An Overview of PROVE IT-TIMI 22 – A Comparison of Intensive Statin Therapy and Moderate Statin Therapy in Acute Coronary Syndrome Patients.

PROVE IT-TIMI 22 Trial Overview[1]

- a multi-center randomized treatment-controlled trial to determine lipid lowering effects of high dose atorvastatin vs. moderate dose pravastatin on 'all-cause mortality/MI/unstable angina/revascularization/stroke' in patients recently hospitalized with an acute coronary syndrome (ACS).
- two treatment arms:
  - **atorvastatin 80mg daily** plus standard treatment for ACS (n=2099)
  - **pravastatin 40mg daily** plus standard treatment for ACS (n=2063)
- 4,162 patients were followed for 24 months (18-36 months) with the following characteristics:
  - males and females recently hospitalized for an ACS (MI or high risk unstable angina within last 10 days)
  - **age**: ~58 years **sex**: ~78% male **baseline LDL levels**: 2.74mmol/l **Peripheral Arterial Disease**: 5%^{ator} vs 6.6% ^{prav}

Table 1: PROVE IT-TIMI 22 results (atorvastatin 80mg daily vs pravastatin 40mg daily)

Endpoints	atorvastatin % (n=2099)	Pravastatin% (n=2063)	ARR %	RRR %	NNT	p value
1° all cause mortality/MI/unstable angina*/revascularization/stroke**	22.4	26.3	3.9	15	**26**	0.005
2° CHD death, nonfatal MI or revascularization	19.7	22.3	2.6	14	38	0.029
2° All-cause mortality	2.2	3.2	1.0	28	NS	0.07
2° Death/nonfatal MI	8.3	10.0	1.7	18	NS	0.06
2° Unstable angina	3.8	5.1	1.3	29	77	0.02
2° Revascularization	18.8	16.3	2.5	14	40	0.04

* requiring hospitalization ** either percutaneous coronary intervention or coronary artery bypass grafting **1°**=primary outcome **2°**=secondary outcome **ARR**=absolute risk reduction **CHD**=coronary heart disease **MI**=myocardial infarction **NNT**=number needed to treat to benefit 1 patient **RRR**=relative risk reduction

Of Note:

- study based on intention to treat analysis
- concomitant meds: ASA$^{(93\%)}$, warfarin$^{(8\%)}$, clopidogrel or ticlodipine $^{(72\%\text{initially, } 20\% @ 1\text{ yr})}$,β-blocker$^{(85\%)}$, ACE-I$^{(69\%)}$, ARB$^{(14\%)}$
- short trial **(~2 years)**; lack data on long term benefits; lack data on adverse reactions
- **LDL** at follow up: pravastatin arm: **2.46 mmol/l** (2.04-2.92 mmol/l); atorvastatin arm: **1.60 mmol/l** (1.29-2.04 mmol/l)
  -75% of patients had not previously been on statin therapy: LDL ↓ 22**%** in the pravastatin arm & ↓ 51% in the atorvastatin arm at 30days $^{(p<0.001)}$
  -25% were on previous statin therapy: LDL was essentially unchanged in the pravastatin arm & ↓ an additional 32% in the atorvastatin arm $^{(p<0.001)}$
  (Statistical benefit only seen in the subgroup with LDL >3.2 mmol/l.)
- C-reactive protein levels were ↓ 83% $^{12.3\rightarrow2.1\text{mg/l}}$ in the pravastatin arm & ↓ 89% $^{12.3\rightarrow1.3\text{mg/l}}$ in the atorvastatin arm
- **SAFETY** : **Creatine kinase** ↑ in 2.7% of pravastatin pts & 3.3% of atorvastatin pts. - NO cases of **rhabdomyolysis** in either arm
  - elevations i**n ALT** levels >3 x ULN occurred in 1.1% of patients in the pravastatin arm and 3.3% in the atorvastatin arm (p<0.001; **NNH=46**)
  - **atorvastatin 80mg** was one treatment arm in the **AVERT**[2,3] trial - 2% of those pts had ALT levels >3 x ULN
  - **atorvastatin 80mg** was one treatment arm in the **MIRACL**[2,4] trial - 2.5% had ALT levels >3 x ULN, and 3 hepatitis cases occurred
- **REVERSAL** (The Reversal of Atherosclerosis with Aggressive Lipid Lowering) trial[5]: compared **atorvastatin 80mg/day** and **pravastatin 40mg/day** in 654 stable coronary dx pts to measure the rate of dx progression over 18 months using intravascular ultrasound (limitation=small # of pts in the trial). The 1° end point (% change in atheroma vol) showed significantly lower $^{(p=0.02)}$ progression rate in the atorvastatin arm. **C-reactive protein** ↓ 5.2% $^{3\rightarrow2.9\text{mg/l}}$ in the pravastatin arm & ↓ 36.4% $^{2.8\rightarrow1.8\text{mg/l}}$ in the atorvastatin arm. $^{(p<0.001)}$ Differences possibly due to greater ↓ in atherogenic lipoproteins and C-reactive protein in those treated with atorvastatin?

What we knew and what these results add to that knowledge:

- There are many large randomized controlled trials that have shown statins reduce the risk of death or CV events in high risk patients. Current guidelines recommend reducing LDL levels to <2.5mmol/l in patients with CAD or diabetes ➔ previous studies using moderate statin doses have shown this is beneficial.[1]
- **PROVE-IT** has demonstrated that an early, more aggressive lipid lowering regimen (atorvastatin 80mg/day) provides greater benefit against 'death or CV events' in ACS patients. An aggressive lipid lowering regimen resulting in LDL levels lower than currently recommended targets may provide greater benefit for these high risk patients.[1, 6] Adverse event rates increase at higher doses, therefore caution is warranted, especially when considering aggressive lipid lowering in patients at lower risk.
- **Magnitude of benefit** was "**one less** 'death or CV event' for every **26 ACS patients** treated over **2 years**"; additional reductions seen in other endpoints such as unstable angina and revascularization.

Questions Remaining:

- Would benefits be seen in lower risk patients? What is the mechanism of the benefit (ie: is it due to ↓ CRP levels/anti-inflammation)[1]? What is the long-term benefit/risk profile of higher aggressive dose statin therapy? Was it the dose of statin or the statin they dosed? What would have happened if they compared atorvastatin 10mg with atorvastatin 80mg?

(See next page for list of upcoming trials.)

Upcoming Trials:

TNT (Treating to New Targets) [7,8]: comparing **atorvastatin 10mg** and **80mg** in ~10,000 CHD pts for 5 years. They are investigating the benefits of aggressive lipid lowering therapy. 1° endpoint=time to occurrence of a major CV event. Results expected in 2005.
IDEAL (Increment Decrease in Endpoints through Aggressive Lipid Lowering)[8]: comparing **atorvastatin 80mg/day** vs **simvastatin 20-40mg/day** in patients with an acute MI or a hx of MI. They are investigating the benefits of aggressive lipid lowering therapy. Results expected in 2005.
SEARCH (The study of the Effectiveness of Additional Reductions in Cholesterol and Homocysteine tests)[8]: comparing **simvastatin 20mg** and **80mg** in CHD patients. Results expected in 2004/2005.
SPARCL (Stroke Prevention by Aggressive Reduction in Cholesterol Levels)[9,10]: evaluating the effects of **atorvastatin 80mg/day** in 4,732 patients with previous stroke or TIA, but no hx of CHD. Results expected in October 2004.
ASPEN (Atorvastatin Study for the Prevention of CHD Endpoints in NIDDM)[11] and **CARDS** (Collaborative AtoRvastatin Diabetes Study)[11]: evaluating if aggressive lipid lowering (using **atorvastatin** vs **placebo**) can lead to 1° prevention of CV events in >4000 type II diabetes pts with no previous MI over 4 years. Also investigating the benefits of ↓ LDL below the current recommended guidelines.

References:
1) Cannon C, Braunwald E, McCabe C, et al. Comparison of Intensive and Moderate Lipid Lowering with Statins after Acute Coronary Syndromes (**PROVE IT-TIMI 22)**. New Engl J Med 2004; 350. Online April 8, 2004.
2) Rath B, Jensen B, Regier L. Lipid Lowering Agents-Evidence, Questions & Comparisons. RxFiles, Feb 2002.
3) Pitt B, Waters D, Brown V, et al. Aggressive Lipid-Lowering Therapy Compared with Angioplasty in Stable Coronary Artery Disease (**AVERT**). New Engl J Med 1999; 341:70-6.
4) Schwartz G, Olsson A, Ezekowitz M, et al. Effects of Atorvastatin on Early Recurrent Ischemic Events in Acute Coronary Syndromes (**MIRACL**). JAMA 2001;285:1711-8.
5) Nissen S, Tuzcu E, Schoenhagen P, et al. Effect of Intensive Compared with Moderate Lipid-Lowering Therapy on Progression of Coronary Atherosclerosis: A randomized Controlled Trial (**REVERSAL)**. JAMA 2004;291:1071-80.
6) Genest J, Frohlich J, Fodor G, McPherson R; Working Group on Hypercholesterolemia and Other Dyslipidemias. Recommendations for the management of dyslipidemia and the prevention of cardiovascular disease: summary of the **Canadian 2003 update**. CMAJ. 2003 Oct 28;169(9):921-4. http://www.cmaj.ca/cgi/data/169/9/921/DC1/1 Full Report.
7) Waters D, Guyton J, Herrington D, et al. Treating to New Targets: Does Lowering Low-density Lipoprotein Cholesterol Levels Below Currently Recommended Guidelines Yield Incremental Clinical Benefit? (**TNT**). Am J Cardiol 2004;93(2):154-8.
8) Brookes L. Reversing Atherosclerosis with Aggressive Lipid Lowering. Medscape: http://www.medscape.com/viewarticle/464440 Date accessed: April 7, 2004.
9) Deanfield J. Clinical Trials: Evidence and Unanswered Questions--hyperlipidaemia. Cerebrovasc Dis 2003; 16 Suppl 3:25-32.
10) Amarenco P, Bogousslavsky J, Callahan A, et al. Design and Baseline Characteristics of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels Study (**SPARCL)**. Cerebrovasc Dis 2003;16(4):389-95.
11) Crespin S. What Does the Future Hold for Diabetic Dyslipidaemia? Acta Diabetol 2001;38 Suppl 1:S21-6.

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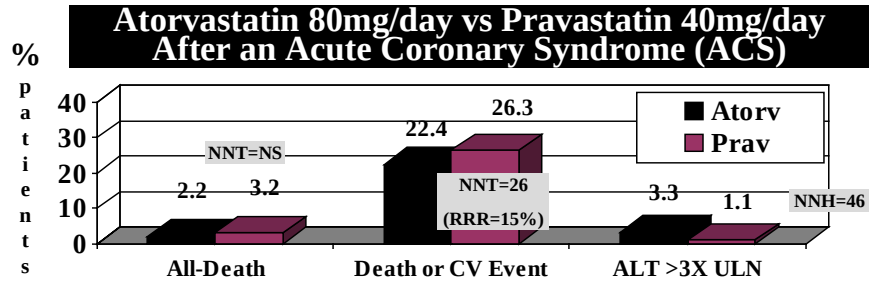
- Intensive vs moderate lipid lowering in high risk ACS patients
- LDL: 2.74 baseline mmol/L ➔ 1.60 atorvastatin vs 2.46 pravastatin
- 1° end point "Death or CV Event": all-cause mortality, MI, unstable angina, revascularization, and stroke



4/7/04 RxFiles-Lipid Agents-Highlights 1

NNT= number needed to treat **NNH**= number needed to harm **NS**= not significant (statistically)
RRR= relative risk reduction **ULN**= upper limit of normal