Four Factors Strongly Predict Ischemic Events

VITALS

Major Finding: Four-year follow-up of a large, atherothrombotic-disease database found four factors that strongly determine risk for new ischemic events: polyvascular disease, ischemic event within the past year, any history of an ischemic event, and current treatment for diabetes.

Data Source: The REACH registry, which enrolled in 44 countries and tracked ischemic events in 45,227 patients with established atherothrombotic disease or multiple risk factors for 4 years during 2003-2008.

Disclosures: REACH is partially sponsored by Sanofi-Aventis and Bristol-Myers Squibb. Dr. Bhatt reported receiving research grants from AstraZeneca, Bristol-Myers Squibb, Eisai, Ethicon, Heartscape, Sanofi-Aventis, and The Medicines Company.

BY MITCHEL L. ZOLER

FROM THE ANNUAL CONGRESS OF THE EUROPEAN SOCIETY OF CARDIOLOGY

STOCKHOLM – Four simple clinical conditions play the biggest role in risk-stratifying outpatients with stable atherothrombotic disease, based on a 45,000-patient, international registry followed for 4 years.

Polyvascular disease heads the list of four factors, followed by history of an ischemic event within the past year, history of an ischemic event at any time, and diabetes, Dr. Deepak L. Bhatt said at the congress. The registry results notably showed polyvascular disease to pose the strongest risk for a subsequent ischemic event, and placed diabetes below the risk from a prior ischemic event, a finding that further dislodges diabetes from its perch as a

myocardial infarction risk equivalent, said Dr. Bhatt, chief of cardiology at the VA Boston Healthcare System.

"It's an important point, but unfortunately the myth lingers on" that diabetes is a myocardial infarction risk equivalent, he said. It is a myth Dr. Bhatt dates to studies reported more than a decade ago.

In the more contemporary database studied by Dr. Bhatt and his associates, with patients followed from 2003 to 2008, diabetes may have been better managed. "It's not that diabetes is not an important risk factor, but a prior ischemic event trumps diabetes," he said in an interview.

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Polyvascular disease is the strongest risk factor, said Dr. Deepak L. Bhatt.

The 4-year results from the Reduction of Atherothrombosis for Continued Health (REACH) registry also added new evidence on the role of polyvascular disease, the study's "most potent predictor of future ischemic events. REACH is the largest and longest registry" to show a strong polyvascular effect, a risk factor that until now has been underappreciated, Dr. Bhatt said.

"A patient with angina and claudication [ischemic disease in two vascular beds] may look stable, but the message from these data is that these patients are at exceedingly high risk for something bad happening over the next 4 years," and so need even tighter medical control of lipids, blood pressure, and other treatable risks.

Dr. Bhatt and his associates are in the final stages of refining a secondary-prevention risk model, a formula to mathematically stratify patients' risk based on the new REACH analysis. While the model isn't ready for release yet, it is based on the four major risk factors he reported. Until now, "there really hasn't been any major attempt to risk-stratify secondary prevention patients, in part because many physicians seem to feel that the risk faced by all secondary-prevention patients is the same. These data show that's not true. There is a wide range of risk in this population."

Higher-risk patients could receive, for example, intensive case management by a nurse, or may be candidates for expensive, new antiatherosclerotic, anti-inflammatory, or antithrombotic therapies, with some nearing the market. "

The REACH registry initially enrolled more than 68,000 people at 5,587 centers in 44 countries during 2003 and 2004. Reports on the baseline and 1-year follow-up data appeared several years ago (JAMA 2006;295:180-9, and JAMA 2007; 297:1197-206). The new analysis used data collected after 4 years' follow-up from 45,227 of the participants.

The database included 21,890 patients with a prior ischemic event (myocardial infarction or stroke) at the time of enrollment into the registry. Another 15,264 patients entered based on having symptomatic, stable atherosclerosis but no event history. The final 8,073 participants had no documented disease but at least three risk factors off this list: current treatment for diabetes; diabetic retinopathy; an ankle-brachial index below 0.9; asymptomatic carotid stenosis with at least 70% occlusion; carotid intima media thickness at least twice that at adjacent sites; systolic blood pressure of at least 150 mm Hg; hypercholesterolemia; current smoker; age 65 or older in men and 70 or older in women.

The average age of the enrollees at baseline was 68; two-thirds were men. Nearly half had a prior ischemic event, 44% had a history of diabetes, 28% had an ischemic event during the prior year, and 16% had polyvascular disease, defined as atherosclerotic disease in at least two vascular beds: coronary, cerebrovascular, or peripheral. During follow-up, the participants had 5,481 events, either cardiovascular death, myocardial infarction, or stroke.

In an analysis, polyvascular disease at baseline linked with a twofold risk for an ischemic event during follow-up, compared with enrollees with risk factors only. Patients with a history of a recent ischemic event had a 70% higher risk for a follow-up event compared with enrollees without an event history. Patients with diabetes at enrollment had a 44% increased risk for a follow-up event compared with participants without diabetes, which did match the increased risk from an older ischemic event. Heart failure also appeared as a strong risk factor.

Concurrently with Dr. Bhatt's report, the results were published online (JAMA 2010 Aug. 30 [doi: 10.1001/jama.2010.1322]). ■

Table 2: Bleeding Rates for Non-CABG-Related Bleeding by Weight and Age (TRITON-TIMI 38)

	Major/Minor		Fatal	
	Effient (%)	Clopidogrel (%)	Effient (%)	Clopidogrel (%)
Weight <60kg (N=308 Effient, N=356 clopidogrel)	10.1	6.5	0.0	0.3
Weight ≥60kg (N=6373 Effient, N=6299 clopidogrel)	4.2	3.3	0.3	0.1
Age <75 years (N=5850 Effient, N=5822 clopidogrel)	3.8	2.9	0.2	0.1
Age ≥75 years (N=891 Effient, N=894 clopidogrel)	9.0	6.9	1.0	0.1

Bleeding Related to CABG - In TRITON-TIMI 38, 437 patients who received a thienopyridine underwent CABG during the course of the study. The rate of CABG-related TIMI Major or Minor bleeding was 14.1% for the Effient group and 4.5% in the clopidogrel group (Table 3). The higher risk for bleeding adverse reactions in patients treated with Effient persisted up to 7 days from the most recent dose of study drug.

Table 3: CABG-Related Bleeding[a] (TRITON-TIMI 38)

	Effient (%) (N=213)	Clopidogrel (%) (N=224)
TIMI Major or Minor bleeding	14.1	4.5
TIMI Major bleeding	11.3	3.6
Fatal	0.9	0
Reoperation	3.8	0.5
Transfusion of ≥5 units	6.6	2.2
Intracranial hemorrhage	0	0
TIMI Minor bleeding	2.8	0.9

[a] Patients may be counted in more than one row.

Bleeding Reported as Adverse Reactions - Hemorrhagic events reported as adverse reactions in TRITON-TIMI 38 were, for Effient and clopidogrel, respectively: epistaxis (6.2%, 3.3%), gastrointestinal hemorrhage (1.5%, 1.0%), hemoptysis (0.6%, 0.5%), subcutaneous hematoma (0.5%, 0.2%), post-procedural hemorrhage (0.5%, 0.2%), retroperitoneal hemorrhage (0.3%, 0.2%), and retinal hemorrhage (0.0%, 0.1%).

Malignancies: During TRITON-TIMI 38, newly diagnosed malignancies were reported in 1.6% and 1.2% of patients treated with prasugrel and clopidogrel, respectively. The sites contributing to the differences were primarily colon and lung. It is unclear if these observations are causally-related or are random occurrences.

Other Adverse Events: In TRITON-TIMI 38, common and other important non-hemorrhagic adverse events were, for Effient and clopidogrel, respectively: severe thrombocytopenia (0.06%, 0.04%), anemia (2.2%, 2.0%), abnormal hepatic function (0.22%, 0.27%), allergic reactions (0.36%, 0.36%), and angioedema (0.06%, 0.04%). Table 4 summarizes the adverse events reported by at least 2.5% of patients.

Table 4: Non-Hemorrhagic Treatment Emergent Adverse Events Reported by at Least 2.5% of Patients in Either Group

	Effient (%) (N=6741)	Clopidogrel (%) (N=6716)
Hypertension	7.5	7.1
Hypercholesterolemia/Hyperlipidemia	7.0	7.4
Headache	5.5	5.3
Back pain	5.0	4.5
Dyspnea	4.9	4.5
Nausea	4.6	4.3
Dizziness	4.1	4.6
Cough	3.9	4.1
Hypotension	3.9	3.8
Fatigue	3.7	4.8
Non-cardiac chest pain	3.1	3.5
Atrial fibrillation	2.9	3.1
Bradycardia	2.9	2.4
Leukopenia (<4 x 10^3 WBC/L)	2.8	3.5
Rash	2.8	2.4
Pyrexia	2.7	2.2
Peripheral edema	2.7	3.0
Pain in extremity	2.6	2.6
Diarrhea	2.3	2.6

7 DRUG INTERACTIONS

7.1 Warfarin: Coadministration of Effient and warfarin increases the risk of bleeding *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

7.2 Non-Steroidal Anti-Inflammatory Drugs: Coadministration of Effient and NSAIDs (used chronically) may increase the risk of bleeding *[see Warnings and Precautions (5.1)]*.

7.3 Other Concomitant Medications: Effient can be administered with drugs that are inducers or inhibitors of cytochrome P450 enzymes *[see Clinical Pharmacology (12.3)]*.

Effient can be administered with aspirin (75 mg to 325 mg per day), heparin, GPIIb/IIIa inhibitors, statins, digoxin, and drugs that elevate gastric pH, including proton pump inhibitors and H_2 blockers *[see Clinical Pharmacology (12.3)]*.

8 USE IN SPECIFIC POPULATIONS

8.1 Pregnancy: Pregnancy Category B - There are no adequate and well controlled studies of Effient use in pregnant women. Reproductive and developmental toxicology studies in rats and rabbits at doses of up to 30 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating human metabolite) revealed no evidence of fetal harm; however, animal studies are not always predictive of a human response. Effient should be used during pregnancy only if the potential benefit to the mother justifies the potential risk to the fetus.

In embryo fetal developmental toxicology studies, pregnant rats and rabbits received prasugrel at maternally toxic oral doses equivalent to more than 40 times the human exposure. A slight decrease in pup body weight was observed; but, there were no structural malformations in either species. In prenatal and postnatal rat studies, maternal treatment with prasugrel had no effect on the behavioral or reproductive development of the offspring at doses greater than 150 times the human exposure *[see Nonclinical Toxicology (13.1)]*.

8.3 Nursing Mothers: It is not known whether Effient is excreted in human milk; however, metabolites of Effient were found in rat milk. Because many drugs are excreted in human milk, prasugrel should be used during nursing only if the potential benefit to the mother justifies the potential risk to the nursing infant.

8.4 Pediatric Use: Safety and effectiveness in pediatric patients have not been established *[see Clinical Pharmacology (12.3)]*.

8.5 Geriatric Use: In TRITON-TIMI 38, 38.5% of patients were ≥65 years of age and 13.2% were ≥75 years of age. The risk of bleeding increased with advancing age in both treatment groups, although the relative risk of bleeding (Effient compared with clopidogrel) was similar across age groups.

Patients ≥75 years of age who received Effient had an increased risk of fatal bleeding events (1.0%) compared to patients who received clopidogrel (0.1%). In patients ≥75 years of age, symptomatic intracranial hemorrhage occurred in 7 patients (0.8%) who received Effient and in 3 patients (0.3%) who received clopidogrel. Because of the risk of bleeding, and because effectiveness is uncertain in patients ≥75 years of age *[see Clinical Studies (14)]*, use of Effient is generally not recommended in these patients, except in high-risk situations (diabetes and past history of myocardial infarction) where its effect appears to be greater and its use may be considered *[see Warnings and Precautions (5.1), Clinical Pharmacology (12.3), and Clinical Studies (14)]*.

8.6 Low Body Weight: In TRITON-TIMI 38, 4.6% of patients treated with Effient had body weight <60 kg. Individuals with body weight <60 kg had an increased risk of bleeding and an increased exposure to the active metabolite of prasugrel *[see Dosage and Administration (2), Warnings and Precautions (5.1), and Clinical Pharmacology (12.3)]*. Consider lowering the maintenance dose to 5 mg in patients <60 kg. The effectiveness and safety of the 5 mg dose have not been prospectively studied.

8.7 Renal Impairment: No dosage adjustment is necessary for patients with renal impairment. There is limited experience in patients with end-stage renal disease *[see Clinical Pharmacology (12.3)]*.

8.8 Hepatic Impairment: No dosage adjustment is necessary in patients with mild to moderate hepatic impairment (Child-Pugh Class A and B). The pharmacokinetics and pharmacodynamics of prasugrel in patients with severe hepatic disease have not been studied, but such patients are generally at higher risk of bleeding *[see Warnings and Precautions (5.1) and Clinical Pharmacology (12.3)]*.

8.9 Metabolic Status: In healthy subjects, patients with stable atherosclerosis, and patients with ACS receiving prasugrel, there was no relevant effect of genetic variation in CYP2B6, CYP2C9, CYP2C19, or CYP3A5 on the pharmacokinetics of prasugrel's active metabolite or its inhibition of platelet aggregation.

10 OVERDOSAGE

10.1 Signs and Symptoms: Platelet inhibition by prasugrel is rapid and irreversible, lasting for the life of the platelet, and is unlikely to be increased in the event of an overdose. In rats, lethality was observed after administration of 2000 mg/kg. Symptoms of acute toxicity in dogs included emesis, increased serum alkaline phosphatase, and hepatocellular atrophy. Symptoms of acute toxicity in rats included mydriasis, irregular respiration, decreased locomotor activity, ptosis, staggering gait, and lacrimation.

10.2 Recommendations about Specific Treatment: Platelet transfusion may restore clotting ability. The prasugrel active metabolite is not likely to be removed by dialysis.

13 NONCLINICAL TOXICOLOGY

13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility: *Carcinogenesis* - No compound-related tumors were observed in a 2-year rat study with prasugrel at oral doses up to 100 mg/kg/day (>100 times the recommended therapeutic exposures in humans (based on plasma exposures to the major circulating human metabolite). There was an increased incidence of tumors (hepatocellular adenomas) in mice exposed for 2 years to high doses (>250 times the human metabolite exposure).

Mutagenesis - Prasugrel was not genotoxic in two *in vitro* tests (Ames bacterial gene mutation test, clastogenicity assay in Chinese hamster fibroblasts) and in one *in vivo* test (micronucleus test by intraperitoneal route in mice).

Impairment of Fertility - Prasugrel had no effect on fertility of male and female rats at oral doses up to 300 mg/kg/day (80 times the human major metabolite exposure at daily dose of 10 mg prasugrel).

17 PATIENT COUNSELING INFORMATION

See Medication Guide

17.1 Benefits and Risks

- Summarize the effectiveness features and potential side effects of Effient.
- Tell patients to take Effient exactly as prescribed.
- Remind patients not to discontinue Effient without first discussing it with the physician who prescribed Effient.
- Recommend that patients read the Medication Guide.

17.2 Bleeding: Inform patients that they:

- will bruise and bleed more easily.
- will take longer than usual to stop bleeding.
- should report any unanticipated, prolonged, or excessive bleeding, or blood in their stool or urine.

17.3 Other Signs and Symptoms Requiring Medical Attention

- Inform patients that TTP is a rare but serious condition that has been reported with medications in this class of drugs.
- Instruct patients to get prompt medical attention if they experience any of the following symptoms that cannot otherwise be explained: fever, weakness, extreme skin paleness, purple skin patches, yellowing of the skin or eyes, or neurological changes.

17.4 Invasive Procedures: Instruct patients to:

- inform physicians and dentists that they are taking Effient before any invasive procedure is scheduled.
- tell the doctor performing the invasive procedure to talk to the prescribing health care professional before stopping Effient.

17.5 Concomitant Medications: Ask patients to list all prescription medications, over-the-counter medications, or dietary supplements they are taking or plan to take so the physician knows about other treatments that may affect bleeding risk (*e.g.*, warfarin and NSAIDs).

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