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Money's Only Part of the COI Story

“Any senior scientist will tell you that the biggest conflict of interest he or she has has nothing to do with the [disclosures] they list on their PowerPoints or in their publications,” Dr. Paul M. Ridker said at his talk on the inflammatory hypothesis of atherosclerosis at the meeting of the International Society on Hypertension in Blacks in Boston. “It has to do with our individual belief in the biology of what we’re doing.”



DIANA MAHONEY

For this reason, his lengthy disclosure slide was less relevant than his fundamental bias, which is his belief that inflammation is “part and parcel, if not the cause,

of atherosclerosis.” That type of bias, not industry support, “is what drives my work, and it is what drives most scientists,” stressed Dr. Ridker of Brigham and Women’s Hospital in Boston.

That contention is likely a nod to the diatribe that followed the 2008 publication of the JUPITER trial results, in which he and his coinvestigators attributed a 44% reduction in cardiovascular events to the ability of rosuvastatin (Crestor) to both lower LDL cholesterol and reduce C-reactive protein (CRP) levels (N. Engl. J. Med. 2008;359:2195-207).

Following the publication of the findings, cardiology colleagues questioned the interpretation and veracity of the data in the face of what they deemed to be an unacceptable degree of commercial bias. They were referring not only to the fact that the study was funded by Astra-Zeneca, the drug’s manufacturer, and that 9 of the 14 authors disclosed financial ties to the company, but also that Dr. Ridker holds the legal patent on CRP testing technology. Without question, the skeptics argued, Dr. Ridker had much to gain from the acceptance of his research.

For his part, Dr. Ridker vigorously defends the quality of the JUPITER data. He has also introduced a salient argument, that the COIs that have the most potential to bias research are the ones that defy enumeration. He does not argue against financial disclosures, but he does warn that they don’t tell the “whole story.” ■

Ms. MAHONEY is the New England Bureau Chief for CARDIOLOGY NEWS.



MITCHEL L. ZOLER

Blognosis

Fan Bids Cypher Stent Adieu

Cypher will soon morph into ciper, and it’s not just about the why, but also the whence and the what once was and the what came next.

Cypher is, of course, the first, the original coronary DES, the one that burst onto the scene a decade ago and launched a new

era in interventional cardiology. And soon it will be no more.

Cypher’s manufacturer, Johnson & Johnson, announced that it would pull the stent off the market by the end of this year, citing “evolving market dynamics.” What they meant was that Cypher’s time has come and gone. I’ve written on this blog on

how the second-generation coronary DES have set new efficacy standards for the field. Cypher had become a 10-year old dinosaur. Presumably the demise of the other first-generation DES, the paclitaxol-eluting Taxus stent, by Boston Scientific, is just around the corner.

But I write not so much to

BRILINTA™ (ticagrelor) Tablets

WARNING: BLEEDING RISK

- **BRILINTA, like other antiplatelet agents, can cause significant, sometimes fatal, bleeding (5.1, 6.1).**
- **Do not use BRILINTA in patients with active pathological bleeding or a history of intracranial hemorrhage (4.1, 4.2).**
- **Do not start BRILINTA in patients planned to undergo urgent coronary artery bypass graft surgery (CABG). When possible, discontinue BRILINTA at least 5 days prior to any surgery (5.1).**
- **Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, percutaneous coronary intervention (PCI), CABG, or other surgical procedures in the setting of BRILINTA (5.1).**
- **If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events (5.5).**

WARNING: ASPIRIN DOSE AND BRILINTA EFFECTIVENESS

- **Maintenance doses of aspirin above 100 mg reduce the effectiveness of BRILINTA and should be avoided. After any initial dose, use with aspirin 75-100 mg per day (5.2, 14).**

BRIEF SUMMARY of PRESCRIBING INFORMATION:

For full Prescribing Information, see package insert.

INDICATIONS AND USAGE

Acute Coronary Syndromes

BRILINTA is a P2Y₁₂ platelet inhibitor indicated to reduce the rate of thrombotic cardiovascular events in patients with acute coronary syndrome (ACS) (unstable angina, non-ST elevation myocardial infarction, or ST elevation myocardial infarction). BRILINTA has been shown to reduce the rate of a combined endpoint of cardiovascular death, myocardial infarction or stroke compared to clopidogrel. The difference between treatments was driven by CV death and MI with no difference in stroke. In patients treated with PCI, it also reduces the rate of stent thrombosis [see Clinical Studies (14) in full Prescribing Information]. BRILINTA has been studied in ACS in combination with aspirin. Maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Avoid maintenance doses of aspirin above 100 mg daily [see Warnings and Precautions (5.2) and Clinical Studies (14) in full Prescribing Information].

DOSAGE AND ADMINISTRATION

Initiate BRILINTA treatment with a 180 mg (two 90 mg tablets) loading dose and continue treatment with 90 mg twice daily. After the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a daily maintenance dose of aspirin of 75-100 mg. ACS patients who have received a loading dose of clopidogrel may be started on BRILINTA. BRILINTA can be administered with or without food. A patient who misses a dose of BRILINTA should take one 90 mg tablet (their next dose) at its scheduled time.

CONTRAINDICATIONS

History of Intracranial Hemorrhage BRILINTA is contraindicated in patients with a history of intracranial hemorrhage (ICH) because of a high risk of recurrent ICH in this population [see Clinical Studies (14) in full Prescribing Information].

Active Bleeding BRILINTA is contraindicated in patients with active pathological bleeding such as peptic ulcer or intracranial hemorrhage [see Warnings and Precautions (5.1) and Adverse Reactions (6.1) in full Prescribing Information].

Severe Hepatic Impairment BRILINTA is contraindicated in patients with severe hepatic impairment because of a probable increase in exposure, and it has not been studied in these patients. Severe hepatic impairment increases the risk of bleeding because of reduced synthesis of coagulation proteins [see Clinical Pharmacology (12.3) in full Prescribing Information].

WARNINGS AND PRECAUTIONS

General Risk of Bleeding

Drugs that inhibit platelet function including BRILINTA increase the risk of bleeding. BRILINTA increased the overall risk of bleeding (Major + Minor) to a somewhat greater extent than did clopidogrel. The increase was seen for non-CABG-related bleeding, but not for CABG-related bleeding. Fatal and life-threatening bleeding rates were not increased [see Adverse Reactions (6.1) in full Prescribing Information]. In general, risk factors for bleeding include older age, a history of bleeding disorders, performance of percutaneous invasive procedures and concomitant use of medications that increase the risk of bleeding (e.g., anticoagulant and fibrinolytic therapy, higher doses of aspirin, and chronic nonsteroidal anti-inflammatory drugs [NSAIDs]). When possible, discontinue BRILINTA five days prior to surgery. Suspect bleeding in any patient who is hypotensive and has recently undergone coronary angiography, PCI, CABG, or other surgical procedures, even if the patient does not have any signs of bleeding. If possible, manage bleeding without discontinuing BRILINTA. Stopping BRILINTA increases the risk of subsequent cardiovascular events [see Warnings and Precautions (5.5) and Adverse Reactions (6.1) in full Prescribing Information].

Concomitant Aspirin Maintenance Dose In PLATO, use of BRILINTA with maintenance doses of aspirin above 100 mg decreased the effectiveness of BRILINTA. Therefore, after the initial loading dose of aspirin (usually 325 mg), use BRILINTA with a maintenance dose of aspirin of 75-100 mg [see Dosage and Administration (2) and Clinical Studies (14) in full Prescribing Information].

Moderate Hepatic Impairment BRILINTA has not been studied in patients with moderate hepatic impairment. Consider the risks and benefits of treatment, noting the probable increase in exposure to ticagrelor.

Dyspnea Dyspnea was reported in 14% of patients treated with BRILINTA and in 8% of patients taking clopidogrel. Dyspnea was usually mild to moderate in intensity and often resolved during continued treatment. If a patient develops new, prolonged, or worsened dyspnea during treatment with BRILINTA, exclude underlying diseases that may require treatment. If dyspnea is determined to be related to BRILINTA, no specific treatment is required; continue BRILINTA without interruption. In a substudy, 199 patients from PLATO underwent pulmonary function testing irrespective

of whether they reported dyspnea. There was no significant difference between treatment groups for FEV₁. There was no indication of an adverse effect on pulmonary function assessed after one month or after at least 6 months of chronic treatment.

Discontinuation of BRILINTA Avoid interruption of BRILINTA treatment. If BRILINTA must be temporarily discontinued (e.g., to treat bleeding or for elective surgery), restart it as soon as possible. Discontinuation of BRILINTA will increase the risk of myocardial infarction, stent thrombosis, and death.

Strong Inhibitors of Cytochrome CYP3A Ticagrelor is metabolized by CYP3A4/5. Avoid use with strong CYP3A inhibitors, such as atazanavir, clarithromycin, indinavir, itraconazole, ketoconazole, nefazodone, nelfinavir, ritonavir, saquinavir, telithromycin and voriconazole [see Drug Interactions (7.1) and Clinical Pharmacology (12.3) in full Prescribing Information].

Cytochrome CYP3A Potent Inducers Avoid use with potent CYP3A inducers, such as rifampin, dexamethasone, phenytoin, carbamazepine, and phenobarbital [see Drug Interactions (7.2) and Clinical Pharmacology (12.3) in full Prescribing Information].

ADVERSE REACTIONS

Clinical Trials Experience

The following adverse reactions are also discussed elsewhere in the labeling:

- **Dyspnea** [see Warnings and Precautions (5.4) in full Prescribing Information]

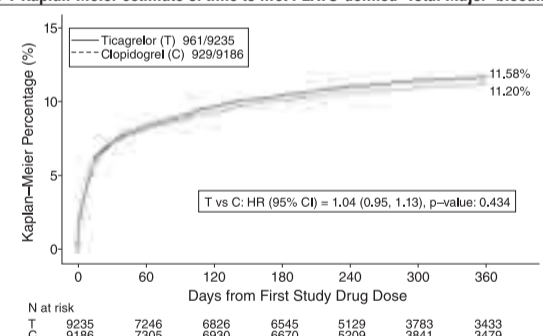
Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. BRILINTA has been evaluated for safety in more than 10000 patients, including more than 3000 patients treated for more than 1 year.

Bleeding PLATO used the following bleeding severity categorization:

- **Major bleed – fatal/life-threatening.** Any one of the following: fatal; intracranial; intrapericardial bleed with cardiac tamponade; hypovolemic shock or severe hypotension due to bleeding and requiring pressors or surgery; clinically overt or apparent bleeding associated with a decrease in hemoglobin (Hb) of more than 5 g/dL; transfusion of 4 or more units (whole blood or packed red blood cells (PRBCs)) for bleeding.
- **Major bleed – other.** Any one of the following: significantly disabling (e.g., intraocular with permanent vision loss); clinically overt or apparent bleeding associated with a decrease in Hb of 3 g/dL; transfusion of 2-3 units (whole blood or PRBCs) for bleeding.
- **Minor bleed.** Requires medical intervention to stop or treat bleeding (e.g., epistaxis requiring visit to medical facility for packing).
- **Minimal bleed.** All others (e.g., bruising, bleeding gums, oozing from injection sites, etc.) not requiring intervention or treatment.

Figure 1 shows major bleeding events over time. Many events are early, at a time of coronary angiography, PCI, CABG, and other procedures, but the risk persists during later use of antiplatelet therapy.

Figure 1 Kaplan-Meier estimate of time to first PLATO-defined 'Total Major' bleeding event



Annualized rates of bleeding are summarized in Table 1 below. About half of the bleeding events were in the first 30 days.

Table 1 Non-CABG related bleeds (KM%)

	BRILINTA N=9235	Clopidogrel N=9186
Total (Major + Minor)	8.7	7.0
Major	4.5	3.8
Fatal/Life-threatening	2.1	1.9
Fatal	0.2	0.2
Intracranial (Fatal/Life-threatening)	0.3	0.2

As shown in Table 1, BRILINTA was associated with a somewhat greater risk of non-CABG bleeding than was clopidogrel. No baseline demographic factor altered the relative risk of bleeding with BRILINTA compared to clopidogrel. In PLATO, 1584 patients underwent CABG surgery. The percentages of those patients who bled are shown in Table 2. Rates were very high but similar for BRILINTA and clopidogrel.

Table 2 CABG bleeds (KM%)

	Patients with CABG	
	BRILINTA N=770	Clopidogrel N=814
Total Major	85.8	86.9
Fatal/Life-threatening	48.1	47.9
Fatal	0.9	1.1