Review Article

Indonesian Journal of Cardiology
Indonesian J Cardiol 2021:42:81-85
pISSN: 0126-3773 / eISSN: 2620-4762
doi: 10.30701/ijc.1143

Cryptogenic Stroke: Cardiac Rhythm Monitoring as An Indispensable Screening Modality

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Abstract
The prevalence of stroke in Indonesia increased over time. Cryptogenic stroke (CS) ranges from 15 to 40% from all ischemic strokes. Atrial fibrillation is predicted as one of the etiologies behind CS. As episodes of AF, in particular paroxysmal AF (PAF), were difficult to diagnose by usual diagnostic modalities, strategies based on longer rhythm monitoring should be considered to evaluate patients with CS. Innovations in digital health technologies will further help the diagnosis and management of patients with PAF.

(Indonesian J Cardiol. 2021;42:81-85)

Keywords: Cryptogenic stroke; Atrial Fibrillation; Holter monitoring; Electrocardiogram

Introdution

The prevalence of stroke in Indonesia increased over time. Cryptogenic stroke (CS) ranges from 15 to 40% from all ischemic strokes. Atrial fibrillation is predicted as one of the etiologies behind CS. As episodes of AF, in particular paroxysmal AF (PAF), were difficult to diagnose by usual diagnostic modalities, strategies based on longer rhythm monitoring should be considered to evaluate patients with CS. Innovations in digital health technologies will further help the diagnosis and management of patients with PAF.

According to the World Health Organization (WHO), stroke is the second most common cause of death and the third most common cause of disability worldwide1. In Indonesia, stroke is the leading cause of death and accounts for 15.4% of death in almost all hospitals.[2] Cryptogenic stroke (CS) is defined as ischemic stroke with undefined etiologies after being evaluated comprehensively.[3] Clinically, the diagnosis of CS can also be considered when assessments are inadequate or etiologies are multiple. CS ranges from 15 to 40% from all ischemic strokes.[4]

Many have hypothesized explanations behind the occurrence of stroke but to no avail. CS poses a particular clinical dilemma as, without clear etiology, an educated guess is the most appropriate treatment modalities subsequently.[5] Moreover, understanding the etiology of ischemic stroke is important to prevent recurrence as stroke has a high cost of illness, with an annual approximation of 27 billion euros (IDR >465 trillion).[1]

Etiology Behind Cryptogenic Stroke

Finding the etiology of ischemic stroke is important to prevent a recurrence. Patent foramen ovale, PAF, aortic arch atherosclerosis, substenotic atherosclerosis, atrial cardiopathy, and LAA dysfunction are several possible pathophysiologies implicated in cryptogenic stroke.[6] A systematic review by McMahon et al.[7] recommended several diagnostic modalities to investigate the cause of cryptogenic stroke, including brain imaging with non-contrast CT scan and MRI, vascular imaging with Coronary Computed Tomography Angiography (CCTA), magnetic resonance angiography (MRA), or Doppler ultrasound, laboratory tests, cardiac imaging, and cardiac monitoring.

The recommended laboratory tests are complete blood count, electrolytes, coagulation, renal function, random glucose, troponin, and others. Echocardiography is done to monitor cardiac structure when a cardioembolic mechanism is suspected. Last but not least, 12-lead ECG is mandatory for all patients to assess the cardiac rhythm. ECG monitoring has to be prolonged in acute embolic ischemic stroke or TIA with an unknown source to prevent the overlook of atrial fibrillation.

Atrial Fibrillation and Cryptogenic Stroke

Despite the recommendation regarding post-stroke rhythm monitoring, the evidence-practice gap still leads to a high number of patients diagnosed with cryptogenic stroke. This fact indicates the failure to diagnose the possible pathophysiology implicated in CS.[8] One of the most underdiagnosed conditions is PAF because of its intermittency and asymptomatic nature. Many times, the first clinical manifestation of PAF is stroke.[9] Data from *the Indonesian Registry on Atrial Fibrillation* (OneAF) showed that more than 30% of outpatient AF patients were asymptomatic.[10,11] Therefore, better cardiac rhythm monitoring for post-stroke AF detection is needed.

Cardiac Rhythm Monitoring for AF Detection

Cardiac rhythm monitoring is comprised of an insertable cardiac monitor (ICM) and ambulatory cardiac monitor. Implantable loop recorder (ILR) is one type of ICM, while 24-hour ECG monitoring and cardiac event recorder using telemetry are examples of conventional ECG monitoring.

Two large randomized controlled trials, the Cryptogenic Stroke and Underlying Atrial Fibrillation (CRYSTAL-AF) and the 30-Day Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) trial have shown that longer ECG monitoring using both types of devices above in patients with cryptogenic stroke led to higher detection rates of AF, which will impact the subsequent treatment option.[9,12,13]

The CRYSTAL-AF trial comprised of 441 patients with cryptogenic stroke were either monitored using ICM ≥6 months or conventional ECG monitoring

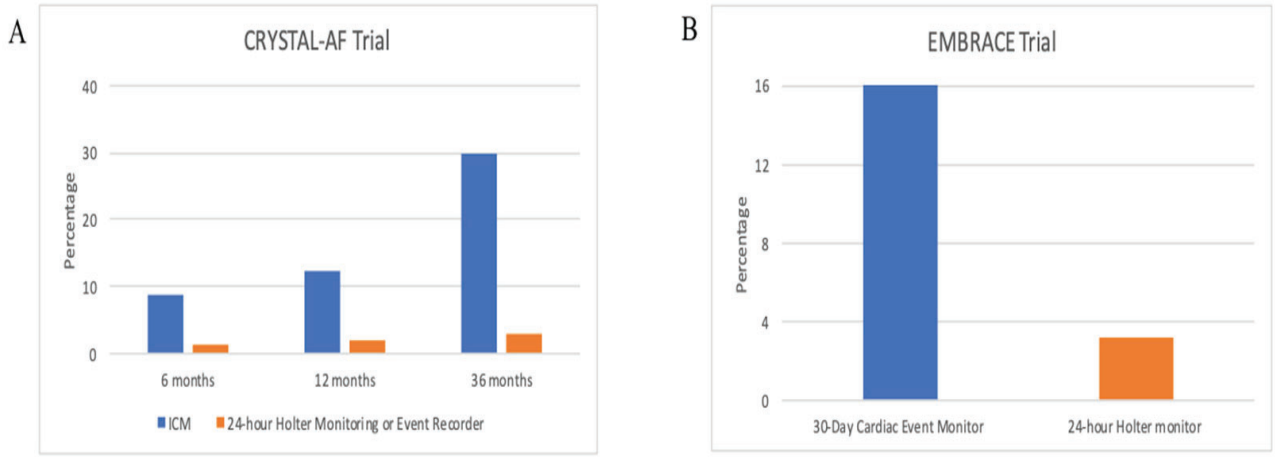

Figure 1. Higher Detection Rate with Prolonged Monitoring from CRYSTAL-AF (Cryptogenic Stroke and Underlying Atrial Fibrillation) and EMBRACE) Cardiac Event Monitor Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event) trials. ICM: insertable cardiac monitor.

(24-hour Holter monitoring or event recorder).[12] The CRYSTAL-AF trial detected AF in 8.9%, 12.4%, and 30.0% of patients who were monitored utilizing ICM at 6, 12, and 36 months compared to 1.4%, 2.0%, and 3.0% of patients who were monitored using conventional ECG monitoring, 24-hour Holter monitoring or event recorder as seen in figure 1A.[12,13] The median time of AF detection at 12 months was 84 days where the majority of these AF were asymptomatic. At 36 months, ICM has a ten times higher ability to detect AF compared to conventional ECG monitoring (30% vs 3% for ICM and conventional ECG, respectively).

On the other hand, the EMBRACE trial comprised of 572 patients with cryptogenic stroke were monitored either using a 30-day event trigger cardiac monitor or a 24-hour cardiac monitor.[9] The EMBRACE trial was able to detect AF in 16.1% of patients who used a 30-day cardiac event monitor compared to 3.2% of patients who used a 24-hour Holter monitor within 90 days. A third of the episodes had a very brief duration as seen in figure 1B.[9,13]

Accordingly, the 2020 ESC guidelines for the diagnosis and management of atrial fibrillation recommend prolonging ECG monitoring using non-invasive cardiac monitors or ICM for patients with a higher risk of developing AF. Those patients are elderly, patients with cryptogenic stroke and suggestive embolic stroke, patients with cardiovascular comorbidities, suspected LA remodeling, and high C2HEST score (a clinical risk score for predicting incident of AF in Asian subjects).[14]

Systematic vs Opportunistic Screening for AF

In addition to the above data that longer cardiac rhythm monitoring will yield a higher chance to detect AF, there are several rationales to do AF screening: 1) many patients with AF were asymptomatic. Data from the OneAF registry showed that ~30% of AF patients who visited the hospital were asymptomatic[11] 2) stroke with AF is more severe and has a higher permanent disability, 3) up to one-third of patients with ischemic stroke had underlying AF, and 4) a significant proportion of patients with stroke (~20%) has AF for the first time.

There are two methods of AF screening, i.e. systematic or opportunistic screening. When the patients/population were invited to go to a health care facility for AF screening is called systematic screening, whereas when the patients were screened during a routine consultation is an opportunistic screening. The Canadian Cardiovascular Society and the European Society of Cardiology recommend opportunistic screening using pulse palpation or rhythm-based devices, especially for patients ≥65 years of age. The systematic screening was recommended in patients >75 years or with high stroke risk.[14]

Pulse palpation was recommended in ESC Guideline as a Class I indication for screening of people ≥65 years of age.[14] Although less specific, this method of

screening has reasonable sensitivity for AF screening. It is therefore useful for ruling out atrial fibrillation.[15]

Digital Health Tools for Atrial Fibrillation Monitoring

The field of digital health has evolved rapidly, bringing transformation into the management of atrial fibrillation. Digital health tools have revolutionized health screening as information can be collected more frequently, increasing the reliability, validity, and ability to detect changes over time. Furthermore, traditional monitors may be ineffective in some cases as duration and time of wear may be incongruent with symptoms.[16] Thus, digital health tools will aid more ad-hoc monitoring. However, the disadvantages that come with these tools are false-positive episodes of AF due to substantial electrical or motion artifact, misclassified rhythms, and unavailability of other arrhythmias classification.[17]

Currently, there are several types of digital health tools available for monitoring, which can be divided into ECG tracing technologies and non-ECG tracing technologies. Handheld devices, smartwatch ECG, and smartphone ECG devices are some examples of ECG tracing technologies while photoplethysmography, oscillometry, and mechanocardiography are some examples of non-ECG tracing technologies.

The current screening paradigm for AF has shifted to only high-risk patients or patients with CS, intending to prevent serious complications. A multicentre, open-label randomized trial by Koh et al.[18] showed 30-day smartphone electrocardiogram monitoring considerably improve AF detection rate in patients with cryptogenic stroke. From 2017 to 2020, the trial observed the diagnostic yield of smartphone ECG recording in cryptogenic stroke patients age 55 years or older without prior history of AF. Participants were randomized in a 1:1 ratio to undergo 30 days ECG monitoring using KardiaMobile recording or additional 24 hour Holter monitoring. Participants in the intervention arm had to monitor their ECG three times a day or when they experienced palpitations. They also had to write down their symptoms and ECG monitoring using a diary. At the end of the monitoring, a blinded electrophysiologist reviewed the ECG recording and the diary. AF was detected 9.5% in the intervention arm and 2% in the control arm with an absolute difference of 7.5% and P = 0.024. The number needed to screen for AF detection was 13. As the detection improve, the number of patients taking oral anticoagulants at three months also increased significantly.

As for screening the general population, the ECG generated from digital health tools is still considered pre-diagnostic. Therefore, verification from the treating physician is needed to prevent overtreatment.[17] The Apple Heart Study is a good example to show that the probability of irregular pulse notification was low in the general population.[19] From 2017 to 2018, the trial observed the identification of AF through a smartwatch application during typical use. Participants were subjects without prior history of AF or who currently do not use oral anticoagulation. If the algorithm identified possible AF, then participants will be scheduled for a telemedicine visit and monitoring using an ECG patch. The study found that 34% of participants who received notification of an irregular pulse had atrial fibrillation on subsequent ECG patch readings with a positive predictive value of 0.8. Nonetheless, the integration of digital health technologies and health care professionals may lead to a bigger value and better care.

Conclusion

Atrial fibrillation is one of the important etiology behind the cryptogenic stroke. Pulse palpation and 12-lead ECG were recommended for AF screening in the high-risk population. A higher detection rate of AF can be achieved with a longer duration of monitoring such as insertable cardiac monitoring and 7- or 21-days Holter monitoring. Lastly, the usage of digital health tools has revolutionized the screening of AF but may generate false-positive rhythm, hence verification is needed to confirm the rhythm.

Conflict of interest

The authors report no conflicts of interest

Sources of funding

This paper received no specific grant from any funding agency, commercial or not-for-profit sectors.

Ethical Clearance

Not applicable

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