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# Antithrombotic Therapy for Atrial Fibrillation

## Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines

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**Table S1—*Studies Assessing Prior Stroke/TIA as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| Pooled estimate[1] | 2.5 (1.8-3.5) | .59 (for heterogeneity) |
| Studies included in pooled estimate: | | |
| AFI[2]/1994 | 2.5 (NR) | < .05 |
| SPAF I-III Aspirin[3]/1999 | 2.9 (NR) | < .001 |
| Stöllberger et al[4]/1998 | 3.7 (1.5-7.5) | .002 |
| Wang et al[5]/2003 | 1.9 (1.1-3.3) | NR |
| Studies not included in pooled estimate: | | |
| AFI Echo[6]/1998[a] | 3.5 (1.8-6.7) | < .001 |
| Aronow et al[7]/1998 | 1.6 (1.1-2.2) | < .009 |
| Hart et al[8]/2000 (intermittent AF) | 4.1 (NR) | .01 |
| Hart et al[8]/2000 (sustained AF) | 2.7 (NR) | < .001 |
| SPAF I[9]/1992 | 2.1 (NR) | .04 |
| Stöllberger et al[10]/2004 | 2.14 (NR) | .045 |
| van Latum et al[11]/1995 | 1.6 (1.0-2.6) | < .05 |
| Van Staa et al[12]/2011 | 2.86 (2.53-3.22) | < .05 |

AF = atrial fibrillation; AFI = Atrial Fibrillation Investigators; NR = not reported; RR = risk ratio; SPAF = Stroke Prevention in Atrial Fibrillation; TIA = transient ischemic attack.

[a]Subset of patients from AFI[6] with echocardiographic data available.



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**Table S2—*Studies Assessing Hypertension as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| Pooled estimate[1] | 2.0 (1.6-2.5) | .29 (for heterogeneity) |
| Studies included in pooled estimate: | | |
| AFI[2]/1994 | 1.6 (NR) | < .05 |
| Moulton[13]/1991 | 1.9 (1.2-3.1) | < .05 |
| SPAF I-III Aspirin[3]/1999 | 2.0 (NR) | < .001 |
| Stöllberger et al[4]/1998 | 3.6 (1.8-8.4) | .001 |
| Studies not included in pooled estimate: | | |
| AFI Echo[6]/1998[a] | 1.5 (0.9-2.5) | .13 |
| Aronow et al[14]/1989 | 12.5 (NR) | < .01 |
| Aronow et al[7]/1998 | NR | NS |
| Cabin et al[15]/1990 | NR | NS |
| Hart et al[8]/2000 (intermittent AF) | 3.4 (NR) | .003 |
| Hart et al[8]/2000 (sustained AF) | 1.8 (NR) | .008 |
| Petersen et al[16]/1990 | NR | NS |
| Seidl et al[17]/1998 | 6.5 (1.5-4.5) | < .05 |
| SPAF I[9]/1992 | 2.2 (1.1-4.3) | .02 |
| SPAF III[18]/1998[b] | 3.3 (1.7-6.9) | .001 |
| Stöllberger et al[10]/2004 | NR | NS |
| Wang et al[5]/2003[c] | NR | NS |
| Studies assessing uncontrolled hypertension only[d]: | | |
| Hart et al[8]/2000 (intermittent AF) | NR | NS |
| Hart et al[8]/2000 (sustained AF) | 2.8 (NR) | < .001 |
| SPAF I-III Aspirin[3]/1999 | 2.3 (NR) | < .001 |
| van Latum et al[11]/1995 | 1.7 (1.0-2.9) | NS |
| Van Staa et al[12]/2011 (≥ 180 vs < 120 mm Hg) | 2.74 (1.21-6.19) | < .05 |
| Van Staa et al[12]/2011 (140-159 vs < 120 mm Hg) | 2.74 (1.21-6.19) | < .05 |
| Van Staa et al[12]/2011 (160-179 vs < 120 mm Hg) | 1.49 (0.55-4.00) | NS |
| Wang et al[5]/2003 | 1.1/10 mm | < .05 |

NS = not significant. See Table S1 legend for expansion of other abbreviations.

[a]Subset of patients from AFI (1994)[2] with echocardiographic data available.

[b]Defines hypertension as diagnosed hypertension.

[c]Defines hypertension as use of BP-lowering medication.

[d]Defined as systolic BP > 160 mm Hg, unless otherwise stated.



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**Table S3—*Studies Assessing Increasing Age as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| Pooled estimate[1] | 1.5 (1.3-1.7)/decade | .59 (for heterogeneity) |
| Studies included in pooled estimate: | | |
| AFI[2]/1994 | 1.4 (NR)/decade | < .05 |
| Moulton et al[13]/1991 (for age > 75) | 1.7 (1.0-2.8) | < .05 |
| SPAF I-III Aspirin[3]/1999 | 1.8 (NR)/decade | < .001 |
| Stöllberger et al[4]/1998 | 1.1 (1.0-1.1)[a] | < .001 |
| Wang et al[5]/2003 | 1.3 (NR)/decade | < .05 |
| Studies not included in pooled estimate: | | |
| AFI Echo[6]/1998[b] | 1.5 (NR)/decade | .006 |
| Cabin et al[15]/1990 (for age > 70) | NR | NS |
| Hart et al[8]/2000 (intermittent AF) | 2.1 (NR)/decade | < .001 |
| Hart et al[8]/2000 (sustained AF) | 1.7 (NR)/decade | < .001 |
| Inoue and Atarashi[19]/2000 (paroxysmal AF; for age > 65 y) | 3.3 (1.92-5.81) | .0001 |
| Nakagami et al[20]/1998 | 1.3 (1.0-1.7)/decade | NS |
| SPAF I[9]/1992 | 1.2 (0.9-1.6)/decade | NS |
| SPAF III[18]/1998 | 1.7 (1.1-2.6)/decade | .01 |
| van Latum et al[11]/1995 | NR | NS |
| Van Staa et al[12]/2011 (age, < 50 vs 60-69 y) | 0.14 (0.06-0.34) | < .05 |
| Van Staa et al[12]/2011 (age, ≥ 80 vs 60-69 y) | 2.22 (1.78-2.76) | < .05 |
| Van Staa et al[12]/2011 (age, 50-59 vs 60-69 y) | 0.44 (0.28-0.69) | < .05 |
| Van Staa et al[12]/2011 (age, 70-79 vs 60-69 y) | 1.42 (1.12-1.78) | < .05 |

See Table S1 and S2 legends for expansion of abbreviations.
[a]Age entered as a continuous variable.
[b]Subset of patients from AFI (1994)[2] with echocardiographic data available.

**Table S4—*Studies Assessing Diabetes as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| Pooled estimate[1] | 1.7 (1.4-2.0) | .69 (for heterogeneity) |
| Studies included in pooled estimate: | | |
| AFI[2]/1994 | 1.7 (NR) | < .05 |
| SPAF I-III Aspirin[3]/1999 | 1.9 (NR) | .02 |
| Stöllberger et al[4]/1998 | NR | NS |
| Wang et al[5]/2003 | 1.8 (1.4-3.1) | NR |
| Studies not included in pooled estimate: | | |
| AFI Echo[6]/1998[a] | 1.7 (1.0-2.9) | .05 |
| Aronow et al[7]/1998 | NR | NS |
| Petersen et al[16]/1990 | NR | NS |
| Seidl et al[17]/1998 | NR | NS |
| SPAF III[18]/1998 | NR | NS |
| Van Staa et al[12]/2011 | 1.33 (1.14-1.55) | < .05 |

See Table S1 and S2 legends for expansion of abbreviations.
[a]Subset of patients from AFI[2] with echocardiographic data available.



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**Table S5—*Studies Assessing Heart Failure as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| AFI[2]/1994 | 1.4 (NR) | NS |
| AFI Echo[6]/1998[a] (with echocardiographic data) | 1.4 (0.8-2.3) | .16 |
| AFI Echo[6]/1998[a] (without echocardiographic data) | 1.7 (1.1-2.7) | .03 |
| SPAF[18]/1998 | NR | NS |
| SPAF I[9]/1992 | 2.6 (1.0-4.2) | .01 |
| SPAF I-III Aspirin[3]/1999 | NR | NS |
| Stöllberger et al[8]/1998[b] | NR | NS |
| Stöllberger et al[10]/2004[b] | NR | NS |
| Van Staa et al[12]/2011 | 1.26 (1.11-1.42) | < .05 |

See Table S1 and S2 legends for expansion of abbreviations.
[a]Subset of patients from AFI[2] with echocardiographic data available.
[b]Defined as New York Heart Association functional class > II.

**Table S6—*Studies Assessing LV Dysfunction/Hypertrophy (Using Echocardiography) as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| AFI Echo[6]/1998 | 1.4 (0.8-2.3) | .16 |
| Aronow et al[7]/1998 | 1.8 (1.2-2.7) | .003 |
| Aronow et al[7]/1998 (LV hypertrophy) | 2.8 (1.8-4.4) | .0001 |
| Aronow et al[14]/1989 (LV hypertrophy) | 6.56 (NR) | < .01 |
| SPAF[21]/1992 | 2.6 (1.4-4.9) | .003 |
| SPAF I-III Aspirin[3]/1999 (using 2D echocardiography) | NR | NS |
| SPAF I-III Aspirin[3]/1999 (using M-mode echocardiography) | NR | NS |
| Stöllberger et al[4]/1998 | NR | NS |

2D = two dimensional; LV = left ventricular. See Table S1 and S2 legends for expansion of other abbreviations.

**Table S7—*Studies Assessing Valvular Heart Disease[a] as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| AFI Echo[6]/1998 (mitral valve prolapse) | 0.29 (NR) | NS |
| AFI Echo[6]/1998 (mitral valve regurgitation) | 1.07 (NR) | NS |
| Aronow et al[7]/1998 (aortic stenosis) | NR | NS |
| Aronow et al[7]/1998 (mitral annular calcifications) | NR | NS |
| Nakagami et al[20]/1998 (mitral valve regurgitation) | 0.45 (0.20-0.97) | < .05 |
| van Staa et al[12]/2011 | 1.65 (1.01-2.71) | < .05 |

See Table S1 and S2 legends for expansion of abbreviations.
[a]Specific type of valvular heart disease in parentheses.



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**Table S8—*Studies Assessing Female Sex as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| AFI[2]/1994 | NR | NS |
| AFI Echo[6]/1998[a] | NR | NS |
| Aronow et al[7]/1998 | NR | NS |
| Aronow et al[14]/1989 | 0.85 (NR) | NS |
| Cabin et al[15]/1990 | NR | .014 |
| Fang et al[22]/2005 (all women) | 1.6 (1.3-1.9) | < .05 |
| Fang et al[22]/2005 (women aged > 75 vs men aged > 75 y) | 1.8 (1.4-2.3) | < .05 |
| Fang et al[22]/2005 (women aged ≤ 75 vs men aged ≤ 75 y) | 1.6 (1.0-2.3) | NS |
| Hart et al[8]/2000 (intermittent AF) | NR | NS |
| Hart et al[8]/2000 (sustained AF) | 1.8 | .004 |
| Inoue and Atarashi[19]/2000[b] (paroxysmal AF) | 0.50 (0.27-0.93) | .0291 |
| Moulton[13]/1991 | NR | NS |
| Nakagami et al[20]/1998 | 0.98 (0.55-1.72) | NS |
| Petersen et al[23]/1990 | NR | NS |
| SPAF III[18]/1998 | NR | NS |
| SPAF I-III Aspirin[3]/1999 (all women) | 1.6 (NR) | .01 |
| SPAF I-III Aspirin[3]/1999 (women aged > 75 y) | 3.0 (NR) | .002 |
| Stöllberger et al[4]/1998 | NR | NS |
| van Latum et al[11]/1995 | 1.5 (1.0-2.4) | .05 |
| Van Staa et al[12]/2011[b] | 1.05 (0.94-1.19) | NS |
| Wang et al[5]/2003 | 1.9 (1.2-3.1) | < .05 |

See Table S1 and S2 legends for expansion of abbreviations.
[a]Subset of patients from AFI[2] with echocardiographic data available.
[b]Reference sex in original study was female; reported values of RR have been inverted to be directly comparable with other studies.

**Table S9—*Studies Assessing Estrogen-Based HRT as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| Fang et al[22]/2005 (22% HRT use) | 1.0 (0.7-1.4) | NS |
| SPAF I-III Aspirin[3]/1999 (33% HRT use at entry) | 3.1 (NR) | .007 |

HRT = hormone replacement therapy. See Table S1 and S2 legends for expansion of other abbreviations.

**Table S10—*Studies Assessing Coronary Artery Disease as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| AFI[2]/1994 (history angina) | NR | NS |
| AFI[2]/1994 (history myocardial infarction) | 1.7 (NR) | NS |
| Aronow et al[14]/1989 (history myocardial infarction) | 4.84 (NR) | < .01 |
| Petersen et al[23]/1990 (history myocardial infarction) | 1.7 (NR) | .0375 |
| SPAF III[18]/1998 | NR | NS |
| SPAF I-III Aspirin[3]/1999 | NR | NS |
| Stöllberger et al[4]/1998 | NR | NS |

Other studies have examined peripheral artery disease as an independent predictor of stroke in patients with AF.[24,25] See Table S1 and S2 legends for expansion of abbreviations.

**Table S11—*Studies Assessing Carotid Artery Stenosis as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| SPAF II[26]/1994 | 1.8 (0.5-3.6) | .55 |

See Table S1 legend for expansion of abbreviations.

**Table S12—*Studies Assessing Left Atrial Thrombus as an Independent Predictor of Stroke in Patients With AF***

| Study/Year | Multivariate OR/RR (95% CI) | *P* Value |
|---|---|---|
| Stöllberger[4]/1998 | 2.4 (0.9-6.9) | .09 |

See Table S1 for expansion of abbreviations.
[a]One-half of the 10 patients with left atrial thrombus received anticoagulant therapy, likely blunting the predictive value.



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**Table S13—*Stroke Risk Stratification Schema***

| Study/Year | Low Risk | Intermediate Risk | High Risk |
|---|---|---|---|
| AFI[2]/1994 | Age < 65 y and no risk factors | Age > 65 y and no other risk factors | Prior stroke/TIA, hypertension, diabetes |
| SPAF[18]/1998 | No risk factors | Hypertension, diabetes | Prior stroke/TIA, women > 75 y, men > 75 y with hypertension |
| $CHADS_2$[27]/2001 | Score 0 | Score 1-2 | Score 3-6 |
| AFI[28]/2003 | No risk factors | No intermediate risk category | Previous stroke/TIA, hypertension, diabetes, angina, previous MI |
| Framingham[5]/2003 | Score 0-7 | Score 8-15 | Score 16-31 |
| NICE guidelines[29]/2006 | Age < 65 y with no moderate/high risk factors | Age ≥ 65 y with no high risk factors<br>Age < 75 y with hypertension, diabetes or vascular disease[a] | Previous stroke/TIA or thromboembolic event<br>Age ≥ 75 y with hypertension, diabetes or vascular disease<br>Clinical evidence of valve disease or heart failure, or impaired left ventricular function |
| ACC/AHA/ESC guidelines[30]/2006 | No risk factors | Age ≥ 75 y, or hypertension, or heart failure, or LVEF < 35%, or diabetes | Previous stroke, TIA or embolism, or ≥ 2 moderate risk factors of (age ≥ 75y, hypertension, heart failure, LVEF ≤ 35%, diabetes) |
| 8th ACCP guidelines[31]/2008 | No risk factors | Age > 75 y, or hypertension, or moderately or severely impaired LVEF and/or heart failure, or diabetes | Previous stroke, TIA or embolism, or ≥ 2 moderate risk factors of (age ≥ 75y, hypertension, moderately or severely impaired LVEF and/or heart failure, diabetes) |
| $CHADS_2$-VASc[32]/2009 | No risk factors | One combination risk factor: (heart failure/LVEF ≤ 40, hypertension, diabetes, vascular disease,[a] female gender, age 65-74) | Previous stroke, TIA or embolism, or age ≥ 75 y, or ≥ 2 combination risk factors (heart failure/LVEF ≤ 40, hypertension, diabetes, vascular disease,[a] female gender, age 65-74) |

ACC/AHA/ESC = American College of Cardiology/American Heart Association/European Society of Cardiology; $CHADS_2$ = congestive heart failure, hypertension, age > 75 years, diabetes, prior stroke or transient ischemic attack [doubled]; LVEF = left ventricular ejection fraction; NICE = National Institute for Health and Clinical Excellence; TIA = transient ischemic attack.
[a]Myocardial infarction, peripheral artery disease, or aortic placque.

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