Trends-in-Medicine

January 2009

by D. Woods

SUMMARY

♦ Abbott's fenofibrate, TriLipix, was shown to be safe when given with a statin. ♦ AstraZeneca's Crestor (rosuvastatin) demonstrated a clear cardiac benefit in normal LDL patients. ♦ Bayer/Johnson & Johnson's new Factor Xa inhibitor, Xarelto (rivaroxaban), missed its primary endpoint in a Phase II trial – and caused so much more bleeding than placebo that the Phase III trial is using only the lowest doses. ♦ Conflicting studies have created confusion about the safety of Sanofi-Aventis/Bristol-Myers Squibb's Plavix (clopidogrel) in combination with a proton pump inhibitor (PPI). ♦ Though there were discussions about the safety of Merck/Schering-Plough's ezetimibe (Zetia and Vytorin) and doctors appeared slightly reassured about safety, there was nothing really new about this issue. ♦ The value of low-dose aspirin for primary prevention remains uncertain. ♦ Vitamins C and E do not reduce major cardiovascular events. ♦ Home INR testing did not improve mortality in warfarin users.

Trends-in-Medicine
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AMERICAN HEART ASSOCIATION (AHA)

New Orleans, LA
November 9-12, 2008

Drug studies dominated the AHA meeting this year, and Abbott's fenofibrate, TriLipix, and AstraZeneca's Crestor (rosuvastatin) got a boost, while vitamins C and E appear not to have a cardiac benefit. Questions were raised about the outlook for a possible warfarin replacement [Bayer/Johnson & Johnson's Xarelto (rivaroxaban)] as well as the safety of combining a proton pump inhibitor (PPI) with Sanofi-Aventis/Bristol-Myers Squibb's Plavix (clopidogrel) and the value of low-dose aspirin for primary prevention. Experts attempted to diffuse concern about the safety of Merck/Schering-Plough's ezetimibe – Zetia and Vytorin (simvastatin + ezetimibe) – and, to a very small extent, they were successful; but a cloud remained over the product, and usage was not expected to increase much if at all over the next few months.

ABBOTT's TriLipix (ABT-335, fenofibric acid) – Safe when given with a statin

A pooled analysis of four trials was presented in poster format. The analysis found the combination of TriLipix (fenofibric acid) plus moderate-dose statins resulted in sustained improvements in multiple lipid parameters with no additional safety concerns and no evidence of cumulative toxicity or emergences of late onset adverse events. In the three Phase III trials – all 12-week, double-blind, randomized studies with a total of 2,316 patients – TriLipix was added to Crestor, Merck's Zocor (simvastatin), or Pfizer's Lipitor (atorvastatin). Long-term safety and efficacy were evaluated in those Phase III trials plus a subsequent pre-specified, 52-week, open-label, 1,911-patient, extension study.

Combination therapy with TriLipix + a statin substantially improved multiple lipid parameters after four weeks, and the improvements were sustained long-term over

Safety Outcomes of Fenofibrate + Statin

Adverse events	TriLipix + Crestor n=1,186	TriLipix + Zocor n=514	TriLipix + Lipitor n=501	Total n=2,201
Treatment-related deaths	0	0	0	0
Total deaths	0.3%	0.4%	0.2%	0.3%
Treatment-related serious adverse events	0.3%	0.6%	0.2%	0.4%
Total serious adverse events	7.2%	7.8%	4.6%	6.7%
Treatment-emergent adverse events	83.1%	86.2%	85.2%	84.3%
Treatment-emergent adverse events leading to discontinuation	12.0%	10.1%	13.8%	11.9%
Treatment-related adverse events	27.7%	27.2%	27.1%	27.4%
Treatment-related adverse events leading to discontinuation	8.3%	6.4%	10.2%	8.3% *

*** 23 patients had ALT elevations, 22 had creatinine elevations, but "many" did not reach pre-defined criteria for clinical relevance**

64 weeks. Mean final lipid values were within optimal levels for high coronary heart disease patients.

None of the six deaths that occurred were considered by the investigator to be treatment related. Eight patients had treatment-related adverse events: 2 cholecystitis, 2 spontaneous abortions, 1 bile duct obstruction, 1 chronic cholecystitis, 1 transient ischemic attack, 1 upper abdominal pain, and 1 choeithiasis in a patient who also experienced cholecystitis. The most frequently reported adverse events were headache, upper respiratory tract infection, nasopharyngitis, and back pain.

The type of statin used in combination therapy did not notably affect the incidence of adverse events or laboratory values related to muscle, hepatic, or renal function. Long-term combination therapy with TriLipix/statin was generally well tolerated, with no evidence of cumulative toxicity or emergence of the late onset adverse events.

AstraZeneca's Crestor (rosuvastatin) – Clear cardiac benefit shown in normal LDL patients

A very large randomized trial has shown that lowering cholesterol with Crestor in healthy people with *normal* cholesterol but high CRP significantly reduces cardiovascular (CV) events. The study participants had baseline lipid levels well below the usual threshold for treatment, but they still benefited from the statin therapy. The JUPITER results were presented at the American Heart Association meeting and simultaneously published in the ***New England Journal of Medicine***.

JUPITER, which was funded by AstraZeneca, was a double-blind, prospective, multicenter, international trial in 17,802 men (>age 50) and women (>age 60) with LDL cholesterol <130 mg/dL and high-sensitivity CRP ≥2.0 mg/L but no history of CV disease. The trial, which was stopped early because of the size of the benefit, found that over 1.9 years, compared to placebo, 20 mg Crestor daily reduced:

- LDL 50%.
- hsCRP 37%.
- Triglycerides 17%.
- MI 54%.
- Stroke 48%.
- Death from any cause 20%.
- Composite primary endpoint of MI, revascularization, stroke, death from CV causes, or hospitalization for unstable angina 44% (women 46%, men 42%).

Previous statin trials have shown ~20% reduction in vascular risk for each 1 mmol/L (38.7 mg/dL) of absolute reduction in LDL. Thus, a reduction of 25% would have been expected in these patients, but the reduction was almost twice as much as that. Dr. Paul Ridker of Harvard Medical School and Brigham & Women's Hospital and colleagues estimated that to prevent one incidence of the primary endpoint, the number needed to treat (NNT) with Crestor was 95 people for 2 years, 31 for 4 years, or probably 25 for 5 years. The effects were consistent in all subgroups evaluated – including women, blacks, and Hispanics – and did not vary by age, race, or ethnic group, region of origin, traditional risk factors, or Framingham score.

The Crestor patients did not have a significant increase in myopathy or cancer, but they did have a higher incidence of physician-reported new diabetes, which is interesting since diabetes was an exclusion factor in the trial. This "small but significant" increase in the rate of physician-reported diabetes with Crestor was not accompanied by any significant difference between the two groups on fasting plasma glucose or glycosuria. Increases in glucose and glycated hemoglobin levels, the incidence of newly-diagnosed diabetes, and worsening glycemic control have been reported in previous trials of pravastatin, simvastatin, and atorvastatin. The

1.9-Year Results of JUPITER Trial

Measurement	Crestor n=8,901	Placebo n=8,901	p-value	Relative risk reduction
Primary endpoint: Composite of MI, revascularization, stroke, hospitalization for unstable angina, or death from CV causes (rate per 100 person-years of follow-up)	0.77	1.36	<0.00001	44%
Secondary endpoints				
Revascularization	0.38	0.71	<0.001	46%
Hospitalization for unstable angina	0.09	0.14	0.09	41%
Any MI	0.17	0.37	0.0002	54%
Any stroke	0.18	0.34	0.002	48%
Death from any cause	1.00	1.25	0.02	20%
Other results				
Nonfatal MI	0.12	0.33	<0.00001	65%
Nonfatal stroke	0.16	0.31	0.003	48%
Revascularization or hospitalization for unstable angina	0.41	0.77	<0.00001	47%
MI, stroke, or death from CV causes	0.45	0.85	<0.00001	47%
Safety				
Adverse events	1,352	1,377	Nss, 0.60	---
Intracranial hemorrhage	6 cases	9 cases	Nss, 0.44	---
Myopathy	19 events	9 events	Nss, 0.82	---
Diabetes, newly diagnosed (physician reported)	3.0% (270 cases)	2.4% (216 cases)	0.01	---
Glycated hemoglobin	5.9%	5.8%	0.001	---
Serious adverse events	15.2%	15.5%	Nss, 0.60	---
Rhabdomyolysis	<0.1% *	0	---	---
Newly diagnosed cancer	3.4%	3.5%	Nss, 0.51	---
Death from cancer	0.4%	0.7%	0.02	---

*** 1 case that occurred after the trial ended.**

JUPITER investigators concluded, "Although the increase… could reflect the play of chance, further study is needed before any causative effect can be established or refuted. Physicians' reports of diabetes were not adjudicated by the endpoint committee…Careful evaluation of participants' records will be needed to better understand this possible effect."

After the trial ended, one nonfatal case of rhabdomyolysis was reported with Crestor in a 90-year-old with febrile influenza, pneumonia, and trauma-induced myopathy. There were no significant differences in muscle weakness, newly diagnosed cancer, or disorders of the hematologic, gastrointestinal, hepatic, or renal systems. The investigators wrote, "We cannot rule out the possibility that the rate of adverse events might increase in this population during longer courses of therapy. However, no such increase was detected in an analysis of participants who continued to receive treatment for four or more years."

The investigators said the JUPITER findings "suggest that the strategy tested (Crestor for normal LDL patients with high CRP) could be cost-effective. And it could reduce the demand for imaging tests in asymptomatic populations." Dr. Ridker et al wrote, "We hope the data presented here spur the further development of targeted anti-inflammatory drugs as potential vascular therapeutic agents and lead to innovative trials that can directly address whether the inhibition of inflammation by agents other than statins can reduce rates of vascular events."

The limitations of the trial were that it was stopped early for benefit and that people with low CRP were not included. Dr. Ridker is the co-inventor of the hsCRP test and holds the patent on the test along with Brigham and Women's Hospital.

In an accompanying editorial in the ***New England Journal of Medicine***, Dr. Mark Hlatky of Stanford pointed out, "The relative risk reductions achieved with the use of statin therapy in JUPITER were clearly significant. However, absolute differences in risk are more clinically important than relative reductions in risk in deciding whether to recommend drug therapy…While the proportion of participants with hard cardiac events in JUPITER was reduced from 1.8% in the placebo group to 0.9% in the Crestor group, 120 patients were treated for 1.9 years to prevent one event. On the other side of the argument, there were significantly higher glycated hemoglobin levels and incidence of diabetes in the Crestor group."

Dr. Hlatky also raised questions about the long-term safety and the expense of this treatment approach, since Crestor costs about $3.45/day. What about routine CRP testing? Dr. Hlatky said, "It is unlikely that high-sensitivity CRP testing is the only way to identify subjects who will benefit from treatment, since statins have reduced the relative risk to a similar extent for every other indicator of cardiovascular risk…(JUPITER provides) only limited and indirect information about the role of high-sensitivity CRP testing in clinical management."

What do these findings mean for clinical practice? Dr. Hlatky said that the JUPITER results "might push the orbit of statin therapy outward to include even more of the general population." Though he said more study is needed, he predicted that the trial results will change clinical practice, "Guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but the appropriate size of the orbit of statin therapy depends on the balance between the benefits of treatment and its long-term safety and cost." Dr. Steven Nissen, director of Cardiovascular Medicine at the Cleveland Clinic, called the JUPITER findings "unprecedented and landscape-changing." He also said the findings should silence those who have suggested that lower cholesterol does not translate into a reduction in hard endpoints – "and lay to rest the talk about statins not benefiting women." In his own practice, he said that he will now measure hsCRP in patients even when LDL is normal.

Another trial released during AHA, the Framingham Heart Offspring Study by the National Heart, Lung, Blood Institute (NHLBI), also found a benefit to measuring hsCRP. In that study, with data from 3,006 people, Dr. Peter Wilson of Emory University in Atlanta and colleagues from NHLBI, Boston University, and Tufts USDA Nutrition Center in Boston found that hsCRP levels provided a more accurate risk assessment than traditional risk scores among people otherwise considered at intermediate risk.

The Framingham researchers said their findings, which were published online in ***Circulation Cardiovascular Quality and Outcomes***, supported a two-step approach to assessing risk – first using traditional risk scores, then measuring hsCRP levels in people at intermediate risk – to guide clinical decisions.

Another NHLBI-funded CRP study – also authored by Dr. Ridker – used data from 10,724 men in the Physicians Health Study II to prospectively develop the Reynolds Risk Score for Men, which added hsCRP levels and parental history of early heart disease to traditional risk factors to assess men's risk. The Reynolds Risk Score for Men was found to be significantly more accurate than traditional risk factors alone in the

Effect on hsCRP and Lipids in JUPITER Trial *

Measurement	Baseline		12 months		24 months		36 months		48 months	
	Crestor	Placebo	Crestor	Placebo	Crestor	Placebo	Crestor	Placebo	Crestor	Placebo
Median hsCRP	4.2	4.3	2.2	3.5	2.2	3.5	2.0	3.5	1.8	3.3
Median LDL	108	108	55	110	54	108	53	106	55	109
Median HDL	49	49	52	50	52	50	50	49	50	50
Median triglycerides	118	118	99	119	99	116	106	123	99	118

* $p<0.001$ for all between-group comparisons except for HDL cholesterol at 36 months ($p=0.003$) and at 48 months ($p=0.34$)

study population, Dr. Ridker and colleagues reported in a paper published online in ***Circulation*** and presented at AHA.

As a result of all three studies, Dr. Elizabeth Nabel, director of the NHLBI, said the NHLBI has formed an expert panel to "review and update the scientific evidence regarding the assessment and management of cardiovascular risk factors." The panel is charged with conducting a rigorous scientific review "to distill the scientific evidence and generate an evidence-based, comprehensive set of clinical guidelines for primary care practitioners to help adult patients reduce their risk for cardiovascular disease."

Will the JUPITER findings be considered a class effect? Yes, doctors said, though they predicted it would give Crestor use a boost.

Asked how the JUPITER trial results would affect current guidelines, AHA president Dr. Timothy Gardner said, "We have to look at how to use the CRP test, so guidelines might change in that area, especially for some of the subgroups…If they are at medium risk, adding the CRP test might be helpful…Other than CRP, specifically the other aspect was the efficacy of statins for patients who had levels previously thought to be okay. JUPITER is more like another aggregate, another interval. It keeps building on the knowledge that we have and gives us an opportunity to build guidelines on better data."

BAYER/JOHNSON & JOHNSON's Xarelto (rivaroxaban) – Missed primary endpoint and more bleeding vs. placebo

In a Phase II study presented at AHA, rivaroxaban, a Factor Xa inhibitor, missed the primary efficacy endpoint and had significantly more bleeding than placebo. Rivaroxaban reduced death, MI, and stroke, a secondary endpoint, but there was so much excess bleeding that Phase III trials will use only the lowest doses.

In the 6-month, randomized, dose-finding, Phase II ATLAS-ACS-TIMI-46 trial in 3,491 acute coronary syndrome (ACS) patients, rivaroxaban failed to show a benefit on the primary efficacy endpoint, a composite of death, MI, stroke, or severe ischemia requiring revascularization. Doses of rivaroxaban vs. placebo that were tested were:

- 5 mg, 10 mg, and 20 mg QD with aspirin alone.
- 2.5 mg, 5 mg, and 10 mg BID with aspirin alone.
- 5 mg, 10 mg, 15 mg, and 20 mg QD with aspirin plus clopidogrel (Sanofi-Aventis's Plavix).
- 2.5 mg, 5 mg, 7.5 mg, and 10 mg BID with aspirin plus clopidogrel.

Factor Xa lies at the intersection of intrinsic and extrinsic pathways that begin the clotting process. Researchers hypothesize that if Factor Xa is blocked, the final pathway to coagulation will be blocked.

There was increased bleeding in the rivaroxaban trial with the higher doses, but most of the bleeding was neither TIMI major nor TIMI minor, and there was no evidence that the drug induced liver injury; liver function tests showed that rivaroxaban is "very safe" for up to six months. ALT 3xULN was numerically less with rivaroxaban than placebo (3.7% vs. 4.5%), and the only cases (3) of ALT >3xULN with bilirubin >2xULN all occurred with placebo.

Although the study failed both its primary endpoints – efficacy and safety – the principle investigator, Dr. C. Michael Gibson of Beth Israel Deaconess Hospital in Boston, emphasized the positive results on a key secondary endpoint, "In the more rigorous (secondary) endpoint – death, MI, and stroke – the risk went down from 5.5% with placebo to 3.9% with rivaroxaban, a 1.6% absolute risk reduction…You need to treat 63 patients with rivaroxaban to prevent 1 event."

6-Month Results of the ATLAS-ACS-TIMI-46 Trial

Measurement	Placebo n=1,160	Rivaroxaban					p-value
		5 mg	10 mg	15 mg	20 mg	All doses n=2,331	
Primary endpoint #1: Death/MI/stroke/severe ischemia requiring revascularization	7.0%	---	---	---	---	5.6% HR=0.79	Nss, 0.10
Secondary endpoint: Incidence of death/MI/stroke	5.5%	---	---	---	---	3.9% HR=0.69	0.028
Primary endpoint #2: Clinically significant bleeding	3.3%	6.1% HR=2.2	10.9% HR=3.4	12.7% HR=3.6	15.3% HR=5.1	---	<0.001 for all doses vs. placebo
Safety: Patients on aspirin only (p<0.01)							
TIMI major	0	0	2.1%	---	0	---	---
TIMI minor	0.4%	0	0	---	0.6%	---	---
Medical attention	1.6%	2.0%	4.1%	---	9.6%	---	---
Safety: Patients on aspirin + clopidogrel (p<0.0001)							
TIMI major	0.2%	0.7%	1.5%	1.7%	2.0%	---	---
TIMI minor	0.2%	0.7%	0.7%	1.1%	0.9%	---	---
Medical attention	3.5%	10.0%	9.8%	10.1%	14.5%	---	---

Dr. Gibson said that the secondary endpoint results justify going forward with a Phase III trial, "Based on the fact that we saw good efficacy at low doses, based on the fact that we saw increased bleeding at high doses, and based on the fact that twice-a-day dosing seemed more effective and safer, we elected to take two doses forward – 2.5 mg and 5 mg twice-a-day. How did they perform in our current ATLAS trial? With aspirin alone, the lower doses brought rates of death, MI, and stroke down from 11.9% to 6.6%. The relative risk reduction was 46% (not statistically significant, p=0.08). That came with a cost of higher bleeding. The absolute risk reduction was smaller, about 1.8%, and a similar rate of bleeding, and there was an increase of 1% in TIMI major bleeding in the aspirin + clopidogrel side."

The Phase II secondary endpoint of death, MI, or stroke will be the primary endpoint in a 13,000- to 16,000-patient, Phase III trial, which was scheduled to begin at the end of November 2008. Because of high rates of bleeding with higher doses – and one case of fatal bleeding in the 10 mg group – the Phase III trial will use 5 mg and an even lower dose, 2.5 mg (both BID), vs. placebo. The Phase III trial will be event-driven and is expected to last 33 months. Dr. Gibson did not say which 10 mg dose had the fatality – QD, BID, with or without Plavix.

Rivaroxaban is being tested against warfarin in two other studies – ROCKET-AF in patients with atrial fibrillation and a study in patients with deep vein thrombosis (DVT). Asked why the Phase III trial won't compare rivaroxaban to warfarin, Dr. Gibson said that ACS patients rarely take warfarin. He would not speculate as to how rivaroxaban would compare to warfarin in terms of efficacy or bleeding.

In the Phase II trial, the most bleeding (15.3%) occurred with the highest dose (20 mg) rivaroxaban, and the 15 mg dose resulted in 12.7% bleeding events. But Dr. Gibson insisted that most of this bleeding was mild and occurred in the first two months of the trial. He noted that 82% of the bleeding events were not classified as either TIMI major or TIMI minor, "There was a dose response curve. All the doses were associated with greater bleeding than placebo. Most of the bleeding was medical-attention bleeding – less severe bleeding (which he called a more sensitive metric of bleeding). The rates of bleeding were higher in patients treated with a background of aspirin and clopidogrel, and there was a dose response curve. Major and minor bleeding were less frequent …It is a very delicate balance between safety and efficacy. In safety, there was one fatal bleed in the 10 mg arm of the active drug (rivaroxaban)."

Results of Low-Dose Rivaroxaban in ATLAS-ACS-TIMI-46 Trial

Measurement	Placebo	Rivaroxaban 2.5 mg BID and 5.0 mg BID	Relative risk reduction	p-value
Aspirin alone (n=761)				
Number of patients	253	254 + 254	---	---
CV death, MI, stroke	11.9%	6.6%	46%	Nss, 0.08
TIMI major bleed	0	1.2%	---	Nss, 0.17
Aspirin + clopidogrel (n=2,730)				
Number of patients	907	912 + 911	---	---
CV death, MI, stroke	3.8%	2.0%	45%	Nss, 0.09
TIMI major bleed	0.2%	1.2%	---	0.03

When the two cohorts in ATLAS are compared – (1) patients who got aspirin alone and (2) patients who got both aspirin and clopidogrel – there were fewer events in the aspirin + clopidogrel group overall. Asked if that could have been due to PCI or to the clopidogrel, Dr. Gibson said, "These are two different patient populations, so you really can't compare stratum 1 to stratum 2. Over time, most studies show that when you add clopidogrel to aspirin, there is about a 20% reduction in events…We're seeing reductions in events, but this is a small study. We really have to do a Phase III study, and 20% seems to be what we expected."

Dr. Elaine Hylek of Boston University Medical Center discussed the trial, calling ATLAS-ACS-TIMI-46 a "terrific, ambitious, and responsible" study and praising it as "thorough and exciting," with a "definite and irrefutable trend in the reduction of cardiovascular events…I do think there is promise. There is a definite and irrefutable trend in the reduction of cardiovascular events. This is an incredibly exciting time for these novel anticoagulants, but again, it is important to appreciate – and we all have our eyes open – but this does come at a cost. As we keep trying and trying to get down to zero for the number of recurring ischemic events, it is difficult."

She pointed out that the trial's definitions of major bleeding were too lenient, "TIMI major definition means a woman with a hematocrit of 34 would bleed down to a hematocrit of 19 before it would be considered a major hemorrhage…There are different criteria to call or deem a major bleed or a hemorrhage, and there are important and significant differences that we should discuss." Dr. Hylek also said that the trial's patient population excluded patients on warfarin, with GI bleeding within six months, and at increased bleeding risk. She also noted that the trial enrolled a lower risk patient population from a bleeding perspective, "If you look at the characteristics of the enrolled population, this younger age of 57 or 60 is about 10 years younger than the atrial fibrillation population. So, it's important to put all the indications in context."

Dr. Hylek concluded that:

- Rivaroxaban exhibited a ***trend*** toward **improved efficacy** in reducing recurrent ischemic events when combined with antiplatelet therapy.
- The addition of rivaroxaban to antiplatelet therapy resulted in a dose-dependent **increase in bleeding**.
- **Uniform reporting** of bleeding across trials and indications would facilitate a more informed assessment of benefit and risk for patients and their providers.

Is triple therapy justified? Dr. Hylek asked, "Is there evidence out there that would literally justify actively pursing an indication for triple therapy for six months in an era of growing awareness of the hazards of triple therapy, particularly among individuals over age 75? I can reassure you that there are robust data to support moving forward in the area of acute coronary syndrome." She pointed out that in-hospital death and reinfarction affects 5%-10% of ACS patients, with the risk persisting during the first month after hospitalization and the risk of death and MI lasting for a year, "So, the question is…will oral anticoagulants add to that? I think that there is a host of data that support the added benefit of anticoagulants to antiplatelet therapy, especially the WARIS-II trial and also to support novel anticoagulants (in the ESTEEM trial). This novel anticoagulant (rivaroxaban) was superior in combination with aspirin compared to aspirin alone."

Overall, Dr. Gibson said that he was "satisfied with the results …moving ahead indicates to all of us that there is enough here to warrant further evaluation."

Asked if bleeding is either a regulatory hurdle or a commercial hurdle, Dr. Gibson said, "It's a doctor issue and a patient issue. Patients don't like bleeding. From the FDA's perspective…they will (approve it) if bleeding doesn't kill you or leave you with permanent residual damage. The bleeding is not as important as in AFib, but we don't want to discount it."

Doctors asked for opinions about the trial results said that it is a small study, adding that rivaroxaban shows promise despite the bleeding problems. Asked about the potential use of rivaroxaban in patients with atrial fibrillation, several doctors said that it has definite advantages vs. warfarin: it starts working within hours, it is more consistent with fewer high peaks and fewer lows, and patients don't have to monitor their INR levels. Doctors refused to compare the rivaroxaban results in ATLAS-ACS-TIMI-46 to historical data and to experience with warfarin, but they offered these comments:

- *Dr. Gibson:* "The intention is (for rivaroxaban) to replace warfarin…(The efficacy/bleeding balance) is the real trick here…A lot of people think that the atrial fibrillation market is bigger than the ACS market, but the ACS market is quite big and substantial."
- *Dr. Sidney Smith of the University of North Carolina, a past president of AHA:* "This phase II trial could be very helpful. We need to see more data, but it is a promising agent."
- *Dr. Raymond Gibbons of the Mayo Clinic, also a past president of AHA:* "It's a Phase II trial, and we have to balance the benefit vs. the risk." He would not compare warfarin to rivaroxaban in terms of bleeding problems, and he seemed surprised to learn that there was a fatal bleeding death with rivaroxaban.
- *Dr. Paul Gurbel of Sinai Hospital in Baltimore:* "Rivaroxaban…has a strong efficacy signal when added to aspirin. It did increase bleeding both in aspirin and patients with aspirin and Plavix, and it was much more significant in the aspirin plus Plavix (arm)…This drug is very interesting when looking at people who are medically treated. It has the possibility to replace clopidogrel and possibly prasugrel (Lilly's Effient)…It is also reassuring that the liver enzymes didn't get elevated. But this drug is similar to what we saw with (Bristol-Myers Squibb's) apixaban in the APPRAISE trial."

An FDA Advisory Committee will consider Xarelto (rivaroxaban) on March 18, 2009.

LILLY/DAIICHI SANKYO's Effient (prasugrel) – Concerns about bleeding still outweigh efficacy claims

At AHA, most doctors questioned agreed that prasugrel has higher efficacy than Plavix in many patients with acute coronary syndrome (ACS) who are being managed with PCI, but they worried about bleeding risks. In TRITON-TIMI-38, a study of more than 13,000 patients, prasugrel was 19% more effective than Plavix in preventing cardiovascular death, nonfatal heart attacks, and strokes, but it was 32% more likely to cause serious bleeding. The risk of cardiovascular death overall was not statistically different between prasugrel and clopidogrel. An FDA Advisory Panel will consider prasugrel on February 3, 2009.

Asked why they think the FDA has not yet approved prasugrel, doctors agreed that it's because of the bleeding problem.

- *California:* "If we are careful about who gets it, it is a valuable tool."
- *Massachusetts:* "It is very effective, but I don't know how much it will be used because of the bleeding."

Doctors also generally agreed that patients who weigh <130 pounds, are ≥age 75, or who have had previous strokes or "mini-strokes" should not take prasugrel. However, Dr. Sanjay Kaul of Cedars-Sinai Heart Institute in Los Angeles said that the TRITON-TIMI-38 trial methodology was "at odds with the scientific facts and that high-risk populations were not accurately defined."

Several prasugrel studies were presented at AHA supporting prasugrel's efficacy compared to Plavix, including:

➢ **An analysis of the "net clinical benefit" of prasugrel in the TRITION-TIMI-38 trial** was presented in a poster. The researchers found:

- The benefit of prasugrel is driven by nonfatal MI, the most prevalent but arguably not the most important component of the composite endpoint of net clinical benefit: death, MI, stroke, or non-CABG TIMI major or minor bleeding.
- Lack of information about the type of MI precludes an informed risk:benefit assessment.

- The wide variability in clinical importance, prevalence, and treatment effect across components challenges the validity of net clinical benefit in the study.

➢ **Prasugrel vs. Plavix in acute coronary syndrome (ACS) patients scheduled for PCI in TRITON-TIMI-38** was presented in another poster. The researchers argued that "clinically important," not just "statistically significant," benefit or harm should influence guideline recommendations and treatment decisions. They concluded that the risk:benefit was good with prasugrel during the first 30 days, suggesting that the optimal approach may be to give prasugrel for the first 30 days as acute induction therapy, followed by maintenance consolidation therapy with a less potent agent (e.g., Plavix).

The study found:

- Both loading and maintenance doses of prasugrel were superior to clopidogrel for reduction of ischemic events.
- Excess major bleeding observed with prasugrel occurred predominantly during the maintenance phase.
- The number needed to treat (NNT) to prevent one ischemic event was 128 from 0-3 days and 148 after 3 days.
- Significant reductions in ischemic events were observed with prasugrel in the first 30 days but not after that. Nearly 75% of the overall treatment benefit with prasugrel was evident in the first 30 days (1.7% of a total of 2.2%).
- TIMI major non-CABG bleeding was similar to Plavix during the first 30 days but significantly greater with prasugrel from 30 days to the end of the study.

➢ **Two TRITON-TIMI-38 substudies** were presented by Dr. Andrew Frelinger of the University of Massachusetts Medical School. The first study, which looked at platelet inhibition measured by vasodilator-stimulated phosphoprotein assay (VASP), followed 31 patients at just four sites. The endpoints were VASP platelet reactivity index (PRI) and hyporesponsiveness (VASP PRI>50). At 30 days, prasugrel-treated patients had lower VASP PRIs vs. Plavix-treated patients (p=0.001). Nearly all (96%) of patients in the Plavix group had VASP PRI levels >50 vs. prasugrel PRI levels of 75 (p=<0.0001). At 30 days, more patients in the Plavix group had VASP PRIs >50 (42% vs. 24% with prasugrel, p=0.003).

Dr. Frelinger also reported that platelet inhibition was greater with prasugrel than Plavix at 1-3 hours ***and*** at 30 days. And thienopyridine hyporesponsiveness was more frequent in Plavix than in prasugrel patients (100% vs. 59%, p=.0373). He concluded: There was a clinical benefit of prasugrel over Plavix, and, though the study was not powered to show a difference in clinical outcomes (and did not), it was sufficiently powered to show differences in platelet function. He said, "Our findings support the hypothesis that greater inhibition of platelet function in ACS patients is likely responsible for both reduced platelet-mediated adverse events and increased bleeding with prasugrel compared to clopidogrel… We think that greater inhibition of platelet functions corresponds to greater risk of thrombosis and greater risk of bleeding…I think this subset of platelet inhibition was greater in prasugrel than in clopidogrel at 1-3 hours and at 30 days."

Asked if he thinks the prevalence of signaling for P2Y12 can predict prasugrel treatment failure, Dr. Frelinger said, "We don't have the data. Patient treatment failures on prasugrel were the same patients who had residual VASP values, but we would hold with the theory that greater inhibition of platelet function corresponds to greater risk of thrombosis and greater risk of bleeding."

Asked about prasugrel and hyporesponders, he said, "That is a question that we are interested in and investigating. There may be some indications that contribute to poor response to prasugrel. The analyses are not finished, but that would be a primary place to look." He said that he wanted to do a much larger substudy that would have allowed him to do those comparisons, but that it ended up not being possible. The panel moderator commented, "It is important to understand platelet physiology and outcomes, particularly when thinking about adding on platelet therapy to aspirin. This is a pivotal area that is under explored and needs further research."

➢ **A comparison of the effects of prasugrel and high-dose Plavix on *in vivo* and *in vitro* platelet activation** – the results of the PRINCIPLE-TIMI-44 – were also presented at AHA. Dr. Frelinger said, "This platelet substudy demonstrated greater inhibition of *in vitro* VASP and platelet aggression assays for prasugrel vs. standard FDA-approved dose clopidogrel-treated ACS patients. A high loading and maintenance dose of clopidogrel rather than an FDA-approved dosing regimen is sometimes used."

PRINCIPLE-TIMI-44 was a randomized, double-blind, double dummy, two phase, crossover trial of prasugrel vs. a high loading and maintenance dose clopidogrel in stable ACS patients. Dr. Frelinger concluded:

- Prasugrel, like clopidogrel, inhibited *in vivo* platelet activation, but unlike clopidogrel, prasugrel inhibition persisted at 24 hours.
- Prasugrel unlike clopidogrel prevented the post-PCI induced increase in the inflammatory marker MPO.
- Prasugrel to a greater degree inhibited ADP.

Asked about dosing, he said, "Higher doses of clopidogrel will speed the rate at which platelet inhibition occurs. 600 mg is greater than 300 mg, but 900 mg does not produce a greater rate of inhibition, so you can't compare between studies. It's probably the 900 mg clopidogrel loaded group that would be closer to the prasugrel group, but I don't think that they would cross over."

➢ **A pharmacokinetic (PK) study** of 1,159 patients, examining exposure to the active metabolite of prasugrel was

presented by Daniel Salazar PhD of Daiichi Sankyo. He said TRITON-TIMI-38 found that prasugrel significantly reduced rates of ischemic events when compared to a standard dose regimen of Plavix, but prasugrel patients had a higher incidence of TIMI bleeding compared to Plavix. Because of that, he said he had to assess the relationship between exposure to prasugrel and TIMI major/minor bleeding in 1,159 patients in a PK substudy.

The investigators took plasma samples and measured TIMI-major and TIMI-minor bleeding and found:

- Increased exposure to prasugrel's active metabolite is associated with increased bleeding risk during maintenance phase but not during loading phase.
- In patients ≥ age 75, increased TIMI major/minor bleeding was confined to patients in the highest exposure quartiles.
- Patients the same age and weight in the lower exposure quartiles had similar TIMI-major and -minor bleeding compared to patients ≥75 who weighed ≤60 kg.

Asked about ischemic risk, Dr. Frelinger said, "We could not find a significant relationship." An audience member asked, "I thought the whole point of giving prasugrel was that it was an expected, anticipated effect. If all those patients had 74% platelet inhibition (as we think), then I'm not sure what that means. If you show there was not 74% inhibition, then the consistence of inhibition is much higher than clopidogrel and may be somewhat less than verified, so which one is it?" Another audience member asked, "Is the implication that a lower dose may be associated with lower bleeding, but we still have to see that efficacy is preserved?" And a third audience member phrased it a different way, "Will you give a lower maintenance dose to elderly and lighter weight patients?" Dr. Frelinger responded, "It depends on if it has the efficacy that we expect…Patients with increased concentrations…we should give them a lower dose, but how often is it proven in all populations that the lower dose has the same efficacy? It's very, very difficult to do, as we all know."

MERCK/SCHERING-PLOUGH'S
Vytorin (ezetimibe + simvastatin) and Zetia (ezetimibe) – Use has stopped falling and appears stabilized

Most doctors interviewed at AHA said that their Vytorin use has leveled out and is not expected to change over the next 6-12 months. Vytorin was mostly seen as a third-, fourth-, or fifth-line drug, usually as a last resort for patients who have failed every other drug.

In the ENHANCE trial, which was presented at the American College of Cardiology in 2008, Vytorin was shown to be ineffective in preventing clogged arteries and was possibly the cause of plaque in some users. Then, in June 2008, the SEAS trial showed that Vytorin not only did not result in additional heart attack prevention, it also was associated with higher rates of cancer than placebo (2.7%/year vs. 1.7%/year). The SEAS investigators convinced the data safety monitoring committees for two other, ongoing Vytorin studies – SHARP and IMPROVE-IT – to allow a pooled analysis of their cancer data by famed biostatistician Richard Peto PhD of Oxford. Dr. Peto found no evidence to support an excess cancer risk with Vytorin. In SHARP and IMPROVE-IT, which together included >20,000 patients, the annual cancer rate was 1.7% in Vytorin patients vs. 1.8% in the simvastatin alone group.

At AHA relatively little time was spent rehashing the debate on the safety of Vytorin. However, a plenary session held on the last afternoon of the conference became testy and contentious, with Vytorin advocate Dr. Rory Collins of Oxford pitted against Vytorin critic Dr. Allen Taylor of Walter Reed Army Medical Center in Washington DC.

- Dr. Collins emphatically insisted that Vytorin does not cause cancer, despite the SEAS findings.
- Dr. Taylor cautioned that there is not enough evidence to show that Vytorin is safe or even effective.
- Dr. Robert Califf, vice chancellor for clinical research at Duke Translational Medicine Institute and the IMPROVE-IT trial principal investigator, participated in the discussion. He later presented a plan to overhaul the way international clinical trials are done.

Dr. Collins, an IMPROVE-IT investigator, criticized the 1,873-patient SEAS trial, in which 101 patients in the Vytorin group got cancer compared to 65 in the placebo group, with a hazard ratio of 1.55 (p=0.006), "The uncorrected p-value was 0.006, and there were so many corrections it was hard to know what was what…This hypothesis needs to be tested independently in a separate set of data to determine whether it (the cancer risk) is likely to be real." He went even further, declaring, "There is no risk of cancer" with Vytorin. He tried to make a $1,000 bet during the session with a doctor who is worried about the potential cancer risk.

Dr. Collins summarized his position:

- There is a lack of credible evidence of cancer with ezetimibe.
- Two hypothesis-testing trials – SHARP and IMPROVE-IT – include about four times as many cancers as the hypothesis-generating SEAS trial.
- An observed 50% increase in the overall incidence of cancer in SEAS (about half within two years) was ruled out by the results of the SHARP and IMPROVE-IT trial analyses.
- No significant excess of cancer incidence or death at any site was found, and there was no emerging trend with more prolonged treatment and follow-up.

Dr. Collins pointed to Dr. Peto's analysis on the SEAS trial, which said that the increased cancer risk was a fluke and an anomaly, "There is…undue alarm being raised by some about treatments that may produce further benefits in terms of

reducing the risks of heart attacks and strokes…In the SEAS trial there were 101 vs. 65 incident cancers with a control rate 1.7% parameter. In the SHARP and IMPROVE-IT trials, the annual rate was similar to the control group in SEAS – 1.8% and control rate 1.7%...They provide no confirmation of the excess observed in the SEAS trial…If we look at the effects by time on fatal and nonfatal cancers in SEAS, there was no significant trend towards an increase with time. The numbers of cancers in each year is similar in SEAS year-by-year, and it's important to note that more than half of the excess in SEAS was observed in Years 1 and 2. In SHARP/IMPROVE-IT, with more than four times as many cancers, there is no difference in cancers and no emerging trend over the period of follow-up."

Dr. Collins said that he is now delving into cancer death year-by-year, "We are torturing the data to see if it will confess and, despite torture, it does not." He said that if one looks at SHARP/IMPROVE-IT, although there is a slight increase in deaths, there is actually a shortfall "in absolute terms" – cancers that have not yet caused death – adding, "You have a bizarre mechanism where you'd have excess of death in a few years. And it does not confirm the trend seen in SEAS."

Dr. Taylor, on the other hand, said, "It is impossible to be completely certain…that there isn't a cancer signal." He said that until ongoing trials prove the safety and effectiveness of the Zetia component of Vytorin that he would only prescribe it as a last-ditch effort. He said that the SEAS data showed "an absolute (cancer) risk increase of 2.9% with the number needed to harm at 34…When I first view the data, it's easy to be skeptical of it. It could be a chance finding, subject to type 1 error from a multiplicity of endpoints, and it is hypothesis-generating. But after a second look, is it plausible that ezetimibe is not fully understood?...Ezetimibe's equipoise is disrupted and may now have risk."

Dr. Taylor argued that neither SHARP nor IMPROVE-IT trial was designed to focus on the cancer hypothesis and questioned whether the cancer question could be truly answered by those trials because there are difference in their controls – including age, sex, disease spectrum, LDL levels, and trial length. He also noted that diabetes and cardiac artery disease were exclusions in SEAS. Dr. Taylor said, "These are very different trials making it very difficult to fully test the hypotheses identified with SEAS."

However, Dr. Taylor said that a cancer signal ***was*** found in SHARP and IMPROVE-IT despite negative bias. The Peto analysis showed a 1.34 hazard ratio for cancer death in Vytorin patients although the difference did not reach statistical significance, "The confidence intervals showed up to an 84% increased risk of cancer death. On the question of p-value…was a two-sided test of significance a fair assessment?...Is the 5% (confidence limit) appropriate when considering an *a priori* hypothesis of harm, or should it be a lower bar, like 0.10 or 0.20?"

As for what to do next, Dr. Taylor said, "I don't have the answer, and we must remain critical. It is simply impossible to be certain, in either direction, of safety or harm…There are two similar signals – difficult to ignore. One is by chance, and one is within a pre-specified hypothesis. It is difficult to deconstruct without other circumstantial evidence."

Dr. Taylor said that some policy issues arise:

- Early ongoing trials are the typical domain of DSMBs but not without a risk of misinterpretation and of the integrity of the ongoing trial.
- First release of detailed adverse events and primary event data occurred through the media.
- What is the implication for consent/disclosure in ongoing trials?

He said that the issues occur in the backdrop of what we know about an agent. With Vytorin, he said that one can focus on ischemic cardiac arterial disease events, where there was a reduction with Vytorin (25%) compared to placebo, "with the percentage of LDL-C reduction in risk, one senses that Vytorin is underperforming."

Dr. Taylor concluded:

- We have a conundrum regarding Vytorin's effect on net healthcare outcomes: The benefit is unmeasured and the absence of harm is uncertain, yet, based on what we know to date, possible.
- The policy issues this episode raises are constructive to address for the future.
- We must keep an open mind.

The panel moderator, Dr. Bruce Psaty of the University of Washington, asked about Vytorin's health benefits compared to risks. Dr. Califf answered, "My main comment should be about the clinical trial. In that setting, we're saying that we don't know that there is a health benefit that exceeds the risk…There is an unproven risk against an unproven benefit. I've been living in the world of the LDL hypothesis, where many people believe, all else being equal, lowering LDL is a really good thing, and many people really do believe that, but when you put that against an unproven horror, people might go the other way in practice. No one knows for sure, and that's true of many of the drugs we use in practice, and it's a matter of judgment and belief."

The discussion continued:

- *Dr. Califf (to Dr. Taylor):* "I've read about this a number of times, and you agree it's a very different issue. If anyone has argued for evidence, Rory (Collins) and I have…On the other hand, it requires long-term trials in chronic disease, and we're going to see continued loss of investment in this field."

- *Dr. Psaty (interrupting):* "I'm not sure that I agree. If (Pfizer's) torcetrapib had come onto the market, the 30% (increase in adverse CV events, including all-cause death) would have been impossible to detect.
- *Dr. Taylor:* "We need a steady voice in this…We need to reassure patients that LDL remains a focus of therapy, but we need to reexamine and focus on the fact that new pharmacological agents need to be fully tested. So, I think that this is the place we find ourselves with ezetimibe."
- *Dr. Califf:* "Can I finish? I feel like I'm on a Sunday morning show…If there's a terror or a really bad risk, that can be done with 100 to 200 events. We just went through this in diabetes, so I'm not arguing willy-nilly to put drugs on the market, but if you're going to wait, we're going to have to change the way we do investments."
- *Dr. Taylor:* "I do respect (Rory Collin's) evidence development; that's not in question. With new therapies, we need to get full evidence before it is widely disseminated, to protect the investment of companies. Perhaps it has to be done through patent-life laws – reform that so that the evidence is first, and the reward for data development can be achieved."

After the panel discussion, an angry Dr. Collins claimed he had been "set up" and that until Dr. Califf intervened the session was going to have Dr. Taylor follow Dr. Collins, with no time for any discussion.

Cardiologist comments at AHA about the Vytorin controversy included:

- *AHA president Dr. Gardner:* "ENHANCE (the trial which first raised questions about the effectiveness of ezetimibe) is done… and I'm not going there."
- *Dr. Deepak Bhatt of Harvard:* "I don't think that there's anything new here on Vytorin. My use hasn't changed. I use it as a second-line drug."
- *Alabama #1:* "I haven't changed my prescribing for Vytorin."
- *Alabama #2:* "If you look at the SEAS trial (which linked ezetimibe to an increased risk of cancer) as a hypothesis-generating trial…I have to agree (that) in terms of safety these days all you have to do is stand up and yell, 'Fire.' You have to prove the cancer risk. But nothing is proven as far as efficacy either."
- *California:* "I will decrease my use, but my use is already very selective. I use it in patients who can't tolerate a statin or an optimal dose, and the LDL hasn't gotten down to a good level. I think that doctors who are cutting back or who have cut back on Vytorin will use more statins. Doctors are using ezetimibe first-line, and now with JUPITER statins are starting to look pretty good."
- *Maryland:* "It shows that the hypothesis that people do well when treated with simvastatin (Zocor) is true."
- *Texas:* "This is not a hard endpoint trial. If you look at the neointimal thickness in the control, it is always better than what you see in the population. I am mostly waiting for IMPROVE-IT and the death and MI data."
- *Illinois:* "The IMPROVE-IT results are still years away."

New Standards Proposal for Clinical Trials

Dr. Califf laid out a global set of standards for large, multinational clinical trials, including strengthening data monitoring committees and moving towards independence from sponsors. He described the beliefs underpinning his suggestions:

- Multinational pragmatic clinical trials are a global imperative.
- The rules of conduct are evolving.
- A global set of standards of conduct and behavior is needed.
- A clinical trial is a human experiment and demands active involvement of health providers with a primary mission of acting on behalf of research subjects and patients as well as sponsors.

He then presented his 10-point plan for improving the clinical trial system:

1. Bolster the role of independent data monitoring committees.
   - NIH and academia need to step up to the plate here – the current DMC workforce is aging out.
   - Committee members should have no financial interest in sponsors or competing sponsors in which personal wealth is tied to the fate of the company.
   - DMC members must have access to the raw database and able to independently analyze it.
2. Bolster a balanced executive committee. Constituents represented on the executive committee, including sponsor, but with the majority investigator.
3. House databases and analyses in not-for-profit institutions.
   - There are many excellent statisticians and data managers in medical products industry and CROs.
   - Fundamental conflict between fiduciary interest to employer and optimal analysis and reporting of human trials.
   - The terms drug-testing and device testing imply that the research subjects are inert – in fact they are human beings who need protection from IRBs and investigators with independence from sponsors.
   - While not-for-profits frequently fall from grace, their societal mission is clear and enforceable – by the tax code – to have the good of society as their primary mission.

- Universities and foundations have not sustained the needed capacity.

4. Transparent reporting of financial relationships.
   - Clinical trials cost money, time, and require people with a high level of scientific, clinical, and project management skills.
   - Consulting with the industry to help modify products to improve health is an important part of professional conduct.
5. Identify conflicts that are not directly financial.
   - Deeply held professional beliefs (like the LDL hypothesis).
   - Professional pride and advancement (hate to be wrong).
   - Working with competitors (other medical products companies, paid work to legal case against sponsors).
   - Being turned down from previous request for funding by previous sponsor.
   - Interpersonal animosity.
   - None of the above are killers in and of themselves.
6. Securities and Exchange Commission – currently the law says that if a company learns about internal information that would change a stock price, they must divulge that information promptly. Promptly is not adequately defined.
7. Commitment to publish.
8. Airing differences of opinion. We should stop using the press as a way to give an opinion.
9. Direct-to-consumer advertising. This should stop until health benefits are proven.
10. Increased public funding of clinical trials.

Dr. Califf ended with this comment: "In a system where money becomes increasingly important in our healthcare system, we need the motto, 'In God We Trust, all others must have data.'"

SANOFI-AVENTIS's Multaq (dronedarone) – May reduce hospitalizations for atrial fibrillation

In the U.S., atrial fibrillation (AFib) is the leading cause of hospitalization for arrhythmias and represents 10% of cardiovascular (CV) admissions. The randomized, double-blind ATHENA trial of more than 4,500 moderate-to-high risk AFib patients found that patients on 400 mg dronedarone BID were hospitalized less frequently for CV reasons than patients on placebo. Dronedarone also showed rate- and rhythm-controlling properties, according to the study investigators.

Dr. Christian Torp-Pedersen of the University Hospital in Copenhagen, Denmark, said, "Dronedarone led to a decrease of 1.26 hospitalization days per patient year. For 1,000 patients treated with dronedarone for one year, the healthcare system would save 1,260 hospital days." He concluded:

- In moderate-to-high risk AFib patients, dronedarone reduced the incidence of CV hospitalizations on top of standard therapy (for AFib-related as well as non-AFib-related reasons).
- Dronedarone did ***not*** increase the incidence of non-CV hospitalizations.
- Dronedarone markedly reduced the total number of hospital nights.
- This favorable effect on global morbidity was assessed with a satisfactory drug reaction profile, including a low risk for pro-arrhythmia.

Hazard Ratio for CV Hospitalization over 21 Months

Measurement	HR	p-value
Primary endpoint: First non-AF-related CV hospitalization	0.86	0.016
Any hospitalization	0.76	0.001
Secondary endpoint: First CV hospitalization	0.75	0.001

Dr. Torp-Pedersen said, "The risk reduction of 24% was highly statistically significant. Furthermore, the secondary endpoint of mortality was 0. For first non-AF related CV hospitalizations, there was a risk reduction of 14% (p=0.016)."

In the question and answer session, Dr. Torp-Pedersen said that a cost-effectiveness analysis is being done but is not complete. Asked about a study that showed an increase in mortality in patients with heart failure, he answered, "I was part of a group that did (that) study…We actually planned to randomize 1,000 heart failure patients, and we only randomized 300 patients. The study was dropped because of the high mortality. At that time, you could consider that the drug was not safe, but the sponsor did another study. That's why the study with 4,000 patients was conducted. It is basically over-powered for the primary endpoint, to provide sufficient

Hospitalizations with Dronedarone

Measurement	Dronedarone	Placebo	p-value
>1 hospitalization	35%	44%	<0.001
Total hospital nights	9,995	13,986	<0.001
Total nights of CV hospitalization	5,875	9,073	<0.001

Reasons for First Non-AF-Related CV Hospitalizations with Dronedarone

Measurement	Dronedarone	Placebo
Any non-AFib CV hospitalization	19%	22%
Worsening CHF	3.9%	4.9%
MI/unstable angina	2.3%	3.1%
Implantation of pacemaker, ICD, or any other CV device	2.0%	2.4%
Stable angina pectoris or atypical chest pain	2.2%	2.3%

safety data. We didn't want to learn the same lesson twice, so we excluded patients with severe heart failure. Not only is this trial positive, it provides a lot of safety data, and I believe this drug is effective and safe in a large group of patients, but I would never give it to a patient with severe heart failure…The heart failure subgroup of ATHENA is not a huge study. I think that the really important thing is that even if you use the drug and your patients have some degree of heart failure, it is still a beneficial drug."

LOW-DOSE ASPIRIN FOR PRIMARY PREVENTION – Still an open question

A randomized trial of Japanese patients with Type 2 diabetes found that low-dose aspirin did not reduce the risk of CV events. Researchers looked at 2,539 Type 2 diabetics without a history of atherosclerosis, randomizing them to either aspirin (81 or 100 mg QD) or placebo and following them for an average of 4.37 years. They reported no significant differences between the two groups, except for fewer fatal MIs and strokes with aspirin, and they speculated that aspirin may benefit patients age ≥65. The results of the JPAD trial were presented at AHA and simultaneously published in the ***Journal of the American Medical Association (JAMA)***.

- There was a 20% non-significant reduction in the primary endpoint – total atherosclerotic events, consisting of coronary, cerebrovas-cular, and peripheral vascular events – with aspirin.
- With the exception of fatal coronary and cerebrovascular events, none of the pre-specified secondary endpoints were reduced significantly in the low-dose aspirin group.
- A benefit of low-dose aspirin was suggested in patients aged ≥65, who had a significant 32% relative reduction in total atherosclerotic events (p=0.047)
- There was a small increase in serious GI bleeding. Four aspirin patients had bleeding that required transfusion, but there was no excess of fatal GI or cerebral hemorrhages.

In an accompanying editorial in ***JAMA***, Dr. Antonio Nicolucci of Italy warned the study should not be considered definite proof that aspirin is less effective in diabetics, "The last meta-analysis on the efficacy of antiplatelet therapy in the prevention of major cardiovascular effects showed a clear benefit for the entire population of more than 140,000 patients (22% reduction in risk), but no statistically significant benefit was documented in the subgroup of about 5,000 diabetic patients (7% risk reduction). The results of the JPAD trial…are compatible with the overall results of the meta-analysis, and a benefit of treatment, at least for the primary study endpoint, cannot be ruled out."

Dr. Nicolucci criticized the study's lack of precision and low statistical power, along with the difficulty of extracting useful conclusions for Western populations, "The epidemiology of cardiovascular disease in Japan is substantially different from that of non-Japanese Western populations." He called the findings relating to elderly patients "encouraging," but he warned that the results should be interpreted with caution, "The risk of major bleeding sharply increases in individuals older than 70 years, making the balance between benefits and harms uncertain."

In subgroup analyses, there were no significant differences based on sex, hypertensive status, smoking status, and lipid status. In patients age ≥65 the incidence of atherosclerotic events was significantly lower with aspirin. However, aspirin therapy was associated with an increased risk of gastro-intestinal bleeding and retinal hemorrhage.

The investigators said that despite the large sample size, the interpretation of the results is challenging. The overall event rate was low – 17 in 1,000 Japanese diabetic patients, which is about a third of the anticipated event rate, "Because of the low event rate in JPAD, our study was underpowered for demonstrating that aspirin had a significant effect on reducing total atherosclerotic events. However, the observation in the JPAD trial of an effect of aspirin on the secondary outcome of fatal cardiovascular events was also seen in the PPP trial. Aspirin did not reduce cardiovascular mortality in the HOT study, and it did not reduce fatal stroke in the Women's Health Study.

4-Year Results of JPAD Trial

Measurement	Aspirin	Non-aspirin	Hazard ratio	p-value
Primary endpoint: All atherosclerotic events	5.4%	6.7%	0.80	Nss, 0.16
Secondary endpoint: Coronary and cerebrovascular mortality	0.08%	0.8%	0.10	.0037
CHD events (fatal + nonfatal)	2.2%	2.7%	0.81	Nss, 0.40
Fatal MI	0	0.4%	1.34	Nss, 0.50
Unstable angina	0.3%	0.8%	0.40	Nss, 0.13
Stable angina	1.0%	0.9%	1.10	Nss, 0.82
Cerebrovascular disease (fatal + nonfatal)	2.2%	2.5%	0.84	Nss, 0.44
Fatal stroke	0.08%	0.4%	0.20	Nss, 0.15
Nonfatal ischemic stroke	1.7%	1.9%	0.93	Nss, 0.80
Nonfatal hemorrhagic stroke	0.4%	0.2%	1.68	Nss, 0.48
Transient ischemic attack	0.4%	0.6%	0.63	Nss, 0.42
Peripheral artery disease	0.6%	0.9%	0.64	Nss, 0.35
Atherosclerotic events in patients age ≥65	6.3%	9.2%	0.68	0.047
Non-cardiac death	23 patients	25 patients	---	---
Death from unknown causes	8 patients	3 patients	---	---
Adverse events				
GI bleeding	5 patients	3 patients	---	---
Retinal bleeding	8 patients	4 patients	---	---
Nose bleeding	6 patients	1 patient	---	---
Non-hemorrhagic gastric ulcer	17 patients	3 patients	---	---
Anemia	4 patients	0	---	---

The reason for the discrepancy in the preventive effect of aspirin on fatal cardiovascular events is not clear at present …A larger trial is needed to determine the efficacy of low-dose aspirin on mortality…The finding of no increase in hemorrhagic stroke in the JPAD trial is of particular clinical importance because hemorrhagic stroke is more common in Japanese populations than in the West."

PLAVIX AND PROTEIN PUMP INHIBITORS – WSJ article and two conflicting presentations created confusion

A ***Wall Street Journal*** article and two studies presented at AHA have created confusion about the safety of Sanofi-Aventis's Plavix (clopidogrel) in patients taking a proton pump inhibitor (PPI). One study, which was quoted online by the ***Wall Street Journal***, found that PPIs block the activity of Plavix. The ***WSJ*** article suggested that the study "could shake the market for several multibillion-dollar-a-year drugs." Then, another study was presented which found no interaction between the two drugs – that Plavix reduces adverse events whether or not patients are taking PPIs.

The session moderator, Harvard's Dr. Bhatt, a noted Plavix researcher, said, "I don't know how the press got the (***WSJ***) study, but people were asking about it. I told them that (the) study said just the opposite, and there is no interaction. (The study) was an observational study and was not placebo controlled. The key here is not to create hysteria. I told doctors that if you have a patient on clopidogrel and PPIs, not to stop."

The controversial study, presented by Dr. Ronald Aubert of Medco Health Solutions in Franklin Lakes NJ, found that PPIs inhibit the effectiveness of Plavix. Dr. Aubert said, "The drug interaction between PPIs and clopidogrel may result in serious adverse outcomes within one year of therapy initiation and further support investigations into the effects of cytochrome P450-2C19 genetic polymorphisms." Clopidogrel's antiplatelet properties are thought to be activated by the isoenzyme cytochrome P450-2C19, which Dr. Aubert said is potently inhibited by PPIs, interfering with clopidogrel activation and its effects.

Medco 1-Year Plavix Outcomes Study in Stent Patients

Major adverse events	Plavix alone n=9,862	Plavix with a PPI n=4,521
Hospitalization for stroke, MI, angina, or CABG but no preceding CV events	21.2%	32.5%
Hospitalization for stroke, MI, angina, or CABG with preceding CV events	26.2%	39.8%

Dr. Aubert's study used the National Medco Integrated Database and followed for one year nearly 15,000 patients who received stents in 2005 or 2006 and who started taking clopidogrel when they received the stent. The researchers reported that the relative risk of a major adverse event was 50% higher, and the relative risk of a heart attack specifically was 74% higher in patients taking clopidogrel with PPIs. Medco said that it will begin alerting physicians, so that they can reconsider the risk:benefit of concurrent prescribing of clopidogrel and PPIs.

Immediately after Dr. Aubert's presentation, Dr. Steven Dunn of the University of Kentucky presented his study in which Plavix reduced adverse events, regardless of PPI use. His study analyzed the primary endpoints for the CREDO trial – 28-day death/MI/urgent TVR and one-year death/MI/stroke – based on PPI use at study entry. Dr. Dunn said, "*Ex vivo* data suggest a pharmacokinetic (PK) interaction may exist between PPIs and clopidogrel, decreasing the antiplatelet effect of the latter…Baseline PPI was associated with an increase in cardiovascular events at one year in both patients receiving clopidogrel and the overall trial population. However, clopidogrel reduced adverse events at one year to an approximately similar degree whether or not patients were on a PPI."

On January 26, 2009, the FDA notified healthcare professionals that studies will be done to better understand how genetic factors and other drugs – especially proton pump inhibitors (PPIs) – affect the effectiveness of Plavix. There have been published reports that Plavix is less effective in some patients than it is in others, and that could be due to genetic differences in the way the drug is metabolized, to drug-drug interactions, or a combination of the two.

The FDA said it is anxious to get the data "promptly" and indicated that the manufacturers have agreed to a timeline for completing the studies. The FDA promised to review the new information expeditiously and to communicate its conclusions and any recommendations to the public but warned that this could take several months.

In the meantime, the FDA recommended that

- Healthcare providers continue to prescribe – and patients continue to take – Plavix as directed.
- Healthcare providers re-evaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC (omeprazole), in patients taking Plavix.
- Patients taking Plavix should consult with their healthcare provider if they are currently taking or considering taking a PPI, including Prilosec OTC.

VITAMINS C AND E
– Do not reduce major CV events

A large, long-term trial of male doctors showed that neither vitamin E nor vitamin C supplements reduced the risk of major cardiovascular events (CV). The results of the Physicians' Health Study II were presented at AHA and concurrently published in the ***New England Journal of Medicine***. It was a randomized, double-blind, placebo-controlled trial of the two vitamins in 14,641 male physicians age ≥50, including 754 men with prevalent CV disease who took supplements of 400 IU vitamin E every other day and 500 mg vitamin C daily.

During a mean follow-up of eight years, there were 1,245 confirmed major cardiovascular events. Neither vitamin C nor E had an effect on the incidence of major cardiovascular events vs. placebo, total stroke, or CV mortality. In both groups, the overall rates of major CV events were 10.8 for vitamins and 10.9 for placebo per 1,000 person-years. Neither vitamin reduced the incidence of individual CV events, including MI and stroke. However, there was an increase in hemorrhagic strokes with vitamin E (39 vs. 23). There were no significant differences in adverse effects with either vitamin vs. placebo.

HOME INR TESTING
– Safe but doesn't improve mortality

The results of The Home INR Study (THINRS) showed that weekly home international normalized ratio (INR) testing is safe but does not notably improve major health outcomes compared to monthly clinic-based testing (high quality anticoagulation management, or HQACM). The study missed its primary endpoint of time to first major event for stroke, major bleed, and death. Over an average of 54 months and more than 8,000 patient-years of follow-up, there were 544 primary endpoint events: 237 deaths, 263 major bleeds, and 44 strokes. There was no statistical difference in the number of events between the intervention groups.

Study co-chair Dr. Alan Jacobson of Loma Linda University School of Medicine in California said warfarin is effective if managed well, but it is underutilized, "Frequent home INR monitoring (weekly patient self-testing, or PST) is a promising strategy to improve outcomes. Increasing testing frequency allows out-of-target INRs to be quickly identified and addressed, and patients can do their own care."

Asked if patient self-testing notably improves health outcomes of currently recommended practice, he said, "The study was powered to identify a 21% relative risk reduction in annual rate of major events (from 5.5% to 3.75%, or an 1.75% absolute reduction)…The patients were monitored for 8,307 patient-years, and on the primary outcome…the two arms were statistically similar…So, while there was no evidence of harm, we couldn't identify a benefit as large as 1.75%."

Dr. Jacobson said that despite the failure to meet the primary endpoint, "What we did find was that time and target range was significantly improved in home vs. clinic group and this translates to about a 7% improvement during the period, and this measure assesses the negative effects of anticoagulation such as anxiety and hassles, as well as the positive features that might be associated with anticoagulation or monitoring… We concluded that weekly home INR monitoring does not improve the aggregate outcome of stroke, major bleed, or death…(but it) is an acceptable alternative to high quality clinical care and may be preferable when the patient has a disability or geographic distance."

The discussant, Dr. Alan Go of Kaiser Permanente of Northern California, in Oakland, asked if the study was underpowered, "They found very low rates of ischemic stroke in both arms driven mostly to the efficacy of anticoagulant therapy, but also some patients at lower stroke risk. There were no significant differences in the numbers of stroke or intracranial hemorrhage or bleeding in both groups, so there would probably be no difference even if the sample was

8-Year Results of Physicians' Health Study II

Measurement	Vitamin E n=7,315	Placebo n=7,326	HR	p-value	Vitamin C n=7,329	Placebo n=7,312	HR	p-value
Primary endpoint: Major cardiovascular events	620	625	1.01	Nss, 0.86	619	626	0.99	Nss, 0.91
Total MI	240	271	0.90	Nss, 0.22	260	251	1.04	Nss, 0.65
MI death	22	30	0.75	---	30	22	1.37	---
Total stroke	237	227	1.07	Nss, 0.45	218	246	0.89	Nss, 0.21
Stroke death	45	56	0.86	---	44	57	0.77	---
Ischemic stroke	191	196	1.00	---	180	207	0.87	---
Hemorrhagic stroke	39	23	1.74	---	30	32	0.95	0.04
Cardiovascular death	258	251	1.07	Nss, 0.43	256	253	1.02	Nss, 0.86
Congestive heart failure	289	294	1.02	---	293	290	1.02	---
Angina	718	765	0.95	---	718	765	0.93	---
Revascularization	675	709	0.96	---	678	706	0.96	---
Total mortality	841	820	1.07	Nss, 0.15	857	804	1.07	Nss, 0.16

increased. Also, this was all done in the VA system; is this population generalizable to other populations? They are mostly men, mostly white European, somewhat younger than others, with a mean age of 67 years…(Third) Was the right comparison group used? They used high quality anticoagulation management services…which may not be considered the standard care in many practice settings and in many communities." He also noted that it was an unblinded trial, and he asked what the resource utilization and cost differences were.

Dr. Go concluded:

- Delivering high quality anticoagulation regardless of method leads to low rates of ischemic stroke and intracranial bleeding.
- Home INR monitoring in eligible patients only modestly improved percentage of TTR compared with the anticoagulant management service.
- There is no significant change in stroke and major bleeding.
- There were no long-term differences in quality of life.

However, he said, "Medicare expanded the use of these devices, so home INR monitoring is a reasonable alternative for appropriate patients with these indications."

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