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## **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**

Samantha MacLean, Sohail Mulla, Elie A. Akl, Milosz Jankowski, Per Olav Vandvik, Shanil Ebrahim, Shelley McLeod, Neera Bhatnagar and Gordon H. Guyatt

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## 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

Samantha MacLean, MSc; Sohail Mulla, BHSc; Elie A. Akl, MD, MPH, PhD; Milosz Jankowski, MD, PhD; Per Olav Vandvik, MD, PhD; Shanil Ebrahim, MSc; Shelley McLeod, MSc; Neera Bhatnagar, MLIS; and Gordon H. Guyatt, MD, FCCP

**Background:** Development of clinical practice guidelines involves making trade-offs between desirable and undesirable consequences of alternative management strategies. Although the relative value of health states to patients should provide the basis for these trade-offs, few guidelines have systematically summarized the relevant evidence. We conducted a systematic review relating to values and preferences of patients considering antithrombotic therapy.

**Methods:** We included studies examining patient preferences for alternative approaches to antithrombotic prophylaxis and studies that examined, in the context of antithrombotic prophylaxis or treatment, how patients value alternative health states and experiences with treatment. We conducted a systematic search and compiled structured summaries of the results. Steps in the process that involved judgment were conducted in duplicate.

**Results:** We identified 48 eligible studies. Sixteen dealt with atrial fibrillation, five with VTE, four with stroke or myocardial infarction prophylaxis, six with thrombolysis in acute stroke or myocardial infarction, and 17 with burden of antithrombotic treatment.

**Conclusion:** Patient values and preferences regarding thromboprophylaxis treatment appear to be highly variable. Participant responses may depend on their prior experience with the treatments or health outcomes considered as well as on the methods used for preference elicitation. It should be standard for clinical practice guidelines to conduct systematic reviews of patient values and preferences in the specific content area. *CHEST 2012; 141(2)(Suppl):e1S–e23S*

Guideline panels require the best evidence regarding patient values and preferences in making trade-offs between desirable and undesirable consequences of alternative management strategies.<sup>1</sup> We define “values and preferences” as a broad term that includes patient perspectives, beliefs, expectations, and goals for their health and life, including the process that patients go through in weighing the potential benefits, harms, costs, and burdens associated with different treatment or disease management options.<sup>2</sup> Recommendations regarding antithrombotic therapy typically involve trade-offs between decreased risk of thrombosis vs increased bleeding risk and burden of treatment. To inform recommen-

dations of the Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines, we conducted a systematic review to determine what is known regarding patient values and preferences for and experiences with antithrombotic therapy (including prophylaxis and treatment).

#### 1.0 METHODS

##### 1.1 Eligibility Criteria

We included studies that enrolled individuals potentially at risk of or having direct experience with conditions for which antithrombotic therapy may be indicated. We specifically included:

- Studies that examined patient preferences for antithrombotic therapy vs no or alternative antithrombotic therapy, which includes receiving both treatment for thromboembolic disease and prophylaxis as defined previously
- Studies that examined in the context of consideration of antithrombotic therapy how patients value alternative health states and experiences with treatment
- Studies that examined choices patients make when presented with decision aids for management options regarding antithrombotic therapy

We excluded studies of proxy decision makers and health-care professionals and studies that were not available in English.

### 1.2 Search Strategy

We developed electronic search strategies with the help of a health-care librarian (N. B.). We searched Medline, Embase, Psychinfo, HealthStar, CINAHL, CENTRAL, and International Pharmaceuticals Abstracts between August and September 2009, starting with the dates of inception of each database.

We also searched the gray literature, including the International Society for Quality of Life conference abstracts (2000-2008), the Society for Medical Decision Making conference abstracts available online (2001, 2004-2008), PapersFirst, and Dissertations and Theses International. Finally, we reviewed reference lists of all eligible studies.

### 1.3 Selection of Studies

Two reviewers independently screened for eligibility the titles and abstracts of identified articles. S. MacLean served as the first reviewer, whereas six authors split the task of the second reviewer (S. McLeod, S. Mulla, M. J., E. A. A., P. O. V., and S. E.); only

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**Affiliations:** From the Department of Biostatistics and Clinical Epidemiology (Ms MacLean, Messrs Mulla and Ebrahim, and Drs Akl and Guyatt) and Health Sciences Library (Ms Bhatnagar), McMaster University, Hamilton, ON, Canada; Department of Internal Medicine (Dr Jankowski), Faculty of Medicine, Jagiellonian University Medical College, Krakow, Poland; Division of Emergency Medicine (Ms McLeod), Department of Medicine, Schulich School of Medicine and Dentistry, The University of Western Ontario, London, ON, Canada; Department of Medicine (Dr Akl), State University of New York at Buffalo, Buffalo, NY; and Norwegian Knowledge Centre for the Health Services and Department of Medicine Gjøvik (Dr Vandvik), Innlandet Hospital Trust, Gjøvik, Norway.

Ms MacLean is currently at the University of British Columbia, Faculty of Medicine, School of Population of Public Health.

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**Correspondence to:** Samantha MacLean, MSc, McMaster University, 1200 Main St W, Hamilton, ON, L8N 3Z5, Canada; e-mail: [macleast@mcmaster.ca](mailto:macleast@mcmaster.ca)

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one reviewer screened conference abstracts. We conducted calibration exercises to ensure consistency among reviewers. We retrieved the full texts of articles judged as potentially eligible by at least one reviewer. Two reviewers then independently screened all full texts for eligibility using a standardized form with explicit inclusion and exclusion criteria. Reviewers resolved their disagreements by discussion or by consulting a third reviewer (G. H. G.).

### 1.4 Data Abstraction

In pairs, reviewers independently abstracted the following data from each article using a standardized data abstraction form: study design; population and health conditions of interest; antithrombotic medication; outcomes assessed; results; and methodologic characteristics of the study, including systematic biases and potential limitations.

### 1.5 Data Analysis

We planned to conduct a meta-analysis if the treatment outcomes considered were comparable. The variability in methods and the ways outcomes were measured and presented made the generation of pooled estimates impossible. We present the results in narrative and tabular form, stratified by the health condition.

## 2.0 RESULTS

### 2.1 Included Studies

Of 48 studies selected for inclusion, 16 focused on patients with atrial fibrillation,<sup>3-18</sup> five on patients with VTE,<sup>19-23</sup> four on stroke or myocardial infarction prophylaxis,<sup>24-27</sup> six on thrombolysis in acute stroke or myocardial infarction,<sup>28-33</sup> and 17 on the burden of antithrombotic treatment.<sup>34-50</sup> Strategies used to elicit patient preferences include visual analog scales<sup>25,37,42,50</sup>, standard gamble<sup>17,22,23,30</sup>, time trade-off<sup>6-8,15,19-21</sup>, probability trade-off technique<sup>3,4,9,12,25,26</sup>, decision aids<sup>10,13,14,18,31</sup>, the presentation of hypothetical scenarios in which participants are asked to make a treatment decision<sup>5,11,16,24,32,33</sup>, and methods used to elicit information about treatment burden, such as interviews and surveys.<sup>27,29,35-41,43-50</sup>

Of the 48 included studies, 12 provided health state utilities or health state valuations obtained from participants with regard to both long-term and short-term outcomes related to thrombolysis and prophylaxis treatments<sup>6-8,15,17,19-23,25,30</sup> (Table 1). Health state utilities typically are assessed on a scale of 0 to 1, with 0 being equivalent or worse health, and 1 being optimal health. A patient or participant's utility value reflects his or her opinions or attitudes toward a given health state or outcome. Disutility refers to the burden or negative outcomes associated with a particular health state.

### 2.2 Overall Findings

Although there were exceptions,<sup>13,14</sup> participants across the studies tended to place a higher disutility on stroke than GI bleed<sup>3,4,25</sup> and much greater disutility

**Table 1—[Section 2.1] Participant Health State Utility Valuations**

Study/Year	Method of HSU Elicitations	Unit	Well Warfarin (or Unspecified VKA)	Well Aspirin	Severe Stroke	Moderate Stroke	Mild Stroke	Major (or Unspecified) GI Bleed	Mild/ Nonfatal GI Bleed	Other
Alonso-Coello et al <sup>19</sup> /2008	Feeling thermometer (100-point scale) 2 y	Mean ± SD	0.66 ± 0.15	0.8 ± 0.19	0.22 ± 0.16		0.47 ± 0.18		0.44 ± 0.2	
Dranitsaris et al <sup>18</sup> /2009	TTO 3 mo	Median (95% CI) transformed to SD <sup>b</sup>	Warfarin treatment of 10 d: 0.80 (0.02)							Dalteparin for 10 d: 0.98 (0.02) Dalteparin for 35 d: 0.83 (0.02)
Protheroe et al <sup>15</sup> /2000	TTO 1 y	Median (IQR) transformed to SD <sup>c</sup>	1 ± 0		0.1 ± 0		0.5 ± 0.29			Burden with warfarin: 0.8 ± 0.22
Thomson et al <sup>17</sup> /2000	SG 1 y	Mean ± SD	GP managed: 0.948 ± 0.09 Clinic managed: 0.84 ± 0.17		0.19 ± 0.28		0.64 ± 0.27	0.84 ± 0.17		
Gage et al <sup>8</sup> /1998	TTO 10 y	Mean (range) <sup>d</sup>	0.95 (0.92-0.99)	0.99 (0.96-1)	0.51 (0-0.99)		0.85 (0-1)			
Gage et al <sup>6</sup> /1995	TTO 10 y	Mean (range) transformed to SD <sup>e</sup>	0.99 ± 0.02	0.99 ± 0.1	0.39 ± 0.25		0.75 ± 0.25			
Gage et al <sup>7</sup> /1996	TTO/SG 1 y	Mean (10th and 90th percentile)	0.99 (0.95, 1)	0.99 (0.99, 1)	0.11 (0, 0.51)	0.39 (0, 0.99)	0.76 (0.14, 1)			
Lenert and Soetikno <sup>23</sup> /1997	SG Entire life	Mean (95% CI) transformed to SD			CNS bleed: 0.66 ± 0.23					Mild PPS: 1.00 ± 0.02 Severe PPS: 0.93 ± 0.06
Locadia et al <sup>20,21</sup> /2004	TTO 2 y	Median (IQR) transformed to SD	0.92 ± 0.15		CNS: 0.33 ± 0.29			GI bleed: 0.65 ± 0.27		PTS: 0.82 ± 0.23 DVT: 0.84 ± 0.25 Pulmonary embolism: 0.63 ± 0.37
Man-Son-Hing et al <sup>25</sup> /2000	VAS (10 cm) 5 y	Mean ± SD		0.93 ± 0.14	0.16 ± 0.16		0.7 ± 0.18	0.79 ± 0.18		MI: 0.57 ± 0.26
O'Meara et al <sup>22</sup> /1994	SG Participant life expectancy	Mean (range) transformed to SD			CNS: 0.29 ± 0.25					Mild PPS: 0.995 ± 0.03 Severe PPS: 0.982 ± 0.03

(Continued)

Table 1—Continued

Study/Year	Method of HSU Elicitations	Well Warfarin (or Unspecified VKA)	Well Aspirin	Severe Stroke	Moderate Stroke	Mild Stroke	Major (or Unspecified) GI Bleed	Mild/Nonfatal GI Bleed	Other
Slot and Berge <sup>30</sup> /2009	SG Entire life	Unit Median (IQR) transformed to SD		0.1 (0.11)	0.77 (0.15)	0.93 (0.04)			

GP = general practitioner; HSU = health state utility; IQR = interquartile range; MI = myocardial infarction; PPS = postphlebotic syndrome; PTS = postthrombotic syndrome; SG = standard gamble; TTO = time trade-off; VAS = visual analog scale; VKA = vitamin K antagonist.

<sup>a</sup>Rescaled from 0-100-point rating. Alonso-Coello P, Montori VM, Diaz MG, et al, unpublished data, 2008.

<sup>b</sup>Assumed normal distribution (mean = median); 95% CI/3.92 = SD.

<sup>c</sup>IQR/1.349 = SD.

<sup>d</sup>Given that the sample size for Gage et al<sup>6</sup> is < 25 (n = 14), we cannot transform the data to SD.

<sup>e</sup>Range × 0.25 = SD.

on stroke than treatment burden.<sup>6-8</sup> However, there was little consistency in health state utilities and preferences for treatment choices both within and across studies. We outline the range of participant preferences in categories of presentation. Unless otherwise indicated, the term “stroke” refers to the net of nonfatal hemorrhagic and nonfatal thrombotic stroke. The term “bleed” refers to nonfatal GI bleeding.

### 3.0 ATRIAL FIBRILLATION

#### 3.1 Summary of Findings

Three studies reported compelling findings of a higher disutility associated with stroke than with bleed. Alonso-Coello et al<sup>3</sup> found that 19 of 96 participants (20%) were willing to accept > 35 additional bleeds on warfarin for 3% absolute risk reduction of stroke. For this 20%, the disutility associated with one stroke was equal to the disutility associated with 11.6 bleeding episodes. The median threshold that patient-participants were willing to accept was 10 bleeds for a 3% reduction in stroke (range, 1-100). Similarly, Devereaux and colleagues<sup>4</sup> found that 57% of participants were willing to accept 22 additional bleeds to achieve a stroke reduction of 8% (disutility of one stroke equal to 2.8 bleeds). The remaining 43% of participants varied considerably in the number of additional instances of bleed that they were willing to accept. The mean number of bleeds that all participants were willing to accept to achieve this 8% stroke reduction was 17.4.

Man-Son-Hing<sup>12</sup> found that given a bleeding risk of 3% over 2 years, the mean stroke reduction that participants required to accept warfarin was 1.65% over the same time period. Fifty-two percent of participants would accept warfarin for an absolute decrease in stroke risk by 1% over 2 years. The low treatment threshold in this study may be partly due to the fact that 90% of participants had been taking warfarin at the time of the first interview, and all participants had previously been prescribed warfarin.

A number of studies reported a stroke-to-bleed preference ratio of < 2.<sup>11,13,14</sup> Patients enrolled in these studies appeared to place a considerably higher value on avoiding bleeding relative to avoiding stroke than did patients in most other studies.<sup>13</sup>

Another study conducted by Man-Son-Hing and colleagues<sup>14</sup> randomized 199 participants to a qualitative vs quantitative version of a decision aid trial. None of the participants had atrial fibrillation, 31% had experienced aspirin treatment, and 6% had experienced warfarin treatment. The investigators categorized participants in both groups as low risk or moderate risk for stroke. In the low-risk group,

participants were told that warfarin, compared with aspirin, resulted in a 1% reduction in stroke and a 2.5% increase in bleeds. The majority (69%) of participants in this group chose aspirin; 4% chose warfarin, 14% chose no medication, and 13% were unable to make a treatment decision. The majority who chose aspirin placed an implicit value on stroke reduction of < 2.5 times the disutility of bleeding.

In the moderate-risk group, participants were told that warfarin, compared with aspirin, results in a 3% absolute risk reduction in stroke and a 2.5% increase in bleeds. The majority (58.1%) of participants in this group chose aspirin; 11% opted for no treatment, 12% chose warfarin, and 18.4% were unable to make a treatment decision. The majority who chose aspirin placed a value on stroke reduction of < 0.83 times the value placed on bleeding.

Holbrook and colleagues<sup>11</sup> presented participants with information about atrial fibrillation using an audiotape and booklet. In a typical scenario, warfarin provided a 6% absolute risk reduction in stroke (9%-3%) and a 4% absolute risk increase in bleed (2%-6%) compared with no treatment. In this scenario, 65% of participants chose warfarin, and 35% chose no treatment. For the 65% choosing warfarin, the disutility associated with one stroke was at least 1.5 times greater than the disutility associated with a major bleed.

There are several potential explanations for the variability in results among studies. The first concerns participants' previous experience with antithrombotic treatment. The low treatment threshold in the 1996 study by Man-Son-Hing<sup>12</sup> (> 50% had a disutility of stroke vs bleeding > 3:1) may be partly due to the fact that 90% of the participants had been taking warfarin at the time of the first interview and that all participants had previously been prescribed warfarin. In contrast, participants in the 1999 study by Man-Son-Hing et al<sup>13</sup> reported a higher disutility with bleeds. The patients in this study had chosen at enrollment in Stroke Prevention in Atrial Fibrillation III (SPAF) 2 years earlier to receive aspirin prophylaxis alone. Most, if not all, of the participants had not experienced a stroke during the subsequent 2 years. Participants may have believed that whatever the general risk of stroke while taking aspirin, their personal risk was lower (and, at least to some extent, they might have been correct in this deduction)<sup>51</sup> (Table 2).

Some studies do not provide enough information to enable us to make reliable inferences regarding patient preferences. For example, Fuller et al<sup>5</sup> did not report what information they provided patients about the mortality associated with stroke and bleed (presumably, their scenarios referred to nonfatal stroke and bleed), nor did they indicate whether they provided any information about the consequences of a thrombotic stroke

or intracranial bleed. These omissions make the results difficult to interpret. To the extent, however, that patients assumed that the functional consequences of a thrombotic stroke and an intracranial bleed are similar, the results of this study suggest that many patients place a higher value on avoiding an adverse event that occurs as a consequence of treatment vs avoiding an event with the same functional consequences that occurs as a consequence of not using that treatment. Table 2<sup>51-54</sup> provides a summary of all studies that considered atrial fibrillation.

## 4.0 VTE/DVT THERAPY

### 4.1 Summary of Findings

These studies illustrate significant variability in elicited patient values and preferences regarding thrombosis prophylaxis and treatment. Locadia et al<sup>20</sup> described extremely large between-patient variability with regard to participant willingness to accept warfarin treatment at varying thresholds of recurrent DVT. In another study by Locadia et al,<sup>21</sup> the authors concluded that preferences stated in the form of health state utilities varied significantly across the three methods (Table 3).

## 5.0 VTE/DVT THROMBOLYSIS

### 5.1 Summary of Findings

A study by O'Meara et al<sup>23</sup> found that no participant values and preferences were consistent with taking streptokinase, which differs from the findings of Lenert and Soetikno<sup>22</sup> where the majority of participant preferences were consistent with use of streptokinase. Lenert and Soetikno<sup>22</sup> explained these differences in results by arguing that their participants were better educated about the risks and benefits of DVT and its treatment, given that participants were presented with video and audio descriptions. O'Meara et al<sup>23</sup> provided only written material to participants; thus, their participants may have lacked a full understanding of the outcomes associated with antithrombotic treatment. Another factor potentially affecting results is that participants in the Lenert and Soetikno<sup>22</sup> study were younger and, thus, potentially less risk averse than the participants in the O'Meara et al<sup>23</sup> study (Table 4).

## 6.0 STROKE AND MYOCARDIAL INFARCTION PROPHYLAXIS

### 6.1 Summary of Findings

The results of each of these studies illustrate how design features and participant characteristics may

**Table 2—[Section 3.0] Atrial Fibrillation Studies**

Study/Year	Study Population	Study Design	Methods for Eliciting Preferences		Therapy	Outcomes Considered		Summary of Results
			PTOT feeling thermometer	W/A		Major stroke Minor stroke Major bleed Minor bleed Burden (W/A) Cost	Minor bleed Major bleed Minor stroke Major stroke	
Alonso-Coello et al/2008	Random sample of 96 patients at risk for AF	Cross-sectional interview	PTOT feeling thermometer	W/A	W/A	Major stroke Minor stroke Major bleed Minor bleed Burden (W/A) Cost	Given an absolute risk reduction in stroke of 3% over 2 y, the mean number of bleeds that patients were willing to accept on warfarin was 10 (range, 0-100) before switching to aspirin (on average, 1 stroke = 3 bleeds). Participants clustered at the extremes, with ~40% willing to accept <10 bleeds, and 19 (~20%) willing to accept >35 bleeds. See Table 1 for HSUs.	
Devereaux et al/2001	61 at risk for AF (unspecified number may have had previous experience with warfarin)	Cross-sectional interview	PTOT	W/A/NT	W/A/NT	Minor bleed Major bleed Minor stroke Major stroke	Fifty-seven percent of participants were willing to accept 22 extra bleeds in 100 patients over a 2-y period on warfarin given a stroke reduction of eight. The remaining 43% of patients would accept between one and 21 bleeds. Participants may have been willing to accept more bleeds but were not given the option to choose more than 22. Thus, for almost 60% of patients, the relative disutility of stroke vs bleed was ~3:1 or greater.	
Fuller et al/2004	81 patients from general physician clinic (8 were taking warfarin)	Cross-sectional	Presentation of hypothetical scenarios where participants were asked to choose between drug A and drug B	W/P	W/P	Stroke burden (regular blood tests)	With a reduction in thrombotic strokes of 8%, 99% of patients would take warfarin if the ICH risk was 0.1% per year, and 50% of patients would take warfarin if the ICH risk was 4% per year. Without being given information about the inconveniences associated with warfarin (including ICH and weekly blood draws), 100% of participants would accept warfarin treatment. Given a 4% stroke risk on warfarin, 76 (94%) participants would accept treatment if they had to take a daily tablet, 68 (84%) would accept treatment if they had to undergo blood draws every 2 wk, 75 (93%) would accept treatment if they had to undergo blood draws every 6 wk, and 80 (99%) would accept treatment if they had to undergo blood draws every 12 wk.	
Gage et al/1996	70 patients with AF (31 were taking warfarin, 23 were taking aspirin, 5 were taking both)	Cross sectional interview with decision analysis	TTO and SG	W/A	W/A	Mild stroke Moderate stroke Severe stroke Burden	Mean utility of life on warfarin was 0.987 and life on aspirin, 0.998. Participants varied significantly in their health state valuations, especially when valuing moderate stroke. See Table 1 for more complete HSUs.	
Gage et al/1995	57 patients with AF (one-half of whom were taking warfarin)	Cross sectional interview with decision analysis	TTO	W/A/NT	W/A/NT	Well with W Well with A Mild stroke Moderate to severe stroke Recurrent stroke Burden	The utility associated with daily life on warfarin (0.95) and aspirin (0.99) were high, whereas life with stroke was associated with a low utility (0.39 for moderate to severe stroke). See Table 1 for additional HSUs.	

(Continued)

**Table 2—Continued**

Study/Year	Study Population	Study Design	Methods for Eliciting Preferences		Therapy	Outcomes Considered	Summary of Results
			TTOT	PTOT			
Gage et al <sup>19</sup> /1998	69 patients with AF (34 of whom were taking warfarin); 14 patients were interviewed (12 of whom were taking warfarin, aspirin, or some other type of antithrombotic therapy at the time of the study)	Cross sectional interview with decision analysis	TTOT		W/A/NT	Well with W Well with A Mild stroke Moderate to severe stroke Recurrent stroke	Health state valuations are reported for only 14 patients who would benefit from preference-based therapy if they were at low risk for stroke. Participants varied significantly in the utilities that they attached to stroke. See Table 1 for additional HSUs.
Howitt and Armstrong <sup>20</sup> /1999	56 patients with AF (17 were of whom taking warfarin at the time of the study)	Cross-sectional interview	PTOT		W/A/NT	Stroke	Fifteen of 17 warfarin patients would accept warfarin treatment if it reduced stroke risk by 2.4%. Bleed risk was not specified. Twenty patients not taking warfarin would accept warfarin treatment if it reduced stroke risk by 4.1%, suggesting that having previously taken warfarin affected participant treatment thresholds.
Holbrook et al <sup>21</sup> /2007	98 participants without AF at risk for stroke (12 of whom had previously taken warfarin and 39 of whom had previously taken aspirin)	3 × 2 factorial RCT of decision aids	Decision aid (three formats)		W/A/NT	Stroke Major bleed (each explained in terms of severity and impact) Impact on lifestyle	The decision aid was administered first with participants blinded from treatment names and again with knowing treatment names. Of 18 who initially chose no treatment, only five chose no treatment after being aware of their choice. The number of participants choosing aspirin increased from 41 to 66. Overall, 36% of participants changed their treatment preference, and 88% of these switches were to aspirin. After the second decision exercise, 67% of participants chose aspirin (risks of health outcomes not reported).
Holbrook et al <sup>21</sup> /2012	71 patients without AF not taking warfarin at the time of the study	Cross-sectional survey	Five scenarios varying risks and benefit; in each scenario, participants provided treatment choice		W/NT	Stroke Bleed	When warfarin provides a 6% absolute risk reduction in stroke (9%-3%), and a 4% absolute risk increase in bleed (2%-6%), compared with no treatment, 64.8% of participants chose warfarin, and 35.2% chose no treatment. For the 65% choosing warfarin, the disutility associated with one stroke is at least 0.67 times as great as the disutility associated with a major bleed.
Man-Son-Hing et al <sup>22</sup> /1996	64 patients with AF having previously been prescribed warfarin (58 of whom were taking warfarin at the time of the first interview)	RCT of two preference elicitation methods (2 interviews 2 weeks apart)	PTOT (ping-pong method vs known efficacy method)		W	Costs Burden Side effects Minor stroke Major stroke Major bleed	All participants were given the following risks before completing the preference elicitation exercise: Risk of bleed on warfarin: 3% over 2 y Risk of stroke in untreated patients: 10% over 2 y One-half of all participants would accept a mean reduction in absolute stroke risk necessary to accept warfarin of 2% (95% CI, 1.64-2.42). Using the ping-pong method, the reduction was 1.01% smaller, indicating that the preference elicitation method affects reported preference. In the second interview, 31 patients would accept warfarin treatment if it reduced stroke risk by 0.5 in 100 patients in the face of an increase bleeding risk of 3%. Another 32 patients would accept warfarin treatment if it reduces stroke risk between 1% and 8%.

(Continued)



**Table 2—Continued**

Study/Year	Study Population	Study Design	Methods for Eliciting Preferences		Therapy	Outcomes Considered		Summary of Results
			Decision aid booklet vs usual care	W/A		Burden	Side effects	
Man-Son-Hing et al <sup>153</sup> /1999	287 patients with AF (75 of whom had previously taken warfarin and 123 taking aspirin at the time of the study [277 stated treatment preference])	RCT of a decision aid vs usual care to inform treatment preference	Decision aid booklet vs usual care	W/A	Burden Side effects Minor stroke Major stroke Major bleed			Of those patients who were randomized to receive the decision aid, 53% to 80% correctly estimated their risks of stroke and bleeding; in the control group, 16% to 28% were able to do so. Thus, the decision aid group more reliably reflects underlying patient values in that patients were substantially more likely to understand the risks and benefits of the alternatives. Therefore, we focus on the results in patients who received the decision aid.  The 58 patients with hypertension were told that warfarin would reduce stroke risk by 4% relative to aspirin (from 8%–4% over a period of 2 y. Because five of the eight strokes in patients taking aspirin were minor, the reduction in major stroke would be from 3% to 1.5%. Warfarin would increase the risk of serious bleeding from 1% to 3%. Of these patients, 88% chose to continue taking aspirin. Thus, most patients placed an implicit value on avoiding stroke of, at most, one-half of what they placed on avoiding a bleed. In terms of major stroke, one stroke was associated with the disutility of at least 1.3 bleeds. Participants with hypertension were told that warfarin increases risk of serious bleeding from 1% to 3%. Of these patients, 95% chose to continue taking aspirin. Thus, almost all patients placed an implicit value on avoiding stroke of, at most, as great as the value they placed on avoiding a bleed. In terms of major stroke, one stroke was associated with the disutility of at least 2.6 bleeds. Patients who had been taking warfarin prior to enrolling in the SPAF III cohort study were approximately twice as likely to choose warfarin than those who had not taken warfarin prior to SPAF III.
Man-Son-Hing et al <sup>154</sup> /2002	198 volunteers without AF	RCT of qualitative vs quantitative decision aid formats	Decision aid (two versions)	W/A/NT	Minor stroke Major stroke Major bleed Burden Side effects			Among low-risk participants, warfarin relative to aspirin was associated with a risk reduction in stroke of 1% and an increase in bleeds of 2.5%. Risk differences in aspirin vs no treatment were a 1% reduction in stroke and a 0.5% increase in bleeds. 4/100 chose warfarin 69/100 chose aspirin 14/100 chose no treatment 13/100 were unsure

(Continued)

**Table 2—Continued**

Study/Year	Study Population	Study Design	Methods for Eliciting Preferences	Therapy	Outcomes Considered	Summary of Results
Protheroe et al <sup>15</sup> /2000	97 patients with AF	Cross-sectional interview with decision analysis	TTO	W	Major side effects Minor side effects Stroke	This suggests that the majority of patients place a disutility of stroke vs bleed of <2.5 when choosing between aspirin and warfarin. Other results suggest that the majority of patients place a disutility of stroke vs bleed of <0.83 when choosing between aspirin and warfarin. Comparing aspirin and warfarin for low-risk patients, stroke is no more than 2.5 times the value of bleeding for most patients; in moderate-risk patients, it is <1.0, and this is in patients with no prior exposure to either warfarin or aspirin. Applying patient's individual utilities to the decision analysis, 61% of participants preferred treatment with warfarin. Guidelines would have recommended treatment with warfarin to ~80% of the patients who chose not to take warfarin, suggesting that guideline authors placed a higher disutility on stroke and a lower disutility on bleeding and burden with warfarin than did the patients. See Table 1 for additional HSUs.
Sudlow et al <sup>16</sup> /1998	176 patients with AF	Cross-sectional interview	Presentation of hypothetical scenarios; participants asked whether they would accept treatment given fixed risks	W (not named in the study)	Stroke Need for a monthly blood draw	Participants were asked whether they would accept treatment with a monthly blood test, initially without being given any information about impact of treatment on stroke or bleeding. Those who asked for further details were told that their risk of stroke without treatment was 5%, with a 3% absolute risk reduction with treatment. Participants did not receive any information regarding bleeding risks with and without treatment. Given this information, 81% (55/68) of women and 94% (101/108) of men would accept treatment.
Thomson et al <sup>17</sup> /2000	57 patients with AF (of whom one-half were taking warfarin at the time of the study, and 23% had experienced stroke)	Cross-sectional interview with decision analysis	SG	W	Major bleed Minor stroke Major stroke W managed by GP W managed at hospital	Mean $\pm$ SD utility of life on warfarin was $0.95 \pm 0.09$ when managed by a GP, and mean HSU of life on warfarin was $0.94 \pm 0.10$ when managed in an outpatient clinic. See Table 1 for additional HSUs.
Thomson et al <sup>18</sup> /2007	105 patients with AF (72 of whom were taking warfarin at the time of the study)	RCT of paper guidelines vs a decision aid to inform treatment preference	Computer decision aid	W	Stroke on W Stroke off W Bleed	Although the majority (82%) of participants chose warfarin, the choice favoring warfarin was highly associated with having taken warfarin previously. Nineteen of 32 (59%) participants who had not previously been exposed to warfarin chose to begin treatment, whereas 70 of 77 (91%) of warfarin patients chose to continue with warfarin treatment.

A = aspirin; AF = atrial fibrillation; ICH = intracranial hemorrhage; NT = no therapy; PTOT = probability trade-off technique; RCT = randomized controlled trial; SPAF III = Stroke Prevention in Atrial Fibrillation III; W = warfarin. See Table 1 legend for expansion of other abbreviations.

\*Alonso-Coello P, Montori VM, Diaz MG, et al, unpublished data, 2008.

Table 3—[Section 4.0] VTE/DVT Prophylaxis and Treatment Studies

Study/Year	Patient Population	Study Design	Method of Preference	Therapy	Outcomes Considered	Context	Summary of Results
Dranitsaris et al <sup>19</sup> /2009	24 volunteers (general public)	Cross-sectional interview	TTO	D 10 d/D 35 d/W	Major bleed Symptomatic DVT Monitoring requirements	VTE prophylaxis	The disutility associated with one episode of DVT was greater, on average, than the disutility associated with 1.5 bleeds. When asked directly, 45.8% of patients chose dalteparin for 10 d with a 6.6% chance of major GI bleed, followed by warfarin (41.6%) with a 4.5% chance of bleed, and then by dalteparin for 35 d (12.5%) with a 6.6% chance of bleed.
Locadia et al <sup>21</sup> /2004	124 patients receiving VKA	Cross-sectional interviews with decision analysis	TTO	VKA	Nonfatal stroke PTS No treatment DVT Pulmonary embolism GI bleed Muscular bleed Treatment with VKA Burden	VTE treatment (prophylaxis)	Across a range of rates of recurrence of DVT without treatment from 5% to 15% (VTE risk reduced to 2% with treatment and a 3% risk of major bleeding event), participants' treatment thresholds were variable (23% would always choose treatment, 30% would always reject treatment, the remainder would reject treatment between 5% and 15% risk of VTE). See Table 1 for additional HSUs
Locadia et al <sup>21</sup> /2004	54 patients previously or currently being treated with VKA who previously experienced a thrombotic event	Repeated interviews (two interviews conducted 2 wk apart)	1. Conventional TTO method 2. Chained TTO method 3. Rank ordering of health states 4. Direct rating of health states on a 0-100 scale	VKA	Hospitalization after a serious accident DVT Pulmonary embolism GI bleed Muscular bleed Treatment with oral anticoagulant	Use of anticoagulants for VTE, PTS, major bleed (prophylaxis)	Health state values differed significantly among the three methods. All participants ranked five health states; the average ordering of health states was as follows: 1. Treatment with oral anticoagulants (HSU ~0.75-0.95 across three methods of HSU elicitation) 2. DVT (HSU ~0.6-0.85) 3. Muscular bleed (HSU ~0.2-0.6) 4. GI bleed (HSU ~0.15-0.15) 5. Pulmonary embolism (HSU ~0.12-0.5)

D = dalteparin. See Table 1 and 2 legends for expansion of other abbreviations.

**Table 4—[Section 5.0] VTE/DVT Thrombolysis Studies**

Study/Year	Patient Population	Study Design	Method of Preference		Therapy	Outcomes Considered		Context	Summary of Results
			Elicitation	Preference		Stroke	Severe PTS		
Lenert and Soetikno <sup>22</sup> /1997	30 healthy women	Cross-sectional computer interviews with decision analysis	SG	SG	H/SK/H&SK	Stroke Mild PTS Severe PTS	DVT treatment (thrombolysis)	Participants rated CNS bleed with a median utility of 0.66 (SD, 0.23), severe PTS with a median utility of 0.93 (SD, 0.06); and mild PTS with a median utility of 1 (SD, 0.02). After applying health state valuations into a decision model, comparing the gains in quality-adjusted life years found combination therapy (H + SK) to be the optimal choice. See Table 1 for additional HSUs.	
O'Meara et al <sup>23</sup> /1994	36 participants (16/36 had experienced VTE)	Cross-sectional interview with decision analysis	SG	SG	H/H&SK	Stroke Mild PPS Severe PPS	Proximal DVT (thrombolysis)	Compared with SK + H, heparin alone increased life expectancy by 29 d over the predicted life expectancy of 20 y. As well, major bleed with CNS was included as the only relevant outcome. SK + H increases absolute risk of fatal CNS bleed by 0.4% and decreases the absolute risk of PPS by 5.6%. Given participant HSU, participants placed a much higher disutility on death (mean, 0 ± 0) than PPS (mean, 0.982 ± 0.025). Heparin alone was preferred because participants were unwilling to accept a small increase of death to avoid PPS. See Table 1 for additional HSUs.	

H = heparin; SK = streptokinase. See Table 1 and 2 legends for expansion of other abbreviations.

affect reported values and preferences. For example, in the 2001 study by Man-Son-Hing et al,<sup>26</sup> enrollees in the Aspirin for Primary Prevention in the Low-risk Elderly (APPLE) pilot study would accept aspirin to gain a significantly smaller reduction in first-time stroke risk compared with those who did not enroll. This finding may indicate that individuals who enroll in trials may have higher acceptance for treatment than those who do not.

Results from a 2000 study by Man-Son-Hing et al<sup>25</sup> help to defend the claim that differing methods for preference and health state utility valuations may affect reported preferences. Of the 42 participants who rated preferences using two methods, 43% reported that they would base their decision on the results of the probability trade-off technique, and 17% would base their decision on the decision analysis. The remaining 40% had no preference between the two.

Results from a study by Bergus et al<sup>24</sup> suggest that methods used to relay information about risks and benefits of therapy may significantly affect their reported preferences. Participants who received treatment benefits following risks were more likely to accept aspirin than those who received information in the opposite order. This may relate to the concept of loss aversion, which refers to the tendency for individuals to prefer avoiding loss in favor of gaining benefits.<sup>55</sup> The results of a study by Montori et al<sup>2</sup> illustrate that similar to other studies, previous experience with a given treatment affects the valuation of the outcomes or risks associated with that treatment (Table 5).

## 7.0 STROKE THROMBOLYSIS

### 7.1 Summary of Findings

Results from Slot and Berge<sup>30</sup> indicate that compared with individuals who have not experienced a given health event, those who have may associate a higher utility to that event. This factor may be important to consider when eliciting health state valuations for outcomes associated with antithrombotic treatment. These studies also illustrate that other factors such as age, sex, and living situation affect willingness to accept or reject treatment options (Table 6).

## 8.0 MYOCARDIAL INFARCTION THROMBOLYSIS

### 8.1 Summary of Findings

One could infer from the results of Heyland et al<sup>31</sup> that many patients are extremely stroke averse (valuing avoiding stroke to a considerably greater extent than avoiding death). More likely, the results suggest that patients place a higher value on avoiding treat-

ment-induced adverse (eg, hemorrhagic stroke) events than avoiding events prevented as a result of treatment. This latter interpretation is consistent with results from Fuller et al,<sup>5</sup> who examined the relative aversion to thrombotic and hemorrhagic stroke and found that patients placed a greater value on avoiding treatment-induced strokes than on avoiding strokes that treatment could prevent. This finding could relate to the concept of loss aversion.<sup>55</sup>

Stanek et al<sup>32</sup> suggested, in contrast with Heyland et al,<sup>31</sup> that participants were most concerned with mortality as opposed to stroke. Participants were most often unwilling to accept a higher risk of death in exchange for a reduction in stroke risk. Differences in results may be attributed to participant populations, methods, and outcomes considered. For example, Stanek et al<sup>32</sup> used a self-administered questionnaire, whereas Heyland et al<sup>31</sup> conducted a face-to-face preference elicitation exercise, with a research assistant guiding participants through the decision aid. Given that in Stanek, under conditions of no cost and 0% risk of mortality, approximately one-third of participants chose tissue plasminogen activator (which is associated with higher stroke risk), it is possible that at least some of these participants lacked a proper understanding of the risks and outcomes associated with each treatment. Heyland elicited preferences from participants considered at risk for myocardial infarction, whereas Stanek surveyed inpatients undergoing diagnostic coronary angiography. Finally, Stanek considered only hemorrhagic stroke, whereas Heyland included both hemorrhagic stroke and myocardial infarction (Table 7).

## 9.0 TREATMENT BURDEN AND QUALITY OF LIFE

### 9.1 Summary of Findings

Warfarin is, for most patients, associated with relatively limited impact on quality of life and the ability to carry out daily activities. Although some patients report anxiety or worry over the risks that they incur while taking warfarin therapy,<sup>35-37,40,41</sup> they generally are satisfied with this treatment.<sup>39,46</sup> Other elements of burden that patients report include dietary modifications and the inconvenience associated with frequent blood monitoring. Duration of warfarin therapy was positively attributed to satisfaction with treatment.<sup>38,40</sup> Duration of low-molecular-weight heparin or unfractionated heparin therapy was associated with increased patient quality of life.<sup>50</sup>

Injection treatments and compression devices are well tolerated by most patients. However, when given the choice, most patients would prefer injection treatment because of the discomfort associated with compression treatment<sup>44</sup> (Table 8).

**Table 5—[Section 6.0] Stroke and MI Prophylaxis Studies**

Study/Year	Patient Population	Study Design	Method of Preference Elicitation	Therapy	Outcomes Considered	Summary of Results
Bergus et al <sup>24</sup> /2002	217 patients sampled from a GP office	RCT comparing order of risk information on treatment decision	Hypothetical scenario of a 40% carotid arterial stenosis	A	Stroke GI side effects (bleeding, ulcers)	Participants were randomized to receive either (1) benefits of therapy and then risks or (2) risks of therapy and then benefits. Approximately 77% of participants would accept aspirin with 1% stroke risk reduction, 40% rate of GI side effects, and 33% chance of bleeds (of which most would be minor bleeds). After reading identical introductory information about the use of aspirin, favorability ratings were similar between two groups. After being given more-detailed information (eg, risks, benefits), the study arm that received benefits before risks had significantly reduced favorability ratings than those who received information in the opposite order (reduction of 10.9/100 vs a reduction of 5.2/100).
Man-Son-Hing et al <sup>25</sup> /2000	42 patients previously prescribed aspirin as part of an RCT	Cross-sectional interviews (three scenarios with varying risks)	PTOT VAS (HSU)/ decision analysis	A/NT	Minor stroke Major stroke Major GI bleed MI Daily pill	Participants became less favorable to the intervention as they learned more about the risks (as rated on a scale of 0-100, where 100 is most favorable). Health risks associated with stroke were rated 78/100 in terms of the importance that this information plays on decision-making. Health risks associated with the intervention was rated 55/100, and health benefits associated with the intervention was rated 76.5/100.
Man-Son-Hing et al <sup>26</sup> /2001	54 participants, 42 of whom had enrolled in an RCT to examine the efficacy of aspirin to prevent cardiovascular events and 12 who had not	Cross-sectional interviews (three scenarios with varying risks)	PTOT	A/NT	Minor stroke Major stroke Major GI bleed MI Daily pill	Given an increase in serious GI bleeds with aspirin of 2% over 5 y, the mean threshold risk reduction in MI required for patients to take aspirin using PTOT was 0.45% (0.31) and for stroke, 0.32% (0.28). Thus, the disutility patients placed on MI was on average more than four times that of bleeding, and for stroke, it was more than six times that of bleeding. Participant treatment thresholds elicited by the PTOT were consistently lower than using the decision analysis model. See Table 1 for additional HSU's.
Montori et al <sup>27</sup> /2003	206 patients with diabetes	Cross-sectional survey	Survey that included a 5-point Likert scale	A	GI bleed Side effects Stroke MI	There are significant differences in treatment thresholds for those enrolled in the APPLE (Aspirin for Primary Prevention in the Low-risk Elderly) pilot study (n = 42) vs those who were not (n = 12).  Patients taking aspirin placed a statistically significantly higher value on avoiding cardiovascular events than treatment-associated side effects, whereas patients not taking aspirin placed an equal value on the two. On a 5-point Likert scale, participants not taking aspirin vs those taking aspirin rated the importance of avoiding heart attack with a score of 4.3 (IQR, 3.7-5) and 5 (IQR, 4.3-5; P < .001) and stroke with a score of 4.3 (IQR, 3.7-5) and 5 (IQR, 4.3-5; P < .0001).

See Table 1 and 2 legends for expansion of abbreviations.

**Table 6—[Section 7.0] Stroke Thrombolysis Studies**

Study/Year	Patient Population	Study Design	Method of Preference Elicitation	Therapy	Outcomes Considered	Summary of Results
Kapral et al <sup>29</sup> /2006	586 outpatient clinic patients (experience with treatment not reported)	Cross-sectional self-administered survey	Single choice with fixed probabilities	tPA	Ischemic stroke	Seventy-nine percent of women and 86% of men would agree to treatment (tPA) with an increase in the likelihood of recovery from stroke from 38% to 50% (12% absolute increase in chance of recovery) in the face of a 6% risk of another stroke or death in the first day after taking the drug. Women were less confident in their decisions and were more risk averse.
Mangset et al <sup>30</sup> /2009	11 patients with stroke (experience with treatment not reported)	Repeated (two interviews 6 mo apart) qualitative semistructured interviews	Two semistructured interviews that elicited information about willingness to accept treatment and awareness of treatment risks and benefits	tPA	ICH (other risks not reported)	Four of seven patients who were aware of the risks associated with thrombolytic treatment were willing to accept risks. Six of the 11 patients were willing to accept risks associated with treatment. Overall, participants had varying perceptions of the risks associated with thrombolytic treatment, which may indicate that risks need to be related in a comprehensible manner to allow participants to make a more informed decision about their treatment.
Slot and Berge <sup>31</sup> /2009	150 stroke survivors and age-matched controls (experience with treatment not reported)	Case-control study with decision analysis (ischemic stroke survivors vs age-matched controls)	SC/direct treatment preference	tPA	Mild stroke Moderate stroke Severe stroke	Investigators found that stroke survivors attached slightly higher utilities to stroke events (mild, moderate, and severe) as opposed to participants who had not experienced stroke events. Participants who were living alone rated each outcome with a higher disutility than those who did not live independently. All participants would have accepted treatment to avoid a severe stroke, and 13% would have accepted treatment of a mild stroke, given an unspecified increase in risk for ICH. Advanced age and living alone had an impact on willingness to accept treatment. The most significant reason for accepting treatment was the desire to maintain functional independence. See Table 1 for additional HSUs.

tPA = tissue plasminogen activator. See Table 1 and 2 legends for expansion of other abbreviations.

**Table 7—[Section 8.0] MI Thrombolysis Studies**

Study/Year	Patient Population	Study Design	Method of Preference		Therapy	Outcomes		Summary of Results
			Elicitation	Considered		Considered	Considered	
Heyland et al <sup>13</sup> /2000	120 participants at risk for MI	Prospective cross-sectional survey	Decision aid: presentation of hypothetical scenarios where participants were asked to choose between drug A and drug B followed by a Likert scale measuring strength of preference	tPA/SK	Hemorrhagic stroke (mild to severe)	When presented with a scenario in which tPA relative to SK reduced the 30-d risk of death by nine per 1,000 and increased the risk of hemorrhagic stroke by 3.3 per 1,000, 50% of participants chose tPA compared with SK, implying that 50% of patients were valuing avoiding a treatment-induced stroke at least 2.7 times that of avoiding death. When the tPA reduced deaths by 11 per 1,000 and increased strokes by 1.3 per 1,000, 30.8% of patients chose SK, implying a value of avoiding stroke at least 8.5 times as great as the value of avoiding death.		
Stamek et al <sup>12</sup> /1997	101 hospital inpatients (angiography, angioplasty)	Prospective cross-sectional self-administered questionnaire	Presentation of hypothetical scenarios where participants were asked to choose between drug A and drug B	tPA/SK	Hemorrhagic stroke Death Costs	When assessing patient preferences for tPA vs SK for the treatment of MI, 84% of participants preferred tPA and 15% SK when considering only 30-d mortality rates. The tPA was reported to have a 1% mortality advantage compared with SK. When considering stroke only (risks not provided), 33% preferred tPA and 66% preferred SK. When participants considered both stroke and 30-d mortality, 78% preferred tPA and 22% preferred SK. Forty-three percent of participants would continue to choose tPA if they were responsible for drug cost.		
Tsui et al <sup>15</sup> /2005	96 hospitalized patients with acute coronary syndrome	Prospective cross-sectional survey	Presentation of hypothetical scenarios where participants are asked to choose between drug A and drug B	tPA/SK	Death Stroke Costs	<ol style="list-style-type: none"> <li>1. Short-term mortality with tPA: 6.3%</li> <li>2. Short-term mortality with SK: 7.3%</li> <li>3. Risk of disabling hemorrhagic stroke with tPA: 7/1,000</li> <li>4. Risk of disabling hemorrhagic stroke with SK: 5/1,000</li> </ol> <p>In the first scenario, participants were asked to consider only stroke risks attributed to SK and tPA. Eighty-eight percent chose SK given stroke risk information (without being provided risks associated with death).</p> <p>In the second scenario considering risk of death alone, 100% of participants chose tPA.</p> <p>In the third scenario where participants were asked to consider stroke and death risk together, 66.7% chose tPA.</p> <p>Two-thirds of participants (2/1,000 patients) were unwilling to accept a small increased risk of stroke to avoid a 1% decreased risk of death on tPA.</p>		



**Table 8—[Section 9.0] Studies Reporting Treatment Burden and Quality of Life With Antithrombotic Interventions**

Study/Year	Patient Population	Study Design	Method of Preference Elicitation	Therapy	Context	Summary of Results
Anand and Asumu <sup>34</sup> /2007	43 consecutively sampled patients having received hip/knee replacement	Cross-sectional survey	Questionnaire gauging level of agreement toward satisfaction and a VAS to assess level of comfort associated with both treatments	Foot pump Dalteparin injections	Thromboembolism prophylaxis	All patients included in the study received both LMWH injections and foot pumps following their surgery. Almost 14% (13.9%) of patients found foot pumps to be painful, and 11.6% found injections to be painful. Seventy percent would agree to or were neutral about using the foot pump for 4 wk following surgery, whereas 86% of patients would agree to or were neutral about receiving injections. Fifty-one percent of patients found foot pumps comfortable, and 72% would agree to use them again if they were to have another joint replacement. Foot pumps are at least as well tolerated as dalteparin injections and are acceptable to the majority of patients. Participants also rated comfort level associated with each treatment along a 10-cm VAS, with 0 being most uncomfortable and 10 indicating most comfortable. Mean VAS score was 6.3 for the foot pump and 7.3 for the injections (statistically insignificant; $P = .07$ ).
Amsten et al <sup>37</sup> /1997	132 (43 noncompliant and 89 compliant) warfarin patients	Case-control study	Telephone interviews to assess patient satisfaction for warfarin, comparing compliant and noncompliant cases	W	VTE/AF (and other) prophylaxis	Fifty-three percent of noncompliant and 31% of compliant individuals reported that warfarin affected their lifestyle. Thirty percent and 15%, respectively, reported that warfarin restricted physical activity; 49% and 30% worried about bleeding complications while taking warfarin, and 60% and 34% reported that regular blood testing was problematic.
Barcelona et al <sup>36</sup> /2000	264 patients on long-term warfarin	Cross-sectional survey	Questionnaire to assess satisfaction and QOL associated with warfarin treatment	W	VTE prophylaxis	Thirty-eight percent of patients were very worried about bleeding, 21% believed that therapy affected free-time activities, but only 11% reported that therapy limits daily life. Ninety-five percent of patients were happy with continuous therapy monitoring. Overall, anticoagulation therapy was believed to be acceptable.
Casais et al <sup>35</sup> /2005	905 patients having used oral anticoagulants for > 4 wk	Cross-sectional survey	Multiple choice questionnaire (SF 36) to assess knowledge, daily life implications, and treatment burden	W or acenocoumarol	VTE/AF and heart valve prophylaxis	The mean QOL score among participants was 53.69/100 ± 23.17; 87.5% of patients reported that they had not changed their lifestyle or habits after beginning treatment. Patients who felt worse since beginning therapy tended to be more worried about bleeding complications. Alternatively, patients who felt better protected by their therapy tended to have been treated for > 5 y.

(Continued)

**Table 8—Continued**

Study/Year	Patient Population	Study Design	Method of Preference Elicitation	Therapy	Context	Summary of Results
Dantas et al <sup>30</sup> /2004	21 patients taking warfarin for 6 mo	Cross-sectional qualitative interview	Semistructured face-to-face interview with four themes: decision-making, knowledge/education, impact, and satisfaction.	W	VTE/AF prophylaxis	The majority (specific percentage not reported) of participants had not experienced complications due to warfarin. Many participants reported only minor inconveniences, such as taking a pill every day, regular blood tests, and dietary changes. Twenty-five percent of participants reported that warfarin therapy affected their day-to-day lives. Most participants were satisfied with their warfarin regimen, but in some cases, the inconveniences associated with regular blood monitoring were reported as being significant.
Davis et al <sup>37</sup> /2005	52 warfarin patients	Cross-sectional survey	Self-administered survey to assess (among other factors) impact of warfarin on QOL	W	Thromboembolism treatment (thrombolysis)	Nineteen percent of patients believed that warfarin limited their QOL, and although 51% reported being worried about the complications of warfarin treatment and about their laboratory results, 82% were happy with their treatment.
Jaffary et al <sup>40</sup> /2003	89 patients with AF receiving warfarin	Cross-sectional survey	SF-36 and EuroQol surveys and interviews to assess patient QOL and health beliefs	W	AF (prophylaxis)	Of stable and unstable INR groups, 81% and 82%, respectively, did not think that warfarin affected their lifestyle; 54% and 53% believed that their health was better since starting warfarin. Frequent blood monitoring bothered 16% and 12%, respectively. Fifteen percent of stable and 18% of unstable participants reported worrying a lot about side effects, 16% and 12% reported being bothered by frequent blood monitoring, and 29% and 15% reported that warfarin bothered them more in the beginning than at the time of the study.
Koopman et al <sup>50</sup> /1996	400 patients with acute proximal DVT	RCT	MOS-SF-20 and VAS	UFH (given in hospital) and LMWH (given at home)	Secondary VTE prophylaxis	At total of 198 participants were randomized to receive standard heparin, and 202 were assigned to receive LMWH. Comparing the two treatments, QOL scores remained similar throughout the 24-wk study period. Mental health scores improved from ~20 (on a scale of 0-100) to 70. Overall QOL scores increased from ~50 to ~60 for both treatments.
Lancaster et al <sup>41</sup> /1991	333 patients with AF enrolled in an RCT (177 of whom were taking warfarin at the time of the study)	Cross-sectional survey	QOL information obtained using scaling methods as well as rating of problems associated with warfarin therapy	W/NT	Nonrheumatic AF prophylaxis	Patients taking warfarin did not differ significantly from controls in their rating of the physical functioning, well-being, or health perceptions. Of the 177 patients taking warfarin at the time of the study, 85% reported that treatment did not restrict their lifestyle, 75.6% reported that frequent blood testing did not trouble them, and 79.2% did not report worrying about frequent blood monitoring. Thirteen percent of participants taking warfarin worried about its side effects, and another 13% did not think that their health had improved since beginning warfarin treatment.

(Continued)

**Table 8—Continued**

Study/Year	Patient Population	Study Design	Method of Preference Elicitation	Therapy	Context	Summary of Results
Le Sage et al <sup>18</sup> /2008	48 patients receiving at least 3 d of LMWH injections	Cross-sectional survey	Open- and close-ended questions to assess knowledge about and satisfaction with treatment	LMWH	VTE prophylaxis	Satisfaction with LMWH was assessed on a 5-point Likert scale. On average, participants were in favor of receiving LMWH (mean, 4.26 ± 0.64) and believed that the side effects of LMWH were tolerable (mean, 3.98 ± 0.86).
Locadia et al <sup>19</sup> /2003	360 patients receiving VKA	Repeated qualitative semistructured interviews (QOL measured at RCT study entry, 10 d, 3 mo, 6 mo)	VAS MOS-SF-20	VKA (UFH and LMWH)	DVT thrombolysis	QOL while taking VKAs remained between ~40 to 60 along a VAS of 100 at each of the three assessment periods (specific figures not provided). Psychological distress scores remained steady between ~20 and 30/100 as did mental health ratings (60-80/100). Length of treatment (3 vs 6 mo) did not significantly affect QOL scores.
Noble and Finlay <sup>20</sup> /2005	40 cancer patients receiving palliative care	Cross-sectional interview	Semistructured interview	W/H	VTE prophylaxis	Participants considered LMWH injections to be acceptable. Injections were believed to be simpler than frequent INR monitoring on warfarin (which was very disruptive and painful). One patient believed that bruising was an unacceptable side effect (but this patient had not previously taken warfarin).
Noble et al <sup>14</sup> /2006	28 cancer patients receiving palliative care	Cross-sectional interview	Semistructured interview	LMWH/compression stockings	VTE prophylaxis	One patient had previous exposure to LMWH, three with LMWH and compression stockings, and three with only compression stockings. Patients considered heparin an acceptable treatment, and heparin was preferred compared with compression stockings. Although patients reported minor side effects, such as bruising at the injection site, LMWH injections did not reduce QOL.
Maxwell et al <sup>15</sup> /2002	207 gynecologic malignancy surgery patients	RCT of two prophylaxis methods	Questionnaire to elicit treatment preferences and reasons for dissatisfaction	LMWH/pneumatic compression	Thromboembolism prophylaxis	Twenty-six percent of patients experienced discomfort/side effects from the EPC device, whereas only 4% of patients receiving injections experienced discomfort/pain or anxiety. One percent of participants found that the injection treatment made them anxious, and another 1% found injections to be painful. Eleven percent of patients found EPC moderately to extremely inconvenient, 7% found it moderately to extremely uncomfortable, and 11% of patients removed the device because of inconvenience and discomfort. Postoperatively, 78% of the LMWH group and 74% of the EPC group preferred the method to which they had been randomized. LMWH may be more highly tolerated, but this finding was not statistically significant.

(Continued)

**Table 8—Continued**

Study/Year	Patient Population	Study Design	Method of Preference		Therapy	Context	Summary of Results
			Study Design	Elicitation			
Samsa et al <sup>46</sup> /2004	220 anticoagulation patients	Cross-sectional survey	25-item scale (Duke Anticoagulation Satisfaction Scale) to measure satisfaction with warfarin	W	Idraparinux injections and VKA	Mechanical heart valves, valvular heart disease, MI, and AF (systemic embolism prophylaxis)	The possibility of bleeding or bruising did not significantly affect overall QOL (mean, 1.88 on a 7-point Likert scale). Warfarin use also did not appear to significantly affect daily life (mean, 2.2) and was not found to be painful (mean, 1.37). Participants did not find daily and infrequent monitoring tasks to be inconvenient (mean, 1.87 and 2.09, respectively).
Prins et al <sup>49</sup> /2009	652 patients with AF, DVT, or pulmonary embolism participating in an RCT	Cross-sectional survey	PACT-Q2		Idraparinux injections and VKA	VTE prophylaxis	All results pertained to satisfaction with idraparinux injections and VKA. No comparative analysis between the two was conducted. Following 3 mo of treatment, 651 participants rated treatment on a 100-point scale in which a higher score indicated greater satisfaction. Participants rated convenience with a mean of 91.3 ± 10.4; 641 rated satisfaction with treatment with a mean 68.9 ± 17.0. Satisfaction scores reflected experiences with side effects, satisfaction with form of treatment, and satisfaction regarding independence. Ratings for convenience and treatment satisfaction remained stable at the 6-mo point, with means of 90.6 ± 10.4 and 70.6 ± 17.4, respectively (with n = 404 and n = 403, respectively).
Warwick et al <sup>47</sup> /1998	274 total hip replacement patients	RCT (all patients randomized to receive enoxaparin or foot pump)	Questionnaire to assess the acceptability of either treatment	LMWH/A-V Impulse System foot pump	LMWH/A-V Impulse System foot pump	DVT prophylaxis (7 d following surgery)	A total of 124 patients using the foot pump were asked about its acceptability. Five of 147 patients randomized to the foot pump stopped using it because they found it intolerable. Eleven percent found foot pumps quite comfortable, whereas 17% had difficulty sleeping while using the pump. In contrast, 8% found the pump to be very relaxing. A total of 122 patients received LMWH injections and completed the questionnaire. Eleven percent found the injections quite painful, whereas 3% found the injections quite comfortable (additional results not reported).

EPC = external pneumatic compression; INR = international normalized ratio; LMWH = low-molecular-weight heparin; MOS-SF-20 = Medical Outcome Study Short Form 20; PACT-Q2 = Perception of Anticoagulant Therapy Questionnaire 2; QOL = quality of life; SF-36 = Medical Outcome Study Short Form 36; UFH = unfractionated heparin. See Table 1 and 2 legends for expansion of other abbreviations.

## 10.0 BIASES AND LIMITATIONS ASSOCIATED WITH INCLUDED STUDIES

There are a number of limitations associated with the included studies. Only three studies reported comprehension screening of potential participants,<sup>3,4,12</sup> and two used only the data from participants with consistent results.<sup>6,31</sup> Le Sage and colleagues<sup>48</sup> had research assistants walk through the survey with participants to ensure that the participants understood all the questions. It is possible that for those studies that did not pretest for comprehension, preferences elicited using methods such as time trade-off, probability trade-off, and standard gamble may have been compromised because of a lack of participant understanding. For example, Thomson et al<sup>18</sup> designed their study as a three-arm trial, one arm of which elicited patient preferences through the standard gamble method. After realizing that participants were having difficulty understanding the standard gamble, they dropped that arm of the study.

Studies were also inconsistent in the descriptions of health states presented to participants in terms of both the number and the type of health states considered (eg, major bleed, major side effects, stroke). For example, Protheroe et al<sup>15</sup> grouped major and minor side effects together (not typical), whereas other studies did not consider minor side effects at all. As well, when describing the outcomes associated with stroke, some authors centered their descriptions on the physical effects,<sup>30</sup> whereas others considered additional aspects, such as the likelihood of becoming depressed or losing the ability to comprehend language.<sup>21</sup> Given the complexity of the treatment decision in this context, we do not consider studies to be biased if they neglected to consider rare or minor outcomes because including these may overwhelm participants and affect the validity of the outcomes.

The methodologic quality of the included studies is concerning, and most studies are compromised by some form of selection bias. For example, whether patients had previously experienced the condition or health events under consideration may have influenced their preference. Slot and Berge<sup>30</sup> found that those participants who had previously experienced a stroke tended to place a lower disutility on stroke than did those who had not experienced stroke events. Ideally, investigators would have recruited individuals recently given a diagnosis of the condition under study and who had not made a treatment decision. None of the included studies did.

In addition, participants' prior associations with the treatments under study may have affected willingness to accept specific treatment options. For example, Holbrook et al<sup>10</sup> found that 36% of participant treatment preferences changed once given the

treatment names (placebo, aspirin, and warfarin); the majority of these switches were to aspirin.

## 11.0 DISCUSSION

We have carried out a systematic review of studies reporting patient values and preferences with regard to antithrombotic treatment. The results obtained through this review provide direction for guideline developers to base recommendations on patient values. In particular, this review highlights the apparently large variability in participant health state valuations and the factors, other than the impact of alternative management strategies on quantity and quality of life, that influence patient decisions.

A number of factors may explain the large variability in patient preferences both within and across studies. First, whether patients had experienced the treatments under consideration appeared to influence results. Typically, previous exposure with a given treatment was associated with a preference for continuing that same treatment.<sup>12,13,45</sup> Cognitive dissonance occurs when participants are inclined to modify their interpretation of information to ensure that it is consistent with their previous decision.<sup>56</sup> To reduce cognitive dissonance, participants who had previously been exposed to the treatments under consideration may be inclined to continue their treatment, even in the face of information suggesting that it is not the optimal choice. Patients who do not want to believe that they have been taking the wrong treatment may interpret the evidence presented so that it is consistent with their prior choice.

In addition, and perhaps most importantly, the differing methods used to elicit values and preferences may have resulted in differing apparent treatment preferences and health state valuations. Few studies attempted to determine whether methods such as probability trade-off, decision analysis, and differing methods for obtaining health state utilities would result in different choices. Indeed, in two studies,<sup>20,25</sup> investigators found that methods used to elicit preferences significantly affected treatment health state valuations and treatment thresholds.

The relatively small number of studies, their small sample sizes, their methodological limitations, and the large variability in their findings limit the inferences that we can confidently draw. We consider the following conclusions, however, as reasonably robust:

1. Values and preferences for antithrombotic treatment and for health states appear to vary appreciably among individuals.
2. Heterogeneity of results across studies—often difficult to explain—leaves appreciable uncertainty about average patient values.

Study results suggest the following average values for the health states of interest:

3. Although there are troubling inconsistencies across studies, particularly in Man-Son-Hing et al,<sup>14</sup> a reasonable trade-off to assume between stroke and bleeds would be a ratio of disutility of net nonfatal stroke (thrombotic or hemorrhagic) to GI bleeds in the range of 2:1 to 3:1.
4. There is much less information about the relative disutility of myocardial infarction and bleeds, although it is clear that myocardial infarction has substantially less disutility than major stroke (and more than minor stroke). A reasonable trade-off to assume between myocardial infarction and bleeds would be 1:1 to 2:1.
5. The only conclusion that one can make regarding the relative disutility of major bleed vs DVT is that it varies widely among patients.
6. Patients are unwilling to accept a small increase in risk of death to avoid the postthrombotic syndrome.<sup>5,23</sup>

Study results suggest the following preferences for the antithrombotic interventions:

7. For most patients, vitamin K antagonist therapy does not have important negative effects on quality of life, although many patients worry about the side effects associated with vitamin K antagonist treatment.
8. Patient aversion to warfarin treatment may decrease over time after treatment is initiated.
9. Injection treatments are well tolerated.
10. Compression stockings are well tolerated but less preferred compared with injection treatments.

The present study has several limitations. Given the large number of abstracts that were selected for review (N = 17,086), it was not feasible to seek out articles that could not be obtained online. Therefore, this study comprises only articles that could be accessed through the electronic library at McMaster University. Eight articles that we deemed potentially relevant were special ordered; two proved eligible. It is possible that we were unable to capture every eligible study in this review, and we expect that authors may come forward with additional studies to be included in an update of this review. Although we attempted to locate unpublished studies by reviewing the gray literature and contacting experts in the field (which did produce two additional articles), this review risks publication bias.<sup>57</sup>

Our findings have a number of implications for future studies eliciting patient values and preferences. First, investigators should elicit values and preferences from participants who have not previously

made the choices under investigation. Although prior experiences may result in a better understanding of the treatment under consideration, it may introduce factors other than preferences for the health states described in their responses (particularly cognitive dissonance). Second, in order to gain a better understanding of whether differing health state descriptions significantly affect health state valuations, future research may test the impact of different descriptions on participant valuations. Ideally, standard descriptions of bleed and stroke outcomes would be developed and applied across studies. Finally, research should ensure that participants understand the preference elicitation exercise and explore factors that bear significantly on patient decisions.

Our findings also have implications for guideline development. The uncertainty and the variability in values and preferences among patients suggest that the present guideline panels should be circumspect in making strong recommendations. Strong recommendations should be restricted to situations in which the desirable consequences of an intervention substantially outweigh the undesirable consequences.

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*Ms MacLean:* served as Topic Editor.

*Mr Mulla:* served as a panelist.

*Dr Jankowski:* served as a panelist.

*Dr Akl:* served as a panelist.

*Dr Vandvik:* served as a panelist.

*Mr Ebrahim:* served as a panelist.

*Ms McLeod:* served as a panelist.

*Ms Bhatnagar:* served as a panelist.

*Dr Guyatt:* served as a panelist.

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**Endorsements:** This guideline is endorsed by the American Association for Clinical Chemistry, the American College of Clinical Pharmacy, the American Society of Health-System Pharmacists, the American Society of Hematology, and the International Society of Thrombosis and Hematosis.

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Samantha MacLean, Sohail Mulla, Elie A. Akl, Milosz Jankowski, Per Olav Vandvik, Shanil Ebrahim, Shelley McLeod, Neera Bhatnagar and Gordon H. Guyatt

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