Atrial Premature Beats Predict Atrial Fibrillation in Cryptogenic Stroke
Results From the EMBRACE Trial

David J. Gladstone, MD, PhD; Paul Dorian, MD; Melanie Spring, MD; Val Panzov, MD; Muhammad Mamdani, PharmD, MPH; Jeff S. Healey, MD; Kevin E. Thorpe, MMath; for the EMBRACE Steering Committee and Investigators*

Background and Purpose—Many ischemic strokes or transient ischemic attacks are labeled cryptogenic but may have undetected atrial fibrillation (AF). We sought to identify those most likely to have subclinical AF.

Methods—We prospectively studied patients with cryptogenic stroke or transient ischemic attack aged ≥55 years in sinus rhythm, without known AF, enrolled in the intervention arm of the 30 Day Event Monitoring Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) trial. Participants underwent baseline 24-hour Holter ECG poststroke; if AF was not detected, they were randomly assigned to 30-day ECG monitoring with an AF auto-detect external loop recorder. Multivariable logistic regression assessed the association between baseline variables (Holter-detected atrial premature beats [APBs], runs of atrial tachycardia, age, and left atrial enlargement) and subsequent AF detection.

Results—Among 237 participants, the median baseline Holter APB count/24 h was 629 (interquartile range, 142–1973) among those who subsequently had AF detected versus 45 (interquartile range, 14–250) in those without AF (P<0.001). APB count was the only significant predictor of AF detection by 30-day ECG (P<0.0001), and at 90 days (P=0.0017) and 2 years (P=0.0027). Compared with the 16% overall 90-day AF detection rate, the probability of AF increased from <9% among patients with <100 APBs/24 h to 9% to 24% in those with 100 to 499 APBs/24 h, 25% to 37% with 500 to 999 APBs/24 h, 37% to 40% with 1000 to 1499 APBs/24 h, and 40% beyond 1500 APBs/24 h.

Conclusions—Among older cryptogenic stroke or transient ischemic attack patients, the number of APBs on a routine 24-hour Holter ECG was a strong dose-dependent independent predictor of prevalent subclinical AF. Those with frequent APBs have a high probability of AF and represent ideal candidates for prolonged ECG monitoring for AF detection.

Clinical Trial Registration—URL: http://www.clinicaltrials.gov. Unique identifier: NCT00846924.

(Stroke. 2015;46:936-941. DOI: 10.1161/STROKEAHA.115.008714.)

Key Words: atrial fibrillation ■ atrial premature complexes ■ cryptogenic stroke ■ electrocardiography ■ projections and predictions ■ risk

Atrial fibrillation (AF) is the leading cardiac cause of stroke, but it frequently goes undetected and untreated in the routine management of patients with embolic ischemic stroke or transient ischemic attack (TIA).1-3 Screening for AF has typically been limited to short-duration ECG monitoring poststroke (eg, 24 hours) and unless atrial fibrillation occurs during that period, the diagnosis is missed, highly effective anticoagulant therapy is generally not prescribed, and potentially preventable recurrent strokes can result. Longer duration ECG monitoring (eg, for 7 days, 30 days, or up to 3 years) significantly improves AF detection and treatment compared with standard care4-6 and is being recommended by new practice guidelines.2,7,8 However, it is unclear which subgroups benefit most from additional monitoring, how much monitoring should be performed, and for whom it will be most cost-effective.

Continuing medical education (CME) credit is available for this article. Go to http://cme.ahajournals.org to take the quiz.

Received January 9, 2015; final revision received January 23, 2015; accepted January 27, 2015.

From the Division of Neurology (D.J.G.), Department of Medicine (D.J.G., P.D., M.S., M.M.), and Dalla Lana School of Public Health (K.E.T.), University of Toronto, Toronto, Ontario, Canada; University of Toronto Stroke Program, Toronto, Ontario, Canada (D.J.G.); Division of Neurology, Department of Medicine, and the Hurvitz Brain Sciences Program, Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, Toronto, Ontario, Canada (D.J.G.); Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Toronto, Ontario, Canada (D.J.G.); Applied Health Research Centre (AHRC), Li Ka Shing Knowledge Institute of St. Michael’s Hospital, Toronto, Ontario, Canada (M.M., V.P., K.E.T.); and Population Health Research Institute, McMaster University, Hamilton, Ontario, Canada (J.S.H.).

*A list of all EMBRACE Steering Committee members and Investigators are given in the Appendix.

Presented in part at the Canadian Stroke Congress, Montreal, Canada, October 17–20, 2013.

The online-only Data Supplement is available with this article at http://stroke.ahajournals.org lookup/suppl/doi:10.1161/STROKEAHA.115.008714/-/DC1.

Correspondence to David J. Gladstone, MD, PhD, FRCPC, Regional Stroke Prevention Clinic, Sunnybrook Health Sciences Centre, A442-2075 Bayview Ave, Toronto, Ontario M4N 3M5, Canada. E-mail david.gladstone@sunnybrook.ca

© 2015 American Heart Association, Inc.

Stroke is available at http://stroke.ahajournals.org

DOI: 10.1161/STROKEAHA.115.008714
Frequent atrial premature beats (APBs) are an emerging risk marker that can help identify patients in sinus rhythm who are likely to have, or develop, paroxysmal AF, as shown in cohort studies of stroke patients\textsuperscript{6–11} and asymptomatic individuals.\textsuperscript{14–20} Similarly, increasing frequency or duration of nonsustained runs of atrial tachyarrhythmia have been associated with AF.\textsuperscript{12,13,15}

To predict which cryptogenic stroke or TIA patients have the highest probability of subclinical AF, we used data from the EMBRACE trial to investigate the association between Holter-detected atrial ectopic activity, in addition to age and left atrial enlargement, on the subsequent detection of AF by 30-day ECG monitoring, and during clinical follow-up at 90 days and 2 years.

Methods

Design and Participants

This study was a preplanned subanalysis of the 30 Day Event Monitoring Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) study, an investigator-initiated, multicenter randomized controlled trial comparing AF detection strategies in patients with cryptogenic stroke at 16 stroke centers within the Canadian Stroke Consortium.\textsuperscript{7} The trial enrolled patients aged ≥55 years without known AF who had an embolic ischemic stroke or TIA of undetermined cause after a standard etiologic work-up. Prerandomization tests included 12-lead ECG(s) and 24 hours ECG (Holter) monitoring that did not reveal any AF ≥30 s, in addition to echocardiography and neurovascular imaging. Eligible participants were randomly assigned to wear an AF auto-detect ECG loop recorder for ≤30 days (intervention group) or another 24-hour Holter ECG monitor (control group). The protocol was approved by Health Canada and site ethics boards, and participants provided written informed consent.

Intervention

Participants assigned to the intervention group received an event-triggered external loop recorder that automatically recorded episodes of AF by detection of R–R irregularity >30 beats at any ventricular rate (Brancar, Inc., ER910AF). It was attached to a nonadhesive dry electrode belt worn around the chest (Accuheart Electrode Belt; Cardiac Bio-Systems, Inc). Participants were instructed to wear the monitor as much as possible for ≤30 days (intervention group) or another 24-hour Holter ECG monitor (control group). The protocol was approved by Health Canada and site ethics boards, and participants provided written informed consent.

Outcomes

We collected baseline Holter and echocardiogram reports from sites for central review. Automated APB counts from Holter reports were converted to a frequency per 24 hours for each patient. The primary outcome was detection of ≥1 episodes of atrial fibrillation or flutter lasting ≥30 s by 30-day ECG monitoring or clinically within 90 days post-randomization. Secondary outcomes were AF ≥30 s detected by 30-day ECG, AF ≥2.5 minutes detected by 30-day ECG, and AF detected by any means within 2 years of clinical follow-up. AF events were adjudicated centrally by a cardiologist and internist blinded to patient details; any disagreements were resolved with an independent cardiologist.

Statistical Analysis

We used multivariable logistic regression analysis, restricted to the intervention group, to assess the association between preplanned baseline variables on the primary and secondary outcomes of AF detection. Because of the small number of outcome events, we had to limit the number of variables included in the model. We chose the following variables based on previous studies, such as (1) baseline APB count (the primary exposure of interest), defined as the number of APBs/24 h recorded on the prestudy Holter monitor ordered clinically as part of usual care after the index stroke or TIA, (2) the number of Holter-detected runs of nonsustained atrial tachycardia/24 h (≥4 continuous nonsinus beats of atrial origin), (3) age, and (4) left atrial enlargement by echocardiography, defined as diameter ≥40 mm or volume index ≥29 mL/m² or by qualitative description. Nonlinear associations between APB count and the log-odds of the outcome was modeled using a restricted cubic spline with 3 knots. Three knots were chosen given the sample size and as the relationships were expected to change smoothly and gradually. The bootstrap was used to evaluate overfitting and produce corrected indexes of discrimination. Furthermore, we categorized patients into 5 groups based on their baseline 24-hour APB count: <100, 100 to 499, 500 to 999, 1000 to 1499, and ≥1500.

Results

Among 287 participants randomized to wear the 30-day ECG monitor, 280 underwent any duration of monitoring or completed 90-day follow-up, and APB data were available on baseline Holter reports for 237 participants. The qualifying event was a cryptogenic ischemic stroke in two thirds and a cryptogenic TIA in one third. Mean age was 72.2±8.6 years, 46% were women (n=110), 89% were white (n=212), 71% had hypertension (n=168), and 16% had previous stroke(s) before the index event (n=39). The median CHADS\textsubscript{2} (congestive heart failure, hypertension, age, diabetes, prior stroke/transient ischemic attack) score was 3 points (interquartile range [IQR], 3–4).

The median baseline APB count was 66 (IQR, 18–309) in the entire cohort, and it was higher in patients who were subsequently found to have AF (629 beats/24 h [IQR, 142–1973]) compared with those without AF (45 beats/24 h [IQR, 14–250]), P<0.001 (Wilcoxon rank sum test).

In the regression model, APB count was the only statistically significant predictor of the primary outcome of AF detection (P=0.0017 overall; nonlinear component P=0.0099; see online-only Data Supplement for additional details). The predicted probability of AF increased steadily with increasing

Figure 1. Predicted probability of paroxysmal atrial fibrillation according to number of atrial premature beats/24 h on a Holter monitor study. AF indicates atrial fibrillation; APB, atrial premature beat.
APB count up to =1500 APBs/24 h, above which there was a plateau (Figure 1). Similar results were obtained for the secondary outcome of AF ≥30 s on the 30-day ECG monitor alone (P<0.0001) and the more robust outcome of AF ≥2.5 minutes on 30-day ECG (P=0.0005), and for AF detection by any means at 2 years (P=0.0027).

For the primary outcome, the AF detection rate in the intervention group was 16% overall but it was highly dependent on the baseline APB count: the predicted probability of AF was 7% to 9% in patients with <100 APBs/24 h, 9% to 24% in those with 100 to 499 APBs/24 h, 25% to 37% in those with 500 to 999 APBs/24 h, 37% to 40% in those with 1000 to 1499 APBs/24 h, and it reached a plateau ≈40% in those with ≥1500 APBs/24 h. Clinicians can refer to Table to estimate an individual patient’s probability of AF based on the number of APB (see Figure I in the online-only Data Supplement for computational formula).

### Discussion

In this analysis from EMBRACE, the largest AF detection trial in patients with cryptogenic stroke, we found that the number of Holter-detected APBs was a strong independent predictor of AF. The overall 90-day AF detection rate in this cohort was 16%, and the baseline APB count stratified the probability of AF into low-, moderate-, or high-risk categories, ranging from 7% to 40%. The average baseline APB count among our stroke patients who subsequently had AF detected was 14 times higher than in the stroke patients without AF detected, and 10-fold higher than in the general population where the median APB count/24 h is 60 (IQR, 19–228) among individuals aged ≥65 years and 62 (IQR, 29–156) among those aged ≥70 years.18,21

These results validate and extend smaller observational stroke studies that relied on arbitrary dichotomized APB counts, and we provide a practical reference table for clinicians to estimate a patient’s probability of AF for a given APB count (Table). The relationship between APB count and the probability of subclinical AF was dose-dependent and nonlinear, similar to that reported for clinical AF in a longitudinal study over a median follow-up of 13 years,18 and there was no lower APB threshold below which AF could be excluded.

Our findings support the concept that frequent APB represent a proarrhythmic tendency and are a marker of prevalent subclinical AF, in addition to being a precursor of incident AF.9–18,20,22,23 Several recent studies indicate that Holter-detected frequent APBs, or APBs present on a routine 12-lead ECG,19,20 are an independent risk factor for stroke or death; previous studies used different thresholds for defining frequent APBs during a 24-hour recording (>100,19 >218,14 >228 APBs,19 or >720 APBs or episodes of atrial tachycardia >20 beats long15). In our study, we found that nearly 50% patients with cryptogenic stroke had an APB frequency >720/24 h, which is potentially clinically important based on the above literature.19 However, as the aforementioned studies did not use any sensitive long-term monitoring for AF, it is unclear whether the increased stroke or death risks were because of subsequent development of AF. Two cohort studies in pacemaker patients demonstrated that subclinical AF as brief as 5 or 6 minutes in duration is associated with an increased risk of stroke.24,25 However, many strokes in the pacemaker studies occurred without the development of longer-lasting AF episodes or lacked a temporal association with the AF episodes.26,27 Such observations suggest that brief atrial arrhythmias or frequent APBs may be a stroke risk marker independent of causal mechanisms, such as the development of long-lasting AF.

This research has practice implications for secondary stroke prevention. The findings are clinically relevant because 1 in every 4 ischemic stroke patients (and half of TIA patients) are labeled as cryptogenic28 yet a substantial proportion will have undetected and untreated AF.1–3 Prolonged ambulatory

<table>
<thead>
<tr>
<th>No. of APBs/24 h on Baseline Holter Monitor</th>
<th>Probability of AF, %*</th>
<th>Lower CI, %</th>
<th>Upper CI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.6</td>
<td>3.6</td>
<td>11.6</td>
</tr>
<tr>
<td>25</td>
<td>7.2</td>
<td>4.1</td>
<td>12.3</td>
</tr>
<tr>
<td>50</td>
<td>7.9</td>
<td>4.6</td>
<td>13.0</td>
</tr>
<tr>
<td>75</td>
<td>8.6</td>
<td>5.2</td>
<td>13.7</td>
</tr>
<tr>
<td>100</td>
<td>9.3</td>
<td>5.8</td>
<td>14.5</td>
</tr>
<tr>
<td>150</td>
<td>10.9</td>
<td>7.2</td>
<td>16.2</td>
</tr>
<tr>
<td>200</td>
<td>12.6</td>
<td>8.5</td>
<td>18.1</td>
</tr>
<tr>
<td>250</td>
<td>14.4</td>
<td>10.0</td>
<td>20.2</td>
</tr>
<tr>
<td>300</td>
<td>16.2</td>
<td>11.3</td>
<td>22.6</td>
</tr>
<tr>
<td>350</td>
<td>18.1</td>
<td>12.7</td>
<td>25.1</td>
</tr>
<tr>
<td>400</td>
<td>19.9</td>
<td>13.9</td>
<td>27.7</td>
</tr>
<tr>
<td>450</td>
<td>21.8</td>
<td>15.1</td>
<td>30.4</td>
</tr>
<tr>
<td>500</td>
<td>23.6</td>
<td>16.2</td>
<td>33.1</td>
</tr>
<tr>
<td>550</td>
<td>25.4</td>
<td>17.2</td>
<td>35.7</td>
</tr>
<tr>
<td>600</td>
<td>27.1</td>
<td>18.2</td>
<td>38.3</td>
</tr>
<tr>
<td>650</td>
<td>28.6</td>
<td>19.0</td>
<td>40.7</td>
</tr>
<tr>
<td>700</td>
<td>30.1</td>
<td>19.8</td>
<td>42.9</td>
</tr>
<tr>
<td>750</td>
<td>31.5</td>
<td>20.6</td>
<td>45.0</td>
</tr>
<tr>
<td>800</td>
<td>32.8</td>
<td>21.2</td>
<td>46.9</td>
</tr>
<tr>
<td>850</td>
<td>33.9</td>
<td>21.8</td>
<td>48.5</td>
</tr>
<tr>
<td>900</td>
<td>35.0</td>
<td>22.4</td>
<td>50.0</td>
</tr>
<tr>
<td>950</td>
<td>35.9</td>
<td>22.9</td>
<td>51.3</td>
</tr>
<tr>
<td>1000</td>
<td>36.7</td>
<td>23.3</td>
<td>52.5</td>
</tr>
<tr>
<td>1100</td>
<td>38.0</td>
<td>24.1</td>
<td>54.2</td>
</tr>
<tr>
<td>1200</td>
<td>38.9</td>
<td>24.6</td>
<td>55.4</td>
</tr>
<tr>
<td>1300</td>
<td>39.6</td>
<td>25.1</td>
<td>56.1</td>
</tr>
<tr>
<td>1400</td>
<td>39.9</td>
<td>25.4</td>
<td>56.5</td>
</tr>
<tr>
<td>1500</td>
<td>40.2</td>
<td>25.6</td>
<td>56.7</td>
</tr>
<tr>
<td>1600</td>
<td>40.3</td>
<td>25.8</td>
<td>56.7</td>
</tr>
<tr>
<td>1700</td>
<td>40.4</td>
<td>26.0</td>
<td>56.6</td>
</tr>
<tr>
<td>1800</td>
<td>40.5</td>
<td>26.2</td>
<td>56.8</td>
</tr>
<tr>
<td>1900</td>
<td>40.5</td>
<td>26.3</td>
<td>56.6</td>
</tr>
<tr>
<td>2000</td>
<td>40.6</td>
<td>26.5</td>
<td>56.5</td>
</tr>
</tbody>
</table>

*AF indicates atrial fibrillation; APB, atrial premature beat; and CI, confidence interval.

Table. Predicted Probability of Atrial Fibrillation for a Given Number of Atrial Premature Beats in Patients With Cryptogenic Stroke or Transient Ischemic Attack
ECG monitoring significantly improves AF detection compared with the usual practice of short-term ECG monitoring, enabling initiation of anticoagulant therapy aimed at preventing recurrent disabling or fatal strokes. New practice guidelines now call for prolonged ECG monitoring to evaluate patients with cryptogenic stroke or TIA, yet the recommended duration of monitoring varies across different guidelines, ranging from ≥1 weeks to ≥30 days or additional ambulatory monitoring of unspecified duration. Because prolonged monitoring can be costly, difficult to access in some regions, and burdensome for some patients, appropriate selection of patients and monitoring strategy is needed. Both noninvasive and minimally invasive monitoring technologies for AF detection are available, and our data suggest that any approach will be most effective, and cost-effective, when applied to patients with frequent APBs. Our findings may be particularly pertinent to patient selection for costly implantable ECG monitors or repeated noninvasive monitoring over time. Patients with excessive APB who do not have AF detected in the short term may benefit from longer-term surveillance for AF.

In light of our study results, we propose a tiered approach for detecting subclinical AF in patients being investigated after an embolic stroke or TIA (Figure 2). We suggest 24-hour Holter ECG as an initial screen. If AF is not detected and the patient meets criteria for an embolic stroke of undetermined source and is considered an appropriate candidate for additional monitoring and potential anticoagulation (and is not being anticoagulated empirically or randomized in an anticoagulant trial), then we suggest additional noninvasive ECG monitoring using a device capable of continuous recording (mobile outpatient telemetry) or an AF auto-detect loop recorder (note that traditional patient-triggered event recorders that only capture symptomatic episodes will miss subclinical AF). In terms of the target monitoring duration, we suggest 4 weeks of monitoring for patients with frequent APBs; 2 weeks may be reasonable for patients with infrequent APBs given the present analysis and the fact that most AF cases in the EMBRACE trial were detected within the first 2 weeks of monitoring. A threshold of >500 APBs/24 h seems to be a reasonable pragmatic definition for frequent APBs in this population based on the data from this study. For patients with excessive APBs (e.g., >1000 APBs/24 h), if AF is not documented after 4 weeks of monitoring then we would consider further monitoring. The role of empiric anticoagulant therapy for patients with frequent APBs, but without documented AF, is currently unknown; randomized trials of anticoagulation for cryptogenic stroke are currently underway and hopefully will evaluate subgroups with frequent APBs.

This study has several limitations. The sample size could not support the evaluation of additional predictor variables, such as neuroimaging features. Our results reflect detection of AF based on 30-day monitoring in an older, predominantly white, Canadian population. Longer monitoring would have yielded more AF and our 2-year AF rate, therefore, is probably an underestimate. Most of the study monitor-detected AF was brief and subclinical, and may or may not have been causally related to the index stroke, but nevertheless represents a potentially treatable risk factor for recurrent stroke. Increasing age is known to be associated with a greater likelihood of both clinical and subclinical AF, but we found that age was not a significant predictor when APB count is included in the model. However, we did not study patients aged <55 years so the ability to fully assess the effect of age was limited. Also, because most echocardiograms from our study sites reported only atrial diameter, not volume, we probably underestimated atrial size and, therefore, limited the ability of our model to assess the significance of left atrial enlargement, a known predictor of clinical AF.

In summary, the EMBRACE AF prediction formula enables simple, rapid, and powerful AF risk stratification, and external validation in other, more diverse cohorts is needed. It has potential for widespread applicability for patient care because it requires only a 24-hour ECG recording, without needing to rely on echocardiography, MRI, or biomarkers, because APB counts are routinely reported on Holter and other continuous outpatient ECG monitor studies. Holter monitoring is widely available and already recommended as a first-line diagnostic investigation after stroke or TIA; this study affirms its value.
as a prognostic tool for those in sinus rhythm and suggests that it may have value as a triage tool to identify higher-risk patients who may benefit from additional monitoring. Beyond the secondary stroke prevention population, this work also has research implications for predicting AF and targeting AF screening in primary care or special populations (after ablation, cardiac surgery, or apparent transient postoperative AF).36

Appendix

Members of EMBRACE Steering Committee or Operations Committee


ECG Adjudication Committee

P. Dorian, M. Spring, A. Pinter.

EMBRACE Participating Sites, Site Investigators and Coordinators (sites listed according to patient enrollment; names listed alphabetically)

London Health Sciences Centre; London, Ontario: S. Abootalab, R. Chan, S. Cram, L. Fleming, C. Frank, V. Huchinski, K. Hesser, B.S. Kumar, P. Soros, M. Wright.


Sources of Funding

The EMBRACE trial was funded by peer-reviewed operating grants from the Canadian Stroke Network and coordinated at the Applied Health Research Centre, Li Ka Shing Knowledge Institute of St. Michael’s Hospital, and Sunnybrook Research Institute, University of Toronto. Dr Gladstone was supported by a Clinician-Scientist Award from the Heart and Stroke Foundation of Ontario, the Bastable-Potts Chair in Stroke Research at Sunnybrook Health Sciences Centre, the Sam Sorbara Charitable Foundation, the Department of Medicine, University of Toronto and the Eaton Scholar Award, the Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, the Bril Chair in Neurology at the University of Toronto, and the Department of Medicine and Hurvitz Brain Sciences Program at Sunnybrook Health Sciences Centre, Toronto.

Disclosures

Dr Gladstone is principal investigator of the SCREEN-AF trial, a Canadian Institutes of Health Research (CIHR)-funded Canadian Stroke Prevention Intervention Network project; coprincipal investigator of a peer-reviewed Ontario Centres of Excellence provincial government grant; and reports receiving lecture fees and honoraria for ad hoc consulting or advisory board participation from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer and an advisory board honorarium from Daiichi Sankyo; Dr Dorian, consulting fees from Servier, lecture fees from Bristol-Myers Squibb, Bayer, Pfizer, and Boehringer Ingelheim, and grant support through his institution from Bristol-Myers Squibb, Bayer, Pfizer, Boehringer Ingelheim, and Servier. Dr Healey is principal investigator of the ASSET-II trial funded by St. Jude Medical and the ARTESIA trial funded by Medtronic. Dr Mamdani reports fees for participating on advisory boards from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Roche, Novartis, Novo Nordisk, and Pfizer. The other authors report no conflicts.

References

8. Kerman WN, Oviabiole B, Black HR, Bravata DM, Chimowitz MI, Ezekowitz MD. Guidelines for the prevention of stroke in patients with


Atrial Premature Beats Predict Atrial Fibrillation in Cryptogenic Stroke: Results From the EMBRACE Trial

David J. Gladstone, Paul Dorian, Melanie Spring, Val Panzov, Muhammad Mamdani, Jeff S. Healey and Kevin E. Thorpe
for the EMBRACE Steering Committee and Investigators*

*For the EMBRACE Steering Committee and Investigators

Stroke. 2015;46:936-941; originally published online February 19, 2015;
doi: 10.1161/STROKEAHA.115.008714

Stroke is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2015 American Heart Association, Inc. All rights reserved.
Print ISSN: 0039-2499. Online ISSN: 1524-4628

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://stroke.ahajournals.org/content/46/4/936

Data Supplement (unedited) at:
http://stroke.ahajournals.org/content/suppl/2015/03/20/STROKEAHA.115.008714.DC2
http://stroke.ahajournals.org/content/suppl/2016/04/06/STROKEAHA.115.008714.DC3
http://stroke.ahajournals.org/content/suppl/2016/04/07/STROKEAHA.115.008714.DC4

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Stroke can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Stroke is online at:
http://stroke.ahajournals.org//subscriptions/
SUPPLEMENTAL MATERIAL

Atrial Premature Beats Predict Atrial Fibrillation in Cryptogenic Stroke: Results from the EMBRACE Trial

David J. Gladstone MD, PhD, Paul Dorian MD, Melanie Spring MD, Val Panzov MD, Muhammad Mamdani PharmD, MPH, Jeff S. Healey MD, Kevin E. Thorpe MMath, for the EMBRACE Steering Committee and Investigators

Submitted January 28, 2015
Supplemental Results

The initial model was overfit. The C-index (area under ROC curve) for the fitted model was 0.78. The bootstrap corrected C-index was 0.745. We fit a second model that only included the spline terms for APB count. The likelihood ratio test comparing these two models gave a p-value of 0.78 and the APB count remained strongly significant (p<0.0001 overall; nonlinear component p=0.0001). The overfitting was nearly eliminated and the reduced model performed better than the initial model: C-index 0.79; bootstrap corrected C-index 0.79.

Supplemental Figure I. Formula for Estimating the Probability of Paroxysmal Atrial Fibrillation for a Given Number of Atrial Premature Beats/24h.

\[
\text{Prob}\{\text{fibr} = 1\} = \frac{1}{1 + \exp(-X\beta)} \quad \text{where}
\]

\[
X\beta =
-2.65666
+0.003903632\text{apbspd}\text{ay} - 1.328472 \times 10^{-8}(\text{apbspd}\text{ay} - 6.697119)^3
+1.378782 \times 10^{-8}(\text{apbspd}\text{ay} - 66.20061)^3 - 5.031017 \times 10^{-10}(\text{apbspd}\text{ay} - 1637.428)^3
\]

and \((x)_+ = x\) if \(x > 0\), 0 otherwise.
Abstract

Atrial Premature Beats Predict Atrial Fibrillation in Cryptogenic Stroke

Results From the EMBRACE Trial

David J. Gladstone, MD, PhD1,2,3,4,5; Paul Dorian, MD2; Melanie Spring, MD2, et al.

1 Division of Neurology, 2 Department of Medicine, University of Toronto, Toronto, Ontario, Canada; 3 University of Toronto Stroke Program, Toronto, Ontario, Canada; 4 Division of Neurology, Department of Medicine, and the Hurvitz Brain Sciences Program, Sunnybrook Health Sciences Centre, Sunnybrook Research Institute, Toronto, Ontario, Canada; and 5 Heart and Stroke Foundation Canadian Partnership for Stroke Recovery, Toronto, Ontario, Canada.

Background and Purpose: In the EMBRACE study, atrial premature beats (APBs) were detected during 12-lead Holter monitoring in 55% of the 675 cryptogenic stroke patients. The relationship between APBs and subsequent atrial fibrillation (AF) was explored.

Methods: This was a post hoc analysis of EMBRACE patients. APBs were defined as >2 beats per 24 hours. The presence of APBs was compared between AF and non-AF patients by logistic regression.

Results: APBs were significantly more frequent in AF patients vs. non-AF patients (26% vs. 6%, P < 0.001). Multivariate analysis confirmed the association between APBs and AF (odds ratio 2.8; 95% CI 1.4-5.4).

Conclusion: APBs detected during 12-lead Holter monitoring were strongly associated with AF. This supports a role for APBs as a trigger for AF in cryptogenic stroke.
배경과 목적
많은 수의 허혈뇌졸중이나 일과성허혈발작이 원인불명으로 분류되지만, 어쩌면 미처 진단되지 않은 심방세동(atrial fibrillation, AF)을 가지고 있을지도 모른다. 본 연구에서는 무증상 AF의 가능성이 높은 환자를 확인하고자 하였다.

방법
원인불명의 뇌졸중이나 일과성허혈발작을 겪고, 55세 이상이며, 동리듬을 보이고 AF 병력이 없는 환자를 30 Day Event Monitoring Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) 연구의 시험군으로 포함시켜 전향적으로 연구하였다. 연구 참여자는 무작위 선정 전기초 검사로 뇌졸중 후 24시간 Holter 심전도 모니터링을 시행받았고, 그 결과 AF가 발견되지 않은 경우에 AF 자동감지 루프리코더(loop recorder)를 이용해 30일간의 심전도 모니터링을 시행하는 군으로 무작위로 선정되었다. 다변량회귀분석의 방법으로 초기 변수(Holter에서 확인된 심방조동[atrial premature beats, APBs], 심방빈맥이 빠르게 지나가는 것[runs of atrial tachycardia], 연령, 좌심방비대)와 이후 진단된 AF와의 연관성을 분석하였다.

결과
237명의 대상 중, Holter 결과 24시간 동안의 APB 수의 중앙값은, 이후 AF가 진단되지 않은 경우에는 629 (interquartile range, 142–1973), AF가 발견되지 않은 경우는 45 (interquartile range, 14–250)였다(P<0.0001). APB 수만이 30일 심전도(P<0.0001) 및 90일(P=0.0017), 2년 (P=0.0027) 후 AF가 진단될 경우의 유의한 예측인자였다. 전체적으로 90일 동안의 AF 진단 비율이 16%였던 것에 비해 24시간 APBs가 100 미만인 경우는 AF 가능성이 9%였고, 100~499인 경우는 9~24%, 500~999인 경우는 25~37%, 1000~1499인 경우는 37~40%, 1500이 넘는 경우는 40%였다.

결론
연령이 높은, 원인불명의 뇌졸중이나 일과성허혈발작 환자 중에서, 심방세동(atrial fibrillation, AF)은 심인성 뇌졸중의 가장 중요한 원인이다. 심방세동은 일과성허혈발작의 일상적인 치료과정 중에서 종종 실제보다 적게 진단되고 덜 치료된다. 심방세동은 전체적으로, Holter 또는 단기 심전도 감시(예를 들어, 24시간) 정도로 제한적으로 시행되며, 만약 이 기간 중에 AF가 발견되지 않으면, 적절한 진단이 이루어지지 않아 결국 그 환자에게 매우 효과적일 수 있는 항응고 치료가 지연되게 된다.

심방세동(atrial fibrillation, AF)은 심인성 뇌졸중의 가장 중요한 원인은 아님에도, 심방세동은 일과성허혈발작에 있어서 중요한 독립적 예측인자로 작용한다. 심방세동은 일과성허혈발작 환자에서 실제보다 적게 진단되고 덜 치료되므로, 심방세동을 적절히 진단하고 치료하는 것이 중요하다.
것은(예를 들어, 7일, 30일 또는 3년까지) 표준 진료에 비해 AF의 진단 및 치료를 유의하게 개선시키며, 4-6 새로운 임상진료지침에서도 권고되는 추세이다. 그러나, 어떤 사람들이 추가적인 모니터링을 필요로 하며 얼마나 오래 시행해야 하는지, 어떤 경우가 가장 비용효과적일지는 불분명하다.

뇌졸중 환자11-13과 증상이 없는 일반인14-20을 대상으로 한 코호트 연구에서 볼 수 있었던 것처럼 심방조기박동이 잦은 경우가 동리듬 환자 중 발작성 AF가 있거나 발생할 가능성이 있는 환자로 규정하는 데 도움이 될 위험인자로 최근 주목되고 있다. 유사하게, 비정상성 심방 부정비맥의 번도나 지속 시간이 증가하는 것도 AF와 연관이 있다.12,15

원인불명의 뇌졸중이나 일과성혈미발작 환자 중 무증상 AF를 가지고 있을 가능성이 높은 환자를 예측하기 위해, Holter 검사에서 확인된 이소성 심방 운동(atrial ectopic activity)과 연령, 좌심방 비대, 30일 간의 심전도 감시 및 90일, 2년 간의 임상 추적관찰을 통해 진단된 AF 우수의 관계를 조사하고자 EMBRACE 연구의 자료를 사용하였다.

방법

연구 설계와 대상

이 연구는 30 Day Event Monitoring Belt for Recording Atrial Fibrillation After a Cerebral Ischemic Event (EMBRACE) 연구에서 사전에 계획한 하위분석 연구로, EMBRACE 연구는 연구자 주도, 다기관, 무작위 선정 대조군 연구로 Canada Stroke Consortium 내의 16개 뇌졸중센터에서 원인불명 뇌졸중 환자의 AF 진단 전략을 비교한 연구이다.4 55세 이상, AF가 없으며, 색전성혈미뇌졸중이나 일과성혈미발작 이후 일반적인 원인규명 검사에서 원인이 밝혀지지 않은 환자를 대상으로 하였다. 무작위 선정 전 Holter 결과에서 자동 집계된 APB 수를 24시간 동안의 번도로 변환하였다. Holter 결과는 10일 간의 심전도 모니터링에서 30초 이상 지속되었거나 무작위 선정 이후 90일 이내 임상적으로 AF 또는 심방조동이 확인된 경우로 하였다. 무작위 선정 후 본 연구에서의 경우, Holter 검사 및 심장초음파 검사도 시행하였다. EMBRACE 연구에서는 심장전문의와 내과전문의가 환자 상세 정보를 모르는 채로 입원 관찰을 시행하였으며, 의견의 불일치가 있는 경우에는 다른 심장전문의의 결정을 기준으로 하였다.

통계분석

AP 전단의 일자, 이차 결과지표에 대하여 시험군에 국한해서, 미리 결정한 초기 변량들 간의 연관성을 평가하기 위해 다변량 로지스틱회귀분석 방법을 사용하였다. 결과지표가 나타난 경우가 적어서, 분석모형에 포함될 변수의 수를 제한해야만 하였다. 초기 연구결과를 토대로 다음 변수를 선택했는데, (1) 이번 뇌졸중이나 일과성혈미발작 이후 일반적인 치료과정 중의 하나로 시행한 30일 간 Holter 모니터링에서 30초 이상 지속된 APB 수, (2) Holter에서 감지된 24시간 동안의 심방 부정맥 선호(심방에서 기원하는 비정상 심박동)의 수, (3) 연령 및 (4) 심장초음파에서 심방이 40mm 이상이거나 용적 지수 29 mL/m²를 초과하는 경우의 수, 그리고 (5) 임상적 소견에서 심방관찰을 시행할 경우가 해당된다. Holter의 전단은 Holter 보고서, S teenager 우발, Holter에서의 심방관찰을 환자들의 초기 24시간 APB 수에 따라 5개의 군으로 나누었다: <100, 100-499, 500-999, 1000-1499, 그리고 ≥1500.

결과

287명의 참여자가 30일간 심전도 모니터링을 받도록 배정되었고, 280명이 일정 기간 모니터링을 시행 하거나 90일 간의 추적 관찰을 완료하였으며, 237명의 참여자에서 Holter
결과에서 APB 자료를 얻을 수 있었다. 연구에 참여하게 된 임상
사건은 2/3가 원인불명의 뇌졸중이었고, 1/3가 원인불명의 일차
성경歴력이었다. 평균 연령은 72.2±8.6세였고, 46%가 여성이
있으며(n=110), 89%가 벤인이었고(n=212), 71%에서 고혈압
(n=168), 그리고 16%가 이전 뇌졸중 병력을 갖고 있었다(n=38),
CHADS2(응혈성심부전, 고혈압, 연령, 당뇨병, 이전의 뇌졸중/
일차성경歴력) 점수의 중앙값은 3 점이었다(interquartile
range, IQR, 3–4).
전체 코호트에서 초기 APB 수의 중앙값은 66이었다(IQR, 18–309). 이는 추후 AF가 발견된 환자(629 beats/24 h [IQR, 142–1973])에서 AF가 발견되지 않은 환자(45 beats/24 h [IQR, 14–250])에 비해 더 많았다(P<0.001 [Wilcoxon rank sum test]).

회귀모형에서, 단지 APB 수만이 AF 예측 일차 결과지표의
통계적으로 유의한 예측인자였다(P=0.0017 overall; nonlinear
component P=0.0009; on-line-only Data Supplement에서 추
가 세부사항을 볼 수 있음). 예측된 AF의 확률은 APB 수가 24시
간당 1500개로 증가할 때까지 계속 증가하고 이후 비슷하게 유지
되었다(Figure 1). 30일 심전도 모니터링에서 AF가 30초 이상
발견된 경우만을 2차 지표로 했을 때(P<0.0001), 2.5분 이상 AF
가 관찰된 울프 확실한 결과지표를 분석했을 때(P=0.0005), 2년
간 어떤 방법으로든 AF가 확인된 경우를 결과로 했을 때
(P=0.0027) 모두 비슷한 결과를 보았다.

일차 결과지표로, 시험군에서 AF 진단율은 전반적으로 16%이
있었으나, 이는 기저 APB 수에 따라 달랐다. 즉 24시간 당 APB가
100개 미만인 경우는 예측된 AF 확률은 7~9%였고, 100~499개인
경우는 9~24%, 500~999개인 경우는 25~37%, 1000~1499개인
경우 37~40%, 1500개 이상인 경우는 40%가량 되었다. 임상의
들은 기저 APB 수에 따른 각 개별 환자의 AF 확률을 계산하기
위해 table을 참고할 수 있다(Figure 1 in the online-only Data
Supplement for computational formula).

Figure 1. Predicted probability of paroxysmal atrial fibrillation
accordiing to number of atrial premature beats/24 h on a Holter
monitor study. AF indicates atrial fibrillation; APB, atrial prema-
ture beat.

결론

원인불명 뇌졸중 환자의 AF를 발견하기 위한 가장 큰 연구인
EMBRACE 연구를 이용한 이 분석에서, Holter 검사에서 발견된
APB의 수가 AF의 강력한 독립적 예측인자임을 확인하였다. 본
코호트에서 전체적인 90일 간의 AF 진단율은 16%이었고, 기저
APB 수를 이용해 AF의 확률을 예, 중, 고위험 군으로 나누어
7%에서 40%로 이르기까지 위험도를 측정할 수 있었다. 이론
연구의 뇌졸중 환자에서 추후 AF가 발견된 경우의 평균 기저
APB 수는 AF가 발견되지 않은 뇌졸중 환자에 비해 14배 많았고,
65세 이상에서는 24시간 APB 중량이 60 (IQR, 19–228), 70세
이상에서는 62 (IQR, 29–156)인 일반 인구집단에 비해 10배
많았다.23,24

이 결과로 APB 수를 임의로 두 군으로 나누어 분석한 소규모
뇌졸중 관찰연구 결과를 확인하였으며, 이를 확대해보았을 때
있다. 본 연구에서는 임상의를 위해 APB 수에 따라 환자의 AF
확률을 계산할 수 있는 심장검사 참고표를 만들었다(Table).
APB 수와 무증상 AF의 확률 간의 관계는 용량–의존적(dose–
dependent)이고, 비선형이며, 중앙값 13%의 기간 동안 추적
관찰한 장기 연구25에서 임상적 AF가 발견된 정도와 비슷하다.

<table>
<thead>
<tr>
<th>No. of APBs/24 h on Baseline Holter Monitor</th>
<th>Probability of AF, %</th>
<th>Lower CI, %</th>
<th>Upper CI, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>6.6</td>
<td>3.6</td>
<td>11.6</td>
</tr>
<tr>
<td>25</td>
<td>7.2</td>
<td>4.1</td>
<td>12.3</td>
</tr>
<tr>
<td>50</td>
<td>7.9</td>
<td>4.6</td>
<td>13.0</td>
</tr>
<tr>
<td>75</td>
<td>8.6</td>
<td>5.2</td>
<td>13.7</td>
</tr>
<tr>
<td>100</td>
<td>9.3</td>
<td>5.8</td>
<td>14.5</td>
</tr>
<tr>
<td>150</td>
<td>10.9</td>
<td>7.2</td>
<td>16.2</td>
</tr>
<tr>
<td>200</td>
<td>12.6</td>
<td>8.5</td>
<td>18.1</td>
</tr>
<tr>
<td>250</td>
<td>14.4</td>
<td>10.0</td>
<td>20.2</td>
</tr>
<tr>
<td>300</td>
<td>16.2</td>
<td>11.3</td>
<td>22.6</td>
</tr>
<tr>
<td>350</td>
<td>18.1</td>
<td>12.7</td>
<td>25.1</td>
</tr>
<tr>
<td>400</td>
<td>19.9</td>
<td>13.9</td>
<td>27.7</td>
</tr>
<tr>
<td>450</td>
<td>21.8</td>
<td>15.1</td>
<td>30.4</td>
</tr>
<tr>
<td>500</td>
<td>23.6</td>
<td>16.2</td>
<td>33.1</td>
</tr>
<tr>
<td>550</td>
<td>25.4</td>
<td>17.2</td>
<td>35.7</td>
</tr>
<tr>
<td>600</td>
<td>27.1</td>
<td>18.2</td>
<td>38.3</td>
</tr>
<tr>
<td>650</td>
<td>28.6</td>
<td>19.0</td>
<td>40.7</td>
</tr>
<tr>
<td>700</td>
<td>30.1</td>
<td>19.8</td>
<td>42.9</td>
</tr>
<tr>
<td>750</td>
<td>31.5</td>
<td>20.6</td>
<td>45.0</td>
</tr>
<tr>
<td>800</td>
<td>32.8</td>
<td>21.2</td>
<td>46.9</td>
</tr>
<tr>
<td>850</td>
<td>33.9</td>
<td>21.8</td>
<td>48.5</td>
</tr>
<tr>
<td>900</td>
<td>35.0</td>
<td>22.4</td>
<td>50.0</td>
</tr>
<tr>
<td>950</td>
<td>35.9</td>
<td>22.9</td>
<td>51.3</td>
</tr>
<tr>
<td>1000</td>
<td>36.7</td>
<td>23.3</td>
<td>52.5</td>
</tr>
<tr>
<td>1100</td>
<td>38.0</td>
<td>24.1</td>
<td>54.2</td>
</tr>
<tr>
<td>1200</td>
<td>38.9</td>
<td>24.6</td>
<td>55.4</td>
</tr>
<tr>
<td>1300</td>
<td>39.6</td>
<td>25.1</td>
<td>56.1</td>
</tr>
<tr>
<td>1400</td>
<td>39.9</td>
<td>25.4</td>
<td>56.5</td>
</tr>
<tr>
<td>1500</td>
<td>40.2</td>
<td>25.6</td>
<td>56.7</td>
</tr>
<tr>
<td>1600</td>
<td>40.3</td>
<td>25.8</td>
<td>56.7</td>
</tr>
<tr>
<td>1700</td>
<td>40.4</td>
<td>26.0</td>
<td>56.6</td>
</tr>
<tr>
<td>1800</td>
<td>40.5</td>
<td>26.2</td>
<td>56.6</td>
</tr>
<tr>
<td>1900</td>
<td>40.5</td>
<td>26.3</td>
<td>56.6</td>
</tr>
<tr>
<td>2000</td>
<td>40.8</td>
<td>26.5</td>
<td>56.5</td>
</tr>
</tbody>
</table>

AF indicates atrial fibrillation; APB, atrial premature beat; and CI, confidence interval.

*Defined as ≥1 episodes of AF ≥30 s detected by 30-day ECG monitoring
or by any means within 90 days after randomization.
A suggested algorithm for detecting subclinical atrial fibrillation (AF) in patients being investigated after an embolic ischemic stroke or transient ischemic attack. APB indicates atrial pre-mature beat.

Figure 2. A suggested algorithm for detecting subclinical atrial fibrillation (AF) in patients being investigated after an embolic ischemic stroke or transient ischemic attack. APB indicates atrial premature beat.
Canadian Institutes of Health Research (CIHR)-funded Canadian Stroke Prevention Intervention Network project; coprincipal investigator of a peer-reviewed Ontario Centres of Excellence provincial government grant; and reports receiving lecture fees and honoraria for ad hoc consulting or advisory board participation from Bayer, Boehringer Ingelheim, Bristol-Myers Squibb, and Pfizer and an advisory board honorarium from Daichi Sankyo; Dr Dorian, consulting fees from Servier, lecture fees from Bristol-Myers Squibb, Bayer, Pfizer, and Boehringer Ingelheim, and grant support through his institution from Bristol-Myers Squibb, Bayer, Pfizer, Boehringer Ingelheim, and Servier.

Dr Healey is principal investigator of the ASSERT-II trial funded by St. Jude Medical and the ARTESiA trial funded by Medtronic. Dr Mamdani reports fees for participating on advisory boards from AstraZeneca, Bristol-Myers Squibb, Eli Lilly, GlaxoSmithKline, Roche, Novartis, Novo Nordisk, and Pfizer. The other authors report no conflicts.

References


Key Words: atrial fibrillation • atrial premature complexes • cryptogenic stroke • electrocardiography • projections and predictions • risk