Estimating Quality of Life in Acute Venous Thrombosis

Kerstin Hogg, MBChB; Miriam Kimpton, BA; Marc Carrier, MD; Douglas Coyle, PhD; Melissa Forgie, MD; Philip Wells, MD

Importance: Future funding for new treatments in venous thromboembolism will be guided by cost-utility analyses. There is little available information on the utility of acute venous thromboembolism, limiting the validity of economic analyses.

Objective: To measure the quality of life in the health states relating to thromboembolism cost-utility analyses.

Design: A prospective cohort study.

Setting: A single-center, university-affiliated thrombosis clinic.

Participants: Two hundred sixteen thrombosis clinic patients with a history of lower limb deep vein thrombosis (DVT) or pulmonary embolism (PE).

Exposures: Participants consented to take a standard gamble interview. Each participant rated the quality of life in acute DVT, acute PE, and bleeding complication health states.

Main Outcomes and Measures: The standard gamble measured quality of life (utility value) for acute DVT, acute PE, major intracranial bleeding event, minor intracranial bleeding event, and gastrointestinal bleeding event.

Results: Two hundred fifteen responses were included in the analysis. Twenty-six percent had experienced both PE and DVT; 54%, DVT alone; and 20%, PE alone. Forty-two percent had experienced more than 1 episode of thrombosis, and 23% had had cancer-associated thrombosis. We found the median utility for acute DVT was 0.81 (interquartile range [IQR], 0.55-0.94); acute PE, 0.75 (IQR, 0.45-0.91); major intracranial bleeding event, 0.15 (IQR, 0.00-0.65); minor intracranial bleeding event, 0.75 (IQR, 0.55-0.92); and gastrointestinal bleeding event, 0.65 (IQR, 0.15-0.86). The median length of symptoms for DVT or PE was 1 week (IQR, 1-3 weeks).

Conclusions and Relevance: To our knowledge, this is the largest published study on utilities in which the participants had personal experience of venous thromboembolism. We present unique information for economic analyses but have also identified future challenges for research in this area. Our summary results differ from those previously published, and we found wide variation in individual responses.

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Health Care Costs Are Escalating with Predictions that the Rise in Spending Will Be Unsustainable over the Next Decade.1,2 There have been many changes in the approach to diagnosing and treating venous thromboembolic (VTE) disease. New diagnostic modalities for pulmonary embolism (PE) and deep vein thrombosis (DVT) have increased the rate of diagnosis without obvious effects on mortality.3 New treatment options have emerged that are more expensive than traditional anticoagulation with vitamin K antagonists but do not require monitoring. In particular, low molecular weight heparins are now used for prolonged treatment of cancer-associated thrombosis at a much greater cost than warfarin.

See Invited Commentary at end of article

Health funding bodies must decide which programs, management services, and drug treatments to pay for. Government advisory boards frequently base their recommendations for funding of new medications on economic analyses, and the American College of Chest Physicians (ACCP) recommendations4 are influenced by economics.
The recent ACCP systematic review compared the cost per QALY gained for different diseases by comparing the cost per QALY gained. Funding bodies often take into account patient preferences, expectations, and projected improvement in quality of life (QOL) when they recommend particular treatments. Cost-utility analysis uses a common outcome (QOL) for all diseases and interventions, which attempts to capture these dimensions. Quality of life can be measured as a utility value, which is a measurement of strength of preference for a particular health state under uncertainty. Using uncertainty in the measurement process is important because we do not know what our future holds, and we make daily decisions based on our values, preferences, and acceptance of risk (eg, a decision to cross the road at a red light or to buy a new car vs a second-hand car). The utility value is often reported as the quality-adjusted life-year (QALY). One year in perfect health is assigned a QALY value of 1.0, and death is assigned a value of 0.

Cost-utility economic analysis is a standard way to determine the cost of improving QOL. Funding bodies compare the costs and benefits of interventions for different diseases by comparing the cost per QALY gained with treatment. The recent ACCP systematic review encountered a lack of research measuring QOL in acute DVT or PE. If economic analyses are to dictate the future of our diagnostic and therapeutic programs, then we should have access to robust estimates of utility values in acute VTE.

The aim of this study was to measure the QOL in acute DVT and acute PE by interviewing patients with prior experience of the condition, using the standard gamble technique. In addition, we aimed to measure the utility of serious bleeding health states as a complication of thrombosis treatment.

This cohort study was conducted in the Ottawa Hospital Thrombosis Clinic (Ottawa, Ontario, Canada), which is the referral unit for a region of 1.1 million people for thrombosis-related problems. Any patient attending the Thrombosis Clinic who had been diagnosed as having either lower extremity DVT or PE at any time was eligible to participate. Patients with a history of upper extremity thrombosis or unusual site thrombosis alone were not included. Participants were interviewed in either English or French. Patients who could not give informed consent, who did not speak either French or English, or who declined to participate were not included. The study was approved by the Ottawa Hospital research ethics board (protocol No. 2011383-01H).

All interviews took place in a private room with a one-on-one interview. The interview used the standard gamble technique to elicit utility values for 5 health states: acute DVT, acute nonfatal PE, nonfatal major intracranial bleeding event, minor intracranial bleeding event, and nonfatal gastrointestinal (GI) tract bleeding event. The 3 bleeding states were chosen as serious bleeding complications in patients given anticoagulation therapy.

Each participant was interviewed to obtain information on age, history of VTE, dates of diagnosis, cancer status at time of diagnosis, type of anticoagulation treatment, and occupation. They were asked how long they had experienced symptoms following their first diagnosis of thrombosis. They were also asked whether they considered themselves “healthy” at the present time (with the option of answering “yes” or “no”). No data were recorded on prior bleeding events or stroke.

The standard gamble is an interview technique in which the interviewer describes a health state and asks the participants to imagine that this is their current situation and level of functioning. They are asked to imagine that there is a treatment that would immediately cure the disease and return them to perfect health. The treatment comes with a risk of immediate and painless death. The treatment is offered multiple times with the probability of dying from the treatment systematically changed on each occasion using the “ping-pong” method. This starts at the extremes (100% probability of cure, then 100% probability of death) and gradually moves toward 50%. The utility is determined by the point of equipoise: when the person is unable to decide whether to take the treatment or not. There is a theoretical concern that some patients may be unable to comprehend or accept a risk of death in exchange for any health benefit. In addition, the interview can be emotionally exhausting, and the participants are asked to consider their own mortality. It can be easier to weigh up these choices by changing death for severe disability (eg, stroke). In this case, the results are recalibrated to the utility derived from gambling the health state “stroke” vs death.

The health state descriptions were written after a literature review of symptoms. They were reviewed before the study by physicians who treat thrombosis (K.H., M.C, M.F., and P.W.), an economist (D.C.), and patients with thrombosis. We first asked the participants to imagine a health state with severe disability (eg, a decision to cross the road at a red light or to buy a new car vs a second-hand car). The utility value is often reported as the quality-adjusted life-year (QALY). One year in perfect health is assigned a QALY value of 1.0, and death is assigned a value of 0.

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encourage them to focus on the health state rather than to worry about later repercussions on their life.

The standard gamble technique was introduced by asking the person to rate the severe stroke health state using a simple computer visual aid program (Figure 2), which displayed probability of death or cure from an imaginary treatment. The ping-pong technique was applied to determine the utility value. After the participant had valued health state B (severe stroke), all other health states (Figure 1, health states C-F) were rated using the same technique. The remaining health states could be cured by the imaginary treatment, but severe stroke (health state B) was substituted for death. The health states were rated in a random order. The final value was calibrated for the utility for health state B against death.

A previous report7 estimated the utility of acute DVT as 0.86 and acute PE as 0.81. Our sample size estimate established that 200 participants would enable identification of a utility value of 0.85 (95% CI, 0.79-0.89).

The data were analyzed using SPSS statistical software (version 20.0). For each health state, the median utility value and interquartile range (IQR) were reported. A post hoc subgroup analysis was conducted to compare results by age (di-chotomized with cutoff age of 60 years), sex, presence of cancer, and patient perception of being “healthy” or not with the Mann-Whitney U test. A comparison between work type and profession was made using the Kruskal-Wallis 1-way analysis of variance.
and PE, the duration of symptoms was guided by our study participant reports shown in Table 1. For the remaining 3 health states, duration was guided by consensus from experts.

Five participants indicated that health state B (severe stroke) had a QOL equal to 1.0 (perfect health). Calibration of their result from the other health states meant that they scored 1.0 for all 5 health states. Five participants rated QOL as 0.0 (equivalent to death) for all 5 health states. Several of these patients had expressed a rational basis to their preferences at the time of interview; however, to explore the effect on the estimates, the analysis was repeated with the 10 patients removed. The median utility values were unchanged.

We found no statistically significant differences in utility estimates between subgroups; however, those with cancer, those older than 60 years, and participants who did not consider themselves as healthy allocated (nonsignificantly) lower utility ratings to all health states than their comparison groups.

**DISCUSSION**

To our knowledge, this is the largest published study of utility measurements for QOL in acute VTE. Our results show that the standard gamble technique gives a wide distribution of results. When the utility values were combined with estimated duration of symptoms, the QALY for acute PE was 0.98 (IQR, 0.95-0.99), and for acute DVT, 0.98 (IQR, 0.96-0.99). The utility for bleeding complications varied greatly, depending on the site of the bleeding event.

Several findings from our study are of interest. (1) There was large variation in patient values. Five participants rated all health states as perfect health, and 5 other participants rated all health states the same QOL as death. Removal of these patients does not affect the results. (2) The histograms show a spread of preference values, and in the case of PE and DVT, there are 2 peaks, one near 1.0 and a second near 0.0. This suggests that patient personal values strongly influence responses to utility analysis and that applying a single QALY estimate to all patients may be erroneous. A logical way to address this variation would be to assess an individual patient for their own personal preference; however, the challenges with this are several-fold: there is limited time in an outpatient clinic; effectively communicating the probability and consequences of adverse outcomes is challenging; some patients look to the physician to make the best decision;
and, strictly speaking, to make the best economic decision, these preferences should be incorporated into an economic model. To address the heterogeneity in utility values, future economic models should include deterministic threshold and probabilistic analysis to explore the effect of utility uncertainty on the optimal therapy.

To date, only 1 study has interviewed patients with experience of thrombosis. Locadia et al7 used the time tradeoff technique to interview 53 patients with prior VTE, 28 with prior major bleeding events, and 48 with postthrombotic syndrome, to estimate preference values for acute VTE and bleeding health states. This technique produces preference values rather than utilities because it does not incorporate choice under uncertainty. The results showed a similar wide distribution (PE, 0.63 [IQR, 0.36-0.86]; DVT, 0.84 [IQR, 0.64-0.98]). Cykert et al8 interviewed 106 women at churches, libraries, medical clinics, and health fairs. Using the standard gamble, they reported lower QALY estimates of 0.86 for DVT and 0.81 for PE. However, all participants were women older than 50 years, 18% did not have a high school education, and VTE health states were valued simultaneously with 3 different cancer health states. There were no confidence limits for the QALY results.

Quality of life in patients with thrombosis has also been measured by disease-specific, multiattribute questionnaires9,10 and a generic questionnaire.11 However, the multiattribute questionnaires are currently not useful for economic analyses because the results are not regarded as QALYs, and to date only 1 study related to acute VTE.12

Several studies have estimated the utility of mild and severe stroke, quoting QALY estimates of 0.6,13 0.29,14 0.2,8 and 0.015 for severe stroke and 0.7515 and 0.78 for mild stroke. The studies used the standard gamble technique and interviewed between 36 and 106 people; some were patients, some were physicians, and others were from the community. The small sample sizes of these studies limit our ability to use the data for cost-utility analyses.

The 2012 ACCP guidelines used estimates of patient preferences to guide the recommendations for “best treatment.” They derived QOL values by asking the panel experts to give their opinion on a scale of 0 to 100. They state that “on average, we assumed that patients attach equal value to nonfatal thromboembolic and major bleeding events.”8(pE4315) In fact, we found that the utility values in acute DVT or PE differ from those for bleeding states. Furthermore, a major intracranial bleeding event has an associated QALY of 0.15 (IQR, 0.00-0.65) compared with a GI tract bleeding event, which has a QALY of 0.99 (IQR, 0.98-1.00). Therefore, it is impossible to reflect all nonfatal bleeding complications with a single health-related QOL value. It seems that a bleeding event may be a worse complication than a recurrent thrombosis. These results might have influenced the ACCP recommendations in cases in which there was clinical equipoise regarding the need for anticoagulation (eg, isolated distal DVT).

The standard gamble technique is viewed by many economists to be the gold standard method for eliciting health utilities. Features that may influence preference are personality, expectations, prior experience, internal resilience, and dependent children. In our study, objective factors (eg, age, cancer, and health status) did not significantly influence the results; however, there was a trend toward lower utility estimates in older participants, those with cancer and those in poor health.

Like many European countries, Canadian health care is free at the point of access, in contrast to the private US health maintenance organizations, which have differing thresholds for funding new technologies. Our results suggest a relatively small disutility for acute thrombosis. There is a risk that strategies aimed at preventing thromboembolic events may fail to reach cost-effective thresholds if the threshold is low, especially if probabilistic sensitivity analysis is not included in future economic models. Although our summary QALY results for VTE were high, the distributions were wide.

There are several points that merit further discussion. To our knowledge, this is the largest study of utility values in VTE, but the results are still widely distributed. The study was not powered to compare small differences in utilities between subgroups, and we cannot tell if variation in participant demographics other than those studied influenced utility estimates. We believe our data are generalizable because our clinic is the single referral center for all patients with any type of thrombosis in the region (not only for complicated cases). There was at least 1 researcher present at every clinic. Not all patients agreed to an interview; however, patients were not approached preferentially or selected on basis of health states.

Although the standard gamble is a well-established method, there is a relative paucity of research evaluating its performance. Research has shown that the stand-

<table>
<thead>
<tr>
<th>Health State</th>
<th>Utility Value, Median (IQR)</th>
<th>Duration of Health State Applied in This Analysis</th>
<th>Corresponding QALY Valuea</th>
<th>Disutility Value (1-QALY)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deep vein thrombosis</td>
<td>0.81 (0.55-0.94)</td>
<td>1 mo</td>
<td>0.98 (0.96-0.99)</td>
<td>0.02 (0.01-0.04)</td>
</tr>
<tr>
<td>Pulmonary embolism</td>
<td>0.75 (0.45-0.91)</td>
<td>1 mo</td>
<td>0.98 (0.95-0.99)</td>
<td>0.02 (0.01-0.05)</td>
</tr>
<tr>
<td>Minor intracranial bleeding event</td>
<td>0.75 (0.55-0.92)</td>
<td>3 mo</td>
<td>0.94 (0.89-0.98)</td>
<td>0.06 (0.02-0.11)</td>
</tr>
<tr>
<td>Gastrointestinal tract bleeding event</td>
<td>0.65 (0.15-0.86)</td>
<td>1 wk</td>
<td>0.99 (0.98-1.00)</td>
<td>0.01 (0.00-0.02)</td>
</tr>
<tr>
<td>Major intracranial bleeding event</td>
<td>0.16 (0.00-0.65)</td>
<td>Permanent</td>
<td>0.15 (0.00-0.65)</td>
<td>0.85 (1.00-0.35)</td>
</tr>
</tbody>
</table>

Abbreviation: IQR, interquartile range.

a Assumes perfect health for remainder of year.
standard gamble gives higher QOL values compared with the time tradeoff, visual analog scales, and the EuroQol Group’s EQ-5D instrument in patients with macular degeneration, urinary incontinence, and erectile dysfunction. So, although the standard gamble technique is widely held to be the most theoretically sound measure, it remains unclear whether it is the best method to measure QOL.

The wide distribution of our results also raises 2 further questions. First, did the participants fully reflect on each health state prior to making a decision about taking the offered treatments? Second, did all participants fully understand the task? The polarization of responses around 1.0 and 0.0 might occur if participants were too tired or uncomfortable to continue, as the extreme values were offered toward the start of the interview. We did not collect data on acceptability or ease of understanding, so we cannot draw conclusions.

Our results have construct validity in that the utility of DVT was rated higher than PE, followed by minor intracranial, GI tract, and major intracranial bleeding events. To calculate the QALY estimates, we had to estimate the duration of symptoms. We collected data on length of DVT and PE symptoms directly from the patients but had to rely on expert consensus regarding length of symptoms from GI tract and minor intracranial bleeding events. We reported the utility and QALY estimates separately in order to make our calculations transparent.

Our study interviewed people with prior experience of VTE. Many economic analyses choose a societal perspective and therefore prefer to derive model estimates from the general community. We do not know if the responses would differ from those elicited from medical staff or the general population.

In conclusion, we found the median utility for acute DVT was 0.81; for acute PE, 0.75; major intracranial bleeding, 0.15; minor intracranial bleeding, 0.75; and GI tract bleeding, 0.65. There was a wide variation in participant utility results. To our knowledge, this is the largest published study on utilities in which the participants had personal experience of VTE, and as such, it presents unique information for economic analyses but also identifies future challenges for research in this area.

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Correspondence: Philip Wells, MD, Department of Medicine, Ottawa Hospital, General Campus, 501 Smyth Rd, Ottawa, ON K1H 8L6, Canada (pwells@toh.on.ca).

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Additional Contributions: Gaurav Bose, BSc, and Karine Gauthier, BSc (both at the University of Ottawa), performed standard gamble interviews and worked voluntarily on the project.

REFERENCES