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INSIDE

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Carotid Artery Stenting and Endarterectomy Compared

ABSTRACT & COMMENTARY

By John C. Caronna, MD

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Dr. Caronna reports no financial relationship relevant to this field of study.

This article originally appeared in the June 2006 issue of Neurology Alert. It was edited by Matthew E. Fink, MD, and peer reviewed by M. Flint Beal, MD. Dr. Fink is Vice Chairman, Professor of Clinical Neurology, Weill Cornell Medical College; Chief of Division of Stroke and Critical Care Neurology, NewYork-Presbyterian Hospital, and Dr. Beal is Professor and Chairman, Department of Neurology, Cornell University Medical College. Drs. Fink and Beal report no financial relationships relevant to this field of study.

Synopsis: *In this retrospective case-control study, carotid stenting with cerebral protection and carotid endarterectomy were not significantly different in early morbidity and mortality.*

Source: Cao P, et al. Outcome of Carotid Stenting Versus Endarterectomy: A Case-Control Study. *Stroke*. 2006;37:1221-1226.

CAROTID ARTERY ANGIOPLASTY WITH STENTING (CAS) HAS BEEN accepted by many physicians and most patients as a less invasive alternative to carotid endarterectomy (CEA) for the primary and secondary prevention of stroke related to internal carotid artery (ICA) stenosis. The clinical use of CAS has steadily increased despite initial outcome studies that indicated higher morbidity and mortality rates for CAS than for CEA.[1]

Cao and colleagues report the perioperative and midterm (up to 36 months of follow-up) results of CAS vs CEA in a retrospective, matched, case-control study at a single tertiary care hospital in Italy. The primary criterion for treatment was severe ICA stenosis, either symptomatic or asymptomatic. All patients underwent preoperative duplex ultrasound examinations. All patients undergoing CAS had the presence of ICA stenosis confirmed by angiography during the CAS procedure. Patients undergoing CEA had preoperative angiography or CT angiography. Patients with recurrent ICA stenosis, previous cervical radiation therapy, tracheostomy, or ICA stenosis above the C_2 level were excluded from the study.

Table 1

Complications at 30 Days

	Patients (CAS) n = 301	Patients (CAS) %	Patients (CEA) n = 301	Patients (CEA) %	P	OR
Disabling Stroke/Death*	8	2.6	4	1.3	NS	2
Any Stroke	24	7.9	7	2.3	0.001	4
Myocardial Infarction	2	0.6	5	1.6	NS	0.4
TIA**	19	6.3	3	1.0	0.0004	9.5
Local Complications	13	4.3	10	3.3	NS	1.3

(After Cao et al.)

* Treated patients

** Includes intention-to-treat patients

Of 301 patients who had CAS with cerebral protection, 301 were matched with control patients who had CEA during the same period (2001-2004). Matching was by sex, age, symptoms, and coronary artery disease.

Outcome measures were stroke, death, cardiac events, and local complications. Intraprocedure CAS complications were divided into 3 phases:

1) During the passage of the aortic arch and cannulation of the ICA;

2) The crossing of the lesion phase, including placement of the cerebral protection device (CPD); and

3) The stent-ballooning procedure including recovery of the CPD.

There was no evidence of a statistically significant increase in the risk of disabling stroke and death in CAS patients compared with CEA controls (*see Table 1*). The risk of any stroke, however, favored CEA over CAS. Eight disabling strokes (2 fatal) occurred in the CAS group. Four were due to massive embolization during phase one. The remaining 4 strokes occurred during phase 3. Of 16 nondisabling strokes in CAS patients, one occurred during phase one, one during phase 3, 10 within the first 24 hours after CAS, and 4 after 24 hours. The majority of TIAs (18/19) occurred during phase 3 of CAS. Bradycardia or hypotension occurred during the procedure in 34% of CAS patients, despite the use of atropine.

At a mean follow-up of 18 months (range, 3-48 months), there was no significant difference in the rate of restenoses in the CAS group (n = 4, 1.3%) vs the CEA group (n = 10, 3.3%).

COMMENTARY

Although the study is a retrospective analysis of a nonrandomized population, Cao et al's observations provide useful insight into the intraprocedural stroke risk for patients undergoing CAS. Notable, too, was the presence of a learning curve for technical expertise in performing CAS. The first 100 CAS patients had a higher stroke rate than later CAS patients. Therefore, if the first 100 CAS patients are excluded from outcome analysis, then the last 201 CAS patients did not have a stroke risk significantly different from the corresponding 201 CEA-matched controls.

At present, it is not possible to exclude a difference favoring one treatment over the other. Nevertheless, given the appropriate technical expertise and experience, an interventionalist performing CAS can expect outcomes identical to those achieved by the surgeon performing CEA. ■

Reference

1. Endovascular versus Surgical Treatment in Patients with Carotid Stenosis in the Carotid and Vertebral Artery Transluminal Angioplasty Study (CAVATAS): A Randomised Trial. *Lancet*. 2001;357:1729-1737.

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Questions & Comments

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Which Non-Invasive Test is Best for Diagnosing Clinically Significant Carotid Artery Stenosis?

ABSTRACT & COMMENTARY

By Matthew E. Fink, MD

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Dr. Fink reports no financial relationship relevant to this field of study.

This article originally appeared in the July 2006 issue of Neurology Alert. It was peer reviewed by M. Flint Beal, MD.

Synopsis: *All of the currently available non-invasive techniques for carotid artery imaging give accurate results when there is a high-grade stenosis (70-99%), but contrast-enhanced MRA is slightly more sensitive.*

Source: Wardlaw JM, et al. Non-Invasive Imaging Compared with Intra-Arterial Angiography in the Diagnosis of Symptomatic Carotid Stenosis: A Meta-Analysis. *Lancet*. 2006;367:1503-1512.

With improvements in the treatment of extracranial carotid artery stenosis using carotid endarterectomy (CEA) and carotid artery stenting (CAS), it has become important for neurologists to understand the relative accuracy of various non-invasive tests for carotid stenosis that can be used as a screening procedure or as a definitive study prior to referral for treatment. There have been few head-to-head studies that have directly compared Doppler ultrasound (DUS) with MR angiography, with (CEMRA) and without (MRA) contrast enhancement, and CT angiography (CTA). Therefore, Wardlaw and colleagues performed a meta-analysis of all studies in the English language literature from 1980-2004 that evaluated the sensitivity and specificity of various non-invasive carotid studies compared to either NASCET or ECST criteria for angiography. To be included in the analysis, the published studies had to meet the Standards for Reporting of Diagnostic Accuracy, as well as the methods of the Cochrane Database of Systematic Reviews. After excluding all papers from 1980-1986 because of obsolete technology, and eliminating those papers that did not define what proportion of patients or arteries were symptomatic, there were 41 original papers available for inclusion. For each paper, Wardlaw et al computed an estimate for sensitivity and specificity with 95% confidence intervals (CIs) for each non-invasive imaging technique compared with intra-arterial angiography.

In the 41 studies, which represented 2541 patients and 4876 arteries, contrast-enhanced MR angiography was more sensitive (0.94, 95%; CI = 0.88-0.97) and specific (0.93, 95%; CI = 0.89-0.96) for 70%-99% stenosis than Doppler ultrasound, MR angiography without contrast, or CT angiography (sensitivities = 0.89, 0.88, 0.76; specificities 0.84, 0.84, 0.94, respectively). For any degree of stenosis less than 70%, none of the non-invasive tests were deemed reliable when compared to intra-arterial angiography, and data regarding any combination of tests was too sparse to draw any conclusions.

COMMENTARY

Non-invasive testing for carotid artery disease is widely available and liberally utilized as part of the clinical identification of stroke risk factors. In symptomatic patients who have had a TIA or stroke, where treatment decisions are urgent, we often combine tests, commonly DUS with MRA, or DUS with CTA, prior to CEA or CAS. The study by Wardlaw et al seems to indicate that all of the available, non-invasive tests are reasonably sensitive and specific when the degree of stenosis is 70%-99% and, probably, it is not necessary to proceed with intra-arterial angiography before surgery or stenting if a high-grade stenosis in found. CEMRA is slightly more sensitive than the other tests, and CTA is slightly more specific. In those patients who are symptomatic with lesser degrees of stenosis (ie, 50%-69%), the sensitivity and specificity of the non-invasive studies is not very high, but there is a lack of good data to compare the various studies. Because the indications for surgical or endovascular therapy in this group with less than 70% stenosis is not as clear and the therapeutic benefit is small, we would continue to recommend intra-arterial angiography if CEA or CAS is being considered. In addition, we need to continue to collect data in a prospective and blinded fashion in the moderate stenosis group, and compare the results with intra-arterial angiography whenever possible. As morbidity and mortality from CEA and CAS continues to improve, there will be a desire to treat more patients with moderate stenosis, and more accurate non-invasive carotid imaging would be helpful. ■

Endocarditis after Acute Q Fever

ABSTRACT & COMMENTARY

By Patricia Cristofaro, MD, and Maria Mileno, MD

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This article originally appeared in the June 2006 issue of Travel Medicine Advisor. It was edited by Frank Bia, MD, MPH, and peer reviewed by Lin H. Chen, MD. Dr. Bia is Professor of Medicine and Laboratory Medicine; Co-Director, Tropical Medicine and International Travelers' Clinic, Yale University School of Medicine, and Dr. Chen is Assistant Professor, Harvard Medical School; Director, Travel Resource Center, Mount Auburn Hospital, Cambridge, MA. Dr. Bia is a consultant for Pfizer and Sanofi Pasteur, and receives funds from Johnson & Johnson, and Dr. Chen reports no financial relationship relevant to this field of study.

Synopsis: *Acute Q fever may progress to endocarditis in patients with clinically silent valvulopathy. Those at risk require either extended antibiotic prophylaxis or close serological follow-up. All patients with acute Q fever should undergo transthoracic echocardiography, or in some instances transesophageal echocardiography, to exclude occult valvular abnormalities.*

Source: Fenollar F, et al. Endocarditis after Acute Q Fever in Patients with Previously Undiagnosed Valvulopathies. *Clin Infect Dis*. 2006;42:818-821.

Fenollar and colleagues report 3 cases of *Coxiella burnetii* (Q fever) endocarditis which occurred in patients with previously undetected, clinically silent cardiac valvular abnormalities, months to years after documented acute Q fever. These subtle valvulopathies included bicuspid aortic valve, mitral valve prolapse, and minimal valvular leaks.[1]

Patient 1: A 45-year-old male physician was diagnosed with acute Q fever in May 1998, having presented with acute hepatitis and a positive serological test. He had no detected cardiac murmur. He received doxycycline 200 mg daily for 3 weeks and remained healthy until November 2003, when he experienced dyspnea without fever. The murmur of aortic insufficiency was appreciated on auscultation. Transesophageal echocardiography (TEE) confirmed aortic insufficiency and revealed a bicuspid aortic valve. Standard blood cultures were negative. *Coxiella burnetii* serology revealed anti-phase I antibodies characteristic of chronic Q fever. The severity of his aortic insufficiency was such that he required valvular replacement. *C. burnetii* was identified by immunohistochemical staining of the valve specimen; PCR and cultures of this specimen were also positive. He received doxycycline (200 mg/day) and hydroxychloroquine (600 mg per day) and remains well.

Patient 2: A 53-year-old woman presented in July 2003, with hepatitis and Q fever serologies characteristic of acute infection (elevated anti-phase II antibodies). She had no significant medical history; no heart murmur was noted. She received doxycycline 200 mg daily for 3 weeks. Two months later, during September 2003, she presented with fever. Mitral valve prolapse, associated with mitral valve vegetations, was found on TEE. Q fever serology was then characteristic of chronic Q fever, with the presence of anti-phase I IgM antibodies. Standard blood cultures remained negative; however, serum PCR was positive for *C. burnetii*. She also received a regimen of oral doxycycline and hydroxychloroquine and is doing well.

Patient 3: A 50-year-old man was diagnosed with acute Q fever in July 2004, having presented with both hepatitis and serum anti-phase II *C. burnetii* IgM titer of 1:1600. He also was treated with doxycycline 200 mg daily for 3 weeks. Medical history and physical exam were unremarkable. A transthoracic echocardiogram (TTE) was completely normal. Six months later, in February 2005, he presented with fever. Transesophageal echo revealed mitral valve vegetation but only trivial mitral regurgitation. *C. burnetii* serology had evolved to anti-phase I antibodies. He, too, was begun on a regimen of doxycycline and hydroxychloroquine and has remained well.

Fenollar et al conclude that when acute Q fever is diagnosed, it is essential to diagnose any concurrent cardiac valvulopathy, no matter how subtle. With this in mind, all such patients should be subjected to at least transthoracic echocardiography. Those at especially high risk should have transesophageal echocardiography because it affords more sensitive and accurate valvular visualization. Among these are those individuals > 60 years in age and those with a family history of either aortic valve disease or bicuspid aortic valve. Those individuals with abnormal valves should receive either specific long-term antibiotic prophylaxis against the evolution of Q fever or follow-up serology every 3 months, for at least 2 years. A combination of doxycycline (200 mg per day) plus hydroxychloroquine (600 mg per day) administered for 12 months has been suggested as the prophylactic regimen.

COMMENTARY

Q fever represents a nearly worldwide zoonosis caused by the Gram negative, obligate intracellular coccobacillus, *Coxiella burnetii*. Transmission is largely by aerosol; inhalation of virtually a single bacterium may lead to infection. Indeed, *C. burnetii* is listed by the CDC as a Category B bioterrorism agent in part because of this efficiency of transmission.[2] The most common mode of transmission is through inhalation of aerosols originating from the infected products of conception of goats, sheep, cats, and cattle at the time of birth or miscarriage. Cases have also occurred from exposure to hay, straw, dust, and wool that had been in contact with infected animals. Exposure by aerosol has been documented as far as 18 kilometers from the infected source. There is occasional blood-borne and, rarely, person-to-person transmission; consumption of unpasteurized cheese has also been linked to Q fever.[3]

At least 50% of acute Q fever cases are completely asymptomatic, manifesting themselves solely by seroconversion. The most common clinical syndromes are: a flu-like illness with fever, headache, myalgias, pneumonia, and hepatitis.[4] The current recommended therapy is oral doxycycline 200 mg daily for 3 weeks. Although most patients recover completely from Q fever, even without treatment, 1% will go on to develop chronic disease. The majority of these patients will have endocarditis. However, other endovascular infections, osteomyelitis, or joint infections are also possible. Host factors that predispose to these sequelae are pre-existing cardiac and vascular abnormalities, prosthetic valves, grafts, or joint prostheses, and immunosuppressive illnesses such as coexistent malignancy or HIV. Acute Q fever would be expected to result in endocarditis in one-third of individuals with underlying valvular disease.[5]

The transformation from acute to chronic Q fever can be diagnosed by observing the evolution of Q fever serology. Acute infection is characterized by antibodies directed against phase II antigens on the organism. On the other hand, chronic Q fever is diagnosed by detection of antibodies directed against phase I antigens. A titer of antiphase I IgG antibody of > 1:800 and an IgA titer of > 1:100 are diagnostic of chronic Q fever.[6]

Endocarditis is a serious, indeed life-threatening, illness which, untreated, may mandate cardiac surgery as for patient one. It is estimated that risk for the development of endocarditis in patients with known valvulopathy and acute Q fever is about 39%. In a previous publication, Fenollar et al proposed that patients with acute Q fever and known cardiovascular defects be treated with combination doxycycline/hydroxychloroquine therapy for one year and followed every 3 months for at least 2 years.[7]

In the more recent article summarized above, Fenollar et al describe 3 patients with normal cardiac findings on physical exam, including one with a normal transthoracic echo who went on to develop chronic Q fever endocarditis. The underlying valvulopathies, later discovered by transesophageal echocardiography,[8] included mitral valve prolapse, minimal valvular leak, and bicuspid aortic valve. Had underlying pathology been detected earlier, antibiotic prophylaxis and/or close follow-up would have prevented clinical disease.

Conversely, Q fever must be considered a possible etiology of culture-negative endocarditis, accounting for about 5% of these cases. We present a patient from the Miriam Hospital, Providence, RI, in whom Q fever developed in the setting of hypertrophic cardiomyopathy. We know of no other similar case report, but we feel this illustrates the range of underlying pathology which must be considered as predispositions to this disease.

Our patient: A 40-year-old woman with hypertrophic cardiomyopathy, diagnosed at age 20, worked in Kingston, Jamaica from 1993 to 1995, where she taught impoverished children living in improvised housing. She had extensive contact with goats and unpasteurized goat milk. Although she had no documented history of Q fever, in 1996, she had a documented episode of aseptic meningitis. Q fever serologic testing was not performed at that time. In September 2000, she developed fatigue, complete heart block, fever to 102° F, and drenching sweats. Although TTE was similar to a previous study done in March 2000, TEE was remarkable for new mitral valve findings: myxomatous mitral leaflets with a one centimeter, pedunculated mass at the anterior mitral leaflet near the septum, suggesting a vegetation. She also had a thickened aortic valve with severe aortic insufficiency. Several extended blood cultures were negative. *C. burnetii* serum antibody titers were anti-IgG phase I ≥ 1:20148; IgG phase II ≥ 1:2048; IgM phase I 1:64; IgM phase II < 1:16. She has responded over time to extended doxycycline/hydroxychloroquine treatment with size reduction of the vegetation, and no further fever or progression of her aortic insufficiency.

Endocarditis is a serious, not uncommon, yet potentially preventable complication of acute Q fever. Every effort should be made to identify those individuals at risk, including careful, sensitive echocardiography to identify occult cardiac disease. Prolonged antibiotic therapy and/or close serological and clinical observation of these individuals are both reasonable and important strategies to prevent the progression of this disease and the development of life-threatening sequelae. ■

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Amebic Encephalitis—More Common Than You Might Think

ABSTRACT & COMMENTARY

By Stan Deresinski, MD, FACP

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This article originally appeared in the June 2006 issue of Infectious Disease Alert. It was peer reviewed by Connie Price, MD. Dr. Price is Assistant Professor at the University of Colorado School of Medicine. She reports no financial relationship relevant to this field of study.

Synopsis: *Antibody testing successfully identified 7 patients whose encephalitis was due to the free-living amoeba,* Balamuthia mandrillaris*, a pathogen that should be suspected in individuals with soil contact, high CSF protein, and mass-like or ring-enhancing brain lesions.*

Source: Schuster FL, et al. Detection of Antibodies Against Free-Living Amoebae *Balamuthia mandrillaris* and Acanthamoeba Species in a Population of Patients with Encephalitis. *Clin Infect Dis*. 2006;42:1260-1265.

As part of the California Encephalitis Project (CEP), more than 250 serum samples from selected patients were screened for antibodies to amebic pathogens, particularly *Balamuthia mandrillaris*. Overall, the CEP has tested samples for > 1800 cases submitted for extensive testing in attempts to determine the etiology of encephalitis in patients without severe immunocompromise. Samples from individuals with a history of occupational contact with soil, or of swimming or camping, as well as elevated CSF protein level and pleocytosis, hydrocephalus, ring-enhancing lesions, or space-occupying lesions were selected for indirect immunofluorescent antibody testing (IFA) against Balamuthia.

While no cases had elevated IFA to Acanthamoeba species or to *Naegleria fowleri*, serum samples from 7 patients had IFA titers against *B. mandrillaris* of > 1:64, and all 7 were subsequently proven to have *Balamuthia encephalitis* by direct examination of brain tissue obtained at postmortem examination. The latter methods included hematoxylin-eosin staining, immunostaining, and polymerase chain reaction for detection of 16 rRNA. The median CSF protein concentration of 5 patients with Balamuthia infection was 1247 mg/dL, compared to 93 mg/dL ($P < 0.001$) in the seronegative group, while glucose levels (47 mg/dL vs 61 mg/dL) and WBC (106/mm^3 vs 63/mm^3) were not significantly different. All 7 patients with proven balamuthiasis were of Hispanic ethnicity.

One patient with confirmed *Acanthamoeba encephalitis* was identified during the course of the study, but that patient who was receiving corticosteroid therapy for systemic lupus erythematosus had what were considered to be negative antibody titers to this organism.

COMMENTARY

Despite enormous diagnostic efforts, the CEP reported several years ago that the etiology of encephalitis remained unknown in at least 62% of cases.[1,2] This report identifies a small, but significant number of cases that proved to be due to the free-living amoeba, *B. mandrillaris*. A number of additional patients with borderline titers could not be adjudicated because of lack of availability of brain tissue for examination, either because no postmortem examination was performed or the patient survived and was lost to follow-up. Nonetheless, the number of identified cases of encephalitis due to this pathogen exceeded the number of cases of human rabies during a similar time frame. Since the amoebal infection has greater potential for successful therapy[3,4] directed against it than does rabies, *Balamuthia encephalitis* is, at least from one viewpoint, a clinically more important disease. Unfortunately, most cases of *Balamuthia encephalitis* are first diagnosed at post-mortem examination. In California, there were 2 survivors[3] among 12

human cases identified from 1990-2005. The demonstration that infection may be identified by serum antibody testing provides hope that, with improved clinician awareness, cases will be more likely to be diagnosed antemortem in the future.

The onset of *Balamuthia encephalitis* is subacute, with months of symptoms prior to diagnosis or death. In addition to the progressive focal and non-focal central nervous system symptoms and findings, CSF examination generally reveals mild, predominantly lymphocytic pleocytosis, with normal or low glucose concentration, and protein concentrations that commonly exceed 1000 mg/dL. A case of amebic encephalitis due to Acanthamoeba has been diagnosed by visualization of the organism on cytological examination of CSF.[4] Space-occupying, mass-like lesions and multiple ring-enhancing lesions may be seen. As pointed out by Schuster and colleagues, initial presumptive diagnoses have included tuberculosis, neurocysticercosis, viral encephalitis, bacterial brain abscess, tumor, and atypical disseminated encephalomyelitis. Balamuthia are free-living amoebae that are present in soil, and individuals such as construction and agricultural workers, among others, should be considered at increased risk.

At least 3 survivors have been identified. After identification of the organism in skin and brain biopsy specimens of a 64-year-old man, treatment involved 5-fluorocytosis, fluconazole, pentamidine isethionate, sulfadiazine, and clarithromycin, with subsequent improvement. There was worsening after discontinuation of fluconazole, with improvement once again after its reinitiation. The patient was then chronically maintained on therapy with fluconazole and sulfadiazine. A similar initial regimen was associated with improvement in a 5-year-old patient with confirmed brain infection.[3] A 72-year-old apparently immunocompetent woman was successfully treated with pentamidine, sulfadiazine, fluconazole, and clarithromycin.[5]

Be the first on your block to make this diagnosis and save a life! ■

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News About Clopidogrel

ABSTRACTS & COMMENTARY

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This article originally appeared in the June 2006 issue of Clinical Cardiology Alert. It was peer reviewed by Rakesh Mishra, MD. Dr. Mishra is Assistant Professor of Medicine, Weill Medical College, Cornell University; Assistant Attending Physician, NewYork-Presbyterian Hospital. He reports no financial relationship relevant to this field of study.

Synopsis: *Overall, clopidogrel plus aspirin was not significantly more effective than aspirin alone in reducing the rate of myocardial infarction, stroke, or death from cardiovascular disease.*

Sources: Bhatt DL, et al. Clopidogrel and Aspirin versus Aspirin Alone for the Prevention of Atherothrombotic Events. *N Engl J Med*. 2006;354:1706-1717; Wolfram RM, et al. Clopidogrel Loading Dose (300 versus 600 mg) Strategies for Patients with Stable Angina Pectoris Subjected to Percutaneous Coronary Intervention. *Am J Cardiol*. 2006; 97:984-989.

CLOPIDOGREL PLUS ASPIRIN HAVE BEEN SHOWN TO reduce subsequent events in patients with unstable angina, myocardial infarction (MI), and post percutaneous interventions. Its role in long-term prophylaxis in high-risk patients without these acute events is unclear. Thus, the Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management, and Avoidance (CHARISMA) trial was conducted in 15,603 patients with either clinically evident cardiovascular disease or multiple atherothrombotic risk factors. They were randomized in a double-blind fashion to clopidogrel (75mg/d) plus aspirin or aspirin (75-160 mg/d) alone (plus placebo). The primary efficacy end point was death, stoke, or MI. The primary safety end point was severe bleeding. There were a variety of secondary end points and prespecified subgroup analyses. After a median follow-up of 28 months, the primary end point occurred in 6.8% of the clopidogrel group and 7.3% of the placebo group ($P = .22$). The primary safety end point occurred in 1.7% of the clopidogrel patients

and 1.3% of the placebo group ($P = .09$). Bhatt and colleagues concluded that overall clopidogrel plus aspirin was no more effective than aspirin alone at preventing subsequent events in patient with known cardiovascular disease or multiple risk factors for it.

Although clopidogrel is an important adjunct to aspirin therapy in patients undergoing percutaneous coronary interventions (PCI), there has been controversy over the appropriate loading dose. Thus, Wolfram and colleagues compared a 300 mg to a 600 mg loading dose immediately prior to PCI in 445 patients with stable angina. The primary end points were post procedure biomarkers of myocardial necrosis, bleeding, and vascular complications at 30 days. There was no difference in the primary end points between the 2 groups. Wolfram et al concluded that a 600 mg loading dose of clopidogrel pre-PCI is safe, but does not improve 30-day outcomes following PCI as compared to 300 mg.

COMMENTARY

Clopidogrel has become a staple of modern cardiovascular care, but higher doses and more widespread use do not seem to be indicated. With regard to pre-PCI use, a 300 mg load seems adequate. The lingering question is when clopidogrel is given many hours before PCI, what is the appropriate dose? Other trials have shown improved outcomes with a 600 mg load, but only when given hours before, which is not the usual practice in the United States. Also, higher doses may be warranted in patients with unstable syndromes. The patients described above had stable angina. One drawback to this study is that it is retrospective and the dose of clopidogrel was not randomized. Thus, there may have been individual selection biases that influenced the results. In fact, about two-thirds of the patients received 600 mg, suggesting that is/was the conventional wisdom at the Washington Hospital Center.

The idea that if clopidogrel plus aspirin is good for acute cardiovascular event patients, that it must be good for all cardiovascular disease patients seems logical but could not be proven in the CHARISMA trial. In some ways this is not surprising because cardiovascular events and procedures are associated with coronary endothelial damage and a greater risk for thrombotic complications, but stable patients probably have largely intact endothelium, and the risks of clopidogrel outweigh its benefit. There may be subgroups of stable patients who may have damaged endothelium and would benefit, but they may be difficult to identify. This study suggested that symptomatic patients may fall in this category, but such subgroup analyses are often inaccurate, and a prospective trial would be required to confirm this. For now it appears that aspirin alone is sufficient unless an acute coronary syndrome develops or PCI is required in stable cardiovascular disease patients or those with high likelihood of this disease. ■

CME Questions

13. Based on the study by Cao et al., comparing carotid endarterectomy to carotid artery stenting for carotid artery stenosis, patients undergoing carotid artery stenting:

a. have a decreased risk of any stroke compared to patients undergoing carotid endarterectomy.
b. have a decreased risk of disabling stroke or death compared to patients undergoing carotid endarterectomy.
c. have a decreased risk of TIA compared to patients undergoing carotid endarterectomy.
d. have decreased mortality rates compared to patients undergoing carotid endarterectomy.
e. have similar clinical outcomes compared to patients undergoing carotid endarterectomy after adjusting for technical expertise of the interventionalist.

14. In the study by Wardlaw et al, which of the following non-invasive tests had the highest sensitivity in detecting high-grade carotid artery stenosis?

a. Doppler ultrasound
b. MRA
c. Contrast-enhanced MRA
d. CTA
e. None

15. Based on the recent randomized controlled trial by Bhatt et al, in patients with chronic cardiovascular disease or multiple atherothrombotic risk factors:

a. the addition of clopidogrel to aspirin resulted in statistically significantly reduced rates of death, MI, and stroke.
b. the addition of clopidogrel to aspirin resulted in statistically significantly increased rates of severe bleeding.
c. the addition of clopidogrel to aspirin was no more effective than aspirin alone in preventing death, MI, and stroke.
d. the use of 300 mg of clopidogrel daily was more effective than 75 mg daily.
e. the use of 600 mg of clopidogrel daily was more effective than 300 mg daily.

Answers: 13. (e); 14. (c); 15. (c)

CME Objectives

The objectives of *Hospital Medicine Alert* are to:

• review pertinent safety, infection control, and quality improvement practices;

• discuss diagnosis and treatment of acute illness in the hospital setting; and

• review current data on diagnostic and therapeutic modalities for common inpatient problems. ■