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

Egan BM, Zhao Y, Li J, et al. Prevalence of optimal treatment regimens in patients with apparent treatment-resistant hypertension based on office blood pressure in a community-based practice network. Hypertension. 2013;62:691-7. [PMID: 23918752]

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?

James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). JAMA. 2014;311:507-20. [Epub ahead of print 18 December 2013] [PMID: 24352797]

Wright JT, Fine LJ, Lackland DT, et al. Evidence supporting a systolic blood pressure goal of less than 150 mm Hg in patients aged 60 years or older: the minority view. Ann Intern Med. 2014;160:499-503. [Epub ahead of print 14 January 2014] [PMID: 24424788]

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

Ann Intern Med. 2014;160:847-852.
For author affiliation, see end of text.
This article was published online first at www.annals.org on 10 April 2014.

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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.

Cautions: 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 (Valsartan 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

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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.

Intervention

Renal Sympathetic Denervation for Resistant Hypertension

Schlaich MP, Schmieder RE, Bakris G, et al. International expert consensus statement: percutaneous transluminal renal denervation for the treatment of resistant hypertension. J Am Coll Cardiol. 2013; 62:2031-45. [PMID: 24021387]

Background: Resistant hypertension is a common but challenging management problem. A novel interventional treatment using percutaneous transluminal catheter radiofrequency to ablate renal nerves has recently been introduced in Europe, Australia, and other countries and has generated considerable interest. Because published clinical trial data are limited, it is important to summarize the opinions of an international expert panel to provide guidance about the indications, methods, and safety of transluminal renal denervation.

Findings: Evidence from available clinical trials indicates that catheter-based renal denervation improves BP control in resistant hypertension, with an acceptable safety profile to 3 years. The effects of renal denervation seem mediated via interference with both efferent sympathetic and afferent sensory nerves and may extend beyond BP control. Renal denervation should be considered only in patients whose BP cannot be controlled by a combination of lifestyle modification and pharmacologic therapy tailored according to current guidelines.

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 (SYMPLICITY 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

Amin AP, House JA, Safley DM, et al. Costs of transradial percutaneous coronary intervention. JACC Cardiovasc Interv. 2013;6:827-34. [PMID: 23871512]

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.

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Smoking Cessation After PCI Added More Than 2 Years to Patients' Lives

de Boer SP, Serruys PW, Valstar G, et al; Interventional Cardiologists of the Thoraxcentre 1980 to 1985. Life-years gained by smoking cessation after percutaneous coronary intervention. Am J Cardiol. 2013;112:1311-4. [PMID: 23891246]

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 these 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.

CVD Prevention

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

Lindekleiv H, Løchen ML, Mathiesen EB, et al. Echocardiographic screening of the general population and long-term survival: a randomized clinical study. JAMA Intern Med. 2013;173:1592-8. [PMID: 23877591]

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.

Guideline for Obesity Management

Jensen MD, Ryan DH, Apovian CM, et al. 2013 AHA/ACC/TOS guideline for the management of overweight and obesity in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and The Obesity Society. Circulation. [Epub ahead of print 12 November 2013] [PMID: 24222017]

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/m^2) and obesity (BMI $\geq$30 kg/m^2) 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 A_{1c} 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.

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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

Stone NJ, Robinson J, Lichtenstein AH, et al. 2013 ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. Circulation. [Epub ahead of print 12 November 2013] [PMID: 24222016]

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 chronologic 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 high-sensitivity 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

Ruff CT, Giugliano RP, Braunwald E, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383:955-62. [Epub ahead of print 4 December 2013] [PMID: 24315724]

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-

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tients 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

1. **Egan BM, Zhao Y, Axon RN, Brzezinski WA, Ferdinand KC.** Uncontrolled and apparent treatment resistant hypertension in the United States, 1988 to 2008. Circulation. 2011;124:1046-58. [PMID: 21824920]

2. **Mancia G, Fagard R, Narkiewicz K, Redón J, Zanchetti A, Böhm M, et al; Task Force Members.** 2013 ESH/ESC Guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). J Hypertens. 2013;31:1281-357. [PMID: 23817082]

3. **Weber MA, Schiffrin EL, White WB, Mann S, Lindholm LH, Kenerson JG, et al.** Clinical practice guidelines for the management of hypertension in the community: a statement by the American Society of Hypertension and the International Society of Hypertension. J Clin Hypertens (Greenwich). 2014;16:14-26. [PMID: 24341872]

4. **Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al.** Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2013. [PMID: 24315724]

5. **Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al; RE-LY Steering Committee and Investigators.** Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139-51. [PMID: 19717844]

6. **Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al; ROCKET AF Investigators.** Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883-91. [PMID: 21830957]

7. **Granger CB, Alexander JH, McMurray JJ, Lopes RD, Hylek EM, Hanna M, et al; ARISTOTLE Committees and Investigators.** Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981-92. [PMID: 21870978]

8. **Giugliano RP, Ruff CT, Braunwald E, Murphy SA, Wiviott SD, Halperin JL, et al; ENGAGE AF-TIMI 48 Investigators.** Edoxaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2013;369:2093-104. [PMID: 24251359]

FAST-TRACK REVIEW

Annals will consider manuscripts of high quality for expedited review and early publication (Fast Track) if they have findings that are likely to affect practice or policy immediately and if they are judged valid. We give priority to fast-tracking large clinical trials with clinical outcomes and manuscripts reporting results that are likely to have an immediate impact on patient safety. Authors wishing to fast-track their articles should contact Senior Deputy Editor Dr. Cynthia Mulrow (e-mail, cynthiam@acponline.org) and provide an electronic version of their manuscript along with a request and justification for expedited review and, for trials, the protocol and registry identification number.

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