Update in Cardiology: Evidence Published in 2013

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This update summarizes key articles in cardiovascular disease (CVD) published in 2013 (and 1 published on 14 January 2014 that explains reasons for disagreement with another article). These reports were selected because of their potential effect on clinical practice. Specifically, they foster the American College of Physicians’ “high-value care” initiative to encourage physicians to focus on diagnostic and management strategies that balance clinical benefit with cost and harm with the goal of improving patient outcomes. Advances were particularly significant in the fields of hypertension, with multiple new guidelines for management focusing on prevention and anticoagulation to prevent stroke in atrial fibrillation (AF). The year was notable: The percentage of patients with hypertension control increased, and a new procedure for treatment-resistant hypertension and new guidelines to reduce risk for CVD, stroke, heart failure, AF, and diabetes were added.

Hypertension

Characteristics of Patients With Treatment-Resistant Hypertension

Background: Strategies to prevent CVD adverse outcomes are critical. Hypertension is the most prevalent and modifiable risk factor for most CVD, which includes coronary artery disease; cerebrovascular disease, such as stroke and transient ischemic attack; heart failure; peripheral arterial disease; AF; and the related disorders of diabetes and chronic kidney disease (CKD). Although hypertension can be controlled with lifestyle changes and drugs in most patients, a better understanding of those with treatment-resistant hypertension represents a significant unmet need. NHANES (National Health and Nutrition Examination Survey) found that patients with uncontrolled blood pressure (BP) who take 3 or more medications (which is defined as apparent treatment-resistant hypertension) make up approximately 30% of all patients with uncontrolled BP (1). However, the characteristics of patients who received optimal-dose medications in practice were unknown.

Findings: The proportion of patients with apparent treatment-resistant hypertension who receive “optimal therapy” (a diuretic and ≥2 other BP medications at ≥50% of the maximum recommended doses) and clinical factors associated with optimal therapy were determined from electronic medical records of an Outpatient Quality Improvement Network of more than 200 community-based clinics. Treatment adherence and measurement artifacts were not available. Approximately 500,000 patients with hypertension met inclusion criteria. A BP less than 140/90 mm Hg defined “control,” and 31.5% of patients were “uncontrolled.” Among these patients, 30% were prescribed 3 or more BP medications but only 15% were prescribed optimal therapy. Factors associated with optimal therapy included black race, CKD, diabetes, and a risk status equal to that for coronary heart disease. Optimal therapy was prescribed more often when coronary heart disease risk was greater and treatment goals were lower. Only 1 in 7 of all patients with uncontrolled BP and 1 in 2 of those with apparent treatment-resistant hypertension were prescribed 3 or more BP medications in optimal regimens, emphasizing the need for additional therapies.

Cautions: Although evidence shows that better BP control translates to improved outcomes, no outcome evidence was presented to indicate that prescribing more optimal pharmacologic regimens improved outcomes in apparent treatment-resistant hypertension.

Implications: Approximately 30% of treated uncontrolled patients have apparent treatment-resistant hypertension, but one half of them have not been prescribed an optimal regimen. For this suboptimally treated group, treatment optimization could improve BP and reduce risk. Novel therapies are needed for persons using optimal regimens.

New Hypertension Management Guidelines: Consensus or Points of View?


Background: The 2003 Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure hypertension guidelines needed to be updated. The European Society of Hypertension and European Society of Cardiology (2) and
the American Society of Hypertension and International Society of Hypertension also released new guidelines (3).

Findings: The Eighth Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure guidelines include recommendations and a treatment algorithm for evidence-based BP management. Of note:

The BP goal should be less than 150/90 mm Hg in the general population aged 60 years or older.

For patients younger than 60 years, treat to a systolic BP (SBP) less than 140 mm Hg and diastolic BP (DBP) less than 90 mm Hg.

For patients aged 18 years or older with CKD and diabetes, the BP goal should be less than 140/90 mm Hg (because of insufficient evidence for lower goals among patients with CKD aged 70 years or older as well as persons with diabetes).

For initial therapy, use thiazide-type diuretics, calcium-channel blockers, and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers.

For black patients, including those with diabetes, the recommended first-line therapy is a thiazide-type diuretic or calcium-channel blocker. For adults with CKD, regardless of race or diabetes status, an angiotensin-converting enzyme inhibitor or angiotensin-receptor blockers should be included.

If the BP goal is not achieved 1 month after initial therapy, increase the dose or add a second class of drug. Add a third class of drug if needed. If drugs in 3 recommended classes do not produce the BP goal or the patient has contraindications, a drug in a nonrecommended class may be added. If the BP goal still cannot be attained or the patient is complex, refer to a hypertension specialist.

Caution: These recommendations differ from European Society of Cardiology/European Society of Hypertension and American Society of Hypertension/International Society of Hypertension guidelines and contain a treatment algorithm that is not validated to reduce adverse outcomes. The reasons that some committee members disagreed with several of the recommendations were summarized by Wright and colleagues. Increasing the SBP target to less than 150 mm Hg will probably reduce the intensity of antihypertensive treatment in a large population at high risk for CVD, including black persons, those with risks aside from diabetes and CKD, and those with clinical CVD, which will probably increase BP in this population. Also, increasing the SBP target will keep nearly half the untreated patients aged 60 years or older from being treated. Wright and colleagues wrote, "... on the basis of absolute risk, using an age threshold of 60 years to define eligibility for less aggressive treatment lacks consistency."

Furthermore, the recommendation to increase the SBP target to 150 mm Hg in patients aged 60 years or older without diabetes or CKD is inconsistent, with evidence supporting an SBP target of 140 mm Hg for those younger than 60 years and those with diabetes or CKD. The dissenters noted that the SHEP (Systolic Hypertension in the Elderly Program) trial documented benefit from treating to an SBP goal of 140 to 145 mm Hg in those aged 60 years or older. Also, the HYVET (Hypertension in the Very Elderly Trial) found benefit, including reduced mortality rates, with an achieved mean SBP of 144 mm Hg. These trials provided evidence that reducing SBP to approximately 140 mm Hg has substantial benefit without major harm in older persons. Furthermore, JATOS (Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients) and the VALISH (Valsratan in Elderly Isolated Systolic Hypertension) trial, cited by the recommendations as supporting a target of 150 mm Hg, were underpowered and not generalizable to certain groups, such as black persons.

The dissenters also noted that results from the FEVER (Felodipine Event Reduction) trial and 2 meta-analyses support an SBP target of 140 mm Hg but were not considered by the panel. Documents from Europe, Canada, the United Kingdom, the American College of Cardiology/American Heart Association, and the American Society of Hypertension/International Society of Hypertension all support an SBP target of 140 mm Hg for patients younger than 80 years. The documents also show that a higher SBP goal in persons aged 60 years or older may reverse the decades-long decline in CVD, especially reduction in stroke and mortality rates. The dissenters maintained that the evidence for increasing the BP target in high-risk populations should be at least as strong as the evidence required to decrease the recommended target. A reasonable alternative approach would have been to set an SBP goal less than 150 mm Hg for frail persons aged 80 years or older.

Implications: Overall, the guideline's most important message is that evidence, based on objective outcomes of well-conducted trials, is required to assist decision making. These recommendations must be integrated with lifestyle modification guidelines as the foundation to prevent hypertension and control its progression.

Concern remains that the arbitrary threshold change in persons aged 60 years or older for initiating therapy will increase the number of persons who are undertreated and have adverse outcome implications because BP has a direct and persistent relationship with CVD outcomes at all ages. It is unreasonable to assume that an active 61-year-old person will lack the benefit from earlier intervention or a lower BP target experienced by a 59-year-old person with otherwise similar characteristics. The remodeling of small arteries, as well as progression of left ventricular hypertrophy, renal dysfunction, coronary artery disease, and cerebrovascular disease, are directly related to elevated BP at all levels above the optimal and the duration of the BP elevation.

There is also concern with removal of the SBP goal less than 130 mm Hg for patients with diabetes because the ACCORD (Action to Control Cardiovascular Risk in
Diabetes) trial found a reduction in stroke that could have a profound benefit in a large population containing patients at increased stroke risk because of a family history of stroke or because they are black or women.

Differentiations by age, race, and kidney status seem reasonable, but it is unclear why the large population with coronary heart disease was omitted. Combination therapy, although given as an alternative in the algorithm, probably should be considered more appropriate as a first step for most middle-aged and elderly persons with stage II hypertension. Large managed care populations document excellent BP control using first-step combinations with lower drug doses. Some of the age-based differentials are clearly supported by evidence. However, it is difficult to understand why the increasingly large cohort of active persons aged 60 years or older was penalized. Black persons especially have greater rates of CKD, stroke, heart failure, and myocardial infarction (MI), and increasing BP goals may not be optimal for them.

Whether some of the recommendations will have adverse consequences is unclear, but practitioners should recall that in the SHEP trial, which decreased average SBP from 155 to 143 mm Hg in elderly persons, a 32% cardiovascular event reduction resulted at 5 years.

It is not known whether renal denervation may be useful in less severe forms of hypertension or in other conditions characterized by heightened renal sympathetic nerve activity, such as heart failure, the metabolic syndrome, heart arrhythmias (such as AF), and chronic renal disease. Therefore, renal denervation is not recommended for these patients outside of appropriately designed clinical trials. Information on long-term safety and efficacy is being collected in national and international registries.

Cautions: There are many unknowns, which include the magnitude of benefit in more rigorously controlled trials, the longer-term risk–benefit profile, and suitability for patients who are more and less complex than those in existing trials.

Implications: Percutaneous renal denervation is the first truly novel treatment of hypertension to emerge in many decades, and it could rapidly change current hypertension management. Although renal denervation is exciting, practitioners must proceed with caution, recognizing that the phase 3 U.S. trial (SYMPLECTICITY HTN3) of the Symplicity renal denervation device (Medtronic, Minneapolis, Minnesota) documented safety, but the BP results were not as robust as expected.

Transradial Percutaneous Coronary Intervention Associated With Cost Savings

Background: Transradial percutaneous coronary intervention (PCI) is being used more frequently at selected centers, but its cost-effectiveness is unclear. A retrospective cohort study of 7121 patients having PCI was conducted at 5 U.S. hospitals. The primary outcome was cost of PCI hospitalization, defined as direct and indirect costs incurred by the hospital from the day of PCI through hospital discharge. Secondary outcomes included bleeding within 72 hours after PCI, length of stay, and all-cause in-hospital mortality.

Findings: Transradial PCI was associated with shorter lengths of stay, reduced bleeding events, and cost savings averaging $830 per patient. The cost savings increased in direct proportion to the bleeding risk: $642 per patient with low risk (95% CI, $43 to $1236), $706 per patient with medium risk (CI, $104 to $1308), and $1621 per patient with high risk (CI, $271 to $2971).

Cautions: A prospective replication study would help minimize physician inertia in adopting this new approach.

Implications: A hospital where 1000 PCI procedures are done per year could realize annual savings of $80 000 to $160 000 by increasing transradial PCI use from 10% to 20%. An increase in transradial PCI use by 10% across the United States could save hospitals approximately $50 million per year.
Smoking Cessation After PCI Added More Than 2 Years to Patients' Lives


**Background:** Smoking cessation is clearly beneficial overall, but its benefit after PCI is unclear. Data from 856 patients who had PCI between 1980 and 1985 at a center in the Netherlands were analyzed relative to long-term outcomes.

**Findings:** Patients who quit smoking after PCI gained an average of 2.1 years of life versus patients who continued to smoke.

**Cautions:** This cohort received only balloon angioplasty. Stent development, improvements in medical care, and other changes have occurred since this cohort was treated in the early 1980s.

**Implications:** It is important for clinicians to share this data when counseling patients who have had PCI. Too often, patients and physicians omit discussions on smoking cessation after a patient has PCI. This information about prolonged life should provide physicians with an additional tool to convince patients to stop smoking.

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**CVD Prevention**

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Echocardiographic Screening of the General Public Did Not Decrease Death, MI, and Stroke Rates


**Background:** Routine echocardiographic screening has not been considered appropriate for persons at low risk for CVD, yet this practice continues, perhaps because the recommendation against it is based only on consensus opinion. Researchers studied whether population-wide echocardiographic screening would reduce risk for CVD or enhance long-term survival.

**Findings:** Middle-aged participants (n = 6861) from a prospective cohort in Norway were studied. After an initial visit, participants were randomly assigned to either an echocardiographic Doppler screening group or a control group. In the screening group, 290 (8.9% of the total sample) had follow-up examinations because their results showed abnormalities, and 249 (7.6%) were confirmed to have cardiac or valvular conditions. After 15 years of follow-up, 26.9% in the screening group died versus 27.6% in the control group (hazard ratio, 0.97 [CI, 0.89 to 1.06]). Thus, screening was not associated with benefit by reducing the primary outcomes of death, MI, or stroke or the secondary outcomes of sudden death, cardiovascular death, fatal or nonfatal MI, or fatal or nonfatal stroke.

**Cautions:** Screening assumes that early detection will lead to a more favorable outcome, but the prevalence of preclinical disease that may be detected by screening should be high in screened patients. The prevalence of structural heart disease was low (7.6%) and consisted primarily of valvular disease, for which there is no known beneficial preclinical intervention. Also, a normal resting echocardiogram does not exclude coronary artery disease.

**Implications:** There was no benefit from routine echocardiographic screening of a low-risk cohort in terms of death from MI or stroke. Although the results were predictable, these findings add evidence-based data to previous recommendations based on consensus opinion. These negative results are important because they may contribute to reducing overuse of inappropriate echocardiographic screening.

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**Guideline for Obesity Management**


**Background:** Obesity and being overweight are serious problems, and guidelines to help address weight management are needed because most providers are not trained in this field. Also, there is much misinformation about weight management, especially about dietary supplements and diets that promise quick and easy weight loss.

**Findings:** Key recommendations include identifying patients in need of weight loss, calculating body mass index (BMI), and using thresholds for overweight (BMI ≥25 to 29.9 kg/m²) and obesity (BMI ≥30 kg/m²) to find and advise those at increased risk for CVD, all-cause mortality, and diabetes. Waist circumference should be measured at least once a year in overweight or obese patients, who should be counseled about other risk factors for CVD, including hypertension, hyperlipidemia, hyperglycemia, and inactivity.

The guideline strongly recommends counseling patients that lifestyle changes resulting in only modest weight loss can lead to clinically meaningful health improvements, such as decreases in BP, triglyceride and hemoglobin A₁c levels, and diabetes risk. Counseling should emphasize that benefits begin to emerge with weight loss of only 3% to 5%.

**Cautions:** There are sizable cohorts at risk, for whom large randomized, controlled trials have not been done but in whom some data are otherwise available to inform practice. For example, there are limited recommendations for pharmacotherapy and in using a complications-centered model for risk stratification. These guidelines did not emphasize obesity as a disease, a position that several societies advocate.
Implications: These guidelines advance the obesity field by urging all physicians to measure BMI and stratify for risks based on BMI. They recommend that providers counsel patients that lifestyle changes with only modest weight loss translate into meaningful health improvements.

Hypercholesterolemia

New Cholesterol Treatment Guidelines

Background: Recommendations for persons at increased risk for atherosclerotic CVD (ASCVD) needed updating. Findings: On the basis of trial data, the guideline expands the role of statins in primary prevention to include stroke prevention. Instead of focusing solely on total mortality, the guideline emphasizes prevention of major nonfatal ASCVD events to reduce disability. Risk assessment is broadened, the treatment threshold is lowered, and statins are recommended as first-line treatment of low-density lipoprotein (LDL) cholesterol and increased CVD risk. The ASCVD risk calculator adds stroke as a risk during the next decade in addition to MI. Also, separate risk-prediction equations were developed for non-Hispanic white and black men and women.

Because the guideline recommends statins for persons with 7.5% or greater ASCVD risk in the next decade, many more persons will qualify for statins (this threshold is exceeded by more than one half of black and more than one third of white men in their 50s). By their late 60s, virtually all men will surpass this threshold, as will approximately 70% of black and 30% of white women.

The guideline recommends statins when the potential for ASCVD risk reduction clearly exceeds the potential for adverse effects, specifically in adults with clinical ASCVD; persons with LDL cholesterol levels of 4.92 mmol/L or greater (≥190 mg/dL); persons aged 40 to 75 years with diabetes and LDL cholesterol levels of 1.81 to 4.90 mmol/L (70 to 189 mg/dL); and persons aged 40 to 75 years without clinical ASCVD or diabetes but with LDL cholesterol levels of 1.81 to 4.90 mmol/L (70 to 189 mg/dL) and an estimated 10-year ASCVD risk of 7.5% or greater.

Cautions: Because the 7.5% ASCVD risk threshold is key to deciding who should receive statins, risk estimation must be accurate. The discrimination of the risk calculator at the patient level, however, raises concern because it had c-statistics of only 0.6 to 0.75 in MESA (Multi-Ethnic Study of Atherosclerosis) and the REGARD (Reasons for Geographic and Racial Differences in Stroke) trial, perhaps because chronicologic age is not a good surrogate for physiologic age. Many practitioners would welcome better evidence in the form of more randomized trials to make these decisions. Selected use of additional tools, such as highsensitivity C-reactive protein and coronary calcium tests, may improve risk assessment in selected patients, but the evidence is limited. The guideline provides limited information on assessing the adequacy of therapy and follow-up.

Implications: Although there are some concerns, the algorithm for initiating statins is simplified compared with previous guidelines. Recommendations are straightforward and reemphasize primary prevention, which should improve implementation. Many more adults now qualify for statins, but heart-healthy dietary and exercise habits remain the foundation of primary prevention.

New Oral Anticoagulants for Stroke Prevention in AF

Background: Four new oral anticoagulants are alternatives to warfarin for stroke prevention in patients with nonvalvular AF; however, the balance between efficacy and safety in subgroups needed better definition. A prespecified meta-analysis (4) of participants in phase 3 trials of dabigatran (5), rivaroxaban (6), apixaban (7), and edoxaban (8) assessed the relative benefits of new oral anticoagulants in key subgroups.

Findings: Among 42,411 participants receiving a new oral anticoagulant and 29,272 receiving warfarin, the new oral anticoagulants significantly reduced stroke or systemic embolic events by 19% versus warfarin, driven by reduction in hemorrhagic stroke. New oral anticoagulants also reduced all-cause mortality and intracranial hemorrhage but increased gastrointestinal bleeding. No difference for stroke or systemic embolism was found among subgroups, but there was greater reduction in major bleeding with new oral anticoagulants when "time in therapeutic" range for warfarin was less than 66% compared with 66% or greater. Low-dose regimens showed overall reductions in stroke or systemic embolism similar to those with warfarin, with more favorable bleeding profiles but significantly more ischemic strokes. Sensitivity analyses without dabigatran showed similar results, which suggests that drugs that inhibit different coagulation factors produce similar outcomes.

Cautions: Because individual-patient data were not available, the analysis was at the study level. Also, the analysis pooled results from different studies, although there were differences in patient demographic and trial characteristics.

Implications: This is the first analysis to include all 4 new oral anticoagulants that have been studied in phase 3 trials for prevention of stroke or systemic embolism among pa-
patients with AF. These new oral anticoagulants had a favorable overall risk–benefit profile, with reductions in stroke, intracranial hemorrhage, and mortality rates and similar amounts of major bleeding versus warfarin but increased gastrointestinal bleeding. The relative efficacy and safety of the new oral anticoagulants were consistent across a wide range of patients, which should lead to more patients with AF receiving these medications.

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Potential Conflicts of Interest: Disclosures can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M14-0300.

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References
Stroke Prevention in Women: Synopsis of the 2014 American Heart Association/American Stroke Association Guideline

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Description: In February 2014, the American Heart Association/American Stroke Association released their first guideline focused on stroke prevention in women. This new guideline highlights unique risk factors for stroke in women, including oral contraception and hormone therapy, and pregnancy-associated disorders, such as preeclampsia, that may have long-lasting consequences on a woman’s health. It also addresses hypertension; atrial fibrillation; migraine headache with aura; and the epidemiology of types of stroke, such as aneurysmal subarachnoid hemorrhage and cerebral vein thrombosis, that are predominant in women.

Methods: Members of a multidisciplinary expert panel searched, reviewed, and critiqued relevant English-language literature published between 1990 and May 2013. The panel devised evidence tables and developed recommendations using American Heart Association guideline procedures and levels of evidence.

Recommendations: This synopsis of the guideline summarizes the evidence about risk factors for stroke in women and suggests prevention strategies. It also describes the new recommendations relevant to identifying and treating hypertensive disorders in pregnancy that increase risk for stroke.

Sex differences are increasingly recognized in many areas of medicine, and stroke is no exception. An estimated 6.8 million persons in the United States have had a stroke, most of whom are women (3.8 million) (1). At the time of stroke, women are older and more likely to be living alone and have worse premorbid status than men. After stroke, they also are more likely to be institutionalized and have a poorer recovery and worse quality of life than men (2–6).

There are many unique risk factors for stroke in women, such as pregnancy and pregnancy complications, hormonal contraception, and hormone therapy for menopause symptoms. Several other risk factors are more common in women than in men, including hypertension, atrial fibrillation, migraine headache with aura, and depression and psychosocial stress (Table). With these issues in mind, we developed a sex-specific guideline that consolidates recommendations specific to stroke prevention in women from primary and secondary prevention guidelines (7, 8) and emphasizes stroke-specific issues in more detail than previously published cardiovascular prevention guidelines (9).

We assigned topic areas to 1 primary reviewer and 1 or 2 secondary reviewers selected from the panel. These reviewers developed search terms to identify literature relevant to their topic area. Members of the writing group then searched PubMed, MEDLINE, the Cochrane Library, CardioSource, and EMBASE for English-language literature published between 1990 and 15 May 2013.

The reviewers scanned the search results, selected papers relevant to their topic, and abstracted data from selected studies to create evidence tables. All members of the panel then reviewed evidence tables and developed recommendations using the American Heart Association’s ratings for class of recommendation and level of evidence (10). The Stroke Council leadership committee and the Scientific Statements Oversight Committee coordinated extensive peer review of the guideline, and the Science Advisory and Coordinating Committee approved the final draft.

RECOMMENDATIONS

Risk Factors for Stroke

Hypertension in Nonpregnant Women

Hypertension, the most modifiable risk factor for stroke, is more prevalent in women than men (11). Hypertension is more often poorly controlled in older women; only 23% of women versus 38% of men older than 80 years have a blood pressure less than 140/90 mm Hg (12). There is currently no evidence that antihypertensive treatments differentially affect blood pressure response or stroke

See also:

Web-Only
CME quiz
We therefore suggest reducing the frequency of migraine headache as a possible strategy to reduce the risk for stroke, although there is no evidence that specific treatment strategies (for example, calcium-channel blockers, β-blockers, and antiepileptic drugs) reduce the risk for stroke (13). Given a synergistic relationship between smoking and migraine headache with aura, we recommend smoking cessation treatments and counseling for persons who smoke and have migraine headache. Finally, we encourage clinicians to caution women with migraine headache about the use of oral contraceptives (13).

**Hormonal Contraception**

The use of oral contraceptives is a risk factor for stroke in young women, increasing the risk from 1.4- to 2.0-fold compared with that of women who do not use these agents (13). The absolute risk is low—approximately 2 events per 10 000 women per year with the use of the lowest-dose formulation, according to a recent study from Denmark (20). The risk for stroke among women using oral contraceptives increases exponentially from 3.4 per 100 000 women aged 15 to 19 years to 64.4 per 100 000 women aged 45 to 49 years (20). Factors that could further increase risk for stroke include prior thromboembolic events, hypertension, cigarette smoking, hyperlipidemia, diabetes, and obesity. Accordingly, we recommend identifying women with such risk factors and increasing efforts to manage modifiable risk factors in women who use oral contraceptives.

The guideline also addresses prothrombotic mutations and biomarkers that increase the risk for stroke in a synergistic manner. Studies show that markers of endothelial dysfunction, such as von Willebrand factor and ADAMTS13 (a disintegrin and metalloprotease with the thrombospondin type 1 repeat 13), increase the risk for stroke more than 10-fold in women who use oral contraceptives compared with those who do not (21). Although many prothrombotic mutations increase the risk for stroke in women using oral contraceptives, we do not recommend screening for these mutations before starting oral contraceptive therapy because of their low prevalence in otherwise healthy women, especially in the absence of a positive family history (13).

Additional research is needed to better characterize the risk for hemorrhagic stroke with oral contraceptive use, focusing on older women who may use these agents until menopause, members of underrepresented minority groups, genetic makeup, and parity. The study of clinically available biomarkers, such as von Willebrand factor, is warranted in broader populations of women.

**Menopause and Hormone Replacement**

Menopause, particularly younger age at menopause, and risk for stroke may be related, but evidence defining such a relationship is inconsistent. Whether natural versus...
surgical menopause is associated with risk for stroke is also unclear. However, the use of hormone therapy in postmenopausal women is a unique risk factor for stroke in women.

In general, hormone therapy is associated with an increased risk for stroke and is not recommended for primary or secondary prevention of this condition. Many gaps remain in research about the magnitude of harms and tradeoffs between benefits and risks of hormone therapy. These gaps concern treatment of subgroups of women who are at high risk for stroke after menopause; treatment of women who are early in the peri- or postmenopausal period; and the optimum timing, dosage, type, and route of administration that could enhance vascular health (13).

Depression and Psychosocial Stress

Several cohort studies and a meta-analysis have identified depression and psychosocial stress as factors that increase the risk for incident stroke by 25% to 45% in women (22–24). The odds ratios across studies that included both men and women are similar to those of studies that included only men or only women, making it difficult to state conclusively that women with these conditions have a higher risk for stroke than men. More research is needed to understand the subgroups of women at risk, such as those who are treated versus not, and the method of determining depression and psychosocial stress (13).

Stroke Prevention Strategies

Healthy Lifestyle

We advise maintaining a healthy weight, eating a healthy diet, abstinence from smoking, regular physical activity, moderate alcohol intake, and activities and interventions aimed at achieving or maintaining normal blood pressure and cholesterol and blood glucose levels. The guideline highlights the risk for stroke in several high-risk conditions, including obesity, physical inactivity, and the metabolic syndrome, but found few data that suggest these conditions increase risk for stroke disproportionately in women.

However, a recent meta-analysis of studies involving more than 750,000 persons and more than 12,000 strokes found that diabetic women have a 27% greater relative risk for stroke than diabetic men (25). The mechanisms underlying this increased risk are unknown but may be related to a more adverse cardiovascular risk profile during the pre-diabetic phase in women than men (25). This meta-analysis provides further evidence that recognition of risk factors for stroke, especially those that may disproportionally increase risk in women, is critical to prevent stroke. Healthy lifestyle interventions, including regular physical activity, such diets as the Dietary Approaches to Stop Hypertension, abstinence from smoking, moderate alcohol consumption (13), and recognition and treatment of diabetes, are important. Until sex-specific strategies are tested, recommendations for stroke prevention in terms of healthy lifestyle interventions remain the same for men and women.

Carotid Stenosis

Women with symptomatic carotid stenosis (recent ischemic stroke or transient ischemic attack ipsilateral to the carotid stenosis) may be less likely to receive carotid endarterectomy than men (26). Whether benefits and risks of carotid angioplasty and stenting differ between women and men is not known. Data from CREST (Carotid Revascularization Endarterectomy Versus Stenting Trial) showed that women randomly assigned to angioplasty and stenting had a higher proportion of peri-procedural events than men and a possible interaction between the treatment assignment and sex ($P = 0.064$) (27).

There are clear sex differences in carotid artery plaque (women have less inflammatory features) and a higher risk for peri-procedural complications with endarterectomy for asymptomatic stenosis. However, evidence to suggest that women with symptomatic or asymptomatic carotid stenosis should be treated medically versus surgically (with endarterectomy or coronary artery stenting) or differently from men is currently lacking (13). Therefore, the guideline recommendations are the same for both sexes. There are many gaps in our understanding of the sex-specific treatment of carotid disease, so future trials are needed to determine whether surgery is superior to aggressive medical management in women with symptomatic carotid stenosis.

Aspirin for Stroke Prevention

There is no convincing evidence to suggest that a particular antiplatelet therapy or dosage of such therapy is more or less beneficial in women than men, but protection from aspirin may be specific to certain vascular diseases on the basis of sex. For example, the results of the WHS (Women’s Health Study), a trial of 100 mg of aspirin every other day versus placebo, showed that aspirin did not reduce the risk for myocardial infarction or death from cardiovascular causes but did decrease stroke events (relative risk, 0.85 [95% CI, 0.79 to 0.91]), especially ischemic stroke (relative risk, 0.976 [CI, 0.63 to 0.93]) (28). A meta-analysis of aspirin and primary prevention showed that women seem to be protected from stroke, whereas men are protected from myocardial infarction (29). However, the ATT (Antithrombotic Trialists’ Collaboration study) reported no evidence of a sex difference in any of the vascular outcomes after adjustment for multiple comparisons (30).

Consistent with other published recommendations, our guideline suggests considering aspirin in women older than 65 years if blood pressure is controlled and the benefit of preventing ischemic stroke or myocardial infarction outweighs the risk for gastrointestinal bleeding and hemorrhagic stroke (13). Whether a woman younger than 65 years may benefit from aspirin could be addressed if a sex-specific risk score were available.
New Recommendations

Pregnancy and Pregnancy Complications

The risk for stroke during pregnancy is fairly low (about 34 per 100,000 deliveries) (31), but risk is highest in the postpartum period. Although the traditional definition of a postpartum time frame is 6 weeks, a recent study showed that thrombotic events may occur up to 12 weeks after birth (32). Suspicion for a postpartum stroke or vasculopathy (the posterior reversible encephalopathy syndrome or the reversible cerebral vasodilation syndrome) or cerebral venous thrombosis should be heightened for women who develop new-onset headache, blurred vision, or seizures or any new neurologic signs or symptoms during the postpartum period (13).

Preeclampsia and Eclampsia: Preeclampsia occurs in approximately 5% of pregnancies. It is defined as high blood pressure in pregnancy associated with proteinuria (urinary protein excretion ≥300 mg/24 h) or thrombocytopenia, impaired liver function, progressive renal insufficiency, pulmonary edema, or new-onset cerebral or visual disturbances (33). The American Congress of Obstetricians and Gynecologists (formerly the American College of Obstetricians and Gynecologists) published an updated guideline (released after our guideline was in production) that changed the criteria for preeclampsia to include women without proteinuria if one of the other multisystem features is present (33).

Because of evidence that a history of preeclampsia is associated with a 2-fold risk for stroke and a 4-fold risk for hypertension later in life, we recommend documenting preeclampsia as a risk factor (class IIa; level of evidence C) (13). Our intent is to increase awareness that women with a history of preeclampsia would probably benefit from lifestyle change and early assessment of cardiovascular risk and interventions. Although the evidence for an association between preeclampsia and later hypertension with attendant risk for stroke is clear, the current gap in knowledge is identifying which women with preeclampsia will have these complications. More research is needed to understand biomarkers or other characteristics that might identify the women at highest risk (13).

Moderate Hypertension in Pregnancy: Another new recommendation is to consider treating women with a systolic blood pressure between 150 and 159 mm Hg or a diastolic blood pressure between 100 and 109 mm Hg of new onset during pregnancy (class IIa; level of evidence B). This recommendation differs from that of the guideline of the American Congress of Obstetricians and Gynecologists, which recommends only treating patients with a blood pressure greater than 160/110 mm Hg (33). Our new recommendation is based on evidence that treatment of mild to moderately elevated blood pressure in pregnancy is associated with a 50% reduction in risk for severe hypertension (relative risk, 0.5 [CI, 0.41 to 0.61]) (34).

New studies or reanalyses of existing data using the new definition of preeclampsia would be useful to assess the benefit of treating mild to moderately elevated blood pressure during pregnancy. Although safe and effective antihypertensive medications can be used during pregnancy, risk to the fetus must also be considered (13).

Conclusion

These guidelines provide recommendations for the prevention of stroke in women, emphasizing risk factors that are unique or more prevalent in women. Of note, we recognize many gaps in the literature that limit the ability to provide strong (level of evidence A), sex-specific recommendations. Some stroke-specific risk scores, such as the Framingham risk score for stroke (35), take sex into account but do not allow calculation of risk in persons younger than 54 years. Goals for our guideline include identifying unique risk factors and facilitating the development of new sex-specific tools for scoring risk for stroke.

We suggest that a more accurate assessment of risk for stroke is possible if events that occur in young adulthood known to increase this risk in later life, such as preeclampsia, are documented. In addition, risks unique to women (use of oral contraceptives and hormone therapy) and established risk factors that are more prevalent in older women (hypertension and atrial fibrillation) should be recognized. We hope that this guideline will spur additional research to determine the best approaches to stroke prevention for both men and women.

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References

Statins, Primary Prevention, and Overall Mortality

Vinay Prasad, MD

In November 2013, the American College of Cardiology and the American Heart Association published an update to cholesterol guidelines that sparked lively debate about the role of statins in the primary prevention of cardiovascular disease. Statin therapy reduces illness (stroke and myocardial infarction) (1), but attendant harms have been underappreciated (2). One measure of efficacy that is universally considered important is the effect of therapy on overall mortality (1, 2). Only 1 trial (3) among dozens has shown strong evidence of a mortality benefit with statin therapy, and the study was criticized for early stopping (4). Small differences in all-cause mortality may be difficult to capture in individual trials but may be important on a population-wide level. Meta-analyses are well-suited to clarify this issue. In fact, Taylor and colleagues’ updated Cochrane review in 2013 found that statin therapy decreased all-cause mortality by about 14% (5).

Their meta-analysis included 13 trials that reported mortality outcomes. They excluded studies in which more than 10% of participants had cardiovascular disease at baseline to avoid biasing the analysis in favor of treatment. Including secondary prevention patients, who already have an indication for treatment, is a challenge in meta-analyses that try to pinpoint the effects of statins for the general population. Such patients are included in several randomized trials, and outcomes derived from them may skew results. Some authors have used alternative strategies to tease out information relevant to primary prevention from the existing trials. In a 2010 meta-analysis, Ray and coworkers queried primary study authors, obtained individual-patient data, and meticulously excluded secondary prevention patients while examining the effect of statins on mortality rates (4). In doing so, they considered at least 2 trials that the Taylor meta-analysis could not and also more precisely identified primary prevention patients in at least 1 other study.

The Table shows a comparison of trials reviewed by Taylor versus Ray. Of 17 studies, 4 were identical in both publications, 3 had discrepancies in the number of deaths or sample size, 6 were unique to Taylor, and 4 were unique to Ray. The number of deaths ascertained among statin and placebo users was 1077 and 1223, respectively, in Taylor and 1346 and 1447, respectively, in Ray. The mortality rate for statin and placebo groups was 4.41% versus 5.17% in the Taylor analysis and 4.13% versus 4.44% in the Ray analysis. Although Taylor noted a significant risk difference in favor of statins by 0.76%, the difference of 0.31% captured by Ray failed to meet significance in that analysis. Less than half of a percentage point marked the difference between these conclusions: “Meta-analyses now provide extensive evidence that statins reduce... total mortality” (1), and “Data from a meta-analysis... showed no reduction in mortality associated with treatment with statins” (2).

What does the comparison of these meta-analyses tell us? First, the outcome in question—overall mortality—is important, and independent teams have made tremendous efforts to comprehensively estimate this outcome. Second, the ascertainment of mortality varies between studies nearly as much as the groups within each study. Comparing mortality rates between the placebo groups of the 2 analyses reveals a difference of 0.73% (5.17% vs. 4.44%; P < 0.001), suggesting that the control groups are different.

Close examination of the 2 meta-analyses uncovers several additional differences. Three trials reviewed by both groups differed in the number of participants or deaths. Differences reported for WOSCOPS (West of Scotland Coronary Prevention Study) (Table) were substantial—numbers diverged by several hundred deaths and participants. This trial originally included patients with angina and electrocardiographic evidence of coronary heart disease; Ray was able to exclude these patients but Taylor was not (4). In addition, Ray used outcomes from this trial at the end of randomization (4.9 median years of follow-up) (6), but Taylor used long-term outcomes that extended 10 years beyond the trial’s completion, after unmasking and open-label use (7). Two other trials differed only in the number of deaths, which suggested that data were captured at varying durations of follow-up.

Of the trials unique to each meta-analysis, some may be questioned. In Taylor, 1 trial (CERDIA [Cerivastatin in Diabetes]) switched statins midstudy when cerivastatin was withdrawn. Two trials (ACAPS [Asymptomatic Carotid Artery Progression Study] and METEOR [Measuring Effects on Intima Media Thickness; an Evaluation of Rosuvastatin]) mandated some degree of carotid intimal artery thickening; whether this represents true primary prevention can be debated. One trial (KAPS [Kuopio Atherosclerosis Prevention Study]) included fewer than 10% of patients with a history of myocardial infarction, but individual-patient data were not used. Another trial (Bone and colleagues) mandated diminished bone mineral density, although it is unclear how this would affect results. One of the trials unique to Ray (HYRIM [Hypertension High Risk Management]) excluded patients who had switched to a vegetarian diet or a diet rich in ω-3 fatty acids, which precludes assessment of whether drug therapy provides benefit beyond lifestyle modification. Three trials (ALLHAT [Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial], ASCOT [Anglo-Scandinavian Cardiac Outcomes Trial], and PROSPER [Prospective Study of Pravastatin in the Elderly at Risk]) seem eligible only through use of individual-patient data.
Table: Comparison of Clinical Trials, Participants, and Deaths Included in Meta-analyses

<table>
<thead>
<tr>
<th>Variable, by Trial (Year)</th>
<th>Deaths/Participants in Taylor et al, 2013 (5), n/n</th>
<th>Deaths/Participants in Both Meta-analyses, n/n</th>
<th>Deaths/Participants in Ray et al, 2010 (4), n/n</th>
</tr>
</thead>
<tbody>
<tr>
<td>Same data</td>
<td>Statin</td>
<td>Placebo</td>
<td>Statin</td>
</tr>
<tr>
<td>ASPEN (2006)</td>
<td>44/999</td>
<td>41/946</td>
<td>44/999</td>
</tr>
<tr>
<td>Discrepant data</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unique to Taylor et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone et al (2007)</td>
<td>0/485</td>
<td>0/119</td>
<td>0/485</td>
</tr>
<tr>
<td>METEOR (2010)</td>
<td>1/700</td>
<td>0/261</td>
<td>1/700</td>
</tr>
<tr>
<td>PHYLLIS (2004)</td>
<td>1/253</td>
<td>0/254</td>
<td>1/253</td>
</tr>
<tr>
<td>Unique to Ray et al</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALLHAT (2002)</td>
<td></td>
<td></td>
<td>155/4391</td>
</tr>
<tr>
<td>ASCOT (2003)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HYRIM (2005)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total*</td>
<td>1077/24408</td>
<td>1223/23652</td>
<td>1077/24408</td>
</tr>
<tr>
<td>Deaths, %</td>
<td>4.41</td>
<td>5.17</td>
<td>4.13</td>
</tr>
</tbody>
</table>

ACAPS = Asymptomatic Carotid Artery Progression Study; AFCAPS/TexCAPS = Air Force Coronary Artery Calcium Prevention Study/Texas Coronary Atherosclerosis Prevention Study; ALLHAT = Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial; ASCOT = Anglo-Scandinavian Cardiac Outcomes Trial; ASPEN = Aterosclerotic Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes; CARDs = Collaborative Aterosclerotic Diabetes Study; CERDIA = Cervinastatin in Diabetes; HYRIM = Hypertension High Risk Management; JUPITER = Justification of the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin; KAPS = Kuopio Atherosclerosis Prevention Study; MEGA = Management of Elevated Cholesterol in the Primary Prevention of Adult Disease; METEOR = Measuring Effects on Intima Media Thickness: an Evaluation of Rosuvastatin; PHYLLIS = Plaque Hypertension Lipid-Lowering Italian Study; PREVEND IT = Prevention of Renal and Vascular Endstage Disease Intervention Trial; PROSPER = Prospective Study of Pravastatin in the Elderly at Risk; WOSCOPS = West of Scotland Coronary Prevention Study.

* Totals are the sum of the data in the Taylor and Both columns, and the Ray and Both columns. For example, the statin-related deaths data in Taylor (n = 654) plus the statin-related deaths data in Both (n = 383) equals 1077 deaths.

Results that seem to conflict can sometimes be adjudicated by additional analyses. In 2012, the Cholesterol Treatment Trialists’ Collaborators found in a study of more than 134,000 patients that, among persons without vascular disease, statins reduced the risk for all-cause mortality for each 1.0 mmol/L (38.6 mg/dL) reduction in low-density lipoprotein cholesterol level (rate ratio per 1.0 mmol/L [38.6 mg/dL] reduction, 0.91 [95% CI, 0.85 to 0.97]) (8). However, analyzing mortality rates weighted by trial-level low-density lipoprotein cholesterol reduction is flawed because it places more weight on trials with greater decreases in cholesterol level (9). The authors also analyzed overall mortality in trials of statins with varying potency and dose together with trials of statin versus placebo. As such, I do not believe that the Cholesterol Treatment Trialists’ study can adjudicate whether statins improve survival for primary prevention patients.

When the final count matters, and the results are close, recounts are commonplace. Eighteen states mandate automatic recounts in tight political elections (10), typically when the number of votes differs by less than 0.5%. For statins in primary prevention, 2 meta-analyses draw opposite conclusions, although they also differ by less than 0.5%. With results this close, is it time for a recount? All published and unpublished trials may be brought forward, and individual-patient data should be made available from studies in the Table that include secondary prevention patients. The Cholesterol Treatment Trialists’ study has a robust set of deidentified individual-patient data, which can improve our understanding, and those data should be made widely available. Updated results should be considered. For example, JUPITER (Justification of the Use of Statins in Prevention: an Intervention Trial Evaluating Rosuvastatin) was halted at a median follow-up of 1.9 years (3) after showing a statistically significant reduction in overall mortality. Although the trial was unblinded at the time, subsequent mortality data would be interesting to review because early stopping is known to inflate estimates of benefit.

Considering all data on a question of interest is fundamental to the appraisal of medical evidence. The approach described here may be used during the next...