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Reprints in HYPERTENSION

These summaries are reprinted from the Journal Watch series of medical literature-surveillance newsletters. Journal Watch newsletters help clinicians stay informed about the most clinically relevant advances in medicine. Our physician-editors review the medical literature and summarize and provide expert commentary on the most significant research. This issue is a compilation of recent summaries of research in hypertension covered in the Journal Watch newsletters.

Poststroke Blood Pressure Affects Risk for Recurrent Stroke

Risk was elevated with low and high systolic BP.

Risk for a first ischemic stroke is generally proportional to the level of systolic blood pressure (BP), but optimal poststroke BP for prevention of recurrent stroke is less clear. To examine this issue, researchers conducted a post hoc analysis of data from a previously published secondary prevention study that involved about 20,000 patients (mean age, 66; two thirds men) with recent noncardioembolic ischemic stroke (*N Engl J Med* 2008; 359:1225).

The original study addressed the role of various antiplatelet regimens, and BP was managed by investigators at their discretion. Patients were assessed several times during a mean follow-up of 2.5 years, during which the risk for recurrent stroke was about 8%. Compared with patients who had low-normal systolic BP (120–129 mm Hg), risk for recurrent stroke was elevated in patients whose mean systolic BP during the study was very low (<120 mm Hg; 29% relative increase), high (140–149 mm Hg; 23% increase), or very high (≥150 mm Hg; 108% increase); risk with high-normal systolic BP (130–139 mm Hg) was similar to that with low-normal BP. These analyses were adjusted for clinical and demographic factors.

COMMENT

These post hoc analyses are sufficiently strong to support a recommendation to maintain systolic BP in the normal range (120–139 mm Hg) — but not lower — in stroke patients. However, rigorous prospective studies to confirm this conclusion are warranted.

— Thomas L. Schwenk, MD

Originally published in ***Journal Watch General Medicine***

Ovbiagele B et al. Level of systolic blood pressure within the normal range and risk of recurrent stroke. **JAMA** *2011 Nov 16; 306:2137.*

Sodium Excretion of >7 g or <3 g Daily Is Associated with Elevated Cardiovascular Morbidity

By comparison, higher potassium excretion was associated with lower stroke risk.

The WHO recommends daily sodium intake of less than 2 g, based on relatively short trials in which the effect of sodium intake on blood pressure was assessed. In this study, researchers analyzed data for 28,880 patients in two international clinical trials of an angiotensin-receptor blocker; most patients (mean age, 67; 70% men) had histories of myocardial infarction, stroke, hypertension, or diabetes. People with congestive heart failure (CHF), decreased renal function, or uncontrolled hypertension were excluded. Mean daily sodium excretion (a surrogate for sodium intake) was 4.77 g, and daily potassium excretion was 2.19 g.

At 5 years, a composite outcome of cardiovascular mortality, myocardial infarction, stroke, and hospitalization for CHF occurred in 4729 patients. Patients with urinary sodium excretion of 4 to 6 g daily had the lowest risk for the composite outcome. Risk was higher by 21%, 16%, 15%, and 49% for patients with daily excretion of <2 g, 2–3 g, 7–8 g, and >8 g, respectively. Compared with patients who had daily potassium excretion of <1.5 g, risk for stroke was 32% lower in those with excretion of >3 g. These analyses were adjusted for numerous clinical and demographic factors.

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Compiled and published by the Publishing Division of the Massachusetts Medical Society. Send your questions to Journal Watch, 860 Winter Street, Waltham, MA 02451-1413, USA, or e-mail to **JWatch@mms.org**. Information on our conflict-of-interest policy can be found at **JWatch.org/misc/conflict.dtl**.

The 13 newsletters in the Journal Watch series cover cardiology, dermatology, HIV/AIDS, emergency medicine, gastroenterology, general medicine, hospital medicine, infectious diseases, neurology, oncology and hematology, psychiatry, pediatrics and adolescent medicine, and women's health.

COMMENT

This J-shaped relation between sodium intake and cardiovascular outcomes conflicts with current recommendations to limit daily sodium intake to 2 g. However, an editorialist is unconvinced and believes that randomized trials are needed to account for confounding caused by preexisting disease and risk factors. The small number of patients with low sodium intake — 3% of the total sample had urinary excretion <2 g daily — also tempers the results. Consuming a diet high in natural foods and low in processed foods would result in a lower sodium–potassium ratio — which could be more important than the actual intake levels.

— Thomas L. Schwenk, MD

Originally published in ***Journal Watch General Medicine***

O'Donnell MJ et al. Urinary sodium and potassium excretion and risk of cardiovascular events. **JAMA** *2011 Nov 23/30; 306:2229.*

Whelton PK. Urinary sodium and cardiovascular disease risk: Informing guidelines for sodium consumption. **JAMA** *2011 Nov 23/30; 306:2262.*

Postpartum Preeclampsia Requires Prompt Evaluation, Referral, and Treatment

Critical period for developing eclampsia is the first week after discharge.

Although overall incidence of eclampsia has declined with improvements in detection and management of preeclampsia, incidence of delayed postpartum preeclampsia and eclampsia has risen. In a retrospective cohort study in 152 women who were discharged from a Detroit medical center after delivery and then readmitted 2 days to 6 weeks later with diagnoses of preeclampsia, researchers evaluated patient demographics, histories, intra- and postpartum management, symptoms, and complications.

In all, 147 women were black, 88 had vaginal births, and 64 had cesarean deliveries. Ninety-six women had no antecedent diagnoses of hypertensive disease, 7 had gestational hypertension, 14 had chronic hypertension, 28 had peripartum preeclampsia, and 7 had preeclampsia superimposed on hypertension. At readmission, headache was the most common presenting symptom. Most of the 22 women who developed eclampsia (>90%) presented within 7 days of initial discharge. Eclampsia was more common in women who had no antecedent hypertension during pregnancy. Other risk factors for eclampsia included younger age (mean, 23 vs. 28) and lower gravidity (mean, 2 vs. 4).

COMMENT

Women who develop prodromal symptoms (especially headaches) of preeclampsia within the first 6 weeks postpartum require prompt referral, evaluation, and treatment to avert eclampsia. This action is especially important for emergency room physicians and physicians in rural areas with minimal obstetric services. All postpartum women could benefit from counseling before hospital discharge; in particular, they should be encouraged to go to the nearest emergency room or obstetric triage facility if they experience persistent headaches.

— Diane J. Angelini, EdD, CNM, FACNM, FAAN, NEA-BC

Originally published in ***Journal Watch Women's Health***

Al-Safi Z et al. Delayed postpartum preeclampsia and eclampsia: Demographics, clinical course, and complications. **Obstet Gynecol** *2011 Nov; 118:1102.*

Angiotensin-Converting—Enzyme Inhibitors During Early Pregnancy Aren't Significantly Associated with Fetal Malformations

But untreated hypertension was associated with excess risk.

Although angiotensin-converting–enzyme (ACE) inhibitors are teratogenic when used during late pregnancy, early exposure was not thought to be harmful until a 2006 study showed an association between first-trimester use and excess risk for congenital anomalies. Now, investigators have conducted a population-based cohort study in 465,745 mother–infant pairs from a large health plan in California to determine if first-trimester ACE inhibitor exposure is associated with risk for fetal malformations beyond that associated with use of any antihypertensive medication or with hypertension alone.

ACE inhibitors were dispensed in 1.6 per 1000 pregnancies, and other antihypertensives were given in 38 per 1000 pregnancies. In adjusted analysis, use of ACE inhibitors or other antihypertensives only during the first trimester only were associated with higher (but not statistically significant) risk for birth defects in liveborn offspring compared with offspring of normotensive women but not compared with offspring of women who had untreated hypertension. In addition, compared with normotensive women, those with untreated hypertension at any time from 1 year before pregnancy through delivery had significantly higher risk for offspring with birth defects (odds ratio, 1.2): specifically, congenital heart disease (OR, 1.4) and neural tube defects (OR, 1.4).

COMMENT

As noted by the authors, the comparison groups in this study enabled researchers to "examine and disentangle the pharmacological effect of antihypertensive drugs from the effect of underlying hypertension, which was associated with significantly higher risk for anomalies. However, as is common, only live births were assessed. Because the demographics of women who used ACE inhibitors differed from those of the comparator groups, one group might have chosen pregnancy terminations for anomalies more often than another. Still, these findings

indicate that women of reproductive age can remain candidates for this effective class of antihypertensives.

— *Allison Bryant, MD, MPH*

Originally published in ***Journal Watch Women's Health***

Li D-K et al. Maternal exposure to angiotensin converting enzyme inhibitors in the first trimester and risk of malformations in offspring: A retrospective cohort study. **BMJ** *2011 Oct 18; 343:d5931.*

Nifedipine vs. Labetalol for Managing Acute Hypertension of Pregnancy

Oral nifedipine and intravenous labetalol were similarly effective.

Acute control of dangerously high blood pressure (BP) during late pregnancy is critical to good maternal and neonatal outcomes. Investigators in Malaysia conducted a randomized, double-blind trial in 50 pregnant women at ≥24 weeks' gestation with sustained, severe hypertension (defined as ≥160 mm Hg systolic or ≥110 mm Hg diastolic BP measured at least twice within 4 hours) to evaluate efficacy of oral nifedipine (10-mg tablets) versus intravenous labetalol (5 mg/mL). Initial treatments were 10-mg nifedipine plus intravenous placebo or 20-mg labetalol plus oral placebo tablet. Doses were repeated (for nifedipine [maximum cumulative total, 5 tablets]) or escalated (for labetalol [maximum individual dose, 80 mg; maximum cumulative total, 300 mg]) at 15-minute intervals as needed to reach target BPs of ≤150 mm Hg systolic and ≤110 mm Hg diastolic. If target BP was not achieved with 5 dosing cycles, crossover to the other regimen was initiated and continued for as many as 5 cycles; subsequent failure to control BP resulted in open-label treatment of the provider's choice.

Median time to achieve target BP was 30 minutes for nifedipine and 45 minutes for labetalol, a difference that was not statistically significant. Crossover treatment was required in 20% of participants in each group. Mean maternal heart rate rose substantially during the first hour of treatment in the nifedipine group (from 90 to 104 beats per minute). Overall, BP target levels were achieved in 80% of cases within 5 doses or within 75 minutes following treatment initiation. Fetal heart rate remained consistent during the first hour in both groups.

COMMENT

Both oral nifedipine and intravenous labetalol are effective for rapid treatment of severe hypertension in pregnancy. In this study, the starting dose of labetalol was 20 mg, a substantial difference from that in protocols that start at 10 mg. Given that magnesium sulfate is commonly administered to women with preeclampsia, the potential for drug interactions should be considered. Concurrent nifedipine and magnesium sulfate have adverse effects (e.g., severe hypotension, although data are inconsistent), and maternal blood pressure did not drop below 90/60 mm Hg in the present study. **— *Diane J. Angelini, EdD, CNM, FACNM, FAAN, NEA-BC***

Originally published in ***Journal Watch Women's Health***

Raheem IA et al. Oral nifedipine versus intravenous labetalol for acute blood pressure control in hypertensive emergencies of pregnancy: A randomised trial. **BJOG** *2011 Oct 10; 119:78.*

Prehypertension and the Continuum of Stroke Risk

Prehypertension, especially in the higher range, is associated with incident stroke.

To assess whether so-called prehypertension is associated with incident stroke, researchers conducted a meta-analysis of prospective cohort studies. The analysis included 518,520 participants from 12 studies originating in the U.S., China, Japan, and India. Prehypertension was defined as systolic blood pressure of 120–139 mm Hg or diastolic blood pressure of 80–89 mm Hg. In seven of the studies, prehypertension was further subdivided into a low range (120–129 mm Hg systolic or 80–84 mm Hg diastolic) and a high range (130–139 mm Hg systolic or 85–89 mm Hg diastolic).

Overall, prehypertension was associated with a significantly increased risk for stroke (relative risk, 1.55) that was driven by higher-range prehypertension (RR, 1.79). Lower-range prehypertension was not significantly associated with increased stroke risk. In subgroup analyses by baseline characteristics, the association was not affected by race/ethnicity, stroke endpoint (fatal vs. all stroke), stroke subtype (ischemic vs. hemorrhagic), or follow-up duration (<10 vs. ≥10 years). The association did not remain significant for people older than 65 and when study quality was only "fair."

The authors conclude that prehypertension, especially in the higher range, is associated with incident stroke.

COMMENT

Hypertension is associated with stroke on a continuum of risk (*Lancet Neurol* 2002; 1:149). For example, mild, moderate, and severe hypertension are all associated with stroke risk, with the highest relative risk for stroke among those with the highest blood pressure, and the greatest absolute number of strokes in those with mild or "high-normal" blood pressure, a designation that includes prehypertension. The current findings support the concept of a continuum of risk for stroke with increasing blood pressure, especially among patients with higher-range prehypertension. However, whether lowering blood pressure in the

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prehypertension range will reduce stroke risk remains uncertain; this hypothesis deserves additional efficacy, safety, and cost-effectiveness testing. Currently, rigorous lifestyle modification is recommended for people with prehypertension. A blood pressure target <130/80 mm Hg has been recommended for those with, for example, diabetes mellitus, chronic renal disease, or carotid artery disease and for those with 10-year Framingham risk scores of ≥10% (*Circulation* 2007; 115:2761).

— *Philip B. Gorelick, MD, MPH*

Originally published in ***Journal Watch Neurology***

Lee M et al. Presence of baseline prehypertension and risk of incident stroke: A meta-analysis. **Neurology** *2011 Oct 4; 77:1330.*

Even with Anticoagulation Therapy, Higher $CHADS_2$ Scores Predict Worse Outcomes

In a RE-LY substudy, the correlation was present and similar in all treatment arms.

The $CHADS_2$ (Congestive heart failure, Hypertension, Age ≥75, Diabetes, Stroke history [2 points]) risk score for stroke was validated in patients with atrial fibrillation (AF) who were not treated with an anticoagulant. To evaluate $CHADS_2$ as a predictor of stroke in AF patients taking anticoagulants, investigators conducted subgroup analyses of data from the RE-LY trial of dabigatran versus warfarin in patients with AF (*N Engl J Med* 2009; 361:1139).

Dividing the RE-LY cohort (>18,000 patients) into rough tertiles according to $CHADS_2$ score resulted in three subgroups with scores of 0–1, 2, and 3–6, respectively. Baseline characteristics differed significantly among the subgroups; of patients with $CHADS_2$ scores of 3–6, >90% had hypertension, and m ost had a history of stroke or transient ischemic attack or were aged ≥75. Mean percentage of time in therapeutic range (TTR) with warfarin fell slightly but significantly with higher $CHADS_2$ scores. Overall, the annual rate of stroke or systemic embolization (the primary outcome) increased significantly with each 1-point increase in $CHADS_2$ score, as did the annual rates of major bleeding and vascular mortality. Patients with a $CHADS_2$ score of 3 or higher had a >2% annual risk for stroke or systemic embolization, a >4% annual risk for major bleeding, and a >5% annual risk for all-cause death, regardless of anticoagulant type. The reduction in stroke or systemic embolization with 150-mg dabigatran compared with warfarin was consistent across the $CHADS_2$ risk groups.

COMMENT

A $CHADS_2$ score of 3 or higher identifies patients with both the most to gain and the most to lose with anticoagulation therapy. In the RE-LY trial, the benefit of dabigatran compared with warfarin was lowest in older patients and in those with high TTR percentages when on warfarin (*Lancet* 2010; 376:975). All of these factors should be considered when assessing the need for and type of anticoagulation treatment in AF patients. **— *Joel M. Gore, MD***

Originally published in ***Journal Watch Cardiology***

Oldgren J et al. Risks for stroke, bleeding, and death in patients with atrial fibrillation receiving dabigatran or warfarin in relation to the $CHADS_2$ Score: A subgroup analysis of the RE-LY trial. **Ann Intern Med** *2011 Nov 15; 155:660.*

Beyth RJ and Landefeld CS. Learning the respective roles of warfarin and dabigatran to prevent stroke in patients with nonvalvular atrial fibrillation. **Ann Intern Med** *2011 Nov 15; 155:714.*

Reversing the Adverse Cardiovascular Effects of Childhood Obesity Later in Life

Results of four large long-term studies indicate that adults who were obese during childhood can lower their cardiovascular risk by not being obese as adults.

Childhood obesity raises risk for obesity and cardiovascular disease during adulthood. To examine whether cardiovascular risks persist in obese children who are no longer obese as adults, researchers combined data from four longitudinal cohort studies (2 U.S., 1 Australian, and 1 Finnish) in which cardiovascular risk was tracked from childhood into adulthood in 6328 participants. Mean follow-up was 23 years, and adiposity status was based on body-mass index (BMI) measurements taken during childhood and adulthood.

Obese adults — regardless of childhood adiposity status — had significantly higher risk for hypertension, dyslipidemia, and type 2 diabetes mellitus than did participants who had never been obese as children or adults. However, normal-weight adults — regardless of childhood adiposity status — had similar cardiovascular risk as participants who had never been obese. Results were similar for men and women when different definitions of childhood adiposity were used.

COMMENT

These results suggest that obese children can lower their risk for cardiovascular disease if they achieve normal BMIs as adults. Therefore, it's never too late to encourage healthy lifestyles in our patients. We must identify the most effective interventions for preventing and treating childhood obesity as well as for helping patients maintain healthy weight as adults. As stated by an editorialist, "treating and preventing childhood obesity is a cost-effective way of achieving a long-term reduction in atherosclerotic cardiovascular disease."

— *Louis M. Bell, MD*

Originally published in ***Journal Watch Pediatrics and Adolescent Medicine***

Juonala M et al. Childhood adiposity, adult adiposity, and cardiovascular risk factors. **N Engl J Med** *2011 Nov 17; 365:1876.*

Rocchini AP. Childhood obesity and coronary heart diseases. **N Engl J Med** *2011 Nov 17; 365:1927.*

What If MI Patients Got Their Follow-Up Meds for Free?

In a cluster-randomized study, improvement in adherence — and in some outcomes — was significant but small.

Prescription of evidence-based medications after acute myocardial infarction (AMI) has increased substantially over the past decade. However, prescription does not ensure benefit; patients must obtain and take the drugs. In this study, sponsored by a large U.S. commercial insurer, investigators assessed full prescription coverage for evidence-based drug therapy following AMI in 5855 patients (mean age, 54; 75% men). Participants were randomized at the level of the health-plan sponsor to either full or usual coverage for angiotensin-converting–enzyme (ACE) inhibitors, angiotensin-receptor blockers (ARBs), beta-blockers, and statins.

Average monthly co-payments in the usual-coverage group were $13.35 for ACE inhibitors or ARBs, $12.83 for beta-blockers, and $24.92 for statins. At a median follow-up of 394 days, the rate of the primary outcome — first major vascular event or revascularization — was 17.6% per 100 person-years with full coverage and 18.8%

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- Mild to Moderate Hypertension[3]

Important Outcomes in patients with

- Hypertension and LVH in LIFE[4]
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*FORTZAAR 100/25 mg should not be administered as the initial dose.
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When pregnancy is detected, treatment should be discontinued as soon as possible. Not to be used in pregnancy as teratogenicity has been shown in experimental animals. Women of child-bearing age should ensure adequate contraception.

REFERENCES: 1. Salerno C, Demopoulos L. Combination angiotensin receptor blocker/hydrochlorothiazide as initial therapy in the treatment of patients with severe hypertension. J Clin Hypertens. 2004; 6:614–620. 2. Cushman WC, Brady WE, Gazdick LP, Zeldin RK. The effect of a losartan-based regimen on isolated systolic hypertension. J Clin Hypertens. 2002;4:101–107. 3. Monterroso VH, Chavez VR, Carbajal ET, et al, for the Losartan Trial Investigators. Use of ambulatory blood pressure monitoring to compare antihypertensive efficacy and safety of two angiotensin II receptor antagonists, losartan and valsartan. Adv Ther. 2000;17:117–131. 4. Dahlöf B, Devereux RB, Kjeldsen SE, et al. Cardiovascular morbidity and mortality in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. Lancet. 2002;359:995–1003. 5. Brenner BM, Cooper ME, de Zeeuw D, et al, for the RENAAL Study Investigators. Effects of losartan on renal and cardiovascular outcomes in patients with type 2 diabetes and nephropathy. N Engl J Med. 2001;345:861–869.

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Reference: Torgerson JS, Boldrin MN, Hauptman J, Sjöström L. Xenical in the Prevention of Diabetes in Obese Subjects (XENDOS) Study. A randomized study of Orlistat as an adjunct to lifestyle changes for the prevention of type 2 diabetes in obese patients. *Diabetes Care* 2004; 27(1): 155 – 161.

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CLINICAL PRACTICE GUIDELINE WATCH

Focused Update: ACC/AHA Guidelines on Peripheral Arterial Disease

Revised recommendations emphasize early detection of PAD, prevention of cardiovascular events, and the equivalence of surgical and endovascular revascularization.

Sponsoring Organizations: American College of Cardiology, American Heart Association, Society for Cardiovascular Angiography and Interventions, Society of Interventional Radiology, Society for Vascular Medicine, Society for Vascular Surgery

Background and Purpose: Changes to recommendations for the management of lower-extremity arterial and abdominal aortic disease reflect clinical-study evidence published since completion of the 2005 guidelines. The 2005 recommendations regarding renal and mesenteric arterial disease remain unchanged in the absence of new pivotal studies of disease in these segments.

Key Points:

1. Because peripheral arterial disease (PAD) is often underdiagnosed and undertreated before limb ischemic symptoms become severe, **an ankle–brachial index (ABI) should now be obtained in all nondiabetic patients with suspected lower-extremity PAD who are aged ≥65,** rather than ≥70, as previously recommended (Class I).

2. **The range of normal ABI values is defined as 1.0 to 1.4, and the range of abnormal values as ≤0.9.** ABI values >1.4 indicate noncompressible arteries, and values of 0.91 to 0.99 are considered borderline (Class I).

3. No prospective, randomized, controlled trials have examined the effects of smoking-cessation strategies on cardiovascular events in patients with lower-extremity PAD. However, observational studies show that 5.0% of smoking-cessation attempts involving physicians are successful, compared with 0.1% of attempts in individuals who try to quit spontaneously. Therefore, **the recommendations for smoking-cessation interventions have been expanded:**

- The novel agent varenicline demonstrated superior smoking-cessation rates in several randomized, controlled comparisons with nicotine replacement and bupropion (which yield 1-year quit rates of 16% and 30%, respectively) and is now recommended (Class I).
- Caution is advised in the use of bupropion or varenicline, which have been associated with reports of changes in behavior, such as hostility, agitation, depressed mood, and suicidal thoughts.

4. The Class I recommendation for clopidogrel as an alternative to aspirin therapy is unchanged. However, a Class IIb recommendation to consider the combination of aspirin and clopidogrel in patients with symptomatic lower-extremity PAD has been added.

5. Additional evidence has bolstered the Class III recommendation against the use of anticoagulation therapy in addition to antiplatelet therapy in PAD patients.

6. Long-term follow-up shows no significant difference in outcomes of open surgery versus balloon angioplasty, either in amputation-free or overall survival in patients with critical limb ischemia or in rates of overall and aneurysm-related morbidity and mortality in patients with abdominal aortic aneurysm. Lower procedural mortality with endovascular aneurysm repair was not sustained; thus, clinicians should choose the method of aneurysm repair that is deemed to be most appropriate for individual patients.

COMMENT

Since 2005, the major advances in the management of peripheral arterial disease are in its prevention, particularly smoking cessation, for which several viable options are now available. Equally important is diagnosing PAD at an early stage; therefore, ankle–brachial indexes should be obtained regularly in all individuals older than 65. Finally, endovascular repair and surgery appear to provide equivalent outcomes for patients with PAD, so individual patient factors should be paramount in making revascularization decisions.

ADDENDUM

The guideline authors reviewed all evidence available through the end of 2010. Several reports published since then have heightened doubts about the safety of varenicline, which has been associated with possible cardiovascular effects (*CMAJ* 2011; 183:1359) as well as with behavioral and mood effects (*PLoS ONE* 2011; 6:e27016). This evidence suggests that varenicline should be moved to the back of the clinician's arsenal of pharmacologic therapies for smoking cessation. **— *Joel M. Gore, MD***

Originally published in ***Journal Watch Cardiology***

Rooke TW et al. 2011 ACCF/AHA Focused update of the guideline for the management of patients with peripheral artery disease (updating the 2005 guideline): A report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. **J Am Coll Cardiol** *2011 Nov 1; 58:2020.*

per 100 person-years with usual coverage (P=0.21). However, the rate of total major vascular events or revascularization was significantly lower in the full-coverage group than in the usual-coverage group (21.5% vs. 23.3%; P=0.03). Adherence rates for specific medication types ranged from 36% to 49% in the usual-coverage group and were significantly higher by 4% to 6% in the full-coverage group; adherence to all three medications was 44% in the full-coverage group and 39% in the usual-coverage group. Patient costs for drugs and other services during follow-up were significantly lower with full coverage than with usual coverage (by almost $500, or 26%); total spending did not differ significantly between the groups ($66,008 and $71,778 with full and usual coverage, respectively).

COMMENT

Despite this study's failure to demonstrate benefit with respect to the primary endpoint, full secondary-prevention prescription coverage after MI seems compelling: it increases adherence, reduces patient costs, does not increase overall costs, and may improve some outcomes. These findings should convince payers to rethink the structure of their benefit plans. Also notable are the atrocious adherence rates among insured patients, even with no out-of-pocket costs. As editorialists note, much more than innovative insurance design is required to get patients to take their pills.

— Frederick A. Masoudi, MD, MSPH, FACC, FAHA

Originally published in ***Journal Watch Cardiology***

Choudhry NK et al. for the Post-Myocardial Infarction Free Rx Event and Economic Evaluation (MI FREEE) Trial. Full coverage for preventive medications after myocardial infarction. **N Engl J Med** *2011 Dec 1; 365:2088.*

Goldman L and Epstein AM. Improving adherence — Money isn't the only thing. **N Engl J Med** *2011 Dec 1; 365:2131.*

Peripartum Cardiomyopathy: Who's at Risk?

Women 40 or older, certain racial and ethnic minorities, and those with severe anemia had greater likelihood of developing heart failure during pregnancy.

Peripartum cardiomyopathy (heart failure without any alternate etiology during late pregnancy or the puerperium) is associated with substantial risk for maternal death. In addition, this condition can recur; therefore, having accurate information about which women are at risk is important for obstetric and women's health providers alike. Investigators at Kaiser Permanente of Northern California conducted a 10-year retrospective study of its large, diverse obstetric cohort to explore risk factors for peripartum cardiomyopathy.

Incidence of confirmed cases of peripartum cardiomyopathy was 4.8 per 10,000 live births. Mortality among cases was 6.1 per 1000 person-years, 27 times that of women without cardiomyopathy. Women of black, Filipino, and Hispanic backgrounds were at excess risk, as were women of parity ≥4 and those who were 40 or older. Notable independent risk factors included severe anemia, multiple gestations, and hypertensive disorders of pregnancy. Neonatal outcomes associated with maternal cardiomyopathy included preterm birth, 5-minute Apgar scores ≤6, and death.

COMMENT

The incidence of peripartum cardiomyopathy in these participants is higher than has been reported in U.S. population-based studies. Although the current sample might not represent the U.S. population, this well-conducted study provides some additional insight into this condition. With readily available echocardiography, we should consider lowering our screening threshold for this dire pregnancy complication when clinical suspicion arises, particularly among women at high risk. Women with histories of peripartum cardiomyopathy should be evaluated for cardiac function at least 6 weeks postpartum. Those with persistent left ventricular dysfunction are at high risk for progression and should be advised to avoid future pregnancies; contraceptive needs should be addressed in such women. Strategies to mitigate risk for cardiomyopathy (e.g., antihypertensive therapy, prophylactic transfusion for marked but asymptomatic anemia) should be targets for future exploration.

— Allison Bryant, MD, MPH

Originally published in ***Journal Watch Women's Health***

Gunderson EP et al. Epidemiology of peripartum cardiomyopathy: Incidence, predictors, and outcomes. **Obstet Gynecol** *2011 Sep; 118:583.*

Xanthelasmata Signals Excess Risks for Ischemic Vascular Disease and Death

No such association was found for arcus senilis corneae.

Both xanthelasmata (yellow plaques on the upper and low eyelids) and arcus senilis corneae (gray-yellow opacity near the periphery of the cornea; also known as arcus senilis) are rich in lipids. In this prospective population-based cohort study, Danish investigators determined whether xanthelasmata, arcus corneae, or both predicted risks for ischemic vascular disease and death.

Nearly 13,000 people (age range, 20–93) who were free of ischemic vascular disease at enrollment in 1976 to 1978 were followed until 2009 (average follow-up, 22 years). At baseline, 4% had xanthelasmata, and 25% had arcus corneae. After adjustment for multiple potential confounders, people with xanthelasmata had significantly higher risks for myocardial infarction (odds ratio, 1.5), ischemic heart disease (OR, 1.4), severe atherosclerosis (OR, 1.7), and death (OR, 1.1) than people without xanthelasmata. In contrast, people with arcus corneae did not have higher risk for death than people without arcus corneae.

COMMENT

In this study, xanthelasmata, but not arcus corneae, was an independent predictor of adverse cardiovascular outcomes and death. These results suggest that patients with xanthelasmata require aggressive management of modifiable cardiovascular risk factors.

— Paul S. Mueller, MD, MPH, FACP

Originally published in ***Journal Watch General Medicine***

Christoffersen M et al. Xanthelasmata, arcus corneae, and ischaemic vascular disease and death in general population: Prospective cohort study. **BMJ** *2011 Sep 15; 343:d5497.*

Got Heart Disease? Don't Be Depressed

Even in relatively young people, depression and suicidality can worsen outcomes from ischemic heart disease.

Depression is known to be a risk factor for bad outcomes of ischemic heart disease (IHD) in older people, but less is known about its impact on cardiac disease in younger people. In this study, researchers used a national mortality database to determine survival of 7641 people who had undergone structured diagnostic interviews a median of 15 years earlier (at a mean age of 28) as part of a national survey of health and nutrition.

At baseline, 5.4% of the group had a lifetime history of unipolar depression, and 1.6% had a lifetime history of bipolar depression; 5.5% reported a previous suicide attempt. At follow-up, 51 participants had died from cardiovascular disease (IHD, 28). After adjustment for age, sex, and traditional IHD risk factors, death from IHD was significantly more likely to occur in those with a history of depression (relative risk, 3.7), attempted suicide (RR, 7.1), or both (RRs: men, 3.5; women, 14.6).

COMMENT

Depression and suicide attempts have an obvious impact on health behaviors and adherence to medical treatment. Beyond that,

the link between depression and suicide attempt and IHD death may be mediated by physiologic factors such as decreased heart rate variability (an indication of autonomic dysfunction), hypercortisolemia, and inflammation (*Am J Psychiatry* 2011; 168:913, and *JAMA* 2008; 300:2379). Whatever the intervening factors, clinicians should assess even young depressed or suicidal patients carefully for IHD, and evaluate cardiac patients for depression and suicide risk. **— *Steven Dubovsky, MD***

Originally published in ***Journal Watch Psychiatry***

Shah AJ et al. Depression and history of attempted suicide as risk factors for heart disease mortality in young individuals. **Arch Gen Psychiatry** *2011 Nov; 68:1135.*

Are Human Papillomavirus Infection and Cardiovascular Disease Linked?

Survey data in women showed a statistical association between HPV positivity and cardiovascular disease, but causality is unlikely.

Despite many recognized risk factors for cardiovascular disease (CVD) in women, variability in risk remains largely unexplained. Investigators hypothesized that human papillomavirus (HPV) infection could contribute to cardiovascular disease, given that oncogenic viral proteins induce degradation of the tumor-suppressor protein p53, and inactivation of p53 has been associated with atherosclerosis. To test this hypothesis, they examined National Health and Nutrition Examination Survey data from 2450 women (age range, 20–59; mean age, 38) who provided self-collected vaginal swabs for HPV testing.

Forty-seven percent of the cohort was positive for HPV DNA. Of 60 women who reported experiencing myocardial infarctions or strokes, 65% were HPV positive. In various models that included demographic, clinical, and management-related CVD factors, risk for CVD remained significantly higher in HPV-positive women than in HPV-negative women (odds ratios, 2.3 for all HPV genotypes and 2.9 for oncogenic genotypes).

COMMENT

Given that human papillomavirus does not cause viremic infection, HPV proteins should not affect vascular endothelium; thus, the biological mechanism of this association is unclear. Despite their elegant models, the authors were unable to control for pivotal potential confounders (especially low socioeconomic status, which is associated with both HPV infection and cardiovascular disease); and statistically significant associations do not necessarily indicate causal relations. This paper received considerable media coverage, but I think the most appropriate course is to reassure concerned HPV-positive women.

— *Anna Wald, MD, MPH*

Originally published in ***Journal Watch Women's Health***

Kuo H-K and Fujise K. Human papillomavirus and cardiovascular disease among U.S. women in the National Health and Nutrition Examination Survey, 2003 to 2006. **J Am Coll Cardiol** *2011 Nov 1; 58:2001.*

Suboptimal Control of HIV Is Associated with Poor Control of Comorbidities

Poor adherence to treatments is likely the key factor behind the association.

Many HIV-infected individuals on antiretroviral therapy (ART) are now living long enough to experience age-related health problems (*Clin Infect Dis* 2011; 53:1120). Controlling these conditions simultaneously is a challenge and requires strict adherence to multiple treatment regimens. In the present study, researchers hypothesized that patients with better control of their HIV infection would also have better control of their hypertension or diabetes.

The study included 291 patients with hypertension and 70 with diabetes who were being treated for these conditions, were receiving ART, and were being followed at the Johns Hopkins HIV Clinic. The study population was predominantly male and black, with a mean age of 45 and a median CD4 count of 256 cells/mm^3 at enrollment. Comorbidities were highly prevalent: 55% of patients had hepatitis C coinfection, 43% had a history of injection-drug use, and 40% had active psychiatric diagnoses.

Control of HIV, diabetes, and blood pressure were assessed by viral load, HbA_{1c} level, and mean arterial blood pressure measured within 30 days of each other. In a multivariate analysis, the higher a patient's viral load was, the higher his HbA_{1c} level or mean arterial blood pressure: Each 1-log increase in viral load was associated with a 0.47-log increase in HbA_{1c} among diabetic patients and a 1.95-mm-Hg increase in mean arterial pressure among hypertensive patients.

COMMENT

This study shows a direct correlation between poor virologic control and poor control of diabetes and hypertension. As noted by the authors, control rates for these two conditions are suboptimal in the general population as well, and adherence to recommended treatments is a key factor. The dramatic improvements in virologic control previously reported from the Johns Hopkins HIV clinic (*Clin Infect Dis* 2011; 53:600) demonstrate that optimal adherence levels *can* be achieved in patient populations that are typically difficult to manage. The key now is to expand HIV clinic–based adherence programs (which often include key wraparound services, such as case management and pharmacy services) to encompass management of comorbid conditions as well. Unfortunately, new funds to support such expansion are likely to be limited in the present economic climate.

— *Keith Henry, MD*

Originally published in ***Journal Watch HIV/AIDS Clinical Care***

Monroe AK et al. Control of medical comorbidities in individuals with HIV. **J Acquir Immune Defic Syndr** *2011 Dec 15; 58:458.*

HIV and Clinical Manifestations of Accelerated Aging

As HIV-infected patients live longer, more are developing chronic diseases typical of aging — but they appear to be doing so earlier and at a higher rate than the general population.

Since the advent of potent antiretroviral therapy (ART), the primary causes of morbidity and mortality among HIV-infected patients have shifted from AIDS-related illnesses to the chronic noncommunicable conditions typically associated with aging. Two research groups recently described the epidemiology of these conditions in HIV-infected patients.

Guaraldi and colleagues evaluated the prevalence of noninfectious comorbidities among 2854 HIV-infected patients receiving ART in Italy (mean age, 46; 71% with undetectable viral loads; median duration of infection, 16 years; median nadir CD4 count, 170 cells/mm^3; median current CD4

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count, 520 cells/mm^3) and 8562 HIV-uninfected controls matched for age and sex. Compared with the controls, the HIV-infected patients had a higher prevalence of renal failure, bone fracture, and diabetes in every age range evaluated (≤40, 41–50, 51–60, and >60), as well as a higher prevalence of cardiovascular disease and hypertension at ages ≤60. They were also more likely, across all age strata, to have at least two of these conditions simultaneously (which the authors describe as "polypathology"). Of note, the HIV-infected patients appeared to develop polypathology at a younger age than controls, such that a 40-year-old HIV-infected patient had a risk similar to that of a 55-year-old HIV-uninfected person. Among HIV-infected patients, polypathology was significantly associated with increasing age, male gender, nadir CD4 count <200 cells/mm^3, lipoatrophy, and lipohypertrophy.

In a separate study, Hasse and colleagues evaluated the incidence of AIDS-related and non–AIDS-related events among 8444 patients who were followed in the Swiss HIV Cohort Study between 2008 and 2010 (median age, 45; median nadir CD4 count, 190 cells/mm^3; median current CD4 count, 528 cells/mm^3). Approximately 30% of study participants were female, 23% had a prior AIDS diagnosis, and 69% had undetectable viral loads. During follow-up, there were 100 new AIDS-related events in the cohort versus 994 new non-AIDS events, including 39 strokes, 55 myocardial infarctions, 70 cases of diabetes, 115 non–AIDS-defining malignancies, and 160 fractures. Each of these non-AIDS conditions was significantly more common after age 50, even after adjustment for factors related to HIV disease progression and the development of comorbidities.

COMMENT

Many people still believe that HIV infection is confined to young adults, but the patients in these two cohorts were decidedly middle-aged — and experiencing all the same chronic conditions as their uninfected peers, though perhaps at a younger age and greater frequency. Soon, more than half of our HIV-infected patients will be older than 50, which means that as HIV clinicians, we'll be spending an increasing amount of time providing primary care. As Hecht and colleagues noted back in 1999 (*Ann Intern Med* 1999; 131:136), "optimal care of HIV infection requires a combination of disease-specific expertise and primary care skills and organization." Now may be the time for many of us to take a refresher course in primary care for the HIV provider. ***— Carlos del Rio, MD***

Originally published in ***Journal Watch HIV/AIDS Clinical Care***

Guaraldi G et al. Premature age-related comorbidities among HIV-infected persons compared with the general population. **Clin Infect Dis** *2011 Dec 1; 53:1120.*

Hasse B et al. Morbidity and aging in HIV-infected persons: The Swiss HIV Cohort Study. **Clin Infect Dis** *2011 Dec 1; 53:1130.*

Saag MS. HIV now firmly established in the middle ages. **Clin Infect Dis** *2011 Dec 1; 53:1140.*