

New Antiplatelet Rx Bests Clopidogrel in STEMI

BY BRUCE JANCIN

ORLANDO — The investigational reversible oral antiplatelet drug ticagrelor proved superior to clopidogrel in all-cause mortality and other key end points in a major randomized trial involving 8,430 patients with ST-elevation MI.

“We believe that ticagrelor may become a new standard of care for the management of patients with STEMI intended for primary PCI,” Dr. P. Gabriel Steg declared in presenting the results of the Platelet Inhibition and Patient Outcomes (PLATO) STEMI subanalysis at the annual scientific sessions of the American Heart Association.

The primary end point in the new PLATO STEMI prespecified subanalysis was a composite of cardiovascular death, MI, or stroke during 1 year of treatment with aspirin and either twice-daily ticagrelor or once-daily clopidogrel (Plavix), the current standard therapy. The composite end point occurred in 9.3% of the ticagrelor group and 11.0% of those on clopidogrel, for a significant 15% relative risk reduction.

Ticagrelor was also associated with significant advantages over clopidogrel in key secondary end points in PLATO STEMI, including reductions of 18% in all-cause mortality and 39% in definite stent thrombosis. (See box.) Moreover, there was no increase in major bleeding with ticagrelor, reported Dr. Steg, pro-

fessor of cardiology at the University of Paris and director of the coronary care unit at Bichat-Claude Bernard Hospital.

Ticagrelor is a reversible blocker of the P2Y₁₂ platelet receptor with considerably more potent and consistent antiplatelet activity than clopidogrel. It's the first in a new class of agents known as the cyclo-pentyl-triazolo-pyrimidines that is chemically distinct from thienopyridines such as clopidogrel or prasugrel.

In PLATO STEMI, the number of patients who needed to be treated for 1 year with ticagrelor rather than clopidogrel to prevent one additional cardiovascular death, MI, or stroke was 59, Dr. Steg said.

He drew particular attention to the reduction in all-cause mortality with ticagrelor compared with clopidogrel, an advantage that grew over time. “We don't come across treatments in cardiovascular care that reduce all-cause mortality often. It sets ticagrelor apart from other oral inhibitors of platelet function. The mortality reduction here is new, it is important quantitatively, and it may have several explanations,” he said.

For one thing, ticagrelor is probably not solely a platelet inhibitor. It is also an adenosine agonist. “Adenosine has myriad physiologic functions that may be beneficial in the context of acute myocardial ischemia and vascular disease. It improves platelet function and vascular

	Clopidogrel	Ticagrelor	Relative Risk Reduction
All-cause mortality	6.0%	4.9%	18%
Definite stent thrombosis	2.5%	1.6%	39%
Major bleeding	9.3%	9.0%	Not significant

Source: Dr. Steg

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function and may have myocardial protection properties. This is very speculative, but given that other antiplatelet agents that have reduced MI have not decreased mortality, the fact that we see here a decrease in MI and cardiovascular events, and a decrease in mortality, raises the question of whether there are other mechanisms at play,” he said.

Discussant Lisa K. Jennings, Ph.D., a vascular biologist at the University of Tennessee, Memphis, noted that another possible contributor to ticagrelor's all-cause mortality advantage may be its faster onset of action. Unlike the thienopyridines, ticagrelor is not a pro-drug. And PLATO STEMI participants were randomized relatively early—with in the first 24 hours after symptom onset, when their risk of cardiac events was especially high and a mortality difference favoring a faster-acting drug would be particularly evident.

The chief side effect associated with ticagrelor was dyspnea, occurring in

12.9% of patients, compared with 8.3% of patients on clopidogrel. The dyspnea was mild, usually occurred early in the course of treatment, and then resolved.

The reduction in cardiovascular events seen with ticagrelor could be expected to result in considerable financial savings through reduced post-STEMI hospitalizations. In addition, the drug's stronger and more consistent antiplatelet activity compared with clopidogrel could conceivably do away with the need to perform platelet function assays in patients undergoing PCI, as is now guideline-recommended with clopidogrel. That possibility will require further studies.

AstraZeneca, which sponsored PLATO, recently applied for European marketing approval for ticagrelor (Brilinta) for treatment of patients with acute coronary syndrome.

Dr. Steg disclosed that he is a consultant to and on the speakers bureau for AstraZeneca. Dr. Jennings is also a consultant to the company. ■

Calcium Score May Improve Framingham Risk Assessment

BY RICHARD HYER

CHICAGO — The Framingham Heart Study risk algorithm fails to identify a significant number of individuals at high risk of coronary heart disease, and its accuracy could be improved significantly by integrating coronary calcium scoring, according to a new study from the Netherlands.

“Coronary calcium scoring, detected by CT, is a promising way to improve cardiovascular risk prediction. Population-based studies have shown that the calcium score is a strong predictor of coronary events,” said Rozemarijn Vliegenthart Proença, Ph.D., of University Medical

Center Groningen (the Netherlands).

This 7-year-long study of 2,038 patients, conducted at the medical center, is supported by outcomes data demonstrating that nearly two-thirds of patients who would be classified as intermediate risk should actually be reclassified as either high or low risk.

The study questioned whether adding the calcium score to known cardiovascular risk factors would improve risk classification in the population. It was embedded into the population-based Rotterdam Study, and 2,038 individuals aged 55-85 years were invited to participate.

“We assessed as clinical outcome coronary heart disease comprising nonfatal

myocardial infarction, [coronary heart disease] mortality, coronary artery bypass grafting, and percutaneous coronary interventions,” Dr. Vliegenthart Proença said at the annual meeting of the Radiological Society of North America.

Investigators created two prediction models: one with variables of the Framingham risk score, fitted to this patient population, and the other including the calcium score. Risk estimates for coronary events were extrapolated to 10 years, the common time horizon for predicting cardiovascular risk. “Then we calculated reclassification percentages to assess what the actual effect is of adding the calcium score to risk factors. Finally we compared the predicted risk, in the different categories, to the actually observed risk,” Dr. Vliegenthart Proença said.

Patients had a mean age of 70 years, and 1,171 (57%) were women. During the course of the study, 84 men and 45 women had a coronary event.

An elevated calcium score corresponded to significantly increased risk of events. Men with a calcium score over 400 had a sevenfold increased risk, compared with men who had a calcium score of 0-10. “When we adjusted for cardiovascular risk factors, these relative risks did not materially change,” Dr. Vliegenthart Proença said.

The strong association between the amount of coronary calcification and

the risk of coronary heart disease was evident in the women's cohort as well.

When the calcium score was included with the Framingham risk score, almost 30% migrated to different risk categories. Reclassification was most prominent in the intermediate Framingham risk category, where nearly two-thirds of men and women were reclassified as either lower or higher risk.

According to Dr. Vliegenthart Proença, this was one of the study's strengths. “Reclassification was based on the actual events. The observed risk in the different categories were calculated on the basis of our risk model, our prediction model, and on the basis of the actual events occurring in the different risk categories.”

An audience member questioned whether the Netherlands has used this data to change treatment recommendations. “Actually, that's work in progress. At this moment there is no screening for coronary calcium in the Dutch population,” Dr. Vliegenthart Proença said.

Session moderator Dr. Frank John Rybicki III of Harvard Medical School, Boston, agreed. This study “pretty specifically shows that integration of the calcium score has a very high chance of being beneficial in determining one's overall risk.”

The study was sponsored by University Medical Center Groningen. Dr. Vliegenthart Proença had nothing to disclose. ■

Data May Not Fit Younger Patients

The Framingham risk score, which is based on observations of thousands of patients over decades, is particularly useful in determining primary prevention interventions for middle-aged patients.

This study is provocative but it appears to include an older group of individuals who would be at higher risk for



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cardiac events based on their age alone.

It may be premature to extrapolate the findings of this study to younger patients.

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