coronary angiography was performed in 5%. No significant stenosis was found in 82% of patients who underwent CTA and 90% who had MPI.

The 6-month major adverse cardiac event rates in this low-risk CT-STAT population were 0.3% in the standard management group and 0.0% in the CTA arm.

SPECT MPI is at present slightly more widely available in EDs around the country than is CTA. The other two up and coming imaging methods with utility in the setting of chest pain and nondiagnostic ECG in the ED—cardiac MRI and contrast echocardiography perfusion—have only limited availability. In terms of accuracy, they're similar to MPI and CTA, said Dr. Kramer.

CTA is the clear winner in terms of time to diagnosis and cost in the emergency department.

DR. KRAMER

A recent pooled analysis of MPI in ED evaluation of chest pain that included nine studies and nearly 1,900 patients showed the imaging method had 98% sensitivity and 73% specificity for identifying acute coronary syndrome. On the basis of its ability to reduce hospital admissions, it has been estimated that MPI reduces hospital costs by about $800 per patient.

Dr. Kramer serves as a consultant to Siemens Medical Solutions and is the recipient of research grants from Astellas and GlaxoSmithKline. ■

Gadolinium Warnings Reduce NSF

BY KERRI WACHTER

GAITHERSBURG, MD. — Black box warnings added to the labels of all gadolinium-based MRI contrast agents have reduced the number of reported nephrogenic systemic fibrosis events to almost none in the last year, according to Dr. James Kaiser.

"The numbers of new events have tapered dramatically, probably due to public awareness of the association of NSF [nephrogenic systemic fibrosis] with GBCA [gadolinium-based contrast agent] administration," he said at a joint meeting of the Food and Drug Administration's Cardiovascular and Renal Drugs and Drug Safety and Risk Management advisory committees. Event dates are either the date of administration of contrast or the date of diagnosis of NSF.

The FDA began receiving reports of NSF possibly being linked to gadolinium-based contrast agents in 2006 when 194 event dates were reported.

This "probably reflects awareness of the medical community of the potential connection between GBCA administration and NSF and changes in radiologic practice," said Dr. Kaiser of the FDA's office of surveillance and epidemiology. There were 128 reported events in 2007, 55 in 2008, and 6 in 2009 (through September).

In 2007, the FDA asked manufacturers to include a boxed warning on the product labels of all gadolinium-based contrast agents.

Five gadolinium-based contrast agents have been approved for use in the United States: Magnevist (gadopentetate dimeglumine), Omniscan (gadodiamide), OptiMARK (gadoversetamide), MultiHance (gadobenate dimeglumine), and ProHance (gadoteridol).

As of September 2009, 382 reports of NSF had been associated with Omniscan (GE HealthCare), 195 with Magnevist (Bayer HealthCare), 35 with OptiMARK (Covidien), 1 with MultiHance (Bracco Diagnostics), and 0 with ProHance (Bracco Diagnostics).

The FDA asked the committees to consider whether warning labels should continue to be grouped together as a class or if there was adequate evidence to single out agents that increase NSF risk.

"The majority of the group feels that at least two of the agents appear to be different from the other agents," said Dr. Robert A. Harrington, who chairs the Cardiovascular and Renal Drugs Advisory Committee. The majority recommended the use of Omniscan and OptiMARK be contraindicated in patients with severe kidney dysfunction. However, there was uncertainty as to how to define severe kidney dysfunction.

There was less consensus on whether a third agent, Magnevist, might also warrant contraindication language. ■

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 10^9 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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