

# Atrial Fibrillation

*Daniel M. Witt*

## INTRODUCTION

Atrial fibrillation (AF) is a common cardiac rhythm disorder. While AF rarely causes life-threatening hemodynamic compromise, it is an important independent risk factor for cardiogenic embolic stroke and systemic arterial thromboembolism.<sup>1</sup> Approximately 90% of AF thromboembolic complications are stroke related while the remaining 10% are systemic.

The following contribute to thromboembolic risk associated with AF<sup>2</sup>:

- Stasis or turbulence of blood flow within the left atrial appendage leads to thrombus formation.
- Dysfunction of vascular endothelium predisposes to local or systemic hypercoagulability.
- Conversion to normal sinus rhythm (NSR)—spontaneous or intentional—may dislodge any existing left atrial thrombi.

## MORBIDITY AND MORTALITY ASSOCIATED WITH AF<sup>1,3</sup>

- 15% of all strokes occur in people with AF.
- The annual stroke risk in untreated AF patients varies between 3% and 8% (average 4.5%) depending on concurrent individual risk factors.
- Attributable stroke risk in AF increases with age.
  - 1.5% in 50–59 year age group
  - 23.5% in 80–89 year age group
- The 30-day case fatality rate of AF stroke is 24%.

Data from high-quality, randomized controlled clinical trials overwhelmingly demonstrates that long-term, adjusted-dose anticoagulation therapy with vitamin K-antagonists like warfarin virtually eliminates the stroke risk associated with AF.<sup>1,2</sup> Despite the proven efficacy of warfarin therapy in preventing AF-related stroke, only about half of patients who could benefit receive anticoagulation therapy.<sup>1</sup> Increasing age, perceived bleeding risk, and the innate complexity of managing anticoagulation therapy are negative predictors of warfarin use in AF.

**Table 12-1: Classification of Atrial Fibrillation**

|               |  |
|---------------|--|
| Acute AF      | Onset within previous 48 hr  |
| Paroxysmal AF | Terminates spontaneously within 7 days (may recur)                           |
| Recurrent AF  | More than one episode  |
| Persistent AF | Duration for more than 7 days without spontaneous termination                |
| Permanent AF  | Persistence of AF despite electrical or pharmacologic cardioversion attempts |

## TREATMENT OVERVIEW

### *Rate vs. rhythm control*

- Two landmark randomized trials, Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) and Rate Control vs. Electrical cardioversion for persistent atrial fibrillation (RACE) provide evidence that cardioversion of AF to normal sinus rhythm (rhythm control) is not necessary nor preferable to allowing AF to continue while controlling ventricular response rate with AV node blockade (rate control).<sup>4-6</sup>
  - AFFIRM found no difference in mortality or stroke rate between patients assigned to one strategy or the other.
  - RACE found rate control not inferior to rhythm control for prevention of death and morbidity.
  - Rate- or rhythm-control strategies do not seem to affect quality of life significantly or differently.

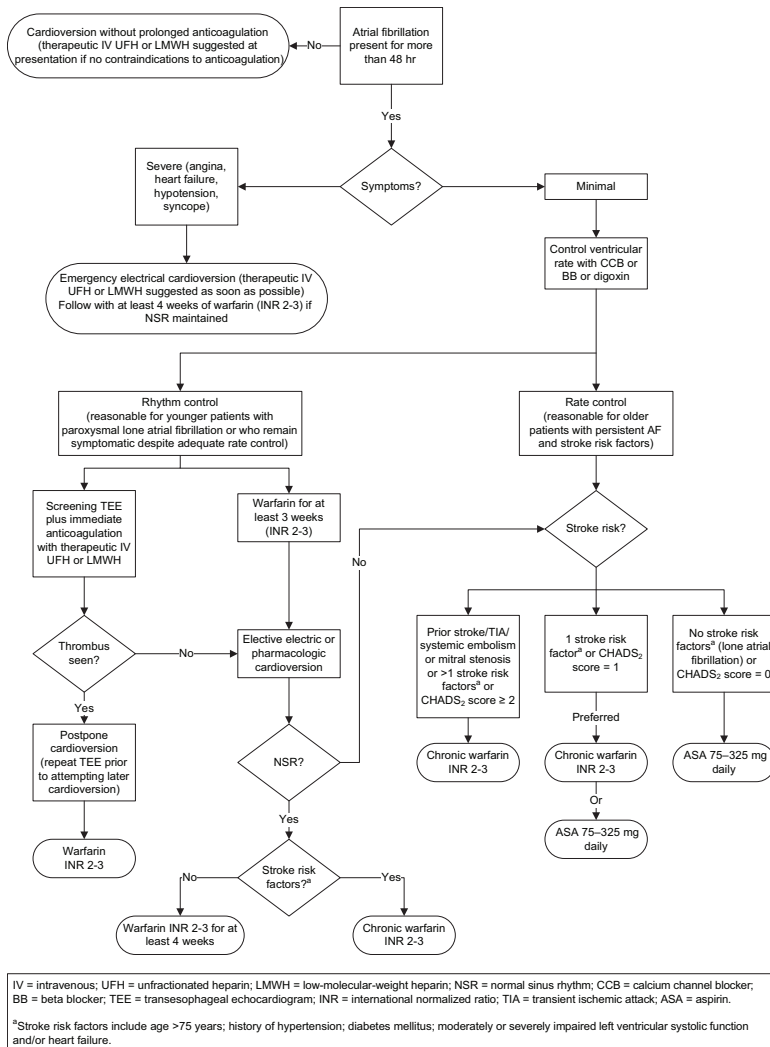


Figure 12-1: Stroke Prevention in Atrial Fibrillation Treatment Algorithm

- Ischemic events occurred with similar frequency with either a rhythm or rate control strategy, especially when warfarin was discontinued or when anticoagulation was subtherapeutic.
- In younger individuals a combined rate and rhythm approach may minimize the risk of related heart failure.
- Whether a rate or rhythm control strategy is employed, AF patients *with thromboembolic risk factors* should probably receive chronic dose-adjusted warfarin anticoagulation.<sup>1,2</sup>

### *Adjusted-dose warfarin vs. daily aspirin (ASA) therapy for stroke prevention in AF*

- ASA provides little protection against stroke in AF and is markedly inferior to adjusted-dose (INR 2–3) warfarin therapy.<sup>1</sup>
- Pooled analysis of trials comparing ASA to placebo yield a relative risk reduction (RRR) estimate of 21% with a 95% confidence interval (CI) of 0% to 38%—compared to a RRR of 68% (95% CI 50% to 79%) with warfarin.<sup>1</sup>
- Compared with ASA alone, the combination of clopidogrel and ASA significantly reduces the rate of major vascular events (mainly stroke) but increases the risk of serious bleeding including ICH<sup>7</sup>—thus, the net effect of the combination is comparable to ASA alone.
- A randomized comparison of warfarin vs. clopidogrel plus ASA was terminated early after showing the superiority of warfarin.<sup>8</sup>
- Adding ASA to warfarin therapy increases the risk of major bleeding and does not provide further protection against ischemic stroke in patients with AF (possible exception is patients with AF and prosthetic heart valve replacement).<sup>9,10</sup>
- **The key decision in AF stroke risk reduction is warfarin, yes or no?**—ASA should only be considered when the answer this question is “warfarin, no” due to either very low stroke risk or contraindications to warfarin therapy (e.g., bleeding risk, inability to comply with the requirements of warfarin therapy).<sup>1</sup>

### *AF stroke risk stratification tools*

- Based on warfarin's superiority over any comparator in preventing stroke in AF, *it is not unreasonable to recommend warfarin therapy for all patients with AF*.<sup>1</sup>

- However, warfarin therapy is associated with bleeding risk, most importantly the risk for intracranial hemorrhage.
- Therefore, various risk stratification schemes have evolved with the following goals<sup>1</sup>:
  - Identifying AF patients at such low risk of stroke that warfarin-associated bleeding risk may outweigh stroke prevention benefit.
  - Encouraging warfarin use in patients at high risk for AF stroke where warfarin's benefit has been clearly demonstrated.
- The CHADS<sub>2</sub> score, which is well validated and easy to use, is the most popular AF stroke risk stratification tool.<sup>11</sup>

| Risk factor                       | Points |
|-----------------------------------|--------|
| Congestive heart failure          | = 1    |
| Hypertension                      | = 1    |
| Age ≥75 years of age              | = 1    |
| Diabetes                          | = 1    |
| Prior Stroke/TIA/systemic embolus | = 2    |

**Example:** an 82-year-old male with hypertension and prior stroke would have a CHADS<sub>2</sub> score = 4.

Higher CHADS<sub>2</sub> score = higher AF stroke risk<sup>1,11</sup>:

| CHADS <sub>2</sub> Score | Stroke Rate (%/year) | Recommended Therapy             |
|--------------------------|----------------------|---------------------------------|
| 0                        | 1.9 (1.2–3.0)        | Daily ASA                       |
| 1                        | 2.8 (2.0–3.8)        | Warfarin (INR 2–3) or daily ASA |
| 2                        | 4.0 (3.1–5.1)        | Warfarin (INR 2–3)              |
| 3                        | 5.9 (4.6–7.3)        |                                 |
| 4                        | 8.5 (6.3–11.1)       |                                 |
| 5                        | 12.5 (8.2–17.5)      |                                 |
| 6                        | 18.2 (10.5–27.4)     |                                 |

- A revised scoring approach (CHA<sub>2</sub>DS<sub>2</sub>VASc) has been proposed<sup>12</sup>:

| Stroke Risk Factor   | Points |
|--|--------|
| Congestive heart failure   | = 1    |
| Hypertension   | = 1    |
| Age ≥75 years of age   | = 2    |
| Diabetes   | = 1    |
| Prior <b>S</b> troke/TIA/systemic embolus  | = 2    |
| <b>V</b> ascular disease (prior MI, PAD, or aortic plaque)   | = 1    |
| Age 65–74  | = 1    |
| Sex category (female)  | = 1    |
| Recommended antithrombotic therapy   |        |
| Score >1: oral anticoagulation (VKA INR 2–3)   |        |
| Score = 1: either oral antithrombotic therapy (INR 2–3)—preferred, or aspirin 75–325 mg/day  |        |
| Score = 0: no anticoagulation therapy (preferred), or aspirin 75–325 mg daily  |        |
| The CHA <sub>2</sub> DS <sub>2</sub> VASc identifies a lower risk population; the impact of the approach over the CHADS <sub>2</sub> has not been determined |        |

**Table 12-2: Risk-Stratified Treatment Recommendations of The American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed.)<sup>1</sup>**

| Risk Category       | Prior ischemic stroke, TIA, systemic embolism, or history of mitral stenosis (valvular AF) or prosthetic heart valve <sup>a</sup> | ≥2 stroke risk factors <sup>b</sup> | Only 1 stroke risk factor <sup>b</sup>    | Age ≤75 years and no other stroke risk factors <sup>b</sup> |
|---------------------|---|-------------------------------------|---|---|
| Recommended Therapy | Warfarin (INR 2–3)  | Warfarin (INR 2–3)                  | Warfarin (INR 2–3) or daily ASA 75–325 mg | Daily ASA 75–325 mg   |

<sup>a</sup>INR target may be higher than 2–3 for patients with prosthetic heart valves.

<sup>b</sup>Stroke risk factors: age > 75 years, history of hypertension, diabetes mellitus, and moderately or severely impaired left ventricular systolic function and/or heart failure.

**Table 12-3: Risk-Stratified Treatment Recommendations of The American College of Cardiology/American Heart Association/European Society of Cardiology 2006 Guidelines for the Management of Patients with Atrial Fibrillation<sup>2</sup>**

| <b>Risk Category</b>       | Any high-risk factor <sup>a</sup> or more than 1 moderate-risk factor <sup>b</sup> | One moderate-risk factor <sup>b</sup>     | No risk factors     |
|----------------------------|--|---|---------------------|
| <b>Recommended Therapy</b> | Warfarin (INR 2–3)   | Warfarin (INR 2–3) or daily ASA 81–325 mg | Daily ASA 81–325 mg |

<sup>a</sup>High-risk factors: previous stroke/TIA/embolism, mitral stenosis, prosthetic heart valve (INR target may be higher than 2–3).

<sup>b</sup>Moderate-risk factors: age  $\geq 75$  years, hypertension, heart failure, left ventricular ejection fraction  $\leq 35\%$ , diabetes mellitus.

- *Echocardiography* is often used in treatment decision making but has limited proven value in determining the need for chronic warfarin therapy.
  - Echocardiography can detect the presence of features associated with thromboembolism. Anticoagulation therapy in patients with these features has been shown to reduce stroke risk (e.g., impaired left ventricular systolic function, left atrial thrombus, dense spontaneous echo contrast, “smoke,” or reduced velocity of blood flow in the left atrial appendage); however, the absence of these echocardiographic abnormalities has not been established as identifying a low-risk group of AF patients who could safely forgo warfarin therapy.<sup>2</sup>
  - Echocardiography is valuable for detecting rheumatic mitral valve disease (there is universal agreement that these patients should receive warfarin therapy).<sup>2</sup>
  - Detection of left atrial thrombus is a contraindication for cardioversion of AF (see below).
  - Transesophageal echocardiography (TEE) far surpasses transthoracic echocardiography (TTE) in the evaluation of cardiogenic risk factors in patients with AF.<sup>2</sup>
- Risk stratification caveats
  - No published risk stratification tool is ideal and all can frequently underestimate stroke risk.<sup>9</sup>

- Risk stratification tools perform less well when limited to patients without prior history of stroke/transient ischemic attack (TIA)/systemic embolism.<sup>1</sup>
- While risk stratification tools identify AF patients who will benefit most and least from warfarin therapy, the stroke vs. bleeding risk tipping point for anticoagulation therapy use is controversial, especially for those at intermediate risk for stroke.<sup>2</sup>
- No tool can incorporate all potential AF stroke risk factors. Risk stratification tools can therefore best be described as “rough guides” to help inform clinicians.<sup>9</sup>
- Validated bleeding risk stratification tools are lacking.
- Patient perspectives and preferences should also factor into clinical decision making.<sup>1</sup>

### *Optimal intensity of anticoagulation for AF<sup>2</sup>*

- Optimal anticoagulation therapy intensity involves a careful balancing between maximizing protection against thromboembolism while minimizing bleeding risk (ICH in particular rivals ischemic stroke in terms of clinical importance).
  - The risk of ischemic stroke is low at INR levels  $\geq 2.0$ .<sup>1</sup>
  - The risk of ICH increases at INR levels of 3.5–4.0 and above, particularly in the elderly.<sup>1</sup>
  - An INR of  $<2.0$  at admission for a new stroke substantially increases the likelihood of death and severe disability from AF-related stroke.<sup>13</sup>
  - There is no decreased risk of ICH at INR levels  $<2.0$ .<sup>1</sup>
- Strong evidence supports the recommended INR target of 2.5 (range 2–3).
  - The American College of Cardiology/American Heart Association/European Society of Cardiology 2006 Guidelines’ suggestion that a lower target INR (1.6–2.5) may be considered in patients unable to tolerate standard intensity warfarin therapy is *not* evidence based.
  - Narrower target ranges have been suggested in certain situations (e.g., INR 2.0–2.5 has been recommended in patients requiring warfarin, ASA, and clopidogrel following percutaneous coronary intervention).<sup>14</sup> Such



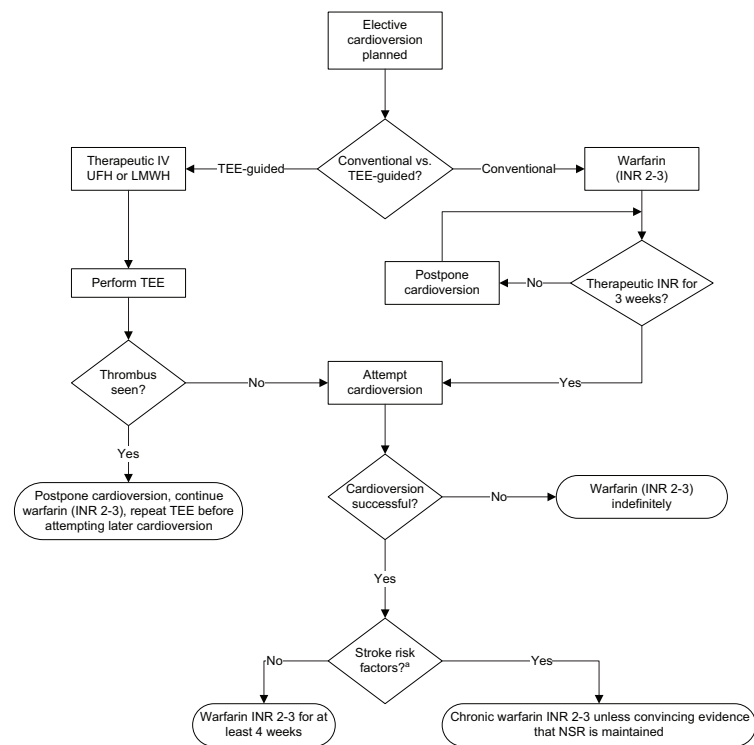
narrow ranges are not supported by good evidence, make achieving therapeutic INRs more difficult, and usually result in the need for more frequent INR testing.

- Target INR range 2–3 should be used for most patients with AF.

### *Stroke prevention considerations during cardioversion*

- Systemic embolism is the most serious complication of cardioversion whether NSR is reestablished by electrical, pharmacologic, or spontaneous means.<sup>1</sup>
- Conversion of AF to NSR, regardless of method, results in transient mechanical dysfunction of the left atrium (“stunning”).<sup>2</sup>
  - Recovery of mechanical function occurs over a period of days to weeks (depending in part on duration of AF prior to conversion).
  - Thrombus formed prior to conversion to NSR or during the period of atrial stunning can be expelled after the return of mechanical functioning resulting in stroke or systemic embolism.
- There is no evidence that cardioversion followed by prolonged maintenance of NSR effectively reduces thromboembolism in AF.<sup>2</sup>
  - Although at least 4 weeks of warfarin therapy (INR 2–3) is recommended following successful cardioversion, patients with risk factors for thromboembolism should continue anticoagulation beyond 4 weeks unless there is convincing evidence that NSR is maintained.<sup>1</sup>
- There are no published data to guide anticoagulation for emergency cardioversion. Expert opinion suggests that hemodynamically unstable patients requiring emergency cardioversion should receive therapeutic anticoagulation with either IV UFH or LMWH started as soon as possible, followed by at least 4 weeks of warfarin therapy (INR 2–3).<sup>1</sup>
  - The optimal strategy for initiating warfarin once patients are hemodynamically stable is not known. Most stable patients do not require cross-coverage with parenteral anticoagulants (“bridge therapy”).<sup>1</sup>
  - Some providers are more comfortable bridging more worrisome AF patients with UFH/LMWH during warfarin initiation. Examples include patients with echocardiographic evidence of left atrial thrombus or those with advanced heart failure.

- Limited data comparing UFH (infusion targeting aPTT ratio 1.5–2.5 times control) to LMWH (enoxaparin 1 mg/kg SC q 12 hr) as a bridge to warfarin with transesophageal echocardiography (TEE) prior to cardioversion (if no thrombus detected) found no differences between strategies.<sup>15</sup>



IV = intravenous; UFH = unfractionated heparin; LMWH = low-molecular-weight heparin; TEE = transesophageal echocardiogram; INR = international normalized ratio; NSR = normal sinus rhythm.

\*Stroke risk factors include age >75 years; history of hypertension; diabetes mellitus; moderately or severely impaired left ventricular systolic function and/or heart failure.

**Figure 12-2: Anticoagulation Therapy for Elective Cardioversion Treatment Algorithm**

### *Electrical vs. pharmacologic cardioversion, implications for anticoagulation therapy*

- Anticoagulation therapy recommendations are similar for electrical and pharmacologic cardioversion.
- Amiodarone is commonly used to maintain NSR in AF patients following successful cardioversion and presents unique challenges for patients on warfarin therapy.<sup>16</sup>
  - Amiodarone inhibits the metabolism of warfarin leading to the potential for excessive anticoagulation and increased bleeding risk.
  - Amiodarone may take hundreds of days to reach steady state due to its very long half-life. In addition, amiodarone can cause hypo- or hyperthyroidism that can also affect warfarin metabolism.
  - Co-administration of warfarin and amiodarone requires vigilant INR monitoring (at least weekly for several weeks and as needed thereafter). Some have advocated empiric warfarin dose reductions (between 35% and 65%) when amiodarone is added to ongoing warfarin therapy.<sup>16</sup>

## **NONPHARMACOLOGIC PREVENTION OF AF STROKE**

- Obliteration of the left atrial appendage by direct surgical truncation, amputation, or closure devices inserted into the left atrial appendage (e.g., the Watchman device) are emerging options for patients who cannot safely undergo anticoagulation therapy.<sup>2</sup>
  - These techniques should be considered investigational until more information is available to establish their efficacy and safety compared to available therapies. The use and duration of anticoagulation therapy with these techniques has yet to be determined.
  - In some cases, small pockets may still be present after the procedure creating a continued risk for thrombus formation.
- Other nonpharmacologic measures aimed at restoring NSR, including the surgical Maze procedure and various catheter ablation techniques, are playing an increasing role in AF management.
  - The current version of the Maze procedure involves cryotherapy or bipolar radiofrequency ablation in the atria along with the amputation

of both atrial appendages to prevent the occurrence of AF and restores NSR in over 90% of patients.<sup>2</sup> The procedure can be done in conjunction with other surgical procedures, such as cardiac valve replacement or independently through a small incision to access the atria.

- Many less invasive alternatives, including thoracoscopic and catheter-based ablation techniques, are under investigation.<sup>2</sup> The primary indication for catheter AF ablation is the presence of symptomatic AF refractory to or intolerant of antiarrhythmic medication.<sup>17</sup>
- Ablation involves placing a catheter into the left atrium and either using a heating or freezing technique to tissues surrounding the pulmonary veins to disrupt their electrical conduction by blocking or destroying abnormal electrical pathways and/or ectopic foci.
  - AF recurrence rates with catheter ablation are high and may be asymptomatic, even among previously symptomatic patients.<sup>1</sup>
  - For this reason, AF patients with stroke risk factors should continue warfarin therapy for a prolonged period after surgery or ablation procedures.<sup>1</sup>
- Embolic stroke complicates from 0% to 5% of catheter-based ablation procedures. Various intravenous unfractionated heparin regimens have been proposed for use during the procedure with those prolonging the activated clotting time (ACT) above 300 seconds, reducing the risk of thrombus formation more than when the ACT was 250–300 seconds.<sup>2</sup>
- The Heart Rhythm Society/European Heart Rhythm Association/European Cardiac Arrhythmia Society Expert Consensus Statement on Catheter and Surgical Ablation of Atrial Fibrillation makes the following recommendations regarding anticoagulation therapy during ablation procedures<sup>17</sup>:
  - Recommendations regarding anticoagulation at the time of cardioversion apply to patients who are in AF at the time of the ablation procedure.
  - Patients with persistent AF who are in AF at the time of ablation should have TEE to screen for thrombus even if warfarin anticoagulation was used prior to the procedure. When warfarin is discontinued for the ablation, some experts recommend 0.5–1 mg/kg of enoxaparin twice daily until the evening prior to the ablation (postprocedure anticoagulation plans may be in part driven by the procedure and potential complications).

- After catheter ablation, anticoagulation is interrupted briefly (e.g., 4–6 hours) to allow sheath removal followed by prompt resumption of warfarin. UFH or enoxaparin should be continued until therapeutic INR is achieved (some experts suggest 0.5 mg/kg enoxaparin twice daily to reduce the risk of postprocedure bleeding complications, such as groin hematoma and retroperitoneal bleeding).
- Warfarin is recommended for all patients for at least 2 months following an AF ablation procedure (consider prolonged therapy for CHADS<sub>2</sub> ≥2).

## REFERENCES

### \*Key articles

- \* 1. Singer DE, Albers GW, Dalen JE, et al. Antithrombotic therapy in atrial fibrillation: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines (8th ed.). *Chest*. 2008;133:546S–592S.
- \* 2. Fuster V, Ryden LE, Cannom DS, et al. ACC/AHA/ESC 2006 Guidelines for the Management of Patients with Atrial Fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines. *Circulation*. 2006;114:e257–e354.
3. Lloyd-Jones D, Adams R, Carnethon M, et al. Heart disease and stroke statistics—2009 update: a report from the American Heart Association Statistics Committee and Stroke Statistics Subcommittee. *Circulation*. 2009;119:e21–181.
4. Van GI, Hagens VE, Bosker HA, et al. A comparison of rate control and rhythm control in patients with recurrent persistent atrial fibrillation. *N Engl J Med*. 2002;347:1834–1840.
5. Wyse DG, Waldo AL, DiMarco JP, et al. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med*. 2002;347:1825–1833.
6. Hagens VE, Ranchor AV, Van SE, et al. Effect of rate or rhythm control on quality of life in persistent atrial fibrillation. Results from the Rate Control Versus Electrical Cardioversion (RACE) Study. *J Am Coll Cardiol*. 2004;43:241–247.
7. Connolly SJ, Pogue J, Hart RG, et al. Effect of clopidogrel added to aspirin in patients with atrial fibrillation. *N Engl J Med*. 2009;360:2066–2078.
8. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. *Lancet*. 2006;367:1903–1912.

9. Lip GY. The balance between stroke prevention and bleeding risk in atrial fibrillation: a delicate balance revisited. *Stroke*. 2008;39:1406–1408.
10. Johnson SG, Rogers K, Delate T, et al. Outcomes associated with combined antiplatelet and anticoagulant therapy. *Chest*. 2008;133:948–954.
- \* 11. **Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA*. 2001;285:2864–2870.**
12. Lip GY, Nieuwlaat R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. *Chest*. 2010;137:263–272.
13. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med*. 2003;349:1019–1026.
14. King SB III, Smith SC Jr., Hirshfeld JW Jr., et al. 2007 Focused Update of the ACC/AHA/SCAI 2005 Guideline Update for Percutaneous Coronary Intervention: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2008;117:261–295.
15. Klein AL, Jasper SE, Katz WE, et al. The use of enoxaparin compared with unfractionated heparin for short-term antithrombotic therapy in atrial fibrillation patients undergoing transoesophageal echocardiography-guided cardioversion: assessment of Cardioversion Using Transoesophageal Echocardiography (ACUTE) II randomized multicentre study. *Eur Heart J*. 2006;27:2858–2865.
16. Lu Y, Won KA, Nelson BJ, et al. Characteristics of the amiodarone-warfarin interaction during long-term follow-up. *Am J Health-Syst Pharm*. 2008;65:947–952.
- \* 17. **Calkins H, Brugada J, Packer DL, et al. HRS/EHRA/ECAS expert Consensus Statement on catheter and surgical ablation of atrial fibrillation: recommendations for personnel, policy, procedures and follow-up. A report of the Heart Rhythm Society (HRS) Task Force on catheter and surgical ablation of atrial fibrillation. *Heart Rhythm*. 2007;4:816–861.**