Research article

Antithrombotic therapy in patients with non-traumatic intracerebral haemorrhage and atrial fibrillation: A retrospective study

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A B S T R A C T

Introduction: The aim of the study was to determine the outcome, prescribed therapy, and localization of non-traumatic intracerebral haemorrhage in patients with atrial fibrillation.
Patients and methods: This retrospective study enrolled patients with atrial fibrillation hospitalised for non-traumatic intracerebral haemorrhage from 2004 to 2013. We compared the patients according to previous antithrombotic therapy, demographics, previous CHADS2 score, comorbidities, the international normalised ration, localisation of intracerebral hamorrhage, stroke severity, prescribed antithrombotic therapy and outcome.
Results: A total of 85 patients were enrolled and assigned to an AT+ group (n = 49; 14 on aspirin, 35 on warfarin) and an AT- group (n = 36; without antithrombotic therapy prior to hospitalisation). The latter had a lower proportion of known atrial fibrillation (90% vs 47%, P < 0.001). The mean INR was 2.6 ± 1.5. The in-hospital mortality rates in both groups were high: 43% in AT+ group and 47% in AT- group. There were no significant differences in any of the predefined comparisons.
Conclusion: Treating patients with intracerebral haemorrhage and atrial fibrillation is challenging due to higher mortality rates and issues regarding the use of antithrombotic treatment in stroke prevention. Based on our data, prior antithrombotic therapy was not associated with increased in-hospital mortality rates or poorer functional outcome at hospital discharge in comparison with no prior antithrombotic therapy.

1. Introduction

Stroke is the leading cause of disability and the third cause of mortality in the world [1]. Approximately 10–15% of first strokes are caused by intracerebral haemorrhage (ICH), which makes it one of the major causes of stroke-related death and disability [2]. Atrial fibrillation (AF) is the most common sustained arrhythmia and a well-established risk factor for ischaemic stroke [3]. AF increases the risk of stroke 4 to 5-fold and accounts for 10–15% of all ischaemic strokes and nearly 25% of strokes in patients aged 80 years and older [4]. The risk for ischaemic stroke is 17 times higher in patients with valvular AF [5]. Shared risk factors for ICH

and ischaemic stroke in patients with AF include age, alcohol intake, arterial hypertension, diabetes mellitus, renal impairment, dementia, and prior stroke or transient ischaemic attack [6]. Antithrombotic therapy (anticoagulant and antiplatelet therapy) is effective for primary and secondary ischaemic stroke prevention [7, 8]. Prior oral antiplatelet or anticoagulant therapy is also a risk factor for ICH [9]. Antiplatelet therapy is commonly used for the prevention of thrombotic stroke, and anticoagulant therapy is strongly recommended for cardioembolic stroke prevention [8].

The aim of this study was to determine the outcome, prescribed therapy, and localization of ICH in patients with AF who were

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hospitalised for non-traumatic ICH. The hypothesis of the study is that mortality rates will be higher for AF patients with ICH who were previously treated with antithrombotic therapy.

2. Patients and methods

2.1. Subjects

This retrospective study enrolled patients with AF who were hospitalised for non-traumatic ICH from January 1, 2004 to December 31, 2013 at the Stroke and Intensive Care Unit, Department of Neurology, University Hospital "Sveti Duh" in Zagreb, Croatia (Figure 1). The inclusion criteria were the presence of ICH and AF (non-valvular or valvular) and age over 18 years. Exclusion criteria were traumatic ICH and haemorrhagic transformation of ischaemic stroke. Ethical approval was received from the "Sveti Duh" University Hospital Ethics Committee. The study protocol followed the principles outlined in the Declaration of Helsinki.

2.2. Methods

Analysis of medical records included age and gender, previous CHADS2 score, previous or newly diagnosed AF, and previous ischaemic stroke. The diagnosis of AF was based on electrocardiographic (ECG)

findings or prolonged ECG monitoring on admission or during hospital stay and analysis of the medical records and medical history. The international normalised ratio (INR) values as a measure of prothrombin time (within 24 h of admission) were collected in patients with prior anticoagulant therapy. The localization of ICH (lobar versus non-lobar bleeding) was evaluated in accordance with the relevant neuroradiologic findings (computerized tomography or magnetic resonance imaging). Stroke severity was assessed on admission, according to the National Institutes of Health Stroke Scale (NIHSS), USA [10]. Stroke outcome was assessed with the modified Rankin scale (mRS) at hospital discharge [11, 12]. A subanalysis was performed in a group of patients with previous oral anticoagulant therapy to determine the intensity of anticoagulation assessed by INR, mortality, outcome, and initial presentation with respect to the NIHSS score [10]. The subanalysis was performed for prescribed antithrombotic therapy at hospital discharge for survived patients, too.

2.3. Statistical analysis

Data were presented in tabular form and analyzed by descriptive statistics and multivariable logistic regression models. We used for estimation and hypothesis testing: the two-sample t-test, chi-squared test, Fisher's exact test, ANOVA, Kruskal-Wallis test, and logistic regression. Statistical computing was performed in R (R Core Team, 2015. R: A
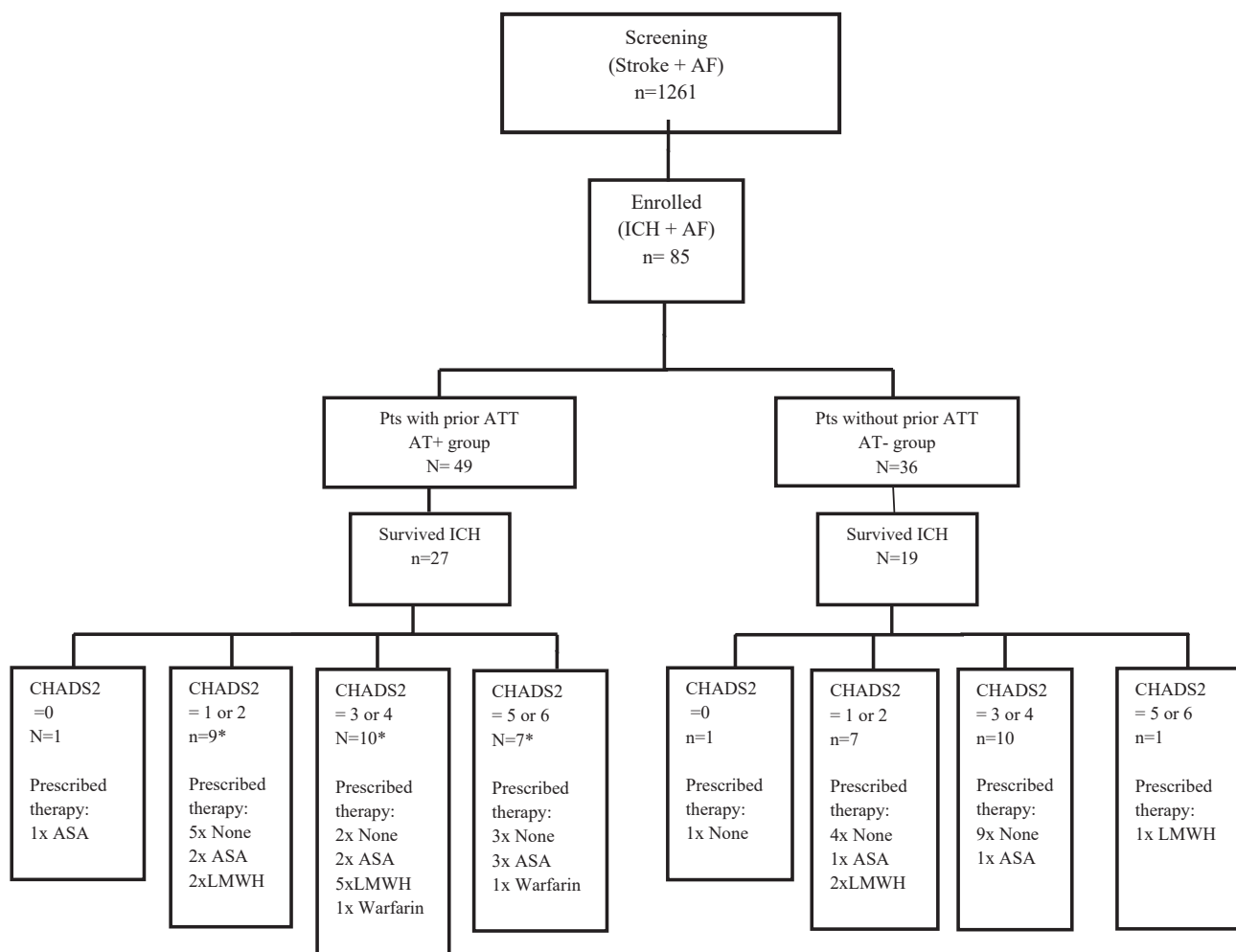
Figure 1. Flow diagram with treatment options regarding CHADS2 score. Legend: Pts – patients. AF – atrial fibrillation; ICH – intracerebral haemorrhage; AT+ the group receiving antithrombotic therapy prior to hospitalisation; AT- - the group without antithrombotic therapy prior to hosipitalisation; ATT-antithrombotic therapy; CHADS2 - (congestive heart failure, hypertension, age, diabetes mellitus, stroke [double risk weight]). ASA – aspirin; LMWH – low molecule weight heparin; * - 1 patient with valvular atrial fibrillation.

language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, version 3.2.1, Austria, http://www.R-project.org/). A testwise false-positive error rate was set at 0.05, thus controlling for potential experimentwise errors.

3. Results

Of 1261 patients with AF and stroke, a total of 85 eligible patients (6.7%) were enrolled. The group receiving antithrombotic therapy prior to hospitalisation (AT+) included 49 patients, 14 of which were on aspirin and 35 were on warfarin therapy. The group without antithrombotic therapy prior to hospitalisation (AT-) included 36 patients. The patients in the AT- group had a lower proportion of previously diagnosed AF (90% vs 47%, $P < 0.001$) and lower disability levels before stroke according to mRS (1.7 ± 1.6 vs 0.8 ± 1.1, $P < 0.001$) in comparison with AT+ group; Table 1 shows characteristics of patients in these groups. Prescribed antithrombotic therapy according to CHADS2 score is provided in Figure 1. Table 2 shows outcome measures by group. The outcome of our patients was poor with moderate to severe disability at discharge (mean $\pm$ SD mRS was 4.95 ± 1.40). Unfavorable outcome (mRS>2) was present in 90.6% of our patients, with in-hospital mortality rates of 56.5% for all enrolled patients (Table 2). The difference in the mean length of stay was not statistically significant across groups (13.0 ± 9.9/AT+/vs 13.8 ± 9.9/AT-/, p = 0.344143). However, 61.5% of patients died during the first week; the median length of stay was significantly longer in patients who survived ICH (17.3 ± 9.8 vs 8.6 ± 7.7, p = .000012). Patients with prior antithrombotic therapy who survived ICH received antithrombotic therapy for ischaemic stroke prevention was

Table 1. Characteristics of patients receiving the antithrombotic therapy (AT+) and those not receiving antithrombotic therapy (AT-) prior to hospitalisation for non-traumatic intracerebral haemorrhage (ICH).

Characteristics	Groups of patients (n, %)		P
	AT+ (n = 49)	AT- (n = 36)	
Age (mean $\pm$ SD, years)	78.0 $\pm$ 7.1	76.2 $\pm$ 9.0	0.302†
Women	29 (59)	20 (56)	0.9101‡
Arterial hypertension	46 (94)	29 (81)	0.123§
Hyperlipidemia	23 (47)	10 (28)	0.117§
Diabetes mellitus	16 (33)	17 (47)	0.256§
Cardiac disease	33 (67)	21 (58)	0.532§
Previous diagnosis of atrial fibrillation	44 (90)	17 (47)	<0.001§
Mechanical heart valves	4 (8.2)	0	0.105§
Previous ischaemic stroke	15 (30)	7 (19)	0.362¶
Dementia	5 (10)	6 (17)	0.289§
CHADS2 score (mean $\pm$ SD)	3.3 $\pm$ 1.4	2.9 $\pm$ 1.2	0.1140‡
mRS (admission)			
Median (range)	2 (0–5)	0 (0–4)	0.00443 II
Mean $\pm$ SD	1.7 $\pm$ 1.6	0.8 $\pm$ 1.1	0.003†
NIHSS			
Median (range)	12 (7–18)	14.5 (10–22)	0.231 II
Mean $\pm$ SD	14.2 $\pm$ 9.8	16.5 $\pm$ 9.0	0.338†
Localization of ICH/survived stroke, n (%)/n			
Lobar	26 (53)/15	21 (58)/12	
Non-lobar	23 (47)/12	15 (42)/7	0.348‡
Basal ganglia	12 (25)/5	12 (33)/5	
Infratentorial	9 (18)/7**	3 (8)/2	
Intraventricular extension of ICH††	13 (27)	13 (36)	0.340‡

Legend: SD – standard deviation; CHADS2 - congestive heart failure, hypertension, age, diabetes mellitus, stroke (double weight); mRS – modified Rankin Scale; NIHSS – National Institute of Health Stroke Scale; IVH – intraventricular haemorrhage; †ANOVA; ‡Two-sample *t*-test; §Yates' correction; ¶ Fisher's exact test; IIKruskal-Wallis rank test; **One patient had IVH; ††Two patients had only isolated IVH; one received prior warfarin; one received prior aspirin.

Table 2. Outcome measures in patients receiving the antithrombotic therapy (AT+) and those not receiving antithrombotic therapy (AT-) prior to hospitalisation for non-traumatic intracerebral haemorrhage (ICH).

Outcome	Groups of patients (n)		P
	AT+ (n = 49)	AT- (n = 36)	
In-hospital mortality	22/49	17/36	0.994§
mRS (discharge)			
Median (range)	5 (0–6)	5 (2–6)	0.59052 II
Mean $\pm$ SD	4.8 $\pm$ 1.6	5.1 $\pm$ 1.1	0.565†
Discharged to:	27/49	19/36	
Palliative care	3	7	
Nursing home	5	1	
Home	6	4	0.197¶
Rehabilitation	10	4	
Other hospital department	3	3	
ATT prescribed in surviving patients	17/27	5/19	0.0188¶
Type of ATT prescribed in surviving patients	27	19	
None	10	14	
ASA	8 (6 lobar/ 2 non-lobar)	2 (1 lobar/ 1 non-lobar)	0.083¶
Warfarin	2 (1 lobar/ 1 non-lobar)	0	
LMWH	7 (3 lobar/ 4 non-lobar)	3 (all lobar)	

Legend: mRS – modified Rankin Scale; ATT – antithrombotic therapy; ASA –aspirin; LMWH – low-molecule-weight heparin; †ANOVA; §Yates' correction; IIKruskal-Wallis test; ¶ Fisher's exact test.

present in 47.8% of the cases (22 out of 46 of surviving patients); ten of these patients had lobar ICH. Warfarin was continued in one patient despite lobar localization of ICH. Bridging therapy with low-molecule-weight heparin (LMWH) was used in 10 patients, in six with lobar and four with non-lobar ICH (Table 2).

We found no association between in-hospital mortality and previous antithrombotic therapy and localization of ICH after adjusting for age, sex, and CHADS2 score in our multivariable logistic regression models. A subanalysis was performed in a group of 35 patients on previous oral anticoagulant therapy (OAT). In this subgroup, mean INR was 2.6 ± 1.5. Seven of 35 patients had an INR>3.0; seven of 35 patients had an INR<1.5; seven patients had an INR between 1.5 and 2.0; 14 patients had INR in the recommended therapeutic window (INR between 2.0 and 3.0). There were no significant differences between patients receiving previous oral anticoagulant therapy regarding in-hospital mortality, outcome, and initial presentation with respect to the NIHSS score. Table 3 is a demographic and clinical characterization of patients who started therapy after ICH.

4. Discussion

We found that less than 7% of all patients with stroke and AF who were treated in the period from 2003 to 2014 had non-traumatic ICH. The previously reported incidence of AF and ICH ranged from 6.0% to 13.9% [6, 13, 14, 15]. AF was more prevalent in women with stroke, as has been observed previously [16]. In-hospital mortality was found in 56.5% of all patients in our study. The outcome of our patients was poor with moderate to severe disability at discharge. Previous investigations have shown that less than 20% of patients who suffered ICH were independent at 6 months after ICH [2, 17], and that mortality after ICH approached 50% at 30 days [18, 19]. One-half of ICH-related deaths were reported to occur in the first 24 hours after initial haemorrhage [20]. In our study the 61.5% of deaths occurred in the first week, and 10.25% of patients died during the first 24 hours. Kuramatsu et al. [21] found that 72.6% of patients with anticoagulant-associated ICH had unfavorable

Table 3. Characteristics of survived patients with intracerebral haemorrhage (ICH) and prescribed therapy.

Characteristics	Groups of patients discharged on (n, %)				P
	ASA (10)	Warfarin (2)	LMWH (10)	No therapy (24)	
Age (mean ± SD, years)	75.5 ± 4.1	84.0 ± 8.5	73.6 ± 7.0	77.6 ± 7.6	0.1870[†]
Women	7 (70)	1 (50)	5 (50)	13	0.8010[¶]
Arterial hypertension	9 (90)	2	9	19	0.8213[¶]
Hyperlipidemia	5 (50)	1	5	10	0.9239[¶]
Diabetes mellitus	4 (40)	0	3	9	0.8872[¶]
Cardiac disease	7 (70)	1	8	12	0.3454[¶]
Previous diagnosis of atrial fibrillation	7 (70)	2	9	14	0.2801[¶]
Mechanical heart valves	2 (20)	0	1	0	0.1030[¶]
Previous ischaemic stroke	3 (30)	2	1	6	0.1273[¶]
Dementia	0	0	2	7	0.2338[¶]
CHADS2 score (mean ± SD)	3.2 ± 1.8	4.5 ± 0.7	2.7 ± 1.3	2.9 ± 1.4	0.4357[†]
Prior antiplatelet therapy	2 (20)	0	2	3	0.7419[¶]
Prior oral anticoagulant therapy	6 (60)	2	5	7	0.0929[¶]
INR (mean ± SD)	2.8 ± 1.9	1.8 ± 0.6	2.2 ± 1.2	2.6 ± 1.6	0.4186[†]
Without prior antithrombotic therapy	2	0	3	14	0.0904[¶]
mRS (admission)					
Median (range)	1 (0–5)	2,5 (2–3)	0.5 (0–4)	1 (0–5)	0.6163[†]
Mean ± SD	1.1 ± 1.5	2.5 ± 0.7	1.1 ± 1.4	1.2 ± 1.4	
NIHSS (admission)					
Median (range)	5.5 (2–18)	7.5 (4–11)	11.0 (7–22)	10.5 (2–20)	0.1075[†]
Mean ± SD	7.2 ± 5.7	7.5 ± 4.9	12.3 ± 5.2	11.3 ± 5.0	
Localization of ICH, n (%)					
Lobar	7	1	6	13	0.8917[¶]
Non-lobar	3	1	4	11	
Basal ganglia	0	1	3	6	0.1746[¶]
Infratentorial	2	0	1	5	0.9175[¶]
Intraventricular extension of ICH[††]	2	1	0	3	0.1754[¶]
mRS (discharge)					
Median	4 (0–5)	4.5 (4–5)	5 (2–5)	5 (1–5)	0.1473[†]
(Mean ± SD)	3.3 ± 1.9	4.5 ± 0.7	4.7 ± 0.9	4.1 ± 1.2	
Discharged to:					
Palliative care	0	0	4	6	0.1011[¶]
Nursing home	0	1	2	3	
Home	3	1	0	6	
Rehabilitation	6	0	3	5	
Other hospital department	1	0	1	4	

Legend: SD – standard deviation; CHADS2 - congestive heart failure, hypertension, age, diabetes mellitus, stroke (double weight); INR - international normalised ratio; mRS – modified Rankin Scale; NIHSS – National Institute of Health Stroke Scale; IVH – intraventricular haemorrhage. mRS – modified Rankin Scale; ASA –aspirin; LMWH – low-molecule-weight heparin; [†]ANOVA; [¶] Exact Fisher Test.

outcomes. The use of antiplatelet agents prior to ICH was associated with increased mortality rates, but not with poorer outcome [22, 23]. In this study, patients on prior antiplatelet agents showed the tendency for better outcome, but without statistical significance.

Most of our patients were candidates for oral anticoagulant therapy in ischaemic stroke prevention according to CHADS2 score and current guidelines [24, 25, 26], although we found that almost half of the patients without previous antithrombotic therapy prior to hospitalisation had known AF and required antithrombotic therapy. Had the decision been made to anticoagulate these 17 patients from the AT- group, at least 14 of them would have required anticoagulant therapy according to CHADS2 score ≥2).

Almost two-thirds of patients with oral anticoagulant therapy in our study had INR >2. Similarly, Poli et al. [27] reported that their patients with AF and ICH (non-traumatic and traumatic) had INR levels >2 in most cases. All our patients had been treated with symptomatic therapy and reversal of warfarin effect with vitamin K, according to current guidelines regarding ICH management [28].

According to risk stratification based on CHADS2 score, we found that antithrombotic therapy was prescribed in patients receiving antithrombotic therapy prior to hospitalisation who had high (CHADS2 score = 3 or 4), and very high CHADS2 scores (CHADS2 score = 5 or 6). Interestingly, among patients without antithrombotic therapy prior to hospitalisation, antithrombotic therapy was prescribed in those with moderate CHADS2 score (CHADS2 score = 1 or 2). Recent studies confirmed that the risk for ischaemic stroke is present in patients with recent ICH, particularly in those with high CHADS2-VASc (congestive heart failure, hypertension, age ≥75 years [doubled risk weight], diabetes mellitus, previous stroke/transient ischaemic attack [doubled risk weight], vascular disease, age 65–74 years, sex) score ≥2 [29].

The resumption of oral anticoagulant therapy for ischaemic stroke prevention after ICH is a challenging issue [34]. In our study, aspirin and LMWH were commonly prescribed; only two patients with warfarin were discharged. Recent ESC guidelines recommend starting oral anticoagulant therapy 4–8 weeks after ICH, and involvement of a multidisciplinary team in the decision process to evaluate ICH-related factors, such as age, prior

anticoagulant therapy, localization of the ICH, microbleeds, white matter lesions, and more [30]. According to the ESC guidelines, one of the therapeutic options is to leave a patient with no antithrombotic therapy [30].

Aspirin use was the most prevalent in patients with lobar ICH, in concordance with current American Heart Association/American Stroke Association guidelines [31]. Antiplatelet therapy is commonly prescribed after ICH [32]. A recent Restart or Stop Antithrombotic Randomised Trial (RESTART) showed that the risk for recurrent ICH does not outweigh the established benefits of antiplatelet therapy for secondary prevention [33]. Flynn et al. [32] showed that subsequent ischaemic stroke or myocardial infarctions were more common than recurrent ICH, and that despite being contraindicated, antiplatelet use was not a major hazard for recurrent ICH [32]. We found that antiplatetelet therapy was administered to 21% of patients at discharge. Recently, Nielsen et al. [34] found that patients with AF are at very high risk for subsequent ischaemic stroke and mortality if they are not receiving antithrombotic therapy. The same study showed that oral anticoagulant treatment was associated with a significant reduction in ischaemic stroke/all-cause mortality rates, supporting re-introduction of the oral anticoagulant treatment after ICH may be recommended [34]. Kuramatsu et al. [21] reported that resumption of oral anticoagulant therapy was associated with significantly lower risk of ischaemic complications, yet oral anticoagulant therapy was prescribed in only one-fifth of AF patients.

Several randomized controlled trials are currently investigating pharmacological treatment options for stroke prevention after ICH in patients with atrial fibrillation [35]. These trials compare oral anticoagulants to aspirin or no antithrombotic agent [35]. The SoSTART (Start or Stop Anticoagulants Randomised Trial) and STATICH (Study of Antithrombotic Treatment After Intracerebral Haemorrhage) trials compare all types of oral anticoagulant therapy versus antiplatelet therapy or no antithrombotic agent [35]. Thus far, direct oral anticoagulants (DOACs) have shown at least non-inferiority in ischaemic stroke prevention, and better safety profile with less major and intracerebral bleeding in comparison to warfarin [36, 37, 38, 39]. New trials already include these agents to investigate their benefits in patients with atrial fibrillation with recent ICH. These trials include the PRESTIGE-AF trial (Prevention of Stroke in Intracerebral Haemorrhage Survivors with Atrial Fibrillation), where DOACs are compared with antiplatelets or on antithrombotic agent, the NASPAF-ICH trial (NOACs for Stroke Prevention in Patients with Atrial Fibrillation and Previous ICH), where DOACs are compared with aspirin, and two trials where apixaban is compared with aspirin or no antithrombotic therapy, the APACHE-AF trial (Apixaban versus Antiplatelet Drugs or no Antithrombotic Drugs after Anticoagulation-associated Intracrebral Haemorrhage in Patients with Atrial Fibrillation), and the ASPIRE trial (Anticoagulation for Stroke Prevention and Recovery after ICH) [35].

This study has the following limitations. As it was a retrospective, single-centre study, it included only patients with non-traumatic ICH treated at our Stroke and Intensive Care Unit, and is therefore not generalizable to the population of such patients. The analysis included only hospital-related data, short-term outcome results and there was no follow-up. No large scale data were emloyed to compare case fatality rate during a longer period with a larger ICH patient population. Some bias may have been induced by the inclusion of the patients having different previous antithrombotic therapy in the same AT+ group. In addition, ICH, CHA2DS2-VASC and HAS-BLED scores could not be determined. The changes in ICH standard of care over this time period might have influenced the outcomes results. The study does not reflect the whole population of patients with intracerebral haemorrhage because patients with traumatic ICH were not included in the analysis because they were treated at a surgical or neurosurgical intensive care unit, and their data were unavailable. Epidemiological data on ICH in patients with AF and the use of antithrombotic therapy in that setting were also unavailable. The subanalysis with patients on warfarin did not show differences in in-hospital mortality, outcome, and initial presentation, which may be biased due to small sample size.

5. Conclusion

Intracerebral haemorrhage and atrial fibrillation are relatively common in routine clinical practice. Treating such patients may be challenging due to higher mortality rates and issues regarding the use of antithrombotic treatment in ischaemic stroke prevention. Based on our data, prior antithrombotic therapy is associated with increased in-hospital mortality rates or poorer functional outcome at hospital discharge, in comparison with patients without prior antithrombotic therapy. Future prospective studies are needed to clarify the role of each parameter in stroke risk scores (eg. CHA2DS2-VASC and/or HAS-BLED) regarding outcome and treatment options.

Declarations

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