NEW INSIGHTS IN HYPERTENSION -

Hypertension is the most common preventable cause of premature death in the world, accounting for 14% of total global mortality. Hypertension is a risk factor for renal and cardiovascular death, with added risk starting at 115/75 mmHg (and doubling with each further 20/10 mmHg elevation in BP). Hypertension-attributed morbidity is accentuated in the presence of other CV risk factors such as diabetes mellitus, chronic kidney disease and coronary artery disease. Hypertension is present in 1 out of 3 adult Americans, and its prevalence increases with age, therefore over 90% of all people will become hypertensive at some point in their lives. Based on NHANES data (Hajjar et al, JAMA 2003) it was estimated that 28.7% of the population were hypertensive, 69% were aware they were hypertensive, 58% were under treatment but only 31% were adequately controlled. To achieve the Healthy People 2010 target of 50% hypertension control, we would need to have 80% of hypertensives being aware of their condition, 90% of hypertensives on drug treatment, and 70% of those treated being controlled (Egan & Basile, J Investigative Med 2003).The financial toll of hypertension is ~$70 billion/yr, and rises to ~$450 billion/yr if morbidity from cardiovascular disease, stroke and CKD are included. It is now clear that control of hypertension results in better outcomes for all risk groups. For all patients, the degree of BP reduction is vastly more important than the drug used to attain that goal. In other words, for an equivalent degree of BP reduction, the differences in primary outcomes attributed to a specific drug is minimal (Chobanian AV, NEJM 2009). That was clearly demonstrated in the STOP-2, ALLHAT, ASCOT and INVEST trials, though a close reading of the LIFE study suggested that ARBs may be superior to beta-blockers, the Australian ANBP2 trial indicated that ACE inhibitors show superior outcomes in comparison to thiazide diuretics in males only, and the ACCOMPLISH study showed that an ACE inhibitor-calcium channel antagonist combination trumped the ACE inhibitor-thiazide combination. So far, we only have a few compelling instances where 1 particular anti-hypertensive is of specific advantage: **1.ACE inhibitor/calcium channel blocker following an acute MI, 2.Beta-blocker/calcium channel blocker in those with CAD, 3.ACE inhibitor or ARB in CKD (especially if proteinuria >1 g/day, 4.ACE inhibitor/ARB/aldosterone antagonis t/ beta-blocker/diuretic in congestive heart failure.**

There are experiential grounds to suspect there is a J-curve (a point of maximal benefit with progressive BP lowering, beyond which clinical benefits decline and adversity slowly increase), but like the existence of paradise, it is difficult to prove. It is wise to be careful in dropping BP under 100/70 mmHg in those with severe coronary artery disease (Messerli & Panjrath, J American College Cardiology, 2009), CKD, vascular dementia or ischemic encephalopathy.

There are different sub-types of chronic hypertension, which must be recognized and treated: 1. pre -hypertension (BP between 125/75-135/85 mmHg) in most would progress into true hypertensive with time, 2. white -coat hypertension (normal BP at home, elevated at the office) accounts for 15-20% of hypertension patients, 3. masked hypertension (normal BP at the office, elevated at home accounts for 10 -15% of hypertension patients.

Based on placebo-controlled trials, drug treatment of hypertension (even if inadequate) will reduce total mortality by ~10%, CAD risk by ~15%, stroke risk by ~30%, CHF risk by ~45% (Psaty et al, JAMA 2003). Any 1 drug can reduce BP up to a maximum of 20/10 mmHg, therefore most patients will need at least 2 or 3 different drugs for adequate BP control. True "resistant" hypertension is uncommon, being found in only 2.9% of patients (Aldermann et al, Hypertension 1988), and "secondary" hypertension is equally rare; the causes of secondary hypertension are most often primary aldosteronism, chronic kidney disease and renal artery stenosis (Lim et al, J Clin Endocrinology Metab 2000). In practice, poor BP control is due to disease-related factors (which are uncommon, but include "secondary" hypertension and presence of CKD), patient-related factors (limited access to care, poor compliance, old age, obesity, lack of exercise, illicit drug use, smoking, alcohol use) and physician-related factors (including limited knowledge of hypertension-related facts, drug preferences, and "clinical inertia"). Though better BP control and proteinuria resolution are common with an ACE inhibitor-ARB combination, the ON TARGET trial demonstrated that it also increases renal adversity and should therefore be avoided (Yusuf et al, NEJM 2008). The HYVET trial shows that treatment of hypertension is beneficial even in the very elderly (>80 years of age) using a diuretic/ACE inhibitor (Beckett NS et al, NEJM 2008).

Treatment of hypertension in pregnancy can be problematic; pregnancy may be associated with abnormal placentation, causing (abnormal) release of vasoactive peptides and autonomic dysfunction, resulting in vasoconstriction, systemic hypertension, and poor maternal-fetal outcomes. Treatment of pregnancy-associated hypertension must be individualized, ACE inhibitors/ ARBs are best avoided because of their teratogenic potential, and typical drugs employed are methyldopa, nifedipine, labetolol and hydralazine, though thiazide diuretics and other calcium channel blockers are probably safe in pregnancy. Strategies for achieving better hypertension control: use a lower threshold for starting drug treatment (strictu sensu, hypertension-related vascular risk starts at 115/75 mmHg, therefore treatment threshold should be at most 140/90 mmHg); monitor and address any drug-related side-effects; audit for drug-drug (e.g. combining diuretics with NSAIDs) and drug-disease (e.g. hydralazine-associated ANA seropositivity in lupus patients) interactions; have a reliable means for checking and recording BP in the out-patient setting; establish an "optimal" BP for the patient; agree on triggers for re-evaluation/medication changes; introduce lifestyle changes early on (no tobacco, limited alcohol, diet modification, physical activity, weight management); emphasize self-management; tailor treatment to individual cultural norms and belief system; consider referral to a hypertension specialist.

SOME NEW KNOWLEDGE :

One of the most common causes of severe proteinuria in adults, "idiopathic" membranous nephropathy, may be due to IgG4 autoantibodies directed against M-type phospholipase A2 receptor (PLA2R) on the podocyte membrane (Beck et al, NEJM 2009). This finding may open an avenue for serologic diagnosis of nephrotic syndrome in the future, without having to perform a renal biopsy.

the SECOND OPINION

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FROM THE EDITOR

"Life is short, the Art is long, opportunity is fleeting, judgment difficult, and experience is dangerous": thus begins the first aphorism of Hippocrates (460-377 B.C.). In the old days- and by that, I mean a scant 15 years ago- the consummate physician was characterized as a "triple threat": bed-side clinical acumen, spell-binding teaching skills, and of course, bench-top laboratory bona fides. From my conversations with old friends still laboring in the vineyards of academic medicine, that concept is slowly but surely receding into medical mythology. The underlying reasons for that change bring us back to the aphorisms of Hippocrates.

In academia as well as in private practice, doctors everywhere are feeling the constraints of time and opportunity. We can expect that for the foreseeable future, our revenue stream will slowly but inexorably decline, even as our patient base increases, new medical discoveries confound, our didactic repertoire erode, expectations from patients rise, bureaucratic hassles overwhelm.... and we still won't get more than 24 hours to complete any given day's work. But make no mistake about it: it is still a rare privilege (and blessing) to practice the healing art, acting as the true intermediary between this world and the next.

Nobody seriously doubts that American medicine is without compare. However, as the raging health-care debate amply illustrates, underlying problems need to be addressed: rising costs, disparities in access, over-reliance on technology, and of course, universal adoption of evidence-based practice. It is time to abandon our ancient superstitions, such as treating infections for 10 days, "weaning" patients off ventilators, using "low-dose" IV dopamine, ordering daily chest films in ICU patients… I could go on.

As someone who has observed first-hand the practice of medicine in different continents, the American model works best for America, not the British, French, Canadian, German, Israeli- or, perish the thought- the Cuban model. The grass might look a lot greener overseas, but trust me, you still won't get to smoke it in peace.

This monthly newsletter hopes to assist you, the Athens physician, in blowing off the smoke, and exposing new medical insights. Let me know your thoughts.
See you Friday lunch-time, at the CME lounge.

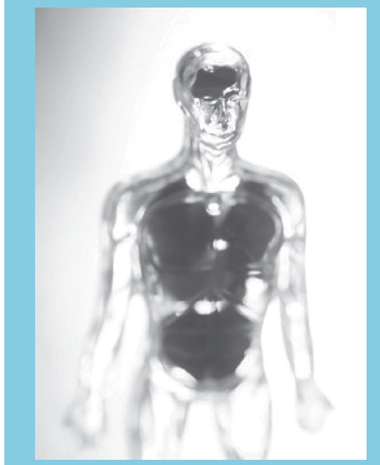
Beze Adogu, MD, Ph.D, FACP

CONSENSUS FROM THE FRONTLINES

Aggrenox (dipyridamole-aspirin 200/25 mg p.o. BID) extends early AV graft patency by 6 weeks in dialysis patients (Dixon et al, NEJM 2009): this benefit will not justify the risk or cost of treatment in our patient population.

PERSPECTIVE: THE BOOGER RULE

Ordering a clinical test is a bit like picking your nose: you have to know what you'd do with the result before you start digging. Consider "boogers" when ordering D-dimers, homocysteine, wound cultures, C2 complement level, plasma iron turnover, et cetera.



A monthly medical newsletter for the Athens medical community

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Protecting Your Kidneys

Chronic kidney disease (CKD) is common, afflicting 1 out of 9 adults, equivalent to 20 million people in the United States. In its extreme form, called end-stage renal disease (ESRD), patients need either long-term dialysis or kidney transplantation to stay alive. There are about 600,000 such people, representing 0.1% of our total population, using up 6% of the entire Medicare budget at a cumulative cost of over $35 billion dollars. But kidney failure can be slowed down or even arrested.

Here are the rules:

1.Control hypertension with BP under 130/80 mmHg
2.Control diabetes with hemoglobin A1c under 6.5%
3.Reduce proteinuria under 1 g/day with either an ACE inhibitor or angiotensin receptor blocker, but do not use both
4.Quit smoking
5.Add an oral statin (target LDL cholesterol under 70 mg/dL)
6.Lose weight (target BMI under 25)
7.Treat anemia (target hemoglobin between 11-12 g/dL)
8.Avoid nephrotoxic drugs and drugs preferentially cleared by the kidneys (especially NSAIDs, narcotics, herbs, tubulotoxic antibiotics, metformin, lithium & neurotropic agents)
9.Avoid hypokalemia (which paradoxically, aggravates interstitial kidney scarring)
10.Consider anti-platelet drugs (at least, start low-dose ASA)
11.Avoid dehydration or hypovolemia (typically from diarrhea, vomiting or polyuria)
12.Promptly treat any UTI

Drug Alert #1

Do not combine both ACE inhibitors (Altace, Prinivil) and angiotensin receptor blockers (Cadesartan, Hyzaar, Diovan): despite improved cardiac outcomes and reduced total proteinuria in such combinations, renal outcomes are paradoxically worse, leading to faster progression to end-stage renal failure (ON TARGET, Salim Yusuf et al, N Engl J Medicine 2008).

Drug Alert #2

Cardiac patients on Clopidogrel (Plavix), a thienopyridine pro-drug, may lose up to 45% of the drug's anti-platelet activity (based on an irreversible block of the platelet P2Y12 ADP receptor) if combined with cytochrome 2C19 inhibitors such as anti-ulcer drugs Omeprazole/Prilosec, cimetidine), anti-fungal drugs ketoconazole, fluconazole, voriconazole), anti-depressants (fluoxetine) and ticlodipine. The available data suggests that Protonix is probably OK. Conversion of Plavix to its active metabolite relies on hepatic cytochrome 2C19 oxidase activity. The 2-step liver-dependent activation of Plavix accounts for its delayed onset of action, variable platelet inhibition, susceptibility to genetic polymorphisms as well as drug-drug interactions. This has made the new triazolopyrimidine anti-platelet drug, Ticagrelor, an attractive option (despite concerns about bronchospasm, bradycardia, hyperuricemia and acute nephropathy).

Hypertensive Crisis

Defined as BP >180/120 (>170/110 in pregnancy), the presence of progressive end-organ damage (brain ischemia/hemorrhage, acute renal failure, encephalopathy, myocardial infarct, aortic dissection, eclampsia, subarachnoid bleed) identifies an "emergency" as opposed to an "urgency".

Treatment should be based on pathophysiology. It is recommended that you choose a few drugs, use them often, know them well.HTN urgencies can be treated in the office/home, with appropriate monitoring, using p.o. medications to slowly reduce BP over 24-48 hrs:

a) Amlodipine 2.5-10 mg p.o. x1
b) Clonidine 0.1-0.4 mg p.o. q 1-2 hrs x 2 doses
c) Labetolol 200-400 mg p.o. q 2 hrs
d) Captopril 25 mg p.o. q 1 hr x 2 doses

HTN emergencies require ICU care with titratable parenteral drugs for immediate BP reduction:

a) Nitroprusside 0.5-2 mcg/kg/min infusion titrated as tolerated (avoid in stroke/intracranial hypertension, liver disease, renal failure, and may worsen cerebral/myocardial ischemia by "steal syndrome")
b) Hydralazine 10 mg IV q 30 mins as needed (acceptable in pregnancy, high risk of tachyphylaxis and lupus syndrome)
c) Fenoldapam 0.1-1.5 mcg/kg/min infusion titrated as needed (avoid in intracranial hypertension/glaucoma and sulfite allergies)
d) Labetolol 1-2 mg/min infusion titrated as needed (ideal for eclampsia)
e) Nicardipine 5-15 mg/hr infusion titrated as needed (common option in stroke and acute MI)
f) Enalaprilat 1.25-5 mg IV q 6 hrs (too slow onset for true "emergency", not in surgical, renal or hypovolemic patient)

Stop the Presses

Early death amongst dialysis patients can be predicted with reasonable accuracy based on 5 independent variables: low albumin, peripheral vascular disease, dementia, old age, response to question ("would you be surprised if this patient died within 6 months?"). Study by Lewis Cohen et al, J American Society Nephrology, December 3, 2009

Paradigm Shift

Using a tunneled/cuffed catheter for chronic dialysis is associated with a 2-3x higher risk of death, 5-10x higher risk of serious infection, as well as higher hospitalization risk and increased likelihood of under-dialysis, when compared to patients using a native AV fistula for dialysis (see Eduardo Lacson et al, American J Kidney Disease, 2009). Therefore, Raheela Rehman et al, Clin J American Society Nephrol 2009, argue that it is both an ethical and legal obligation for doctors to dissuade patients from using long-term dialysis catheters.

Principle of Medicine

Several (environmental) factors are associated with disease, but association does not mean causation. A.B. Hill in Proceedings of Royal Society of Medicine (1965) argued that to prove cause, you must show: specificity of linkage, biologic plausibility, coherence of effect, temporality, consistency of findings, and consideration of alternative explanations.

The Obesity Paradox

Obesity is common, and 70% of the American population are either obese (BMI equal to or above 30) or overweight (BMI 25 to 29.9). Obesity is associated with a higher prevalence of chronic kidney disease (Morales et al, American J Kidney Diseases, 2003) as well as cardiovascular disease as shown in the Renfrew-Paisley study (Murphy et al, European Heart J, 2006). Yet, obesity is paradoxically linked to a better long-term prognosis in both dialysis and cardiac patients.

Checking BNP in Chronic Kidney Disease

BNP is synthesized within left ventricular myocytes as a pro-hormone (pro-BNP), which is split within the circulation into an active C-terminal peptide (BNP) and an inactive N-terminal fragment (NT-proBNP). BNP isremoved from the circulation by binding to its receptor, by neutral endopeptidase enzymes, and kidney clearance. BNP has been found to help diagnose decompensated heart failure in those with unexplained dyspnea, and is prognostic for short-term and long-term outcome in cardiac disease. Levels of BNP are known to correlate with left ventricular mass, presence of coronary/peripheral vascular disease as well as advanced age, and BNP is inversely linked to eGFR (kidney function), anemia and left ventricular ejection fraction. Yet, data from PRIDE as well as BNP studies indicate that even with dialysis-dependent kidney failure, the excess of BNP surge is still linked to cardiac disease, and is therefore still diagnostic as well as prognostic. Surprisingly, despite the near-universal rise in BNP amongst dialysis patients, it does not reflect or predict volume status in CKD, but a high BNP reflects the presence of LVH, low LV ejection fraction, et cetera, and more specifically to dialysis, also reflects the efficiency of dialysis (as measured by Kt/V or URR) and type of dialyzer membrane (Sheen et al, American Heart J, 2007). Therefore, suggested "cut off" levels for BNP are 104 pg/ml for GFR above 60 ml/min (CKD stage I & II), 201 pg/ml for GFR 30-60 ml/min), 225 pg/ml for GFR under 30 ml/min. The **Bottom line: If BNP is above 200 pg/ml, you probably have cardiac disease, irrespective of kidney failure.**