Patient values and preferences for antithrombotic therapy in atrial fibrillation
A Narrative Systematic Review

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Summary
Guidelines recommend that patients’ values and preferences should be considered when selecting stroke prevention therapy for atrial fibrillation (SPAF). However, doing so is difficult, and tools to assist clinicians are sparse. We performed a narrative systematic review to provide clinicians with insights into the values and preferences of AF patients for SPAF antithrombotic therapy. Narrative systematic review of published literature from database inception. Research questions: 1) What are patients’ AF and SPAF therapy values and preferences? 2) How are SPAF therapy values and preferences affected by patient factors? 3) How does conveying risk information affect SPAF therapy preferences? and 4) What is known about patient values and preferences regarding novel oral anticoagulants (NOACs) for SPAF? Twenty-five studies were included. Overall study quality was moderate. Severe stroke was associated with the greatest disutility among AF outcomes and most patients value the stroke prevention efficacy of therapy more than other attributes. Utilities, values, and preferences about other outcomes and attributes of therapy are heterogeneous and unpredictable. Patients’ therapy preferences usually align with their values when individualised risk information is presented, although divergence from this is common. Patients value the attributes of NOACs but frequently do not prefer NOACs over warfarin when all therapy-related attributes are considered. In conclusion, patients’ values and preferences for SPAF antithrombotic therapy are heterogeneous and there is no substitute for directly clarifying patients’ individual values and preferences. Research using choice modelling and tools to help clinicians and patients clarify their SPAF therapy values and preferences are needed.

Keywords
Atrial fibrillation, anticoagulation, antiplatelet, antithrombotic, stroke, bleeding, values, preferences, medication

Introduction
There are many effective antithrombotic therapies for stroke prevention in atrial fibrillation (SPAF): warfarin (1), dabigatran (2), rivaroxaban (3), apixaban (4), and edoxaban (5). Each option has efficacy, safety, monitoring, dosing, and lifestyle implications. These therapeutic distinctions pose a challenge when selecting the best treatment for each patient. Therapeutic guidelines from various countries have recognised the importance of patients’ values and preferences and recommend that they be taken into account when selecting SPAF antithrombotic therapy (6–9). Doing so is a fundamental principle of patient-centred care (10), and may also help address low patient knowledge about their AF and its treatment (11–14), non-adherence to SPAF therapy (15–20), and ultimately SPAF failure (21). However, incorporating patients’ values and preferences into decision making is difficult, and few tools exist to assist clinicians. In this context, “values” refers to the absolute or relative weight patients place on attributes of their condition (e.g. stroke) and/or its therapy (e.g. cost), and “preferences” concerns the selection of one treatment over another (including no therapy) or ranking of treatment options.

Although a review was previously published on this topic (22), it did not focus specifically on patients with atrial fibrillation (AF), and a significant body of literature has emerged since. This includes research involving new oral anticoagulants (NOACs), antidotes to OACs, and emerging methods to study patient preferences and attributes of therapy other than stroke and bleeding. Furthermore, previous authors have identified large inter-individu-
ual variability in patients’ values and preferences related to antithrombotic therapy (22). Since few have attempted to rationalise the observed heterogeneity, a systematic review is ideal to access these contributing factors.

**Objective**

Twas the review’s objective to provide clinicians, guideline developers, and policymakers with insights into the values and preferences of AF patients for stroke prevention therapy and the patient-specific factors which affect those values and preferences.

**Research questions**

Literature related to patient values and preferences for SPAF antithrombotic therapy was systematically reviewed to answer the following research questions:

- What are patients’ values and preferences regarding AF and its therapy-related attributes (e.g. stroke, major bleeding)?
- How are SPAF antithrombotic therapy values and preferences affected by patient factors (e.g. sex, previous stroke)?
- How does conveying risk information affect SPAF therapy preferences?
- What is known about patient values and preferences regarding novel oral anticoagulants (NOACs) for SPAF?

**Methods**

A systematic review was conducted according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) guidelines (23). The project was prospectively registered with the PROSPERO database of systematic reviews (#29231) (24). Literature indexed in PubMed, Medline, and Embase since each database’s inception up to June 2016 was searched. Keywords and MeSH terms related to “preference”, “values”, “satisfaction”, “utility”, “decision”, “shared decision-making”, “anticoagulants”, “antithrombotics”, “warfarin”, “vitamin K antagonist”, “dabigatran”, “rivaroxaban”, “apixaban”, “edoxaban”, and “stroke prevention” combined with “atrial fibrillation” were used. Reference lists of included studies and all articles citing the included studies were searched using Google Scholar.

English-language reports involving all study designs were included if they involved evaluation of individuals’ values or preferences related to health states (e.g. stroke), choice of SPAF antithrombotic therapy (including no therapy), and therapy attributes (e.g. bleeding risk). “Values” was defined as quantifying the extent to which attributes of AF (e.g. stroke) or SPAF antithrombotic therapy (e.g. cost) were important to the patient (25), using utilities, ranking, or discrete choice experiments. Studies which identified thresholds required for patients to select one option over another were included in this category. “Preferences” were defined as the selection of one treatment over another (including no therapy) or ranking of treatment options. Studies were included if participants had AF or if they were asked to respond as though they had AF. Studies including people with and without AF were included if the AF cohort was ≥50% or discrete results for AF patients were reported. Studies were excluded if the population mix of AF vs non-AF was not reported or if they did not provide information about actual patient values or preferences (e.g. base-case analyses, quality-of-life studies).

Eligible abstracts were evaluated by three authors (AJ, AK, PL) to select for full-text review. Data was extracted from full-text articles by two authors (AJ, AK) into a standardised database. Three authors (PL, AK, AJ) reviewed the database and collectively resolved discrepancies, identified missing data, consulted original publications, and arrived at consensus through group discussion regarding inclusion and exclusion criteria.

Risk of bias was assessed at the study level using accepted study design-specific quality of reporting critical appraisal instruments. CONSORT was used for randomised controlled trials (26), STROBE extensions for cohort and cross-sectional studies (27), COREQ for qualitative studies (28), and the ISPOR Good Research Practices checklist for conjoint analyses (29). Three authors (PL, AK, AM) critically appraised all included studies and disagreements about appraisal items were resolved by consensus. A point was given for each checklist item met and all other items were judged as unmet or not applicable. For example, studies that did not include subgroup analyses were exempt from checklist items about reporting and quality of subgroup analyses. Because each instrument has a different number of items, to summarise across checklists a score was computed for each study as the number of items satisfactorily met divided by the total number of applicable items and expressed as a percentage. Using the method of Stevanovic et al., overall quality of reporting was summarised as “low” for scores <50%, “moderate” for scores 50%-80%, and “high” for scores >80% (30). Additional content-specific critical appraisal to identify potential for bias from framing effects and conflicts of interest were performed by all authors and also noted.

Due to lack of commonality of quantitative endpoints in the included studies, the synthesis was qualitative and the systematic review narrative. The primary units of organisation for synthesis were studies about values and studies about preferences. All authors independently coded the attributes (for values studies) and therapies (for preference studies) and each study’s results were tagged for applicability to our research questions. These results were qualitatively synthesised by all authors to generate the narrative answers to each research question, cross-referencing therapy attributes/therapy options with each research question. Results from “low” quality studies were flagged and denoted as such in the narrative if similar result(s) did not also appear in higher-quality studies.

**Results**

**Study selection and characteristics**

The literature search identified 895 candidate articles. Sixty-eight articles were selected for full-text review and 43 of these were excluded. Twenty-five studies were included in the review (Figure 1). Several
Figure 1: Study flow diagram.

1145 candidate articles identified through database search

895 articles screened after duplicates removed

827 articles excluded based on title/abstract review (125 because of non-English)

61 articles for full-text review

7 candidate articles identified from reference lists

68 articles for full-text review

43 full text articles excluded: study population not clear (5), AF cohort <50% (5), study method quality-of-life only or no actual patients assessed (base-case analysis, modeling) (33)

25 articles included in systematic review

15 articles focused on patient values
Methods used (multiple methods possible):
- Standard gamble (n=6)
- Time/therapy trade off (n=6)
- Discrete choice experiment (n=5)
- Conjoint analysis (n=1)
- Scenario ranking (n=1)

10 articles focused on patient preferences
Methods used:
- Questionnaires (n=5)
- Simple choices based on scenarios (n=2)
- Comparisons of information presentation formats (n=3)
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<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Patient population</th>
<th>Attributes studied</th>
<th>Therapy</th>
<th>Values results (primary analysis)</th>
<th>Appraisal instrument</th>
<th>Comments</th>
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<tr>
<td>USA</td>
<td>DCE</td>
<td>N=74; mean age 70; 86% male; 100% with AF; 50% had previous warfarin use</td>
<td>Mild stroke, Moderate stroke, Major stroke</td>
<td>ASA, Warfarin</td>
<td>Utilities (median): Mild stroke: 0.94, Moderate stroke: 0.07, Major stroke: 0.0, Warfarin: 0.997, ASA: 1.0</td>
<td>ISPOR 82% (Moderate) 3.1, 3.2, 4.2, 5.3, 6.3</td>
<td>No bleeding risk information provided. Death was mentioned as a possible stroke outcome.</td>
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<td>Canada</td>
<td>Cross-sectional</td>
<td>N=64; mean age 69; 70% male; 100% with AF; 91% had previous warfarin use</td>
<td>Stroke</td>
<td>No treatment, Warfarin</td>
<td>Based on a baseline 10% risk of stroke over 2 years</td>
<td>STROBE cross-sectional 77% (Moderate) 5, 9, 10, 14b</td>
<td>Death was not mentioned as a possible stroke/major bleed outcome.</td>
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<td>Howitt and Armstrong, 1999 (57)</td>
<td>Cross-sectional</td>
<td>N=56; 100% with AF</td>
<td>Stroke</td>
<td>No treatment, Warfarin</td>
<td>Only 63% could decide on an MCID. MCID (warfarin users): 2.4%/year, MCID (warfarin naïve): 4.1%/year</td>
<td>STROBE cross-sectional 76% (Moderate) 9, 10, 12c, 12d, 13c, 14a, 14b, 16b</td>
<td>Incomplete reporting. Possible selection bias. No bleeding risk information. Death was not mentioned as a possible stroke outcome.</td>
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<td>Protheroe, 2000 (32, 58)</td>
<td>DCE</td>
<td>N=97; mean age 77; 51% male; 100% with AF; 39% taking ASA; 48% taking warfarin</td>
<td>Stroke, Major/minor &quot;side effects&quot;</td>
<td>No treatment, Warfarin</td>
<td>Utilities of health states: No treatment: +no CVA: 1; +CVA with no residual sx: 0.7; +CVA with residual sx: 0.1. Warfarin: +side effects +no CVA: 0.8; +side effects +CVA with no residual sx: 0.5; +side effects +CVA with residual sx: 0.1; +no side effects +CVA with no residual sx: 0.7; +no side effects +CVA with residual sx: 0.1; +no side effects +no CVA: 1</td>
<td>ISPOR 63% (Moderate) 2.3, 3.1, 3.2, 4.1, 4.2, 5.1, 5.3, 6.2, 8.2, 10.2</td>
<td>Definition of &quot;side effects&quot; not reported. No specific bleeding risk information. Death was not mentioned as a possible outcome.</td>
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<td>Country</td>
<td>Study design</td>
<td>Patient population N; mean age (years); % male; % with AF; % with prior stroke; % with prior major bleed; OAC use</td>
<td>Attributes studied</td>
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<td>Values results (primary analysis)</td>
<td>Appraisal instrument Appraisal score* Deficient items</td>
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<td>Devereaux, 2001 (37)</td>
<td>DCE</td>
<td>N=61, 57% male, 0% with AF; no prior strokes or bleeds; 0% OAC experienced. Not reported: mean age</td>
<td>Stroke</td>
<td>No treatment</td>
<td>Patients required 1.8 (SD 1.9) strokes be prevented over 2 years to take warfarin. Patients required 1.3 (SD 1.3) strokes be prevented over 2 years to take ASA. Patients were willing to tolerate 17.2 (SD 7.1) extra major bleeds over 2 years with warfarin and 14.7 (SD 8.5) extra major bleeds over 2 years with ASA. 57% of patients would accept 22 additional major bleeds for an 8% absolute stroke risk reduction over 2 years.</td>
<td>ISPOR</td>
<td>86% (High) 3.3, 4.1, 4.2, 5.3</td>
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<td>Robinson, 2001 (35)</td>
<td>DCE</td>
<td>N=57; mean age 73; 54% male; 100% with AF; 23% prior stroke; 49% on warfarin Not reported: % with prior stroke or bleed</td>
<td>Stroke Major bleeding</td>
<td>Warfarin</td>
<td>Utilities (mean): • GP managed warfarin 0.95 • Hospital managed warfarin 0.94 • Major bleed 0.84 • Mild stroke 0.64 • Severe stroke 0.19 Severe stroke considered worse than death by 56%; mild stroke considered worse than death by 9%. Major bleed considered worse than death by one patient; 12% of patients chose a major bleed over GP or hospital managed warfarin.</td>
<td>ISPOR</td>
<td>74% (Moderate) 3.3, 4.2, 6.1, 6.3, 7.1, 8.3, 10.2</td>
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<td>Wild, 2009 (39)</td>
<td>Qualitative</td>
<td>N=60; mean age 60; 57% male; 47% with AF; 7% prior major bleed; 100% on warfarin Not reported: % with prior stroke</td>
<td>Bleeding &amp; bruising INR monitoring Dietary &amp; alcohol restriction Psychological impact Expectations and knowledge of VKA</td>
<td>Warfarin Hypothetical NOAC (no INR monitoring, food or alcohol interactions, or interaction with other medications)</td>
<td>• Bleeding &amp; bruising: 89% &amp; 97% experienced, respectively; 7% experienced “severe or long-lasting bleeding” • INR monitoring: 50% considered it a burden. 20% would feel apprehensive without it. • Dietary &amp; alcohol restriction: ~44% acknowledged there were restrictions (22% diet, 40% alcohol). • Psychological impact: embarrassment about bruises, 18% worried about bleeding/bruising, 50% concerned about drug interactions • Expectations and knowledge of VKA: 40% understood why they were on warfarin. 10% could explain that it was to reduce heart attacks or strokes. 57% found it complicated to follow regimen. 39% of patients would consider switching to the hypothetical NOAC.</td>
<td>COREQ</td>
<td>71% (Moderate) 1, 5, 7, 13, 21, 23, 24, 25, 28</td>
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<td>Country</td>
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<td>Alonso-Coello, 2014 (38)</td>
<td>DCE</td>
<td>N=96; mean age 72; 50% male; 0% with AF; 0% OAC experienced</td>
<td>Mild stroke, Major stroke, Non-fatal GI bleed, Burden of treatment</td>
<td>ASA, Warfarin</td>
<td>Median 10 extra bleeds accepted for absolute stroke risk reduction of 3% over 2 years</td>
<td>ISPOR 94% (High) 4.1b, 8.2</td>
<td>Death was not mentioned as a possible stroke/bleed outcome</td>
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<td>Ghijben, 2014 (41)</td>
<td>DCE</td>
<td>N=76; mean age 53; 34% male; 8% with AF; 1.3% prior stroke; 2.6% prior major bleed; 16% had prior ASA, warfarin, or NOAC use.</td>
<td>Untreated stroke risk (4 levels from 0 to 2.4%/year), Treated bleed risk (4 levels from 2 to 5% per year), Antidote availability, Need for monthly blood tests, Dosing frequency per day, Presence or absence of drug-food interactions, Cost (4 levels, from AUD$0 to AUD$120 per month)</td>
<td>No treatment ASA, Warfarin, Apixaban, Dabigatran, Rivaroxaban</td>
<td>Attribute ranking: Efficacy (stroke risk) was more important than safety (bleed risk, antidote), which were both more important than convenience factors (blood tests, dose frequency, drug or food interactions). Participants were willing to pay AUD$50.00 per month for a reduction in absolute stroke risk or bleed risk of 1%/year, and AUD$35–75 for an antidote, depending on the risk of bleeding. WTP to eliminate blood testing: $2.74/month.</td>
<td>ISPOR 100% (High)</td>
<td>Death was not mentioned as a possible stroke/bleed outcome</td>
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instances of duplicate and iterative publication were encountered and we grouped and describe these as a single report wherever possible. Fifteen studies were classed as “patient values” and 10 as “patient preferences”. Characteristics of patient values and patient preferences studies are summarised in Table 1 and Table 2, respectively. Each study is narratively summarised in the Online Appendix (available online at www.thrombosis-online.com). Studies in the patient values category used standard gamble (31–36), time or probability trade-off (31, 33, 34, 36–38), qualitative (39), discrete choice experiment (40–44), conjoint analysis (45), and scenario ranking methods (46). The patient preferences studies used questionnaires (47–51), simple choices based on scenarios (52, 53), and comparisons of information presentation formats (54–56).

Critical appraisal results are included in Table 1 and Table 2. Of the studies, 32% were of “high” quality, 64% were “moderate”, and one study’s quality was “low”. The mean appraisal score was 74% (SD 13.8) overall, 76% (SD 13.4) for “values” studies, and 71% (SD 14.5) for “preferences” studies. Potential risks of bias across studies are described in the Discussion.

**Synthesis of results**

The following observations were made using the research question framework.

1. **What are patients’ values and preferences regarding AF and its therapy-related attributes?**

Patients with or without AF consistently consider disabling stroke to have a utility worse than death and non-disabling strokes to have fairly little disutility (31, 35, 36). The value placed on moderate strokes was more variable (35, 36). Overall, stroke avoidance is
highly valued by patients. In studies focusing only on OACs, where efficacy and safety between therapies are relatively similar, stroke avoidance was not a prominent therapy attribute in comparison to factors such as the availability of an antidote or interactions with foods or drugs (45).

In studies evaluating the trade-off between stroke and major bleeding, patients accepted many serious bleeds to avoid one stroke (e.g. 2, 5.6, 10, 16, 17, 22 or >33 bleeds per stroke) (36–38) and were willing to pay two times more per month in medication cost for every 1% reduction in stroke risk compared to bleed risk.

Table 1: Continued

<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Patient population N; mean age (years); % male; % with AF; % with prior stroke; % with prior major bleed; OAC use</th>
<th>Attributes studied</th>
<th>Therapy</th>
<th>Values results (primary analysis)</th>
<th>Appraisal instrument</th>
<th>Appraisal score* Deficient items</th>
<th>Comments</th>
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<tbody>
<tr>
<td>LaHaye, 2014 (36)</td>
<td>Cross-sectional</td>
<td>N=172; mean age 73; 67% male; 100% with AF; 22% prior stroke; 20% prior bleed; 59% on warfarin</td>
<td>• Stroke • Major bleeding</td>
<td>ASA Warfarin</td>
<td>Utility scores: • Major stroke –0.36 • Death 0.00 • Moderate stroke 0.09 • Minor stroke 0.47 • Major bleed 0.60</td>
<td>STROBE cross-sectional</td>
<td>77% (Moderate) 7, 9, 10, 12c, 12d, 13b, 16b</td>
<td>Death was not mentioned as a stroke/major bleed outcome</td>
</tr>
<tr>
<td>Bottger, 2015 (42)</td>
<td>DCE</td>
<td>N=486; mean age 74; 57% male; 100% with AF; 7% prior stroke in last 5 years; 1.4% prior bleed 1.4%; 52% on warfarin; 48% on rivaroxaban</td>
<td>• Need of bridging (for surgical procedures) • Interactions with food/nutrition • Need of INR controls/dose adjustment • Dosing frequency per day</td>
<td>Warfarin Rivaroxaban</td>
<td>Importance (% influence): • Frequency of intake: 29% • Need for bridging: 26% • Interaction with food/nutrition: 26% • INR control/dose adjustment: 6%</td>
<td>ISPOR 88% (High) 4.1b, 5.2b, 5.3, 8</td>
<td>Sponsored by Bayer, manufacturer of rivaroxaban. Unclear why other NOACs (all BID dosing) were excluded, since authors performed hypothetical analyses of dabigatran and apixaban, which they found to be inferior to rivaroxaban</td>
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(43). None of these studies disclosed the risk of death from major bleeding to participants. This likely exaggerates the value placed on stroke avoidance over major bleeding and the preference for OAC over ASA or no therapy. The only studies that mentioned death from major bleeding showed respondents to be more sensitive to bleeding risk (51, 56).

Studies evaluating the minimum stroke risk reduction patients required to choose OAC over no therapy (36–38, 40, 57) found it to be smaller than the actual effect of warfarin (1). Some of these
Table 1: Continued

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<thead>
<tr>
<th>Country</th>
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<th>Patient population N; mean age (years); % male; % with AF; % with prior stroke; % with prior major bleed; OAC use</th>
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<tr>
<td>USA</td>
<td>DCE</td>
<td>N=201; 50% male; 100% with AF; prior experience: 29% ASA, 34% warfarin, 7% apixaban, 7% dabigatran, 12% rivaroxaban</td>
<td>Stroke; Major bleeding; Convenience (regular blood testing, diet restrictions); Cost; Dosing frequency per day</td>
<td>Warfarin Apixaban Dabigatran Edoxaban Rivaroxaban</td>
<td>WTP: $30.28 per month for 1% reduction in stroke risk per year; $16.49 for 1% reduction in major bleed risk; $8.79 per month to reduce dosing from twice to once daily</td>
<td>ISPOR 67% (Moderate) 2.1, 3.1, 3.3, 4.1, 4.2, 5.2, 5.3, 7.1, 8.1, 8.2</td>
<td>ISPOR 67% (Moderate)</td>
<td>2.1, 3.1, 3.3, 4.1, 4.2, 5.2, 5.3, 7.1, 8.1, 8.2</td>
<td>Funded by Bristol-Myers Squibb and Pfizer, manufacturers of apixaban, 3 authors are employees of the companies</td>
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<td>Not reported: mean age, % with prior stroke or bleed</td>
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DCE: discrete choice experiment; NOAC: novel oral anticoagulant; MCID: Minimal clinically important difference; GI: gastrointestinal; WTP: willingness to pay; CVA: cardiovascular accident; ARR: absolute risk reduction; QoL: quality of life. CONSORT (26); STROBE cohort (27); STROBE cross-sectional (27); ISPOR (29); COREQ (28). *appraisal score: <50% = "low"; 50–80% = "moderate"; >80% = "high".

Table 2: Summary of included patient preferences studies.

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<tr>
<th>Country</th>
<th>Study design</th>
<th>Patient population N; mean age (years); % male; % with AF; % with prior stroke; % with prior major bleed; OAC use</th>
<th>Preference options</th>
<th>Preference results (primary analysis)</th>
<th>Appraisal instrument</th>
<th>Appraisal score*</th>
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<tr>
<td>USA</td>
<td>RCT (audiobooklet DA vs usual care)</td>
<td>N=287; mean age 66; 76% male; 100% with AF; 62% on ASA; 37% ever used warfarin</td>
<td>ASA Warfarin</td>
<td>Overall 91% chose ASA. More patients in the usual care group chose warfarin (11% vs. 8%). Patients with hypertension were more likely to choose warfarin than normotensives (21% vs. 12%). Previous warfarin use was associated with choosing warfarin over ASA (OR 2.18). 6-month adherence to chosen therapy was 94%.</td>
<td>CONSORT 88% (High) 13b, 23, 24</td>
<td>Stroke risk information was not individualised. Death was not mentioned as a possible stroke/major bleed outcome.</td>
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<td>Not reported: % with prior stroke or bleed</td>
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<td>UK</td>
<td>Cross-sectional</td>
<td>N=176; 100% with AF Not reported: mean age, % male, % with prior stroke or bleed, OAC experience</td>
<td>No treatment Warfarin Location of INR monitoring (home, clinic, or hospital)</td>
<td>89% chose warfarin therapy. Home-based testing was preferred to hospital based (99% vs. 79% acceptance).</td>
<td>STROBE cross-sectional 54% (Moderate) 4, 5, 7, 9, 10, 11, 12b, 12c, 13b, 13c, 14b</td>
<td>STROBE cross-sectional 54% (Moderate) 4, 5, 7, 9, 10, 11, 12b, 12c, 13b, 13c, 14b</td>
<td>STROBE cross-sectional 54% (Moderate) 4, 5, 7, 9, 10, 11, 12b, 12c, 13b, 13c, 14b</td>
<td>Bleeding was not mentioned as a risk. Stroke risk information was not quantitative or individualised. Death was not mentioned as a stroke/major bleed outcome.</td>
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<td>Stroke risk information was not individualised. Death was not mentioned as a possible stroke/major bleed outcome.</td>
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<td></td>
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<td>Not reported: % with prior stroke or bleed</td>
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studies disclosed no description of bleeding risk (57) or major bleeding (36), whereas others presented bleeding risks devoid of the risk of death (37, 38, 40). Consequently, these studies likely overestimated patients' willingness to take OAC for SPAF. Furthermore, patients' preference for taking OAC vs no therapy may not align with guideline recommendations (58), and physician preferences are often different from patient preferences in unpredictable directions (37, 38, 43–45).

Values and preferences related to International Normalised Ratio (INR) monitoring are extremely heterogeneous, though most studies found it to be relatively unimportant compared to other attributes of therapy (41, 42, 45, 48, 56). Whereas some patients find INR testing burdensome (53), there is a subset (15–20% in one study) who prefer the assurance INR monitoring provides (39). Supporting this notion, avoidance of INR testing and dietary restrictions (combined as "convenience") (43) had a negative willingness-to-pay value, a finding consistent with an excluded study which found no willingness to pay to avoid blood testing (59). In spite of this, studies consistently showed that physicians ascribe higher value to INR testing avoidance than patients (43, 45).

Antidote availability for OAC bleeding was included as an attribute in three studies and was defined as: "Serious bleeding, although rare, can occur in your brain or in your gut… The doctor

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<th>Country</th>
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<th>Preference options</th>
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</tr>
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<tr>
<td>Canada</td>
<td>RCT (quantitative vs qualitative risk information)</td>
<td>N=198; mean age 71; 49% male; 0% with AF; 4% prior stroke; 4% prior GI bleed; 31% prior ASA use; 6% prior warfarin use</td>
<td>No treatment ASA Warfarin</td>
<td>ASA was preferred in all groups (52–71% choosing it, depending on the arm), and warfarin was preferred by more in the moderate risk group than in the low risk group (12% vs. 4%; p=0.03). Quantitative presentation resulted in a more realistic understanding of risks, but did not affect treatment choices. Warfarin preference was associated with no GI bleed history, female gender, and stroke risk awareness</td>
<td>CONSORT 84% (High)</td>
<td>8a, 10, 14a, 23</td>
<td>Death was not mentioned as a possible stroke/major bleed outcome.</td>
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<tr>
<td>Canada</td>
<td>RCT (6 formats of information presentation), blinded then unblinded to treatment identity</td>
<td>N=98; mean age 74; 38% male; 0% with AF; 7% prior stroke; 9% prior major bleed; 40% prior ASA use; 12% prior warfarin use</td>
<td>No treatment ASA Warfarin</td>
<td>Preferred while blinded: ASA (42%), warfarin (40%), no therapy (18%). Unblinded: ASA (67%), warfarin (28%), no therapy (5%). Reasons for switching to warfarin included fear of stroke and knowing someone who had a stroke. Reasons for switching to ASA included the aforementioned reasons and no INR monitoring.</td>
<td>CONSORT 85% (High)</td>
<td>8a, 10, 13b, 14a, 23</td>
<td>Stroke and bleed risk information was not individualized. Death was not mentioned as a possible stroke/major bleed outcome.</td>
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<tr>
<td>USA</td>
<td>Cross-sectional</td>
<td>N=147; mean age 68; 50% male; 71% with AF; 100% on warfarin</td>
<td>Warfarin Hypothetical NOAC (more expensive than warfarin, twice daily dosing, no INR monitoring)</td>
<td>Patients were satisfied with warfarin (80%) and 58% would switch to hypothetical NOAC. Older age and male gender were more willing to switch.</td>
<td>STROBE cross-sectional 78% (Moderate)</td>
<td>10, 12b, 12c, 12d, 13b, 13c</td>
<td>No bleeding risk information was provided. Death was not mentioned as a possible stroke/major bleed outcome.</td>
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Note: Uncorrected proof, epub ahead of print online

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Table 2: Continued

<table>
<thead>
<tr>
<th>Country</th>
<th>Study design</th>
<th>Patient population N; mean age (years); % male; % with AF; % with prior stroke; % with prior major bleed; OAC use</th>
<th>Preference options</th>
<th>Preference results (primary analysis)</th>
<th>Appraisal instrument</th>
<th>Appraisal score*</th>
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| Canada  | RCT          | N=71; mean age 70; 49% male; 0% with AF; 7% prior stroke; 10% prior major bleed; 7% prior warfarin use | No treatment       | Scenarios: preference  
  : average benefit/harm: 65% warfarin  
  : high benefit/low harm: 62% warfarin  
  : low benefit/high harm: 23% warfarin  
  : high benefit/high harm: 41% warfarin  
  : individualised risk profile: 27% warfarin  
  Decisional conflict: not different between presentation types (p=0.097)  
  Participants were significantly less likely to choose warfarin when risks were presented as the chance of NOT having a stroke or bleed. Disclosing the chance of death ("2-year risk of death, 32% for no treatment, 25% for warfarin") significantly swayed participants to choose warfarin. Factors most influencing patient decision were, "I am afraid of having/know someone who has had, a stroke" (87%), "I am afraid of having/know someone who has had, a serious bleeding complication" (49%), "I don't like the idea of having to take another pill" (28%), "I don't want to have regular blood tests" (14%).  
  83% preferred warfarin over dabigatran.  
  Decisional conflict: mean 18.9 (SD=14.2) ("low") after using the DA.  
  Cited factors in making the decision:  
  Fear of stroke 89%  
  Fear of MI 83%  
  Once daily dosing 74%  
  Fear of major bleed 72%  
  Cost concerns 51%  
  Would consider switching their medication: Dabigatran users 10.7%; Warfarin users 32%. Reasons for dabigatran users to consider switching: cost (62.5%), inadequate insurance coverage (18.8%). Reasons for warfarin users to consider switching: "too much of a hassle" (19.5%), “interfering with my lifestyle” (12.2%).  
  Supported by Janssen, manufacturer of rivaroxaban. Death was not mentioned as a possible stroke/major bleed outcome. | CONSORT 50% (Moderate)  
  1a, 4b, 5, 6a, 7a, 8a, 9, 10, 11a, 12b, 13a, 13b, 14a, 15, 23, 24 | |
| Hong, 2013 (49) | | | | |
| Canada  | Prospective observational | N=35; mean age 63; 63% male; 0% with AF; 74% taking ASA; patients excluded if using anticoagulant  
  Not reported: % prior stroke or bleed | Warfarin         | 83% preferred warfarin over dabigatran.  
  Decisional conflict: mean 18.9 (SD=14.2) ("low") after using the DA.  
  Cited factors in making the decision:  
  Fear of stroke 89%  
  Fear of MI 83%  
  Once daily dosing 74%  
  Fear of major bleed 72%  
  Cost concerns 51%  
  Would consider switching their medication: Dabigatran users 10.7%; Warfarin users 32%. Reasons for dabigatran users to consider switching: cost (62.5%), inadequate insurance coverage (18.8%). Reasons for warfarin users to consider switching: "too much of a hassle" (19.5%), “interfering with my lifestyle” (12.2%).  
  Supported by Janssen, manufacturer of rivaroxaban. Death was not mentioned as a possible stroke/major bleed outcome. | STROBE cohort 80% (Moderate)  
  1a, 3, 12c, 13c, 14b, 22 | |
| Choi, 2014 (50) | Cross-sectional | N=364; mean age 65; 69% male; 100% with AF; 56% on warfarin; 44% on dabigatran  
  Not reported: % prior stroke or bleed | Warfarin         | Would consider switching their medication: Dabigatran users 10.7%; Warfarin users 32%. Reasons for dabigatran users to consider switching: cost (62.5%), inadequate insurance coverage (18.8%). Reasons for warfarin users to consider switching: "too much of a hassle" (19.5%), “interfering with my lifestyle” (12.2%).  
  STROBE-cross sectional 57% (Moderate)  
  5, 6, 8, 9, 10, 12c, 12d, 13a, 13b, 14b, 16a, 16b, 20 | STROBE-cross sectional 57% (Moderate)  
  5, 6, 8, 9, 10, 12c, 12d, 13a, 13b, 14b, 16a, 16b, 20 | |

Loewen et al. Patient values and preferences for stroke prevention in AF
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<td>Elewa, 2014</td>
<td>Cross-sectional</td>
<td>N=260; 45% male; 50% with AF; 50% on warfarin</td>
<td>Warfarin Hypothetical NOAC (resembling dabigatran)</td>
<td>89% were satisfied with their warfarin therapy. 40–60% would switch to the hypothetical NOAC, depending on the attribute question. Most important switch attributes: lack of food interactions, lower cost, and potential for fewer follow-up visits were the most potent factors driving preference for a new drug over warfarin. 63% were not willing to pay more than $10 more per month for the new drug vs. warfarin.</td>
<td>STROBE cross-sectional</td>
<td>77% (Moderate)</td>
<td>5, 9, 12c, 12d, 13c, 22</td>
<td>Results from patients with AF were not reported separately. Overall switch preference proportion not evaluated. Death was not mentioned as a possible stroke/major bleed outcome.</td>
</tr>
<tr>
<td>Fatima, 2016</td>
<td>Prospective observational DA validation</td>
<td>N=81; mean age 75; 64% male; 93% with AF; 9% prior major bleed; 77% prior anticoagulant use; 35% taking antiplatelet or NSAID</td>
<td>No treatment ASA Warfarin Dabigatran 110/150 mg Rivaroxaban Apixaban</td>
<td>Preferences based on individualised stroke and bleeding risk: • warfarin 41% • apixaban 33% • rivaroxaban 15% • dabigatran 110 mg 4% • dabigatran 150mg 4% • no therapy 3% • ASA 1% Factors that “somewhat” or “greatly” influenced treatment decision: • &quot;comparisons between the benefits and harms of the drugs“ (81%), • “does not want regular blood tests“ (42%), “afraid of having a stroke” (41%) • “afraid of having a heart attack“ (38%) • “afraid of having a bleed“ (36%) • “cost of drug“ (35%) • “prefer taking an older, more known drug“ (31%) • “prefer taking pill once/day rather than twice/day“ (28%) • “greatly“ influenced NOAC-choosers: • “does not want regular blood tests done (36%)“ • “comparison between the benefits and harms of the drugs“ (31%) • “prefer taking pill once/day rather than twice/day“ (20%). • 36% of current warfarin users selected “prefer taking an older, more known drug“ (0% of NOAC patients reported this)</td>
<td>STROBE cohort</td>
<td>59% (Moderate)</td>
<td>1a, 3, 5, 9, 12c, 13a, 13b, 13c, 14b, 20, 21</td>
<td>Death was mentioned as a possible stroke/major bleed outcome.</td>
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RCT: randomised controlled trial; DA: decision aid; ICH: intracranial haemorrhage. DCS: decisional conflict score. CONSORT (26); STROBE cohort (27); STROBE cross-sectional (27); ISPOR (29); COREQ (28). *appraisal score: <50% = “low”; 50–80% = ”moderate“; >80% = “high”.

Loewen et al. Patient values and preferences for stroke prevention in AF

Table 2: Continued

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The importance of dosing frequency for SPAF antithrombotic therapy (once vs twice daily dosing) is unclear. In one study, once daily dosing was not a significant choice factor between warfarin and a NOAC (41), there was variation in the willingness-to-pay for once daily dosing vs twice in another (43), and two studies showed dosing frequency was of low-intermediate importance (45, 56). Conversely, in a study without safety or efficacy attributes, patients demonstrated a preference for once daily dosing above all else (42). When only OAC options were presented, patients’ preference for once daily dosing vs twice superseded fear of major bleeding (49).

Lack of dietary restrictions or food-drug interactions were among the highest rated attributes for patients when choosing between OACs (45) and a major incentive for patients to switch from warfarin to a NOAC (53). Other studies found that drugs with food-drug interactions were less favoured and the absence of these interactions was of intermediate importance (41, 42).

2. How are SPAF antithrombotic therapy values and preferences affected by patient factors?

Patients ascribe similar disutility to different severities of stroke depending on whether or not they have experienced one, or know someone who has (31, 38). This suggests peoples’ perceptions about how a stroke may impact their life are accurate. It is not clear whether this is true for major bleeding, although one study indicated that prior gastrointestinal bleeding was associated with an increased preference for no therapy over warfarin (54).

AF-related values and preferences do not appear to differ between patients with and without AF (37, 38, 41, 49, 54), and few generalisable differences between treatment naïve and treatment experienced patients were identified (35). Prior warfarin use was associated with preference for warfarin over no therapy (52), and with acceptance or preference for INR testing over no testing (39, 43).

The effect of sex is not clear. One study found that females ascribed much more disutility to major bleeding, had a higher treatment threshold, and would tolerate far fewer major bleeds per stroke avoided compared to males (36), while another showed that female sex was associated with increased preference for warfarin over no therapy (54). One study determined males were more decisive about therapy and more inclined to make all-or-none decisions such as refusing therapy despite its efficacy or disregarding bleeding risk (36). Other studies detected no association between sex and SPAF values or preferences (38, 43, 45, 47).

3. How does conveying risk information affect SPAF antithrombotic therapy preferences?

Although the methods and information presented to patients varied widely between studies, overall the available evidence shows that patients choose stroke-prevention therapy primarily based on the presented risk of stroke, with the propensity to choose OAC varying in proportion to increased stroke risk (36, 41, 52, 54, 56). However, there are significant cohorts of people who do not follow this pattern. One study found that 20% of patients would not choose warfarin even when benefits were high and risks low, and a similar proportion chose warfarin even when the risks outweighed the benefits (56). In another study, 12% of patients said they would not take antithrombotic therapy even if it was 100% effective, 15% were completely unconcerned about bleeding, and 42% said they would not take OAC if there was any increased risk of bleeding (36). Even when no bleeding risk information was presented, 50% of patients were unwilling to take warfarin at any level of stroke risk (57). Patients have even been shown to change treatment preference based solely on drug name (55).

Presentation of each patient’s individualised stroke and bleeding risk affects treatment choice compared to giving only generic information, usually in a manner that comports with the patient’s stated values (56). Framing also affects decisions. For example, presenting risks as the chance of not having an event causes fewer patients to select OAC (56), and the exclusion of bleeding risk information increases OAC preference (32, 47). However, presenting quantitative risk information did not affect treatment choice compared to qualitative presentation (e.g. “your stroke risk is moderate”) (54). Individualised education about benefits and risks of therapy, framing effects, and latent beliefs appear to have important impacts on patients’ SPAF antithrombotic therapy decisions.

4. What is known about patient values and preferences regarding novel oral anticoagulants (NOACs) for SPAF?

The above findings can be applied to patient preferences regarding NOACs, whose attributes include similar or slightly better efficacy for stroke prevention, major bleeding, no INR monitoring, once or twice-daily dosing, fewer dietary restrictions and drug interactions, and potentially higher cost. Ten studies addressed patient values or preferences regarding actual or hypothetical NOACs (39, 41–43, 45, 46, 48–50, 53), five of which were sponsored by NOAC manufacturers (39, 42, 43, 50, 60).

In a qualitative study, half of long-time warfarin users said they would switch to a hypothetical NOAC, though no cost information was presented (39). Switchers were most influenced by “less frequent monitoring”. When comparing warfarin and dabigatran users, dabigatran users were less likely to consider switching (11% vs 32%, respectively), more confident in their medication’s stroke-prevention, more worried about side effects, and slightly more satisfied overall (50). Furthermore, in a cohort of warfarin and rivaroxaban users, frequency of intake was the most important among four convenience-related therapy attributes (both once daily) and lack of INR monitoring was the least important (42). When presented with data for warfarin and dabigatran, 83% of patients preferred warfarin (49). Rivaroxaban-taking patients were less likely to consider stopping treatment than warfarin, dabigatran, or apixaban-takers (45). Based on a blinded drug profile, warfarin was the most preferred OAC among warfarin non-users (78% vs 8.3% for apixaban, the next most preferred) and warfarin users (27% vs 26% for apixaban, the next most preferred) (43). Most of these studies were sponsored by the manufacturer of the actual or hypo-
thetical NOAC involved, and are susceptible to biases due to study design or framing effects.

Patients are drug cost sensitive. Australian patients were willing to pay for stroke and bleed risk reductions and for an antidote to a hypothetical NOAC when compared to warfarin (41). Their preference for NOAC over warfarin increased significantly when the NOAC cost was reduced, from 40% at the highest cost to 70% at the lowest. Warfarin users were 80% satisfied and 58% were willing to switch to a hypothetical dabigatran-like NOAC when cost information was excluded, but only 36% were willing to switch when cost information was given (48). Likewise, warfarin users found attributes of a hypothetical dabigatran-like NOAC appealing but 63% were not willing to pay more than $10 extra monthly for it (53). Comparing warfarin to a hypothetical NOAC, when a $20-$40 NOAC co-pay was introduced, preference for warfarin increased from 50% to 65% while preference for the NOAC decreased from 25% to 19% (43). Patients were willing to pay out-of-pocket for stroke and bleeding risk reductions for a hypothetical NOAC, but not for fewer daily doses, and relinquishing INR testing and dietary restrictions had negative willingness-to-pay.

Discussion
Implications for decision-making

Clinically relevant conclusions based on the evidence include: 1) Across all SPAF antithrombotic therapy options, stroke prevention efficacy is the most important value for patients; 2) The importance of major bleeding is extremely variable, unpredictable, and confounded by lack of disclosure of the risk of death in most studies; 3) After efficacy and safety, one vs two daily doses, antidote availability, absence of dietary restrictions and drug-drug interactions are of intermediate and variable importance; 4) Patient preferences for INR testing or no INR testing are largely unpredictable; 5) Prior stroke, bleed, or OAC use does not affect patient values significantly, although prior experience with warfarin increases preference for warfarin over no therapy and for INR testing over no INR testing; 6) Presentation of individualised stroke and bleeding risk results in therapy choices that usually align with the patient’s values; 7) Significant cohorts of patients’ treatment choices are unpredictable, probably due to latent beliefs and framing effects; 8) Patient preferences for NOAC over warfarin are highly variable and published studies are susceptible to bias based on sponsorship; 9) Patient preferences for NOAC over warfarin are overwhelmed by even small increases in out-of-pocket drug cost.

We infer from the available evidence that there is no substitute for directly clarifying patients’ actual values and preferences related to the attributes of SPAF antithrombotic therapy (e.g. stroke risk, bleeding risk, cost of therapy, number of daily doses, need for regular blood testing, drug-drug interactions, dietary restrictions, lifestyle implications, antidote availability). Even though many patients select SPAF antithrombotic therapy based primarily on the risk of stroke presented, many do not. Cultural or familial attitudes and personal experiences are latent sources of inter-individual variability in values and preferences and may include stigma of taking medication, perceptions of cost, and risk aversion, among others. Reported data are also affected by measurement effects like lack of numeracy and framing effects (12). All of these sources of variability are understudied in AF.

Clinicians require tools and skill to help patients clarify their values and preferences. Currently available decision aids convey combinations of patient-specific stroke and bleeding risk information, drug information, and patient-specific preference factor information, but none help patients map their values to options or use formal methods to address the trade-offs that are at the centre of SPAF antithrombotic therapy choices (51, 61–66).

Limitations of this review

This review is primarily limited by gaps in the available evidence and selection bias. Because SPAF antithrombotic decisions require making trade-offs (e.g. between stroke prevention efficacy and bleeding risk, lack of INR monitoring vs cost) between therapies that each have several attributes, multi-attribute methods of study (e.g. choice modelling, conjoint analysis, or discrete choice experiments) are required to reveal the relative importance of the individual attributes of the options, something which studies involving only choosing one drug over another do not capture (67–69). We found few published studies using choice modelling for SPAF antithrombotic therapies, particularly concerning preferences. Although some such evidence exists in other populations (e.g. venous thromboembolism, acute coronary syndromes) (22), we are reluctant to extrapolate because the underlying motivations for SPAF antithrombotic therapy are very different. AF-specific evidence is necessary though limited. Our restriction to English-language literature may have led to neglect of important perspectives on the study questions arising from some countries or cultures. Other gaps in the literature are the relative lack of studies which include ASA as a therapeutic option despite its efficacy compared to no therapy (1, 70), and the dearth of studies in which the risk of death associated with major bleeding was disclosed (5–15% for extracranial bleeding) (71–73). Such lack of disclosure may contribute to a bias across the literature valuing OAC efficacy over bleeding risk and selection of OAC over other options, including no therapy. Similar framing effects may have biased the results of studies in which investigators had conflicts of interest related to the study OACs, whether or not the study was industry-sponsored. Selection bias in our review may have arisen from our choice to exclude quality-of-life studies analysing patients’ overall experience, drug information, and patient-specific preference factor information, but none help patients map their values to options or use formal methods to address the trade-offs that are at the centre of SPAF antithrombotic therapy choices (51, 61–66).
Conclusions

Most AF patients value the stroke prevention efficacy of SPAF antithrombotic therapy above all other attributes. Values and preferences about other attributes of therapy are extremely heterogeneous and unpredictable, and therefore must be ascertained directly from patients. When individualised risk information is presented, patients’ SPAF antithrombotic therapy preferences usually align with their values, although divergence from this is common. Preferences research using choice modelling methods is needed, as are tools to help clinicians and patients clarify their SPAF antithrombotic therapy values and preferences.

Author contributions

Loewen (PI): Conception, protocol development, data collection, data extraction, analysis, interpretation, manuscript writing. Ji: Data collection, data extraction, analysis, manuscript writing. Kapanen: Conception, protocol development, data extraction, analysis, interpretation, manuscript writing. McClean: Data collection, data extraction, analysis, interpretation, manuscript writing.

Conflicts of interest

None declared.

References
