(heating, freezing, intralesional antimony compounds, paramomycin ointment) and the "gold standard" of systemic therapy with antimony compounds.[7,8]

The case reported here highlights the need to consider leishmaniasis in anyone returning from a tropical destination who has a progressive ulcer that does not respond to local care and systemic antibiotic therapy.

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Long-term management of atrial fibrillation: Rhythm or rate control?

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Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) Investigators. A comparison of rate control and rhythm control in patients with atrial fibrillation. *N Engl J Med* 2002;347:1825-33.

Background: Atrial fibrillation may produce symptoms that are thought to be due to the poorly controlled ventricular rate or the irregular rhythm, or both. Although anticoagulation reduces the risk of stroke, it is not known whether treatment strategies to maintain sinus rhythm are superior to those that simply maintain rate control. In theory, rhythm-control strategies might result in fewer symptoms, better exercise tolerance, lower risk of stroke, eventual discontinuation of anticoagulation, better quality of life and improved survival. Atrial fibrillation, however, often responds poorly to antiarrhythmic drugs, which themselves can be associated with adverse effects.

Question: In the long-term management of atrial fibrillation is it preferable to start with a rhythm-control strategy or a rate-control approach?

Design: This multicentre, randomized, nonblinded trial compared rhythm-control and rate-control strategies in patients with atrial fibrillation who were at least 65 years of age or had other risk factors for stroke or death. Eligible patients had atrial fibrillation that was judged clinically by the investigators to likely be recurrent and cause illness or death, such that long-term treatment was deemed warranted.

In the rhythm-control group, the treating physician was free to choose one or more antiarrhythmic drugs from among amiodarone, disopyramide, flecainide, moricizine, procainamide, propafenone, quinidine, sotalol and dofetilide. Cardioversion was allowed as necessary to maintain sinus rhythm. In the rate-control group, the choice of one or more drugs was allowed from among β-blockers, calcium-channel blockers (verapamil and diltiazem) and digoxin, with the aim of maintaining a heart rate not exceeding 80 beats/min at rest or 110 beats/min during a 6-minute walk. After failure of at least 2 trials of a rhythm-control or rate-control drug, patients could be considered for nonpharmacologic therapy as appropriate to their group assignment.

Although both groups were given warfarin to reach an international normalized ratio (INR) of 2.0–3.0, the treating physicians of patients in the rhythm-control group were free to stop the warfarin once sinus rhythm had been maintained for at least 4 weeks. The primary analysis was an intention-to-treat comparison of the time to death from any cause, adjusted for interim analyses.

Results: The 4060 patients enrolled in the study had a mean age of 69.7 years and similar baseline characteristics. In

all, 70.8% had a history of hypertension, and 38.2% had coronary artery disease. For 35.5% of the patients the qualifying episode of atrial fibrillation was also the first episode of this arrhythmia. The duration of the qualifying episode was at least 2 days in 69.2% of cases, and in more than 90% the patients were enrolled within 6 weeks after the qualifying episode.

Failure of an antiarrhythmic drug before randomization was seen in 17.6% of cases. Of 3311 patients who underwent echocardiography, the left atrium was enlarged in 64.7% and left ventricular function was depressed in 26.0%. A significant number of crossovers occurred in both directions, but more often from the rhythm-control to the rate-control group because of adverse drug effects or failure to maintain sinus rhythm. Combinations of drugs were often required in both groups. At 5 years, 34.6% of patients in the rate-control group were in sinus rhythm and over 80% of those in atrial fibrillation had adequate rate control. The prevalence of sinus rhythm declined over time in the rhythm-control group, being only 62.6% at 5 years.

The mean follow-up was 3.5 years, and by 5 years 23.8% of patients in the rhythm-control group had died, as compared with 21.3% in the rate-control group (hazard ratio 1.15, 95% confidence interval 0.99–1.34, $p = 0.08$). This trend persisted after adjustment for various covariates. The rates of the composite endpoint of death, disabling stroke, disabling anoxic encephalopathy, major bleeding or cardiac arrest were similar in both groups ($p = 0.33$). Significantly more patients in the rhythm-control group than in the rate-control group had drug side effects and required hospital care. The rates of ischemic stroke were low (about 1% per year) in both groups, and most occurred after warfarin had been stopped or when the INR was below the therapeutic range. Scores on tests of cognitive ability and selected measures of quality of life were similar in both groups.

Commentary: In this well-designed study enrolled patients were representative of those seen in practice and drugs were those used in common practice. The high number of crossovers also mimiced the situation in normal practice, and the intention-to-treat analysis assessed the appropriateness of the initial strategy for long-term management. Unfortunately, data about specific symptom control (i.e., palpitation and dyspnea) were not provided. It also would have been helpful to test the usefulness of periodic 24-hour Holter monitoring in detecting recurrence of atrial fibrillation in the rhythm-control group, since one reason for a rhythm-control strategy is to avoid long-term anticoagulation therapy. The authors nonetheless highlight the importance of appropriate anticoagulation in both strategies to avoid ischemic stroke.

Practice implications: There appears to be no survival advantage to establishing and maintaining sinus rhythm with the currently available drug therapies. The trend toward increased mortality and the significantly higher prevalence of hospital admissions in the rhythm-control group suggests that rate-control strategies and appropriate anticoagulation is more cost-effective. Rhythm-control strategies should still be considered for patients who remain symptomatic from the irregular rhythm despite adequate rate control, those with congestive heart failure or hemodynamic instability and younger patients with "lone" atrial fibrillation. In the event of availability of less toxic antiarrhythmic drugs or more widespread use of nonpharmacologic therapies, these recommendations may change.

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