Milestones in the management of atrial fibrillation

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Over the past decades, interest in atrial fibrillation (AF) has greatly increased, and the understanding of its pathophysiology and potential treatment modalities is constantly growing. This article summarizes findings that the authors deem milestones in the clinical management of the arrhythmia.

The first milestone was the observation that AF is not a benign entity; rather, it is associated with an increased risk of death and morbidity. While no trial had previously shown that patients live longer if AF is suppressed, the epidemiological association is very consistent among several populations. The second milestone was the discovery that thromboembolic strokes can be prevented by warfarin or (to a lesser extent) antithrombotic therapy. The third milestone was the finding that—with contemporary treatment—rhythm control did not improve patient outcomes and, in fact, that with regard to mortality, rate- and rhythm-control strategies are largely interchangeable. Fourth, the description of a specific trigger of the arrhythmia localized in the pulmonary veins has driven efforts to curatively treat AF. While no survival benefit has so far been shown for patients treated with catheter ablation, this technique has progressed from an innovative investigational procedure to routine clinical practice. The fifth milestone is the addition of outcome data to the current body of evidence. In the ATHENA trial, for the first time, an antiarrhythmic agent proved to reduce cardiovascular mortality and morbidity.

In summary, the development of novel treatment strategies for AF is highly dynamic and productive. Years to come will likely witness significant changes in perspective and prognosis of affected patients.

KEYWORDS Heart failure; Hypertension; Atrial fibrillation ablation; Anticoagulation; Rhythm control

ABBREVIATIONS **AF** = atrial fibrillation; **AV** = atrioventricular; **CHF** = congestive heart failure; **CI** = confidence interval; **HR** = hazard ratio; **INR** = international normalized ratio; **LVEF** = left ventricular ejection fraction; **LV** = left ventricular; **NNT** = number needed to treat; **NS** = not significant; **RR** = relative risk

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In recent years, clinicians and scientists have witnessed an actual explosion of knowledge on atrial fibrillation (AF) with respect to understanding its pathophysiological basis, clinical consequences, and evolving treatment modalities. This increase in scientific interest is indicated by an almost exponentially increasing number of publications related to AF in indexed, peer-reviewed journals (Figure 1A). Epidemiological data clearly indicate that this interest is not simply the result of a "*l'art pour l'art*" attitude but of the growing number of affected individuals in Western populations[1] (Figure 1B). This observation is very consistent with that made by other investigators in several other populations.[2–4] The present review tries to distill key clinical observations from this large body of evidence with respect to the management of AF.

It is the personal view of the authors that five specific milestones of paramount importance blazed the trail to the current state-of-the-art therapy.

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Milestone 1: Awareness of prognostic implications of atrial fibrillation

AF is not a benign entity—in fact it is associated with an increase in mortality as evidenced by epidemiological data.[5] Among over 5200 subjects initially recruited to the Framingham Heart epidemiological study, AF was associated with excess mortality that was almost twice as high as in the population without AF (1.5- to 1.9-fold mortality risk after adjustment for preexisting cardiovascular conditions). This increased risk could be demonstrated regardless of age and gender.

Similar findings were subsequently found in other studies. For instance, during the 20-year follow-up of the Renfrew/Paisley study[6] in women, AF was an independent predictor of cardiovascular events (relative risk [RR] = 3.0; 95% confidence interval [CI], 2.1–4.2), fatal or nonfatal strokes (RR = 3.2; 95% CI 1.0–5.0), and heart failure (RR = 3.4; 95% CI 1.9–6.2). Corresponding RR values among men were 1.8 (95% CI 1.3–2.5) for cardiovascular events, 2.5 (95% CI 1.3–4.8) for strokes, and 3.4 (95% CI 1.7–6.8) for heart failure. With respect to mortality, AF was associated with increased all-cause mortality in women (RR = 2.2; 95% CI 1.5–3.2) and in men (RR = 1.5; 95% CI 1.2–2.2).

While these studies demonstrate an association of AF with mortality and morbidity—which is pathophysiologically credible and sound—no intervention trial to date has

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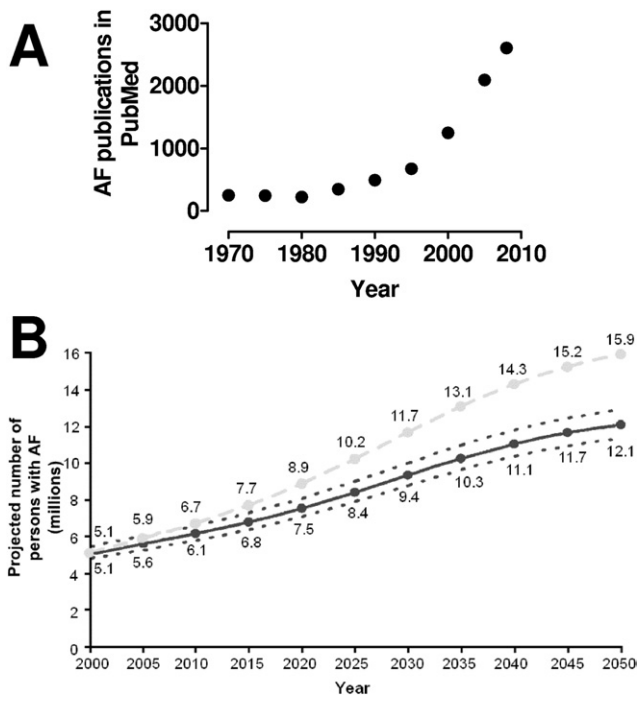

Figure 1 This slide illustrates the increase in AF-related publications indexed in PubMed (**A**) and the epidemiological changes projected to 2050 based on observations from Olmsted county (**B**). Panel B was adapted from reference 1 with permission. The *solid curve* indicates the projected increase in AF prevalence if no further increase in AF incidence occurs. The *dotted curve* indicates the increase in AF prevalence if the increase in incidence rate continues to rise to a similar extent as it rose between 1980 and 2000.

demonstrated that patients live longer if their physicians eradicate AF.

Milestone 2: Prevention of thromboembolic strokes

The association of AF and ischemic stroke is strong, and depending on risk factors, some patients may have a stroke risk as high as 10% per year[7] (Figure 2). A series of now classical trials comparing warfarin or aspirin therapy to placebo or control treatment was conducted in the 1980s and early 1990s.[8–13] The aim of these trials was to determine whether oral anticoagulation or aspirin could prevent ischemic strokes and the peripheral arterial embolism associated with nonvalvular AF. Each of these trials indicated the superiority of either antithrombotic or adjusted-dose warfarin therapy over placebo/control, with warfarin being substantially more efficacious than antiplatelet therapy with aspirin. Hart and coworkers[14] performed a first meta-analysis in 1999, summarizing data from 16 trials that included almost 10,000 patients. The results of their study indicated that during a mean follow-up of 1.7 years, adjusted-dose warfarin reduced stroke by 62% (95% CI 48%–72%), which translates into absolute risk reductions of 2.7% per year for primary prevention and 8.4% per year for secondary prevention.[14] A more recent meta-analysis of this group found highly consistent results in data obtained from 29 trials that had included 28,044 patients (mean follow-up 1.5 years).[15] According to this more recent meta-analysis, adjusted-dose warfarin was associated with a 64% (95% CI 49%–74%) reduction in stroke. The absolute risk reduction in all strokes was 2.7% per year (number needed to treat [NNT] for 1 year to prevent one stroke was 37) for primary prevention and 8.4% per year (NNT = 12) for secondary prevention. In line with these findings from the meta-analysis, analyses from the European Atrial Fibrillation (EAFT) trial indicated that in particular for patients with a high risk of stroke (secondary prevention), warfarin was more effective than aspirin, while in the group of low to intermediate risk, both agents had similar effects.[13]

The problems with warfarin, however, are many, and the drug is disliked by patients and physicians. Its narrow therapeutic range, the need for frequent international normalized ratio (INR) checks, the interaction with food and other medications, and the associated bleeding risk are among the

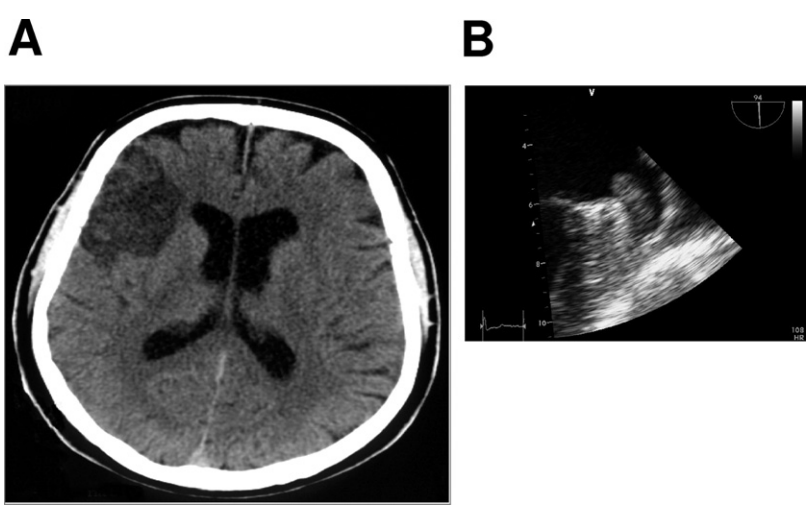

Figure 2 **A:** Computed tomography scan of a patient with ischemic stroke in the territory of the middle cerebral artery owing to AF. **B:** Corresponding, typical clot formation in the left atrial appendage (visualized by transesophageal echocardiogram).