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SURF (stroke with underlying risk of atrial fibrillation): Proposals for a definition

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ABSTRACT

Objectives: Diagnosis of occult atrial fibrillation (AF) in stroke patients remains challenging. Several scores predictive of occult AF in stroke patients have been proposed, all based on the positive predictive value of clinical, biological, and radiological parameters, but they failed to modify the management of AF detection after stroke. The aim of this study was to identify a group of **S**troke patients with **U**nderlying **R**isk of Atrial **F**ibrillation (SURF) excluding stroke patients with low risk of AF.

Patients and methods: We enrolled consecutive AF-naive stroke patients without indication of long-term anticoagulation. AF was adjudicated after prolonged Holter ECG and 2 years of follow-up. The negative predictive value (NPV) was determined for each relevant parameter in the acute phase. Firstly, clinico-radiological parameters with NPV > 95% defined the initial exclusion criteria of SURF. Secondly, the ultimate exclusion criterion of SURF was defined by a composite criterion constructed using the beta-coefficient of independent predictive parameters of AF determined by logistic regression.

Results: Among 773 AF-naïve patients without indication of anticoagulation, 111(14.4%) AFs were found. Initial SURF exclusion criteria, determined by NPV ≥ 95%, are: symptomatic atherosclerotic stenosis ≥50%, symptomatic arterial dissection or lacunar stroke. The SURF definition was completed by a composite exclusion criterion [Age*10 + BNP < = 700] (NPV: 96.8%[92.6–98.9]). In the SURF group, 93/195(47.7%) AFs were diagnosed.

Conclusions: In the SURF group, nearly half of the stroke patients had AF. The criteria used to define such a group are easily obtained in all stroke units, in the acute phase. SURF is a new concept proposal, which aims to improve the effectiveness of AF diagnosis after stroke.

1. Introduction

Atrial fibrillation-naïve stroke patients without clear indication of anticoagulation are treated with antiplatelet agents. However, diagnosis of occult atrial fibrillation in this group remains challenging. It is now recognized that some cardiac investigation strategies increase the atrial fibrillation diagnosis rate [1–5]. However, an extensive cardiac work-up, including prolonged Holter monitoring or implanted devices cannot be offered to every patient, particularly in settings with limited resources [6]. Indeed, there is a need to identify a sub-group of patients at higher risk of AF, who are most likely to benefit from extensive cardiac work-up and/or anticoagulation. Determining a specific pattern could help to better address the most appropriate instrumental work-up required for selected stroke patients and consequently to improve secondary prevention.

The aim of this study was to identify criteria to define stroke patients with underlying risk of paroxysmal atrial fibrillation (SURF group). Until now, the main strategy to identify stroke patients with a high risk of paroxysmal AF was based on AF predictive parameters [7–16] or scores [17–20]. However, these scores have been proven insufficient when applied to cryptogenic strokes [7,21,22]. To avoid this problem, another pertinent method to identify patients at high risk of delayed AF relies on the exclusion of patients at lower risk to develop AF in the stroke patient group. In this study, we opted for this innovative method in which the SURF definition is based only on AF exclusion criteria.

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2. Patients and methods

2.1. Patient selection

In this study, we enrolled AF-naive stroke patients without indication of long-term anticoagulation treatment who were included in TARGET-AFIII cohort. TARGET-AFIII is a prospective cohort of 1038 patients with consecutive ischemic strokes, hospitalized in acute phase at the stroke unit of Nice (France) between November 2010 and November 2013. Eligibility criteria for the TARGET-AF III cohort were ischemic strokes confirmed by CT or MRI imaging. Exclusion criteria were defined as stroke patients with undetermined etiology due to incomplete evaluation (TOAST classification; [23]), and patients where the prolonged Holter ECG duration was inferior to 3 days. Exhaustive data were collected according to the standard definition including the following parameters: demographic data, medical history, vascular risk factors, clinical stroke characteristics, AF detection, biology at admission, extra and intra-cranial vascular data (CT scan and/or echo-Doppler) and cardiologic transthoracic echocardiography. The research was conducted according to the principles of the Declaration of Helsinki. Ethics approval was obtained from the local institutional review board. The board waived the need for specific patient consent for this non-interventional study.

2.2. Method of AF detection

Prolonged Holter ECG monitoring was started immediately upon admission, performed throughout the stay at the stroke unit, and stopped at discharge. Prolonged Holter ECG monitoring was performed for a minimum of 3 consecutive days. An ECG recording system (5 electrodes) was connected to the central station: Siemens SC6002XL bedside monitors for the intensive care stroke unit and Infinity M300 telemetry for the conventional stroke unit. We used an Infinity Central Station (Drager Medical, Lubeck, Germany) to collect all ECG data. Using a Holter viewer (VF8 software installed on the Infinity Central Station), Holter ECG data were analyzed daily on a 2-lead ECG for each inpatient by neurologists and cardiologists of the stroke unit. Presence of AF (or atrial flutter) was defined by convention as at least one period lasting more than 30 s according to the guidelines of the European Society of Cardiology [24]. Timing and duration of the prolonged Holter ECG were collected. Patients included in TARGET-AF III cohort were followed over the next 2 years by phone interview with AF status requests. Modalities of AF detection after discharge were not collected. AF diagnosis was adjudicated at the termination of this follow-up.

2.3. SURF criteria definition strategy

SURF's construction strategy was based on the principle of excluding stroke patients at low risk of AF using all of the assessed variables. The initial study population was defined by AF-naïve patients without indication of long-term anticoagulation, who were included in the TARGET-AF III cohort. The ability to predict the paroxysmal AF for each variable was determined by calculating the negative predictive value (NPV). SURF exclusion criteria were adjudicated using variables with negative predictive value (NPV) $\geq$ 95%. Determination of SURF exclusion criteria was stratified in two steps: Firstly, we only studied the clinico-radiological stroke characteristics that were available upon patient admission and used these to establish the first exclusion criteria to define SURF. Secondly, we applied previously determined exclusion criteria to our initial population. In the remaining population, independent predictive parameters of paroxysmal AF were identified by backward stepwise logistic regression. The ultimate SURF exclusion criterion was a composite score generated by using the β coefficient of the logistic regression equation. Cutoff was determined with an NPV $\geq$ 95%.

2.4. Statistical analyses and validation

Statistical analyses were conducted using the statistical package STATA SE 10.0. To determine the statistically significant differences between clinical and paraclinical variables according to AF status, a univariate analysis was carried out using the Chi-Square test to compare discontinuous variables and the Mann-Whitney U test or Student's *t*-test to compare continuous variables. Nonparametric continuous variables are represented by medians and interquartile ranges and medians and SD for parametric variables. Categorical variables are stated by absolute numbers (%). $P < 0.05$ was considered significant.

Discriminant predictive values of SURF were calculated (PPV, NPV, area under receiver operating characteristic curve). External validation of SURF was confirmed in a previous similar cohort (TARGET-AF, n = 373) and considered as a validation dataset. The SURF criteria were applied to this cohort of 373 stroke consecutive patients whose characteristics have been previously published [9]. Discriminant predictive values of SURF in this validation dataset were calculated and compared to the original study.

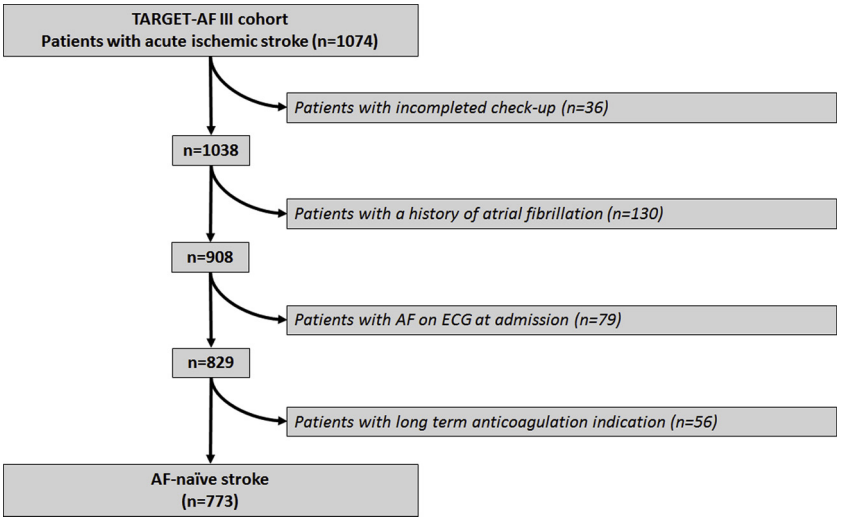

Fig. 1. Flow chart showing patient selection in TARGET-AFIII cohort.

Table 1
Baseline characteristics.

		All ischemic stroke (IS)	IS without AF	IS with AF	*p*
		n = 773	n = 662 (85.64%)	n = 111 (14.36%)	
Demographics					
	Age (years)	65 [53-75]	63 [50-73]	76 [71-81.5]	< 0.001
	Male sex	480 (62.10%)	438 (66.16%)	42 (37.84%)	< 0.001
Comorbidities – risk factors					
	Hypertension	365 (47.22%)	298 (45.02%)	67 (60.36%)	0.003
	Diabetes mellitus	127 (16.43%)	115 (17.37%)	12 (10.81%)	0.084
	Dyslipidemia	269 (34.80%)	220 (33.23%)	49 (44.14%)	0.026
	Obesity	49 (6.34%)	43 (6.50%)	6 (5.41%)	0.663
	Coronary heart disease	78 (10.09%)	64 (9.67%)	14 (12.61%)	0.340
	Heart failure	6 (0.78%)	3 (0.45%)	3 (2.70%)	0.012
	Ischemic stroke (or TIA)	114 (14.75%)	93 (14.05%)	21 (18.92%)	0.180
	Peripheral artery disease	29 (3.75%)	27 (4.08%)	2 (1.80%)	0.243
Stroke characteristics					
	NIHSS score	4 [1–11]	3 [1–10]	10 [3-18.5]	< 0.001
	Anterior circulation stroke	555 (71.80%)	465 (70.24%)	90 (81.08%)	0.019
	Posterior circulation stroke	196 (25.36%)	182 (27.49%)	14 (12.61%)	< 0.001
	Anterior and posterior circulation stroke	22 (2.85%)	15 (2.27%)	7 (6.31%)	0.018
	Lacunar stroke	136 (17.59%)	136 (20.54%)	0 (0.00%)	–
Vascular data					
	Symptomatic atherosclerosis stenosis	247 (31.95%)	234 (35.35%)	13 (11.71%)	< 0.001
	Asymptomatic atherosclerosis stenosis	47 (6.08%)	37 (5.59%)	10 (9.01%)	0.163
	Symptomatic arterial dissection	41 (5.30%)	41 (6.19%)	0 (0.00%)	0.007
New AF detection strategy					
	Time to start Holter ECG (days)	0.70 [0.18-1.81]	0.76 [0.23-1.88]	0.19 [0.10-0.91]	< 0.001
	Duration of Holter ECG (Days)	6.48 [3.99-11.04]	6.08 [3.86-10.60]	8.60 [4.95-12.79]	0.001
	New AF diagnosed on prolonged Holter ECG	106 (13.71%)	0 (0.00%)	106 (95.50%)	< 0.001
	New AF diagnosed in follow-up	5 (0.65%)	0 (0.00%)	5 (4.50%)	< 0.001
Biology at admission					
	Hemoglobin (mmol/l)	8.87 [8.19-9.50]	9.00 [8.31-9.56]	8.32 [7.90-8.94]	< 0.001
	Glycemia (mmol/l)	6.17 [5.38-7.40]	6.14 [5.36-7.40]	6.32 [5.54-7.37]	0.436
	Creatinine clearance (MDRD) (ml/mn/1.73m2)	84.58 [69.34-102.77]	86.85 [72.04-105.76]	72.76 [60.37-85.29]	< 0.001
	HbA1c (%)	5.7 [5.45-6.2]	5.7 [5.4-6.2]	5.8 [5.5-6.1]	0.404
	BNP (pg/ml)	67 [31-153]	56 [28-121.75]	216 [136-295.5]	< 0.001
	HDL-cholesterol (mmol/l)	1.29 [1.04-1.62]	1.27 [1.03-1.58]	1.46 [1.11-1.82]	0.001
	LDL-cholesterol (mmol/l)	3.14 [2.48-3.86]	3.18 [2.52-3.91]	2.84 [2.20-3.61]	0.006
	Triglyceridemia (mmol/l)	1.22 [0.92-1.69]	1.24 [0.95-1.74]	1.05 [0.79-1.44]	< 0.001
	TSH ultrasensitive (mUI/l)	1.31 [0.77-2.04]	1.32 [0.79-2.06]	1.25 [0.62-1.91]	0.049
Trans thoracic echographia					
	Left ventricular hypertrophy	123 (15.91%)	103 (15.56%)	20 (18.02%)	0.512
	Left atrial dilatation	98 (12.68%)	56 (8.46%)	42 (37.84%)	< 0.001

3. Results

3.1. Study population and AF detection

Among 1038 stroke patients, 773 AF-naïve patients had no indication of anticoagulation (Fig. 1). In this group, 111 (14.4%) AFs were found, 100 using Holter ECG (Median [IQR]: 6.48[3.99–11.04] days) and 11 during the 2 follow-up years (Median [IQR]: 2.4[1.7–3.2] years). Characteristics of the study population according to AF status are presented in Table 1.

3.2. SURF exclusion criteria determination

Firstly, according to the methodology, we determined all clinico-radiological parameters and the NPV of AF diagnosed during follow-up for the study population (Table 2). Three parameters obtained an NPV ≥ 95% and were adjudicated as SURF's first exclusion criteria: symptomatic atherosclerotic stenosis ≥50% (95.0 [92.2–97.2]), symptomatic arterial dissection (100.0 [91.3–100.0]) or lacunar stroke (100.0 [97.3–100.0]. Active smoking also obtained an NPV ≥ 95% (95.6 [92.8–97.6]).

Secondly, previously determined exclusion criteria were applied to our initial population. In the remaining population (n = 349), independent predictive parameters of paroxysmal AF were identified by backward stepwise logistic regression ($p < 0.001$). Two parameters were identified: age (by 10 years; OR: 1.89[1.45–2.45]) and baseline BNP value (by 100 pg/ml; 1.86[1.44–2.29]. Using the β coefficient of the logistic regression equation, these two parameters were combined into a composite score: Age (y) × 10 + BNP (pg/ml). The area under the curve was 0.857. At the Youden plot (700), the NPV was 96.8% [92.6–98.9].

3.3. SURF definition proposal and validation

Based on previous results, SURF criteria are outlined in Fig. 2. Discrimination of the model was evaluated by Area Under Receiver Operating Characteristic Curve (AUC: 0.842[0.814 − 0.867]). In the SURF group, about half of the patients presented paroxysmal AF (93/195, PPV: 47.7% [40.5–54.9]) (Fig. 3). The NPV was 96.9% [95.1–98.1]. Predictive values (NPV, PPV) were calculated from a validation dataset by applying SURF defined criteria to the TARGET-AF cohort [9]. Among 373 consecutive ischemic strokes, 300 patients were AF-naïve. AF was found in 52 patients (17.3%) with the same strategy used in this present study. 121 patients had SURF criteria, of which 50 patients had AF (PPV: 41.3% [32.4–50.6]) (Fig. 3). The NPV was 98.9% [96.0–99.8]. AUC in the validation dataset was 0,838 [0,791 − 0,878] and was not statistically different to the AUC calculated in the present study ($p < 0.05$).

4. Discussion

In our study, we have identified a group of stroke patients with

Table 2
AF predictive values of clinico-radiological parameters of stroke patients at admission.

		Youden plot cutoff	Positive predictive value (PPV)	Negative predictive value (NPV)
Demographics				
	Age (years)	> 70	29.7 [24.4-35.4]	94.5 [92.1-96.3]
	Male sex		23.5 [18.8-28.8]	91.3 [88.4-93.6]
Comorbidities – risk factors				
	Hypertension		18.4 [14.5-22.7]	89.2 [85.8-92.1]
	Diabetes mellitus		15.30 [12.6-18.3]	90.6 [84.1-95.0]
	Dyslipidemia		18.2 [13.8-23.4]	87.7 [84.5-90.4]
	Obesity		14.5 [12.0-17.3]	87.8 [75.2-95.3]
	Coronary heart disease		17.9 [17.2-28.3]	86.0 [83.2-88.5]
	Heart failure		50.0 [12.4-87.6]	85.9 [83.3-88.3]
	Ischemic stroke (or TIA)		18.4 [11.8-26.8]	86.3 [83.5-88.9]
	Peripheral artery disease		14.7 [12.2-17.4]	93.1 [76.8-99.0]
Stroke characteristics				
	NIHSS score	> 7	24.2 [19.2-29.7]	91.0 [88.1-93.4]
	Anterior circulation stroke		16.8 [13.8-20.1]	92.9 [88.3-96.0]
	Posterior circulation stroke		16.2 [13.2-19.6]	90.4 [85.7-93.9]
	Anterior and posterior circulation stroke		31.8 [13.9-54.9]	86.2 [83.5-88.5]
	Lacunar stroke		17.4 [14.6-20.6]	100.0 [97.3-100.0]
Vascular data				
	Symptomatic atherosclerosis stenosis		18.6 [15.4-22.2]	95.0 [92.2-97.2]
	Asymptomatic atherosclerosis stenosis		21.3 [10.7-35.7]	86.1 [83.4-88.5]
	Symptomatic arterial dissection		15.2 [12.6-18.0]	100.0 [91.3-100.0]

underlying risk of atrial fibrillation. This SURF group can be defined as AF-naïve stroke patients with the following exclusion criteria: major cardio embolic source, lacunar stroke, symptomatic arterial dissection or symptomatic atherosclerotic stenosis (> 50%) and [Age (y) x 10 + baseline BNP (pg/ml)] < 700. In the group thus defined, the risk of finding a paroxysmal AF is 47%. This risk is very high compared to the risk of 14% observed among the initial 773 AF-naïve stroke patients. Therefore, in the SURF group, to find one AF, only three patients required screening. These results were validated when SURF criteria were applied in a previously published similar cohort (TARGET-AF; 9).

In order to define SURF, we have chosen a strategy based only on the negative predictive value of each parameter. It is quite different from previously published methods using positive predictive values for paroxysmal AF. These clinical, biological, echographic, electrocardiographic and radiological parameters have now been described and have been combined to build predictive scores [7–16,19]. For example, we have suggested a composite score called STAF [18]. However, we learned that these scores revealed themselves to be insufficient when applied to cryptogenic strokes [7,21,22]. In such situations, scores like STAF are neither specific enough nor sufficiently sensitive. Indeed, to be useful in selecting patients for ECG monitoring or anticoagulation, such a score would need to have sensitivity close to 100%. Otherwise, a substantial number of patients at risk of AF would be missed. Combining our experience and data from the literature, we noticed that predictive parameters of AF have a negative predictive value, which is often stronger than their positive predictive value. With SURF, the screening strategy of AF after a stroke is innovative. This method aims to exclude stroke patients at low risk of AF, and thus to increase the diagnosis rate of AF in the stroke patient cohort without altering the sensitivity of the diagnosis.

For the stroke physician, suspicion of paroxysmal AF is often discussed in the case of cryptogenic strokes in particular. It will not have escaped the reader that the clinical and radiological criteria defining SURF are similar to those defining the new concept of "Embolic Stroke of Undetermined Source", created in 2014, which had not yet been suggested when we started this study in 2010–2013 [25]. ESUS is defined as a non-lacunar brain infarct without proximal arterial stenosis or cardioembolic sources, and without a clear indication for anticoagulation. Consequently, SURF can be defined as ESUS with Age (y) × 10 + BNP (pg/ml) > 700. Several publications have demonstrated that BNP levels correlate with the risk of developing atrial fibrillation in a variety of clinical situations, including strokes [9–11,26]. Compared to other clinical, radiologic and electrocardiographic parameters, BNP levels have a higher predictive value [9,27,28]. In the literature, BNP levels in plasma were recognized as pertinent biomarkers in order to rule out AF [9–11,26]. In fact, BNP levels were found to be correlated with AF alone, but also with conditions that promote AF as well as AF thromboembolism criteria. BNP is a confounding factor for numerous parameters that contribute to predict AF [9]. It is noteworthy that BNP, in our study, is an independent and statistically significant predictive factor of AF, that it is independent to age but that it does have a synergistic impact on AF. The role of age itself is explained by AF epidemiology [29]. We can conclude that SURF represents a sub group of ESUS with a high risk of paroxysmal AF. This explains why AF is often found in ESUS [30–32].

Therefore, the question of the best strategy to apply in this group is raised. It would be possible to track AF with cardiac recordings, knowing that the costs related to ECG monitoring could be reduced in such a group for optimum cost-effectiveness. In our study, 14.4% of new AF were found in the cohort of AF-naïve stroke patients without

Criteria of SURF (Stroke with Underlying Risk of atrial Fibrillation) group:

- AF-naive stroke without indication of long term anticoagulation
- No symptomatic atherosclerotic stenosis ≥50%
- No symptomatic arterial dissection
- No lacunar stroke
- Age (years) × 10 + BNP (pg/ml) at admission > 700

Fig. 2. Proposal of SURF (**S**troke with **U**nderlying **R**isk of Atrial **F**ibrillation) group definition.

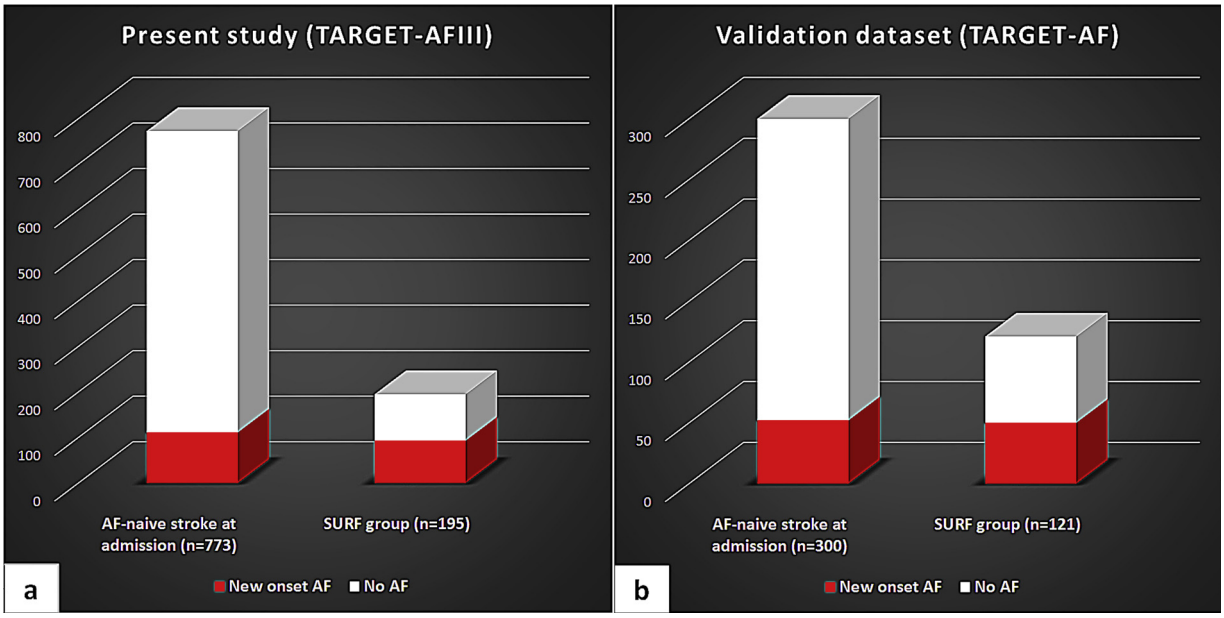

Fig. 3. AF distribution before and after using SURF criteria in the original TARGET-AFIII cohort **(a)** and dataset validation of the TARGET-AF cohort [9] **(b)**.

indication of long-term anticoagulation. This is consistent with the result of a recent meta-analysis study (10.7% [5.6–17.2]; 1). The majority (90%) of new AF were diagnosed early after admission in the stroke unit thanks to prolonged Holter ECG (median: 6.48[3.99–11.04] days). The first weeks after the stroke seem to be the optimal time period where patients are more prone to be diagnosed with AF [33,34]. The stroke guidelines recommend Holter cardiac monitoring for at least 24H [35], but it is generally admitted that 24H Holter ECGs have a low sensitivity in AF detection after strokes (4.6%[0–12.7]; 1, 36). In randomized, controlled trials, the utility of prolonged Holter monitoring and implanted devices was demonstrated with better AF detection rates (compared to 24H Holter ECG; 1, 2, 5). Yet, the optimal duration and timing of prolonged monitoring is not clear and the gold standard AF detection strategy following a stroke is not known [37]. However, our approach of a prolonged Holter ECG, started immediately, with a good detection rate, is in agreement with the optimum detection modality advocated in the literature and very recently, in the European Society of Cardiology, which recommended 72 h of Holter after a stroke or transient ischemic attack [38]. In our study, the significantly longer duration of monitoring in the AF group is explained by the longer hospital stay for those patients who are clinically more severe.

On the other hand, the good tolerance of non-vitamin K oral anticoagulants (OAC) allows us to discuss a pragmatic approach. In particular, the AVERROES study well demonstrated the safety of Apixaban compared to aspirin, since the rate of hemorrhagic complications was comparable in the two groups [39]. This discussion has already been conducted for ESUS and led to randomized trials comparing the OAC to aspirin in large clinical trials (NAVIGATE-ESUS, RESPECT-ESUS; 40,41). Recently, results of NAVIGATE-ESUS concluded that Rivaroxaban* was not superior to aspirin with regard to the prevention of recurrent stroke after an initial embolic stroke of undetermined source and was associated with a higher risk of bleeding [42]. We hypothesize that the SURF group might be constitute a target population for a randomized clinical trial testing the superiority of OAC versus aspirin for the secondary prevention of cryptogenic stroke. Because the incidence of AF in the SURF group is very high, testing the superiority of OAC in this group versus aspirin could be an alternative to shunt the costly and uncertain diagnosis of occult AF in the cryptogenic stroke group. In the SURF group, one in two patients will have AF and benefit from anticoagulation. In SURF, the number patients needed to demonstrate the superiority of anticoagulation over anti-platelets would be significantly smaller.

We have proposed the first definition of SURF, a new concept to manage AF detection after stroke. Because it is a single center study, validation in prospective multicenter stroke studies are necessary, in order to confirm our definition proposal in independent cohorts and to eventually adjust the cut-off.

5. Conclusions

We have identified a group of stroke patients at underlying risk of paroxysmal atrial fibrillation. The criteria used to define such a group are simple, available in all stroke units, and in the first days after admission. SURF is a new, easy to use concept proposal, which aims to improve the effectiveness of AF diagnosis after stroke. This result should allow an increase of the AF diagnosis rate after a stroke but also a cost reduction for ECG monitoring. It appears to be a feasible approach allowing a pragmatic management of stroke patients with optimum cost-effectiveness.

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Conflict(s)-of-Interest

None.

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