Preadmission oral anticoagulant therapy and clinical outcome in patients hospitalised with acute stroke and atrial fibrillation

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ABSTRACT

INTRODUCTION: Information about the effect of preadmission oral anticoagulant therapy (OAT) on stroke outcome in patients with atrial fibrillation (AF) is scarce. A systematic review was done of the existing data on the association between preadmission OAT and stroke outcome in patients with AF.

METHOD: We performed a systematic search in the PubMed Database, the Embase Database and the Cochrane Database of Systematic Reviews identifying 13 studies that met the inclusion criteria.

RESULTS: The studies included a total of 18,523 patients with AF and admission with stroke. Of these, 1,169 had a haemorrhagic stroke. The proportion of patients in preadmission OAT varied from 5 to 37%, and the proportion who did not receive any antithrombotic therapy (AT) varied from 22 to 75%. The risk of having a severe stroke for patients with an international normalised ratio (INR) < 2 ranged from 26 to 43% compared with a 15-36% range for patients with an INR ≥ 2. The risk of death or disability among patients not receiving any AT ranged from 22 to 56% compared with 15-59% for those on platelet inhibitors, 16-48% for those on OAT with an INR < 2 and 6-37% among patients with an INR ≥ 2. These patterns were confirmed after adjustment for confounding factors.

CONCLUSION: Only a minority of AF patients with stroke received OAT at the time of hospitalisation. Overall, preadmission OAT was associated with less severe strokes and a lower risk of death or disability. Further efforts seem warranted to ensure OAT for all eligible AF patients.

Atrial fibrillation (AF) is the most common cardiac arrhythmia and a major risk factor for ischaemic stroke [1, 2]. The prevalence of AF increases dramatically with age and affects approximately 9% of the population aged 80 years or more. The prevalence is expected to more than double by year 2050 [3, 4]. Stroke is the most feared complication in AF patients, and AF is associated with a higher risk of an adverse outcome following a stroke [5, 6].

Antithrombotic therapy is the primary prevention strategy for cardioembolic stroke in patients with AF. The efficacy of oral anticoagulation therapy (OAT) for prevention of cardioembolic stroke in patients with AF was documented in several clinical trials [7]. OAT use has been shown to reduce the incidence of clinical stroke with an acceptable bleeding risk and to be three times as effective as aspirin [8-11]. Less is known about the possible effect of preadmission OAT on stroke outcomes in patients with AF. It is necessary to study the possible impact of OAT on stroke outcomes to fully understand the effectiveness and safety associated with this treatment. Although clinical guidelines recommend OAT for all eligible AF patients, several studies have reported insufficient use and intensity of OAT, mainly due to concerns among clinicians and patients about the safety of OAT [12]. Additional insight into the safety and effectiveness of OAT in routine care settings is therefore needed.

We here aim to provide a systematic review elucidating the association between preadmission OAT and stroke outcomes in patients with AF. To our knowledge, this is the first systematic review to examine the literature on this topic.

METHOD

A systematic search was conducted using the "patient, intervention, comparison, outcome" (PICO) model in the search strategy [13]. The overall research question was defined as follows: "How does preadmission OAT treatment influence the clinical outcome among patients with AF who are hospitalised with acute stroke?" The population was defined as patients hospitalised with stroke and diagnosed with AF either before or after admission. The intervention was defined as use of OAT or other types of antithrombotic therapy (AT) prior to admission. Furthermore, comparison should be possible between different treatment regimens of OAT, different antithrombotic drugs or no AT. Outcome should be measured as either stroke severity at admission, disability or mortality obtained within the hospital stay or after discharge. All types of human studies were eligible for inclusion.

SYSTEMATIC REVIEW

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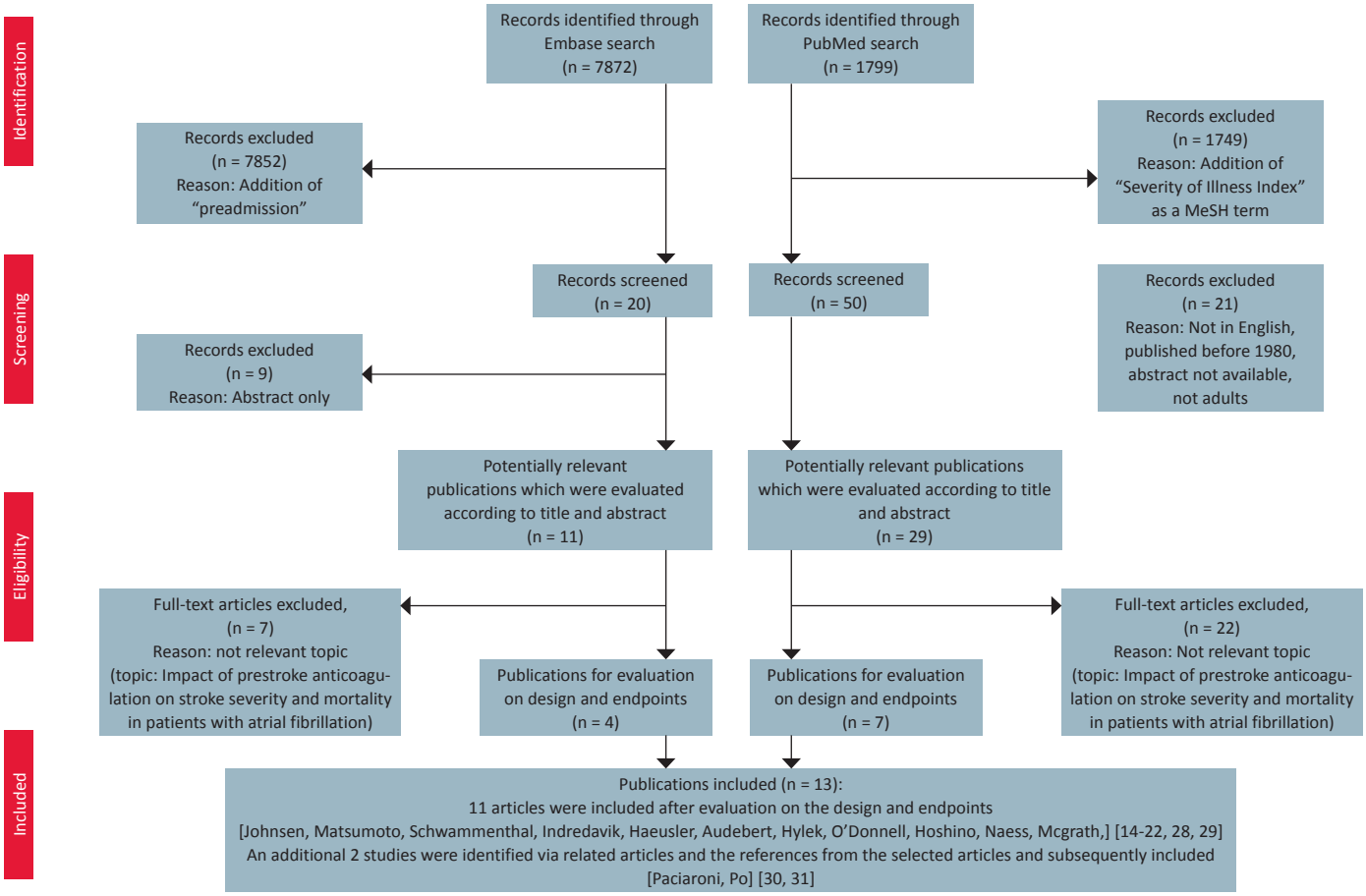
Dan Med J 2014;61(9):A4904

FIGURE 1

PRISMA 2009 Flow Diagram



The systematic search was conducted in the PubMed Database, the Embase Database and the Cochrane Database of Systematic Reviews. In all databases, the following keywords were used in the initial free text search, both individually and combined: "stroke", "atrial fibrillation", "anticoagulants". Papers focusing on patients having a stroke and having either AF or receiving anticoagulation were reviewed, but only those including outcome measures on mortality, disability or stroke severity were included.

After the initial search, the MeSH term "stroke" (MeSH) was combined with ("anticoagulants" (MeSH) AND "atrial fibrillation" (MeSH)) in a search within the PubMed database.

This search identified 1,799 publications. Next, the MeSH term "Severity of Illness Index" was included to narrow the search to papers including the outcome measurements of interest. This was followed by exclusion of papers not published in English, published before 1980, without available abstract and not focusing on adults. This resulted in 29 potentially relevant publications, and seven of these were included for evaluation of design and endpoints.

The initial search in the Embase database search identified 7,872 publications and was followed by addition of the search term "preadmission". This resulted in 20 publications relevant for screening, but nine lacked an abstract, which resulted in 11 publications that were potentially relevant for inclusion. Seven of these were already known from the PubMed database search, but the remaining four relevant studies were included.

The search in the Cochrane Database of Systemic Reviews did not identify any relevant publications.

We identified two additional studies from the reference lists, related articles and citation lists of the papers included from the initial database search. After this procedure, a total of 13 studies were selected for this systematic review. The search was conducted on 7 March 2014. The flow chart of the search can be seen in **Figure 1**.

Patients on OAT therapy are presented as using any OAT therapy or divided according to their admission in-

TABLE 1

Characteristics of included studies regarding patients with atrial fibrillation and stroke.

		Type of stroke, n (%)		Atrial fibrillation, n (%)		Preadmission antithrombotic therapy (AT), %		Oral anticoagulant therapy (OAT)		
Autor (published year)	[Ref.]	Ischaemic	Haemorrhagic	Diagnosed before admission	Diagnosed during admission	Nothing	Platelet inhibitors alone	Any	Known AF before admission	Known AF before admission, INR ≥ 2
Hylek (2003)	[20]	596 (100)	–	596 (10ç0)	–	42	27	31	31	12
Paciaroni (2005)	[31]	314 (100)	–	238 (76)	76 (24)	52[a]	36[a]	–	12	5
Indredavik (2005)	[17]	394 (100)	–	394 (100)	–	28	43	29	29	16
O'Donnell (2006)	[21]	948 (100)	–	741 (78)	207 (22)	32	31	37	47	15
Naess (2009)	[28]	117 (100)	–	89 (78)	28 (22)	–	–	23	29	–
Po (2010)	[30]	152 (100)	–	124 (82)	28 (18)	56[a]	38[a]	–	6	3
Schwammenthal (2010)	[16]	324 (100)[b]	–	324 (100)	–	28	38	34	34	15
Audebert (2010)	[19]	718 (89)	86 (11)	–	804 (100)	75[c]	–	25	–	–
Haeusler (2011)	[18]	506 (95)	28 (5)	348 (65)	186 (35)	51	35	14	21	8
Matsumoto (2011)	[15]	68 (100)	–	–	68 (100)	41	25	34	–	–
Hoshino (2012)	[22]	162 (100)[b]	–	–	162 (100)	22	43	35	–	–
Macgrath (2013)	[29]	2,754 (100)	–	1,887 (69)	867 (31)	68[c]	–	32	47	14
Johnsen (2013)	[14]	10,301 (91)	1,055 (9)	6,679 (59)	4,677 (41)	43	35	22	32	–

a) Preadmission antithrombotic therapy obtained on the proportion who had atrial fibrillation at admission
b) Ischaemic + transient ischaemic attack patients
c) Unknown whether some of these received platelet inhibitors

ternational normalised ratio (INR) level with INR < 2 or INR ≥ 2, respectively. Furthermore, patients were categorised by the use of platelet inhibitors or no use of antithrombotic therapy.

RESULTS

All of the included 13 studies contributed with information about the treatment status of patients with AF admitted with stroke. Six studies provided information about stroke severity on admission, whereas nine studies contributed with information about mortality or disability at discharge.

Treatment status

Table 1 shows the characteristics of the 13 studies, including information about population size, stroke subtypes, known history of AF and the use of AT.

A total population of 18,523 patients with AF and hospitalisation with stroke was obtained from the 13 studies, among which the largest study by Johnsen et al [14] contributed with 11,356 patients and the smallest study by Matsumoto et al [15] contributed with 68 patients. Of all the patients, 1,169 had a haemorrhagic stroke, whereas the rest were ischaemic. Of all included patients, 11,420 corresponding to 62% were known to have AF prior to admission.

The proportion of patients on preadmission AT differed between the studies. The proportion, which did not receive any AT before admission, ranged from 22 to 75%. The proportion of patients receiving platelet inhibitors ranged from 25 to 43%, and the proportion receiving any OAT on admission varied from 14 to 37%. The proportion of patients in adequate OAT treatment, with an INR ≥ 2, ranged from 3 to 16%.

Stroke severity

Table 2 shows stroke severity on admission in the six studies that reported this outcome. The different scales used to define stroke severity were the proportion of patients with reduced consciousness, the Canadian neurological scale score < 7, the baseline National Institutes of Health Stroke Scale (NIHSS) > 5, NIHSS > 10, NIHSS ≥ 11 and the Scandinavian Stroke Scale score < 30.

The probability of having a severe stroke compared with having a mild or moderate stroke in patients not receiving any preadmission AT ranged from 27 to 65%. The adjusted relative risk estimates when compared with the OAT-treated group with INR ≥ 2 were 1.3 (95% confidence interval (CI) 0.6-2.7) and 4.1 (95% CI 1.8-9.9), respectively, for the two studies that provided this information [16, 17].

Of all the patients receiving platelet inhibitors, 30 to 54% had a severe stroke according to the individual study definitions [16-18]. Using the group without treatment as reference, the adjusted relative risk estimates for therapy with platelet inhibitors were 0.7 (95% CI 0.5-1.0) and 1.1 (95% CI 0.7-1.6), respectively [18, 19]. In the two studies using OAT with an INR ≥ 2 as reference, the risk of a severe stroke with preadmission use of platelet inhibitors was increased, but the differences were not statistically significant [16, 17].

The probability of having a severe stroke compared

TABLE 2

Preadmission therapy among atrial fibrillation patients and the impact on stroke severity at admission

			No AT use		Platelet inhibitors		Oral anticoagulant therapy Any		INR < 2		INR ≥ 2	
Stroke severity Autor (published year)	[Ref.]	Study outcome	%	Adjusted relative risk estimate (95% CI)	%	Adjusted relative risk estimate (95% CI)	%	Adjusted relative risk estimate (95% CI)	%	Adjusted relative risk estimate (95% CI)	%	Adjusted relative risk estimate (95% CI)
Indredavik (2005)	[17]	Patients with reduced consciousness	27	1.3 (0.6-2.7)	30	1.5 (0.8-3.0)	–	–	33	1.7 (0.8-4.0)	22	Reference
O'Donnell (2006)	[21]	Canadian neurological scale ≤ 7	–	Reference	–	0.7 (0.5-1.0)	–	–	–	0.7 (0.1-1.0)	–	0.4 (0.2-0.6)
Schwammenthal (2010)	[16]	Baseline NIHSS > 5	65	4.1 (1.8-9.9)	54	2.1 (1.0-4.6)	–	–	43	1.5 (0.6-8.3)	36	Reference
Audebert (2010)	[19]	Probability for severe stroke, NIHSS > 10	30	Reference	–	–	–	–	28	1.0 (0.6-1.7)	16	0.4 (0.2-0.7)[a]
Haeusler (2011)	[18]	Probability for severe stroke, NIHSS ≥ 11	39	Reference	44	1.1 (0.7-1.6)	–	–	26	0.5 (0.2-1.1)	15	0.3 (0.1-0.8)
Johnsen (2013)	[14]	Scandinavian Stroke Scale score < 30	40	Reference	–	–	–	–	36	0.9 (0.6-1.3)	26	0.5 (0.4-0.8)[a]

a) Estimate for patients with Ian NR between two and three.
AT = Atrial fibrillation; CI = Confidence interval; INR = International normalised ratio

TABLE 3

Preadmission therapy among AF patients and the impact on stroke mortality or disability

			No AT use		Platelet inhibitors		Oral anticoagulant therapy Any		INR < 2		INR ≥ 2	
Stroke severity Autor (published year)	[Ref.]	Study outcome	%	Adjusted relative risk estimate (95% CI)	%	Adjusted relative risk estimate (95% CI)	%	Adjusted relative risk estimate (95% CI)	%	Adjusted relative risk estimate (95% CI)	%	Adjusted relative risk estimate (95% CI)
Hylek (2003)	[20]	30-day mortality	24	4.9 (1.8-13.7)	15	2.5 (0.9-7.4)	–	–	16	3.4 (1.1-10.1)	6	Reference
Indredavik (2005)	[17]	In-hospital mortality or sent to nursing home	28	2.4 (1.1-5.5)	29	2.6 (1.2-5.6)	–	–	35	3.1 (1.3-8.0)	14	Reference
O'Donnell (2006)	[21]	Mortality or disability at discharge mRS (4-6)	56	Reference	50	0.8 (0.5-1.1)	–	–	48	0.7 (0.5-1.1)	37	0.5 (0.3-0.9)
Schwammenthal (2010)	[16]	3-month mortality	32	4.0 (1.3-15.9)	22	3.1 (1.0-11.8)	–	–	16	2.0 (0.6-8.3)	12	Reference
Audebert (2010)	[19]	Mortality at discharge or during 90 days	–	Reference	–	–	–	0.5 (0.4-0.8)	–	–	–	–
Haeusler (2011)	[18]	Long-term mortality, mean 38 months (0-68)	42	Reference	59	1.9 (1.2-2.8)	–	–	43	1.3 (0.7-2.5)	27	0.7 (0.3-1.9)
Hoshino (2012)	[22]	Discharge mRS (0-2) versus (3-6)	–	Reference	39	–	21	1.95 (1.3-3.0)	–	–	–	–
Macgrath (2013)[a]	[29]	30-day mortality (baseline: mild stroke)	–	1.6 (1.0-2.6)	–	1.9 (1.2-3.1)	–	–	–	1.1 (0.6-2.1)	–	0.7 (0.2-1.8)
		30-day mortality (baseline: moderate stroke)	–	1.3 (0.8-2.0)	–	1.6 (1.0-2.4)	–	–	–	1.5 (0.9-2.5)	–	1.4 (0.9-2.7)
		30-day mortality (baseline: severe stroke)	–	1.2 (0.9-1.5)	–	1.3 (1.0-1.7)	–	–	–	1.4 (1.0-1.9)	–	1.6 (0.9-2.7)
Johnsen (2013)	[14]	30-day mortality	22	Reference	–	–	–	0.8 (0.7-1.0)	17	0.7 (0.4-1.1)	18	0.8 (0.5-1.1)[b]

a) Reference category is no AF diagnosis.
b) Estimate for patients with INR between two and three.
AT = Atrial fibrillation; CI = Confidence interval; INR = International normalised ratio

with a mild or moderate stroke in patients receiving pre-admission OAT and having an INR < 2 ranged from 26 to 43%, whereas the risk for patients with an INR ≥ 2 ranged from 15 to 36%. The adjusted relative risk estimates showed that patients using OAT and having an INR ≥ 2 experienced a lower risk of severe stroke than patients with an INR < 2 or using platelet inhibitors. Examples of this are the results from Audebert et al [19],

Haeusler et al [18] and Johnsen et al [14], who found adjusted relative risk estimates of 1.0 (95% CI 0.6-1.7), 0.5 (95% CI 0.2-1.1) and 0.9 (95% CI 0.6-1.3), respectively, for those with an INR < 2, compared with 0.4 (95% CI 0.2-0.7), 0.3 (95% CI 0.1-0.8) and 0.5 (95% CI 0.4-0.8), respectively, for patients with an INR ≥ 2, when those without treatment were used as reference.

Death or disability

Table 3 shows the mortality or disability according to preadmission use of AT. Nine studies reported on these outcomes. Their measures differed including 30-days mortality, in-hospital mortality or sent to nursing home, modified Rankin Scale (mRS) score of 4-6 (covering patients being unable to walk unassisted to death), 3-month mortality, long-term mortality and a discharge mRS (0-2) versus mRS (3-6).

The risk of death or disability for patients not receiving any preadmission AT ranged from 22 to 56%, compared with a 15-59% range for those on platelet inhibitors. For those on OAT with INR < 2, the risk of death or disability ranged from 16 to 48% compared with a range from 6 to 37% among patients in OAT therapy with INR ≥ 2.

This pattern was confirmed by the adjusted relative risk estimates. For the three studies [16, 17, 20] using patients with an INR ≥ 2 as reference, all point estimates in the remaining three categories (no use of AT, use of platelet inhibitors and OAT use with INR < 2) showed a higher risk of death or disability. For the four studies [14, 18, 19, 21] that used patients with no preadmission AT as reference, the risk estimates decreased for patients receiving preadmission platelet inhibitors or OAT. An example of this is O'Donnell et al [21], who reported a relative risk estimate of 0.7 (95% CI 0.5-1.1) among patients with an INR < 2 and 0.5 (95% CI 0.3-0.9) for patients with an INR ≥ 2. Hoshino et al [22] compared discharge mRS (0-2) versus (3-6), used patients without treatment as reference and found that patients with any OAT treatment had a relative risk estimate of 1.95 (95% CI 1.3-3.0) for ending up within the favourable mRS (0-2) category.

Impact of haemorrhagic stroke

Only two studies, Audebert et al [19] and Johnsen et al [14], included haemorrhagic stroke in their analysis of stroke severity and mortality or disability. Both used patients without AT as reference, regarding both stroke severity and mortality, and both reported an overall association between preadmission OAT use and lower stroke mortality, even though they included haemorrhagic stroke patients in their analysis.

Audebert et al [19] found that the relative risk of a severe stroke with OAT therapy and an INR < 2 was 1.0 (95% CI 0.6-1.7); and for an INR ≥ 2, it was 0.4 (95% CI 0.2-0.7) compared with 0.9 (95% CI 0.6-1.3) and 0.5 (95% CI 0.4-0.8) with an INR < 2 and INR ≥ 2, respectively, as reported by Johnsen et al [14].

For stroke mortality, Audebert et al [19] reported a relative risk estimate of 0.5 (95% CI 0.4-0.8) with any OAT use compared with no antithrombotic therapy. For comparison, Johnsen et al [14] reported an estimate of 0.8 (95% CI 0.7-1.0).

DISCUSSION

Insufficient use of OAT among patients with AF was observed in all studies included in this systematic review. Overall, only around one in four patients with AF used OAT at the time of admission with stroke, although the patients in general had a high predicted risk of thromboembolic evensts. Even among patients previously diagnosed with AF, only an average of 10% were being treated with OAT and had an INR value ≥ 2, which is the lower threshold of the therapeutic target interval. The low use of OAT among AF patients admitted with stroke is comparable with that seen in patients with AF in general [12]. Within the 10-year period covered by the included studies, there was no clear trend towards improvements in the proportion of AF patients being treated with OAT prior to their stroke. The largest of the studies included did observe improvements over time [14], but the proportion of insufficiently treated AF patients remained high; also by the end of the study period, particularly when the intensity of the OAT was taken into account.

The less protective effect of platelet inhibitors on the risk of developing stroke in AF patients [11] is supported in this review by results showing that compared with antithrombotic treatment, platelet inhibitors are associated neither with lower stroke severity nor with a lower rate of disability or mortality. These findings support current clinical guidelines, which do not recommend use of platelet inhibitors for stroke prevention in patients with AF.

The studies included in the present review indicate that insufficient use of OAT in AF is a global problem and that we need more knowledge about the recommended use of OAT in AF patients and about how to organise the monitoring of these patients. A key challenge in the efforts to achieve a more sufficient treatment with OAT in AF patients is the concern about bleeding risk and inadequate knowledge of the lower severity of stroke in patients with AF who receive OAT. The risk of inducing a fatal or severe intracerebral haemorrhage (ICH) due to OAT is a particular concern in this context. Only two studies [14, 19] included haemorrhagic stroke in the outcome measurements. In the study by Johnsen et al [14], approx. one in five strokes among patients with AF was

FACTBOX

Atrial fibrillation is the most common cardiac arrhythmia and a major risk factor for ischaemic stroke. The prevalence is expected to more than double by 2050.

Oral anticoagulation therapy has been shown to reduce the risk of cardioembolic stroke in patients with atrial fibrillation.

Only around one in four patients with atrial fibrillation used oral anticoagulant treatment at the time of admission with stroke, although the patients were generally characterised by a high predicted thromboembolic risk.

Among patients previously diagnosed with atrial fibrillation, only on average of 10% were treated with oral anticoagulants and having an INR value ≥ 2, which is the lower threshold of the therapeutic target interval.

Overall preadmission oral anticoagulant treatment was associated with a less severe stroke and a lower mortality or disability rate.

an ICH. They found a higher mortality among hospitalised patients with ICH using OAT at the time of admission, but the increased risk did not offset the substantially lower mortality among the much higher number of patients with ischaemic stroke using preadmission OAT. Their results and data from Audebert et al [20] support the finding that OAT use has an overall positive impact on the mortality and disability associated wi th stroke.

Thus, the insufficient use of OAT in AF is not only problematic considering the marked effect of this treatment on stroke risk, but also considering the association between OAT and clinical outcome related to stroke among patients with AF found in this systematic review. It is important to note that none of the included studies indicate an overall negative impact of preadmission OAT on clinical outcome in AF patients. This further supports the argument for improving the efforts to identify and treat eligible AF patients with OAT. The most recent version of the widely used clinical guidelines from the European Society of Cardiology may hopefully prove helpful in this context as these guidelines are more explicit and focused on practical issues than previous versions were [23].

The current scoring systems to determine whether AF patients are candidates for OAT (i.e. the CHA2-DS2-VASc score [24] to estimate the risk of stroke or systemic embolism, and the HAS-BLEED score [25] to estimate the risk of bleeding) are based on many identical risk factors, which makes it difficult to weight the value of these opposing systems against each other. To increase the proportion of AF patients being appropriately treated, we may well need to improve the available tools to identify the patients who will definitely not benefit from AT due to their risk of bleeding.

This review only included studies with conventional OAT use, since no studies have evaluated the preadmission use of non-vitamin K oral antagonists (NOACs) and their impact on clinical outcome. Studies with data on NOACs are required to clarify whether the apparently beneficial effects of OAT also include these newer drugs. The NOACs are of major interest because the use of these drugs is increasing and they have shown favourable results in preventing non-haemorrhagic stroke in patients with non-valvular AF, and because they are also generally associated with a lower risk of intracranial bleeding than warfarin in randomised clinical trials [26, 27].

This systematic review has limitations. First, the definition of antithrombotic therapy differed between the studies, and the use of platelet inhibitors, in particular, was not clearly defined in all studies. Second, we were unable to get information about the proportion of patients with AF in the no-treatment category who had an OAT treatment contraindication.

Studies reporting an estimate on stroke severity typically defined severe stroke individually and data for this outcome may therefore differ between the studies according to the different types of scales used. Definition of disability also differed between the included studies; and, furthermore, the use of different ways to obtain mortality data prevented us from making a direct comparison of the impact on mortality or disability between the studies.

CONCLUSION

In conclusion, only few patients with an acute stroke and AF received OAT at the time of hospitalisation. Furthermore, only one in ten patients with known AF before admission was treated appropriately with OAT at the time of the stroke. Additional education and improvements of the available tools used to identify patients who will not benefit from OAT due to their bleeding risk may be required to reap the full potential of OAT. Overall, preadmission OAT was associated with a less severe stroke and a lower mortality or disability rate. These effects appeared not to be set off when haemorrhagic strokes were included. Further efforts seem warranted to ensure OAT to all eligible patients with AF, because OAT not only reduces the risk of cardioembolic stroke, but also appears to be associated with a more favourable clinical outcome should a stroke occur.

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ACCEPTED: 2 July 2014

CONFLICTS OF INTEREST: Disclosure forms provided by the authors are available with the full text of this article at www.danmedj.dk

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