

Off-Pump CABG Bests PCI in Cognitive Scores

BY BRUCE JANCIN

ORLANDO — Patients treated with off-pump coronary artery bypass graft surgery had significantly better long-term neurocognitive function than did those who got percutaneous coronary intervention in the first-ever randomized head-to-head comparison of the revascularization methods focusing on cognitive outcome.

At 7.5 years' follow-up in the Dutch multicenter Octopus Study, overall scores on a standardized neurocognitive test battery were significantly better in the off-pump coronary artery bypass (OPCAB) group, Dr. Jakub J. Regieli said at the annual scientific sessions of the American Heart Association.

The OPCAB group scored significantly higher on four of the seven cognitive domains measured: visual memory, motor capacity, divided attention, and learning. Scores on the other domains—reaction time, decision making, and working memory—also consistently favored the OPCAB patients, but the advantage fell short of statistical significance, said Dr. Regieli, a cardiology fellow at the University of Utrecht (the Netherlands).

But discussant Robert C. Robbins was not buying Octopus.

"I really have to question whether PCI would give worse neurocognitive function. I can tell you as a surgeon that if I had the choice of having a stent versus CABG, I'd take a stent every time—and I think I'd be smarter in the end," said Dr. Robbins, professor and chairman of the department of cardiothoracic surgery at Stanford (Calif.) University.

"This discussion is different than any



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DR. ROBBINS

I've ever participated in," he added. "You've got a cardiologist telling you how bad PCI is, and I'm a surgeon and I'm defending the results of PCI versus CABG."

There are sound reasons for a patient to opt for OPCAB rather than PCI—a lower repeat revascularization rate, vessels unsuitable for stenting—but an expectation of better cognitive outcome is not one of them, Dr. Robbins said.

The Octopus population comprised

280 low-risk patients with preserved left ventricular function, single-vessel disease, and a mean age of 60.

The composite cardiac end point of death, stroke, or MI occurred in 17.4% of the PCI group over the course of 7.5 years and was not significantly different, at 19.2%, in the OPCAB group. Mortality was 8.7% with PCI and 13.4% with OPCAB, a nonsignificant difference. But the 21.7% repeat revascularization rate in the PCI group was significantly higher than the 11.3% rate with OPCAB.

Manipulation of the aorta occurred in 100% of PCI patients but in only 15% of those who received OPCAB. That difference plays a key role in the Octopus investigators' interpretation of the cognitive outcome differences.

Imaging data show "that microemboli do occur during PCI," Dr. Regieli said. "Subclinical cerebral injury during repeated cardiac catheterization in the PCI-treated patients may have led to worse cognitive performance in that group."

Dr. Regieli added a caveat: PCI in Octopus was performed in the bare-metal stent era. Contemporary PCI with drug-eluting stents has a lower repeat revascularization rate, and that might well spell better neurocognitive performance.

None of the cardiac findings is really

surprising, in Dr. Robbins' view. The neurocognitive results are a different matter. He noted that 25% of patients in the PCI group did not undergo neurocognitive testing, compared with 13% in the OPCAB group—a difference that could have influenced the results. Also, no baseline neurocognitive testing was done prior to revascularization.

More than 8 years ago, when Octopus was being planned, there was widespread high hope that OPCAB was the answer to the neurocognitive impairment that often follows CABG when performed on pump. But the pendulum has swung the other way. Most heart surgeons consider the Veterans Affairs Randomized On/Off Bypass (ROOBY) Study the definitive statement, according to Dr. Robbins.

ROOBY randomized 2,203 patients scheduled for CABG to OPCAB or on-pump surgery. No significant differences between the techniques were found in neurocognitive outcomes (N. Engl. J. Med. 2009;361:1827-37). And there has never been any evidence that on-pump CABG is associated with less neurocognitive impairment than PCI, he noted.

The Octopus Study was funded by The Netherlands National Health Insurance Council. Dr. Regieli reported having no conflicts of interest. ■

Bosentan was teratogenic in rats given oral doses two times the maximum recommended human dose [MRHD] (on a mg/m² basis). In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses 2 and 10 times the MRHD (on a mg/m² basis). Although birth defects were not observed in rabbits given oral doses of up to the equivalent of 10.5 g/day in a 70 kg person, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs [see **Nonclinical Toxicology**].

Nursing Mothers

It is not known whether Tracleer is excreted into human milk. Because many drugs are excreted in human milk, and because of the potential for serious adverse reactions in nursing infants from Tracleer, a decision should be made to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother.

Pediatric Use

Safety and efficacy in pediatric patients have not been established.

Geriatric Use

Clinical studies of Tracleer did not include sufficient numbers of subjects aged 65 and older to determine whether they respond differently from younger subjects. Clinical experience has not identified differences in responses between elderly and younger patients. In general, caution should be exercised in dose selection for elderly patients given the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy in this age group.

Hepatic Impairment

Because there is *in vitro* and *in vivo* evidence that the main route of excretion of bosentan is biliary, liver impairment could be expected to increase exposure (C_{max} and AUC) of bosentan. Mild liver impairment was shown not to impact the pharmacokinetics of bosentan. The influence of moderate or severe liver impairment on the pharmacokinetics of Tracleer has not been evaluated. There are no specific data to guide dosing in hepatically impaired patients; caution should be exercised in patients with mildly impaired liver function. Tracleer should generally be avoided in patients with moderate or severe liver impairment [see **Dosage and Administration, Warnings and Precautions**].

Renal Impairment

The effect of renal impairment on the pharmacokinetics of bosentan is small and does not require dosing adjustment.

Patients with Low Body Weight [see **Dosage and Administration**].

NONCLINICAL TOXICOLOGY

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenesis and Mutagenesis

Two years of dietary administration of bosentan to mice produced an increased incidence of hepatocellular adenomas and carcinomas in males at doses as low as 450 mg/kg/day (about 8 times the maximum recommended human dose [MRHD] of 125 mg twice daily, on a mg/m² basis). In the same study, doses greater than 2000 mg/kg/day (about 32 times the MRHD) were associated with an increased incidence of colon adenomas in both males and females. In rats, dietary administration of bosentan for two years was associated with an increased incidence of brain astrocytomas in males at doses as low as 500 mg/kg/day (about 16 times the MRHD). In a comprehensive battery of *in vitro* tests (the microbial mutagenesis assay, the unscheduled DNA synthesis assay, the V-79 mammalian cell mutagenesis assay, and human lymphocyte assay) and an *in vivo* mouse micronucleus assay, there was no evidence for any mutagenic or clastogenic activity of bosentan.

Reproductive and Developmental Toxicology

Bosentan was teratogenic in rats given oral doses ≥60 mg/kg/day. In an embryo-fetal toxicity study in rats, bosentan showed dose-dependent teratogenic effects, including malformations of the head, mouth, face and large blood vessels. Bosentan increased stillbirths and pup mortality at oral doses of

60 and 300 mg/kg/day. Although birth defects were not observed in rabbits given oral doses of up to 1500 mg/kg/day, plasma concentrations of bosentan in rabbits were lower than those reached in the rat. The similarity of malformations induced by bosentan and those observed in endothelin-1 knockout mice and in animals treated with other endothelin receptor antagonists indicates that teratogenicity is a class effect of these drugs.

Impairment of Fertility/Testicular Function

The development of testicular tubular atrophy and impaired fertility has been linked with the chronic administration of certain endothelin receptor antagonists in rodents.

Treatment with bosentan at oral doses of up to 1500 mg/kg/day (50 times the MRHD on a mg/m² basis) or intravenous doses up to 40 mg/kg/day had no effects on sperm count, sperm motility, mating performance or fertility in male and female rats. An increased incidence of testicular tubular atrophy was observed in rats given bosentan orally at doses as low as 125 mg/kg/day (about 4 times the MRHD and the lowest doses tested) for two years but not at doses as high as 1500 mg/kg/day (about 50 times the MRHD) for 6 months. Effects on sperm count and motility were evaluated only in the much shorter duration fertility studies in which males had been exposed to the drug for 4-6 weeks. An increased incidence of tubular atrophy was not observed in mice treated for 2 years at doses up to 4500 mg/kg/day (about 75 times the MRHD) or in dogs treated up to 12 months at doses up to 500 mg/kg/day (about 50 times the MRHD).

PATIENT COUNSELING INFORMATION

Advise patients to consult the Medication Guide on the safe use of Tracleer.

Important Information

• Monthly monitoring of serum aminotransferases

The physician should discuss with the patient the importance of monthly monitoring of serum aminotransferases.

• Pregnancy testing and avoidance of pregnancy

Patients should be advised that Tracleer is likely to cause birth defects based on animal studies. Tracleer treatment should only be initiated in females of childbearing potential following a negative pregnancy test. Females of childbearing potential must have monthly pregnancy tests and need to use two different forms of contraception while taking Tracleer and for one month after discontinuing Tracleer. Females who have a tubal ligation or a Copper T 380A IUD or LNG 20 IUS can use these contraceptive methods alone. Patients should be instructed to immediately contact their physician if they suspect they may be pregnant and should seek contraceptive advice from a gynecologist or similar expert as needed.

• Drug Interactions

The physician should discuss with the patient possible drug interactions with Tracleer, and which medications should not be taken with Tracleer. The physician should discuss the importance of disclosing all concomitant or new medications.

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