

Delaying Surgery After PCI Cuts Kidney Injury

BY MITCHEL L. ZOLER

FORT LAUDERDALE, FLA. — Combining coronary artery catheterization and cardiac surgery in the same hospital admission was linked to a significantly increased risk for acute kidney injury, compared with performing the surgery during a second, later hospitalization, a single-center study of more than 600 patients showed.

Acute kidney injury (AKI) in cardiac surgery patients represents an important complication. Results from an earlier study linked it to significantly worse long-term survival, Dr. Robert S. Kramer said at the annual meeting of the Society of Thoracic Surgeons.

“If there is a way to safely manage patients medically between catheterization and surgery, that should be done, to mitigate the potential for acute kidney in-

jury,” said Dr. Kramer, director of cardiac surgery research at Maine Medical Center in Portland. He acknowledged that some patients have urgent medical reasons to undergo cardiac surgery within days of their percutaneous coronary intervention (PCI), such as patients with an acute MI, life-threatening coronary anatomy, or another acute syndrome that mandates quick surgery. However, in many other cases, cardiac surgery be-

comes scheduled during the same hospital admission as PCI because of convenience for the patient, the surgeon, or other physicians involved with the case.

“We want cardiac surgeons to look at the whole picture and consider whether it would be better for the patient to go home and settle down if there is no reason to act right now,” he said in an interview. “We hypothesize that there may be an opportunity to reduce the incidence of acute kidney injury by moving patients who may be safely changed from the urgent to nonurgent category.”

The study reviewed 722 consecutive patients who underwent cardiac surgery subsequent to PCI at Maine Medical Center during 2008. The analysis excluded 41 patients who required emergency procedures while hospitalized, 5 who were on dialysis, and 8 who did not have cardiac catheterization in the days or weeks before their surgery, leaving 668 patients in the study. Surgery occurred during a subsequent hospitalization following catheterization in 211 patients, while in 457, surgery followed catheterization during the same hospitalization. Among patients with delayed surgery, the period between catheterization and surgery averaged 39 days. In patients who had both procedures in one admission, the delay between catheterization and surgery averaged 3 days.

The patients’ average age was 68 years, and about a quarter were women. Patients with immediate surgery and those with delayed surgery were similar in the prevalence of most comorbidities and clinical characteristics. The immediate-surgery patients had a significantly higher prevalence of coronary artery disease, 83% compared with 75%; a higher prevalence of MI during the week preceding surgery, 25% compared with 1%; a higher prevalence of a left ventricular ejection fraction of less than 40%, 14% compared with 8%; and a higher prevalence of an elevated white cell count.

The rates of elective and urgent surgery, respectively, were 86% and 14% in the patients whose surgery was deferred for a second hospitalization, compared with 13% and 87% in patients who had their catheterization and surgery in a single hospitalization. Coronary bypass surgery alone occurred in 53% of the deferred patients and 60% of those with a single hospitalization, with the other surgeries divided between valve alone or valve plus bypass.

The incidence of AKI during or immediately after surgery was 34% in the patients who came back to the hospital a second time for their surgery and 50% in those who had their surgery soon after their catheterization, a statistically significant difference. Dr. Kramer and his associates used an AKI definition devised by the AKI Network: a creatinine measure that increased by at least 50% over baseline or that rose by at least 0.3 mg/dL over baseline. All patients in the review had their serum creatinine levels measured at baseline and several

Continued on following page

Once-A-Day

■ ■ CUBICIN® ■ ■ (daptomycin for injection)

Brief summary of prescribing information.

INDICATIONS AND USAGE CUBICIN (daptomycin for injection) is indicated for the following infections (see also **DOSE AND ADMINISTRATION** and **CLINICAL STUDIES** in full prescribing information): **Complicated skin and skin structure infections (cSSSI)** caused by susceptible isolates of the following Gram-positive microorganisms: *Staphylococcus aureus* (including methicillin-resistant isolates), *Streptococcus pyogenes*, *S. agalactiae*, *S. dysgalactiae* subsp. *equisimilis*, and *Enterococcus faecalis* (vancomycin-susceptible isolates only). Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms. **Staphylococcus aureus bloodstream infections** (bacteremia), including those with right-sided infective endocarditis, caused by methicillin-susceptible and methicillin-resistant isolates. Combination therapy may be clinically indicated if the documented or presumed pathogens include Gram-negative or anaerobic organisms. The efficacy of CUBICIN in patients with left-sided infective endocarditis due to *S. aureus* has not been demonstrated. The clinical trial of CUBICIN in patients with *S. aureus* bloodstream infections included limited data from patients with left-sided infective endocarditis; outcomes in these patients were poor (see **CLINICAL STUDIES** in full prescribing information). CUBICIN has not been studied in patients with prosthetic valve endocarditis or meningitis. Patients with persisting or relapsing *S. aureus* infection or poor clinical response should have repeat blood cultures. If a culture is positive for *S. aureus*, MIC susceptibility testing of the isolate should be performed using a standardized procedure, as well as diagnostic evaluation to rule out sequestered foci of infection (see **PRECAUTIONS**). CUBICIN is not indicated for the treatment of pneumonia. Appropriate specimens for microbiological examination should be obtained in order to isolate and identify the causative pathogens and to determine their susceptibility to daptomycin. Empiric therapy may be initiated while awaiting test results. Antimicrobial therapy should be adjusted as needed based upon test results. To reduce the development of drug-resistant bacteria and maintain the effectiveness of CUBICIN and other antibacterial drugs, CUBICIN should be used only to treat or prevent infections that are proven or strongly suspected to be caused by susceptible bacteria. When culture and susceptibility information are available, they should be considered in selecting or modifying antibacterial therapy. In the absence of such data, local epidemiology and susceptibility patterns may contribute to the empiric selection of therapy.

CONTRAINDICATIONS CUBICIN is contraindicated in patients with known hypersensitivity to daptomycin.

WARNINGS *Clostridium difficile*-associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including CUBICIN, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon, leading to overgrowth of *C. difficile*. *C. difficile* produces toxins A and B, which contribute to the development of CDAD. Hypertonic-producing strains of *C. difficile* cause increased morbidity and mortality, since these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary because CDAD has been reported to occur over 2 months after the administration of antibacterial agents. If CDAD is suspected or confirmed, ongoing antibiotic use not directed against *C. difficile* may need to be discontinued. Appropriate fluid and electrolyte management, protein supplementation, antibiotic treatment of *C. difficile*, and surgical evaluation should be instituted as clinically indicated.

PRECAUTIONS **General** The use of antibiotics may promote the selection of non-susceptible organisms. Should superinfection occur during therapy, appropriate measures should be taken. Prescribing CUBICIN in the absence of a proven or strongly suspected bacterial infection is unlikely to provide benefit to the patient and increases the risk of the development of drug-resistant bacteria. **Persisting or Relapsing *S. aureus* Infection** Patients with persisting or relapsing *S. aureus* infection or poor clinical response should have repeat blood cultures. If a culture is positive for *S. aureus*, MIC susceptibility testing of the isolate should be performed using a standardized procedure, as well as diagnostic evaluation to rule out sequestered foci of infection. Appropriate surgical intervention (eg, debridement, removal of prosthetic devices, valve replacement surgery) and/or consideration of a change in antibiotic regimen may be required. Failure of treatment due to persisting or relapsing *S. aureus* infections was assessed by the Adjudication Committee in 19/120 (15.8%) CUBICIN-treated patients (12 with MRSA and 7 with MSSA) and 11/115 (9.6%) comparator-treated patients (9 with MRSA treated with vancomycin and 2 with MSSA treated with anti-staphylococcal semi-synthetic penicillin). Among all failures, 6 CUBICIN-treated patients and 1 vancomycin-treated patient developed increasing MICs (reduced susceptibility) by central laboratory testing on or following therapy. Most patients who failed due to persisting or relapsing *S. aureus* infection had deep-seated infection and did not receive necessary surgical intervention (see **CLINICAL STUDIES** in full prescribing information).

Skeletal Muscle In a Phase 1 study examining doses up to 12 mg/kg q24h of CUBICIN for 14 days, no skeletal muscle effects or CPK elevations were observed. In Phase 3 cSSSI trials of CUBICIN at a dose of 4 mg/kg, elevations in CPK were reported as clinical adverse events in 15/534 (2.8%) CUBICIN-treated patients, compared with 10/558 (1.8%) comparator-treated patients. In the *S. aureus* bacteremia/endocarditis trial, at a dose of 6 mg/kg, elevations in CPK were reported as clinical adverse events in 8/120 (6.7%) CUBICIN-treated patients compared with 1/116 (<1%) comparator-treated patients. There were a total of 11 patients who experienced CPK elevations to above 500 U/L. Of these 11 patients, 4 had prior or concomitant treatment with an HMG-CoA reductase inhibitor. Skeletal muscle effects with CUBICIN were observed in animals (see **ANIMAL PHARMACOLOGY** in full prescribing information). Patients receiving CUBICIN should be monitored for the development of muscle pain or weakness, particularly of the distal extremities. In patients who receive CUBICIN, CPK levels should be monitored weekly, and more frequently in patients who received recent prior or concomitant therapy with an HMG-CoA reductase inhibitor. In patients with renal insufficiency, both renal function and CPK should be monitored more frequently. Patients who develop unexplained elevations in CPK while receiving CUBICIN should be monitored more frequently. In the cSSSI studies, among patients with abnormal CPK (>500 U/L) at baseline, 2/19 (10.5%) treated with CUBICIN and 4/24 (16.7%) treated with comparator developed further increases in CPK while on therapy. In this same population, no patients developed myopathy. CUBICIN-treated patients with baseline CPK >500 U/L (N=19) did not experience an increased incidence of CPK elevations or myopathy relative to those treated with comparator (N=24). In the *S. aureus* bacteremia/endocarditis study, 3 (2.6%) CUBICIN-treated patients, including 1 with trauma

associated with a heroin overdose and 1 with spinal cord compression, had an elevation in CPK >500 U/L with associated musculoskeletal symptoms. None of the patients in the comparator group had an elevation in CPK >500 U/L with associated musculoskeletal symptoms. CUBICIN should be discontinued in patients with unexplained signs and symptoms of myopathy in conjunction with CPK elevation >1,000 U/L (5x ULN), or in patients without reported symptoms who have marked elevations in CPK >2,000 U/L (≥10x ULN). In addition, consideration should be given to temporarily suspending agents associated with rhabdomyolysis, such as HMG-CoA reductase inhibitors, in patients receiving CUBICIN. In a Phase 1 study examining doses up to 12 mg/kg q24h of CUBICIN for 14 days, no evidence of nerve conduction deficits or symptoms of peripheral neuropathy was observed. In a small number of patients in Phase 1 and Phase 2 studies at doses up to 6 mg/kg, administration of CUBICIN was associated with decreases in nerve conduction velocity and with adverse events (eg, paresthesias, Bell's palsy) possibly reflective of peripheral or cranial neuropathy. Nerve conduction deficits were also detected in a similar number of comparator subjects in these studies. In Phase 3 cSSSI and community-acquired pneumonia (CAP) studies, 7/989 (0.7%) CUBICIN-treated patients and 7/1,018 (0.7%) comparator-treated patients experienced paresthesias. New or worsening peripheral neuropathy was not diagnosed in any of these patients. In the *S. aureus* bacteremia/endocarditis trial, a total of 11/120 (9.2%) CUBICIN-treated patients had treatment-emergent adverse events related to the peripheral nervous system. All of the events were classified as mild to moderate in severity; most were of short duration and resolved during continued treatment with CUBICIN or were likely due to an alternative etiology. In animals, effects of CUBICIN on peripheral nerve were observed (see **ANIMAL PHARMACOLOGY** in full prescribing information). Therefore, physicians should be alert to the possibility of signs and symptoms of neuropathy in patients receiving CUBICIN.

Drug Interactions **Warfarin** Concomitant administration of CUBICIN (6 mg/kg q24h for 5 days) and warfarin (25 mg single oral dose) had no significant effect on the pharmacokinetics of either drug, and the INR was not significantly altered. As experience with the concomitant administration of CUBICIN and warfarin is limited, anticoagulant activity in patients receiving CUBICIN and warfarin should be monitored for the first several days after initiating therapy with CUBICIN (see **CLINICAL PHARMACOLOGY, Drug-Drug Interactions** in full prescribing information). **HMG-CoA Reductase Inhibitors** Inhibitors of HMG-CoA reductase may cause myopathy, which is manifested as muscle pain or weakness associated with elevated levels of CPK. There were no reports of skeletal myopathy in a placebo-controlled Phase 1 trial in which 10 healthy subjects on stable simvastatin therapy were treated concurrently with CUBICIN (4 mg/kg q24h) for 14 days. In the Phase 3 *S. aureus* bacteremia/endocarditis trial, 5/22 CUBICIN-treated patients who received prior or concomitant therapy with an HMG-CoA reductase inhibitor developed CPK elevations >500 U/L. Experience with co-administration of HMG-CoA reductase inhibitors and CUBICIN in patients is limited; therefore, consideration should be given to temporarily suspending use of HMG-CoA reductase inhibitors in patients receiving CUBICIN (see **ADVERSE REACTIONS, Post-Marketing Experience, Drug-Laboratory Test Interactions**). There are no reported drug-laboratory test interactions.

Carcinogenesis, Mutagenesis, Impairment of Fertility Long-term carcinogenicity studies in animals have not been conducted to evaluate the carcinogenic potential of daptomycin. However, neither mutagenic nor clastogenic potential was found in a battery of genotoxicity tests, including the Ames assay, a mammalian cell gene mutation assay, a test for chromosomal aberrations in Chinese hamster ovary cells, an in vivo micronucleus assay, an in vitro DNA repair assay, and an in vivo sister chromatid exchange assay in Chinese hamsters. Daptomycin did not affect the fertility or reproductive performance of male and female rats when administered intravenously at doses up to 150 mg/kg/day, which is approximately 9 times the estimated human exposure level based upon AUCs. **Pregnancy** **Teratogenic Effects: Pregnancy Category B** Reproductive and teratology studies performed in rats and rabbits at doses of up to 75 mg/kg, 2 and 4 times the 6 mg/kg human dose, respectively, on a body surface area basis, have revealed no evidence of harm to the fetus due to daptomycin. There are, however, no adequate and well-controlled studies in pregnant women. Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. **Nursing Mothers** It is not known if daptomycin is excreted in human milk. Caution should be exercised when CUBICIN is administered to nursing women. **Pediatric Use** Safety and efficacy of CUBICIN in patients under the age of 18 have not been established. **Geriatric Use** Of the 534 patients treated with CUBICIN in Phase 3 controlled clinical trials of cSSSI, 27.0% were 65 years of age or older and 12.4% were 75 years of age or older. Of the 120 patients treated with CUBICIN in the Phase 3 controlled clinical trial of *S. aureus* bacteremia/endocarditis, 25.0% were 65 years of age or older and 15.8% were 75 years of age or older. In Phase 3 clinical studies of cSSSI and *S. aureus* bacteremia/endocarditis, lower clinical success rates were seen in patients ≥65 years of age compared with those <65 years of age. In addition, treatment-emergent adverse events were more common in patients ≥65 years old than in patients <65 years of age.

ADVERSE REACTIONS Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared with rates in the clinical trials of another drug and may not reflect the rates observed in practice. The adverse reaction information from clinical trials does, however, provide a basis for identifying the adverse events that appear to be related to drug use and for approximating rates. Clinical studies sponsored by Cubist enrolled 1,667 patients treated with CUBICIN and 1,319 treated with comparator. Most adverse events reported in Cubist-sponsored Phase 1, 2, and 3 clinical studies were described as mild or moderate in intensity. In Phase 3 cSSSI trials, CUBICIN was discontinued in 15/534 (2.8%) patients due to an adverse event, while comparator was discontinued in 17/558 (3.0%) patients. In the *S. aureus* bacteremia/endocarditis trial, CUBICIN was discontinued in 20/120 (16.7%) patients due to an adverse event, while comparator was discontinued in 21/116 (18.1%) patients. **Gram-Negative Infections** In the *S. aureus* bacteremia/endocarditis trial, serious Gram-negative infections and nonserious Gram-negative bloodstream infections were reported in 10/120 (8.3%) CUBICIN-treated and 0/115 comparator-treated patients. Comparator patients received dual therapy that included initial gentamicin for 4 days. Events were reported during treatment and during early and late follow-up. Gram-negative infections included cholangitis, alcoholic pancreatitis, sternal osteomyelitis/mediastinitis, bowel infarction, recurrent Crohn's disease, recurrent line sepsis, and recurrent urosepsis caused by a number of different Gram-negative organisms. One patient with sternal osteomyelitis following mitral valve repair developed *S. aureus* endocarditis with a 2 cm mitral vegetation and had a course complicated with bowel infarction, polymicrobial bacteremia, and death. **Other Adverse Reactions** The incidence (%) of adverse events that occurred in ≥2% of patients in either CUBICIN 4 mg/kg (N=534) or comparator (N=558) treatment groups in Phase 3 cSSSI studies were as follows: *Gastrointestinal disorders*: constipation 6.2% and 6.8%; nausea 5.8% and 9.5%; diarrhea 5.2% and 4.3%; vomiting 3.2% and 3.8%; dys-

pepsia 0.9% and 2.5%; *General disorders*: injection site reactions 5.8% and 7.7%; fever 1.9% and 2.5%; *Nervous system disorders*: headache 5.4% and 5.4%; insomnia 4.5% and 5.4%; dizziness 2.2% and 2.0%; *Skin/subcutaneous disorders*: rash 4.3% and 3.8%; pruritus 2.8% and 3.8%; *Diagnostic investigations*: abnormal liver function tests 3.0% and 1.6%; elevated CPK 2.8% and 1.8%; *Infections*: fungal infections 2.6% and 3.2%; urinary tract infection 2.4% and 0.5%; *Vascular disorders*: hypotension 2.4% and 1.4%; hypertension 1.1% and 2.0%; *Renal/urinary disorders*: renal failure 2.2% and 2.7%; *Blood/lymphatic system disorders*: anemia 2.1% and 2.3%; *Respiratory disorders*: dyspnea 2.1% and 1.6%; *Musculoskeletal disorders*: limb pain 1.5% and 2.0%; arthralgia 0.9% and 2.2%. *Comparators included vancomycin (1 g IV q12h) and anti-staphylococcal semi-synthetic penicillins (ie, nafcillin, oxacillin, cloxacillin, fluclloxacillin; 4 to 12 g/day IV in divided doses). The incidence (%) of adverse events that occurred in ≥5% of patients organized by system organ class (SOC), in either CUBICIN 6 mg/kg (N=120) or comparator (N=116) treatment groups in the *S. aureus* bacteremia/endocarditis study were as follows: *Infections and infestations*: 65 (54.2%) and 56 (48.3%); urinary tract infection NOS 8 (6.7%) and 11 (9.5%); osteomyelitis NOS 7 (5.8%) and 7 (6.0%); sepsis NOS 6 (5.0%) and 3 (2.6%); bacteraemia 6 (5.0%) and 0 (0%); pneumonia NOS 4 (3.3%) and 9 (7.8%); *Gastrointestinal disorders*: 60 (50.0%) and 68 (58.6%); diarrhoea NOS 14 (11.7%) and 21 (18.1%); vomiting NOS 14 (11.7%) and 15 (12.9%); constipation 13 (10.8%) and 14 (12.1%); nausea 12 (10.0%) and 23 (19.8%); abdominal pain NOS 7 (5.8%) and 4 (3.4%); dyspepsia 5 (4.2%) and 8 (6.9%); loose stools 5 (4.2%) and 6 (5.2%); gastrointestinal haemorrhage NOS 2 (1.7%) and 6 (5.2%); *General disorders and administration site conditions*: 53 (44.2%) and 69 (59.5%); oedema peripheral 8 (6.7%) and 16 (13.8%); pyrexia 8 (6.7%) and 10 (8.6%); chest pain 8 (6.7%) and 7 (6.0%); oedema NOS 8 (6.7%) and 5 (4.3%); asthenia 6 (5.0%) and 6 (5.2%); injection site erythema 3 (2.5%) and 7 (6.0%); *Respiratory, thoracic, and mediastinal disorders*: 38 (31.7%) and 43 (37.1%); pharyngolaryngeal pain 10 (8.3%) and 2 (1.7%); pleural effusion 7 (5.8%) and 8 (6.9%); cough 4 (3.3%) and 7 (6.0%); dyspnoea 4 (3.3%) and 6 (5.2%); *Skin and subcutaneous tissue disorders*: 36 (30.0%) and 40 (34.5%); rash NOS 8 (6.7%) and 10 (8.6%); pruritus 7 (5.8%) and 6 (5.2%); erythema 6 (5.0%) and 6 (5.2%); sweating increased 6 (5.0%) and 0 (0%); *Musculoskeletal and connective tissue disorders*: 35 (29.2%) and 42 (36.2%); pain in extremity 11 (9.2%) and 11 (9.5%); back pain 8 (6.7%) and 10 (8.6%); arthralgia 4 (3.3%) and 13 (11.2%); *Psychiatric disorders*: 35 (29.2%) and 28 (24.1%); insomnia 11 (9.2%) and 8 (6.9%); anxiety 6 (5.0%) and 6 (5.2%); *Nervous system disorders*: 32 (26.7%) and 32 (27.6%); headache 8 (6.7%) and 12 (10.3%); dizziness 7 (5.8%) and 7 (6.0%); *Investigations*: 30 (25.0%) and 33 (28.4%); blood creatine phosphokinase increased 8 (6.7%) and 1 (<1%); *Blood and lymphatic system disorders*: 29 (24.2%) and 24 (20.7%); anaemia NOS 15 (12.5%) and 18 (15.5%); *Metabolism and nutrition disorders*: 26 (21.7%) and 38 (32.8%); hypokalaemia 11 (9.2%) and 15 (12.9%); hyperkalaemia 6 (5.0%) and 10 (8.6%); *Vascular disorders*: 21 (17.5%) and 20 (17.2%); hypertension NOS 7 (5.8%) and 3 (2.6%); hypotension NOS 6 (5.0%) and 9 (7.8%); *Renal and urinary disorders*: 18 (15.0%) and 26 (22.4%); renal failure NOS 4 (3.3%) and 11 (9.5%); renal failure acute 4 (3.3%) and 7 (6.0%); *Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (ie, nafcillin, oxacillin, cloxacillin, fluclloxacillin; 2 g IV q4h), each with initial low-dose gentamicin. The following events, not included above, were reported as possibly or probably drug-related in the CUBICIN-treated group: *Blood and Lymphatic System Disorders*: eosinophilia (1.7%), lymphadenopathy (<1%), thrombocythaemia (<1%), thrombocytopenia (<1%); *Cardiac Disorders*: atrial fibrillation (<1%), atrial flutter (<1%), cardiac arrest (<1%); *Ear and Labyrinth Disorders*: tinnitus (<1%); *Eye Disorders*: vision blurred (<1%); *Gastrointestinal Disorders*: dry mouth (<1%), epigastric discomfort (<1%), gingival pain (<1%), hypoaesthesia oral (<1%); *Infections and Infestations*: candidal infection NOS (1.7%), vaginal candidiasis (1.7%), fungaemia (<1%), oral candidiasis (<1%), urinary tract infection fungal (<1%); *Investigations*: blood phosphorus increased (2.5%), blood alkaline phosphatase increased (1.7%), INR ratio increased (1.7%), liver function test abnormal (1.7%), alanine aminotransferase increased (<1%), aspartate aminotransferase increased (<1%), prothrombin time prolonged (<1%); *Metabolism and Nutrition Disorders*: appetite decreased NOS (<1%); *Musculoskeletal and Connective Tissue Disorders*: myalgia (<1%); *Nervous System Disorders*: dyskinesia (<1%), paraesthesia (<1%); *Psychiatric Disorders*: hallucination NOS (<1%); *Renal and Urinary Disorders*: proteinuria (<1%), renal impairment NOS (<1%); *Skin and Subcutaneous Tissue Disorders*: heat rash (<1%), pruritus generalized (<1%), rash vesicular (<1%). In Phase 3 studies of community-acquired pneumonia (CAP), the death rate and rates of serious cardiorespiratory adverse events were higher in CUBICIN-treated patients than in comparator-treated patients. These differences were due to lack of therapeutic effectiveness of CUBICIN in the treatment of CAP in patients experiencing these adverse events (see **INDICATIONS AND USAGE**). The incidence of decreased renal function based on creatinine clearance levels in CUBICIN 6 mg/kg (N=120) and comparator (N=116) was as follows: Days 2 to 4, 2/96 (2.1%) and 6/90 (6.7%); Days 2 to 7, 6/115 (5.2%) and 16/113 (14.2%); Day 2 to End of Therapy, 13/118 (11.0%) and 30/114 (26.3%). *Comparator: vancomycin (1 g IV q12h) or anti-staphylococcal semi-synthetic penicillin (ie, nafcillin, oxacillin, cloxacillin, fluclloxacillin; 2 g IV q4h), each with initial low-dose gentamicin. **Post-Marketing Experience** The following adverse reactions have been reported with CUBICIN in worldwide post-marketing experience. Because these events are reported voluntarily from a population of unknown size, estimates of frequency cannot be made and causal relationship cannot be precisely established. *Immune System Disorders*: anaphylaxis; hypersensitivity reactions, including pruritus, hives, shortness of breath, difficulty swallowing, truncal erythema, and pulmonary eosinophilia. *Musculoskeletal System*: rhabdomyolysis; some reports involved patients treated concurrently with CUBICIN and HMG-CoA reductase inhibitors.

OVERDOSAGE In the event of overdosage, supportive care is advised with maintenance of glomerular filtration. Daptomycin is slowly cleared from the body by hemodialysis (approximately 15% recovered over 4 hours) or peritoneal dialysis (approximately 11% recovered over 48 hours). The use of high-flux dialysis membranes during 4 hours of hemodialysis may increase the percentage of dose removed compared with low-flux membranes.

DOSE The recommended dosage of CUBICIN (daptomycin for injection) in adult patients is as follows: *Creatinine clearance (CL_{CR})* ≥30 mL/min: 4 mg/kg once every 24 hours (cSSSI) or 6 mg/kg once every 24 hours (*S. aureus* bloodstream infections); *Creatinine clearance (CL_{CR})* <30 mL/min, including hemodialysis or CAPD: 4 mg/kg once every 48 hours (cSSSI) or 6 mg/kg once every 48 hours (*S. aureus* bloodstream infections).



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Primary PCI in STEMI: Stick to Culprit Lesions

BY BRUCE JANCIN

SNOWMASS, COLO. — Primary percutaneous coronary intervention for patients with ST-elevation MI and multivessel disease is best limited to the culprit vessel in hemodynamically stable patients, according to the first large population-based study on this issue to include long-term outcomes.

Staged PCI of other lesions causing residual ischemia can safely be done later during the same hospitalization or during the next few months, Dr. Spencer B. King III reported at a conference sponsored by the American College of Cardiology. Indeed, the analysis of New York State PCI Registry data showed that risk-adjusted mortality with a strategy of staged PCI on additional vessels within 60 days was comparable to that of culprit-vessel primary PCI alone.

Prior studies examining the topic of culprit-vessel versus multivessel PCI in STEMI patients have generally been small, short-term, and conflicting in their findings. As a result, practices vary widely, with some cardiologists restricting themselves to opening only the culprit vessel, others opting to treat additional lesions at the time of primary PCI, and still others waiting a day, several weeks, or months before addressing lesions shown on the basis of stress testing or

fractional flow reserve to be a likely source of residual ischemia.

"There are a host of different opinions out there on how to deal with this," observed Dr. King, the conference program director and president of St. Joseph's Heart and Vascular Institute, Atlanta.

To help bring clarity to the situation, he and his coinvestigators compared mortality through 42 months of follow-up in STEMI patients with multivessel disease who underwent primary PCI in New York State, where reporting of PCI outcomes is mandatory, from January 2003 through June 2006 (JACC Cardiovasc. Interv. 2010;3:22-31).

Mortality rates were significantly lower in 458 hemodynamically stable patients whose revascularization was limited to the culprit vessel than in an equal number of propensity-matched patients who underwent multivessel revascularization at the time of primary PCI. (See box.)

On the other hand, mortality rates in hospital and at 12, 24, and 42 months of follow-up were similar in 259 patients who underwent culprit-vessel PCI only and in 259 propensity-matched patients who had staged multivessel revascularization during the index hospitalization; in fact, the staged multivessel PCI group showed a consistent trend for fewer deaths at all time points.

Similarly, among 538 patients who un-

derwent culprit-vessel PCI only and were alive at 60 days, mortality rates at 12, 24, and 42 months of follow-up were not statistically different compared with those in an equal number of propensity-matched patients who had staged multivessel revascularization within 60 days on a nonemergency basis. Once again, there was a consistent albeit nonsignificant trend for lower mortality in the staged multivessel revascularization group.

A staged PCI approach to STEMI patients with multivessel disease makes solid sense to Dr. David O. Williams. "When I was at Rhode Island Hospital, the mean time it took from when the patient hit the door of the cath lab, often fully dressed, to the balloon going up, was 18 minutes,"

observed Dr. Williams, who is now at Brigham and Women's Hospital, Boston.

"It's very tough to learn much about the patient who's undergoing primary PCI—and their ability to take dual antiplatelet therapy—given the haste with which we do these cases. We're on the clock. When you talk about multiple stents, multiple lesions, I think it might be good to have an opportunity to get to know a little bit more about the background of the patient," he said.

Disclosures: Dr. King is a consultant to BG Medicine, Celonova Biosciences, Cordis, Medtronic, and NorthPoint Domain. Dr. Williams is a consultant to Abbott Vascular, Cordis, and Volcano.

Mortality Following Culprit- vs. Multivessel PCI in STEMI

	Culprit-Vessel Revascularization at Time of Primary PCI	Multivessel Revascularization at Time of Primary PCI
In-hospital	0.9%	2.4%
12 months	4.2%	5.8%
24 months	4.9%	7.2%
42 months	6.7%	10.4%

Notes: Based on New York State PCI Registry data from 2003 to June 30, 2006.

Differences are statistically significant.

Source: Dr. King

Continued from previous page

times during and after surgery.

No other perioperative outcome parameters differed significantly between the two groups, including death, Q-wave MI, or stroke. The perioperative mortality rate was 2% in patients with deferred surgery and 4% in those with more immediate surgery.

In an analysis that adjusted for baseline demographic and clinical differences, patients with deferred surgery had a significant, 45% relative reduction in their rate of AKI, compared with patients with more immediate surgery.

Dr. Kramer and his associates documented the potential importance of AKI in a study they reported at the American Heart Association scientific sessions last November in Orlando. During 5-year follow-up of about 4,000 cardiac surgery patients, the survival rate was about 95% in patients who did not have any AKI perioperatively, compared with about 80% in those who experienced AKI.

"Creatinine levels and AKI are surrogates for bad epiphenomenon" in patients following cardiac surgery. "The kidney is the canary in the mine shaft," Dr. Kramer said.

It's unclear what it is about

scheduling cardiac surgery several days or weeks following coronary catheterization that cuts the risk of AKI. Contrast administered during coronary catheterization "is a major player, but other factors also play a role. It's not that the contrast clears, but contrast causes tubular injury that has to heal and does heal within a few days." Based on other studies, he speculated that a delay of at least 5 days is ideal.

He cautioned that the finding was limited by the retrospective, single-center nature of the study. But it involved a relatively large number of patients, and creatinine level checks occurred prospectively and uniformly for all patients, eliminating potential ascertainment bias.

Although the findings are just hypothesis generating, Dr. Kramer contended that the findings are compelling enough to warrant an immediate change in practice: Limit cardiac surgery within a few days after catheterization to patients who clearly need rapid intervention. ■

Disclosures: Dr. Kramer said he had no disclosures relevant to this study.

■ A related video is at www.youtube.com/HospitalistNews (search for 72164).

Time to Shut Down Low-Volume Heart Transplantation Centers?

BY BRUCE JANCIN

SNOWMASS, COLO. — Heart transplantation is one of the greatest operations ever devised—but the number of heart transplant centers in the United States needs to be cut by about two-thirds.

That's the considered opinion of Dr. Bruce W. Lytle, professor and chair of cardiothoracic surgery at the Cleveland Clinic Foundation, who notes that International Society for Heart and Lung Transplantation (ISHLT) data show persuasively that transplant program volume is an independent predictor of survival, both short term and at 5 years.

With more than 140 heart transplant programs now in place in the United States, relatively few centers have a reasonable case volume. In fact, the number of high-volume centers is actually declining as centers compete for the extremely limited number of donor organs.

It's a situation that cries out for national regulation, Dr. Lytle said at a conference sponsored by the American College of Cardiology.

"My guess is that organ allocation and utilization will probably be a lot more efficient under those circumstances. So I'd say in this area we've met the enemy and they is us. This is not a local issue, this is really a national issue," the surgeon said.

The ISHLT data show that 30-day mortality is doubled at cardiac transplant centers performing fewer than 10 procedures per year. Of all U.S. centers, 45% consistently do fewer than

10 procedures annually, and during a recent 8-year period fully 66% of centers failed to reach the 10-case mark in all 8 years (Ann. Thorac. Surg. 2008;86:1250-9).

"Any normal person can see we need about a third as many transplant programs as we have in America," Dr. Lytle commented.

Survival 5 years following transplant is currently about 80%, with superb quality of life.

"Cardiac transplantation is really one of the great operations of all time, particularly in this day and age, now that a lot of the immune suppression problems have been dealt with. When we do conservative operations for heart failure, we try to make bad heart failure into better heart failure. Transplantation is the only operation we have that takes someone who is really underwater and can make them absolutely normal. It is a terrific operation," he said.

The trouble is, from a public health perspective cardiac transplantation is relatively ineffective, Dr. Lytle added. Although an estimated 250,000-300,000 Americans under age 75 have class IIIb/IV heart failure and are thus potential candidates for cardiac replacement therapy, the limited donor organ supply means that only about 3,000 transplants can be done annually.

Mechanical replacement using left ventricular assist devices as destination therapy will have a much greater impact in this population than will organ transplantation, he predicted. ■

Disclosures: Dr. Lytle reported no relevant financial interests.