Is an outpatient workup safe for patients with a transient ischemic attack?

■ EVIDENCE-BASED ANSWER
There is no compelling evidence that outpatient diagnostic workup of patients with transient ischemic attack (TIA) is less safe than inpatient workup, or that hospitalization prevents stroke or improves stroke outcomes after TIA (strength of recommendation [SOR]: C, based on case series studies). Because the risk of stroke is substantial in the week following a TIA (SOR: A, based on a prospective cohort study), evaluation and treatment for reversible stroke risk factors should be initiated urgently and completed within a week of initial presentation (SOR: C, based on expert consensus opinion).

Risk factors for patients at highest risk for stroke or other cardiovascular events after TIA include age >60 years, diabetes, TIA lasting longer than 10 minutes, and a TIA associated with weakness or speech impairment (SOR: B, based on retrospective cohort study). Hospitalization may be prudent for patients at high risk for cardiovascular events or for those with mental status changes, an inadequate home situation, or the physician’s inability to obtain expedient evaluation (SOR: C, based on case series studies).

■ EVIDENCE SUMMARY
Transient ischemic attack (Figure) is a temporary, focal brain or retinal deficit caused by vascular disease that clears completely in less than 24 hours.1 A large prospective cohort study recently estimated the risk of stroke after a TIA or minor stroke to be 8% to 12% at 7 days and 11% to 15% at 1 month.2

In a large retrospective cohort study, 5% of TIA patients returned to the emergency department with a stroke within the first 2 days after TIA.3 Another 6% returned with a stroke within 90 days. Five independent risk factors were identified: age >60 years, diabetes mellitus, duration of TIA longer than 10 minutes, signs or symptoms of weakness, and speech impairment. Thirty-four percent of patients with all 5 risk factors, and none of the patients without any risk factors, had a stroke within 90 days. Of note, 13% of the TIA patients had an arrhythmia, congestive heart failure, unstable angina, myocardial infarction, stroke, or recurrent TIA within 4 days of initial presenting with a TIA. Twenty-five percent of the patients experienced 1 of these cardiovascular events during the 3 months of follow-up.

In a retrospective case review of TIA and stroke patients, the hospital admissions of 4 of 21

What are Clinical Inquiries?
Clinical Inquiries answer real questions that family physicians submit to the Family Practice Inquiries Network (FPIN), a national, not-for-profit consortium of family practice departments, residency programs, academic health sciences libraries, primary care practice-based research networks, and other specialists.

Questions chosen for Clinical Inquiries are those that family physicians vote as most important through a web-based voting system.

Answers are developed by a specific method:
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• FPIN clinician authors select the research articles to include, critically appraise the research evidence, review the authoritative sources, and write the answers.
• Each Clinical Inquiry is reviewed by 4 or more peers and editors before publication in JFP.
• FPIN medical librarians coauthor Type I Clinical Inquiries that have required a systematic search.
• Finally, a practicing family physician writes an accompanying commentary.
TIA patients were retrospectively categorized as medically justified. Admission was categorized as medically justified if the patient had 1 or more of the following criteria: another diagnosis that warranted admission, inadequate home situation, altered mental status, an adverse event during hospitalization including worsening of the deficit, and if the patient underwent some hospital-based treatment that could not be provided on an outpatient basis. Ease and rapidity of evaluation was not considered medically justifiable and outcome improvement (stroke prevention) was not studied.

Two retrospective chart reviews of TIA found considerable practice variability in the evaluation of TIA patient. In 1 study of TIA patients presenting to an emergency department, 81% had a computed tomography scan, 75% had electrocardiogram, and 74% had a complete blood count. Carotid Doppler imaging was performed in the emergency department in 16%, and 26% were referred for outpatient Doppler studies. One percent had an ECG in the emergency department, and 16% were given ECGs as outpatients.

Risk of stroke is greatest in the week following a TIA, particularly if the event lasted more than 10 minutes or caused weakness or speech impairment, or if the person is older than 60 years or has diabetes.

Hospitalization is probably most important for patients at risk for cardiovascular events, exhibiting changes of mental status, or unable to receive adequate work-up in the outpatient setting.

Symptoms vary with the arterial system involved.

Vertebral involvement usually leads to confusion or dizziness, or affects vision in both eyes.

Carotid involvement may cause unilateral blindness or weakness.

Internal carotid at the bifurcation or common carotid are frequently affected.

Atherosclerotic plaque, emboli, or arterial spasm may precipitate the event.

The American Heart Association (AHA) recommends that physicians use a stepwise approach to TIA evaluation as outlined in the Table. The AHA also recommends that the diagnostic evaluation of patients seen within 7 days of a TIA should be completed within 1 week or less. The AHA leaves the decision whether to hospitalize a patient up to the physician based on a patient’s circumstances. The goals of diagnostic testing are to identify or exclude causes of TIA requiring specific therapy, to assess modifiable risk factors, and to determine prognosis.

The National Stroke Association recommends that patients with known high-grade stenosis in a
vascular territory appropriate to the symptoms, and patients with recurrent symptoms, undergo urgent evaluation. Evaluation includes imaging and ruling out other causes of TIA. Patients should be admitted to the hospital if imaging is not immediately available. If indicated, carotid endarterectomy should be performed without delay.\(^a\)

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**Clinical Commentary:**

Make the patient aware of the risks of TIA and quickly complete the work-up

It is important to remember that a diagnosis of TIA can only be made retrospectively. All patients with ongoing focal neurologic signs must be evaluated immediately and (if the symptom duration is less than 3 hours) considered potential candidates for emergent thrombolytic therapy. The vast majority of TIA patients are asymptomatic during their evaluation. Because they feel well and may have a considerable element of denial, it can be hard to get them to rapidly complete their evaluation in either the inpatient or outpatient setting. It is therefore critical that the patient be made aware that the highest risk period is soon after the TIA and that failure to quickly complete the work-up could have serious negative consequences.

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**References**

Does combining aspirin and warfarin decrease the risk of stroke for patients with nonvalvular atrial fibrillation?

### EVIDENCE-BASED ANSWER

Adjusted-dose warfarin (international normalized ratio [INR]=2.0–3.0) remains the most efficacious antithrombotic regimen for the primary and secondary prevention of cardioembolic stroke in high-risk patients with nonvalvular atrial fibrillation (NVAF) (strength of recommendation [SOR]: A, based on randomized controlled trials).

Aspirin therapy at a dose of 75 to 325 mg reduces the risk of stroke to a lesser degree and may be useful for low-risk patients with NVAF or patients at high risk for bleeding (SOR: A, based on randomized controlled trials).

Combination therapy with low, fixed-dose warfarin (1–2 mg) and aspirin has not been shown to be superior to aspirin therapy alone. Moreover, this combination appears to be inferior to adjusted-dose warfarin (SOR: A, based on randomized controlled trials). To date, no clinical trials have investigated the efficacy and safety of combining adjusted-dose warfarin and aspirin for the prevention of stroke from NVAF.

### EVIDENCE SUMMARY

Thromboprophylaxis with warfarin for patients with NVAF has been studied in 5 major clinical trials. Pooled analysis with more than 2900 patients revealed an annual stroke risk of 4.5% for control patients and 1.4% for patients receiving adjusted-dose warfarin (number needed to treat [NNT] for 1 year=32). Studies comparing aspirin with placebo for treatment of NVAF are less robust and have heterogeneous results. Combined data from the Atrial Fibrillation Aspirin Anticoagulation Study (AFASAK-1), the European Atrial Fibrillation Trial, and the Stroke Prevention in Atrial Fibrillation (SPAF) I studies revealed a small but statistically significant reduction in stroke rates (relative risk reduction [RRR]=21%; 8.1% vs 6.3% annual stroke rate; NNT=55), with no increase in major bleeding risk.

The SPAF III investigators further compared adjusted-dose warfarin with low-intensity, fixed-dose warfarin plus aspirin in high-risk patients with NVAF. An interim analysis at 1.1 years revealed superiority in the reduction of ischemic strokes and systemic embolisms with adjusted-dose warfarin (7.9% vs 1.9% per year, respectively; NNT=16), which led to the trial’s termination. Rates of major hemorrhage did not differ between treatment groups (2.4% per year with combination vs 2.1% per year with warfarin).

Two similar studies published in 1998 were terminated early, in light of the SPAF III results. The Second Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation Study completed 3 of the scheduled 6 years; it compared warfarin 1.25 mg/d, warfarin 1.25 mg/d plus aspirin 300 mg, aspirin 300 mg alone, and adjusted-dose warfarin (INR=2.0–3.0) to treat NVAF for patients with a median age of 74 years (range, 44–89). The cumulative stroke event rate after 1 year was 5.8% on fixed-dose warfarin, 7.2% on combination, 3.6% on aspirin, and 2.8% on adjusted-dose warfarin. The researchers concluded that while the difference was not statistically significant, adjusted-dose warfarin seemed superior to other treatments after 1 year.

In a similar fashion, Pengo et al randomized patients with NVAF aged >60 years to fixed-dose (1.25 mg/d) or adjusted-dose warfarin (INR=2.0–3.0) to evaluate ischemic stroke rates and major bleeding. This trial enrolled 303 patients who were followed up for 14.5 months before discontinuation of the trial. The rate of ischemic stroke was significantly higher in the fixed-dose warfarin group compared with the adjusted warfarin group (3.7%...
vs 0% per year; NNT=27). Major bleeds were more frequent in the adjusted warfarin group (2.6% vs 1% per year, number needed to harm=63). While the combined primary endpoint did not show a significant benefit for adjusted-dose warfarin, this study suggests that fixed-dose warfarin does not protect against ischemic stroke in NVAF patients.

The intensity of warfarin therapy and stroke severity has recently been studied for patients with NVAF.12 A subtherapeutic INR (<2.0) on the day of admission was independently associated with severe stroke (odds ratio=1.9; 95% confidence interval [CI], 1.1–3.4), and risk of death at 30 days (hazard ratio, 3.4; 95% CI, 1.1–10.1) compared with an INR of 2.0 or greater. Furthermore, an admission INR of 1.5–1.9 had a similar mortality rate (18%) as an INR of <1.5 (15%), and for those patients on aspirin (15%). These findings further support the importance of achieving therapeutic INR goals for patients with NVAF.

### RECOMMENDATIONS FROM OTHERS

The American Heart Association, the American College of Cardiology,13 and the American College of Chest Physicians (ACCP)14 recommend adjusted-dose warfarin for nonvalvular atrial fibrillation patients at high risk for ischemic stroke. Risk stratification is a key component in order to maximize efficacy while minimizing bleeding risk.

The **Table** summarizes the ACCP guidelines for prevention of ischemic stroke based on patient risk factors.

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<table>
<thead>
<tr>
<th>Atrial fibrillation stroke profile</th>
<th>Risk factors</th>
<th>Treatment guidelines</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>High risk</strong></td>
<td><em>One or more of the following:</em></td>
<td>Warfarin (INR=2.5; range, 2–3)</td>
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<tr>
<td></td>
<td>Age 75 years</td>
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<td></td>
<td>History of hypertension</td>
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<td></td>
<td>Cerebrovascular accident/transient ischemic attack</td>
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<td></td>
<td>Arterial thromboembolism</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Poor left ventricular systolic dysfunction (ejection fraction &lt;40%)</td>
<td></td>
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<tr>
<td></td>
<td>Rheumatic mitral valve disease</td>
<td></td>
</tr>
<tr>
<td></td>
<td>or prosthetic heart valve</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2 or more moderate risk factors</td>
<td></td>
</tr>
<tr>
<td><strong>Moderate risk</strong></td>
<td><em>No high risk factors and 1 of the following:</em></td>
<td>Warfarin (INR=2.5, range, 2–3) or Aspirin 325 mg/d</td>
</tr>
<tr>
<td></td>
<td>Age 65–74 years</td>
<td></td>
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<tr>
<td></td>
<td>Diabetes</td>
<td></td>
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<tr>
<td></td>
<td>Coronary artery disease</td>
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</tr>
<tr>
<td><strong>Low risk</strong></td>
<td><em>No high or moderate risk factors and:</em></td>
<td>Aspirin 325 mg/d</td>
</tr>
<tr>
<td></td>
<td>Age &lt;65 years</td>
<td></td>
</tr>
</tbody>
</table>

INR, international normalized ratio
CLINICAL COMMENTARY:

When warfarin is started, aspirin should be stopped

The lack of evidence to support the combined use of aspirin and warfarin creates an excellent opportunity to remove an unnecessary drug from a patient’s medication list. Patients who were taking aspirin for thrombosis prophylaxis occasionally develop atrial fibrillation. Many patients who take aspirin for prophylaxis do so because they are already at moderate to high risk for embolic stroke. The onset of atrial fibrillation in these patients appropriately leads to the initiation of warfarin. At the time of warfarin initiation, the aspirin should be stopped. By stopping the aspirin at the initiation of the warfarin, one can reduce the number of medications that the patient must take, avoid the interactions of aspirin and warfarin, and eliminate the side effects of the aspirin.

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REFERENCES


Do statins reduce the risk of stroke?

EVIDENCE-BASED ANSWER

HMG Co-A reductase inhibitors (statins) are effective for primary prevention of ischemic stroke in people who have a history of occlusive artery disease, coronary artery disease, or diabetes without history of cerebrovascular disease (strength of recommendation [SOR]: A, based on 1 randomized controlled trial [RCT]).

Statins reduce the risk of ischemic stroke in hypertensive patients with multiple cardiovascular risk factors and nonfasting total cholesterol <250 mg/dL (SOR: A, based on RCT). Statins also reduce the risk of ischemic stroke for patients with coronary disease or equivalents (such as diabetes or peripheral artery disease), including patients who have a normal fasting lipid profile (SOR: A, based on RCT). For patients with ischemic stroke who have coronary disease, statins prevent recurrent ischemic stroke; evidence is conflicting about whether this benefit is proportional to initial cholesterol levels (SOR: A, systematic review). Statins do not prevent hemorrhagic stroke (SOR: A, based on RCTs).

CONTINUED
Statins reduce the risk of ischemic stroke for patients with coronary disease or equivalents

**EVIDENCE SUMMARY**

We found no studies evaluating statins for the primary prevention of stroke. An observational study of 433 patients with ischemic stroke found that patients who were taking statins before hospital admission more often had better outcomes (51%) than those who were not taking statins (38%). However, the groups differed in many respects.\(^1\) Many coronary event prevention and treatment trials using statins include the risk of primary and recurrent ischemic stroke as secondary endpoints for patients with high cardiac risk.

**Primary prevention of stroke in vascular disease.** The Heart Protection Study followed 20,536 patients in the United Kingdom (aged 40–80 years), 3280 with a history of cerebrovascular disease (defined as nondisabling stroke, transient cerebral ischemic attack, or carotid endarterectomy or angioplasty) and 17,256 with other occlusive arterial disease, coronary artery disease, or diabetes. Patients were randomized to receive either simvastatin 40 mg or placebo for an average of 5 years. The endpoint was major vascular events: myocardial infarction, stroke of any type, and revascularization procedure.

Simvastatin reduced the combined risk of nonfatal or fatal ischemic stroke for patients with no history of cerebrovascular disease (3.2% for simvastatin vs 4.8% with placebo; relative risk reduction=33%, number needed to treat [NNT]=63; \(P=0.0001\)).\(^2\) As noted in other well-done studies, the Heart Protection Study showed no difference in the number of hemorrhagic strokes between treatment and placebo groups. There were 3500 subjects with pretreatment low-density lipoprotein (LDL) cholesterol <100 mg/dL; lowering LDL to 65 mg/dL reduced major vascular event risk by about 25%.\(^3\)

**Hypertension with multiple cardiovascular risk factors and cholesterol <250 mg/dL.** The ASCOT-LLA study compared atorvastatin with placebo in 10,305 hypertensive Caucasian patients with multiple cardiovascular risk factors and a total nonfasting cholesterol of 250 mg/dL (6.5 mmol/L) or less. Patients were aged 40 to 79 years and had at least 3 other cardiovascular risk factors (left ventricular hypertrophy, abnormal electrocardiogram, type 2 diabetes, peripheral artery disease, stroke or transient ischemic attack, male sex, age >55 years, proteinuria or microalbuminuria, smoking, family history of premature coronary heart disease). The study was stopped early at a median of 3.3 years because atorvastatin significantly reduced cardiac events. Atorvastatin also significantly reduced ischemic strokes when compared with placebo (relative risk [RR]=0.73, 95% confidence interval [CI], 0.56–0.96; \(P=0.024\)). This study did not differentiate between first or second stroke. The NNT was 155.\(^4\)

**Ischemic stroke and coronary disease.** The LIPID trial randomized 9014 patients with a history of acute coronary syndromes and total cholesterol of 150 to 270 mg/dL (4 to 7 mmol/L) to either pravastatin or placebo and followed them for 6 years. Among the 350 patients with prior ischemic stroke, there were 388 new ischemic strokes over the course of the study. When adjusted for risk factors (atrial fibrillation, history of cerebrovascular accident, diabetes, hypertension, cigarette smoking, body mass index, and male sex), pravastatin reduced recurrent ischemic stroke by 21% relative to placebo (\(P=0.024\)). The reduction was not modified by baseline lipid level.\(^5\)

A meta-analysis of 15 randomized placebo-controlled trials using various statins (32,684 participants) assessed the risk of strokes for patients with a history of coronary disease. Among patients who had cerebrovascular disease, statins significantly reduced recurrent ischemic stroke (RR=0.74; 95% CI, 0.64–0.86). One recurrence of ischemic stroke would be prevented for every 110 coronary disease patients treated with a statin. Achieving final total cholesterol <232 mg/dL correlated with reduced
risk of recurrent stroke. Three of the studies evaluated primary prevention of stroke and did not show a significant risk reduction (RR=0.85; P=.4). Statins did not reduce the rate of hemorrhagic stroke or fatal strokes.

**Risks of statins.** In 1 study involving 35,000 participants and 158,000 person-years of observation, there were 8 cases of rhabdomyolysis in the treatment groups vs 5 in the placebo groups. Forty-three deaths attributed to statin therapy have been reported to the Food and Drug Administration from 1987 to 2001, or 1 per million person-years of use. The Heart Protection Study found simvastatin and placebo users reported myopathy or muscle pain at the same annual rate of 0.01%.

**RECOMMENDATIONS FROM OTHERS**

We found no recommendations specifically regarding the use of statins to prevent stroke. However, the Third Report of the National Cholesterol Education Program, Adult Treatment Panel III (NCEP-ATP III) describes symptomatic carotid artery disease as a coronary heart disease risk equivalent and recommends therapy to reduce the LDL below 100 mg/dL.

**REFERENCES**


**CLINICAL COMMENTARY:**

Statins prevent cerebrovascular accidents and have low adverse event rates

Statins are effective for primary and tertiary cardiovascular disease prevention. For those with vascular disease or significant risks, statins prevent cerebrovascular accidents and have low adverse event rates.

While no evidence is available about primary prevention of cerebrovascular accidents for those at lower risk, in practice statins are often appropriately initiated. NCEP-ATP III, the key guideline on when to start statins, is based more on cardiac benefits. Most studies evaluating statins use a triple outcome of mortality, myocardial infarction, or cerebrovascular accident. Since myocardial infarction is more common than the other adverse endpoints, there is a greater demonstrated cardioprotective effect (prevention of myocardial infarction: NNT=95; prevention of cerebrovascular accidents: NNT=735). However, regardless of whether the benefits are cardiac or cerebrovascular, statins will prevent disease for many patients.

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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 (\(P<.001\) 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.\(^6\)\(^,\)\(^7\)
Digoxin was ineffective during exercise and less effective than beta-blockers or calcium-channel blockers at rest. The combination of digoxin plus a calcium-channel blocker or beta-blocker may have increased benefit compared with either drug alone. Evidence was insufficient to recommend propafenone, clonidine, or amiodarone for rate control.

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. There was moderate evidence for quinidine and insufficient evidence for disopyramide and sotalol. Studies of pharmacologic conversion suffer from small sample size, short follow-up, and variable duration of atrial fibrillation. 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.

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. (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. 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.”

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**REFERENCES**
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.

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). 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; , .05; number needed to treat [NNT]=6). 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. 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
Oral or topical NSAIDs, topical heparin, and topical nitroglycerin all alleviate symptoms of SVTP

an extension or recurrence of their SVTP or a DVT, compared with 16% to 17% of treated patients (NNT=6). There was no significant difference in outcome between subcutaneous enoxaparin at fixed (40 mg/d) or adjusted doses (1.5 mg/kg), or 20 mg/d oral tenoxicam. In a small randomized trial (n=40), intramuscular defibrotide provided better symptom resolution than low-dose heparin for patients with uncomplicated SVTP of the leg.4

For infusion-related SVTP, a randomized controlled trial of 120 patients found both oral and topical diclofenac effective in reducing symptoms (NNT=3), although oral diclofenac had significantly more gastrointestinal side effects (number needed to harm=3 for dyspepsia).5 Two double-blind trials of topical heparin showed it to be superior to placebo in reducing symptoms and speeding healing.6,7

In the larger study (n=126), 44% of patients treated with 1000 IU/g heparin gel 3 times a day were symptom-free at 1 week, compared with 26% on placebo (NNT=6).7 A randomized trial of infusion-related SVTP (n=100) found that 2% nitroglycerin gel eliminated pain in 50 hours vs 72 hours with topical heparin (P<.05).8 A smaller, underpowered double-blind trial of topical heparin, piroxicam gel, and placebo (22 to 24 patients in each treatment arm) failed to find efficacy with either therapy.9

RECOMMENDATION FROM OTHERS

For SVTP of the leg that does not include the proximal saphenous vein, Up To Date recommends compression and oral NSAIDs, noting that NSAIDs are inexpensive, help with symptom control, and appear comparable to low-molecular-weight heparin in limiting complications.10

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CLINICAL COMMENTARY:

Those with symptoms in the thigh need closer follow-up, more aggressive therapy

Patients with a red, swollen, painful extremity are commonly encountered in my practice. I see this among patients with venous stasis due to obesity, aging, and varicosities. I find ready access to a D-dimer blood test and a venous Doppler can help me rule out DVT. I end up treating many of these patients with both an NSAID and an antistaphylococcal antibiotic, because of the lack of certainty in differentiating superficial phlebitis from cellulitis.

Upper extremity phlebitis is less common. It can occur in a delayed fashion several days after a patient has received intravenous therapy. The characteristic on exam is a knotty, red, ropey painful structure correlating to the course of the basilic or cephalic vein.

This review is helpful to me; it reinforces that the patients I see with symptoms in the thigh need closer follow-up and more aggressive therapy with anticoagulation, no matter what the Doppler shows. I usually hold off on anticoagulating other patients until they show no improvement with a trial of the NSAIDs and compression. Topical heparin and nitroglycerin gel are therapies new to me and appear worth looking into for the patient who is not improving. In a quick search for topical heparin, I could not find a US source, and it is not used locally.

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REFERENCES

Does moderate exercise prevent MI for patients with coronary heart disease?

**EVIDENCE-BASED ANSWER**

Moderate exercise reduces mortality for patients with known coronary heart disease but does not significantly decrease the risk of recurrent nonfatal myocardial infarction (MI) (strength of recommendation [SOR]: A, based on systematic review of randomized controlled trials). Exercise-based cardiac rehabilitation also reduces all-cause mortality (SOR: A, based on systematic review).

For patients with stable angina, a daily exercise program is more effective than percutaneous transluminal coronary angioplasty (PTCA) with stenting in preventing major cardiovascular events (number needed to treat [NNT]=5.5; SOR: A, based on a single randomized controlled trial).

**EVIDENCE SUMMARY**

A systematic review of cardiac rehabilitation programs evaluated 14 randomized controlled trials with exercise-based interventions.¹ An updated review added 5 more for a total of 2984 patients with coronary heart disease.² Patients with coronary heart disease comprised those with prior MI, prior coronary artery bypass graft surgery, or PTCA, and those with angina pectoris and angiographically confirmed coronary heart disease.

Exercise-based cardiac rehabilitation significantly reduced all-cause mortality (relative risk [RR]=0.76; 95% confidence interval [CI], 0.59–0.98) compared with usual care (NNT=66; 95% CI, 35–273). Cardiac mortality also decreased significantly with exercise (RR=0.73; 95% CI, 0.56–0.96) compared with usual care (NNT=49; 95% CI, 26–120).

Six studies showed particularly significant improvement in total cardiac mortality.³⁻⁸ Exercise was variably defined. Training sessions lasted 30 minutes and occurred on 2 to 5 days per week. Intensity was typically 75% to 85% of a maximum work capacity determined on an exercise test before initiating the training sessions. The type of exercise ranged from cycling alone to circuit training with 6 stationary devices. Patients were trained with supervision 1 to 36 months and followed for a mean of 24 months (range, 6–60 months).

A trend was observed toward decreased recurrence of nonfatal MI with exercise-based cardiac rehabilitation, which did not reach significance (RR=0.78; 95% CI, 0.59–1.03). An inadequate number of subjects is the most likely reason; however, other possibilities include an increase in the frequency of nonfatal MI after rehabilitation, or an increased rate of survival after MI for patients undergoing exercise-based rehabilitation.

The studies included in these reviews had several limitations. The population appears skewed in age (mean=54 years, with patients aged >65 years excluded from most studies) and gender (4.9% female); ethnicity was rarely reported. The adequacy of randomization was poor or unclear in 71% of studies, and only 4 trials reported blind assessment of outcomes. Finally, in 34% of studies the loss of participants to follow-up was more than 20%.

A well-done study randomized 101 male patients (age <70 years) with stable angina to
either a daily exercise program or standard PTCA with stenting. After 12 months, event-free survival was significantly greater among patients randomized to exercise than in those randomized to PTCA with stenting (88% vs 70%; \( P = .023; \text{NNT} = 5.5 \)). Cardiovascular events were defined as percutaneous interventions, hospitalizations, acute MI, cerebrovascular accidents, coronary artery bypass graft operation, and death.

**RECOMMENDATION FROM OTHERS**

The American Heart Association (AHA) supports aggressive risk factor management for patients with coronary heart disease, and recommends a minimum of 30 minutes of exercise 3 to 4 days per week as well as an increase in daily lifestyle activities. The American College of Cardiology endorses the position of the AHA.

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**REFERENCES**