Trends-in-Medicine

April 2005
by Lynne Peterson

SUMMARY

Sanofi-Aventis's diet drug Acomplia continues to look like a winner, and demand is likely to be high among cardiologists. ♦ Sanofi-Aventis's Plavix got a boost at ACC: adding it to a fibrinolytic +aspirin is an effective and safe way to reduce ischemic complications, and doubling the loading dose to 600 mg before stenting cuts the MI risk in half. ♦ Lilly's prasugrel could become a major challenger to Plavix. Though development is still early, it appears to be a much more powerful platelet inhibitor than Plavix. ♦ Prescriptions for Pfizer's Lipitor may go up after the results of the TNT trial, which proved lowering LDL cholesterol levels below current guidelines reduces the risk of heart attacks and strokes. ♦ Data are building that Pfizer's torcetrapib, a CETP inhibitor, raises HDL both as monotherapy and in combination with a statin, but Pfizer reportedly only plans to offer it in combination with Lipitor. The thing to watch with torcetrapib is the systolic blood pressure.

Trends-in-Medicine
Stephen Snyder, Publisher
1879 Avenida Dracaena
Jensen Beach, FL 34957
772-334-7409 Fax 772-334-0856
www.trends-in-medicine.com

AMERICAN COLLEGE OF CARDIOLOGY: DRUGS

Orlando, FL
March 5-10, 2005

Stents dominated this meeting of the American College of Cardiology (ACC), but there also was news on several drugs, including Sanofi-Aventis's Acomplia and Plavix; Lilly's platelet inhibitor, prasugrel (a potential Plavix competitor); Pfizer's Lipitor, torcetrapib, and Viagra; and Actelion's tezosentan.

SANOFI-AVENTIS'S Acomplia (rimonabant)

Weight loss and metabolic benefits maintained through second year

Two-year data from the Phase III RIO-Europe weight loss trial of Sanofi-Aventis's Acomplia (rimonabant) confirmed and replicated the one-year results of that trial, which were presented at the European Society of Cardiology meeting in September 2004. RIO-Europe was a two-year, multicenter, randomized, double-blind, placebo-controlled, parallel group study of 1,507 patients in Belgium, Finland, France, Germany, the Netherlands, Sweden, and the U.S. (~350-400 U.S. patients). All patients were on a non-specific hypocaloric diet with a 600 kcal/day deficit. Researchers reported that the benefits obtained at one year were maintained out through two years.

- **5 mg Acomplia.** Less weight loss achieved in Year 1, but that weight loss was maintained in Year 2.
- **20 mg Acomplia.** More weight loss in Year 1, but ~16% of this was given back in Year 2, though patients still had significantly more weight loss than with 5 mg at either the end of Year 1 or Year 2.

At ACC, Sanofi-Aventis officials very carefully described Acomplia as a drug to treat metabolic syndrome, emphasizing the overall health benefits rather than just the weight loss. The FDA does not currently recognize metabolic syndrome, but a Sanofi official said the company will continue to work to convince the FDA to recognize metabolic syndrome even as it submits Acomplia to the FDA in April 2005, "Metabolic syndrome is not recognized by the FDA, but we need to move in that direction which we are doing." Another Sanofi official said, "Whether we get an indication for metabolic syndrome or obesity depends on how fast we can educate the FDA."

The discussant at the formal presentation of the RIO-Europe data called the findings "truly a landmark study in the field of obesity," but he raised several concerns:

- **On efficacy:** "The two-year data suggest a 50% relative reduction from about 40% to 20% in the prevalence of metabolic syndrome, which is extremely important…But if you look at the (Kaplan-Meier weight loss) curves at two

years, the curves are starting to head upwards…We would really like to know what happens after two years …We want to see more post-marketing studies to see if the effect is maintained long-term."

- **On safety:** "It was very heartening that in these 1,500 patients the safety profile was quite good. But I would also raise for your consideration a hypothetical and provocative question: What if the drug now hits the market, and we have five million prescriptions and get all the wonderful positive effects, but one person per million dies related to the drug? What should reasonable people do? Should they say it is an acceptable risk:benefit? Or should we handle it like previous anorexants, with punitive measures? And who makes this decision?…This is just one of a number of medications that may, emphasize may, have this problem. We have no evidence of this now. How do we deal with something that is good for the vast majority, but may not, in post-marketing studies, be as safe as it was in the original 1,500 or 3,000?"
- **On marketing:** "It is important to have medications to treat the scourge of obesity, but we have to decide who should get these medications. The data are strong for the 20 mg (Acomplia) but not so for the 5 mg. Should it be anyone defined as obese, or should we require additional risk factors?...I would hate to see a prescription drug reduce efforts toward healthy eating and lifestyle measures."

There was no discussion at ACC about other issues that have been raised about Acomplia, including the effect on neuropsychiatric/mood/cognition (anxiety, depression). The SF-36 quality of life results also still have not been presented for this or the RIO-North America trial.

At an off-site session on Acomplia, the audience was asked several questions that are useful in understanding the outlook for Acomplia:

- 74% said that from 30%-70% of the patients in their practice are overweight.
- 72% said from 20%-50% of their patients have metabolic syndrome.
- 68% currently assess BMI.

2-Year RIO-Europe Trial Results of Acomplia

Measurement	Placebo n=305	Acomplia 5 mg QD n=603	Acomplia 20 mg QD n=599
Secondary endpoint: **Absolute weight loss at 2 years**			
Absolute weight loss Completers (per protocol)	-2.5 kg -5.5 pounds	-4.6 kg -10.1 pounds (p<.007 vs. placebo)	-7.2 kg -15.8 pounds (p<.001 vs. placebo)
By ITT with LOCF	-1.2 kg -2.6 pounds	-2.9 kg -6.4 pounds	-5.5 kg -12.1 pounds
Other results			
Completers losing >10% of body weight	10.9%	N/A	32.1%
Waist circumference in Completers – average decrease	-3.4 cm -1.34 inches	-5.3 cm -2.09 inches	-7.5 cm -2.96 inches (p<.001 vs. placebo)
Waist circumference by ITT with LOCF – average decrease	-1.8 cm -0.71 inches	-3.5 cm -1.38 inches	-6.7 cm -2.64 inches
Metabolic effects			
% of subjects with metabolic syndrome at two years	N/A	N/A	21.5% (vs. 42.0% at baseline and 19.6% at one year)
Change in HDL in Completers	+16.8%	+21.7%	+28.2%
Change in HDL by ITT with LOCF	+12.6%	+17.2%	+22.6% (p<.001)
Change in triglycerides (TGL) in Completers	+6.3%	-0.1%	-8.8%
Safety			
Psychiatric disorders	5.9%	3.8%	8.8%
Depressive disorders	2.0%	2.0%	3.7%
Any adverse event	84.9%	85.4%	89.1%
Any serious adverse event	9.2%	8.3%	10.9%
Death	2 patients	0	1 patient
Discontinuations for adverse events	13.1%	10.9%	18.9%

1-Year vs. 2-Year Results of RIO-Europe Trial

Measurement	Acomplia 20 mg		Placebo	
	1 year	2 years	1 year	2 years
Weight loss by Completers	-18.9 pounds	-15.8 pounds	-7.9 pounds	-5.5 pounds
Weight loss by ITT	-14.5 pounds	-12.1 pounds	-4 pounds	-2.6 pounds
Completers losing >10% of body weight	39%	32.1%	12.4%	10.9%
Average decrease in waist circumference in Completers	-3.3 inches	-2.96 inches	-1.8 inches	-1.34 inches
Average decrease in waist circumference by ITT	-2.5 inches	-2.64 inches	-0.9 inches	-0.71 inches
% of patients with metabolic syndrome	19.6%	21.5%	31.4%	N/A
Increase in HDL	22.3%	22.6%	13.4%	12.6%

- At the beginning of the session, 74% said they currently do not measure waist circumference. By the end of the session, 100% said that waist circumference is important in assessing the risk for metabolic syndrome. A speaker quipped, "The tape measure has become the new stethoscope." Another speaker said waist measurement is a better measure than CT or MRI. A third expert said, "If we want this to work, the nurse or dietician has to do the waist circumference measurement."
- 63% said cholesterol/lipid profile has the greatest impact on patient care decisions.
- Based on the RIO-Europe two-year data, 57% said from 20%-30% of their patients would be eligible for Acomplia if it were available today.

Data from the RIO-Diabetes trial will be presented at the American Diabetes Association meeting in June 2005.

The outlook for Acomplia

Ten doctors were interviewed about their plans for Acomplia, and all said they would prescribe it if it was available. A doctor said, "My patients will want it, and I'll prescribe it…It also helps patients stop smoking. A patient has to be motivated for Zyban (GlaxoSmithKline, bupropion) to work, and a drug that helps with motivation would be good." A Midwest cardiologist said, "It seems safe and effective, the efficacy seems long-lasting. It would be an adjunct in our treatment of metabolic syndrome because statins are not a cure for metabolic syndrome." An Illinois cardiologist said, "It is a tremendously promising agent, and it will be widely used for metabolic syndrome patients and diabetics in particular. The effects are quite attractive. It could have a huge impact on metabolic syndrome." An Arizona cardiologist said, "I have patients who will ask for it, but not as many as for statins, at least in the beginning. It is a new drug, and I don't believe in being first or last to use a new drug." Another doctor said, "This is not a drug for thin women. It is a serious drug. It is not something to make women look good in a swimsuit."

Acomplia could be bigger than a statin, several sources predicted. On average, these doctors estimated that 29% of their patients would be eligible for Acomplia.

Medical cardiologists are not the only doctors who see a role for Acomplia in their practice. Even some electrophysiologists are interested in it. A Midwest electrophysiologist said, "Since metabolic syndrome is prevalent in the highest risk population – diabetics, it is hugely important to be able to control it." Sources also pointed out that primary care physicians are likely to be big prescribers of Acomplia. An Arizona doctor said, "This is going to be a primary care drug! Primary care physicians will jump on the bandwagon first."

The depression side effect was not a major concern among these doctors. One said, "Depression could be an issue, but you need to pick the patient population." A Midwest doctor said, "It is a safety issue, but we need to see if it is more noticeable in patients on antidepressants. If there were suicides, then it would be a problem." Another doctor said, "It won't be an issue if there is no suicidality."

Smoking cessation

Acomplia also is being developed as an aid to help people quit smoking. The results of a smoking cessation trial, STRATUS-Worldwide, was to be presented at the Society for Research on Nicotine and Tobacco in Prague March 20-23, 2005. It appears only the 20 mg dose is effective at helping people stop smoking, but either dose will maintain the smoking abstinence for up to one year after the person has quit. And only the 20 mg dose reduced weight gain in individuals who quit smoking.

SANOFI-AVENTIS'S Plavix (clopidogrel)
Good additive therapy for MI patients with ST-segment elevation

Adding Plavix to fibrinolytic therapy (e.g., tPA, streptokinase), aspirin, and, when appropriate, weight-based heparin, is an effective – and safe – way to improve the patency of the infarct-related artery and to reduce the rate of ischemic complications. That was the finding in two large, randomized, double-blind, placebo-controlled clinical trials.

CLARITY-TIMI-28

The results of the CLARITY-TIMI-28 trial were presented at ACC and simultaneously published in the ***New England Journal of Medicine***. CLARITY was conducted at 319 sites in 23 countries, and compared clopidogrel (300 mg loading dose followed by 75 mg QD) to placebo in 3,491 patients age 18-75 who presented within 12 hours of the onset of ST-elevation MI (STEMI) and who were headed for the cardiac cath lab within 48-192 hours. All patients also received a fibrinolytic agent (e.g., tPA), aspirin (ASA), and, in some cases, weight-adjusted heparin.

Researchers found that 36 patients needed to be treated to prevent one CV death, MI, or recurrent ischemia leading to urgent revascularization. The results were consistently in favor of clopidogrel by every subgroup – age, gender, etc. Dr. Marc Sabatine, the principal investigator, said, "CLARITY has demonstrated that more intensive, dual antiplatelet therapy with clopidogrel on top of ASA results in significant improvement in perfusion in STEMI patients."

The discussant pointed out that the findings were in a non-U.S. STEMI population who did not receive prompt invasive diagnosis or therapy, which he said "replicates the circumstances at a U.S. hospital without on-site interventional capability." He concluded that clopidogrel is a "valid adjunctive therapy that should be beneficial, particularly in settings where prompt PCI is not available."

- **On benefit:** He agreed that the primary endpoint is "strongly positive," but he noted that it is only a surrogate for CV morbidity/mortality.
- **On safety:** He said the lack of an increase in intracranial hemorrhage is "very reassuring." He added, "In that fraction of patients who require surgery, there was no increase in surgical bleeding. This is a finding that might not have been anticipated, since very often surgeons are reluctant to operate on a patient who has recently received clopidogrel."

In an accompanying editorial in the ***New England Journal of Medicine***, Dr. Richard Lange and Dr. L. David Hillis suggested:

- For patients on fibrinolytic therapy, adding clopidogrel and aspirin appears to be effective and safe. Clopidogrel+ fibrinolytic+aspirin+heparin did not appear to increase the incidence of bleeding complications – a finding in clear contrast to previous studies of combination therapy with reduced-dose fibrinolytic therapy, aspirin, and a IIb/IIIa inhibitor.
- Clopidogrel is easier to administer, less expensive, and safer than a IIb/IIIa inhibitor.
- Of the individual components of the PEP (i.e., death, recurrent MI, and occlusion of the infarct-related artery), clopidogrel exerted its greatest effect in reducing the rate of occlusion of the infarct-related artery. The mechanism by which clopidogrel did this is unknown. It may have:
  - **Enhanced early reperfusion.**
  - **Improved late reperfusion.**
  - **Prevented re-occlusion.** The reduction in risk of recurrent MI suggests that its primary mechanism of action is the prevention of re-occlusion.

The editorial also offered several caveats concerning the study:

1. The safety in CABG patients could not be assessed because there were too few of such patients.
2. The benefit when an early invasive strategy is routinely used is unknown.

CLARITY Trial Results Through The Day After Angiography

Measurement	Clopidogrel	Placebo	p-value	Odds Reduction
Angiography performed (mean 84 hours after randomization)	93.9%	94.2%	---	---
PCI	57.2%	56.6%	---	---
CABG	5.9%	6.0%	---	---
Primary endpoint: Composite of occluded infarct-related artery on angiography, death from any cause, or recurrent MI before angiography	15.0%	21.7%	.00000036	Down 36%
Composite endpoint of cardiac death, recurrent MI, or recurrent ischemia leading to urgent revascularization ***at 30 days***	11.6%	14.1%	.03	Down 20%
Recurrent MI	2.5%	3.6%	.08 (Nss)	Down 30%
Intracoronary thrombus	N/A	N/A	<.001	Down 27%
TIMI flow grade 0-1	11.7%	18.4%	<.001	Down 41%
TIMI flow grade 3	55.8%	51.2%	<.001	Up 36%
TIMI myocardial-perfusion grade 3	N/A	N/A	.008	Up 21%
Mean stenosis	68.4%	70.8%	.001	Down
Mean minimal luminal diameter	0.82 mm	0.75 mm	.001	Up
Death from any cause	2.6%	2.2%	.49 (Nss)	No difference
Resolution of ST-segment elevation by 180 minutes	59%	61%	.22 (Nss)	No difference
Need for early angiography (within 48 hours after randomization)	15.4%	18.6%	.01	Down 21%
Need for urgent revascularization during index hospitalization	19.5%	23.3%	.005	Down 21%
Stroke	N/A	N/A	.052 (Nss)	Down 46%
Death	2.6%	2.2%	.49 (Nss)	No difference
Recurrent MI	2.5%	3.6%	.08 (Nss)	No difference
Safety				
Major bleeding	1.3%	1.1%	.64 (Nss)	No difference
Minor bleeding	1.0%	0.5%	.17 (Nss)	No difference
Intracranial hemorrhage	0.5%	0.7%	.38 (Nss)	No difference

30-Day Results of CLARITY Trial

Measurement	Clopidogrel	Placebo	p-value	Odds Reduction
Composite endpoint of cardiac death, recurrent MI, or recurrent ischemia leading to urgent revascularization ***at 30 days***	11.6%	14.1%	.026	Down 20%
CV death	4.4%	4.5%	Nss	Down 3%
Recurrent MI	4.1%	5.9%	.02	Down 31%
Recurrent myocardial ischemia leading to urgent revascularization	3.5%	4.5%	.11 (Nss)	Down 24%
Stroke	0.9%	1.7%	.052(Nss)	Down 46%
Safety at 30 days				
Major bleeding	1.9%	1.7%	.80 (Nss)	---
Minor bleeding	1.6%	0.9%	.12 (Nss)	---
Intracranial hemorrhage	3.4%	2.7%	.24 (Nss)	---

3. It was a low-risk patient population (both treatment groups had 30-day mortality <5%, which is among the lowest reported for any study of patients who have MI with ST-segment elevation. It is unknown whether unselected MI patients with ST-segment elevation will benefit from clopidogrel without an increased incidence of bleeding.

4. Elderly and thin patients (those at increased risk of bleeding) were treated with a standard, non-weight-based dose of heparin, and prior-CABG patients were excluded. Thus, it is unknown whether such patients should receive clopidogrel in combination with full-dose fibrinolytic therapy and aspirin.

5. The timing of clopidogrel administration in PCI patients may have affected the study outcome. Clopidogrel patients had adequate serum concentrations of the drug at the time of PCI, but placebo patients did not, which may explain, at least in part, why the PEP prior to angiography was 8.3% vs. 9.3% (p=.27) but favored clopidogrel at 30 days.

COMMIT/CCS-2

The findings in CLARITY were reinforced by the positive findings of this large study conducted in China. The COMMIT/CCS-2 trial compared 75 mg clopidogrel daily to placebo (with all patients receiving 162 mg aspirin as well) in 45,852-patients who presented with suspected AMI within 24 hours of symptom onset. The trial excluded patients who got primary PCI or were at high-risk of bleeding. Mean treatment and follow-up was 16 days.

Researchers found adding clopidogrel to aspirin reduced the risk of a future CV event by 9%, with no increased risk in bleeding – even in elderly patients. They estimated that for each million MI patients treated for ~2 weeks, 5,000 deaths and 5,000 non-fatal events would be avoided.

16-Day Results of COMMIT/CCS-2 Trial

Measurement	Clopidogrel	Placebo	p-value	Relative risk reduction
Time delay MI<6 h	33.8%	33.7%	---	---
Primary endpoint #1: Death	9.3%	10.1%	.002	9%
Primary endpoint #2: All cause death	7.7%	8.1%	.03	7%
Outcome after re-MI				
Death	0.9%	1.0%	---	---
Stroke	0.9%	1.1%	---	14%
Any major bleed	0.58%	0.54%	Nss	---

ARMYDA-2 – A higher loading dose cuts MI risk

The 255-patient ARMYDA-2 trial found that doubling the standard 300 mg dose of clopidogrel can halve the risk of MI shortly after PCI with stenting. Patients scheduled to undergo PCI were randomized to either a 600 mg or 300 mg dose of clopidogrel four to eight hours before PCI.

30-Day Results of ARMYDA-2 Trial

Measurement	Clopidogrel 600 mg n= 126	Clopidogrel 300 mg n= 129	p-value
Multi-vessel procedures	20%	9%	---
Primary endpoint: Combination of death, MI, and TVR	4%	12%	0.041
Death	0	0	---
MI	5	15	---
TVR	1	0	---
Secondary endpoints			
Peak values of CK-MB (ng/mL)	3.0	4.9	0.038
Periprocedural CK-MB increase >2xULN	5%	15%	0.014
% of patients with CK-MB elevation	14%	26%	.036
Peak values of Troponin I (ng/mL)	.33	.81	0.021
% of patients with Troponin I elevation	26%	44%	0.004
Peak values of myoglobin (ng/mL)	84	113	0.002
% of patients with myoglobin elevation	30%	46%	0.015
Risk reduction for MI	52% not on statins 78% on statins	---	---
Groin hemotomas	9	6	Nss
Major bleed	0	0	Nss
Minor bleed	0.8%	0.8%	Nss

LILLY'S Prasugrel (CS-747, LY-640315)

Looks more powerful than Plavix, but still in early development

Data from two Phase I trials were presented on this potential challenger to Sanofi-Aventis's Plavix (clopidogrel), and prasugrel handily beat Plavix in both. Lilly researchers reported that prasugrel (sometimes called "son of Plavix") produced a significantly higher level of inhibition of platelet aggregation (IPA) – and more consistent inhibition – than Plavix, and prasugrel had a superior responder rate. Prasugrel, which Lilly licensed from Sankyo, is a novel thienopyridine $P2Y_{12}$ antagonist. Thus, from these two trials it appears the optimal loading dose is 60 mg, and the maintenance dose is 10 mg.

The first trial was a randomized, two-way, open-label, crossover comparison in healthy adults. Patients first received a loading dose of 60 mg

prasugrel or 300 mg Plavix, followed by a two week washout period, and then treatment arms were reversed and each arm received the opposite drug. The study evaluated the response to loading doses of each drug, measured by IPA. Responders were prospectively defined as either:

1. Inhibition of platelet aggregation >25% at both 4 and 24 hours post-dose.
2. >10% decrease in MPA at both 4 and 24 hours post-dose.

Regardless of which definition was used, prasugrel demonstrated a significantly higher responder rate than Plavix.

The second trial, presented in poster form, was a Phase Ib dose-ranging study of IPA comparing prasugrel and clopidogrel in aspirin-treated subjects with atherosclerotic vascular disease, mainly stable coronary disease. Patients were given a loading dose, followed by a lower maintenance dose. Lilly researchers concluded that:

- A prasugrel loading dose of 40 mg or 60 mg achieved higher IPA than clopidogrel 300 mg.
- Prasugrel maintenance doses of 10 mg and 15 mg achieved higher IPA than clopidogrel 75 mg.
- The percent of non-responders was lower in patients treated with prasugrel than clopidogrel.
- Both prasugrel and clopidogrel were well-tolerated, with no discontinuations due to adverse events.
- The highest prasugrel maintenance dose (15 mg) was associated with a higher number of bleeding events than clopidogrel.

A Lilly researcher addressed several issues that have come up about prasugrel:

- **Death.** The company has determined that the three deaths seen in earlier trials of prasugrel are not drug-related.
- **QT prolongation.** The QT studies the FDA requires are still not complete, but no signal of QT prolongation has been seen in very early studies.
- **Over-inhibition.** There is no evidence that prasugrel inhibits the $P2Y_{12}$ receptor too much. The moderator at the session where this data were presented asked, "Your degree of platelet inhibition looks dangerously close to that achieved with (oral) IIb/IIIa inhibitors. Isn't there a potential for this being a double-edged sword, especially for long-term treatment?" The Lilly researcher responded, "Obviously, we are concerned about a two-edged sword, that great inhibition may be associated with great bleeding…Another prasugrel study (also presented at ACC 2005) suggested that at least out to 30 days, the response to prasugrel, especially at higher levels of IPA, is well tolerated…And data from a Phase II trial (JUMBO-TIMI-26) that was presented at the European Society of Cardiology meeting (in September 2004) found no significant difference in major bleeding or major/minor bleeding, including the 60 mg dose. This will again be carefully examined in the Phase III trial, but so far it looks like it is well tolerated."
- **Comparison to higher dose Plavix.** Even a higher (600 mg) loading dose of Plavix, which is gaining popularity, probably would not provide greater – or even comparable – IPA as prasugrel. He said, "The IPA achieved with 600 mg Plavix is similar to 300 mg; it is just that you move the time to when you achieve peak inhibition from 6-12 hours to two hours…More recent data suggest there is about a 10% increase in IPA following a 600 mg loading dose…That would take you from ~30%-40% IPA…And that is only an estimate…We are up at a level of ~78% inhibition (with prasugrel), so I think we would still be significantly higher, but that has to be tested in a head-to-head study."
- **Optimal dose.** The dose going forward is 60 mg.

Results of Phase Ib Dose-Ranging Study of Prasugrel

Measurement	Prasugrel				Clopidogrel
	40 mg/5 mg n=19	40 mg/7.5 mg n=19	60 mg/10 mg n=19	60 mg/15 mg n=21	300 mg/75 mg n=101
Bruising	12%	13%	12%	15%	11%
Bleeding	2%	4%	2%	6%	5%
Bruising and bleeding	13%	15%	13%	17%	15%
Epistaxis	1%	1%	1%	5%	2%
Non-responders to loading dose	0 (p=.00002)*		~3% (p=.00002)*		~52%
Non-responders to maintenance dose	0	~20%	0 (p=.0007)*	0 (p=.0007)*	~45%

* vs. clopidogrel

PFIZER'S Lipitor (atorvastatin) Proves lower LDL is better, but perhaps just as big a win for SCHERING-PLOUGH/MERCK's Zetia

The results of the TNT (Treating to New Targets) trial show that lower-is-better in LDL cholesterol. Reducing cholesterol below 100 mg/dL in coronary heart disease patients with high-dose statin therapy was found to reduce major cardiovascular events by 22%. But Schering-Plough/Merck may be as big a winner with the results as the trial sponsor, Pfizer; a ***New England Journal of Medicine*** editorial suggested that Zetia (ezetimibe) might be a better choice than high dose Lipitor for additional lipid lowering.

TNT was a five-year, 10,001-patient, double-blind, parallel group study comparing 10 mg and 80 mg Lipitor. Once patients with a starting LDL <130 reached an LDL of ~100 mg/dL on 10 mg Lipitor, they

TNT Trial Results

Measurement	Lipitor 10 mg n=5,006	Lipitor 80 mg n=4,995	p-value	Relative risk reduction
Mean LDL during treatment	101	77	---	---
Primary endpoint: Total major cardiovascular events	10.9%	8.7%	<.001	Down 22%
Death from CHD	2.5%	2.0%	.09	---
Non-fatal, non-procedure-related MI	6.2%	4.9%	.004	Down 22%
Resuscitation after cardiac arrest	0.5%	0.5%	0.89	---
Fatal or non-fatal stroke	3.1%	2.3%	.02	Down 25%

were randomized to either 10 mg or 80 mg Lipitor. Patients were followed an average of 4.9 years. The 10 mg Lipitor patients maintained their cholesterol at an average of 101 mg/dL, and the 80 mg Lipitor patients achieved and maintained an average LDL of 77 mg/dL. Compared to low dose Lipitor, high dose Lipitor reduced total major cardiovascular events (the primary endpoint) by 22%, strokes by 25%, and MIs by 22%.

Investigators estimated that if 1,000 patients had their LDL reduced from 101 to 77, it would prevent 34 major CV events over five years. Thus, ~30 patients would need to be treated to prevent one event. The principal investigator, Dr. John LaRosa of SUNY Downstate Medical Center in Brooklyn NY said, "Treating to a (LDL) goal of 77 mg/dL with 80 mg atorvastatin daily from a starting LDL of 100 provided a highly significant reduction in the risk of major cardiovascular events. The results indicate the linear relationship between reduced LDL and reduced coronary heart disease risk holds true even at very low LDL levels."

Current cholesterol guidelines recommend an LDL goal of <100 mg/dL. The Heart Protection Study (HPS) comparing placebo and Merck's Zocor (simvastatin), and the PROVE-IT trial – which compared standard dose (40 mg) pravastatin (Bristol-Myers Squibb's Pravachol) and 80 mg Lipitor – both found a lower LDL goal would be beneficial. However, a goal of LDL 70 mg/dL remained an option, not a recommendation, in the ACC's cholesterol guidelines. A speaker, Carl Vaughn, a pharmacologist at the University College Cork in Ireland, concluded, "This trial calls for lower cholesterol targets… TNT will be remembered as a proof-of-concept study."

However, Dr. Bertram Pitt of the University of Michigan School of Medicine, in a ***New England Journal of Medicine*** editorial, concluded that cholesterol guidelines should still not be changed. He wrote, "While TNT proves a reduction in CV events with aggressive Lipitor therapy to an LDL of 77 mg/dL, we need further reassurance as to the safety of this approach before we can advocate a major shift in our current goals for LDL cholesterol levels in patients with stable CHD."

The one concern in TNT is that non-cardiovascular death increased slightly with high dose Lipitor, so the trial did not show an overall reduction in mortality. The trial was not powered to determine an effect on overall mortality between the two doses of Lipitor, and it was not clear this was due to the drug, but there was no identifiable cause for the extra deaths. Dr. LaRosa, said, "No single cause of death and no single cancer type drove the non-significant difference in all-cause mortality between the two groups…There was no significant decline in cardiovascular mortality and no statistically significant increase in non-cardiovascular mortality. It is not valid to draw any conclusions beyond that about mortality…Morbidity is important…If I told you that you have X years to live, and you can live with a debilitating stroke or all your attributes in place, you wouldn't have trouble making that choice. We must talk not only about mortality but also about morbidity."

However, Dr. Pitt wrote in his ***New England Journal of Medicine*** editorial: "Although this increase in deaths from non-cardiovascular causes could be due to chance, it is a matter of concern…Until the safety and effectiveness of an 80 mg daily dose of atorvastatin have been established, patients and their physicians will need to carefully weigh the benefits of a reduction in the risk of cardiovascular events, including myocardial infarction and stroke, with their attendant disability, against the uncertainty of an increase in the risk of death from non-cardiovascular causes."

Dr. Pitt also suggested that other approaches to cholesterol reduction, such as Zetia, might be preferable to 80 mg Lipitor, "It is reasonable to ask whether other means of achieving an LDL cholesterol level of 70 mg/dL will be equally beneficial with respect to cardiovascular events but possibly safer… Some clinicians may choose to add an agent such as ezetimibe." At the Zetia booth and elsewhere, Zetia sales reps

Additional Results from TNT Trial

Measurement	Lipitor 10 mg	Lipitor 80 mg	p-value
Secondary endpoints			
Major coronary event	8.3%	6.7%	.002
Cerebrovascular event	5.0%	3.9%	.007
Hospitalization for CHF	3.3%	2.4%	.01
Peripheral artery disease	5.6%	5.5%	Nss (p=.76)
All-cause mortality	5.6%	5.7%	Nss (p=.92)
Any CV event	33.5%	28.1%	<.001
Any coronary event	26.5%	21.6%	<.001
Non-cardiac death			
All-cause mortality	5.6%	5.7%	Nss (p=.92)
CV death	3.1%	2.5%	Nss (p=.08)
Non-CV death	2.5%	3.2%	Nss (p=.06)
Cancer	1.5% 75 patients	1.7% 85 patients	Nss (p=.42)
Trauma	0.2%	0.3%	Nss
Non-traumatic causes other than cancer	0.9%	1.2%	Nss (p=.13)

wouldn't talk about the TNT findings, but they were grinning from ear to ear.

PFIZER'S torcetrapib
Increases HDL but will only be available in combination with Lipitor

A study presented at ACC shows that torcetrapib, a novel cholesteryl ester transfer protein (CETP) inhibitor, increased HDL cholesterol in healthy patients without vascular disease but with low HDL levels. The results were positive both when CETP was used alone and when given in combination with Pfizer's Lipitor (atorvastatin). However, Pfizer reportedly plans to market only the combination tablet.

Patients were given eight weeks of 20 mg/day Lipitor followed by eight weeks of combination Lipitor+ torcetrapib. Researchers reported that HDL increased in the torcetrapib monotherapy patients as well as in the combination therapy patients. They said the effect on HDL cholesterol occurred quickly, increasing levels within two weeks of initiation of therapy. Treatment with the 60 mg and 90 mg dose of torcetrapib also resulted in modest LDL reductions in those not taking Lipitor, but greater reductions were observed in those treated with the statin.

A Pfizer official said, "HDL increased >54% with torcetrapib, and when it is added to Lipitor, LDL and triglycerides go down as well…We don't want to offer it as monotherapy because we don't want to address just HDL…Torcetrapib is ideal for a secondary prevention patient – where you know the patient needs this…and you can also stabilize plaque."

The one concern with torcetrapib is blood pressure elevation. Researchers said there was a tendency for torcetrapib to increase systolic blood pressure vs. placebo. At the highest dose tested (90 mg), systolic blood pressure increases ranged from 1.8 mmHg to 2.8 mmHg, but increases of systolic blood pressure >15 mmHg were rare. A Pfizer official said a blood pressure increase of 3 mmHg is considered significant.

PFIZER'S Viagra (sildenafil)

A poster from Thai researchers reported that patients taking Viagra for erectile dysfunction who also need an ICD should have the energy level of the ICD set higher than usual.

ACTELION'S tezosentan
No benefit in heart failure

The VERITAS study was ended in November 2004 at the 75% interim analysis when it was apparent it would not meet its primary endpoint. VERITAS-I and -II were identical randomized trials that compared the IV tezosentan with placebo in 1,449 patients with acute heart failure who required IV therapy. The studies found no difference in death or worsening heart failure between the two groups at both 7 and 30 days, and there was no difference in dyspnea at 24 hours between the two groups. There also was no difference in survival at six months.

6-Month Results of VERITAS Trials

Measurement	IV tezosentan 5 mg/hr for 30 min., followed by 1 mg/hr for 24-72 hrs n=727	Placebo 5 mg/hr for 30 min., followed by 1 mg/hr for 24-72 hrs n=708	p-value
Primary endpoint #1: Death or worsening heart failure at 7 days	26.3%	26.4%	.95
Primary endpoint #2: Death or worsening heart failure at 30 days	31.9%	33.2%	0.61
Primary endpoint #3: Change in dyspnea from baseline over the first 24 hours, as assessed by area under the curve	No difference		Nss
Serious adverse events	40.4%	42.4%	Nss

♦