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Maastricht University

Faculteit Geneeskunde en Levenswetenschappen
School voor Levenswetenschappen

master in de biomedische wetenschappen

Masterthesis

Assessing patient characteristics and detection methods for underlying atrial fibrillation in cryptogenic stroke

Dimitri Vanhaen

Scriptie ingediend tot het behalen van de graad van master in de biomedische wetenschappen, afstudeerrichting klinische biomedische wetenschappen

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Assessing patient characteristics and detection methods for atrial fibrillation in cryptogenic stroke*

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*Running title: *Cryptogenic stroke characterization and follow-up*

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Keywords: Cryptogenic stroke, atrial fibrillation, phenotyping, follow-up, ICM, mobile health, FibriCheck

ABSTRACT

ENGLISH

BACKGROUND – In 20-40% of all ischemic strokes, no underlying cause can be found. The stroke is then classified as "cryptogenic". Paroxysmal atrial fibrillation (AF) is linked with cryptogenic stroke (CS) but is often not detected due to its asymptomatic nature. During this study, CS patient characteristics, the current follow-up methods for detecting AF, and the use of mobile health for CS patients' follow-up were assessed.

METHODS – A retrospective analysis was performed on 391 CS patients. Several risk factors and comorbidities, and the standard of care AF detection methods were assessed. A prospective study was carried out to investigate the use of mobile health (i.e., FibriCheck) in CS patients' follow-up. CS patients were monitored for six months with both a guideline-recommended insertable cardiac monitor (ICM) and FibriCheck. The performance of both methods was compared.

RESULTS – Smoking and obesity were significant predictors for AF in CS patients (p = 0.017, p = 0.037). The combination of smoking and obesity remained significant (p < 0.001). The ICM had the highest AF detection rate (24.0%). However, the low usage (25 patients) should be considered. AF and one-year mortality (p = 0.007) were strongly associated. Preliminary results of the prospective study showed AF detection in two patients so far.

CONCLUSION – Smoking and obesity were associated with a higher risk of AF in CS patients. Therefore, when these factors are present, prolonged monitoring should be highly recommended. FibriCheck might be a worthy, non-invasive add-on for the ICM. However, more results are needed for further confirmation.

NEDERLANDS

ACHTERGROND – In 20-40% van alle ischemische beroertes wordt geen onderliggende oorzaak gevonden. Men spreekt dan van een cryptogene beroerte (CB). Er is een link tussen (paroxysmale) voorkamerfibrillatie (VKF) en CB's, maar de detectie van VKF wordt vaak bemoeilijkt door de asymptomatische aard van de aandoening. Tijdens deze studie werden karakteristieken van CB-patiënten, de huidige opvolgingsmethodes voor VKF-detectie en het gebruik van een mobiele gezondheidstoepassing als opvolgingsmethode voor CB-patiënten onderzocht.

METHODEN – Een retrospectieve analyse werd uitgevoerd op 391 CB-patiënten. Verschillende risicofactoren en comorbiditeiten werden onderzocht, alsook de huidige VKF-detectiemethodes. Een prospectieve studie werd uitgevoerd om te onderzoeken of een mobiele gezondheidstoepassing (FibriCheck) kan gebruikt worden voor de opvolging van CB-patiënten. De patiënten werden zes maanden opgevolgd met een implanteerbare cardiale monitor (ICM) én FibriCheck. De ICM is volgens de richtlijnen aanbevolen. De performantie van beide methodes werd vergeleken.

RESULTATEN – Roken en obesitas waren significante voorspellers voor VKF in deze patiëntenpopulatie (p = 0.017, p = 0.037). De combinatie ervan bleef significant (p < 0.001). De ICM had het hoogste VKF-detectiepercentage (24.0%). Er dient wel rekening gehouden te worden met het gelimiteerde gebruik (25 patiënten). VKF en één-jaar-mortaliteit waren sterk geassocieerd (p = 0.007). In de prospectieve studie werd tot dusver bij twee patiënten VKF gedetecteerd met FibriCheck. De studie is nog lopende.
CONCLUSIE – Roken en obesitas verhoogden het risico op VKF bij CB-patiënten. Bijgevolg zou bij aanwezigheid van deze factoren langdurige opvolging sterk aangeraden moeten zijn. FibriCheck is mogelijk een waardige, niet-invasieve toevoeging naast de ICM. Maar, meer resultaten zijn nodig voor bevestiging.

INTRODUCTION

Background

A stroke is nowadays defined as an acute episode of focal neurological dysfunction of the brain, retina, or spinal cord which lasts longer than 24 hours, or of any duration if computed tomography (CT) imaging, magnetic resonance imaging (MRI), or autopsy show focal infarction or hemorrhage relevant to the experienced symptoms (1). A focal dysfunction lasting less than 24 hours and with no imaging evidence of infarction is defined as a transient ischemic attack (TIA) (1).

In 2015, the prevalence of stroke in Belgium was estimated at 63,535 strokes, which comes down to 348.5 strokes per 100,000 inhabitants, or 19,000 yearly stroke patients (2). Globally, the annual mortality rate of stroke is around 5.5 million, making it the second leading cause of death worldwide (3). Above that, high morbidity is related to stroke since it is the third leading cause of loss of disability-adjusted life-years (DALYs) (1). As a result, 50% of stroke survivors are chronically disabled (3). Due to the loss of DALYs, health care costs are negatively influenced. In Belgium, the total health care cost related to stroke was €393.7 million in 2015 (2).

There are two major categories of stroke: hemorrhagic and ischemic (1, 3). A hemorrhagic stroke is caused by a rupture of a blood vessel or an abnormal vascular structure. On the other hand, an ischemic stroke is caused by an embolism from the heart, artery-to-artery embolism, or in situ small vessel disease, which leads to a disruption of the blood supply to a specific part of the brain and ultimately to loss of function (1, 3). Because of insufficient blood supply to the part of the brain in question, symptoms such as unilateral weakness, numbness, visual loss, diplopia, altered speech, etc. are very common in stroke (1).

In order to find the underlying cause of the stroke, several clinical investigations need to be carried out. Brain imaging using a CT scan and MRI is one approach (1, 3, 4). CT is a more sensitive technique to detect intracranial hemorrhages, whereas MRI detects brain ischemia more sensitively (1). A transesophageal echocardiogram (TEE) should be carried out in order to detect thrombi in the left atrial appendage or patent foramen ovale (PFO) (4). PFO is a congenital heart abnormality that is present in approximately 25% of all adults worldwide (5). It results from the failed closure of the foramen ovale, which is a small tunnel that exists in the fetus to direct blood flow directly from the left to the right atrium (5). PFO is associated with an increased risk of stroke, because venous thrombi may shunt through the PFO to the left atrium. This is called a paradoxical embolism (4, 5). Furthermore, duplex ultrasound of the carotids is a possible screening method for carotid artery stenosis, which is another risk factor of stroke (1, 6). It is also important to assess the blood glucose and cholesterol levels since these markers are also risk factors for developing a stroke (1, 3). Also, hyperglycemia is associated with worse outcomes (7). Therefore, blood glucose levels need to be assessed since it provides an opportunity to treat hyperglycemia in order to achieve normoglycemic blood levels (7). Above that, when patients younger than 55 years suffer from an ischemic stroke, screening for hypercoagulable states is also suggested (8, 9).

Problem statement

About 20-40% of all ischemic strokes are cryptogenic (1, 4, 9, 10). A cryptogenic stroke (CS) is defined as an ischemic stroke with an undetermined cause. This can be due to incomplete or delayed clinical investigation, multiple causes or because no cause can be found, meaning the stroke is truly cryptogenic (1, 4). Cryptogenic strokes can be further classified as non-embolic and embolic (4). Several studies have found a link between (paroxysmal) atrial fibrillation (AF) and embolic strokes of undetermined source (ESUS), which is a type of cryptogenic stroke (4, 9-13). AF is a cardiac arrhythmia in which the upper chambers are dysfunctional due to abnormal electric signaling. Because of this, the blood in the atria remains static, which promotes blood clot formation and increases the risk of developing a stroke (14). Therefore, AF is the most common cause of cardio-embolism (13).

Depending on device-related and study design-related factors, AF detection yields of up to 33.7% were reached in CS patients who were monitored for 281 ± 212 days (12). However, AF detection yields may vary due to different follow-up durations (12). Several risk factors contribute to the emergence of AF. These risk factors can be unmodifiable (e.g., genetics) or modifiable (e.g., smoking). Cardiovascular disease, such as heart failure and myocardial infarction, can be a risk factor as well as an adverse clinical outcome associated with AF (15). Paroxysmal AF is a type of AF which occurs spontaneously and resolves by itself or with treatment within seven days (14). Consequently, heart rhythm monitoring should also be carried out, in addition to the investigations mentioned above, with the aim of detecting AF (4). The first line procedures for this are acute continuous electrocardiogram (ECG) monitoring for at least 24h after stroke onset, 12-lead ECG, 24-hour holter and prolonged ECG monitoring after discharge (4, 16). However, due to the asymptomatic nature of paroxysmal AF, it is often not detected during these standard of care clinical investigations (9-11, 17).

It is important to mention that CSs caused by AF have a higher burden, i.e., more severe consequences and a worse prognosis (18). Above that, ischemic strokes due to AF double the mortality risk and the risk of a future neurologic event (18). This type of patients is also more likely to have a prolonged hospital stay and more issues with picking up daily activities due to impairment, dependency or other complications (18). Therefore, follow-up of CS patients with the aim of detecting AF is critical. AF detection in CS patients is crucial because it creates a window of opportunity to initiate anticoagulant therapy instead of antiplatelets and hereby reducing the risk of a recurrent stroke (9-13).

According to the current European Society of Cardiology (ESC) guidelines for the diagnosis and management of AF, an insertable cardiac monitor (ICM) is recommended for the follow-up of CS patients (19). An ICM is a small, insertable device that continuously monitors the heart rhythm through ECG for up to three years (20). Implantation of an ICM is a minimally invasive procedure, which occurs under local anesthesia (21). The price of these devices ranges from €3,640–€4,554, but ICMs are reimbursed in Belgium (22, 23). Several studies have concluded that the use of an ICM is superior to short-term and/or intermittent monitoring strategies (e.g.,12-lead ECG, Holter monitoring) for the detection of AF in CS patients (9, 10, 16). *De Angelis et al.* detected AF in 41% of CS patients, after a mean time of six months after receiving an ICM and eight months after the CS (9).

Despite the abovementioned benefits, ICMs are still not used very often because of their invasiveness, cost and insufficient real-life data (9, 19). On top of that, there are several limitations bound to using an ICM. The implantation of the device is a minimally invasive procedure, but, albeit rarely, patients receiving an ICM can develop local complications (21). The small size of the device and the lack of device fixation could also lead to spontaneous ICM migration along the tissue plane, which could lead to loss of signal (20). Furthermore, artifacts can mimic AF and lead to false positives (9). However, revision of the diagnosis by an expert can contain this problem (9).

Mobile health technology: the solution?

To solve the abovementioned problems, the idea of using non-invasive, inexpensive mobile health (mHealth) technology arose. In 2018, mHealthBelgium was launched by the Belgian government (24). This is a platform specifically for mobile applications that are CE-certified as a medical tool, with the goal of integrating these mHealth applications in Belgian health care settings. Therefore, the mHealth validation pyramid was introduced in mid 2018. The pyramid consists of three levels that can be obtained by mHealth applications when they meet certain criteria (24). The first level can be obtained when the application is CE-certified. Next, when the application shows safe connection and interoperability with other (mobile) applications in healthcare, it can climb to the second level. Lastly, when the application can prove its added social-economic value, it will be reimbursed by *Rijksinstituut voor ziekte- en invaliditeitsverzekering* (RIZIV), and the third and upper level of the pyramid is reached (24).

Different mHealth methods are available for the detection of AF. First of all, there are several applications. The KardiaMobile app is one example of an application that can be used for the detection of AF. However, supplementary equipment is needed for this application. This equipment consists of finger pad sensors for the left and right hands, which need to be attached to the smartphone. This equipment then transmits the information to the application, which produces an ECG trace in order to register the heart rhythm (25). CardiioRhythm is another example of an app for AF detection. This app uses photoplethysmography (PPG) signals acquired from finger and face to register the heart rhythm (25). Preventicus is another application that uses PPG signals obtained from the index fingertip (26).

Several studies investigated the use of microelectromechanical (MEMS) sensors, present in mobile phones, for AF detection. The patient needs to lie down in supine position, with their phone placed on their chest. The accelerometer of the phone can detect cardiogenic movements that are caused by the opening of the aortic valve. The interval between each successive opening is used to determine if AF is present or not (25).

Furthermore, smartwatches can be used for AF detection. In order to register the heart rhythm, either PPG or electrodes are used. The Apple Watch is an example of a smartwatch that is used for AF detection. To achieve this, it uses both PPG and a two-lead ECG (27).

Lastly, other mHealth devices can be used for AF detection. One example of such a device is MyDiagnostick. This is a rod-shaped device with two electrodes on the endings. By holding the device by the endings, a single-lead ECG is recorded and stored, after which it is analyzed by the algorithm for the presence of AF (27-29).

The smartphone application FibriCheck also uses PPG for the detection of AF (30). PPG measures the amount of light absorbed or reflected by the blood in the blood vessels (31). For the smartphone application, this means that the change in blood volume that flows through the capillaries in the fingertip is measured. When the blood vessels stretch out, this implicates that there is more blood present. Consequently, the absorption of light is increased. When the blood vessel shrinks again, the volume of blood flowing through the vessel is smaller. Hence, the light absorption is decreased. This is what happens during a cardiac cycle. With every heartbeat, blood vessels are stretched out. Between two heartbeats, the blood vessels decrease in size (30). The PPG signals that are generated, are used by the application software to capture the heart rhythm. Above that, the software is capable of detecting AF in the acquired PPG signals (30). Nowadays, FibriCheck is also available on Fitbit smartwatches.

Proesmans et al. performed a health economic assessment of the implementation of FibriCheck for AF monitoring in CS patients specifically (32). Sixty-three patients who experienced a CS needed to perform measurements with FibriCheck twice a day for a period of three months. This was compared to a 12-lead ECG, which is standard of care. At the end of the study, 3 new AF cases and 1 recurrent AF case were reported with FibriCheck, whereas AF was not detected with 12-lead ECG.

Using a Markov model, the cost-effectiveness of monitoring CS patients was investigated. FibriCheck was found superior to standard of care AF screening in terms of cost-effectiveness. More specifically, implementing FibriCheck in a population of 1,000 resulted in 26 QALYs and a reduction of -€ 1,189/QALY (32). This supports the idea of using mHealth, more specifically FibriCheck, for prolonged monitoring for AF in CS patients.

It is important to mention that the AF burden differs between mHealth and the ICM. The AF burden is defined in many ways, such as the AF episode with the longest duration or the number of AF episodes during a monitoring period (33). However, the amount of time a patient is in AF during a certain monitoring period, expressed as a percentage, is the most complete definition. Evidence suggests that a higher AF burden is associated with a higher risk of stroke (33). Currently, the AF episode threshold is set at 30 seconds (34). *Nölker et al.* used a threshold of ≥ 2 minutes when assessing ICMs for the detection of paroxysmal AF (35). *Sanna et al.* also investigated the performance of ICMs for the detection of paroxysmal AF after CS and used the AF duration threshold of ≥ 30 seconds (10). In contrast to ICMs, an mHealth method like FibriCheck cannot use a threshold of ≥ 2 minutes since a measurement only lasts one minute (36). The debate about which AF episode threshold should be employed is still ongoing. It is not yet established whether or not short episodes of AF lasting 30 seconds are clinically relevant and if the risk of thrombo-embolic events in CS patients is a function of the AF burden (4, 12). Needless to say, more research is necessary to validate AF episode thresholds that are associated with an increased risk of stroke and to determine when oral anticoagulation is indicated (18, 33).

Objectives

In this paper/thesis, the results of two studies, FOOTSTEP and REMOTE, will be presented and discussed. The goal of the FOOTSTEP study (i.e., Follow-up of cryptogenic stroke patients), a retrospective study, is to phenotype patients who suffered from a cryptogenic stroke or TIA to get a clearer view of the efficiency of AF detection methods which are currently used as standard of care investigations. The results of this study will also provide better insights into which patients would benefit from prolonged heart rhythm monitoring. The overall aim of the REMOTE study (i.e., A new strategy for early detection of atrial fibrillation in cryptogenic stroke patients using mobile technology to improve secondary prevention), a prospective, interventional study, is to investigate if mHealth technology can replace or be an addition to the ICM for the follow-up of CS patients as an AF detection method. The CS patients in this study were monitored with both an ICM and FibriCheck, the mHealth application, for a period of six months. The ICM continuously monitored the heart rhythm of the patient. With FibriCheck, patients performed two daily measurements with their smartphone or received a smartwatch which automatically performed measurements every three minutes. We hypothesize that the AF detection rates of mHealth technology are non-inferior to the ICM (= control). Furthermore, the patients' vision on mHealth technology and their opinion about using mHealth for their follow-up were assessed with a questionnaire.

METHODS

FOOTSTEP study – retrospective study

Study population

Data of 391 cryptogenic stroke (CS) patients admitted to the stroke unit of Ziekenhuis Oost-Limburg (ZOL), Genk, between January 1st, 2017 and January 1st, 2020, was collected in this retrospective study. Patients were at least 18 years old. CS patients who died during admission were excluded. Patient selection is explained in ***Figure 1***.

Study set-up

A database was constructed with information from the electronic health record (EHR) of 391 CS patients. Several parameters and characteristics were assessed, of which the most important were gender, age, medical history, cardiovascular risk

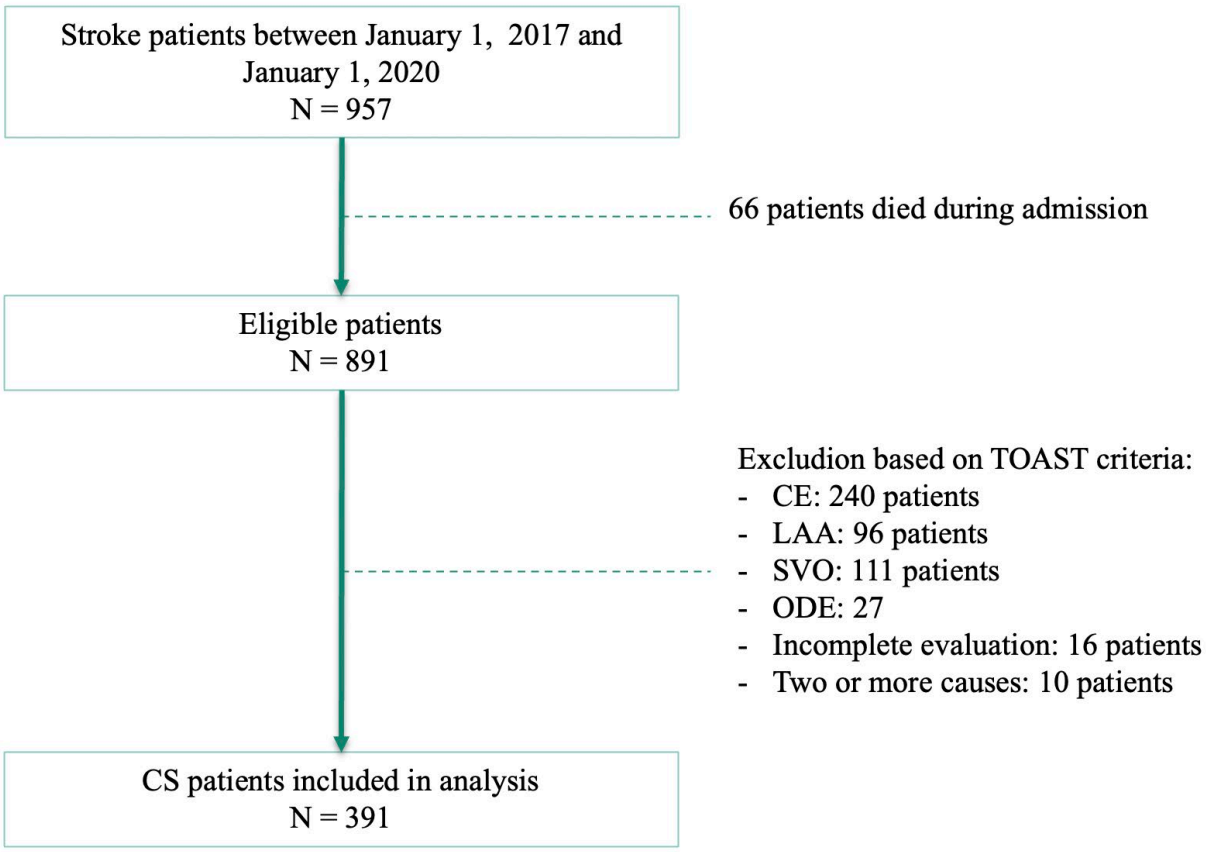

Figure 1: CONSORT flowchart of patient selection. *CE, Cardio-embolic; LAA, Large Artery Atherosclerosis; SVO, Small Vessel Occlusion; ODE, Other Defined Etiology; CS, Cryptogenic Stroke.*

factors, comorbidities, mortality, ASPECTS score, collateral score and use of atrial fibrillation (AF) detection methods (cardiac monitoring, 12-lead ECG, 24-hour holter, 7-day holter, insertable cardiac monitor (ICM), pacemaker (PM), implantable cardioverter defibrillator (ICD) and FibriCheck). The goal was to phenotype patients who suffered from a cryptogenic stroke or TIA to get a clearer view on the efficiency of AF detection methods which are currently used as standard of care investigations.

Statistical analysis

Statistical analysis of the acquired data was carried out with IBM SPSS Statistics version 26 (IBM® SPSS® Inc., Chicago, Illinois, USA). Continuous data were expressed as means ± standard deviation (S.D.) or medians and interquartile range (IQR) when appropriate. Categorical data were expressed as numbers and percentages and compared with the Pearson Chi-square or Fisher's exact when appropriate. Non-parametric tests were carried out to compare the AF detection methods in pairs (e.g., cardiac monitoring with ECG). For the ICM, a Kaplan-Meier analysis was carried out in order to visualize the time between ICM insertion and AF detection. A Kaplan-Meier analysis was also performed for all AF detection methods to visualize the time between stroke onset and AF detection. The log-rank test was used to compare the methods. Furthermore, non-parametric tests such as the Mann Whitney U test as well as binary and ordinal logistic regression analyses were carried out when appropriate. All assumptions were checked before carrying out the concerning statistical test. A p-value < 0.05 was considered statistically significant.

Ethical Approval

Approval from the local medical ethical committee was obtained (reference: 20/0037R), with a waiver of informed consent.

REMOTE study – prospective, interventional study

Study population

Ischemic stroke patients admitted to the stroke unit of Ziekenhuis Oost-Limburg (ZOL), Genk, were categorized as CS patients when no underlying cause could be found during standard of care clinical investigations. CS patients were eligible for the REMOTE study depending on whether or not they met the inclusion- and exclusion criteria. Eligible patients had to voluntarily give their informed consent before inclusion in the study.

Study set-up

In the context of this study, the follow-up of CS patients happened with both an ICM (control) and FibriCheck. The latter method is not according to the state-of-the-art and represents this study's novelty. The ICM is the state-of-the-art, because it continuously monitors the patient's heart rhythm through ECG. The nurses checked irregular ECG parts on a weekly basis to filter out all false positives. When an irregular heart rhythm occurred, the cardiologist was warned.

With FibriCheck, the patients were randomized in two groups: smartphone or smartwatch. With the smartphone, the patient needed to perform measurements of one minute. By holding the fingertip against the camera flash, heart rhythm registration occurred. Then, the software analyzed the heart rhythm and detected AF in the acquired PPG-signals when it was present. The patient had to do this twice a day and when the patient experienced AF symptoms (e.g., palpitations). With the smartwatch, a Fitbit Versa 2 or Fitbit Ionic, measurements were automatically performed on a semi-continuous basis, i.e., every three minutes. The results from these measurements were blinded for the patient and caregiver.

In total, the patient was monitored for six months, starting from the day of the ICM implantation. A comparison between the two methods was made at the end of the six-month follow-up. This experiment aimed to compare the AF detection rates of both follow-up methods and to investigate whether mHealth technology is a reliable method for CS patients' follow-up in order to detect AF. Above that, this experiment was carried out to demonstrate that mHealth technology is non-inferior to an ICM and can therefore replace it or be an add-on for AF detection during the follow-up of CS patients.

Furthermore, the patients' opinion on the application and mHealth technology in general was assessed. More specifically, patients had to fill out two questionnaires, one at the start of the follow-up and one after the follow-up of six months. The questionnaires provided information about how the patients perceived the application in terms of ease of use, satisfaction with the application, and their personal opinion on being monitored with mHealth technology. Above that, the patients needed to indicate if there was a difference in willingness to use an mHealth application depending on whether or not this would be advised by a governmental health platform such as mHealthBelgium.

Statistical analysis

Statistical analysis of the acquired data was carried out with IBM SPSS Statistics version 26 (IBM® SPSS® Inc., Chicago, Illinois, USA). Continuous data were expressed as means ± standard deviation (S.D.) or medians and interquartile range (IQR) when appropriate. Categorical data were expressed as numbers and percentages.

Ethical Approval

This study was approved by the Medical Ethics Committees of Ziekenhuis Oost-Limburg (ZOL), Genk and Hasselt University (2019/106). All procedures were performed in accordance with the Declaration of Helsinki.

RESULTS

FOOTSTEP

Demographics and patient characteristics

Between January 2017 and January 2020, a total of 957 stroke patients were admitted to Ziekenhuis Oost-Limburg (ZOL), Genk. A CONSORT flowchart of patient selection is depicted in ***Figure 1***. After assessing the Trial of ORG 10172 in Acute Stroke Treatment (TOAST) criteria and exclusion of patients who deceased during admission, 391 CS patients were identified. Demographics and patient characteristics are shown in ***Table 1***. The mean age of stroke onset was 69.63 ± 0.69 years. The gender distribution in this study population was rather equal (male: 47.31%, female: 52.68%). Hypertension and hypercholesterolemia were the most common risk factors, respectively present in 62.4% and 46.3% of this CS patient population. Vascular disease (i.e., including peripheral vascular disease, myocardial infarction, and atherosclerosis) was the most prevalent comorbidity in this population (52.9%). If the patient suffered from at least one of these comorbidities, they automatically suffered from vascular disease. This might explain why vascular disease was most commonly present. It is important to mention the descriptive nature of ***Table 1***. A statistical comparison with another group or population was not made. Therefore, no conclusions can be drawn.

Comorbidities

In order to investigate the effect of certain risk factors and/or comorbidities on the likelihood of developing AF in this population of CS patients, a binomial logistic regression was performed. The results of this test are shown in ***Table 2***. The overall model was statistically significant when compared to the null model, (χ^2 (15) = 27.174, p = 0.027), explained 13% of the variation of in AF (Nagelkerke R^2) and correctly predicted 86.3% of cases. Diabetes, smoking, and obesity added significantly to this regression model (p = 0.003, p = 0.017, p = 0.037 respectively). More specifically, diabetes was associated with a reduced likelihood of exhibiting AF. Smokers were 3.394 times more likely to have AF than non-smokers. Obese CS patients were 2.499 times more likely to exhibit AF. Another binomial logistic regression was performed to assess if a combination of these variables contributes to developing AF as well. In ***Supplementary Table 1***, the results of this test are demonstrated. The overall model was statistically significant when compared to the null model, (χ^2 (3) = 15.050, p = 0.002), explained 7.1% of the variation of in AF (Nagelkerke R^2) and correctly predicted 86.2% of cases. The combination of obesity and smoking was a significant predictor for AF in this population of CS patients ($p < 0.001$), whereas the combinations diabetes-smoking and diabetes-obesity were not (p = 0.633, p = 0.085 respectively). Thus, a smoking, obese CS patient was 4.127 times more likely to develop AF.

Because 36.1% of the patients in this population had at least one old infarction area according to CT- and MRI-scans, an investigation was carried out to see if there was an association between comorbidities and number of old infarctions. A Chi-square test was performed to assess this. The results in ***Supplementary Table 2*** show that there was a significant association between previous stroke/TIA (χ^2 (2, N = 391) = 8.992, p = 0.011) hypercholesterolemia (χ^2 (2, N = 376) = 8.135, p = 0.017), familial history (χ^2 (2, N = 385) = 7.565, p = 0.023), PFO (χ^2 (2, N = 377) = 7.218, p = 0.027), atherosclerosis (χ^2 (2, N = 383) = 6.167, p = 0.046), vascular disease (χ^2 (2, N = 391) = 6.040, p = 0.049) and heart failure (χ^2 (2, N = 383) = 6.052, p = 0.049), and the number of old infarctions. Moreover, when the patient suffered from hypercholesterolemia, previous stroke/TIA, heart failure, familial history, atherosclerosis or vascular disease, they were more likely to have old infarctions. When the patient suffered from PFO, they were less likely to have old infarctions (***Supplementary Figure 1***). The other comorbidities showed no significant association with the number of old infarctions.

To establish if certain risk factors/comorbidities predict the presence of old infarctions in the brain, an ordinal regression was carried out. In ***Table 3***, the results of this analysis are given. There was a statistically significant result for alcohol abuse,

Table 1: Demographics and patient characteristics.

	CS patients (N = 391)
CHARACTERISTICS	
Age onset (mean ± SD)	69.63 (± 0.69)
Gender	
Female	206 (52.7%)
Male	185 (47.3%)
Stroke	273 (68.8%)
TIA	118 (30.2%)
AF	57 (14.6%)
Stroke recurrence	13 (3.3%)
Old infarction	141 (36.0%)
RISK FACTORS	
Hypertension	244 (62.4%)
Hypercholesterolemia	181 (46.3%)
Obesity	98 (25.1%)
Smoking	88 (22.5%)
Diabetes	87 (22.3%)
Alcohol abuse	32 (8.2%)
COMORBIDITIES	
Vascular Disease	207 (52.9%)
Atherosclerosis	182 (46.5%)
Family history	111 (28.4%)
CKD	87 (22.3%)
PFO	69 (17.6%)
PFO closure	7 (10.2%)
Previous Stroke/TIA	61 (15.6%)
MI	42 (10.7%)
PVD	33 (8.4%)
Heart Failure	22 (5.6%)

SD, Standard Deviation; TIA, Transient Ischemic Attack; AF, Atrial Fibrillation; CKD, Chronic Kidney Disease; MI, Myocard Infarction; PVD, Peripheral Vascular Disease; PFO, Patent Foramen Ovale.

hypercholesterolemia, previous stroke/TIA and heart failure. Patients who did not abuse alcohol were less likely to have old brain infarctions (OR = 0.431 (95% CI, 0.192 to 0.968), Wald χ^2 (1) = 4.158, p = 0.04). Patients with no hypercholesterolemia were less likely to have old infarctions (OR = 0.586 (95% CI, 0.370 to 0.930), Wald χ^2 (1) = 5.149, p = 0.02). Also, when patients had not suffered from a previous stroke/TIA, they were less likely to have old brain infarctions (OR = 0.519 (95% CI, 0.291 to 0.927), Wald χ^2 (1) = 4.917, p = 0.03). Lastly, patients who did not suffer from heart failure, were less likely to have old brain infarctions (OR = 0.370 (95% CI, 0.145 to 0.942), Wald χ^2 (1) = 4.350, p = 0.04). In conclusion, when these comorbidities were not present in the patient, they were less likely to have old infarctions.

The association between comorbidities and having an ICM was investigated with a Chi-square test for all risk factors and comorbidities separately. As tabulated in ***Supplementary Table 3***, only previous stroke/TIA turned out to be significant. Thus, there was a significant relationship between previous stroke/TIA and having an ICM. Patients with an ICM were more likely to have experienced a previous stroke/TIA, χ^2 (1, N = 387) = 12.075, p = 0.002. A visual representation is given in ***Supplementary Figure 2***.

Another Chi-square test was performed to evaluate the relationship between any risk factor/comorbidity and gender. The results are tabulated in ***Supplementary Table 4***. Hypertension, diabetes and peripheral vascular disease were significantly associated with gender. Females were more likely to suffer from hypertension and diabetes, χ^2 (1, N = 384) = 4.145, p = 0.042 and χ^2 (1, N = 385) = 4.042, p = 0.044 respectively. The relationship between gender and peripheral vascular disease was significant as well χ^2 (1, N = 384) = 4.014, p = 0.045. Males were more likely than females to have peripheral vascular disease. A visual representation is given in ***Supplementary Figure 3***.

Atrial fibrillation and its detection methods

In 57 patients (14.6%) of this population, AF was detected, as shown in ***Table 1***. Considering that these patients had a stroke between January 1, 2017 and January 1, 2020, AF detection was within three years after stroke onset. A Chi-square test was carried out to see if gender was associated with AF. However, this was not the case (p = 0.556)

Table 2: Binary Logistic Regression: AF and risk factors/comorbidities.

	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Smoking	1.222	0.514	5.646	1	**0.017***	3.394	1.239	9.299
Alcohol	-0.054	0.673	0.007	1	0.936	0.947	0.253	3.540
Hypertension	-0.445	0.357	1.551	1	0.213	0.641	0.318	1.291
Diabetes	-1.140	0.379	9.048	1	**0.003****	0.320	0.152	0.672
Hypercholesterolemia	0.424	0.341	1.545	1	0.214	1.528	0.783	2.981
Obesity	0.916	0.439	4.351	1	**0.037***	2.499	1.057	5.908
Previous stroke/TIA	0.323	0.458	0.496	1	0.481	1.381	0.562	3.390
Heart failure	0.096	0.739	0.017	1	0.897	1.100	0.258	4.685
Familial	0.105	0.353	0.089	1	0.766	1.111	0.556	2.220
CKD	0.317	0.413	0.589	1	0.443	1.373	0.611	3.084
PVD	-0.705	0.525	1.800	1	0.180	0.494	0.177	1.384
MI	-0.652	0.548	1.415	1	0.234	0.521	0.178	1.526
Atherosclerosis	-1.146	0.761	2.265	1	0.132	0.318	0.071	1.414
Vascular disease	0.749	0.831	0.811	1	0.368	2.114	0.414	10.782
PFO	0.370	0.465	0.635	1	0.425	1.448	0.583	3.601

AF, Atrial Fibrillation; S.E., Standard Error; df, degrees of freedom; Sig., significance; Exp(B), Odds Ratio; CI, Confidence Interval; TIA, Transient Ischemic Attack; CKD, Chronic Kidney Disease; MI, Myocardial Infarction; PVD, Peripheral Vascular Disease; PFO, Patent Foramen Ovale.
*$p < 0.05$, **p < 0.01

(***Supplementary Table 5***). The distribution of AF in the different age categories of stroke onset was also assessed by means of a Mann-Whitney U test. Age of stroke onset was divided into 3 categories: <65 years old, 65-74 years old and ≥ 75 years old. As can be seen in ***Supplementary Table 6*** there is a significant difference (U = 12,177; $p < 0.001$) between the categories age of onset for patients with AF compared to patients who did not exhibit AF. The mean rank was higher when CS patients were in the AF group (249.40 compared to 187.26), which implicates that the age category, and thus age, was higher when patients exhibited AF.

Table 3: Ordinal regression analysis: comorbidities predicting old infarctions.

		Estimate	SE	Wald	df	Sig.	95% Confidence Interval		Exp(B)	Lower	Upper
							Lower Bound	Upper Bound			
Threshold	Number of old infarctions=0	-2.050	0.891	5.296	1	0.021	-3.796	-0.304	0,129	0,022	0,738
	Number of old infarctions =1	-1.273	0.886	2.062	1	0.151	-3.009	0.464	0,280	0,049	1,591
Location	Smoking=0	0.274	0.277	0.978	1	0.323	-0.269	0.817	1,315	0,764	2,263
	Smoking=1	0			0				1		
	Alcohol=0	-0.842	0.413	4.158	1	**0.041***	-1.651	-0.033	0,431	0,192	0,968
	Alcohol=1	0			0				1		
	Hypertension=0	-0.153	0.247	0.383	1	0.536	-0.636	0.331	0,858	0,529	1,392
	Hypertension=1	0			0				1		
	Diabetes=0	0.059	0.282	0.043	1	0.835	-0.494	0.612	1,060	0,610	1,843
	Diabetes=1	0			0				1		
	Hypercholesterolemia=0	-0.534	0.235	5.149	1	**0.023***	-0.995	-0.073	0,586	0,370	0,930
	Hypercholesterolemia=1	0			0				1		
	Obesity=0	-0.436	0.266	2.691	1	0.101	-0.957	0.085	0,647	0,384	1,089
	Obesity=1	0			0				1		
	PreviousstrokeTIA=0	-0.656	0.296	4.917	1	**0.027***	-1.235	-0.076	0,519	0,291	0,927
	PreviousstrokeTIA=1	0			0				1		
	Heartfailure=0	-0.995	0.477	4.350	1	**0.037***	-1.930	-0.060	0,370	0,145	0,942
	Heartfailure=1	0			0				1		
	Familial=0	-0.230	0.245	0.885	1	0.347	-0.710	0.249	0,794	0,492	1,283
	Familial=1	0			0				1		
	CKD=0	0.423	0.288	2.159	1	0.142	-0.141	0.988	1,527	0,868	2,686
	CKD=1	0			0				1		
	PVD=0	-0.648	0.380	2.900	1	0.089	-1.393	0.098	0,523	0,248	1,103
	PVD=1	0			0				1		
	MI=0	0.154	0.392	0.154	1	0.695	-0.614	0.922	1,166	0,541	2,513
	MI=1	0			0				1		
	Atherosclerosis=0	-0.298	0.233	1.631	1	0.202	-0.754	0.159	0,743	0,470	1,172
	Atherosclerosis=1	0			0				1		
	PFO=0	0.565	0.324	3.038	1	0.081	-0.070	1.201	1,760	0,932	3,323
	PFO=1	0			0				1		

SE, Standard Error; df, degrees of freedom; Sig., Significance; TIA, Transient Ischemic Attack; CKD, Chronic Kidney Disease; PVD, Peripheral Vascular Disease; MI, Myocardial Infarction; PFO, Patent Foramen Ovale.
*$p < 0.05$

Table 4: Mann-Whitney U: Difference between AF detection methods.

Group	N	Mean Rank	Sum of Ranks	U	P-value
Short-Term	831	430.18	35,7475.50	11779.50	**<0.001*** **
Long-Term	34	502.04	17,069.50		
Long-Term	34	92.19	3,134.50	1982.50	**0.039***
7d Holter	133	81.91	10,893.50		
Short-Term	831	479.64	398,581.50	52885.50	**0.027***
7d Holter	133	500.36	66,548.50		

AF, Atrial Fibrillation; 7d Holter, 7-day Holter. *$p < 0.05$, ***$p < 0.001$

Table 5: Association between atrial fibrillation and one-year mortality.

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	8.980[a]	1	0.003		
Continuity Correction[b]	7.339	1	0.007		
Likelihood Ratio	7.092	1	0.008		
Fisher's Exact Test				**0.007***	**0.007***
Linear-by-Linear Association	8.957	1	0.003		
N of Valid Cases	391				

a: 1 cell (25.0%) has an expected count of less than 5. The minimum expected count is 3.79.
b: Computed only for a 2x2 table
**$p < 0.01$

During hospital admission, stroke patients underwent several standard of care clinical investigations, one of which was the transesophageal echocardiography (TEE). During this examination, the left ventricular function and ejection fraction (EF) was assessed. Also, the left atrium (LA) was evaluated, more specifically whether or not it was dilated. EF was divided into categories: category 1, preserved EF (50-70%); category 2, borderline normal EF (40-49%) and category 3, reduced EF (<40%). Left atrial diameter was divided into categories as well: category 1, normal; category 2, mildly dilated; category 3, moderately dilated. For EF, 95.6% of CS patients were in category 1, 4.1% in category 2 and 0.3% in category 3. For LA diameter, 72.6% were in category 1, 20.4% in category 2 and 7.0% in category 3 (***Supplementary Figure 4***). Whether EF and LA diameter differed based on exhibiting AF was evaluated with a Mann-Whitney U test. The results are tabulated in ***Supplementary Table 7***. For both EF and LA diameter there was a significant difference ($U = 6817.00$, $p < 0.001$; $U = 8271.00$, $p < 0.001$) between AF patients compared to non-AF patients. Based on the mean ranks, AF patients were in a higher category of EF and LA diameter. Thus, AF patients had a lower EF and more dilation of their LA.

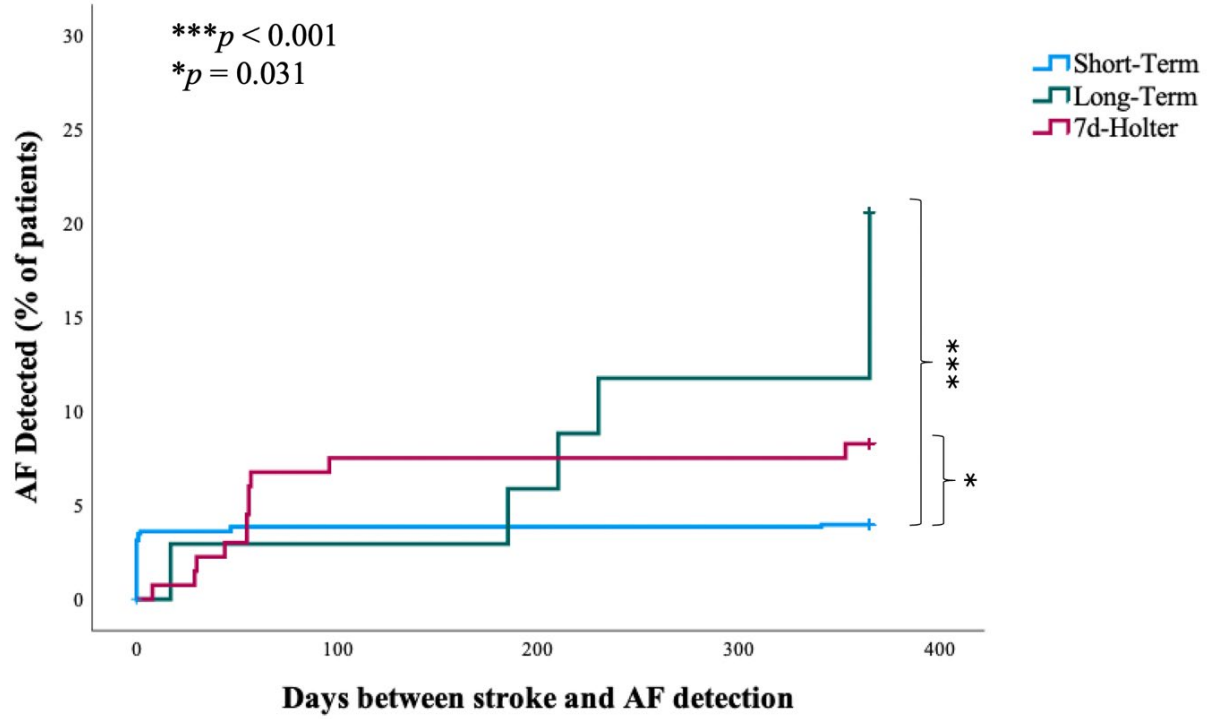

Figure 2: Kaplan-Meier analysis of AF detection methods. *The curves of short-term monitoring (blue), long-term monitoring (green) and 7-day holter monitoring (red) are depicted. The event in this analysis was AF detection. A log-rank test was carried out to test if the curves were significantly different. The curves of long-term and 7-day holter were significantly different from short-term monitoring ($p < 0.001$; $p = 0.031$, respectively).*
**p < 0.05, ***p< 0.001*

Furthermore, a binomial logistic regression was carried out to examine if a higher National Institutes of Health Stroke Scale (NIHSS) and/or a higher CHA_2DS_2-VASc score predicts the detection of AF. The NIHSS is used to assess the severity of stroke, whereas the CHA_2DS_2-VASc score is used to estimate the stroke risk of AF patients (37, 38). NIHSS was again divided into 6 categories (category 1: 0-5, category 2: 6-10, category 3: 11-15, category 4: 16-20, category 5: 21-25, category 6: 26-30). The CHA_2DS_2-VASc score in this study population ranged from 0 to 5. The overall model was statistically significant when compared to the null model, (χ^2 (9) = 20.880, p = 0.013), explained 10.9% of the variation of in AF (Nagelkerke R^2) and correctly predicted 84.5% of cases. As shown in ***Supplementary Table 8***, an NIHSS score between 6 and 10 and 21 and 25 (p = 0.03 and p = 0.01 respectively) added significantly to the model. Thus, patients with an NIHSS score ranging from 6 to 10 and 21 to 25 were respectively 2.505 and 6.553 times more likely to have AF.

To examine if there was a difference in AF detection between the methods, a pairwise comparison was carried out by means of a McNemar test. Stroke unit monitoring, 12-lead ECG, 24-hour holter, 7-day holter, FibriCheck and prolonged monitoring with ICM/ICD/PM were the detection methods in question. Each possible combination was tested. The results are shown in ***Supplementary Table 9***. There was a significant difference in AF detection between stroke unit monitoring and 7-day holter (p <0.001), 12-lead ECG and 7-day holter (p = 0.022), and 12-lead ECG and ICM/ICD/PM (p = 0.016). Then, the different methods were divided into categories. More specifically, a distinction was made between short-term monitoring (i.e., stroke unit monitoring, 12-lead ECG and 24-hour holter), long-term

monitoring (i.e., ICM and FibriCheck) and the 7-day holter, which monitors for a rather intermediate period of time. A Mann-Whitney U test was performed to detect possible statistical differences in AF detection between short-term, long-term and 7-day holter monitoring. The results are demonstrated in ***Table 4***. Based on the mean ranks, AF was significantly more detected with long-term monitoring compared to short-term monitoring (U = 11,779.50; $p < 0.001$). Similarly, long-term monitoring detected more AF than 7-day holter monitoring (U = 1,982.50; $p = 0.039$) and 7-day holter monitoring detected more AF than short-term monitoring (U = 52,885.50; $p = 0.027$).

Above that, a Kaplan-Meier analysis was performed. In this way, the percentage of AF detection in patients with short-term monitoring, long-term monitoring and the 7-day holter were compared. Also, the timing of the event is taken into account with a Kaplan-Meier analysis, in contrast to previously performed statistical tests. A log-rank test was carried out to test if there was a difference in AF detection between the three groups. The Kaplan-Meier curves are shown in ***Figure 2*****.** The function of long-term monitoring shows the highest AF detection percentage (20.6 %) after one year. The curves of short-term and long-term monitoring ($\chi^2(1) = 20.028$, $p < 0.001$), and short-term monitoring and 7-day holter were significantly different ($\chi^2(1) = 4.673$, $p = 0.031$).

A Kaplan-Meier analysis was carried out for the ICM alone, since this method is guideline-recommended for prolonged monitoring of CS patients (***Supplementary Figure 5*****).** Within one year, AF was detected in 24% of patients with an ICM. However, only 25 patients out of 391 had an ICM, therefore these results should be regarded with caution.

Lastly, a Cox regression was performed to predict the probability that the event of interest, AF detection, occurred at a given time. In this way, an estimate of the hazard ratio and its confidence interval were provided. When looking at the AF detection methods separately, 12-lead ECG was indicated as the reference category. The overall model was statistically significant when compared to the null model, (χ^2 (5) = 23.061, p < 0.001). As shown in ***Supplementary Table 10***, ICM had a significant effect ($p < 0.001$). It was 4.832 times more likely to detect AF with the ICM than with the 12-lead ECG. When categorizing the AF detection methods again in short-term, long-term and 7-day holter, short-term monitoring was indicated as the reference category. The results are shown in ***Supplementary Table 11***. The overall model was statistically significant when compared to the null model, (χ^2 (2) = 20.734, p = 0.001). Long-term monitoring and 7-day holter were respectively 5.200 ($p < 0.001$) and 2.086 ($p = 0.035$) times more likely to detect AF compared to 12-lead ECG.

Mortality

To investigate if there was an association between AF and one-year mortality in this population of CS patients, a Chi-Square test was performed. The results are shown in ***Table 5***. There is a significant association between AF and one-year mortality in this population of CS patients (χ^2 (1, N = 391) = 8.980, $p = 0.007$). Patients with AF were more likely to die within one year after stroke onset (***Supplementary Figure 6***). Furthermore, another Kaplan-Meier analysis was done to compare one-year mortality between patients with and without AF. The functions are depicted in ***Figure 3***. A log-rank test was carried out to test if the functions were significantly different. However, the survival times for AF and non-AF patients were significantly different ($p = 0.002$).

To investigate if there was a difference in NIHSS category and age category of stroke onset between patients who died within one year after stroke and patients who were still alive, a Mann-Whitney U test was carried out. ***Supplementary Table 12*** shows the results of the Mann-Whitney U tests for the difference in NIHSS categories and age of onset categories. Based on the mean ranks, NIHSS and age of onset category were significantly higher for patients who died within one year after stroke onset compared to those who did not (U = 7,328.50, $p < 0.001$; U = 11,254.0, $p < 0.001$).

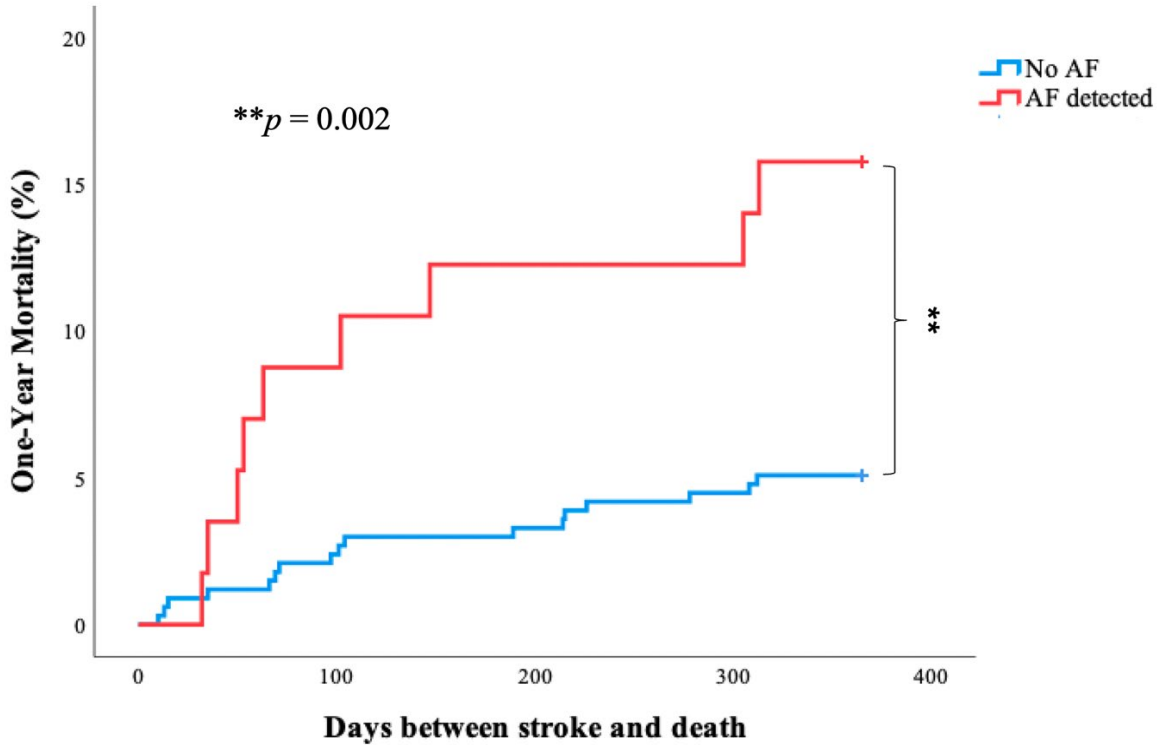

Figure 3: Kaplan-Meier analysis of one-year mortality. *The curves of patients with AF (red) and patients without AF (blue) are depicted. The event in this analysis was death within one year after stroke onset. A log-rank test was carried out to test if the curves were significantly different. The curves of AF and non-AF patients were significantly different (p = 0.002).*
**p < 0.01

To evaluate if the CHA_2DS_2-VASc score differed between patients who died within one year after stroke onset and those who did not (i.e., one-year mortality), a Mann-Whitney U test was performed. ***Supplementary Table 12*** shows that the distribution of CHA_2DS_2-VASc score was the same in patients who died within one year after stroke onset and those who did not (U = 8596.50, p = 0.155).

REMOTE

Demographics and patient characteristics

At the moment of writing, 33 CS patients were included in the REMOTE trial, of which 28 are in the smartphone group and 5 in the smartwatch group. Demographics and characteristics are displayed in ***Table 6***. The mean age of the total population was 65.76 ± 12.67. Currently, more men than women are included in the study (72.7% versus 27.3%). The mean height and median weight were respectively 1.72 ± 0.09 m and 77.00 (19) kg. The median Body Mass Index (BMI) was 25.39 (5) kg/m^2. Comorbidities and risk factors were assessed as well. Worth mentioning is that 72.7% had hypertension. Hypercholesterolemia was present in 60.6% of patients. PFO was present in 36.4% of these patients. The majority (78.8%) did not have a history of stroke or TIA. However, 6.1% (2 patients) experienced a previous stroke and 15.2% (5 patients) had a TIA in the past. Lastly, 27.3% of the patients were smokers and 9.1% were former smokers. The mentioned results are of a descriptive nature. Therefore, no conclusions can be drawn. The two groups were also assessed separately. These results are also tabulated in ***Table 6***.

Patients' vision on and opinion about mobile health

To investigate if the participants were aware of mobile health, they needed to fill out a questionnaire (***Supplementary Table 13***) before the start of the six-month follow-up with the ICM and FibriCheck (i.e., mobile health). Above that, the patients needed to indicate if there was a difference in willingness to use a mobile health application depending on whether or not this would be advised by a governmental health platform such as mHealthBelgium. The results are tabulated in ***Supplementary Table 13***. The first question assessed the patients' awareness about the availability of mobile health applications for smartphones. The results show that 73.9% knew about the existence of these apps. Furthermore, the patients were asked which type of application they downloaded on their smartphones. Social media, news apps, health and lifestyle and economic were the most downloaded categories (69.6%, 65.2%, 60.9% and 56.5% respectively. Also, patients were asked which type of health apps they downloaded on their phone. The most downloaded categories were fitness (i.e., pedometer) and diet/nutrition (respectively 60.9% and 17.4%). Lastly, advice from a governmental institution (i.e., mHealthBelgium) did not influence the decision of patients to use a mobile health application. When the application is not recommended by a governmental health platform, 56.5% agreed to still use it, 34.8% had no opinion and 4.3% strongly agreed. When the application is recommended, 56.5% agreed to use it, 30.4% had no opinion and 13.0% strongly agreed.

Currently, 5 out of 33 patients were allocated in the smartwatch group, of which 4 patients started the six-month follow-up. Important to mention is that after 13 days of follow-up, an average of 133.75 data points (i.e., measurements) per day per patient were generated. Furthermore, 4 out 33 patients have completed the six-month follow-up with both the ICM and FibriCheck thus far. In two out of these four patients, AF was detected.

Case report 1

The first patient is a 59 year old male admitted to ZOL, Genk, with a stroke on October 7, 2020. The man was 1.79 m tall and weighed 78.0 kg. Consequently, a BMI of 24.34 kg/m^2 was calculated. The patient was a former smoker. Only arterial hypertension was present in this patient. The Modified Rankin Scale (MRS) was zero. NIHSS and CHA_2DS_2-VASc score were both one. The Alberta Stroke Programme Early CT score (ASPECTS) was not calculated.

The patient underwent standard of care clinical investigations, being cardiac monitoring (telemetry), a Computed Tomography (CT) scan of the brain, brain Magnetic Resonance Imaging (MRI), carotid artery examination and TEE. Telemetry showed a normal, sinusal heart rhythm. The results of the CT scan demonstrated recent ischemia in the left temporoparietal region. This was further established with MRI, which showed diffusion restriction in the cortico-subcortical posterior region of the temporal lobe and thus a recent infarction in the circulation area of the left middle cerebral artery (M3). The patient's carotid arteries showed no stenosis or occlusion. No structural abnormalities were found with TEE. PFO was not present. However, there was a central thickening in the left coronary cusp of the aortic valve, resulting in grade ¼ aortic valve insufficiency. Furthermore, a blood sample was collected for laboratory investigations. Glycemia level was 128 mg/dL, HbA1c was 5.7% and LDL-cholesterol was 78 mg/dL. In-hospital blood pressure (BP) was 127/93 mmHg. In conclusion, no clear cause was found for the stroke. Therefore, the stroke was classified as cryptogenic.

In-hospital treatment consisted of dual antiplatelet therapy (DAPT), antihypertensives and hypolipidemics. DAPT was reduced to one antiplatelet agent after 21 days. The other treatments were continued in the same way four weeks after discharge. The patient was scheduled for further investigations, which were a 7-day holter and 24-hour BP measurement. The goal of the 7-day holter was to detect AF. However, no AF was detected. BP was normal as well. Therefore, the patient qualified for implantation of an ICM.

Table 6: REMOTE trial: Patient characteristics and demographics.

	Smartphone group (N = 28)	***Smartwatch group (N = 5)***	***Total (N = 33)***
CHARACTERISTICS			
Age (years)	63.50 (17)	74.80 ± 8.32	65.76 ± 12.67
Gender			
Male	21 (75.0%)	2 (40.0%)	24 (72.7%)
Female	7 (25.0%)	3 (60.0%)	9 (27.3%)
Height (m)	1.72 ± 0.10	1.70 ± 0.05	1.72 ± 0.09
Weight (kg)	76.0 (20)	75.80 ± 13.63	77.00 (19)
BMI (kg/m²)	25.39 (5)	26.27 ± 3.95	25.39 (5)
COMORBIDITIES/RISK FACTORS			
Smoking			
Never	18 (64.3%)	3 (60.0%)	21 (63.6%)
Former	2 (7.1%)	1 (20.0%)	3 (9.1%)
Current	8 (28.6%)	1 (20.0%)	9 (27.3%)
Hypertension	21 (75.0%)	3 (60%)	24 (72.7%)
Diabetes	5 (17.9%)	1 (20%)	6 (18.2%)
Hypercholesteremia	18 (64.3%)	2 (40.0%)	20 (60.6%)
Dyslipidemia	2 (7.1%)	0 (0.0%)	2 (6.1%)
Family history	5 (17.9%)	1 (20.0%)	6 (18.2%)
Heart failure	1 (3.6%)	0 (0.0%)	1 (3.0%)
CKD	1 (3.6%)	0 (0.0%)	1 (3.0%)
Alcohol abuse	1 (3.6%)	0 (0.0%)	1 (3.0%)
PAD	2 (7.1%)	0 (0.0%)	2 (6.1%)
Angina pectoris	1 (3.6%)	0 (0.0%)	1 (3.0%)
MI	1 (3.6%)	1 (20.0%)	2 (6.1%)
Atherosclerosis	0 (0.0%)	0 (0.0%)	0 (0.0%)
PFO	9 (32.1%)	3 (60.0%)	12 (36.4%)
PFO closure	1 (11.1%)	0 (0.0%)	1 (8.3%)
CAD	2 (7.1%)	1 (20.0%)	3 (9.1%)
No comorbidities	2 (7.1%)	0 (0.0%)	2 (6.1%)
History of Stroke/TIA			
Stroke	1 (3.6%)	1 (20.0%)	2 (6.1%)
TIA	5 (17.9%)	0 (0.0%)	5 (15.2%)
No history	22 (78.6%)	4 (80.0%)	26 (78.8%)

CKD, Chronic Kidney Disease; PAD, Peripheral Artery Disease; MI, Myocardial Infarction; PFO, Patent Foramen Ovale; CAD, Coronary Artery Disease.

The ICM implantation took place on November 24, 2020. On the same day, the patient started performing measurements with FibriCheck, twice a day, for a period of six months. The results of these measurements were blinded for the patient and caregiver. On November 27, 2020, AF was detected for the first time with both the ICM and FibriCheck. According to ICM data, the patient was in AF for 28 hours and 22 minutes. For FibriCheck, the AF burden was the amount of time patients performed measurements on which AF was detected (i.e., red measurements) plus half of the amount of time between the last normal measurement (i.e., green measurement) and the first red measurement and half of the amount of time between the last red and first green measurement, after the AF episode (***Supplementary Figure 7***). The first episode on FibriCheck was 36 hours and

18 minutes. Consequently, antiplatelet therapy was replaced with anticoagulant therapy, as described by the guidelines. However, there were several days between the first episode and the verification of the irregular ECG parts by the nurses. Therefore, initiation of anticoagulant therapy was also several days later. Afterwards, the patient had four more episodes, which lasted 28 hours and 44 minutes, 26 hours and 14 minutes, 20 hours and 4 minutes and 37 hours and 14 minutes, respectively, according to the ICM. For FibriCheck, the AF burden for the corresponding episodes was 41 hours and 24 minutes, 26 hours and 46 minutes, 18 hours and 51 minutes and 34 hours and 19 minutes. In conclusion, the total AF burden for FibriCheck was 8.5%, whereas the total AF burden for the ICM was 7.6% (***Supplementary Table 14***).

On February 8, 2021, the patient underwent ablation as a treatment for AF. After this procedure, no more AF episodes were detected by the ICM nor FibriCheck. Above that, the patient did not suffer from stroke recurrence thus far. On May 25, 2021, the six-month follow-up with FibriCheck came to an end and follow-up proceeded with solely the ICM.

Important to mention is the quality of the data gathered with FibriCheck. The majority of the measurements (92%) were of good quality. However, signal quality was insufficient in 8% of the measurements. Also, the motivation percentage of the patient was calculated by dividing the number of times the patient performed two or more measurements by the total number of days the patient had to use FibriCheck. This percentage is an indication of how well the patient performed its daily measurements. The motivation percentage for this patient was 42.5 %.

Case report 2

The second patient was admitted to ZOL, Genk, on July 26, 2020. The patient of interest is a 53 year old male, 1.70m of height, 77.00kg of weight, resulting in a BMI of 24.22 kg/m^2. The patient was an active smoker. Two comorbidities were present in this patient: arterial hypertension and type 2 diabetes. This patient had an MRS of 1. The NIHSS was 25 and CHA_2DS_2-VASc score was 2. The ASPECTS was 10.

This patient underwent standard of care clinical investigations as well. The telemetry conclusion was a normal, sinusal heart rhythm. The CT scan could not demonstrate ischemia nor hemorrhage. However, a stop image was detected at the middle cerebral artery, at the transition between M1 and M2. The results of the MRI showed limited signs of recent ischemia in the circulation area of the right middle cerebral artery (ACM 1). No stenosis was found in the carotid arteries. No abnormalities were detected during TEE. The patient did not have PFO. Laboratory investigations showed a glycemic level of 117 mg%, HbA1c of 6.5% and LDL-cholesterol of 152 mg/dL. In-hospital BP was 150/78 mmHg. As with the first patient, no clear cause was found, and the stroke was classified as cryptogenic.

At discharge, the NIHSS had decreased to two. The treatment of the patient consisted of thrombolysis and thrombectomy, antiplatelet therapy, antihypertensives and hypolipidemics. Hypolipidemic medication was added to his treatment after discharge. This patient underwent 7-day holter monitoring but was not scheduled for a 24-hour BP measurement. The result of the 7-day holter was negative for AF. Therefore, the patient qualified for ICM implantation.

On November 20, 2020, the ICM was inserted in the patient. On the same day, the patient started the simultaneous follow-up with FibriCheck, for a period of six months. In February 2021, transmission issues arose with the ICM. Consequently, the department of cardiology did not receive any data from the patient's ICM. These issues were not resolved, despite multiple attempts reaching the patient or his family. Above that, the patient was not consistent with performing FibriCheck measurements. Nevertheless, AF was detected with FibriCheck for the first time on April 19, 2021. It is not clear yet if the ICM also detected this, due to the transmission issues mentioned before. However, when the device is read out, this might come to light. Because it is not yet clear if the ICM detected this AF episode, anticoagulant therapy was not started in this patient.

In total, four AF episodes were detected with FibriCheck. The AF burden was not calculated yet. On May 15, 2021, the six-month follow-up with FibriCheck was ended and the patient was further monitored with the ICM alone. However, there are still transmission issues that need to be resolved. So far, the patient did not suffer from a recurrent stroke.

The quality of the data gathered with FibriCheck was good in 56.8% of the measurements, whereas in 43.2% of the measurements, signal quality was too low to eventually yield good-quality data. The motivation percentage in this patient was 39.8 %.

DISCUSSION

Our findings from the binomial logistic regression showed that CS patients with a smoking habit and CS patients with obesity were more likely to develop AF. When these two factors were combined, the likelihood of developing AF was even higher. CS patients with diabetes were less likely to develop AF. In contrast, Gender was not associated with AF. Furthermore, there was a significant association between several comorbidities and the presence of old brain infarctions in these CS patients. The CS patients in our population were more likely to have old brain infarctions when they suffered from hypercholesterolemia, a previous stroke/TIA, heart failure, family history, atherosclerosis or vascular disease. A further, in-depth ordinal regression analysis was carried out to establish these risk factors and comorbidities and showed that CS patients who did not drink excessively and who did not suffer from hypercholesterolemia or a previous stroke/TIA were less likely to have old brain infarctions. Then, we also found that when AF was detected in these patients, they were significantly older. It was more likely to detect AF in CS patients with an NIHSS ranging from 21 to 25. When assessing the AF detection methods, we found that AF detection rates were significantly higher for long-term monitoring (ICM) compared to 7-day holter and short-term monitoring (12-lead ECG, cardiac monitoring, 24-hour holter). This suggests that long-term monitoring is superior in detecting AF. This was further established in a Kaplan-Meier analysis, which showed that long-term monitoring had the highest AF detection percentage up to one year after stroke onset, which was expected. However, the AF detection percentage of the ICM would have been higher if the year after insertion instead of year after stroke onset was investigated, since the average amount of days between stroke and insertion was 190.5 days. Also, a cox regression demonstrated that it was more likely to detect AF with long-term monitoring and 7-day holter monitoring compared to short-term monitoring. Furthermore, AF and one-year mortality were strongly associated. More specifically, CS patients who developed AF were more likely to die within one year after stroke onset. This was further established with a Kaplan-Meier analysis. CS patients with a higher NIHSS score and a higher age were more likely to die within one year after stroke onset as well. The interim results of the REMOTE trial indicate that most of the patients are aware of the existence of mobile health and that recommendation of a mobile health implication by a governmental institution such as mHealthBelgium does not influence the willingness of the patient to use the application in question. In two patients, AF was detected with FibriCheck. These are already promising results. However, the trial is still ongoing and conclusions can only be drawn after the trial is fully completed.

Previous studies already reported that smoking and obesity are associated with AF (15). Both former and current smokers had a higher AF incidence, but the incidence was highest in current smokers (15). According to findings from the ARIC-study, the multivariable-adjusted hazard ratio (HR) for AF was 2.05 when compared to non-smokers (15, 39). Moreover, secondhand exposure to tobacco and exposure during gestational development or during early childhood are also associated with an increased risk of AF (15). Obesity was independently associated with an increased risk of AF when conditions such as MI, hypertension, etc. were accounted for, since obesity predisposes to these established risk factors for AF (15). Previous studies also found that diabetes increases the risk of AF (15). However, our findings suggest that patients with diabetes were less likely to develop AF. We also did not find an association between gender and AF, whereas multiple studies found that AF incidence is higher in men (15). Age

is also a commonly known risk factor (15). Our findings indicate that CS patients who developed AF were significantly older and are therefore in line with what is already known. Thus, CS patients with the above-mentioned risk factors may benefit from prolonged monitoring to detect AF. An attempt was made to create a score to assess CS patients' risk of AF based on several risk factors and comorbidities. *Zhao et al.* created the HAVOC score, which is computed by assessing obesity, hypertension, age, valvular heart disease, coronary artery disease (CAD) and congestive heart failure (40). The HAVOC score successfully stratified the AF risk after CS or cryptogenic TIA (40). These risk factors and comorbidities are in line with our findings. CS patients with a higher NIHSS, i.e. a more severe stroke (38), were more likely to have AF. Existing evidence has already demonstrated that strokes caused by AF are associated with increased morbidity and mortality (15). Therefore, this finding is in accordance with what is known.

We found that several comorbidities were associated with old brain infarctions, which is in line with previous studies. Hypercholesterolemia, alcohol abuse, cardiovascular diseases are known risk factors of stroke and thus brain infarctions (1, 3). Furthermore, previous stroke is a significant risk factor for a subsequent stroke (3). Family history is also associated with a higher risk of stroke (41).

Our results concerning the performance of AF detection methods are in accordance with results of previous studies. The CRYSTAL-AF study showed that the ICM was superior in detecting AF compared to 24 hours ECG monitoring after stroke (10). *Choe et al.* used the data from the CRYSTAL-AF study and performed an analysis to assess the sensitivity and negative predictive value (NPV) of other monitoring strategies in comparison with the ICM (42). The monitoring strategies were 24-hour holter, 48-hour holter, 7-day holter, 21-day event recorder and 30-day event recorder, periodic monitoring (i.e., quarterly) through 24-hour holter, 48-hour holter and 7-day holter, and monthly 24-hour holters (42). For all these strategies, the sensitivity and NPV were significantly lower compared to continuous monitoring with ICM (42). *De Angelis et al.* demonstrated the superiority of prolonged monitoring in CS patients as well. In 41% of the included CS patients, AF was detected with the ICM after a mean time of six months (9). *Haeusler et al.* reported that a first episode of AF is detected with prolonged monitoring using an ICM in up to one-third of all CS patients (43). *Poli et al.* reported that the AF detection rate is one-third after a year when candidates for an ICM after CS or cryptogenic TIA were selected on the basis of presence of one of the following AF risk factors: CHA_2DS_2-VASc score ≥ 4, atrial runs, LA size > 45 mm and the presence of left atrial appendage (LAA) flow ≤ 0.2 m/s, or spontaneous echo contrast in the LAA (44). In short, ICMs have dramatically increased the ability to detect paroxysmal AF in CS patients (21).

Strokes in patients with known AF are associated with an increased mortality rate (15). Moreover, one-year survival after stroke was worse in AF patients when compared to non-AF patients (15). The patients in the FOOTSTEP study suffered from CS. These individuals were considered non-AF patients at the time of stroke onset. However, the patients who eventually developed AF may have had previous, asymptomatic episodes due to the paroxysmal nature. Therefore, our findings, which indicate that CS patients who developed AF were more likely to die within one year after stroke onset, are considered to be in line with results from previous studies.

We found that a higher NIHSS score and a higher age were associated with one-year mortality. *Farooque et al.* reported that NIHSS score and age are important predictors for acute ischemic stroke outcomes (45). To assess outcomes after stroke, patients were followed for 90 days after hospital admission (45). This is in contrast with our results, which describe one-year mortality. Nevertheless, previous studies have already indicated that NIHSS score and age are strongly associated with post-stroke outcome and are therefore important for clinical decision-making (45, 46).

Since only four patients have completed the six-month follow-up during the REMOTE trial, no statistical analyses were performed. However, AF was detected with FibriCheck in two patients. The first patient was a former smoker and had arterial hypertension. The second patient was an active smoker and suffered from type 2 diabetes and

hypertension. As stated above, smoking was a significant predictor for AF in our CS patient population. Type 2 diabetes and arterial hypertension are important risk factors according to existing evidence (15), but are not in line with our findings. Even though no conclusions can be drawn from this, it shows the potential of mHealth technology. Prolonged monitoring with the ICM, which is guideline-recommended in CS patients, was applied in only 25 out of 391 patients. Moreover, 133 patients received a 7-day holter, from which 122 were negative for AF. Out of these 122 patients, 103 patients did not receive an ICM. However, these patients should have been monitored with an ICM. This indicates that the ICM is not always used when indicated. This may be due to the invasive nature of the procedure and the costs (21). Therefore, if the results of the REMOTE trial continue to evolve in this way, mHealth might be a worthy, cost-effective add-on or alternative for the ICM. With mHealth, the patient is involved with its own follow-up, contributing to patient empowerment. Furthermore, no medical infrastructure is needed, and no elaborate training is necessary to successfully perform measurements (30). On top of that, the smartwatch automatically performs measurements, which is even more convenient for the patient. As mentioned before, FibriCheck was health-economically assessed as a monitoring strategy for AF detection in CS patients and turned out to be a cost-effective method (32). Furthermore, several mHealth technologies designed for AF detection, including FibriCheck, showed great sensitivity and specificity (30, 47).

Limitations

Several limitations should be stated. Data from FOOTSTEP study was collected retrospectively. Consequently, the disadvantages that come along with retrospective studies should be taken into account. Also, five patients who suffered from CS in 2019, received an ICM in 2020. Thus, they did not complete the three-year follow-up with the ICM yet. Therefore, AF detection rates might be higher. Furthermore, the REMOTE trial is still ongoing. At the moment, four patients have completed the six-month follow-up with mHealth and the ICM. Therefore, conclusions can only be made when the trial is fully completed with the intended, precalculated sample size (N = 226).

CONCLUSION

Several risk factors and comorbidities increase the likelihood of AF in CS patients. Furthermore, NIHSS, age and AF are associated with one-year mortality. Therefore, when these factors are present in patients admitted due to CS, prolonged monitoring should be strongly indicated. However, prolonged monitoring with ICMs, which is guideline-recommended, is carried out insufficiently in practice. Therefore, mHealth might be a possible add-on monitoring method. Preliminary results showed that FibriCheck can detect AF in CS patients, with a similar AF burden. Above that, it is non-invasive, cost-effective, patient-friendly, and can improve patient empowerment. Nevertheless, more results from the REMOTE-trial and other studies are necessary to establish this. Above that, a distinction could be made between patients with a high or low risk of AF, based on risk factors and comorbidities that are present in patients. A possible hypothesis might be that high-risk patients might benefit more from continuous monitoring, whereas mHealth monitoring could suffice for low-risk patients. However, future studies are necessary to demonstrate this.

REFERENCES

1. Hankey GJ. Stroke. Lancet. 2017;389(10069):641-54.
2. The burden of stroke in Europe - Report. King's College London for the Stroke alliance for Europe (SAFE). 2017.
3. Donkor ES. Stroke in the 21(st) Century: A Snapshot of the Burden, Epidemiology, and Quality of Life. Stroke Res Treat. 2018;2018:3238165.
4. Fonseca AC, Ferro JM. Cryptogenic stroke. Eur J Neurol. 2015;22(4):618-23.
5. Homma S, Messe SR, Rundek T, Sun YP, Franke J, Davidson K, et al. Patent foramen ovale. Nat Rev Dis Primers. 2016;2:15086.
6. Shafaat O, Sotoudeh H. Stroke Imaging. StatPearls [Internet]: Treasure Island (FL): StatPearls Publishing; 2020.
7. Powers WJ, Rabinstein AA, Ackerson T, Adeoye OM, Bambakidis NC, Becker K, et al. Guidelines for the Early Management of Patients With Acute Ischemic Stroke: 2019 Update to the 2018 Guidelines for the Early Management of Acute Ischemic Stroke: A Guideline for Healthcare Professionals From the American Heart Association/American Stroke Association. Stroke. 2019;50(12):e344-e418.
8. Jamieson DG. Diagnosis of ischemic stroke. Am J Med. 2009;122(4 Suppl 2):S14-20.
9. De Angelis MV, Di Stefano V, Franciotti R, Furia N, Di Girolamo E, Onofrj M, et al. Cryptogenic stroke and atrial fibrillation in a real-world population: the role of insertable cardiac monitors. Sci Rep. 2020;10(1):3230.
10. Sanna T, Diener HC, Passman RS, Di Lazzaro V, Bernstein RA, Morillo CA, et al. Cryptogenic stroke and underlying atrial fibrillation. N Engl J Med. 2014;370(26):2478-86.
11. Gladstone DJ, Spring M, Dorian P, Panzov V, Thorpe KE, Hall J, et al. Atrial fibrillation in patients with cryptogenic stroke. N Engl J Med. 2014;370(26):2467-77.
12. Sanna T, Ziegler PD, Crea F. Detection and management of atrial fibrillation after cryptogenic stroke or embolic stroke of undetermined source. Clin Cardiol. 2018;41(3):426-32.
13. Dalen JE, Alpert JS. Silent Atrial Fibrillation and Cryptogenic Strokes. Am J Med. 2017;130(3):264-7.
14. Xu J, Luc JG, Phan K. Atrial fibrillation: review of current treatment strategies. J Thorac Dis. 2016;8(9):E886-E900.
15. Staerk L, Sherer JA, Ko D, Benjamin EJ, Helm RH. Atrial Fibrillation: Epidemiology, Pathophysiology, and Clinical Outcomes. Circ Res. 2017;120(9):1501-17.
16. Burkowitz J, Merzenich C, Grassme K, Bruggenjurgen B. Insertable cardiac monitors in the diagnosis of syncope and the detection of atrial fibrillation: A systematic review and meta-analysis. Eur J Prev Cardiol. 2016;23(12):1261-72.
17. Ziegler PD, Rogers JD, Ferreira SW, Nichols AJ, Richards M, Koehler JL, et al. Long-term detection of atrial fibrillation with insertable cardiac monitors in a real-world cryptogenic stroke population. Int J Cardiol. 2017;244:175-9.
18. Akrawinthawong K, Venkatesh Prasad K, Mehdirad AA, Ferreira SW. Atrial Fibrillation Monitoring in Cryptogenic Stroke: the Gaps Between Evidence and Practice. Curr Cardiol Rep. 2015;17(12):118.
19. 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 of Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2020.
20. Ciconte G, Giacopelli D, Pappone C. The Role of Implantable Cardiac Monitors in Atrial Fibrillation Management. J Atr Fibrillation. 2017;10(2):1590.
21. Giancaterino S, Lupercio F, Nishimura M, Hsu JC. Current and Future Use of Insertable Cardiac Monitors. JACC Clin Electrophysiol. 2018;4(11):1383-96.
22. Implantaten en invasieve medische hulpmiddelen : Lijst van de verstrekkingen en nominatieve lijsten van de individuele hulpmiddelen. 2020.

23. Miller DJ, Shah K, Modi S, Mahajan A, Zahoor S, Affan M. The Evolution and Application of Cardiac Monitoring for Occult Atrial Fibrillation in Cryptogenic Stroke and TIA. Curr Treat Options Neurol. 2016;18(4):17.
24. mHealthBelgium 2020 [cited 2021 April 12th, 2021]. Available from: https://mhealthbelgium.be/nl/.
25. Li KHC, White FA, Tipoe T, Liu T, Wong MC, Jesuthasan A, et al. The Current State of Mobile Phone Apps for Monitoring Heart Rate, Heart Rate Variability, and Atrial Fibrillation: Narrative Review. JMIR Mhealth Uhealth. 2019;7(2):e11606.
26. Brasier N, Raichle CJ, Dorr M, Becke A, Nohturfft V, Weber S, et al. Detection of atrial fibrillation with a smartphone camera: first prospective, international, two-centre, clinical validation study (DETECT AF PRO). Europace. 2019;21(1):41-7.
27. Giebel GD, Gissel C. Accuracy of mHealth Devices for Atrial Fibrillation Screening: Systematic Review. JMIR Mhealth Uhealth. 2019;7(6):e13641.
28. Vaes B, Stalpaert S, Tavernier K, Thaels B, Lapeire D, Mullens W, et al. The diagnostic accuracy of the MyDiagnostick to detect atrial fibrillation in primary care. BMC Fam Pract. 2014;15:113.
29. Tieleman RG, Plantinga Y, Rinkes D, Bartels GL, Posma JL, Cator R, et al. Validation and clinical use of a novel diagnostic device for screening of atrial fibrillation. Europace. 2014;16(9):1291-5.
30. Proesmans T, Mortelmans C, Van Haelst R, Verbrugge F, Vandervoort P, Vaes B. Mobile Phone-Based Use of the Photoplethysmography Technique to Detect Atrial Fibrillation in Primary Care: Diagnostic Accuracy Study of the FibriCheck App. JMIR Mhealth Uhealth. 2019;7(3):e12284.
31. Elgendi M, Fletcher R, Liang Y, Howard N, Lovell NH, Abbott D, et al. The use of photoplethysmography for assessing hypertension. NPJ Digit Med. 2019;2:60.
32. Proesmans T, Desteghe L, Berti D, Nuyens D, De Cock D, Soufflet V, et al. Health economic assessment of smartphone implementation for atrial fibrillation monitoring in cryptogenic stroke patients. . 2018.
33. Chen LY, Chung MK, Allen LA, Ezekowitz M, Furie KL, McCabe P, et al. Atrial Fibrillation Burden: Moving Beyond Atrial Fibrillation as a Binary Entity: A Scientific Statement From the American Heart Association. Circulation. 2018;137(20):e623-e44.
34. Jones NR, Taylor CJ, Hobbs FDR, Bowman L, Casadei B. Screening for atrial fibrillation: a call for evidence. Eur Heart J. 2020;41(10):1075-85.
35. Nolker G, Mayer J, Boldt LH, Seidl K, V VAND, Massa T, et al. Performance of an Implantable Cardiac Monitor to Detect Atrial Fibrillation: Results of the DETECT AF Study. J Cardiovasc Electrophysiol. 2016;27(12):1403-10.
36. Verbrugge FH, Proesmans T, Vijgen J, Mullens W, Rivero-Ayerza M, Van Herendael H, et al. Atrial fibrillation screening with photo-plethysmography through a smartphone camera. Europace. 2019;21(8):1167-75.
37. Coppens M, Eikelboom JW, Hart RG, Yusuf S, Lip GY, Dorian P, et al. The CHA2DS2-VASc score identifies those patients with atrial fibrillation and a CHADS2 score of 1 who are unlikely to benefit from oral anticoagulant therapy. Eur Heart J. 2013;34(3):170-6.
38. Kwah LK, Diong J. National Institutes of Health Stroke Scale (NIHSS). J Physiother. 2014;60(1):61.
39. Chamberlain AM, Agarwal SK, Folsom AR, Duval S, Soliman EZ, Ambrose M, et al. Smoking and incidence of atrial fibrillation: results from the Atherosclerosis Risk in Communities (ARIC) study. Heart Rhythm. 2011;8(8):1160-6.
40. Zhao SX, Ziegler PD, Crawford MH, Kwong C, Koehler JL, Passman RS. Evaluation of a clinical score for predicting atrial fibrillation in cryptogenic stroke patients with insertable cardiac monitors: results from the CRYSTAL AF study. Ther Adv Neurol Disord. 2019;12:1756286419842698.
41. Boehme AK, Esenwa C, Elkind MS. Stroke Risk Factors, Genetics, and Prevention. Circ Res. 2017;120(3):472-95.

42. Choe WC, Passman RS, Brachmann J, Morillo CA, Sanna T, Bernstein RA, et al. A Comparison of Atrial Fibrillation Monitoring Strategies After Cryptogenic Stroke (from the Cryptogenic Stroke and Underlying AF Trial). Am J Cardiol. 2015;116(6):889-93.
43. Haeusler KG, Tutuncu S, Schnabel RB. Detection of Atrial Fibrillation in Cryptogenic Stroke. Curr Neurol Neurosci Rep. 2018;18(10):66.
44. Poli S, Diedler J, Hartig F, Gotz N, Bauer A, Sachse T, et al. Insertable cardiac monitors after cryptogenic stroke--a risk factor based approach to enhance the detection rate for paroxysmal atrial fibrillation. Eur J Neurol. 2016;23(2):375-81.
45. Farooque U, Lohano AK, Kumar A, Karimi S, Yasmin F, Bollampally VC, et al. Validity of National Institutes of Health Stroke Scale for Severity of Stroke to Predict Mortality Among Patients Presenting With Symptoms of Stroke. Cureus. 2020;12(9):e10255.
46. Saber H, Saver JL. Distributional Validity and Prognostic Power of the National Institutes of Health Stroke Scale in US Administrative Claims Data. JAMA Neurol. 2020;77(5):606-12.
47. O'Sullivan JW, Grigg S, Crawford W, Turakhia MP, Perez M, Ingelsson E, et al. Accuracy of Smartphone Camera Applications for Detecting Atrial Fibrillation: A Systematic Review and Meta-analysis. JAMA Netw Open. 2020;3(4):e202064

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SUPPLEMENTARY

Supplementary Table 1: Binomial logistic regression: diabetes, obesity and smoking.

	B	S.E.	Wald	df	Sig.	Exp(B)	95% CI for Exp(B)	
							Lower	Upper
Diabetes - Smoking	-0.208	0.437	0.228	1	0.633	0.812	0.345	1.910
Obesity - Smoking	1.417	0.388	13.367	1	**<0.001*** **	4.127	1.930	8.823
Diabetes - Obesity	-0.770	0.446	2.974	1	0.085	0.463	0.193	1.111

The combination of smoking and obesity is a significant predictor for having AF ($p < 0.001$).
S.E., Standard Error; df, degrees of freedom; Sig., Significance; CI, Confidence Interval
***$p < 0.001$

Supplementary Table 2: Association between comorbidities and number of old infarctions.

Comorbidities	Pearson Chi Square p-value
Previous Stroke/TIA	**0.011***
Hypercholesterolemia	**0.017***
Family History	**0.023***
PFO	**0.027***
Atherosclerosis	**0.046***
Vascular Disease	**0.049***
Heart Failure	**0.049***

The comorbidities that are mentioned are significantly associated with the number of old infarctions in this CS patient population.
CS, Cryptogenic Stroke; TIA, Transient Ischemic Attack; PFO, Patent Foramen Ovale.
*$p < 0.05$

Supplementary Table 3: Chi-Square test: association between previous stroke/TIA and having an ICM.

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	12.075[a]	1	0.001		
Continuity Correction[b]	10.177	1	0.001		
Likelihood Ratio	9.390	1	0.002		
Fisher's Exact Test				**0.002****	**0.002****
Linear-by-Linear Association	12.044	1	0.001		
N of Valid Cases	391				

a: 1 cell (25,0%) has expected count less than 5. The minimum expected count is 3.90.
b: Computed only for a 2x2 table
There was a significant association between previous stroke/TIA and having an ICM (p = 0.002).
TIA, Transient Ischemic Attack; ICM, Insertable Cardiac Monitor; df, Degrees of Freedom; Sig., Significance.
**$p < 0.01$

Supplementary Table 4: Chi-square test: association between comorbidities and gender.

Comorbidity	Significance
Smoking	0.092
Alcohol abuse	0.079
Hypertension	**0.042***
Diabetes	**0.044***
Hypercholesteremia	0.627
Obesity	0.109
Previous stroke/TIA	0.381
Heart failure	0.771
Family history	0.569
CKD	0.766
PVD	**0.045***
MI	0.679
Atherosclerosis	0.083
Vascular disease	0.152
PFO	0.241

Hypertension, diabetes and PVD were significantly associated with gender ($p = 0.042$, $p = 0.044$, $p = 0.045$ respectively).

TIA, Transient Ischemic Attack; CKD, Chronic Kidney disease; PVD, Peripheral Vascular Disease; MI, Myocardial Infarction; PFO, Patent Foramen Ovale.

*$p < 0.05$

Supplementary Table 5: Chi-square test: association between gender and AF.

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	0.347[a]	1	0.556		
Continuity Correction[b]	0.197	1	0.657		
Likelihood Ratio	0.348	1	0.555		
Fisher's Exact Test				0.564	0.329
Linear-by-Linear Association	0.346	1	0.556		
N of Valid Cases	391				

a: 0 cells (0.0%) have expected count less than 5. The minimum expected count is 26.02.
b: Computed only for a 2x2 table.
There was no association between gender and having AF (p = 0.556).
AF, Atrial Fibrillation; df, Degrees of Freedom; Sig., Significance.

Supplementary Table 6: Mann-Whitney U Test: Distribution of age in patients with and without AF.

Independent-Samples Mann-Whitney U Test Summary	
Total N	391
Mann-Whitney U	12,177
Wilcoxon W	13,717
Test Statistic	12,177
Standard Error	726.524
Standardized Test Statistic	4.043
Asymptotic Sig. (2-sided test)	**<0.001*** **

Age was significantly different for patients with and without AF (p < 0.001).
AF, Atrial Fibrillation; Sig., Significance.
***$p < 0.001$

Supplementary Table 7: Mann-Whitney U Test: AF and Ejection Fraction/LA Diameter.

Independent-Samples Mann-Whitney U Test Summary			
Ejection Fraction		**LA Diameter**	
Total N	342	**Total N**	343
Mann-Whitney U	6,817.00	**Mann-Whitney U**	8,271.50
Wilcoxon W	7,597.00	**Wilcoxon W**	9,091.50
Test Statistic	6,817.00	**Test Statistic**	8,271.50
Standard Error	206.16	**Standard Error**	459.84
Standardized Test Statistic	4.407	**Standardized Test Statistic**	4.809
Asymptotic Sig. (2-sided test)	<0.001***	**Asymptotic Sig. (2-sided test)**	<0.001***

Ejection fraction ($p < 0.001$) and LA diameter ($p < 0.001$) were significantly different for patients with and without AF.
AF, Atrial Fibrillation; Sig., Significance; LA, Left Atrium.
***$p < 0.001$

Supplementary Table 8: Binomial logistic regression: NIHSS and CHA_2DS_2-VASc as predictors for AF.

	B	**S.E.**	**Wald**	**df**	**Sig.**	**Exp(B)**	**95% C.I. for Exp(B)**	
							Lower	**Upper**
NIHSS category			10.562	5	0.061			
NIHSS = 6-10	0.918	0.422	4.725	1	**0.030***	2.505	1.095	5.734
NIHSS = 11-15	0.679	0.472	2.068	1	0.150	1.972	0.782	4.974
NIHSS = 16-20	0.875	0.634	1.905	1	0.168	2.399	0.692	8.313
NIHSS = 21-25	1.880	0.733	6.582	1	**0.010***	6.553	1.559	27.553
NIHSS = 26-30	-19.172	23,194.136	0.000	1	0.999	0.000	0.000	.
CHA_2DS_2-VASc			8.343	4	0.080			
CHA_2DS_2-VASc = 2	-0.326	0.741	0.194	1	0.659	0.721	0.169	3.082
CHA_2DS_2-VASc = 3	0.241	0.679	0.126	1	0.722	1.273	0.336	4.819
CHA_2DS_2-VASc = 4	0.408	0.697	0.342	1	0.559	1.503	0.383	5.897
CHA_2DS_2-VASc = 5	1.457	0.789	3.407	1	0.065	4.294	0.914	20.179
Constant	-2.330	0.622	14.014	1	0.000	.097		

This analysis showed that CS patients with an NIHSS score between 6 and 10 and between 21 and 25 were respectively 2.505 and 6.553 times more likely to have AF ($p = 0.03$ and $p = 0.01$ respectively).
AF, Atrial Fibrillation; S.E., Standard Error; df, Degrees of Freedom, Sig. Significance; C.I., Confidence Interval; NIHSS; National Institutions of Health Stroke Scale.
*$p < 0.05$

Supplementary Table 9: McNemar's Test: AF detection methods.

Comparison	N	Exact Sig. (2-tailed)
SM – 12-lead ECG	359	0.227
SM – 24h Holter	100	0.250
SM – 7d Holter	129	**<0.001*** **
SM – FC	9	1.000
SM – ICM/ICD/PM	37	0.070
12-lead ECG – 24h Holter	97	1.000
12-lead ECG – 7d Holter	126	**0.022***
12-lead ECG – FC	9	1.000
12-lead ECG – ICM/ICD/PM	35	**0.016***
24h Holter – 7d Holter	18	1.000
24h Holter – FC	1	1.000
24h Holter – ICM/ICD/PM	3	1.000
7d Holter – FC	7	1.000
7d Holter – ICM/ICD/PM	20	0.375

There was a significant difference in AF detection between stroke unit monitoring and 7-day holter, 12-lead-ECG and 7-day holter and 12-lead ECG and ICM/ICD/PM ($p < 0.001$, $p = 0.022$, $p = 0.016$ respectively).

Sig., Significance; AF, Atrial Fibrillation; SM, Stroke Unit Monitoring; ECG, Electrocardiogram; ICM, Insertable Cardiac Monitor; ICD, Implantable Cardioverter Defibrillator; PM, Pacemaker; FC, FibriCheck.

*$p < 0.05$

***$p < 0.001$

Supplementary Table 10: Cox Regression: AF detection methods compared to 12-lead ECG.

Variables in the Equation								
	B	S.E.	Wald	df	Sig.	Exp(B)	95.0% C.I. for Exp(B)	
							Lower	Upper
AF detection method			15.579	5	**0.008****			
7-day Holter	0.516	.383	1.817	1	0.178	1.675	0.791	3.547
SM	-0.182	.350	0.271	1	0.603	0.834	0.420	1.654
ICM	1.575	.471	11.167	1	**0.001****	4.832	1.918	12.174
FibriCheck	0.834	1.027	0.659	1	0.417	2.302	0.307	17.246
24-hour Holter	-12.615	243.220	0.003	1	0.959	0.000	0.000	3,55E+204
Chi-Square	23.061							

This analysis shows that it was 4.832 times more likely to detect AF with the ICM than with a 12-lead ECG (p = 0.001).

AF, Atrial Fibrillation; ECG, Electrocardiogram; S.E., Standard Error; df, Degrees of Freedom, Sig. Significance; C.I., Confidence Interval; SM, Stroke Unit Monitoring; ICM, Insertable Cardiac Monitor.

**$p < 0.01$

Supplementary Table 11: Cox Regression: AF detection method categories compared to short-term monitoring.

Variables in the Equation								
	B	S.E.	Wald	df	Sig.	Exp(B)	95,0% C.I. for Exp(B)	
							Lower	Upper
AF detection method category			17.415	2	0.000			
Long-term monitoring	1.649	0.416	15.695	1	**<0.001*****	5.200	2.300	11.755
7-day Holter	0.735	0.348	4.458	1	**0.035***	2.086	1.054	4.127
Chi-Square	13.498							

This analysis shows that it was respectively 5.200 and 2.086 times more likely to detect AF with long-term monitoring and 7-day holter monitoring than with a 12-lead ECG (p < 0.001, p = 0.05 respectively).

ECG, Electrocardiogram; S.E., Standard Error; df, Degrees of Freedom, Sig. Significance; C.I., Confidence Interval.

*$p < 0.05$

***$p < 0.001$

Supplementary Table 12: Mann-Whitney U Test: NIHSS, age, and CHA_2DS_2-VASc score and one-year mortality.

Independent-Samples Mann-Whitney U Test Summary			
	NIHSS category	**Age of onset category**	**CHA_2DS_2-VASc score**
Total N	322	391	391
Mann-Whitney U	7,328.50	11,254.00	8,596.500
Wilcoxon W	8,069.50	12,244.00	9,586.500
Test Statistic	7,328.50	11,254.00	8,596.500
Standard Error	456.72	660.37	677.633
Standardized Test Statistic	4.231	5.482	1.420
Asymptotic Sig. (2-sided test)	**<0.001*** **	**<0.001*** **	0.155

NIHSS ($p < 0.001$) and age ($p < 0.001$) were significantly different for patients who died within one year and those who did not.

NIHSS, National Institutes of Health Stroke Scale; Sig., Significance.

***$p < 0.001$

Supplementary Table 13: Questionnaire patient's vision on mhealth.

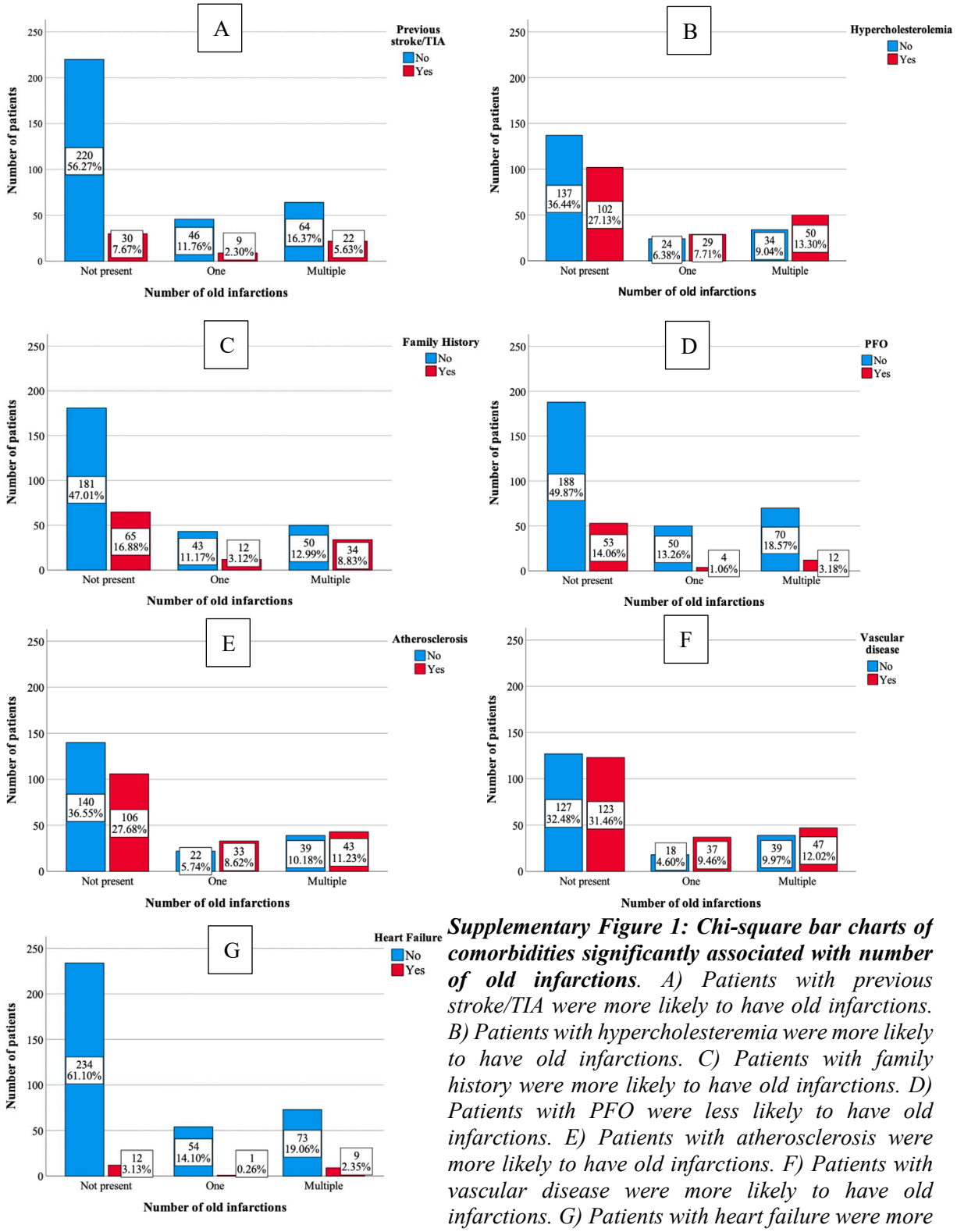
Patient study ID: Timing: ☐ Before use of mHealth (1 month after discharge)	
1. Are you aware of the availability of health applications for smartphones?	☐ Yes **(73.9%)** ☐ No **(26.1%)**
2. What type of applications do you download?	☐ Games **(30.4%)** ☐ Education **(21.7%)** ☐ Books **(4.3%)** ☐ News (**65.2%)** ☐ Social **(69.6%)** ☐ Health and lifestyle **(60.9%)** ☐ Economic (**56.5%)** ☐ Other (**4.3%)**
3. What kind of app do you download when you download a health app?	☐ BMI/alcohol units **(13.0%)** ☐ Smoking cessation **(4.3%)** ☐ Diet and nutrition **(17.4%)** ☐ Fitness (e.g., pedometer) **(60.9%)** ☐ Relaxation **(4.3%)** ☐ None **(30.4%)** ☐ Other **(0%)**
4. Check the box that suits your opinion the most. a) I would use a health application that is **NOT** supported by a recognized health institution such as mHealthBelgium.	☐ Strongly agreed **(4.3%)** ☐ Agreed **(56.5%)** ☐ Neutral **(34.8%)** ☐ Disagreed **(4.3%)** ☐ Strongly disagreed **(0%)**
b) I would use a health application that is supported by a recognized health institution such as mHealthBelgium.	☐ Strongly agreed **(13.0%)** ☐ Agreed **(56.5%)** ☐ Neutral **(30.4%)** ☐ Disagreed **(0%)** ☐ Strongly disagreed **(0%)**

The questions and possible answers are shown. Furthermore, the percentage of patients that chose a particular answer are given.
mHealth, Mobile Health.

Supplementary Table 14: Comparison of AF burden on Fibricheck and ICM.

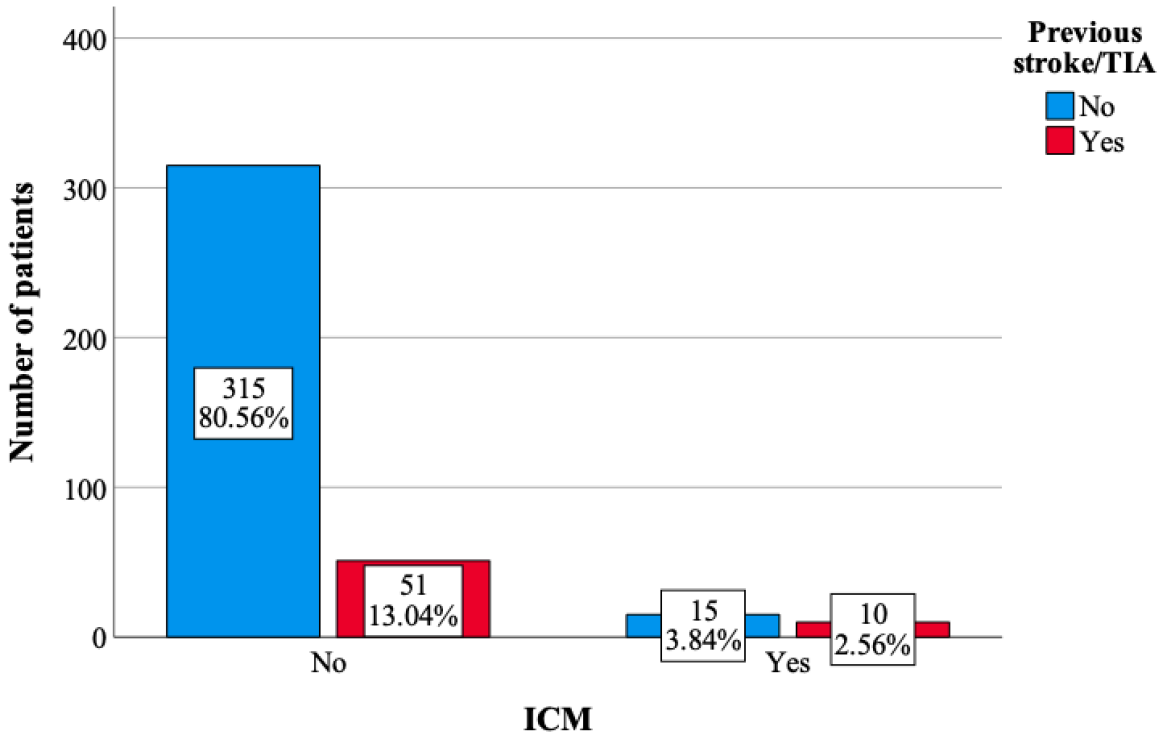
Episode	FibriCheck	ICM
1	36h18	28h22
2	41h24	28h44
3	26h46	26h14
4	18h51	20h04
5	34h19	37h14
AF burden	**8.5%**	**7.6%**

In this table, the AF burden (= amount of time in AF) from the ICM and FibriCheck are compared.
ICM, Insertable Cardiac Monitor; AF, Atrial Fibrillation.

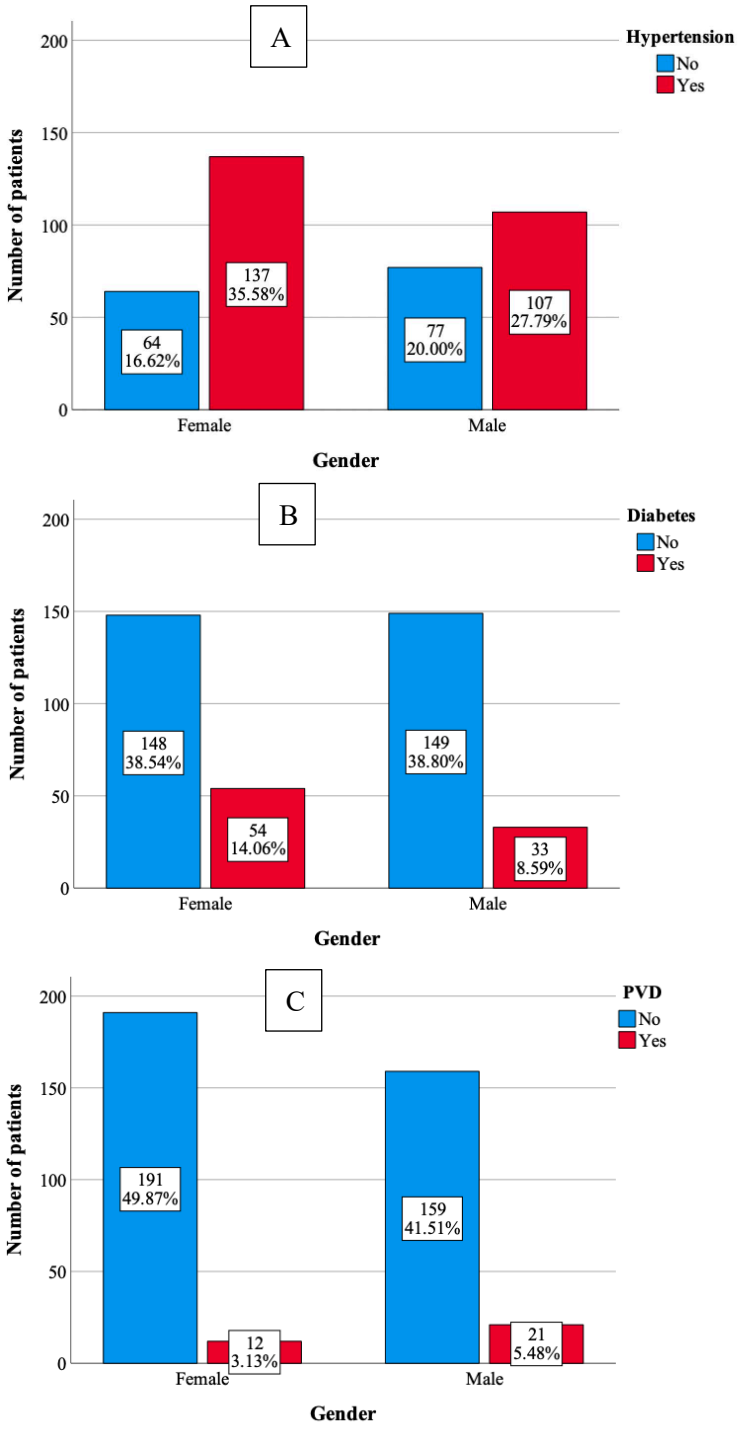


Supplementary Figure 1: Chi-square bar charts of comorbidities significantly associated with number of old infarctions*. A) Patients with previous stroke/TIA were more likely to have old infarctions. B) Patients with hypercholesteremia were more likely to have old infarctions. C) Patients with family history were more likely to have old infarctions. D) Patients with PFO were less likely to have old infarctions. E) Patients with atherosclerosis were more likely to have old infarctions. F) Patients with vascular disease were more likely to have old infarctions. G) Patients with heart failure were more likely to have old infarctions.*

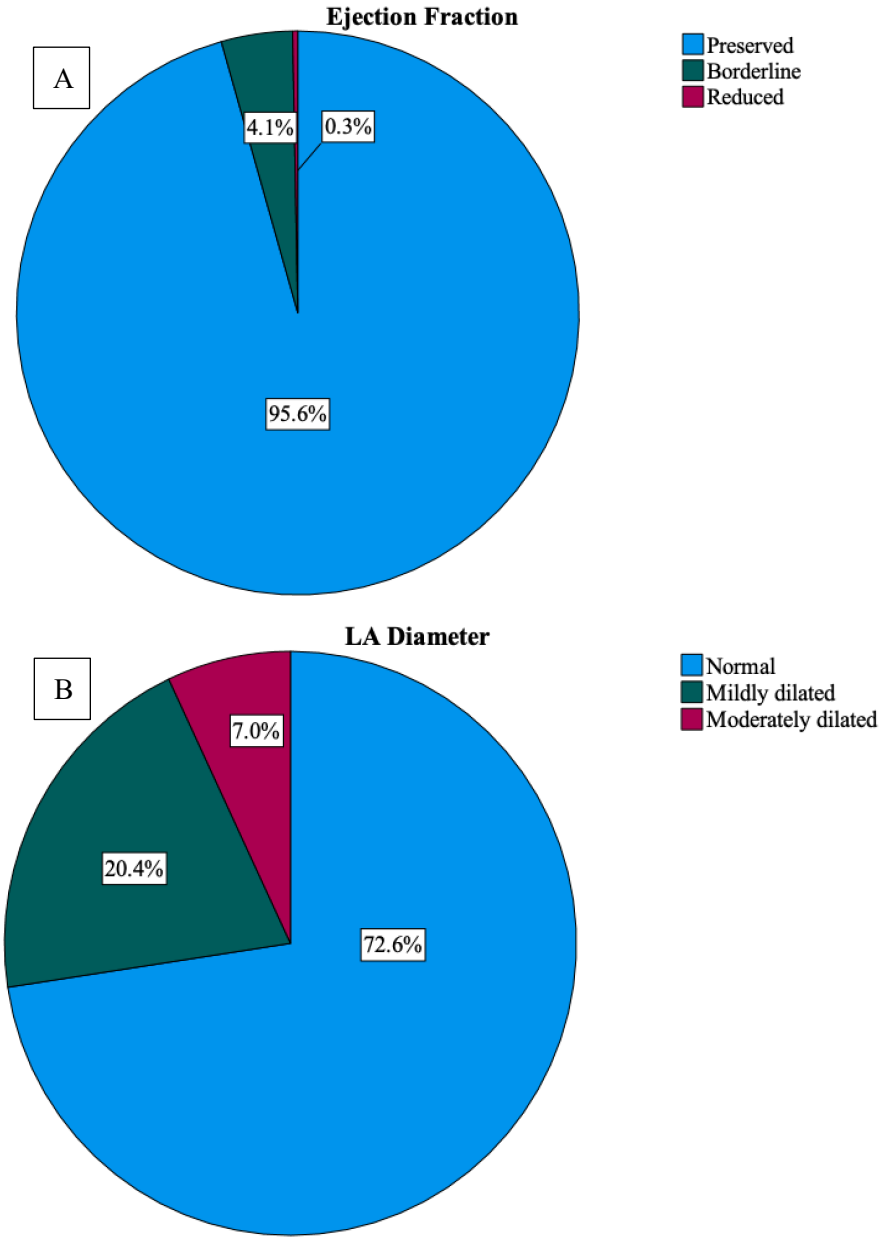
TIA, Transient Ischemic Attack; PFO, Patent Foramen Ovale.



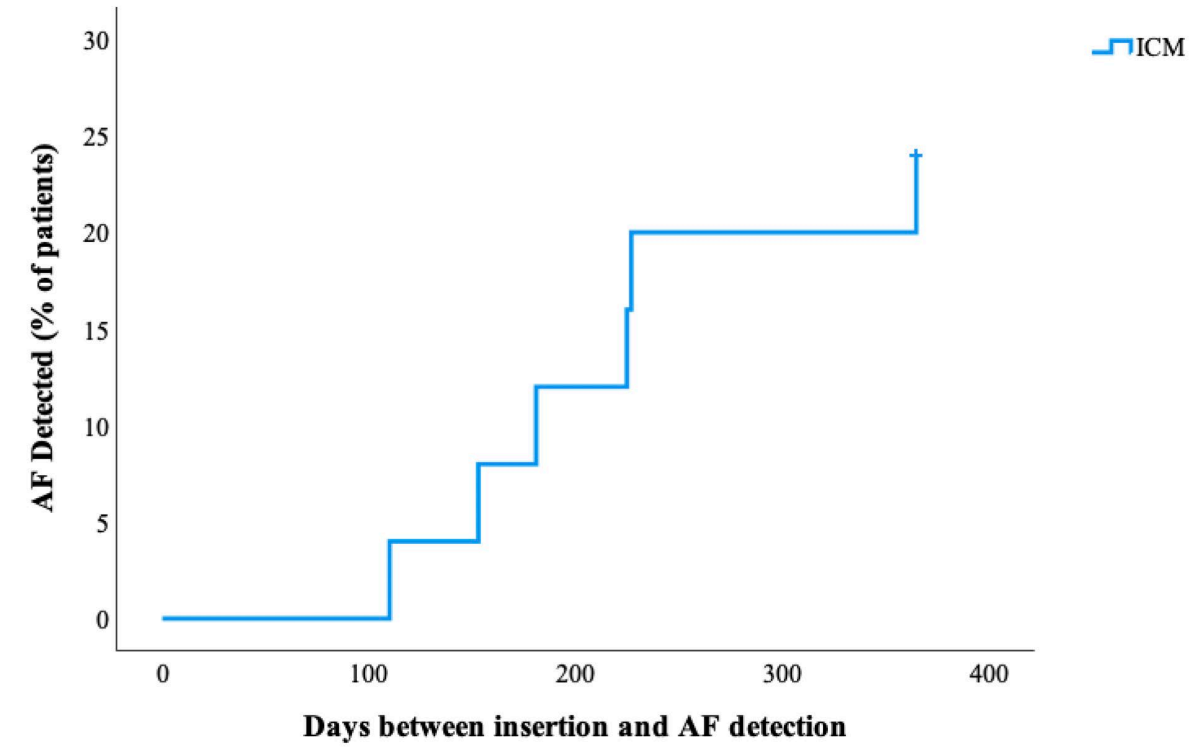
Supplementary Figure 2: Chi-square bar charts for the association between previous stroke/TIA and having an ICM. *When CS patients suffered from a previous stroke/TIA, they were more likely to have an ICM. TIA, Transient Ischemic Attack.*



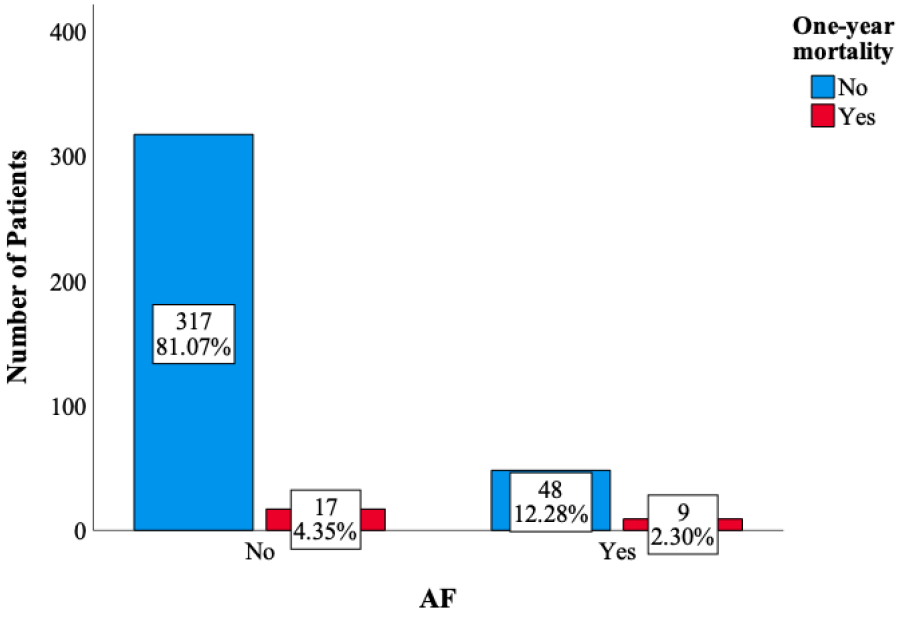
Supplementary Figure 3: Chi-square bar charts of comorbidities significantly associated with gender. *A) Females were more likely to suffer from hypertension. B) Female were more likely to have diabetes. C) Male patients were more likely to have PVD. PVD, Peripheral Vascular Disease.*



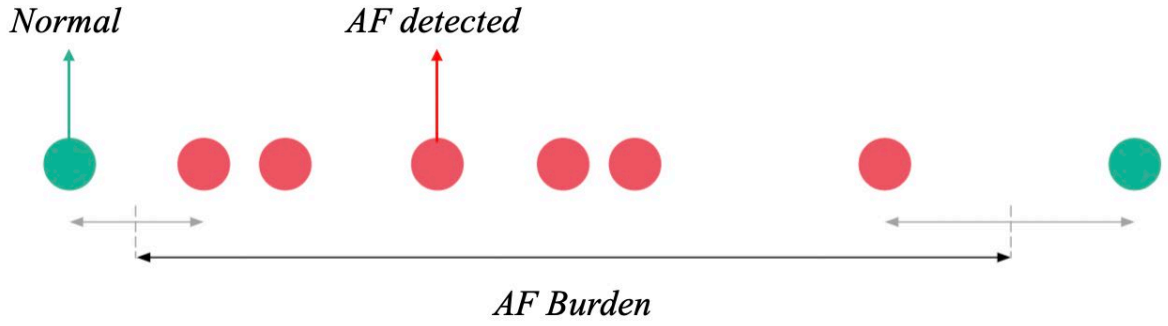
Supplementary Figure 4: Distribution of CS patients across categories of ejection fraction and LA diameter*. A) The majority of CS patients had a preserved EF, i.e., 95.61%. From the remaining patients, 4.09% and 0.29% respectively had a borderline and reduced EF. B) The majority had a normal LA diameter. In 20.41% of patients, the LA was mildly dilated. In 7.00% the LA was moderately dilated.*
EF, Ejection Fraction; LA, Left Atrium.



Supplementary Figure 5: Kaplan-Meier analysis of ICM. One year after ICM insertion, in 24% of the patients, AF was detected.



Supplementary Figure 6: Chi-square bar chart for the association between AF and one-year mortality. *Patients with AF were more likely to die within one year after stroke onset.*



Supplementary Figure 7: Visualization of AF burden calculation for FibriCheck. *Red circles represent measurements on which AF was detected. Green circles represent normal measurements. The AF burden was the sum of the amount of time patients performed red measurements, half of the amount of time between the last green measurement and the first red measurement, and half of the amount of time between the last red and first green measurement after the AF episode.*