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ABSTRACT & COMMENTARY

Risk of NSAID Use in Patients Receiving Antithrombotic Therapy After Myocardial Infarction

By Harold L. Karpman, MD, FACC, FACP

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Dr. Karpman reports no financial relationships related to this field of study.

SYNOPSIS: Among patients receiving antithrombotic therapy after MI, the use of NSAIDs was associated with increased risk of bleeding and excess thrombotic events, even after short-term treatment.

SOURCE: Schjerning Olsen AM, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. JAMA 2015;313:805-814.

Numerous published studies have demonstrated an increased risk of thrombotic cardiovascular events associated with the use of anti-inflammatory drugs (NSAIDs).[1-3] Current guidelines discourage the use of NSAIDs in patients with cardiovascular disease,[4] yet up to 44% of patients with a history of myocardial infarction (MI) are treated with these agents[5,6] for a variety of clinical conditions. Current management guidelines also advise that all patients with MI should be prescribed dual antithrombotic therapy (aspirin and clopridogel) for up to 12 months, and since a substantial proportion of patients have additional indications for oral anticoagulants, adding NSAIDs to the treatment regimen may further increase bleeding risks in these patients and may also increase the risk of recurrent cardiovascular events. As a result, Olson and her associates[7] mounted a prospective study to investigate the association of the concomitant use of NSAIDs with risk of bleeding and cardiovascular events in patients receiving antithrombotic treatment after suffering a MI.

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A total of 61,971 patients who suffered a first MI in Denmark between 2002 and 2011 and who filled at least one NSAID prescription were included in this study. The number of deaths during a median follow-up of 3.5 years was 18,105 (29.2%). In addition, a total of 5288 bleeding events (8.5%) and 18,568 cardiovascular events (30%) also occurred. Bleeding events occurred in 4.2% of those patients receiving concomitant NSAID therapy and in only 2.2% of those patients not receiving NSAID therapy. The authors concluded that an increased risk of bleeding and cardiovascular events occured with concomitant use of NSAID therapy regardless of the type of antithrombotic treatment administered, the type of NSAID utilized, and/or the duration of NSAID use.

■ COMMENTARY

In this Danish nationwide study, the concomitant use of NSAIDs was associated with an increased risk of bleeding in patients who had experienced a first MI and were also being treated with antithrombotic drugs. The study facilitators observed an increased risk regardless of which antithrombotic drugs were used. The results of the Olson study[7] support the guideline recommendations from the American Heart Association[4] as well as published European guidelines.[6] It is important to point out that the Olson study results are limited because of its observational design, and because only prescription data were utilized in reaching its conclusions. Therefore, one cannot avoid the uncertainty that exists about patient adherence to treatment recommendations in the individual patient, which obviously is important since the definition of NSAID therapy in this study was based only on prescription data. However, despite these limitations, it is important to recognize that in patients receiving antithrombotic therapy after MI, there is likely a significantly increased risk of bleeding and excess thrombotic events when NSAIDs are used, even after short-term treatment with these anti-inflammatory drugs.

In conclusion, clinicians should be aware of the increased risks of bleeding and/or thrombosis when using NSAIDs in patients following an acute or recent myocardial infarction. Physicians obviously need a properly controlled prospective research study not dependent only on prescription data to answer the important question about whether it is safe to prescribe NSAIDs to patients who recently have suffered a myocardial infarction. ■

REFERENCES

1. Brophy JM, et al. The coronary risk of cyclo-oxygenase-2 inhibitors in patients with a previous myocardial infarction. *Heart* 2007;93:189-194.
2. Gislason GH, et al. Risk of death or reinfarction associated with the use of selective cyclooxygenase-2 inhibitors and nonselective nonsteroidal anti-inflammatory drugs after acute myocardial infarction. *Circulation* 2006;113:2906-2913.
3. McGettigan P, Henry D. Cardiovascular risk with nonsteroidal anti-inflammatory drugs: Systematic review of population-based controlled observational studies. *PLoS Med* 2011;8:e1001098.
4. Antman EM, et al. Use of nonsteroidal anti-inflammatory drugs: An update for clinicians: A scientific statement from the American Heart Association. *Circulation* 2007;115:1634-1642.
5. Schjerning Olsen AM, et al. Duration of treatment with nonsteroidal anti-inflammatory drugs and impact on risk of death and recurrent myocardial infarction in patients with prior myocardial infarction: A nationwide cohort study. *Circulation* 2011;123:2226-2235.
6. European Medicines Agency. PRAC Recommends the Same Cardiovascular Precautions for Diclofenac as for Selective COX-2 inhibitors. Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages/news_and_events/news/2013/06/news_detail_001816.jsp&mid=WC0b01ac058004d5c1. Accessed January 28, 2015.
7. Schjerning Olsen AM, et al. Association of NSAID use with risk of bleeding and cardiovascular events in patients receiving antithrombotic therapy after myocardial infarction. *JAMA* 2015;313:805-814.

ABSTRACT & COMMENTARY

Utility of the New Cholesterol Guidelines

By Michael H. Crawford, MD

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Dr. Crawford reports no financial reltionships relevant to this field of study.

SYNOPSIS: The authors concluded that under the new guidelines, the risk:benefit ratio is much better for moderate- than high-intensity statins.

SOURCE: Yeboah J, et al. Implications of the new American College of Cardiology/American Heart Association cholesterol guidelines for primary atherosclerotic cardiovascular disease event prevention in a multi ethnic cohort: Multi-Ethnic Study of Atherosclerosis (MESA). *Am Heart J* 2015;169:387-395.

The American College of Cardiology/American Heart Association (ACC/AHA) released new guidelines for the use of statin drugs to prevent atherosclerotic cardiovascular disease (CVD) in 2013. Because these guidelines increase the number of apparently healthy people who are eligible for statin therapy, there is concern among practitioners that the potential adverse effects of statins may outweigh the imputed benefits. Since any randomized trial to test this hypothesis is years away from completion, these investigators analyzed the Multi Ethnic Study of Atherosclerosis (MESA) database to assess the impact of the new guidelines on the number of patients eligible for statin therapy. Also, using randomized trial data for statin therapy, they analyzed primary prevention statin trials to estimate the reduction in CVD risk for these patients and the risk of adverse effects of using moderate- or high-intensity statins. MESA subjects aged 40-75 years at baseline enrollment who were not on a statin were selected, which resulted in a population of 5437; mean age was 61 years.

Using the 2001 National Cholesterol Education Program/adult treatment panel III (NCEP/ATP III) guidelines, 25% of these patients would have been eligible for statin therapy. This increased to 56% under the new guidelines and 66% if the optional category was added. Only 5% who were eligible under the old guidelines were no longer eligible under the new guidelines. Among the newly eligible 1742 patients, 127 (7%) had a CVD event during 10 years of follow-up. If you assume 10 years of moderate statin therapy, the absolute reduction in events would be 2%, number needed to treat (NNT) 49, the absolute increase in diabetes would be 0.9%, and the number needed to harm (NNH) 111. If high-intensity statins were chosen, the absolute reduction would be 3% (NNT 38), with a diabetes increase of 3% (NNH 39). Under the old guidelines, the reduction in events would be 3% (NNT 32) and new diabetes 1% (NNH 94). The incidence of rhabdomyolysis estimated to occur in the MESA cohort with the new guidelines is < 1%. The authors concluded that under the new statin treatment for primary prevention guidelines, the risk:benefit ratio is much better for moderate- than high-intensity statins.

■ COMMENTARY

The lack of supportive data for the new guidelines and the estimation that more subjects will be eligible for statin therapy, which is often a tough sell in asymptomatic individuals, has led to reluctance on some practitioners' part to embrace these guidelines. Thus, the data presented in this analysis of the MESA database and recent primary prevention statin trials are informative.

As predicted, the number of patients eligible for statin therapy doubled. Based on statin primary prevention trial data, with moderate-intensity statin therapy, CVD events would decrease and new diabetes rates would increase. With high-intensity statin use, CVD events would decrease more but diabetes rates would be higher; rhabdomyolysis rates would be negligible. Other adverse events were not studied such as cognitive impairment, liver abnormalities, and muscle aches. Thus, under the new guidelines, those with a predicted 10 event rate of > 7.5% should be treated with moderate-intensity statins.

These estimates assume high statin compliance, but the literature suggests it is 50-65% in primary prevention patients. Most patients stop statins because of muscle aches and liver function test abnormalities, even though routine liver blood tests are no longer recommended in asymptomatic patients. These side effects were not studied, and the rate of statin discontinuation is not known in this study. If the adherence rate were lower, then the assumed overall benefit would be reduced, but so would the incidence of diabetes.

The strengths of this study are the large size of the MESA database, the knowledge of 10-year event rates, and the multiethnic make-up of the population. Weaknesses include that MESA is an observational community-based study and the statin trials are a more select group of patients that may not be comparable. Also, MESA doesn't include all the ethnicities seen in the United States, but comes closer than most studies. One difference between the new guidelines and the old is that the old guidelines were based on hard endpoints only (death and myocardial infarction). The cutoff for considering statin therapy was a predicted 10-year incidence of hard endpoints of > 20%. The new guidelines include stroke, which is perhaps more relevant since trials have shown reduced stroke rates in some patient groups with statins, and uses a 10-year incidence cutoff of > 7.5%. This design fact alone increases the number of patients in whom statin therapy should be considered. Although this analysis supports the conclusions of the new guidelines, only prospective, randomized trials will confirm this approach. ■

ABSTRACT & COMMENTARY

Clindamycin vs. Trimethoprim-Sulfamethoxazole for Uncomplicated Skin Infections

By Dean L. Winslow, MD, FACP, FIDSA

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Dr. Winslow reports no financial relationships relevant to this field of study.

SYNOPSIS: Five hundred twenty-four children and adults with either cellulitis or abscesses larger than 5 cm (smaller for children) were enrolled in a multisite prospective study of clindamycin vs. trimethoprim-sulfamethoxazole dosed for 10 days. Cure rates did not differ between the treatments, and rates of adverse events were similar in the two groups.

SOURCE: Miller LG, et al. Clindamycin versus trimethoprim-sulfamethoxazole for uncomplicated skin infections. N Engl J Med 2015;372:1093-1103.

Five hundred twenty-four patients (including 155 children) were enrolled in a prospective, double-blinded, randomized trial of clindamycin vs. trimethoprim-sulfamethoxazole in uncomplicated skin infections. Fifty-three percent had cellulitis, 31% had abscesses, and 16% had mixed cellulitis/abscess. *Staphylococcus aureus* was isolated from 41% of patients, and 77% of these were methicillin-resistant *S. aureus* (MRSA). Overall, cure rates were 80% in the clindamycin group and 78% in the trimethoprim-sulfamethoxazole group. Cure rates did not differ significantly between the two antibiotics in the subgroups of children, adults, and abscess vs cellulitis. Rates of adverse events were similar in the two groups.

■ COMMENTARY

While this study is a bit difficult to interpret due to a mix of cellulitis (non-suppurative) and abscess (suppurative), the data are important since it is a large study and addresses a real-world question of which of two reasonable choices of antibiotics works best in uncomplicated skin infections commonly encountered in the primary care and emergency department (ED) setting.

It could be argued that inclusion of a placebo arm would have been helpful since previous studies suggest that incision and drainage alone is appropriate treatment for small abscesses and antibiotics are not necessary. However, an earlier study performed in children demonstrated that abscesses larger than 5 cm were often associated with treatment failure unless adjunctive antibiotics were administered.[1] As expected, cultures were not obtainable in patients with cellulitis without abscess (and presumably were almost always due to beta-hemolytic streptococci). The surprisingly high response rate of cellulitis to trimethoprim-sulfamethoxazole suggests that the historical concern about poor activity of trimethoprim-sulfamethoxazole against streptococci may be unfounded. Interestingly, a recent study showed that *S. pyogenes* are generally trimethoprim-sulfamethoxazole susceptible if low-concentration thymidine agar is used for susceptibility testing.[2]

The rates of *S. aureus* resistance to clindamycin and trimethoprim-sulfamethoxazole were 5.2% and 0.2%, respectively, and although a slightly lower cure rate was seen with clindamycin in those rare clindamycin-resistant strains of staph (73% with clindamycin vs. 92% with trimethoprim-sulfamethoxazole), this should not necessarily preclude the empiric use of clindamycin in uncomplicated skin infections where close follow up can be assured. Interestingly, no cases of *C. difficile* infection were seen in either arm of the study, suggesting that this is not a serious concern in this relatively young and healthy population when only a 10-day course of therapy is prescribed.

The results of this study did reinforce a couple of things I teach the residents and fellows.[1] Clindamycin is a great antibiotic for skin (and bone) infections as long as one knows that the *S. aureus* is susceptible in vitro. Clindamycin is just as effective and as well tolerated as linezolid — and much less expensive.[2] It adds further evidence to support my dislike of the common ED practice of prescribing both cephalexin and trimethoprim-sulfamethoxazole to patients with skin infections. (My fear is that when a patient treated with this combination develops a rash, then they are often labeled for life as being "allergic to beta-lactam antibiotics and sulfonamides.") This should reassure the practitioner that despite our previous concerns, trimethoprim-sulfamethoxazole probably treats uncomplicated streptococcal skin infections adequately. ■

REFERENCES

1. Lee MC, et al. Management and outcome of children with skin and soft tissue abscesses caused by community-acquired methicillin-resistant *Staphylococcus aureus*. *Pediatr Infect Dis J* 2004;23:123-127.
2. Bowen AC, et al. Is *Streptococcus pyogenes* resistant or susceptible to trimethoprim-sulfamethoxazole? *J Clin Microbiol* 2012;50:4067-4072.

PHARMACOLOGY UPDATE

Ivabradine Tablets (Corlanor®)

By William T. Elliott, MD, FACP, and James Chan, PharmD, PhD

Dr. Elliott is Chair, Formulary Committee, Northern California Kaiser Permanente; and Assistant Professor of Medicine, University of California, San Francisco. Dr. Chan is Pharmacy Quality and Outcomes Manager, Kaiser Permanente, Oakland, CA

Drs. Elliott and Chan report no financial relationships relevant to this field of study.

Ivabradine blocks the hyperpolarization-activated cyclic nucleotide-gated channel responsible for the cardiac pacemaker.[1,2] The drug acts mainly at the sinoatrial node. Ivabradine was reviewed under the FDA's priority review program and received fast track designation, which provides for expedited review and approval. Ivabradine is marketed by Amgen as Corlanor®.

INDICATIONS

Ivabradine is indicated to reduce the risk of hospitalization for worsening heart failure in patients with stable, symptomatic chronic heart failure with left ventricular ejection fraction ≤ 35% in patients who are in sinus rhythm with resting heart rate of ≥ 70 beats per minute and either are on maximally tolerated doses of beta-blockers or have a contraindication to beta-blocker use.[1]

DOSAGE

The recommended starting dose is 5 mg twice daily with meals.[1] After 2 weeks, based on heart rate, the dose should be adjusted. The maximum dose is 7.5 mg twice daily. In patients with conduction defects or in whom bradycardia could compromise hemodynamics, the starting dose should be 2.5 mg twice daily. No dosage adjustment is required for patients with mild or moderate liver impairment or those with creatinine clearance 15 to 60 mL/min. It is contraindicated in patients with severe hepatic impairment. Ivabradine is available as 5 mg and 7.5 mg tablets.

POTENTIAL ADVANTAGES

Ivabradine offers an agent with a different mechanism of action for treatment of heart failure. Treatment resulted in a reduction of hospitalization.[1]

POTENTIAL DISADVANTAGES

Ivabradine did not show benefit in overall mortality or cardiovascular mortality.[1] Common adverse events (compared to placebo) were

hypertension (8.9% vs 7.8%) and atrial fibrillation (8.3% vs 6.6%). Visual brightness (phosphenes) was reported in 2.8% compared to 0.5%. Ivabradine is contraindicated or should be avoided in patients on strong or moderate cytochrome CYP3A4 inhibitors or 3A4 inducers.[1] Embryo-fetal toxicity and teratogenicity have been shown in animal reproductive studies.[1]

COMMENTS

The efficacy and safety of ivabradine were evaluated in a randomized, double-blind, placebo-controlled study (n = 6558) in adult participants with stable NYHA class II to IV heart failure with left ventricular ejection fraction of ≤ 35% and resting heart rate ≥ 70 bpm.[1,3] Participants had to be clinically stable for at least 4 weeks but hospitalized for heart failure within the past 12 months. Eighty-nine percent were on beta-blockers; however, only 26% were on guideline-defined target daily doses. Participants were randomized to ivabradine 5 mg twice daily or matching placebo. The dose could be increased to 7.5 mg twice daily or decreased to 2.5 mg twice daily. The primary efficacy endpoint was combined hospitalization for worsening heart failure or cardiovascular death based on time-to-event. The annual incidence rate was 14.5% patient-year for ivabradine compared to 17.7% for placebo (hazard ratio, 0.82; 95% confidence interval, 0.75-0.90). The drug effect was primarily in decreased hospitalization (9.2% patients-year vs 12.7%). The benefit of ivabradine appears to be inversely related to the dose of beta-blockers on board. Little benefit is observed in patients on guideline defined target dose of beta-blockers.[1] Ivabradine showed no benefit in two large studies in subjects with stable coronary artery disease with or without stable heart failure.[4,5] The first study (n = 12,473) enrolled subjects with coronary artery disease (CAD) and a left ejection fraction of ≤ 40%.[4] After a median follow-up of 19 months, the addition of ivabradine did not improve the primary composite outcome (CV death, hospital admission for acute MI, or new onset/worsening heart failure) compared to placebo. The second study (n = 19,103) enrolled subjects with stable CAD without heart failure and heart rate of 70 beats per min or greater.[5] In addition, about two-thirds had activity-limiting angina. Similarly, after a median follow-up of 27.8 months, the addition of ivabradine showed no improvement in outcomes (CV death or nonfatal MI) compared to placebo.

> Ivabradine's effect in reducing heart rate was most prominent at a higher heart rate thus minimizing the risk of bradycardia.

CLINICAL IMPLICATIONS

Ivabradine is the first-in-class drug for the treatment of heart failure. Its effect in reducing heart rate, by acting on the SA node, was most prominent at a higher heart rate thus minimizing the risk of bradycardia. Its role in therapy seems limited to those who need heart rate reduction and are unable to tolerate an effective dose of a beta blocker. The wholesale cost is $375 for a 30-day supply. n

REFERENCES

1. Corlanor Prescribing Information. *Amgen*. April 2015.
2. Nawarskas JJ, et al. Ivabradine: A unique and intriguing medication for treating cardiovascular disease. *Cardiol Rev* 2015; April 1 Epub ahead of print].
3. Swedberg K, et al. Ivabradine and outcomes in chronic heart failure (SHIFT): A randomised placebo-controlled study. *Lancet* 2010;376:875-885.
4. Fox K, et al. Ivabradine for patients with stable coronary artery disease and left-ventricular systolic dysfrunction (BEAUTIFUL): A randomised, double-blind, placebo-controlled trial. *Lancet* 2008;372:807-816.
5. Fox K, et al. Ivabradine in stable coronary artery disease without clinical heart failure. *N Engl J Med* 2014;371:1091-1099.

Clinical Briefs

By Louis Kuritzky, MD

Ongoing Saga of Homocysteine and Vasculopathy

SOURCE: Catena FC, et al. *J Am Soc Hypertens* 2015;9:167-175.

The relationship between homocysteine (hCYS) and vascular disease has been recognized for at least 2 decades. Indeed, the strength of the association between plasma hCYS levels and coronary atherosclerosis surpasses that of cholesterol. Once this relationship was publicized, a flurry of enthusiasm for modulation of hCYS ensued, based largely on the strong observational data and the simplicity with which hCYS can be lowered: supplementation with folate and B vitamins. Since these treatments are not associated with meaningful toxicity at appropriate doses, there appeared to be much to celebrate: an easy, inexpensive fix for an important health problem.

After a bevy of trials in which hCYS lowering failed to show risk reduction for cardiovascular events, need for revascularization, etc., one editorialist confidently announced "The homocysteine hypothesis is dead!". Well, apparently some still feel a faint pulse.

Catena et al published their data looking at the relationship between hCYS and carotid disease among hypertensive patients. They found that carotid intima-media thickness was linearly related to hCYS levels, independent of age, blood pressure, and C-reactive protein.

Since no clinical trials have shown a favorable impact of hCYS modulation, why should clinicians care? The authors bring up the interesting proposition that since elevated hCYS is a recognized risk factor for vasculopathy, it might help influence treatment decisions for management of persons at risk for cardiovascular disease. Perhaps, for instance, elevated hCYS might tip the balance of a treatment decision for persons with a strong family history of vascular disease, but borderline risk factors (e.g., blood pressure, lipids, glucose). ■

Roflumilast for Acute Exacerbations in COPD

SOURCE: Martinez FJ, et al. *Lancet* 2015; 385:857-866

Acute exacerbations of chronic obstructive pulmonary disease (AE-COPD) are potentially highly consequential: In-hospital mortality is approximately 10%, and up to 25% of patients admitted to the ICU die. Additionally, AE-COPD is associated with a decline in pulmonary function that is not regained once the exacerbation is resolved. Fortunately, several of the tools we use to treat COPD are associated with reduced frequency of exacerbations.

Roflumilast (ROF) is a PDE-4 inhibitor that has been shown to reduce AE-COPD and has FDA labelling for that indication. Martinez et al have published the results of their multicenter randomized, double-blind, placebo-controlled trial that sought to determine whether ROF reduces exacerbations compared to placebo in severe COPD patients who are already on background combination therapy of inhaled long-acting beta-agonist plus inhaled corticosteroid (n = 1945).

After 1 year of treatment, the rate of AE-COPD was statistically significantly lower in persons who were treated with ROF than those receiving placebo. The adverse events rates were similar in the ROF and placebo groups. Additionally, hospital admissions for AE-COPD were significantly reduced in the ROF group vs placebo. The addition of ROF to the regimen of patients with severe COPD already using combination therapy with beta-agonists and inhaled corticosteroids can reduce exacerbations and hospitalizations related to exacerbations. ■

Treatment of OSA Reduces Risk of Repeat Revascularization After PCI

SOURCE: Wu X, et al. *Chest* 2015;1478:708-718.

Obstructive sleep apnea (OSA) is associated with numerous comorbidities and downstream consequences, not the least of which are increased cardiovascular events, hypertension, and arrhythmias. The increased sympathetic tone associated with OSA is usually considered a major culprit in the evolution of such adversities. Although the associations between OSA are strong and consistent across numerous reports and diverse populations, outcomes trials showing concrete endpoint reduction through successful treatment of OSA are less evident.

The clinical trial data reported by Wu et al confirm very favorable results in a very specific population: Persons with sleep laboratory-confirmed OSA (n = 390) who had undergone PCI were followed over 4.8 years (median). The primary endpoint of interest was whether treatment of OSA affected the incidence of revascularization compared to untreated OSA. Treatment of OSA by CPAP was confirmed at 3-monthly intervals for the first year, and annually thereafter.

The incidence of coronary revascularization was almost twice as high in the untreated OSA group than in the treated OSA group (26.1% vs 14.1%, $P = 0.019$). Although there were statistically significant differences between groups as far as overall mortality or cardiovascular events, outcomes at 5 years tended to favor the CPAP-treated OSA patients. OSA treatment reduces the need for revascularization in persons who have undergone PCI. ■

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CME QUESTIONS

1. The use of NSAIDs among the patients receiving antithrombotic therapy after MI:

a. is not associated with an increased risk of bleeding or thrombotic events.

b. can be used safely at any time.

c. should be avoided if at all possible.

d. may be safely used at any time starting two weeks after hospital discharge.

2. The risk:benefit ratio for statin therapy in primary prevention patients is most favorable for:

a. lower-intensity therapy.

b. moderate-intensity therapy.

c. high-intensity therapy.

d. no statin therapy.

3. Which of the following is true regarding the findings of Miller et al about the treatment of uncomplicated skin infections?

a. Clindamycin was significantly superior to trimethoprim-sulfamethoxazole.

b. Trimethoprim-sulfamethoxazole was significantly superior to clindamycin.

c. Trimethoprim-sulfamethoxazole was entirely ineffective in the treatment of cellulitis.

d. There was no overall significant difference in outcomes with use of either antibiotic regimen.

CME OBJECTIVES

Upon completion of this educational activity, participants should be able to:

- describe new findings in the differential diagnosis and treatment of various diseases;
- describe the advantages, disadvantages and controversies surrounding the latest advances in the diagnosis and treatment of disease;
- identify cost-effective treatment regimens;
- explain the advantages and disadvantages of new disease screening procedures.

[IN FUTURE ISSUES]

Inpatient and Outpatient Care Providers

Dietary Supplements