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Published in:
European Journal of Internal Medicine

DOI (link to publication from Publisher):
10.1016/j.ejim.2023.12.010

Publication date:
2024

Document Version
Publisher's PDF, also known as Version of record

European Journal of Internal Medicine 122 (2024) 61–67

Contents lists available at ScienceDirect

European Journal of Internal Medicine

journal homepage: www.elsevier.com/locate/ejim

Original Article

Adherence to an integrated care pathway for stroke is associated with lower risk of major cardiovascular events: A report from the Athens Stroke Registry

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ARTICLE INFO

Keywords:
Stroke
Mortality
Integrated care
Major adverse cardiac events

ABSTRACT

Background: A recent European Society of Cardiology (ESC) Council on Stroke position paper proposed a holistic integrated care management approach for stroke patients, to improve cardiovascular outcomes. The impact of implementing the ABC_{stroke} pathway 'concept' on clinical outcomes has never been estimated before. In order to investigate the potential effect of ABC_{stroke} pathway adherence to cardiovascular outcomes post stroke, we performed a post-hoc analysis from the Athens Stroke Registry.

Methods and results: This analysis was performed in the Athens Stroke Registry, which includes all consecutive patients with acute first-ever ischemic stroke. The Kaplan–Meier product limit was used to estimate the cumulative hazard of each outcome according to adherence with the ABC_{stroke} pathway.

We studied 2513 patients [median (IQR) age 71 (62–78) years; 37.7 % female] with ischemic stroke with median follow-up period of 30 (6–75) months. Full adherence to the ABC pathway was identified in 156 (6.2 %) of the patients, while 192 (7.6 %) did not adhere to any of the therapeutic pillars of ABC_{stroke}. Full adherence to ABC treatment pathway was associated with significant reduction of stroke recurrence, compared to patients with no or partial adherence (aHR: 0.61; 95 %CI: 0.37–0.99), as well as a lower risk of MACE (HR: 0.59; 0.39–0.88) and death (aHR: 0.22; 95 %CI: 0.12–0.41).

Conclusion: Full adherence to the ABC_{stroke} pathway based on the current guidelines was evident in only 6.2 % of our ischaemic stroke cohort but was independently associated with lower risks of stroke recurrence, major cardiovascular events and mortality. This highlights a potential opportunity to improve clinical outcomes post-stroke with a holistic or integrated care management approach.

1. Introduction

Despite improvements in overall stroke survival, patients surviving an ischaemic stroke are at increased risk of cardiovascular complications, both in the acute and chronic phase, and one-third of deaths occurring after the incident event are cardiovascular [1,2]. Approximately 20 % of these patients newly develop heart failure, cardiac arrhythmia, or acute coronary syndrome within the first 30 days after stroke, a phenomenon termed the 'stroke-heart syndrome' [3,4]. Such patients with stroke-heart syndrome (SHS) are at highly increased risk of further long-term cardiovascular events [5,6].

Our previous data show that of 365,383 persons with stroke with 5-year follow-up, more than 20 % developed a manifestation of SHS within 4 weeks of incident ischaemic stroke, which included acute coronary syndrome (11.1 %), atrial fibrillation/flutter (8.8 %); heart failure (6.4 %), severe ventricular arrhythmias (1.2 %), and Takotsubo syndrome 0.1 %. The odds of 5-year all-cause mortality were significantly higher in stroke patients with acute coronary syndrome (odds ratio, 1.49 [95 % CI,

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https://doi.org/10.1016/j.ejim.2023.12.010
Received 21 August 2023; Received in revised form 14 November 2023; Accepted 11 December 2023
Available online 16 December 2023

1.44–1.54]), atrial fibrillation/flutter (1.45 [1.40–1.50]), heart failure (1.83 [1.76–1.91]), and severe ventricular arrhythmias (2.08 [1.90–2.29]), compared with matched controls [5].

Given this higher risk, a recent European Society of Cardiology (ESC) Council on Stroke position paper proposed a holistic integrated care management approach for stroke patients, to address SHS and improve cardiovascular outcomes [6]. This holistic, integrated care approach follows the ABC pathway ('ABC_{stroke}') [7]: (A) Appropriate antithrombotic therapy in all stroke/TIA patients to avoid recurrent stroke; (B) Better functional (cardiac and post-stroke) and psychological status, including the assessment of post-stroke cognitive and physical impairment, depression, and anxiety as part of routine post-stroke work-up in every person; and (C) Cardiovascular risk factors and comorbidities management includes optimizing risk factor management and lifestyle changes [6].

The potential impact of implementing the ABC_{stroke} pathway concept on clinical outcomes has never been previously estimated. In view of this, we performed a post-hoc analysis on a prospectively collected ischaemic stroke registry, the Athens Stroke Registry, in order to investigate the effect of implementation or adherence to the ABC_{stroke} pathway on outcomes post stroke.

2. Methods

2.1. Study population and definitions

This analysis was performed in the Athens Stroke Registry, which includes all consecutive patients with acute first-ever ischemic stroke admitted in Alexandra University Hospital, Athens, Greece, between June 1992 and December 2012 [8]. Patients with transient ischemic attack or recurrent stroke were not included in this registry. The scientific use of the data collected in the Athens Stroke Registry was approved by the local Ethics Committee. Detailed data were prospectively recorded including demographics, medical history and associated cardiovascular risk factors, laboratory findings on admission, medication at admission and at discharge, and in-hospital treatment.

Among the included patients, paroxysmal or permanent atrial fibrillation (AF) was diagnosed by admission and repeated standard 12-lead ECGs, continuous ECG monitoring for 1 week or until discharge for patients treated in the acute stroke unit and 24 h Holter ambulatory ECG monitoring during hospitalization.

2.2. Adherence to the integrated stroke pathway

For the purposes of the analysis, we defined the ABC_{stroke} pathway according to the position paper of the ESC on the integrated care for the management of stroke [6]. In the present analysis we used all associated available data from the Athens Stroke Registry as follows:

- **"A" Criterion:** Appropriate Antithrombotic therapy. Stroke patients were considered adherent to the "A" criterion if they have been prescribed the appropriate antithrombotic treatment after stroke at discharge. Thus, patients with AF or prosthetic valve were adherent to "A" if they have been prescribed at baseline with OAC according to the baseline thromboembolic risk, whereas stroke patients without AF or any other reason for anticoagulation, were adherent if they have been prescribed with antiplatelet therapy. All other patients were considered non-adherent.
- **"B" Criterion:** Better functional and psychological status. To be adherent with the "B" criterion, all stroke patients with any deficit at discharge, defined based on the modified Rankin Scale (mRS) $\geq$1, should have been prescribed with any kind of physiotherapy, speech therapy or ergotherapy.
- **"C" criterion:** Cardiovascular risk factors and Comorbidity optimization. For the "C" criterion in stroke patients we considered the use of statin, treatment of hypertension and diabetes mellitus and whether they were treated with revascularization of the ipsilateral to stroke carotid was identified with stenosis $\geq$70 %.

2.3. Outcomes and follow-up

The outcomes of this analysis were stroke recurrence, a composite outcome of major adverse cardiovascular events (MACE) comprising of recurrent stroke, myocardial infarction, aortic aneurysm rupture or sudden cardiac death, all-cause mortality and major bleeding comprised by intracranial, intestinal and other major bleeding. Patients were prospectively followed-up at 1, 3, and 6 months after discharge and yearly thereafter up to 10 years. Follow-up was routinely performed in the outpatient clinic. In case of patients with severe handicap who had difficulty in visiting the outpatient clinic, follow-up was assessed by telephone interview or at patient's residence.

All patients in the Athens Stroke registry who were discharged from the hospital after the index stroke were divided according to the number of ABC_{stroke} pathway criteria which they fulfilled, from 0 (none) to 3 (full adherence). Additionally, we compared full adherence vs. non-adherence to ABC_{stroke} pathway and the association of each ABC_{stroke} pathway criterion adherence with each of the outcomes.

2.4. Statistical analysis

Continuous variables are presented as mean value ($\pm$ standard deviation, SD) or median (Inter quartile range, IQR) and categorical covariates as absolute numbers and proportion (%). For patients lost during follow-up, survival data were censored at the last time known to be alive. Patients who experienced more than one MACE were censored at the time of the first event. Student's t-test was applied for continuous variables; chi-square or Fisher's exact test was applied for categorical variables. Logistic regression analysis was performed to evaluate the effect of sex or stroke severity in adherence to ABC_{stroke}. Multivariable Cox- regression analyses were performed to evaluate the effect of adherence to the ABC_{stroke} pathway on the risk of each outcome, after adjustment for age (linear variable), sex, major comorbidities (hypertension, diabetes mellitus, CHF, CAD, PAD, prior stroke) and stroke severity reported based on the NIHSS on admission. Results were reported as Odds Ratio (OR) or Hazard Ratio (HR) and 95 % Confidence Intervals (CI). Additionally, to investigate the effect of each criterion in the outcomes of interest we performed a multivariable analysis including each criterion as different variable. The Kaplan–Meier product limit was used to estimate the cumulative hazard of each outcome according to adherence with the ABC_{stroke} pathway and survival distributions were compared using Log–Rank test. Statistical analyses were performed with the StataCorp. 2015. *Stata Statistical Software: Release 14*. College Station, TX: StataCorp LP.

3. Results

From the original study cohort of 3304 hospitalized acute stroke patients, 2513 patients had ischemic stroke and discharged from the hospital (Fig. 1). The cohort population had a median (IQR) age of 71 (62–78) years and consisted of 949 (37.7 %) women with median follow-up period of 30 (6–75) months. AF was reported in 842 (33.5 %) patients. History of paroxysmal or permanent AF was reported in 254 (10.1 %) whereas 588 (23.4 %) were diagnosed with AF after the ischemic stroke. Among them, 63 were diagnosed on admission, 128 during hospitalization (60 with monitor, 39 with ECG and 29 with in hospital Holter) and 65 after discharge (42 on follow-up visit ECG, 13 with Holter and 10 on stroke recurrence).

Among the included patients, 192 (7.6 %) did not adhere to any of the therapeutic pillars of ABC_{stroke}, while 956 (38 %) and 1209 (48.1 %) patients had partial adherence to one or two characteristics of the integrated care stroke pathway. Full adherence to the ABC_{stroke} pathway was identified in 156 (6.2 %) patients, which was not influenced by sex

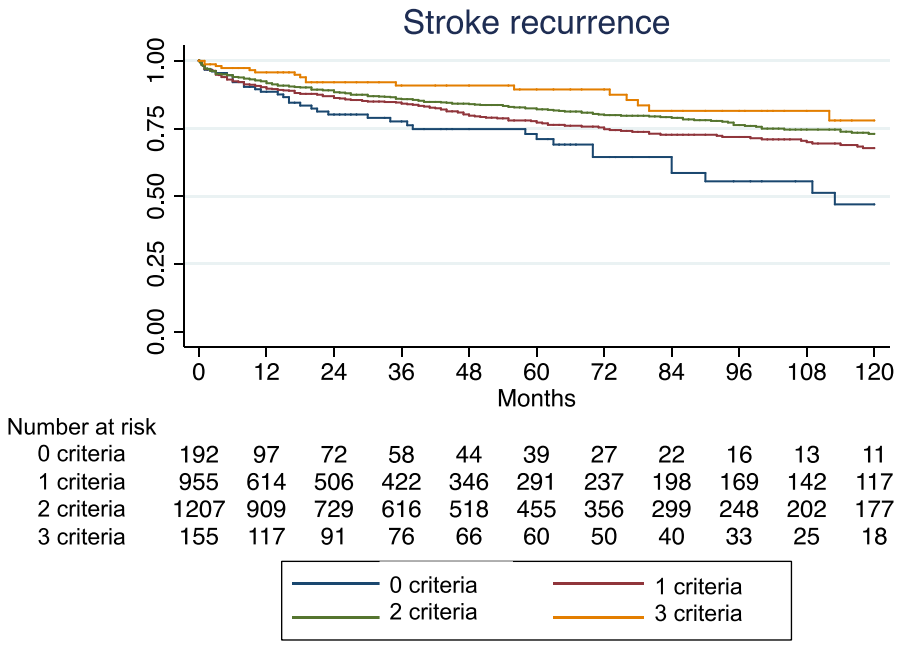

Fig. 1. Stroke recurrence in relation to adherence of with components of the ABC_{stroke} pathway.

Table 1
Baseline characteristics based on the adherence on the ABC integrated care pathway.

ABC criteria adherence Patients: 2513	0 192	1 956	2 1209	3 156	*p*
Year of admission, median (IQR)	2002 (1994–2007)	2000 (1995–2007)	2002 (1997–2007)	2008 (2006–2010)	<0,001
Female, *n*(%)	96 (50)	361 (37.8)	435 (36)	56 (35.9)	0.003
Age, median (IQR)	75 (67–83)	72 (63–80)	70 (62–77)	68 (59–75)	<0.001
NIHSS, median (IQR)	5 (2–21)	4 (2–10)	6 (3–14)	6 (2–13)	<0.001
Obesity, *n*(%)	50 (26.2)	289 (30.3)	473 (39.2)	100 (64.1)	<0.001
Hypertension, *n*(%)	131 (68.2)	682 (71.3)	892 (73.8)	133 (85.3)	0.001
Atrial fibrillation, *n*(%)	138 (71.9)	372 (38.9)	298 (24.7)	34 (21.8)	<0.001
Diagnosed on admission	17 (8.9)	24 (2.5)	18 (1.5)	4 (2.6)	<0.001
Diagnosed during hospitalization	22 (11.5)	63 (7)	38 (3.1)	5 (3.2)	
Diagnosed on follow-up	12 (6.3)	32 (3.4)	19 (1.6)	2 (1.3)	
Known atrial fibrillation	87 (45.3)	253 (26.5)	223 (18.4)	23 (14.7)	
OACs prior to stroke, *n*(%)	10 (5.2)	55 (5.8)	78 (6.5)	16 (10.3)	0.169
AF treated with OACs prior to stroke	7 (3.7)	45 (4.7)	69 (5.7)	13 (8.3)	<0.001
Antiplatelet prior to stroke, *n*(%)	33 (17.2)	182 (19)	196 (16.2)	32 (20.5)	0.273
Diabetes Mellitus, *n*(%)	43 (22.4)	268 (28)	339 (28)	20 (12.8)	<0.001
Hyperlipidemia, *n*(%)	50 (26)	292 (30.5)	469 (38.8)	101 (64.7)	<0.001
Coronary artery disease, *n*(%)	28 (14.6)	200 (20.9)	228 (18.9)	34 (21.8)	0.170
Peripheral artery disease, *n*(%)	6 (3.1)	41 (4.3)	62 (5.1)	4 (2.6)	0.332
Prior stroke, *n*(%)	13 (6.8)	54 (5.6)	73 (6)	15 (9.6)	0.283
Heart failure, *n*(%)	20 (10.4)	73 (7.6)	78 (6.5)	7 (4.5)	0.111
Prosthetic valve, *n*(%)	4 (2.1)	9 (0.9)	26 (2.2)	1 (0.6)	0.103
Smoking, *n*(%)	47 (25.5)	307 (32.1)	408 (33.8)	63 (40.4)	<0.001
Alcohol, *n*(%)	7 (3.7)	78 (8.2)	95 (7.9)	20 (12.8)	0.019
Treatment at discharge					
Antiplatelet at discharge, *n*(%)	91 (4.9)	703 (73.5)	952 (78.7)	125 (80.1)	<0.001
Anticoagulation at discharge, *n*(%)	18 (9.4)	160 (16.7)	343 (28.4)	41 (26.3)	<0.001
Antihypertensive at discharge, *n*(%)	68 (6.1)	395 (41.3)	520 (43)	133 (85.3)	<0.001
Antidiabetic at discharge, *n*(%)	5 (2.6)	38 (4)	67 (5.5)	20 (12.8)	<0.001
Statin at discharge, *n*(%)	8 (4.2)	100 (10.5)	240 (19.9)	156 (100)	<0.001
Endarterectomy, *n*(%)	2 (1)	17 (1.78)	26 (2.15)	3 (1.9)	0.745
Diuretics at discharge, *n*(%)	38 (19.8)	197 (20.6)	225 (18.6)	62 (39.7)	<0.001
Beta-blockers at discharge, *n*(%)	10 (5.2)	82 (8.6)	125 (10.3)	40 (25.6)	<0.001
ACE/ARB at discharge, *n*(%)	38 (19.8)	298 (24.9)	354 (29.3)	113 (72.4)	<0.001
Physiotherapy, *n*(%)	0	347 (36.3)	929 (76.8)	112 (71.8)	<0.001
MRS at discharge, median (IQR)	1 (1–5)	1 (1–4)	3 (1–4)	3 (0–4)	<0.001
MRS at 3 months, median (IQR)	1 (1–5)	1 (1–3)	2 (1–3)	1 (0–3)	<0.001

IQR, interquartile range; NIHSS, national institute of health stroke scale; OACs, anticoagulants; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blockers; MRS, modified rankin scale.

(OR: 1.08, 95 % CI 0.78–1.52) and stroke severity based on NIHSS or mRS at discharge (OR: 1.01, 95 % CI: 0.98-1.02 and OR:0.97, 95 %CI: 0.88–1.06, respectively). Baseline characteristics and therapeutic interventions are summarized in Table 1

3.1. Stroke recurrence

During the follow-up period, there were 431 (17.5 %) stroke recurrences. Among 156 patients with full adherence to the ABC_{stroke} pathway, 18 (11.5 %) experienced a recurrent ischemic stroke and full adherence to the ABC_{stroke} pathway was associated with significantly lower risk of stroke recurrence compared to partial or no adherence (HR: 0.58; 0.36–0.94).

Compared to patients with no adherence to any of the criteria of the ABC_{stroke} pathway, patients who fulfilled 1, 2 or 3 out of 3 criteria, had lower risk of stroke recurrence during follow-up (HR:0.68; 95 % CI:0.48–0.97 and 0.56; 95 %CI:0.39–0.79 and HR: 0.37; 95 %CI: 0.20–0.65, respectively; log-rank test <0.001) (Fig. 1). On the multivariable analysis, full adherence to ABC_{stroke} pathway was associated with significant reduction of stroke recurrence, compared to patients with no or partial adherence (aHR: 0.61; 95 %CI: 0.37–0.99) (Table 2).

Adherence to A criterion was associated with significant reduction on the risk of stroke recurrence (HR:0.65; 95 %CI:0.53-0.82), whereas adherence to B and C criteria was not (HR:0.99;95 %CI:0.79–1.21 and HR:0.76, 95 %CI:0.53–1.07, respectively) (Fig. 2).

3.2. Major cardiovascular events

During the follow-up period, there were 659 (26.2 %) MACE. Among 156 patients with full adherence to the ABC_{stroke} pathway, 26 (16.7 %) experienced a new MACE and full adherence to the ABC_{stroke} pathway was associated with significantly lower risk of MACE compared to partial or no adherence (HR: 0.55; 0.37–0.81). Compared to patients with no adherence to any of the criteria of the integrated stroke pathway, patients who fulfilled 1, 2 or 3 out of 3 criteria, had lower risk of MACE recurrence during follow-up (HR:0.74; 95 %CI:0.55–0.99 and 0.63; 95 %CI:0.48–0.85 and HR: 0.38; 95 %CI: 0.23–0.61, respectively; log-rank test <0.001) (Fig. 3).

On multivariable analysis full adherence to ABC_{stroke} pathway was associated with significant reduction of MACE recurrence, compared to patients with no or partial adherence (aHR: 0.58; 95 %CI: 0.39–0.86) (Table 2). Adherence to A and C criteria were associated with significant reduction on the risk of future MACE (HR:0.74; 95 %CI:0.61–0.88 and HR: 0.70;95 %CI:0.52–0.94, respectively), while adherent to B criterion was not (HR:0.93;95 %CI:0.52–0.94) (Fig. 2)

3.3. Death

During the follow-up period, 877 (34.9 %) patients died. Among 156 patients with full adherence to the ABC_{stroke} pathway, 11 (7.05 %) patients died during follow-up and full adherence to the ABC_{stroke} care pathway was associated with significantly lower risk of death compared to partial or no adherence (HR: 0.18; 0.10–0.34).

Compared to patients with no adherence to any of the criteria of the ABC_{stroke} pathway, patients who fulfilled 1, 2 or 3 out of 3 criteria, had lower risk of death during follow-up (HR:0.59; 95 %CI:0.47–0.74 and 0.42; 95 %CI:0.33–0.53 and HR: 0.10; 95 %CI: 0.05–0.18, respectively; log-rank test <0.001) (Fig. 4). On multivariable analysis, full adherence to ABC_{stroke} pathway was associated with significant reduction of death, compared to patients with no or partial adherence (aHR: 0.23; 95 %CI: 0.12–0.41) (Table 2). Adherence to each of the A, B or C criteria was associated with significant reduction on the risk of death (HR:0.57; 95 % CI:0.49–0.66 and HR: 0.77;95 %CI:0.66–0.91 and HR:0.28;95 % CI:0.18–0.43, respectively) (Fig. 2).

3.4. Major bleeding

During the follow-up period, 69 (2.75 %) patients experience a major bleeding. Among 156 patients with full adherence to the ABC_{stroke} pathway, 7 (4.5 %) patients had a major bleeding during follow-up and full adherence to the ABC_{stroke} care pathway was not associated with lower risk of major bleeding compared to partial or no adherence (HR: 1.67; 95 %CI 0.75–3.67).

4. Discussion

In this study, our principal findings are as follows: (i) full adherence to the ABC_{stroke} pathway was evident in only 6.2 % of our ischaemic stroke cohort; and (ii) full adherence with the ABC_{stroke} integrated care pathway was independently associated with lower risks of stroke recurrence, major cardiovascular events and mortality. Partial adherence provided some improvement, but full adherence was associated with the best outcomes. This illustrates the potential for optimization of management of post-stroke patients to save lives, reduce cardiac events and recurrence of strokes.

As far as we are aware, this is the first demonstration that ABC_{stroke} pathway adherence was associated with improved clinical outcomes. Current guidelines on stroke prevention recommend the use of antithrombotic therapy, with oral anticoagulation (OAC) when AF is present, or with antiplatelet drugs in the absence of AF [9,10]. Indeed, the use of an integrated pathway in AF patients is associated with a 64 % reduction in stroke, and a 26 % reduction in all-cause mortality compared to control or placebo [11]. In patient post-stroke, prolonged monitoring is associated with a greater detection of incident AF, although the impact of systematic screening is not established [12].

Post-stroke care also recommended the used of stroke rehabilitation and organized care packages in specialized stroke units, with rehabilitation being associated with improved clinical outcomes from death or dependency when compared to general medical wards [13,14]. Indeed, improved functional (cardiac and post-stroke) and psychological status, including the assessment of post-stroke cognitive and physical impairment, depression, and anxiety as part of routine post-stroke work-up in every person [6].

Cardiovascular risk factors and comorbidities management includes optimizing risk factor management and lifestyle changes. In the general population, healthy lifestyle based on smoking cessation, alcohol reduction and increased physical activity have been associated with a reduction in incident AF, as well as AF-related complications such as MACE, stroke, heart failure, dementia and mortality [15–17]. Vigilance for new onset AF is important, as early rhythm control in patients with

Table 2
Outcomes based on ABC adherence.

	Number of ABC criteria adherence adjHR (95 %CI)				Full- Vs. no or partial adherence
	No (192/7.6 %)	1 (956/38 %)	2 (1209/48.1 %)	3 (156/6.2 %)	156 Vs. 2357
Stroke recurrence	38 (19.8) Ref.	173 (18.1) 0.71 (0.50 1.02)	202 (16.7) 0.62 (0.43 0.88)	18 (11.5) 0.41 (0.23 0.74)	0.61 (0.37 0.99)
MACE	52 (27.1) Ref.	262 (27.4) 0.74 (0.55 0.99)	319 (26.4) 0.65 (0.49 0.88)	26 (16.7) 0.41 (0.25 0.66)	0.59 (0.39 0.88)
Death	101 (52) Ref.	396 (41.4) 0.56 (0.45 0.70)	410 (33.9) 0.33 (0.26 0.42)	11 (7.1) 0.10 (0.05 0.18)	0.22 (0.12 0.41)
Major bleeding	2 (1) Ref.	29 (3) 2.8 (0.54 9.6)	31 (2.6) 1.56 (0.37 6.59)	7 (4.5) 2.97 (0.61 14.46)	1.67 (0.76 3.67)

DOAC, direct oral anticoagulants; VKA, vitamin K antagonists; HR, hazard ratio; CI, confidence intervals; MACE, major adverse cardiovascular events.

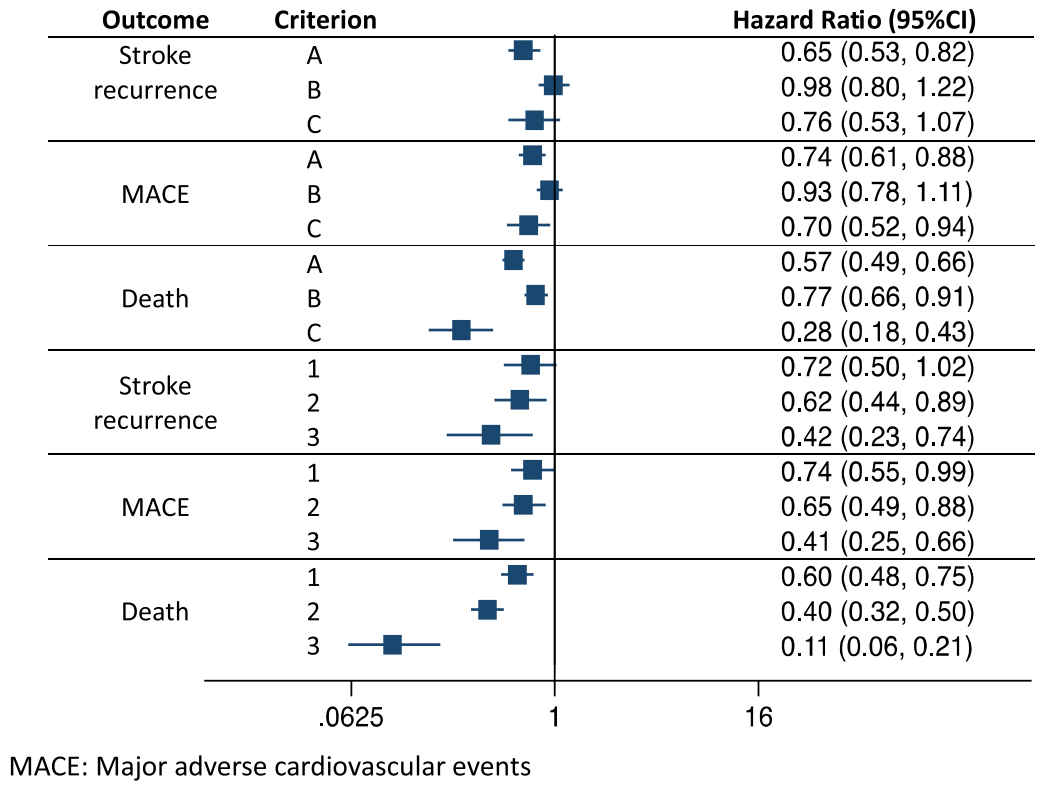

Fig. 2. Adjusted hazard ratios and 95 % Confidence intervals based on each components of the ABC_{stroke} pathway.
MACE: Major adverse cardiovascular events.

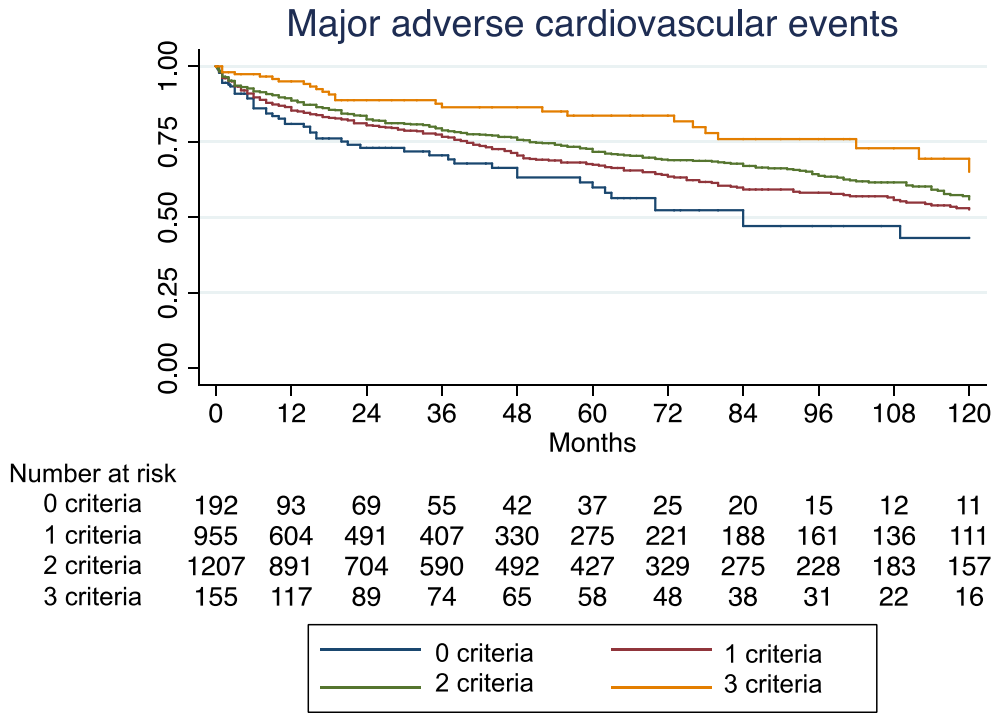

Fig. 3. Major cardiovascular events in relation to adherence of with components of the ABC_{stroke} pathway.

incident AF post-stroke has been associated with a lower risk of recurrent stroke [18,19]. In the present study, ischemic stroke patients underwent screening for AF with several modalities especially during hospitalization with continuous monitoring or Holter ECGs which resulted in the identification of a significant proportion of patients with AF. Nevertheless, during the extended study period (2992–2012) guidelines have changed over time, suggesting longer and more robust screening modalities for AF, especially during the later years. Adherence to integrated care management in AF patients leads to a lower risk of incident dementia (a common sequelae post-stroke), whether vascular

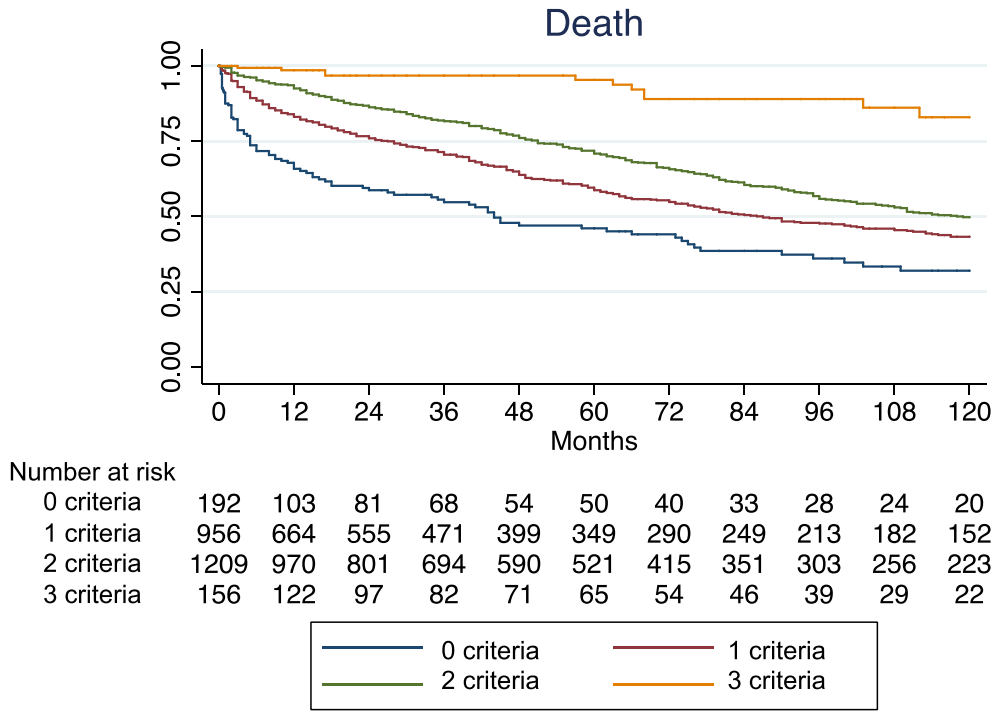

Fig. 4. Death in relation to adherence with components of the ABC_{stroke} pathway.

dementia or Alzheimer's Disease [20]. Greater patient and family/-caregiver involvement in planning actions and their input and feedback on optimizing stroke care pathways is needed.

Proactive management of comorbidities such as hypertension or diabetes leads to a lower risk of incident stroke and dementia. Especially hyperlipidemia treatment with the use of statin among ischemic stroke patients is associated with significantly lower risk of stroke or cardiovascular outcomes [21]. Despite the clear benefit of statin treatment in ischemic stroke patients, in a recent real-world study including 59,588 stroke patients, almost 27 % were not treated with statins within 3 months after ischemic stroke [22]. Of note, in the present study, only a small proportion of stroke patients was treated optimally based on the current guidelines, which was driven by the low proportion of patients treated with statins at discharge., in a period in which a) statin treatment was not established in secondary stroke prevention, and b) the LDL-cholesterol treatment goals were much higher than today [23,24]. The beneficial role of statins in secondary prevention of non-cardioembolic strokes was established in 2006 by the SPARCL randomized trial [25]. Nevertheless, still there are no data from randomized trials suggesting the universal use of statins in secondary stroke prevention among patients with AF or ESUS and the beneficial role of statins is extrapolated by cardiovascular prevention trials or is based on observational studies. Thus, the low proportion of "optimally" treated patients, does not reflect the physicians' low adherence to guidelines [26], but rather the evolution in the related evidence-based secondary stroke and cardiovascular prevention, especially due to the extended use of statins.

As clearly shown in the present study, the best outcomes are evident with full adherence to the ABC_{stroke} pathway. Indeed, our previous data show that more than 20 % developed a manifestation of SHS within 4 weeks of incident ischaemic stroke, leading to a higher 5-year all-cause mortality and recurrent stroke [5]. Although overall, the risk for 5-year mortality, recurrent stroke, and acute myocardial infarction were similar for females and males, the risk tended to be higher for those with certain modifiable risk factors (i.e., hypertension, type 2 diabetes mellitus, and high LDL cholesterol) [27]. Hence, proactive clinical assessments and review, as well as improved risk stratification and implementation of the ABC_{stroke} pathway in such patients would mitigate such risks of mortality and MACE in post-stroke patients, often referred to as the 'stroke-heart syndrome'.

However, there is no established risk prediction tool for SHS in clinical practice, and accurate risk prediction has challenges. In a prospective U.S. population of 3,435,224 patients with/without AF, and common clinical risk assessments only had moderate predictive value, while machine learning (ML) models accounting for the dynamic nature of changing multimorbidity risk factors yielded the highest discriminant validity values showing how AI can account for dynamic changes in risk and improve risk prediction [28].

Guideline adherent care translates to better clinical outcomes. In patients with AF, a holistic integrated care approach to AF management based on the Atrial fibrillation Better Care pathway has been associated with improved clinical outcomes, whether from retrospective or prospective cohorts or post hoc analyses of clinical trial data, as well as one prospective cluster randomised trial [29,30]. The data remained consistent irrespective of country where the study was based. This has led to its recommendations in guidelines from USA, Europe and Asia-Pacific [9,31,32]. The principles of such holistic integrated care can be extended to various chronic long-term conditions [33,34]. In the case of stroke, the high risk of post-stroke cardiovascular complications has led to the ESC Council on Stroke position paper recommendations of a broader post-stroke ABC_{stroke} pathway to reduce the risk of cardiovascular complications post-stroke [6]. We now show for the first time that full adherence to such an approach translates to improved clinical outcomes, albeit in a post-hoc analysis of a modest sized ischaemic stroke registry.

4.1. Limitations

This study is limited by its retrospective post-hoc analysis of a single-center prospective observational hospital-based registry with some potential selection bias and confounding by indication. Adherence to ABC pathway was based on the treatment of the patients at discharge, thus we did not take in account several changes that may have happened during follow-up and potentially influenced the results of our study.

Echocardiography was not applied universally to all patients, so underlying associated heart failure could not be ascertained. Treatment choices were based on the decision of the managing physician taking into account patients' comorbidities and stroke severity.

A potential limitation of the present study is the very low prevalence of patients who were optimally managed after ischemic stroke based on the current guidelines, representing only 6.2 % of the included patients. Although this raises serious concerns on the reflection of the study in the current era, since it was based on patients' data recorded from 1992 to 2012, it simultaneously provides us the ability to compare long term outcomes of patients who, based on current guidelines, were not optimally treated compared to those treated based on current guidelines. Similarly, an important proportion of patients with AF was not treated with anticoagulation at discharge. Unfortunately, there were no data on the specific reason for the use of the antithrombotic at discharge and whether there was a contraindication for the use of anticoagulation. Detailed rhythm monitoring was not universally documented, and we did not have data on the exact screening duration for AF, which may have affected the results of our study. Also, we did not perform systematic screening for AF on follow-up, and compliance and adherence to treatment after discharge may have affected the outcomes of the study.

5. Conclusion

Full adherence to the ABC_{stroke} pathway was evident in only 6.2 % of our ischaemic stroke cohort, but was independently associated with lower risks of stroke recurrence, major cardiovascular events and mortality. This highlights a potential opportunity to improve clinical outcomes post-stroke with a holistic or integrated care management approach.

References

[1] Ntaios G, Papavasileiou V, Makaritsis K, Milionis H, Michel P, Vemmos K. Association of ischaemic stroke subtype with long-term cardiovascular events. Eur J Neurol Off J Eur Fed Neurol Soc 2014;21:1108–14.

[2] Rutten-Jacobs LC, Arntz RM, Maaijwee NA, Schoonderwaldt HC, Dorresteijn LD, van Dijk EJ, et al. Long-term mortality after stroke among adults aged 18 to 50 years. JAMA J Am Med Assoc 2013;309:1136–44.

[3] Scheitz JF, Sposato LA, Schulz-Menger J, Nolte CH, Backs J, Endres M. Stroke-heart syndrome: recent advances and challenges. J Am Heart Assoc 2022;11:e026528.

[4] Scheitz JF, Nolte CH, Doehner W, Hachinski V, Endres M. Stroke-heart syndrome: clinical presentation and underlying mechanisms. Lancet Neurol 2018;17:1109–20.

[5] Buckley BJR, Harrison SL, Hill A, Underhill P, Lane DA, Lip GYH. Stroke-heart syndrome: incidence and clinical outcomes of cardiac complications following stroke. Stroke J Cereb Circ 2022;53:1759–63.

[6] Lip GYH, Lane DA, Lenarczyk R, Boriani G, Doehner W, Benjamin LA, et al. Integrated care for optimizing the management of stroke and associated heart disease: a position paper of the European society of cardiology council on stroke. Eur Heart J 2022;43:2442–60.

[7] Lip GYH, Ntaios G. Novel clinical concepts in thrombosis": integrated care for stroke management-easy as abc. Thromb Haemost 2022;122:316–9.

[8] Vemmos KN, Takis CE, Georgilis K, Zakopoulos NA, Lekakis JP, Papamichael CM, et al. The Athens Stroke Registry: results of a five-year hospital-based study. Cerebrovasc Dis 2000;10:133–41 (Basel, Switzerland).

[9] Chao TF, Joung B, Takahashi Y, Lim TW, Choi EK, Chan YH, et al. 2021 focused update consensus guidelines of the Asia pacific heart rhythm society on stroke prevention in atrial fibrillation: executive summary. Thromb Haemost 2022;122:20–47.

[10] NICE. National institute for health and care excellence. Stroke rehabilitation in adults. Clinical guideline [cg162]published: 12 June 2013. 2022:https://www.nice.org.uk/guidance/cg162.

[11] Hart RG, Pearce LA, Aguilar MI. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med 2007;146:857–67.

[12] Kalarus Z, Mairesse GH, Sokal A, Boriani G, Sredniawa B, Arroyo RC, et al. Searching for atrial fibrillation: looking harder, looking longer, and in increasingly sophisticated ways. An ehra position paper'. Europace 2022;25:185–98.

[13] Langhorne P, Ramachandra S, Stroke Unit Trialists C. Organized inpatient (stroke unit) care for stroke: network meta-analysis. Stroke J Cereb Circ 2020;51:e349–50.

[14] Pollock A, Farmer SE, Brady MC, Langhorne P, Mead GE, Mehrholz J, et al. Interventions for improving upper limb function after stroke. Cochrane Database of Syst Rev 2014;2014:Cd010820.

[15] Lee SR, Choi EK, Ahn HJ, Han KD, Oh S, Lip GYH. Association between clustering of unhealthy lifestyle factors and risk of new-onset atrial fibrillation: a nationwide population-based study. Sci Rep 2020;10:19224.

[16] Lee SR, Choi EK, Park SH, Lee SW, Han KD, Oh S, et al. Clustering of unhealthy lifestyle and the risk of adverse events in patients with atrial fibrillation. Front Cardiovasc Med 2022;9:885016.

[17] Park SH, Lee SR, Choi EK, Lee H, Chung J, Choi J, et al. Low risk of dementia in patients with newly diagnosed atrial fibrillation and a clustering of healthy lifestyle behaviors: a nationwide population-based cohort study. J Am Heart Assoc 2022;11:e023739.

[18] Lee SR, Choi EK, Lee SW, Han KD, Oh S, Lip GYH. Early rhythm control in patients with incident atrial fibrillation who had a prior stroke. JACC Clin Electrophysiol 2023;9:1121–33.

[19] Sagris D, Korompoki E, Ntaios G, Tzeis S, Manios E, Kanakakis J, et al. Sinus rhythm restoration and improved outcomes in patients with acute ischemic stroke and in-hospital paroxysmal atrial fibrillation. Eur Stroke J 2022;7:421–30.

[20] Yang PS, Sung JH, Jang E, Yu HT, Kim TH, Uhm JS, et al. The effect of integrated care management on dementia in atrial fibrillation. J Clin Med 2020;9:1696.

[21] Sagris D, Ntaios G, Milionis H. Beyond antithrombotics: Recent advances in pharmacological risk factor management for secondary stroke prevention. J Neurol Neurosurg Psychiatry 2023:jnnp-2022-329149.

[22] Åivo J, Ruuskanen JO, Tornio A, Rautava P, Kytö V. Lack of statin therapy and outcomes after ischemic stroke: a population-based study. Stroke 2023;54:781–90.

[23] Sagris D, Ntaios G, Georgiopoulos G, Kakaletsis N, Elisaf M, Katsiki N, et al. Recommendations for lipid modification in patients with ischemic stroke or transient ischemic attack: a clinical guide by the hellenic stroke organization and the hellenic atherosclerosis society. Int J Stroke 2021;16:738–50.

[24] Mach F, Baigent C, Catapano AL, Koskinas KC, Casula M, Badimon L, et al. 2019 ESC/EAS guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J 2020;41:111–88.

[25] High-dose atorvastatin after stroke or transient ischemic attack. N Engl J Med 2006;355:549–59.

[26] Dawson J, Béjot Y, Christensen LM, De Marchis GM, Dichgans M, Hagberg G, et al. European Stroke Organisation (ESO) guideline on pharmacological interventions for long-term secondary prevention after ischaemic stroke or transient ischaemic attack. Eur Stroke J 2022;7. I–II.

[27] Buckley BJR, Harrison SL, Lane DA, Hill A, Lip GYH. Stroke–heart syndrome: mechanisms, risk factors, and adverse cardiovascular events. Eur J Prev Cardiol 2023.

[28] Lip GYH, Genaidy A, Tran G, Marroquin P, Estes C, Sloop S. Improving stroke risk prediction in the general population: a comparative assessment of common clinical rules, a new multimorbid index, and machine-learning-based algorithms. Thromb Haemost 2022;122:142–50.

[29] Romiti GF, Pastori D, Rivera-Caravaca JM, Ding WY, Gue YX, Menichelli D, et al. Adherence to the 'atrial fibrillation better care' pathway in patients with atrial fibrillation: Impact on clinical outcomes-a systematic review and meta-analysis of 285,000 patients. Thromb Haemost 2022;122:406–14.

[30] Romiti GF, Guo Y, Corica B, Proietti M, Zhang H, Lip GYH, et al. Mobile health-technology-integrated care for atrial fibrillation: a win ratio analysis from the MAFA-II randomized clinical trial. Thromb Haemost 2023;123:1042–8.

[31] Hindricks G, Potpara T, Dagres N, Arbelo E, Bax JJ, Blomstrom-Lundqvist C, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European association for cardio-thoracic surgery (EACTS): the task force for the diagnosis and management of atrial fibrillation of the European society of cardiology (ESC) developed with the special contribution of the European heart rhythm association (EHRA) of the esc. Eur Heart J 2021;42:373–498.

[32] Lip GYH, Banerjee A, Boriani G, Chiang CE, Fargo R, Freedman B, et al. Antithrombotic therapy for atrial fibrillation: chest guideline and expert panel report. Chest 2018;154:1121–201.

[33] Field M, Kuduvalli M, Torella F, McKay V, Khalatbari A, Lip GYH. Integrated care systems and the aortovascular hub. Thromb Haemost 2022;122:177–80.

[34] Buckley BJR, Lip GYH. Current concepts: comprehensive "cardiovascular health" rehabilitation-an integrated approach to improve secondary prevention and rehabilitation of cardiovascular diseases. Thromb Haemost 2022;122:1966–8.