

- You are seeing a 58y/o male with CAD. He is s/p CABG but has no chest pain. He has HTN, and Dyslipidemia. Although he has been on statin and has an LDL cholesterol of 98; he has read that a greater reduction in cholesterol is associated with an improved outcome. He want to know what you recommend.

- In a 58y/o male with CAD does further does reducing the LDL cholesterol from the previous target of 100 to a lower target result in less cardiac events.

- Are the results valid?
- Will the Results Help me in caring for my patients?
- What are the results?
- How do you do the calculation?

1. Was the assignment of patients to treatment randomized?

- Yes No Can't Tell
- **2. Were all patients who entered the trial properly accounted for and attributed at its conclusion?**
- **was follow-up complete?**
- **were patients analyzed in the groups to which they were randomized (intention to treat analysis)?**
- Yes No Can't Tell
- **3. Were patients, their clinicians, and study personnel 'blind' to treatment?**
- Yes No Can't Tell

- **4. Were the groups similar at the start of the trial?**
- **Baseline prognostic factors (demographics, co-morbidity, disease severity, other known confounders) balanced?**
- **If different, were these adjusted for?**
- Yes No Can't Tell
- **5. Aside from the experimental intervention, were the groups treated equally?**
- **Co-intervention?**
- **Contamination?**
- **Compliance?**
- Yes No Can't Tell
- **6. Overall, are the results of the study valid?**
- Yes No Can't Tell

- **1. Can the results be applied to my patient care?**
- **Patients similar for demographics, severity, co-morbidity and other prognostic factors?**
- **Compelling reason why the results should not be applied?**
- Yes No Can't Tell
- **2. Were all clinically important outcomes considered?**
- **Are substitute endpoints valid?**
- Yes No Can't Tell
- **3. Are the likely treatment benefits worth the potential harms and costs?**
- **NNT for different outcomes?**
- Yes No Can't Tell

- **What are the Results**
- **1. How large was the treatment effect?**
- **Absolute risk reduction?**
- **Relative risk reduction?**
- **2. How precise was the estimate of the treatment effect?**
- **Confidence intervals?**

- The magnitude of effect is usually expressed as one of the following, where:
- **Yes No Exposed** a **Not Exposed** b **Control event rate** (CER) = $c/c+d$
- **Experimental event rate** (EER) = $a/a+b$
- (a) **Relative Risk** (RR) = $EER/CER = (a/a+b)/(c/c+d)$
- (b) **Relative Risk Reduction** (RRR) = $CER - EER / CER$
(commonest reported measure of dichotomous treatment effect)
- (c) **Absolute Risk Reduction** (ARR) = $CER - EER$
- (d) **Number Needed to Treat** (NNT) = $1/ARR$

Intensive Lipid Lowering with Atorvastatin in Patients with Stable Coronary Disease

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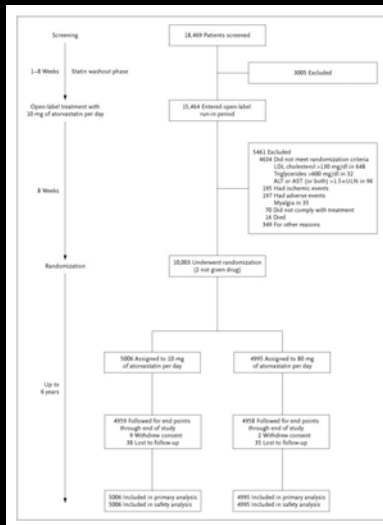
• **ABSTRACT**

- *Background* Previous trials have demonstrated that lowering low-density lipoprotein (LDL) cholesterol levels below currently recommended levels is beneficial in patients with acute coronary syndromes. We prospectively assessed the efficacy and safety of lowering LDL cholesterol levels below 100 mg per deciliter (2.6 mmol per liter) in patients with stable coronary heart disease (CHD).
- *Methods* A total of 10,001 patients with clinically evident CHD and LDL cholesterol levels of less than 130 mg per deciliter (3.4 mmol per liter) were randomly assigned to double-blind therapy and received either 10 mg or 80 mg of atorvastatin per day. Patients were followed for a median of 4.9 years. The primary end point was the occurrence of a first major cardiovascular event, defined as death from CHD, nonfatal non-procedure-related myocardial infarction, resuscitation after cardiac arrest, or fatal or nonfatal stroke.

- *Results* The mean LDL cholesterol levels were 77 mg per deciliter (2.0 mmol per liter) during treatment with 80 mg of atorvastatin and 101 mg per deciliter (2.6 mmol per liter) during treatment with 10 mg of atorvastatin. The incidence of persistent elevations in liver aminotransferase levels was 0.2 percent in the group given 10 mg of atorvastatin and 1.2 percent in the group given 80 mg of atorvastatin ($P<0.001$). A primary event occurred in 434 patients (8.7 percent) receiving 80 mg of atorvastatin, as compared with 548 patients (10.9 percent) receiving 10 mg of atorvastatin, representing an absolute reduction in the rate of major cardiovascular events of 2.2 percent and a 22 percent relative reduction in risk (hazard ratio, 0.78; 95 percent confidence interval, 0.69 to 0.89; $P<0.001$). There was no difference between the two treatment groups in overall mortality.
- *Conclusions* Intensive lipid-lowering therapy with 80 mg of atorvastatin per day in patients with stable CHD provides significant clinical benefit beyond that afforded by treatment with 10 mg of atorvastatin per day. This occurred with a greater incidence of elevated aminotransferase levels

- Patients with stable coronary artery disease may benefit from therapy to lower low-density lipoprotein (LDL) cholesterol levels, but optimal target levels are unknown
- This study showed that intensive lowering of LDL cholesterol levels to a mean of 77 mg per deciliter (2.0 mmol per liter) with 80 mg of atorvastatin per day produced greater clinical benefit than lowering levels to a mean of 101 mg per deciliter (2.6 mmol per liter) with 10 mg of atorvastatin per day
- These results could affect practice patterns by redefining target levels of LDL cholesterol in patients with stable coronary disease

Screening, Enrollment, and Outcomes



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Baseline Characteristics of the Patients

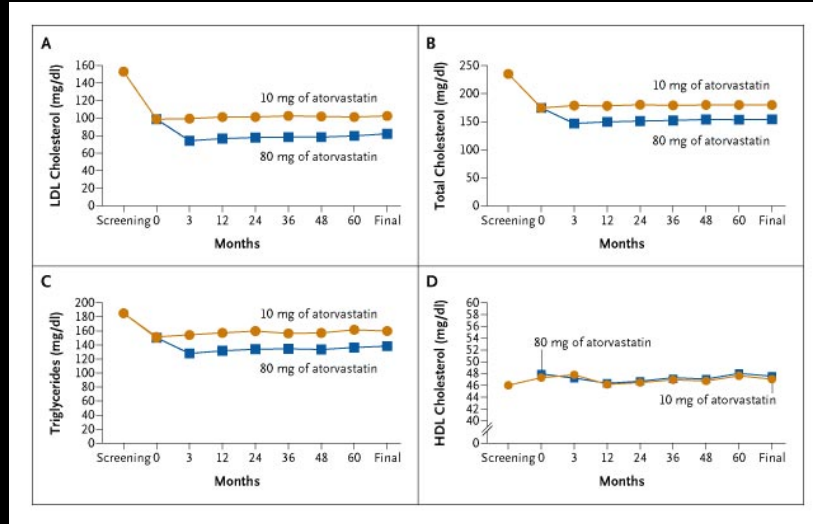
Table 1. Baseline Characteristics of the Patients.*

Characteristic	10 mg of Atorvastatin (N=5000)	20 mg of Atorvastatin (N=4995)
Age — yr	60.9±8.8	61.2±8.8
Male sex — no. (%)	4045 (80.8)	4054 (81.2)
White race — no. (%)†	4711 (94.1)	4699 (94.1)
Systolic blood pressure — mm Hg	131±17	131±17
Diastolic blood pressure — mm Hg	78±10	78±10
Body-mass index‡	28.6±4.7	28.4±4.5
Cardiovascular history — no. (%)		
Current smoker	672 (13.4)	669 (13.4)
Former smoker	3167 (63.3)	3155 (63.2)
Systemic hypertension	2721 (54.4)	2692 (53.9)
History of diabetes mellitus	753 (15.0)	748 (15.0)
Myocardial infarction	2888 (57.7)	2945 (59.0)
Angina	4067 (81.2)	4084 (81.8)
Cerebrovascular accident	263 (5.3)	255 (5.1)
Peripheral-artery disease	570 (11.4)	605 (12.1)
Congestive heart failure	408 (8.1)	377 (7.6)
Atrial fibrillation	927 (18.5)	967 (19.2)
Coronary revascularization		
Angioplasty	2719 (54.3)	2688 (53.8)
Bypass	2338 (46.7)	2317 (46.4)
Lipids — mg/dL§		
LDL cholesterol	98±18	97±18
Total cholesterol	175±24	175±24
Triglycerides	151±72	151±70
HDL cholesterol	47±11	47±11

* Plus-minus values are means ±SD.
 † Race was self-designated.
 ‡ Body-mass index is the weight in kilograms divided by the square of the height in meters.
 § To convert values for cholesterol to millimoles per liter, multiply by 0.02586; to convert values for triglycerides to millimoles per liter, multiply by 0.0113. LDL denotes low-density lipoprotein, and HDL high-density lipoprotein.

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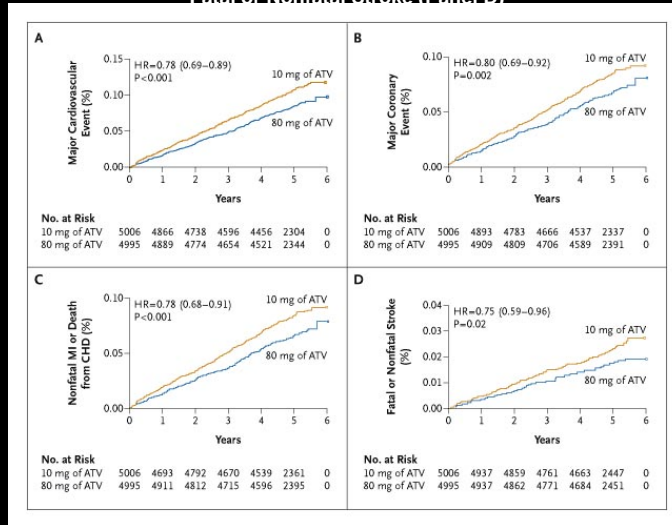
Mean Lipid Levels during the Study



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Cumulative Incidence of a First Major Cardiovascular Event (Panel A), a First Major Coronary Event (Panel B), Nonfatal Myocardial Infarction (MI) or Death from CHD (Panel C), and a First Fatal or Nonfatal Stroke (Panel D)



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Estimated Hazard Ratio for Individual Components of the Primary and Secondary Efficacy Outcomes

Table 2. Estimated Hazard Ratio for Individual Components of the Primary and Secondary Efficacy Outcomes.^a

Outcome	10 mg of Atorvastatin (N=5006)	80 mg of Atorvastatin (N=4995)	Hazard Ratio (95% CI)	P Value
<i>no. with first event (%)</i>				
Primary outcome				
Total major cardiovascular events	548 (10.9)	434 (8.7)	0.78 (0.69–0.89)	<0.001
Death from CHD	127 (2.5)	101 (2.0)	0.80 (0.61–1.03)	0.09
Nonfatal, non-procedure-related myocardial infarction	308 (6.2)	243 (4.9)	0.78 (0.66–0.93)	0.004
Resuscitation after cardiac arrest	26 (0.5)	25 (0.5)	0.96 (0.56–1.67)	0.89
Fatal or nonfatal stroke	155 (3.1)	117 (2.3)	0.75 (0.59–0.96)	0.02
Secondary outcomes				
Major coronary event [†]	418 (8.3)	334 (6.7)	0.80 (0.69–0.92)	0.002
Cerebrovascular event [‡]	250 (5.0)	196 (3.9)	0.77 (0.64–0.93)	0.007
Hospitalization for congestive heart failure	164 (3.3)	122 (2.4)	0.74 (0.59–0.94)	0.01
Peripheral-artery disease [§]	282 (5.6)	275 (5.5)	0.97 (0.83–1.15)	0.76
Death from any cause	282 (5.6)	284 (5.7)	1.01 (0.85–1.19)	0.92
Any cardiovascular event	1677 (33.5)	1405 (28.1)	0.81 (0.75–0.87)	<0.001
Any coronary event [¶]	1326 (26.5)	1078 (21.6)	0.79 (0.73–0.86)	<0.001

^a In each row, only the first event for each patient is counted. CI denotes confidence interval.
[†] This was the original primary outcome (death from CHD, nonfatal non-procedure-related myocardial infarction, or resuscitation after cardiac arrest).
[‡] A cerebrovascular event was defined as fatal or nonfatal stroke or transient ischemic attack.
[§] Peripheral-artery disease was defined as any new diagnosis of peripheral-artery disease, any admission related to its treatment, or any incidental discovery of plaques or stenosis.
[¶] Any coronary event was defined as a major coronary event, revascularization procedure, procedure-related myocardial infarction, or documented angina.

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 THE NEW ENGLAND
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- All Primary Outcomes. ARR= 10.9%-8.7%=2.2% NNT=1/ARR=1/2.2%=45.4
- Any Coronary Event. ARR=26.5%-21.6%=4.9% NNT=1/ARR=1/4.9%=20.4

- To reduce one of primary outcomes you must treat 45.4 people for 4.9 years.
- To reduce any coronary event you must treat 20.4 people for 4.9 years.
- Atrovastin 10 mg cost \$79 per month.
- Atrovastin 80 mg cost \$114 per month
- The difference is \$35 per month
- Therefore the cost of this intervention is $\$35 \times 45.4 \times 59 = 93000$ for one of there primary intervention
- The cost of this intervention is $\$35 \times 20.4 \times 59 = 42126$ for any cardiac event.

- Adverse events related to treatment occurred in 406 patients in the group given 80 mg of atorvastatin, as compared with 289 patients in the group given 10 mg of atorvastatin (8.1 percent vs. 5.8 percent, $P < 0.001$).
- The respective rates of discontinuation due to treatment-related adverse events were 7.2 percent and 5.3 percent ($P < 0.001$).
- Treatment-related myalgia was reported by 241 patients in the group given 80 mg of atorvastatin and by 234 patients in the group given 10 mg of atorvastatin (4.8 percent and 4.7 percent, respectively; $P = 0.72$).

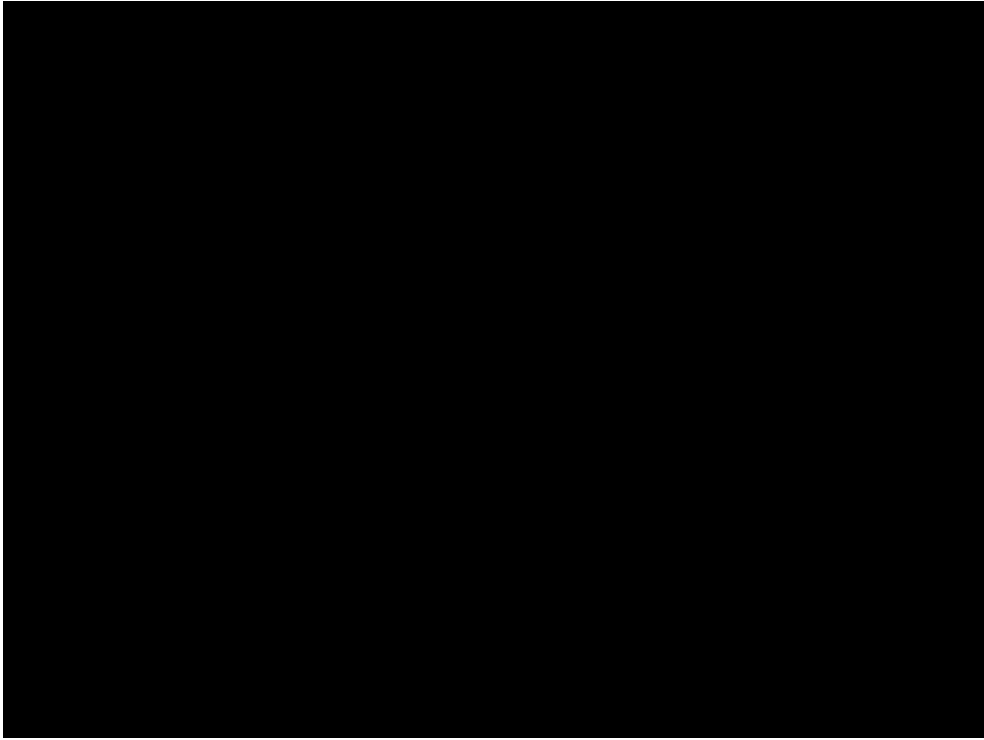
- A total of 60 patients receiving 80 mg of atorvastatin had a persistent elevation in alanine aminotransferase, aspartate aminotransferase, or both (defined as two consecutive measurements obtained 4 to 10 days apart that were more than three times the upper limit of the normal range), as compared with 9 patients receiving 10 mg of atorvastatin (1.2 percent vs. 0.2 percent, $P<0.001$).
- There were no persistent elevations in creatine kinase (defined as two consecutive measurements obtained 4 to 10 days apart that were more than 10 times the upper limit of the normal range).
- Five cases of rhabdomyolysis were reported (two in the group given 80 mg of atorvastatin and three in the group given 10 mg of atorvastatin)

Characteristics of Five Patients with Rhabdomyolysis

Table 3. Characteristics of Five Patients with Rhabdomyolysis.*

Characteristic	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Clinical presentation	Congestive heart failure, MI, respiratory failure, pneumothorax	Accidental fall	Pneumonia and sepsis	Weakness with concomitant ingestion of alcohol and ceftriaxone	Postoperative thromboembolic disease; occluded arterial supply to right arm and left leg
Atorvastatin group	80 mg	10 mg	10 mg	10 mg	80 mg
Muscle symptoms	No	Yes	No	Yes	No
Creatine kinase (U/liter)					
Peak	4228	611	4913	7265	Not available
Normal range	25–195	55–170	Not available	<180	Not available
Creatine kinase >10×ULN	Yes	No	Yes	Yes	Not available
Creatinine elevation (or urinary abnormalities)	Undetermined	Yes (marginal increase in creatinine)	Not available	Undetermined	Renal failure

* The criteria of the American College of Cardiology, American Heart Association, and National Heart, Lung, and Blood Institute for rhabdomyolysis are muscle symptoms plus a creatine kinase level that is more than 10 times the upper limit of the normal range (>10×ULN) plus an elevation in creatinine or urinary abnormalities (e.g., myoglobinuria).⁹ Cases were identified by the investigator with direct responsibility for the patient; none of the cases were believed to be related to the study drug. MI denotes myocardial infarction.



- Intensive lipid-lowering therapy with 80 mg of atorvastatin per day in patients with stable CHD provides significant clinical benefit beyond that afforded by treatment with 10 mg of atorvastatin per day
- This occurred with a greater incidence of elevated aminotransferase levels