). In the high-dose lovastatin group, higher BMI appeared to be protective against clinical events (p trend = 0.06, test of interaction: 0.02). CONCLUSIONS: Higher BMI is strongly associated with atherogenic progression after CABG surgery. Aggressive statin therapy may be protective against obesity-related acceleration of coronary heart disease.

Elevated total cholesterol: its prevalence and population attributable fraction for mortality from coronary heart disease and ischaemic stroke in the Asia-Pacific region⁵⁴.

BACKGROUND: About half of the world's cases of cardiovascular disease occur in the Asia-Pacific region. The contribution of serum total cholesterol (TC) to this burden is poorly quantified. DESIGN: The most recent nationally representative data on TC distributions for countries in the region were sought. Individual participant data from 380,483 adults in the Asia Pacific Cohort Studies Collaboration were used to estimate associations between TC and cardiovascular disease. METHODS: High TC was

defined as ≥ 6.2 mmol/l, and nonoptimal TC as ≥ 3.8 mmol/l. Hazard ratios for fatal coronary heart disease (CHD) and ischaemic stroke (IS) were found from Cox models. Sex-specific population attributable fractions for high TC and nonoptimal TC were estimated for each country. The former used conventional methods, based on single measures of TC and a fixed dichotomy of risk strata; the latter took account of the continuous positive association between TC and both CHD and IS and regression dilution. RESULTS: Data were available from 16 countries. Where reported, the prevalence of high TC ranged from 4 to 27%. The fraction of fatal CHD and IS attributable to high TC ranged from 0 to 14% and 0 to 15%, respectively. Although leaving the relative ranking of countries much the same, the fractions estimated for nonoptimal TC were typically at least twice as big, ranging from 0 to 47% and 0 to 35%, respectively. CONCLUSION: Conventional methods for estimating disease burden severely underestimate the effect of TC. Cholesterol-lowering strategies could have a tremendous effect in reducing cardiovascular deaths in this populous region.

[The influence of simvastatin on hsCRP and some parameters of hemostasis in patients with ischemic heart disease]⁵⁵

Inflammation and disturbances of the hemostatic system may play a role in pathogenesis and complications of ischemic heart disease. More and more reports indicate that apart from their cholesterol-lowering effect statins also exert other beneficial effects in cardiovascular diseases. Taking this into consideration, the aim of the study was to assess the influence of simvastatin (20 mg per day) on a marker of inflammation - CRP and some parameters of coagulation and fibrinolysis in 22 patients with ischaemic heart disease. Serum lipids, levels of hsCRP, thrombomodulin (TM), vWF, prothrombin fragment 1+2 (F1+2), thrombin-antithrombin complex (TAT), thrombin activatable fibrinolysis inhibitor (TAFI), t-PA, plasmin-antiplasmin complex (PAP) and TAFI activity were assessed before and after one, three and six months simvastatin treatment. After one month therapy of simvastatin, there have been significant reduction of levels of total cholesterol, LDL-cholesterol and triglycerides and these values have remained until the end of the study. No influence on the level of HDL-cholesterol has been observed. After 6 months of treatment significant decrease in the level of hsCRP and increase of the levels TM and vWF with reference to baselines results have been observed. After a 1-and 6-month therapy, the level of TAFI have been significantly increased. Other hemostatic parameters, i.e. levels of F1+2, TAT, t-PA, PAP and TAFI activity have not changed significantly. This prospective study has confirmed high efficacy of lipid-lowering effect and anti-inflammatory properties of simvastatin. Simvastatin influenced some hemo-static parameters, however, these effects were not, in majority, significant.

National improvements in low-density lipoprotein cholesterol management of individuals at high coronary risk: National Health and Nutrition Examination Survey, 1999 to 2002⁵⁶

BACKGROUND: This study sought to evaluate national levels of elevated low-density lipoprotein cholesterol (LDL-C) before and after publication of the Adult Treatment Panel III (ATP III). The ATP III guidelines intensified LDL-C targets and defined additional high-risk conditions. These recommendations are expected to have a noticeable impact on US cholesterol levels. METHODS: Coronary heart disease (CHD) risk was determined per ATP III guidelines for US residents aged 20 to 79 years in the 1999 to 2000 and 2001 to 2002 surveys. For those at high risk, the LDL-C mean percentage < 100 mg/dL and percentage ≥ 130 mg/dL, although not taking lipid-lowering therapy, were compared between the 2 surveys. In addition, subsets with and without CHD were evaluated. RESULTS: Of all high-risk US residents, the mean LDL-C dropped from 129 mg/dL in 1999 to 2000 to 120 mg/dL in 2001 to 2002 ($P = .003$). Those < 100 mg/dL increased from 23% to 32% ($P = .003$). Those ≥ 130 mg/dL and not on medication dropped from 36% to 27% ($P = .001$). Goal achievement and improvements were more favorable in the subset with CHD compared with those at high risk due to high-risk equivalent conditions. CONCLUSIONS: The sharp increase in high-risk US residents at the goal and the drop in the untreated percentage of those above treatment threshold illustrate national improvements in the management of LDL-C for those at high coronary risk. High-risk subjects without CHD displayed less significant improvements, suggesting an opportunity for better recognition and management of these individuals.

Atorvastatin induces associated reductions in platelet P-selectin, oxidized low-density lipoprotein, and interleukin-6 in patients with coronary artery diseases⁵⁷

The development and progression of atherosclerosis comprises various processes, such as endothelial dysfunction, chronic inflammation, thrombus formation, and lipid profile modification. Statins are 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors that have pleiotropic effects in addition to cholesterol-lowering properties. However, the mechanisms of these effects are not completely understood. Here, we investigated whether atorvastatin affects the levels of malondialdehyde-modified low-density lipoprotein (MDALDL), an oxidized LDL, the proinflammatory cytokine interleukin-6 (IL-6), or platelet P-selectin, a marker of platelet activation, relative to that of LDL cholesterol (LDL-C). Forty-eight patients with coronary artery disease and hyperlipidemia were separated into two groups that were administered with (atorvastatin group) or without (control group) atorvastatin. The baseline MDA-LDL level in all participants significantly correlated with LDL-C ($r = 0.71$, $P < 0.01$) and apolipoprotein B levels ($r = 0.66$, $P < 0.01$). Atorvastatin (10 mg/day) significantly reduced the LDL-C level within 4 weeks and persisted for a further 8 weeks of administration. Atorvastatin also reduced the MDA-LDL level within 4 weeks and further reduced it over the next 8 weeks. Platelet P-selectin expression did not change until 4 weeks of administration and then significantly decreased at 12 weeks, whereas the IL-6 level was gradually, but not significantly, reduced at 12 weeks. In contrast, none of these parameters significantly changed in the control group within these time frames. The reduction (%) in IL-6 between 4 and 12 weeks after atorvastatin administration significantly correlated with that of MDALDL and of platelet P-selectin ($r = 0.65$, $P < 0.05$ and $r = 0.70$, $P < 0.05$, respectively). These results suggested that the positive effects of atorvastatin on the LDL-C oxidation, platelet activation and inflammation that are involved in atherosclerotic processes are exerted in concert after lowering LDL-C.

Cholesterol lowering, sudden cardiac death and mortality⁵⁸

Sudden cardiac death is the main cause of cardiac mortality. Is blood cholesterol a determinant of sudden cardiac death? Does cholesterol lowering result in fewer sudden cardiac deaths? Answering these two questions may shed a new light on the epidemiology of coronary heart disease and on prevention options. In fact, careful analysis of the available data, including randomised trials, indicates that, contrary to a widespread opinion, cholesterol lowering does not appear to be a very effective way of reducing cardiac and overall mortality in the general population.

Simvastatin vs therapeutic lifestyle changes and supplements: randomized primary prevention trial⁵⁹

OBJECTIVE: To compare the lipid-lowering effects of an alternative regimen (lifestyle changes, red yeast rice, and fish oil) with a standard dose of a 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitor (statin). **PATIENTS AND METHODS:** This randomized trial enrolled 74 patients with hypercholesterolemia who met Adult Treatment Panel III criteria for primary prevention using statin therapy. All participants were randomized to an alternative treatment group (AG) or to receive simvastatin (40 mg/d) in this open-label trial conducted between April 1, 2006, and June 30, 2006. The alternative treatment included therapeutic lifestyle changes, ingestion of red yeast rice, and fish oil supplements for 12 weeks. The simvastatin group received medication and traditional counseling. The primary outcome measure was the percentage change in low-density lipoprotein cholesterol (LDL-C). Secondary measures were changes in other lipoproteins and weight loss. **RESULTS:** There was a statistically significant reduction in LDL-C levels in both the AG (-42.4%±15%) ($P < .001$) and the simvastatin group (-39.6%±20%) ($P < .001$). No significant differences were noted between groups. The AG also demonstrated significant reductions in triglycerides (-29% vs -9.3%; 95% confidence interval, -61 to -11.7; $P = .003$) and weight (-5.5% vs -0.4%; 95% confidence interval, -5.5 to -3.4; $P < .001$) compared with the simvastatin group. **CONCLUSION:** Lifestyle changes combined with ingestion of red yeast rice and fish oil reduced LDL-C in proportions similar to standard therapy with simvastatin. Pending confirmation in larger trials, this multifactorial, alternative approach to lipid lowering has promise for a subset of patients unwilling or unable to take statins.

Atorvastatin administration after percutaneous coronary intervention in patients with coronary artery disease and normal lipid profiles: impact on plasma adiponectin level⁶⁰

BACKGROUND: There is controversy about the effects of statins on plasma adiponectin, and the impact of percutaneous coronary intervention (PCI) on plasma adiponectin level is still unknown. We

investigated the impact of Atorvastatin on plasma adiponectin levels in coronary artery disease (CAD) patients with stable angina and normal lipid profiles after PCI. **METHODS:** Sixty CAD patients with stable angina and normal lipid profiles scheduled for PCI, and not on statins, were randomly assigned to either no treatment (control group) or the Atorvastatin treatment (Atorvastatin group). Atorvastatin administration was started immediately after PCI. Blood samples were obtained immediately after PCI and again 3 and 6 mo later. Fasting plasma adiponectin concentrations were measured using a radioimmunoassay kit. **RESULTS:** After PCI, there were statistically significant decreases in adiponectin levels in the Atorvastatin group at 3 and 6 mo (8.66 +/- 0.69 versus 6.87 +/- 0.55 and 7.12 +/- 0.71 microg/mL at 0, 3, and 6 mo, respectively), despite the anti-inflammation and lipid-lowering effects of Atorvastatin. There were no statistically significant changes in adiponectin levels in the control group. There was significant positive association between baseline plasma adiponectin and high-density lipoprotein (HDL) levels. Changes of adiponectin level were not associated with the changes of high-sensitivity C-reactive protein (hs-CRP) and lipid profiles in the Atorvastatin group. **CONCLUSIONS:** Our study confirmed the benefits of Atorvastatin on anti-inflammation and anti-atherosclerosis, but we also found that Atorvastatin had a negative effect on the adiponectin system. The anti-inflammatory, anti-atherogenic effects of Atorvastatin are not affected by decreased adiponectin levels.

Role of n-3 fatty acids in the treatment of hypertriglyceridemia and cardiovascular disease⁶¹

n-3 Fatty acids (FAs) when used in doses of 3-4 g/d eicosapentaenoic acid and docosahexaenoic acid have profound effects on triacylglycerol (TG) concentrations. The mechanism for their TG reduction relates to their favorable effects on reducing hepatic production and secretion of VLDL and VLDL apolipoprotein B particles, along with favorable effects on plasma lipolytic activity through lipoprotein lipase-mediated clearance, as well as stimulation of beta-oxidation of other FAs in the liver. Their hypotriglyceridemic properties are related to both the dose of n-3 FAs used and the baseline TG concentrations of the population. In patients with TG concentrations >500 mg/dL, 4 g n-3 FAs have been shown to reduce TGs by 45%, VLDL by 42%, and non-HDL by 10.2%. A recent pooled meta-analysis with multiple doses of n-3 FAs ranging from 0.8 to 5.4 g revealed changes in TGs of -27 mg/dL (95% CI: -33, -20), in HDL of +1.6 mg/dL (95% CI: + 0.8, +2.3), and in LDL cholesterol of +6 mg/dL (95% CI: + 3, +8). The clinical uses of n-3 FAs include treatment of severe and moderate hypertriglyceridemia, use in statin-treated patients with elevated TG concentrations or non-HDL cholesterol (mixed hyperlipidemia), and use in the secondary and primary prevention of cardiovascular disease. Existing large-scale clinical trials such as the GISSI-Prevenzione Study and JELIS with low doses of n-3 FAs (1-2 g) show clinical benefit in reducing coronary heart disease without substantial changes in concentrations of TGs or other lipids. Future clinical trials need to determine whether the TG-lowering doses of n-3 FAs (3-4 g/d) result in additional risk reduction.

Lipids, apolipoproteins, and their ratios in relation to cardiovascular events with statin treatment⁶²

BACKGROUND: Low-density lipoprotein (LDL) cholesterol is the principal target of lipid-lowering therapy, but recent evidence has suggested more appropriate targets. We compared the relationships of on-treatment levels of LDL cholesterol, non-high-density lipoprotein (HDL) cholesterol, and apolipoprotein B, as well as ratios of total/HDL cholesterol, LDL/HDL cholesterol, and apolipoprotein B/A-I, with the occurrence of cardiovascular events in patients receiving statin therapy. **METHODS AND RESULTS:** A post hoc analysis was performed that combined data from 2 prospective, randomized clinical trials in which 10,001 ("Treating to New Targets") and 8888 ("Incremental Decrease in End Points through Aggressive Lipid Lowering") patients with established coronary heart disease were assigned to usual-dose or high-dose statin treatment. In models with LDL cholesterol, non-HDL cholesterol and apolipoprotein B were positively associated with cardiovascular outcome, whereas a positive relationship with LDL cholesterol was lost. In a model that contained non-HDL cholesterol and apolipoprotein B, neither was significant owing to collinearity. Total/HDL cholesterol ratio and the apolipoprotein B/A-I ratio in particular were each more closely associated with outcome than any of the individual proatherogenic lipoprotein parameters. **CONCLUSIONS:** In patients receiving statin therapy, on-treatment levels of non-HDL cholesterol and apolipoprotein B were more closely associated with cardiovascular outcome than levels of LDL cholesterol. Inclusion of measurements of the antiatherogenic lipoprotein fraction further strengthened the relationships. These data support the use of

non-HDL cholesterol or apolipoprotein B as novel treatment targets for statin therapy. Given the absence of interventions that have been proven to consistently reduce cardiovascular disease risk through raising plasma levels of HDL cholesterol or apolipoprotein A-I, it seems premature to consider the ratio variables as clinically useful.

Implementing electronic clinical reminders for lipid management in patients with ischemic heart disease in the veterans health administration: QUERI Series ⁶³.

ABSTRACT: BACKGROUND: Ischemic heart disease (IHD) affects at least 150,000 veterans annually in the United States. Lowering serum cholesterol has been shown to reduce coronary events, cardiac death, and total mortality among high risk patients. Electronic clinical reminders available at the point of care delivery have been developed to improve lipid measurement and management in the Veterans Health Administration (VHA). Our objective was to report on a hospital-level intervention to implement and encourage use of the electronic clinical reminders. METHODS: The implementation used a quasi-experimental design with a comparison group of hospitals. In the intervention hospitals (N = 3), we used a multi-faceted intervention to encourage use of the electronic clinical reminders. We evaluated the degree of reminder use and how patient-level outcomes varied at the intervention and comparison sites (N = 3), with and without adjusting for self-reported reminder use. RESULTS: The national electronic clinical reminders were implemented in all of the intervention sites during the intervention period. A total of 5,438 patients with prior diagnosis of ischemic heart disease received care in the six hospitals (3 intervention and 3 comparison) throughout the 12-month intervention. The process evaluation showed variation in use of reminders at each site. Without controlling for provider self-report of use of the reminders, there appeared to be a significant improvement in lipid measurement in the intervention sites (OR 1.96, 95% CI 1.34, 2.88). Controlling for use of reminders, the amount of improvement in lipid measurement in the intervention sites was even greater (OR 2.35, CI 1.96, 2.81). Adjusting for reminder use demonstrated that only one of the intervention hospitals had a significant effect of the intervention. There was no significant change in management of hyperlipidemia associated with the intervention. CONCLUSION: There may be some benefit to focused effort to implement electronic clinical reminders, although reminders designed to improve relatively simple tasks, such as ordering tests, may be more beneficial than reminders designed to improve more complex tasks, such as initiating or titrating medications, because of the less complex nature of the task. There is value in monitoring the process, as well as outcome, of an implementation effort.

Application of the screening for Heart Attack Prevention and Education Task Force recommendations to an urban population: observations from the Dallas Heart Study ⁶⁴.

BACKGROUND: The Screening for Heart Attack Prevention and Education (SHAPE) Task Force recommends noninvasive atherosclerosis imaging of all asymptomatic men (aged 45-75 years) and women (aged 55-75 years), except those at very low risk, to augment conventional cardiovascular risk assessment algorithms. METHODS: Among 2611 participants in the Dallas Heart Study aged 30 to 65 years who underwent computed tomography to measure coronary artery calcification, low-density lipoprotein cholesterol (LDL-C) therapeutic targets were calculated using both National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) and SHAPE algorithms. The proportion of subjects reclassified as being "at goal" for LDL-C vs "not at goal" after implementation of the SHAPE recommendations was determined. RESULTS: More subjects were identified with LDL-C levels greater than or equal to goal based on SHAPE than on NCEP-ATP III (27.4% vs 21.6%), with 7.0% of individuals reclassified as having unmet LDL-C goals and 1.1% of individuals reclassified as at goal. When more aggressive optional LDL-C goals were implemented, 31.7% had LDL-C levels greater than or equal to goal using SHAPE recommendations vs 28.1% using NCEP-ATP III recommendations, with 6.3% of subjects reclassified as being not at goal and 2.7% as being at goal. CONCLUSIONS: The SHAPE recommendations resulted in bidirectional reclassification of eligibility for lipid-lowering therapy in subjects aged 30 to 65 years. While broad implementation of these recommendations would modestly increase cholesterol-lowering drug use in this age range, the magnitude of the increase depends on whether standard or optional LDL-C goals are targeted.

Intensive lipid-lowering with atorvastatin for secondary prevention in patients after coronary artery bypass surgery ⁶⁵.

OBJECTIVES: The aim of this post hoc analysis from the TNT (Treating to New Targets) trial is to determine whether patients with previous coronary artery bypass grafting (CABG) surgery achieved clinical benefit from intensive low-density lipoprotein (LDL)-cholesterol lowering. **BACKGROUND:** The development and progression of atherosclerosis is accelerated in coronary venous bypass grafts. **METHODS:** A total of 10,001 patients with documented coronary disease, including 4,654 with previous CABG, were randomized to atorvastatin 80 or 10 mg/day and were followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event (cardiac death, nonfatal myocardial infarction, resuscitated cardiac arrest, or stroke). **RESULTS:** A first major cardiovascular event occurred in 11.4% of the patients with prior CABG and 8.5% of those without prior CABG ($p < 0.001$). In CABG patients, mean LDL-cholesterol levels at study end were 79 mg/dl in the 80-mg arm and 101 mg/dl in the 10-mg arm, and the primary event rate was 9.7% in the 80-mg arm and 13.0% in the 10-mg arm (hazard ratio 0.73, 95% confidence interval 0.62 to 0.87, $p = 0.0004$). Repeat revascularization during follow-up, either CABG or percutaneous coronary intervention, was performed in 11.3% of the CABG patients in the 80-mg arm and 15.9% in the 10-mg arm (hazard ratio 0.70, 95% confidence interval 0.60 to 0.82, $p < 0.0001$). **CONCLUSIONS:** Intensive LDL-cholesterol lowering to a mean of 79 mg/dl with atorvastatin 80 mg/day in patients with previous CABG reduces major cardiovascular events by 27% and the need for repeat coronary revascularization by 30%, compared with less intensive cholesterol-lowering to a mean of 101 mg/dl with atorvastatin 10 mg/day. (A Study to Determine the Degree of Additional Reduction in CV Risk in Lowering LDL Below Minimum Target Levels [TNT]; NCT00327691).

Can we cause regression of coronary atherosclerosis? ⁶⁶

With the advent of effective antiatherosclerotic therapies, especially lipid lowering agents, cardiovascular morbidity and mortality rates associated with coronary atherosclerosis can be reduced. A growing body of evidence suggests such therapies can retard the progression of coronary atherosclerosis and with aggressive treatment regimens can cause regression. Antiatherosclerotic, and especially lipid lowering therapies, have the potential to become an alternative to invasive interventions. This report examines clinical studies that have addressed the regression of human coronary atherosclerosis by medical therapy.

The LDL to HDL cholesterol ratio as a valuable tool to evaluate coronary heart disease risk ⁶⁷.

The current National Cholesterol Education Program Adult Treatment Panel III guidelines recommend specific target levels of LDL cholesterol (LDL-C) and HDL cholesterol (HDL-C) for determining cardiovascular disease (CVD) risk and evaluating the effectiveness of lipid-lowering therapies. While there is a growing consensus that levels of apolipoprotein (apo) B and the ratio of apo B/apo A-I are more accurate predictors of CVD risk, the question has been raised as to whether it is realistic to expect patients and health professionals to switch from cholesterol-based guidelines to apolipoprotein-based guidelines. Because it will take time before apolipoprotein terminology is recognized by the general public and recommended by the NCEP Adult Treatment panel to evaluate risk, it may be more efficacious to continue adhering to the already familiar and proven measurements of the LDL-C/HDL-C ratio. The following review provides evidence that the LDL-C/HDL-C ratio continues to be a valuable and standard tool to evaluate CVD risk in all populations.

The benefits of intensive lipid lowering in patients with stable coronary heart disease with normal or high systolic blood pressure: an analysis of the Treating to New Targets (TNT) study ⁶⁸

This post-hoc analysis of the Treating to New Targets (TNT) study evaluated the joint effects of managing low-density lipoprotein cholesterol (LDL-C) and systolic blood pressure (SBP) on cardiovascular outcomes. Patients (N=9739) with clinically evident, stable coronary heart disease (CHD) were randomized to atorvastatin 10 or 80 mg/d. The primary end point was occurrence of a first major cardiovascular event. At 3 months' follow-up, patients were stratified according to SBP (< 140 mm Hg vs ≥ 140 mm Hg) and tertiles of LDL-C. At 4.9 years' median follow-up, the rate of major cardiovascular events was reduced most in patients with lower LDL-C ($P < .001$) and in patients with SBP < 140 mm Hg ($P = .014$). A 42% relative risk reduction was observed for patients in the lowest LDL-

C tertile with an SBP < 140 mm Hg, compared with patients in the highest LDL-C tertile with an SBP > or = 140 mm Hg. The effect of lower SBP on stroke was most pronounced in the lowest LDL-C tertile.

Fluvastatin improves arterial stiffness in patients with coronary artery disease and hyperlipidemia: a 5-year follow-up study⁶⁹.

BACKGROUND: The present study was designed to test the hypothesis that fluvastatin might improve arterial stiffness, as assessed with pulse wave velocity (PWV), in patients with coronary artery disease (CAD) and hyperlipidemia over the long term. **METHODS AND RESULTS:** Ninety-three patients were randomly assigned to either fluvastatin (group A, n=50) or bezafibrate (group B, n=43) and followed for 5 years. There was no difference in the clinical findings between the 2 groups. In group A, there was a progressive reduction in the brachial-ankle PWV along with a decrease in serum low-density lipoprotein-cholesterol (LDL-C) and C-reactive protein (CRP) by 12 months after fluvastatin, and the improvement was maintained until 5 years after treatment. In group B, despite identical lowering of the serum lipid, PWV was progressively increased. In group A, the percentage change in PWV correlated significantly with that of the serum CRP ($r=0.49$, $p<0.001$), but not with that of the serum LDL-C after treatment. **CONCLUSIONS:** The beneficial vascular effects of fluvastatin persisted for a long period in patients with CAD and hyperlipidemia. Its anti-inflammatory action might contribute to the favorable effects on arterial stiffness.

Cholesterol lowering is more important than pleiotropic effects of statins for endothelial function in patients with dysglycaemia and coronary artery disease⁷⁰.

AIMS: The importance of pleiotropic effects of statins on endothelial function and inflammatory markers was investigated in patients with dysglycaemia and coronary artery disease (CAD). **METHODS AND RESULTS:** Thirty-nine patients were randomized to simvastatin 80 mg daily (S80; n = 20) or ezetimibe 10 mg and simvastatin 10 mg daily (E10/S10; n = 19) for 6 weeks, aiming at similar cholesterol reduction. Endothelial function, evaluated by brachial artery flow-mediated vasodilatation (FMD) and the effect of endothelin receptor blockade, serum lipids, and inflammatory markers were evaluated at baseline and follow-up. At follow-up, low-density lipoprotein cholesterol decreased from 3.1 (2.8-3.4) (median and quartiles) to 1.5 mmol/L (1.4-1.7) and from 3.0 (2.5-3.4) to 1.3 mmol/L (1.1-1.8), in the S80 and E10/S10 groups, respectively. In the entire study group, FMD increased from 4.3% (3.4-6.1) at baseline to 5.5% (3.4-6.6) at follow-up, while C-reactive protein decreased from 3.1 (1.7-7.6) to 2.3 mg/L (0.9-6.5). The changes in FMD and C-reactive protein from baseline to follow-up were not significantly different between patients on S80 and E10/S10 groups. Endothelin blockade enhanced endothelium-dependent vasodilatation both at baseline and follow-up. **CONCLUSION:** Lipid lowering is more important than pleiotropic effects of statins for improvement in endothelial function and inflammatory markers in patients with dysglycaemia and CAD.

Factors associated with discharge lipid-lowering drug prescription in patients hospitalized for coronary artery disease (from the Get With the Guidelines database)⁷¹.

Lipid-lowering therapy prevents morbidity and mortality in patients with coronary artery disease (CAD), but little is known regarding ordering practices in patients hospitalized with CAD events. Patients at participating hospitals of Get with The Guidelines-CAD, a hospital performance improvement program, were entered into a registry. Factors associated with discharge lipid-lowering therapy prescription were identified and the effect of in-hospital low-density lipoprotein cholesterol measurement on therapy prescription was evaluated. A total of 98,880 patients were enrolled at 405 hospitals. At discharge, lipid-lowering therapy was prescribed in 84.7% of patients and was associated with percutaneous coronary intervention and angiotensin-converting enzyme inhibitor, aspirin, and beta-blocker therapies at discharge, but not cardiac rehabilitation referral or coronary artery bypass grafting (all $p<0.0001$). After adjustment for patient characteristics, men were more likely (odds ratio [OR] 1.23, 95% confidence interval [CI] 1.18 to 1.29; $p<0.0001$) and patients with heart failure were less likely to be prescribed lipid-lowering therapy (OR 0.64, 95% CI 0.59 to 0.69, $p<0.0001$). Patients who had low-density lipoprotein cholesterol measured during hospitalization were more likely to be prescribed lipid-lowering therapy (OR 1.56, 95% CI 1.48 to 1.65, $p<0.0001$). Lipid-lowering therapy prescription was associated positively with

higher body mass index, history of dyslipidemia, and previous myocardial infarction and negatively with history of renal insufficiency, stroke, and hypertension. In conclusion, despite consistent benefits of lipid-lowering therapy in patients hospitalized for CAD events, discharge prescription varied by patient characteristics, in-hospital assessment, and treatment decisions. Additional efforts are needed to improve evidence-based lipid-lowering therapy prescription for eligible patients.

Effects of modifying triglycerides and triglyceride-rich lipoproteins on cardiovascular outcomes

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Elevated levels of triglycerides (and triglyceride-rich lipoproteins) are increasingly being recognized as treatment targets to lower cardiovascular risk in certain patient subgroups, including individuals receiving HMG-CoA reductase inhibitors (statins). Evidence suggests that these agents reduce the risk of coronary events more markedly in patients with elevated triglycerides and low levels of high-density lipoprotein cholesterol (HDL-C). Further, intensive long-term statin therapy that reduces both low-density lipoprotein cholesterol (LDL-C) to <70 mg/dL and triglycerides to <150 mg/dL results in a decreased risk of cardiovascular events compared with more moderate statin treatment. Long-term therapy with fibric-acid derivatives, which lower triglycerides and raise HDL-C, appears to reduce mortality in patients with elevated triglycerides and/or those experiencing the most marked reductions in triglycerides on therapy. However, randomized clinical trials involving fibrates have not shown consistent benefit. Niacin (nicotinic acid), which is the most effective available medication for raising HDL-C and also lowers triglycerides, has not been as extensively studied as fibrates in long-term randomized controlled trials. Initial reports (eg, Coronary Drug Project) demonstrated a reduction in coronary disease but not total mortality in patients randomized to niacin. However, a 15-year follow-up demonstrated that all-cause mortality was significantly reduced in those initially randomized to niacin. At the pathophysiologic level, elevated triglycerides and triglyceride-rich lipoproteins are recognized as potential factors in driving atherosclerotic progression, particularly in mild-to-moderate lesions. Elevated triglycerides also constitute a plausible therapeutic target in certain patients with coronary heart disease (and/or insulin resistance) but without profound LDL-C elevations. The foregoing and other evidence has led consensus panels to lower the upper limit for "normal" triglycerides to 150 mg/dL. Adequately powered randomized controlled trials that specifically assess the effects of lowering triglycerides and raising HDL-C, and trials that target individuals with high triglycerides and low HDL-C, may provide data for recommending specific treatment targets for triglycerides and HDL-C, as well as effective and well-tolerated therapies to achieve these goals.

Adjunctive interventions in myocardial infarction: the role of statin therapy ⁷³

Statin therapy has reduced cardiovascular morbidity and mortality across the spectrum of atherosclerosis. The administration of statins has been demonstrated to be effective in primary and secondary prevention clinical trials evaluating patients with high and low risk-factor profiles. The presumed mechanism of benefit of hypolipidemic therapy in the prevention of atherosclerotic disease was a reduction in the deposition of atherogenic lipoproteins in vulnerable areas of the coronary vasculature. Subsequent experimental studies with statins demonstrated a variety of potentially beneficial effects that would extend clinical benefit beyond lipid-lowering per se. Statin therapy beneficially alters inflammation, coagulation and fibrinolytic parameters, endothelial function, vasoreactivity, and platelet function. The demonstration of the non-lipid or pleiotropic effects provided the theoretical basis for a possible role as an adjunctive therapy in acute coronary syndromes. Retrospective analysis of a variety of early trials indicated a potential benefit of statins during acute ischemic syndromes. Recent clinical trials have addressed this important clinical question in a prospective controlled manner. The Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering (MIRACL) and the Thrombolysis In Myocardial Infarction (TIMI)-22 studies present strong clinical evidence in favor of the administration of statins as adjunctive therapy in acute ischemic syndromes.

Cholesterol goal attainment in patients with coronary heart disease and elevated coronary risk: results of the Hong Kong hospital audit study ⁷⁴

OBJECTIVE: We sought to determine 1) long-term lipid-lowering treatment patterns; 2) cholesterol goal attainment rates and possible determinants of goal achievement; and 3) effects of cholesterol goal

attainment on coronary events in hospitalized Hong Kong patients. **METHODS:** In this retrospective cohort analysis, records of two public Hong Kong hospitals were reviewed for 196 adults (69% with coronary heart disease (CHD) or CHD-risk equivalent) who received at least one lipid-lowering therapy during hospitalization. Low-density lipoprotein cholesterol (LDL-C) targets were <2.6 mmol/l (<100 mg/dL) for patients with CHD or CHD risk equivalents and <3.37 mmol/l (<130 mg/dL) for those without. **RESULTS:** Most participants were initiated on regimens of low to mid-potency doses and never had their regimens adjusted to higher potency. Approximately 44% of patients not at LDL-C at baseline failed to achieve goal during a median follow-up of 1.9 years. Patients with higher coronary risk and/or LDL-C levels at baseline were less likely than their lower-risk counterparts to achieve goal; for each 1-mmol/l (38.7-mg/dL) increase in LDL-C at baseline, the likelihood of attaining goal declined by 64%. Patients achieving cholesterol goal had significantly longer cardiovascular event-free times. **CONCLUSIONS:** A total of 44% of Hong Kong patients not at LDL-C goals at baseline did not achieve them over 1.9 years. More effective and well-tolerated therapies, including adjunctive regimens (e.g., ezetimibe-statin, niacin-statin), may be necessary to enhance LDL-C goal achievement and increase event-free time.

Lipid levels after acute coronary syndromes⁷⁵

OBJECTIVES: This analysis from the LUNAR (Limiting UNdertreatment of lipids in ACS with Rosuvastatin) study assessed lipid changes 1 to 4 days after onset of acute coronary syndromes (ACS), before initiation of study treatment. **BACKGROUND:** Early studies indicated that cholesterol levels decrease significantly after ACS. However, most studies were small or did not measure low-density lipoprotein cholesterol (LDL-C) directly, and many used nonfasting or retrospective data. More recent studies suggest less pronounced changes in cholesterol levels after ACS. **METHODS:** The LUNAR trial is a prospective, multicenter, randomized, open-label study in adults hospitalized for acute ST-segment elevation myocardial infarction (STEMI), non-STEMI, or unstable angina (UA). Blood samples were taken at median times after onset of ACS symptoms of 26 h (Day 1, fasting or nonfasting sample), 43 h (Day 2, fasting sample), and 84 h (Day 4, fasting sample) for direct measurement of serum lipid levels before study treatments were started. **RESULTS:** Of 507 patients available for analysis, 212 were admitted for STEMI, 176 for non-STEMI, and 119 for UA. The LDL-C levels decreased in the 24 h after admission (from 136.2 to 133.5 mg/dl), followed by an increase over the subsequent 2 days (to 141.8 mg/dl). These changes did not seem to be clinically meaningful. Similar changes were observed for total cholesterol and smaller changes for high-density lipoprotein cholesterol; fasting triglyceride levels did not change. **CONCLUSIONS:** Mean lipid levels vary relatively little in the 4 days after an ACS and can be used to guide selection of lipid-lowering medication.

Statin use is associated with decreased CD-40 ligand expression on T lymphocytes of coronary atheroma plaque in patients with stable coronary artery disease⁷⁶

OBJECTIVE: Atherosclerosis is a chronic inflammatory disease. Statins suppress the inflammation in the plaque. This cross-sectional study was planned to evaluate the effect of statins on plaque T cell activation markers in patients with stable angina pectoris undergoing coronary intervention and atherectomy procedures. **METHODS:** Twenty-six patients with stable angina with suitable for atherectomy coronary lesions were enrolled in the study. Fourteen of 26 patients who had been taking statin treatment for at least six months were assigned to the Group 1 (Statin group) and 12 patients who had not received any lipid lowering treatment comprised the Group 2 (Control group). Atherectomy specimens were studied with single and double immunohistochemical staining (CD25, CD69, and CD40L). Statistical analysis was performed using Student's t-test and Fisher's exact test. **RESULTS:** There was no significant difference between the total tissue area of sections (Group 1: 8.4 ± 0.9 mm², Group 2: 7.8 ± 0.9 mm², $p > 0.05$). CD3, CD25, CD69, and CD40L positive cells did not show statistically significant difference between the groups in unit area (mm²). There was no significant difference between the groups for percentage of T lymphocytes expressing CD25 (Group 1: $7.8 \pm 4.6\%$, Group 2: $7.8 \pm 5.9\%$, $p = 0.97$) and CD 69 (Group 1: $12.9 \pm 4.6\%$, Group 2: $15.5 \pm 5.2\%$, $p = 0.203$). The expression of CD40L was significantly lower in Group 1 than in Group 2 (Group 1: $4.8 \pm 3.9\%$, Group 2: $11.2 \pm 8.7\%$, $p = 0.034$). **CONCLUSION:** We concluded that, statin treatment may decrease the expression of CD40L on plaque T lymphocytes in patients with stable angina pectoris.

Effect of APOE genotype on lipid levels in patients with coronary heart disease during a 3-week inpatient rehabilitation program⁷⁷

It has been suggested that the apolipoprotein E (APOE) genotype modifies the effect of dietary and pharmacological interventions for lowering lipid levels. We wanted to determine whether APOE genotyping information would be useful in making lipid-lowering treatment decisions in clinical practice. We included 981 patients with coronary heart disease (CHD) enrolled in an inpatient 3-week standardized rehabilitation program. Of these, 555 (57%) patients received continued statin therapy and 232 (24%) patients received newly initiated statin therapy. Dietary intervention was part of the program only for 194 (20%) patients. Total cholesterol (TC) and low-density lipoprotein cholesterol (LDLC) levels decreased in all the groups of patients during rehabilitation. The decreases were less pronounced among the APOE E2 carriers. However, the observed variation among the groups with respect to reduction of lipid levels was accounted for mainly by the initial lipid levels (30-47%) and only marginally on the APOE genotype (1%). We therefore found no evidence that APOE genotyping will be useful in guiding dietary or pharmacological lipid-lowering treatment decisions.

Association of circulating leukocyte count with coronary atherosclerosis regression after pravastatin treatment⁷⁸

Epidemiological studies have demonstrated that the peripheral blood leukocyte count could be used as a marker of the progression of atherosclerosis. Few data exist regarding the relationship between inhibition of the progression of coronary atherosclerosis and the anti-inflammatory effects of statins, especially the drugs' effects on the leukocyte count in patients with coronary artery disease. A 6-month prospective study was, therefore, conducted in 50 patients treated with pravastatin. The plaque volume, as assessed by volumetric analysis using intravascular ultrasound, reduced significantly by 14% ($p < 0.0001$, vs. baseline) following the treatment, furthermore, a corresponding decrease of the leukocyte count (8.9%, $p < 0.01$, vs. baseline) was also seen. No correlation was found between the change in the leukocyte count and any of the changes in the lipid levels; changes in either of these are known to be associated with the rate of progression of atherosclerosis. A multivariate regression analysis using other traditional risk factors and medications as covariates revealed that the decrease in the leukocyte count was an independent predictor of inhibition of the progression of coronary atherosclerosis. In conclusion, a reduction of the leukocyte count as one of the non-lipid-lowering effects of pravastatin may be a novel marker of regression of coronary atherosclerosis.

Rationale and design of a study to examine lower targets for low-density lipoprotein-cholesterol and blood pressure in coronary artery disease patients⁷⁹

BACKGROUND: The benefits of coronary risk modification through medication and other methods have been shown in many clinical studies. Recently, aggressive lowering of low-density lipoprotein-cholesterol (LDL-C) has been shown to confer additive benefits in patients with coronary artery disease (CAD). However, it has not been shown in Japanese patients with CAD if multiple aggressive medical interventions for coronary risk factors are beneficial compared with standard regimens, so a prospective, randomized, open-label, blinded-endpoint (PROBE) multicenter study was designed to evaluate whether aggressive lowering of LDL-C and blood pressure in Japanese hypertensive, hypercholesterolemic CAD patients bestows additional benefits compared with regimens based on current Japanese guidelines. **METHODS AND RESULTS:** Seventeen hospitals in Japan are participating in the Japanese Coronary Artery Disease II (JCADII) study. Hypertensive and hypercholesterolemic patients who have $\geq 75\%$ stenosis in at least one major coronary artery according to American Heart Association guidelines will be allocated randomly to receive either conventional or aggressive therapy. Standard therapy for hypertension and hypercholesterolemia aims to reduce blood pressure to $< 140/90$ mmHg and LDL-C concentration to < 100 mg/dl. Aggressive therapy aims for targets of $< 120/80$ mmHg and < 80 mg/dl, respectively. We plan to recruit 500 patients and follow them up for 3 years. Antihypertensive agents, when used, include the angiotensin receptor blockers candesartan and/or losartan. Antihypercholesterolemic agents, when used, include at least one of the following statins: pravastatin, simvastatin, and atorvastatin. **CONCLUSION:** The JCADII study will provide important information concerning medical treatment of coronary risk factors in Japanese patients with CAD (UMIN-ID: UMIN000000571).

Prescription omega-3 fatty acids and their lipid effects: physiologic mechanisms of action and clinical implications⁸⁰

Hypertriglyceridemia is a risk factor for atherosclerotic coronary heart disease. Very high triglyceride (TG) levels (> or =500 mg/dl [5.65 mmol/l]) increase the risk of pancreatitis. One therapeutic option to lower TG levels is omega-3 fatty acids, which are derived from the oil of fish and other seafood. The American Heart Association has acknowledged that fish oils may decrease dysrhythmias, decrease sudden death, decrease the rate of atherosclerosis and slightly lower blood pressure, and has recommended fish consumption or fish oil supplementation as a therapeutic strategy to reduce cardiovascular disease. A prescription omega-3-acid ethyl esters (P-OM3) preparation has been available in many European nations for at least a decade, and was approved by the US FDA in 2004 to reduce very high TG levels (> or =500 mg/dl [5.65 mmol/l]). Mechanistically, most evidence suggests that omega-3 fatty acids reduce the synthesis and secretion of very-low-density lipoprotein (VLDL) particles, and increase TG removal from VLDL and chylomicron particles through the upregulation of enzymes, such as lipoprotein lipase. Omega-3 fatty acids differ mechanistically from other lipid-altering drugs, which helps to explain why therapies such as P-OM3 have complementary mechanisms of action and, thus, complementary lipid benefits when administered with statins. Additional human studies are needed to define more clearly the cellular and molecular basis for the TG-lowering effects of omega-3 fatty acids and their favorable cardiovascular effects, particularly in patients with hypertriglyceridemia.

The efficacy and safety of intensive statin therapy: a meta-analysis of randomized trials⁸¹

BACKGROUND: Recent lipid guidelines recommend aggressive low-density lipoprotein (LDL) cholesterol lowering in patients with coronary artery disease. To clarify the evidence for this recommendation, we conducted a meta-analysis of randomized controlled trials that compared different intensities of statin therapy. **METHODS:** We searched electronic databases (MEDLINE, EMBASE, Cochrane Central Registry of Controlled Trials, Web of Science) for randomized controlled trials published up to July 19, 2007, that compared statin regimens of different intensities in adults with coronary artery disease and that reported cardiovascular events or mortality. Data were pooled using random-effects models to calculate odds ratios (OR). **RESULTS:** A total of 7 trials (29 395 patients) were included. Compared with less intensive statin regimens, more intensive regimens further reduced LDL levels (0.72 mmol/L reduction, 95% confidence interval [CI] 0.60-0.84 mmol/L), and reduced the risk of myocardial infarction (OR 0.83, 95% CI 0.77-0.91) and stroke (OR 0.82, 95% CI 0.71-0.95). Although there was no effect on mortality among patients with chronic coronary artery disease (OR 0.96, 95% CI 0.80-1.14), all-cause mortality was reduced among patients with acute coronary syndromes treated with more intensive statin regimens (OR 0.75, 95% CI 0.61-0.93). Compared with lower intensity regimens, more intensive regimens were associated with small absolute increases in rates of drug discontinuation (2.5%), elevated levels of aminotransferases (1%) and myopathy (0.5%), and there was no difference in noncardiovascular mortality. All 7 trials reported events by randomization arm rather than by LDL level achieved. About half of the patients treated with more intensive statin therapy did not achieve an LDL level of less than 2.0 mmol/L, and none of the trials tested combination therapies. **INTERPRETATION:** Our analysis supports the use of more intensive statin regimens in patients with established coronary artery disease. There is insufficient evidence to advocate treating to particular LDL targets, using combination lipid-lowering therapy to achieve these targets or for using more intensive regimens in patients without established coronary artery disease.

High-density lipoprotein cholesterol, high-density lipoprotein particle size, and apolipoprotein A-I: significance for cardiovascular risk: the IDEAL and EPIC-Norfolk studies⁸²

OBJECTIVES: This study was designed to assess the relationship of high-density-lipoprotein cholesterol (HDL-C), HDL particle size, and apolipoprotein A-I (apoA-I) with the occurrence of coronary artery disease (CAD), with a focus on the effect of very high values of these parameters. **BACKGROUND:** High plasma levels of HDL-C and apoA-I are inversely related to the risk of CAD. However, recent data suggest that this relationship does not hold true for very high HDL-C levels, particularly when a preponderance of large HDL particles is observed. **METHODS:** We conducted a post-hoc analysis of 2 prospective studies: the IDEAL (Incremental Decrease in End Points through Aggressive Lipid Lowering; n = 8,888) trial comparing the efficacy of high-dose to usual-dose statin treatment for the secondary prevention of cardiovascular events, and the EPIC (European Prospective Investigation into Cancer and

Nutrition)-Norfolk case-control study, including apparently healthy individuals who did (cases, n = 858) or did not (control patients, n = 1,491) develop CAD during follow-up. In IDEAL, only HDL-C and apoA-I were available; in EPIC-Norfolk, nuclear magnetic resonance spectroscopy-determined HDL particle sizes were also available. RESULTS: In the IDEAL study, higher HDL-C proved a significant major cardiac event risk factor following adjustment for age, gender, smoking, apoA-I, and apoB. A similar association was observed for HDL particle size in EPIC-Norfolk. Increased risk estimates were particularly present in the high ends of the distributions. In contrast, apoA-I remained negatively associated across the major part of its distribution in both studies. CONCLUSIONS: When apoA-I and apoB are kept constant, HDL-C and HDL particle size may confer risk at very high values. This does not hold true for very high levels of apoA-I at fixed levels of HDL-C and apoB. These findings may have important consequences for assessment and treatment of CAD risk.

Can dysfunctional HDL explain high coronary artery disease risk in South Asians? ⁸³

BACKGROUND: Coronary artery disease (CAD) is the leading cause of mortality and morbidity in United States, and South Asian immigrants (SAIs) have a higher risk for CAD compare to Caucasians. Traditional risk factors do not completely explain high risk, and some of the unknown risk factors need to be explored. We assessed dysfunctional pro-inflammatory high density lipoprotein (HDL) in SAIs and assessed its association with sub-clinical CAD using carotid intima-media thickness (IMT) as a surrogate marker for atherosclerosis. METHODS: Cross-sectional study on SAIs aged 40-65 years. Sub-clinical CAD was measured using carotid intima media thickness (IMT) as a surrogate marker of atherosclerosis. Dysfunctional or pro-inflammatory HDL was determined by novel cell free assay and HDL inflammatory Index. RESULTS: Dysfunctional HDL was found in the 50% participants, with HDL-inflammatory index of ≥ 1.00 , suggesting pro-inflammatory HDL (95% CI, 0.8772-1.4333). The prevalence of sub-clinical CAD using carotid IMT (≥ 0.80 mm) was seen in 41.4% (95% CI, 0.2347-0.5933). On logistic regression analysis, positive carotid IMT was found to be associated with dysfunctional HDL after adjusting for age, family history of cardiovascular disease, and hypertension ($p=0.030$). CONCLUSIONS: The measurement of HDL level as well as functionality plays an important role in CAD risk assessment. Those SAIs with dysfunctional HDL and without known CAD can be a high risk group requiring treatment with lipid lowering drugs to reduce future risk of CAD. Further large studies are required to explore association of dysfunctional HDL with CAD and identify additional CAD risk caused by dysfunctional HDL.

Secondary prevention with bezafibrate therapy for the treatment of dyslipidemia: an extended follow-up of the BIP trial ⁸⁴

OBJECTIVES: This study was designed to evaluate the long-term cardiovascular benefit of bezafibrate therapy in coronary heart disease patients enrolled in the BIP (Bezafibrate Infarction Prevention) trial. BACKGROUND: The BIP trial yielded a nonsignificant 7.3% reduction in the rate of major cardiac events after a mean follow-up period of 6.2 years, possibly owing to an increasing unbalanced usage of nonstudy lipid-lowering drugs (LLDs) during the course of the trial. METHODS: The adjusted risk for the combined end point of cardiac death or nonfatal myocardial infarction during an extended mean 8.2-year follow-up period of the BIP trial was assessed in 3,090 patients allocated to the original bezafibrate (n = 1,548) and placebo (n = 1,542) groups of the trial. RESULTS: During the extended follow-up period, nonstudy LLDs were administered to a significantly greater proportion of placebo-allocated patients (57%) than bezafibrate-allocated patients (53%; $p = 0.02$). Interaction-term analysis demonstrated that the benefit of bezafibrate therapy was pronounced (18% risk reduction; $p = 0.03$) without or before treatment with nonstudy LLDs initiated during follow-up and attenuated (hazard ratio 1.05; $p = 0.85$) after therapy with nonstudy LLDs initiated during the observation period. Consistent with these findings, treatment with bezafibrate was shown to be associated with a significant 17% risk reduction ($p = 0.03$) when study patients were censored from the analysis upon initiation of therapy with nonstudy LLDs. CONCLUSIONS: The data demonstrate that bezafibrate therapy in the BIP trial was associated with significant long-term cardiovascular protection that was attenuated by an unbalanced usage of nonstudy LLDs during the course of the trial.

Beneficial effects of aggressive low-density lipoprotein cholesterol lowering in women with stable coronary heart disease in the Treating to New Targets (TNT) study ⁸⁵

OBJECTIVE: To examine by secondary analysis of the Treating to New Targets (TNT) study whether the benefits of intensive versus standard levels of lipid lowering are equally applicable to women. **METHODS:** A total of 10 001 patients (1902 women) with stable coronary heart disease (CHD) were randomised to double-blind treatment with atorvastatin 10 or 80 mg/day for a median follow-up of 4.9 years. **RESULTS:** In women and men, intensive treatment with atorvastatin 80 mg significantly reduced the rate of major cardiovascular events compared with atorvastatin 10 mg. Among women, the relative and absolute reductions were 27% and 2.7%, respectively (hazard ratio (HR) = 0.73, 95% confidence interval (CI) 0.54 to 1.00, $p = 0.049$). In men, the corresponding rate reductions were 21% and 2.2% (HR = 0.79, 95% CI 0.69 to 0.91, $p = 0.001$). The number needed to treat value (to prevent one cardiovascular event over 4.9 years compared with patients treated with atorvastatin 10 mg) for atorvastatin 80 mg was 29 for women and 30 for men. Rates of death of non-cardiovascular origin in the atorvastatin 80 mg and atorvastatin 10 mg were 3.6% and 1.6%, respectively ($p = 0.004$) among women, and 2.8% and 3.1% ($p = 0.47$) among men. **CONCLUSION:** Intensive lipid-lowering treatment with atorvastatin 80 mg produced significant reductions in relative risk for major cardiovascular events compared with atorvastatin 10 mg in both women and men with stable CHD.

Inflammation, statin therapy, and risk of stroke after an acute coronary syndrome in the MIRACL study⁸⁶

OBJECTIVE: Patients with acute coronary syndromes have an increased risk of stroke. We measured markers of inflammation in the MIRACL study, a randomized trial of atorvastatin versus placebo in acute coronary syndromes, to assess the relationship of inflammation to stroke. **METHODS AND RESULTS:** Baseline C-reactive protein (CRP), serum amyloid A (SAA), and interleukin-6 (IL-6) were collected in 2926 (95%) subjects. Baseline markers were related to stroke risk over the 16 weeks of the study. Subjects who subsequently experienced a stroke had higher CRP (27.5 versus 10.2 mg/L, $P=0.0032$), SAA (30.5 versus 16.0 mg/L, $P=0.031$), IL-6 (11 231 versus 6841 pg/L, $P=0.004$), and troponin (6.03 versus 3.19 ng/mL $P=0.0032$). The risk of stroke was related to greater CRP, SAA, and IL-6 in the placebo group only. Similarly, there was a graded increase in risk of stroke across quartiles of inflammatory markers in the placebo patients only. **CONCLUSIONS:** In acute coronary syndromes, the early risk of stroke relates to both heightened inflammation and size of myocardial necrosis. Treatment with atorvastatin abrogated the risk associated with elevated markers of inflammation in this study, a finding that provides a novel rationale for the use of statins in acute coronary syndromes.

The role of lipid-lowering therapy in preventing coronary heart disease in patients with type 2 diabetes⁸⁷

Coronary heart disease is the most common cause of death among diabetic patients. The increased risk of coronary heart disease in type 2 diabetes is due, in part, to lipid abnormalities often present in the diabetic patient. Diabetic dyslipidemia is characterized by elevated triglycerides, low high-density lipoprotein cholesterol (HDL-C) and an increased preponderance of small, dense low-density lipoprotein cholesterol (LDL-C) particles. Current guidelines for the prevention of coronary heart disease in diabetic patients identify elevated LDL-C as the primary target of lipid-lowering therapy, and recommend statins as the first-line treatment for diabetic dyslipidemia. This review evaluates the large statin trials that have included diabetic patients, and discusses the role of combination therapy in managing dyslipidemia in diabetic patients.

Treatment potential for cholesterol management in patients with coronary heart disease in 15 European countries: findings from the EUROASPIRE II survey⁸⁸

BACKGROUND: During the last decade, the evidence of beneficial effects of cholesterol lowering in patients with coronary heart disease (CHD) has been proven in several clinical trials. This has prompted international guidelines on prevention of CHD to include recommendations on dietary and pharmacological treatment of hyperlipidaemia with set goals on total- and LDL-cholesterol. **METHODS:** The first EUROASPIRE survey performed in 1995/1996 showed poor adherence to the European recommendations on lipid-lowering in patients with CHD. The second survey was carried out in 1999/2000 in 15 European countries and enrolled 8181 patients with CHD. Medical records were assessed and clinical examinations of risk factors including serum lipids were performed. The aim of this survey is to describe the treatment of hyperlipidaemia among CHD patients in Europe. **RESULTS:** The

proportion of patients not reaching the target of 5.0mmol/l was 58.3% with significant variations between countries. The use of lipid-lowering drugs was relatively high (60.9%). However, the most frequently used doses of lipid-lowering agents were much lower than the doses of proven effect used in clinical trials. CONCLUSIONS: Although the treatment of hyperlipidaemia in CHD patients seems to be improving as compared to the first survey, a significant number of patients do not reach treatment goals. If the full potential of lipid-lowering therapy was utilised with all eligible patients treated and doses titrated correctly, more patients would benefit in terms of reduced morbidity and mortality of CHD.

Coenzyme Q10 in patients undergoing CABG: Effect of statins and nutritional supplementation

89

BACKGROUND: The hydroxymethylglutaryl coenzyme A reductase inhibitors (statins) are effective cholesterol lowering medications, however, statins may interfere with CoQ(10) biosynthesis. We examined the effect of statin therapy as well as nutritional supplements on plasma, cardiac and skeletal muscle concentrations of CoQ(10). **METHODS:** Forty patients with left ventricular dysfunction had fasting blood samples collected at baseline and following four weeks of supplementation (150mg/day of CoQ(10)). Cardiac and skeletal muscle biopsies were collected at the time of surgery and frozen in liquid nitrogen until analyzed for CoQ(10) levels by high performance liquid chromatography. **RESULTS:** Nutrient supplementation significantly increased plasma [(1.8 (1.2, 2.7) vs 0.8 (0.6, 0.94) mug/ml plasma, median+IQR; p=0.001)] and cardiac tissue concentrations of CoQ(10) [(120.5 (76.5, 177.1) vs 87.3 (60.5, 110.8) nmol/g wet weight, p=0.04)]. No effect of supplementation was seen on samples of skeletal muscle from the chest wall. Statin therapy was not found to influence plasma, cardiac or chest wall levels of CoQ(10). **CONCLUSION:** Nutrient supplementation significantly increased plasma and cardiac tissue levels of CoQ(10) but did not influence chest wall muscle concentrations. Statin therapy did not significantly influence tissue concentrations of CoQ(10). Longer term studies are needed to confirm this observation.

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