

# Clinical Briefs in **Primary Care**<sup>TM</sup>

The essential monthly primary care update

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## Treatment of Periodontitis and Endothelial Function

Tonetti MS et al. *N Engl J Med.*  
2007;356:911-920

**T**HAT THERE IS A LINK BETWEEN inflammation and atherosclerosis is no longer in dispute. Whether modulation of inflammation might change the process of atherosclerosis, or even better, reduce vascular endpoints, remains a challenging question. To date, efforts to reduce inflammation by means of antioxidants, reduction of homocysteine or antibiotics has not proven to favorably alter the course of vasculopathy.

Periodontitis (PDT) is a common inflammatory process often seen at midlife and beyond, and observational studies indicate an association with endothelial dysfunction, atherosclerosis, and cardiovascular endpoints. PDT merits treatment in its own right, and its treatment might reduce the systemic—and hence vascular—burden of inflammation.

A single-blind randomized trial was performed to compare the impact of intensive periodontal disease treatment (i-PDT) vs community-based treatment (c-PDT) as a control. All patients had severe PDT.

At six months, the group who received i-PDT showed significantly greater flow-mediated brachial artery dilation (indicative of improved endothelial function) than the control group.

PDT is associated with elevated CRP, fibrinogen, and cytokine levels. This data suggests that skillful intensive management of PDT may produce benefits beyond improved oral hygiene. ■

## Does Cost-Conscious Prescribing Hamper Clinical Outcomes?

Usher-Smith JA. *Int J Clin Pract.*  
2007;61(1):15-23

**L**IMITED RESOURCES REQUIRE SKILLFUL utilization of the most cost-effective resources that will achieve desired clinical outcomes. Policies in the UK have recently put greater focus on the opportunities to achieve similar outcomes with less expensive medications. Whenever medications are switched, even when a “class effect” is anticipated, clinicians would like to be assured that there is no cost-efficacy tradeoff.

The National Health Service Primary Care Practice in Hertfordshire, UK, provided an opportunity to study the impact of two simultaneous medication switches in a geographically localized population.

Seventy patients originally on atorvastatin (ATORVA) were switched to an equipotent dose of Simvastatin (SIMVA). Excluding one patient who developed new SIMVA-associated visual symptoms, all the others were followed for 10 months. During this time there was no significant change in total or HDL cholesterol. The calculated savings, adjusted for additional time spent by pharmacists and explanation time by physicians associated with the switch, still added up to over \$20,000 in one year.

Patients (n = 115) on Losartan (LOS) were switched to equipotent doses of candesartan (CAN). At followup, systolic BP was slightly better with CAN, otherwise BP was unchanged, and no serious outcomes

(eg, MI, stroke) were attributable to medication change. In one year, the practice netted savings greater than \$20,000.

These data are reassuring that within class medication substitution may be cost-saving without compromising patient well-being. ■

## Induction of Macrolide-Resistant Streptococci

Malhotra-Kumar S, et al. *Lancet.*  
2007;369:482-490

**R**ESISTANCE OF PATHOLOGIC streptococci (pStrep) to macrolide antibiotics produces barriers to successful outcomes. In theory, the longer half-life of AZI might predispose to greater risk for development of resistance than CLA, but this remains to be conclusively established.

Commensal non-pathologic streptococcal flora (np-Strep), because they possess similar macrolide resistance genes as pStrep, provides a useful and readily accessible model to evaluate the effects of macrolide antibiotics on resistance.

Healthy volunteers (n = 244) were randomized to CLA (500 mg qd for 3 days), AZI (500 mg b.i.d for 7 days) or placebo with appropriate blinding and masking of doses. Macrolide resistance was assessed in more than 1000 pharyngeal samples obtained over a 180 day interval.

In the first 28 days after drug administration, there was a statistically significantly greater percentage of resistant strep in persons receiving AZI than CLA (17.4% more common in the former). However, by the

study final measurement point (180 days), there was no difference between the antibiotic groups in overall frequency of resistant strains. On the other hand, the presence of the erm gene is indicative of high-level resistance to macrolides: AZI did not impact levels of erm gene; CLA induced a 2.5 fold increase in this gene by 180 days.

Macrolide antibiotics induce prompt and enduring effects on genetic patterns of resistance. This knowledge should help shape therapeutic choices for patients having recently received macrolides. ■

## Pulse Pressure and Risk of New-Onset Atrial Fibrillation

Mitchell GF et al. *JAMA*. 2007;297(7):709-715.

**R**ISK FACTORS FOR ATRIAL FIBRILLATION (AF) most prominently include age, hypertension, diabetes, valvular disease, and heart failure. It has been theorized that the progressive increase in aortic stiffness that occurs with age, which leads to increased vascular resistance, greater cardiac workload, and ventricular hypertrophy, might be a fundamental underlying mecha-

nism for development of AF. Pulse pressure (systolic BP minus diastolic BP) reflects vascular stiffness. Using data from the Framingham Heart Study, Mitchell et al studied the relationship between pulse pressure (PSP) and incidence of AF.

Over a 20-year period of observation, 698 participants developed AF. The incidence of AF in the highest quintile of PSP (> 61 mmHg) was more than 4-fold greater than the lowest PSP quartile (< 40 mm Hg).

Even after adjusting for multiple confounding risk factors (eg, smoking, diabetes, LVH, HTN), for every 20 mmHg increment in pulse pressure, there was a 26% increase in risk of AF. PSP appears to be a prominent risk factor for AF; whether treatment that reduces PSP will reduce endpoints remains to be determined. ■

## Challenges to the Stages of Grief Theory

Maciejewski PK, et al. *JAMA*. 2007;297:716-723.

**T**HE MOST WELL-ACCEPTED MODEL for stages of grief (SOG) associated with bereavement or terminal illness describes the following 5-step sequence: denial/dissociation/isolation, anger, bargaining, depression, and acceptance. Not all experts confirm that this sequence is consistent. For instance, several reports have demonstrated that depression is not always part of the bereavement process. Defining boundaries for the normal grief process helps to define those who have not resolved grief in a healthful fashion; additionally, it may identify persons who require intervention due to failure to progress through normal SOG.

The Yale Bereavement Study invited Connecticut residents identified as suffering bereavement due to loss of a loved one (n = 233), and collected data up to 24 months post-loss. Interviewers periodically assessed and scored levels of yearning, disbelief, anger, and acceptance of death during this interval.

Contrary to current theory, instead of disbelief being the most common initial stage, acceptance was. A “map” of bereavement indicators derived from this population shows that yearning, anger, and depression peak sequentially at 4, 6, and 8 months, respectively, and progress to resolution by 24 months. The authors suggest that the DSM-IV may

need revision with respect to normal patterns of bereavement. Clinicians may wish to use this metric for progression of bereavement to help identify patients whose healing process is not advancing in a healthy fashion. ■

## EKG Abnormalities in Asymptomatic Women: Association with CV Events

Denes P, et al. *JAMA*. 2007;297:978-985.

**D**ATA FROM MOSTLY-MALE POPULATIONS indicates that EKG abnormalities in asymptomatic persons are associated with adverse cardiovascular outcomes. The Women’s Health Initiative (WHI) has provided a large population of healthy women among whom the association between EKG abnormalities and subsequent CV health can be studied. Denes, et al provide data on women from the estrogen and progestogen replacement arm of the WHI (women with uterus intact, n = 14,749, of whom half received placebo).

Women participating in the WHI were free of known CHD at baseline when their initial EKG was obtained. Follow up data was obtained every six months, as well as another EKG at years 3 and 6.

Abnormalities on EKG were categorized as “minor” or “major” according to criteria from the Pooling Project, a national US study. Minor abnormalities included such findings as 1st or 2nd degree heart block, or left atrial enlargement; major abnormalities included such findings as atrial fibrillation, LBBB, or LVH with ST segment abnormalities. At baseline, 66% of women had a normal EKG, 27.8% had minor abnormalities, and 6.2% had major abnormalities.

Women with minor EKG abnormalities at baseline had a 55% relative risk increase of incident CHD compared to women who did not have abnormalities. Incident CHD was increased 3-fold in women with major abnormalities at baseline.

Based upon this data, clinicians may wish to factor EKG abnormalities into their risk stratification scheme for asymptomatic women. ■

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