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INSIDE

What You Can't See Will Hurt You (and Your Patient)

ABSTRACT & COMMENTARY

Synopsis: *Concealed renal insufficiency is common and contributes to adverse drug reactions from hydrosoluble medications.*

Source: Corsonello A, et al. *Arch Intern Med*. 2005;165:790-795.

Aging affects drug metabolism. The physiology behind this includes decreased liver and renal reserve, changes in body composition favoring a greater percentage of fat,[1] and decreased perfusion of the liver and kidneys. Drugs that undergo a high degree of first-pass extraction have a decreased rate of metabolism.[2] The glomerular filtration rate (GFR) falls by 10 mL/min/decade, resulting in a 50% decline between the ages of 30 to 80 years.[3] Renal insufficiency in the elderly can be missed if we rely solely on measurement of serum creatinine (Cr). They have a smaller percentage by weight of muscle mass than young adults and inefficiently filter a lower concentration of Cr. The physiologic corollary to this is that the elderly have a smaller water mass than younger people (50% vs 60-65%, respectively). This means that the volume of distribution of hydrophilic drugs (or, as Corsonello and colleagues describe them, hydrosoluble drugs) is smaller in the elderly. The incidence of adverse drug reactions (ADRs) is higher in the elderly. Corsonello et al hypothesize that these 2 observations are linked.

The Gruppo Italiano di Farmacovigilanza nell'Anziano (GIFA) has conducted a large observational study of ADRs. They collected data between 1993 and 1998 and enrolled 17,186 hospitalized patients. After excluding patients who died during hospitalization, those on whom data were not available, and those who were not on geriatric or internal medicine services, the population was reduced to 11,687 patients.

Corsonello et al used the World Health Organization's definition of ADR, and the patients' physicians determined whether or not an ADR occurred. GFR was estimated by the Modification of Diet and Renal Disease Study (MDRD) formula (*see Table*). Corsonello et al defined 3 conditions: normal renal function (NRF, Cr ≤ 1.2 mg/dL

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Table

MDRD Study Formula

$$170\ [Cr]^{-0.999} \times [Age]^{-0.176} \times [Urea\ Nitrogen]^{-0.170} \times [Albumin]^{0.318} \times 0.762\ (\text{if female}) \times 1.180\ (\text{if black})$$

Source: *Levey A, et al. Ann Intern Med. 1999;130:461-470.*

and GFR ≥ 60 mL/min), concealed renal insufficiency ([CRI], Cr ≤ 1.2 mg/dL and GFR < 60 mL/min), and overt renal insufficiency ([ORI], Cr > 1.2 mg/dL and GFR ≥ 60 ml/min). The patients were grouped into 3 classes based on renal function. The NRF class had 7195 patients (62%); CRI, 1631 (14%); and ORI, 2861 (24%).

In addition to the usual demographic measures, the other variables included body mass index (BMI), serum albumin, functional status by activities of daily living (ADL), and cognitive status.

The percentage of patients older than 80 years was greater in the concealed and overt renal insufficiency groups than in the normal group (23% NRF, 44% CRI, 42% ORI), as were the percentage of male patients (47% NRF, 53% CRI, 64% ORI). Patients in the normal group were less dependent in ADLs, less cognitively impaired, less likely to be prescribed more that 4 medications, and less likely to have more than 4 diagnoses. They were less likely to have hypoalbuminemia, diabetes, congestive heart failure, and hypertension.

During hospitalization, 941 patients (8.0%) had an ADR. Significant risk factors for ADRs included age older than 65 years, female gender, hypoalbuminemia, having more than 4 diagnoses, taking more than 4 medications, having a length of stay in excess of 14 days, and having ORI (but not CRI). When the ADRs were grouped by hydrosolubility, age was associated with hydrosoluble drugs and female gender with non-hydrosoluble drugs, and the other risk factors appeared with statistically equivalent frequencies. ADRs to non-hydrosoluble drugs were not associated with renal function. Patients afflicted with an ADR to a hydrosoluble drug were more likely to have CRI (odds ratio, 1.61) or ORI (odds ratio, 2.02). Hydrosoluble drugs accounted for 301 of 941 ADRs. The hydrosoluble drugs most likely to cause an ADR (and the reaction) were diuretics (hypokalemia), digitalis (bradycardia), angiotensin-converting enzyme inhibitors (hypotension), and hypoglycemic agents (hypoglycemia).

COMMENT BY ALLAN J. WILKE, MD

GIFA previously published results of a study showing that ADRs were responsible for 3.4% of all hospital admissions and that the greatest risk factor was the number of medications taken.[4] This study also points to polypharmacy as an ADR risk factor. Polypharmacy probably results from drug-drug interactions,[5] often with the same drugs implicated in this study. Although several other risk factors were identified, only polypharmacy and hypoalbuminemia are potentially modifiable. Faced with this, what should clinicians do? Calculating GFR on all elderly patients is a necessary first step. Fully one patient in 7 in this population had CRI. If you don't look for it, you won't see it. (If you are unable to perform MDRD calculations in your head, get a medical calculator. I use MedMath, a Palm OS program, available as a component of Epocrates® or as a free stand-alone download.[6] A Pocket PC version[7] from the National Kidney Foundation or Epocrates® and an online calculator[8] from the National Kidney Disease Educa-

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tion Program, an initiative of the National Institutes of Health, are available for free.) Patients with NRF comprised 62% of the population, but suffered only 55% of the ADRs. In patients with ORI or CRI or who are hypoalbuminemic, a review of all medications (but especially hydrosoluble ones) with an eye to reducing the number or dosage of drugs to a bare minimum is good geriatric medicine. Although there is no evidence for this, switching from a hydrosoluble drug to an equivalent non-hydrosoluble one may reduce the occurrence of ADRs. Intuitively, correcting hypoalbuminemia seems reasonable, but there is no evidence for this, either.

Some factors that may have skewed these results are the exclusion of patients who died and the physician's judgment when deciding whether an ADR had occurred. What prevented physicians from not recognizing, ignoring, or not reporting an ADR when it occurred? All could have reduced the number of ADRs identified. Another thing to keep in mind is hydrosolubility is not an all-or-nothing proposition. Finally, Corsonello et al did not distinguish between ADRs based on the severity of the reaction. ■

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Asymptomatic Mitral Regurgitation—When is it Appropriate to Repair or Replace?

ABSTRACT & COMMENTARY

Synopsis: *Patients with an effective regurgitant orifice of at least 40 mm^2 should promptly be considered for cardiac surgery.*

Source: Enriquez-Sarano M, et al. *N Engl J Med*. 2005;352: 875-883.

In most medical centers, the timing of surgery for asymptomatic primary mitral valve regurgitation has been based on both the appearance of significant symptomatology and the hemodynamic effects of the lesion (ie, the response of the left ventricle to chronic volume overload).[1] The timing of surgical intervention is critical since frequently, by the time any symptoms occur, irreversible left ventricular systolic dysfunction may already have developed after which surgical outcomes are frequently quite poor and the patient may be left with persistent symptoms of left ventricular dysfunction and progressive heart failure even if surgery is performed.

Enriquez-Sarano and colleagues at the Mayo Clinic prospectively studied 456 patients with an ejection fraction of at least 50% with asymptomatic isolated (ie, without aortic valve disease) and pure (ie, without significant stenosis) mitral regurgitation due to organic valve disease identified by echocardiography.[2] Independent determinants of survival were increasing age, the presence of diabetes and an increasing effective regurgitant orifice, a measurement which was found to have a predictive power that superseded all other qualitative and quantitative echocardiographic measures of mitral regurgitation. Finding an effective regurgitant orifice of at least 40 mm^2 proved to be a powerful predictor of the clinical outcome of patients with mitral regurgitation in that significantly improved survival occurred in this group of patients when subjected to mitral valve replacement and/or repair even if asymptomatic before surgery.

■ COMMENT BY HAROLD L. KARPMAN, MD

It now appears that we must we rethink our approach to the follow-up and treatment of patients with asymptomatic chronic mitral regurgitation. Patients with symptomatic severe mitral regurgitation usually require surgical intervention; however, once left ventricular contractility has become impaired, symptoms of ventricular dysfunction and progressive heart failure may persist even after surgery has been performed. The data from the landmark Enriquez-Sarano study strengthen the concept that asymptomatic mitral regurgitation is a serious illness with a 5-year rate of death from any cause of 22% and a 33% incidence of adverse cardiovascular events including death from cardiac causes, heart failure and new onset of atrial fibrillation. Focusing on regurgitant severity as a predictor of clinical outcome in patients with primary mitral regurgitation, the data demonstrated that patients with an effective regurgitant orifice area of greater then 40 mm^2 had more than 5 times the risk of death from cardiac events (ie, death from cardiac causes, congestive heart failure, or new onset atrial fibrillation) then did those patients with a regurgitant orifice area of < 20 mm^2.

In summary, in appropriately selected patients, mitral valve surgery is associated with a considerably decreased risk of mortality and heart failure[2] and it now appears that even after correcting for age, sex, presence or absence of diabetes and atrial fibrillation at baseline, and ejection fraction, assessment of mitral regurgitation by determining the effective regurgitant orifice provides a powerful predictor of the clinical outcome among patients with isolated, asymptomatic organic mitral regurgitation. Certainly, patients with an effective regurgitant orifice area of 40 mm^2 or more should be at least monitored more closely and, in fact, since surgery in these patients often results in a normalization of life expectancy,[3] surgery should be strongly considered especially if the likelihood is that the valve can be repaired rather than replaced based upon the echocardiographic findings.[4] However, if valve replacement is likely to be needed or the surgical risk is high because of age and/or the presence of significant comorbid conditions, watchful waiting and careful follow-up may be a more appropriate choice. Final answers to this dilemma will come when a prospective, randomized, clinical study comparing the early surgery in asymptomatic patients with effective regurgitant mitral orifice areas of greater than 40 mm^2 with a group of patients whose surgery was performed based upon conventional indications, usually after they became symptomatic. But, for the time being, physicians should strongly consider sending asymptomatic mitral regurgitation patients with mitral orifice areas of greater than 40 mm^2 to surgery before they become symptomatic. ■

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Bad News About the COX-2 Inhibitors

SPECIAL REPORT

THERE HAS BEEN ENORMOUS CONTROVERSY REGARDing the benefit/safety relationship of the COX-2 inhibitors, which were initially introduced in 1999. A recent FDA panel garnered considerable national publicity and "rendered an ambivalent verdict on the future of the cyclo-oxygenase-2 (COX-2) inhibitors." It initially appeared that the Merck drug, rofecoxib (ROF), was the only 1 of the 3 marketed COXIBS, including celecoxib (CEL) and valdecoxib (VAL), whose safety was questioned. Recent issues of the *New England Journal of Medicine* contain numerous articles (3 original reports, 2 editorials) that deal with this complex and unhappy story.

Is Rofecoxib Safe? One of the first hints suggesting increased cardiovascular risk with COX-2 inhibitors came from the VIGOR trial, published in 2000, demonstrating more cardiovascular (CV) events in individuals randomized to ROF compared to naproxen. This study generated enormous controversy regarding ROF, ultimately culminating in Merck's withdrawal of the drug from the market. APPROVe, a recent study of 2600 individuals with a history of colorectal adenoma, randomized subjects to 25 mg ROF or placebo, was terminated prematurely because of increased cardiovascular risk in the ROF cohorts, with more confirmed serious atherothrombotic events during follow-up of 2.5 years vs placebo, relative risk of 1.9, $P = 0.008$. The event curves separated after 18 months of treatment. There also was a nonadjudicated 5-fold increase in congestive heart failure. APPROVe is the first placebo-controlled study to document a substantial risk for ROF; many other reports had not shown any increase in CV events vs conventional NSAID. Okie and colleagues discuss the conflicting data in the literature, including contradictory meta-analyses, and conclude that there is "an increased risk of confirmed thrombotic events associated with the long-term use of rofecoxib."

Is Celecoxib Associated with CV Risk? The answer apparently is yes, and it is strongly supported by the APC (Adenoma Prevention with Celecoxib) study of 2000 patients with a history of colorectal cancer; a trial comparing 2 doses of CEL (200 mg or 400 mg BID) or placebo for prevention of colorectal adenoma. After 3 years, the composite CV end point was 1% in the placebo group, compared to 2.3% in the 200 mg BID cohort and 3.4% in the 400 mg BID cohort. Because of these findings, early discontinuation of the trial was recommended. This study appears to be a smoking gun, indicating that ROF is not the only culprit in the COX-2 armamentarium. Okie et al suggest "there may be a real increase in cardiovascular risk associated with the use of celecoxib in particular, and the class of selective COX-2 inhibitors in general."

Are valdecoib and parecoxib safe? A late-breaking trial was presented at the American College of Cardiology meeting in Orlando, which employed 2 COXIBS to treat post operative pain following coronary bypass surgery.

Seventeen hundred patients were randomly assigned intravenous parecoxib (PAR) for at least 3 days, followed by oral valdecoxib (VAL) through day 10. Three cohorts, placebo-placebo, PAR-placebo, and VAL-placebo, were studied. The primary end points included a broad composite of CV events.

Results: Both groups using active coxibs were associated with increased CV risk, 7.4% in each vs 4.0% in the placebo group, resulting in a risk ratio of 1.9 for all comparisons $P = 0.002$. Okie et al conclude "short term COX-2 inhibitors are associated with a significant risk of thromboembolic events in patients with high risk of such events." They note that prior studies have suggested possible adverse effects of these 2 COXIBs. They state "selective COX-2 inhibitors should be avoided in patients undergoing CABG. . . and probably. . . in patients undergoing any vascular procedure for atherosclerotic disease."

Two editorials discuss the FDA COX-2 meeting and the question as to whether other NSAIDs may be harmful; much discussion is on the role of naproxen in this controversy.[1,5] "The members (advisory committee) sense that the cardiovascular risk with celecoxib appeared smaller than that with rofecoxib and valdecoxib."[1] The vote was 31 to 1 in favor of keeping CEL on the market and a split vote for ROF 17-15 and VAL 17-13, staying on the market. Criticism of both Merck and Pfizer came for some committee members who urged that manufacturers be prohibited from direct to consumer advertising (the FDA apparently can not ban this as such, but can require a black box warning on COX-2 labeling). This is a sobering report about the special FDA hearing, with little good news for the COX-2 agents.

A second editorial by a law professor is particularly critical of the Merck decision not to act on the early warnings that ROF might be hazardous.[5] There is emphasis on the financial profits from the sales of these drugs that complicates this unhappy saga and fuels the controversy and publicity attending the removal of Vioxx from the market. [On April 7, 2005 Bextra (VAL) was withdrawn from the market by Pfizer].

COMMENT BY JONATHAN ABRAMS, MD

The remarkably intense focus on the COX-2 drugs over the past several years is well documented in this series of articles. There have now been several COX-2 meta-analyses which are in conflict. It appears clear, through the retrospectroscope, that these drugs do impart hazard via putative interactions regarding prostacycline, thromboxane inhibition, etc. These agents may have been allowed to stay on the market for too long after early warning systems were activated. It is likely, but not proven, that patients with increased CV risk have a higher likelihood of having an adverse event with a COXIB. We do not know whether short duration of therapy is safer than long duration. We do not know whether high doses are more hazardous than low doses, although recent trials with both ROF and CEL would suggest that is the case. Reports that some patients only appear to respond to COX-2 agents for relief of pain are subjective. Helping our patients is one of our primary objectives! If there is an increased risk, it should be clearly stated and understood by all. This issue is, of course, heightened by the enormous success of COXIB sales, attributed by critics to the intense widespread direct consumer advertising campaigns on television and magazines. Patient choice of a COX-2 inhibitor may also be related to their long duration of action, requiring once or twice daily therapy when compared to some traditional NSAIDs. While there has been no evidence that short term use of these drugs, eg, a few days to 2 weeks, imparts risk, the CABG trial suggests this may be the case.[4]

This is a cautionary tale. Use of COX-2 drugs for arthritis, inhibition of potentially precancerous colonic polyps, or reducing the risk of GI bleeding compared to other NSAIDs, cannot be supported by current data. Millions of dollars in lawsuits against Merck and possibly Pfizer are likely, relating to presumed drug related major cardiovascular events that some believe have been prevented by earlier cessation of marketing. There does not appear to be any winner in this evolving story. ■

Dr. Abrams is Professor of Medicine, Division of Cardiology; University of New Mexico, Albuquerque

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Pharmacology Update

Micafungin Infusion (Mycamine™)

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

THE FDA HAS APPROVED A NEW INTRAVENOUS ANTIfungal agent. Micafungin is a member of the

echinocandin class that inhibits the formation of fungal cell walls. It is the second member of the class after caspofungin. Micafungin is marketed by Fujisawa as Mycamine™.

Indications

Micafungin is indicated for the prophylaxis of *Candida albicans* infections in patients undergoing hematopoietic stem cell transplantation. It is also indicated for the treatment of patients with esophageal candidiasis.[1]

Dosage

The recommended dose for the treatment of esophageal candidiasis is 150 mg IV daily. The mean duration of treatment from clinical studies was 15 days (range, 10-30 days). For prophylaxis, the recommended dose is 50 mg per day with a mean duration of 19 days (range, 6-51 days).[1]

Intravenous infusion should be over a period of 1 hour. No dosage adjustment is required for severe renal or mild-to-moderate hepatic dysfunction.

Micafungin is available as 50 mg single-dose vials.

Potential Advantages

Micafungin (50 mg daily) has been shown to be more effective than fluconazole for prophylaxis of fungal infections during neutropenia in patients undergoing hematopoietic stem cell transplantation (n = 882).[2] Absence of invasive fungal infection occurred in 80% of patients in the micafungin arm and 73% in the fluconazole group. Micafungin is well tolerated and has a low potential for drug interactions,[3,4] and is active against a broad range of Candida species including azole-resistant strains.[4] Cross resistance to azole and amphotericin B has not been shown.[3] Micafungin appears less likely to interact with cyclosporine than caspofungin resulting in elevation of liver enzymes.[3]

Potential Disadvantages

Micafungin is not available as an oral formulation. Patients receiving concomitant therapy with sirolimus or nifedipine should be monitored for toxicity due to increased bioavailability of these drugs.[1] Adverse events associated with micafungin include leukopenia, neutropenia, nausea, vomiting, diarrhea, abdominal pain, rash, pyrexia, and rigor. The frequencies ranged from 1-3%.[1] Elevations of liver enzymes, hyperbilirubinemia, and injection site reactions have also been reported.

Comments

Micafungin is the second member of the class, echinocandin. These drugs are inhibitors of -1.3-D-glucan synthase enzyme complex resulting in damaging fungal cell wall. It's activity is mainly directed at *Candida* and *Aspergillus* spp. The minimum inhibitory concentration is lower than amphotericin B and fluconazole against common *Candida* spp.[3] It's generally fungicidal against Candida and fungistatic against *Aspergillus* spp. Phase III studies involved treating candidiasis and the prophylaxis of fungal infections in patients undergoing hematopoietic stem cell transplantation. Micafungin (50 mg daily) was found to be more effective than fluconazole (400 mg daily) in prophylaxis. For treatment of esophageal candidiasis micafungin in HIV-positive patients (150 mg daily) was comparable to fluconazole 200 mg daily (89.8% vs 86.7%).[4] Micafungin is generally well tolerated and is at least as well tolerated as fluconazole. The wholesale cost of micafungin is $93.50 per 50 mg vial.

Clinical Implications

Current fluconazole is the standard for esophageal candidiasis and prophylaxis in neutropenic patients.[5] Micafungin provides an effective alternative and appears to be more effective than fluconazole in prophylaxis in neutropenic patients. About 10% of *Candida albicans* and 48% of nonalbican spp. (eg, *C. krusei*, *C. glabrata*) are resistant to fluconazole and mycafungin may be an active option.[4] The role of combination therapy (with amphotericin B or fluconasole) requires more study, but some degree of synergy has been reported.[3,6] Caspofungin is also approved for esophageal candidiasis and has also shown comparable efficacy to fluconazole.[7] However the role of this echinocandin is likely reserved for its other approved indications, candidemia and invasive aspergillosis refractory to or intolerant of other antifungal drugs. ■

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CME Questions

26. Quantitative assessment of mitral regurgitation is best achieved by measuring:

a. regurgitant volume.
b. ejection fraction.
c. effective regurgitant orifice.
d. mitral and aortic stroke volume.

27. Choose the false statement.

a. Concealed renal insufficiency is more common in females.
b. Age greater than 65 years is a risk factor for adverse drug reactions.
c. Patients suffering adverse drug reactions to a hydrosoluble drug were more likely to have concealed renal insufficiency.
d. Polypharmacy is a risk factor for adverse drug reactions.
e. Hypoalbuminemia is a risk factor for adverse drug reactions.

28. Despite their potential risks, COX-2 inhibitor drugs have been popular because of:

a. celebrity advertising on TV.
b. less GI adverse effects.
c. once-a-day dosing.
d. All of the above

Answers: 26 (c); 27 (a); 28 (d)

By Louis Kuritzky, MD

Daily vs As-Needed Steroids for Asthma

Management of asthma in America remains problematic, with as many as 5,000 deaths annually in recent years. Current guidelines suggest that for anyone with any degree of persistent asthma, maintenance anti-inflammatory medication is appropriate. The first-line recommended anti-inflammatory medication is inhaled corticosteroids (ICS), which are generally prescribed for daily use. Despite clinician advice to use ICS daily, prescription patterns indicate that this advice is often not heeded.

Reflecting upon the observed pattern of ICS administration, Boushey and colleagues randomized 225 adult asthmatics to receive 1) daily ICS, or 2) daily zafirlukast, or 3) brief steroid bursts with worsening asthma symptoms (10 days ICS or 5 days oral steroids), but no daily asthma maintenance medications. Subjects were followed for one year.

The primary end point of the study, change in morning peak expiratory flow rate, did not differ amongst the 3 groups. As anticipated, ICS did provide more favorable effects upon pulmonary inflammatory cellular changes (eg, degree of sputum eosinophilia). The number of asthma exacerbations did not differ between the groups. Although the daily administration of ICS did result in a greater number of symptom-free days than other regimens (26 days per year), this must be counterbalanced with the lack of impact of ICS upon exacerbations. Boushey et al caution that their results should be considered preliminary; larger studies would be required before such an approach could be endorsed. ■

Boushey HA, et al. N Engl J Med. 2005;352:1519-1528.

Intensive Lipid Lowering with Atorvastatin

The vasculopath—anyone with established vascular disease such as previous MI, stroke, PAD, or type 2 diabetes—is known to be at increased risk for subsequent vascular events and mortality. A large body of encouraging data of late have indicated that use of statins to lower lipids has favorable effects in diverse populations, including primary and secondary prevention, and even impressive results in acute coronary syndromes (ACS). Statin data from the ACS studies may not accurately reflect risk reductions that might be attained in stable patient populations. Additionally, although the PROVE IT trial suggested that lower lipid levels achieved were responsible for more favorable outcomes in a pravastatin vs atorvastatin trial, there still remained the possibility that there was some inherent difference between statins. So, 2 critical questions remained: Is lower better? Do persons with stable coronary disease benefit similarly to other populations?

Patients with stable demonstrated coronary heart disease and modest levels of LDL (< 130 mg/dL mean) were enrolled and randomized to 10 mg or 80 mg of atorvastatin daily for a median of 4.9 years (n = 10,00).

The relative risk reduction in the primary end point (first major cardiovascular event) was 22% (absolute risk reduction 2.2%). These favorable effects were achieved with a mean LDL of 77 mg/dL on 80 mg/dL atorvastatin, vs an LDL of 101 mg/dL on 10 mg/d. Lower is better. ■

LaRosa JC, et al. N Engl J Med. 2005;352:1425-1435.

The Polymeal: Natural Strategy to Reduce CVD

You may recall spirited discussion prompted by commentary in the *British Medical Journal* (Wald NJ. *BMJ*. 2003;326:1419-1423) that in theory, a sound public health measure would simply be to administer to everyone at age 55, regardless of health status, a multicomponent pill containing a statin, HCTZ, and ACE inhibitor, Beta Blocker, and Folic acid, all at half-standard dose. Administered population-wide, such a 'polypill' could conceivably provide radical reductions in cardiovascular disease end points.

Franco and colleagues believe there is perhaps a better, less expensive, less adverse effect-laden method that is substantially more palatable: The Polymeal. Based upon their literature review of favorable data on individual components of diet, the following ingredients of the Polymeal would have a beneficial effect: wine (150 mL/d), fish (114 g 4×/week), dark chocolate (100 g/d), fruits and vegetables (400 g/d), garlic (2.7 g/d), and almonds (68 g/d).

Based upon the Framingham life table data, Franco et al calculate the Polymeal reducing cardiovascular disease by 76%. Omitting any component might reduce the benefits; for instance, simply by omitting the wine,one might lose 11% of that benefit! They also calculate a 4.8 years (women), 6.6 years (men) increase in life expectancy from the Polymeal. Cost, of course, will be highly variable depending upon one's tastes in wine and chocolate, but could certainly conform to the most modest of economic settings. Bon appetite! ■

Franco O, et al. BMJ. doi:10.1136/bmj.329.7480.1447.

In Future Issues: Cardiac Resynchronization Therapy in CHF