Trends-in-Medicine

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by Lynne Peterson

SUMMARY

There is so much news is this report – on devices as well as drugs and even a look at the European view of U.S. healthcare reform – that we thought you needed a table of contents to help you find things:

Trends-in-Medicine
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EUROPEAN SOCIETY OF CARDIOLOGY (ESC)

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The official theme of ESC this year was prevention, but the practice-changing findings of several important trials overshadowed that message. ESC President Prof. Roberto Ferrari of Italy said it isn't a revolution like angioplasty was, "People will go back (from ESC) and change their practice, not immediately, but they will have a new opportunity to treat patients."

ESC has been bucking the trend by growing in size while attendance has been shrinking at other major medical conferences. This year, 31,371 delegates attended the meeting, of which 25,104 were active participants, so the increase was not simply inflated by industry. Prof. Ferrari said, "I was very worried (about attendance) because of the economic crisis. All the other scientific associations in cardiology – but not only in cardiology – are experiencing a decline in attendance and participation…Here in Barcelona, we had more participants than last year in Munich, and this is extraordinary…We have more delegates and less industry than the American College of Cardiology (ACC) or the American Heart Association (AHA)."

Why is attendance up at ESC? Prof. Ferrari cited three reasons: "Barcelona is a lovely city, we are providing a good congress with a brand, and we have increased patients' lifespan in cardiology by 7 years vs. 2.4 months in oncology. (But) we haven't solved the (cardiac) problem, just delayed it."

European views on general cardiovascular (CV) health topics

How has the lifespan increase been achieved? Prof. Ferrari credited the move to quick reperfusion (either primary PTCA or thrombolysis), improvements in cardiac intensive care units, and the discovery that thrombi cause myocardial infarctions (MIs) and of pharmacologic and mechanical ways to eliminate thrombi. In addition, he said, cardiology is a well organized system. However, Prof. Ferrari warned, "Don't consider us magicians. We cannot provide a magical solution every year."

***Asked about healthcare advances in China*,** Prof. Ferrari said, "I've been to China 2-3 times, and I was quite amazed at the amount of smoking going on in China, and that is not good for prevention…I was also amazed at the (pollution) which also is not very good for prevention…So, I think (China has) to do a lot, and (it is) in a good position to learn from our mistakes, learn from the mistakes we are making in our western civilization."

***Asked about U.S. restrictions on gifts to doctors by the pharmaceutical industry and whether those limits will spread to Europe*,** Prof. Ferrari told reporters, "We do have a code of conduct (in Europe) agreed with the companies…I do believe the situation going on in the States at the moment perhaps is going a little bit to the extreme as always is the case. In a way the drug companies are, at least for me, extremely important. Without them, we would have no drugs. And the drug companies are not humanitarian enterprises. They have to make money and sell their drugs…I don't think you can bribe a doctor with a pen…so I believe common sense will be important. Companies are used to using educational materials, written by doctors, often reviewed by associations, and I don't see anything wrong with that…Here, I hope you will appreciate that we have a very clear-cut session which is independently organized by us, and symposia which are organized by companies. We have press conferences which are independent and organized by us, and you go to press conferences organized by the companies. Will you be influenced by the companies? That is up to you. Here, you can't go to every hotel and get a company-run session with food. We don't allow anyone to do this. So, in a way I think we have a good policy based on common sense."

***Asked if there is a message for the food industry with respect to cardiology*,** Prof. Ferrari said, "We have a lot of messages for the food industry as much as we have messages for the tobacco industry. Whether we can influence this highly-economically important institution is very, very difficult. For example, in Ferrara (Italy) we convinced bread makers to produce a bread with no salt, high fiber, and a lot of omega-3. The bread is tasty, and we call it 'healthy bread.' Will we change anything? I don't know, but at least there is a possibility…The drug industry has to make a profit. Let's try to do it together and provide some healthier food than by letting them go alone."

KEY TAKE-AWAYS FROM ESC

At the conclusion of ESC, Prof. Joep Perk of Sweden outlined what the ESC views as the key messages from the meeting:

- Strong attendance at sessions on prevention.
- A lot of data showing the close relationship between lifestyle and cardiovascular disease (CVD), but CVD awareness needs to start during childhood, and there is an urgent need to transform knowledge into action.
- Change in clinical practice will not occur overnight but step-by-step. "Trials such as SYNTAX show relevant results, but the impact cannot be immediate."
- Interesting research findings, including:
  - Drinking half a bottle of wine vs. water has an immediate impact on the right atrium.
  - Watching championship football games does not, as previously thought, increase CVD risk.
  - Hair is the mirror of health – e.g., patients with AMI (acute myocardial infarction) have 25% more cortisol in their hair months prior to the incident.

Four trials presented at ESC have the potential to change practice, but they each also had issues that could derail their impact.

1. **RE-LY**, which showed Boehringer Ingelheim's direct thrombin inhibitor Pradaxa (dabigatran) could become the first replacement for warfarin in atrial fibrillation (AFib). It was shown to be superior to warfarin and easier to give, leading everyone to call it a "game changer." However, (a) it also was an open-label trial, (b) the drug has its own side effects (mostly dyspepsia), and (c) the MI rate was significantly higher than warfarin, which would mean a delay if the FDA requested additional data before approval.
2. **PLATO**, which showed that AstraZeneca's P2Y12 inhibitor Brilinta (ticagrelor) could displace both Sanofi-Aventis's Plavix (clopidogrel) and Lilly's Effient (prasugrel) as the leading antiplatelet inhibitor. It was shown to be superior to Plavix and safer than Effient. However, North American patients had a lesser response, raising questions about FDA approvability; some doctors are concerned about the BID dosing; and it, too, has its own side effects (dyspnea, ventricular pauses, increases in serum creatinine and serum uric acid, and a slight trend to a higher risk of hemorrhagic stroke).
3. **CURRENT-OASIS-7**, which showed that double-dose Plavix for 7 days in percutaneous coronary intervention (PCI) patients is more effective than low-dose Plavix – and it is surprisingly safe. Many hospitals are already using a double loading dose but not this 7-day regimen. While this is expected to be adopted quickly, it doesn't eliminate all Plavix resistance.
4. **MADIT-CRT**, which showed that CRT-Ds reduce hospitalizations in heart failure patients with mild disease (NYHA Class I-II). However, they do not improve survival, and many of the experts at ESC argued that the results – and the cost – don't justify changing guidelines yet.

PLATO, CURRENT-OASIS-7, and RE-LY trials – all game changers

Will PLATO and RE-LY change the standard of care? Will Brilinta replace both prasugrel and clopidogrel? Will Pradaxa replace warfarin? Cardiologists at ESC were asked to predict how the new agents will impact use of the existing standard-of-care agents. The bottom line was that, if these agents are both approved, there will still be a role for clopidogrel, prasugrel, and warfarin, just a reduced role.

KEY Trials at ESC

Trial	Company/product	Class	Advantages	Concerns
RE-LY	Boehringer Ingelheim's Pradaxa (dabigatran)	Direct thrombin inhibitor	Superior to warfarin and easier to give; no monitoring required	MI rate Dyspepsia and GI bleeding BID dosing Only one trial, though it was large
PLATO	AstraZeneca's Brilinta (ticagrelor)	Factor Xa inhibitor	Superior to Plavix with no increase in major bleeding Fast on/fast off effect	Open-label trial design Decreased effect in North American patients BID dosing Dyspnea Loss of efficacy if a patient is non-compliant
CURRENT-OASIS-7	Sanofi-Aventis's Plavix (clopidogrel)	Thienopyridine	Better efficacy in PCI with no additional bleeding risk	Some patients still resistant
MADIT-CRT	Boston Scientific	CRT-D	Reduces heart failure hospitalizations	No impact on survival Cost

How are guidelines likely to change in the U.S.? New ACC/AHA guidelines have already been written, are in the late stages of fine-tuning and approval, and are likely to be finalized in November 2009, so the information from PLATO, RE-LY, CURRENT-OASIS-7, and MADIT-CRT will not be incorporated in them, though there may be a mention of some of the findings, particularly MADIT-CRT. Dr. Elliott Antman of Brigham & Women's Hospital, an AHA spokesman, said, "CURRENT-OASIS-7 won't change guidelines at least until it is peer reviewed. You couldn't change a recommendation because it is not published, but you could discuss it in the text. Ultimately, you will see it (OASIS-7) make its way into the guidelines…(But) it is a very reasonable assumption that prasugrel will be in the new guidelines."

ASTRAZENECA's Brilinta

Brilinta is expected to largely replace prasugrel, though prasugrel may still have a small role. Brilinta also will largely replace Plavix as well as generic clopidogrel in the acute setting because of its reversibility. There are no data yet on long-term use, but the reversibility also makes this an attractive option for long-term patients. While the lower cost of generic clopidogrel will be enticing (especially to payers), cardiologists are likely to use Brilinta liberally long term, even in the face of lower-cost generic clopidogrel.

- *U.S. #1:* "In the U.S. we are producing a lot of me-too drugs and not necessarily better drugs…Ticagrelor was non-inferior to Plavix, which means non-inferior to placebo…I think the drug (Brilinta) is a potential game changer because of its reversibility. I think that is a huge advantage…(Compared to prasugrel), because of reversibility, it…has substantial advantage…In patients presenting with ACS (acute coronary syndrome), and you want rapid onset and reversibility, this drug will have an important impact in our treatment of ACS. In patients needing a thienopyridine longer term (≥1 year), then you start looking at cost issues. Then, trying to be a cost-effective physician, I can see utilizing generic clopidogrel in long-term situations and using the new drug in acute situations."
- *U.S. #2:* "What distinguishes (ticagrelor) is its reversibility…It will be the preferred option in the acute setting – patients undergoing angioplasty or even in some more elective settings where there is the potential for CABG in coming days. You can't always identify patients prior to angiography…In patients where we don't know enough about what the angiogram will show, there is a strong role for this compound in preference to prasugrel. But in patients with prior angioplasties, etc. – where bypass is not in the mix – prasugrel may still have an important role."
- *U.S. #3 (prasugrel investigator):* "(It is) not so straightforward (that Brilinta will leapfrog prasugrel). Prasugrel QD is irreversible, which is a concern in surgery patients. Ticagrelor's reversibility is an advantage, but BID is a problem if patients forget a dose. I'm delighted to see the ticagrelor results because it means an array of options… How much the dyspnea and ventricular pauses will affect clinical thinking remains to be seen…I think there is still a role for prasugrel."
- *Netherlands:* "PLATO is a dream outcome – better efficacy (with Brilinta) and no excess bleeding like with prasugrel…Between now and the availability of ticagrelor, prasugrel may get wide use – but only until ticagrelor is available. Prasugrel is very effective for the first two weeks, and then there is a leveling off of effect. Ticagrelor has a little less early benefit but more effect over time…The reversibility of ticagrelor gives it a big edge. Fast off/fast on is an advantage, but fast off is also a disadvantage if a patient forgets a pill…Ticagrelor will change the guidelines."
- *Austria:* "It looks good for AstraZeneca, but it is only one study…Prasugrel is just being introduced in Europe, but I'm not sure of its future because of the bleeding. I think it has a limited uptake outlook. In one year, 25% of patients may be on prasugrel, but in two years 100% will be on the new drug (Brilinta)…I don't think Bristol-Myers Squibb should give up on apixaban, but it will have to beat ticagrelor."

- *U.S. #4:* "The keys to this drug (Brilinta) are (1) reversibility, so it is much more easily used in patients where you might have to go to surgery, and (2) rapid action. So, in an acute setting, there might be more benefit to it (Brilinta)."
- *U.K.:* "Prasugrel has not attracted people, but ticagrelor will…PLATO is a practice changer…I was surprised at the strong result in PLATO – the mortality, the continued separation of the curves, and the consistent safety and efficacy. What convinced me it will change practice is the mortality benefit. If I were making a decision, I would be keen on the new product vs. double-dose clopidogrel."
- *France:* "In the beginning, I thought it would be difficult to accept prasugrel because of the increased bleeding and fatal bleeding. It is a very good drug, but perhaps it should be restricted to diabetics and STEMI patients. It is too early to say how we will actually use it, but probably there will be limited use until ticagrelor is approved. Remember Lilly (prasugrel) is a U.S. company, and ticagrelor is a European company (AstraZeneca)."

Will doctors start patients on Brilinta and then switch to generic clopidogrel at some point (perhaps 30 days)? Possibly, but there are no data on switching, and none of the U.S. cardiologists questioned was promoting that idea.

- "At the moment, based on the trial (PLATO), the benefit is in the acute setting. In the future, whether there are longer term benefits remain to be shown…There is a potential for long-term use…But there is also more burden on the patient for compliance. There isn't much danger when a patient misses a Plavix dose…A short-acting agent has the potential to avoid toxicity but creates the potential for problems related to non-compliance."
- "This trial (PLATO) didn't address that (long-term use), but the reversible nature and short-duration of action could be quite useful for chronic disease…Cardiologists are constantly being called by gastroenterologists who want to do a colonoscopy, and this (Brilinta) allows that …A little more experience with this drug would be useful."
- "It's a choice of either…Ticagrelor is BID, and clopidogrel is QD. For some patients that may be an issue…I look at these (ticagrelor, prasugrel, and clopidogrel) a little like the statins – three different drugs with slightly different profiles."
- "The question is whether it will be cost effective."
- *Netherlands:* "Switching from prasugrel to clopidogrel at 30 days would be good for safety, but that won't happen with ticagrelor because the efficacy is so good over time. The only issue will be cost."
- *Dr. Spencer King, past president of the ACC:* "(Brilinta) isn't easier to use than clopidogrel or prasugrel. It is a pill…I thought it was reversible really quickly, and that concerned me on how this trial would come out because in the real world patients don't take medicine every day… I've been told the off is a lot slower than originally thought. It takes some days. If it was rapid off, you can think of needed applications – people where you don't want it to interfere with surgery. But it is not reversible like a short-acting IIb/IIIa inhibitor. In that regard, it might have some advantage, but it is much less than I had envisioned. But reversibility may have some advantage in chronic use. Compliance also is an issue because in the real world people forget to take their medications. And we have a trial here of ticagrelor vs. clopidogrel; we don't yet have a trial of ticagrelor vs. prasugrel. So how do we know?...From my perspective, we have prasugrel, and we won't have ticagrelor for a while, so it is not an immediate issue…If you need more anticoagulation, you need the agent that gives it to you. But do you need it in everyone? My argument is there are all kinds of needs. Going forward, the focus in on personalized medicine. Both this agent (ticagrelor) and prasugrel raise the question of whether we should be identifying patients who are having an antiplatelet effect who need it."

In PLATO, what is the importance of the reduced benefit in North American patients with Brilinta? AstraZeneca reportedly is putting together a scientific panel to study this. Most cardiologists questioned at ESC were not very worried about this issue. Dr. Timothy Gardner of Christiana Health Care System in Wilmington DE, immediate past president of the American Heart Association, said, "PLATO got dinged a bit on the North American subgroup. It is something that has to be considered – whether it is just a chance variance or represents some signal in the way North American patients with coronary artery disease are treated…The only theory I've heard is some difference in the dosing of aspirin. In Europe the standard aspirin dose tends to be lower (160 mg) than the dose in the U.S. (325 mg)…I think that has to be sorted out…but it is still a very important development." AHA President Dr. Clyde Yancy, a heart failure specialist from Baylor University Medical Center in Texas, said, "There is a signal that the North American cohort didn't show a benefit. All of us have learned that subgroup analyses are fraught with issues. In the absence of additional analyses, it is hard to make anything out of it…In the MERIT-HF trial, the North American subset for Toprol XL (AstraZeneca, metoprolol succinate controlled release) did not meet the North American standard, but it was approved (by the FDA)."

From the FDA's perspective, the failure of a therapeutic drug to show a statistically significant benefit among North American patients is unlikely to have any impact on approval if the overall results were positive, and the rest of the trial was in Canada and/or Europe. However, if the trial has an active comparator, the FDA is likely to give the analysis of the North American patients a little more scrutiny and may put the information in the label.

Asked generally if the subgroup of U.S. patients in a global trial needs to be positive for FDA approval, Dr. Robert Temple, director of the FDA's Office of Drug Evaluation I in the Center for Drug Evaluation and Research (CDER), said, "The FDA can, by regulations, rely on foreign data and has often done so, although we are more comfortable with more familiar sites. ICH E-5, however, gives us the clear ability to expect some U.S. data. The FDA has historically accepted data from Western Europe as 'U.S. equivalent,' so a pivotal Phase III trial doesn't necessarily have to have any U.S. patients in it to meet FDA approval standards."

However, if, for example, a company ***wanted*** to make a claim about a particular ethnic group (e.g., African Americans), it would need to have a subset of patients in that ethnic group that was large enough to be powered to show a positive effect in that ethnic group. The study would also need to have a subset hypothesis. This is not something that comes up very often or in a typical study.

Where this issue does come up is in large outcomes studies done globally. Once in a while, in those studies, the results are significantly different in some country, including sometimes in the U.S. That is not necessarily a bar to approval. For example, the FDA approved Toprol XL in heart failure where the global trial, MERIT-HF, showed a statistically significant improvement in the primary endpoint of death/hospitalization overall and a clear effect on mortality but no effect at all on cardiovascular (CV) mortality among U.S. patients. The FDA noted the differences in the label, but Dr. Temple said, "We noted the difference, but we couldn't decide if it was a play of chance…There is no doubt that we get nervous when we see major differences like this."

MERIT-HF was a 3,991-patient trial vs. placebo, which showed:

- All-cause mortality was 7.3% with Toprol XL vs. 10.8% with placebo, a 34% risk reduction.
- All-cause hospitalization was 32% for Toprol XL vs. 38% for placebo, a 19% reduction.
- CV mortality was 10.1% for Toprol XL vs. 6.4% for placebo, a 38% reduction.
- The risk of death from worsening heart failure was 1.5% for Toprol XL vs. 2.9% for placebo, a 49% reduction.
- In the U.S. subgroup (n=1,071 of ~25% of trial patients) and in women (n=898, also ~25% of patients), the CV mortality was not significantly reduced. Indeed the rates were almost identical.

Assuming a U.S. or North American subgroup analysis was planned in a global trial, and assuming the subgroup was large enough to be powered to show any effect, would that subgroup have to be positive for approval? This was discussed in a recent Q&A update of ICH E-5. Dr. Temple said, "Generally even very large multinational trials are underpowered for any given country, so we would not expect significance. Large differences, though, would worry us. We would wonder if the way people might be treated is different in the U.S., if the standard of care is the same, if the use of other (background) drugs is different. But this is mostly for outcomes studies. A symptomatic drug is different, and we would be very concerned if U.S. studies failed. We've seen antidepressants that seemed to work nicely in Latin America and Eastern Europe, but when they moved to the U.S., the drug didn't work any more, and we didn't approve it."

For drugs in large, global, outcomes studies, the issue for the FDA is more what to say in the label if the U.S. results differ. Dr. Temple said, "If a drug wins overall, our big debate is how much to say in the label – whether to say it is a real worry or probably chance. More and more we are putting forest plots – graphical displays illustrating the strength of treatment effects in various demographic or other subgroups – into labeling. The question is how much to make of them (the forest plots) when one subgroup seems different."

Another example: The LIFE hypertension study which compared losartan (Merck's Cozaar) to atenolol. Losartan won overall on stroke reduction, except in African Americans, where it was almost significantly worse. The FDA handled that by approving losartan but putting the information in the label, saying the Agency didn't know if it was true, but drawing attention to the data.

The limitations of subgroup analyses were highlighted by a tongue-in-cheek analysis by the noted biostatistician Sir Richard Peto of Oxford which showed a drug beating placebo in one of the ISIS studies except under two zodiac signs.

Would it make a difference if the comparator were an active drug instead of placebo? Would that make the failure of the U.S. subgroup to meet the primary endpoint of more consequence? Dr. Temple said it would be more problematic if the trial was against an active control than placebo because the Agency worries more about whether the drugs were used the same way, "In an active control trial, the biggest worry is if the active control had the usual effect…But we usually have set a reasonably tough standard (in the primary endpoint), a fairly conservative approach, so we would be moderately concerned in that situation."

Double-dose clopidogrel

Double-dose clopidogrel is likely to become commonplace if not standard of care in cardiac cath labs, but just until Brilinta is available and perhaps after that for *some* patients, but it does not solve the problem of Plavix resistance. And one cardiologist pointed out that prasugrel is likely to be cheaper than double-dose *generic* clopidogrel.

- *U.S. #1:* "Even double the Plavix dose doesn't assure you will get the same benefit as using one of these more potent antiplatelet agents. Surely, giving the higher clopidogrel dose gives you more protection than 300+75 mg, but OASIS-7 doesn't say that would be as good as prasugrel or ticagrelor."

- *U.S. #2:* "Doubling the daily dose of clopidogrel gets you a little further along but not as far along as prasugrel… Theoretically, this is a good place for a comparative effectiveness study. The question will become an economic one. If you have adequate antiplatelet therapy with 75 mg or 150 mg clopidogrel, do you go to a more expensive drug?...Do you want to double everyone…or test people? You improve your responsiveness a bit with double-dose…So, you gain something, but you don't fix it. Doubling the dose doesn't cure the problem, it lowers the number of non-responders somewhat."
- *Netherlands:* "Overall, OASIS-7 was an ACS trial, and in the overall results, there was no difference with high vs. low dose clopidogrel, and no difference with high vs. low dose aspirin. Only with a post hoc analysis was there a benefit with (high dose clopidogrel in) PCI. You never know when a patient comes in if the patient will get a stent. Double-dose clopidogrel should not be given to everyone – only after a patient receives a stent. That is a bit disappointing…In the cath lab, we may double dose clopidogrel for a week, but that is a short period. It was a positive trial, but it won't change practice or guidelines."
- *Austria:* "OASIS-7 will have a major impact, with high-risk patients getting double dose immediately…Ticagrelor is very expensive, and clopidogrel is going generic, so we'll probably give all patients double-dose clopidogrel."
- *U.K.:* "Double-dose clopidogrel will now go ahead of prasugrel but not ahead of ticagrelor."

BOEHRINGER INGELHEIM's Pradaxa

Pradaxa is expected to be the first-line choice ahead of warfarin if it is priced right (equal or less than the cost of warfarin plus monitoring, which most sources agreed is hard to estimate and varies geographically within the U.S. but generally is under $500/month in most places). Yet, even with proper pricing, warfarin will still have a role in patients who cannot tolerate the side effects of Pradaxa (dyspepsia) or who are not compliant with the BID dosing of Pradaxa.

- "You are likely to see a sea change in clinical practice with the data on dabigatran in RE-LY…RE-LY is the headline of ESC."
- "I agree with the (***New England Journal of Medicine***) editor that the main primary endpoint and the other endpoints all favor efficacy. You do have side effects and a modest infarct increase. In my patients, who have been looking for an alternative to Coumadin (warfarin) and periodic blood tests, presented with this information and asked, 'Would you like to try a drug with an increase in GI side effects but which no longer requires blood tests, diet restrictions, or a worry about every other drug you are put on and interaction?' I think most patients will look at me and say, 'Are you serious, doctor?' Every one of my sophisticated patients on Coumadin ask me yearly how the alternatives to Coumadin are coming."
- "Use (of Pradaxa) depends on the pricing."
- "This would be an ideal type of thing for a comparative effectiveness study."
- *Dr. Anthony DeMaria of the University of California, San Diego, editor-in-chief of the* ***Journal of the American College of Cardiology*** *(JACC):* "RE-LY is far and away, hands-down, the headline story of ESC. Warfarin is a hateful drug. It really is…We've been looking for an alternative to warfarin forever. Many think there has been an under-utilization because it is a difficult drug to use… As a strategy, I would start with the easier drug to use (Pradaxa), and then, if a patient didn't tolerate it, go to the more problematic drug (warfarin)…Every doctor, I think, would choose to start with dabigatran rather than warfarin."
- *Netherlands:* "RE-LY was a landmark study…I like that we will have a low dose for patients at risk of bleeding and a high dose for low bleeding risk patients – a high dose for high stroke risk patients…Warfarin will be dead."
- *Dr. John Camm of the U.K.:* "I strongly urge the results of RE-LY not derail other agents (under investigation)."
- *U.K. #2:* "Because it is likely to cause such a sea change, maybe another trial would be good. But patients really want a drug without testing."

How concerning is the MI signal with Pradaxa? Most cardiologists questioned were not very worried about it.

- *Dr. Ray Gibbons, AHA past president:* "There is a signal there, and it deserves further attention. We need to watch it. It is a signal, not a hard finding. It was a blip in the results…Whether or not another trial is needed is for the regulators to decide, but for me, I'll watch how it develops with additional patient exposure."
- *Dr. DeMaria was startled to learn about the MI signal:* "It is a very small incremental risk…but you wouldn't expect that in an AFib population…The difference in AMI from 0.53% to 0.7%...that 0.2% increase is incredibly small…That small difference in a huge number of patients might be more magnified in a group of patients who had high-risk coronary artery disease (unstable angina, etc.)…So, it might be very reasonable to say that maybe warfarin might still have a role in patients who have high-risk coronary artery disease…If you segment them out, the risk might be high enough that, in that subset, you might elect to use warfarin – in perhaps 15% of the population…I still think this (RE-LY) is a fabulous result for an alternative to a problematic drug, but the blip with the AMI has to be watched, and it might only be relevant to a patient population with high risk of AMI."
- *Netherlands:* "The MI rate does concern me!"
- *U.K.:* "I could imagine a black box on MI."

- *Austria:* "The MI rate doesn't take the excitement away. There is much less need for monitoring with dabigatran. A drug that avoids monitoring will be very important. Less bleeding and fewer strokes for more MI might be a fair trade-off."

There is no established FDA position on how much of an MI elevation/signal in a pivotal Phase III trial would be concerning. There is no cut-point that raises the level of concern similar to a drug that increases blood pressure >5 mmHg or QT prolongation >500 mc.

In the recently issued guidance for diabetes drugs on this issue, the drug's database was to rule out an excess risk of 80% (HR 1.8) prior to approval. Postmarketing, the company has to do a bigger study or pool data to rule out a risk of 30% (HR 1.3). Speaking generally on this topic, the FDA's Dr. Temple said, "This is a disease (diabetes) that has major CV consequences, and you really want to know (if there is an MI risk). If you look at what people are doing with the databases for NSAIDs, they are getting 10,000-20,000 patients, which could rule out a quite small risk. The question you might ask is if we are looking at calling for this anywhere else, and the answer is, 'We haven't said.'"

Oral hypoglycemics is not the first class where the FDA has had concerns. The FDA is particularly concerned about CV medications because patients are already at risk, and some drugs have recognized risk, such as antiarrhythmics and drugs for heart failure. Dr. Temple said, "We have been nervous about certain classes for some time – antiarrhythmics and heart failure drugs – and we insist that whatever symptomatic benefit you get, you rule out an excess of deaths."

Is one trial sufficient for Pradaxa? One very large outcomes trial with a strong p-value is likely to be sufficient for FDA approval. It is unlikely the FDA would ask for another trial unless there were a safety issue (e.g., MI) that could only be resolved with another trial or if there were uncertainty about the result. Generally, the FDA does not expect companies to conduct more than one ***large*** outcomes study, provided the results are clear. Dr. Temple said, "We generally say that if the p-value is very low (<0.01), that might suffice if there is nothing to worry about. It gets unrealistic to expect two 10,000-patient trials. So, if the results are very strong, we certainly accept it (one trial). And if it is a familiar class with known pharmacologic effects, that gives us comfort. The nature of the outcomes also matter; we are more generous if it is a mortality trial. Those large trials have huge safety databases."

Generally, most cardiologists thought RE-LY was large so that a second trial, a confirmatory study, should not be required. Dr. De Maria said, "It is a very large, multicenter, multicountry, statistically robust trial. It comes in the context of a congener drug, ximelagatran (AstraZeneca's Exanta), that showed the same kind of efficacy but had a higher incidence of side effects (particularly liver failure). If you are willing to say ximelagatran also proved to be equally effective as warfarin, then this is, in that context, maybe not the only study…I think there is more analysis needed (on Pradaxa and RE-LY). It would be useful to analyze whether the increased risk of MI existed primarily in the patient population that had symptomatic coronary artery disease or if, in fact, the risk of MI was higher in the group of patients with coronary artery disease than without. That might identify a subgroup of patients where you might prefer warfarin."

Competition is on the horizon. Cardiologists questioned all agreed that there is still room for other competitors in this space, and there are several, including:

- **Bristol-Myers Squibb/Pfizer's apixaban.**
- **Daiichi Sankyo's edoxaban (DU-176b).** A Phase III trial of this antiplatelet agent (in AFib) is ongoing. An investigator said, "Based on the Phase II data, which has very important PK data that identified dosing, two doses were taken into Phase III…Warfarin will remain the comparator. RE-LY is a very encouraging sign because it was important to know there are drugs that can compete with warfarin, and it will encourage people to enroll patients (in other trials)."
- **Portola/Merck's betrixaban.**

What do cardiologists think the positive data at ESC from the PLATO and RE-LY trials mean for betrixaban and Portola/Novartis's elinogrel? Doctors repeatedly emphasized that they want competitors to continue development, insisting that there is room for more agents and suggesting that the competitors may have advantages over Brilinta and Pradaxa. In particular, they emphasized elinogrel is:

- The only P2Y12 being developed with both IV and oral formulations, which may make the transition from IV to oral antiplatelet dosing.
- Reversible.
- QD, a real advantage over Pradaxa's BID dosing.

MADIT-CRT – marketing hype?

Cardiologists generally agreed that the results of this cardiovascular resynchronization therapy trial are unlikely to significantly boost the volume of device implants in the short term, though heart failure patients may more often get a CRT-D than an ICD going forward.

Will MADIT-CRT change the American College of Cardiology/American Heart Association heart failure guidelines? Dr. Mariell Jessup, a heart failure specialist from the University of Pennsylvania and chair of the ACC/AHA heart failure guidelines committee, said, "If the indication for CRT is expanded to all stage C patients with a low LVEF and a QRS duration more than 120 msec, regardless of current symptoms or the duration of medical therapy, the potential 'indication creep' in patients who are unlikely to derive a

mortality benefit will alter the benefit-to-safety ratio and tip the score on cost-effectiveness even further in the wrong direction. Given the sobering facts about the costs of healthcare confronting us now and in the future, it appears prudent that any expanded indication for CRT in less symptomatic patients should be confined to patients with a QRS duration of more than 150 msec and in whom previous marked symptoms have been controlled with optimal medical therapy."

Will the FDA approve this new indication for CRT-D, and will CMS cover the cost for Medicare patients? MADIT-CRT investigators were confident that the devices will get approved by both agencies. However, the FDA had some issues with the trial design that were ignored, and CMS is likely to be difficult to convince. Dr. David Cannom of Good Samaritan Hospital in Los Angeles CA, a MADIT investigator, said, "The FDA wanted us to turn off a fraction of the CRT devices at Year 1, which we all thought was a crazy idea, and we refused to do it. They (FDA) didn't come back and reprimand us (for not doing it)." Dr. Cannom said it would have cost another $20 million to do the trial the way the FDA wanted.

DRUGS

ANTICOAGULANTS

BOEHRINGER INGELHEIM's Pradaxa (dabigatran etexilate), a direct thrombin inhibitor – a game changer

- **high dose superior to warfarin and easier to give**
- **low dose non-inferior to warfarin and easier to give**
- **both doses easier to give than warfarin but more side effects (MI and dyspepsia) and higher dropout rate**

The results of the Phase III RE-LY trial – published in the ***New England Journal of Medicine*** and presented at ESC – showed that both dabigatran doses tested (110 mg BID and 150 mg BID) were non-inferior to warfarin in patients with atrial fibrillation (AFib), and the 150 mg BID dose was superior to warfarin. While the stroke rate was lower with dabigatran, there was a price in terms of an increase in MI and dyspepsia.

RE-LY – with 18,113 patients, the largest AFib stroke prevention trial so far – was a multicenter study at 951 centers in 44 countries, sponsored by Boehringer Ingelheim. The dose of dabigatran was blinded, but warfarin use was not blinded, and warfarin patients had regular INR monitoring. The mean CHADS score was 2.1, and there was no difference in response to dabigatran based on the CHADS score.

Dr. Stuart Connolly of McMaster University in Canada, co-principal investigator for RE-LY, commented, "The results of dabigatran in RE-LY exceeded all our expectations. We now have an oral treatment which offers superior protection from stroke with less bleeding and without the need for routine monitoring…On top of the efficacy, dabigatran has shown equally impressive safety results, offering a wider safety margin."

Dr. Michael Ezekowitz of Pennsylvania, a RE-LY investigator, called it an "absolute game changer," predicting that Brilinta will "replace warfarin in most patients." He added, "From a purely personal level, when I was unblinded, I was amazed by the results of this trial. When we designed the trial, we had no anticipation of any of the dose being superior…It was designed as a non-inferiority trial. We felt that warfarin is an outstanding drug in terms of efficacy…and we felt that it would be highly unlikely that any novel drug would beat warfarin on efficacy and at the same time be as safe or safer. With that in mind, we designed the trial as an equivalency trial. The drug is so much more user friendly that we felt the characteristics of the drug would carry the day and make it acceptable to the FDA. The characteristics of the drug are user friendliness, rapid onset of action, very, very few drug/drug interactions, and no requirement for monitoring."

Key Results of RE-LY Trial of Pradaxa in Atrial Fibrillation

Measurement	Pradaxa 150 mg BID	Pradaxa 110 mg BID	Warfarin
Discontinuation rate per year	1.11%	1.53%	1.69%
Primary efficacy endpoint: Systemic embolism or stroke	1.11% (p<0.001 for ***superiority***)	1.53% (p<0.001 for ***non-inferiority***)	1.69%
Primary safety endpoint: Major hemorrhagic (stroke)	0.10% (p<0.001)	0.12% (p<0.001)	0.38%
Primary net clinical benefit: Composite of stroke, systemic embolism, pulmonary embolism, MI, death, or major hemorrhage	6.91% (p=0.04)	7.09% (Nss, p=0.10)	7.64%
Non-hemorrhagic stroke	0.92%	1.34%	1.20%
Extracranial hemorrhage	2.84%	2.51%	2.67%
Major bleeding (per year)	3.11% (Nss, p=0.31)	2.71% (p=0.003)	3.36%
Major or minor bleeding (per year)	16.42% (p=0.002)	14.62% (p<0.001)	18.15%
All-cause mortality	3.64% (Nss, p=0.051)	3.75% (Nss, p=0.13)	4.13%
Hospitalization	20.2% (Nss, p=0.34)	19.4% (p=0.003)	20.8%
Safety			
MI	0.74%	0.72%	0.53%
Dyspepsia	11.3%	11.8%	5.8%
ALT or AST >3xULN	1.9%	2.1%	2.2%
Hepatobiliary disorder	0.6%	0.5%	0.5%
Discontinuations			
1 year	16%	15%	10%
2 years	21%	21%	17%

Asked about the open-label design, Dr. Ezekowitz said, "The company communicated the design of the trial to the FDA, and the FDA commented on the design of the trial and found that the design was acceptable to them, but they made no commitments…There have been many unblinded trials of anticoagulation…The reason we did an unblinded trial is that it was a very carefully considered decision. In fact, the decision was made in concert with the FDA. They clearly allowed us to do the trial…but the reason we made this decision was that the blinded trials of anticoagulation in atrial fibrillation have results that were exactly comparable to unblinded trials…Also we felt that a blinded trial in anticoagulation represents an artificial situation, and an unblinded trial more accurately represents a practice situation…However, we also, in anticipation of questions about this, embedded scientific safeguards in the trial design – all the endpoints would be adjudicated by an independent committee blinded to the drug assignment and dose. 100% of endpoints were adjudicated."

Asked about the increase in MI, Dr. Ezekowitz said, "The incidence of MI was very low – 0.7% with dabigatran and ~0.5% with warfarin…We are unsure of the mechanism, but when I looked at patients with a prior history of coronary disease, the massive stroke reduction in these patients far outweighed the slight increase in MI. But we are looking into this in much more detail, and we haven't fully analyzed the data yet. The trial was just unblinded ~8 weeks ago."

Asked about the dyspepsia side effect, Dr. Ezekowitz said it ranged from abdominal pain to slight nausea but was a very non-specific symptom, "By taking the drug after food, there seemed to be some relief of symptoms, but for 4% of patients in both arms, the symptoms were severe enough to discontinue therapy. This is an issue that requires more in-depth evaluation…But the massive reduction in the primary endpoint for the 150 mg dose, and the massive safety improvement for the 110 mg dose – and the massive reduction in intracerebral bleeds for both doses – far outweigh the problem (dyspepsia) that some patients unfortunately might encounter."

Asked why the high dropout rate was higher than for warfarin, Dr. Ezekowitz said, "Dyspepsia was one reason, but there were other reasons – patient preference and doctor preference…We want to look into that in more detail. We suspect that (it was concern about an unknown drug)."

Asked if another Phase III trial is planned, Dr. Ezekowitz said that RE-LY was so large that the company believes one trial will be sufficient for regulatory approval in Europe and the U.S., "It is very clear the results in this study were absolutely definitive."

Asked how he would use dabigatran in his practice if it were approved, Dr. Ezekowitz said, "Dabigatran is much more user friendly (than Plavix) for the patient and for the doctor. So, as I do with all my patients, it is always an individual decision with an individual patient. What RE-LY has done is that, for the first time in 60 years, it has given the patient an option of whether to remain on Coumadin or switch. I suspect a large number of patients, given the option, will switch."

Asked if insurance companies and Medicare will pay for dabigatran if it gains FDA approval, Dr. Ezekowitz said he thinks patients will pressure insurance companies to cover it.

Asked which dose should go forward or be approved, Dr. Ezekowitz said, "That is an interesting question…We intend to look at that in great detail to determine if there are subgroups of patients in whom one may be better than the other. For the time being we are unsure about that. Both dosages are better than warfarin…Should we leave it up to the physician or choose the dose?...150 mg is far superior but slightly safer; 110 mg is vastly safer and slightly better. So, the question is unresolved. There are enough patients on both doses to do a rigorous comparison between the doses, and that is my (recommendation)." Asked if only one dose is chosen, if it would be 150 mg, he said, "That's undecided."

Asked what the RE-LY results mean for:

- *The outlook for Bayer/Johnson & Johnson's Xarelto (rivaroxaban) in the ongoing ROCKET-AF trial*, Dr. Ezekowitz said, "I think it raises the bar because ROCKET is being evaluated as a single dose, and my sense is that if dabigatran is approved, dabigatran will become the new standard against which any new agent will have to be compared."
- *The outlook for Mercks/Portola's betrixaban*, Dr. Ezekowitz said, "Betrixaban is in very early development. It has an interesting profile in that it is minimally cleared by the kidney. But it is too early to tell. (What betrixaban has to use as a comparator in Phase III) depends on the indication they go for and the results of the (ongoing) Phase II trial."

In an accompanying ***NEJM*** editorial, Dr. Brian Gage of Washington University School of Medicine pointed out that warfarin prevents 64% of strokes but is prescribed to only two-thirds of appropriate AFib candidates due to drug and dietary interactions, the need for INR monitoring, and concerns about real-world effectiveness, which is estimated to be ~35%. Dr. Gage estimated that more than 350 patients would have to be treated with high-dose dabigatran to prevent one more even than warfarin, but he still believes there is value in dabigatran use, particularly because of poor warfarin compliance. He noted that warfarin patients in the trial were in the therapeutic INR range 64% of the time, but he estimated that warfarin patients would have needed to be in range ~79% of the time to have a stroke rate as low as high-dose dabigatran – a goal he called "unlikely."

Dr. Gage also said the drug-drug interactions of dabigatran need to be considered. These include verapamil, amiodarone, and quinidine, all of which raise dabigatran serum levels

"considerably." But he noted that:

- 150 mg dabigatran is more efficacious and prevents more strokes.
- 110 mg dabigatran caused fewer hemorrhages and is safer, especially in patients taking amiodarone, etc. This dose may also be safer in petite, elderly, or renally-impaired patients.

Dr. Gage concluded, "Patients already taking warfarin with excellent INR control have little to gain by switching to dabigatran. In contrast, many other patients who have atrial fibrillation and at least one additional risk factor for stroke could benefit from dabigatran."

The number needed to treat (NNT) to benefit from dabigatran is very high (>350), but it is against an active comparator, not placebo. Other studies have shown a number needed to treat of 18-37 for warfarin to prevent 1 hemorrhagic stroke vs. placebo.

Dr. Gage's Estimate of NNT with Pradaxa

Comparison	NNT with Pradaxa 150 mg vs. warfarin
To prevent 1 non-hemorrhagic stroke	357
To prevent 1 hemorrhagic stroke	370
To have an MI	500

Overall, dabigatran is easier to use than warfarin because it doesn't require INR monitoring, and there is a non-significant trend to improved mortality, but it isn't a home run. Compared to warfarin, MI and dyspepsia are higher with dabigatran, and the 2-year dropout rate is higher with dabigatran. So, Dr. Gage's recommendation appears to be the best way to use this new agent.

However, it is likely that, if approved, doctors will not take this conservative approach to usage. Instead, dabigatran will largely replace warfarin – provided, in the U.S., that Medicare and insurance companies cover it.

Approvability is a question despite the positive data because of the open-label trial design. While patients were blinded to the dose of dabigatran, they were not blinded to dabigatran vs. warfarin. Approvability may be more of an issue in the U.S. than in Europe. European cardiologists predicted that the EMEA (European Medicines Agency) will approve dabigatran based on RE-LY. While the FDA prefers double-blind trials, it may accept an open-label trial provided the warfarin arm was in line with historic rates, and in this case the warfarin rate does seem in line with what would be expected.

Comments on the RE-LY data and the outlook for dabigatran included:

- *Dr. Fausto Pinto of Portugal, ESC program chairman, stopped short of calling it a home run:* "The hope is that the strength, size, and strong conclusions (in RE-LY) will be sufficient (for EU approval). I think there is enough evidence to establish dabigatran as a new option. RE-LY will provide more evidence that can help to change practice. (Dabigatran) is certainly a big step forward. It is a very good alternative to warfarin and will probably replace warfarin…There is strong evidence that this is a strong alternative to warfarin. It is easier to manage, and the results are very good."
- *Dr. Douglas Weaver of Michigan, immediate past president of the ACC:* "For me, it is a major breakthrough…The MI signal is small, and no one knows the significance…The most important endpoint – alive or dead – is going in the right direction…Now, you have a drug that actually seems to save lives, so I suspect physicians will be a little more generous applying the drug in some borderline populations."
- *Dr. Alfred Bove of Temple University Medical Center, current ACC president:* "The price of the drug (dabigatran) will be higher. Warfarin is very inexpensive, and I think the insurers will put a lot of pressure on doctors not to use it until the price comes down…We will be on the phone quite a lot trying to justify that drug…For a while it is going to be tough (to get it approved)…It is definitely a game changer…This is the first evidence that an alternative to warfarin works…Patients are going to demand it…In terms of the GI 'upset,' there is a population of patients who can't use warfarin and who are at risk of stroke and may be willing to tolerate the GI problems…There are a bunch of patients who dropped out of warfarin who we would like to have on an anticoagulant where this drug is an alternative…The reason it won't be first line is the insurance companies won't pay for it for some period of time. It will have to be introduced and take some time. In a couple of years, I think it will be the first-line drug we all will want to use."
- *Dr. Ralph Brindis of Kaiser Permanente in northern California, president-elect of the ACC:* "This may be a significant tipping point to decrease the number of patients not receiving an anticoagulant who should – and increasing the ability of both physicians and patients to utilize a drug that doesn't require the hassle of frequent drug testing…I would think there will be a lot of excitement that a huge untreated population will get treatment…For patients already on Coumadin and tolerating it well, I wouldn't jump ship, but new people who are first-timers with AFib or people I couldn't get on warfarin before would be excellent candidates for this new drug."
- *AHA's Dr. Yancy:* "I think RE-LY potentially is a game changer…because you are talking about a therapy that reduces the risk of stroke without the need for periodic testing or dose titration…Warfarin makes patients crazy…Patients are reluctant to go on (warfarin) and stay on it. That is why it is a game changer."
  - "The things that give people hesitancy in saying this is a game changer are the small incremental benefit and the unknown cost."

- "The big issue here is going to be the cost comparison, but standard of care has to include not only the cost of the drug but also the cost of the monitoring" – which he estimated at an average of $250/month (range $50-$500) for warfarin.
- "BID dosing is a compliance issue."
- "The excess MI also is a reason for pause. There is no plausible explanation for an uptick in MI. It is statistically significant, but is that a statistical fluke, a play of chance, or a real phenomenon? Why would a drug with anticoagulant properties end up pro-thrombotic?...But the signal is there, and we've learned in cardiovascular medicine not to ignore signals."
- *On the open-label trial design:* "That is something the FDA has to consider…The difference in bleeding between low and high dose will come into play and be a big part of the FDA deliberation. And these were older individuals; this is not an all-comers trial. This is a higher risk group. I would anticipate the FDA would come forward with somewhat restrictive labeling, particularly if there is concern about MI."
- "The dyspepsia (an increase in gastric acid) may be the reason the drug is more effective because the moiety to which it binds is one that generates dyspepsia."
- *What is the take-away message?* "If it is approved, it would have to be considered in the framework for which it is approved, likely high-risk patients – older patients and people with heart failure or a previous stroke. But the cost issues have to be resolved… Potentially for a not small cohort of AFib patients this could change how they are managed…Even a year (after approval), this will not be a dramatic uptake…There will be some hesitancy for patients doing well. But for patients who failed Coumadin (warfarin) or at high risk to take Coumadin, this is (a better option)…For any patients for whom you can avoid the weekly (INR) tests, this is a game changer...but if someone is doing very well (on warfarin) and tolerating it, why go through the disruption and switch?"

The MI issue with Pradaxa

There was a similar signal with another direct thrombin inhibitor, AstraZeneca's Exanta (ximelagatran), which could suggest a mechanistic explanation for the MI, which could make it more concerning.

At the Exanta FDA Advisory Committee meeting in 2003, MI and coronary artery disease (CAD) with Exanta were an issue. This was overshadowed by the liver toxicity problem that eventually killed Exanta, but FDA reviewers concluded that there was about a three-fold higher incidence of acute MI/CAD with Exanta short-term use (<35 days) vs. warfarin. There were also MI/CAD safety issues raised about long-term use (12 months) for VTE and AFib.

The panel voted that the MI risk requires further study ***before approval***, not just as part of postmarketing surveillance.

FDA question 1 to the panel: Regarding the potential risk of myocardial infarction/coronary artery disease (MI/CAD) with short-term exposure to ximelagatran (mean 8 days) in patients undergoing TKR (total knee replacement), do you recommend further studies to assess the risk of MI/CAD? If yes, what type of study(ies) do you recommend? **YES, the recommendation was for a 30-day pre-approval study with 90-day follow-up.**

FDA question 2 to the panel: Do you have other safety concerns (other than liver safety) with the long-term use of ximelagatran (e.g., cardiac)? Regarding the short-term use of ximelagatran? **YES for both, particularly cardiac safety, but some panel members were also concerned with bleeding.**

Dr. Steven Nissen, chairman of the Department of Cardiovascular Medicine at the Cleveland Clinic, was on the Exanta panel. Asked recently about the MI issue with dabigatran, he said, "It is the one category where warfarin looks better. I served on the Exanta panel and made this very point, but we noted something a little different with Exanta – many MIs occurred shortly after stopping the drug! I questioned whether this was a 'rebound' phenomenon. Because warfarin is longer acting, I wondered whether a short-acting direct thrombin inhibitor might show rebound. In RE-LY, I don't know the timing of the MIs…Bottom line: I would interpret RE-LY based upon the totality of benefit, rather than parsing different endpoints. Remember that individual endpoints are also 'subgroups' and subject to…

FDA View of MI/CAD Adverse Events with Exanta

Adverse Events	EXULT-A+B Trials	
	Exanta n=2,677	**Warfarin n=1,907**
Short-term use (<35 days)		
MI	16 patients (0.60%)	4 patients (0.21%)
Other CAD (angina/ischemia)	4 patients (0.15%)	1 patient (0.05%)
CAD events leading to discontinuation	20 patients (0.75%)	5 patients (0.26%)
Longer term use (>35 days)		
	Exanta n=6,931 for 370 days n=5,024 for ≥6 months n=3,509 for ≥12 months	**Warfarin n=4,967 for 455 days Placebo n=1,249**
MI (non-fatal) during treatment	26.3%	27.1%
CAD adverse events	7.0% for AFib patients 1.3% for VTE-T patients 2.6% for VTE-P patients	6.7% for AFib patients 0.1% for VTE-T patients 2.0% for VTE-P patients

statistical issues…You rarely see complete uniformity in any trial. I think both RE-LY and PLATO are robust results, and I'm not a pushover…Both drugs will achieve widespread usage."

Is there any rebound effect with dabigatran? A Boehringer official said the company doesn't know yet. Those analyses are ongoing, "This is an 8,113-patient trial. This is a huge trial. With trials of this magnitude, you will have data that doesn't come with a clear explanation…The study (PLATO) had a two-year duration. That is fairly long. Right now, we don't believe that (there is rebound), but we will continue to monitor patients in the extension study, but we don't believe there is."

When did the MIs occur? Again, that is still in the analysis phase.

What is the cause of the dabigatran MI? Again, a Boehringer official said the company doesn't know yet, but he commented, "The rate of MI in the trial was very low in general. One thing we are looking at and trying to understand is if this is related to a certain type of patient. There is definitely a lot of work (going on) to analyze the data and find some explanation…Different products act differently."

➢ **Net clinical benefit.** The Boehringer official emphasized that the net clinical benefit – which takes into account both safety and efficacy – favored dabigatran, "Overall, the benefit you get – taking pluses and minuses together – vs. warfarin is in favor of dabigatran. This compares to other products that require a significant number of patients to prevent an event, and stroke is one of the most devastating of those events."

➢ **Regulatory plans.** A company official confirmed that the current plan is to submit both doses to regulatory authorities (U.S. and Europe) by the end of this year. If approved, Boehringer plans to launch the drug itself, without a partner.

➢ **Reimbursement.** Boehringer has already started working on its reimbursement strategy. An official said, "We will have a lot of good health economics data…The team is working on a robust publication plan from the health economics side as well as a reimbursement strategy. The fact that we have been able to demonstrate a reduction in stroke as well as no incremental bleeding cost, we believe gives us a very good story."

The Boehringer official agreed with Dr. Yancy's estimate that the typical cost of a month of warfarin therapy, including testing, is in the range of $50-$500, but he pointed out that there are also a lot of other indirect costs, such as time taken off of work to get testing done, caregiver time, etc.

THE MEDICINE COMPANY's Angiomax (bivalirudin) – benefits hold up longer term

One-year data from the HORIZONS-AMI trial showed that Angiomax reduces clinical events in heart attack (STEMI) patients undergoing PCI. The data were published in ***The Lancet*** and presented at ESC.

Researchers, led by Dr. Roxana Mehran of Columbia University Medical Center in New York, reported that the initial 30-day results with Angiomax (reported last year) – lower rates of major hemorrhagic complications and net adverse clinical events (NACE) vs. heparin plus a GP IIb/IIIa inhibitor – were maintained at 1 year of follow-up. The researchers concluded, "In high-risk patients with STEMI undergoing primary PCI, procedural anticoagulation with bivalirudin alone seemed to reduce hemorrhagic complications, late reinfarction, and early and late cardiac and all-cause mortality compared with unfractionated heparin plus the routine use of a GP IIb/IIIa inhibitor. This finding has important clinical implications for the selection of optimum treatment strategies for patients with STEMI."

HORIZONS-AMI was a multicenter, open-label, randomized trial in 3,602 patients. It met both primary endpoints – efficacy and safety. The reduction in mortality was unrelated to the type of stent used (bare or drug-eluting). Interestingly, the study also provides reassurance that Angiomax does not increase the incidence of stent thrombosis at one year.

In an accompanying commentary in ***The Lancet***, Dr. Ranil de Silva and Professor Kim Fox of the U.K. said the HORIZON-AMI 1-year results "provide the rationale for considering bivalirudin monotherapy in patients with ST elevation acute coronary syndromes receiving primary PCI. This strategy should be the preferred option in patients with the highest bleeding risk but might be less appropriate in those with acute stent thrombosis, large thrombus burden, or no reflow." They added that this strategy "should be preferred in patients with the highest bleeding risk."

1-Year Results of HORIZONS-AMI Trial

Measurement	Angiomax n=1,696	UFH+IIb/IIIa n=1,702	p-value
Primary endpoint #1: Major bleeding	5.8%	9.2%	RRR 39%
TIMI major or minor bleeding	6.5%	10.2%	<0.0001
Primary endpoint #2: NACE (major bleeding or composite MACE: death, reinfarction, target vessel revascularization for ischemia, or stroke)	15.6%	18.3%	0.022 HR 0.83 RRR 17%
MACE	11.9%	11.9%	Nss, 0.98
Cardiac mortality	2.1%	3.8%	0.005
All-cause mortality	3.5%	4.8%	0.037
Reinfarction	3.6%	4.4%	Nss, 0.22
Non-Q-wave reinfarction	1.4%	2.7%	0.009
Stent thrombosis	3.1%	3.5%	Nss, 0.53

PORTOLA/MERCK's betrixaban, an oral direct Factor Xa inhibitor

Top line data from the Phase II EXPLORE-Xa trial in AFib is expected by the end of 2009, with a Phase III trial starting by the end of 2010. The company hopes to get betrixaban on the market in 2014.

While a year might seem a long time between the end of the Phase IIb trial and the beginning of the Phase III trial, both Portola and Merck officials agreed that is the likely timeframe. Anne Hermanowski Vosatka of Merck said the regulatory-imposed "quiet period" just ended, and Merck had only been able to really talk to Portola for about 1.5 weeks, so Merck really needs to get in and figure things out, including incorporating the new data on dabigatran. She said starting the Phase III trial "can take a year, and this probably won't be faster…The comparator will be warfarin…and that will remain so until dabigatran is approved. And it is a global filing, so we have to consider that."

Bayer/J&J's Xarelto (rivaroxaban) is further along in development in AFib than betrixaban, but neither Portola nor Merck appears concerned about that. Portola CFO Dier said, "In RE-LY, dabigatran is superior and safer than warfarin, and if dabigatran gets approved, having something beat warfarin in a controlled setting, we think is fabulous. Physicians hate using warfarin. We would be very excited (about the approval) …We think it gives us an advantage to learn from the compounds ahead of us. They are pushing a short half-life drug into once-daily. We think a real QD drug will be an advantage. And we have no CYP450 interactions, and no CYP450 2C19*2 effect at all (like Plavix)."

Dier speculated on how betrixaban can play in this space, "It is a huge market. The AFib market could grow, and we think the characteristics of our drug are such that it will again be the best-in-class compound when approved. Betrixaban has a long half-life – 19-25 hours – so it is a true once-a-day. The very low peak-to-trough ratio (3:1) is one of the lowest out there. I think there will be a lot of discussion of whether the rivaroxaban dose is too high and whether you will see spikes and too much bleeding. Our philosophy is to keep the peak-to-trough ratio lowest. And we have the lowest renal clearance – 15% vs. 80% for dabigatran. So, we don't have to carve out renal patients except for dialysis patients… Physicians will grab the drug that is easiest to prescribe and to the broadest patient population…I think betrixaban will be for AFib. Some doctors are comfortable with enoxaparin (Sanofi-Aventis's Lovenox) in the short-acting setting, but I think there will be tremendous uptake of Factor Xas once they are approved."

Asked what PLATO means for betrixaban, Merck's Vosatka said, "Obviously, we need to think carefully about this very positive study…And we are conscious of the fact that, because we are not one of the first agents in this indication, that we will have to watch the other agents and how they do in development…We will spend a lot of time and attention poring over the data."

What does Merck see as the advantages of betrixaban over dabigatran? Vosatka cited three things:

1. **Betrixaban targets Factors Xa instead of thrombin.** As a result, they may have non-overlapping benefits…It seems unlikely that giving both would necessarily have a benefit, but that has to be considered (as, for example, with an ACE inhibitor and an ARB)."
2. **Betrixaban is likely to be able to be used without restriction in patients with renal impairment.** "Many of the AFib patients are elderly, and many elderly patients have compromised renal function, so in this particular population, where you are trying to prevent stroke, renal compromise is quite common."
3. **Betrixaban offers once-daily dosing.**

REGADOBIOSCIENCES and DUKE UNIVERSITY's REG1 System, a reversible Factor IXa inhibitor – very early but interesting

According to a poster at ESC by Duke researchers, this synthetic, single-strand oligonucleotide is metabolized in blood with no "active" metabolites and no protein binding. The REG1 System is composed of two parts:

1. RB006, an anticoagulant with a half-life of >24 *hours* and a specific affinity for Factor IXa.
2. RB007, an active control agent with a half-life of <5 *minutes* and specific affinity for RB006.

In a Phase IIa open-label, PCI study, the researchers looked at 24 patients and found:

- All procedures were successful.
- The treatment was well tolerated.
- No cath or guidewire thrombosis occurred.
- RB007 facilitated early sheath removal.
- RB006 (1 mg/kg) demonstrated rapid onset with consistent coagulation during PCI.

A Phase IIb trial will evaluate safety and efficacy in ACS patients undergoing cardiac catheterization.

Phase IIa Results with REG1 System

Measurement	Partial reversal n=10	Total reversal n=10	UFH n=4
Primary endpoint: Modified acuity bleeding events	0/10	0/10	1/4
Death/MI/urgent TVR through Day 14	1/10	1/10*	1/4

* Not related to REG1

SANOFI-AVENTIS's otamixaban – positive news but not a home run, almost a "who cares"

The SEPIA-ACS-1-TIMI-42 trial showed that intravenous (IV) administration of the direct Factor Xa inhibitor otamixaban was effective in patients with non-ST-elevation ACS. The results were pub-ished in ***The Lancet*** and preented at ESC. SEPIA was a randomized, double-blind, Phase II, parallel group, dose-ranging, active-controlled trial with 3,241 patients sponsored by Sanofi-Aventis.

Dr. Marc Sabatine of Brigham and Women's Hospital in Boston and colleagues compared five otamixaban doses (a 0.08 mg/kg bolus followed by infusions of 0.035, 0.070, 0.105, 0.140, or 0.175 mg/kg/hour) to the combination of unfractionated heparin (UFH) and an IV GP IIb/IIIa inhibitor [in this case, Schering-Plough's Integrilin (eptifibatide)], which is the current standard of care for ACS. The lowest dose group was stopped early at the recommendation of the data safety monitoring board (DSMB), due to higher numbers of patients going on to have full heart attacks and/or dying.

The researchers found that, "in all of the otamixaban dosage groups, except the lowest one, the rate of death, second heart attack, or additional coronary complications tended to be lower with otamixaban than with heparin plus eptifibatide." The results at 7 days held up out to 180 days.

The intermediate doses of otamixaban (0.105 or 0.140 mg/kg/h) appeared the best, resulting in:

- A 40% lower rate of death, second heart attack, or additional coronary complications vs. UFH + Integrilin.
- A ≥45% reduction in death or a second heart attack.

In terms of adverse events, the researchers reported a signif-icant increase in bleeding across the 5 otamixaban dosage groups, but the rate with the intermediate doses of otamixaban was similar to UFH + Integrilin.

The researchers concluded, "Our study offers additional preliminary evidence for the efficacy and safety of direct Factor Xa inhibition with otamixaban in patients with coronary disease…These findings will need to be tested in a large Phase III trial to establish the definitive role of otamixaban in the treatment of acute coronary syndromes."

What does this mean for the Phase III trial? The researchers suggested, though the company has not confirmed, that a bolus of 0.08 mg/kg, followed by an infusion of 0.105-0.140 mg/kg/h is the likely dose. They argued that otamixaban may be superior to heparin + a IIb/IIIa, Angiomax, or fondaparinux (GlaxoSmithKline's Arixtra) because otamixaban is reversi-ble, may result in a lower rate of ischemic events, may not require dose modification in renally-impaired patients, and is not associated with catheter-related thromboses at the proposed dose.

However, in an accompanying commentary, Dr. John Eikelboom and Dr. Jeffrey Weitz of McMaster University in Canada questioned the need for this drug, "These findings suggest that, like bivalirudin, otamixaban may be a useful alternative to heparin for patients with acute coronary syndromes who are undergoing PCI. However, do we need another parenteral agent for this indication? Without safety or convenience advantages, otamixaban would need to demon-strate efficacy that is superior not only to heparin but also to bivalirudin before it would be adopted for clinical use. To our knowledge, there are no on-going Phase III trials to explore these possibilities, nor is otamixaban under development for other clinical indications."

Results of SEPIA-ACS-1-TIMI-42 Trial of Otamixaban

Measurement	Otamixaban (mg/kg/h)					UFH + Integrilin
	0.035	0.070	0.105	0.140	0.175	
Primary efficacy endpoint: Composite of death, heart attack, urgent treatment to increase blood flow in the artery, or bailout IIb/IIIa inhibitor use up to 7 days	7.2% (RR 1.16)	4.6% (RR 0.74)	3.8% (RR 0.61)	3.6% (RR 0.58)	4.3% (RR 0.69)	6.2%
Death	0.8%	1.3%	1.2%	1.2%	1.2%	1.8%
MI	4.0%	1.6%	1.4%	2.0%	1.8%	3.1%
Urgent revascularization	0.8%	0.3%	0.8%	0.3%	0.6%	0.7%
Primary safety endpoint: Major or minor bleeding not related to CABG	1.6%	1.6%	3.1%	3.4%	5.4%	2.7%
Bailout IIb/IIIa use for recurrent ischemia or thrombotic complication	3.2% (RR 2.87)	2.2% (RR 1.99)	1.4%	0.8%	1.2%	1.1%
Thrombotic complication during PCI	6.2%	5.0%	2.9%	3.5%	3.2%	2.4%

PLATELET AGGREGATION INHIBITORS

A survey of 500 European cardiologists showed that as many as 40% of their ACS patients on oral antiplatelet therapy (aspirin or aspirin + Plavix) are at significant risk for having another cardiovascular event. The survey was conducted in July 2009 by Harris Interactive for Schering-Plough. Oral antiplatelet therapy is the standard of care for ACS patients according to 90% of the doctors questioned, and 96% said that some of their patients are at risk for having another cardiovascular event. More than half (62%) estimated that 11%-40% of their ACS patients may still be at risk for having another cardiovascular event.

Three-quarters of the physicians said that bleeding is a disadvantage of current oral antiplatelet therapy in ACS patients.

Most cardiologists said that they would use an oral antiplatelet therapy that does not have an incremental bleeding risk:

- 87% would choose an oral antiplatelet therapy that does not have incremental major bleeding risk over a therapy that does.
- 95% described a novel oral antiplatelet therapy that reduces cardiovascular events without an incremental increase in the risk of major bleeding as a therapeutic advance.
- 93% would adopt a novel antiplatelet therapy if it significantly reduces cardiovascular events without incremental bleeding risk when used with standard-of-care regimens.

ASTRAZENECA's Brilinta (AZD-6140, ticagrelor), a P2Y12 inhibitor – looks better than Plavix and safer than prasugrel, but it has problems of its own

The results of the PLATO trial – published online in the ***New England Journal of Medicine*** and presented at ESC – showed that Brilinta significantly reduced death from vascular causes, MI, and stroke without increasing major bleeds but with an increase in non-procedure related bleeding. PLATO trial chair Dr. Lars Wallentin of Uppsala Clinical Research Center University Hospital in Sweden and colleagues said the advantage to Brilinta was evident within the first 30 days and persisted throughout the study period.

Brilinta is an oral, reversible, direct-acting, P2Y12 inhibitor. PLATO was a randomized, international, multicenter, double-blind trial comparing Brilinta (180 mg loading dose, followed by 90 mg BID daily) vs. Plavix (either 300 or 600 mg loading dose, followed by 75 mg daily) in 18,624 patients with ACS (with or without ST-segment elevation). Nearly all the patients (95.7% of Brilinta and 95.3% of Plavix) underwent PCI either during index hospitalization or within 24 hours of randomization.

The key findings were:

- Brilinta showed superiority to Plavix, significantly reducing the composite rate of death from vascular causes, MI, or stroke (a 16% relative risk reduction).
- Major bleeding was not decreased, but it also was not increased (as with prasugrel).
- Brilinta was effective without regard to STEMI status, the Plavix loading dose, or whether invasive management was planned.
- All-cause death was reduced 22% at 1 year.
- The treatment effects were the same in the first 30 days as out to Day 360.
- The concerns with Brilinta are dyspnea, ventricular pauses, increases in serum creatinine and serum uric acid, and a slight trend to a higher risk of hemorrhagic stroke.

Results of the PLATO Trial of Brilinta in ACS Patients

Measurement	Brilinta	Plavix	p-value
Primary endpoint: Composite of death ***from vascular causes***, MI, or stroke	9.8%	11.7%	0.0003
Secondary endpoints			
Composite of death ***from any cause***, MI, or stroke	10.2%	12.3%	<0.001
MI	5.8%	6.9%	0.005
Death from vascular causes	4.0%	5.1%	0.001
Stroke	1.5%	1.3%	Nss, 0.22
Hemorrhagic stroke	0.2%	0.1%	Nss, 0.10
Other results			
Major bleeding (by study criteria)	11.6%	11.2%	Nss, 0.43
Major bleeding (by TIMI criteria)	7.9%	7.7%	Nss, 0.57
Non-CABG major bleeding (by study criteria)	4.5%	3.8%	0.03
Non-CABG major bleeding (by TIMI criteria)	2.8%	2.2%	0.03
Non-intracranial fatal bleeding	0.1%	0.3%	0.03
Intracranial bleeding	0.3%	0.2%	Nss, 0.06
Death from any cause	4.5% (RRR 22%)	5.9%	<0.001
Results in patients for whom invasive treatment was planned			
Composite of time to first occurrence of death ***from vascular causes***, MI, or stroke	8.9%	10.6%	0.003
Stent thrombosis (definite by ARC)	1.3%	1.9%	0.009
Stent thrombosis (probably/definite by ARC)	2.2%	2.9%	0.02
Adverse events			
Dyspnea	13.8%	7.8%	<0.001
Ventricular pauses ≥3 sec in first week	5.8%	3.6%	0.01
Ventricular pauses ≥3 sec at 30 days	2.1%	1.7%	Nss, 0.52
Increase in serum uric acid from baseline at 12 months	15%	7%	<0.001
Increase in serum creatinine from baseline at 12 months	11%	9%	<0.001
Discontinuations			
Overall	23.4%	21.5%	0.002
Due to adverse events	7.4%	6.0%	<0.001
Due to dyspnea	1.0%	0.3%	<0.001

The benefits of Brilinta were less in 3 of 33 subgroups:

1. Patients weighing less than the median weight for their sex.
2. Patients not taking lipid-lowering drugs at time of randomization.
3. North American patients.

How do Brilinta, Effient, and Plavix compare? Each has advantages and disadvantages. *(See chart on right)*

Comparison of Brilinta and FDA-Approved Antiplatelets

Measurement	Plavix	Effient	Brilinta
Reversibility	Irreversible	Irreversible	Reversible
Bleeding	Some	Increased	No increase
Variability in response	An issue	Less an issue	Less an issue
Onset of action	Delay	---	Fast
Stent thrombosis	Increased risk	Possibly less	---
Mortality in ACS patients	No significant improvement	No significant improvement	Improved survival
Spontaneous bleeding	No increase	Increased	Increased
Drug-drug interactions	Yes	Yes	Less
Genetic polymorphisms that affect response	Yes	No	No
New side effects	No	No	Dyspnea, elevated uric acid and creatinine, bradyarrhythmia, trend to more hemorrhagic stroke
Cost	Will be generic soon	More expensive	More expensive

Dr. Wallentin put the findings in perspective, "All of the time event rates were lower with ticagrelor than clopidogrel, driven by MI, where you also see a continuous lower risk, and by CV death, which showed a continual benefit with better survival during the whole treatment. The largest benefit was in total death, and there was a significant difference in total mortality: 4.0% vs. 5.1%, favorg ticagrelor…Based on 1,000 patients admitted to the hospital for a heart attack, using ticagrelor leads to: 14 fewer deaths, 11 fewer MIs, 6-8 fewer stent thromboses, and no increasing bleeding requiring transfusion. Nine patients may switch to thienopyridine treatment because of reversible symptoms."

Dr. Wallentin said the results for Brilinta hold up among the subgroups evaluated – men, women, bodyweight, age, prior TIA/stroke, "It seems to be a similar effect across the board."

How does Brilinta compare to double-dose Plavix? Dr. Wallentin said, "The results are the same in patients with the double dose and the single dose (Plavix). You get the same benefit of ticagrelor in double-dose Plavix…That suggests using ticagrelor (instead of double-dose Plavix)."

Comparison of Antiplatelet Trials *

Measurement	Relative risk reduction		
	Plavix in CURE	Effient in TRITON-TIMI-38	Brilinta in PLATO
Death from any cause	0.93	0.95	0.78
CV death	0.93	0.89	0.79
MI	0.77	0.76	0.84
CV death, MI, or stroke	0.80	0.81	0.84
Major bleeding	1.38	1.45	1.04

* Source: Dr. Schömig editorial in NEJM

In an accompanying ***NEJM*** editorial, Dr. Albert Schömig of Munich, Germany, said the availability of three antiplatelet agents may make it possible to individualize antiplatelet therapy. He speculated on how Brilinta may be used:

- As with prasugrel, avoid it in patients with a high bleeding risk.
- As with prasugrel, avoid it in patients with a history of stroke or transient ischemic attacks.
- Use it for patients whose coronary anatomy is unknown and for whom a CABG proce-dure is deemed probable.
- Switch patients to it from clopid-ogrel or prasugrel if they need elective surgery for 5-7 days before the operation.
- Avoid it in patients with COPD, hyperuricemia, moderate or severe renal failure, bradyarrhythmias unprotected by a pacemaker, a history of syncope, or the need for prolonged (>1 year) treatment.
- Make either it or prasugrel the preferred therapy in all other ACS patients until there is head-to-head data comparing Brilinta and prasugrel.

Cardiologists were generally very enthusiastic about the PLATO findings. Their comments included:

➢ *New York:* "Clopidogrel was a game changer…Suddenly we have two very attractive alternatives to Plavix (prasu-grel and ticagrelor). The fact that ticagrelor was able to lower death rates is very powerful. We didn't see that with prasugrel in the TRITON trial…Bleeding increases with the more effective drugs, but it's a small number of people who have trouble. The benefit of taking a stronger agent is going to outweigh the increased bleeding risk for more patients. One concern using ticagrelor in patients getting stents is the risk of stent thrombosis. Although it was lower with ticagrelor in PLATO, in the real world patients miss pills sometimes. Since the drug effect wears off after 24 hours or so, the chance of stent thrombosis should go up in people who have trouble taking a pill twice a day…There's no doubt that Plavix is in for real competition. I wouldn't be surprised to see prasugrel take a significant market share over the next 24 months, with ticagrelor being used in patients at risk of bleeding complications or who plan to have surgery soon after they suffer a coronary problem."

- *Michigan:* "This drug appears to be even better than prasugrel."
- *AHA president Dr. Yancy:* "PLATO was very interesting, but it is a little complicated. It basically means we now have a third antiplatelet drug for ACS. That means that practitioners and ultimately patients will have to recognize that there is no one treatment du jour when antiplatelet therapy is desired."
  - "It is tempting to compare CURE, TRITON, and PLATO…and see if we can come up with a statement about one being more effective or safer than the others, and the answer is no (we can't)…If you look at just the clopidogrel arms in the three studies, the bleeding rates are vastly different, which means either the definitions or the patient cohorts are very, very different…So, the only way we will know the relative efficacy or relative risk is in the exact same patient population, head-to-head."
  - "(Brilinta) almost totally bypasses the liver, so genetic metabolism and drug-drug interaction may be less of an issue. In those situations, especially if someone had previous difficulty managing clopidogrel, this may be an option. I envision a circumstance where someone doing fine on clopidogrel develops a problem, and this would be an option that avoids one of the very big issues with clopidogrel."
  - "The hesitancy with ticagrelor is the unusual, unintended issue of bradycardia that has to be sorted out. So, it is likely that patients predisposed to sinus pauses or unprotected AV block – anyone at risk for bradycardia – would not be a candidate for this newest thrombin inhibitor."
  - "We do see an increase in renal problems (in PLATO)…(As a heart failure expert), I am always concerned with renal problems…Is it play of chance? Is the metabolism so different that we actually have to consider it kind of a thrombin inhibitor and understand more about its pharmacology?"
  - "These two side effects are real – bradycardia and renal. It may be another situation where the right approach here would be iterative. Where you go forward in patients who fail other drugs."
  - "One of the things in the study that kind of jumped off the page was that in the subgroup analysis, the North American cohort did not show a favorable response. Is that a statistical fluke? Or, is that a circumstance where, because of contemporary treatment patterns in the U.S., whatever benefit you might have expected from this is masked in the morass of everything else we do?"
  - *He suggested Brilinta is* **unlikely** *to be a game changer:* "There is already one incredibly effective drug that has become standard of care. Now there is prasugrel…which has a bleeding risk…And is there is a third drug with fewer issues of variability but unintended consequences that give us reason for pause."
  - "I think in this case we absolutely need a head-to-head trial…Without that, decisions will be based on practicality, cost, reversibility, freedom from bleeding, freedom from bradycardia, etc."
  - "The 50,000-foot view is that three strong studies have demonstrated that antiplatelet therapy is clearly very effective in ACS patients…If I were an ACS patient I would want aspirin and an antiplatelet drug. That is the take-home message. Convincingly, dual antiplatelet therapy is the standard of care. Between the three drugs, the differences are nuances…I really don't think this is a game changer. It is an extra option, but not a game changer."

PORTOLA/NOVARTIS's elinogrel (PRT-060128), a direct-acting, reversible P2Y12 inhibitor

Top line data are expected in 1Q10, with the Phase III starting by the end of 2010 (most likely in ACS) and completing in 2013. The company hopes to have it on the market in 2014. Portola chief financial officer (CFO) Mardi Dier said, "We believe the method of action allows superior efficacy and similar or less bleeding (vs. warfarin or prasugrel)…The IV/oral combination allows doctors to have the flexibility to treat patients upstream, right when they come into the hospital."

What impact will the PLATO trial (of ticagrelor) have on the design of the elinogrel Phase III trial? Dier said she doesn't know. While the company has been discussing whether this will change the comparator, Dier said there are definitely no plans to compare elinogrel to prasugrel because Portola will seek a broader label than prasugrel, including a claim for secondary prevention. It is likely that the elinogrel Phase III trial could start before ticagrelor is approved, so it appears likely that the comparator will be Plavix.

What will cardiologists want to see in the elinogrel data? A lower bleeding risk than warfarin or prasugrel. A lower thrombosis risk using the same drug first IV, then orally, would be a plus.

Dr. Paul Gurbel of the Sinai Center for Thrombosis in Baltimore MD presented first-in-man data on elinogrel at ESC. He said the effect of elinogrel in patients with high platelet reactivity (HPR) was not entirely known, so he studied it in 5 coronary artery disease (CAD) patients with a prior stent who were taking dual antiplatelet therapy (75 mg clopidogrel + 81 mg aspirin daily), using a variety of platelet aggregation methods.

He found:

- HPR (Plavix resistance) is reversibly overcome by a single 60 mg oral dose of elinogrel in 24 hours.

- The PK data follow the PD data. Maximum plasma con-centration is at 4 hours. Thus, elinogrel acts quickly (in 4 hours), and the effect is maintained out to 7 days (with repeat dosing).
- Elinogrel has "promise as an important future anti-platelet agent" and may overcome Plavix resistance.
- The first data on the use of Accumetrics' VerifyNow to assess the reversibility of a P2Y12 inhibitor was concordant with VASP analyses.
- 44% of patients examined had the CYP450 2C19*2 allele, indicating this is a common problem for Plavix. Furthermore, 7% of patients with HPR had the allele. Among patients without HPR, the prevalence of the allele was only 16%. He concluded, "Irrespective of the genotype, the presence of CYP450 2C19*2 doesn't appear to affect response to elinogrel in this small study."
- There was a good correlation between peak plasma concentration and the observed PD inhibition.
- The major limitations of this study were that it studied only one dose; the dose was not the formulation being used in Phase II.
- An immediate release (IR) formulation of elinogrel will be used for the INNOVATE-PCI study, and he said that should be associated with less variability in AP effect.

Asked how the 60 mg elinogrel dose will compare to a 600 mg loading dose of Plavix, Dr. Gurbel said the company has not yet compared 60 mg elinogrel to 600 mg Plavix.

SANOFI-AVENTIS's Plavix (clopidogrel) – doubling dose for 7 days *safely* boosts efficacy

The results of the CURRENT-OASIS-7 trial, which was presented at ESC and will be published in the future in a major medical journal, showed that double-dose Plavix (600 mg loading dose, followed by 150 mg x 7) administered for 7 days results in a higher and more rapid antiplatelet effect than standard dosing (300 mg loading dose, then 75 mg x 7). The primary investigator, Dr. Shamir Mehta of McMaster University in Canada said the message for clini-cians is:

➢ Patients not undergoing PCI should continue to use the standard Plavix dose.

Comparison of Results of CURRENT-OASIS-7 and TRITON-TIMI-38 Trials

Measurement	CURRENT n=17,232 PCI patients	TRITON n=13,608
CV death, MI, or stroke	Down 15% (Down 21% with high dose ASA)	Down 19%
Definite stent thrombosis	Down 42% (Down 51% with high dose ASA)	Down 58%
TIMI major bleed	No increase	Up 32%
CABG-related bleeding	No increase	Up 4-fold
Fatal bleeding	No increase	Up 4-fold

Aspirin (ASA) Results in the CURRENT-OASIS-7 Trial in ACS Patients

Measurement	ASA 75-100 mg	ASA 300-325 mg	p-value	HR
Primary endpoint: Composite of death, MI, or stroke	4.4%	4.2%	Nss, 0.47	0.96
Death/MI/stroke in PCI patients	4.2%	4.1%	Nss, 0.76	0.98
Death/MI/stroke in non-PCI patients	4.7%	4.4%	Nss, 0.44	0.92
Stent thrombosis	2.1%	1.9%	Nss, 0.37	0.91
TIMI major bleed	1.03	0.97	Nss, 0.71	0.94
CURRENT-defined major bleed	2.3	2.3	Nss, 0.90	0.99
GI bleeds	0.24%	0.38%	Nss, 0.51	---

Plavix 30-Day Results in the CURRENT-OASIS-7 Trial in ACS Patients

Measurement	Standard dose (300 mg + 75 mg)	Double dose (600 mg + 150 mg)	p-value	HR
Primary endpoint: **Composite of CV death, MI, or stroke**	**4.4%**	**4.2%**	**Nss, 0.37**	**0.95**
Death/MI/stroke in PCI patients	4.5%	3.9%	**0.036**	0.85
Death/MI/stroke in non-PCI patients	4.2%	4.9%	Nss, 0.14	1.17
MI	**2.2%**	**1.9%**	**Nss, 0.097**	**0.86**
MI in PCI patients	2.6%	2.0%	0.012	0.78
MI in non-PCI patients	1.4%	1.7%	Nss, 0.23	1.25
CV death	**2.2%**	**2.1%**	**Nss, 0.682**	**0.96**
CV death in PCI patients	1.9%	1.9%	Nss, 0.68	0.96
CV death in non-PCI patients	2.8%	2.7%	Nss, 0.77	0.96
Stroke	**0.5%**	**0.5%**	**Nss, 0.95**	**0.99**
Stroke in PCI patients	0.4%	0.4%	Nss, 0.59	0.88
Stroke in non-PCI patients	0.8%	0.9%	Nss, 0.67	1.11
Bleeding				
TIMI major bleed	0.95%	1.04%	Nss, 0.50	1.09
CURRENT-defined major bleed *	2.0%	2.5%	**0.01**	1.25
CURRENT-defined severe bleed	1.5%	1.9%	**0.03**	1.23
Fatal bleed	0.11%	0.13%	Nss, 0.71	1.15
RBC transfusion ≥2 units	1.76%	2.21%	**0.01**	1.26
Stent thrombosis				
Overall	2.3%	1.6%	**0.002**	0.71
ARC definite	1.2%	0.7%	**0.001**	0.58

*** Driven almost entirely by red blood cell transfusions**

- For every 1,000 ACS patients receiving PCI, using double-dose clopidogrel for 7 days instead of standard dose will prevent an additional 6 MIs and 7 stent thromboses, with an excess of 3 severe bleeds and no increase in fatal, CABG-related or TIMI major bleeds.

CURRENT-OASIS-7 was a randomized trial in 25,087 ACS patients, of whom 70% received PCI. The key findings of the trial were:

- In patients not undergoing PCI, double-dose clopidogrel was comparable to the standard dose.
- Double-dose clopidogrel significantly reduced stent thrombosis and major CV events (CV death, MI, or stroke) in PCI patients.
- There was a "modest" increase in major bleeds using the trial's definition, but no increase in TIMI-defined major bleeds, ICH, fatal bleeds, or CABG-related bleeds.
- There was no difference in efficacy or bleeding rates between high dose (300-325 mg) and low dose (75-100 mg) aspirin in these patients.

Will the Plavix dosing guidelines change? New ACC/AHA guidelines are in the final stages of preparation, so these findings will not be part of the new guidelines, though one guidelines committee member said the results will probably be mentioned in the text of the new guidelines. Dr. Mehta said, "Virtually every interventionalist is using clopidogrel today… After these results, they will have to decide what to do…It is simple going from one pill a day to two. The cost implications are negligible, and the benefits are large. This could improve outcomes in PCI, so I think it will have an impact."

What does the trial mean for aspirin use? Dr. Mehta said, "The rationale we used in the past for low dose aspirin was that there would be more bleeding with high dose, and observational data suggested that. We showed no increased bleeding with the high dose, and, in fact, the higher dose aspirin group consistently did better for the primary outcome and in the PCI group. We have been an advocate of low dose aspirin for a decade, and we will probably switch to high dose aspirin…There was no downside to using the higher dose, and there may have been a benefit."

PROTON PUMP INHIBITORS (PPI)
– do *not* interfere with efficacy of clopidogrel or prasugrel

In contrast to earlier studies – and FDA and EMEA warnings – a new observational study published in ***The Lancet*** and presented at ESC found that PPIs do ***not*** interfere with the benefits of thienopyridines (Plavix and Effient) in ACS patients and do not need to be avoided in patients taking those drugs. Light transmission aggregometry, not point-of-care testing, was used to determine platelet aggregation in these studies.

Dr. Michelle O'Donoghue of Brigham and Women's Hospital in Boston and colleagues studied the effects of PPIs in two trials:

- The 13,608-patient **TRITON-TIMI-38** trial. The researchers found that use of a PPI in combination with either Plavix or Effient did not increase the risk of cardiovascular events, including death, heart attack, or stroke.
- The smaller, 201-patient **PRINCIPLE-TIMI-44** trial. In this double-blind, two-phase, crossover study, the researchers found that mean platelet inhibition was significantly lower for patients on a PPI than those not on a PPI at 6 hours after a 600 mg loading dose of Plavix, but a "more modest" difference was seen after a 60 mg loading dose of Effient.

In patients with the CYP450 2C19*2 allele (which is associated with Plavix resistance), there was actually a numerically lower rate (but not statistically significant) of CV death, MI, or stroke (10.2%) in patients on a PPI vs. 13.0% of patients not on a PPI. The researchers noted, "We did not show a higher risk of adverse outcomes for patients on a PPI with diminished CYP2C19 activity caused by a reduced-function allele."

The researchers concluded, "The current findings do not support the need to avoid concomitant use of proton pump inhibitors, when clinically indicated, in patients receiving clopidogrel or prasugrel."

In an accompanying commentary in ***The Lancet***, Dr. Dirk Sibbing and Dr. Adnan Kastrati of Technische Universität München in Germany agreed that patients with a risk profile similar to those patients in the TRITON-TIMI-38 study can be safely treated with a PPI in addition to Plavix or Effient, but they warned, "Caution is, however, required when prescribing proton pump inhibitors in selected high-risk patients with intrinsic reduced response to thienopyridines."

Cardiologists at ESC called the findings "reassuring." Their comments included:

- *ACC president-elect Dr. Brindis of Kaiser Permanente estimated that 10% of patients going to the cath lab will now get a PPI:* "As a clinician, I think this makes us less worried about the PPI issue…Many centers (had) stopped routine use of PPIs for prophylaxis for patients undergoing procedures, but we were still worried about the patients who actually needed PPIs in terms of safety and how to deal with them. This (research) has helped us. Again, the swing of the pendulum back to reality…(Now) we can use PPIs in the patients who need them, but I think physicians will be cautious and not use PPIs routinely as prophylaxis…This paper is very reassuring to clinicians… We have a million angiographies a year in the U.S., and PPIs were prescribed all the time…What we are learning now is maybe this signal is not as much a problem as we thought it was. Even though we can show in the test tube

that PPIs do decrease the ability of (Plavix), it does not appear to be at a clinical level…Maybe we should not give PPIs routinely, but only in high-risk patients or patients with demonstrated bleeding problems."

- *Dr. Robert Bonow of Northwestern University, past president of the AHA:* "It is not definitive, but it is reassuring…There is still some cause for concern, but at least these data are reassuring."
- *Dr. Jonathan Halperin of Mt. Sinai Medical Center in New York, an AHA spokesman:* "I think physicians and patients need to be alert to this potential drug-drug interaction, but there are people who can get away with it, for reasons we don't entirely understand."

DEVICES

CARDIAC RESYNCHRONIZATION THERAPY (CRT)

MADIT-CRT: CRT-Ds reduce heart failure hospitalizations but do not improve survival in NYHA Class I-II patients

- **preaching to the choir or marketing hype?**
- **results unlikely to significantly boost volume of device implants in short term**

The full results of the MADIT-CRT trial were published in the ***New England Journal of Medicine*** and presented at ESC, and, while they were positive, they also generated some controversy and even a little sparring between very prominent U.S. cardiologists.

MADIT-CRT is a 4.5-year trial at 110 centers in the U.S., Canada, and Europe that enrolled 1,820 symptomatic NYHA Class I or II patients with EF ≤30, QRS ≥130, comparing the use of a CRT-D with an ICD (programmed VVI for single chamber devices and DDI for dual chamber units) on top of best medical care. The trial, which was sponsored by Boston Scientific and utilized Boston Scientific devices, was stopped early on June 22, 2009, for efficacy by the independent DSMB.

Because prolonged ICD use is associated with an increased risk for first and recurrent heart failure events, cardiac resynchronization therapy is often added to an ICD (a CRT-D) to reduce the rate of hospitalization in symptomatic patients with heart failure in NYHA Class III and IV patients. MADIT-CRT was designed to determine whether the same benefits of CRT-D would be shown in cardiac patients with less advanced heart failure. Experts agreed that it did – but just how much and at what cost are the issues.

At an average follow-up of 2.4 years, the trial met its primary endpoint – all-cause mortality or heart failure event (whichever occurred first) – showing a 34% reduction on this combined endpoint. The researchers, led by Dr. Arthur Moss of the University of Rochester (New York), reported, "The benefit from resynchronization therapy was driven by a 41% reduction in risk of heart failure events." However, the benefit was primarily in patients with a QRS ≥150 and in female patients.

MADIT-CRT researchers defended their trial, pointing out that reducing heart failure hospitalizations is a target for President Obama. The researchers concluded that their trial supports the use of a CRT-D as a preventive measure in patients with minimal heart failure symptoms. They found that the results of the trial "document the effectiveness of resynchronization therapy in reducing the risk of heart failure events in asymptomatic or mildly symptomatic cardiac patients… Reduction in heart failure events with resynchronization was not associated with reduction in mortality in this prevention trial, possibly because of the low annual mortality rate of 3% in each treatment group."

On the **positive** side, in NYHA Class I and II heart failure patients, CRT-D devices, compared to an ICD alone:

- **Reduced heart failure hospitalizations and events.** In the trial, 87% of events were hospitalizations, and 13% were outpatient treatments. Dr. Cannom of California, a MADIT-CRT investigator, estimated that the average heart failure patient experiences 5-10 hospitalizations in five years and then gets a CRT device, "I think this is just moving the expense early." He called it a matter of: "Use it now, or use it later."
- **Improved ejection fraction (EF)**. This is a hard endpoint, and the data were good. However, critics said, "This is a hard endpoint, but the FDA will not allow us to use EF as an endpoint. They call it a surrogate. If it is so good, why didn't they (MADIT-CRT) show any benefit in mortality? That is the argument the FDA is going to make."
- **Reduced left ventricle size** (reverse remodeling). Dr. Cannom said, "If you reverse (ventricular dilatation), the patient will have less heart failure and will live longer. And these changes (with CRT-D) were pretty dramatic. The heart shrinks and pumps more efficiently and forcefully." Over time, he suggested that some patients might be able to reduce their diuretic dose as their heart remodeled, but there are no data to support this yet.

On the **negative** side, experts raised a number of issues with the MADIT-CRT results, including:

- **No mortality benefit.** Mortality was equally low (2.7%) with both therapies. The trial may be too short to show a survival benefit, but patients will continue to be followed, and investigators are hopeful that with time a mortality benefit will emerge.
- **High cost and questionable cost-effectiveness** of the devices for this patient population. An ICD costs ~$25,000 in the U.S. and a CRT-D another ~$7,500. A heart failure expert said Medicare pays ~$4,500 for the

first heart failure hospitalization. Thus, experts said a cost-benefit analysis, based on reduction in repeat heart failure hospitalizations, will be important. Dr. Moss said that this analysis is being done but won't be completed for a couple of months. Dr. Cannom said, "What CMS is looking at is the hospital readmission rate. That is the heart failure story. And we will have that data…I don't think the cost of the device is an issue. I think it is under $50,000 quality-adjusted life year (QALY). Ultimately, the device will pay for itself in terms of what it would normally cost to treat these patients." Dr. Jessup said, "Maybe it is cheaper to have a call center than put a CRT in." Dr. Moss added, "We are working on repeat hospitalization (data)…I would hope to have that data in a month or two…The statisticians say this is a tricky analysis to get right…The question is whether to use 7 days or 30 days (to measure rehospitalization)." Asked about CMS's use of 30 days, Dr. Moss said, "Yes, but who says they are right?…If we can prevent recurrent heart failure events as well as the first event, this will add a great deal to the study."

- The appropriateness of **patient selection** – exactly which heart failure patients should get the devices, etc. Dr. Jessup said trial patients weren't really naïve mild heart failure patients. She wondered, "How did they decide if someone was asymptomatic or mildly symptomatic? I don't know how they did that. They had investigators saying that. And that is a little bit of a problem…Who are these patients and how do they differ from patients we have been putting CRTs into already?" Dr. Moss said 90% of patients in the trial had no prior heart failure, though 10% had NYHA Class III or IV at some time in the "distant" past (≥3 months before trial entry).
- Why **women got more benefit** than men from the devices. Dr. Cannom speculated, "QRS of 130 may be more important to a woman than a man because their hearts are smaller, so we are underestimating the severity of QRS 130 in a woman."
- **The number needed to treat (NNT).** In an accompanying ***NEJM*** editorial, Dr. Jessup said, "In MADIT-CRT, 12 patients would need to be treated to prevent a single heart failure event…Is this money that could be spent more wisely?" Dr. Moss responded, "(That NNT of 12) is essentially correct. Our calculations are 10, but I won't argue over 10 or 12…but she didn't say over what time. If we do NNT over three years, it comes to 10."

The debate turned a bit personal, though. Dr. Moss leveled rather personal criticism against Dr. Jessup, charging, "Somehow she got the wrong percent and (was) misled…I don't know if she got wrong information or misread (the manuscript)…She said the ones with the worst heart failure had the best benefit. That is exactly wrong…I don't know why she didn't see it…I sent a letter to the editorial board of the ***New England Journal of Medicine*** and said, 'I wonder where she got that figure.'"

Of the 7 pre-specified subgroups analyzed, only two showed a difference – CRT-D had more effect in females and in patients with QRS ≥150. Interestingly, an exploratory analysis found that patients who had NYHA Class III or IV symptoms or atrial fibrillation prior to enrollment did not do as well with CRT-D as patients without those conditions.

MADIT-CRT Results

Measurement	CRT-D n=1,089	ICD n=731	p-value, hazard ratio, relative risk reduction
Received no device	1%	2.6%	---
Device removal	1.3%	0.7%	---
Completers	96%	92%	---
Primary endpoint: All-cause mortality or heart failure event	17.2%	25.3%	0.001 HR 0.66 RRR 34%
First heart failure event	---	---	RRR 41%
Death	3%	3%	Nss
Left ventricular volume	More with CRT-D		---
Ejection fraction increase	More with CRT-D		---
Adverse events			
Death during hospitalization	1	0	---
Pneumothorax	1.7%	0.8%	---
Infection	1.1%	0.7%	---
Pocket hematoma requiring evacuation	3.3%	2.5%	---
Coronary venous dissection with pericardial effusion during implantation	0.5%	0	---
Repositioning of left ventricular lead	4%	---	---
Serious adverse events >30 days per 100 device-months	4.5%	5.2%	---

MADIT-CRT Subgroup Results

Subgroup	CRT-D vs. ICD	p-value
Pre-specified analyses		
Females	HR 0.37	0.01
Males	HR 0.76	
QRS ≥150	HR 1.06	0.001
QRS <150	HR 1.52	
Centers with high vs. low enrollment	Nss	---
Blood urea nitrogen ≥26 mg/dL	Nss	---
Ischemic vs. non-ischemic disease	Nss	---
Exploratory analyses		
NYHA Class III or IV symptoms >3 months prior to enrollment (n=182)	Did not do as well as patients without these symptoms	
Atrial fibrillation prior to enrollment (n=213)	Did not do as well as patients without these symptoms	

How many heart failure patients potentially would be eligible for a CRT-D according to MADIT-CRT criteria? Dr. Moss estimated three million patients, though he added (with a chuckle), "That doesn't mean three million patients are going to get a device." However, other experts put the number much, much lower.

- *Dr. Jessup said the number of eligible patients could be as high as 300,000, but the low hanging fruit has already been plucked.* She said she is not sure if this will increase the number of patients identified, "The take-away message from the study is that heart failure patients need to hear there is a specific group of patients with very wide QRS who, if that is persistent despite optimal medical therapy, may benefit from CRT – not necessarily with an ICD, though they will all get (the ICD)…I think use will go up a lot…CRT is used inappropriately a lot in our country. It gets put in before a patient is on optimal medical therapy. Physicians see wide QRS and don't think twice about whether a patient fits the guidelines…It is a costly procedure. You (doctors) get a lot of money, and you get to follow the patients. It is a winner…It will take a while for this word to get out, but I think many more people will get CRT (now)…It is a winner."
- *AHA's Dr. Yancy, a Texas heart failure specialist:* "We don't know…Probably 60% of heart failure patients fall into Class I and II…Mild heart failure continues to be the disease entity we see most commonly…(But) I think we will see the number of patients who fit this (MADIT-CRT) profile (EF ≤30 and QRS ≥150) is not a large number."
- *Dr. Cannom put the number at 100,000-200,000 patients a year:* "It does not apply to every NYHA Class I-II patient. It will apply to maybe 30% (of those patients)… Device acceptance has not been what we thought it would be for defibrillators, and I think part of the problem for that is we were looking for a mortality benefit and not a symptomatic benefit…Here, I think the acceptance will be high because it has benefit symptomatically…They have a real chance of feeling better. The heart failure people on the (MADIT-CRT) steering committee were abundantly excited about this…It may be accepted by them more than the average cardiologist. Overall, I think it will be a real advance for the device world."

Why have device referrals been relatively flat? Dr. Cannom contended that a turf war is going on, with different cardiology subspecialties fighting over patients, "I don't think the chief problem is with primary care. I think the chief problem is with cardiologists. All the indications are the chief problem is with the cardiologists...For a variety of reasons, cardiologists have dismissed interest in devices at this point…There will be more acceptance (post-MADIT-CRT), but I'm not sure this will translate into more implantations. It is always slower than you think it will be…The loss of patients to electrophysiologists is a big issue…It is a turf issue…The only way manufacturers can deal with this is to educate cardiologists about the benefits (of CRT-D)."

What do the MADIT-CRT results mean for the outlook for future CRT-D use? Some experts predicted that the trial will have little impact on overall CRT-D volume, while others expect it to gradually but significantly increase CRT-D use in heart failure patients. Even the trial investigators didn't agree on this.

- *Dr. Moss:* "I think there will be a progressive avalanche (of use)."
- *ACC past president Dr. Douglas Zipes, an electrophysiologist from Indiana School of Medicine:* "This study may widen the net to capture more patients for CRT-ICD, but whether that is appropriate should be questioned. It is likely that our indications for ICD and now, maybe for CRT as well, are already too broad. Hence, only a third or so of patients with ICD indications receive the device because many physicians are concerned about appropriate utilization, and only about a third of those who receive an ICD actually use the device after several years. We need better patient-specific identifications for who actually will benefit from these expensive devices."
- *ACC president Dr. Bove of Pennsylvania:* "This study shows a small but significant benefit to a new patient population; however, it will likely not immediately affect practice…Previous device studies have shown us that it takes time to consider benefits for real-world populations. Even if costs were not a factor, we still do not have enough information to expand treatment right away."
- *AHA president Dr. Yancy:* "A CRT plus ICD appears to have benefit in less ill patients and is something we have to consider…For symptomatic patients in NYHA Class I with EF<30 and a wide QRS (≥150), the data suggest a CRT-D might be a reasonable strategy to reduce heart failure events. These data give practitioners some latitude …It is not the same as saying we are going to put CRT-D in all-comers with heart failure and wide QRS…There is general reluctance to utilize CRT technology in patients with heart failure, and these data say, yet again, another patient cohort exists that has benefit…So, we are getting closer to a level of evidence to increase use…I'm not advocating across the board, widespread use…We have to be very sensitive to cost issues…My sense is that there are many patients under very good care of primary care physicians where device therapy has not been contemplated…because of a reluctance to accept this as part of standard therapy. If these data provide anything, it may be that they are another piece of compelling evidence that device therapy is beneficial…Do we embrace this and spend the money to widely apply CRT?…I don't know that we do. I think we accept this as another piece of information…I would temper the enthusiasm about any significant change in practice or use by saying this reflects a smaller cohort of patients than what you've been led to believe."

- *Dr. Gardner of Delaware, AHA past president:* "I think it is another area where we just don't have adequate data, where we have data that is suggestive but not definitive…We need a community to help analyze this (MADIT-CRT). We need health economists, anthropologists, etc."
- *Dr. Gibbons of the Mayo Clinic, another AHA past president:* "There are a variety of ways where one could deal with the difficult problem of patients with heart failure and prevent hospitalizations – better coordination of care, better use of nurse managers, etc., all of which take more resources than we have…Should our resources be devoted to those measures or to CRT-D?"
- *Dr. Jessup:* "In my own practice I will put more CRT in as a result of this." She added that the devices are likely to be heavily marketed – and marketing has already started, "Boston Scientific clearly feels they won't have a problem with CMS. They are moving ahead and pushing hard…(But) this is big, expensive therapy…(and) it is a very compelling argument."
- *Dr. Cannom:* He said the reluctance of other cardiologists to refer heart failure patients for device therapy is a key roadblock to increasing implant volume. One reason for this is fear patients will get inappropriate shocks from the ICD, "We have another MADIT trial that will look at shocks. That trial (MADIT-RIT) is starting in (September 2009)."

DRUG-ELUTING STENTS(DES)

At EuroPCR in May 2009, European cardiologists said DES volume was holding fairly steady vs. bare metal stents (BMS), and they expected that to continue over the next 6-12 months. James Tobin, then Boston Scientific CEO, estimated that in Europe Abbott's Xience V had >30% market share, Promus ~12%, Taxus ~20%, for a total Boston Scientific share of ~32%. At ESC, Mark Fligge, group marketing manager for DES at Boston Scientific, said Taxus share has remained stable at ~20%, while Promus share has increased to 15% – taking a little market share from Xience, a little from Medtronic's Endeavor, and a little from Johnson & Johnson's Cypher. Thus, Boston Scientific's total share is now 32%-35%, he said.

BIOCOMPATIBLES' BioDivYsio stent eluting Avastin (bevacizumab)

A poster reported on the first-in-man experience with this DES in 20 patients. The conclusion was that it is safe. At 34 months, there was no death, MI, TVR, stent thrombosis, restenosis, or malapposition. At 24 months, in-stent late loss was 0.15 mm, in-lesion late loss 0.03 mm, and neointimal hyperplasia 0.82 mm.

BOSTON SCIENTIFIC

Boston Scientific is expecting a C.E. Mark for both Promus Element and Taxus Element later this year (4Q09), and he said the company is "deep in the throes of preparation" and plans to launch immediately upon approval. Boston Scientific held an all-day planning session for staff during ESC, and post-ESC planning efforts are being stepped up.

Taxus Element was launched in what Boston Scientific calls "premier" countries – United Arab Emirates, Tunisia, Singapore, Malaysia, Lebanon, Saudi Arabia – in March 2009, and Fligge said, "It is doing well there. People love the deliverability." He said it has expanded their share, not just been a switch-out for Taxus. However, Promus Element is ***not*** being sold anywhere in the world yet.

What are the advantages to Promus Element? Fligge said, "Half the recoil, very strong, thinner stent struts. We entirely changed the design; now there are more stent segments, so it tracks better."

Boston Scientific is cutting it pretty close on Promus Element. The agreement with Abbott to supply Promus expires in November 2009, and Boston Scientific needs to have Promus in the market by then, and that is now by no means certain. But Fligge is optimistic, "The build is in place, and we are expecting approval. All the feedback we get is that it is on track…This may be easier (to get approved) because it is the same drug and polymer."

On September 18, Boston Scientific announced that enrollment is complete in the "workhorse portion" of its PLATINUM trial of Promus Element, with 1,532 patients. PLATINUM compares Promus Element to Promus/Xience. Like Promus, Promus Element is an everolimus-eluting stent, but it is made out of platinum instead of cobalt chromium.

How can Boston Scientific get approval for Promus Element with almost no data, particularly since the stent is a new material (platinum)? Fligge said, "There are two Element trials: the PLATINUM trial for Promus Element and PERSEUS for Taxus Element. The PERSEUS data will be at the American College of Cardiology meeting in 2010, and the PLATINUM data about a year later; that trial just started in November 2008…Xience Prime just got a C.E. Mark, and we can leverage the data for Taxus Liberté because it is the same drug and polymer…There are also DSMB reports on Promus Element. The EMU (European regulators) will consider that those regulatory bodies (DSMBs) met and considered it… When you launch a product without brand new data, we will talk about the features and the benefits of the stent and platform. Xience Prime had a new platform – they changed the stent a little and used a new balloon, but they stayed with cobalt chromium…There are no platinum stents approved, but there are platinum products – coils, leads, orthopedic products. We have compatibility data from animals and preclinical data to make sure it is biocompatible."

Taxus Labcoat has been implanted in a few patients in Europe, and the company plans to launch in Europe in about 18 months – provided new, one-year data from the JAC-TAX trial to be presented at TCT 2009, looks good.

Will there be bare Element? Fligge said yes, with a European market launch probably in late 2010 or early 2011.

How will the transition from the current Promus to Promus Element be handled? Fligge said it will be a fast conversion, "The technology is a step forward, so people will want to do it quickly. We have been preparing for a rapid launch…We plan to convert almost immediately."

DES pricing appears to be holding steady in Europe. Fligge said, "It is a competitive marketplace, but it is fairly stable. New technologies will help stabilize pricing." But there appears to be a trend toward use of fewer DES brands in individual cath labs. Fligge said, "We are seeing more and more cath lab consolidation. Rarely do a group of doctors agree on one stent, but administrators like to consolidate, which gives us an advantage right now. We offer both paclitaxel and a limus, and that has good appeal. People like choice, especially physicians."

JOHNSON & JOHNSON's Nevo

J&J's goal is still to file for C.E. Mark by the end of 2009 and the FDA in 2011 for this next-generation DES with multiple hundreds of small reservoirs filled with a combination of polymer/sirolimus. There was no news on Nevo at ESC, but during the meeting J&J announced in a press release that the first patient had been enrolled in the 2,000-patient CYPRESS trial, J&J's contribution to a ~20,000-patient, dual antiplatelet (DAPT) study in which all four DES manufacturers in the U.S. are collaborating with the FDA.

CYPRESS is divided into two phases. In Phase I, patients get a Cypher stent and receive 12 months of dual antiplatelet therapy with aspirin plus either Plavix or Effient. The primary endpoint of this portion of the trial is target lesion failure at 12 months.

In Phase II, patients treated with 12 months of dual antiplatelet therapy from Phase I, who remain free from death, heart attack, stroke, revascularization, stent thrombosis, and major bleeding are then eligible for randomization to aspirin plus either placebo or an additional 18 months of thienopyridine (Plavix or Effient) therapy. The primary endpoints of Phase II are MACCE, stent thrombosis, and bleeding.

DES safety – no increased risk with DES after all

The Swedish (SCAAR) registry caused a great deal of concern in 2006 when it showed a 30% increase in mortality long term with DES. It now appears that much of that concern was misplaced. The five-year data show similar rates of death and MI between DES and bare metal stent (BMS) patients and an improvement in the rate of restenosis in high-risk patients with a DES. In fact, the survival curves were almost superimposed, with no increased risk of death at five years. Patients with the highest risk for restenosis had a 70% relative risk reduction with DES vs. BMS.

However, the SCAAR investigators said that late stent thrombosis remains a concern, "Most registry studies suggest a lower risk of death or MI with DES. However, late occurring stent thrombosis still remains higher and seems to be uniquely associated with these stents."

The investigators said that, despite the heartening news, "All observational data comparing treatment options should be interpreted with caution because of possible concealed confounders, and there is no registry that can replace any large, well-performed, randomized trial with long-term follow-up.

Yet, there does appear to be a continuing risk of stent thrombosis with DES, while the stent thrombosis risk levels off at 1 year with bare metal stents. A speaker noted, "Stent thrombosis…is highest with Taxus Express, lowest with Xience. There have only been 4 cases with Xience…Cypher and Taxus Liberté event curves are superimposed and lower than Taxus Express…We don't need to be particularly worried about stent thrombosis because, overall, mortality is not increased…There are some positive and some negative signs. We may lose some patients to stent thrombosis, but we gain some on reduction in the need for new interventions…I don't think we need to be that worried, but we need to be aware of it and to select the right patients and to avoid DES in patients with limitations – who can't take dual antiplatelet therapy or who we aren't sure will be able to take it in the future."

PCI for unprotected left main (LM) disease

Dr. Gilles Montalescot of France said there are few studies in unprotected LM, and he doubts there will ever be a randomized clinical trial in these patients, which account for only about 4% of ACS patients. However, LM is a serious situation with in-hospital mortality of 7.7%. Over the past 10 years, there has been a steady shift to more PCI, which now is the most common strategy for revascularization of these patients and is the preferred therapy in emergency/serious cases.

Biodegradable polymers

Dr. Julinda Mehilli of Munich, Germany, reported on the results of the ISAR-TEST-4 study of a stent utilizing a biodegradable polymer and eluting rapamycin. The stent is not intended for commercial production; it was designed to look at biodegradable polymers. It is coated in-house. The project was supported by Bayerische Forschungsstiftung.

Compared to other DES, this biodegradable stent had comparable all-cause mortality, MI, stent thrombosis, in-stent restenosis, and in-segment restenosis. Dr. Mehilli said, "Out

to 12 months, the biopolymer DES is non-inferior to two leading permanent polymer-based DES in a large-scale study powered for clinical endpoints."

Will there be a lower rate of late stent thrombosis with this approach? Dr. Mehilli said, "Theoretically a biodegradable polymer, which is only on the stent for 9 weeks, won't have the problems of a permanent polymer, so theoretically we will have safety advantages. However, one year is a short time for this. That is why we are waiting for longer term data…We believe the limus family is more promising, and we are not testing any paclitaxel."

SYNTAX Trial – CABG still better than PCI in Year 2

You may see notes saying that the SYNTAX 2-year data comparing PCI (DES) to CABG showed no statistically significant difference between PCI and CABG in the composite safety endpoint (all-cause death, stroke, and MI). While this is true, it is very misleading because:

1. The trend appears to favor CABG. (p=0.98 in first year, 0.11 in second year, and 0.44 overall). Numerically DES is worse in second year (3.5% DES vs. 2.2% CABG) though comparable in the first year (7.6% vs. 7.7%).
2. That was ***not*** the primary endpoint of SYNTAX. On the primary endpoint of MACCE (all-cause death, stroke, MI, and revascularization), the data improved slightly over the second year, but it remains statistically better for CABG (12.4% vs. 17.8%, p<0.001 overall). DES vs. CABG was 8.3% vs. 5.7% (p=0.03) in Year 2, which compares to 17.8% vs. 12.4% (p=0.002) in Year 1.

Furthermore, MI also worsened. There was no statistical difference in Year 1, but DES was significantly worse (1.2% vs. 0.1%, p=0.008) in Year 2, and now the overall difference statistically favors CABG (p=0.01).

On the other hand:

- Stroke actually ***improved*** and was not statistically significantly worse with DES in Year 2. Though, overall CABG is still statistically lower, it would appear that by Year 3 or 4, there will no longer be any overall difference between the two therapies.
- There remains no statistical difference in all-cause death between DES and CABG.
- Repeat revascularization did not statistically favor CABG in Year 2, though overall it still is lower than for DES.
- In the pre-defined subgroup with:
  - Left main (LM) disease, safety and MACCE were similar between PCI and CABG, but revascularization was lower with CABG.
  - 3-vessel disease (3VD) safety was similar between PCI and CABG, but revascularization and MACCE favored CABG.

TRANSCATHETER AORTIC VALVE IMPLANTATION (TAVI)

At a Medtronic-sponsored session speakers described in detail the new subclavian approach with the CoreValve ReValving System. An Edwards-sponsored session focused on patient selection, the importance of a team approach, a review of some of the Sapien data to date, and a look at the company's new, lower profile delivery system. Dr. Helmut Baumgartner of Germany said, "For 2009, patient selection for TAVI needs to be based on aortic stenosis severity and aortic-stenosis-related symptoms, then on technical and anatomical considerations. Patients should have an elevated risk with a conventional valve replacement, and there should be a reasonable likelihood of a significant improvement in quality of life…It is my experience now that when you get to an age >80, the percent of patients who are good candidates for surgery decreases dramatically. Even an 85-year-old patient where you calculate a EuroScore <20, both surgeons and we (interventional cardiologists) are reluctant to do surgery."

Asked if he is considering doing TAVI on an emergency basis, Dr. Baumgartner said, "That is limited by logistical reasons. That is the main reason we haven't done it in emergency situations."

Edwards' speakers took a bit of a dig at the CoreValve subclavian approach, referring to it as the "transjugular" approach. Dr. Alain Cribier of France, an Edwards investigator and a leader in the TAVI field, said, "Today 50% of Edwards cases and 70% of CoreValve cases are performed transfemorally."

Edwards' pivotal U.S. trial, PARTNER-US, is now fully enrolled, with results expected in 2010.

2-Year Results of SYNTAX Trial

Measurement	Overall			Year 1			Year 2		
	CABG	PCI	p-value	CABG	PCI	p-value	CABG	PCI	p-value
Primary endpoint: MACCE	**16.3%**	23.4%	<0.001	**12.4%**	17.8%	0.002	**5.7%**	8.3%	0.03
All-cause death/CVA/MI	9.6%	10.8%	Nss, 0.44	7.7%	7.6%	Nss, 0.98	2.2%	3.5%	Nss, 0.11
CVA	2.8%	**1.4%**	0.03	2.2%	**0.6%**	0.003	0.6%	0.7%	Nss, 0.82
Repeat revascularization	**8.6%**	17.4%	<0.001	**5.9%**	13.5%	<0.001	3.7%	5.6%	Nss, 0.06
MI	**3.3%**	5.9%	0.01	3.3%	4.8%	Nss, 0.11	**0.1%**	1.2%	0.008

Some of the other new aortic valves in development are repositionable. Dr. Cribier dismissed the importance of this, but other interventional cardiologists predicted that would be an important advance. Dr. Cribier said, "My feeling is that positioning today is very well done. If you take the last 50-100 (Edwards) patients, valve positioning is not that much of an issue today."

Asked about the future of other new aortic valves in development, Dr. Cribier said, "Today, we absolutely don't know the future of these new devices."

Comments by other cardiologists about TAVI included:

- *Dr. Michel Bertrand, France:* "TAVI will be approved in France in the next few weeks. The government will allow 1,000-1,200 a year. They will limit it initially, as they did with DES…There are no new safety issues with percutaneous valves…If you ask young interventional cardiologists, they are more interested in TAVI than PCI."
- *Dr. Baumgartner, Germany:* "There are no new safety issues with these valves…There is still only data on high-risk patients…Mortality is 6%-7% with both Edwards and CoreValve…Reimbursement is still an issue in Germany. It is limiting the number we will do this year. With no limit we would do 80-100. But many patients are not referred because the cardiologists are not aware or TAVI is not known. The difficult question now is who should get a percutaneous valve. In the (Edwards) registry, only 120 of 230 patients were eligible…Right now, it has to be reserved for high-risk patients, and most people are following that…We are only using Edwards, but that is more a personal decision than anything else. If you look at the outcomes, Edwards and CoreValve are pretty comparable, but they have a different philosophy to the approach…The need for a pacemaker is an issue with CoreValve…Pricing is holding steady."

ABBOTT/EVALVE's MitraClip

Just after ESC, Abbott announced it was entering the valve field with the purchase of Evalve. MitraClip was not a major focus at ESC, but a German cardiologist, who is about to start using MitraClip, said, "There are not enough data and no European trials. I don't think we should get the impression that it is not a promising option for the future. Use will increase. But patient numbers are small. For patients not at high risk for surgery, we have a good surgical option. People think twice about offering something new to these patients. With aortic stenosis (aortic valves), there are no alternatives."

STEM CELLS

Cardiologists are interested in stem cells but see them as still very far away from clinical application. Dr. Pinto of Portugal, ESC program chair, said, "There was a lot of hope and expectations for stem cells in heart failure. Regenerative medicine is a dream of cardiologists. But it is still a work in progress…It is a great hope for the future, but not the next 1-2 years. It will take some time to get real results."

Several companies have been investigating the use of stem cells to treat cardiac conditions. Among these are Cytori, TCA Cellular, Angioblast. Dr. Patrick Serruys of the Netherlands said, "It is a difficult field. The basic scientists keep saying it is too early to go clinically, but clinicians want to help patients. The truth is in between. We have to do something in patients to stimulate science and research…I don't know if it will be clinically useful in the next decade."

CYTORI THERAPEUTICS – adipose-derived cells

Dr. Serruys said, "I did my first patient with myoblasts in May (2009)…It is easy to detect what is not correct but not easy to fix that. Six-minute walk improved but ejection fraction was unchanged...You need a sham treatment or there is a huge placebo effect."

He said Cytori is planning a trial with 4 cohorts of 12 patients each that will be sham and double-blind. Some data from this may be available at the American College of Cardiology in 2010. He added, "The ***but*** is that it is quite heavy – patients get a huge abdomen. If a patient is on a IIb/IIIa inhibitor or clopidogrel, they could get a serious hematoma or bleed… They plan to progressively increase the number of cells injected, but they can't go beyond the level of the first cohort (10 million cells), and you can't harvest more cells from the abdomen, so if they need a higher dose, it will be a problem."

ANGIOBLAST SYSTEMS – shelf-stable mesenchymal stem cells

To be successful Dr. Serruys believes a stem cell therapy needs to be an off-the-shelf product, and that is the advantage to this product. Dr. Serruys said, "There is no liposuction of bone marrow." So far all the data are in animals, but a human trial is expected to start shortly, probably in transplant patients, "They will inject the cells before removing the heart – to prove the cells are incorporated in the myocardium… These are cells which are very undifferentiated. There is no immunological reaction, so you can use animal cells. If it works, on-the-shelf will make if very, very different."

TCA CELLULAR – mesenchymal + hematopoietic stem cells

TCA Cellular medical director Dr. Gabriel LaSala, an interventional cardiologist, said that what differentiates his company is its combination of autologous mesenchymal and hematopoietic stem cells obtained from iliac crest bone

marrow, "We are the only company combining two different kinds of stem cells."

The TCA Cellular procedure has several steps. First, hematopoietic stem cells are harvested from a patient and sent to a company facility where they are grown (incubated) for 2-3 weeks in a germ-free environment. Then, mesenchymal cells, which can't be grown, are harvested from the same patient in a second procedure and combined with the cultured hematopoietic cells.

The company has tried its stem cell therapy in dogs as well as several patients in Chile and in a few patients in the U.S., including some FDA-approved studies. However, in neurologic patients only mesenchymal cells are used, not the combination with hematopoietic cells:

- Chronic coronary ischemia – Phase I is completed, and Phase II is about to finish.
- AMI – Phase I.
- Patients undergoing CABG and having a scar in the heart – Phase I.
- Limb ischemia – A Phase I trial is completed, and a 30-patient Phase II is nearly finished. The company has already submitted a protocol for a Phase III trial to the FDA and is waiting for a response.
- Amyotrophic lateral sclerosis (ALS, Lou Gehrig's disease) – The company has submitted a protocol to the FDA for this study. So far, two patients have been treated in the U.S., and six patients have been "successfully" treated in Chile, with their symptoms and motion improved. Dr. LaSala said, "It is not a cure, but they are doing better."
- Spinal cord injuries – The company also is waiting for FDA approval for this study. So far, two spinal cord injury patients have been treated, and Dr. LaSala said one improved, and the other showed very little improvement, "One was a patient with a T7 injury, a 54-year-old man paralyzed from the waist down. He recovered all sensory feeling lost in his lower extremities. He is able to move his legs again 2.5 years after his injury. The other was a 62-year-old woman with a completely severed spinal cord at the T11 level. She was completely paralyzed. She can move her feet up and down now, which she couldn't do before, and she did get skin sensory feeling back."
- Duchene muscular dystrophy – One patient has been tried, a 13-year-old boy. Dr. LaSala said, "There is no cure for this disorder…We injected stem cells into his paralyzed muscles, and we believe we formed a chimera, where the new cells fused with the diseased cells, and the nucleus of the stem cell fuses with the nucleus of the other cell…Now, this child is walking with assistance with bars and can ride on a stationary bike for six miles."

The therapy sounds promising, but Dr. LaSala is quick to point out that it is still very early. And other stem cell therapies have looked promising only to fizzle out. Dr. LaSala said, "There was a theory six years ago that there could be transdifferentiation. That theory was turned down 2-3 years ago. Still, some of those trials are running using hematopoietic CD34 stem cells, and they aren't going to work…There is a trial in Houston using allogeneic mesenchymal stem cells in patients with coronary ischemia, funded by Osiris. We don't know those results…We think ours is better because we use two types of stem cells. You need the hematopoietic stem cells to form the endothelium of the blood vessels, and the mesenchymal to form the walls and the membrane."

Shortly after ESC, Osiris announced that its stem cell program failed in two late-stage clinical trials, dealing a blow not only to Osiris but to the whole stem cell field. Osiris Prochymal (mesenchymal stem cells) did not show any benefit vs. placebo in treated host vs. graft disease, though there may be a subset of patients who benefited.

To do its Phase III trial, TCA Cellular needs to raise money. In Phase II, each patient cost the company $11,000, and Phase III is likely to be more expensive. Plus the company needs to build a new, bigger lab. Dr. LaSala said, "The problem with the Phase III (limb ischemia) trial is that we don't have the funds for it. We need money for that…We have applied for orphan drug status because Duchene's, ALS, and certain types of spinal cord injuries are very rare. But we don't have approval to do trials in orphan indications yet…To do more patients, we need a larger lab. Our current lab couldn't handle more than 10-50 patients. We would need at least six clean rooms for a (Phase III) study."

And there are no key opinion leaders in cardiology involved in this yet, which could raise some credibility issues.

Ramping TCA Cellular's therapy up for widespread use could be an issue. The hematopoietic cells have to be grown at a company facility, and that has to be within a few hours of any hospital where they are harvested. So, either the company would have to build multiple sites around the country, or, more likely, patients would have to travel to their facility. Dr. LaSala thinks patients would come, "Patients would need to come to our facility. It requires a 24-hour admission, though that probably won't be required in the future…Three thousand Americans went to Singapore and Bangkok to be treated at $39,000 each in 2007…For now, for Phase I the FDA requires a 24-hour observation, and in Phase II we have 24-hour observation, but in Phase III we are requesting a six-hour observation because the safety is proven already."

On the positive side, TCA Cellular owns 50% of Lifesource Cryobank, the only company to cryopreserve adult mesenchymal stem cells. For $20,000 a person can have his/her mesenchymal stem cells expanded and stored. So far, ~180 people have done just that.

This therapy is still a long ways away from FDA approval. For the Phase III limb ischemia trial, the company's proposal is for 600 patients to be enrolled at five hospitals in Louisiana, all within four hours of the company lab. It is likely to take at least two years to enroll that many patients, then at least a year of follow-up (or perhaps the FDA will want more). Thus, assuming the Phase III trial started in January 2010 and all went perfectly, Dr. LaSala estimates it will probably be 2014 or later before the therapy is approved, assuming it could be approved on one trial.

European View of U.S. Healthcare Reform

European cardiologists are watching the U.S. healthcare reform debate with amazement. They generally believe the U.S. should adopt a European-type system, perhaps along the lines of the U.K. or Spain, though they doubt that is politically viable.

- **Prof. Ferrari, ESC President**, defended the European approach to healthcare, saying, "I was born in a country where healthcare is the prerogative of every individual. It comes first. Everyone in Italy, if sick, will be treated free by the healthcare system. This is not happening in the U.S. The U.S. has a fantastic system for a few and a less than fantastic system for most people…So far we (in Europe) have been able to afford the economic burden (of free healthcare)… Cardiovascular disease is down in most of Europe. And that is the ultimate test…We don't have a cardiovascular waiting list in Italy, France, or Spain."

- **Dr. Heinz Drexel of Austria** said, "My U.S. friends think there must be a way between the European and U.S. approaches. President Obama's suggestion that all kids should be covered is well-accepted now…I am very optimistic that it can be improved for everyone (in the U.S.)."

- **Dr. Martin Cowie of the U.K.** commented, "I'm amazed how vitriolic healthcare reform has been (in the U.S.). It has been widely reported in Europe, and that level of argument amazes us in Europe. I'm disappointed in the misinformation on our National Health Service (NHS). I think the U.S. has to increase coverage. I'm also amazed President Obama is tackling this because it may grind him to a stop. I expect the U.S. will end up with a dual system – basic coverage and then topped off with a private system – as in most European countries. So, what is the fuss?...I'm pleased America is focused on healthcare reform and on rising costs, but the more I'm amazed that the wealthiest country has a system with so many people without access to basic healthcare."

- **Dr. John Martin of the U.K.**, an ESC spokesman, defended the European healthcare system, "The general view in Europe is that healthcare is a human right, it should be delivered by the state, and it generally works well. There are several different models in Europe. My own is the NHS, where, as a doctor, I deliver healthcare free when it is needed at the point of contact. Money never comes into it. The poorest or richest man receives from me the treatment he needs. Even if it is a $103,000 operation, the money doesn't come into play. And it is wonderful for me as a doctor to work in that situation. And it is good for my patients, and they like it. There are some problems of chronic disease and waiting, but if you have an acute problem, it works very well. If you have a heart attack, it is fantastic. Last year, I went into my outpatient room and sitting waiting for me was a Nobel prize winner, a conductor of a national symphony orchestra, and ~10 other patients who were a mixture of middle class and poor people, all with health problems. And I like that very much. Americans might say this is socialism. Yes, it is, but it is good for the poor and the patient."

Dr. Martin charged that the U.S. healthcare system has lost its focus, "The U.S. is a country based on freedom and generating wealth through capitalism, both of which I believe in. But the use of that wealth and freedom, I think, has gotten out of balance. A critical example is the vaccination against swine flu. In the U.K. everyone will be vaccinated for free through NHS, paid for by taxes, and that will decrease the chances of both rich and poor people getting swine flu. But in a system (U.S.) where you have to pay for vaccination, everyone suffers. It is such a short-sighted view of health – even the health of the richest people."

Asked what they fear might happen with healthcare reform in the U.S., European cardiologists generally did not have many concerns. Dr. Martin, however, said, "I'm afraid with the recession fewer people will pay for healthcare, and therefore there will be a decrease in the health of the population over 10-15 years…for example, heart disease, an increase in infectious disease, immunizable disease, and this in the future might cause economic problems by affecting the work force… I think economically even it is very short-sighted, and America should do the sums about the cost of cardiovascular disease on the economy and the benefit of preventing it properly in the population…I think short-sightedness related to short-term political gain is one of the major problems of American healthcare."

Asked how U.S. healthcare reform will affect pharma research and development, Dr. Martin said, "We have no problem in Europe with pharma research dollars…I don't think research dollars will dry up. They are flexible capitalistic machines, and they will do what is necessary for their wealth. But big pharma research dollars have not been productive over the last 10 years. Pfizer is spending $6 billion a year, and the others are spending $2-6 billion a year, and nothing has come out of it in the last 10 years. They are using their cash pile to buy smaller companies and ideas, and you cannot survive like that. Money carries with it social responsibility. We didn't use to think this until the banks collapsed. Governments clearly thought banks were too important, but they have been nationalized in Europe and the U.S. Is big pharma too important to leave to big pharma? Will big pharma collapse as banks collapsed because of lack of their productivity in producing new medicines for society and for not fulfilling their social contract?"

What's Dr. Martin's suggestion for the U.S.? Nationalizing pharmaceutical companies. He said, "We need a completely new model on how we approach pharmaceutical research…I would nationalize the pharmaceutical industry. I would also suggest future tax credits should be given to pharma if they liberate their cash piles – and their average cash reserves are $150 billion each for the top 20 firms – to go to university research. University research is starved of funding, and it is enormously effective."

MISCELLANEOUS

MERCK's rolofylline, an oral adenosine A1 receptor antagonist – why it failed in acute heart failure

Dr. Marco Metra of Italy provided details on the PROTECT study, in which rolofylline, an IV loop diuretic, showed no benefit over placebo in acute heart failure patients with fluid overload. PROTECT was a >2,000-patient trial comparing 30 mg rolofylline IV vs. placebo IV for 3 days. The trial failed to meet the primary endpoint as well as all the secondary endpoints. Dr. Metra said, "Numerically more rolofylline patients experienced marked/moderate improvement of dyspnea, but this was counterbalanced by the number of patients with persistent renal impairment…The overall safety profiles were similar. Rolofylline was associated with…no increase in cardiac adverse events but a higher incidence of seizures and a trend to a higher incidence of stroke."

Merck has officially discontinued any research and development of rolofylline, but it has a follow-on compound in development. What is the lesson from the PROTECT trial, Dr. Metra said, "We had a pathological and pharmacological basis to expected improvement in renal dysfunction or to expect protection from worsening dysfunction…This was found in a pilot study and in smaller studies. As frequently happens, these results were not replicated." Asked what the results mean for the class of drugs, he said, "There was improvement in symptoms, but there were also side effects…It is impossible to extrapolate to other compounds."

Dr. Daniel Bloomfield, executive director of cardiovascular clinical research at Merck said, "It is very definitive that this trial failed. You could say we opened the door by showing it is safe. The seizures were mechanistically-based, which means they are manageable. The stroke was totally unexpected, and we don't understand it. It is hard to say if it is chance…We believe there are strong data on how this class works in the kidney."

Results of PROTECT Trial of Rolofylline in Heart Failure

Measurement	Placebo n=666	Rolofylline n=1,336	p-value
Treatment success	26.0%	40.6%	Nss
Patients unchanged	44.2%	37.5%	Nss
Treatment failure	19.8%	21.8%	Nss
Dyspnea improvement at 24 and 48 hours	51.2%	44.5%	Nss
Death	9.5%	8.9%	Nss
Persistent renal impairment	13.7%	15.0%	Nss, 0.441
Time to death/renal failure at Day 60	---	---	Nss, 0.861 (HR 0.98)
Rehospitalization	25.6%	25.7%	Nss
Adverse events	61.4%	62.9%	Nss
Serious adverse events			
Any	14.7%	13.8%	Nss
Cardiac disorder	9.0%	7.2%	---
Nervous system disorder	0.6%	1.5%	---
Seizure	0	0.8%	---
Stroke (hemorrhagic and ischemic)	0.5%	1.2%	HR 0.7

Heart failure in AFib – an ARB is not the answer

Dr. Salim Yusuf of McMaster University presented the results of the ACTIVE-I trial in AFib, which found irbesartan lowered blood pressure but had no other benefit in AFib patients. ACTIVE-I was a large study (9,016 patients), and the rationale for testing irbesartan was that high blood pressure is the commonest reason for AFib. However, a non-pre-specified, post hoc analysis found that the composite endpoint of stroke/TIA/non-CNS embolism was significantly reduced with irbesartan. Dr. Yusuf commented, "Maybe there is something that even small blood pressure lowering will prevent intracranial bleeds…Although we didn't reach our primary endpoint, we had clinically useful results. The other surprise was that the number of hospital admissions were substantially reduced and total days in hospital were reduced…Studies have shown in this population where 80% have hypertension, it makes sense to use an ARB…and perhaps it reduced intracranial bleeds."

Asked if there is any mechanistic explanation for why adding an ARB reduced hemorrhagic events, Dr. Yusuf said, "I think it is blood pressure reduction. The relationship between blood pressure and intracranial bleeds is (strong)…So, these results shouldn't be a surprise."

Results of ACTIVE-I Trial of Irbesartan in AFib

Measurement	Irbesartan 300 mg/day	Placebo	p-value
Primary endpoint: First stroke/MI/vascular death	5.4%	5.4%	Nss, 0.846 (HR 0.99)
Change in SBP	- 6.94	- 3.23	---
Stroke	2.1%	2.3%	Nss, 0.213 (HR 0.92)
TIA	0.7%	0.8%	Nss, 0.208
Non-CNS embolism	0.3%	0.4%	Nss, 0.114 (HR 0.74)
Stroke/TIA/non-CNS embolism	2.9%	3.4%	0.024
Hospital admissions	2,817	4,050	0.003

Fractional Flow Reserve (FFR) – gaining importance

A survey by ***CRTonline*** earlier this month found that FFR is still used very little despite growing evidence of its value.

FFR Usage *

% cath lab usage	Doctors using
<5%	61.82%
<10%	16.36%
<20%	7.27%
>20%	14.55%

*** Source *CRTonline* survey**

Is there consistency between the measurements with St. Jude/Radi Medical Systems' and Volcano's FFR pressure wires? Interventional cardiologists asked about this were unaware of any comparison testing, but they all assumed they are comparable. One said, "I imagine they are similar. That's my best guess. Whether it would matter if they are different depends on how different they are and whether it moves patients much in terms of whether they have a good or bad responses. If patients have a low FFR, that would suggest significant stenosis and that something needs to be done. If one device registers low FFR and the other is near normal, that is a concern, but I don't think we will see that much difference." Another said, "They should be (the same). It is a scale. You are measuring a pressure, and the pressure should be the same if it is giving you the correct pressure."

Hemodynamic Support – useful in limited number of patients

What percent of high-risk PCI and AMI cases use hemodynamic support? U.S. interventional cardiologists questioned about this insisted it is very few.

How do cardiologists choose among the available options for hemodynamic support – Abiomed's Impella, CardiacAssist's TandemHeart, or IABP (intra-aortic balloon pump)? One doctor said, "I use all three, each when appropriate…Studies are ongoing comparing balloon pump and Impella in left main, but the vast majority of (left main) cases are being done without hemodynamic support. So, it is unclear how many of those need hemodynamic support. This is more an 'experience of the operator' kind of thing…The greatest use is when a patient has hemodynamic collapse – emergency situations, cardiogenic shock, etc. It is unclear how helpful these support systems are for elective interventions." Another cardiologist said, "We do TandemHeart, and we've had reasonable success. It is all a matter of which patients you pick. Impella is for high-risk procedures; TandemHeart is for longer term…The amount of hemodynamic support with Impella is far greater than with IABP. Impella enables interventional cardiologists to take on riskier cases than they might have done – unprotected left main or critical stenosis in the graft supplying the whole coronary circulation."

Impella is being used in cath labs outside of clinical trials, but cardiologists said they are not feeling any pressure from hospital administrators about the cost of either Impella or TandemHeart when they use those devices. A doctor said, "The hospital doesn't say anything when we use them as indicated – and because our use is for a very small number of patients." Another said, "There is no hospital push back."

Robotic Guidance: INTUITIVE SURGICAL's da Vinci Robot – catching on slowly in cardiac surgery

Interest in robotic surgery for cardiac procedures remains very low. A da Vinci is expensive, and most cardiac surgeons questioned at ESC do not see a need for it. However, some sources suggested that a da Vinci may be an option that surgeons will get for new hybrid operating rooms (combination interventional cath labs and cardiac surgery ORs). Hybrid ORs are catching on, but slowly due to both the cost and the need for a change in the relationship between cardiac surgeons and interventional cardiologists.

- *U.S. doctor whose hospital has a cardiac da Vinci in its hybrid OR:* "We have it because of patient demand. Patients want smaller incisions and better recovery time. The hybrid OR actually saves a number of procedures and time in the hospital. You can have a stent and a valve done in one room. We have had situations where patients went in for an angiogram, a decision was made, a stent placed, and then valve surgery performed. And some of our cardiac surgeons are now certified in interventional cardiology…We've had a coronary surgeon do an angioplasty and then an aortic valve, but he was prepared to do CABG if significant stenosis was found. That is quite efficient."
- *Dr. Pinto of Portugal:* "The da Vinci doesn't have a major role in cardiac surgery."

Genetic testing – may help prevent heart attacks but not in the near future

Although there are 13 genetic variants found that affect risk of heart attacks, several dozen are expected to be discovered. Each variant increases the risk by 10%-30%. Risk variants are common. Some scientists envision a future in which people will be tested for a panel of risk variants, the results of which could add to risk assessment and influence decisions about whether to do primary prevention with, for example, statins. At an individual level, overall genetic risk may be determined by the proportion of risk variants one carries within all the genes that affect the risk of heart attacks, and those are not yet known, making any accurate risk prediction algorithms difficult.

European Heart Health Charter – issues new guidelines

The Joint European Societies' task forces on CVD prevention guidelines, published in 2007, are being implemented in Europe on a wide scale and include more attention to health promotion and CVD prevention within existing healthcare and

insurance systems. The guidelines have been adopted by 24 national cardiac societies, translated into 19 languages, and published in 19 scientific national journals. Nationwide prevention strategies in 17 countries focus on education about balanced diet, physical exercise, and avoiding tobacco. Challenges include the need for adequate healthcare and insurance systems. Also, most European health systems provide acute care, and there is a need to focus more on prevention. A second European summit will convene in 2010.

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