Patient (2017) 10:17–37
DOI 10.1007/s40271-016-0185-9

SYSTEMATIC REVIEW

Patient Preferences for Oral Anticoagulation Therapy in Atrial Fibrillation: A Systematic Literature Review

Thomas Wilke[1] · Sabine Bauer[2] · Sabrina Mueller[2] · Thomas Kohlmann[3] · Rupert Bauersachs[4,5]

Published online: 26 July 2016

Abstract

Objectives Since the introduction of non-vitamin K antagonist (VKA) oral anticoagulants (NOACs), an additional treatment option, apart from VKAs, has become available for stroke prevention in patients with atrial fibrillation (AF). For various reasons, it is important to consider patients' preferences regarding type of medication, particularly in view of the established relationship between preferences towards treatment, associated burden of treatment, and treatment adherence. This review aimed to systematically analyse the scientific literature assessing the preferences of AF patients with regard to long-term oral anticoagulant (OAC) treatment.

Methods We searched the MEDLINE, Scopus and EMBASE databases (from 1980 to 2015), added records from reference lists of publications found, and conducted a systematic review based on all identified publications. Outcomes of interest included any quantitative information regarding the opinions or preferences of AF patients towards OAC treatment, ideally specified according to different clinical or convenience attributes describing different OAC treatment options.

Results Overall, 27 publications describing the results of studies conducted in 12 different countries were included in our review. Among these, 16 studies analysed patient preferences towards OACs in general. These studies predominantly assessed which benefits (mainly lower stroke risk) AF patients would require to tolerate harms (mainly higher bleeding risk) associated with an OAC. Most studies showed that patients were willing to accept higher bleeding risks if a certain threshold in stroke risk reduction could be reached. Nevertheless, most of the publications also showed that the preferences of AF patients towards OACs may differ from the perspective of clinical guidelines or the perspective of physicians. The remaining 11 studies included in our review assessed the preferences of AF patients towards specific OAC medication options, namely NOACs versus VKAs. Our review showed that AF patients prefer easy-to-administer treatments, such as treatments that are applied once daily without any food/drug interactions and without the need for bridging and frequent blood controls.

Conclusion Stroke risk reduction and a moderate increase in the risk of bleeding are the most important attributes for an AF patient when deciding whether they are for or against OAC treatment. If different anticoagulation options have similar clinical characteristics, convenience attributes matter to patients. In this review, AF patients favour attribute levels that describe NOAC treatment.

✉ Thomas Wilke
thomas.wilke@ipam-wismar.de

[1] IPAM-Institut für Pharmakoökonomie und Arzneimittellogistik, Alter Holzhafen 19, 23966 Wismar, Germany

[2] Ingress-Health HWM GmbH, Alter Holzhafen 19, 23966 Wismar, Germany

[3] Institute for Community Medicine, University Medicine Greifswald, Walther-Rathenau-Straße 48, 17475 Greifswald, Germany

[4] Department of Vascular Medicine, Klinikum Darmstadt GmbH, Grafenstr. 9, 64283 Darmstadt, Germany

[5] Centre for Thrombosis and Hemostasis, University of Mainz, Mainz, Germany

Key Points for Decision Makers

For patients with atrial fibrillation (AF), stroke risk reduction and a moderate increase in bleeding risk are the most important attributes of anticoagulation treatment. AF patients are willing to accept higher bleeding risks for significant stroke risk reductions.

When the clinical characteristics of anticoagulation treatments are similar, patients with AF prefer easy-to-administer treatments (i.e. once-daily application, no food/drug interactions, no need for bridging, and no need for frequent blood controls).

1 Introduction

With a prevalence of 1–3 % in the general population, atrial fibrillation (AF) is the most common cardiac disorder [1–7], and its prevalence is expected to increase markedly in most countries in the next few years [5–8]. AF patients have been reported to be at high risk for heart failure and thromboembolic events [8, 9]. In particular, the risk of ischaemic strokes is up to fivefold higher than in the general population [6, 8–10]. Current AF guidelines recommend the assessment of thromboembolic event/stroke risk and, if a certain risk exists in a patient, lifelong oral anticoagulant (OAC) treatment [7, 11]. To assess the risk of stroke in patients with AF, the $CHADS_2$ score [12] or the CHA_2DS_2-VASc score instruments have been recommended [13]. Based on these, patients with a $CHADS_2$/CHA_2DS_2-VASc score $\geq$1 are at mild or high risk of stroke and should consequently receive OAC treatment, while patients with a score equal to 1 may receive aspirin [7, 11].

For several decades, vitamin K antagonists (VKAs) have been the only OAC treatment option for AF patients; however, in 2011, the first non-VKA oral anticoagulant (NOAC) became available for these patients as an alternative to VKA treatment. To date, four NOACs have been approved for stroke prevention in non-valvular AF (dabigatran, rivaroxaban, apixaban, edoxaban). Most clinical studies have shown that NOAC treatment in AF patients with a need for anticoagulation is at least as effective and safe as VKA treatment [14–16]; however, former studies also indicate that a difference in patient perception may exist with regard to the treatment options mentioned [17–19]. This may be of particular importance because, inherently, every treatment should be centred on the patient. This is especially relevant in the long-term treatment of chronic diseases such as AF because patient preferences may influence not only the long-term adherence of patients but also the physician–patient relationship and, finally, the real-world effectiveness of a particular type of treatment [20].

Consequently, it is important to know which anticoagulation treatment characteristics AF patients prefer. In line with this, clinical guidelines highly recommend taking into account the views and preferences of an AF patient when deciding on OAC therapy options [7, 11, 21, 22]. In this way, the patient is enabled to make an informed decision, in partnership with the healthcare professionals, about their upcoming treatment. In turn, this will enable healthcare professionals to understand the patient's view, which can be assumed to be of utmost importance, especially in the long term [22].

Little is known about the preferences of AF patients with regard to OAC therapy; therefore, the objective of this analysis was to conduct a systematic literature review summarising the results of studies dealing with the preferences of AF patients towards OAC treatment.

2 Methods

The methods applied in this review are consistent with those proposed in the Preferred Reporting Items for Systemic Reviews and Meta-Analyses (PRISMA) statement [23].

2.1 Study Selection

We searched the MEDLINE, Scopus and EMBASE databases (from 1980 to 2015), added records from reference lists of publications found, and conducted a systematic review based on all identified publications. All in all, we conducted a literature search on the basis of 20 queries, which included the terms 'preferences', 'atrial fibrillation' and 'discrete choice experiment', amongst others.[1] Inclusion criteria for studies were defined as follows:

[1] Search strings entered in MEDLINE were 'discrete AND choice AND experiment AND atrial AND fibrillation', 'discrete AND choice AND experiment AND anticoagulation', 'treatment AND preferences AND atrial AND fibrillation', 'treatment AND preferences AND atrial AND fibrillation', 'discrete AND choice AND experiment AND af', 'discrete AND choice AND experiment AND ac', 'dce AND atrial fibrillation', 'dce AND anticoagulation', 'discrete AND choice AND experiment AND cardiac AND arrhythmia', 'treatment AND preference AND cardiac AND arrhythmia', 'treatment AND preferences AND cardiac AND arrhythmia', 'anticoagulant AND discrete AND choice', 'anticoagulant AND patient AND preference', 'discrete AND choice AND anticoagulation', 'discrete AND choice AND anticoagulant', 'conjoint AND preference AND anticoagulation', 'trade off AND preference AND anticoagulation', 'preference AND atrial fibrillation', 'preference AND anticoagulation', 'preference AND anticoagulant'.

- The study was published between 1980 and 2015, and written in either German or English.
- The study quantitatively assessed the opinions or preferences of AF patients towards OAC therapy; qualitative studies, authors' opinions regarding patient opinions or preferences, as well as studies dealing with physicians' opinions only, were excluded.
- We excluded all studies that did not describe the questionnaire used or the applied preference elicitation technique in sufficient detail.

Outcomes of interest included any quantitative information about the opinions or preferences of AF patients towards OAC treatment. If studies provided detailed insights, or even a trade-off assessment of different (partly competing) attributes describing OAC treatment options, results of these assessments were included.

2.2 Assessment of Study Eligibility and Inclusion

All titles and abstracts identified through the initial search in the digital literature were reviewed independently by two reviewers, and any disagreements were resolved through discussion and/or referral to a third reviewer if necessary. Articles were excluded when they were obviously considered irrelevant, which was decided on the basis of their titles and abstracts. Eligibility of the remaining articles was assessed on the basis of the inclusion criteria listed above. Systematic reviews and meta-analyses that met the inclusion criteria were not included in our review but were used to identify any other potentially relevant articles. A comparison of our results with those of identified systematic reviews or meta-analyses addressing similar topics is presented in the Discussion section of this paper.

The methodological quality and the main characteristics of the included studies were evaluated on the basis of the following types of information:

- Addressed disease (AF only or additional diseases).
- Single-centre versus multicentre study.
- Selection of surveyed patients (random, consecutive or convenience sample).
- Sample size (number of patients).
- Type of surveyed persons (AF patients, patients with other cardiovascular diseases, general public).
- OAC experience of surveyed persons.
- Main study objective (assessment of patient preferences towards OACs in general versus preferences towards specific OAC medication types, i.e. mainly VKAs versus NOACs).
- Preference elicitation technique used, with a focus on how potential trade-offs between different treatment attributes associated with different anticoagulation options were dealt with. Here we differentiated between studies using simple descriptive methods (e.g. self-developed questionnaires investigating the importance of specific attributes, based on Likert scales), trade-off/threshold/standard gamble techniques or, more recently, developed preference elicitation techniques (e.g. analytical hierarchy method, traditional conjoint analysis or discrete choice analysis). In addition, we assessed whether the included studies primarily dealt with clinical attributes associated with different anticoagulation options (mainly thromboembolic events and bleeding rates), respective convenience attributes (e.g. frequency of intake, interaction with other drugs/food, regular blood controls), or both.

2.3 Data Extraction

Information regarding study design (including sample definition and methodology), characteristics of study participants (sample size, addressed disease), analysed attributes or attribute levels in the study, and study results (qualitative or quantitative data with regard to patient opinions/preferences) were collected for each included publication and are listed in Table 1.

2.4 Statistical Analysis and Synthesis

Our main focus was to investigate which anticoagulation treatment would be preferred by AF patients. This was done on a per-study basis; no meta-analysis was conducted due to the expected diversity of studies in terms of analysed samples and methodology used to elicit preferences.

3 Results

3.1 Study Selection and Characteristics

The electronic search identified 4577 records, including duplicates, and 1249 records after duplicates were removed (Fig. 1). Based on the screening of titles, a further 1184 records (94.8 %) were removed, with an additional 19 records being removed after screening of the abstract, and 19 being removed after reading the manuscript, resulting in 27 studies being included in the review. An overview of selected study characteristics, as well as study methodology and study results, are provided in Table 1.

All studies used patient surveys to elicit patient preferences, with six studies including additional physician surveys. The number of patients included varied between 32 and 1507, and the identified studies were conducted in 12 different countries.

Table 1 Summary of the studies included in the systematic literature review

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Alonso-Coello et al., 2014, Spain [24]	Values and preferences for oral antithrom-botic therapy in patients with atrial fibrillation: physician and patient perspectives.	n = 96 outpatients n = 96 physicians; Atrial Fibrillation; VKA (warfarin), aspirin	Characterise the distribution of patient and physician values and preferences relevant to decisions regarding anticoagulation in patients with AF. Elicit the maximum risk of bleeding (threshold risk) that respondents would tolerate with VKA vs. Aspirin to achieve a reduction in three strokes in 100 patients over a 2-year period.	Multi-centre study; Quantitative	Trade-off/ threshold technique: Interviews with outpatients and physicians.	Stroke risk, bleeding risk	Median threshold risk for both patients and physicians was 10 additional bleeds in 100 patients in 2 years. In both groups, there was a large variability in the threshold number of bleeds observed, with wider variability in patients than clinicians [patient range: 0-100, physician range: 0-50]. One cluster of patients and physicians was observed who would tolerate <10 bleeds and another cluster of patients, but not physicians, who would accept more than 35.	Stroke risk, bleeding risk	Wide variability in patient and physician values and preferences regarding the trade-off between strokes and bleeds.	Yes	Yes	Partly	Yes	No	NA	NA
Sudlow et al., 1998, UK [25]	A community survey of patients with atrial fibrillation: associated disabilities and treatment preferences.	n = 207; Atrial Fibrillation; VKA (Warfarin)	Investigate the prevalence of disability, cognitive impairment, and problems with compliance in a representative sample of the elderly with atrial fibrillation To determine whether these patients would want treatment and how they would like services to be arranged.	Multi-centre study; Quantitative	Preference question-naire: Views on treatment were obtained using a structured interview.	Stroke risk reduction	Almost all subjects expressed a willingness to undergo treatment to prevent stroke and preferred blood testing performed outside of the hospital.	Stroke risk	Most elderly people with AF would accept treatment to prevent stroke.	Yes	Yes	No	Yes	No	NA	NA
Najafzadeh et al., 2014, USA [26]	Patients' preferences in anticoagulant therapy: discrete choice experiment.	n = 341 Selection of a sample of US patients with cardiovascular disease from an online panel; Cardiovascular Disease; Anticoagulation therapy	Elicit cardiovascular disease patients' relative preferences for specific benefits and risks of anticoagulant therapy.	Cross-sectional study; Quantitative	Conjoint analysis: Discrete Choice Experiment	Non-fatal stroke, non-fatal myocardial infarction, cardiovascular death, minor bleeding, major bleeding, bleeding death, and need for regular monitoring.	Patients valued a 1% increased risk of a fatal bleeding event the same as a 2% increase in non-fatal myocardial infarction risk, a 3% increase in non-fatal stroke risk, a 3% increase in cardiovascular death risk, a 6% increase in major bleeding risk, and a 16% increase in minor bleeding risk.	Fatal bleeding risk, non-fatal MI risk, non-fatal stroke risk, cardiovascular death risk	Patients' preferences for various outcomes of anticoagulant therapy vary and depend on their previous experiences with myocardial infarction or stroke.	Yes	Yes	Partly	Yes	No	NA	NA

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Devereaux et al., 2001, Canada [27]	Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study.	n = 63 physicians who were treating patients with AF n = 61 patients at high risk for AF; Atrial Fibrillation; VKA (warfarin) and aspirin	Determine and compare physicians' and patients' thresholds for how much reduction in risk of stroke is necessary and how much risk of excess bleeding is acceptable with antithrombotic treatment in people with AF.	Prospective observational Study; Quantitative	Trade-off/ threshold technique: Scenario analysis using threshold analysis (probability trade-off tool)	Stroke risk, bleeding risk.	Minimum number of strokes that needed to be prevented in 100 patients over two years for VKA to be justified was significantly lower for patients than for physicians (1.8 (SD 1.9) v 2.5 (1.6)) Maximum number of excess bleeds acceptable in 100 patients over two years for use of VKA was significantly higher for patients than for physicians (warfarin 17.4 (7.1) v 10.3 (6.1)).	Stroke risk, bleeding risk	Patients at high risk for AF placed greater value on the avoidance of stroke and less value on the avoidance of bleeding than did physicians who treat patients with atrial fibrillation.	Yes	Yes	Partly	Yes	No	NA	NA
Man-Son-Hing et al., 1996, Canada [28]	Warfarin for Atrial Fibrillation. The Patient's Perspective	n = 64 patients; Atrial Fibrillation; VKA (Warfarin)	Determine the minimal clinically important difference of VKA therapy for the treatment of AF from the perspective of patients.	Observational study, survey; Qualitative & quantitative	Trade-off/ threshold technique: Identifica-tion of the minimal clinically important difference in outcomes associated with VKA therapy.	Stroke risk, bleeding risk	Given a baseline risk of experiencing a stroke in the next 2 years, if not taking warfarin, of 10 of 100, the mean MCID was 2.01 of 100 (95% CI, 1.60-2.42). 52% of the patients would take VKAs for an absolute decrease in stroke risk of 1% over 2 years.	Stroke risk, bleeding risk	Patients want to get a clear clinical benefit when accepting the burden of an anticoagulation therapy	Yes	Yes	Yes	Yes	No	NA	NA
Prothero et al., 2001, England [29]	Effects of patients' preferences on the treatment of atrial fibrillation: observational study of patient-based decision analysis.	n = 97 Randomly selected AF patients aged 70 to 85 years; Atrial Fibrillation; VKA (warfarin)	Investigate patients' preferences towards anticoagulation therapy.	Observational study; Quantitative	Preference question-naire: Interviews with patients in 8 general practices.	Stroke risk, bleeding risk	61% of the interviewed patients would prefer anticoagulation treatment, considerably fewer than those who would be recommended treatment according to guidelines. Of 38 patients whose decision analysis indicated a preference for anticoagulation, 17 (45%) were being prescribed VKA. 28 (47%) of 59 patients were not being prescribed VKA, although the results of their decision analysis suggested they wanted to be.	Patients obviously weigh clinical advantages and disadvantages of anticoagulation treatment differently than clinical guidelines	Based on patients' preferences, there would be fewer prescriptions for VKA than under published clinical guideline recommendations	Yes	No	Partly	Yes	No	NA	NA

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Gonzáles-Rojas et al., 2012, Spain [30]	Preferences for oral anticoagulant treatment in the medium and long-term prevention of stroke in non-valvular atrial fibrillation.	n = 295; Atrial Fibrillation; Oral anticoagulants	Analyse the preferences of patients with non-valvular AF for oral anticoagulants.	Observational , multi-centre study; Quantitative	Preference questionnai re: focus groups and semi-structured interviews with physicians and patients to define the required attributes of OACs and their levels. Clusters analysis to identify population groups by their preferences	Efficacy, safety, dosage (fixed, variable), need for coagulation checks and interactions with diet and medication.	The most preferred attribute was the smaller number of embolisms in a year (importance: 30.15%), followed by the fixed dose of the OAC (25.45%) and the smaller number of intracranial haemorrhage in a year (21.57%). The maximum amount patients were willing to pay for the OAC was 66.76 ± 54.64 € (mean) per month.	Small number of embolisms per year was rated as the most important attribute.	Efficacy and a fixed dose scheme are the attributes of an OAC most valued by AF patients.	Yes	No	Partly	Yes	No	NA	NA
Palacio et al., 2015, USA [31]	Patient values and preferences when choosing anticoagulants.	n = 137; Atrial Fibrillation or being at risk of AF; VKA (warfarin) and Dabigatran	Evaluate the preferences of AF patients with regard to anticoagulants; patients had already made a decision regarding anticoagulation.	Cross-sectional study; Quantitative	Trade-off/ threshold technique: Survey containing a hypo-thetical scenario of the risk of AF and the attributes of each anticoagu-lant.	Options in the survey: 1) has better efficacy at reducing risk of stroke; 2) has been in the market for a long period of time; 3) has an antidote to reverse the rare case of bleeding; 4) has better quality of life profile with no required frequent laboratory tests; 5) I want to follow physician recommenda-tions.	36% of those exposed and 37% of those unexposed to anticoagulants reported that they would select a medication that has an antidote even if the risk of bleeding was very small. 23% of the unexposed and 22% of the exposed groups reported that they would prefer the medication that gives the best quality of life (no coagulation checks).	Availability of antidote	Patients who may be exposed to an anticoagulation decision prefer to actively participate in the decision-making process, and have individual values for making a decision.	Yes	No	Partly	Yes	No	NA	NA

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Levitan et al., 2013, USA [32]	Patient and physician preferences in the United States for benefits and risks of anticoagulant use in atrial fibrillation - results from a conjoint-analysis study.	n = 186; Atrial Fibrillation; Hypothetical anticoagulants	To quantify and compare US patient and physician preferences for benefits and risks associated with anticoagulants in AF.	Multi-centre study; Quantitative	Web-based, choice-format conjoint survey	Attributes were defined by event risks: disabling and non-disabling stroke, myocardial infarction, embolism, and major and non-major clinically-relevant bleeding.	Patients considered disabling stroke as the least desirable outcome, while physicians regarded death as least desirable. Relative to the risk of disabling stroke, patients considered death 60% (95% CI 39%-80%) as important, and non-fatal major bleeding and non-major clinically-relevant bleeding 47% (28%-65%) and 17% (10%-23%) as important, respectively. For physicians, relative to the risk of disabling stroke, death was 150% (82%-218%) as important, and non-fatal major bleeding and non-major clinically-relevant bleeding were 66% (47%-84%) and 14% (8%-20%) as important. Non-fatal embolism and myocardial infarction were of intermediate importance between the two levels of bleeding for both groups.	Disabling stroke, death, non-fatal major bleeding and non-major clinically-relevant bleeding	US patient decisions on anticoagulant treatment in AF may be more motivated by avoiding strokes, while physicians may focus more on avoiding death. The difference in perspective on relative importance of bleeding and stroke may lead to different benefit-risk assessments by patients and physicians.	Yes	No	Partly	Yes	No	NA	NA
Najafzadeh et al., 2015, USA [33]	Patient versus general population preferences in anticoagulant therapy.	n = 341 Cardiovascular Disease; Hypothetical anticoagulants	To elicit and compare anticoagulant treatment outcomes preferences between patients and the general population.	Multi-centre study; Quantitative	Discrete choice experiment	Attributes described hypothetical treatments randomly labeled "new drug," "old drug," or "no drug": non-fatal stroke, non-fatal myocardial infarction (MI), cardiovascular death, minor bleeding, major bleeding, bleeding death, and need for therapeutic monitoring.	On average, patients perceived a 1% increased risk of a fatal bleeding equivalent to a 2% increase in non-fatal MI, a 3% increase in non-fatal stroke, a 3% increase in cardiovascular death, a 6% increase in major bleeding, or a 16% increase in minor bleeding. As compared to the patients, the general population had similar preferences except that they perceived a 3% increase in non-fatal MI or a 13% increase in minor bleeding equivalent to a 1% increase in risk of bleeding death. Patients were less likely to choose "no drug" (odds ratio, 0.72; 95% confidence interval, 0.61- 0.84) or "old drug" (odds ratio, 0.86; 95% confidence interval, 0.81-0.93) than "new drug." The general population sample was indifferent to the drug labels.	Fatal bleeding, non-fatal MI, non-fatal stroke, cardiovascular death, major bleeding, minor bleeding	Patients and the general population had similar relative preferences for anticoagulant treatment outcomes but were more likely to choose "new drug," irrespective of its relative benefits and risks.	Yes	No	Partly	Yes	No	NA	NA

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Okumura et al., 2015, USA, Japan [34]	Comparing patient and physician risk tolerance for bleeding events associated with anticoagulants in atrial fibrillation - evidence from the United States and Japan.	USA: n = 186 patients and n = 107 physicians; Japan: n = 152 patients; Atrial Fibrillation; Anticoagulants	To quantify the perceived relative importance of treatment-related benefits and risks and how these perceptions vary between patients and physicians in different countries.	Multi-centre study; Quantitative	Discrete choice experiment	Minor stroke, major stroke that results in permanent disability, blood clot in the leg (non-CNS, systemic embolism), heart attack (myocardial infarction), moderate bleeding (non-major clinically relevant bleeding), non-fatal major bleeding (extracranial major bleeding), all-cause death	Japanese patients were relatively less averse than US patients to bleeding risks. Physicians in both countries did not distinguish between non disabling and disabling strokes. US patients were less tolerant than physicians of non-major clinically relevant bleeding risk when this risk was a consequence of preventing non disabling strokes. Japanese patients were generally more tolerant than physicians of bleeding risks when the risks were consequences of preventing both non disabling and disabling strokes.	US patients: disabling non-fatal stroke, all-cause death, extracranial major bleeding, nondiasbling stroke. Japanese patients: all-cause death, disabling non-fatal stroke, nondisabling stroke, extracranial major bleeding.	Overall, preferences for anticoagulant benefits and risks were not statistically different between patients and physicians in the United States, nor were there differences in preferences for different stroke risks between physicians in the United States and Japan; however, preferences were different between patients and physicians in Japan.	Yes	No	Partly	Yes	No	NA	NA
Okumura et al., 2012, Japan, [35]	Japanese patients and physicians' preferences for anticoagulants use in atrial fibrillation - results from a conjoint-analysis study.	n = 152 Atrial Fibrillation; Anticoagulants	To quantify Japanese patients and physicians' preferences for benefits and risks associated with the use of anticoagulants in AF and to enable cross-patient and physician comparison.	Multi-centre study; Quantitative	Conjoint-Analysis: web-enabled, choice-format conjoint survey that included a series of trade-off questions.	Minor stroke, major stroke that results in permanent disability, blood clot in the leg (non-CNS, systemic embolism), heart attack (myocardial infarction), moderate bleeding (non-major clinically relevant bleeding), non-fatal major bleeding (extracranial major bleeding), all-cause death	Overall patients and physicians considered all-cause death to be the least desirable outcome. Among non-fatal outcomes, patients considered the risk of disabling stroke to be 2.6 times more important than extra-cranial major bleeding and 16 times more important than non-major clinically relevant bleeding compared to 1 time and 2.7 times for physicians.	Disabling stroke, extra-cranial major bleeding, non-major clinically relevant bleeding	Japanese patients and physicians have different preferences for non-fatal outcomes associated with anticoagulants, with patients willing to tolerate a greater risk of bleeding for stroke prevention than physicians.	Yes	No	Partly	Yes	No	NA	NA

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Protheroe et al., 2000, UK [36]	The impact of patients' preferences on the treatment of atrial fibrillation: observational study of patient based decision analysis.	n = 97 Atrial Fibrillation; Warfarin	To investigate the impact of patients' preferences on the treatment of atrial fibrillation, by using individualised decision analysis combining probability and utility assessments into a decision tree.	Multi-centre study; Quantitative	Time trade-off method: Nine health states (outcomes) from a decision tree were shown and ranked in order of preference.	Levels in the decision tree: treatment with warfarin, experience of side effects, experience of cardiovascular accidents, affected or unaffected after an event	Among the 97 patients, the decision analysis indicated that 59 (61%; 95% CI: 50% - 71%) would prefer anticoagulation treatment - considerably fewer than those who would be recommended treatment according to guidelines. There was marked disagreement between the decision analysis and guideline recommendations (k = 0.25 or less). Of 38 patients whose decision analysis indicated a preference for anticoagulation, 17 (45%) were being prescribed warfarin; on the other hand, 28 (47%) of 59 patients were not being prescribed warfarin although the results of their decision analysis suggested they wanted to be.	Majority (61%; 95% CI: 50% - 71%) preferred treatment with warfarin	Based on patients' preferences, these would receive fewer prescriptions for warfarin than under published guideline recom-mendations.	Yes	No	No	Yes	No	NA	NA
Robinson et al., 2001, UK [37]	How patients with atrial fibrillation value different health outcomes: a standard gamble study.	n = 69 Atrial Fibrillation; Warfarin	To elicit patient valuations of health states relevant to assessment of the prevention of stroke by warfarin anticoagulation therapy.	Multi-centre study; Quantitative	Standard gamble method: elicitation of the patient health state values	General practitioner-managed warfarin treatment, hospital-managed warfarin treatment, major bleed, mild stroke and severe stroke	Median (mean) utility values were for GP-managed warfarin treatment 0.986 (0.948), hospital-managed warfarin treatment 0.984 (0.941), major bleed 0.880 (0.841), mild stroke 0.675 (0.641) and severe stroke 0 (0.189). There was wide variation in values between patients and the distributions were highly skewed.	Highest utility: GP-managed warfarin treatment, hospital-managed warfarin treatment, major bleed, mild stroke, severe stroke	Patients prefer GP-based warfarin management.	Yes	No	Partly	Yes	No	NA	NA
Casais et al., 2004, Argentina [38]	Patients' perceptions regarding oral anticoagulation therapy and its effect on quality of life.	n = 905 All reasons for anticoagulation were included (i.e. AF, VTE, MHVP, mitral stenosis, coronary heart disease, among others); Warfarin or acenocoumarol	To evaluate prospectively patients' perceptions and quality of life in patients chronically anticoagulated.	Cross-sectional study; Quantitative	Assessment of perceptions from the specific OAC questionnai re to the General Health SF-36 score, to the patient's characterist ics, the absolute bleeding, duration of therapy and medical attention.	OAC questionnaire included: daily life implications and the economic burden of OAC; general epidemiological and socio-economical aspects, OAC itself (duration, indication, bleeding complications) and medical attention (contention, trust, knowledge and time devoted to patients, need for emergency calls and solution of problems by the doctor on-call); additionally, SF-36 questionnaire was filled out	Most patients felt protected and better since the beginning of therapy (71.5% and 61.5%, respectively). Patient characteristics associated with negative perceptions were; female sex (Odds Ratio [OR] 1.58, 95% Confidence Interval [CI] 1.06–2.36, p = 0.01); patients with less than 1 year of therapy (OR 2.16, 95% CI 1.34–3.48, p = 0.006); those not satisfied with medical attention (OR 2.86, 95% CI 1.53–5.18, p = 0.0001); and those that modified their lifestyle (OR 2.75, 95% CI 1.49–4.91, p = 0.0002). Patients with a lower bleeding risk (INR 2.0–3.0) had more negative perceptions than those with a higher risk. Patients with negative perceptions achieved the lowest score in the SF-36 survey. Haemorrhages did not affect patients' perception or QOL.	No ranking of attributes performed in terms of importance.	Patients' perceptions correlate with QOL.	No	NA	Yes	Yes	No	NA	NA

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Lahaye et al., 2014, Canada [39]	Evaluation of patients' attitudes towards stroke prevention and bleeding risk in atrial fibrillation.	n = 172 Hospitalised in-patients with documented non-valvular AF in whom anticoagulant therapy was considered; Atrial Fibrillation; Not specified	Determine the minimal clinically important difference (treatment threshold). Assess the maximum number of major bleeding events that a patient would be willing to endure in order to prevent one stroke for the initiation of antithrombotic therapy.	Cross-sectional study; Quantitative	Standard gamble technique: iPad question-naire	Major bleeding events that a patient would be willing to endure in order to prevent one stroke (Bleeding Ratio)	12% of AF patients were 'medication averse' and were not willing to consider antithrombotic therapy, even if it was 100% effective in preventing strokes. Of the other patients, 42% were identified as 'risk averse' and 15% were 'risk tolerant'. Patients required at least a 0.8% annual absolute stroke risk reduction and a 15% relative stroke risk reduction to accept antithrombotic therapy Patients were willing to endure 4.4 major bleeds in order to prevent one stroke.	Stroke risk, bleeding risk	Substantial amount of inter-patient variability, and often extreme differences in opinion regarding tolerance of bleeding risk.	No	NA	No	Yes	No	NA	NA
Barcellona et al., 2015, Italy [40]	The criteria of the Italian Federation of Thrombosis Centres on DOACs: a 'real world' application in non-valvular atrial fibrillation patients already on vitamin K antagonist.	n = 525 NVAF patients treated with VKA; Atrial Fibrillation; VKA	Evaluate the number of patients with non-valvular AF, anticoagulated with vitamin K antagonists (VKA), and monitored in a Thrombosis Centre, who could replace VKA with NOACs based on the Italian Federation of Thrombosis Centres (FCSA) consensus criteria.	Cross-sectional study which included a patient survey; Quantitative	Preference question-naire: Patients' preferences were evaluated through the administrati on of a specifically developed question-naire.	Need for laboratory checks, possible concerns about the consumption of NOACs by patients accustomed to periodic clinical and laboratory control, lack of specific antidote for NOACs, difficulties in taking two new tables daily.	Only 20 % of the patients would move from VKA to NOACs, mainly because of the lack of an antidote and laboratory checks during NOACs therapy. 33% of patients were worried that they would forget to take the tablets twice a day. About 2 % of patients could not use NOACs since their glomerular filtration rate was less than 30 ml/min, while in 23.6 % of the patients a reduction in the daily dose of NOACs would have been required due to renal failure. The proposal for a control of anticoagulant activity through dedicated laboratory tests every 4–5 months is considered too long by about 60 % of the patients.	Lack of laboratory checks, absence of an antidote and twice-daily intake may be barriers to use NOACs	The main concerns for the majority of patients currently treated with VKAs were the lack of a laboratory check and the absence of an antidote.	Yes	Yes	Yes	No	Yes	Yes	Yes

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Böttger et al., 2015, Germany [41]	Preferences for anticoagulation therapy in atrial fibrillation: the patients' view	n = 486 All participants were diagnosed with AF; Atrial Fibrillation; 48.1 % of Participants rivaroxaban; 51.9 % of Participants VKA	Assess AF patients' preferences with regard to the convenience attributes of different anticoagulation treatment options.	Multi-centre survey among randomly selected physicians; Quantitative	Conjoint analysis: Computer-assisted telephone interviews based on a discrete choice design	Need of bridging, interactions with food/nutrition, need of INR checks/dose adjustment, frequency of intake; additionally, one neutral comparator attribute (distance to practitioner: <1 km/>15 km) was analysed	Patients significantly preferred the attribute levels (in order of patients' importance) 'once daily intake' (Level: once = 1 vs. twice = 0; Coefficient = 0.615; $p < 0.001$), 'bridging necessary' (yes = 1 vs. no = 0; -0.558; $p < 0.001$), 'distance to practitioner of ≤1 km' (>15 km = 0 vs. ≤1 km = 1; 0.494; $p < 0.001$), 'interactions with food/nutrition' (yes = 1 vs. no = 0; -0.332; $p < 0.001$) and 'need of INR controls/dose adjustment' (yes = 1 vs. no = 0; -0.127; $p < 0.001$).	'Once daily frequency of intake' was the most important OAC-convenience attribute for patients' choice followed by 'no bridging necessary' and 'no interactions with food/nutrition'.	Patients with AF seem to prefer treatment options which are easier to administer.	Yes	Yes	Yes	No	Yes	Yes	Yes
Andrade et al., 2016, Canada [42]	Values and preferences of physicians and patients with non-valvular atrial fibrillation who receive oral anticoagulation therapy for stroke prevention.	n = 266 Atrial Fibrillation; Apixaban, dabigatran, rivaroxaban, or warfarin	To assess the values, preferences, and experience of patients who receive OAC therapy, and of physicians who prescribe OAC therapy.	Multi-centre study; Quantitative	Conjoint analysis	Bleeding rates, stroke-free survival, requirement for blood testing, dosing regimen, reversal, clinical experience, and drug/food interaction	Preferences of patients and physicians regarding OAC therapy differed but largely focused on characteristics related to safety and efficacy. When based solely on the basis of the attribute profile (blinded to the specific agent), physicians were more likely to select apixaban (61%), whereas patients showed no significant preference among apixaban, rivaroxaban, and warfarin. Despite this, 49% of physicians spontaneously stated rivaroxaban as their preferred agent (vs 25% apixaban). Patients prescribed and taking once daily medications (rivaroxaban or warfarin) showed better compliance with their OAC therapy (approximately 30% of twice daily medications being taken once daily, with significantly more missed doses compared with once daily medications).	Efficacy of the medication for stroke prevention, the safety of the medication, and the recom-mendation by their treating physician (average of 9.0 on a 10-point scale). Pharmacist recom-mendation, and longstanding clinical experience were rated as less important (average of < 7.5 on a 10-point scale).	Real-world prescriptions do not reflect reported values, which suggests that other factors influence patient-physician decision-making around OAC therapy. Data on self-reported adherence and discordance in the use of OACs from prescribed regimens are concerning.	Yes	Yes	Yes	No	Yes	Yes	Yes
Zamorano et al., 2012, France, Germany, Italy, Spain, UK [43]	Patient preferences for chronic treatment for stroke prevention: results from the European Patient Survey in Atrial Fibrillation (EUPS-AF).	n = 1,507 Atrial Fibrillation; VKA/Warfarin and NOACs	To assess the burden of current, primarily VKA-based treatment for stroke prevention in AF and explore patient preferences for AF therapy in France, Germany, Italy, Spain and the UK.	Multi-centre study; Quantitative	Structured telephone interviews: Adapted version of the questionnaire "2008 Commonwealth Fund International Health Policy Survey of Chronically Ill Adults", questions relevant to patients with AF were included.	Questions were asked on the following aspects: anticoagulation monitoring, dose adaptation, dosing regimen	Prompted recall of oral anticoagulation medication revealed substantial differences in VKA utilisation among the surveyed countries. Overall, 67% of the 789 respondents who regularly had their anticoagulation status monitored responded positively to the possibility of reduced anticoagulation monitoring. 55% of the 1138 patients receiving medication for AF were positive about the possibility of no longer needing dose adaptation for oral anticoagulation. 80.7% of respondents taking medication for AF expressed a preference for once-daily dosing.	NA, since survey was administered	Most patients surveyed responded positively to the possibility of reduced coagulation monitoring and absence of requirement for dose adaptation associated with NOACs.	Yes	Yes	Partly	No	Yes	No	No

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Gebler-Hughes et al., 2014, Australia [44]	Patients' perspectives regarding long-term warfarin therapy and the potential transition to new oral anticoagulant therapy.	n = 290 Patients on VKA therapy, among them atrial fibrillation; VKA	To examine patients' perspectives regarding long-term vitamin K antagonist (VKA) therapy and the potential transition to new oral anticoagulants (NOACs) such as dabigatran and rivaroxaban, and to determine if any factors affect these opinions.	Multi-centre study; Quantitative	Preference Question-naire: Interviews with patients in 6 general practices who were waiting for their INR results and were on VKA therapy	Questionnaire included: demographic details such as age and gender, it comprised sections on current therapy and a hypothetical switch from warfarin to a NOAC.	The majority of the sample (79.5%, 229/288) were either satisfied or very satisfied with current VKA therapy. The mean score for the potential benefits of transition to NOACs was 7.6 (±4.2) out of a possible 20, which was significantly lower than the mean score 10.9 (±4.5) for the perceived deterrents to transition ($p < 0.001$). Rural patients (82.0%, 82/100) were significantly more likely ($p = 0.001$) to have not heard of NOACs than metropolitan patients (50.3%, 95/189) and also perceived significant less benefits in a transition to NOACs ($p = 0.001$).	Rank order of potential problems with warfarin therapy: frequent changes to dose (21.4%), frequency of medical appointments (19.7%), frequency of INR testing (15,5%); Rank order of potential benefits and deterrents associated with transition to NOAC: Fewer alterations to medication dose (22.9%), INR monitoring not required (21.9%), fewer interactions with other medications (14.3%), anticoagulation unable to be reversed (41.9%), potential side effects (38.2%), No regular INR monitoring required (34.7%).	When considering potential transition from VKAs to NOACs it is important for prescribers to consider that some patients, in particular those from a rural location, may not perceive a significant benefit in transitioning or may have particular concerns in this area.	Yes	No	Yes	No	Yes	Yes	No
Ghijben et al., 2014, Australia [18]	Preferences for oral anticoagu-lants in atrial fibrillation: a best-best discrete choice experiment	n = 76 Study participants were members of the general public with or without AF aged ≥ 40 years, those without AF were seen as proxy for newly-diagnosed AF patients; Atrial Fibrillation; VKA (warfarin), NOACs	Examine patient preferences with regard to attributes of VKA and NOAC treatment Assess which attributes are most important Determine whether current anticoagulation under-treatment is likely to improve with the new oral anticoagulants.	Cross-sectional patient survey: Quantitative	Conjoint analysis: Compute-rised discrete choice experiment (including one follow-up interview)	Efficacy (stroke risk), safety (bleeding risk, antidote), convenience factors (blood tests, dose frequency, drug or food interactions)	Anticoagulation under-treatment may decrease with NOAC use if NOAC prices are not so high that they form a treatment barrier	Efficacy (stroke risk) was more important than safety (bleed risk, antidote); both were considerably more important than convenience factors (blood tests, dose frequency, drug or food interactions). Cost was also important.	The overall profiles of the NOACs were preferred to warfarin as their cost decreased. Public subsidisation and the development of antidotes for the NOACs may have a positive effect on the under-treatment of AF.	No	NA	Not known	No	Yes	Yes	Yes

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/random sample of study sites with consecutive/random selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Boom et al., 2015, Netherlands [45]	When do patients prefer a direct oral anticoagulant over a vitamin K antagonist?	n = 200 Random sample of AF patients treated with VKAs, taken from the Thrombosis Service in Amsterdam; Atrial Fibrillation; VKA	Assess AF patients' preferences with regard to anticoagulation treatment.	Cross-sectional study; Quantitative	Trade-off/ threshold technique: Patient survey.	Survey included 4 scenarios: 1 (no need for laboratory controls); 2 (less bleeding); 3 (less interactions); 4 (more effective).	Under scenario 1, 57% of the patients would have made the switch, with a further increase to 65% with scenario 2 (trend value, p = 0.006, 95% CI 1.11-1.85). In each scenario, patients who were less satisfied with their current treatment were more likely to switch to a NOAC compared with satisfied patients. The variables: duration of treatment, gender, age and educational level did not affect the preference for a NOAC.	No requirement for regular laboratory control and lower risk of bleeding were considered most important attributes to switch to a NOAC.	Patients considered no requirement for regular laboratory checks and a lower risk of bleeding the most important arguments to switch to a NOAC.	No	NA	Yes	No	Yes	Yes	Yes
Cottrell et al., 2009, UK [46]	Preference and willingness-to-pay study to assess the value of an anticoagulation therapy modelled on dabigatran etexilate using discrete choice analysis: a UK pilot study of warfarin-naive atrial fibrillation patients	n = 32 Atrial Fibrillation; Warfarin, Dabigatran	To assess preferences for and valuation of attributes of an anticoagulation therapy (ACT) modelled on the oral direct thrombin inhibitor dabigatran etexilate (DAB) relative to warfarin in UK atrial fibrillation (AF) patients, naïve to warfarin.	Cross-sectional study; Quantitative	Discrete choice analysis: patients made pair-wise medication choices between a fixed scenario representing warfarin and 12 alternatives	Dose frequency; anticoagulation monitoring; diet, alcohol and certain analgesic restrictions; use of different tablet strengths to make up correct daily dose. Stroke risk was assumed not to differ between Dabigatran and warfarin.	When cost was not considered, respondents showed significant preference for an ACT modelled on DAB over warfarin (OR = 3.65 [95%CI: 1.09–12.22]). Avoiding different tablet strengths was a significant choice driver (p = 0.006). Rational traders (n = 18) were willing to pay an incremental £73.90 [95%CI: 17.30–141.40] per month for DAB. A demand curve indicated that 88.4% would choose DAB over warfarin at zero incremental cost and >50% would choose DAB at an incremental of £49.	Avoiding INR was a significant choice driver (p = 0.039)	Warfarin-naïve AF patients showed a strong preference for an ACT modelled on DAB over warfarin. Among respondents who were willing to trade (62.5%), there was a significant WTP for the convenience of DAB.	No	NA	No	No	Yes	Yes	Yes
Attaya et al., 2012, USA [47]	Study of Warfarin Patients Investigating Attitudes Toward Therapy Change (SWITCH Survey)	n = 155 Atrial fibrillation, DVT/PE, Valvular heart disease; 76% of patients on warfarin	To conduct a survey of the attitudes of patients enrolled in a warfarin clinic towards switching to a novel anticoagulant	Cross-sectional study; Qualitative	Descriptive interviews mainly addressing willingness to switch to a novel anticoagulant.	Self-reported data on age, gender, indication for warfarin use, and satisfaction with warfarin therapy; willingness to replace warfarin with a costlier drug that needed to be taken twice a day but did not need international normalised ratio monitoring; out of pocket cost.	Fifty-eight percent of patients were willing to switch anticoagulants. Women were significantly less willing to switch from warfarin than men (31 of 71, 44% vs. 54 of 78, 69%; P = 0.003). Patients older than 70 years were significantly more willing to switch anticoagulants than those younger than 70 years (48 of 68, 71% vs. 38 of 75, 51%; P = 0.017).	80% of patients reported satisfaction with warfarin treatment; most frequent reason for dissatisfaction was 'inconvenience of frequent doctor visits'	There are significant differences across age and gender in the initial willingness of patients to accept novel anticoagulants. These differences may have important implications in the prevention and treatment of thromboembolic events.	No	NA	Yes	No	Yes	No	Yes

Table 1 continued

Author/ Year of Publication/ country	Title	Study population; addressed disease area; Medication	Study objective(s)	Study Type	Method for Preference Measure-ment	Analysed attributes	Results	Most important attributes, based on the patient view	Conclusions	Represen-tative AF patient selection: multi-center study?	In case of multi-center study: representative/ran dom sample of study sites with consecutive/rando m selection of patients?	Were surveyed patients current OAC users?	Study analyzes general attitudes of AF patients towards OAC?	Different medication options addressed in study?	If different medication options are explored: questionnaire reflects all relevant attributes of treatment alternatives including convenience attributes?	If different medication options are explored: questionnaire reflects trade-offs between OAC treatment options?
Wang et al., 2015, Canada [49]	Patient-reported health preferences of anticoagulant-related outcomes.	n = 100 Patients on VKA therapy, among them atrial fibrillation; Warfarin, Dabigatran, Rivaroxaban	To use direct measures to elicit patient-reported utilities (i.e. preferences) for anticoagulant-related outcomes.	Cross-sectional study; Quantitative	Visual analogue scale (VAS) and standard gamble (SG) methods: six long-term and four short-term anticoagula nt-related health states were elicited by these methods	The long-term health states included ''well on warfarin'', ''well on dabigatran'', ''well on rivaroxaban'', major ischaemic stroke, minor ischaemic stroke and intracranial haemorrhage (ICH). Short-term health states included: transient ischaemic attack (TIA), major extracranial haemorrhage (ECH), minor ECH and myocardial infarction (MI).	Health states with the highest SG-derived mean utility values were ''well on rivaroxaban'' (mean ± SD = 0.90 ± 0.15), ''well on warfarin'' (0.86 ± 0.17), and ''well on dabigatran'' (0.83 ± 0.18). Approximately half of the patients considered major ischaemic stroke (-1.57 ± 6.77) and intracranial haemorrhage (-1.99 ± 6.98) to be worse than death. The percentages of patients who considered a particular health state worse than death ranged from 0 to 55% among various health states assessed. The VAS had similar findings. Ischaemic stroke and intracranial haemorrhage had a significant impact on patients' HRQoL. Greater variation in patients' preferences was observed for more severely impaired health states, indicating the need for individualised medical decision-making	Highest utility: well on rivaroxaban, well on warfarin, well on dabigatran	Patients prefer treatment that works well and is safe	No	NA	Yes	No	Yes	No	Yes
Wang et al., 2013, Singapore [48]	Utility evaluation of health states related to stroke and stroke prophylaxis.	n = 100 Atrial Fibrillation; Warfarin, Dabigatran, Rivaroxaban	To use the visual analogue scale (VAS) and standard gamble (SG) to elicit patient-reported utilities for health states related to stroke and stroke prophylaxis by the three anticoagulants.	Cross-sectional study; Quantitative	Standard gamble method: elicitation of the patient health state values including seven chronic and four temporary health states.	The long-term health states included ''well on warfarin'', ''well on dabigatran'', ''well on rivaroxaban'', major ischaemic stroke, minor ischaemic stroke and intracranial haemorrhage (ICH). Short-term health states included: transient ischaemic attack (TIA), major extracranial haemorrhage (ECH), minor ECH and myocardial infarction (MI).	When the SG was used, the three health states with the highest mean utilities were "well on rivaroxaban" (0.90), "current health state" (0.86) and "well on warfarin" (0.86). The three health states with the lowest mean utilities were intracranial bleeding (ICH) (-0.09), major ischaemic stroke (IS) (-0.01) and myocardial infarction (0.45).	Highest utility: well on rivaroxaban, current health state and well on warfarin	The elicited utilities of the anticoagulants were, in a decreasing order, rivaroxaban, warfarin and dabigatran.	No	NA	Yes	No	Yes	No	Yes

AF atrial fibrillation, *OAC* oral anticoagulant, *NA* not applicable, *VKA* vitamin K antagonist, DCE discrete choice experiment, *MI* myocardial infarction, *SD* standard deviation, *MCID* minimal clinically important difference, **CI** confidence interval, *OR* odds ratio, *CNS* central nervous system, *GP* general practitioner, *VTE* venous thromboembolism, *MHVP* mechanical heart valve prosthesis, *CHD* coronary heart disease, *SF-36* Short-Form 36, *INR* international normalised ratio, *QOL* quality of life, *DOACs* direct oral anticoagulants, *NVAF* non-valvular atrial fibrillation, *NOACs* non-VKA oral anticoagulants, *WTP* willingness to pay, *DVT* deep vein thrombosis, *PE* pulmonary embolism, *HRQoL* health-related quality of life, *EUPS-AF* European Patient Survey in AF, *NK* not known, *ACT* anticoagulation therapy, *DAB* dabigatran etexilate, *VAS* visual analogue scale, *SG* standard gamble, *ICH* intracranial haemorrhage, *TIA* transient ischaemic attack, *ECH* extracranial haemorrhage

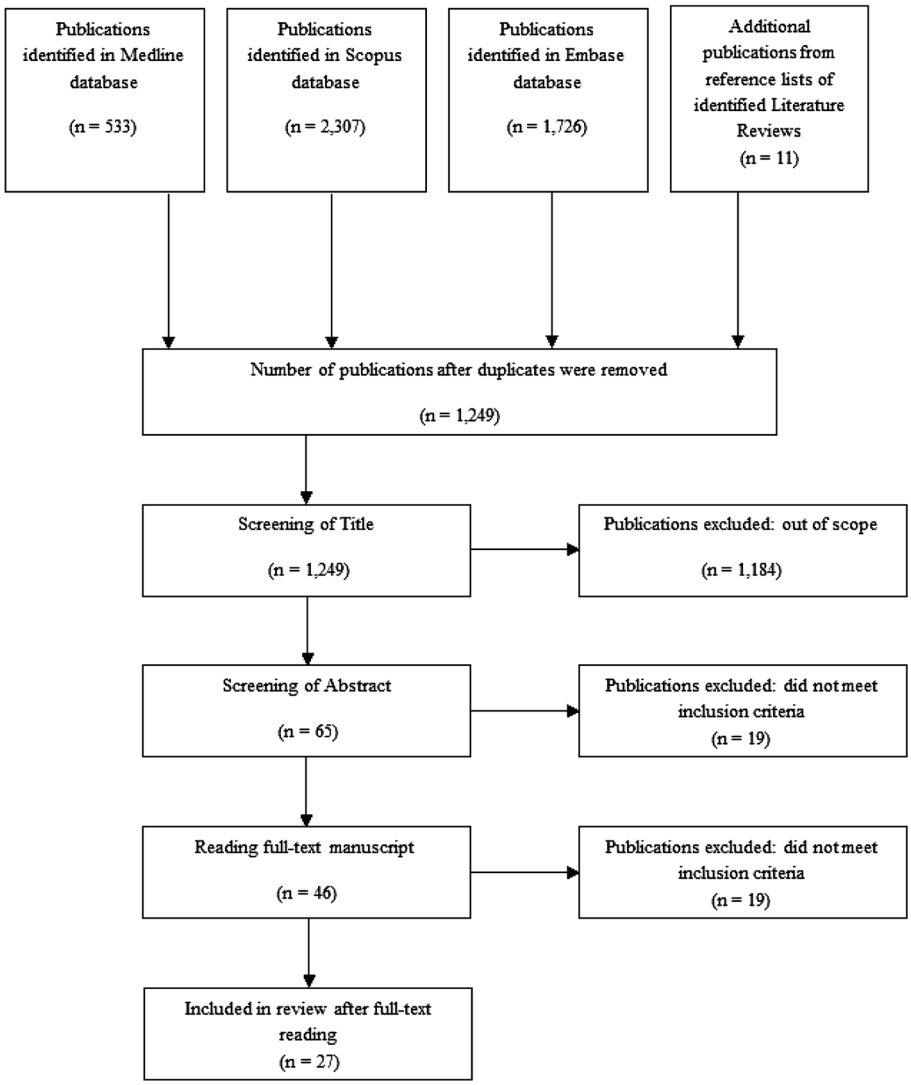

Fig. 1 PRISMA flowchart illustrating the study selection process

Figure 2 describes the main types of included studies; 16 studies analysed patient preferences towards OAC in general [24–39]. These studies predominantly assessed which benefits (mainly lower stroke risk) AF patients would require to tolerate harms (mainly higher bleeding risk) associated with an OAC. Five of these studies were multicentre studies that applied different techniques to ensure a representative inclusion of patients (mean number of patients 154) [24–28]. In these studies, the majority of surveyed patients were current OAC users. In addition, the majority of these five studies used a trade-off methodology for the survey.

An additional nine studies could also be characterised as multicentre studies but they applied a convenience sample of patients (mean number of patients 182) [29–37]. As previously, the majority of surveyed patients were OAC users, and the preference elicitation technique used most commonly was conjoint analysis. Finally, two of the studies assessing general preferences towards OAC use were single-centre studies (mean number of patients 538) [38, 39]. In these studies, one used a trade-off technique surveying OAC-naïve patients, and the other used a preference questionnaire interviewing current OAC users.

The remaining 11 included studies assessed AF patient preferences towards specific OAC medication options, namely NOACs versus VKAs (Fig. 2) [18, 40–49]. Three of these could be characterised as multicentre studies ensuring a representative inclusion of patients and applying a methodology that addressed most of the known differences between VKAs and NOACs (mean number of patients 426) [40–42]. All of these three studies addressed OAC users only. One study used a descriptive preference questionnaire, while two others used conjoint analysis.

One additional multicentre study including a representative sample of 1507 AF patients (partly OAC users) used a descriptive preference questionnaire [43]; however, this study did not include all known differences between NOACs and VKAs as attributes. Another study in the

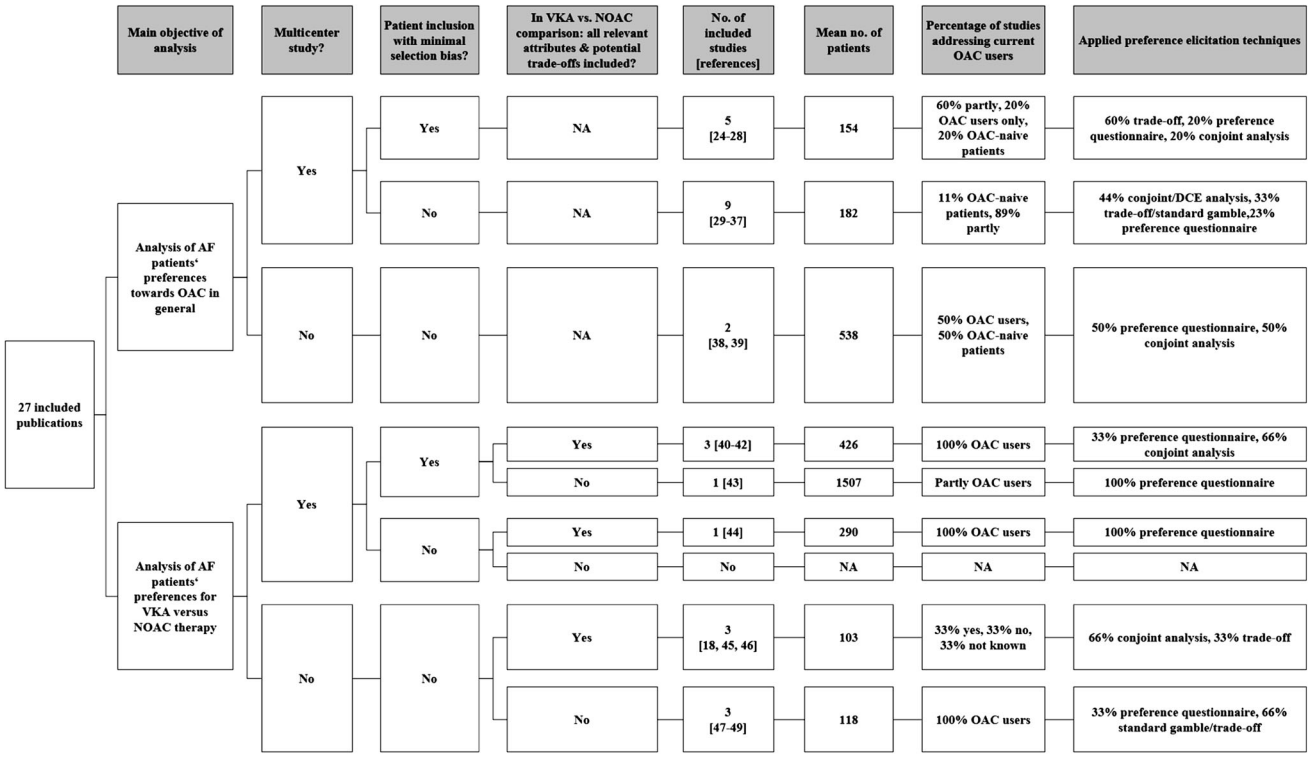

Fig. 2 Main characteristics of the included studies. *VKA* vitamin K antagonist, *NOAC* non-VKA oral anticoagulant, *OAC* oral anticoagulant, *AF* atrial fibrillation, *NA* not applicable, *DCE* discrete choice experiment

group of multicentre studies analysing preferences towards NOACs or VKAs was based on a convenience sample of OAC users. This study used a descriptive preference questionnaire (290 patients) [44].

In three additional single-centre studies that included most of the known differences between NOACs and VKAs as attributes of the preference survey (mean number of patients 103), one study used the trade-off technique, and two others used conjoint or discrete choice analysis [18, 45, 46]. One study addressed current OAC users, one study addressed OAC-naïve patients, and one study addressed members of the general public without known OAC status.

Finally, three single-centre studies including a convenience sample of AF patients (100 % OAC users; mean number of patients 118) mostly used a standard gamble/trade-off technique (two studies), while one study used a preference questionnaire [47–49]. None of these studies addressed all known differences between NOAC or VKA treatment.

3.2 Preferences of Atrial Fibrillation (AF) Patients Towards Oral Anticoagulation Therapy

In the 16 included studies that dealt with the preferences of AF patients towards OAC therapy in general, the main question addressed was what degree of stroke risk reduction AF patients would require in order to accept an anticoagulation therapy-associated higher bleeding risk.

The five studies with the highest methodology ranking as indicated above showed that AF patients are willing to accept certain bleeding risks for a decrease in the probability of experiencing a stroke. However, there was substantial variability in the threshold number of bleeds observed for the acceptance of OAC, both between the different studies and, more so, between surveyed participants within the studies. A Spanish survey reported a threshold of 10 additional bleeds in 2 years, while a Canadian survey reported 17 additional bleeds in 2 years (both for acceptance of OACs) [24, 27]. In the same survey, the minimum required stroke prevention rate for the acceptance of OAC with its associated higher bleeding risk was 1.8 strokes per 100 patient years. An additional Canadian survey reported 52 % of AF patients would accept warfarin treatment if it was associated with a 1 % stroke risk reduction over 2 years [28]. A recent US survey showed that AF patients valued a 1 % increased risk of a fatal bleeding event the same as a 2 % increase in non-fatal myocardial infarction risk, a 3 % increase in non-fatal stroke risk, a 3 % increase in cardiovascular death risk, a 6 % increase in major bleeding risk, and a 16 % increase in minor bleeding risk [26].

The results of the 11 studies with a lower methodological quality were generally in line with the above results. In another Canadian survey, patients required at least a 0.8 % annual absolute stroke risk reduction and a 15 % relative stroke risk reduction to accept antithrombotic therapy. Patients were willing to endure 4.4 major bleeds in order to prevent one stroke [41]. This study identified different patient segments on the basis of general attitudes towards anticoagulation; 12 % of patients were seen as 'medication averse', meaning that they would not be willing to consider anticoagulation therapy even if it were to be 100 % effective. Among the other patients, 42 % were identified as 'risk averse', indicating that the patients were not willing to consider antithrombotic therapy if there was any increased risk of bleeding compared with the 'no therapy option', and 15 % were 'risk tolerant', denoting that these patients did not appear to care about the risk of bleeding at all. The remaining patients could not be assigned to either of these categories [39].

Interestingly, studies comparing the general willingness of patients to accept OAC treatment with clinical guidelines concluded that significantly fewer patients (61 %) would be willing to accept such a therapy than is recommended in clinical guidelines [29]. Furthermore, several studies found that patients and physicians evaluate stroke and bleeding risks differently, with physicians interpreting bleeding risks as more important and stroke risk as less important than patients do [27, 32, 35].

3.3 Preferences of AF Patients Towards Specific OAC Attributes

Eleven identified studies analysed patient preferences towards OAC treatment and included, either additionally or separately, attributes that were different from either stroke/thromboembolic event or bleeding risk. Overall, these attributes can be called 'convenience attributes' describing NOACs and VKAs as alternative treatment options.

Among the three studies with the highest methodological quality, one German survey analysed the preferences of AF patients towards convenience attributes of anticoagulation options [41]. Based on a discrete choice analysis of AF patients receiving either VKAs or therapy with one specific NOAC agent, a once-daily frequency of intake was the most important attribute describing different treatment options, followed by 'no bridging necessary', and 'no interactions with food/nutrition'. The authors of this particular survey concluded that German AF patients would be willing to accept an additional distance of 29.3 km to see the treating physician in order to receive treatment that would incorporate once-daily intake, no necessary bridging in case of surgeries, less food/drug interaction and an absence of monthly blood tests, if such a treatment was compared with VKA treatment [41]. However, in an Italian study, only 20 % of AF patients stated they would be willing to move from VKA to NOAC therapy. Patients not willing to switch to an NOAC agent mentioned that the lack of an antidote and the absence of regular laboratory checks were the main reasons for their preference towards VKA treatment. The majority of patients indicated that they would prefer regular coagulation laboratory monitoring during treatment with NOACs. The absence of such monitoring would be a source of concern for patients because they would be afraid of suffering a thrombotic or haemorrhagic complication. Thirty-three percent of the study population indicated that they were concerned about forgetting to take the two daily tablets and about the associated risk of non-adherence [40]. The third of these studies, a recent Canadian survey, concluded that real-world OAC prescriptions do not reflect reported patient preferences, which suggests that other factors influence patient–physician decision making around OAC therapy. The authors additionally concluded that data on self-reported adherence to OAC therapy and discordance in the use of OACs from prescribed regimens raise important concerns and warrant further investigation [41].

Here too, and as mentioned earlier, the results of the studies with a lower methodological quality were generally in line with the above results. With regard to their results, no substantial differences were observed between studies surveying different patient types (OAC users versus OAC-naïve patients) or between studies using different preference elicitation techniques. In the majority of studies, AF patients preferred an OAC treatment that, based on convenience attributes, was in line with an NOAC treatment. All in all, of the 11 studies addressing patient preferences towards either NOACs or VKAs, 8 concluded that AF patients prefer NOAC therapy.

However, as illustrated by an Australian survey that analysed AF patient preferences using a discrete choice design including both clinical and convenience attributes associated with either VKA or NOAC treatment, the majority of the above studies also showed that clinical efficacy and safety associated with an OAC alternative are of paramount importance with respect to convenience factors such as regular blood tests, dose frequency, or drug or food interactions [18].

4 Discussion

4.1 Main Results and Comparison with the Literature

Several studies analysed the attitudes of AF patients towards OAC treatment in general, especially the view of

AF patients towards the trade-off between a lower stroke and higher bleeding risk. Most of the literature shows that patients are willing to accept higher bleeding risks if a certain threshold in reduced stroke risk can be reached. Nevertheless, the majority of the publications also showed that many AF patients may weigh bleeding risk and stroke risk differently from both physicians and clinical guidelines. Therefore, based on the preferences of AF patients only, fewer patients would receive anticoagulation treatment than may be expected on the basis of recommendations found in clinical guidelines. Consequently, preferences of AF patients may be one important and potentially modifiable explanation for the often observed OAC undertreatment of patients [50, 51]. Therefore, it is of utmost importance to not only identify but also to understand patient preferences with regard to anticoagulation treatment in order to improve adherence to guideline recommendations. Besides that, it is also important that the treating physician educates and informs the patient about stroke and bleeding risks since, in that way, adherence to guideline recommendations can be further improved. All the publications we analysed reported a high variability of AF patient preferences towards anticoagulation treatment; some of the analyses even identified specific AF patient segments, defined by different degrees of bleeding risk aversion.

The above-mentioned results were confirmed by two previous systematic reviews. The authors of the first review concluded that higher patient values and preferences regarding thromboprophylaxis treatment may depend on patients' prior experience with the treatments, as well as on the methods used for preference elicitation [52]. The second review argued that AF patient preferences may indicate that fewer patients would take VKAs compared with the recommendations of the guidelines. Based on this review, at a stroke rate of 1 % with aspirin, half of the participants would prefer VKAs and, at a rate of 2 % with aspirin, two thirds would prefer VKA treatment [53].

As shown in our review, a second part of the scientific literature analysed the preferences of AF patients towards OAC treatment by including 'convenience' attributes, which characterise the alternative OAC treatment options, VKAs and NOACs. Generally, the published data show that AF patients, in accordance with clinical guidelines, weigh clinical attributes such as stroke or bleeding risk more heavily than convenience attributes. Therefore, it is in line with the preferences of AF patients that a treating physician first investigates the clinical effectiveness and safety of the recommended anticoagulant before suggesting alternative treatment choices to the patient. However, this review also showed that if alternative OAC treatments are similar in terms of efficacy and safety, as is the case with many anticoagulation options in AF, convenience attributes such as mode of application, interactions with food or drugs, availability of an antidote, need for bridging, or frequency of application may matter to patients. Furthermore, patients may not only have a preference for a more convenient mode of application but the adherence of patients may also depend on the convenience of medication therapy. Thus, it has been shown that a less frequent dosing schedule, such as once daily on chronic cardiovascular disease medication, is associated with higher treatment adherence [54].

We also identified a variability of results with regard to preferences towards these convenience attributes, which could be explained by several reasons. First, patients analysed in the included studies were different from each other in terms of sociodemographic characteristics, study site characteristics (inpatient versus outpatient treatment, general practitioners [GPs] versus cardiologists) and current anticoagulation treatment, or in terms of the treatment experience of surveyed patients. For example, one German study found that AF patients currently treated with VKAs for at least 3 months (which may be an indicator of stable anticoagulation) did not show any clear preference for or against monthly blood checks, whereas patients treated with an NOAC agent had a clear preference against such checks [41]. Thus, it is important to inform the patient about the differences between NOACs and VKAs, which are apparent in the need for regular blood checks, amongst others. With VKAs, regular checks are necessary, whereas with NOACs, no regular checks are needed.

Second, study methodologies differed markedly between the different studies in terms of the number of included study sites, patient inclusion criteria and patient selection, and the preference elicitation technique used. Because of this, it cannot be ruled out that the selected questions in the descriptive questionnaires used in several studies also influenced reported results. In some studies, interviews were conducted face-to-face, whereas others used phone, written or online interviews, therefore interviewer bias cannot be excluded in these studies [29]. On the other hand, when questionnaires were sent out to participants, there was the risk of non-response bias, potentially leading to skewed results of the study [25].

Three studies analysing preferences towards NOACs versus VKAs used trade-off/standard gamble techniques. These comprise a method that offers the opportunity to compare therapy preference between two different options [45]. The hypothetical efficacy of the intervention is systematically varied until the lowest risk reduction, the point at which patients are willing to take the therapy, is found [28]. A disadvantage of this method is that the consideration of more than two options might generate confusion or fatigue in respondents, resulting in a notable proportion of respondents indicating initial choices that were internally inconsistent [55].

Finally, four studies applied a conjoint analysis/discrete choice experiment (DCE) to analyse preferences towards either NOACs or VKAs. DCE was introduced into health economics as a technique to identify the key characteristics of alternative treatments because patients were concerned with aspects of healthcare other than only clinical outcomes. This method has been used to elicit preferences for health and healthcare in a range of contexts and is now, to a certain degree, seen as a gold-standard technique. The method assumes that the value of medical treatments depends on a number of characteristics. DCE allows one to simultaneously weigh various characteristics of different therapeutic options and to establish the relative importance of each characteristic in the implementation of that therapeutic option. It can also be used to estimate how individuals trade these characteristics; for instance, the rate at which they are willing to give up one characteristic for an increase in another [56]. The main reason for applying a DCE is that simply asking patients to rate treatment-related attributes generally yields no substantial information since patients will state in such a survey that they want all the benefits and none of the indirect/direct costs [57]. One advantage of applying a DCE is that patients are forced to make a trade-off between two or more options and that they have to choose, as is the case in reality, between options that may be associated with utility-increasing and utility-decreasing attribute levels [58].

The studies included in our review that used a DCE technique came to similar conclusions. An Australian study that included both clinical and convenience attributes concluded that the overall profiles of NOACs, compared with VKA treatment, are preferred by patients, especially if an antidote exists and if there are reasonable costs for NOAC treatment [18]. Similarly, in an Italian study that included bleeding risk as an attribute, patients preferred once-daily tablet treatment without regular monitoring [56]. In a German DCE study, AF patients also favoured attribute levels that are best presented by a once-daily NOAC treatment [41].

In addition to the above-mentioned difficulties in comparing the identified studies, due to differences in their methodology, we acknowledge two additional limitations. First, our research was based on a review of publications available in the selected databanks only and, second, due to methodological differences between the studies, we did not conduct a quantitative meta-analysis.

5 Conclusions

Our review of the preferences of AF patients towards anticoagulation shows that stroke risk reduction and limited bleeding risk are the most important attributes for an AF patient when deciding whether they are for or against a certain treatment. In the stroke risk/bleeding risk trade-off assessment, physicians may be more sensitive to bleeding risk than patients. AF patients are willing to accept higher bleeding risks if a certain threshold in reduced stroke risk can be reached.

Treating physicians should take patient preferences into account when deciding on the type of OAC treatment. If different anticoagulation options have similar clinical characteristics, convenience attributes matter to patients. In this review, AF patients favour attribute levels that describe NOAC treatment (e.g. once-daily intake, no regular blood tests and less drug/food interaction). Whether these convenience advantages may also contribute to improving the percentage of patients in need of lifelong OACs in order to receive such a treatment is open for future research.

Compliance with Ethical Standards

Conflicts of interest Thomas Wilke has received honoraria from various pharmaceutical companies, including Novo Nordisk, GlaxoSmithKline, Bayer, Bristol-Myers Squibb, and Sanofi-Aventis; Thomas Kohlmann has received honoraria from Bayer Vital GmbH, Germany; Rupert Bauersachs has acted as a consultant for Boehringer Ingelheim Pharma, Bayer Vital GmbH, Germany, and Bristol-Myers Squibb. Sabine Bauer and Sabrina Müller have no conflicts of interest to declare.

Funding This study was financially supported by Bayer Vital GmbH, Germany.

Author Contributions Thomas Wilke participated in the conception, planning and interpretation of this study, drafted the manuscript, and approved the final version. He also acts as overall guarantor for this work.
Sabine Bauer participated in the planning and analysis of the data, critically reviewed the draft manuscript, and approved the final version.
Sabrina Müller participated in the conception and planning of the work, critically reviewed the manuscript, and approved the final version.
Thomas Kohlmann participated in the conception of the work, critically reviewed the manuscript, and approved the final version.
Rupert Bauersachs participated in the conception of the work, critically reviewed the manuscript, and approved the final version.

References

1. Ryder KM, Benjamin EJ. Epidemiology and significance of atrial fibrillation. Am J Cardiol. 1999;84:R131–8.

2. Chugh SS, Blackshear JL, Shen WK, Hammill SC, Gersh BJ. Epidemiology and natural history of atrial fibrillation: clinical implications. J Am Coll Cardiol. 2001;37:371–8.
3. Chien K, Su T, Hsu H, Chang W, Chen P, Chen M, et al. Atrial fibrillation prevalence, incidence and risk of stroke and all-cause death among Chinese. Int J Cardiol. 2010;139:173–80.
4. Fang MC, Go AS, Chang Y, Borowsky L, Pomernacki NK, Singer DE. Comparison of risk stratification schemes to predict thromboembolism in people with nonvalvular atrial fibrillation. J Am Coll Cardiol. 2008;51:810–5.
5. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Incidence and prevalence of atrial fibrillation: an analysis based on 8.3 million patients. Europace. 2013;15:486–93.
6. Davis RC, Hobbs FDR, Kenkre JE, Roalfe AK, Iles R, Lip GYH, et al. Prevalence of atrial fibrillation in the general population and in high-risk groups: the ECHOES study. Europace. 2012;14:1553–9.
7. Camm AJ, Kirchhof P, Lip GYH, Schotten U, Savelieva I, Ernst S, et al. Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). Eur Heart J. 2010;31:2369–429.
8. Kirchhof P, Auricchio A, Bax J, Crijns H, Camm J, Diener H, et al. Outcome parameters for trials in atrial fibrillation: executive summary. Eur Heart J. 2007;28:2803–17.
9. Stewart S, Hart CL, Hole DJ, McMurray JJV. A population-based study of the long-term risks associated with atrial fibrillation: 20-year follow-up of the Renfrew/Paisley study. Am J Med. 2002;113:359–64.
10. Friberg L, Hammar N, Rosenqvist M. Stroke in paroxysmal atrial fibrillation: report from the Stockholm Cohort of Atrial Fibrillation. Eur Heart J. 2010;31:967–75.
11. Fuster V, Rydén LE, Cannom DS, Crijns HJ, Curtis AB, Ellenbogen KA, et al. 2011 ACCF/AHA/HRS focused updates incorporated into the ACC/AHA/ESC 2006 guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology Foundation/American Heart Association Task Force on practice guidelines. Circulation. 2011;123:e269–367.
12. Gage BF, Waterman AD, Shannon W, Boechler M, Rich MW, Radford MJ. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. JAMA. 2001;285:2864–70.
13. Lip GYH, Nieuwlaat R, Pisters R, Lane DA, Crijns HJGM. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the euro heart survey on atrial fibrillation. Chest. 2010;137:263–72.
14. Connolly SJ, Ezekowitz MD, Yusuf S, Eikelboom J, Oldgren J, Parekh A, et al. Dabigatran versus warfarin in patients with atrial fibrillation. N Engl J Med. 2009;361:1139–51.
15. Patel MR, Mahaffey KW, Garg J, Pan G, Singer DE, Hacke W, et al. Rivaroxaban versus warfarin in nonvalvular atrial fibrillation. N Engl J Med. 2011;365:883–91.
16. Granger CB, Alexander JH, McMurray JJV, Lopes RD, Hylek EM, Hanna M, et al. Apixaban versus warfarin in patients with atrial fibrillation. N Engl J Med. 2011;365:981–92.
17. Fumagalli S, Cardini F, Roberts AT, Boni S, Gabbai D, Calvani S, et al. Psychological effects of treatment with new oral anticoagulants in elderly patients with atrial fibrillation: a preliminary report. Aging Clin Exp Res. 2015;27:99–102.
18. Ghijben P, Lancsar E, Zavarsek S. Preferences for oral anticoagulants in atrial fibrillation: a best-best discrete choice experiment. Pharmacoeconomics. 2014;32:1115–27.
19. Bakhai A, Sandberg A, Mittendorf T, Greiner W, Oberdiek AMS, Berto P, et al. Patient perspective on the management of atrial fibrillation in five European countries. BMC Cardiovasc Disord. 2013;13:108.
20. van der Pol M, Hennessy D, Manns B. The role of time and risk preferences in adherence to physician advice on health behavior change. Eur J Health Econ. [**Epub 16 Apr 2016**].
21. Jones C, Pollit V, Fitzmaurice D, Cowan C. The management of atrial fibrillation: summary of updated NICE guidance. BMJ. 2014;348:g3655.
22. National Institute for Health and Clinical Excellence (NICE). NICE guidelines (CG180), atrial fibrillation (update): the management of atrial fibrillation. 2014. Available at: http://guidance.nice.org.uk/CG180. Accessed 15 June 2016.
23. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med. 2009;6(7):e1000097.
24. Alonso-Coello P, Montori VM, Díaz MG, Devereaux PJ, Mas G, Diez AI, et al. Values and preferences for oral antithrombotic therapy in patients with atrial fibrillation: physician and patient perspectives. Health Expect. 2014;18(6):2318–27.
25. Sudlow M, Thomson R, Kenny RA, Rodgers H. A community survey of patients with atrial fibrillation: associated disabilities and treatment preferences. Br J Gen Pract. 1998;48:1775–8.
26. Najafzadeh M, Gagne JJ, Choudhry NK, Polinski JM, Avorn J, Schneeweiss SS. Patients' preferences in anticoagulant therapy: discrete choice experiment. Circ Cardiovasc Qual Outcomes. 2014;7:912–9.
27. Devereaux PJ, Anderson DR, Gardner MJ, Putnam W, Flowerdew GJ, Brownell BF, et al. Differences between perspectives of physicians and patients on anticoagulation in patients with atrial fibrillation: observational study. BMJ. 2001;323:1218–22.
28. Man-Son-Hing M, Laupacis A, O'Connor A, Wells G, Lemelin J, Wood W, et al. Warfarin for atrial fibrillation. The patient's perspective. Arch Intern Med. 1996;156:1841–8.
29. Protheroe J, Fahey T, Montgomery AA, Peters TJ. Effects of patients' preferences on the treatment of atrial fibrillation: observational study of patient-based decision analysis. West J Med. 2001;174:311–5.
30. González-Rojas N, Gimenez E, Fernandez MA, Heineger AI, Martinez JL, Villar J, et al. Preferences for oral anticoagulant treatment in the medium and long term prevention of stroke in non valvular atrial fibrillation [in Spanish]. Rev Neurol. 2012;55:11–9.
31. Palacio AM, Kirolos I, Tamariz L. Patient values and preferences when choosing anticoagulants. Patient Prefer Adherence. 2015;9:133–8.
32. Levitan B, Yuan Z, González JM, Hauber AB, Lees M, Piccini JP, et al. Patient and physician preferences in the United States for benefits and risks of anticoagulant use in atrial fibrillation: results from a conjoint-analysis study. Value Health. 2013;16:A11.
33. Najafzadeh M, Gagne JJ, Choudhry NK, Polinski J, Avorn JL, Schneeweiss S. Patient versus general population preferences in anticoagulant therapy. Value Health. 2015;18:A9–10.
34. Okumura K, Inoue H, Yasaka M, Gonzalez JM, Hauber AB, Levitan B, et al. Comparing patient and physician risk tolerance for bleeding events associated with anticoagulants in atrial fibrillation: evidence from the United States and Japan. Value Health Reg Issues. 2015;6:65–72.
35. Okumura K, Inoue H, Yasaka M, Gonzalez JM, Hauber AB, Iwamoto K, et al. Japanese patients and physicians preferences for anticoagulants use in atrial fibrillation: results from a conjoint-analysis study. Value Health. 2012;15(7):A380.
36. Protheroe J, Fahey T, Montgomery AA, Peters TJ. The impact of patients' preferences on the treatment of atrial fibrillation: observational study of patient based decision analysis. BMJ. 2000;320:1380–4.

37. Robinson A, Thomson R, Parkin D, Sudlow M, Eccles M. How patients with atrial fibrillation value different health outcomes: a standard gamble study. J Health Serv Res Policy. 2001;6:92–8.
38. Casais P, Meschengieser SS, Sanchez-Luceros A, Lazzari MA. Patients' perceptions regarding oral anticoagulation therapy and its effect on quality of life. Curr Med Res Opin. 2005;21:1085–90.
39. Lahaye S, Regpala S, Lacombe S, Sharma M, Gibbens S, Ball D, et al. Evaluation of patients' attitudes towards stroke prevention and bleeding risk in atrial fibrillation. Thromb Haemost. 2014;111:465–73.
40. Barcellona D, Luzza M, Battino N, Fenu L, Marongiu F. The criteria of the Italian Federation of Thrombosis Centres on DOACs: a "real world" application in nonvalvular atrial fibrillation patients already on vitamin K antagonist. Intern Emerg Med. 2015;10:157–63.
41. Böttger B, Thate-Waschke I, Bauersachs R, Kohlmann T, Wilke T. Preferences for anticoagulation therapy in atrial fibrillation: the patients' view. J Thromb Thrombolysis. 2015;40:406–15.
42. Andrade JG, Krahn AD, Skanes AC, Purdham D, Ciaccia A, Connors S. Values and preferences of physicians and patients with nonvalvular atrial fibrillation who receive oral anticoagulation therapy for stroke prevention. Can J Cardiol. 2016;32:747–53.
43. Zamorano JL, Greiner W, Sandberg A, Oberdiek AMS, Bakhai A. Patient preferences for chronic treatment for stroke prevention: results from the European Patient Survey in Atrial Fibrillation (EUPS-AF) [poster]. Presented at the European Society of Cardiology Congress; 25–29 Aug 2012: Munich.
44. Gebler-Hughes ES, Kemp L, Bond MJ. Patients' perspectives regarding long-term warfarin therapy and the potential transition to new oral anticoagulant therapy. Ther Adv Drug Saf. 2014;5:220–8.
45. Boom MS, Berghuis EM, Nieuwkerk PT, Pinedo S, Ba Ller HR. When do patients prefer a direct oral anticoagulant over a vitamin K antagonist? Neth J Med. 2015;73:368–72.
46. Cottrell S, LeReun C, Tilden D, Robinson P. Preference and willingness to pay study to assess the value of an anticoagulation therapy modelled on dabigatran etexilate using discrete choice analysis: a UK pilot study of warfarin-naive atrial fibrillation patients. Value Health. 2009;12:A339.
47. Attaya S, Bornstein T, Ronquillo N, Volgman R, Braun LT, Trohman R, et al. Study of warfarin patients investigating attitudes toward therapy change (SWITCH Survey). Am J Ther. 2012;19:432–5.
48. Wang Y, Kong MC, Ko Y. Utility evaluation of health states related to stroke and stroke prophylaxis. Value Health. 2013;16:A292.
49. Wang Y, Xie F, Kong MC, Lee LH, Ng HJ, Ko Y. Patient-reported health preferences of anticoagulant-related outcomes. J Thromb Thrombolysis. 2015;40:268–73.
50. Wilke T, Groth A, Mueller S, Pfannkuche M, Verheyen F, Linder R, et al. Oral anticoagulation use by patients with atrial fibrillation in Germany. Adherence to guidelines, causes of anticoagulation under-use and its clinical outcomes, based on claims-data of 183,448 patients. Thromb Haemost. 2012;107:1053–65.
51. Wilke T, Groth A, Pfannkuche M, Harks O, Fuchs A, Maywald U, et al. Real life anticoagulation treatment of patients with atrial fibrillation in Germany: extent and causes of anticoagulant underuse. J Thromb Thrombolysis. 2015;40:97–107.
52. MacLean S, Mulla S, Akl EA, Jankowski M, Vandvik PO, Ebrahim S, et al. Patient values and preferences in decision making for antithrombotic therapy: a systematic review. Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141:e1S–23S.
53. Man-Son-Hing M, Gage BF, Montgomery AA, Howitt A, Thomson R, Devereaux PJ, et al. Preference-based antithrombotic therapy in atrial fibrillation: implications for clinical decision making. Med Decis Mak. 2005;25:548–59.
54. Coleman CI, Roberts MS, Sobieraj DM, Lee S, Alam T, Kaur R. Effect of dosing frequency on chronic cardiovascular disease medication adherence. Curr Med Res Opin. 2012;28:669–80.
55. Llewellyn-Thomas HA, Williams JI, Levy L, Naylor CD. Using a trade-off technique to assess patients' treatment preferences for benign prostatic hyperplasia. Med Decis Mak. 1996;16:262–82.
56. Moia M, Mantovani LG, Carpenedo M, Scalone L, Monzini MS, Cesana G, et al. Patient preferences and willingness to pay for different options of anticoagulant therapy. Intern Emerg Med. 2013;8:237–43.
57. Clark MD, Determann D, Petrou S, Moro D, de Bekker-Grob EW. Discrete choice experiments in health economics: a review of the literature. Pharmacoeconomics. 2014;32:883–902.
58. Reed Johnson F, Lancsar E, Marshall D, Kilambi V, Muhlbacher A, Regier DA, et al. Constructing experimental designs for discrete-choice experiments: report of the ISPOR Conjoint Analysis Experimental Design Good Research Practices Task Force. Value Health. 2013;16:3–13.