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AHA SCIENTIFIC STATEMENT

Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity

A Scientific Statement From the American Heart Association

ABSTRACT: Our understanding of the risk factors and complications of atrial fibrillation (AF) is based mostly on studies that have evaluated AF in a binary fashion (present or absent) and have not investigated AF burden. This scientific statement discusses the published literature and knowledge gaps related to methods of defining and measuring AF burden, the relationship of AF burden to cardiovascular and neurological outcomes, and the effect of lifestyle and risk factor modification on AF burden. Many studies examine outcomes by AF burden classified by AF type (paroxysmal versus nonparoxysmal); however, quantitatively, AF burden can be defined by longest duration, number of AF episodes during a monitoring period, and the proportion of time an individual is in AF during a monitoring period (expressed as a percentage). Current guidelines make identical recommendations for anticoagulation regardless of AF pattern or burden; however, a review of recent evidence suggests that higher AF burden is associated with higher risk of stroke. It is unclear whether the risk increases continuously or whether a threshold exists; if a threshold exists, it has not been defined. Higher burden of AF is also associated with higher prevalence and incidence of heart failure and higher risk of mortality, but not necessarily lower quality of life. A structured and comprehensive risk factor management program targeting risk factors, weight loss, and maintenance of a healthy weight appears to be effective in reducing AF burden. Despite this growing understanding of AF burden, research is needed into validation of definitions and measures of AF burden, determination of the threshold of AF burden that results in an increased risk of stroke that warrants anticoagulation, and discovery of the mechanisms underlying the weak temporal correlations of AF and stroke. Moreover, developments in monitoring technologies will likely change the landscape of long-term AF monitoring and could allow better definition of the significance of changes in AF burden over time.

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Atrial fibrillation (AF) is a serious public health problem because of its increasing incidence and prevalence in the aging population[1] and its association with elevated risks of cardiovascular events and death.[2–7] Our understanding of the risk factors and complications of AF is based mostly on studies that have evaluated AF in a binary fashion (present or absent) and have not investigated AF burden (quantity or amount of AF that a person has). The optimal method of measuring AF burden, the prognostic significance of AF type (paroxysmal, persistent, or permanent)[8] or AF duration, and the relationship of lifestyle and intensive risk factor modification to AF burden are all important knowledge gaps that require clarification. This scientific statement comprehensively discusses the published literature and knowledge gaps related to (1) methods of defining and measuring AF burden, (2) relationship of AF type or device-detected AF duration to cardiovascular and neurological outcomes, and (3) effect of lifestyle and risk factor modification on AF burden. We will also propose future directions for research to address knowledge gaps.

It is not the goal of this scientific statement to provide specific formal clinical recommendations. Instead, the general goal of this scientific statement is to increase knowledge and awareness by healthcare professionals of effective, state-of-the-art science related to the causes, prevention, detection, management, and future research needs related to AF burden. The information presented here represents the synthesis of data and a consensus of experts convened on the writing committee. Members of the writing committee performed detailed literature searches using PubMed, Web of Science, and Scopus to identify relevant original articles, guideline statements, and review articles in the literature. We restricted literature searches to articles published in English from the year 2000 and later. Search terms included but were not limited to *atrial fibrillation*, *atrial fibrillation burden*, *atrial fibrillation frequency*, *atrial fibrillation duration*, *atrial fibrillation type or pattern*, *device-detected atrial fibrillation*, *device-detected atrial tachyarrhythmias*, *pacemaker-detected atrial tachycardia or atrial fibrillation*, *pacemaker-detected atrial tachyarrhythmias*, *atrial high-rate episodes*, *subclinical atrial fibrillation*, *silent atrial fibrillation*, and *subclinical atrial tachyarrhythmias*. The document was peer reviewed by official external reviewers representing experts in population-based, clinical, and translational research on AF.

DEFINITION OF AF BURDEN

In the simplest sense, AF burden refers to the amount of AF that an individual has. By considering AF burden, we regard AF as a quantitative entity and move beyond merely treating AF as a binary condition (presence or absence of AF). There are many ways one can define AF burden, such as the duration of the longest AF episode or number of AF episodes during a certain monitoring period. Intuitively, the best definition for AF burden is the proportion of time an individual is in AF during a monitoring period, expressed as a percentage. Literature on AF burden using the latter definition is sparse simply because continuous ambulatory monitoring would be required to meet this definition. Consequently, the majority of studies that have addressed AF burden have mostly focused on AF type or pattern (paroxysmal, persistent, and permanent)[8] or device-detected AF duration as measured from cardiac implantable electronic devices (CIEDs).

AF PATTERN OR TYPE AND RISK OF STROKE

Although one would expect that AF burden should be directly proportional to stroke risk, current guidelines recommend assessing stroke risk on the basis of the individual patient risk profile, not on AF type, pattern, or burden. The approach to risk stratification has been constrained by the fact that the decision to anticoagulate is binary (we prescribe an oral anticoagulant [OAC], or we do not), and risks attributable to patient characteristics (those included in the CHA_2DS_2-VASc score, for instance) have been thought to overwhelm the risk attributable to AF pattern. On its own, a particular AF pattern is unlikely to spare high-risk patients from anticoagulation or warrant OAC use for low-risk patients. Nonetheless, understanding the relationship between AF pattern and stroke risk might yield some pathophysiological insight into this disease process and motivate further investigation in stroke prevention.

Clinical Trials (OACs)

Current practice guidelines make identical recommendations for anticoagulation regardless of AF pattern; however, the large, heterogeneous prospective trials in the direct OAC era have afforded an opportunity to revisit this paradigm. Post hoc analyses of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation), ENGAGE-AF (Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation), and ROCKET-AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation) trials have all shown consistently lower stroke rates for patients with paroxysmal AF than for those with persistent AF, even after adjustment for baseline characteristics (ARISTOTLE: adjusted hazard ratio [HR], 0.70 [95% confidence interval (CI), 0.51–0.93], P=0.015[9]; ROCKET: adjusted

HR, 0.79 [95% CI, 0.63–1.0], *P*=0.048[10]; and ENGAGE-AF: adjusted HR, 0.79; *P*=0.015[11]). In the RE-LY trial (Randomized Evaluation of Long-Term Anticoagulation Therapy), the stroke rates were numerically lower in paroxysmal versus persistent AF (1.32% versus 1.55%, respectively), but no formal adjusted comparisons were made, and patients with paroxysmal AF tended to have lower $CHADS_2$ scores.[12]

Older data on anticoagulated patients in SPORTIF (Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation) III and V (randomized to either vitamin K antagonist or ximelagatran) demonstrated an annual stroke/systemic embolic event rate of 1.73% for persistent AF and 0.93% for paroxysmal AF (adjusted HR, 1.87 [95% CI, 1.04–3.36]; *P*=0.037 for persistent versus paroxysmal AF).[13] Similarly, the AMADEUS trial (Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation) demonstrated higher rates of a composite of cardiovascular death and stroke or systemic embolism among anticoagulated patients with nonparoxysmal AF (HR, 1.68 [95% CI, 1.08–2.55]; *P*=0.02).[14] However, SPORTIF III and V demonstrated similar stroke rates in patients with at least 2 risk factors for stroke, which suggests that at the higher end of the risk spectrum, the paroxysmal AF pattern is not associated with significantly lower stroke risk.

Clinical Trials (Antiplatelet Agents)

Although antiplatelet therapy currently plays only a very small role in the prevention of stroke in AF, a reexamination of studies involving antiplatelet therapy can shed some light on the relationship between AF pattern and stroke in patients who have not undergone anticoagulation. Analyses of aspirin-treated patients in the ACTIVE-A (Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events) and AVERROES (Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment) trials suggest that the pattern of AF is related to stroke risk among patients who have not undergone anticoagulation.[15] This study demonstrated yearly ischemic stroke rates of 2.1%, 3.0%, and 4.2% for paroxysmal, persistent, and permanent AF, respectively, with an adjusted HR of 1.83 (*P*<0.001) for permanent versus paroxysmal AF and 1.44 (*P*=0.02) for persistent versus paroxysmal AF.[15]

Conversely, analysis of aspirin-treated patients in the SPAF trial (Stroke Prevention in Atrial Fibrillation) demonstrated a comparable annualized rate of ischemic stroke in those with intermittent (3.2%) and sustained (3.3%) AF.[16] Similarly, analysis of the ACTIVE-W study, which examined patients being treated with combined antiplatelet therapy or OACs, demonstrated a similar annualized risk of stroke or systemic embolism in paroxysmal AF and sustained AF (adjusted relative risk, 0.94 [95% CI, 0.63–1.40]; *P*=0.755).[17] These mixed data suggest that the differences in stroke rate by AF pattern could be less consistent in a population not treated with OAC; however, these studies were comparatively small, including only 460 patients with paroxysmal AF in SPAF and 1202 patients in ACTIVE-W, and might be less representative of contemporary practice outcomes. Furthermore, a greater proportion of patients with persistent AF were randomized to warfarin rather than combination antiplatelet therapy in ACTIVE-W (65% for paroxysmal AF versus 85% for sustained AF, *P*=0.0001), which could have attenuated some difference attributable to the underlying AF pattern.

AF Registries

Data from AF registries and population-based studies are also mixed. This likely speaks to the complexity in risk adjustment between AF type and differential treatment patterns (eg, anticoagulation rate), which confounds the relationship between AF type and stroke risk. It is well established that patient characteristics differ significantly by AF type, generally trending toward higher-risk features in persistent AF,[18,19] which makes rigorous adjustment critical for all epidemiological studies.

In the Loire Valley Atrial Fibrillation Project AF cohort, the rates of stroke differed significantly by pattern of AF; however, clinical factors, not AF pattern, independently increased the risk of stroke in multivariate analyses.[20] On the basis of this finding, the authors concluded that stroke risk is similar across all patterns of AF and that antithrombotic therapy should be based on clinical risk factors, not on AF pattern. Similarly, both the EORP-AF (EURObservational Research Programme–Atrial Fibrillation) General Pilot Registry and the J-RHYTHM (Japanese Rhythm Management Trial for Atrial Fibrillation) Registry demonstrated higher death rates with nonparoxysmal AF; however, in the multivariable Cox model, nonparoxysmal AF was not an independent predictor of death during follow-up.[21,22] In the Euro Heart Survey, paroxysmal AF had comparable risk for thromboembolic events as persistent and permanent AF.[23,24]

Conversely, in a large cohort of Japanese patients (Fushimi AF Registry), paroxysmal AF was independently associated with lower incidence of stroke/systemic embolism than sustained AF.[25] Also, a secondary prevention study demonstrated a nearly 2-fold increased risk of stroke with persistent AF, even after adjustment for age, sex, previous anticoagulation, and National Institutes of Health Stroke Scale severity of the index event.[26] Finally, a meta-analysis of 12 studies (nearly 100 000 patients) demonstrated a multivariable adjusted HR for thromboembolism of 1.38 (95% CI, 1.19–1.61) for nonparoxysmal AF compared with paroxysmal AF.[27]

Impact on Stroke Severity

One study demonstrated more severe neurological deficits and poorer outcomes in patients with persistent AF (versus paroxysmal AF) who have had a cardioembolic stroke.[28–30] Patients with persistent AF might also be at higher risk of a recurrent stroke.[26,31] However, perhaps because of its higher prevalence than persistent AF and the fact that many patients with paroxysmal AF are not treated with anticoagulation,[32,33] paroxysmal AF remains the most common AF pattern among all patients presenting with acute stroke.[34] Table 1 presents a list of randomized controlled trials (RCTs) comparing outcomes according to AF pattern.

Conclusions

- Current guidelines recommend using vascular risk factors (as measured by the CHA_2DS_2-VASc score) and not considering AF burden when making decisions regarding anticoagulation for stroke prevention in AF.
- The strongest evidence, however, suggests that patients with persistent AF are at higher risk of stroke than those with paroxysmal AF.
  - This relationship holds among contemporary patients treated with appropriate anticoagulation:
    - Post hoc analyses of the ARISTOTLE, ENGAGE-AF, and ROCKET-AF trials have all shown consistently lower stroke rates for patients with paroxysmal than for persistent AF, even after adjustment for baseline characteristics.
  - The relationship is also present in patients not treated with anticoagulation:
    - Analyses of aspirin-treated patients in the ACTIVE-A and AVERROES trials showed higher stroke risk in persistent and permanent AF than in paroxysmal AF.
    - However, older studies (SPAF and ACTIVE-W) did not demonstrate this relationship, but these studies might be comparatively underpowered and potentially less representative of contemporary practice outcomes.
  - Data from AF registries and population-based studies are also mixed, but the largest meta-analysis (12 studies and nearly 100 000 patients) demonstrated an HR of 1.38 for nonparoxysmal AF compared with paroxysmal AF (Table 1).

DEVICE-DETECTED AF DURATION AND STROKE RISK

Patients with CIEDs are at particularly high risk of AF,[35] likely related to the high prevalence of underlying cardiac pathology such as sinus node dysfunction and cardiomyopathy, which predispose to AF. Unlike ambulatory electrocardiographic monitoring devices of specific intervals (1 day to 4 weeks), CIEDs provide full-time continuous monitoring of atrial and ventricular arrhythmias. In devices with atrial leads, cumulative AF burden is tracked, and individual atrial arrhythmias can be stored by the device by autotriggered alerts. A full array of diagnostic information is available, including date, time, duration, and atrial arrhythmia cycle length, as well as day-level AF burden. Because many implantable cardioverter-defibrillators implanted for primary prevention of sudden death are single-chamber devices (with only a ventricular lead), newer technologies have emerged to allow for AF detection based on R-R cycle length irregularity with conventional leads.[36]

Caution is needed in interpreting device-detected AF and using atrial high-rate episodes (AHREs) as a surrogate for AF. False detection of AF can occur because of far-field R-wave oversensing by the atrial lead or sustained runs of premature atrial complexes or atrial tachycardia. Implantable loop recorders or implantable cardiac monitors, which rely on R-R intervals for arrhythmia detection, have lower sensitivity and specificity for AF identification than limb-lead–based ambulatory electrocardiography monitors and CIEDs with atrial leads.[37] Newer-generation algorithms, although improved, are still dependent on the background incidence rate of the monitored population, programmed sensitivity, and the duration of detected AF episodes.[38] AF can be missed by transvenous lead CIEDs if episodes of AF are very brief or slow. In the ASSERT trial (Asymptomatic Stroke and Atrial Fibrillation Evaluation in Pacemaker Patients and the Atrial Fibrillation Reduction Atrial Pacing Trial), 17.3% of AHREs at >190 bpm that lasted >6 minutes were found to be false positive for AF.[39] Nevertheless, given the continuous monitoring for long periods of time, CIEDs afford a potential opportunity to examine the relationship between AF burden and risk of stroke, both for estimating risk of stroke and for the expected benefit of stroke prevention therapy. Studies have generally shown that higher AF burden is associated with a higher risk of stroke; however, thresholds have not been reproducibly identified. Confounding the observation is that patients with higher AF burden also tend to have a higher prevalence of other conditions that increase risk of stroke, such as advanced age or heart failure (HF).

In studies that evaluate risk based on AF duration, the cut points were generally arbitrarily prespecified rather than empirically derived. In a secondary analysis of the MOST trial (Mode Selection Trial) of 316 patients with sinus node dysfunction and dual-chamber pacemakers, an AHRE (atrial rate >220 bpm) cutoff of 5 minutes was chosen to avoid false-positive results from oversensing.[40,41] Presence of 5-minute AHREs was associated with increased risk of death or nonfatal stroke (HR, 2.79; 95% CI, 1.51–5.15; P=0.0011) and of AF.

This study was limited by its small size, retrospective design, and the fact that only AHREs that lasted >5 minutes were considered; thus, the prognostic significance of shorter episodes or much longer episodes (eg, hours) was not evaluated. The TRENDS study (A Prospective Study of the Clinical Significance of Atrial Arrhythmias Detected by Implanted Device Diagnostics) was a prospective, observational study of 2846 patients with CIEDs and risk factors for stroke.[42] In TRENDS, compared with no atrial tachyarrhythmias (ATs)/AF, the stroke risk was doubled in those with high AT/AF burden (≥5.5 hours on any single day in a 30-day window) but not in those with low AT/AF burden (<5.5 hours on any single day in a 30-day window), which suggests that stroke risk is a quantitative function of AT/AF burden. The 5.5-hour threshold was chosen as the cutoff because it was the median AT/AF burden and not an empirical threshold of risk.

In ASSERT, subclinical episodes of AT (defined as atrial rates ≥190 bpm lasting >6 minutes) were associated with an increased risk of ischemic stroke (HR, 1.76; 95% CI, 0.99–3.11).[43] The cutoff of 6 minutes was prespecified. The increase in risk was similar for episodes >6 hours (HR, 2.00; 95% CI, 1.13–3.55). A follow-up analysis demonstrated that subclinical AT only increased the risk of stroke or systemic embolism for episodes >24 hours (adjusted HR, 3.24; 95% CI, 1.51–6.95)[44] and that risk of stroke in patients with subclinical AT between 6 minutes and 6 hours (adjusted HR, 0.75; 95% CI, 0.29–1.96) and between 6 hours and 24 hours (adjusted HR, 1.32; 95% CI, 0.40–4.37) was not significantly different from that for patients without subclinical AT. Cutoffs were based on manufacturer categories for classification of subclinical AT.

To evaluate further whether AF burden correlates with stroke risk, the SOS AF project (Stroke Prevention Strategies Based on Atrial Fibrillation Information From Implanted Devices) performed a pooled analysis of individual patient data from 5 prospective studies comprising 10 016 patients without permanent AF and previously implanted with CIEDs.[45] The annual stroke risk for different categories of AF burden (0 to <5 minutes, ≥5 minutes to <1 hour, ≥1 hour to <6 hours, ≥6 hours to <12 hours, ≥12 hours to <23 hours, and ≥23 hours) was 0.24%, 0.08%, 0.34%, 0.26%, 0.30%, and 0.23%, respectively.

In a case-crossover analysis involving 9850 patients with CIEDs remotely monitored in the Veterans Administration Health Care System between 2002 and 2012, Turakhia and colleagues[46] found that AF burden of ≥5.5 hours in a given day raised the short-term risk of stroke 4- to 5-fold. Moreover, they found a strong relationship of temporal proximity of AF with ischemic stroke: the risk was highest in the 5 to 10 days after the episode of AF; by 30 days, the risk of stroke events was no longer elevated. The cutoff of 5.5 hours was based on the previous TRENDS study.[42] When the AF cutoff was changed from 30 minutes to 6 hours in increments, there was no risk threshold identified. Finally, the majority of strokes that occurred were temporally dissociated from AF. Therefore, although a transient increase in risk based on AF onset was identified, the overall attributable risk was low.

Table 2 presents a list of studies of CIEDs evaluating the association of AF burden and risk of stroke.

Conclusions

- In virtually all studies, cutoffs for AF burden were arbitrarily prespecified rather than empirically derived.
- The effect of very brief AF episodes (<5 to 6 minutes) on stroke risk has not been rigorously evaluated and remains unknown.
- Although increasing AF burden is generally associated with an increasing risk of stroke, the relationship is not well characterized with respect to functional form (eg, threshold or monotonicity) or duration of any transient risk.
- Among patients with CIEDs, the majority of ischemic strokes are temporally discordant from AF episodes.
- AHREs in MOST[40] and AT/AF in TRENDS[42] and ASSERT[43] might have included atrial flutter. It is unclear whether the ischemic stroke risk of atrial flutter is the same as that of AF. As such, some caution is needed in interpreting AF burden–related ischemic stroke risk from these studies (Table 2).

AF TYPE, AF DURATION, AND NONSTROKE OUTCOMES

Nonstroke outcomes of AF that have been described include HF,[3] cognitive impairment and dementia,[52] myocardial infarction,[6,7] chronic kidney disease progression to end-stage renal disease,[53,54] sudden cardiac death,[5] and all-cause death.[4] Whereas a clear association exists between AF and cardioembolic stroke, the relationships between AF and other cardiac and noncardiac outcomes, quality of life, and death are more complex. As such, inferring directional relationships between AF and most nonstroke outcomes is treacherous. Despite these challenges, understanding the correlations between AF type and AF duration with nonstroke outcomes provides additional prognostic information regarding AF burden. However, the data are scarce in this area.

Heart Failure

HF and AF are highly concordant. They represent overlapping epidemics, with AF occurring in more than half of individuals with HF and HF occurring in more than

Table 1. RCTs Comparing Outcomes According to AF Pattern

Study	Aim of Study and Study Size	Patient Population	Study Intervention/ Study Comparator
ARISTOTLE[9]	Aim: To determine whether the benefit from apixaban varies by type and duration of AF Size: 18 201	Inclusion criteria: Nonvalvular AF or flutter. Patients had to have ≥1 of the following risk factors for stroke: age ≥75 y; prior stroke, TIA, or systemic embolism; symptomatic HF within 3 mo or LVEF ≤40%; DM; and hypertension requiring pharmacological treatment Exclusion criteria: Moderate or severe mitral stenosis; AF attributable to a reversible cause; a contraindication to oral anticoagulation because of an increased bleeding risk; conditions other than AF that required anticoagulation, such as prosthetic heart valve; persistent uncontrolled hypertension; or planned AF or atrial flutter ablation	Intervention: Apixaban twice daily, administered in 5-mg pills or 2.5-mg doses for patients with ≥2 of the following factors: age ≥80 y, body weight ≤60 kg, and serum creatinine ≥1.5 mg/dL (133 mmol/L) Comparator: Warfarin (or matching placebo) was administered in 2-mg tablets and was adjusted to achieve a target INR of 2.0–3.0 Substudy compared outcomes by AF pattern
ROCKET-AF[10]	Aim: To compare outcomes in patients with persistent vs paroxysmal AF receiving oral anticoagulation treated with rivaroxaban or warfarin in ROCKET-AF Size: 14 264	Inclusion criteria: All patients randomized in ROCKET-AF (ITT). Patients were grouped according to AF type at baseline enrollment (paroxysmal or persistent) according to prespecified diagnostic criteria and before any data analysis. Exclusion criteria: Patients with new-onset AF at baseline (1.4% [n=202]) were excluded from this analysis.	Intervention: Rivaroxaban Comparator: Warfarin (INR 2–3)
ENGAGE AF[11]	Aim: To determine whether AF pattern modifies risk-benefit of anticoagulation Size: 21 105	Inclusion criteria: Age ≥21 y, ≥1 episode of documented AF of any duration in preceding 12 mo, $CHADS_2$ score ≥2 Exclusion criteria: AF because of a reversible disorder, creatinine clearance <30 mL/min, high risk of bleeding, use of dual-antiplatelet therapy, moderate to severe mitral stenosis, other indications for anticoagulation, acute coronary syndrome, or coronary revascularization or stroke within 30 d	Intervention: Edoxaban Comparator: Warfarin (INR 2–3)
AMADEUS[14]	Aim: To determine the prognosis of anticoagulated patients with permanent AF and nonpermanent AF according to preexisting HF Size: 4556	Inclusion criteria: Nonvalvular AF and an indication for long-term anticoagulation, based on presence of ≥1 of the following risk factors: previous ischemic stroke, TIA, or systemic embolism; hypertension requiring drug treatment; LVD; age >75 y, or age 65–75 y with either DM or symptomatic CAD Exclusion criteria: Inability to provide consent; contraindication or other requirement for anticoagulation; calculated creatinine clearance <10 mL/min, breastfeeding, pregnancy, and recent or anticipated invasive procedures with potential for uncontrolled bleeding	Intervention: Fixed-dose idraparinux Comparator: Conventional anticoagulation by dose-adjusted oral VKA therapy
SPORTIF III and V[13]	Aim: To test the hypothesis that stroke and SEEs in SPORTIF III and V are different between paroxysmal and persistent AF Size: 13 822	Inclusion criteria: Age ≥18 y, persistent or paroxysmal AF and ≥1 risk factor for stroke: hypertension; age ≥75 y; previous stroke, TIA, or SEE; LVD (EF <40% or symptomatic HF); age ≥65 y and CAD; and age ≥65 y and DM Exclusion criteria: Planned cardioversion	Intervention: Ximelagatran Comparator: Warfarin

(*Continued*)

Table 1. Continued

Primary End Points	Relevant Secondary End Points, Study Limitations, and Adverse Events	Results Relative to AF Pattern	Comments
Primary end point: Composite of ischemic or hemorrhagic stroke or systemic embolism Safety end point (if relevant): ISTH major bleeding	Secondary efficacy end point was all-cause mortality	There was a consistent reduction in stroke or systemic embolism (*P* for interaction=0.71), all-cause mortality (*P* for interaction=0.75), and major bleeding (*P* for interaction=0.50) with apixaban compared with warfarin for both AF types. Apixaban was superior to warfarin in all studied end points, regardless of AF duration at study entry (*P* for all interactions=0.13). Rate of stroke or systemic embolism was significantly higher in patients with persistent or permanent AF than in patients with paroxysmal AF (1.52 vs 0.98%; *P*=0.003, adjusted *P*=0.015). There was also a trend toward higher mortality in patients with persistent or permanent AF (3.90 vs 2.81%; *P*=0.0002, adjusted *P*=0.066).	Analyses comparing outcomes by AF pattern adjusted for age; sex; region; prior myocardial infarction; HF; prior stroke; TIA or systemic embolism; DM; hypertension; prior clinically relevant or spontaneous bleeding; time from first documented occurrence of AF to randomization (ie, duration of AF); whether a VKA was used before enrollment; vascular disease; and baseline use of aspirin, statins, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, and amiodarone
Primary end point: Stroke or systemic embolism Safety end point: Major bleeding	All-cause mortality	Patients with persistent AF had higher adjusted rates of stroke or systemic embolism (2.18 vs 1.73 events per 100 patient-years, *P*=0.048) and all-cause mortality (4.78 vs 3.52, *P*=0.006). Rates of major bleeding were similar (3.55 vs 3.31, *P*=0.77). Rates of stroke or systemic embolism in both types of AF did not differ by treatment assignment (rivaroxaban vs warfarin, *P* for interaction=0.6).	Efficacy end point models were adjusted for the following: age, sex, BMI, region, DM, prior stroke/TIA, vascular disease, myocardial infarction, peripheral artery disease, carotid occlusive disease, CHF, hypertension, chronic obstructive pulmonary disease, DBP, creatinine clearance, heart rate, and abstinence from alcohol. Safety end point models were adjusted for the following: prior stroke/TIA; anemia; prior gastrointestinal bleed; chronic obstructive pulmonary disease; DBP; creatinine clearance; platelets; albumin; and prior aspirin, VKA, or thienopyridine use.
Primary end point: Stroke/SEE Safety end point: Major bleeding	All-cause mortality	Primary end point of stroke/SEE was lower in patients with paroxysmal AF (1.49% per y) than in persistent AF (1.83% per y; adjusted *P*=0.015) and permanent AF (1.95% per y; adjusted *P*=0.004)	Analyses by AF pattern were adjusted for sex, age, race, geographic region, BMI, smoking status, alcohol use, prior stroke or TIA, hypertension, CAD, dyslipidemia, CHF, DM, increased risk of falling, hepatic disease, neuropsychiatric disease, prior nonintracranial bleed, use of antiplatelet agents at randomization, and creatinine clearance at randomization.
Primary end point: Composite of cardiovascular death and stroke or systemic embolism Safety end point: Major bleeding, defined as bleeding that was fatal, intracranial, or affecting another critical anatomic site, or overt bleeding with a drop in hemoglobin ≥20 g/L or requiring transfusion of ≥2 U of erythrocytes		HR (for primary outcome) for permanent vs nonpermanent AF was 1.68 (95% CI, 1.08–2.55; *P*=0.02)	Multivariate model included adjustment for age, sex, creatinine (log transformed), hypertension, DM, and previous stroke/TIA/thromboembolism, and CAD
Primary end point: Stroke and SEEs Safety end point: Major bleeding	Mortality	Annual event rates for stroke/SEE were 1.73% for persistent AF and 0.93% for paroxysmal AF. In multivariate analysis, after adjustment for stroke risk factors, sex, and aspirin usage, differences remained statistically significant, with higher HR for stroke/SEE in persistent AF (vs paroxysmal AF: HR, 1.87; 95% CI, 1.04–3.36; *P*=0.037).	Adjustment was performed for 7 predefined risk factors from clinical study protocol: previous stroke, TIA, or systemic embolism; hypertension; LVD (EF <40% or symptomatic systolic or diastolic HF); age ≥75 y; or age ≥65 y with known coronary disease or DM together with sex, VKA use, and aspirin use at study entry

(*Continued*)

Table 1. Continued

Study	Aim of Study and Study Size	Patient Population	Study Intervention/ Study Comparator
ACTIVE W[17]	Aim: To determine risk of stroke or noncerebral embolism associated with paroxysmal compared with sustained AF Size: 6697	Inclusion criteria: AF and ≥1 risk factor for stroke (age ≥75 y; on treatment for hypertension; prior stroke, TIA, or non-CNS systemic embolus; LVEF ≤45%; peripheral arterial disease; if patients were between the ages of 55 and 74 y, requirement to have either DM requiring drug therapy or previous CAD)	Intervention: Combined antiplatelet therapy with aspirin (75–100 mg/d) and clopidogrel (75 mg/d) Comparator: Warfarin (INR 2–3)
SPAF I, II, and III[16]	Aim: Characterize the risk of stroke in elderly patients with recurrent intermittent vs sustained AF Study type: Longitudinal cohort study Size: 2012	Inclusion criteria: Participants in SPAF I, II, and III (1987–1997) assigned to aspirin (325 mg/d) or to a combination of aspirin plus inefficacious fixed-dose warfarin in SPAF III Exclusion criteria: Age <60 y without associated cardiovascular disease ("lone AF") and those who were heavy alcohol users (precluding safe anticoagulation) were not eligible	Intervention: Intermittent AF Comparator: Sustained AF

(*Continued*)

one third of individuals with AF.[55] The incidence of HF is ≈2-fold greater than the incidence of stroke in patients with AF. AF is known to promote symptomatic HF through multiple mechanisms and vice versa.[56] It is unknown to what extent AF drives subsequent HF (eg, tachycardia-mediated cardiomyopathy and loss of atrioventricular synchrony) versus AF merely manifesting before HF from common underlying pathophysiology (eg, primary myocardial hypertrophy, fibrosis, and apoptosis leading to neurohormonal activation, electrical abnormalities, and elevated filling pressures). AF and HF, as well as downstream morbidity and mortality, share common risk factors: obesity, diabetes mellitus, tobacco use, hypertension, prior myocardial infarction, chronic obstructive pulmonary disease, and renal disease.

The data are scarce on the relationship of burden and type of AF to incident HF. In a contemporary American registry of AF, incident HF developed in 3.6% of patients over the 2-year follow-up period (ejection fraction was >40% in 64%, ≤40% in 13.5%, and unmeasured in the remainder).[57] In multivariable analysis, compared with paroxysmal AF, the presence of permanent AF was associated with a higher rate of incident HF (HR, 1.60; 95% CI, 1.18–2.16), which suggests that a higher burden of AF is associated with a greater risk for HF. In a global AF registry, prevalent HF was 33% in paroxysmal AF, 44% in persistent AF, and 56% in permanent AF, which suggests a higher burden of AF is associated with a greater prevalence of HF.[18]

Cognitive Impairment and Dementia

Although there is compelling evidence to support an association of AF with greater cognitive decline and risk of dementia,[52] there is a paucity of data on the relationship between AF burden and cognitive performance. A small, cross-sectional study based on the ARIC cohort (Atherosclerosis Risk in Communities) provided evidence that persistent AF might be associated with lower cognitive function than paroxysmal AF.[58] This study included 325 participants (mean age, 76.9±5.2 years; 53% women) who underwent cognitive tests and heart rhythm recording using a 14-day patch monitor. AF was detected in 26 participants (8.0%): 14 with low AF burden (range, 1%–6%) or paroxysmal AF and 12 with high burden (100%) or persistent AF. Compared with no AF, persistent AF, but not paroxysmal AF, was independently associated with lower *z* scores on the Digit Span Backward test (executive function), the Trail Making Test part B (executive function), and Animal Naming (verbal fluency). Prospective evaluation of AF burden in relation to longitudinal change in cognitive scores and incident dementia is needed to confirm this association.

Quality of Life

AF is associated with lower quality of life, both directly and through its association with other factors that affect quality of life. The AFEQT (Atrial Fibrillation Effect on Quality-of-Life) health status measure was assessed in 2007 AF patients from the ORBIT registry (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation).[59] The median AFEQT summary score was 82 (interquartile range [IQR], 67–94; 0 worst to 100 best). Multiple factors were independently associated with lower AFEQT score: female sex, younger age, new-onset AF, higher heart rate, obstructive sleep

Table 1. Continued

Primary End Points	Relevant Secondary End Points, Study Limitations, and Adverse Events	Results Relative to AF Pattern	Comments
Primary end point: Stroke, noncerebral systemic embolism, myocardial infarction, or vascular death Safety end point: Major bleeding, defined as any bleeding requiring transfusion of ≥2 U of red blood cells or equivalent of whole blood, or as bleeding associated with death; drop in hemoglobin ≥5 g/dl; significant hypotension with need for inotropic support; intraocular bleeding; bleeding requiring surgery; or symptomatic intracranial hemorrhage		Similar annualized risk of stroke or systemic embolism in paroxysmal AF and sustained AF (adjusted RR, 0.94 [0.63–1.40]; *P*=0.755)	Analyses by AF pattern were adjusted for age, hypertension, HF, valvular heart disease, and DM
Primary end point: Ischemic stroke		In SPAF aspirin-treated patients, there was a comparable annualized rate of ischemic stroke in those with intermittent (3.2%) and sustained (3.3%) AF	Primary analyses were unadjusted. Differences in age-adjusted RRs between patients with intermittent and sustained AF were evaluated by fitting the model, adjusted for age, pattern of AF, and factor of interest, and then testing significance of the interaction term for pattern of AF and factor of interest.

ACTIVE indicates Atrial Fibrillation Clopidogrel Trial With Irbesartan for Prevention of Vascular Events; AF, atrial fibrillation; AMADEUS, Evaluating the Use of SR34006 Compared to Warfarin or Acenocoumarol in Patients With Atrial Fibrillation; ARISTOTLE, Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation; BMI, body mass index; CAD, coronary artery disease; CHF, congestive heart failure; CI, confidence interval; CNS, central nervous system; DBP, diastolic blood pressure; DM, diabetes mellitus; EF, ejection fraction; ENGAGE AF, Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation; HF, heart failure; HR, hazard ratio; INR, international normalized ratio; ISTH, International Society of Thrombosis and Hemostasis; ITT, intention to treat; LVD, left ventricular dysfunction; LVEF, left ventricular ejection fraction; RCT, randomized controlled trial; ROCKET-AF, Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation; RR, relative risk; SEE, systemic embolic event; SPAF, Stroke Prevention in Atrial Fibrillation; SPORTIF, Stroke Prevention Using Oral Thrombin Inhibitor in Atrial Fibrillation; TIA, transient ischemic attack; and VKA, vitamin K antagonist.

apnea, symptomatic HF, chronic obstructive pulmonary disease, and coronary artery disease. Of note, patients with new-onset AF had worse symptoms than those with permanent AF.[59]

Interventions aimed at reducing AF burden have not translated proportionally to improvement in quality of life. A strategy of rhythm control for patients with AF, even if successful, was not shown to result in better quality of life than in patients treated with rate control,[60] for older patients or for patients with HF and reduced ejection fraction.[61] In an AF cohort, patients undergoing cardioversion compared with matched patients without cardioversion did not exhibit greater symptom improvement (34% versus 42%) or less symptomatic progression (15% versus 4%) by European Heart Rhythm Association scores.[62] In patients randomized to antiarrhythmic drug therapy versus ablation, quality of life was similar after treatment, despite less AF in the ablation group.[63] Overall, these data suggest that higher AF burden is not necessarily related to lower quality of life.

Mortality

AF is associated with an increased risk of mortality.[4,5,64] Importantly, higher AF burden is associated with higher risk of mortality. In a systematic review of 12 studies of nearly 100 000 patients that compared outcomes by type of AF, overall unadjusted all-cause mortality was higher in patients with nonparoxysmal AF than in those with paroxysmal AF (relative risk, 1.46; 95% CI, 1.26–1.70); multivariable adjustment only partially attenuated this association (HR, 1.22; 95% CI, 1.09–1.37).[27]

The data are less clear on how AHREs relate to mortality, with a suggestion that these low-burden events carry lower mortality risk, in part because studies have been smaller with less precision. In one study of 394 patients with cardiac resynchronization therapy, although the 20% of patients with AHREs (compared with those without) had an increased risk of clinical AF (HR, 2.35; 95% CI, 1.47–3.74) and thromboembolic events (HR, 2.30; 95% CI, 1.09–4.83; *P*=0.028), the risk of mortality was not higher (HR, 0.97; 95% CI, 0.64–1.45).[50] By contrast, in a study of 224 patients with pacemakers, 17% had AHREs of ≥5-minute duration within 6 months of pacemaker implantation; in multivariate analysis adjusted for age, sex, and cardiovascular diseases, presence of AHREs was associated with a significant increase in cardiovascular mortality (HR, 2.80; 95% CI, 1.24–6.31) and stroke mortality (HR, 9.65; 95% CI, 1.56–59.9), with a trend toward increased all-cause mortality (HR, 1.79; 95% CI, 0.98–3.26).[65] The subgroup of patients with AHREs of ≥5-minute but <1-day duration also had a significantly increased cardiovascular mortality (HR, 3.24; 95% CI, 1.37–7.66).

Table 2. Studies of CIEDs Evaluating Association of AF Burden and Risk of Stroke

First Author (Year)	Patients, n	Study Design	Means of AF Detection	Mean/Median Follow-Up	Primary Exposure Definition	Outcome
Glotzer et al (2003)[40]	312	Secondary analysis of RCT	Dual-chamber PPM	27 mo	AHRE ≥5 min	HR=2.79 for death or nonfatal stroke (*P*=0.001)
Capucci et al (2005)[47]	725	Prospective registry	Dual-chamber PPM	22 mo	AF >24 h	Adjusted HR of 3.1 for TE events (*P*=0.044) No association of AF episodes 5 min to 24 h with TE events
Botto et al (2009)[48]	568	Prospective observational study	Dual-chamber PPM	12 mo	AF <5 min AF 5 min to 24 h AF >24 h	Risk of stroke/systemic embolism increased in proportion to $CHADS_2$ score and AF burden
Glotzer et al (2009)[42]	2486	Prospective observational study	Dual-chamber PPM or ICD	1.4 y	AF ≥5.5 h	HR=2.20 (95% CI, 0.96–5.05) for TE events
Healey et al (2012)[43]	2580	RCT	Dual-chamber PPM or ICD	2.5 y	AT/AF >6 min	HR=1.76, *P*=0.05 for TE events
Shanmugam et al (2012)[49]	560	Prospective, multicenter, observational studies	Biventricular PPM or ICD	370 d	AHRE ≥3.8 h/d	HR=9.4, *P*=0.006 for stroke or systemic embolism
Boriani et al (2014)[45]	10016	Pooled analysis of 3 prospective studies	PPM or ICD	24 mo	AF >5 min	AF ≥1 h vs <1 h, HR=2.11, *P*=0.008 for ischemic stroke AF ≥5 min vs <5 min, HR=1.76, *P*=0.041 for ischemic stroke
Turakhia et al (2015)[46]	9850	Case-crossover	PPM or ICD	Case period: 1–30 d before stroke Control period: 91–120 d before stroke	AF ≥5.5 h	Warfarin-adjusted OR, 4.2 (95% CI, 1.5–13.4)
Witt et al (2015)[50]	394	Retrospective registry study	CRT	4.6 y	AHRE >6 min	HR=2.30 (95% CI, 1.09–4.83)
Swiryn et al (2016)[51]	5379	Retrospective registry study	PPM or ICD	22.9 mo	Long episodes of atrial tachyarrhythmia/AF (onset and offset not within the same EGM recording) Short episodes of atrial tachyarrhythmia/AF (onset and offset within the same EGM recording)	Long episodes: HR=1.51 (95% CI, 1.03–2.21) for stroke or TIA Short episodes: HR=0.87 (95% CI, 0.58–1.31) for stroke or TIA
Van Gelder et al (2017)[44]	2455	Secondary analysis of RCT	Dual-chamber PPM or ICD	2.5 y	AF >6 min to 6 h AF >6–24 h AF >24 h	Both AF >6 min to 6 h and AF >6–24 h not associated with higher risk of stroke/systemic embolism. AF >24 h: HR=3.24 (95% CI, 1.51–6.95)

AF indicates atrial fibrillation; AHRE, atrial high-rate episode; AT, atrial tachycardia; CI, confidence interval; CIEDs, cardiac implantable electronic devices; CRT, cardiac resynchronization therapy; EGM, electrogram; HR, hazard ratio; ICD, implantable cardioverter-defibrillator; OR, odds ratio; PPM, permanent pacemaker; RCT, randomized controlled trial; TE, thromboembolic; and TIA, transient ischemic attack.

Conclusions

- Compared with paroxysmal AF, nonparoxysmal AF is associated with higher prevalence and incidence of HF.
- Although 1 small cross-sectional study reported that persistent AF was associated with lower cognitive function than paroxysmal AF, data on the relationship between AF burden and cognitive function are scarce, which represents a critical knowledge gap that demands more attention.
- Higher AF burden is not necessarily related to lower quality of life; new-onset AF is associated with worse quality of life than reported in patients with permanent AF. Interventions aimed at reducing AF burden have not translated to improvement in quality of life.

- Compared with paroxysmal AF, nonparoxysmal AF is associated with higher risk of mortality. The data are less clear with device-detected AHRE.
- High-quality research is needed to understand how maintenance of sinus rhythm and anticoagulation relate to cardiac function, quality of life, and mortality in patients with various types and durations of AF, particularly among the population at risk of HF or who have coexistent HF.

ATHEROSCLEROTIC AND LIFESTYLE RISK FACTORS AND AF BURDEN

Physical inactivity, obesity, and hypertension have all been linked to increased incidence of AF[66,67]; however, the degree to which atherosclerotic and lifestyle factors contribute to AF burden is not well established. There is emerging evidence that comprehensive approaches to reduce obesity, improve physical activity, and appropriately manage obstructive sleep apnea can reduce recurrence of AF after ablation, but the degree to which AF burden is reduced has been reported in only a few studies. The following section presents the limited evidence that has been generated from observational studies and single-center, small, RCTs in which a variety of methods to measure AF burden or recurrence were used.

Comprehensive Risk Factor Management

Australian investigators reported the results of a study in which participants with AF and body mass index (BMI) ≥27 kg/m^2 opted for comprehensive risk factor management or standard management and were followed up for 15 months,[68] 2 years,[69] and 5 years (LEGACY study [Long-term Effect of Goal-Directed Weight Management on Atrial Fibrillation Cohort: A 5-Year Follow-up Study]).[70,71] AF burden was measured by 7-day Holter monitoring. For 75 participants in the risk factor intervention group, the probability of experiencing 1 or more 30-second episodes of AF decreased from baseline (0.6; 95% CI, 0.5–0.7) to the 15-month follow-up (0.2; 95% CI, 0.1–0.3). In comparison, the probability of experiencing 1 or more 30-second episodes of AF did not significantly decrease from baseline to 15-month follow-up (0.6 [95% CI, 0.5–0.7] to 0.5 [95% CI, 0.4–0.6]) in 75 participants who received usual care.[68] A significant group-by-time interaction (P<0.001) was demonstrated. In a subsequent report,[69] freedom from AF 2 years after catheter ablation was greater in those who chose to participate in the risk factor management program than in those who chose not to participate. The structured weight loss component of the risk factor modification intervention produced the greatest benefit for reduction of AF burden (without additional catheter ablation or drug therapy) in those whose weight loss was >10% of their baseline weight, progressive, and linear and did not fluctuate more than 2% over the 5-year follow-up.[70]

The benefit of cardiorespiratory fitness for reducing AF burden was evaluated in 308 subjects who participated in the risk factor management program. Over the 5-year follow-up, AF-free survival was greater (P<0.001) in those who improved their cardiorespiratory fitness by ≥2 metabolic equivalents than in those whose metabolic equivalent gain was <2.[71] Although the most powerful components of this comprehensive risk factor management intervention appear to be the weight loss and physical activity programs, it is not clear how other components of the intervention might have interacted with weight loss and exercise programs to contribute to decreased AF burden.

Exercise Training

There is evidence to suggest that a lower level of cardiorespiratory fitness is associated with a higher risk of AF.[72] The benefit of structured exercise programs for reducing AF symptoms and improving cardiorespiratory capacity has been reported,[73,74] but RCTs reporting the benefit of exercise training to reduce AF burden are limited. Malmo et al[75] reported that in 25 participants assigned to a 12-week aerobic interval training program with 3-month follow-up, the mean time in AF decreased from 8.1% to 4.8% compared with an increase from 10.4% to 14.6% in the 25 participants assigned to the control group (P=0.009). Although this study was limited by a relatively small sample size and short follow-up, the use of an implantable loop recorder to quantify AF throughout the study was a strength compared with studies that used 7-day Holter monitor recordings[68–70] to quantify AF.

Weight Reduction

Obesity is associated with a higher risk of AF.[76–78] Other than LEGACY,[70] most studies investigating the relationship between adiposity and AF have focused on AF incidence or recurrence and not AF burden. For example, in Look AHEAD (Action for Health in Diabetes), an intensive lifestyle intervention designed to achieve and maintain weight loss did not reduce the risk of developing AF compared with diabetes mellitus support and education in patients with type 2 diabetes mellitus.[79] Moreover, findings have been mixed, with some studies reporting no increased risk for AF recurrence with higher BMI[80,81] and others reporting increased risk for AF recurrence with higher BMI after catheter ablation.[82–84] A meta-analysis of 6 observational studies (2358 participants) that used either event monitors or 24-hour Holter monitor recordings to detect AF revealed that a BMI ≥25 kg/m^2 was associated with a 31% increased

risk of AF recurrence after ablation.[85] Compared with participants with normal BMI (<25 kg/m^2), those categorized as obese (≥30 kg/m^2) had a 38% increased risk of AF recurrence.[85]

One limitation of the above studies was the short follow-up time, with only 2[80,83] of the 6 studies following participants for at least 24 months. A recent study conducted follow-up on 2715 participants for 5 years after ablation to examine the association of BMI with ablation outcomes.[86] A BMI >35 kg/m^2 was a significant predictor of AF recurrence. As BMI increased over the 5 years, there was a linear increase in the proportion of participants with persistent AF, from 46.2% to 65.1% (*P*<0.001); this finding would suggest that not only was increased BMI a risk factor for AF recurrence, but it also might have contributed to an increased AF burden. By contrast, a retrospective study of 1558 patients who underwent ablation revealed that over 3 years of follow-up, there was a trend for but no statistically significant relationship between increased BMI and increased risk of AF recurrence after ablation.[84] Findings from this study, however, are limited by its retrospective approach and lack of an objective method to detect AF episodes during follow-up.

Authors of a recent meta-analysis[87] reported associations of measures of adiposity with postablation AF: 1-SD higher values for epicardial fat volume, waist-to-hip ratio, waist circumference, and BMI were associated with a 2.69 (95% CI, 1.66–4.07), 1.32 (95% CI, 1.25–1.41), 1.11 (95% CI, 1.08–1.14), and 1.22 (95% CI, 1.17–1.27) fold increased risk of postablation AF, respectively. However, details such as timing and method of postablation detection of AF were not reported. The effect of these adiposity variables was not reported in terms of AF frequency and duration, but findings highlight the importance of considering measures beyond BMI to elucidate the influence of obesity on AF burden.

Blood Pressure Lowering

Although the link between hypertension and higher AF risk is well recognized,[66] it is unclear whether intensive blood pressure (BP) lowering would be associated with a lower incidence of AF. The ACCORD (Action to Control Cardiovascular Risk in Diabetes) BP trial showed that intensive BP lowering reduced the risk of a composite outcome of AF and abnormal P-wave indices[88]; however, given the composite outcome in this study, more definitive studies that specifically evaluate AF incidence are needed. Moreover, the data are scarce on whether intensive BP lowering or treatment with specific BP-lowering agents would reduce AF burden. In a 1-group crossover trial, Deftereos et al[89] reported that participants (n=60) with paroxysmal AF experienced a significant (*P*<0.01) reduction (from 82 mm Hg [IQR, 74–87 mm Hg] to 78 mm Hg [IQR, 71–82 mm Hg]) in diastolic BP when treated with moxonidine, but that reduction was not associated with reduced AF burden. However, participants who were monitored with 48-hour Holter recordings experienced fewer episodes (*P*<0.01) and minutes (*P*<0.01) of AF per day, respectively, when treated with moxonidine (1 episode [IQR, 1–3 episodes] and 16.5 minutes [IQR, 15.0–57.8 minutes]) compared with periods when they used the placebo (3 episodes [IQR, 2–3 episodes] and 28.0 minutes [IQR, 15.0–57.8 minutes]).

Stress Management

Theoretically, cognitive behavioral therapies that counteract the stress response could reduce sympathetic stimulation and diminish arrhythmogenic triggers that can stimulate AF. Lampert et al[90] reported an association between experiencing negative emotion and subsequent AF episodes, documented by a nonlooping event recorder. Yet few investigators have explored the effect of cognitive and behavioral therapies on reducing AF burden. Using a prospective pre-post cohort design, Lakkireddy et al[91] evaluated the influence of yoga on the number of AF episodes experienced by participants with paroxysmal AF who participated in a 3-month yoga program. AF episodes were measured by a nonlooping event recorder that participants used at least once daily and if symptoms were experienced. The frequency of AF episodes decreased significantly from baseline to study completion for both symptomatic (3.8±3.0 to 2.1±2.6, *P*<0.001) and asymptomatic (0.12±0.44 to 0.04±0.20, *P*<0.001) AF. These findings suggest a benefit from the yoga intervention, but the lack of a control group and short follow-up period limit the strength of the evidence. In a descriptive study,[92] 65% of participants endorsed stress or worry as a cause of their AF, yet the science to explain the relationship between perceived stress and AF burden is underdeveloped.

Conclusions

Tables 3 and 4 present a list of studies that have investigated comprehensive risk factor management programs and risk factor modification interventions as they relate to AF burden.

- A structured and comprehensive risk factor management program targeting atherosclerotic risk factors is effective in reducing AF burden (Table 3).
- More RCTs of exercise training interventions with longer follow-up are needed to confirm whether exercise training is effective in reducing AF burden. More research is also needed to determine the dose (frequency, duration, and intensity) of physical exercise required to reduce AF burden.

Table 3. Key Nonrandomized Trials, Observational Studies, and Registries of Comprehensive Risk Factor Management Programs and AF Burden

Study	Study Type/Design/Size	Patient Population	Primary End Point and Results	Summary/Conclusion Comments	Results
ARREST-AF[69]	Study type: Nonrandomized Intervention: Comprehensive physician-led risk factor management program targeting weight, physical activity, hypertension, lipids, glucose control, obstructive sleep apnea Size: N=149 n=61 opted for risk factor management intervention; n=88 declined intervention and formed control group who received risk factor management information and whose care was managed by their own provider Follow-up: 24 mo	Inclusion criteria: Symptomatic AF patients who had undergone ablation Exclusion criteria: Myocardial infarction or cardiac surgery in previous 12 mo; previous ablation; active malignancy; autoimmune or systemic inflammatory disease; severe renal or hepatic failure	Primary end point: AF-free survival 24 mo after ablation	Patients who chose to participate in the risk factor management program were more likely to be free of AF 24 mo after ablation than those who declined to participate. Method of AF detection was ECG, with 7-d Holter monitor every 3 mo during first year and every 6 mo thereafter. Risk factors such as lipids, hypertension, blood glucose, and weight were improved to a greater degree in the risk factor management group.	AF-free survival was defined as freedom from atrial arrhythmia ≥30 s after 3-mo blanking period; the risk factor management program was an independent predictor of AF-free survival (HR=4.8 [95% CI 2.04–11.4], *P*<0.001).
LEGACY[70]	Study type: Observational Size: N=825 Intervention: Structured weight loss physician-led program combined with comprehensive risk factor management program. Groups were categorized as ≥10% weight loss, 3%–9% weight loss, <3% weight loss, and 5-y follow-up	Inclusion criteria: Patients with BMI ≥27 kg/m^2 treated for AF Exclusion criteria: Permanent AF; myocardial infarction or cardiac surgery in previous 12 mo; previous ablation; active malignancy; autoimmune or systemic inflammatory disease; severe renal or hepatic failure	Primary end point: AF-free survival, defined as freedom from atrial arrhythmia ≥30 s after 3-mo blanking period without use of antiarrhythmic drugs	AF-free survival was greatest in participants who lost ≥10% of body weight and maintained the loss over 5 y. Method of AF detection was ECG and 7-d Holter monitor, but frequency was not reported. Progressive linear weight loss was associated with greater AF-free survival. Program required patients to maintain food and activity diaries; attrition was substantial. These findings are notable because they provide insight into the threshold of weight loss that reduces AF recurrence.	At 5 y: ≥10% weight loss, 45.5% AF-free; 3%–9% weight loss, 22.2% AF-free; and <3% weight loss, 13.4% AF-free (*P*<0.001)
CARDIO-FIT[71]	Study type: Observational, prospective Size: N=308 Grouped according to MET change at end of study Intervention: Tailored structured exercise program that was part of a comprehensive risk factor management program Follow-up: 5 y	Inclusion criteria: Patients with BMI ≥27 kg/m^2 treated for AF Exclusion criteria: Permanent AF; myocardial infarction or cardiac surgery in previous 12 mo; previous ablation; active malignancy; autoimmune or systemic inflammatory disease; severe renal or hepatic failure; those who could not perform exercise because of neuromuscular limitations	Primary end point: AF-free survival, defined as freedom from atrial arrhythmia ≥30 s after 3-mo blanking period without use of antiarrhythmic drugs	≥2 MET gain in cardiorespiratory fitness increased AF-free survival in patients who participated in an exercise training program in the context of a comprehensive risk factor management program. Method of AF detection was ECG and 7-d Holter monitor, but frequency was not reported. METs were estimated by a treadmill exercise test using the standard Bruce protocol. These findings are notable because they provide insight into the threshold of exercise and cardiorespiratory fitness that reduces AF recurrence. Program required patients to maintain food and activity diaries, and there was substantial attrition by years 4–5 of follow-up.	At study completion: 89% of patients with ≥2 MET gain were AF-free; 40% of patients with <2 MET gain were AF-free (*P*<0.001). In multivariate analysis, every MET gained from baseline was associated with a 12% decrease in risk of AF recurrence (HR per 1-MET change=0.88 [95% CI, 0.80–0.96], *P*=0.005).

AF indicates atrial fibrillation; ARREST-AF, Aggressive Risk Factor Reduction Study for Atrial Fibrillation and Implications for Outcome of Ablation; BMI, body mass index; CARDIO-FIT, Impact of Cardiorespiratory Fitness on Arrhythmia Recurrence in Obese Individuals With Atrial Fibrillation; CI, confidence interval; HR, hazard ratio; LEGACY, Long-term Effect of Goal-Directed Weight Management in an Atrial Fibrillation Cohort: A Long-term Follow-up Study; and MET, metabolic equivalents.

- Weight loss and maintaining a healthy weight are effective in reducing AF burden.
- Adiposity measures such as epicardial fat, waist circumference, and waist-to-hip ratio could improve our understanding of the contribution of obesity to AF burden.
- Published data regarding whether intensive BP lowering would reduce AF burden are lacking.
- RCTs are needed to determine whether interventions to manage stress (eg, yoga, mindfulness meditation) would reduce AF burden (Table 4).

KEY KNOWLEDGE GAPS AND FUTURE DIRECTIONS

Defining AF Burden

Current guidelines define presence of AF as electrocardiographic documentation of absolutely irregular RR intervals and no discernible, distinct P waves lasting for at least 30 seconds.[94] As such, manufacturers of ambulatory heart rhythm monitors, such as iRhythm Technologies, have used the 30-second cutoff to define presence of AF. It might be more useful, however, to consider AF not as a binary state but rather on a spectrum of atrial disease severity, defined in part by a factor of how much time or burden one is in this state. As has been discussed thoroughly in this document, the amount of time spent in AF has a direct effect on outcomes such as stroke. How one measures burden of AF beyond paroxysmal or nonparoxysmal AF types, however, needs consensus.

A reasonable and convenient definition of AF burden is the amount of time spent in AF divided by the total amount of time a patient is monitored. Most commercial loop monitors report AF burden using this definition. In many studies, AF burden is defined as the maximum amount of time in AF over a 24-hour period. In the present era of long-term continuous monitoring, however, this convenient definition of AF burden becomes problematic. With long-term monitoring, a single but prolonged episode of AF could be interpreted as low AF burden, and very frequent but brief episodes of AF could be interpreted as high AF burden, which calls into question whether it is the duration of the longest single episode or total AF burden that is prognostically more important.

The concept of temporal AF burden aggregation, or AF density, was defined by Charitos et al[95] as a measure of the concentration of AF episodes. More precisely, AF density was defined as the absolute cumulative deviation of the patient's actual burden development from the hypothetical uniform burden development divided by the minimum time required for development of all AF episodes. Given the same AF burden, a patient with a small number of prolonged episodes of AF has a higher AF density than a patient with many brief episodes of AF. In this study, the authors demonstrated that detection of AF in patients with a high density of AF is more challenging with intermittent monitoring. Moreover, how AF density affects risk of stroke and other outcomes is not well studied.

Therefore, the definition of AF burden must take into account not only the percentage of time in AF but also the monitoring time window. For example, one definition of AF burden that can be adopted is 7-day peak AF burden: the maximum percentage of time in AF during any 7-day window. This is a modification of the commonly used definition of maximum AF burden in a 24-hour monitoring window, which has obvious limitations because of the short monitoring time. Using a 24-hour monitoring window, patients with a single 24-hour episode over the span of 1 year will have the same AF burden as patients with sustained AF over the span of 1 year, although they would likely have different prognoses.

Validating Measures of AF Burden

A critical knowledge gap that needs to be addressed is the threshold of AF burden that results in an increased risk of stroke that warrants anticoagulation. The answer to this question might depend on the context in which AF is being measured. In standard clinical settings, where AF is identified with intermittent monitoring and in response to symptoms, the clinical burden of AF might not impact stroke risk.[16,17,24,96] It is possible that by the time patients reach a clinical diagnosis, they have already crossed a yet unspecified threshold of elevated stroke risk. In these patients, AF burden might play a less critical factor in determining stroke risk and need for anticoagulation.

However, there is a trend toward more widespread use of long-term monitoring for subclinical or asymptomatic AF. As summarized earlier, in trials such as ASSERT, atrial tachyarrhythmias lasting >6 minutes were associated with higher stroke risk.[43] More recently, long-term implantable monitors in targeted high-risk patient populations, such as those with cryptogenic strokes, have revealed high rates of subclinical AF.[97] The key knowledge gap that remains, therefore, is this: In patients without overt clinical AF, how much AF burden is necessary to justify initiation of anticoagulation? Results from the CRYSTAL AF study (Cryptogenic Stroke and Underlying AF) imply that a single episode lasting >6 minutes might be sufficient to increase risk; however, as summarized earlier, studies of device-detected AF have found thresholds of elevated risk that vary from 5 minutes to >24 hours (Table 2). Prospective long-term monitoring studies are needed to determine the AF burden threshold at which the risk of stroke increases. Ultimately, randomized anticoagulation clinical trials in asymptomatic patients who meet a predefined AF burden threshold on long-term monitoring will be needed

Table 4. Key RCTs Comparing Risk Factor Modification Intervention With Standard Care to Reduce AF Burden

First Author (Year)	Aim of Study, Study Type, and Study Size	Patient Population	Study Intervention/ Study Comparator	End Point Results	Relevant Secondary End Points, Study Limitations, and Adverse Events
Abed et al (2013)[68]	Aim: To determine whether weight reduction and cardiometabolic risk factor management reduces AF burden Study type: RCT Size: N=150 (n=75 intervention and n=75 control) Median follow-up 15 mo	Inclusion criteria: Symptomatic AF; BMI ≥27 kg/m^2; waist circumference >100 cm for men and 90 cm for women; ages 21–75 y Exclusion criteria: Participation in weight loss program within 3 mo; DM requiring insulin treatment; significant cardiac valve disease; unstable INR	Intervention: Tailored physician-led weight loss program supported by a software-based obesity management system plus interventions delivered to comparison group Comparator: Lifestyle modification advice; self-directed general lifestyle measures; management of cardiometabolic risk factors	Primary end point: Symptom burden and severity measured by AFSS; secondary AF frequency and duration Safety end point (if relevant): NA Results: At 12 mo, mean number of AF episodes decreased in intervention group from 3.3 (95% CI, 1.16–4.9) to 0.62 (95% CI, 0.19–1.0), and duration decreased from 1176 (95% CI, 720–1632) to 491 (95% CI, 159–822) min. For control group, episodes decreased from 2.8 (95% CI, 1.7–4.0) to 2.0 (95% CI, 1.1–3.0) and duration increased from 1393 (95% CI, 785–1994) to 1546 (95% CI, 782–2308) min. There were significant group differences for frequency and duration (P<0.001).	Holter recordings at baseline and 12 mo were used to quantify AF. Those participating in the tailored weight loss program experienced less AF burden than those who did not participate. The weight loss program was intense, requiring use of meal replacements when weight loss was not adequate. Improvements for symptom severity scores were greater in the weight loss group (P<0.001). Waist circumference was reduced to a greater degree in the weight loss group (P<0.001). Catheter ablation was performed on 14 patients in the control group and 10 in the intervention group during the conduct of the study. Investigators conducted sensitivity analyses and claimed that the results pertaining to AF frequency and duration were not affected.
Malmo et al (2016)[75]	Aim: To assess the effects of aerobic interval training on time in AF, AF symptoms, cardiovascular health, and quality of life Study type: RCT Size: N=51 (n=26 intervention, n=25 control) Follow-up 20 wk	Inclusion criteria: Symptomatic patients referred for first ablation Exclusion criteria: Performing endurance training; prior cardiac surgery; valve disease; ejection fraction <45%; pacemaker implantation; unable to perform exercise	Intervention: Walking or running on treadmill in 45-min sessions 3 times per wk for 12 wk. Sessions included warm up with four 4-min high-intensity intervals alternated with 3-min recovery and cool down. Activity was monitored with actigraph worn on the wrist. Comparator: Usual exercise habits	Primary end point: Time in AF from baseline to follow-up at 20 wk Safety end point: Not specified Result: Time in AF decreased in intervention group from baseline 8.1% (95% CI, 4.1%–12.8%) to end 4.8% (95% CI, 2.0%–7.6%; P<0.05). Time in AF increased in control group from baseline 10.4% (95% CI, 4.6%–17.8%) to end 14.6% (95% CI, 6.4%–24.9%). Change from baseline to follow-up between groups: P<0.01	Those participating in the exercise training experienced reduced time in AF compared with those who did not. This study is noteworthy because AF burden was measured by an implanted loop recorder, which allowed AF burden to be objectively quantified.
Parkash et al (2017)[93]	Aim: To determine whether aggressive BP reduction prevents AF recurrence after ablation Study type: RCT parallel, open-label; 13 sites in Canada Size: N=184 (aggressive control n=92, standard control n=92) Median follow-up 14 mo	Inclusion criteria: Baseline BP >130/80 mm Hg; symptomatic AF; scheduled for catheter ablation Exclusion criteria: Severe renal dysfunction; intolerance to angiotensin receptor II antagonist	Intervention: Treatment before ablation to maintain BP at ≤120/80 mm Hg Comparator: Treatment before ablation to maintain BP at <140/90 mm Hg	Primary end point: Recurrence of symptomatic AF lasting >30 s that occurred 3 mo after catheter ablation Safety end point: 26% of intervention and 0% of standard care patients experienced hypotension that required medication adjustment Results: There was no significant difference in AF recurrence between intervention (70.5%) and control (63.5%) groups 3 mo after ablation (HR, 0.94; 95% CI, 0.65–1.38; P=0.76)	Aggressive hypertension control did not reduce AF recurrence after catheter ablation

(*Continued*)

Table 4. Continued

First Author (Year)	Aim of Study, Study Type, and Study Size	Patient Population	Study Intervention/ Study Comparator	End Point Results	Relevant Secondary End Points, Study Limitations, and Adverse Events
Deftereos et al (2013)[89]	Aim: To determine whether the effect of moxonidine as a central nervous sympathetic activation modulator affects AF burden in hypertensive patients with AF Study type: Not an RCT; prospective double-blind, single-group cross-over Size: N=56	Inclusion criteria: Hypertensive patients with symptomatic AF in whom at least 5 min of AF had been documented on a baseline 24-h Holter Exclusion criteria: Age <25 or >80 y; known hypersensitivity to moxonidine; sinus node dysfunction; bradycardia <50 bpm at rest; glomerular filtration rate <30 mL·min^{-1}·1.73 m^{-2}; history of angioneurotic edema; ejection fraction <0.40; angina pectoris; known peripheral artery disease; and others	Intervention: Each participant received treatment for two 6-wk periods: 1 period with moxonidine and 1 period with placebo, with 2-wk washout between treatments Comparator: Cross-over study	Primary end point: AF burden: min spent in AF per d when measured by three 48-h Holter recordings in moxonidine and placebo treatment periods Secondary: Number of AF episodes per d. When treated with moxonidine, AF min per d were reduced from 28 to 16.5 (P<0.01). AF duration was reduced by 41% and frequency by 66% while taking moxonidine. Safety end point: No serious adverse events were documented	In this cross-over study, min of AF per d and episodes per d were reduced during treatment with moxonidine. AF detection method was 48-h Holter recordings 3 times during moxonidine and placebo treatment. AF symptoms were also reduced during moxonidine treatment. Compliance with treatment was monitored by pill counts.

AF indicates atrial fibrillation; AFSS, Atrial Fibrillation Severity Scale; BMI, body mass index; BP, blood pressure; CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; INR, international normalized ratio; NA, not applicable; and RCT, randomized controlled trial.

to answer this question. Ongoing trials include ARTESiA (Apixaban for the Reduction of Thrombo-Embolism in Patients With Device-Detected Subclinical Atrial Fibrillation)[98] and NOAH (Non–Vitamin K Antagonist Oral Anticoagulants in Patients With Atrial High Rate Episodes).[99] Similarly, future studies to determine the threshold of AF burden that results in increased risk of other outcomes such as HF and dementia will also be needed (Table 5).

Most of what is known about the effects of AF burden and consequences of AF comes from studies in patients with permanent pacemakers or implantable cardioverter-defibrillators or those who have had prior strokes. Prospective studies of the effects of AF burden on stroke and other outcomes will be necessary in broader community-based cohorts. Studies such as National Institutes of Health–funded projects to better define the prevalence of subclinical AF and the risks associated with AF burden using external loop monitors in the ARIC (R01HL126637), Women's Health Initiative (R01HL136390), and Multi-Ethnic Study of Atherosclerosis (R01HL127659) cohorts are ongoing.

Table 5. Knowledge Gaps in the Study of AF Burden

Key Knowledge Gaps
1. Optimal monitoring frequency and duration to measure AF burden
2. Threshold of AF burden that results in an increased risk of stroke, heart failure, dementia, and other AF-related outcomes
3. Prevalence of subclinical AF and effects of AF burden in broad community-based cohorts
4. Risk factors and determinants of AF burden in broad community-based cohorts
5. Lack of temporal relationship between AF burden and stroke in AF patients
6. How AF burden will need to be redefined in the era of widespread, long-term continuous cardiac monitoring
7. Threshold of AF burden that indicates need for anticoagulation in patients with higher risk of stroke (eg, CHA_2DS_2-VASc score ≥2)

AF indicates atrial fibrillation.

Link Between AF Burden and Stroke

The concept that AF-related strokes are caused by formation of left atrial clots that embolize has been considered dogma. It is believed that the risk of a clot forming and embolizing increases significantly after 48 hours of AF. This notion is based in part on studies in which stroke risk related to cardioversion is mitigated by ruling out left atrial clots with transesophageal echocardiogram in patients who have been in AF for >48 hours.[100]

However, studies in patients with long-term device monitoring reveal that the temporal relationship between AF burden and strokes might not be as strong as we have assumed.[46,49] In the Veterans Administration Health Care System study,[46] 83% of patients with a stroke had no AF detected in the previous 120 days. Although most of the remaining patients with AF detected during this monitoring period had an AF event that lasted >5.5 hours in the 30 days before the stroke, a handful only had AF detected remotely, between 90 to 120 days prior.

On the one hand, these observations affirm existing dogma that AF burden is associated with immediate

short-term risk of AF; however, these studies also raise questions regarding the lack of a temporal relationship between AF and stroke in other patients. This lack of a temporal relationship can be explained either by the ability of left atrial clots to form and remain dormant for prolonged periods before embolizing or by the ability of AF to predispose patients to embolic events originating outside the left atrial appendage. One leading hypothesis is that patients with AF might have associated endothelial dysfunction that leads to an inflammatory response and release of prothrombotic molecules such as von Willebrand factor.[101,102] Studies focused on how AF burden affects endovascular function are needed to further explore these hypotheses. Another possible explanation could be related to the emerging concept that AF is on a continuum of atrial disease, or atriopathy.[103] It is plausible that stroke could occur at any stage of this continuum and that AF burden could simply be a marker of the severity of atriopathy and stroke risk.

AF Burden and Future Monitoring Techniques

The technologies used to monitor AF are advancing at a rapid pace. Several commercially available loop monitors the size of a small patch are now available, and their ease of use results in excellent patient compliance.[104] Implantable loop recorders have become small enough and easy enough to implant that it is feasible to perform the procedure in-office.[105] As both wearable and implantable technologies become smaller and more affordable, long-term continuous cardiac monitoring will become pervasive. It is conceivable that in the near future, most people, with and without known AF, will be continuously and indefinitely monitored.

As is often the case, improvements in medical technology outpace our ability to study their clinical implications. New questions and additional knowledge gaps are bound to arise. For example, as greater numbers of young and low-risk populations are monitored continuously, AF burden and the clinical consequences will need to be studied and redefined. Long-term monitoring in large populations will also allow us to better define the significance of changes in AF burden over time.

CONCLUSIONS

- Many studies examine outcomes by AF burden classified by AF type (paroxysmal versus nonparoxysmal, persistent, long-standing persistent, or permanent). However, quantitatively, AF burden can be defined by longest duration, number of AF episodes during a monitoring period, and perhaps more comprehensively by the proportion of time an individual is in AF during a monitoring period, expressed as a percentage.
- Current guidelines recommend using vascular risk factors (as measured by the CHA_2DS_2-VASc score), and not considering AF burden, when making decisions regarding anticoagulation for stroke prevention in AF.
- The strongest evidence suggests that patients with persistent AF are at higher risk of stroke than those with paroxysmal AF; however, the relationship of increasing AF burden with risk of stroke is not well characterized. CIED-based studies conclude that higher AF burden is associated with higher risk of stroke, but it is unclear whether the risk increases continuously or whether a threshold exists, in large part because of variable AF duration cutoffs, which were mostly arbitrarily prespecified rather than empirically derived. The effect of very brief AF episodes of <5 to 6 minutes on stroke risk has not been rigorously evaluated and remains unknown.
- Although one small cross-sectional study reported that persistent AF was associated with lower cognitive function than paroxysmal AF, data on the relationship between AF burden and cognitive function are scarce, which represents a critical knowledge gap that demands more attention.
- Compared with paroxysmal AF, nonparoxysmal AF is associated with higher prevalence and incidence of HF and higher risk of mortality. The data are less clear with device-detected AHRE.
- Higher AF burden is not necessarily related to lower quality of life; new-onset AF is associated with worse quality of life than reported in patients with permanent AF. Interventions aimed at reducing AF burden have not translated to improvement in quality of life.
- A structured and comprehensive risk factor management program targeting atherosclerotic risk factors, weight loss, and maintaining a healthy weight is effective in reducing AF burden.
- Remaining knowledge gaps indicate the need for future studies, including those focused on validation of definitions and measures of AF burden, determination of the threshold of AF burden that results in an increased risk of stroke that warrants anticoagulation, and discovery of the mechanisms underlying the weak temporal correlations of AF and stroke.
- Developments in monitoring technologies will likely change the landscape of long-term AF monitoring and could allow better definition of the significance of changes in AF burden over time.

ARTICLE INFORMATION

The American Heart Association makes every effort to avoid any actual or potential conflicts of interest that may arise as a result of an outside relationship or a personal, professional, or business interest of a member of the writing panel.

Specifically, all members of the writing group are required to complete and submit a Disclosure Questionnaire showing all such relationships that might be perceived as real or potential conflicts of interest.

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Writing Group Disclosures

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*Modest.

†Significant.

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†Significant.

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Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity: A Scientific Statement From the American Heart Association

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