Athens Kidney Center
1440 North Chase Street
Athens, GA 30601

RETURN SERVICE REQUESTED

SAFETY OF HOSPITAL DISCHARGE AFTER ED-CARDIOVERSION

New-onset atrial fibrillation is a common ailment in the ED, and its incidence is almost guaranteed to rise with an aging population, high prevalence of ischemic heart disease and cardiotoxicity from diverse clinical interventions. ED management of such new-onset AF often involves pharmacologic or electric cardioversion, either of which may risk ventricular proarrhythmia or bradyarrhythmia, respectively. Besser and Mills, *Ann Emerg Med*, 2011, review the literature on "drive-by" cardioversion: a total of 5 studies were analyzed, each demonstrated that hemodynamically stable patients with AF of less than 48 hours duration could be safely cardioverted in the ED and discharged home without pre-procedural echocardiography (looking for thrombi) and with minimal risk. This important review reinforces the appropriateness of "drive-by" cardioversion in stable patients, a practice that is clearly advantageous to the society with respects to appropriate resource allocation, potential patient satisfaction and spiraling hospitalization costs.

GETTING WITH THE PROGRAM: FIRST-LINE ANTI-HIV TREATMENT

As treatment of HIV gets more complicated by the day, most practitioners depend on expert panel recommendations in choosing a workable cocktail. First-line treatment may be either NNRTI-based (non-nucleoside reverse transcriptase inhibitor) or PI-based (protease inhibitor) or InSTI-based (integrase strand transfer inhibitor). Once the major element from those 3 options is chosen, then 2 additional NRTIs (nucleoside reverse transcriptase inhibitor) are added to complete the cocktail. The recommended NRTIs are tenofovir and emtricitabine used in combination. Presently, 2 PIs (of which is typically Ritonavir) must be used together in combination as must be 2 NRTIs.

1. NNRTI-based: Efavirenz plus [Tenofovir plus Emtricitabine]
2. PI-based: Atazanavir and Ritonavir plus [Tenofovir plus Emtricitabine]
   Darunavir and Ritonavir plus [Tenofovir plus Emtricitabine]
3. InSTI-based: Raltegravir plus [Tenofovir plus Emtricitabine]

OVERUSE OF HEAD SCANS

There is some anecdotal evidence of systematic misuse of neuroimaging at measurable risk of patient safety and healthcare cost. Raja et al, *Arch Intern Med*, 2011, set out to examine this problem. Analyzing data which was representative of the estimated 117 million ED visits in 2007 covering 4891 emergency departments, it was noted that head CT scans were performed in 6.7% of such visits (1 out of 14 patients) and head MRIs in 0.26% (1 out of 400 patients). Higher neuroimaging use was associated with advanced patient age, non-Hispanic white race, urban/city-based EDs and non-profit hospitals (as opposed to government-owned hospitals). Most scans were ordered as part of the evaluation of trauma, headache and dizziness. An accompanying editorial by Tabas and Hsia underlines the vast disparity in using radio-imaging facilities: for similar ED presentations with relatively minor complaints, variability amongst physicians in ordering expensive neuroimaging tests ranged from 6% to 80%, and 16% to 70% amongst hospitals. Therefore, there is both an individual as well as institutional bias to investigative "overkill". As Brenner and Hall, N Eng J Med, 2007, had previously demonstrated, there has been a 20-fold rise in medical imaging over the last 25 years in the United States with a full third of all CT scans being medically unnecessary. It's either we are getting sicker, smarter, more thorough, more adept (and comfortable with new technology), or we are all becoming more careless?

the SECOND OPINION

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FROM THE EDITOR

A favorite parlor trick in medieval times was to ask if it was possible for God to create a stone so huge that He himself could not move it. It was exactly the kind of question that earned you a place as the guest of honor at the witches' stake. You see, if you answered Yes, it meant God was not omnipotent, as He ought to be able to do anything, including moving stones. If you answered No, it meant God was not omniscient, and could not create anything he so pleased. I thought of this old riddle when news came forth that Erasmus University, Rotterdam, had dismissed Professor Don Poldermans, a leading cardiologist and gifted researcher, for scientific fraud. He joins other recent Dutch firings for similar transgressions.

There are more colorations of scientific fraud than there are stripes on a rainbow. The laity are understandably outraged at the more obvious strokes, such as conflict of interest, as was rightfully directed at Amgen for its behind-the-scenes manipulation of trials involving Epogen; falsification of data, which effectively ended the once-promising careers of Naoyuki Nakao (of COOPERATE infamy), Andrew Wakefield (pointman for the autism-vaccine debacle), and almost certainly derailing any future Nobel pretensions of Robert Gallo, of the LAV-HTLV saga, whose major flaw was probably carelessness rather than chicanery. Equally detestable is plagiarism, the unacknowledged pillage of others' words or ideas, a crime which owes more to intellectual indolence than creative larceny.

More difficult for the general public to engage are the fairly common- though hardly innocuous- misdeeds of our science culture: token authorship (where citation privileges are bestowed as an act of reverence, appreciation, loyalty, or simply as a gesture of fraternal goodwill) and its mirror-image, the unacknowledged appropriation of intelligence, where another's ideas are repackaged and festooned in bespoken plummage. Then, you have citation bias, where relevant knowledge is either purposefully suppressed to advance a contrary viewpoint or outrageously highlighted for dramatic effect. In the fight for tenure and peer accolades, redundancy is a common tactic, where the same old experiment or idea is serially recreated as new insight in lesser journals, pretty much like a herpetic eruption of stale ideas. More subtle is the act of self-publication, which encourages editors (as well as reviewers and friends-of-editors) to effectively bypass rigorous peer review by including self-originating papers of cursory import within their own journals.

We, as a society, should all care about scientific misconduct. Once published, it is difficult, if not impossible, to repair any damage published in an authoritative outlet. The moving finger of scientific thought brooks no recall. Nine years after Nakao et al published their improbable findings in Lancet, suggesting that combining an ACE inhibitor and angiotensin receptor blocker was superior to either drug used alone in slowing the progression of renal disease, there are still a lot of patients on that particular regimen and there are a lot of nephrologists who still believe Nakao was right. Imagine how many kidneys that have been consigned to an early Valhalla from that singular publication. Similarly, everyone now acknowledges that Andrew Wakefield was a fraud, driven by a vision of uncontested research grants, money from expert witness testimony at personal injury courts on autism, and dreams of a potentially lucrative diagnostic assay to detect vaccine-related complications in children. Yet, most parents are understandably uneasy about given the "full Monty" of triple vaccines to their young infants. What if he was slightly right? What if Sahel nomads in West Africa, already suspicious of Western efforts in polio immunization, also learnt that children in Europe (and America) were no longer being vaccinated? By his singular act, Wakefield has probably pushed back the cause of disease prevention in children by 3 decades or more.

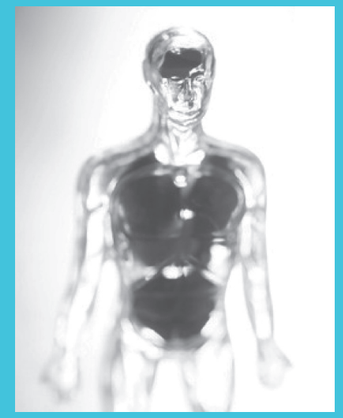
What can be done to end- or at least, mitigate- scientific misconduct? I believe 4 rules ought to be adopted as soon as possible: no more direct funding of research by pharmaceuticals or other "interested" parties; academic ascendancy should be based on more tangible indices not a "publish or perish" culture (indeed, 1 notable finding of direct clinical impact should trump a multiplicity of second-rate observations usually published in relatively obscure journals); all authorship must be proven and verifiable, not bestowed; criminal proceedings should be considered for egregious acts of scientific misinformation.

By the way, the answer to that riddle concerning the immovable stone is the human ego. Think about it. I'll see you Friday lunch-time, at the CME lounge.

Beze Adogu, MD, PhD, FACP

PREDICTING DEATH FOLLOWING DISCHARGE FROM THE ED

Early death within 7 days of discharge from the ED is not uncommon (30,000 per annum in the United States) and presents an opportunity for quality control initiatives. Gabayan et al, *Ann Emerg Med*, 2011 were able to collate data from 12 hospitals over a 2 year period. There was 0.05% early mortality following ED evaluation and discharge in this southern California population. Predictors of early death were: advanced age, male gender, multiple pre-existing co-morbidities, non-infectious lung disease at presentation, renal disease at presentation and ischemic heart disease at presentation.



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Athens Kidney Center
1440 North Chase Street • Athens, GA 30601
706-227-2110 (p) • 706-227-2116 (f)
www.athenskidneycenter.com

ACUTE CORONARY SYNDROME IN DIALYSIS PATIENTS

The clinical concurrence of cardiac and renal disease is well recognized in the various types of cardio-renal syndrome. Cardiac disease, not uremic syndrome or other manifestation(s) of renal failure, is the most common cause of death in ESRD patients. Specific knowledge of acute coronary syndrome in ESRD is patchy at best, but a new study by Gurm et al, *Am J Cardiol*, 2012, derived from the multi-national GRACE registry provides some insight. Non-ST segment elevation acute MI is the most common type of acute coronary syndrome in ESRD patients (accounting for 50% of ACS in this population but only 33% in non-ESRD populations), recurrent acute MIs were more common in the ESRD population (with repeat performances in 7.6% of ESRD patients and only 2.9% of non-ESRD patients), and mortality was uniformly worse amongst dialysis patients (in-hospital mortality being 12% and 6-month mortality at 13% with ESRD in comparison to 4.8% and 4.2% respectively amongst those without ESRD). Also, the prognostic GRACE risk score grossly underestimated the risk of major complications amongst ACS patients on dialysis. The reasons for such a pervasively poor outcome in ESRD are unclear, but probably relate to a higher burden of (atherosclerotic) disease at presentation, higher likelihood of prognostic risk factors (such as hypertension, type 2 diabetes mellitus, dyslipidemia), atypical clinical presentation (with heart failure symptoms rather than angina pectoris), under-treatment by physicians out of a sense of uncertainty or futility (or both), and the dilemma of drug titration and/or altered pharmacokinetics as a consequence of impaired renal excretion. Next stage: a randomized controlled trial of what works (or does not) in ACS within the ESRD population.

CLINICAL CONSIDERATIONS IN DECODING PANCYTOPENIA

Pancytopenia is not uncommon in the critically ill. A recent evaluation of a middle-aged African-American lady with critical anemia plus moderate leukopenia and mild thrombocytopenia led to a clinical review of the important causes of pancytopenia.

1. Multiple Etiologies: though not often listed in medical texts, this might actually be 1 of the more common causes of pancytopenia (anemia secondary to erythropoietin-deficient renal failure, leukopenia secondary to acute viremia, thrombocytopenia due to heparin-induced thrombocytopenia).
2. Reduced Blood Cell Production: either as a result of aplastic anemia (which can either be inherited as in the Fanconi anemia or acquired following viral infections, chemical exposure or other toxic insults to marrow) or bone marrow infiltration/replacement by disease, a.k.a. myelophthisis (such as myelofibrosis, leukemia, lymphoma, metastatic carcinomatosis, myelomatosis, storage disorders such as Gaucher's syndrome, granulomatous diseases such as sarcoidosis/tuberculosis, infections such as hepatitis C/HIV).
3. Increased Blood Cell Destruction: as a consequence of overwhelming inflammation (in sepsis or collagen-vascular disease or other autoimmune conditions) and hypersplenism (denoted by splenomegaly) and paroxysmal nocturnal hemoglobinuria.
4. Ineffectual Blood Cell Synthesis: from lack of vital cofactors in cell formation/maturation such as folic acid deficiency, vitamin B12 deficiency and myelodysplastic syndrome.

WHY DO PATIENTS FAIL TO TAKE MEDICATIONS?

A review by Brown & Bussell, *Mayo Clin Proc*, 2011, analyzes long-term medication adherence in the general population. Therapeutic success hinges on medication compliance, and only an estimated 50% of patients in the developed world exhibit long-term drug adherence. The reasons are diverse: disease-related (asymptomatic diseases such as arterial hypertension, diseases that require extended therapy before obvious clinical improvement such as AIDS/tuberculosis), patient-related (poor understanding of disease process/drug benefit, lack of involvement in decision-making, negative socio-cultural assumptions about disease/treatment, prior experience with drug therapies, lack of motivation, high cost of treatment, poor family/social support structure, psychiatric co-morbidity including depression and anxiety), physician-related (ignorance of specific drug use, failure to recognize non-compliance, prescription of complex treatment protocols, failure to explain/describe drug-related adversity, failure to describe intended drug benefits, poor communication skills, failure to examine potential drug-drug and drug-herb interactions) and system-related (fragmented/multi-provider clinical care, long waiting times at pharmacy, lack of drug coverage benefits, lack of physician-support resources). There can be no silver bullet to correct non-adherence: any effort should aim to simplify health delivery, educate and motivate the patient, and encourage physicians to inquire and follow-up on appropriate drug use by their patients whilst avoiding the parallax pitfall of poly-pharmacy.

UNDERSTANDING HYPOTENSION IN CRITICAL ILLNESS

Mortality in hypotensive (septic) shock remains high despite advances in treatment and early initiation of critical care support. It is thought that (inducible) nitric oxide synthesis which is up-regulated in sepsis leads to profound systemic vasodilation and hypotension in shock-like conditions. Yet, as therapeutic inhibition of nitric oxide synthetase activity has not improved clinical outcomes in trials of septic shock patients, it is likely that other pathways are involved in shock. Another inducible enzyme in shock-like conditions is indoleamine 2,3-dioxygenase 1, which metabolically converts tryptophan (an essential amino acid) to kynurenine contributing to systemic vasodilation and hypotension. Changsirivathanathamrong et al, Crit Care Med, 2011, report on indoleamine 2,3-dioxygenase activity in septic shock which they correlated to severity of hypotension and requirement for IV inotropes. Hopefully, this may provide a clinically remediable metabolic pathway in the future management of sepsis.

PROPERLY INTERPRETING HEMOGLOBIN A1C LEVELS

Hemoglobin A1c has been traditionally used to assess long-term glycemic control (over 3 months) though there are moves to adopt this test for the initial diagnosis of diabetes mellitus. The result of hemoglobin A1c assays can be influenced by various factors:

1. Abnormal erythrocyte longevity: the "normal" erythrocyte lifespan of 120 days may be drastically altered in hemoglobinopathies (hemolysis will reduce hemoglobin A1c values), hemolytic anemias (same effect), reticulocytosis (reduced hemoglobin A1c values), iron deficiency (increased erythrocyte longevity leading to higher hemoglobin A1c levels).
2. Altered biochemistry: reduction of glycation reaction by vitamins C and E can reduce hemoglobin A1c levels without changing average blood glucose levels; carbamylation of hemoglobin in uremia can cause higher assay readings as increased hemoglobin A1c levels; acetylation of hemoglobin by ASA can cause assay artifact read as higher hemoglobin A1c levels; high hemoglobin F levels increase assay result as high hemoglobin A1c (conversely, hemoglobin C, E, D, S all decrease hemoglobin A1c levels).
3. Hemoglobin A1c is higher in hyperlipidemia (particularly hypertriglyceridemia), hyperbilirubinemia (jaundice), elderly (age-related increase is up to 0.4%), Blacks (higher by about 0.4%) but lower in pregnancy (by 0.4%), chronic liver disease/cirrhosis, and those on HAART for AIDS.

EMPOWERING PATIENTS ON COUMADIN SELF-MONITORING

Use of vitamin K antagonists is an established intervention in prophylaxis against thrombo-embolic disease. However, it can be expensive, prone to complications, and associated with multiple treatment barriers, including frequent MD review, office-based monitoring of INR (which has to be kept within a narrow pre-determined range), illogical adjustments in dose (without considering intake of vitamin K agonists and precursors) and limited patient involvement (which breeds poor therapeutic compliance). There is some data that self-monitoring of INR/coumadin dose by patients is effective but not universally adopted. In this meta-analysis by Heneghan et al, *Lancet*, 2011, randomized trials of self-monitored coumadin treatment were retrieved using both Medline and Embase, with a focus on the comparative effects on time to death, time to first major bleeding event, and time to first thrombo-embolic event. In the pooled analyses, self-monitoring cut the risk of thrombo-embolism by roughly 50% when compared to physician/institutional monitoring (in doctors' offices or coumadin clinics). Also, time to first major bleeding episodes as well as mortality were no worse (and probably better) amongst those who self-monitored. Self-monitoring was associated with particularly superior outcomes for adults under 55 years of age and patients with mechanical valve prostheses, but least impressive for treatment of atrial fibrillation. In the largest cohort, 80% of patients were found able to self-monitor coumadin treatment with the most common grounds for exclusion being patient preference, judgment of primary MD (of patient's competence), inability of patient to train and learn monitoring protocol, advanced age, poor cognition and poor manual dexterity. Which begs the question, why then do 20% of German patients self-monitor their own coumadin dose but only 1% of American patients?

WHAT SHOULD REPLACE THE AUTOPSY?

When cause of death is uncertain- and the acceptable degree of certainty in these matters depends in part on unexpectedness of death, rarity of proposed etiology, familial grief, medico-legal squabbling, suspicion of felony- the autopsy has long been the accepted mode of reconciliation. However, the fraught and somewhat grisly picture painted by an anatomical dissection of a loved one has dimmed public acceptance of the autopsy. Public objection to autopsy has fomented a search for less invasive alternatives: a kinder, gentler examination of the deceased. The virtuopsy- radio-imaging of the cadaver by CT or MRI- has become the procedure of choice. A timely study by Roberts et al, *Lancet*, 2011, examined 182 unselected cases to confirm cause of death by 1 of 3 methods (CT scan of cadaver, MRI of cadaver, consensus report by 4 radiologists after both CT plus MRI of cadaver) before obtaining a formal autopsy. Shockingly, there were huge discrepancies in alleged cause of death: 32% in CT evaluations, 43% for MRI evaluations, 30% for "consensus reports" by 4 radiologists. Tellingly, even in cases where radiologists felt certain an autopsy was not necessary after full radiologic imaging (of which 34% were after a CT report, 42% after completing an MRI, and 48% after a deliberative consensus report), discrepancies persisted with 16% of CT scans being discrepant, 21% of MRIs and 16% of consensus reports. The following findings were of particular interest: though radiologists appeared most confident of their conclusions following MRI tests, that modality was actually the most unreliable; most erroneous virtuopsy results were for either of 4 separate conditions (ischemic heart disease, pulmonary embolism, pneumonia and intra-abdominal pathologies); using an autopsy as "gold standard" depends on the skills of the pathologist (which, knowing that these studies were carried out at Manchester and Oxford, UK, suggests that the pathologists were definitely "better than average").

ADVERSE DRUG MORBIDITY: ARE WE MISSING THE TARGET?

Using the National Electronic Injury Surveillance System-Cooperative Adverse Drug Event Surveillance database, Budnitz et al, *N Engl J Med*, 2011, reached some pretty compelling (and astounding) conclusions about hospitalizations for drug-related adversity amongst the older population. Each year, nearly 100,000 seniors are hospitalized with drug-related complications. The majority of those are very old, about 50% in this cohort being 80 years or older. About two-thirds (65.7%) are unintentional overdoses. A full 67% were accounted for by 4 drug groups only: coumadin (33.3%), insulins (13.9%), oral anti-platelet drugs (13.3%) and oral hypoglycemic drugs (10.7%). In case you are also wondering, all those high-risk medications listed in formularies and Beer's criteria, accounted for a whopping 1.2% of such hospitalizations. Take home messages: major bleeding and hypoglycemia are the 2 important complications arising from geriatric pharmacotherapy; check for bleeding manifestations, and check it often; beware hypoglycemia, especially in the elderly, where warning signals may have blunted with chronic illness or neuropathy. Finally, could someone please revise the Beer's list?

NOVEL TREATMENT FOR NORVASC/AMLODIPINE OVERDOSE

Amlodipine is a potent, long-acting dihydropyridine calcium channel blocker which acts by blocking intracellular calcium influx through L-type calcium channels. Overdose commonly results in severe hypotension. Treatment should be graded: IV saline or other available crystalloid; IV boluses of 10% calcium gluconate; IV bolus of glucagon; inotropic agents (such as IV norepinephrine); insulin-euglycemia protocol (1 unit insulin/kg IV bolus followed by 0.5-1 unit/kg/hour plus glucose). Jang et al, *Ann Emerg Med*, 2011, report on the added benefit of methylene blue (2 mg/kg IV bolus followed by 1 mg/kg/hour maintenance infusion). Rationale: calcium channel antagonists such as amlodipine are thought to mediate systemic hypotension in part through blockade of L-type calcium channels in vascular smooth muscle cells, but also through stimulation of endothelial nitric oxide synthetase activity which results in high nitric oxide levels, which in turns stimulates guanylate cyclase activity which leads to increased generation of cyclic guanosine monophosphate (cGMP), a direct mediator of vasodilatation in shock as well as following hypotensive drug therapy with calcium antagonists. Methylene blue inhibits guanylate cyclase, inhibits nitric oxide synthetase activity, and also "scavenges" for nitric oxide within the microcirculation.

PALLIATIVE CARE IN CHILDHOOD CANCER: HOPE OFTEN TRUMPS SCIENCE

The decision to end potentially life-saving or life-extending treatment is always an emotional event. When parents act on behalf of their children, a difficult issue becomes even more intractable. Tomlinson et al, *CMAJ*, 2011, report that parents of children with incurable cancers were more likely to choose aggressive chemotherapy rather than palliative end-of-life care. Indeed, 54.5% of parents opted for aggressive care in stark contrast to 15.6% of healthcare professionals who recommended palliation. Patients ranked hope as the more important factor in decision making, as opposed to healthcare professionals. Recognizing those different priorities and attitudes might improve the long-term acceptability of palliative care in the pediatric setting.

COFFEE AND DEPRESSION IN WOMEN

It turns out that the most frequently ingested psycho-stimulant is caffeine, the active ingredient of coffee. In a recent study by Lucas et al, *Arch Intern Med*, 2011, 50,739 women were followed over 10 years in the United States for new-onset depression and self-reported coffee intake. The risk of being diagnosed with depression fell with increased coffee consumption. This held true for caffeinated coffee, not for the decaffeinated beverage. Women of the world, please pass the cup on the left-hand side....