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STATE-OF-THE-ART PAPER

Age as a Risk Factor for Stroke in Atrial Fibrillation Patients

Implications for Thromboprophylaxis

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The prevalence of atrial fibrillation (AF) is related to age and is projected to rise exponentially as the population ages and the prevalence of cardiovascular risk factors increases. The risk of ischemic stroke is significantly increased in AF patients, and there is evidence of a graded increased risk of stroke associated with advancing age. Oral anticoagulation (OAC) is far more effective than antiplatelet agents at reducing stroke risk in patients with AF. Therefore, increasing numbers of elderly patients are candidates for, and could benefit from, the use of anticoagulants. However, elderly people with AF are less likely to receive OAC therapy. This is mainly due to concerns about a higher risk of OAC-associated hemorrhage in the elderly population. Until recently, older patients were under-represented in randomized controlled trials of OAC versus placebo or antiplatelet therapy, and therefore the evidence base for the value of OAC in the elderly population was not known. However, analyses of the available trial data indicate that the expected net clinical benefit of warfarin therapy is highest among patients with the highest untreated risk for stroke, which includes the oldest age category. An important caveat with warfarin treatment is maintenance of a therapeutic international normalized ratio, regardless of the age of the patient, where time in therapeutic range should be ≥65%. Therefore, age alone should not prevent prescription of OAC in elderly patients, given an appropriate stroke and bleeding risk stratification. (J Am Coll Cardiol 2010; 56:827–37) © 2010 by the American College of Cardiology Foundation

Atrial fibrillation (AF) is a common cardiac arrhythmia that confers substantial mortality and morbidity from stroke, thromboembolism, and heart failure, and a significant impairment of quality of life (1,2). The prevalence of AF increases markedly with older age (3,4): about 5% of people over 65 years and 10% of people age ≥80 years suffer from AF (4). The lifetime risk of AF is approximately 1 in 4 among people age 40 years and older (2,5). AF is more prevalent in men than in women, although the absolute number of women and men with AF is similar, given that women outnumber men in the older age groups (6). The prevalence of AF is projected to rise exponentially as the population ages and the prevalence of cardiovascular risk factors increases (4).

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AF is a major risk factor for stroke, increasing the risk of ischemic stroke by approximately 5-fold (6), with approximately 15% of all strokes in the U.S. being attributable to AF (6). Further, age is also a risk factor for stroke, with the lifetime probability of suffering a stroke increasing steadily with age, from 5.9% at 55 to 59 years, to 22.3% at 80 to 84 years in men, and from 3.0% to 23.9% over this age range in women (1). Therefore, the combination of increasing age and AF means that stroke prevention in elderly people with AF is paramount.

The objective of this systematic review is to provide an overview of published studies that have examined the relation between age and stroke/thromboembolism in AF. We appreciate that perioperative AF is also an important predictor of post-operative stroke, thromboembolism, and mortality, as highlighted in various reviews (7–9), but the focus of this paper will be thromboprophylaxis in the nonsurgical setting, and more on the outpatient nonacute clinical setting.

Age and Risk of Stroke in Studies

The importance of age as a risk factor for stroke in AF populations has been specifically evaluated in 17 studies (Table 1) examining the independent risk associated with

Abbreviations and Acronyms

AF = atrial fibrillation
CI = confidence interval
HR = hazard ratio
ICH = intracranial hemorrhage
INR = international normalized ratio
OAC = oral anticoagulation
RCT = randomized controlled trial
RR = relative risk
TIA = transient ischemic attack
TTR = time in therapeutic range

age, either as a continuous variable (1,10–12) or incrementally by decade (13–21), or by employing an arbitrary cutoff (e.g., >75 years) (22–25). Twelve studies found increasing age to have an independent effect on the stroke risk (1,10,11,13–17,21–23,25), whereas 5 studies failed to find such an association (12,18–20,24).

In a pooled analysis of 5 randomized controlled trials (AFASAK [Copenhagen Atrial Fibrillation, Aspirin, and Anticoagulation], SPAF [Stroke Prevention in Atrial Fibrillation Investigators trial], BAATAF [Boston Area Anticoagulation Trial For Atrial Fibrillation], CAFA [Canadian Atrial Fibrillation Anticoagulation study], and SPINAF [Stroke Prevention In Nonrheumatic Atrial Fibrillation]), the overall relative risk (RR) of stroke associated with age (by increasing decade) was 1.4 (95% confidence interval [CI]: 1.1 to 1.8) (13). Age also emerged as an independent predictor of ischemic stroke in prospective cohort or case-control studies (15,22,26–40) (Table 2).

Being age 65 years or older was associated with a 3-fold increased risk of stroke (RR: 3.3, 95% CI: 1.92 to 5.81) in an observational study (22), with the Framingham study demonstrating that age (per decade) was independently associated with stroke, with a RR of 1.32 (95% CI: 1.02 to 1.76) (15). Among the 4 studies that evaluated thresholds of age to define age-related stroke risk (22–25), only 1 (24) did not find that being >70 years of age was a significant stroke risk factor. In this study, as in AFASAK I (12), hypertension—which is a well-known risk factor for stroke—also failed to emerge as an independent risk factor for stroke in AF (24).

Further, the recent van Walraven et al. meta-analysis of randomized controlled trials (RCTs) (41) demonstrated that age independently (adjusted for sex, year of randomization, history of cerebrovascular disease, diabetes mellitus, hypertension, and congestive heart failure) increased the risk of ischemic stroke (1.45, 95% CI: 1.26 to 1.66 per decade).

Therefore, the balance of evidence suggests that age is an independent risk for stroke, with the magnitude of risk varying dependent on whether an incremental risk per decade or an age cutoff is employed (Table 2). There is a steep increase in the lifetime incidence of stroke with age both in men and women. The risk starts to rise at age 55 to 59 years from 5.9% in men and 3.0% in women to 11.0% and 7.2%, respectively, in the next decade, reaching an incidence of 22.3% and 23.9% in the 80- to 84-year-old group (1). Studies that have dichotomized age suggest a 1.4-fold increased risk of stroke per decade (13).

Risk Stratification Schemes

The absolute risk of stroke varies widely among patients with AF and is dependent not only on chronological age, but also on existing comorbidities and other clinical features. Indeed, multiple stroke risk stratification schemes for AF patients have been proposed (42) that vary substantially in complexity and incorporate different combinations of clinical and echocardiographic parameters. However, at the core of all the existing and most frequently employed schemes are 3 key features that have been independently and consistently associated with stroke in AF patients: advancing age (1,10–25), previous stroke or transient ischemic attack (TIA) (13,15–18,43–48), and hypertension (13,16,17,43–48).

Table 1 Increasing Age as a Risk Factor For Stroke

Study (Ref. #)	n	Age Criteria Employed	Risk (95% CI) Associated With Age	p Value
Flegel and Hanley, 1989 (25)	91	Age >75 yrs	HR: 2.51 (1.14–5.51) >75 yrs	<0.05
Cabin et al., 1990 (24)	272	Age >70 yrs	*	NS
Petersen et al., 1990 (12)	336	Correlation with increasing age	*	NS
Wolf et al., 1991 (1)	5,070	Age 80–90 yrs	*	<0.001
Moulton et al., 1991 (22)	2,516	Age >75 yrs	OR: 1.76 (1.08–2.89)	<0.05
SPAF Investigators, 1992 (19)	568	Incremental risk per decade	RR: 1.2 (0.9–1.6)	>0.20
AFI, 1994 (13)	1,593	Incremental risk per decade	RR: 1.4 (1.1–1.8) per decade	<0.05
Van Latum et al., 1995 (18)	375	Incremental risk per decade	HR: 1.3 (0.5–3.0) ≥70 yrs	NS
Yoshida et al., 1996 (11)	122	Correlation with increasing age	RR: 1.11 (1.04–1.19)	0.0052
SPAF III, 1998 (14)	829	Incremental risk per decade	RR: 1.7 (1.1–2.6) per decade	0.01
AFI, 1998 (17)	1,066	Incremental risk per decade	RR: 1.5 (1.1–1.9) per decade	0.008
Naghami et al., 1998 (20)	290	Incremental risk per decade	OR: 1.33 (1.04–1.71) per decade	NS
Hart et al., 1999 (16)	460	Incremental risk per decade	RR: 2.0‡ per decade	<0.001
Hart et al., 2000 (21)	2,010	Incremental risk per decade	RR: 2.1/1.7†‡ per decade	<0.001
Inoue et al., 2000 (23)	740	Age >65 yrs	RR: 3.33 (1.92–5.81)	0.0001
Wang et al., 2003 (15)	705	Incremental risk per decade	*	<0.05
Stollberger et al., 2004 (10)	409	Correlation with increasing age	RR: 1.06 (1.04–1.08)	0.0006

*Not reported; †intermittent AF/sustained AF; ‡confidence intervals not reported.
AFI = Atrial Fibrillation Investigators; HR = hazard ratio; NS = not significant ($p > 0.05$); OR = odds ratio; RR = relative risk; SPAF = Stroke Prevention in Atrial Fibrillation Study.