Trends-in-Medicine

December 2009

by Lynne Peterson

SUMMARY

There was a lot of news at AHA, but the key things were:

♦ More bad news for Merck's ezetimibe – lack of efficacy and a safety signal in the ARBITER-6-HALTS trial. ♦ Niacin and HDL-raising drugs are getting new attention, though cardiologists are waiting for the AIM-HIGH trial to prove that raising HDL is beneficial. ♦ More data were presented confirming the efficacy and safety of AstraZeneca's antiplatelet agent Brilinta (ticagrelor) and Boehringer Ingelheim's anticoagulant Pradaxa (dabigatran). But the CHAMPION trials of The Medicines Company's cangrelor didn't hold out much hope for that IV platelet inhibitor, and platelet resistance testing is unlikely to take off without data from a large outcomes trial, if ever. ♦ In anemia, more bad news for Amgen's Aranesp, with new data that mortality was higher in stroke survivors who took Aranesp vs. placebo. But IV iron may be more helpful than previously thought, especially in non-anemic heart failure patients. ♦ CardioDx has an interesting gene test for obstructive coronary artery disease, Corus CAD, but so far cardiologists are skeptical. ♦ Continuous flow LVADs – and destination therapy – got a big boost with new data on Thoratec's HeartMate-II showing 58% two-year survival.

Trends-in-Medicine
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AMERICAN HEART ASSOCIATION (AHA) SCIENTIFIC SESSIONS

Orlando, FL
November 15-18, 2009

Attendance at AHA was down this year, and while the numbers weren't dramatically lower, the impact was clear. Sessions had lighter attendance, the exhibit floor was smaller, fewer companies were exhibiting, and hallways weren't as busy. There were even fewer reporters covering the meeting.

AHA Scientific Sessions Attendance

Measurement	2009	2008	Change
Total	20,548	23,256	Down 12%
Professionals	15,650	17,422	Down 10%
Physicians	9,400	10,279	Down 9%
Research scientists	6,250	2,875	Down 13%
Non-healthcare		1,394	
Other		2,874	
Exhibitors	N/A	300+	Down 17%
Exhibitor space	---	---	Down 15%
Media	246	340	Down 28%

Yet, AHA is not the only major medical conference facing this problem. While some medical meetings have seen an increase in attendance, more have seen fewer people coming this year, and most – but not all − have seen shrinking and poorly attended exhibit halls. Exhibit halls used to be a great place for reporters to find random doctors to interview, but that has changed. Many exhibitors are thinking of downsizing their booths even further or not attending some meetings next year. Siemens and Philips, for example, were noticeably missing from the AHA exhibit floor. At least one medical society is considering asking all its exhibitors if they want to downsize proportionally.

Several reasons appear to account for these changes, including:

- **Attendance is down.** The doctors who do attend often stay at the meeting for fewer days and bring fewer staff members.
- **Booths are smaller, less glitzy, and offer fewer reasons to visit.** At many meetings, including AHA, most booths have had nothing but signage, no senior officials hanging out, no new products on display to see and handle. There are fewer booth lectures. A Virginia doctor at AHA said, "I usually visit the exhibit floor, but I haven't been there this year. There just isn't the ***value*** to going any longer. My time is better spent in other ways."
- **Some doctors are reluctant to be seen on the exhibit floor**, eschewing even the appearance of an association with industry.

- **New regulations limit pharmaceutical company give-aways.** No longer are there free engraved pens and laser pointers, t-shirts, notepads, flash drives, etc. At AHA this year, doctors could find a free cup of cappuccino, a chocolate strawberry, a fruit smoothie, an occasional cookie, or aspirin at the Bayer booth, but that's about it. At AHA, there were no "learning" games to play, no magicians or mentalists, and no golf-putting greens, but Novo Nordisk was doing free HbA_{1c}/cholesterol/blood pressure screenings, and another company was taking doctors' pictures.

  While it would be easy to blame the exhibit hall problems on this issue alone, some meetings which traditionally have had very few give-aways, like the American Academy of Ophthalmology meeting, had very good exhibit floor traffic this year, making it clear this is a multifactorial problem.

- **Budgets are tight, and doctors may not be shopping.** Many hospital budgets have been frozen, and many private practice doctors have battened down the hatches and limited purchases during the recession. Thus, there is less need to go see the latest, greatest device on the exhibit floor. Thus, doctors are concentrating more on educational sessions.

- **Doctors have gotten somewhat wary of new drugs.** More and more doctors are taking a wait-and-see attitude toward new drugs, even ones that promise to be practice-changing blockbusters. In addition, many doctors have said that they now prefer to learn about new drugs from their colleagues (in lectures) or in medical journals rather than from industry sales reps or on the exhibit floor.

DRUGS

LIPID-LOWERING MEDICATIONS

LOWERING LOW DENSITY LIPOPROTEIN (LDL) – decreasing in the U.S. but screening still very low

The prevalence of high LDL in adults dropped by about a third from 1999 to 2006. That was the finding of a study by Centers for Disease Control and Prevention (CDC) researchers which was presented at AHA and simultaneously published in the ***Journal of the American Medical Association (JAMA)***. Overall, 31.5% of the 7,044 people studied had high LDL in 1999, and this dropped to 21.2% in 2006.

LDL Prevalence in the U.S.

Measurement	1999-2000	2005-2006	p-value for linear trend
High-risk patients with chronic heart disease (CHD)	69.4%	58.9%	Nss, 0.06
Intermediate-risk patients (≥2 risk factors)	51.3%	30.2%	<0.001
Low-risk patients (≤1 risk factor)	15.5%	11.0%	0.02
Use of lipid-lowering medications	8.0%	13.4%	<0.001

However, the number of adults getting screened for high cholesterol did not change, remaining at <70% throughout the study. Among the people with high LDL, 35.5% were unscreened, 24.9% undiagnosed, and 39.6% untreated or inadequately treated in 2006. The researchers speculated that screening may be hindered by the lack of consensus regarding the age at which screening should start.

MERCK/SCHERING-PLOUGH's Zetia (ezetimibe) and Vytorin (ezetimibe + simvastatin) – ineffective plus a safety question

In the ARBITER-6-HALTS trial, presented at AHA and simultaneously published in the ***New England Journal of Medicine (NEJM)***, ezetimibe performed significantly worse than niacin in patients already on a statin. The cardiovascular safety of ezetimibe was also worse, although that may have been due to its lack of effect on HDL compared to a positive effect for niacin. There are several shortcomings and confounding issues with the trial, but the bottom line is that ezetimibe/statin had ***higher*** rates of cardiovascular events and was associated with a slight but temporary ***increase*** in carotid intima-media thickness (CIMT).

ARBITER-6 was a 208-patient, randomized, parallel-group, open-label, comparative effectiveness trial in patients with coronary heart risks or actual coronary disease with good LDL cholesterol control (<100 mg/dL) but low HDL (<50 mg/dL for men and <55 mg/dL for women). Patients at two sites – Walter Reed Army Medical Center and Washington Adventist Hospital − were randomized to either extended-release niacin (Abbott's Niaspan 2000 mg/day) or ezetimibe (Zetia 10 mg/day). The trial enrolled 363 patients, but data were only available on 208 patients because it was stopped early at 14 months for efficacy. The study was sponsored by Abbott, but it was run by the investigators who also did the data analysis.

In the study:

- **CIMT** initially increased then declined back to just barely below baseline with ezetimibe, whereas CIMT steadily and significantly decreased with niacin.

- **HDL** increased significantly with niacin but decreased with ezetimibe.

- **LDL** and **total cholesterol** decreased much better with ezetimibe than niacin. In the first two months, both drugs reduced LDL and total cholesterol sharply, but during the rest of the trial both LDL and total cholesterol increased slightly but steadily, though staying well below baseline.

- **Triglycerides** decreased sharply and significantly in the first two months with niacin, and remained low out to 8 months, then began to steadily increase a little. Ezetimibe decreased triglycerides only a little, and that returned to baseline by the end of the trial.

- **Quality of life** was not significantly different between the drugs.

In a post hoc analysis, the researchers, led by Dr. Allen Taylor of Walter Reed Army Medical Center, looked at LDL change and CIMT and found a significant inverse relationship. That is, as LDL decreased with ezetimibe, CIMT increased – which did not occur in the niacin patients. The researchers speculated that the unexpected and paradoxical increase of CIMT with ezetimibe "is biologically plausible if it is associated with the unintended disruption of reverse cholesterol transport…This hypothesis-generating finding is not an indictment of the overall importance of reducing LDL…Rather, this adverse relationship may be attributable to the net effect of ezetimibe."

The researchers concluded, "Our findings challenge the usefulness of LDL cholesterol reduction as a guaranteed surrogate of clinical efficacy, particularly reduction achieved through the use of novel clinical compounds…We believe that prudent clinical practice currently favors the avoidance of ezetimibe, with consideration of further restriction on its use in lieu of clinically validated regimens, until its net effect on clinical outcomes can be fully ascertained."

There are three potential explanations for why ezetimibe looked so bad in this trial:

1. **HDL lowering is what counts**, and that's what niacin, but not ezetimibe, does.
2. **CIMT is a bad surrogate marker** and perhaps should not be used in the future.
3. **Ezetimibe simply is a bad drug**, which, at this point, looks like the most likely answer.

The ***NEJM*** also published two editorials on this trial.

1. Dr. Roger Blumenthal and Dr. Erin Michos, both from Johns Hopkins University School of Medicine, called it a "thought-provoking study." They said the positive results for niacin were "not that surprising." While they do not believe the study conclusively shows that raising HDL is more beneficial than augmenting the decrease in LDL, they concluded that when a patient is unable to reach the target LDL with the maximum dose of a potent statin, then – for now – "niacin is the preferred adjunctive agent."

Among their criticisms of this study were:

- Premature termination, which "may exaggerate" any potential niacin benefit.
- Use of CIMT, which they described as a controversial surrogate for coronary atherosclerosis.
- "Unsubstantiated" putative effects of ezetimibe on CIMT.
- Lack of information on whether more aggressive LDL lowering (with higher statin doses) is as effective as adding a second agent. They said other trials such as AIM-HIGH, HPS2-THRIVE, and IMPROVE-IT should address this issue.

In an interview at AHA, Dr. Blumenthal said, "We are seeing some better-than-expected effects of niacin but at a dose very few people tolerate in the U.S. – 2 grams…It will lead many more doctors like myself to think niacin will be the preferred second agent…In the community doctors (generally) don't make niacin their second agent…This study has elevated niacin to the preferred second drug status over ezetimibe…but we also have to keep in mind that (the trial) used 2 g of niacin, and that lowers LDL almost as much as ezetimibe…In my mind, for high-risk individuals, especially those with average or low HDL, most clinicians will view these two studies that niacin is the preferred second-line agent…There is still a role for Zetia in patients with relatively high LDL…I think we really won't know for sure the role of Zetia until IMPROVE-IT…People will not only look at niacin as the preferred agent but will try to push the dose higher…This is good news for niacin, not bad news for Zetia…The impact on clinical practice will be that more individuals will try to use niacin as a

14-Month Results of ARBITER-6-HALTS Trial

Measurement	Ezetimibe + statin n=111	Niacin + statin n=97	p-value
Demographics			
Family history of CHD	38%	49%	0.09
Percutaneous corony intervention (PCI)	44%	30%	0.05
Simvastatin use	39%	54%	0.09
Atorvastatin use	57%	40%	---
Key results			
Primary endpoint: CIMT change	Down 0.0007 (Nss, p=0.84)	Down 0.0142 (p=0.001)	0.003
Secondary endpoint #1a: HDL	Down 2.8 mg/dL	Up 7.5 mg/dL to 50 mg/dL **Up 18.4%** (p<0.001)	<0.001
Secondary endpoint #1b: LDL	Down 17.6 mg/dL to 66 mg/dL **Down 19.2%** (p<0.001)	Down 10.0 mg/dL	0.01
Secondary endpoint #2: Discontinuation due to adverse events	3 of 9 patients	17 of 27 patients	Nss, 0.12
Secondary endpoint #3: Health-related quality of life	N/A	N/A	Nss
Secondary endpoint #4: MACE [myocardial infarction (MI), revascularization, hospitalization for acute coronary syndrome, and cardiac death]	5% 9 patients	1% 2 patients	0.04
MI	3 patients	1 patient	---
Revascularization	3 patients	0	---
Cardiovascular (CV) death	5 patients	1 patient	---
Other results			
Discontinuations	9%	15%	0.09
Medication adherence	95%	88%	<0.001

second agent because of the potential benefit in reducing atherosclerotic events, and where Zetia used to be used second-line, it will be more apt to be used third- or fourth-line."

Asked about the MACE rate in ARBITER-6, Dr. Blumenthal said, "I'm not concerned because the (ongoing) IMPROVE-IT study (with ezetimibe) is the most highly watched study in history. They have 15,000+ patients, and they are looking carefully at cancer, stroke, and cardiovascular events…We will hear again soon officially from them, but they have seen no hint of (excessive) adverse events…so it is disingenuous to say there is real harm with this medication with a 208-patient study."

Asked about the slight uptick in CIMT with ezetimibe at 8 months in ARBITER-6, Dr. Blumenthal said, "Well, it went up slightly. It didn't go up as much as niacin did at 1 year with 1 g (in ARBITER-2)…People think of this as Drano, but this is 0.14 mm in a highly precise research setting."

2. Two Dutch doctors, Dr. John Kastelein from the University of Amsterdam and Dr. Michiel Bots of the University Medical Center Utrecht, called ARBITER-6 an "important and provocative" trial and the results "intriguing," saying they show "a clear superiority of niacin over ezetimibe." However, they made several points about the trial, including:

- The CIMT assessment was careful and well designed.
- The early trial termination reduced the power of the trial.
- The post hoc analysis of the relationship between changes in LDL and CIMT was "not the most rigorous," so firm conclusions about the relationship should await the findings of larger studies.

Dr. Kastelein and Dr. Bots concluded, "The primary results are likely to be correct although the magnitude of the difference between the treatment arms may be over-estimated. Whether these results are due to the effect of niacin on HDL cholesterol, LDL cholesterol, remnants, Lp(a) lipoprotein, high-sensitivity C-reactive protein, or any combination of these cannot be answered by the current data."

Dr. Kastelein, who has received consulting and/or lecture fees from Merck/Schering-Plough, called the CIMT assessment "truly impeccable" and recommended that niacin, not Zetia, be the second-line treatment, "These (and other trials) support the concept that the use of statins to reduce LDL to target and the subsequent addition of extended-release niacin, as compared with ezetimibe (which offers only LDL) lowering, will provide more effective treatment of high-risk patients…We should first use statins to reduce LDL to target or close to target and then add niacin to provide more effective treatment of high-risk patients."

Safety of Zetia

Asked if it is safe for patients to take Zetia until the IMPROVE-IT results are known, Dr. Taylor said, "AHA is driven by science, and at this time we have no evidence the drug does harm…(but) I see no reason at this time to use ezetimibe as an LDL lowering treatment…It does cost money. It is not free...The data are clear that niacin is superior to ezetimibe. How people make clinical decisions is up to them, but the cost needs to be considered." AHA spokesperson Dr. Robert Eckel of the University of Colorado added, "Patients should be encouraged to contact their physicians about those kinds of decisions."

Dr. Taylor disclosed that he has received more than $10,000 in consulting and lecture fees from Abbott, which sponsored the trial, but he wouldn't say how much more. The American College of Cardiology (ACC) only requires members to disclose that they receive more or less than $10,000.

Asked about the status of IMPROVE-IT, Dr. Luciano Rossetti, a Merck senior vice president and head of Merck's global science strategy and franchise head of cardiovascular, said, "Recruitment is going well. We now have more than 15,000 of the 18,000 planned patients enrolled. The DSMB (data safety monitoring board) just met, and recruitment is going well. Close to 2,300 events have accrued, so we are close to the interim analysis which occurs when 50% of events occur." He predicted the interim analysis will occur in a few months, perhaps in March or April 2010. Dr. Eckel said, "IMPROVE-IT should continue because, at this point, getting LDL lower is still a strategy and recommended in the AHA/ACC/SCAI (Society for Cardiovascular Angiography and Interventions) guidelines…I would caution the public and the prescribing community about reaching conclusions too early on a trial of comparative agents." He also warned doctors and patients against the idea of doing serial CIMT measures, "CIMT is useful in assessing plaque burden, but we don't have any information that serial measurements of CIMT actually predict events."

Implications of ARBITER-6 – increase in use of niacin over Zetia

ARBITER-6 is likely to lead to another significant drop in Zetia use. Most doctors questioned said the trial confirmed their current use of niacin and will expand it. They also predicted that doctors not using niacin much or at all will start and that Zetia use will fall. Some were very critical of Merck/Schering-Plough's marketing of Zetia, which could have implications for any new cardiovascular drug that Merck launches – unless IMPROVE-IT gives Zetia a reprieve. Remember that cardiologists have a history of "punishing" pharmas when problems come up with a drug or marketing gets out of hand [e.g., Johnson & Johnson's ReoPro (abciximab), Merck's Aggrastat (tirofibran) launch].

Physician reactions to the ARBITER-6 results included:

- *Dr. Mariell Jessup, program chair for the AHA annual meeting:* "I tend not to use a lot of Zetia…Niacin is not well tolerated, so the decision (on what to use) is not as clear cut as it might appear."
- *An IMPROVE-IT investigator:* "(This is) yet another surrogate endpoint trial that demonstrates the efficacy of niacin to 'stabilize' plaque…(It) further validates my use of niacin. I try it often, though it is not always successful due to the side effect profile. Small studies with hand-selected patients will have better adherence with this difficult drug. I am waiting for the large trials to see what it (niacin) does in a more 'general' population… (ARBITER-6) should lower the threshold for considering niacin as an adjunct therapy to statins for prevention. We await the ongoing large clinical trials to evaluate the clinical endpoint efficacy of the treatments to move them to a 1a ('proven') indication…However, one needs to put the LDL lowering in context. In other intimal progression trials, once LDL is lowered to a goal, further lowering has not resulted in further reduction in thickening…To me, this means one can see an effect on initiation of aggressive LDL lowering but not with further lowering (of LDL)."
- *Connecticut:* "It adds to the void of evidence to support ezetimibe, a drug that has sales of $3-4 billion and has yet to show that it does more than lower cholesterol. This study is small and has a surrogate outcome as its primary endpoint, but what is important is that the evidence that is here is not reassuring about the benefit of this still popular drug. Merck surrogates will try to turn this into a squabble about a small study rather than a third study that fails to provide any support for this drug that was marketed heavily through a campaign to the public and with academic leaders − and ultimately adopted quickly…We still do not know if the drug reduces risk, is an expensive placebo, or is harmful. The studies, together and individually, are not powerful enough to render a verdict on the drug, but they provide no reassurance that it is beneficial. The company says we should disregard the study and not change practice. I believe the study should make us question the current practice…The likelihood that it will eventually be shown to be beneficial is lower, though it is not out of the question…I believe every patient on this drug should know that there is no evidence that it lowers risk, that there are safety questions/controversies, and that better information about it will not be available for years …the company says it is safe, but that is not known…We cannot tell if it increases the risk of common problems like heart attacks or cancer. This study does not help in that regard. The increased events compared with niacin raise a concern but, again, are not definitive…I already consider (ezetimibe) a drug of last resort, and patients on it should know they are taking a gamble that it will eventually be shown to be safe and effective in lowering risk…Practice needs to change."
- *Dr. Eckel:* "I'll pause some and be thinking a little more …I will keep LDL below 100, but perhaps use more niacin. I'll still use Zetia, but I will think earlier of using niacin…This (ARBITER-6) could make the FDA re-think using LDL as a surrogate."
- *Dr. Taylor:* "This trial established the combination of statin-niacin is superior to statin-ezetimibe. Prudent clinical practice presently favors avoidance of this agent because its net effect to clinical outcomes is unknown, and its relative efficacy is now known to be inferior…The ezetimibe clinical efficacy remains unproven."
- *Louisiana:* "There is no question that we really care a lot more about clinical event reduction than (carotid) IMT, and this trial is really too small to adequately assess event reduction. Nevertheless, this study suggests better event reduction when adding Niaspan to a statin instead of Zetia, and the main study finding (regarding the IMT) also is strongly in favor of the niacin…I personally already use a lot of niacin…but I have generally reserved this for patients with HDL under 40 (especially those) who also had high triglycerides…I believe that this study will encourage clinicians and patients to use more niacin, to fight through the initial non-life threatening side effects (mainly flushing)…as well as using niacin in addition to statins in patients with a little higher baseline HDLs. This will increase the use of over-the-counter niacin as well as (Niaspan)."
- *Maryland (investigator):* "The study is very convincing …The study was extremely well designed, orchestrated, and executed…We can be very confident in these data… (The trial) will have great impact for using niacin-based therapy…(Depending on the results of the AIM-HIGH trial), statins and niacin may turn out to be the…power combination needed to effectively treat cholesterol and combat heart disease."
- *Massachusetts:* "The issue is that (ARBITER-6) is a small, mechanistic study – not one that would drive clinical care…Thus, it should not change clinical care. I find it encouraging – the fifth small, mechanistic study to show changes in the artery wall with niacin. But…we need to wait for the outcomes trials to see what to use."
- *Michigan:* "The findings are not surprising…Will this be a blockbuster and change clinical practice and the guidelines? Not likely, but it will (should) change practice patterns of a significant number of physicians…There are two large outcomes trials underway to assess the benefit of adding niacin to a statin (simvastatin): the AIM-HIGH study…and the HPS2-THRIVE study…It will be those studies that change the guidelines…The (CIMT) finding supports the previous observations that ezetimibe may not provide value…It also begs the question whether the comparison with ezetimibe biased toward the success of niacin…I expect the results to influence the practitioners who use ezetimibe as well as those who have been reluctant to use niacin because of side effects."

- *Vermont:* "(ARBITER-6) is very well done, and the results are provocative. I am particularly impressed that the primary result, carotid intimal thickness, which favored use of niacin, was supported by decreased clinical events."
- *Minnesota:* "The study is well done and will be of considerable scientific interest…Public interest is limited because for most patients LDL <100 is the goal, so this study doesn't apply, it's not clear whether patients were at 'maximum' tolerated dose of a statin at the time of enrollment, and CIMT is a surrogate endpoint...In my practice…niacin is the preferred second agent if statins at the maximum tolerated dose do not get patients to target."
- *New York:* "This appears to be a very well designed study by an accomplished researcher…I think that this… potentially will change practice. It could be the final nail in the Zetia coffin. Prior to (ARBITER-6), I was not convinced (based on one study, ENHANCE) that Zetia should not be used, but I have to say that (ARBITER-6) supports ENHANCE and suggests that there is something in the mechanism of Zetia that is adverse."
- *Pennsylvania:* "This study supports the concept that adding niacin to a statin in patients with low HDL and high risk may be beneficial in reducing cardiovascular risk. Many physicians, including me, have prescribed niacin in addition to a statin for such patients for some time without hard clinical evidence of benefit. Of course, the caveat is that carotid IMT is a surrogate…The bottom line for the consumer is that niacin, which can be hard to take, probably has benefit in this setting."
- *Wisconsin:* "For patients who are on statins, niacin is the next best drug to treat lipids, if additional medical therapy is needed. It has a wealth of evidence for preventing cardiovascular events and delaying progression of atherosclerosis – more than for all the other classes of non-statin lipid-altering medications. It has earned its place as second-in-line therapy after high doses of statins. This study, combined with previous studies showing niacin benefits and ezetimibe's lack of efficacy, clearly make it important information…(ARBITER-6) will have very little impact on my clinical practice. I rarely use ezetimibe …Doctors need to stop using so much ezetimibe. Using this drug is not practicing evidence-based medicine. It is taking a path of least resistance, the easy way out of getting numbers to targets. But we don't treat numbers; we treat patients and are obligated to use drugs that are proven in clinical trials to reduce things they care about – heart attacks, strokes, and death – and to do so safely."

The value of CIMT

A major imaging trial is expected to be presented at the American College of Cardiology 2010 comparing different imaging modalities, and it may be critical of CIMT as a measurement, which would be good news for Zetia/Vytorin, but that is still not expected to boost use, though it could slow the slide in prescriptions. The future of Zetia/Vytorin now appears to hinge on the IMPROVE-IT trial.

Some things to keep in mind about IMPROVE-IT:

- The DSMB's decision to allow the trial to continue doesn't mean the trial doesn't have a safety issue, just that there is no safety issue that has risen to the stopping point, whatever that may be. Thus, it could show a statistically significant detriment in CV safety just as ARBITER-6 did without being stopped early.
- After the ENHANCE and SEAS trials, Dr. Rory Collins, professor of medicine and epidemiology from the University of Oxford and chairman of the SHARP steering committee, and Sir Richard Peto, the Oxford epidemiologist/cancer biostatistician who analyzed the SEAS cancer data, both were quoted as saying that IMPROVE-IT is expected to be positive in favor of ezetimibe. However, at AHA they were both hedging this, suggesting the trial is now likely to fail.

HDL-Raising Agents

While niacin effectively raises high-density lipoprotein (HDL), the side effects – particularly flushing − are too difficult for many patients to tolerate. One possible solution is Merck's Tredaptive (nicotinic acid/laropiprant), which has the added agent, laropiprant, to reduce the flushing. Another is a new class of agents, cholesteryl ester transfer protein (CETP) inhibitors. Unfortunately, the first of these agents, Pfizer's torcetrapib, failed dramatically, raising safety questions about the entire class. However, several companies are continuing to work on CETP inhibitors, including Merck and Roche.

Asked about the tolerability of niacin, Dr. Taylor said, "Tolerability was very high for both (niacin and ezetimibe)… Tolerability tended to be higher for ezetimibe…Flushing is common with niacin, yet adherence to treatment, including titration to 2 g of niacin, and overall retention was very high …Patients faithfully participated in the trial…On a clinical plane, these are not trials that answer questions of tolerability …and they track with reported data on tolerability…The AHA has a clear statement that over-the-counter niacin is not a useful alternative to prescription niacin because the safety and viability is unknown. While niacin is available as an over-the-counter supplement, it is not advised that patients do that."

There is also another problem: there is no proof that raising HDL is beneficial. It seems almost intuitive that it is, but it isn't proven, and the experience with homocysteine makes some experts nervous. Elevated homocysteine emerged some years ago as a marker of adverse cardiac outcomes, and drugs were developed that could lower homocysteine, but AHA officials and experts insisted that it hadn't been proven that lowering homocysteine was beneficial. Outcomes trials were done, and, indeed, it turned out that lowering homocysteine is not helpful. Experts doubt the same thing will prove true with HDL, especially given the experience with niacin, which

raises HDL, but they aren't sure. Dr. Taylor commented, "Drugs are not licensed to raise HDL. Niacin is licensed on low-density lipoprotein (LDL) lowering and regression of atherosclerosis. It is an open question on the clinical effect of HDL raising with niacin, and that's why the ongoing AIM-HIGH study is needed."

Merck's Dr. Rossetti urged doctors to remember that "LDL (lowering) saves lives…The problem we have in front of us is more than 50% of people don't achieve the LDL goal, despite our having multiple statins…The idea of changing the practice of LDL lowering based on a very small biomarker study and (then) say it is better to raise HDL (is wrong)…I have no objection to trying niacin or something else when patients are at goal on LDL (<100)…but (raising) HDL remains to be fully validated."

Dr. Rossetti defended the safety of ezetimibe and urged people to look at the ARBITER-2 study before drawing conclusions about ARBITER-6, "There is massive evidence of the safety of our drug. It is very well tolerated, and there is evidence it lowers LDL…We have more than 16,000 patients who took ezetimibe in randomized clinical trials, more than 15,000 patients in IMPROVE-IT, with a DSMB monitoring them, plus multiple small studies bigger than ARBITER-6 with a total lack of imbalance (in safety)…For a small study like this to create a safety issue is almost unethical in my opinion."

Merck has its own niacin in development, Tredaptive. Dr. Rossetti said, "I think what is the big story here is that maybe we have a resurgence of the HDL hypothesis. That is really the big story for lipid management at this meeting…We believe Tredaptive will be a great drug – the best way for us to get people to use niacin because it is better tolerated, so we can get people to use a higher dose. Our (Tredaptive) dose is 2 g, and patients tend to tolerate it fairly well. Of the patients who currently accept niacin, only 10% get to a 2 g dose."

MERCK – positioned well if HDL-raising drugs get established

➢ Tredaptive

Merck officials at AHA were very upbeat about the company's cardiovascular pipeline, which has 8 late-stage programs, including Tredaptive, betrixaban, SCH-530348 (TRA), Kynapid (oral vernakalant for AFib), and anacetrapib. Dr. Rossetti said, "There is no other company with a CETP inhibitor and a best-in-class niacin in late-stage development, so if HDL comes back (as a key target), Merck will be positioned in a way to benefit in cardiovascular disease enormously. So, even though we staunchly believe in the safety and efficacy of ezetimibe, we shouldn't lose the fact that Merck is best positioned with HDL-raising drugs."

There were no new data on this at AHA, but Merck officials were trying to be sure it stayed on everyone's radar. Asked about the tolerability of Tredaptive, which has less flushing than extended-release niacin but no zero flushing, Dr. Rossetti said, "In clinical trials it is extremely rare to demonstrate a big difference in compliance and sticking to a medication. Patients in trials try hard to stick with the medications. But, overall, only 10% of patients on Niaspan achieve the high dose of 2 grams. The majority of (Niaspan) patients drop out entirely, and the ones who stay are at 500 mg to 1000 mg. We hear from the Tredaptive European launch that it is very well tolerated, and people are pretty happy and surprised by how well tolerated it is. In the first few weeks we see a marked blunting of flushing (with Tredaptive). The other difference is longer term. While Niaspan still causes three times the flushing of placebo, Tredaptive gets back to placebo level."

A cardiologist commented, "Niacin tolerability is a big issue with patients, so there will be interest in this." Another cardiologist said, "The good news for Tredaptive is that, if niacin does do very well, they actually got fully enrolled before the AIM-HIGH (niacin outcomes) trial, so you would think that those (Tredaptive) results will come sooner than AIM-HIGH, so it is a potential big win for the field if (Merck) can show that on top of statins and LDL in the range of 80 g/dL, you can get further significant improvement…The ACCORD [a large, National Institute of Health- (NIH) sponsored cardiovascular outcomes trial of fibrates] data were supposed to be at this meeting, and that was delayed until March 2010 (at the American College of Cardiology meeting), so we are assured there are no JUPITER-like effects [where AstraZeneca's Crestor (rosuvastatin) showed excellent benefits]."

➢ Anacetrapib

Dr. Rossetti said he is optimistic about this CETP inhibitor, which is proceeding with a Phase III trial.

ROCHE's dalcetrapib, a CETP inhibitor to raise HDL

New pre-clinical data were presented on dalcetrapib at AHA, showing it is safe and effective, at least in the early stages. Roche also announced the start of the two-year, 900-patient, Phase III, dal-PLAQUE-2 study of dalcetrapib in delaying, regressing, or preventing atherosclerosis progression. dal-PLAQUE-2 will use both IMT and IVUS imaging to measure the thickness of artery walls.

Roche also is conducting the 15,600-patient dal-OUTCOMES morbidity and mortality study to evaluate dalcetrapib's effects on the reduction of cardiovascular events vs. best standard of care. So far, more than 9,000 patients have been enrolled. The pre-clinical data were related to mechanism of action, molecular structure, binding site, and interaction with CETP. There were also data differentiating dalcetrapib and other CETP inhibitors. In an animal model, dalcetrapib binds to a unique site of CETP inducing a conformational change of CETP and promotes reverse cholesterol transport.

ANTIPLATELET AND ANTICOAGULATION AGENTS

ASTRAZENECA's Brilinta (ticagrelor) – more positive news

The key findings from the PLATO trial were presented at the 2009 European Society of Cardiology (ESC) meeting, but data from a pre-planned substudy of ST elevation myocardial infarction (STEMI) patients with planned PCI were presented at AHA, and the data looked similarly positive. In both PLATO and PLATO-STEMI, there was:

- A reduction in the composite of CV death, MI, or stroke.
- A reduction in MI and stent thrombosis.
- A reduction in total mortality.
- No increase in major bleeding.

In PLATO-STEMI, the number needed to treat (NNT) to avoid one primary endpoint was 59. Leading principal investigator, Dr. Gabriel Steg of France, said, "The results are very clear and actually very consistent with the overall trial results of the larger PLATO trial…The good news is that there was no sign of increased major bleeding regardless of how we defined it…The bleeding was absolutely identical in the two study arms."

The side effects to watch for with Brilinta are dyspnea and bradycardia. Dyspnea occurred more often with Brilinta in PLATO-STEMI, but Dr. Steg said, "It is mild, usually observed early in the course of therapy, and patients didn't discontinue…Granted, it was five times the rate with clopidogrel (Sanofi-Aventis/Bristol-Myers Squibb's Plavix), but it was still a very rare event…Dyspnea occurred in 1 in 8 or 9 patients, but it is mild, transient, and early in the course of treatment. After a few weeks or even a few days of treatment, it is gone. It (the dyspnea) is what we see with adenosine scans or echos. There is no abnormality of pulmonary function testing, no abnormality in lung morphology…So, while the dyspnea is there, patients will get used to this, like statins cause muscle pain and beta blockers may give cold fingers. It is there, a genuine side effect, more common than with clopidogrel, but mild, transient, and reversible." Dr. Robert Harrington of Duke Clinical Research Institute agreed, "There is a 4% increase in discontinuation in the ticagrelor group vs. clopidogrel over a year. That's it. And that is attributable to a difference in dyspnea. Virtually all of it is transient and goes away pretty quickly, leading to discontinuation in 1% or so of patients."

Dr. Steg also said bradycardia, pacemaker placement, syncope, and heart block were not a concern in PLATO-STEMI.

Asked about the lack of a benefit in North American patients – which is unlikely to matter to the FDA – Dr. Steg said, "North American patients are on the wrong side of the line. There has been a lot of speculation and questions about this. It is important to remember the North American group is rather small (~1,800 patients), and chance is a very, very possible explanation for this finding…I think there is nothing unique about North America, but with the company we have looked at potential explanations – body weight, BMI, different practice patterns, and different doses of aspirin. There is some very modest indication that aspirin dose may play a role, but that is still being explored. It would be excessive to say we have pinpointed the answer. I am personally dubious that the issue is aspirin." Dr. Harrington explained, "The challenge in sorting this out is the aspirin dose tracks very much by region. The only region using 325 mg is North America…We need further analytic work and mechanistic work at the bench top to see if there is interaction of different aspirin doses and ticagrelor." Dr. Clyde Yancy, AHA president, added, "Given the overall results, I think we should remain circumspect about the North American cohort until a lot more information is in hand."

The discussant, Lisa Jennings, PhD, from the University of Tennessee Health Science Center, suggested the findings look better than prasugrel (Lilly's Effient) but worries a little about the BID dosing, "While you can't always compare data from two different trials…you can see with prasugrel vs. clopidogrel, there was an increase in major bleeding, but with ticagrelor there was no increased risk of major bleeding. But this (ticagrelor) is BID, which might be a challenge in patients who are not fully compliant."

Asked about the reduction in total mortality, Dr. Steg said, "We don't come across a treatment that reduces all-cause mortality often, and when we find one, we should take a good look at it…The mortality

Results of the PLATO-STEMI Substudy of Brilinta

Measurement	Overall PLATO			PLATO-STEMI		
	Brilinta	Plavix	p-value	Brilinta	Plavix	p-value
Primary endpoint: Composite of death ***from vascular causes***, MI, or stroke	9.8%	11.7%	.0003	9.3%	11.0%	0.02
Death from any cause	4.5% (22% RRR)	5.9%	<0.001	4.9%	6.0%	0.04
Stent thrombosis – definite (by ARC)	1.3%	1.9%	0.009	1.6%	2.5%	0.01
Stent thrombosis – probable/definite (by ARC)	2.2%	2.9%	0.02	2.5%	3.6%	0.01
Stent thrombosis – possible/probable/definite (by ARC)	N/A	N/A	---	3.2%	4.4%	0.02
Major bleeding (TIMI)	7.9%	7.7%	Nss, 0.57	9.0%	9.3%	Nss, 0.63
Adverse events						
Dyspnea	13.8%	7.8%	<0.001	12.9%	8.3%	<0.0001
Discontinuation due to dyspnea	1.0%	0.3%	<0.001	0.5%	0.1%	0.0003
Bradycardia-related events	---	---	---	4.6%	4.9%	Nss, 0.57
Ventricular pauses ≥3 sec in first week	5.8%	3.6%	0.01	---	---	---

effect is seen overall and in STEMI patients…It does set ticagrelor apart from other oral platelet inhibitors because in previous trials some P2Y12s did reduce MACE or MI but not mortality. This mortality reduction is new and important quantitatively." He offered several possible reasons for the mortality finding:

- "It could be due to chance, though that is a small possibility."
- "It could be due to reduced bleeding or lack of increased bleeding…These patients were randomized and entered into the trial somewhat early in the treatment of ACS (acute coronary syndrome), which is different from TRITON, where patients first had to undergo angiography. In a sense, there is a selection for survivors in TRITON…Here patients are randomized earlier."
- "Most speculative but most tantalizing is the possibility that ticagrelor is probably not solely a platelet inhibitor. It is structurally very similar to adenosine…which explains the side effects of dyspnea and bradycardia …This is very speculative, but other agents that reduced MI have not reduced mortality, but we see it here, begs the question of whether there are other factors at play."

Were the data analyzed based on clopidogrel dose? Dr. Steg said the findings are very consistent for both doses of clopidogrel (300 mg and 600 mg).

The day after AHA, AstraZeneca filed Brilinta with the FDA, so the PDUFA date will be September 2010.

BOEHRINGER INGELHEIM's Pradaxa (dabigatran etexilate), an oral direct thrombin inhibitor – results holding up

The results of the RE-DEEM trial confirmed the benefits of dabigatran that were seen in the RE-LY trial at the ESC meeting in September 2009. RE-DEEM was a 6-month, dose-finding, double-blind, placebo-controlled, Phase II study comparing four different doses of dabigatran in 1,861 ACS patients. All patients also received aspirin plus clopidogrel.

Dabigatran Results in RE-DEEM Trial

Measurement	Dabigatran				Placebo
	50 mg BID n=369	75 mg BID n=368	110 mg BID n=406	150 mg BID n=347	n=371
Primary endpoint: Major bleeding and clinically relevant minor bleeding	3.5%	4.3%	7.9%	7.8%	2.4%
Major bleeding	0.8%	0.3%	2.0%	1.2%	0.5%
Clinically relevant minor bleeding (by ITT)	9%	14%	23%	23%	7%
Composite of CV death, non-fatal MI, and stroke	4.6%	4.9%	3.0%	3.5%	3.8%
Serious adverse events	9%	8%	9%	6%	9%
Discontinued study treatment	20%	16%	19%	18%	14%
Discontinued study treatment due to adverse events	9%	8%	12%	10%	8%
Fatal bleed	0	0	1 patient	0	1 patient
ICH bleed	0	0	0	0	0

Asked about the possible MI signal in the RE-LY trial, Dr. Jonas Oldgren of Sweden, the RE-DEEM principal investigator, said, "There is a very low event rate for clinical events …MI might be higher with dabigatran…but there is no significant difference. It's only a handful of events (in RE-DEEM)…We don't think it reveals anything about the MI issue from RE-LY…In RE-LY, there was a small increase, but that is compared to warfarin, which is an excellent drug in preventing MI…so warfarin might be a little better than dabigatran in preventing MI…From RE-DEEM we cannot draw any conclusions."

Dr. Oldgren concluded, "All dosage levels are promising… The top two doses (110 mg BID and 150 mg BID) had more bleeding…but the major bleeding increase was <1%...so we think all doses are safe despite this dose-dependent increase… Dabigatran up to 150 mg BID can be used on top of dual antiplatelet therapy with a modestly increased bleeding risk. This is of relevance for atrial fibrillation (AFib) patients after ACS and stenting."

The discussant, Dr. Elaine Hylek of Boston University Medical Center, noted that the addition of dabigatran to dual-antiplatelet therapy results in a dose-dependent increase in bleeding, but ISTH (International Society on Thrombosis and Haemostasis) major bleeding is "acceptably low." However, she emphasized that the small number of events precludes a definitive statement on efficacy. She also offered some cautions:

- The time course and reasons for the nearly 20% discontinuation rate need to be better understood. "Clinically relevant non-major bleeding is not to be dismissed because this is often the reason patients come off the drug or physicians get skittish and take patients off the drug. The FDA is concerned with all categories of bleeding."
- Care should be taken in extrapolating the RE-DEEM data in ACS patients to AFib patients because of an ~10-year mean age difference between the two patient populations.
- Longer term (two- to 5-year) safety is still a question.
- Will clopidogrel be the right comparator as new, more potent antiplatelet drugs get approved?
- Is there an adequate rationale or unmet need for triple therapy for patients?

LILLY's Effient (prasugrel)

New AHA/ACC guidelines should make it easier for cardiologists to decide to use prasugrel. The guidelines recommend a 60 mg loading dose of prasugrel as an alternative to clopidogrel for patients with STEMI who undergo primary PCI. The guideline writers determined, "Despite the increase in bleeding, the net clinical-benefit endpoint, which included all-cause mortality, ischemic events, and major bleeding events, favored prasugrel."

However, the guidelines also say prasugrel should not be used as part of dual antiplatelet therapy in patients with a history of stroke or transient ischemic attack (TIA).

The new guidelines were presented at the AHA meeting and simultaneously published in three major medical journals: ***Circulation: Journal of the American Heart Association***, ***Journal of the American College of Cardiology***, and ***Catheterization and Cardiovascular Interventions***.

THE MEDICINES COMPANY's cangrelor – 2 failed trials but investigators still see potential

In May 2009, The Medicines Company halted two large, multicenter, randomized, double-blind, double-dummy, international Phase III trials of cangrelor, a fast-acting intravenous P2Y12 platelet inhibitor (which had been licensed from AstraZeneca) after interim analyses of the data concluded the studies were futile. At AHA, the results of both CHAMPION-PCI and CHAMPION-PLATFORM were presented in detail and simultaneously published in the ***NEJM***.

Both trials were non-inferiority as well as superiority studies, and both failed on superiority but met the criteria for non-inferiority, which was a 50% margin, but experts doubted that this degree of non-inferiority would be viewed by the FDA as approvable. One expert predicted that the company will submit cangrelor to the FDA based on these data. And the investigators of both trials as well as other experts agreed that The Medicines Company shouldn't give up on cangrelor. They see a role for it, although that is likely to be a niche role.

The key differences between the two trials were the time when cangrelor was administered and the inclusion of STEMI patients.

Comparison of CHAMPION Trials

Measurement	CHAMPION-PCI	CHAMPION-PLATFORM
Design	Superiority vs. placebo and standard of care	
Patients	9,000	6,400
Type of patients	Stable angina Unstable angina NSTEMI STEMI	Stable angina Unstable angina NSTEMI
Comparator	Clopidogrel 600 mg at start of PCI	Clopidogrel 600 mg at end of PCI
Event rate	7%	7.7%
Effect size	22.5%	25%

➢ **CHAMPION-PCI** was an 8,877-patient, active-control trial of 600 mg cangrelor vs. oral clopidogrel (600 mg) administered prior to PCI in ACS patients. Cangrelor was given 30 minutes before PCI and continued for 2 hours after PCI, and the clopidogrel was given 30 minutes before PCI only. The study showed no benefit to cangrelor on the composite primary endpoint, and not even a trend on any of the components of that composite. Furthermore, there was a trend to an increase in major bleeding with cangrelor.

In the ***NEJM*** article, Dr. Harrington and colleagues called the lack of superiority of cangrelor over clopidogrel "unexpected," but they held out hope for cangrelor as a "bridging" agent for patients who require platelet blockage but cannot take an oral agent. At AHA Dr. Harrington commented, "Using standard non-inferiority methods, we estimate that cangrelor preserves 62.4% (of the effect of clopidogrel 600 mg vs. placebo."

Dr. Alan Michelson of the University of Massachusetts Medical School discussed the CHAMPION-PCI results at AHA, offering several possible reasons why cangrelor did not demonstrate a clinical benefit over clopidogrel:

1. The 600 mg dose of clopidogrel. In the TRITON trial of prasugrel, the clopidogrel dose was 300 mg, and in the PLATO trial of Brilinta both 300 and 600 mg doses were used. Dr. Michelson said this might be relevant in light of the OASIS-7 findings that 600 mg clopidogrel had benefits over 300 mg.

CHAMPION-PCI Results with Cangrelor

Measurement	Cangrelor n=4,433	Clopidogrel n=4,444	p-value
Results at 48 hours (*modified intent-to-treat population*)			
Primary endpoint: Composite of all-cause death, MI, and ischemia-driven revascularization at 48 hours	7.5%	7.1%	Nss, 0.59
MI	7.1%	6.6%	Nss, 0.36
All-cause death	0.2%	0.1%	Nss, 0.42
Ischemia-driven revascularization	0.3%	0.6%	Nss, 0.10
Stent thrombosis	0.2%	0.3%	Nss, 0.34
Stroke	0.2%	0.2%	Nss, 0.77
Q-wave MI	0.1%	0.3%	Nss, 0.12
Safety at 48 hours			
Hematoma at puncture site ≥5 cm	1.9%	1.7%	Nss, 0.48
ICH	<0.1%	0	---
Bleeding requiring surgery	<0.1%	<0.1%	Nss, 1.00
Ecchymosis	6.5%	5.4%	**0.03**
Oozing at puncture site	9.1%	7.3%	**0.002**
Blood transfusion	1.1%	1.0%	Nss, 0.68
Major bleeding (ACUITY criteria)	3.6%	2.9%	Nss, 0.06
Major bleeding (TIMI criteria)	0.4%	0.3%	Nss, 0.39
Exploratory endpoints			
Composite of all-cause death, Q-wave MI, and ischemia-driven revascularization	0.6%	0.9%	Nss, 0.14
Composite of all-cause death, Q-wave MI, and stent thrombosis	0.5%	0.6%	Nss, 0.42

2. The definition of MI.
3. The transition of patients to clopidogrel. There was no transition in either TRITON or PLATO. The effect wears off quickly with cangrelor.

➢ **CHAMPION-PLATFORM** was a 5,362-patient trial comparing cangrelor (30 µg/kg bolus, then an infusion of 4 µg/kg/minute) to placebo during PCI, with a minimum infusion duration of 2 hours and a maximum duration of 4 hours. A 600 mg dose of clopidogrel was given to all patients – at the end of the cangrelor infusion for cangrelor patients and at the end of the procedure for placebo patients. The study showed no benefit to cangrelor on the primary endpoint, but cangrelor did beat placebo on two secondary endpoints – all-cause death and stent thrombosis. However, once again, bleeding was higher with cangrelor, and in this case the difference was statistically significant, though it did not lead to an increase in transfusions.

In the ***NEJM*** article, Dr. Deepak Bhatt of the Boston VA and colleagues concluded that the mixed findings left open the door for further study of cangrelor, "Taken together, the two CHAMPION trials may provide insight into the optimal timing of periprocedural antiplatelet blockade with clopidogrel …It appears that the 600 mg loading dose of clopidogrel may provide incremental benefit when given at the start of the procedure vs. only at the end, though this conclusion remains speculative. However, even when clopidogrel is given at the start of the procedure, the additional antiplatelet blockage conferred by cangrelor may provide clinical benefit."

CHAMPION-PLATFORM Results with Cangrelor

Measurement	Cangrelor n=2,654	Clopidogrel n=2,641	p-value
Results at 48 hours (*modified intent-to-treat population*)			
Primary endpoint: Composite of all-cause death, MI, and ischemia-driven revascularization at 48 hours	7.0%	8.0%	Nss, 0.17
MI	6.7%	7.2%	Nss, 0.42
Secondary endpoint #1: All-cause death	0.23%	0.68%	**0.02** *
Ischemia-driven revascularization	0.7%	0.9%	Nss, 0.44
Secondary endpoint #2: Stent thrombosis	0.19%	0.61%	**0.02** **
Stroke	0.3%	0.2%	Nss, 0.57
Q-wave MI	0.2%	0.3%	Nss, 0.25
Safety at 48 hours			
Hematoma at puncture site ≥5 cm	4.3%	2.7%	**0.001**
ICH	0.1%	<0.1%	Nss, 0.57
Bleeding requiring surgery	<0.1%	<0.1%	Nss, 1.00
Ecchymosis	3.6%	2.2%	**0.002**
Oozing at puncture site	4.7%	3.4%	**0.02**
Major bleeding (ACUITY criteria)	5.5%	3.5%	**<0.001**
Major bleeding (TIMI criteria)	0.2%	0.3%	Nss, 0.17
Exploratory endpoints			
Composite of all-cause death, Q-wave MI, and ischemia-driven revascularization	0.9%	1.6%	**0.03**
Composite of all-cause death, Q-wave MI, and stent thrombosis	0.5%	1.3%	**0.003**

* Not significant at 30 days ** Significant at 30 days

At AHA, Dr. Bhatt emphasized the benefits in terms of stent thrombosis and mortality, "On stent thrombosis…this is the real thing…On mortality, the curves parallel what happened in stent thrombosis. In the first 48 hours, there is a significant reduction. The event rates from Days 2-30 are not statistically different, and there is no evidence of any rebound…The lower rates of stent thrombosis and mortality are biologically plausible…The effect on 'harder' endpoints but not periprocedural MI is intriguing and calls into question the definition of periprocedural MI used…We do believe further study of cangrelor is warranted."

In a ***NEJM*** editorial accompanying the data from both these trials, two German cardiologists, Dr. Adnan Kastrati and Dr. Gjin Ndrepepa, suggested that cangrelor should be studied further to find "more suitable clinical niches" where it might be beneficial and provide "more appropriate approaches to its use." Perhaps, they said, cangrelor should be given "immediately after diagnostic angiography established an indication for PCI," though newer oral agents may obviate the need for cangrelor in ACS patients.

Dr. David Faxon of Brigham & Women's Hospital, a former AHA president, discussed the findings, saying, "Interpreting CHAMPION-PLATFORM as a negative trial is misleading. I think they were unlucky." He also offered several reasons why the trial may have missed the primary endpoint:

- The primary endpoint was lower than expected in the control arm.
- The duration of cangrelor infusion (2.1 hours) may have been too short.
- The crossover to clopidogrel may have resulted in inadequate platelet inhibition.
- The time from admission to PCI was "remarkably" short (6 hours), which may have made it difficult to interpret periprocedural MI.
- The definition and determination of periprocedural MI may not have been accurate enough.

With Brilinta on the near horizon, is there a need for cangrelor? The cangrelor investigators think so. Dr. Harrington said, "Ticagrelor and cangrelor came out of the same platelet inhibitor development effort at AstraZeneca. The cangrelor Phase II studies were sponsored by AstraZeneca before The Medicines Company got the rights…If you look at the structure of the two, you will note a lot of similarities. Ticagrelor has some adenosine-

like features, and cangrelor is an ATP analog…The major advantage of cangrelor is that it is available (via) IV…What can cangrelor add? The answer is we don't know. Will delivering a more rapidly acting agent in the acute setting, where not everyone is able to take an oral, (be beneficial)? If cangrelor were commercially available, I think there is a lot of interest in the interventional cardiology community…(because of) the rapidity of onset…There are some provocative findings (in PLATFORM), particularly in regard to stent thrombosis and perhaps on death in the first 48 hours…that would get the attention of the interventional community who are looking for a rapidly acting platelet inhibitor…The caution is we have two trials that didn't meet the primary endpoint and were stopped early…but the data are provocative." Dr. Faxon agreed comparing the difference between cangrelor and clopidogrel to that between IV heparin and fondaparinux or enoxaparin, "This drug (cangrelor) comes off rapidly, so…you can turn it off when you have to go to the operating room. I think it has the advantage of being much more flexible in management." But Dr. Elliott Antman of Brigham & Women's Hospital and Harvard Medical School suggested that cangrelor now should be tested against Effient and Brilinta.

MERCK

- **SCH-530348 (TRA), a thrombin receptor antagonist or protease activated receptor-1 (PAR-1) inhibitor – Phase III trial fully enrolled**

During AHA, Merck announced that it had reached its target of ≥26,000 patients in the global, randomized, double-blind, placebo-controlled, multinational Phase III TRA-2°P-TIMI-50 trial of TRA. Merck now prefers that TRA be called SCH-530348. In this CV outcomes study, SCH-530348 is being compared to placebo in patients with a prior MI or stroke or who have peripheral arterial disease to see if it will prevent major cardiovascular events when added to current antiplatelet regimens (either aspirin alone or aspirin plus an ADP inhibitor). Dr. Eugene Braunwald, chairman of the TIMI Study Group, which is conducting the trial, said it is "the largest and most rapidly enrolling trial in our 25-year history."

The other ongoing pivotal Phase III trial is TRA-CER, a 1-year, multinational, randomized, placebo-controlled, double-blind study in patients with non-STEMI ACS. Patients are being randomized to standard medical care (including aspirin or clopidogrel) ± SCH-530348 (40 mg loading dose, followed by a 2.5 mg maintenance dose). The primary endpoint of TRA-CER is the composite of cardiovascular death, MI, rehospitalization for ACS, urgent coronary revascularization, or stroke. Merck's Dr. Rossetti said more than 8,000 of the planned 12,500 patients have been enrolled, "We have a good shot of finishing in 2011. That is a very exciting mechanism. It is likely to give us additional benefits with small or no incremental bleeding…TRA is a major priority (for Merck).

- **Betrixaban – data coming soon**

Merck is developing this oral direct Factor Xa inhibitor with Portola. Phase IIb data should be reported soon. Dr. Rossetti said the EXPLORE-Xa trial is fully enrolled and should be complete in mid-December 2009, with results expected in 2010. Dr. Rossetti said dose selection will be critical, "If we picked the right dose, it will be a big winner. We are not convinced all the ones (Factor Xas) ahead of us have picked the dose correctly, and they may have trouble with bleeding in some of their studies…We are very excited about betrixaban …The (Portola and Merck) teams are working very, very well together. It is a very exciting molecule. We won't be the first-in-class, but I think we have the best Factor Xa for many reasons. We might not be competitive on timing, but we can be competitive on best-in-class…Prevention of stroke in AFib is very serious, and warfarin is the therapy, but it is very difficult to take, and 50% of patients don't bother taking it… Renal excretion with betrixaban is minimal, so this will be the drug of choice for that segment (of patients). This is a real QD drug, and it could have less bleeding risk."

Dr. Rossetti said Portola has developed a "sophisticated thrombin generation assay" that still needs to be validated but looks to be a good tool to understand the pharmacodynamics of Factor Xas and perhaps direct thrombin inhibitors, "I don't expect it to be used to monitor a patient's coagulation status, but it would be very helpful for drug development."

PLATELET RESISTANCE TESTING – not all tests are created equal

Up to 36% of patients are less responsive to clopidogrel, so the idea of using platelet function tests to identify these patients has appeal. At AHA, Dutch researchers presented the results of the POPular trial, a head-to-head study comparing five different methods of measuring platelet function, and they found that Accumetrics' VerifyNow, Helena Laboratories' Plateletworks, and light transmittance aggregometry (LTA) – but not Diomed's Impact-R or Siemen's PFA-100 – are able to identify patients at higher risk for death, MI, stent thrombosis, or stroke. However, none of the tests were able to identify patients at risk for TIMI major or minor bleeding.

Dietmar Trenk, PhD, of Germany discussed the findings, noting that platelet aggregation appears suitable for clinical decision-making but adhesion methods are not useful. He also pointed out that two other methods of measuring platelet function − Vasodilator-stimulated phosphoprotein (VASP) and multiple electrode platelet aggregometry − were not included in this study.

What will it take for these tests to gain widespread use? Four things are clouding the outlook: lack of a large outcomes trial, concern over variability in the different tests, newer medications coming, and cost. Dr. Jurrien Berg, a POPular investigator, said, "The trials so far have been relatively small and only one test has been used, so we really don't know the best test to predict clinical outcome…Most of the (available) tests are not used in clinical practice. It is still for research. This study shows some of the tests are predictive, but we have to wait for randomized clinical trials using them to see if they

Comparison of Platelet Function Tests

Test	Measures	Type of test	Comments	Number of patients	Primary endpoint (survival)*	Odds ratio
LTA – 5 µmol/L and 20 µmol/L	Aggregation in platelet-rich plasma	Laboratory	Time consuming, must be done in lab	1,049-1,051	<0.0001	2.05-2.09
VerifyNow	Aggregation based, whole blood	Fully automated bedside test	Very quick and truly automated	1,052	<0.0001	2.53
Plateletworks	Aggregation, single platelet count, whole blood	Semi-automated bedside test	Can be done in cath lab but laborsome and highly time-dependent (must perform within 10 minutes)	606	0.002	2.22
Impact-R and R-ADP	Cone plate analyzer, shear-induced platelet adhesion, whole blood	Laboratory	Very laborious; with extensive sample handling	905-910	Nss, 0.17 and 0.22	1.11-1.34
PFA-100 (both COL/ADP and Innovance)	Shear-stress-based, whole blood	Bedside	Fully automated and can be done in cath lab	588-812	Nss, 0.42 COL/ADP 0.001 Innovance	0.77 COL/ADP 1.59 Innovance

* Survival free of death, non-fatal MI, definite stent thrombosis, and stroke

will change outcomes for patients…LTA is used the most often, but not in a clinical setting…VerifyNow (use is) widespread but as a research tool." Dr. Michelson added, "This is a very controversial area. These tests are not being used broadly. The one most commonly used is VerifyNow because it is true point-of-care, which makes it easy to use…LTA is used, but it is somewhat more cumbersome. The other tests studied (in POPular) are hardly used at all – Plateletworks and Impact not at all − and PFA-100 was previously shown not beneficial in this area."

Variability

There are also concerns about the variability in the test results. Dr. Berg said, "VerifyNow is one of the best tests, but the correlation of the tests is not good. VerifyNow doesn't correlate with Plateletworks. On the other hand, you don't need trained personnel to do VerifyNow, and it has the best correlation with LTA…Plateletworks and VerifyNow have different results, and that is very hard to explain."

Outcomes studies

Experts insisted that these tests will not find wide adoption until and unless a large clinical trial shows a beneficial effect on outcomes. The GRAVITAS trial is underway, with outcomes data expected in 2010. GRAVITAS is a double-blind, placebo-controlled, randomized study in PCI patients getting a drug-eluting stent. The trial is testing all patients for Plavix resistance, then randomizing resistant patients to either standard (75 mg daily) or double-dose (150 mg daily) Plavix. The primary endpoint is MACE (major adverse cardiac events − CV death, non-fatal MI, or ARC definite/probable stent thrombosis) at 6 months. Comments included:

- *Dr. Yancy, AHA President:* "High platelet inhibition or high platelet resistance is something important in this field, and we need to grow the database and see how it is affected by the different compounds…We need more data."
- *Dr. Berg:* "If you can use one of these tests and can change medication to, for instance, prasugrel, that would (increase use)…We need a large Phase III trial to show benefit before we adopt a test in the cath lab…Should you just put all patients on prasugrel and not test?...No, because studies such as the platelet substudy of TRITON say the variability of platelet function is less, but there is still variability, so even with agents like prasugrel, we will have to use a platelet function test to adjust medications…GRAVITAS has to be positive for VerifyNow to be used commonly, but that is a well-powered trial…Even if GRAVITAS is negative but shows a positive trend, platelet function testing will be adopted."
- Dr. Faxon: "Even GRAVITAS won't answer the question. We need a lot of other information first…These tests have a 16% predictive value, which is really, really bad…The additional predictive value of these tests (for individual patients) is low. They provide no additional information…We currently use the test (VerifyNow) in our cath lab but in a very restricted way."
- *Dr. Antman:* "There isn't a single platelet study that is giving us a number to achieve, like a range of 2-3 for international normalized ratio (INR) with warfarin, and GRAVITAS is not looking at titrating a dose to a platelet level. It is not a tailored treatment…And no platelet test predicts bleeding."

Newer medications, such as Brilinta

Dr. Berg insisted that even if Brilinta, for example, is approved, there will be a need for testing, but perhaps less need, "There is still variability in response, and compliance will be an issue with twice-a-day ticagrelor." Dr. Antman said, "It is possible we won't need testing if a really potent agent gets approved." Dr. Faxon added, "The new agents look good enough that we won't need the tests except in very rare cases."

Cost

Dr. Berg said cost is an issue. VerifyNow, he said, costs about $75 (50 euros). When Plavix goes generic, that could make testing more cost-effective, Dr. Berg speculated. However, Dr. Antman said the cost of the test would have to be figured into the cost of generic Plavix, so adding the cost of the test to generic clopidogrel "makes the equation not as favorable."

ANEMIA

AMGEN's Aranesp (darbepoetin alfa) – more bad news

The main results of TREAT were presented at Renal Week in October 2009 by Dr. Marc Pfeffer of Harvard Medical School and Brigham & Women's Hospital and simultaneously published in the ***NEJM***, but there was another full presentation at AHA, which brought the bad news message to an additional group of doctors.

In addition, a pre-specified subgroup analysis of the TREAT trial presented at AHA found that mortality was higher in stroke survivors who took Aranesp than placebo: 47% of the stroke survivors taking Aranesp (109 of 231 patients) had a cardiac event or died vs. 37% of the placebo group (79 of 216 patients).

TREAT found that intensive treatment with Aranesp was no more effective – and far less safe – than placebo in chronic kidney dialysis patients with anemia and Type 2 diabetes. TREAT was a 4,038-patient, randomized, double-blind, placebo-controlled trial at 623 sites in 24 countries evaluating the effect of Aranesp vs. placebo. Amgen, which sponsored the trial, hoped it would demonstrate that, with a hemoglobin (Hgb) target of 13 g/dL, Aranesp would lower the risk of death and non-fatal CV events (non-fatal MI, congestive heart failure, stroke, or hospitalization for MI). It did not. While Aranesp improved hemoglobin, it did not lower the risk of CV events (death, MI, MI ischemia, heart failure, or stroke), which were 31.4% with Aranesp vs. 29.7% with placebo (Nss, p=0.41), the risk of stroke was increased (5.0% vs. 2.6%, p<0.001), and Aranesp was associated with a ***higher*** rate of transfusions and cancer.

The AHA discussant, Dr. Mary Cushman of the University of Vermont, said one option would be for doctors to give up on erythopoietin-stimulating agents (ESAs), but she dismissed that idea, noting that "fatigue can be devastating."

When to transfuse

The FOCUS study found that an aggressive transfusing approach in elderly surgery patients is not better than a more restrictive approach. Cardiovascular outcomes were not better in patients who got a transfusion when their hemoglobin (Hgb) was ≤10 g/dL vs. only transfusing patients who were either symptomatic or had Hgb <8 g/dL.

Dr. Jeffrey Carson of the University of Medicine and Dentistry of New Jersey's Robert Wood Johnson Medical School, the principal investigator for FOCUS, said, "Post-operative anemia is common after major surgery. There is no doubt that blood transfusions are beneficial to patients who are severely anemic with Hgb levels <5-6 g/dL. However, there are few studies and no large, randomized trials such as this one that investigated the effect of transfusion in asymptomatic patients with moderate anemia (8-10 g/dL)…We found no statistically significant difference between groups…Many clinicians base their decision only on the Hgb level. This trial seems to say that you need to look at every patient individually, to evaluate their symptoms."

FOCUS enrolled 2,106 patients with an average age of 81.6 undergoing hip fracture repair surgery at 47 medical centers in the U.S. and Canada. When patients' Hgb fell <10 g/dL, they were randomized to either blood transfusions to maintain Hgb >10 g/dL or to only receive transfusions if their hemoglobin fell <8 g/dL or if they had symptoms of anemia such as chest pain, low blood pressure, rapid heartbeat unresponsive to a fluid challenge, or congestive heart failure.

6-Year Results of FOCUS Trial

Measurement	Transfusion at Hgb <10 g/dL n=1,007	Transfusion in symptomatic patients or Hgb <8 g/dL n=1,009
Transfused patients	97%	41.5%
Total units transfused	1,866 units	652 units
MI	2.3%	3.8%
Death (in hospital)	2.0%	1.4%
MI/death/unstable angina	4.3%	5.2%

LUITPOLD's Injectafer/Ferinject (ferric carboxymaltose) – IV iron beneficial even if heart failure patients not anemic

In March 2008, the FDA rejected Injectafer, citing concerns about the risk:benefit ratio in postpartum women and women with heavy menstrual bleeding, the target population. However, a study presented at AHA and simultaneously published in the ***NEJM*** suggests that there may still be a role for this drug – ***or other IV irons*** − in a different patient population – heart failure patients even those not anemic.

The FAIR-HF trial, sponsored by Vifor Pharma, found that IV iron improved symptoms, functional capacity, and quality of life in chronic heart failure patients with iron deficiency – whether or not they had anemia. And the side effects were described as "acceptable."

FAIR-HF was a 459-patient, randomized, double-blind, multi-center trial in New York Heart Association (NYHA) Class II or III patients with left ventricular ejection fraction (LVEF) ≤40%-45%, iron deficiency (measured by ferritin level), and hemoglobin 9.5-13.5. Traditional thinking has been that iron deficiency is only clinically meaningful if the patient also has

anemia, an assumption that this trial refutes. The study found that IV iron:

- Rapidly increased ferritin levels to normal.
- Modestly increased hemoglobin in anemic patients but not in patients without anemia.
- "Convincingly" improved the quality of life measures.
- Was effective within 4 weeks, with the effect maintained out to 24 weeks.
- Was beneficial in patients with anemia and in those without anemia (hemoglobin <12).

The European investigators, led by Dr. Stefan Anker of Germany, concluded that IV iron deficiency is a valid independent therapeutic target. They also called for further studies to figure out why treating iron deficiency can improve symptoms even without changing hemoglobin. Dr. Anker said, "Using the definition of functional iron deficiency, we estimate 20%-35% of ambulatory heart failure patients have iron deficiency." However, Dr. Anker and his colleagues did not recommend IV iron for heart failure patients with iron deficiency whose hemoglobin is <13.5 g/dL, though they thought that should be studied.

In a ***NEJM*** editorial accompanying the results, Dr. G. William Dec of Massachusetts General Hospital concluded the study suggests IV iron "may have merit in patients with moderately symptomatic heart failure and documented iron deficiency." However, he pointed out several limitations to the study, including:

- The dropout rate (8.6% for IV iron, 12.9% for placebo).
- Subjective and "less convincing" primary endpoints.
- Too few patients with mild symptoms (NYHA Class II).
- The small symptomatic benefit in patients with anemia.
- No information on whether oral iron would be a cheaper but equally effective alternative.

FAIR-HF 24-Week Results of IV Iron in Heart Failure Patients

Measurement	IV iron n=304	Placebo (saline) n=155	p-value
Primary endpoint #1: Patient Global Assessment much or moderately improved at Week 24	50%	27%	<0.0001
Primary endpoint #2: NYHA Class I-II at Week 24	47%	30%	<0.0001
Secondary endpoint #1: 6-minute walk	Up 39 meters	Up 8 meters	<0.001
Secondary endpoint #2a: EQ-5D Visual analog scale (VAS)	Up 9 points	Up 3 points	<0.001
Secondary endpoint #2b: Kansas City Cardiomyopathy questionnaire	Up 14 points	Up 6 points	<0.001
Safety			
Hospitalizations for cardiac reasons	10.4%	20.0%	Nss, 0.08
Hospitalization for worsening heart failure	4.1%	9.7%	Nss, 0.11
GI disorder	16.9%	6.9%	Nss, 0.06
Premature discontinuation	5.3%	9%	---

Asked about the implication for other injectable irons, Dr. Anker said, "We have a rule in iron: you shouldn't assume a class effect until you have a proven class effect, but I would still warn that considering safety, you really should do a trial before using any agent in heart failure, and here we have results with ferric carboxymaltose."

Asked about the validity of iron as a treatment target in heart failure patients, Dr. Marvin Konstam of New England Medical Center in Boston said, "Based on these results, I would say yes…It is fascinating to think the iron itself is a key therapeutic element, so I am pretty interested in (these) results." Another expert said, "This is intriguing and thought-provoking…We know the association between anemia and fatigue, cognition, reduced quality of life, change in LV (left ventricular) size. What we don't know is if it is the correction of anemia or the iron itself…So, it is intriguing…But there are things I would be interested in evaluating. If it is the iron itself, let's do mechanistic studies and see if it is iron replacement that is associated with increased exercise capacity, patient outcomes, and LV remodeling, etc."

Asked what the development plans are for this drug, Dr. Anker said, "This was a Phase III trial for symptom improvement. It absolutely was not a pivotal trial for morbidity and mortality. If I were the company and had unlimited funds…I would consider strongly doing an outcomes study…but that is far beyond what I can decide."

Asked what the mechanism of action might be for the positive results with IV iron, Dr. Anker said, "Mitochondria need iron to use oxygen to generate energy and muscle function… Cardiac and skeletal muscle may need iron…Mitochondria need iron."

MISCELLANEOUS

LILLY's Cialis (tadalafil) – a possible new use in Type 2 diabetes

Researchers at Virginia Commonwealth University (VCU) presented mouse data at AHA suggesting that Cialis may be beneficial for glucose control in Type 2 diabetics. So far, these are investigator-led studies, but that's how Pfizer's Viagra/ Revatio (sildenafil) got its start in pulmonary arterial hypertension (PAH). The VCU researchers plan to continue work on Cialis in Type 2 diabetes. They pointed out that Cialis is approved for daily use, and they insisted that it would not be unreasonable to expect patients to take daily Cialis for diabetes.

DEVICES

ANGINA

As many as 16.5 million Americans have stable angina, and 500,000 more are diagnosed each year. However, Dr. William Kraus of Duke University School of Medicine called the diagnosis of angina "abysmal." A complex variety of tests are used to diagnose angina, but Dr. Kraus said that these tests "have significant variability in interpretation, even within institutions, and some patients are not good imaging candidates. And there are obvious concerns over radiation and contrast (agent) exposure…It would be nice to have a test that gives us a good indication of the likelihood of a patient having angina."

CARDIODX's Corus CAD, a PCR gene expression test for coronary artery disease (CAD)

Corus CAD is an algorithm based on an assay of 23 genes in peripheral blood that purportedly can diagnose obstructive CAD in non-diabetic patients, factoring in age and gender. It is a CLIA-certified test and is currently available in at least nine states through the company's California lab, and the company plans to expand to other states in 2010.

The test costs $1,195, but under an introductory special, the company is guaranteeing that patients will not have to pay more than $75 out-of-pocket and is offering to file the insurance claim for patients. Asked if insurance companies are covering the test, CardioDx medical affairs director, Dr. Hsiao Lieu of the University of California, San Francisco, said, "A few are paying. There is no official coverage policy, but a few carriers are paying." He also said the company is working on collecting cost-effectiveness data as well as outcomes data. The outcomes data will come from an ~12,000-patient study that is just beginning, which will use Corus CAD in a subgroup of patients.

At AHA, the results of the PREDICT trial, a validation study of Corus CAD, were presented. A second validation study, COMPASS, is planned, and CardioDx is "in discussions with a big (physician) group to run it."

PREDICT was a multicenter trial in which patients underwent non-invasive imaging, then blood collection, followed by catheterization and coronary angiography, with a core lab reading the results. Patients (symptomatic and asymptomatic) were enrolled who had suspected CAD but had not been previously diagnosed and did not have an acute MI.

The final Corus CAD gene algorithm is multifactorial, using particular genes with coefficient that are put into the final score. The genes are gender-specific and age-specific, depending on coronary risk factors, and the assay incorporates genes from leukocytes as well as gene expression changes within a given cell type. One comparator was the Diamond-Forrester (DF) scoring system for the presence of obstructive CAD, a system published in 1979 and validated in 1981. Dr. Kraus said, "It (DF) represents the most significant clinical model and is underutilized (to reclassify patients) in clinical practice, which is unfortunate." In addition to the Diamond-Forrester scoring system, Corus CAD was compared to the Framingham risk score (FRS) and to myocardial perfusion imaging (MPI).

According to Dr. Kraus, even when the other tests indicated a high likelihood of coronary artery disease, only 50% had significant coronary disease according to Corus CAD.

Even key investigators aren't using Corus CAD much if at all.

- The principal investigator was Dr. Eric Topol of Scripps Research Institute, but he reportedly isn't using Corus CAD.
- Dr. Kraus and other Duke cardiologists aren't using it often. Dr. Kraus said, "We are using it but not extensively, not as extensively as the company would like. I am a very aggressive treater. If you are my patient and have high cholesterol, and everything else is in the ones (low), I will still treat you because medications and risk factor modification, no matter how minor, will benefit you. So, I don't use classification schemes as much as some others."
- Dr. Lieu said it isn't being used at UCSF, "I haven't had a chance to convince them. The problem at big academic centers is that you need to go through committees. Right now, we are targeting private practices – the sites that used it in the PREDICT trial…The drawback at UCSF is they spent a lot of money on nuclear equipment, and they get paid for it, so they don't want to give up a revenue stream…Private interventional cardiologists don't want to cath normal patients, so they are using the test to eliminate patients who don't need catheterization."

The key market for Corus CAD is not cardiologists, Dr. Kraus said, but primary care physicians, "It is not a cardiology thing. Primary care doctors see 15 patients in a morning and half have chest pain. They wonder, 'Is that something I need to worry about?'" Dr. Lieu said, "About 500 tests have been done so far, 60% by cardiologists and 40% by internal

PREDICT Trial Validation Study of Corus CAD

Corus measure	DF low	DF moderate	DF high	FRS low	FRS medium	FRS high	MPI negative	MPI positive
Low	13%	**25%**	21%	14%	**26%**	0	17%	11%
Medium	22%	30%	48%	14%	43%	44%	26%	27%
High	70%	**52%**	63%	33%	**62%**	58%	47%	56%
All	22%	39%	51%	15%	49%	53%	25%	34%

medicine/family practice doctors. One family practice doctor did more than 36 tests…Internal medicine doctors will use it for patients they are not sure about, patients with chest pain, and asymptomatic patients with ≥2 risk factors. Cardiologists will use it for patients with an inconclusive stress test." Another CardioDx official said, "A family practice doctor could do our test in a patient with chest pain. If the score is low, he could treat the patient's clinical symptoms, and if the score is intermediate to high, then he could refer the patient to a cardiologist."

Corus CAD sounds complicated for physicians to use, but Dr. Kraus said he doesn't believe there is a steep learning curve, "In the clinical setting is that people are more familiar with the Framingham risk score…That is fine for a group but not for individuals. The challenge in cardiology is the people in the Framingham medium (10-20) range. Do we exposure them to statins unnecessarily? When people come with chest pain that I am not convinced is cardiac, I would send them on to another test. The misconception is that stress testing is valid…(Corus CAD) does a better job of classifying individuals of having CAD than current technologies, and it is blood-based, with no radiation exposure. It is not perfect; no test is."

Asked what it will take to get Corus CAD into a main session at AHA or get wider recognition among physicians, Dr. Kraus said, "That takes a lot of marketing…These things do take time…I don't know how long or what it will take (to get widespread use)."

Asked about other genetic tests that are valid but rarely used such as the test for warfarin resistance, Dr. Kraus said, "I think it is criminal that people are not using it."

Cardiologists questioned about the test were uniformly negative about it. In particular, they took strong exception to suggestions by both Dr. Lieu and another CardioDx official that the test could be used to determine whether a patient should get a catheterization or not.

While cost might be one reason, Dr. Kraus pointed out that it is less than MPI, which he said costs $2,200 per test, "We are faced with a dilemma. We don't know what healthcare will be like and what will be covered and what won't be covered (under healthcare reform). If something is covered by insurance, physicians really don't care (about the cost). They will use it more if patients aren't burdened with the cost. If you could get the warfarin test at no cost, and all payers covered it, people would be using it a lot more…(But) cardiologists make money on tests."

In another lecture at the same session, James Wingrove, PhD, of CardioDx discussed the impact of promoter and 9p21 single nucleotide polymorphisms (SNP) on peripheral blood cell expression of genes responsive to levels of obstructive CAD, using samples from the PREDICT trial. He examined 35 SNPs within promoter regions of 20 CAD responsive genes, testing for interaction in two independent datasets – Set 1 with 515 Caucasians and Set 2 with 460 Caucasians.

Dr. Wingrove said the strongest association with Rs2410300 is IL18RAP, which accounts for 50% of overall variation in expression ($p=2.9x10^{-82}$). He cautioned, "Genetics accounts for a range of observed variability (1.4% to 50.5% of overall variability). It is important to understand the impact of genetics when measuring gene expression as it can add unwanted variability."

Dr. Wingrove said he and his colleagues also looked at the association of 9p21 on gene expression, "9p21 is associated with increased risk of CAD, MI, and AAA (abdominal aortic aneurysm). 9p21 affects expression levels of three genes in the same neighborhood as well as affecting the expression of genes on other chromosomes. We wanted to look at the impact of 9p21 expression on Rs10757278 in Set 1 and Set 2. We saw significant interaction in seven genes, which all were down-regulated ($p<0.05$), which suggests the effect of 9p21 may be cell-specific…The presence of 9p21 disease allele is associated with lower lymphocyte counts, so we wanted to look at the impact of 9p21 on cell counts. We saw a statistically significant decrease in lymphocyte count in the presence of this allele, which suggests two things to us: (1) a decrease in lymphocyte count may be one way 9p21 is increasing risk, and (2) the disease allele may be associated with alterations in cell proliferation/cell cycle…We studied it and found CDKN2A is significantly affected in both Sets 1 and 2…CDKN2A may play a role in cell proliferation…The presence of 9p21 is associated with decreased lymphocytes, which is associated with increased risk."

Impact of 9p21 Expression on Rs10757278

Corus measure	# of SNPs	# of significant SNPs	# of genes tested	# of genes with significant SNPs
Set 1	35	23	20	16
Set 2	20	19	16	15

CARDIAC RESYNCHRONIZATION THERAPY (CRT)

Biventricular pacing – biventricular pacing better and safer than right ventricular apical pacing

It has long been known that right ventricular apical pacing can be deleterious for left ventricular function. However, the PACE study − performed in China but presented at AHA and simultaneously published in the ***NEJM*** − found that biventricular pacing does not have the same negative effects. In the 12-month, prospective, double-blind, multicenter, 177-patient PACE trial, conventional right ventricular apical pacing was compared to biventricular pacing, and biventricular pacing was significantly better in terms of left ventricular remodeling and in LVEF.

12-Month PACE Trial Results

Measurement	Biventricular pacing n=89	Right ventricular apical pacing n=88	p-value
Primary endpoint #1: LVEF	62.2%	54.8%	<0.001
Primary endpoint #2: Left ventricular end-systolic volume	27.6 ml	35.7 ml (25% increase)	<0.001
Ejection Fraction (EF) <45%	1%	9%	0.02
Death	0	1 patient	---
Hospitalization for heart failure	5 patients	6 patients	Nss, 0.74
Other results			
6-minute walk (meters)	+ 39	+ 35	Nss, 0.81
SF-36 physical functioning	+ 6	+ 2	Nss, 0.75
SF-36 physical	+ 23	+ 30	Nss, 0.14
SF-36 bodily pain	+ 4	- 1	Nss, 0.21
Adverse events			
Periprocedural deaths	0	0	--
Hospitalization for heart failure	5 patients	6 patients	Nss, 0.74
Hospitalization for ACS	0	3 patients	---
Hospitalization for stroke	2 patients	0	---
Diaphragmatic pacing	7 patients	0	---

In an accompanying editorial in the ***NEJM***, Dr. Bruce Lindsay of the Cleveland Clinic noted that "more aggressive pharmacologic therapy might have reduced the changes" with right ventricular pacing. He pointed out that the results do not say whether the deleterious effects would continue to worsen beyond 12 months. Dr. Lindsay also questioned whether it was ethical to intentionally pace the right ventricle in the patients in this trial.

Why is right ventricular pacing deleterious? Dr. Lindsay said the prevailing hypothesis is that biventricular pacing prevents or reverses cardiac dyssynchrony and that right ventricular pacing makes it worse. Yet, Dr. Lindsay pointed out that several practical issues limit the benefit of biventricular pacing: implantation skill, no agreed optimal position for the lead, variations in coronary anatomy, cost, and longevity of biventricular pacing systems/generators.

The bottom line, according to Dr. Lindsay, is that "most of the adverse remodeling reported in patients with sinus-node dysfunction would be avoided by adherence to standards of care that minimize right ventricular pacing. There is no compelling evidence that biventricular pacing should be selected at the time of implantation in all patients who have normal ventricular function and high grade atrioventricular block." Instead, he suggested following patients carefully with annual echocardiograms, converting to biventricular pacing systems "only if a clinically significant change" in LV function or functional capacity is observed. Guidelines should not change, Dr. Lindsay said.

LEFT VENTRICULAR ASSIST DEVICES (LVADS)

Continuous flow vs. pulsatile flow LVADS – continuous flow a big advance

Dr. David Markham of the University of Texas Southwestern Medical Center in Dallas compared the physiology of pulsatile and continuous flow devices in a one-day experiment in 9 patients (4 pulsatile and 5 continuous flow) at his center, using electrocardiography (ECG) and blood pressure measurements as well as transcranial Doppler (sitting and standing). He found higher muscle sympathetic nerve activity (MSNA) with continuous flow devices, which he said could lead to adverse events over time, such as stroke, high blood pressure, or renal effects. But he noted that it may be possible to develop a surrogate measure of sympathetic activity to guide therapy in these patients. His conclusion: "Patients may need ***some*** pulsatile activity."

Comparison of Continuous Flow and Pulsatile Flow LVADs

Measurement	Continuous flow LVAD	Pulsatile flow LVAD
Weight	390 gm	1,250 gm
Volume	63 ml	450 ml
Noise	Silent	Audible
Moving parts	One	Many
Maximal flow	10 liters/min	10 liters/min
Clinical durability	>2 years	18 months
Valves	No	Yes

A heart failure expert asked, "Do you think this is a bad thing or a good thing?…In heart failure, there is an elevated resting level of sympathetic tone, but it is a blunted response. Where are these patients in this cycle of having adrenergic tone withdrawn, or are they still in heart failure mode, and what do we want these patients to have?" Dr. Markham responded, "The pulsatile folks seem to have fairly normal MSNA…I think we are seeing folks with advanced heart failure who, if they get a pulsatile device, don't have heart failure any more. With continuous flow devices, they don't have heart failure, but…there isn't normal baroreceptor function."

Comparison of Continuous Flow and Pulsatile Flow Physiology

Measurement	Continuous flow LVAD n=5	Pulsatile flow LVAD n=5
MSNA	Consistently higher than control and higher than pulsatile flow. Also higher peaks	Consistently higher than control but fairly normal
Cardiac output	Similar	
Mean arterial pressure during head-up tilting	Nss difference	Nss difference

THORATEC's HeartMate-II – good 2-year survival data

The two-year survival with this continuous-flow ventricular assist device (LVAD) is good enough that it is likely to boost use as destination therapy. Data from a randomized U.S. trial (HMII) were presented at AHA and simultaneously published in the ***NEJM***, showing that HeartMate-II was more effective than the currently approved pulsatile-flow device (HeartMate-XVE) in advanced heart failure patients ineligible for a heart transplant. The researchers, led by Dr. Mark Slaughter of Advocate Christ Medical Center in Oak Lawn IL, found that HeartMate-II appears to have solved many of the issues that have kept LVADs from becoming commonly used as destination therapy.

2-Year Results with the HeartMate-II Left Ventricular Assist Device

Measurement	Continuous flow (HeartMate-II) n=134	Pulsatile flow (HeartMate-XVE) n=66	p-value
Primary endpoint: Survival free from disabling stroke and reoperation to repair or replace the device at 2 years	46%	11%	<0.001
Secondary endpoint: Survival	58%	24%	0.008
Discharged from hospital with device in place	86%	76%	---
Mean length of stay in hospital	27 days	28 days	---
Time out of the hospital after device implantation	88%	74%	0.02
First event that prevented patient from reaching the primary endpoint			
Disabling stroke	11%	12%	Nss, 0.56
Reoperation to repair or replace pump	10%	36%	<0.001
Death within 2 years of implantation	33%	41%	0.048
Any event	54%	89%	<0.001
Secondary endpoint: **Adverse events**			
Stroke	18% (0.13 events per patient-year)	14% (0.22 events per patient-year)	Nss, 0.21
Rehospitalization	94%	96%	0.02
LVAD-related infection	35%	36%	0.01
Bleeding requiring transfusion	81%	76%	Nss, 0.06
Bleeding requiring surgery	30%	15%	Nss, 0.57
Cardiac arrhythmia	56%	59%	0.006
Respiratory failure	38%	41%	<0.001
Renal failure	16%	24%	<0.001
Other *secondary endpoints:* Quality of life/functional capacity			
6-minute walk	Up 190 meters	Up 134 meters	<0.001
Minnesota Living with Heart Failure Questionnaire score (down is better)	Down 46.4	Down 15.1	<0.001
Leading cause of death			
Hemorrhagic stroke	9%	10%	---
Right heart failure	5%	8%	---
Multisystem organ failure	---	7%	---
Sepsis	4%	---	---
Ischemic stroke	---	5%	---
External power interruption	4%	---	---
Respiratory failure	3%	---	---
Cardiac arrest	3%	---	---
Bleeding	3%	---	---

In the study, HeartMate-II:

- Significantly improved 2-year survival.
- Had a rate of pump repair/replacement of 6 events per 100 patient-years, nearly one-eighth the incidence with the pulsatile HeartMate-XVE, and mainly due to lead issues.
- Significantly reduced adverse events.
- Had a risk of stroke comparable to what is expected in advanced heart failure patients.
- Had a lower infection rate.

In an editorial in ***NEJM*** accompanying the results, Dr. James Fang of Case Western University called the improvement in the probability of survival "truly remarkable," adding, "The use of continuous-flow left ventricular assist devices appears to have quadrupled the survival of these patients in the past decade." However, he also noted that stroke remains a "major challenge," postoperative mortality remained high, and rehospitalization was common.

How can these results be applied to clinical practice? Dr. Fang said the first priority is to make more doctors aware that these devices are "available, effective, and safe for well-selected patients." He also urged doctors not to delay referral until patients are too sick to benefit from the devices, "Any patient in whom IV inotropic support is required should be considered a candidate for destination therapy."

The discussant on the HMII trial was Prof. George Wieselthaler of Vienna, Austria, who is on the advisory board of a competitor, HeartWare. He said, "Overall, this clinical trial really demonstrated that the new technology of a rotarized pump is superior to older displacement pumps…but I believe with a reduction in adverse events… Even better results can be achieved in the very near future (an apparent reference to HeartWare's HVAD device, which is smaller than HeartMate-II)."

Asked about the economic impact of these devices, Dr. Mark Rogers of Duke University Medical Center, who presented the HMII trial results at AHA, said, "At the present time the cost is fairly trivial because so few patients are being implanted with the device…We have collected a fairly large amount of cost data which has not yet been analyzed…but preliminarily it looks like it is in line with cardiac transplantation, which is

an accepted cost for patients with advance heart failure." Dr. Wieselthaler said the cost environment is very different in Europe, "The most striking difference is that in the U.S. you have to label devices as either bridge-to-transplant or destination therapy, and that is why trials like this (HMII) have to be performed. In Europe, we lack donor organs and the patients who go to bridge-to-transplant usually wait 1.5-2.5 years for their organs. That means they would go for the endpoint of this trial as well. So, there is some economic impact as well… And we have to keep in mind that transplant per se is very cost-effective. If you can reduce the rehospitalization rate for patients on the transplant list, that also has a very large impact on economic issues." An Italian doctor added, "It is very important that we don't have to decide if a device is bridge-to-transplant or destination therapy before implantation…I have patients who, once they have the device, refuse the transplantation because of their quality of life. We must consider the (cost) savings vs. transplantation."

Stroke remains a concern, though the rate is lower with HeartMate-II than earlier devices. Dr. Rogers said, "This is an area we are still trying hard to understand…Hemorrhagic stroke was the most common cause of death in both groups… With pulsatile flow, you really only need to use a single antiplatelet agent. The anticoagulation protocol for the HeartMate-II included perioperative heparin followed by two antiplatelet drugs plus warfarin, and what we found was many more bleeding events than thrombotic events…So, investigators cut back on the anticoagulation and antiplatelet therapies during the study…This probably is a much more complicated question…There may be interesting and important impacts of the way we provide flow that we have not yet explored."

Asked what these devices mean for Abiomed's Abiocor artificial heart, Dr. Rogers said, "Most of us in this field believe the majority of these patients will have sufficient support with an LVAD…I have no practical experience with Abiocor…but I think the patient population will be relatively limited in the big picture of advanced heart failure."

What does LVAD destination therapy mean for the transplant list? Will LVAD patients jump ahead of other patients? An expert said that in the U.S. the sickest patients are transplanted first. HeartMate-II patients get 30 days of highest priority on the transplant list – any thirty days, either at the beginning or some later time – and then they drop to a lower level.

Asked if there has been any hospital pushback on LVAD use, doctors generally said no. But there has been some pushback from insurance companies. Experts are hopeful that cost-effectiveness data will convince those payers. An expert said, "The hospital constraint is the infrastructure for the program – the nurses, etc. Financially, most programs at least break even; that has to do with the team experience. The device cost is ~$100,000, and the total patient cost is ~$140,000-$180,000. The Medicare approved reimbursement is ~$160,000…But many commercial carriers will not pay for a study device."

Cardiologists predicted that these data will spur wide user of HeartMate-II, but probably a gradual increase, not a dramatic jump in use. Among their comments were:

- *Dr. Yancy, AHA President:* "(This shows) destination therapy is truly an effective treatment for advanced heart failure patients. Before mechanical support was underused because of the question of risk and longevity. This is a good step ahead, not just an incremental step…This also opens the opportunity for more new technology…For now at least, it may be appropriate for 10s of thousands of patients, not hundreds of thousands of patients…I hope they find even smaller devices, though…But we still can't use it as destination therapy without FDA approval, but my sense is that, given these findings, the FDA will look at this very carefully…If it gets FDA approval, payers and Centers for Medicare and Medicaid Services (CMS) would be a lower bar. CMS already accepts destination therapy with a pulsatile device…With these (HeartMate-II) results, cost may favor destination therapy…Currently, about 1,000 patients a year get destination therapy. This opens it to considerably more patients, but the treatment still must remain in the hands of experienced centers. Because of technology and management concerns, our view is it should remain in experienced centers. There is no rush for new centers, but more centers will get involved."
- *Dr. Jessup:* "This new trial will pave the way for patients more ideally suited for destination therapy…We already use HeartMate-II extensively. It will allow some third party payers to give us more flexibility for destination therapy. It will also open even more hospitals getting into LVADs for destination therapy. A lot of hospitals will be interested because they won't need a transplant program as they do with bridge-to-transplant (devices)."
- *Dr. Wieselthaler:* "This trial reflects reality. Seventeen percent of patients recovered (from transplant ineligible to eligible)."
- *Dr. Rogers:* "(HMII) won't change anything in the short term because FDA approval is needed. But I hope that we have shown enough positive data that general cardiologists will now refer more patients…Heart failure cardiologists are the converted; they realize these devices save lives. But three-quarters of heart failure patients are cared for by primary care doctors. The message now is we have good data, and this is a viable treatment option."
- *Dr. Sidney Smith, University of North Carolina at Chapel Hill, past president of the AHA:* "Some patients are very comfortable on an LVAD and choose to stay with that rather than have a transplant…It is an increase in mechanical assist, and that will be an advantage for patients with end-stage heart failure who are not eligible for transplant…When you see results like this, it is a step forward and a sign that supports use beyond bridge-to-transplant…This will increase use."

- *Kentucky:* "The biggest downside to growth is lack of awareness that this is a safe and effective treatment among the primary care and internal medicine doctors and cardiologists who take care of the patients who are candidates…Twice a month I do outreach, visiting practicing doctors and spending 2-4 hours going over data. I frequently take a patient with me. And that has increased referrals…Even five years ago, if you offered an LVAD to patients, they wanted it, but it wasn't offered to most patients."
- *Dr. Alfred Bove, president of the American College of Cardiology:* "We have been using this second-generation device for a few years. Anecdotal observations showed they had longer lifetimes, and the early use showed they were much more easily tolerated than the bigger early model devices. We had a sense that these smaller devices were going to have better long-term outcomes, and this trial proves it. These devices are now used as final destination therapy as well as a bridge to heart transplant. These devices have come a long way in five years. I expect that technology will continue to move things forward, and they will be even better five years from today."
- *Dr. Ray Gibbons, past president of AHA:* "This is a highly technical area, and it will take time for the clinical cardiology community to digest what it means from a practical, clinical standpoint. It won't drive changes in referrals until that happens. It is awfully technical."
- *New England:* "HeartMate-II is the device of choice already. A lot of centers want to start using it, but I'm skeptical it will be a step increase. I think there will be moderate, steady growth. The complexity of getting a program up and running is complex, and the drive-line still requires a lot of patient education. The uptake as destination therapy will be gradual."

Several doctors who do LVAD implants were questioned about the outlook for LVAD use generally and HeartMate-II specifically. Most sources said they rarely use pulsatile devices any longer, with most devices implanted either HeartMate-II or an investigational device in a study. Most sources agreed that use will gradually increase, not show steep step jumps.

What does "gradual" growth mean? On average, doctors who implant LVADs predicted that use, in the 12 months after HeartMate-II gets FDA approval – which some experts were predicting would come in 1Q10 – would go up ~75%, but that is from a low base number of ~1,000-1,200 LVADs a year, but that will include investigational devices, so it won't be all HeartMate-II. In particular, there is real interest in the HeartWare device, which is even smaller than HeartMate-II. Plus the Jarvik continuous flow device has three settings, allowing patients to adjust it to accommodate their activity level, and that appeals to doctors and patients.

An expert said there are 71 centers currently approved to do destination therapy, and there are 110 transplant centers. If each of these centers did an extra 4-10 LVADs a year that would be an additional ~500 devices/year. If every center did 10 more, the number would climb to about 2,000/year total. Some centers are expected to increase just a few, while others may go up 30-40 devices. So, an estimate of a 700-750 device increase in one year is considered gradual. Furthermore, more centers are expected to start doing LVADs when HeartMate-II is approved because it is expected to be able to be done at sites that do not do heart transplants.

How big can the market get eventually? Some experts predicted that 20,000-50,000 patients a year will be implanted, but a more conservative implanter put the number at 8,000-10,000.

Comments included:

- *Dr. Rogers:* "There will be continued slow adoption because it is expensive and complicated. Over five years, there will be a slow, steady adoption but no sudden burst of use…The HeartWare device is the next evolution. You put it in the pericardium, and it may lower the infection rate."
- *Dr. Slaughter, Kentucky:* "We will put in 70 HeartMate LVADs this year and 100 next year, compared to 15-20 transplants this year…Access is still a potential problem in many parts of the country…And there is tremendous misperceptions about this therapy. Many people only remember Barney Clark (the first person to be implanted with the Jarvik-7 artificial heart, surviving 112 days) or the REMATCH trial (which had only 28% survival at 2 years)…It is completely different now. The majority of patients live, have quality of life, and are at home doing activities of daily living."
- *Dr. Markham, Texas:* "With this destination data, we'll see use increase dramatically. It could double at our center from the current 10-15/year. Within 1-2 years, VADs could double, but some centers haven't bought into the destination therapy approach."
- *Dr. Randall Starling, Cleveland Clinic:* "At the Cleveland Clinic, in 2009 for the first time, we've done more destination therapy than heart transplants: 80 destination therapies and 50 heart transplants year-to-date. The HeartMate-II results are increasing confidence. Bridge-to-transplant is also increasing in sicker patients with better devices. Until HeartMate-II gets FDA approval, it will only be used for bridge-to-transplant, bridge-to-decision, or a clinical trial. Once it is approved, we'll have more ready access, and reimbursement will improve. Total device numbers will go up, but transplants are flat. Overall, we'll do 90 devices this year, compared to 49 last year, but, for us, that will level off. My threshold for a VAD is lower than my colleagues, but I'm seeing even my most conservative colleagues have a lower threshold."

- "We are doing 40-50 destination therapy devices a year and 50-55 transplants a year, and we have an aggressive transplant program. Destination therapy will increase 30%-40%, but not double or triple…The people who need to hear about it aren't hearing it. Over the next 1-2 years, use could double and approach 3,000 in another couple of years, but it will take more convincing to move en masse and to do it in less sick patients…I think the maximum annual rate will be 8,000-10,000. Medicare won't allow 20,000-40,000 devices, especially in the current health-care environment."
- *Minnesota:* "We do ~40 heart transplants and 80 VADs a year, and that will increase, but the HeartMate-II 2-year survival was 58%, and people hoped it would be better."

HEARTWARE's HVAD, a continuous flow LVAD – potentially a major competitor for HeartMate-II

This is the LVAD that experts were most excited about – because it is smaller than HeartMate-II, intrapericardial, and has no touching parts. But until it is proven, HeartMate-II will dominate the market. An investigator said the HeartWare trial is "quickly enrolling" for bridge-to-transplant. He predicted there is room in this market for two devices – HeartMate-II and HeartWare.

Dr. Wayne Levy of the University of Washington reviewed data to date on this LVAD. He said that survival with this LVAD is 90% at 180 days and 85% at one year, which is similar to the 87% one-year survival with transplant.

Asked about the outlook for growth in the use of LVADs, Dr. Levy said, "The real problem with LVADs now is we are stuck with the ACC/AHA guidelines of >50% mortality risk (to be eligible) ...and I think most of us are comfortable with using >30% mortality risk …If you want people walking around, they are in the (mortality risk greater than) 20%-40% range, not the >50% range." Another LVAD surgeon said, "HeartWare has half the operating room (OR) time, less bleeding, and fewer infections. It will boost VAD use as destination therapy." A third surgeon said, "We will continue to use HeartMate-II for the majority of our patients, but we will do HeartWare, too."

Comparison of HVAD to Medical Therapy

Measurement	HeartWare HVAD bridge-to-transplant	Medical therapy (predicted)
Predicted survival		
At 1 year	58%	58%
At 2 years	40%	40%
At 3 years	30%	---
Reduction in mortality	~ 70% - 75%	---
Predicted survival in less sick patients (mortality risk <50%)		
At 1 year	76%	---
At 2 years	60%	---

Causes of LVAD mortality

Elizabeth Genovese, BS, of the University of Pittsburgh reported on a study at her center of what predicts mortality during LVAD use. In a retrospective review of patients who survived ≥60 days with an LVAD from 1996 to 2008, the researchers found that actuarial survival was 60% and steadily decreased after 60 days. The five key predictors of increased mortality after 60 days were renal failure, respiratory failure, bleeding, reoperation, and right ventricular failure. Mortality increased with the addition of each new adverse event. The strongest predictors of 1 year mortality were renal failure and right ventricular failure.

Main Causes of Death in LVAD Patients

Cause	Death
CNS	37.1%
Infection	31.4%
Multiorgan failure	11.4%
Cardiovascular	8.6%
Pulmonary	5.7%

12-Month Mortality with LVADs

Device	Death
HeartMate-II	6%
HeartMate-XVE	13%
Jarvik	1%
VentrAssist	10%
Novacor	21%
Overall actuarial survival	60%

Adverse Event Predictors of Mortality in LVAD Patients

Adverse event	Occurrence in first 60 days	Univariate survival analysis		Multivariate survival analysis
		≥1 adverse event	No adverse event	
Infection	44.8%	53.9%	64%	---
Bleeding	44.2%	48.3%	70.3% *	---
Cardiovascular dysfunction	38.0%	---	---	---
Reoperations	33.1%	47.9%	67.3%	---
Neurological events	28.2%	59.9%	N/A	---
Right ventricular failure	27.1%	38.7%	66.7% *	---
Renal failure	---	32.0%	64.7%	2.8 HR, p=0.03
Respiratory	---	35.3%	68.2% *	---

* $p<0.05$

LVAD as bridge-to-weight loss

LVADs may be a way to help obese patients lose weight and qualify for the transplant list. Dr. Pavittarpaul Dhesi of Cedars-Sinai Medical Center in Los Angeles reported on a study of 13 obese patients not eligible for transplant who got a HeartMate-XVE as a bridge-to-weight loss compared to 6 obese patients treated with medical management. He said that obese patients have increased morbidity and mortality after transplant, but obese patients successfully implanted with an LVAD do not have any different complications or decreased survival compared to other weight groups.

Several experts said combining an LVAD with bariatric surgery is where the real weight loss – and better outcomes – are achieved. The question is the order in which these should

Obese Patients ±LVAD

Measurement	Obese patients with LVAD n=13	Obese patients on medical management n=6
Average age	49.1	56
BMI	36.1	39.1
Weight loss at 6 months	4.3 kg (p=0.002)	No change
On transplant list at 12 months	7 listed	0 listed (due to persistent obesity)
Cardiac hospitalization over 12 months	1.7	2.2
All hospitalizations	1.9	2.5

be done − simultaneous, bariatric first, or LVAD first – and the experts didn't agree.

Among the comments were:

- "Some people are comfortable transplanting at BMI ≤35, and most are pushing it to BMI 40 with LVADs."
- "The HeartMate-XVE is difficult to put in an obese patient…We prefer the HeartWare device. We found that in someone obese, the HeartMate-II goes on an angle, and with HeartWare that doesn't happen. HeartWare is a great device for the obese patient."
- "We had 4-5 patients under age 30 who were supposed to be bridge-to-transplant that we had to de-list because their BMI was in the high 30s or low 40s, and all gained weight on the HeartMate-II. The patients feel good (and eat). You don't change the patient with the device. These are obese patients, and you don't change that with an LVAD."
- "We have a fairly big LVAD experience, and we noticed that no one loses weight with a VAD – at least not in our program. I suspect hearts supplemented with a VAD burn fewer calories."
- "We had a similar experience. Everyone gained weight on a VAD…But we put in the HeartMate, not with banding, but with gastric bypass…These guys lost weight, including a 400-pounder who lost 50-60 pounds. We give them three months (on the VAD), and if they don't lose weight, then we give gastric bypass."

LVAD cost-effectiveness

Dr. Daniel Sims of Columbia University Medical Center compared the cost of the HeartMate-II and older HeartMate-XVE, finding that the HeartMate-II is most cost-effective due mostly to a shorter length of stay in the cardiothoracic-intensive care unit (CT-ICU). An expert commented, "I think this is a very important topic you've raised…I don't think it has come to the attention of third-party payers yet…Currently, the incentive on reimbursement in bridge-to-transplant is to put in the VAD, send the patient home, get paid, have the patient come back for transplant…With length of stay for transplant ~17 days and for VAD all-comers >50 days but dropping." Another expert said, "What we've noticed is that length of stay was 30 days with HeartMate-1 (XVE) and decreased to ~17 days now with HeartMate-II. We need to get them out in less than 20 days or we lose money on Medicare patients."

PERCUTANEOUS VALVES

DIRECT FLOW MEDICAL

European first-in-man data on this bovine pericardial valve were presented at AHA on 31 patients, and the data looked acceptable but not great. The attraction of this valve is that it is repositionable and retrievable. Only 22 of the 31 patients were able to be implanted – a 71% success rate. There were two in-hospital deaths, but an investigator, Dr. Joaquim Schofer, said they were not related, and two patients went to surgery.

The major adverse events post-discharge were: 3 deaths, 1 stroke, 4 AV block requiring a pacemaker (an 18% pacemaker rate). At one year, all-cause mortality was 23% and procedure related mortality was 13%. Most patients in this study improved to NYHA Class I. Dr. Schofer said there was only a small amount of paravalvular leakage, "In contrast to other devices, we didn't see any signs of aortic regurgitation."

Dr. Schofer concluded:

- The valve is safe and effective, with an effective orifice of 1.46 cm^2 which decreases to 1.22 cm^2 at one year, but mean and peak gradients remained stable.
- The success rate points to the importance of pre-assessment of calcification quantity and pattern, both in the peripheral vasculature and within the native valve apparatus.

Asked how the valve heals over time, Dr. Schofer said no autopsy data are available.

Asked why there is less paravalvular leak, Dr. Schofer said, "I think it is the design. The rings are much more flexible than the metal valves."

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