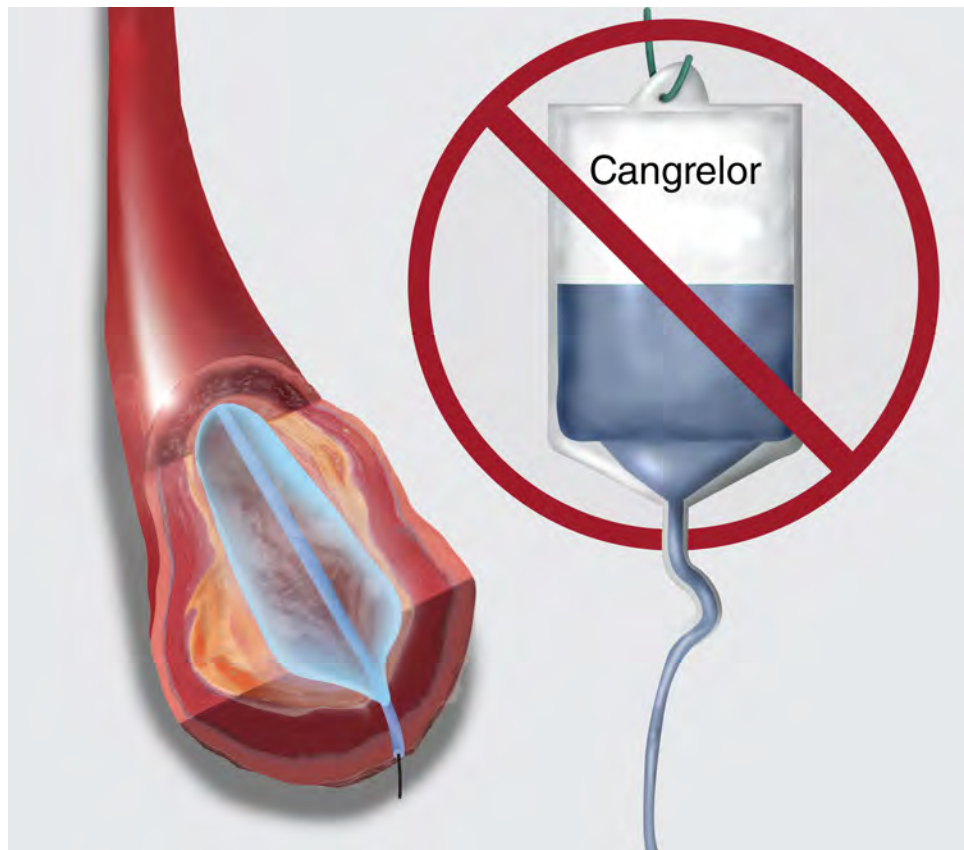


US FDA panel votes against approval of cangrelor for PCI patients

A US FDA advisory panel has voted 7:2 against the approval of cangrelor in patients with coronary artery disease undergoing percutaneous coronary intervention (PCI). Cangrelor, an intravenous (IV) antiplatelet agent, has been suggested to reduce the number of thrombotic cardiovascular events in this particular patient subset but the majority of the panel believed that the risk/benefit profile was not sufficiently strong enough to recommend approval.

Despite the positive results with the CHAMPION-PHOENIX trial in demonstrating the benefits of cangrelor use, other clinical trials, including CHAMPION-PCI and CHAMPION-PLATFORM, yielded negative results and were in fact stopped early in 2009 after interim analyses suggested neither study would show a benefit.

The CHAMPION-PHOENIX study was sponsored by the Medicines Company to address issues raised about those earlier trials – namely, that they were negative owing to problems adjudicating new myocardial infarctions (MIs) in patients with elevated biomarkers at baseline. The 11,000-patient trial tested cangrelor in patients undergoing PCI for stable angina or for acute coronary syndromes, including ST-elevated MI. Overall, treatment with cangrelor reduced the composite efficacy end point of all-cause mortality, MI, ischemia-driven coronary revascularization and stent thrombosis by 22% compared with patients treated with a 300- or 600-mg loading dose of clopidogrel. The risk of stent thrombosis was reduced 38% and the risk of MI reduced by 20%.



In a FDA review of the trial results, PHOENIX received mixed comments, with some reviewers being particularly critical of the data while others believed that the trial showed mixed results. However, the ultimate conclusion was that there was a 'marginal' benefit in the PCI setting that was driven by a reduction in periprocedural MIs.

Members of the advisory panel were troubled by the type of MIs prevented with cangrelor and whether or not they were clinically meaningful. Even with the uncertainty about benefits, they struggled to identify the most clinically significant bleeding end point. In PHOENIX, there were more bleeds with cangrelor, depending on the definition used, although the study's primary safety end point, GUSTO severe non-coronary artery bypass graft or severe/moderate bleeding, did not differ between cangrelor- and clopidogrel-treated patients.

In addition, some committee members struggled to make sense of the benefits of cangrelor, given variations in the comparator arm. Patients in the PHOENIX control arm received either a 300- or 600-mg loading dose of clopidogrel at the physician's discretion, while those in the cangrelor arm received clopidogrel 600 mg that was initiated immediately following the discontinuation of the IV drug.

One panel member, Dr Milton Packer (University of Texas Southwestern Medical Center, TX, USA), voted against the approval of the drug but went on to explain how he had really wanted to vote yes. "The concept behind this drug was so intuitively appealing. You have an antiplatelet drug, and the minute you turn it on, it works, and the minute you turn it off, it stops. The problem I had was that if that were the basis for approving drugs, we would always approve drugs based on surrogate end points. We would approve drugs based on what we think they ought to do and hope they would do that. And then you have to think about that you'll have to treat 1000 patients to prevent, maybe, three MIs or deaths at the cost of three or four major bleeds," he said. "It does not add to a favorable benefit to risk."

In addition, the advisory panel recommended rejecting the application for a cangrelor bridging indication. Specifically, the nine panel members voted against approving cangrelor for use in patients with stents at increased risk for thrombotic events who have to stop oral P2Y₁₂ inhibition because they are undergoing surgery. There were zero votes in favor of approving cangrelor as a 'bridge' therapy, mainly as the panel members again felt there wasn't sufficient evidence to provide an assessment of the risks and benefits.

Source: Press release: The Medicines Company. <http://ir.themedicinescompany.com/phoenix.zhtml?c=122204&p=irol-news-Article&ID=1899593&highlight=>

Paclitaxel-eluting stent study: 4-year results presented in Paris

The 4-year results of the Zilver® PTX® (Cook Medical, IN, USA) randomized controlled trial of paclitaxel-eluting stents for femoropopliteal disease were recently presented for the first time during the Controversies and Updates in Vascular Surgery Congress 2014 in France.

Designed to evaluate bare metal stents (BMS) and percutaneous transluminal angioplasty (PTA)-coated stents as treatments for peripheral arterial disease in the superficial femoral artery, the study is the first of its kind with long-term data.

The results indicate that paclitaxel-eluting stents continue to demonstrate consistent, superior results when compared with BMS and PTA in terms of primary patency, restenosis reduction and revascularization rates.

Patients treated with Zilver PTX demonstrated 75% primary patency in the superficial femoral artery compared with 57.9% patency for patients with pro-

visional BMS placement in the study. Furthermore, 4-year restenosis was reduced by 41% in patients with the paclitaxel-coated stent versus those with BMS. A total of 83.2% of patients with femoropopliteal lesions who were treated with Zilver PTX did not require revascularization after 4 years. In comparison, 69.4% of patients treated with acutely successful PTA or provisional BMS placement did not require revascularization.

"These long-term results show that this paclitaxel-eluting stent consistently has a higher efficacy profile compared to bare metal stents in the treatment of femoropopliteal disease in lesions less than 14 cm. Restenosis, which can reappear within the first year, is a major issue in treating these patients. The significant reduction of restenosis shown in this study, in particular claudicants, with three out of four peripheral artery patients remaining free from restenosis over a 4-year period, underlines the therapeutic interest of this treat-

ment approach to femoropopliteal disease,” said Patrick Lermusiaux, vascular surgeon at Centre Hospitalier Universitaire de Lyon (Lyon, France), who presented the data in Paris.

The 5-year data of the Zilver PTX Randomized Trial of Paclitaxel-Eluting Stents for Femoropopliteal Disease in PAD Patients will be unveiled by the company this Autumn.

Source: *The Zilver PTX® Randomized Controlled Trial of Paclitaxel-Eluting Stents for Femoropopliteal Disease: 4-year results. Presented at: CACVS 2014 Annual Congress. Paris, France, 13 January 2014.*

Retrospective study indicates shift in cause of death after percutaneous coronary intervention

A large, single-center study has reported that the cause of long-term death after percutaneous coronary intervention (PCI) has shifted from cardiac to noncardiac causes over the last two decades.

Researchers performed a retrospective study of close to 20,000 consecutive patients who underwent an index PCI at the Mayo Clinic (MN, USA) and examined the 5-year mortality rates during three 6-year periods: 1991–1996, the balloon angioplasty era; 1997–2002, the bare-metal stent era; and 2003–2008, the drug-eluting stent, or modern, era.

In the most recent era, only 36.8% deaths at 5 years after PCI were cardiac related: congestive heart failure or structural heart disease (12.9%), myocardial infarction (MI; 12.0%), sudden cardiac death (9.3%), and surgical or other cardiac causes (2.6%). While death from MI or sudden cardiac arrest had dropped, death from heart failure remained the same. The noncardiac deaths were largely from cancer (26.2%) and chronic disease such as renal failure, pulmonary disease, liver or multiorgan failure, or neurologic disease (16.0%). Other noncardiac causes included vascular disease, sepsis, suicide, trauma and accidents (19.1%).

Of the 19,077 patients who survived hospitalization, 6988 patients (37%) died during follow-up.

Over the three time periods, the incidence of cardiac deaths at 5 years declined from 9.8% to 7.4% to 6.6%, while noncardiac deaths increased from 7.1% to 8.5%

to 11.2%. These trends occurred in all age groups, in single and multivessel disease, and in PCI performed for stable angina or acute coronary syndromes. The authors commented that the results were somewhat unexpected owing to PCI patients becoming progressively older and sicker, with more complex disease.

Across these time periods, the mean age increased from 64.7 to 66.3 years and the Charlson index increased from 1.8 to 2.6. The predominant indication for PCI changed from stable angina to acute coronary syndrome. At hospital discharge, more patients were being given medications for secondary prevention: ACE inhibitor use increased from 19 to 63% and lipid-lowering drug use increased from 25 to 90%.

Senior author Rajiv Gulati (Mayo Clinic) has proposed improved medications such as antiplatelets, statins, β -blockers and ACE inhibitors as the main drivers in the reduction of cardiac deaths. According to Gulati, the findings have two major implications. “First, we need to think more in detail about noncardiac causes of death and partner with our noncardiac physician colleagues to target that as an opportunity to improve mortality,” he said. “Second ... maybe as we design new drugs and devices and implement our therapies, [heart failure] is a target that we might have more opportunity to reduce, given that there’s already been a decline in MI and sudden cardiac death.”

Sources: *Spoon DB, Psaltis PJ, Singh M et al. Trends in cause of death after percutaneous coronary intervention. Circulation 129(12), 1286–1294 (2013).*

Blood transfusions may lead to worse PCI outcomes

A nationwide analysis of percutaneous coronary intervention (PCI) suggests there is wide variability in the practice of blood transfusions and that patients who received blood transfusions fared significantly worse following PCI than those who did

not receive them. Furthermore, for patients undergoing PCI who received a blood transfusion, there was a significantly increased risk of MI, stroke and in-hospital death, regardless of bleeding complications.

Led by Matthew Sherwood (Duke Clinical Research Institute, NC, USA), researchers observed that the overall transfusion rate was 2.14% among 2.2 million patients who underwent PCI between 2009 and 2013 in the CathPCI Registry. After adjustment for multiple variables, receipt of blood was associated with significantly increased risk of myocardial infarction (MI), stroke or in-hospital death. In the overall population, transfusion was associated with a more than 3.5-fold increased risk of the combined cardiovascular end point, and this increased risk was observed in patients with bleeding (odds ratio [OR]: 1.16; 95% CI: 1.11–1.22) and those without bleeding (OR: 3.66; 95% CI: 3.63–3.69). As individual end points, MI, stroke and in-hospital deaths were all significantly increased in the overall population, irrespective of bleeding complications.

They also found that the risk-standardized rate of transfusion in PCI patients treated at the 1485 centers ranged from 0.3 to 9.3%. Just over 96% of hospitals gave blood transfusions to less than 5% of their patients. Sherwood explained that there is a lack of definitive evidence on the risks and/or benefits of blood transfusion in the setting of acute coronary syndrome (ACS), and as a result, most physicians tend to adopt hospital practices.

“When we looked at the outcomes, it turns out that blood transfusion, whether the patient bleeds or not, is associated with worse cardiovascular outcomes,” said Sherwood. “We don’t have a lot of randomized clinical trial evidence about transfusion strategies in PCI patients. Our observational research, though confounded, does point to the need for more data, specifically more randomized data to answer the question.”

Recently, the American Association of Blood Banks published new clinical guidelines, but these new guidelines were unable to address hospitalized, hemodynamically stable acute coronary syndrome patients, given the low-quality evidence available.

Given the absence of guideline recommendations for blood transfusions in PCI patients, Sherwood said their center tends to treat patients conservatively. “What we suggest is a conservative strategy with transfusion, and in PCI our goal would be to use bleeding-avoidance strategies so that we can minimize bleeding events and minimize physicians wanting to transfuse. Physicians are much more likely to transfuse a patient who is having a bleeding event. We just don’t know which type of patient transfusion would help and which patient it would harm,” he added.

Source: Sherwood MW, Wang Y, Curtis JP, Peterson ED, Rao SV. Patterns and outcomes of red blood cell transfusion in patients undergoing percutaneous coronary intervention. *JAMA* 311, 836–843 (2014).

– All stories written by Emma Sinclair

– Illustration by Claire Dolan

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