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Should atrial fibrillation patients with hypertension as an additional risk factor of the CHA2DS2-VASc score receive oral anticoagulation?

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Abstract

Hypertension has been found to be increased a risk of stroke in atrial fibrillation (AF). Both the European and U.S. guidelines advocate the use of the CHA_2DS_2-VASc (congestive heart failure, hypertension, age > 75 years, diabetes mellitus, stroke/transient ischemic attack, vascular disease, age 65–74 years, sex category) scheme for risk stratification. Although vitamin K antagonists is more effective than acetylsalicylic acid at preventing ischaemic stroke, its benefit is offs by an increased haemorrhage risk. The risk of ischemic stroke in patients with AF and a CHA_2DS_2-VASc score of 1 are considered to be low risk and may be not expected to benefit from anticoagulation therapy. Hypertension carries an increased risk of ischemic stroke, however, it is also a clear risk factor for hemorrhage in AF. Therefore, the optimal antithrombotic management is highlighted in patients with AF with only one risk factor especially hypertension.

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1 Introduction

Hypertension is the most common comorbid condition in patients with atrial fibrillation (AF). In particular, it was found in 49%–90% of individuals in AF trials.[1–4] Stroke prevention is a major goal in the treatment of patients with AF. Hypertension has been found to be an independent risk factor for stroke and patients with both AF and hypertension have an increased risk of stroke. Both the European and U.S. guidelines[5,6] advocate the use of the CHA_2DS_2-VASc [congestive heart failure, hypertension, age > 75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category] scheme for risk stratification. However, for low risk patients with a score of 1 on the CHA_2DS_2-VASc the guidelines are inconsistent. The European Society of Cardiology (ESC)[5] recommends treatment with either adjusted-dose vitamin K antagonists (VKAs) (e.g., warfarin) or, preferably, one of the non–vitamin K antagonist oral anticoagulants (NOACs) (i.e., dabigatran, rivaroxaban, apixaban). While the 2014 American Heart Association/American College of Cardiology (AHA/ACC) guideline[6] states that aspirin may be considered for AF patients with a CHA_2DS_2-VASc score of 1 as a potential alternative to oral anticoagulants (OACs) or no therapy. The recent Canadian guidelines[7] dichotomized individuals into those with versus without one risk factor for stroke, based on the CHA_2DS_2-VASc score. Although some of the CHA_2DS_2-VASc risk factors (e.g., age) are easy to validate, others such as hypertension are more complex. Uncontrolled hypertension leads to more strokes, whether in AF or non-AF patients. However, when anticoagulants are used, uncontrolled blood pressure increases the risk of serious bleeding. In addition, racial/ethnic also affect the optimal anticoagulation therapy. Incidence in intracranial hemorrhage (ICH) during warfarin treatment was approximately four times greater in the Asian than in the Caucasian. Asians were at successively greater ICH risk than whites.[8] Thus, it is of value to examine the strength of the data on hypertension alone as a risk factor for thromboembolism in AF.

2 Hypertension and thrombosis

Previous studies[9–11] have found that patients with hypertension demonstrate abnormalities of vessel wall (endothelial dysfunction or damage), blood constituents (abnormal levels of haemostatic factors, platelet activation and

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fibrinolysis) and blood flow (rheology and flow reserve), suggesting that hypertension does indeed confer a prothrombotic or hypercoagulable state. In addition to the increased risk of thrombogenesis, hypertension also increases the risk of atherosclerosis, since both thrombogenesis and atherogenesis are intimately related. Thus, the pathophysiological changes in hypertension contribute to an intravascular microenvironment which promotes platelet adhesion, aggregation and thrombus formation, which is probably responsible for the excess risk of myocardial infarction, strokes and peripheral vascular disease. The rationale for the use of antithrombotic therapy on pathophysiological grounds alone would therefore seem highly plausible.

3 Stroke assessment in hypertensive patients with AF

Hypertension is frequently seen in patients with AF as those included in major clinical trials. Furthermore, hypertension has been frequently documented in patients (49%–90%) as those included in major AF clinical trials.[3,4,12,13] Compared with the general population, patients with AF have a 3- to 6-fold increase in stroke risk.[14] Hypertension worsens the stroke rate by an additional 2- to 3-fold in patients with AF.[15–17] Untreated or suboptimally treated hypertension leads to the development of left ventricular hypertrophy, which is one of the most important expressions of subclinical organ damage, and is an independent risk factor for cardiovascular events, including the development of AF. In the presence of left ventricular hypertrophy, left ventricular compliance is reduced, left ventricular stiffness and filling pressure increase, coronary flow reserve is decreased, wall stress is increased and there is activation of the sympathetic nervous system and of the renin–angiotensin–aldosterone system. In the atria, proliferation and differentiation of fibroblasts into myofibroblasts lead to the left atrial mechanical remodeling. It has been demonstrated that hypertension is associated with reduced left atrial appendage flow velocity, spontaneous echo contrast, and thrombus formation in patients with nonvalvular AF, thus resulting in cardioembolic stroke.[18,19] Nonetheless, hypertension can also increase the risk of non-cardioembolic stroke due to hypertensive damage to brain vessels leading to lacunar infarcts in patients with AF.[20,21] However, hypertension is not always detected as an independent predictor of thromboembolism or hemorrhagic complications. In previous reports in patients with nonvalvular AF who were not receiving anticoagulation therapy, hypertension was an independent risk factor for ischemic stroke,[22] whereas it was not in patients treated with warfarin.[23, 24] Since these analyses were performed post hoc on data from prospective clinical studies, patient characteristics varied among studies. More recently, systolic blood pressure (SBP) of ≥ 136 mmHg at the time closest to the event rather than the history of hypertension was an independent risk for thromboembolism and major hemorrhage.[25] The presence of AF in hypertensive patients should therefore prompt physicians to control the blood pressure. Given that uncontrolled elevation in SBP is a risk factor for intracranial hemorrhage and patients taking anticoagulants are at high risk for bleeding, it is not only relevant to determine the association between a history of hypertension requiring therapy, but also to determine whether patients with AF and hypertension benefit from anticoagulation treatment in the same way as those without.

4 Anticoagulation treatment in hypertension patients

Since hypertension is part of CHA_2DS_2-VASc risk score for stroke, and according to the guidelines, most of them should receive unless contra-indications exist, OACs to prevent stroke and other embolic events.[5] The risk of stroke in patients with AF can be reduced with anticoagulation, and VKAs have historically been the most commonly used therapy. Recently NOACs, including dabigatran, apixaban, rivaroxaban, and edoxaban, were approved for stroke prevention in nonvalvular AF.[3,4,26,27] All four NOACs share additional clinical advantages over warfarin due to better known and reproducible pharmacological profiles, fewer drugs to drugs interactions, absence of dietary effects, and substantially reduced risk of intracranial bleeding compared with warfarin. Indeed, in daily clinical practice a large proportion of patients with hypertension are older than 65, or are women therefore having a risk score of 2 or greater. Anticoagulation treatment should be given not only to patients with persistent or permanent AF, but also to those with paroxysmal AF, who should be regarded as having the same risk.

5 Antithrombotic therapy in AF with hypertension as the only risk factor

All guidelines[6,28–31] recommend that patients with a CHA_2DS_2-VASc score of 2 or higher should be treated with OACs because the risk of ischaemic stroke outweighs the increased risk of bleeding induced by anticoagulation therapy. However, guidelines are less confirmed in their recommendations concerning patients with a CHA_2DS_2-VASc score of 1, reflecting uncertainty about the benefits of OACs

in this population. Recent guidelines' update[5] strongly recommends focusing on the identification of "truly low-risk" patients with AF, instead of "high-risk" patients. Indeed, patients with AF who have stroke risk factor (s) ≥ 2 are recommended to receive effective stroke prevention therapy, which is OACs with either well-controlled VKA therapy [international normalized ratio (INR) 2–3, with a high percentage of time in the therapeutic range (TTR), for example, at least 70%] or one of the NOACs.[32] The important unresolved issue is whether the CHA_2DS_2-VASc score improves risk discrimination in patients in whom it is unclear if treatment with anticoagulants is beneficial (i.e. those with a CHA_2DS_2-VASc score of 1). Hypertension, a common disease and the most frequent comorbidity in patients with AF, should be assessed for the risk of stroke or systemic embolism. However, most clinical trials of OACs did not usually have hypertension as the only entry criteria. In addition, for low risk patients with a score of 1 on the CHA_2DS_2-VASc, the thromboprophylaxis is inconsistent in guidelines. For low risk patients with a score of 1 on the CHA_2DS_2-VASc, the ESC recommends treatment with either an adjusted-dose VKAs (e.g., warfarin) or, preferably, one of the NOACs (i.e., dabigatran, rivaroxaban, apixaban).[29] The 2014 National Institute for Health and Care Excellence (NICE) guidelines recommend a similar approach, and aspirin is not recommended.[31] However, the 2014 ACC/AHA guidelines recommend OACs for patients with a CHA_2DS_2-VASc score ≥ 2 and no therapy for those with a CHA_2DS_2-VASc score of 0; for patients with a CHA_2DS_2-VASc score of 1, no therapy, aspirin, or OACs is recommended.[6]

There are limit data on some patients with AF and a CHA_2DS_2-VASc score of 1 (which would include hypertension alone) who have very low stroke rates (Table 1). Coppens, *et al*.[33] have first showed that patients with AF and a CHA_2DS_2-VASc score ≤ 1 (which would include hypertension alone) have very low stoke rates (0.9% or less per year) and they demonstrated these patients may not benefit from treatment with VKA therapy. Similarly, Friberg, *et al*.[34] found that AF patients with CHA_2DS_2-VASc score of 1 had an annual stroke risk between 0.5% and 0.9%, even the endpoint was enriched with diagnoses of TIA, pulmonary embolism, arterial embolism, and stroke not specified as ischemic or hemorrhagic, the annual event rate for men was 1.3%, well below the 1.7% and 0.9% limits,[35] therefore anticoagulation treatment benefit is unlikely with warfarin or even with the newer drugs (dabigatran, rivaroxaban, or apixaban). Subsequently, the cost effectiveness of treatment will be low, or even negative, if treatment causes more harm than good. Lip, *et al*.[36] conducted a retrospective study of 39,400 Danish patients discharged with incident nonvalvular AF and 0 or 1 CHA_2DS_2-VASc score reported that about 50% of patients with one risk factor had age as the only risk factor (> 65 years), and 90% had either age or hypertension as the main risk factors. Stroke event rates for untreated low-risk patients [CHA_2DS_2-VASc=0 (man), 1 (woman)] were 0.49% at one year and 0.47% at full follow-up (intention-to-treat; 5.9 years). However, with one additional stroke risk factor, stroke event rates at one year were 1.55% per year on intention-to-treat and increased by 3.01-fold without treatment. Otherwise, both aspirin and warfarin have reduced death significantly but increase bleeding at full follow up and the reduction in stroke is neutral in

Table 1. Hypertension in the risk factors of cohort studies that reported patients with AF and a CHA_2DS_2-VASc score of 1.

Characters	Coppens, *et al* 2013	Huang, *et al* 2014	Friberg, *et al* 2015	Lip, *et al* 2015	Suzuki, *et al* 2015
Study Type	Clinical trial of Asprin	Investigative Study	Retrospective Health Registry Study	Retrospective Health Registry	Prospective, Observational Registry
Sample Size	4670	548	140, 420	39400	3588
Hypertension	79%	12%	43.8%	17.3%	50.4%
Heart failure	6%	4.5%	31.9%	1.8%	15%
Diabetes mellitus	3%	2.5%	16.4%	25.6%	15.3%
$CHADS_2$-Vasc = 0		35%	7%	51.6%	17.2
$CHADS_2$-Vasc = 1	26%	65%	8.80%	48.4%	20%
Stroke rate for $CHADS_2$-Vasc = 1	0.9%	6.6%	0.5%–0.9%	0.49%	0.5%
Women	34%	19.2%	50.1%	37.8%	33.9%
Men					
Asprin	48%	0	0	13.6%	41.8%
Warfarin	0	0	40%	26.6%	0

CHA_2DS_2-VASc: congestive heart failure, hypertension, age > 75 years, diabetes mellitus, stroke/transient ischemic attack (TIA), vascular disease, age 65–74 years, sex category.

patients with one additional stroke factor. In addition, Huang, *et al*.[37] in a cohort of 9727 Chinese AF patients, of which, 548 patients were entered into analysis, reported an annual incidence of stroke of 2.4 and 6.6% for patients with CHA_2DS_2-VASc score of 0 and 1, respectively, showing that patients with hypertension were at the highest risk of stroke [hazard ratio (HR): 9.8, 95% confidence intervals (CI): 2.7–35.6], followed by patients aged 65–74 (HR: 3.9, 95% CI: 2.3–6.6) and female sex (HR: 2.3, 95% CI: 1.1–4.8). The study showed that hypertension conferred the highest risk for stroke among other risk factors comprising the score.

A more aggressive thromboprophylaxis strategy may be justified among AF patients with CHA_2DS_2-VASc score of 1 due to hypertension. The presence of hypertensive in AF patients should therefore prompt physicians to control the blood pressure and consider anticoagulation therapy, particularly if there are other risk factors present, e.g. older age (> 75 years), heart failure or left ventricular dysfunction. However, hypertension is a clear risk factor for hemorrhagic stroke in the general population.[38] An increase in blood pressure levels during antithrombotic treatment was positively associated with the development of ICH, suggesting that adequate blood pressure control was important for avoiding ICH.[39] Furthermore, uncontrolled hypertension is an important risk factor for bleeding in anticoagulated subjects.[40] Previous analysis of pooled data from five randomized controlled trials demonstrated that the effect of aspirin was seen mainly among patients with a history of hypertension. In these patients the frequency of strokes was decreased by 59% (95% CI, 28% to 77%; $P = 0.002$), while among patients with no history of hypertension it was increased by 10% (95% CI, 40% to 100%; $P = 0.76$). The difference in the effectiveness of aspirin in patients with and without a history of hypertension was statistically significant ($P = 0.02$).[41] At present, no direct comparisons have been made between clopidogrel and aspirin and the new oral anticoagulants that have lower bleeding risks than warfarin in AF patients with CHA_2DS_2-VASc score of 1. Aspirin has been used as an alternative for thromboprophylaxis in AF, and although the data are inconsistent, aspirin is probably useful in younger patients with AF who do not have risk factors.[42] However, oral anticoagulation is essential in the vast majority of heart failure patients with AF with non-vitamin K based anticoagulants being suitable alternative to warfarin. In contrast, aspirin alone does not provide adequate stroke prevention in such patients.[43]

In the future, more studies are warrant to focus on the role of hypertension in stroke in AF and to expand the dialogue on the use of risk factors in guiding antithrombotic options for AF. We recognize that treatment adherence/discontinuation is an important consideration for patient management, but a thorough analysis is beyond the scope of this paper. Further studies are warranted to illustrate the question of whether patients with AF and CHA_2DS_2-VASc of 1 in particular when that risk factor is hypertension would be best managed with "nothing, aspirin, or warfarin".

6 Conclusions

Although the stroke risk of AF patients with CHA_2DS_2-VASc score of 1 was low, antithrombotic drugs options in these patients were inconsistent. Hypertension and AF commonly coexist and their combination carries an increased risk of stroke or systemic embolism. Hypertension in the presence of AF should be assessed for the risk of stroke or systemic embolism as a risk factor alone. In this review, we highlight the problems with using one factor such as hypertension as the only criterion for institution of antithrombotic therapy for patients with AF. Accurate antithrombotic therapy management may reduce the risk of ischemic stroke in these apparently low-risk patients with hypertension as the risk factor alone.

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