

# the SECOND OPINION

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A monthly medical newsletter for the Athens medical community.

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## THE GREAT BREAST CANCER DEBACLE (CONT.)

older age at first live birth (younger age if positive family history of breast cancer); early menarche; Caucasian or Ashkenazi ethnicity; mutation in BRCA1/BRCA2 gene; prior therapeutic chest radiation; dense breast tissue on mammogram; high fat diet; high alcohol intake; low physical activity; obesity; exposure to environmental toxins; use of exogenous estrogens (as contraception or hormone replacement treatment).

7. Between 40-49 years of age, 3.5 women out of 1000 die from breast cancer over 10 years; screening mammography cuts this down to 3.0 out of 1000 screened (Mandelblatt et al, Ann Intern Medicine, 2009).
8. Over a 10 year period, screening mammography saves 1 life out of 2000 screened from breast cancer-related death (Mandelblatt et al, Ann Intern Medicine, 2009)
9. In the 40-49 y.o. cohort you would need to screen 1000 women to prevent 1 cancer death.
10. Mammography in common with all medical interventions has risks & benefits. Risks from screening include false-positives (with attendant anxiety, unnecessary biopsies/evaluation, cumulative radiation exposure, post-surgical scarring) as well as false negatives (fostering a false sense of security) and potential treatment of non-threatening cancers.
11. Mammograms are prone to over-diagnosis of clinically latent disease in the young with 2-10 such over-diagnosis for every breast cancer death prevented (Zackrisson et al, British Med J, 2006; Gotzche et al, Cochrane Rev 2009).
12. The unexplained excess in total mortality (HPI study, Stockholm trial, Canadian National Breast Screening Study) amongst ladies 40-49 y.o. screened with mammograms is not necessarily a statistical artefact.

## CONTRAST-INDUCED NEPHROPATHY

Administration of iodinated radiocontrast dye is now 1 of the most common causes of drug-related acute kidney injury. The rise in serum creatinine may occur within 24 hours, but typically takes up to 5 days to fully manifest. Contrast-associated nephropathy is common (the third most common cause of hospital-acquired kidney failure), potentially serious (may result in dialysis-dependence or death), occurs in up to 7% of all contrast exposures, and is eminently preventable.

**At Athens Kidney Center, our success rate in preventing this morbidity is about 100%. This is how we do it.**

1. Prophylax everybody, more so if contrast dye is to be given intra-arterially or infra-diaphragmatically.
2. Limit contrast dye volume to [5 mL x Weight in kg]/serum creatinine (Cigarroa et al, American J Medicine, 1989)
3. Consider use of less toxic alternatives, including low-osmolar non-ionic dye, carbon dioxide and gadolinium (we'll talk about nephrogenous systemic fibrosis on another day).
4. Focus especially on high-risk patients. such patients may be anemic, hypotensive, elderly, diabetic or with premonitory CKD (serum creatinine >1.5 mg/dL). Additionally, select those with prior contrast-related adversity, hypoalbuminemia, ethnic minorities, polyarteritis nodosa, chronic liver disease, solitary kidney, HIV associated nephropathy, myeloma, severe proteinuria or clinical dehydration.
5. Stop high-risk drugs at least 5 days prior to intervention (Metformin, angiotensin receptor blockers, ACE inhibitors, diuretics, Tylenol, NSAIDs, et cetera).
6. Volume expansion with saline (Mueller et al, Archives Internal Medicine, 2002) best given continuously IV over >6 hours for at least 2 liters; the data on sodium bicarbonate at 154 mEq/L, dosed at 3 mL/kg/hr is controversial (Merten et al, JAMA 2004).
7. Medications of uncertain benefit: (a) Mucomyst 600 mg p.o. BID (Tepel et al, N England J Medicine, 2000) and may be given as 150 mg/kg IV in 500 mL of saline over 30 mins followed by infusion of 50 mg/kg in 500 mL of saline over 4 hours in an emergency (Baker et al, J American College Cardiology, 2003); (b) Ascorbic acid 3 g p.o. x 1, then 2 g p.o. BID (Spargias et al, Circulation, 2004); © Lipitor or other statin, 10-80 mg p.o. QHS (Khanal et al, American J Medicine, 2005); Misoprostol 200 mcg p.o. QID x 3 days before test and 2 days after (Gurkowski et al, American J Therapeutics, 1995).
8. Not all renal failure following coronary angiography is attributable to contrast nephrotoxicity: do not forget renal athero-embolism from dislodged arterial plaques.

## FROM THE EDITOR

Medicine, as with the other classic professions, is steeped in historic provenance. Even a cursory reading of our professional antecedents would forcefully remind us of the impermanence of life and fortune, as well as the unique role played by the ancient professions (of law, medicine, and the priesthood) in the ascent of mankind. Distinct from the "trades", these classic learned professions are obliged to give back to the society that sustains them: lawyers call it *pro bono publico*, priests call it alms or *caritas*, and we call it *service*. True, we never took monastic vows of chastity, poverty and obedience, but our daily clinical practice is a testament to the sublimation of self (to say nothing of health) to our chosen vocation. As we walk the plank of our ER gauntlet dispensing care to "unassigned" patients, with no hope of compensation and an above-average risk of legal liability, it is worth remembering that we tread a singular path. The public struggles of today over "professional courtesy", fee-for-service, euthanasia, abortion, privacy/HIPAA, malpractice are but iterations of ancient disputations. Just ask Hippocrates.

*I swear by Apollo physician, by Aesculapius, by Hygiea, by Panacea, and by all the gods and goddesses, calling upon them to bear witness that according to my ability and judgment, I will in every particular keep this covenant.*

*To regard he who taught this art as equal with my parents. To share my substance, and if need be, to relieve his necessities, and to regard his offspring equally with my brethren, and to teach his art if they should wish to learn it without fee or stipulation. To impart my knowledge by precept and by lecture and by every other mode of instruction to my sons, to the sons of my teacher, and to my pupils who are bound by stipulation and oath according to the law of medicine, and to no other.*

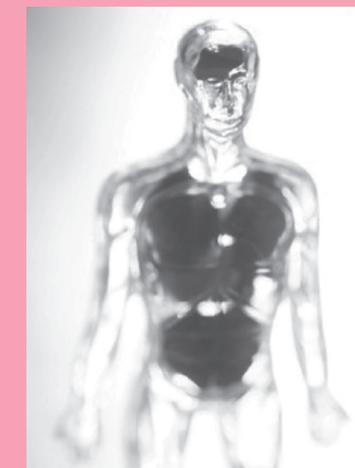
*I will use that regimen, which according to my ability and judgment shall be for the welfare of the sick, and I will refrain from that which may be baneful or injurious. If any should ask of me a drug to produce death, I will not give it; nor will I suggest such counsel. In like manner, I will not give a woman a destructive pessary. With purity and holiness will I watch closely my life and my art. I will not cut for stone, but will give way to those who practice that work. Into whatever houses I enter, I go only to aid the sick, abstaining from acts of injustice or corruption, and from lasciviousness with women or men, free or slave.*

*Whatever in the lives of men I see or hear in my practice which should not be made public, that I will hold in silence, believing such things should not be spoken of.*

*While I keep this oath inviolate and unbroken, may I be granted a joyous life and art, forever honored by all men. But should I by transgression violate this oath, may the reverse be mine.*

Enough said. See you Friday lunch-time, at the CME lounge.

*Beze Adogu, MD, Ph.D., FACP*



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### Editor:

Beze Adogu, MD, PhD, FACP

### Associate Editors:

Khudr Burjak, MD  
Harini Chittineni, MD

### Athens Kidney Center

1440 North Chase Street  
Athens, GA 30601  
706-227-2110 (p) • 706-227-2116 (f)

## PRINCIPLE OF MEDICINE

Occam's Razor- the law of parsimony- posits that the simplest explanation accounting for all the known facts is more likely to be true, than multiple or complex explanations. Offshoots from this cardinal principle include: rare complications of a common disease are more common than common complications of a rare disease; multiple complications from 1 disease are more likely than multiple diseases without added complications. Prosaically put: God can send you fleas or He can send you lice- but He wouldn't send you both fleas and lice at the same time. The philosophic counterpoise to Occam's razor is found in Hickam's dictum: "A patient can have as many darn diseases as he damn well pleases".

## PERSPECTIVE: POLYPHARMACY

Polypharmacy is defined as concurrent use of >5 medications (Colley & Lucas, J General Internal Medicine, 1993). Impact is greatest amongst vulnerable populations (elderly or severe organ dysfunction, including liver or kidney failure). Significance is tragic where medications were not even necessary. Polypharmacy results in increased drug-related adversity, higher medication errors, less therapeutic compliance and higher re-admission rates following hospital discharge. The "average" senior takes 4.5 different pills daily. At least 15% of hospitalizations in the elderly are related to drug adversity. Most of these are avoidable! Have you done a pill audit today?

## OSTEOPOROSIS

Osteoporosis is common (afflicting over half of those over 50 y.o.), chronically disabling (causing more than 2 million fractures q year), costly (\$18 billion is spent on osteoporosis-related fractures q year), serially under-diagnosed (less than 30% of high-risk patients ever get evaluated for osteoporosis) and under-treated (even with proper diagnosis, drug selection is often poor, compliance is limited, follow-up is marginal). The key to management is early diagnosis *before* a fracture occurs and early treatment to *prevent* any fracture(s).

High risk patients are: elderly (over 65 y.o.), post-menopausal state, history of previous bone fracture(s), history of smoking/steroid use/alcohol use, history of rheumatoid arthritis, parental history of hip fracture, and those with low body weight.

High risk patients should undergo bone mineral density (BMD) evaluation using a dual-energy x-ray absorptiometer (DEXA), and compared to a sex-specific Caucasian bone reference score taken either at the lumbar spine/hip or distal radius or femoral neck: any score under -1.0 is abnormal (osteopenia) and scores under -2.5 denote osteoporosis.

Any fragility (non-traumatic) fracture is by itself adequate to diagnose osteoporosis without a DEXA scan.

### Management of osteoporosis:

- oral calcium 300-600 mg p.o. TID-QID (minimum daily intake is 1200 mg daily, but avoid using over 600 mg at 1 sitting);
- vitamin D3 1000 units p.o. q daily or higher, titrated to serum 25-hydroxy-vitamin D level >30 ng/mL
- stop tobacco/alcohol use
- prevent falls (e.g., use walking aides, avoid sedative use, et cetera)
- encourage weight-bearing exercises;
- institute drug *prophylaxis* if DEXA score under -2.5 using (1) conjugated estrogens as Premarin 0.3 mg p.o. q daily in post-menopausal (risk of breast cancer, acute MI, DVT or stroke); (2) selective estrogen receptor modulators (SERMs) for *both prophylaxis and treatment* in post-menopausal as Evista/raloxifen 60 mg p.o. q d; (3) bisphosphonates for both prophylaxis and *treatment* in all types of osteoporosis as Fosamax/alendronate 10 mg p.o. q d or 70 mg p.o. q wk (50% of that dose is used for prophylaxis; the efficacy of Fosamax in steroid-induced osteoporosis is controversial) vs. Actonel/risedronate 5 mg p.o. qd or 35 mg p.o. q wk or 150 mg p.o. q month vs. Boniva/lbandronate 150 mg p.o. q month or 3 mg IV q 3 months vs. Reclast/zoledronic acid 5 mg IV q yr
- **for treatment** use either (1) bisphosphonates (usable for all types of osteoporosis, including steroid-induced disease), (2) SERMs (only for post-menopausal disease), (3) Miacalcin/calcitonin as nasal spray 200 IU q d using alternate nares or 100 IU sq given alternate days, (4) anabolic steroids such as Forteo/teriparatide 20 mcg sq q daily x 2 years (usable in both post-menopausal and male osteoporosis)
- Avoid bisphosphonates in those with a history of esophageal disease/reflux.
- Repeat DEXA scan after 2 years of treatment for improvement in BMD score

## STATIN INTOLERANCE

Statins are effective in reducing serum LDL cholesterol but 5% of patients are intolerant of this class of drugs. Several strategies have been suggested:

1. Once weekly Crestor at 1-40 mg p.o. q weekly (Backes et al, American J Cardiol, 2007)
2. Artichoke extract 600 mg p.o. TID (beware of GI symptoms & flatulent dyspepsia)
3. Barley bran flour (or oil extract) 3-30 g p.o. q daily (lower doses for oil extract)
4. Metamucil 5 g p.o. BID
5. Garlic extract 300 mg p.o. TID (worsens GERD and gives bad breath)
6. Red Yeast Rice (actually contains Lovostatin/Mevacor at low doses, therefore not a unique treatment)
7. Beta-sitosterol 2 g p.o. BID (beware of diarrhea and flatulence)

## HOT FROM THE TRENCHES

New guidelines from the WHO and NIH advocate starting HAART on HIV-infected patients when CD4 counts fall under 350 cells/mcl. Consensus is shifting to earlier treatment (between 350-500 cells/mcl) for better long-term outcomes. Cons: higher cost (as treatment typically begin 1-2 years earlier than hitherto using 200 cells/mcl threshold), more drug-related adversity, and higher risk of drug-resistance virus selection. Pros: reduced HIV-related illness and end-organ damage (including CNS, cardiac, liver and renal dysfunction), reduced viral transmission (to susceptible partners), and possibly reduce overall cancer risk. *Treatment should be offered to all pregnant women (from the 14th week of gestation) and all HIV-associated nephropathy (HIVAN) and all HIV-hepatitis B virus co-infection regardless of CD4 count.*

## PRIMUM NON NOCERE: THE CASE AGAINST ERYTHROPOIETIN

Anemia is common in chronic illness, including chronic kidney disease, heart failure and cancer. The pathogenesis of anemia is often multifactorial, from the combined effect of nutritional hypovitaminoses, iron deficiency, bone marrow dysfunction (due to uremic toxins or hyperparathyroidism), reduced erythropoietin synthesis in kidney failure (or bone marrow resistance to endogenous erythropoietin), multiple blood tests ("vampire syndrome") and chronic inflammatory conditions.

Erythropoietin is an endogenous glycoprotein synthesized by renal interstitial cells in response to circulating hypoxia-inducible factor 1 (HIF-1) which in turn binds to erythrocytic precursor cells within the bone marrow to trigger RBC proliferation and differentiation.

## PRIMUM NON NOCERE: THE CASE AGAINST ERYTHROPOIETIN (CONT.)

Anemia has been thought to be deleterious to long-term renal survival (Kuriyama et al, Nephron 1997). Treatment of anemia with exogenous erythropoietin (Epogen and other ESAs) has dramatically reduced transfusion requirements, and led to an improved quality of life, retained cognitive function and regression of left ventricular hypertrophy for most patients.

But there are new worries:

1. Since the original publication by Henke et al, Lancet 2003, that ESAs worsened survival in head/neck cancer patients, similar findings have been reported for metastatic breast cancer and non-oat cell cancer of the lungs. A recent meta-analysis by Bohlius et al, Lancet 2009 calculates an average 17% higher mortality with ESAs in cancer patients, possibly reflecting faster tumor growth in recipients.
2. Normal Hematocrit Study (NHS) first showed that dialysis patients with underlying ischemic heart disease or congestive cardiac failure being treated with Epogen to a "normal" hematocrit had worse cardiovascular outcomes (Besarab et al, N England J Medicine, 2004). That finding was replicated in the CHOIR study (Singh et al, N England J Medicine, 2006) which was also prematurely terminated after 16 months. Next came the TREAT study which did show a non-significant trend towards poorer CVS outcomes with ESA treatment as well as a significantly higher risk of stroke and thrombo-embolism (Pfeffer et al, N England J Medicine 2009).

What is a physician to do? First, use ESAs only where there is a clear indication, i.e. absolute or relative erythropoietin deficiency. Second, start with low ESA doses and slowly titrate upwards to avoid the potential hemodynamic and rheologic consequences of (relative) polycythemia. Third, aim to relieve symptoms of anemia, targeting a lower hematocrit of 10-12 g/dL, and no higher. Fourth, consider holding ESAs for tumors with a high growth fraction or manifesting high degrees of vasculotropism (e.g. Kaposi's sarcoma, renal cell cancer, et cetera) or are refractory to chemotherapy. Fifth, correct erythropoietin resistance, which is typically due to an underlying inflammatory process or absolute/relative/functional iron deficiency.

## PERSPECTIVE: ASPIRIN RESISTANCE

ASA blocks the generation of thromboxaneA2 via irreversible acetylation of platelet-derived cyclo-oxygenase enzyme (COX-1). ASA is shown to substantially reduce athero-thrombotic events by up to 25% in high risk individuals, but about 15% of patients do not respond to conventional ASA treatment. Such treatment failure in ASA-treated patients is referred to as ASA resistance. ASA resistance is multi-factorial, and is actually a continuous variable (i.e., every patient has some degree of relative resistance) not a dichotomous yes/no status, which varies both temporally and quantitatively. Components of ASA resistance include obesity, under-dosing, poor GI absorption (e.g. admixture with "binding agents", cathartics or chelating drugs), therapeutic non-compliance, drug-drug interaction with NSAIDs, drug-disease interactions (e.g., type 2 diabetes mellitus is associated with up-regulated P2Y12 pathway of platelet aggregation, which is inhibited by exogenous insulin), genetic polymorphisms involving COX-1/von Willebrand factor/GP IIb/IIIa tissue expression, as well as poorly-defined cellular factors (mediated in part by tissue over-expression of COX-2 mRNA, high serum levels of norepinephrine, and erythrocyte-dependent platelet activation).

Treatment of ASA resistance is unknown, though supplementation with omega-3 fatty acids is gaining currency. Current data suggests that ASA resistance is only partly related to COX-1 inhibition, therefore using higher doses of ASA is probably ineffective. The CURE and BRAVO data-base suggest that higher ASA doses worsen bleeding/gastrotoxic adversity without added anti-platelet effect.

## THE GREAT BREAST CANCER DEBACLE

The recent USPSTF recommendations have sadly generated more heat than light, becoming a ready foil for talk-show hosts and political hacks. How did a colorless, non-partisan, scientific advisory group become so controversial?

USPSTF recommended against *routine* screening mammograms in women aged 40 to 49 years with *average* cancer risk, asking that specific decisions ought to be *individualized* based on *benefit-harm analysis*. That nuanced proposition was lost in the public outcry, and as with every politicized debate, declarations were mostly short on facts but long on opinion. Perversely, in public debate, half truths like half bricks carry a lot better and travel further.

**Here are the facts, again:**

1. The USPSTF used randomized controlled trials, which are universally accepted as the standard for scientific evidence, for their analysis.
2. An ideal screening test must be cheap, accurate, widely available, accessible, easily interpretable plus effective, with high sensitivity (able to pick up testees with disease) and high specificity (able to exclude testees without disease); the disease tested must be common, associated with substantial morbidity, and have an identifiable "at risk" population with a high pretest prevalence (i.e. prior odds) of the condition.
3. Screening mammograms do not actually *prevent* breast cancer, but aims to *detect* disease at an early, easily treatable, pre-metastatic stage (if you believe in the Bernard-Fisher model, cancer is a systemic micro-metastatic disease even at the time of earliest detection).
4. The risk of breast cancer increases with age, therefore benefits of screening equally increase with age (the 5-yr risk for breast cancer is 0.4% for a 40 y.o. with "average" risk but rises to 6% for a 50 y.o. with "multiple" risk).
5. Sensitivity for cancer detection is typically over 80% in specialized centers (lower by up to 25% in younger women with denser breast mass) and specificity is over 95% (under 90% in the young, because of a higher incidence of benign breast disease).
6. Those with higher (than average) risk of breast cancer have: personal or family history of breast/ovarian cancer; breast cancer in first-degree relative; history of breast mass/prior breast biopsy; history of atypical hyperplasia of breast tissue;