Other than anticoagulation, what is the best therapy for those with atrial fibrillation?

EVIDENCE-BASED ANSWER

Rate control with long-term anticoagulation is recommended for most patients with atrial fibrillation (strength of recommendation [SOR]: **A**, based on randomized controlled trials [RCTs]). A rhythm-control strategy provides no survival or quality-of-life benefit when compared with rate control and causes more adverse drug effects and increased hospitalizations (SOR: **A**, based on RCTs).

Non-dihydropyridine calcium-channel blockers (diltiazem, verapamil) and most beta-blockers are effective for controlling heart rate both at rest and during exercise (SOR: **A**, based on RCTs). Digoxin is only effective for rate control at rest and should be reserved for patients with systolic dysfunction or as an adjunct for those inadequately rate-controlled on calcium-channel blockers or beta-blockers (SOR: **B**, based on RCTs).

Subgroups in whom rhythm control may be superior are patients with persistent fatigue and dyspnea despite ventricular rate control and those unable to achieve adequate rate control. Both pharmacologic conversion (SOR: **B**, based on RCTs) and direct-current cardioversion (SOR: **B**, based on observational studies) are appropriate options in these patients.

Long-term anticoagulation is necessary for high-risk patients even if they are successfully managed with rhythm control (SOR: **A**, based on RCTs).

EVIDENCE SUMMARY

Five recent RCTs have demonstrated similar mortality and cardiovascular morbidity in atrial fibrillation patients treated with either a rate-control or rhythm-control strategy.[1–5]

The AFFIRM trial, the largest (n=4060), was a nonblinded, randomized, multicenter study with an average follow-up of 3.5 years.[1] The patients were aged 65 years or older and had at least 1 other risk factor for stroke. The rhythm-control group was given an antiarrhythmic medication chosen by the treating physician, while the rate-control group was given either a beta-blocker, a calcium-channel blocker, digoxin, or a combination of these as needed. Heart-rate goals were a resting pulse under 80 beats per minute, and a pulse after a 6-minute walk under 110 beats per minute. An intention-to-treat analysis was followed.

There was no difference between the 2 groups for the composite endpoints of death, disabling stroke, disabling anoxic encephalopathy, major bleeding, or cardiac arrest. A nonsignificant trend was observed for mortality favoring the rate-control group (relative risk [RR]=1.15; 95% confidence interval [CI], 0.99–1.34). Quality-of-life measures were equivalent in the 2 groups at all points in the study.[1]

More patients in the rhythm-control group required hospitalization (number needed to harm [NNH]=12.3; $P<.001$) and had adverse drug effects ($P\leq.001$ for each of pulmonary events [NNH=18], gastrointestinal events [NNH=17], bradycardia [NNH=56], and prolonged QT [NNH=63]). This trial did not include younger patients without stroke risk factors, or those with paroxysmal atrial fibrillation.[1]

The 4 other RCTs also found no greater benefit with a rhythm-control strategy vs rate-control for most patients with atrial fibrillation.[2–5]

Two systematic reviews have looked at the efficacy of medications for ventricular rate control in atrial fibrillation.[6,7] The first analyzed 54 trials involving 17 agents and focused on digoxin calcium-channel blockers and beta-blockers. The second systematic review evaluated 45 trials with similar agents. Both reviews were unable to perform mathematical pooling due to the heterogeneity of the studies. However, both showed strong evidence for superior ventricular rate control at both exercise and rest with verapamil and diltiazem compared with placebo.[6,7]

All beta-blockers tested were effective in rate-control during exercise and most (excluding labetalol and celiprolol) were effective at rest.[6,7]

A rhythm-control strategy provides no survival or quality-of-life benefit when compared with rate control

Digoxin was ineffective during exercise and less effective than beta-blockers or calcium-channel blockers at rest.[6–8] The combination of digoxin plus a calcium-channel blocker or beta-blocker may have increased benefit compared with either drug alone.[6] Evidence was insufficient to recommend propafenone, clonidine, or amiodarone for rate control.[7]

In select patients, a rhythm-control approach may be desirable. A meta-analysis of 60 RCTs evaluated 8 drugs for acute cardioversion. Ibutilide, flecainide, dofetilide, propafenone, and amiodarone were found to have the strongest evidence of efficacy.[6] There was moderate evidence for quinidine and insufficient evidence for disopyramide and sotalol.[6] Studies of pharmacologic conversion suffer from small sample size, short follow-up, and variable duration of atrial fibrillation.[6] A review of limited research reveals an 80% to 85% immediate success rate for DC cardioversion, with rare side-effects of ventricular tachycardia, transient AV node dysfunction, and significant skin blistering.[6]

For patients who elect a rhythm-control approach, RCTs demonstrate the need for continued long-term anticoagulation in high-risk patients even if they are maintained in sinus rhythm.[1,4,5] (High-risk patients are defined as those aged >65 years, or those <65 years with 1 or more stroke risk factors: diabetes, hypertension, heart failure, prior transient ischemic attack or stroke or systemic embolism, or echocardiographic evidence of a left atrium >50 mm, a shortening fraction <25%, or an ejection fraction <40%.)

RECOMMENDATION FROM OTHERS

The American Academy of Family Practice/American College of Physicians' clinical guidelines support a rate-control strategy for most patients with atrial fibrillation and recommend atenolol, metoprolol, diltiazem, or verapamil as the first-choice drugs.[8] Digoxin is recommended as a second-line agent. DC cardioversion and pharmacologic conversion for patients who desire a rhythm-control strategy are described as "appropriate options."[8]

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CLINICAL COMMENTARY: Rate control best for atrial fibrillation

AFFIRMed at last, it's rate-controlling and not rhythm-controlling drugs that get the evidence-based nod for most types of atrial fibrillation. While rate and rhythm control were equally efficacious in most patient-oriented outcomes, the antiarrhythmics sent more people to the hospital and, potentially, killed more people than the rate controlling medications. The antiarrhythmics, especially amiodarone,[9] do have a place in maintaining sinus rhythm in select patients with atrial fibrillation; but that role is limited and may be best managed with the help and support of a cardiologist.

The atrial fibrillation evidence also suggests that we need to place beta-blocker and non-dihydropyridine calcium-channel blockers (ie, verapamil and diltiazem) as first-line choices for rate-control therapy. Digoxin still has a place in our medical armamentarium; but its role is as an adjunct or backup to the blockers for most patients.

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What is the best therapy for superficial thrombophlebitis?

EVIDENCE-BASED ANSWER

For proximal saphenous vein thrombosis, anticoagulation is more effective than venous ligation (with or without stripping) in preventing deep venous thrombosis (DVT) and pulmonary embolus (PE) (strength of recommendation [SOR]: **C**, qualitative systematic review of primarily case series).

For patients with superficial venous thrombophlebitis (SVTP) distal to the saphenous vein of the thigh, tenoxicam (a nonsteroidal anti-inflammatory agent [NSAID]) and low-molecular-weight heparin are similarly effective for reducing extension and subsequent DVT when administered along with compression therapy (SOR: **B**, 1 randomized controlled trial). Oral or topical NSAIDs, topical heparin, and topical nitroglycerin all alleviate symptoms and speed resolution of SVTP caused by infusion catheters (SOR: **B**, smaller, occasionally conflicting randomized trials).

EVIDENCE SUMMARY

Superficial thrombophlebitis refers to erythema, pain, induration, and other findings of inflammation in superficial veins, usually due to infection or thrombosis. Typically, SVTP is localized problem, but some lower-extremity SVTP is associated with increased risk of DVT and PE, particularly the long saphenous vein. This review will not address thrombosis in the superficial femoral vein, a portion of the deep venous system, which requires full DVT therapy.[1]

Since saphenous vein thrombosis above the knee is associated with DVT and PE, 1 systematic review looked at papers comparing anticoagulation (IV heparin followed by 6 weeks to 6 months of warfarin) with surgical ligation of the saphenous vein (either alone or combined with vein stripping or with vein stripping and perforator ligation).[1] The review included primarily case series with widely varying protocols. According to the authors, the data "suggests that medical management with anticoagulants is somewhat superior" to surgery for preventing DVT and PE. However, the fewest extensions of SVTP occurred when vein ligation was combined with stripping of the thrombosed vein and interruption of perforators.

In a more recent trial, patients randomized to subcutaneous heparin at 12,500 units twice daily for a week followed by 10,000 units twice daily had fewer vascular complications of proximal saphenous vein thrombosis than those receiving heparin at 5000 units twice daily (6/30 in the low-dose group and 1/30 in the high-dose group; $P<.05$; number needed to treat [NNT]=6).[2] There were no bleeding complications in either group.

One large double-blind randomized controlled trial compared tenoxicam (an NSAID available in Canada, similar to piroxicam), enoxaparin (Lovenox), and placebo for 8 to 12 days in 427 patients with SVTP of the leg measuring 5 cm or more.[3] Patients were also treated with compression hose. Patients who required immediate anticoagulation or venous ligation were excluded. Within 3 months, 35% of patients taking placebo developed

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