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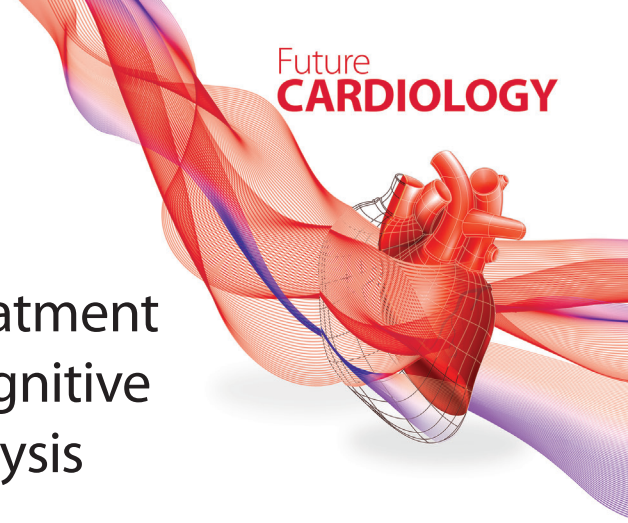

The effect of antihypertensive treatment on the incidence of stroke and cognitive decline in the elderly: a meta-analysis

Christine Parsons[1], Mohammad Hassan Murad[2], Stuart Andersen[1], Farouk Mookadam*[,3] & Helene Labonte[1]

Aim: To evaluate the effectiveness of antihypertensives in reducing neurocognitive outcomes in elderly patients. **Patients & methods:** We conducted a systematic literature search of randomized trials in which hypertensive patients with a mean age ≥65 years received antihypertensive or control treatment. Outcomes were stroke, transient ischemic attack, cognitive decline and dementia. We included 14 trials for meta-analysis. **Results:** Compared to placebo, antihypertensive treatment reduced the risk of stroke (RR: 0.67 [95% CI: 0.57–0.79]). Reduced risk was significant for transient ischemic attack, fatal stroke, nonfatal stroke and total stroke. There were insufficient data to compare individual agents. **Conclusion:** Antihypertensive treatment is associated with a significant reduction in stroke in elderly individuals. Reductions in dementia and cognitive decline were not significant; however, there was short follow-up. Comparative effectiveness evidence is limited.

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KEYWORDS
• aged • cognition • dementia • hypertension • stroke

Background

Cardiovascular disease is the leading cause of mortality worldwide [1]. Chronic disease is on the rise due to the growing elderly population. One aim of the WHO is to reduce the burden of chronic diseases through drug therapy, especially to reduce the prevalence of risk factors for myocardial infarction and stroke [2]. Hypertension is an established risk factor for cerebrovascular and ischemic heart disease and abundant evidence from clinical trials shows that treatment of hypertension of all degrees of severity reduces cardiovascular morbidity and mortality [3].

The elderly population has a higher prevalence of hypertension and is more likely to have isolated systolic hypertension, which is more closely related to cardiovascular risks than diastolic hypertension [4,5]. The absolute risk associated with hypertension and adverse cardiovascular and stroke outcomes is highest in elderly patients [5]. Studies have also shown significant relationships between hypertension and cognitive decline, although the relationship between blood pressure, cognition and dementia is complex and not fully established. Study results on the efficacy of blood pressure control in the elderly in preventing cognitive decline are inconsistent [6]. Despite the higher incidence of hypertension and associated complications, the elderly population is less well represented in clinical trials assessing the effect of antihypertensive treatment on cardiovascular and cerebrovascular outcomes.

We designed the present study to systematically review randomized trials on the effect of antihypertensive treatment on stroke, transient ischemic attack, dementia and cognitive decline in hypertensive patients with a mean age of ≥65 years.

[1]Deptartment of Internal Medicine, Mayo Clinic, 5777 E Mayo Blvd, Phoenix, AZ 85054, USA
[2]Division of Preventive Medicine, Mayo Clinic, 200 1st St SW, Rochester, MN 55905, USA
[3]Division of Cardiovascular Diseases, Mayo Clinic, 13400 E Shea Blvd, Scottsdale, AZ 85259, USA
*Author for correspondence: Tel.: +1 480 301 6907; Fax: +1 480 301 8018; mookadam.farouk@mayo.edu

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• Objective

In hypertensive elderly patients, to assess the effects of blood pressure lowering treatments for the prevention of stroke, transient ischemic attack, cognitive decline, and dementia.

Patients & methods

• Eligibility criteria

We included randomized controlled trials with primary and secondary end points of interest that were published in English. Eligible trials had to fulfill the following criteria: prospective study involving elderly persons with a mean age of ≥65 years who underwent randomized treatment with antihypertensive monotherapy or combination therapy compared with another antihypertensive therapy or placebo; treatment duration was ≥2 years and sample size in each treatment arm was ≥200 subjects; outcomes assessed included cerebrovascular accident, transient ischemic attack (TIA) and dementia or cognitive decline. Dementia was diagnosed according to standard diagnostic criteria and cognitive decline was defined as a negative cognitive change from baseline as assessed by any standardized test of cognition, including the Mini-Mental State Examination (MMSE).

• Study identification

We identified studies by searching electronic databases and manual review of all reference lists from of articles included in the analysis. The search was applied to Embase, MEDLINE and CINAHL (1 January 1990–1 June 2014) by three investigators with a second search completed independently by a medical librarian. The search was limited to studies in human subjects and the English language. We used the following medical subject headings (MeSH) terms: 'aged'; 'hypertension'; 'hypertension', 'malignant'; 'vascular resistance'; 'antihypertensive agents'; 'stroke'; 'cerebrovascular disorders'; 'intracranial embolism'; 'dementia'; 'dementia, multi-infarct'; 'dementia, vascular' and 'cognition disorders.' We used the following key terms: 'geriatric patients'; 'aging senescence'; 'high blood pressure hypertensive state'; 'hypertension drug therapy'; 'antihypertensive drug treatment' and 'stroke cerebrovascular disorders.'

Three investigators assessed basic trial eligibility via title and abstract screening utilizing the inclusion criteria. The full text of remaining articles was assessed for eligibility and the reference lists of these articles were reviewed for additional articles.

• Data collection

Data extracted from each trial included: demographic characteristics and baseline blood pressure; intervention (including drug type, dose, duration and protocol for dose titration and addition of other drugs to meet blood pressure goals); and outcome measures (including final blood pressure, how cognitive decline was defined, and how dementia and other neurocognitive outcomes were diagnosed).

We assessed the risk of bias in included studies using the Cochrane Collaboration's tool for assessing risk of bias.

• Statistical analysis

An intention-to-treat meta-analysis was performed in accordance with recommendations from the Cochrane Collaboration. Meta-analyses were performed using Comprehensive Meta-analysis, Version 2 (NJ, USA). The I^2 statistic of inconsistency was used to assess heterogeneity between studies. Substantial heterogeneity was defined as an I^2 statistic >50%. Pooled estimates of relative risks (RRs) with their 95% CIs were estimated using the random effects model. Publication bias could not be assessed due to the small number of studies included in each analysis.

Results

• Study identification

Figure 1 depicts the search and selection procedures. Thirty-one articles were identified from the screen and 15 new articles were identified from the reference lists of screened articles. Supplementary searches were conducted to capture additional publications of two trials, the Japanese Trial to Assess Optimal Systolic Blood Pressure in Elderly Hypertensive Patients (JATOS) and the Systolic Hypertension in the Elderly: Long-term Lacidipine treatment (SHELL) trial. Thus, 48 articles in total (25 randomized trials) met our inclusion criteria. The only subanalyses of the main trial results from the 25 identified trials that were of interest and consequently included were those that isolated different treatment regimens within a trial (as a result of add-on therapies in certain trials). Also, subanalyses done by mean age ≥65 years were included even if the overall trial did not meet the mean age requirement.

Fourteen trials were included in the meta-analysis for treatment versus placebo [7–20]. There were insufficient trials to conduct a

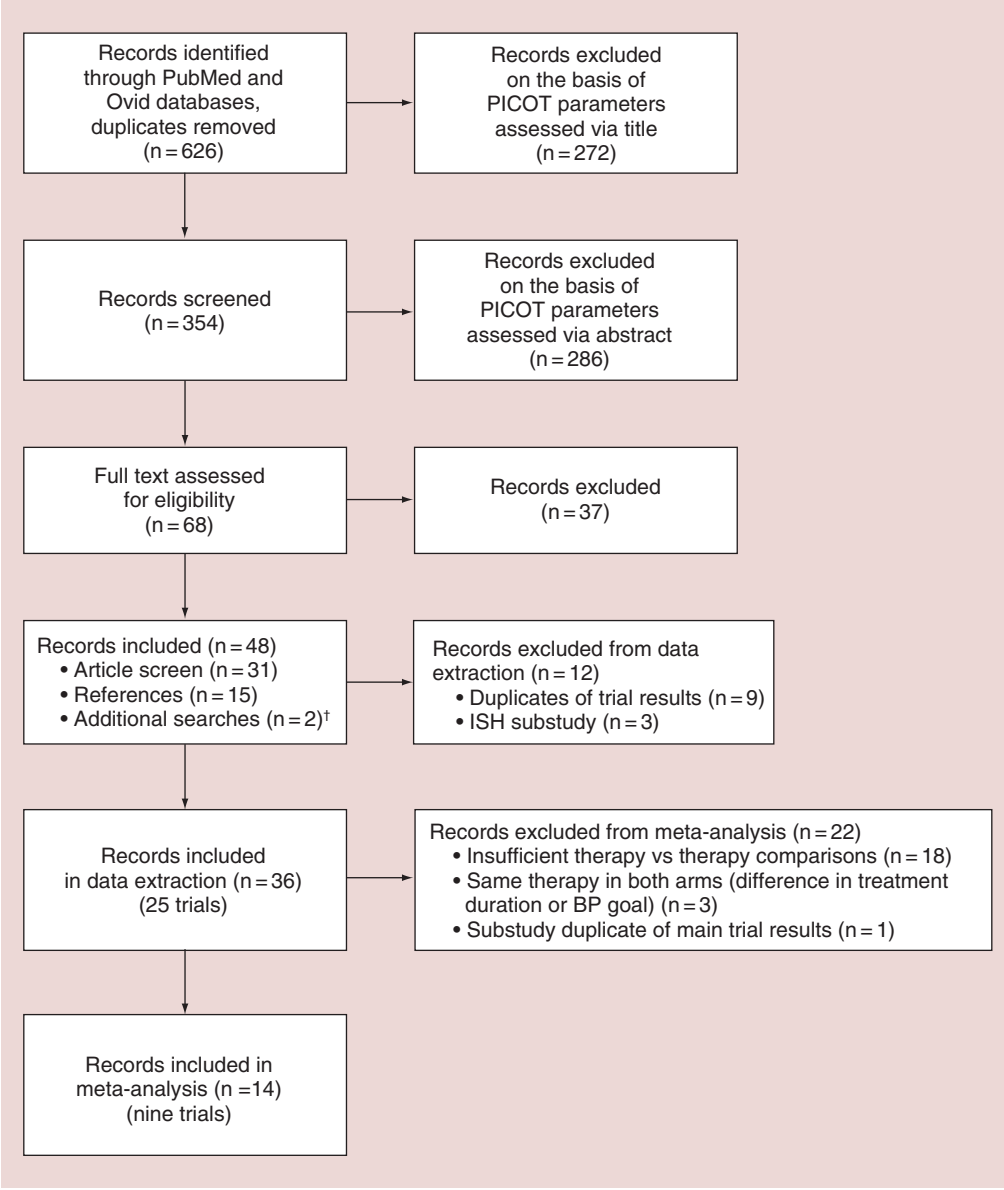


Figure 1. Preferred reporting items for systematic reviews and meta-analyses flow diagram of study selection.

†Additional searches were conducted to capture additional publications of the JATOS and the SHELL trials.

BP: Blood pressure; ISH: Isolated systolic hypertension; PICOT: Patient population of interest, intervention of interest, comparison with another intervention, outcome of interest, time frame.

network meta-analysis and provide pairwise comparisons. The characteristics of the trials included in the meta-analysis are summarized in **Table 1**. Those trials reporting stroke had a total of 15,531 placebo control and 15,245 intervention hypertensive subjects, with a mean age 73 years for both groups. The average duration of follow-up was 3.5 years. Those trials reporting dementia outcomes had a total of 7660 placebo control and 7767 intervention hypertensive subjects, with a mean age of 75 years for both groups. The average duration of follow-up was 3.1 years. Those trials reporting cognitive decline had a total of 5375 placebo control and 5471 intervention hypertensive subjects, with a mean age of 77 years for both groups. The average duration of follow-up was 3.5 years.

Table 1. Characteristics of studies included in meta-analysis.

Study (year)	Subgroup	Outcome	n	Mean age (sd)	Male (%)	Follow-up (years)	Mean initial BP (sd)	Mean final BP (sd)	Ref.
FEVER (2011)	DHP-CCB and diuretic	Stroke	1631	69.5 (3.3)[†]	65.5[†]	3.3	156.3 (11.9)/89.1 (8.1)[†]	139.7/81.2	[18]
	Placebo		1548					145.5/83.6	
HYVET (2008)	Diuretic	Fatal stroke, total stroke	1933	83.6 (3.2)	39.3	2.1	173 (8.4)/90.8 (8.5)	143.5/77.9	[19]
	Placebo		1912	83.5 (3.1)	39.7		173 (8.6)/90.8 (8.5)	158.5/84	
HYVET-COG (2008)[‡]	Diuretic	CD, dementia	1687	83.5 (3.1)[†]	39.4	2.2	173.1 (8.5)/90.8 (8.5)	143.5/77.7	[17]
	Placebo		1649		39.7		172.9 (8.5)/90.8 (8.5)	158.3/83.6	
MRC (1992); MRC (2012)	DHP-CCB and diuretic	Stroke	1081	70.3	42.0	5.8	185/90.7	151/76.2	[15,16]
	BB[§]		1102	70.4	41.0		184.5/90.6	152/75.6	
	Placebo		2213	70.3	42.0		184.5/90.7	165/84.7	
SCOPE (2003)	ARB	CD[#], dementia, nonfatal, fatal and total stroke	2477	76.4	35.2	3.7	166 (8.9)/90.3 (6.6)	145.2 (16.1)/79.9 (8.7)	[13]
	Placebo		2460	76.4	35.8		166.5 (9)/90.4 (6.6)	148.5 (16.8)/81.6 (8.8)	
SHEP (1991); SHEP (2001)	Diuretic	CD[¶], dementia, TIA, nonfatal, fatal and total stroke	2365	71.6 (6.7)	43.7	4.5	170.5 (9.5)/76.7 (9.6)	144 (19.3)/67.7 (10.2)	[7,8]
	Placebo		2371	71.5 (6.7)	42.7		170.1 (9.2)/76.4 (9.8)	155.1 (20.9)/71.1 (12.8)	
STONE (1996)	DHP-CCB	Stroke	801	66.2 (5.1)	50.1	2.5	168.5 (13)/98.5 (7)	146.8/85.4	[12]
	Placebo		774	66.6 (5)	43.7		168.6 (15)/97.4 (7)	156.3/89.8	
STOP-Hypertension (1991)	BB and DHP-CCB	TIA, stroke	812	75.6 (3.7)	37.2	5.4	195 (14)/102 (7)	167 (21)/87 (9)	[9]
	Placebo		815	75.7 (3.7)	37.5		195 (14)/102 (7)	186 (22)/96 (10)	
Syst-China (1998)	DHP-CCB	Nonfatal, fatal and total stroke	1253	66.4 (5.4)	65.0	2	170.7 (10.9)/86.1 (6.7)	150.7/81.1	[14]
	Placebo		1141	66.7 (5.7)	63.6		170.2 (11.4)/85.9 (7)	159.3/84	
Syst-Eur (1998)[††]	DHP-CCB	Dementia	1238	69.9 (6.5)	33.6	2	173.5 (10.1)/86.1 (5.6)	151.8/79.7	[10]
	Placebo		1180	69.9 (6.2)	35.0		173.4 (10.1)/86 (5.7)	160/83.4	
Syst-Eur (1997)	DHP-CCB	Nonfatal, fatal and total stroke	2398	70.3 (6.7)	32.5	2	173.8 (9.9)/85.5 (5.8)	150.8 (14.7)/79.4 (8.4)	[11,20]
	Placebo		2297	70.2 (6.7)	33.8		173.9 (10.1)/85.5 (5.9)	162.4 (17.2)/83.5 (8.3)	

[†]Values for combined treatment groups; values for individual treatment groups were not readily available in the literature.
[‡]Cognitive outcome reporting for HYVET.
[§]Diuretic and/or BB treatment group; n = 1575.
[#]ARB n = 2416; placebo n = 2409.
[¶]Diuretic n = 1368; placebo n = 1317.
[††]Dementia outcome reporting for Syst-Eur.
ARB: Angiotensin receptor blocker; BB: β-blocker; BP: Blood pressure; CD: Cognitive decline; DHP-CCB: Dihydropyridine calcium channel blocker; sd: Standard deviation; TIA: Transient ischemic attack.

• Excluded studies

Of the 48 studies that met inclusion criteria, nine were excluded in the analysis as they reported the same main trial results as in other included studies. Three studies were excluded as they reported isolated systolic hypertension subanalyses of certain main trial results, which were not a variable of particular interest in this review. Three studies were excluded because they either had the same treatment strategy for both arms for strict versus mild blood pressure targets or a different duration of therapy for both arms. One study was excluded as it reported a subgroup of the main trial.

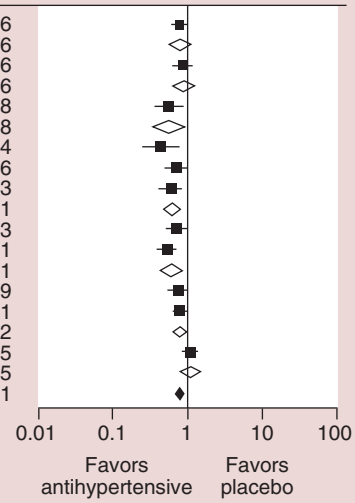
• Risk of bias

The domains of random sequence generation, allocation concealment, blinding (participants, personnel, outcome assessment), incomplete outcome data (loss to follow-up) and reporting bias (selective reporting) were assessed for each included study. The risk of bias was generally low and is summarized in **Supplementary Tables 2 & 3**. Paired reviewers demonstrated adequate chance-adjusted agreement (κ) for the different components of the risk of bias assessment (0.78 overall). Of studies included in the meta-analysis **(Supplementary Table 2)**, all were randomized, most concealed allocation via central allocation (including telephone and web-based controlled randomization), and all blinded participants although some studies had a proportion of participants with eventual open-label follow-up (i.e., withdrew from study medication). Most blinded personnel had a centralized group of blinded investigators that evaluated end points. Stroke and dementia outcomes were less likely to be influenced by a lack of blinding as these outcomes are largely physiologic with standardized diagnostic criteria. However, cognitive decline as assessed by various screening exams is more likely to be influenced by lack of participant blinding. Most trials in the meta-analysis had small loss to follow-up that were comparable across the active treatment and placebo groups.

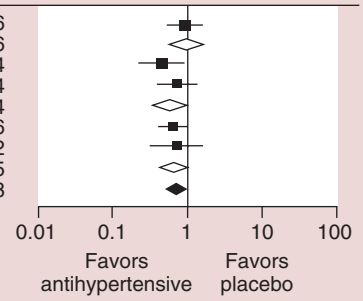
The Medical Research Council (MRC) Elderly Hypertension trial had a high loss to follow-up (25%); however, the RR was similar to that of the other studies included in the meta-analysis and thus would not be expected to skew the overall result or conclusion. The risk of bias due to incomplete outcome data in the MRC trial was also thought to be lower as the loss to follow-up was balanced across the three treatment groups and the authors employed an intention-to-treat analysis. The authors thought that the loss to follow-up was likely due to a long duration of follow-up (mean: 5.8 years) compared with other similar studies. Furthermore, it was noted that definitions used in the MRC trial to define loss to follow-up were broader than those used in similar studies and that redefinition of MRC losses in terms used by European trialists (such as in the European Working Party on High Blood Pressure in the Elderly [EWPHE] trial) reduces the figure from 25 to 11.7% [21]. The loss to follow-up for the cognitive assessment of participants in the Systolic Hypertension in the Elderly Program (SHEP) trial was not reported, although 219 (16.0%) and 266 (20.1%) participants in the active treatment and placebo groups were not assessed during the fourth year of the study. The authors stated that there was possible selective attrition as the behavioral assessment was frequently limited to those who were healthier and able to reach the study clinic. The group not assessed was not differentiated, thus the loss to follow-up may have been less and the trial results were similar to those of the Hypertension in the Very Elderly Trial Cognitive Function Assessment (HYVET-COG), which also employed a diuretic regimen for the active treatment. The risk of bias due to incomplete outcome data was also thought to be lower as the loss to follow-up was relatively balanced across the treatment groups and the authors employed an intention-to-treat analysis. The Systolic Hypertension in China (Syst-China) trial had a 9.3 and 10.7% loss to follow-up in the active treatment and placebo groups; however, the associated risk of bias was judged to be low as the RR was similar to that of the Shanghai Trial of Nifedipine in the Elderly (STONE) and Systolic Hypertension in Europe (Syst-Eur) trial, which also utilized a dihydropyridine calcium channel blocker (DHP-CCB) regimen for the active treatment group. Also, attrition was similar across groups and the analysis was by the intention-to-treat principle.

Of studies evaluating treatment versus treatment comparisons **(Supplementary Table 3)**, all were randomized, concealed allocation via central allocation (including telephone and web-based controlled randomization) and had a centralized group of blinded investigators that evaluated end points. Nine of these studies did not blind participants and personnel, employing the Prospective Randomized Open-label

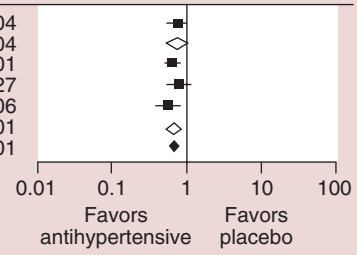
Group by intervention	Study (year)	Outcome	Statistics for each study: Risk ratio	Lower limit	Upper Limit	p-value
ARB	SCOPE (2003)	Stroke	0.77	0.59	1.01	0.06
ARB	–	–	0.77	0.59	1.01	0.06
BB	MRC BB (2012)	Stroke	0.84	0.62	1.14	0.26
BB	–	–	0.84	0.62	1.14	0.26
BB and DHP-CCB	STOP-HTN (1991)	Stroke	0.55	0.35	0.86	0.008
BB and DHP-CCB	–	–	0.55	0.35	0.86	0.008
DHP-CCB	STONE (1996)	Stroke	0.43	0.24	0.77	0.004
DHP-CCB	Syst-China (1998)	Stroke	0.70	0.48	1.02	0.06
DHP-CCB	Syst-Eur (1999)	Stroke	0.59	0.41	0.83	0.003
DHP-CCB	–	–	0.60	0.47	0.75	<0.001
DHP-CCB and diuretic	MRC (2012)	Stroke	0.69	0.49	0.96	0.03
DHP-CCB and diuretic	FEVER (2011)	Stroke	0.52	0.39	0.69	<0.001
DHP-CCB and diuretic	–	–	0.59	0.45	0.78	<0.001
Diuretic	HYVET (2008)	Stroke	0.73	0.51	1.04	0.09
Diuretic	SHEP (1991)	Stroke	0.77	0.63	0.94	0.01
Diuretic	–	–	0.76	0.64	0.91	0.002
Diuretic and/or BB	MRC (1992)	Stroke	1.06	0.83	1.36	0.65
Diuretic and/or BB	–	–	1.06	0.83	1.36	0.65
Overall	–	–	0.74	0.67	0.82	<0.001



Group by intervention	Study (year)	Outcome	Statistics for each study: Risk ratio	Lower limit	Upper limit	p-value
ARB	SCOPE (2003)	Fatal stroke	0.92	0.53	1.59	0.76
ARB	–	–	0.92	0.53	1.59	0.76
DHP-CCB	Syst-China (1998)	Fatal stroke	0.46	0.21	0.97	0.04
DHP-CCB	Syst-Eur (1997)	Fatal stroke	0.73	0.38	1.40	0.34
DHP-CCB	–	–	0.60	0.37	0.98	0.04
Diuretic	HYVET (2008)	Fatal stroke	0.64	0.39	1.03	0.06
Diuretic	SHEP (1991)	Fatal stroke	0.72	0.32	1.61	0.42
Diuretic	–	–	0.66	0.43	0.99	0.05
Overall	–	–	0.69	0.53	0.91	0.008



Group by intervention	Study (year)	Outcome	Statistics for each study: Risk ratio	Lower limit	Upper limit	p-value
ARB	SCOPE (2003)	Nonfatal stroke	0.73	0.53	0.99	0.04
ARB	–	–	0.73	0.53	0.99	0.04
DHP-CCB	SHEP (1991)	Nonfatal stroke	0.65	0.50	0.83	<0.001
DHP-CCB	Syst-China (1998)	Nonfatal stroke	0.78	0.50	1.21	0.27
DHP-CCB	Syst-Eur (1999)	Nonfatal stroke	0.56	0.37	0.84	0.006
DHP-CCB	–	–	0.65	0.53	0.79	<0.001
DHP-CCB	–	–	0.67	0.57	0.79	<0.001
Overall						



Group by intervention	Study (year)	Outcome	Statistics for each study: Risk ratio	Lower limit	Upper limit	p-value
BB and DHP-CCB	STOP-HTN (1991)	TIA	0.27	0.09	0.80	0.02
BB and DHP-CCB	–	–	0.27	0.09	0.80	0.02
Diuretic	SHEP (1991)	TIA	0.76	0.55	1.05	0.10
Diuretic	–	–	0.76	0.55	1.05	0.10
Overall	–	–	0.70	0.51	0.95	0.02

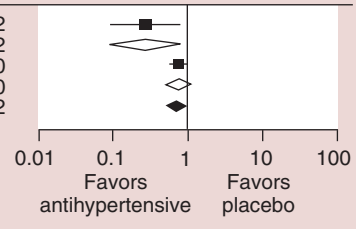


Figure 2. Meta-analysis by treatment and overall meta-analysis for outcomes of total stroke, nonfatal stroke, fatal stroke and transient ischemic attack (see facing page).
ARB: Angiotensin receptor blocker; BB: β-blocker; DHP-CCB: Dihydropyridine calcium channel blocker; TIA: Transient ischemic attack.

with Blinding of End point (PROBE) design. The majority of studies that made treatment versus treatment comparisons had small losses to follow-up that were comparable across the active treatment and placebo groups. The Combination Therapy of Hypertension to Prevent Cardiovascular Events (COPE) trial did not state the loss to follow-up. The SHELL trial had a 12.3 and 11% loss to follow-up in the lacidipine and chlorthalidone groups; however, the risk may be low as the attrition was similar across groups and the analysis was by the intention-to-treat principle.

• Effect of antihypertensive treatment compared with placebo on neurologic & cognitive outcomes

Meta-analysis demonstrated that compared with placebo, antihypertensive treatment reduced the risk of overall stroke (RR: 0.67 [95% CI: 0.57–0.79]), fatal stroke (RR: 0.69 [95% CI: 0.53–0.91]) and nonfatal stroke (RR: 0.74 [95% CI: 0.67–0.82]) **(Figure 2)**.

In terms of the individual trials, a significant reduction in total stroke was found in six clinical trials [8–9,11–12,16,18]. Diuretic, β-blocker (BB) and DHP-CCB regimens, including DHP-CCB regimens that involved addition of an angiotensin-converting enzyme inhibitor (ACEI), were among those treatments that resulted in significant reductions in stroke as compared with placebo. There were several other trials comparing similar treatment regimens to placebo that did not demonstrate a significant effect on stroke reduction [14–16,19]. There was a significant reduction in nonfatal stroke for angiotensin receptor blocker (ARB) compared with placebo, however, this reduction was not significant for fatal and total stroke [13]. The RR was lower for DHP-CCB regimens compared placebo than that of other drug classes, which were all fairly similar in magnitude. There were sufficient studies to conduct a meta-analysis on total stroke outcome for diuretic, DHP-CCB and DHP-CCB and diuretic regimens compared with placebo. A significant reduction in total stroke was found for these treatments versus placebo **(Figure 2)**. The DHP-CCB regimens had similar risk ratios that were lower than those of the diuretic regimens in meta-analysis. There were sufficient studies to conduct a meta-analysis on fatal and nonfatal strokes for the DHP-CCB drug class compared with placebo, and a significant reduction was found for both outcomes **(Figure 2)**. A significant reduction in fatal stroke was also found in meta-analysis of the diuretic drug class compared with placebo. The relative lack of evidence for ACEIs and ARBs compared with placebo is likely explained by the risk reduction found in earlier studies for diuretics and CCBs versus placebo, making antihypertensive compared with placebo unethical in later studies. The overall meta-analysis of antihypertensive treatment versus placebo found a significant reduction in nonfatal, fatal and total stroke.

The Swedish Trial in Old Patients with Hypertension (STOP-Hypertension) found that a BB regimen resulted in fewer TIAs as compared with placebo [9]. Another study evaluating a diuretic regimen compared with placebo found a nonsignificant reduction in TIA [8]. The overall meta-analysis of antihypertensive treatment versus placebo found a significant reduction in TIA **(Figure 2)**.

Studies that compared antihypertensive treatment to placebo on the development of cognitive decline or dementia did not show significant reductions [7–8,10,13,17]. Meta-analysis of individual drug classes and overall meta-analysis of antihypertensive treatment versus placebo found small, nonsignificant reductions in cognitive decline and dementia **(Figure 3)**. The Systolic Hypertension in Europe trial 2 (Syst-Eur 2) showed that early as opposed to delayed antihypertensive treatment resulted in a significant decrease in dementia (OR: 0.46; CI: 0.27–0.78) [10]. It is important to note that conclusions should not be drawn about the relationship between cognitive decline and blood pressure control based on the data as the follow-up periods may be insufficient to infer a causal effect.

There were few comparisons of sufficient studies with the same intervention to apply the I^2 statistic of inconsistency. The I^2 statistic for DHP-CCB versus placebo in nonfatal and fatal stroke was 0% indicating that substantial heterogeneity between studies (defined as an I^2 statistic >50%) was not present.

• Head-to-head studies of antihypertensive treatment effect on neurologic & cognitive outcomes

The Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) demonstrated that an ACEI regimen resulted in a significant increase in total stroke as compared with conventional antihypertensives, such as DHP-CCB, BB and diuretic regimens [22,23], while other studies with similar comparisons did not demonstrate significant outcomes [24,25]. The Second Australian National Blood Pressure Study (ANBP2) found that ACEI treatment compared with diuretic treatment had significantly higher fatal stroke outcomes, however, this relationship was not significant for total stroke [25]. The Losartan Intervention For Endpoint reduction in hypertension (LIFE) trial demonstrated that an ARB regimen resulted in a significant decrease in total stroke and fatal stroke as compared with conventional antihypertensives [26], while other studies with similar comparisons did not demonstrate significant outcomes [27–29]. The Morbidity and Mortality After Stroke, Eprosartan Compared With Nitrendipine for Secondary Prevention (MOSES) trial showed that an ARB regimen resulted in a significant reduction in stroke and TIA as compared with a DHP-CCB regimen [30]. The ALLHAT demonstrated that an α-blocker regimen was significantly less effective in preventing total and fatal stroke as compared with a diuretic regimen [31]. The Anglo-Scandinavian Cardiac Outcomes Trial – Blood Pressure Lowering Arm (ASCOT-BPLA) demonstrated that a DHP-CCB regimen compared with a BB regimen resulted in significantly fewer strokes [32]. The SHELL trial found that diuretic and DHP-CCB regimens showed no significant difference in the incidence of stroke [33]. Strict treatment (SBP <140 mmHg) versus mild treatment (SBP <160 mmHg) with DHP-CCB regimens did not result in a significant difference in stroke incidence in the JATOS trial [34]. Studies meeting inclusion criteria that described nonfatal stroke outcomes among different therapies did not show significant outcomes. Studies comparing the effect of different treatment regimens on TIA incidence did not have significant results [33–36].

No studies met inclusion criteria that compared different antihypertensive treatments on the incidence of cognitive decline or dementia. There were insufficient studies comparing one drug class or regimen versus another for meta-analysis for all outcomes of interest.

Discussion

We conducted a systematic review and meta-analysis of randomized trials to evaluate the effects of antihypertensive treatment on neurological and cognitive outcomes in elderly patients. Meta-analysis demonstrates that antihypertensive treatment significantly reduced fatal, nonfatal and total stroke. The confidence in the presented estimates is moderate to high. There were insufficient trials in this systematic review to compare any effect between drug classes. Individual head-to-head comparisons varied in their findings and significance. Antihypertensive treatment did not result in significant reductions in the incidence of cognitive decline or dementia. The effect of antihypertensive treatment on cognitive decline or dementia may not be reliably assessed based on the included trials as the duration of follow-up may be insufficient for the development of these conditions. Studies with longer follow-up are needed to evaluate this association.

The results of this analysis are grossly consistent with earlier reviews. A Cochrane review assessing the long-term effects of antihypertensive drug therapy as compared with control in the elderly indicated a significant reduction in cerebrovascular morbidity and mortality (OR: 0.63 [95% CI: 0.55–0.72]; number of events prevented by treating 1000 patients for approximately 5 years = 20 [95% CI: 14–25]) [37]. Most of the ten included trials evaluated diuretic and BB therapies. Another meta-analysis concluded that placebo-controlled trials provided strong evidence of the benefits of ACEIs and calcium antagonists in preventing stroke in the elderly, but that there was weak evidence of the differences between treatment regimens of differing intensities or different drug classes [38].

Observational epidemiological studies have shown a positive association between hypertension and incident dementia; however, controlled trials have shown conflicting results on the effect of antihypertensive treatment on cognition. Meta-analyses of the trials have not elucidated this effect. These findings were reflected in our review. The incidence of dementia after 8 years in the long-term follow-up of the Syst-Eur study was 55% lower in the nitrendipine group compared with control [39]. However, chlorthalidone had no effect on cognitive function in the SHEP trial [8], and no difference was noted between the candesartan group and controls in the Study on Cognition and Prognosis in the Elderly (SCOPE) [13]. The Hypertension in the Very Elderly Trial (HYVET)

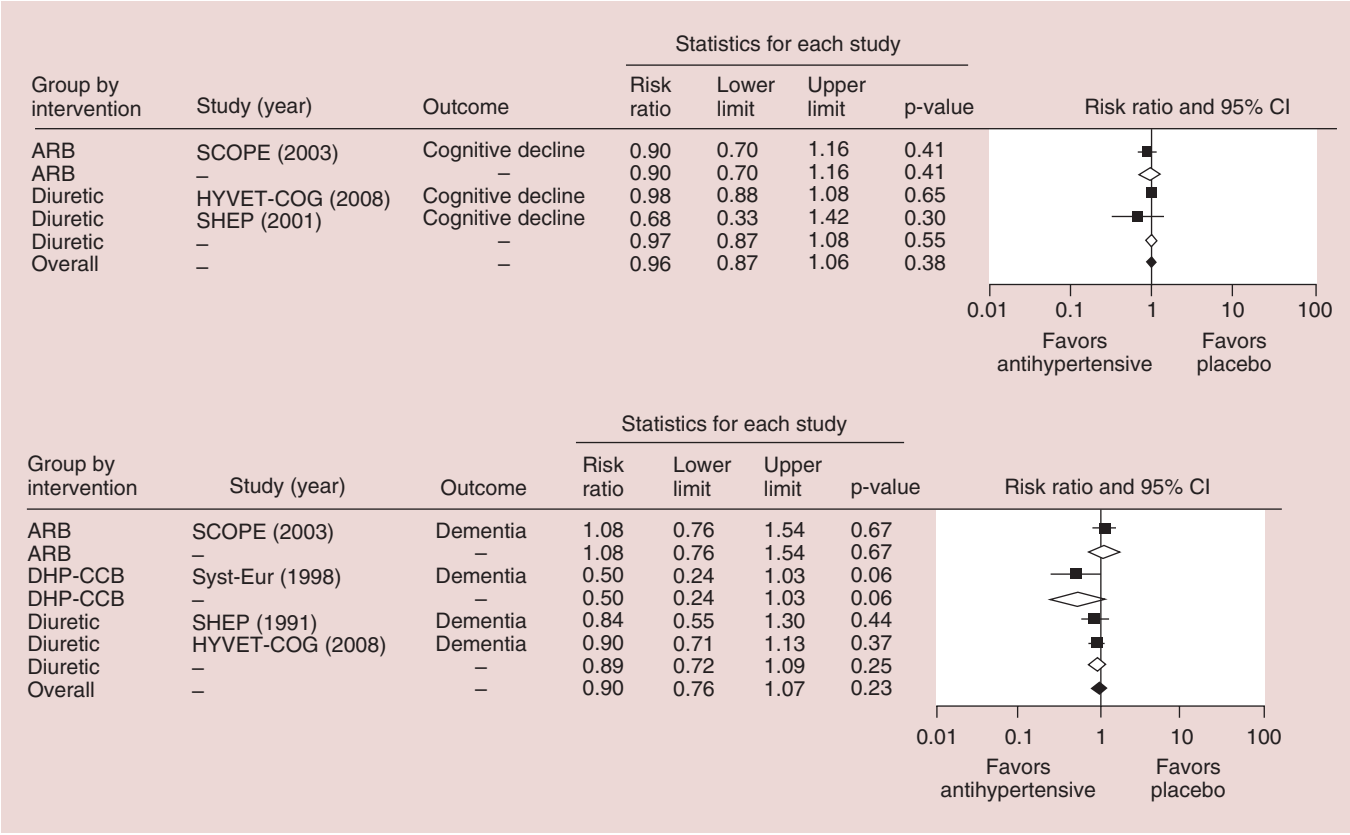


Figure 3. Meta-analysis by treatment and overall meta-analysis for outcomes of cognitive decline and dementia.
ARB: Angiotensin receptor blocker; DHP-CCB: Dihydropyridine calcium channel blocker.

also found that antihypertensive treatment with diuretic and add-on ACEI in elderly patients does not statistically reduce the incidence of dementia [17]. There may be varied efficacy among antihypertensives in diminishing the risk for dementia; however, there were insufficient trials to conduct a meta-analysis of different antihypertensive drug classes versus placebo and no trials met inclusion criteria that compared different treatments. The difference may also reflect the longer follow-up of the Syst-Eur study. A Cochrane review assessing the effects of antihypertensive treatment on the prevention of dementia and cognitive decline in those without a history of cerebrovascular disease found that the combined result of four trials including 15,936 hypertensive subjects (mean age: 75.4 years) indicated no significant difference between treatment and placebo [40]. A meta-analysis assessing this effect in patients with cardiovascular and cerebrovascular disease also found no significant risk reduction and stated there was noticeable heterogeneity between the included trials [41]. More well-designed clinical trials of sufficient power and follow-up duration are needed to investigate if antihypertensive treatment in the elderly improves cognitive outcomes and if this effect varies significantly across drug classes. Furthermore, the HYVET was the only trial meeting inclusion criteria with a mean age or subjects greater than 80 years. Data are particularly lacking in this age group.

• Limitations

Antihypertensive regimens and dosages were heterogeneous across trials. Control subjects may have received antihypertensive treatment, usually with an older class of antihypertensive than that of the active treatment arm, if their blood pressures exceeded preset values. Additionally, numerous trials had add-on therapy to both the treatment and control arms if certain blood pressure goals were not met, that could cloud the effect of the main antihypertensive regimen.

The definitions of high blood pressure and cognitive decline varied across the studies and may limit comparability. The methods used to screen and diagnose cognitive decline were heterogeneous, although the diagnosis of

dementia followed established, standardized criteria.

Conclusion & future perspective

The elderly population is widely affected by hypertension and its associated neurocognitive effects, representing a major target for preventative health improvements. Meta-analysis of existing randomized trials shows that antihypertensive treatment is associated with a significant reduction in stroke in the elderly. Reductions in dementia and cognitive decline were not significant, but fewer high-quality trials were available for this analysis and follow-up duration may have been insufficient. Longer trial periods may reveal that antihypertensive treatment improves cognitive outcomes, recommending treatment of hypertension in the elderly despite adverse effects and possible polypharmacy in order to improve this significant quality of life factor. Further trials are needed to better direct management of hypertension in the elderly, especially to guide choice of agent and goal blood pressures to achieve significant improvement in clinical end points and minimize adverse effects. Data are particularly sparser on the newer agents. Antihypertensive drugs with renin–angiotensin blockade may prove more efficacious in improving neurocognitive outcomes owing to vascular effects beyond blood pressure control. We suspect that strict blood pressure targets will not be advisable based on existing evidence.

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EXECUTIVE SUMMARY

- Meta-analysis of antihypertensive treatment versus placebo found a significant reduction in transient ischemic attack, total stroke, nonfatal stroke and fatal stroke in the elderly.
- Meta-analysis of antihypertensive treatment versus placebo found no significant reduction in cognitive decline or dementia in the elderly; however, this may reflect an inadequate duration of follow-up in included studies.
- Insufficient studies met inclusion criteria that utilized the same antihypertensive class compared with placebo to facilitate meta-analysis of all antihypertensive drug classes.
- A significant reduction in total stroke was found for meta-analysis of diuretic, dihydropyridine calcium channel blocker (DHP-CCB) and DHP-CCB and diuretic regimens compared with placebo.
- The DHP-CCB-pooled risk ratio for total stroke was lower than that of the diuretic.
- Few head-to-head trials of antihypertensive therapies were available with insufficient data for meta-analysis.
- More high-quality randomized controlled trials comparing antihypertensive treatments on neurocognitive outcomes in the elderly are needed in order to guide clinical decision-making in this population.

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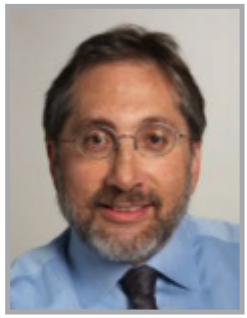
Future NEUROLOGY

EDITORIAL

Central post-stroke pain: theories, diagnosis and treatment



"Central post-stroke pain treatment is typically based on trial and error until pain relief is found and the result is usually a combination of several pharmaceutical and non-pharmaceutical treatments."

Jonathan Singer*[1] & Steven R Levine[1]

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KEYWORDS
• central post-stroke pain • thalamic stroke

Theories, diagnosis & treatment of central post-stroke pain in thalamic strokes

Stroke is the fourth leading cause of death and is the number one cause of disability worldwide [1]. Post-stroke pain (PSP) is an uncomfortable and disabling condition that has been reported to occur between 14 and 49% in ischemic stroke patients [2]. Numerous articles have reported that a third of PSP occurrences affect patients who have suffered a thalamic ischemic stroke [3–5]. In general, patients with pain experience greater cognitive and functional decline, lower quality of life (QoL), fatigue and depression compared with patients without pain [4–6]. Furthermore, patients tend to under-report their pain. As central PSP (CPSP) is not well recognized among many care providers, we provide a brief overview of this topic.

PSP has been classified into two different types: CPSP, believed to be due to primarily CNS mechanisms [7] and pain following stroke triggered by peripheral/mechanical mechanisms (e.g., shoulder, arm and neck pain). We focus on the suspected causes of CPSP in thalamic strokes, diagnostic criteria and treatments.

Strokes affecting the thalamic region have a tendency to yield a higher rate of CPSP [3,8] than nonthalamic strokes. In the late 1800s, CPSP was originally described by two French neurologist, Dejerine and Roussy, who labeled it as an 'unusual pain syndrome' [9]. There are many hypotheses as to why CPSP is more common in thalamic strokes. Four general theories have come to the forefront: disinhibition, central imbalance, alterations in spinothalamic tract function and central sensitization [7].

Disinhibition theory was one of the earliest proposed mechanisms. In 1911, Holmes and Head hypothesized that injury to the lateral thalamus disinhibits its medial thalamus activity and causes pain by disrupting inhibitory pathways between lateral and medial routes [10,11]. However, this theory is outdated. More recently, it was proposed that burning pain and cold allodynia are due to loss of normal inhibition of the thermal system

[1]SUNY Downstate Medical Center & Stroke Center, 450 Clarkson Avenue, MSC 1213, Brooklyn, NY 11203-2012, USA
*Author for correspondence: Tel.: +1 718 270 7687; jonathan.singer@downstate.edu

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of nociceptive neurons [8]. This theory appears to be more fitting because thalamic stroke has been shown to lead to burning pain and cold allodynia.

The central imbalance theory and the alterations in spinothalamic tract function are based on the same premise: spinothalamic pathway alterations and damage are the reasons for CPSP. Patients with CPSP exhibit difficulty with pain and temperature sensitivity, including sensitivity to touch, vibration and other phenomena, which are believed to course mainly through lemniscus pathways [12] of the spinothalamic tract. Moreover, impaired spinothalamic function is associated with pathogenesis of CPSP and that medial lemniscus involvement is neither necessary nor sufficient [11–14].

"It appears that the development of new, high-resolution imaging technology, longitudinal-based observation and clinical trial research may lead us to a more consolidated understanding of central post-stroke pain while also providing a standard of care."

The central imbalance theory goes further and suggests that when a stroke affects the thalamic region, an imbalance between the lateral and medial pain systems occur [11]. This theory is supported by research, which has found that insular activity and decreased anterior cingulate cortex activity in CPSP patients can occur [5]. Also, imbalance occurs between the spinothalamic and medial lemniscus pathways. It has been shown that spinothalamic tract damage results in the transmission of pain signals through alternative pathways and proposed that the medial lemniscus pathway probably undertakes these functions [12–14]. Therefore, these pain pathways could produce tactile allodynia and result in CPSP.

Central sensitization theory is characterized by the hyperexcitability of central nociceptive neurons, which may be responsible for spontaneous pain and allodynia. In a study that examined microelectrode recordings in patients, there was abnormal spontaneous evoked bursting activity within deafferented regions of lateral and medial thalamic nuclei in some patients with CPSP [11]. The abnormal firing of thalamic neurons leads to a lack of generalized increase in thalamic excitation, and therefore, causes a decrease in thalamic activity and may be the root of CPSP. This theory is built on the basis that NMDA antagonists, GABA agonist and channel blockers are effective in reducing pain associated with CPSP [5].

There is neither a consolidated definition nor clinical characteristics that have been generally agreed upon when investigating CPSP. There are a number of studies that have attempted to formulate diagnostic criteria for CPSP. However, a consensus remains elusive. In a recent study, it was stated that suffering from pain could be related to the meaning of the pain as much as it is due to the intensity [15]. A systematic review combined main points from the literature and established reoccurring trends, which were organized into mandatory and supportive criteria [7]. Yet, they stated that a definite diagnosis is difficult due to the heterogeneous clinical picture, the many types of pain and the lack of diagnostic criteria for CPSP. The mandatory criterion they identified was that pain must be in an area of the body that corresponds to the lesion in the CNS, and other causes of the pain, such as a nociceptive or peripheral neuropathic pain, should be ruled out. They defined supportive criteria as having no primary relation to movement, inflammation or other local tissue damage. They also stated that descriptors such as burning, painful cold, electric shocks, stinging and allodynia or dysesthesia to touch should be considered.

More recently, it was stated that the diagnosis of CPSP should be based on a combination of history, sensory examination, findings obtained by applying multiple somatosensory stimuli and neuroimaging findings of the brain lesion [5]. They concluded that if available, measurements of somatosensory-evoked potentials, laser evoked potentials and contact heat-evoked potentials should all be utilized.

Notwithstanding the studies outlined above, the diagnostic criteria for CPSP needs to be consolidated and new studies need to be developed to formulate a more precise definition. Also, creating a more accurate diagnostic schema could yield better treatment and management practices.

A number of different treatments and management practices for CPSP have been reported. However, CPSP treatment is typically based on trial and error until pain relief is found and the result is usually a combination of several pharmaceutical and nonpharmaceutical treatments [7]. Antidepressants, specifically adrenergically active antidepressants, are usually the first pharmaceutical treatment prescribed for CPSP [5,6,13]. However, to our knowledge, there are no published clinical trials on polypharmacy for CPSP and the only study on prevention of CPSP was a small study of 39 patients. This prospective, double-blinded, placebo-controlled study of amitriptyline (75 mg per day) found no significant prophylactic

that was effective [14]. Depending on different factors (e.g., doctor's opinions, the severity of the pain, effect on QoL), a patient with CPSP may also be given empiric nonpharmaceutical treatments.

The three main, nonpharmaceutical treatments are motor cortex stimulation, deep brain stimulation and transcranial magnetic stimulation. The motor cortex stimulation regulates neuronal pathways involved in pain. There have been numerous case studies that have reported that motor cortex stimulation is a safe, invasive therapy, and significant changes occur in cerebral blood flow including in the thalamus after this treatment [5,7,16]. Two studies found this treatment to produce a 1-year success rate, 45 and 50%, with rare complications including infections and seizures [5,16]. Therefore, many doctors have tried to implement motor cortex stimulations, but have to determine a long-term treatment after a year depending on the patient.

Deep brain stimulation is a procedure that involves the insertion of deep stimulation electrodes within the periaqueductal area, specific thalamic nuclei or the internal capsule [5,7,17]. This invasive neurosurgical procedure targets the thalamus and the periventricular grey matter. In a small study of 15 patients with post-stroke pain, it was found that 49% of the patients reported improvement [18]. This is consistent with other studies where the range of efficacy has been reported between 25 and 67% [7]. However, the invasive nature of this procedure and the wide range of efficacy that has been reported are troublesome for doctors prescribing to CPSP patients.

Transcranial magnetic stimulation is a noninvasive stimulation of the brain. The stimulation is produced by generating a brief, high-intensity magnetic field by passing an electric current through a magnetic coil. The problem with this procedure is that results have found that mitigation of pain is limited and short lasting [7]. However, adverse events have been reported as rare and sessions of repetitive transcranial magnetic stimulation of the motor cortex have been shown to prolong pain relief [15]. Transcranial magnetic stimulation seems to be effective in the short term, but it should be used with other treatments for long-lasting pain.

There has been one study to our knowledge that has addressed the differences between transcranial magnetic stimulation and motor cortex stimulation with CPSP. Five daily sessions of transcranial magnetic stimulation were found to produce longstanding pain relief compared with motor cortex stimulation [19].

Studies have shown that nonpharmaceutical treatments for CPSP can be effective; however, they can be evasive and most of them only last a short time with a sizeable range of efficacy. Therefore, future research is still needed as doctors are treating CPSP patients on a trial and error basis. Research has not addressed the clinical efficacy of other treatment options including the use of combinations of pharmaceutical and nonpharmaceutical treatments, which could help with management of pain for these patients. It has been proposed that pain intensity is not the best measure of the success of pain treatment, which makes diagnosing and finding a treatment even more complex [15].

CPSP may result in significant impact on patients' QoL and is understudied from a patient-centered perspective. Research suggests that thalamic strokes have a much higher (~threefold) rate of CPSP than nonthalamic strokes; however, the reasons are still highly debated. Furthermore, a uniform set of diagnostic criteria for the disorder remains elusive. Research conducted over the last decade shows promise with rates of pharmaceutical and nonpharmaceutical treatments being effective as much as 60% of the time. However, there is no understanding of which treatment works for a specific patient so that treatment is empiric. Finding the underlying cause of why thalamic strokes produce more CPSP may be the root to treating CPSP. It appears that the development of new, high-resolution imaging technology, longitudinal-based observation and clinical trial research may lead us to a more consolidated understanding of CPSP while also providing a standard of care.

Financial & competing interests disclosure

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RESEARCH ARTICLE

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Future NEUROLOGY

Efficacy, safety and tolerability of rivaroxaban for the secondary prevention of stroke in patients with atrial fibrillation in clinical practice

María Monteagudo*[,1], Eva Fernández-Díaz[1], Jorge García-García[1,2], Óscar Ayo-Martín[1,2], Francisco Hernández-Fernández[1] & Tomás Segura[1,2]

Aim: To evaluate the efficacy, safety and tolerability of rivaroxaban for the secondary prevention of stroke in patients with atrial fibrillation in clinical practice. **Methods**: Patients treated with rivaroxaban for secondary prevention of stroke/transient ischemic attack attended at a cerebrovascular disease unit were consecutively included in a noninterventional and prospective study. **Results**: 89 patients (median age 77 years, $CHADS_2$ = 4, HAS-BLED = 3, follow-up = 15 months) were included. Rivaroxaban was started early after the cerebrovascular event (median 5 days for stroke and 3 days for transient ischemic attack). Stroke recurrence occurred in only one patient (annual rate, 0.82%). Eight cases of clinically significant bleeding were recorded (annual rate, 6.58%), of which two were major (annual rate, 1.64%) and one intracranial (annual rate, 0.82%). Medication persistence was very good. **Conclusion**: Our data show that the early treatment with rivaroxaban is well tolerated, efficacious and safe for secondary prevention of real-life atrial fibrillation patients.

KEYWORDS:
• clinical practice • real-world • rivaroxaban • ROCKET-AF • secondary prevention • stroke • transient ischemic attack

Atrial fibrillation (AF) is the most common arrhythmia in clinical practice. It has been estimated that the prevalence of AF is around 1–2% of the general population, but rises with age, reaching 5–15% in individuals aged >80 years. AF is associated with a five-fold increased risk for stroke. Moreover, stroke caused by AF is more severe and leads to greater disability and mortality compared with stroke resulting from other causes [1]. Most patients with AF require anticoagulation for preventing the development of stroke. Traditionally, vitamin K antagonists (VKAs) have been used for this purpose. Since warfarin was approved for human use in 1954, several studies have demonstrated its efficacy and safety compared with placebo, aspirin and the combination of aspirin and clopidogrel [2]. These studies have shown that warfarin significantly reduces the rate of systemic embolic events, especially those affecting the central nervous system (absolute reduction in the annual risk of stroke, 2.7%). However, this reduction is achieved at the cost of an increased annual risk of bleeding, namely, 0.3–0.5% for major bleeding and 0.2% for intracranial bleeding [3–10].

In addition to the increased risk of bleeding complications, VKAs have many disadvantages (i.e., narrow therapeutic window, multiple interactions with food and other drugs, highly variable metabolism, frequent dose adjustments) that limit their use in clinical practice, leading to the search for new drugs that are safer and simpler to manage and capable of preventing systemic embolisms [11–13]. New direct oral anticoagulants (DOACs), with a more selective mechanism of action than VKAs, have been approved for the prevention of stroke in patients with nonvalvular AF. The results from pivotal clinical trials (ROCKET-AF [14], ARISTOTLE [15], RELY [16] and ENGAGE-AF-TIMI 48 [17]) have shown that DOACs (rivaroxaban, apixaban, dabigatran and edoxaban, respectively) are at least as effective as warfarin for the prevention of stroke and systemic embolism,

[1]Department of Neurology, Hospital General Universitario de Albacete, Spain
[2]Universidad de Castilla-La Mancha, Facultad de Medicina de Albacete, Calle Almansa nº14, Albacete, Spain
*Author for correspondence: mmonteagudog@sescam.jccm.com

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but with a lower risk of intracranial hemorrhage. However, as they have recently been marketed, data regarding efficacy and safety of these drugs in real-life patients are very scarce and in some cases (i.e., elderly patients, subjects with many comorbidities or polymedication, patients with recent stroke, etc.) remain controversial.

The objective of this study was to evaluate the efficacy, safety and tolerability of rivaroxaban for the secondary prevention of stroke in real-life patients with nonvalvular AF.

Methods

For this purpose, a noninterventional and prospective study was performed. Patients who had nonvalvular AF, treated with rivaroxaban for the secondary prevention of stroke/transient ischemic attack (TIA), attended at the cerebrovascular disease unit of our hospital over a 24-month period (from October 2012 to October 2014) were consecutively included. All patients were followed for at least 3 months. Rivaroxaban was administered at a dose of 20 mg once daily (15 mg once daily in case of creatinine clearance 15–49 ml/min).

Clinical and demographic data were collected. The risk of stroke was evaluated using the $CHADS_2$ score, and the risk of bleeding was measured using the HAS-BLED score. The efficacy endpoint was the recurrence of stroke. The safety endpoint included the following: clinically significant bleeding (i.e., bleeding that required medical attention); major bleeding (i.e., bleeding in a key anatomical region, such as cranial, spinal column, eye, pericardium, joints, retroperitoneal space and muscles [compartment syndrome]); bleeding that leads to a decrease in hemoglobin >2 g/dl or requires transfusion of at least 2 units of red cell concentrates or fatal bleeding; intracranial bleeding.

Side effects and tolerability were also evaluated in all patients. Data were obtained from the electronic clinical history of patients using the computerized records of Castilla-La Mancha regional health system, which provided information of all visits to hospitals and healthcare centers of the region. Patients' database was registered and approved by the Albacete General Hospital Research Ethics Committee.

• Statistical analysis

Continuous variables were expressed as median and interquartile range. Categorical variables were expressed as a percentage. Clinical and demographic data, as well as efficacy and safety endpoints from our study were compared with that of the subgroup of patients with history of stroke or TIA from ROCKET-AF trial treated with rivaroxaban [18]. The data design was subjected to internal consistency rules and ranges to control for inconsistencies/inaccuracies in the collection and tabulation of data. Statistical significance was set at a p-value < 0.05. The statistical analysis was performed using the SPSS statistics package, version 22.0 for Windows (SPSS, Chicago, IL, USA).

Results

A total of 89 patients, of whom 56% had a history of stroke and 44% a history of TIA, were included in the study. Median (interquartile range) follow-up was 15 (9–21) months. The clinical characteristics of patients were shown in **Table 1**. Median age was 77 (72–82) years, and 52.8% of patients were women. The median $CHADS_2$ score was 4 (3–4), and the median

Table 1. Baseline clinical characteristics of the study population.

	TIA (n = 39)	Stroke (n = 50)	Overall (n = 89)
Median (IQR) age, years	76 (71–81)	79 (72–83)	77 (72–82)
>75 years	64%	70%	67%
>80 years	28%	46%	38%
Men	43.6%	50.0%	47.2%
$CHADS_2$ score, median(IQR)	4 (3–4)	4 (3–4)	4 (3–4)
HAS-BLED score, median (IQR)	3 (2–3)	3 (2–3)	3 (2–3)
Delay in starting DOAC, median (IQR)	3 days (2–5)	5 days (2–7)	4 days (2–6)
Previous treatment with VKA	28%	16%	22%

DOAC: Direct-acting oral anticoagulant; IQR: Interquartile range; TIA: Transient ischemic attack; VKA: Vitamin K antagonist.

HAS-BLED score was 3 (2–3) **(Table 1** and **Figures 1** and **2)**.

In 78% of patients no other anticoagulant therapy had been previously prescribed before the use of rivaroxaban; in the remainder 22%, rivaroxaban was started after therapeutic failure of VKAs. Anticoagulant therapy was started early after the stroke or TIA episodes (median 5 [2–7] days for stroke and 3 [2–5] days for TIA) **(Table 1)**.

Compared with the subgroup of patients with previous stroke or TIA treated with rivaroxaban from ROCKET-AF trial, our patients were older, more commonly women and a lesser proportion of patients had been previously treated with VKAs. By contrast, $CHADS_2$ score was similar in both groups **(Table 2)**.

With regard to the efficacy endpoint (stroke recurrence), only one recurrence was detected (annual rate, 0.82%). No hemorrhagic transformation was observed. The clinical presentation of this patient was described in **Box 1**. Rates of stroke recurrence of our patients compared with that of patients with previous stroke or TIA taking rivaroxaban in ROCKET-AF were shown in **Table 3**.

With regard to the safety endpoints, eight cases of clinically significant bleeding were recorded (annual rate, 6.58%), of which two were major (annual rate, 1.64%) and one was intracranial (annual rate, 0.82%) **(Table 3)**. The clinical presentation of the patient with intracranial bleeding was described in **Box 1**. Rates of bleeding of our patients compared with that of patients with previous stroke or TIA taking rivaroxaban in ROCKET-AF were shown in **Table 3**. The type of bleeding in our patients was described in **Table 4**.

Nine patients died during follow-up (annual rate, 7.4%). Of these, only one was referred because of a bleeding complication (subdural hematoma following head injuries **[Box 1]**). Other causes of death were refractory status epilepticus (n = 2), pneumonia (n = 2), respiratory failure (n = 1), pulmonary edema (n = 1), hip fracture (n = 1) and hypernatremia (n = 1).

Tolerability and persistence were both good, and in two cases treatment with rivaroxaban was withdrawn (2.25%, one case due to skin rash and one case because of increased liver enzymes). In both cases, the conditions resolved after withdrawal of treatment.

Discussion

Several studies have proven the efficacy and safety of warfarin for the prevention of stroke in patients with AF [3,7,9]. Thus, a meta-analysis

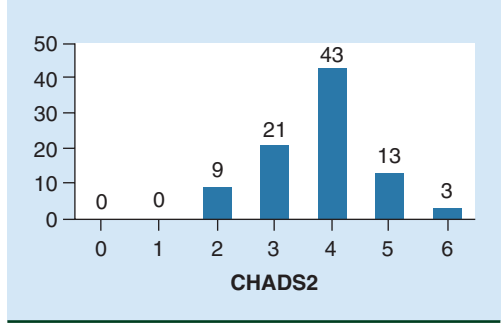

Figure 1. Distribution of the study population according to $CHADS_2$ score.

published in 2007 revealed a 64% reduction in the relative risk of stroke with warfarin (2.7% annual absolute risk reduction), 67% when only ischemic stroke was taken into consideration [3]. However, its use was associated with an increased risk of bleeding. In addition to possible bleeding complications, management of VKAs is not easy in clinical practice. Anticoagulation activity must be closely monitored, since bioavailability is affected by food, other treatments and genetic differences between patients and frequent dose adjustments are required [11]. This often leads to an overload in care work and affects patient quality of life, and more importantly, that many patients with a clear indication of anticoagulation are not taking anticoagulant therapy [19].

These limitations have been mitigated by the development of DOACs, since these drugs have a more predictable pharmacokinetic and pharmacodynamic profile. Moreover, they have few interactions with other drugs and do not interact with food [11,20], although in the case of rivaroxaban, it is important to remember that bioavailability increases with food [20]. As a result, in patients taking rivaroxaban, periodic monitoring is unnecessary and dose adjustments are only required in patients with renal insufficiency [11]. Moreover, the meta-analysis of Ruff *et al.* [21]

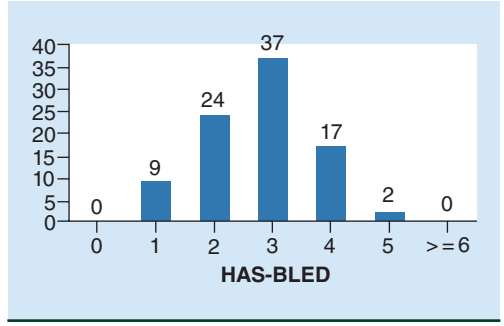

Figure 2. Distribution of the study population according to HAS-BLED score.

Table 2. Baseline clinical characteristics of the study population compared with that of the subgroup of patients with previous stroke or transient ischemic attack treated with rivaroxaban from ROCKET-AF trial.

	Study population (n = 89)	Rocket-AF (n = 3.754)	p-value
Age (years)	77 (72–82)	71 (64–76)	<0.001
Men (%)	47.2	61.0	0.01
$CHADS_2$ score, median (IQR)	4 (3–4)	4 (3–5)	NS
Previous treatment with VKAs (%)	22	59	<0.001

IQR: Interquartile range; VKA: Vitamin K antagonist.

that analyzed the results of pivotal clinical trials comparing DOACs with warfarin showed that taken in combination, DOACs were noninferior to warfarin for preventing ischemic stroke or reducing major bleeding, but considerably reduced the risk of intracranial bleeding with respect to warfarin. They therefore have a clear clinical advantage, leading neurologists to consider them as almost 'cerebroprotective' drugs. In this setting, DOACs will probably prove most advantageous in secondary prevention of stroke or in more elderly patients [22] and when treating patients with a history of cerebral lesions.

The ROCKET-AF trial showed that in patients with nonvalvular AF, rivaroxaban was noninferior to warfarin for the prevention of stroke or systemic embolism, with similar rates of major bleeding, but a lesser risk of intracranial and fatal bleeding [14]. A substudy of ROCKET-AF showed that the relative efficacy and safety of rivaroxaban compared with warfarin was consistent with the overall results regardless the history of previous stroke or TIA [18]. Thus, in ROCKET-AF, rates of major and nonmajor clinically relevant bleeding were 14.9/100 patient-years for rivaroxaban and 14.5/100 patient-years for warfarin (p = 0.44). In patients with previous stroke or TIA, these numbers were 13.31 and 13.87 patient-years, respectively (HR 0.96; 95% CI 0.87–1.07). Rates of major bleeding were 3.6 and 3.4%, respectively (in the subgroup of patients with previous stroke or TIA, 3.13 and 3.22%, respectively), and for intracranial hemorrhage 0.5 and 0.7%, respectively (in the subgroup of patients with previous stroke or TIA, 0.59 and 0.80%, respectively) [14,18].

Although our knowledge of DOACs is now consolidated, it is gained mainly from controlled clinical trials. However, patients included in clinical trials are somewhat different to those attended in daily clinical practice [23]. As a result, it has been postulated that some of the theoretical advantages of DOACs in clinical practice may not actually exist, given that real-life patients are older, have multiple conditions, including renal insufficiency. Our data showed that in clinical practice, patients with AF and a history of stroke or TIA were older, and had a very high risk of stroke recurrence (median $CHADS_2$ score of 4) and bleeding (median HAS-BLED score of 3). Compared with ROCKET-AF trial, our patients were older, but $CHADS_2$ score was similar. Despite that, there was a trend to a lower risk of annual recurrence of stroke in our patients compared with ROCKET-AF [18]. These data confirm the efficacy of rivaroxaban in real-life patients.

Despite in ROCKET-AF rivaroxaban reduced the risk of intracranial hemorrhage by 33% (p = 0.02) and fatal bleeding by 50% (p = 0.003) [14], one of the most important concerns about the use of rivaroxaban in clinical practice is its impact on hemorrhagic episodes in real-life patients. Of note, in our study median HAS-BLED score was 3. This translated into a high risk of bleeding [1]. However, despite the fact that the patients were older and anticoagulant therapy was started early after stroke or TIA events (median only 4 days), the risk of clinically significant bleeding was significantly lower than that observed in ROCKET-AF, without significant differences in the risk of intracranial hemorrhage. In addition, there was a trend to a lower risk of major bleeding in our patients [18]. These favorable results regarding the rate of bleeding complications, better than those achieved with rivaroxaban in ROCKET-AF trial, could have been due to the recommendation of taking the drug immediately after a meal and the concomitant use of omeprazole. In addition, we cannot rule out a favorable idiosyncrasy of our population that would be more resistant, especially to gastrointestinal bleeding complications. Anyway, the safety of rivaroxaban in real-life world has been confirmed in three observational studies performed in Germany, Canada and USA, respectively [24–26].

Box 1. Clinical presentation of the patient with stroke recurrence and the patient with intracranial bleeding.

Patient with stroke recurrence

- The patient was an 84-year-old man with nonvalvular atrial fibrillation who had started rivaroxaban after a cardioembolic stroke affecting the left middle cerebral artery territory. The NIHSS score of the patient was 2 and the $CHADS_2$ score 5 (estimated annual stroke rate, 12.5%).
- 14 months later he visited the emergency department at 10:30 a.m. for abrupt onset of symptoms that progressed with right homonymous hemianopsia, global aphasia and right hemiparesis. No acute lesions were observed on the computed tomography scan. The patient had last taken rivaroxaban at 9:00 a.m. that morning and denied having forgotten to take this medication during the previous days.

Patient with intracranial bleeding

- The patient was an 84-year-old woman who started anticoagulant therapy after a cardioembolic stroke resulting from nonvalvular atrial fibrillation with an NIHSS score of 4 at discharge and a high risk of bleeding (HAS-BLED, 4).
- 15 months later, a fall from bed was followed by reduced consciousness. Patient was taken to the emergency department. The computed tomography scan revealed an acute frontoparietal subdural hematoma with mass effect and clotting abnormalities (INR, 2.66; prothrombin activity, 34%). The patient died 12 h later.

Another concern about the use of DOACs is the medication adherence (forgotten doses, discontinuation of medication) because of a lesser follow-up by the healthcare system. Since DOACs require less medical follow-up, it is reasonable to think that adherence could be poorer, with the result that many patients would be exposed to the risk of stroke despite having started anticoagulant therapy. Nevertheless, our results revealed good persistence to treatment (97%), even though our patients were older and had experienced cerebral ischemia. Both findings support the use of rivaroxaban for secondary prevention of cerebral ischemia in patients in our setting. This good persistence was even better than that observed in ROCKET-AF [18]. Importantly, it has been reported that in nonvalvular AF patients, rivaroxaban is also associated with a significantly lower risk of treatment nonpersistence compared with warfarin [25,27]. This is very relevant taking into account that it has been observed that persistent secondary prevention treatment declines rapidly during the first 2 years after stroke, particularly for warfarin [28]. Therefore, rivaroxaban is not associated with a lower medication adherence. By contrast, medication persistence with rivaroxaban is good, and markedly better than with warfarin. Another advantage of rivaroxaban is that it is taken only once daily, in contrast to dabigatran and apixaban that are taking twice daily. In fact, it has been reported that nonvalvular AF patients treated with once-daily dosing regimens for chronic medications are associated with a higher likelihood of adherence compared with subjects on twice-daily regimens [29]. On the other hand, although administration of a single dose has raised doubts about the potential loss of anticoagulant effect at the end of the day, this has not been confirmed in ROCKET-AF [14] or in observational studies [25], including our study. Ongoing multicenter registries and noninterventional studies [30,31] will further consolidate our findings regarding efficacy, safety and medication persistence of rivaroxaban in clinical practice.

Our study had some relevant limitations. This study was performed in only one center, and the sample size was quite small. However, since patients included in clinical trials are somewhat different to those attended in daily clinical practice, studies performed in real-life patients are mandatory. AF patients with previous stroke or TIA are at very high risk of both stroke and bleeding complications. In this context, analyzing the efficacy and safety of anticoagulation in clinical practice is essential. Since the information currently available in this population is scarce, we consider that the information provided by our study is of interest. In fact, it did enable us to improve patient management, since it reaffirmed our belief that in our daily clinical practice, and as shown in controlled

Table 3. Recurrence of stroke and bleeding complications in our study compared with that of the subgroup of patients with previous stroke or transient ischemic attack treated with rivaroxaban from ROCKET-AF trial.

	Study population (n = 89)	Rocket-AF (n = 3.754)
Annual recurrence of stroke (%)	0.82	2.79
Annual clinically significant bleeding (%)*	6.58	13.31
Annual major bleeding (%)	1.64	3.13
Annual intracranial bleeding (%)	0.82	0.59
Withdrawal rate (%)**	2.25	15

*$p < 0.05$.
**$p < 0.001$.
AF: Atrial fibrillation.

clinical trials, DOACs, particularly rivaroxaban, are safe and efficacious and more convenient both for the patient and for the healthcare system. Rivaroxaban was used in this study, since in ROCKET-AF rivaroxaban markedly reduced the risk of intracranial hemorrhage compared with warfarin. In addition, in ROCKET-AF more than a half of patients included had a history of stroke or TIA. As a result, the experience regarding the use of rivaroxaban in this population was important. Moreover, its simplicity of use (once-daily dose; easy dose adjustment, only according to renal function) makes rivaroxaban an ideal oral anticoagulant for elderly patients, as those observed in our unit.

Conclusion

In real-life patients with nonvalvular AF and a history of stroke or TIA, rivaroxaban was well tolerated, efficacious and safe, even in elderly patients (67% were aged >75 years) with a high HAS-BLED score and almost no delay in starting DOACs after the stroke. These results were even more favorable than those reported from the ROCKET-AF study regarding efficacy, safety and medication persistence.

Future perspective

Clinical trials have shown that DOACs are noninferior to warfarin for preventing ischemic stroke or reducing major bleeding, but with a marked lesser risk of intracranial bleeding. This great advantage makes neurologists to consider DOACs as almost 'cerebroprotective' drugs. In this context, it is likely that in the following years, DOACs will be considered as the treatment of choice for secondary prevention of stroke or even for primary prevention in patients with nonvalvular AF and a history of brain damage (i.e., radiological leukoaraiosis or history of cognitive impairment). Ongoing clinical trials performed in patients with embolic stroke of undetermined source will determine whether DOACs are useful for secondary prevention in this population [32].

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Table 4. Bleeding complications.

Type of bleeding	Number of patients (%)
Epistaxis	2 (25%)
Cephalohematoma	1 (12.5%)
Periorbital hematoma	1 (12.5%)
Hematuria	2 (25%)
Hemoptysis	1 (12.5%)
Intracranial	1 (12.5%)
Total	8 (100%)
Decrease in hemoglobin levels >2 points	1 (12.5%)
Transfusion of red cell concentrates	0
Fatal bleeding	1 (12.5%)

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved.

EXECUTIVE SUMMARY

- Direct oral anticoagulants (DOACs) are at least as effective as warfarin for the prevention of stroke and systemic embolism, but with a lower risk of intracranial hemorrhage.
- Since DOACs have recently been marketed, data regarding efficacy and safety of these drugs in clinical practice are very scarce and in some cases remain controversial.
- The aim of this study was to evaluate the efficacy, safety and tolerability of rivaroxaban for the secondary prevention of stroke in patients with nonvalvular atrial fibrillation (AF) in clinical practice.

Methods

- For this purpose, a noninterventional and prospective study was performed.
- A total of 89 patients (median age 77 years, median $CHADS_2$ score 4, median HAS-BLED score 3) were included.

Results

- Compared with the subgroup of patients with previous stroke or TIA treated with rivaroxaban from ROCKET-AF trial, our patients were older, more commonly women and a lesser proportion of patients had been previously treated with vitamin K antagonists. By contrast, $CHADS_2$ score was the same in both groups.
- Rivaroxaban was well tolerated, efficacious and safe, even in elderly patients, with a high HAS-BLED score and almost no delay in starting DOACs after the stroke.

Discussion & future perspective

- The results of our study, performed in real-life patients, were even more favorable than those reported from the ROCKET-AF study regarding efficacy, safety and medication persistence.
- The great advantage of DOACS over warfarin (similar efficacy for preventing ischemic stroke or reducing major bleeding, but with a marked lesser risk of intracranial bleeding) makes neurologists to consider DOACs as almost 'cerebroprotective' drugs.
- It is likely that in the following years, DOACs will be considered as the treatment of choice for secondary prevention of stroke or even for primary prevention in patients with nonvalvular AF and a history of brain damage (i.e., radiological leukoaraiosis or history of cognitive impairment).

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