A Survey of the Use of Empiric Novel Anticoagulants During Investigation of Stroke

Stephen van Gaal, Marc Carrier, Rosendo A. Rodriguez, Mukul Sharma, Ranjeeta Mallick, Grant Stotts, Dar Dowlatshahi

Keywords: Atrial fibrillation, anticoagulants, electrocardiography, ambulatory, methodology, survey, stroke

doi:10.1017/cjn.2015.14

Atrial fibrillation (AF) is a strong risk factor for ischemic stroke but anticoagulation significantly reduces this risk. Screening for atrial fibrillation is therefore a key component of stroke / transient ischemic attack (TIA) evaluation. Current guidelines recommend a 24-48 hour Holter monitor, but the yield is only 5–7%.1 Extended duration recorders have recently been shown to have a yield of 12.4–16.1% when used after an initial negative stroke / TIA evaluation (including 24-hour Holter).2,3 Given the time needed to obtain these investigations, including the possibility of wait lists with increasing test utilization, it may be necessary to specifically consider how to manage patients pending these investigations.

The empirical use of anticoagulation during this ‘peri-investigational’ period would offer greater interim protection to the subset of patients with underlying AF. However, due to the increased risk of bleeding of warfarin over acetylsalicylic acid (ASA), empirical anticoagulation with warfarin would likely not be safe. Three novel oral anticoagulants ((NOAC); apixaban, dabigatran, and rivaroxaban) share an approximate 50% lower risk of intracranial hemorrhage compared to warfarin despite non-inferior stroke prevention in AF.4 Apixaban specifically demonstrated a risk of hemorrhage comparable to ASA in AVERROES, a trial of ASA vs. apixaban in patients with AF deemed ineligible for anticoagulation with warfarin.5 The empirical use of the NOACs during this period might therefore be an efficacious and safe strategy.

As a first step toward exploring the potential value of this, we surveyed academic Canadian neurologists. We asked them to respond to a hypothetical case of stroke with possible underlying AF. Then, in the context of the results of the AVERROES trial, we asked respondents to comment on their appraisal of the empirical use of apixaban in this circumstance.

METHOD

Population

The target population was neurologists affiliated with one of the 16 Canadian academic health centres. A representative from each division of neurology distributed our questionnaire to each of their members by forwarding a generic e-mail invitation. To prevent double counting, we did not use alternative methods of distribution. One reminder was issued, and no incentives were provided.

Survey

Ethics approval was obtained from the Ottawa Hospital Research Ethics Board. Before the beginning of the study, the investigators reached a consensus on the design and content of the survey questionnaire. Feedback from internal and external vascular neurologists was used to establish the face validity of the survey. The survey consisted of 11 closed-ended questions with multiple-choice responses, three of which used a Likert-type format. In the first three questions, we asked respondents to indicate the diagnostic tests and antithrombotic they would recommend for a patient with a potentially cardioembolic TIA. The next two questions surveyed preferences toward the potential empirical use of apixaban, discussed in the context of the AVERROES clinical trial. The last question required respondents to estimate the equivalent number of hemorrhages that would be needed to cancel out the benefit of an arbitrary number of strokes prevented. Demographic data was collected at the end of the survey. The final survey was programmed in Survey Monkey (www.surveymonkey.com) for electronic distribution. The survey was open for three months (August – October 2013). Survey respondents remained anonymous at all times. The final survey instrument is provided as an online supplement.

Statistics

Individual-level data was exported directly from the electronic survey application to PASW Statistics (SPSS, Chicago, IL, version 18). Descriptive statistics (frequencies and proportions) were calculated for each demographic and response variable. Post-hoc chi-square statistics were used to assess between-group differences.

RESULTS

Fourteen out of sixteen academic Neurology Divisions agreed to participate. Sixty-three of 469 (13%) of neurologists completed
the questionnaire, and 57 of the 63 responded to all questions. Demographic information is provided in Table 1.

Responses to the clinical vignette are provided in Table 2. Respondent estimates of the time needed to complete investigations varied with the investigations they requested; 52% of respondents requesting extended monitoring anticipated waiting at least one month, compared to 19% of respondents not requesting this investigation ($\chi^2 = 8.8, \text{df} = 1, p = 0.003$). Recommendation for extended rhythm monitoring did not vary with sub-specialist status ($\chi^2 = 0.091, \text{df} = 2, p = 0.956$).

Most respondents believed that apixaban would be more effective than ASA for stroke prevention (31/58, 54%), and as safe or safer with respect to intracranial hemorrhage (42/58, 72%). Respondents were split on their perception of the overall risk-benefit ratio (17/58; 29% in favor of ASA, 20/58; 34% in favor of apixaban, 21/58; 36% balanced).

Our respondents identified a number of potential barriers to the empirical use of anticoagulation with apixaban, including lack of evidence (47/58, 81%), colleague perceptions of practice patterns (38/58, 65%) and medicolegal concerns (28/58, 48%). Increased risk of hemorrhage was not an absolute barrier; considering an arbitrary benefit of six ischemic strokes prevented per 100 patients, 34/58 (59%) respondents were willing to accept up to two excess intracranial hemorrhages. Half of respondents indicated that they would participate in a clinical trial of empirical anticoagulation versus antiplatelet therapy pending investigation of stroke / TIA with suspected underlying atrial fibrillation (28/58; 49%).

DISCUSSION

The recent EMBRACE and CYRSTAL-AF trials have demonstrated the efficacy of prolonged rhythm recorders for detecting AF in patients with stroke / TIA and negative initial work-up.\(^2\,^3\) It is likely that these recorders will be increasingly used in the investigation of stroke/TIA without an immediately obvious cause. Given the time needed to obtain these investigations, it is now reasonable to explicitly address anti-thrombotic choice in the peri-investigational period. The empirical use of apixaban during this time may be beneficial, given available data demonstrating a bleeding risk comparable to ASA despite superior protection against stroke and systemic embolism due to AF.\(^5\)

In this study, we sought an appraisal of this strategy. We asked a group of academic Canadian neurologists to respond to a clinical vignette depicting a patient with a TIA and possible underlying atrial fibrillation: recommended investigations (Q1), turn-around time (Q2), and empiric antithrombotic (Q3).

Note: No missing responses.

<table>
<thead>
<tr>
<th>Question and responses</th>
<th>N (% of responses)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Requested investigations (Q1, multiple choices)</td>
<td>63 responses</td>
</tr>
<tr>
<td>Echocardiogram (TTE/TEE)</td>
<td>56 (88.9%)</td>
</tr>
<tr>
<td>Holter monitor (24/48 hour)</td>
<td>46 (73.0%)</td>
</tr>
<tr>
<td>Extended rhythm recorder</td>
<td>27 (42.9%)</td>
</tr>
<tr>
<td>MRI (+/- MRA)</td>
<td>18 (28.6%)</td>
</tr>
<tr>
<td>Expected turn-around time (Q2, single choice)</td>
<td>63 responses</td>
</tr>
<tr>
<td>Less than 1 week</td>
<td>11 (17.5%)</td>
</tr>
<tr>
<td>1–2 weeks</td>
<td>13 (20.6%)</td>
</tr>
<tr>
<td>2–4 weeks</td>
<td>17 (27.0%)</td>
</tr>
<tr>
<td>1–3 months</td>
<td>20 (31.8%)</td>
</tr>
<tr>
<td>More than 3 months</td>
<td>2 (3.2%)</td>
</tr>
<tr>
<td>Empiric antithrombotic (Q3, single choice)</td>
<td>63 responses</td>
</tr>
<tr>
<td>ASA</td>
<td>43 (68.3%)</td>
</tr>
<tr>
<td>ASA &amp; clopidogrel</td>
<td>15 (23.8%)</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>1 (1.6%)</td>
</tr>
<tr>
<td>Novel oral anticoagulant</td>
<td>3 (4.8%)</td>
</tr>
<tr>
<td>Warfarin</td>
<td>1 (1.6%)</td>
</tr>
</tbody>
</table>

Note: 6/63 missing responses.

<table>
<thead>
<tr>
<th>Demographic characteristics of survey respondents</th>
</tr>
</thead>
<tbody>
<tr>
<td>Demographic</td>
</tr>
<tr>
<td>----------------</td>
</tr>
<tr>
<td>Practice specialization</td>
</tr>
<tr>
<td>General neurology</td>
</tr>
<tr>
<td>Vascular neurology</td>
</tr>
<tr>
<td>Other subspecialty</td>
</tr>
<tr>
<td>Practice location</td>
</tr>
<tr>
<td>Academic hospital</td>
</tr>
<tr>
<td>Academic office practice</td>
</tr>
<tr>
<td>Community hospital</td>
</tr>
<tr>
<td>Community office practice</td>
</tr>
<tr>
<td>Volume of stroke patients</td>
</tr>
<tr>
<td>0-5</td>
</tr>
<tr>
<td>6-10</td>
</tr>
<tr>
<td>11-20</td>
</tr>
<tr>
<td>20+</td>
</tr>
</tbody>
</table>

Note: 6/63 missing responses.
data will be needed before either of these questions can be con-

fidently answered.

To our knowledge, this is the first survey of neurologist atti-

tudes and practices toward the use of anticoagulation as empiric

therapy for stroke and suspected underlying AF. As such, it pro-

vides a first impression of a group of practicing neurologists on

this emerging clinical question. The results of our survey are

strengthened by the inclusion of clinicians from across Canada

and by the inclusion of a large number of vascular neurologists.

Our survey also has some important limitations. We were only

able to achieve a response rate of 13%. This is below average for

physician surveys but within reported ranges. We attempted repeat

mailings but this had minimal impact. This low response rate may

in part be attributable to individual practice patterns, such that some

academic neurologists may not manage a significant vascular

practice. In the final question of our survey we asked respondents to

identify a threshold at which the relative benefit of strokes pre-

vented would be outweighed by hemorrhages caused. We provided

simplified estimates for the purpose of relative weighting; these are

higher than the likely absolute values and may have introduced

bias. We think that this is mitigated by the position of this question

as the last of survey and by the clear task of relative weighting

against risks. Finally, we appreciate that our survey of academic

Canadian neurologists may not be representative of community

neurologists or neurologists practicing outside of Canada.

This study suggests that the empiric management of suspected

cardioembolic stroke could be an avenue for further research. Our

clinicians appeared optimistic that apixaban would be more effective

than ASA for the prevention of stroke in patients with suspected

underlying AF but would not use it given the lack of evidence.

Such work would complement ongoing efforts to determine the

prevalence of paroxysmal AF in patients with stroke or TIA.

CONCLUSION

Neurologists practicing in academic Canadian centers
demonstrated equipoise for the empirical use of apixaban during
the investigation of possible cardioembolic stroke / TIA.

FUNDING

DD is supported by a Heart and Stroke Foundation of Canada
New Investigator Award, and by the University of Ottawa
Department of Medicine.

MC is a recipient of a New Investigator Award from the Heart
and Stroke Foundation of Canada and of a Tier 2 Research Chair
from the University of Ottawa.

DISCLOSURES

DD has received speaker honoraria from Boehringer Ingelheim
and Octapharma, and has served on advisory boards for Bayer and
BMS/Pfizer.

MS has received speaker honoraria and/or advisory boards for
Boehringer Ingelheim, BMS/Pfizer, Bayer. No ownership interest.

MC has received speaker honoraria from Boehringer Ingelheim
and Bayer.

SUPPLEMENTARY MATERIAL

To view supplementary material for this article, please visit
http://dx.doi.org/10.1017/cjn.2015.14.

REFERENCES


   cardiac monitoring for detecting paroxysmal atrial fibrillation or
   flutter after acute ischemic stroke: a systematic review. Stroke.

2. Gladstone DJ, Spring M, Dorian P, et al. Atrial fibrillation in

   patients with cryptogenic stroke. New Engl J of Med. 2014;370:
   2467-2477.


   and underlying atrial fibrillation. New Engl J Med. 2014;370:
   2478-2486.


   anticoagulants and the risk of intracranial hemorrhage: traditional
   and Bayesian meta-analysis and mixed treatment comparison of
   randomized trials of new oral anticoagulants in atrial fibrillation.
