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STATINS & DIABETES

Despite the well documented beneficience of statins- discussed under the generic nostrum of pleiotropic effects in the earlier article- new studies indicate that statins, as with all medical interventions, have a significant side effect/risk profile. We already knew about liver disease, myopathy and rhabdomyolysis. A recent meta-analysis derived from 13 placebo-controlled studies by Sattar et al, *Lancet* 2010, showed a 9% increased risk of developing diabetes mellitus following 4 years of statin treatment. This adverse metabolic profile is mediated by reduced insulin secretion and worsened insulin resistance, most likely through reduced adiponectin levels, reduced glucose-mediated intracellular calcium spikes in pancreatic beta cells and blocked expression of GLUT-4 transporter in adipocytes. Paradoxically, this adversity is not apparently found in less lipophilic statins such as pravastatin, which seem not to be diabetogenic (Freeman et al, *Circulation* 2001). Lipophilic statins now join other potentially diabetogenic agents also used in treating vascular diseases (thiazide diuretics, beta-blockers and niacin being prime examples). Extrapolating from the CTTC data-base, the risk of diabetes with lipophilic statin treatment is 1 per 1000 patient-years of exposure, whilst 5 deaths or MIs are avoided per 1000 patient-years in addition to 4 strokes or coronary revascularization procedures prevented per 1000 patient-years.

DEATH IN PREGNANCY: BEWARE PULMONARY EMBOLISM

Viability of life- for both mother & child- in the pregnant state relies on a hypercoagulable state, a physiological imperative for successful delivery. In developing countries, the chief causes of maternal death are sepsis and peri-partal bleeding. In developed countries, it is pulmonary embolism. Both are different sides of the same coin. Tracking maternal death in our hospitals is 1 of the prime indicators of the new health-care initiative.

Pregnancy is associated with a 8x higher risk of venous thromboembolism in comparison to age-matched controls, rising to 20-35x the incidence in age-matched controls during the post-partum stage. Pregnancy-related DVT is left-sided in 85% of cases, a substantial minority of thrombi is localized within the pelvic veins, and a third of DVTs potentially result in pulmonary embolism. As the mortality rate of untreated pregnancy-related PE is high, it is important to start heparin treatment (preferably, LMWH) immediately PE is suspected, even before completing the requisite diagnostic tests. Risk factors for PE include personal or family history of DVT/PE, immobilization, obesity, history of smoking or thrombophilia, prolonged post-partum bleeding, ceasarean delivery, infection or pre-eclampsia. Strongly consider prophylaxis with Lovenox for those patients. Patients with limb symptoms consistent with DVT should undergo a compression ultrasonographic exam, those without localizing symptoms should obtain a V/Q scintigram or CT pulmonary angiogram.

SURGICAL RISK IN RENAL PATIENTS: WHO WOULD HAVE THOUGHT THAT?

After adjusting for co-morbidities, age, race and gender, University of Maryland researchers found that CKD was associated with worse post-surgical outcomes, including a 4x higher risk of metabolic derangements, 2.3x higher infection risk with "minor" procedures and 39% higher sepsis risk after major surgeries, 60% higher anesthesia complications, 37% higher post-operative respiratory failure, 18% higher incidence of post-operative acute MI and 53% higher mortality even with "routine" low-risk surgeries.

OXYGEN FOR ACUTE CORONARY SYNDROMES: CAVEAT EMPTOR

Routine (and reflexive) oxygen administration, causing hyperoxemia, may lead to reduced coronary artery blood flow by up to 29% of basal flow in susceptible patients (Farquhar et al, *American Heart J*, 2009; Wijesinghe et al, Heart, 2009). Therefore, to avoid an iatrogenic extension of myocardial infarct, Sheikh et al, British Med J 2010, remind us that oxygen supplementation during myocardial infarcts is indicated only if the patient is hypoxemic. *Caveat emptor!*

the SECOND OPINION

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FROM THE EDITOR

First, in the spirit of Pentecost, the good news: doctors do think. Actually, we think a lot, endlessly worrying about ethical conundrums relating to our practice of medicine (Torke et al, *J American Ger Soc* 2010, 58, 533-538). Now, the bad news: doctors do not like following directives, even when those directives are called evidence-based (Brace et al, *J Clin Oncology*, early online release, March 30, 2010). That, despite the preponderance of evidence that those same guidelines lead to better clinical outcomes.

Perversely enough, that brought to mind the spirited on-line debate we all recently enjoyed on the (f)utility of treating pre-hypertension. As much as I enjoy the *sturm und drang* of informed argumentation, I suspect that as doctors, we are a pretty tough crowd to convince. We would think nothing of dancing on the grave of Thomas Bayes. Which got me thinking more about evidence-based medicine, and its role in modern practice.

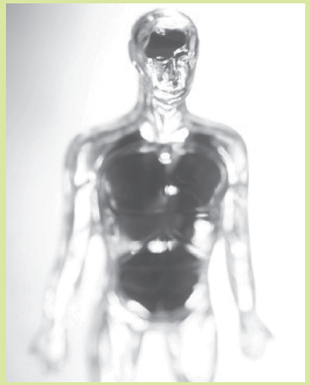
The golden age of evidence-based medicine has certainly come; come, as in the ides of March, but not gone. At its best, evidence-based medicine guards against the excesses of therapeutic optimism, institutional resistance (to new ideas) and the idiosyncracies of professional inbreeding. Doctors who train or practice together, share more than fond memories of "the good old days"; they also indulge in similar practices, for good or ill. Therefore, evidence-based medicine can be an indispensable tool in constructing medical opinion. It affords us an objective, informed, conscientious, explicit, balanced use of the avalanche of ideas (and information) out there. At its best, it integrates clinical expertise and data from relevant systematic reviews, adopting the rules of good science, solid economics and public welfare to extend our clinical reach. But it is still a tool- and no doubt, a very useful one- but like all tools, its usefulness will depend on the skills (and character) of the user.

And critics abound. The chief reservations include a lurking suspicion that it removes physician autonomy, substituting the inferred worship of the citizen-doctor with the worship of the prospective randomized controlled clinical trial. There is a fear of an overly aggressive proselytism by "true believers", and the implied conclusion that governmental regulation based on "evidence" cannot be far behind. Other skeptics insist that evidence-based medicine, like other new-fangled ideas, will someday lose its luster.

Perhaps. Yet, one cannot but be pleased that an objective benchmark is finally being applied to the riot of clinical observations published daily through many outlets. Am I alone in thinking that if we actually had real trials, maybe we would not have subjected generations of gullible patients to such incongruous ministrations as blood-letting, leeches, scarifications, prophylactic tonsillectomy, and other superstitious mumbo-jumbo? When was the last time you saw someone using "renal dose" dopamine? Can hyperbaric oxygen be too far behind?

We may have elevated the prospective, randomized, controlled clinical trial into deity, and made numbers needed to treat (NNT) our secular gospel, but imagine the confusion that reigned in years past, without any meaningful reference point. Like Santayana's dreamer, we are much better off being shepherded by the facts than piloted by our hallucinations. May the *p* value reign for ever.

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



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LABILE HYPERTENSION IS WORSE THAN STABLE HYPERTENSION

Hypertension is a cardinal risk factor for vascular events. Variable (or labile) hypertension tends to be dismissed or treated less aggressively in clinical practice. Indeed, several guidelines, including JNC VII and European Society of Hypertension recommend monitoring for episodic hypertension. A new study shows that variability in systolic blood pressure is more predictive of vascular events (especially strokes) than mean systolic blood pressure elevation (Rothwell et al, *Lancet*, 2010) especially in the young.

PLEIOTROPIC EFFECTS OF STATINS

Statins (3-hydroxy-3-methyl glutaryl coenzyme A [HMG Co A] reductase inhibitors) are amongst the most commonly prescribed drugs. These drugs block the rate-limiting step in cholesterol biosynthesis in the liver and elsewhere, resulting in marked reductions in serum LDL cholesterol levels (and a reciprocal increase in tissue expression of LDL receptors) which are linked to improved outcomes in epidemiologic studies of coronary artery disease. Those added effects of statin drugs which go beyond their known lipid lowering function are referred to as *pleiotropic* properties. Those include anti-proliferative, anti-inflammatory, immuno-modulatory and endothelial effects, mediated through non-lipid pathways.

1. Anti-inflammatory effects are mediated by attenuated levels of pro-inflammatory molecules such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), gamma interferon (IF-gamma) and nuclear factor kappa B (NF-kB), which is a transcription factor needed for both inflammation and apoptosis (Cho et al, *Int J Cancer* 2008). Statins also block the cellular expression of adhesion molecules (thus eliminating interactions between endothelial cells and neutrophils via P/E-selectins) whilst inhibiting *ras* and *rho* isoprenylation, a critical step in the inflammatory cascade that requires post-translational modification of GTP-binding proteins (Lee et al, *NeuroScience Lett*, 2008).

2. Stabilization of atheromatous plaque: multiple trials, including HPS and JUPITER (Ridker et al, *N Engl J Med* 2001), have shown that cardiac outcomes are improved by statins regardless of LDL cholesterol levels. As statin effect may be predicted by high levels of inflammatory biomarkers such as C-reactive peptide, it is hypothesized that this is an anti-inflammatory effect of statins. Additionally, statins reduce inflammatory cell proliferation, improve endothelial function, and block accumulation of cholesteryl esters within macrophages (Vaughan et al, *J American Coll Cardiol* 2000).

3. Angiogenesis: statins activate endothelial protein kinase enzymes (such as *Akt*, which act downstream of most known angiogenic growth factors including vascular endothelial growth factor [VEGF]) which upregulate nitric oxide (NO) synthase leading to increased production of nitric oxide, a cellular signal for angiogenesis (Kureshi et al, *Nature Med* 2000).

4. Statins induce apoptosis through the NF-kB pathway, affecting both normal and neoplastic cells; this has led to observable inhibition of cancer growth in cell cultures (Cho et al, *Int J Cancer* 2008). Furthermore, by increased phagocytosis of "scavenger" blood cells (Salman et al, *Biomed Pharmacothet* 2008), cell cycle arrest at G1/S phase in Alzheimer-vulnerable cerebral lymphoctyes, and reducing beta-amyloid synthesis via its inhibition of *ras* and *rho* isoprenylation as described earlier, statins can retard the development of amyloid plaques in Alzheimer's disease (Ostrowski et al, *J Biol Chem* 2007).

Despite the accumulated experimental evidence, no study has yet shown a uniform protection against most cancers from statin use. Individually, there is some data supporting protection against lung and colon cancer ((Farwell et al, *J National Cancer Inst* 2008; Khurana et al, *Chest* 2007) and perhaps, using lipid-soluble statins such as Lovostatin, Simvastatin or Fluvastatin (Cauley et al, *J National Cancer Inst* 2006). Similarly, the data on Alzheimer's disease is unconvincing (Arvanitakis et al, *Neurology* 2008) despite initial interest (Sparks et al, *Acta Neurol Scand* 2006) as was the case with sepsis treatment (Gao et al, Br J Anesth 2008).

REFEEDING SYNDROME IN ICU

Refeeding syndrome describes severe shifts in fluids/electrolytes in malnourished or critically ill patients receiving artificial feeds, either enterally or parenterally.

The biochemical hallmark of refeeding syndrome is hypophosphatemia, but may include hypokalemia, hypomagnesemia, hypovitaminoses and other complex changes in fat, protein and glucose metabolism.

The underlying cause is rapid refeeding; the undernourished patient who has become chronically adapted to intracellular mineral deficits and reduced insulin production suddenly faces a surge in insulin secretion with re-reversal from ketogenesis (as ketone bodies are displaced once more as the preferred energy substrate of the brain). As glucose is internalized within cells, water and minerals are co-transported, resulting in potentially fatal drops in serum levels of those minerals.

Management relies in identifying high risk patients (undernourished, elderly, alcoholic, cancer patients, post-operative cases and those on long-term diuretic treatment or oral phosphate-binding antacids), resume feeding at 50% of energy requirements and slowly increase over 1 week, add vitamin supplements x 2 weeks, maintain volume status, treat catabolic risks (such as infection, ulcers, et cetera) and closely monitor weight gain.

FEAR OF HEPARINOIDS IN KIDNEY DISEASE

Deep vein thrombosis is common in the acutely ill. Low molecular weight heparins (heparinoids) have become the standard of care in DVT prophylaxis, because of their higher efficacy in high-risk patients (Geerts et al, *ACCP Conf Stmt*, 2004) and low risk of heparin-induced thrombocytopenia. Unfractionated heparin is often preferred in CKD patients based on concerns about reduced heparinoid drug clearance. The data does not support this practice. The DIRECT study using dalteparin 5000 units q daily did not demonstrate excessive bleeding or excessive anticoagulation attributable to drug accumulation in CKD (Douketis et al, *Arch Int Med* 2008) and several other studies do not support the contention that heparinoids accumulate in CKD anyway (Kani et al, *J Crit Care* 2006, Tincani et al, *Hematologica* 2006).

POST-STROKE MENTAL RECOVERY

Escitalopram (Lexapro) helps stroke victims recover some cognitive function within 1 year, including visual and verbal memory, based on a University of Iowa study published by Jorge et al, *Arch General Psychiatry* 2010. Interestingly, this was reportedly independent of the drug's known anti-depressant effect.

POLYCYSTIC KIDNEYS: NEW THERAPEUTIC APPROACHES

Autosomal dominant polycystic kidney disease (ADPKD) is the most common hereditary cause of kidney failure accounting for 5% of all dialysis cases. Being a systemic and progressive condition, its protean manifestations become more apparent with time (and age). This disorder is attributed to a genetic mutation involving *pkd* 1 (on the short arm of chromosome 16) or pkd 2 (on the long arm of chromosome 4) which encode the epithelial transmembrane glycoproteins, polycystin 1 and polycystin 2 respectively. Remember that 5-7% of patients will not have a family history of ADPKD.

Making the diagnosis requires *ultrasonographic* demonstration of 2 or more cysts in 1 kidney or 1 cyst in each kidney in a young adult under 30 y.o. with a positive family history (or 5 cysts in total for both kidneys, if no family history); 2 or more cysts in each kidney in a middle-aged adult aged 30-59 y.o. with a positive family history (or 5 cysts in total in both kidneys, if no family history); 4 or more cysts in each kidney in an elderly adult (>60 y.o.) with or without a positive family history (Ravine et al, *Lancet* 1994). If still in doubt, obtain DNA linkage analysis.

Treatment entails (a) adequate BP control with either an ACE inhibitor or Angiotensin Receptor Blocker; (b) prompt detection and treatment of urosepsis with lipophilic antibiotics (such as quinolones, Bactrim, clindamycin); © appropriate pain management with avoidance of NSAIDs; (d) routine AHA antibiotic prophylaxis if evidence of mitral regurgitation; (e) treatment and prophylaxis for (urate) kidney stones; (f) CT angiogram and neurosurgery referral if family history of cerebral aneurysm/stroke; (g) increased dietary roughage and bulk laxatives for colonic diverticulosis; (h) reduce cAMP generation by reducing vasopressin synthesis (*increase water intake* to 3L daily or use vasopressin V2 receptor blockers) and *low salt diet* (under 2 g daily) and *avoiding phosphodiesterase inhibitors* (restrict tea, coffee and chocolate); (i) avoid hypokalemia, which is associated with cyst formation and increased interstitial renal fibrosis; (j) mTOR pathway inhibitors (such as rapamycin) are the focus of current research for future treatment of ADPKD.

THROMBOPHILIA: HYPERCOAGULABLE STATES

Adequate clotting capacity is essential to life: otherwise, we'd all bleed to death. Some have a physiologic tendency to clotting, mostly protective in nature, seldom pathologic. We recognize those at high risk for clotting with the medical school mnemonic 5Ps HAD CAUSED CLOTS: **p**regnancy/**p**ost-partum, **p**olycythemia vera, **p**aroxysmal nocturnal hemoglobinuria, **p**rotein C/S deficiencies, **p**rothrombin G20210 mutation, **s**moking, **h**eparin-induced thrombocytopenia, **h**yperhomocysteinemia, **a**ntithrombin III deficiency, **d**ysfibrinogenemia/**d**yslipidemia, congestive cardiac failure, **a**ntiphospholipid antibody syndrome, **u**remia, **s**urgery, **e**strogens, **d**iabetes, **c**ancer, **L**eiden factor V mutation, **o**besity, **t**rauma/**t**ravel, **t**hyroid disease/**t**hrombocytosis, **t**halassemia, **s**epsis/**s**ickle cell disease.

Testing for anticoagulant defects has a low predictive value in the general population, therefore these tests are only indicated in those with: (a) personal or family history of idiopathic venous thrombosis before age 50 years, (b) history of recurrent venous thrombosis, © recurrent unexplained fetal loss. These tests are not useful for population screening: the vast majority of those with clear clotting factor defects will never have blood clots.

The prevalence of those defects in thrombophiliacs are: activated protein C resistance (12-40%), hyperhomocysteinemia (10-20%), prothrombin G20210A mutation (6-18%), anti-thrombin III/protein C/protein S deficiencies (5-15%), anti-phospholipid antibody syndrome (5-10%)

Tests to order include: (a) Activated Protein C resistance, (b) Anti-thrombin III deficiency, © Protein S and Protein C deficiencies, (d) Prothrombin G20210 mutation, (e) Anti-phospholipid antibody/lupus anticoagulant and anti-cardiolipin screen, (f) Homocysteine, (g) PT/PTT, (h) Lipoprotein(a)

The goal of treatment is effective but safe clinical intervention, resolution of clot with low bleeding risk: with coumadin aim for an INR of 2-3 but consider extended duration of 6-12 months in thrombophilia (or life-long treatment in those with either 2 or more separate genetic defects predisposing to thrombophilia, or patients with potentially fatal venous thrombosis or clot at an unusual vascular bed, such as within the mesenteric, renal, hepatic, cerebral or portal venous systems).

Monitoring treatment can be challenging: usually, drugs will not affect genetic tests, but acute vein thrombosis will transiently reduce plasma levels of anti-thrombin III as well as protein C and protein S; heparin can precipitate up to 30% reduction in anti-thrombin III levels; coumadin can reduce the functional activity of protein C and protein S, as well as increase plasma levels of anti-thrombin III in those with anti-thrombin III deficiency. It is recommended to wait at least 2 weeks after being anticoagulant-free before repeating coagulation tests.

PRE-OPERATIVE CARDIAC CONSULTATIONS

Having been trained to order "cardiac clearance" for all but the stablest patients scheduled for surgery, the latest guidelines from the American College of Cardiology (Chopra et al, *Ann Internal Medicine*, 2010) comes as a kick to the gut!

1. Cardiac screening is not required for stable patients undergoing non-cardiac surgery.

2. Cardiac testing may identify CAD but that does not necessarily identify high peri-surgical risk (i.e. severe CAD is not equal to peri-operative cardiac risk) and PTCA/CABG prior to surgery does not lower peri-operative cardiac risk (i.e. treating CAD does not help you, either).

3. Peri-operative beta-blockers are useful in high-risk patients only (not for every patient) with CAD but must be titrated to BP and HR for maximum benefit.

FRINGE BENEFITS

Routine screening of asymptomatic patients by CT colonography reveals previously unsuspected cancer in 0.56% of patients. Only a third actually had colon cancer, the majority of patients, about two-thirds, had cancers discovered elsewhere: most often renal cell cancer, lung cancer and non-Hodgkin's lymphoma (Pickhardt et al, *Radiology*, 2010, 255, 83-88).