REVERSAL AND PROVE-IT
Frequently Asked Questions
VHA Pharmacy Benefits Management Strategic Healthcare Group and the Medical Advisory Panel

1. What are the recommendations from the MAP based upon the results of REVERSAL and PROVE-IT?

a. Ensure statin therapy is used in appropriate individuals, especially those with acute coronary syndrome and other cardiovascular diseases.
b. Utilize a "high-potency" formulary statin (lovastatin, or simvastatin) whenever possible. Initiate these statins at a dose of 20 or 40 mg daily, unless there are safety issues requiring lower doses or requiring a non-CYP 3A4 metabolized statin (e.g. drug-drug interaction). Titrate to the appropriate LDL-C goal in individual patients or as tolerated.
c. If the LDL-C goal is not reached, add-on therapy with other lipid-lowering therapies (e.g. niacin, resins or nonformulary ezetimibe) or a nonformulary switch to atorvastatin (http://www.vapbm.org/criteria/Fluva-prava-atorva-r.pdf) should be considered.
d. Continue using recommended LDL-C lowering treatment goals until the results of the 3 ongoing trials designed to determine whether a lower LDL-C is better than current recommendations.

2. What are REVERSAL and PROVE-IT?[1,2]

REVERSAL and PROVE-IT are acronyms for 2 recently published trials comparing fixed doses of pravastatin 40 mg to atorvastatin 80 mg daily. REVERSAL stands for reversal of atherosclerosis with aggressive lipid lowering and PROVE-IT stands for pravastatin or atorvastatin evaluation and infection therapy.

3. What was the research question each study set out to answer?

The REVERSAL trial was undertaken to determine if there is a difference in coronary artery atherosclerosis burden and progression in patients receiving moderate versus intensive lipid-lowering therapy with statins.
The PROVE-IT trial had 2 main goals which included determining whether lowering LDL-C to 100 mg/dL with pravastatin versus to an LDL-C of 70 mg/dL with atorvastatin results in a difference to time to occurrence of death or major cardiovascular events in patients with acute coronary syndrome (ACS). The second goal of PROVE-IT was to examine the role of chlymadia pneumoniae (C. pneumoniae) infection in cardiovascular disease. The effect of the antibiotic portion of the trial is not presented with this data.

4. What were the study designs?

REVERSAL was a prospective, randomized (allocation concealed), double-blind (all patients and study personnel including those performing intravascular ultrasound), double-dummy trial with a planned follow up of 18 months.

PROVE-IT was a prospective, randomized (allocation concealed), double-blind, double-dummy trial with a planned follow up of between 18-36 months. The trial was continued until 925 events were reported to the coordinating center. The average duration of follow up was 24 months.

5. What was the setting in each study?

REVERSAL was a multicenter trial conducted in 34 community and tertiary sites within the Unites States.
PROVE-IT was a multicenter trial conducted at 349 sites in 8 countries.

6. What was the patient population in each study?

Eligible patients in the REVERSAL trial included men and women aged 30-75 years who required coronary angiography for a clinical indication. Patients were screened and those with at least one

obstruction with luminal narrowing of 20% or more were randomized. The vessel for study "target vessel" was not to have undergone angioplasty or have luminal narrowing of more than 50% throughout a "target segment" with a minimum length of 30 mm. Patients were required to have an LDL-C of 125-210 mg/dL after a 4-10 week washout period. Six hundred and fifty-seven patients met the eligibility requirements and were randomized. Demographic and lipid baseline characteristics did not differ between groups.

Eligible patients in the PROVE-IT trial included men and women aged 18 years or older who had been hospitalized for an acute coronary syndrome, either acute myocardial infarction (AMI) with or without ST-segment elevation or high risk unstable angina within the preceeding 10 days. In PROVE-IT, there were multiple exclusion criteria including shortened-life expectancy, use of any statin at a dose of 80 mg daily at the time of the index event, receiving fibrates or niacin that could not be discontinued, receiving known cytochrome P450 (CYP) 3A4 inhibitors or were anticipated to need, etc. Forty-one hundred and sixty-two patients met the eligibility requirements and were randomized. Baseline demographic and lipid characteristics were similar between groups with the exception of a statistically higher percentage of patients with a history of peripheral vascular disease in the pravastatin group.

7. What was the intervention in each study?

In REVERSAL, after coronary angiography, patients meeting all eligibility criteria were randomized to receive either pravastatin 40 mg daily or atorvastatin 80 mg daily for 18 months. At 18 months, repeat cardiac catheterization was performed. The reason pravastatin 40 mg daily was chosen was because that was the highest FDA approved dose at the time the study began and because it was well studied in secondary prevention. Furthermore, the mean LDL-C of patients in the trial was 150 mg/dL and it was considered that pravastatin 40 mg daily had the ability to reduce LDL-C to 100 mg/dL or less. Atorvastatin 80 mg daily was considered to be capable of lowering LDL-C greater than any other available therapy (to about 70 mg/dL in these patients with a mean baseline LDL-C 150 mg/dL).

For PROVE-IT, in addition to aspirin and other standard medications and interventional treatments for acute coronary syndromes, patients were randomized to receive pravastatin 40 mg daily or atorvastatin 80 mg daily. Patients were also randomly assigned to receive a 10-day course each month of gatifloxacin or placebo with the use of a 2X2 factorial design.

Pravastatin was increased to 80 mg daily in a blinded fashion if LDL-C exceeded 125 mg/dL on 2 consecutive visits and the patient was deemed compliant with medications and study visits. The dose of either drug could be reduced in half in response to elevated LFTs or CK or myalgias.

8. What were the outcome measures?

REVERSAL: After diagnostic coronary angiography, intravascular ultrasound was performed in both the longest and least angulated target vessel having met inclusion criteria and then again after 18 months in those patients still actively participating in the study. Since there were 6 intravascular ultrasound reviewers, the investigators took steps to determine intraobserver and interobserver variability.

The primary endpoint was percentage change in total atheroma volume. Measurement of total atheroma volume is different from other atherosclerotic progression trials that measured change in minimum luminal diameter. A secondary endpoint was nominal change in percentage atheroma volume. Other efficacy measures included nominal change in atheroma volume for the 10 contiguous cross-sections with the greatest and the least atheroma volume.

REVERSAL was not powered to find a difference in clinical events between groups.

PROVE-IT: The primary outcome measure was the time from randomization to first occurrence of a component primary event: death from any cause, MI, documented USA requiring hospitalization, revascularization via PCI or CABG (performed at least 30 days after randomization) and stroke.

Secondary endpoints were the risk of death from CHD, nonfatal MI, or revascularization, risk of CHD death or nonfatal MI and the risk of the individual components of the primary outcome. PROVE-IT was an event driven trial designed to last until a prespecified number of events (925) had occurred.

9. What were the results?

REVERSAL:
Of the 657 patients randomized, only 502 had evaluable intravascular ultrasound examinations at baseline and at 18 months (249 prava and 253 atorva). As a result, only those 502 patients were included in the efficacy analysis.

Laboratory: % Mean Change From Baseline (150 mg/dL) and Mean Lipid Value

	Pravastatin	Atorvastatin	P-value
Total Cholesterol	-18.4 / 187.5 mg/dL	-34.1 / 151.3 mg/dL	<0.001
LDL-C	-25.2 / 110 mg/dL	-46.3 / 78.9 mg/dL	<0.001
HDL-C	5.6 / 44.6 mg/dL	2.9 / 43.1 mg/dL	0.06
TG	-6.8 / 165.8 mg/dL	-20 / 148.4 mg/dL	<0.001
APO B100	-22 / 118.1 mg/dL	-39.1 / 91.8 mg/dL	<0.001
C-reactive protein	-5.2 / 2.9 mg/L	-36.4 / 1.8 mg/L	<0.001

Percentage change in total atheroma volume from baseline was 2.7% in the pravastatin group (95% CI 0.24-4.47%) vs. –0.4 in the atorvastatin group (95% CI –2.35-1.49). The difference was significant with a p-value of 0.02 indicating no disease progression with atorvastatin but progression with pravastatin.

A secondary endpoint of change in percentage atheroma volume was also observed to be statistically different between atorvastatin and pravastatin with atorvastatin having no disease progression and pravastatin having some progression.

In those coronary arteries with the greatest atheroma burden, there was net regression of disease in both atorvastatin and pravastatin. However, the percent regression was significantly greater with atorvastatin. In those arteries with the least atheroma burden, there was no difference between atorvastatin and pravastatin.

The authors noted in their discussion that some patients in the REVERSAL trial experienced marked regression in disease burden, however, they also reported that significant progression was observed in both groups.

The authors commented that the trial was not powered to determine a difference in clinical outcomes between interventions. There weren't differences between groups with regard to serious adverse events or drug discontinuations. No cases of rhabdomyolysis were reported.

PROVE-IT:

Of the 4,162 patients enrolled, 8 (0.2%) were lost to follow up.

1. The index-event was unstable angina in 1/3 of patients, MI without ST segment elevation in 1/3 and MI with ST segment elevation in the final 1/3.
2. 69% of patients underwent PCI
3. ¼ had been on statins at the time of the index event.
4. The median LDL-C after the index event and prior to treatment with study statins was 106 mg/dL. The median LDL-C during follow-up was 95 in the pravastatin and 62 in the atorvastatin group.
5. CRP was reduced from a median of 12.3 mg/L to a median of 2.1 in pravastatin and 1.3 for atorvastatin.

Primary endpoint:
For all randomized patients, the Kaplan-Meier event rates of the primary endpoint at 2 years was 26.3% in the pravastatin vs. 22.4% in the atorvastatin group (p=0.005, 95% CI 5-26%). The relative risk reduction was reported to be 16% with an absolute risk reduction of 3.9%. The number needed to treat (NNT) was 25

individuals for 2 years. Numeric differences were apparent as early as the first 30 days but this was not statistically different.

Secondary endpoints:

1. The risk of the secondary endpoint of death due to CHD, MI or revascularization was reduced statistically greater in the atorvastatin vs. pravastatin group (p=0.029, 95% CI not provided, RRR 14%, ARR 2.6%, NNT 38).
2. Among individual components of the primary endpoint, the only statistically significant difference favoring atorvastatin were in the need for revascularization and recurrent unstable angina.
3. A reduction in occurrence of all individual components of the primary endpoint were seen in favor of the atorvastatin vs. pravastatin group with the exception of stroke which favored pravastatin slightly.

Of interest, in those patients with baseline LDL-C 125 or greater, there was a much greater reduction in the hazard ratio of 34% (20.1% vs. 28.2%= ARR 8.1% NNT 12) compared to those patients with a baseline LDL-C of less than 125 mg/dL with a RRR of 7% (23.5 vs. 25.6=ARR 2.1%, NNT 47). Additionally, there were no differences in the primary outcome between treatment groups in the 25% of patients receiving statins prior to enrollment in the study.

Withdrawal for adverse events (ADE) did not differ between groups. However, the number of patients experiencing clinically significant elevation in liver function tests (LFTs) was significantly greater in the atorvastatin vs. pravastatin group (3.3 vs. 1.1%, p<0.001). There was no difference in CK elevations and no patients developed rhabdomyolysis.

10. What are the limitations of the 2 studies?

In both REVERSAL and PROVE-IT, compliance with study medications or study visits was not reported.

In REVERSAL, 23% of randomized patients were not included in the efficacy analysis due to a variety of reasons that were reported by the investigators. However, sensitivity analyses were performed demonstrating that a statistically significant difference still existed.

In PROVE-IT, authors reported the numbers of patients that were lost to follow up (n=8) and the percentage of patients withdrawing from the study. Thirty to thirty-three percent of study participants discontinued treatment in both groups after 2 years. However, the actual number of patients withdrawing from the study for a particular reason was not provided (e.g. adverse event (ADE), noncompliance with study protocol, protocol violation, etc.).

In PROVE-IT, the numbers of patients in each group (at baseline and end of study) receiving aspirin, beta-blockers and other medications and/or interventions (e.g. angioplasty, coronary stenting) proven to reduce events after myocardial infarction were not provided. As a result, the differences between atorvastatin and pravastatin being explained by aggressive versus moderate LDL-C lowering is less clear.

11. Is the more intensive reduction in LDL-C responsible for the differences in atherosclerotic progression or occurrence of events in REVERSAL or PROVE-IT, or is it an independent additional benefit of atorvastatin?

In REVERSAL, the mean LDL-C in the pravastatin group was 110 mg/dL and 78.9 mg/dL in the atorvastatin group. The current recommendations for both groups with coronary artery disease (CAD) is <100 mg/dL. As a result, the mean LDL-C for pravastatin was above the recommended range. Furthermore, the reduction in C-reactive protein (CRP) from baseline was significantly greater in the atorvastatin versus the pravastatin group (36.4% vs. 5.2%, respectively). Triglycerides were also reduced to a greater extent in the atorvastatin versus pravastatin group (20% vs. 6.8%). In an accompanying editorial, the author noted that the reduction in LDL-C and CRP in the pravastatin group was lower than expected based upon results

from other large, long-term outcome trials. However, laboratory results were only reported for those 502 patients completing the entire trial and did not include the results for the 23% of subjects who withdrew.

On page 1078 of the article, authors utilized graphs to compare the percentage LDL-C reduction and change in atheroma burden between the 2 drugs. It appeared that for a given percent reduction in LDL-C, atorvastatin was associated with a lower degree of disease progression. The authors noted that it is possible that there may be other factors contributing to the difference including TG and CRP reduction.

In PROVE-IT, the median LDL-C cholesterol was as anticipated, 95 mg/dL in the pravastatin vs. 62 mg/dL in the atorvastatin group. C-reactive protein was reduced significantly in both groups.

It is difficult if not impossible to determine if the differences observed between pravastatin and atorvastatin can be explained solely by aggressive versus moderate reduction in LDL-C or if there are individual or inherent differences in the statins themselves. There are 2 large ongoing clinical outcome trials comparing the effect of intensive versus moderate LDL-C reduction with statins that will help to better answer the question of whether "lower is better". These studies are designed to compare whether "lower is better" with a low versus high dose of the same statin [1)SEARCH: simvastatin 20 vs. 80 mg, 2)TNT: atorvastatin 10 vs. 80 mg]. Projected completion dates for both trials are in 2004. Another ongoing study designed to determine if "lower is better" is called the IDEAL study. IDEAL is comparing the LDL-C lowering ability and clinical outcomes between simvastatin 40 mg daily and atorvastatin 80 mg daily. In addition to SEARCH, TNT, REVERSAL and PROVE-IT, IDEAL may help to further clarify if any differences between individual statins exist, aside from LDL-C lowering.

12. Will these results change the choice of formulary statin in the VA?

At this time, there is no evidence to suggest that atorvastatin has an advantage over the current VA National Formulary "high-potency" statin simvastatin, aside from an average 5-6% greater reduction in LDL-C at the 80 mg dose of both agents. If an individual does not achieve their LDL-C goal on the maximum daily dose of simvastatin, addition of other lipid-lowering therapies (e.g. niacin, resins, or nonformulary ezetimibe) or a nonformulary switch to atorvastatin should be considered.

13. Will these results significantly lower the current LDL-C goal of <100 mg/dL in those patients at high risk for coronary heart disease CHD (e.g. those with CHD or CHD risk equivalents)?

In PROVE-IT, patients with a baseline LDL-C of 125 mg/dL or higher experienced the greatest reduction in the primary composite endpoint of 34% compared to those with a baseline LDL-C of <125 mg/dL who experienced a relative risk reduction of only 7%. On the other hand, in the Heart Protection Study[3], patients receiving simvastatin at a dose of 40 mg daily experienced a similar significant reduction in clinical events regardless of their baseline LDL-C (e.g. < or > 100 mg/dL). A reminder of caution that although informative, subgroup analyses are typically hypothesis generating and aren't statistically as reliable as data from the entire trial population.

Until the results from the clinical outcome trials, involving a low and a high dose of the same statin, the LDL-C goal for high-risk patients will remain at <100 mg/dL.

14. Should all veteran patients receive the maximum dose of a particular statin?

It is well accepted that as you increase the dose of any statin, the risk of adverse events is also increased. In PROVE-IT, there were numerous exclusion criteria in an attempt to avoid the potential for increasing serum concentrations of atorvastatin above that achieved with the 80 mg dose. Authors went on to discuss that the recommended routine LFT monitoring is important when using higher statin doses due to the apparent increased risk for liver function test abnormality. In REVERSAL, ALT was increased more than 3 times the upper limit of normal in 5 of the pravastatin vs. 7 of the atorvastatin recipients.

There are 2 studies comparing the LDL-C lowering abilities of 80 mg of atorvastatin and simvastatin. In the first study, 826 patients with hypercholesterolemia to atorvastatin 20mg or simvastatin 40mg daily for 6 weeks; followed by atorvastatin 40mg or simvastatin 80mg daily for 6 weeks; then atorvastatin 80mg or simvastatin 80mg daily for the remaining 24 weeks.[4] Mean baseline LDL-c was 206mg/dl in the atorvastatin versus 206mg/dl in the simvastatin group. At a dose of 80mg daily for each statin, atorvastatin reduced LDL-c by 53.6% compared to 48.1% for simvastatin ($p \leq 0.001$). With regard to safety, a greater number of patients in the atorvastatin 80mg as opposed to the simvastatin 80mg group ($p<0.001$) reported clinical adverse effects (primary gastrointestinal-diarrhea). There was no significant difference in withdrawal rates due to adverse effects between groups. With regard to laboratory safety, a greater number of patients in the atorvastatin 80mg versus the simvastatin 80mg daily group experienced adverse laboratory events ($p<0.001$). Furthermore, withdrawal from the study due to adverse laboratory events occurred more often in the atorvastatin 80mg compared to the simvastatin 80mg daily group ($p<0.05$). Clinically important ALT elevation (> 3 times the upper limit of normal) occurred statistically more often in the atorvastatin 80mg compared to the simvastatin 80mg group (17 vs. 2 cases, respectively, $p=0.002$) and was especially pronounced in women (there were statistically more women randomized to atorvastatin than simvastatin). Aminotransferase elevation generally occurred within 6 to 12 weeks after initiation of the 80mg statin dose.

In a second study, comparing maximum doses of atorvastatin and simvastatin, Karalis and colleagues randomized 1,732 patients with hypercholesterolemia to treatment with atorvastatin 10mg or 80mg daily or simvastatin 20mg or 80mg daily for 6 weeks.[5] In this study, a total of 432 patients received either atorvastatin or simvastatin at a dose of 80mg daily. At a dose of 80mg daily for each statin, LDL-c was reduced by 53% in the atorvastatin versus 47% in the simvastatin group ($p<0.0001$). With regard to safety at the 80mg dosage for each statin, atorvastatin was associated with a higher incidence of adverse effects compared to simvastatin (46% vs. 39%) and a higher rate of study discontinuation due to adverse effects (8% vs. 5%). However, neither of these differences was statistically significant.

In AVERT[6], and MIRACL[7], there were 2 and 2.5% of patients in the atorvastatin 80 mg daily group who experienced clinically important elevations in liver transaminases which was significantly greater than that seen in the angioplasty or placebo groups. In GREACE [8], there were 5 patients out of 25 who received atorvastatin 80 mg daily who experienced clinically significant increases in liver function tests. In all cases (GREACE), the transaminase elevations were reversible upon discontinuation or reduction in dose of atorvastatin. In PROVE-IT, 3.3% of patients receiving atorvastatin 80 mg experienced clinically significant elevation in LFTs vs. 1.1% in the pravastatin 40 mg group ($p<0.001$). In the majority of studies reporting health outcomes involving fluvastatin, lovastatin, pravastatin or simvastatin, the maximum daily dose was not used.

As a result of the increased risk for adverse events with maximum statin doses, especially in patients receiving concomitant medications that may increase the statin serum concentration, initiation of a reasonable statin dose followed by appropriate titration to LDL-C goals is recommended.

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