improvement in stroke prevention and a significant increase in both hemorrhage and death. Thus, the long-term use of clopidogrel in combination with aspirin is not recommended for stroke prevention.

The short-term combination of clopidogrel with aspirin may be effective in preventing second stroke, however. A trial of 5170 Chinese patients enrolled within 24 h of TIA or minor ischemic stroke found that a clopidogrel-aspirin regimen (clopidogrel 300 mg load then 75 mg/d with aspirin 75 mg for the first 21 days) was superior to aspirin (75 mg/d) alone, with 90-day stroke risk decreased from 11.7 to 8.2% ($p < .001$) and no increase in major hemorrhage. An international NIH-sponsored trial of similar design is ongoing.

Dipyridamole is an antiplatelet agent that inhibits the uptake of adenosine by a variety of cells, including those of the vascular endothelium. The accumulated adenosine is an inhibitor of aggregation. At least in part through its effects on platelet and vessel wall phosphodiesterases, dipyridamole also potentiates the antiaggregatory effects of prostacyclin and nitric oxide produced by the endothelium and acts by inhibiting platelet phosphodiesterase, which is responsible for the breakdown of cyclic AMP. The resulting elevation in cyclic AMP inhibits aggregation of platelets. Dipyridamole is erratically absorbed depending on stomach pH, but a newer formulation combines timed-release dipyridamole, 200 mg, with aspirin, 25 mg, and has better oral bioavailability. This combination drug was studied in three trials. The European Stroke Prevention Study (ESPS) II showed efficacy of both 50 mg/d of aspirin and extended-release dipyridamole in preventing stroke, and a significantly better risk reduction when the two agents were combined. The open-label ESPRIT (European/Australasian Stroke Prevention in Reversible Ischaemia Trial) trial confirmed the ESPS-II results. After 3.5 years of follow-up, 13% of patients on aspirin and dipyridamole and 16% on aspirin alone (hazard ratio 0.80, 95% confidence index [CI] 0.66–0.98) met the primary outcome of death from all vascular causes. In the Prevention Regimen for Effectively Avoiding Second Strokes (PRoFESS) trial, the combination of extended-release dipyridamole and aspirin was compared directly with clopidogrel with and without the angiotensin receptor blocker telmisartan; there were no differences in the rates of second stroke (9% each) or degree of disability in patients with median follow-up of 2.4 years. Telmisartan also had no effect on these outcomes. This suggests that these antiplatelet regimens are similar and also raises questions about default prescription of agents to block the angiotensin pathway in all stroke patients. The principal side effect of dipyridamole is headache. The combination capsule of extended-release dipyridamole and aspirin is approved for prevention of stroke.

Many large clinical trials have demonstrated clearly that most antiplatelet agents reduce the risk of all important vascular atherothrombotic events (i.e., ischemic stroke, MI, and death due to all vascular causes) in patients at risk for these events. The overall *relative* reduction in risk of nonfatal stroke is about 25–30% and of all vascular events is about 25%. The *absolute* reduction varies considerably, depending on the particular patient's risk. Individuals at very low risk for stroke seem to experience the same relative reduction, but their risks may be so low that the "benefit" is meaningless. Conversely, individuals with a 10–15% risk of vascular events per year experience a reduction to about 7.5–11%.

Aspirin is inexpensive, can be given in low doses, and could be recommended for all adults to prevent both stroke and MI. However, it causes epigastric discomfort, gastric ulceration, and gastrointestinal hemorrhage, which may be asymptomatic or life threatening. Consequently, not every 40- or 50-year-old should be advised to take aspirin regularly because the risk of atherothrombotic stroke is extremely low and is outweighed by the risk of adverse side effects. Conversely, every patient who has experienced an atherothrombotic stroke or TIA and has no contraindication should be taking an antiplatelet agent regularly because the average annual risk of another stroke is 8–10%; another few percent will experience an MI or vascular death. Clearly, the likelihood of benefit far outweighs the risks of treatment.

The choice of antiplatelet agent and dose must balance the risk of stroke, the expected benefit, and the risk and cost of treatment. However, there are no definitive data, and opinions vary. Many authorities believe low-dose (30–75 mg/d) and high-dose (650–1300 mg/d) aspirin are about equally effective. Some advocate very low doses to avoid adverse effects, and still others advocate very high doses to be sure the benefit is maximal. Most physicians in North America recommend 81–325 mg/d, whereas most Europeans recommend 50–100 mg. Clopidogrel and extended-release dipyridamole plus aspirin are being increasingly recommended as first-line drugs for secondary prevention. Similarly, the choice of aspirin, clopidogrel, or dipyridamole plus aspirin must balance the fact that the latter are more effective than aspirin but the cost is higher, and this is likely to affect long-term patient adherence. The use of platelet aggregation studies in individual patients taking aspirin is controversial because of limited data.

ANTICOAGULATION THERAPY AND EMBOLIC STROKE

Several trials have shown that anticoagulation (INR range, 2–3) in patients with chronic nonvalvular (nonrheumatic) atrial fibrillation (NVAF) prevents cerebral embolism and stroke and is safe. For primary prevention and for patients who have experienced stroke or TIA, anticoagulation with a VKA reduces the risk by about 67%, which clearly outweighs the 1–3% risk per year of a major bleeding complication. VKAs are difficult to dose, their effects vary with dietary intake of vitamin K, and they require frequent blood monitoring of the PTT/INR. Several newer oral anticoagulants (OACs) have recently been shown to be more convenient and efficacious for stroke prevention in NVAF. A randomized trial compared the oral thrombin inhibitor dabigatran to VKAs in a noninferiority trial to prevent stroke or systemic embolization in NVAF. Two doses of dabigatran were used: 110 mg/d and 150 mg/d. Both dose tiers of dabigatran were noninferior to VKAs in preventing second stroke and systemic embolization, and the higher dose tier was superior (relative risk 0.66; 95% CI 0.53–0.82; $p < .001$) and the rate of major bleeding was lower in the lower dose tier of dabigatran compared to VKAs. Dabigatran requires no blood monitoring to titrate the dose, and its effect is independent of oral intake of vitamin K. Newer oral factor Xa inhibitors have also been found to be equivalent or safer and more effective than VKAs in NVAF stroke prevention. In the Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation (ARISTOTLE) trial, patients were randomized between apixaban, 5 mg twice daily, and dose-adjusted warfarin (INR 2–3). The combined endpoint of ischemic or hemorrhagic stroke or system embolism occurred in 1.27% of patients in the apixaban group and in 1.6% in the warfarin group ($p < .001$ for noninferiority and $p < .01$ for superiority). Major bleeding was 1% less, favoring apixaban ($p < .001$). Similar results were obtained in the Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared with Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation (ROCKET-AF). Here, patients with NVAF were randomized to rivaroxaban versus warfarin: 1.7% of the factor Xa group and 2.2% of the warfarin group reached the endpoint of stroke and systemic embolism ($p < .001$ for noninferiority); intracranial hemorrhage was also lower with rivaroxaban. Finally, the factor Xa inhibitor edoxaban was also found to be noninferior to warfarin. Thus, oral factor Xa inhibitors are at least a suitable alternative to VKAs, and likely are superior both in efficacy and perhaps compliance.

For patients who cannot take anticoagulant medications, clopidogrel plus aspirin was compared to aspirin alone in the Atrial Fibrillation Clopidogrel Trial with Irbesartan for Prevention of Vascular Events (ACTIVE-A). Clopidogrel combined with aspirin was more effective than aspirin alone in preventing vascular events, principally stroke, but increased the risk of major bleeding (relative risk 1.57, $p < .001$).

The decision to use anticoagulation for primary prevention is based primarily on risk factors (Table 446-3). The history of a TIA or stroke tips the balance in favor of anticoagulation regardless