Assessing patients' anticoagulation preferences for the treatment of cancer-associated thrombosis using conjoint methodology

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ABSTRACT

Low molecular weight heparins have demonstrated superiority over coumarins in the extended treatment of cancer-associated thrombosis and are recommended as first-line therapy in clinical guidelines. Non-vitamin K oral antagonists are yet to be evaluated against low molecular weight heparin for this indication. Nevertheless, a perception that patients favor oral anticoagulants over injections may lead to an increased prescribing of warfarin or non-vitamin K oral antagonists despite the evidence gap. There has been no evaluation of cancer patient preferences for anticoagulants and whether such an evidence gap is an acceptable trade-off for patients prescribed orals. We conducted a study to assess what features are most important to CAT patients regarding their choice of anticoagulant. Two modules were applied: Initial in-depth interviews with 9 patients diagnosed with cancer-associated thrombosis, and thereafter quantitative research, where a further 100 patients completed a choice-based-conjoint exercise, where 15 different scenarios were presented to identify the most important attributes of an anticoagulant. Seventy percent of the patients were treated with injected medication (low molecular weight heparin) and 30% with oral medications. Patients most valued an anticoagulant with minimal interference with their cancer treatment (39%), low thrombosis recurrence rate (24%), and low risk of major bleed (19%). Preference for oral administration over injection had moderate importance (13%). The results show that patients prefer an anticoagulant that does not interfere with their cancer treatment, suggesting the primacy of the cancer disease over venous thromboembolism in these patients. Patients also favor efficacy and safety over convenience of route of administration.

Introduction

Venous thromboembolism is a common complication of the cancer journey and exacerbated by surgery, chemotherapy and disease progression.[1] The treatment of cancer associated thrombosis (CAT) by anticoagulation is likewise more complex than in non cancer patients since there is an increased risk of bleeding and recurrent VTE.[2,3] Furthermore, both bleeding and thrombotic risks are likely to fluctuate over time, especially in patients receiving chemotherapy or those with a progressive disease.[4] The use of warfarin for this indication is particularly challenging in many patients receiving chemotherapy due to drug-drug interactions rendering the INR unstable.[4] Clinical guidelines recommend low molecular weight heparins (LMWH) as the first-line treatment of CAT, since it has demonstrated superiority over warfarin efficacy with respect to preventing recurrent VTE without an increase in bleeding complications.[5-7] In addition, LMWH has fewer drug-drug interactions than warfarin, and rarely requires monitoring.[8] The last five years has seen the introduction of new oral anticoagulants including the oral factor IIa inhibitor dabigatran and the factor Xa inhibitors rivaroxaban and apixaban.[9-11] These non-vitamin K antagonist oral anticoagulants, collectively known as NOACs, have demonstrated non-inferiority with respect to warfarin for the treatment of conventional VTE. Requiring neither monitoring nor dose adjustments, and with significantly fewer drug-drug interactions, the NOACs are an attractive alternative to warfarin.[12] However, there are insufficient data to recommend NOACs as a first-line treatment of CAT since they have not been evaluated against LMWH, the current gold standard. One post-hoc subgroup analysis of cancer patients suggested rivaroxaban to be as effective as warfarin, but the patients studied had markedly better prognostic indices and fewer thrombotic risk factors than the populations in the LMWH studies.[13]

The 9th edition of the American College of Chest Physicians (ACCP) antithrombotic guidelines included a systematic review of patient values and preferences in decision making for antithrombotic therapy.[14] The authors identified limited data specific to the treatment and secondary prophylaxis of CAT. One qualitative paper on patients with advanced cancer reported LMWH to be preferable to warfarin, which was associated with frequent complications and an increased need for monitoring. However, the interviewed patients had only been receiving LMWH for a mean of forty-two days, which is perhaps an insufficient amount of time to evaluate the impact of six months anticoagulation.[15]

Two qualitative studies conducted on similar populations have since been published.[16,17] Both studies suggested patients found the experience of a symptomatic VTE extremely distressing and, in this context, LMWH was found to be an acceptable intervention.

Despite the established evidence-base supporting LMWH as the first-line therapy in the treatment of CAT and the qual-

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itative data supporting its use, it is possible that some patients may prefer an oral anticoagulant to a LMWH purely because it avoids a daily injection, even if such therapy brings with it a theoretical reduction in efficacy. To date, it is unknown whether this suggestion is a true representation of cancer patients' views or whether such patients may accept a degree of trade-off between convenience and efficacy.

Conjoint analysis surveys offer an empirical solution to estimate a patient's willingness to accept such trade-offs, and therefore to assess the importance patients place on treatment attributes that drive their preference. To our knowledge, to date there has been no evaluation of the attributes that form the basis of cancer patients' VTE treatment preferences.

We therefore undertook a study to identify and evaluate the values and preferences of patients with CAT regarding anticoagulant treatments using a conjoint methodology, and to assess their potential influence on future prescribing practices.

Methods

Study design

This preference based study was designed in accordance with, and in adherence to, the applicable standard for opinion research: ISO 20252.[18] The conduct of the study and primary analysis of data was carried out independently by Kantar Health in line with ISO 20252.

A choice-based conjoint (CBC) methodology was chosen to establish the most important attributes of anticoagulants when treating CAT, and the degree of importance placed on each one. This is an established method of identifying patient preferences and has been undertaken across a breadth of disease populations.[19-21] It comprised an initial qualitative component followed by a quantitative evaluation. Participants meeting the inclusion criteria were sequentially recruited through participating primary care and oncology centers and via patient associations in Germany and the United Kingdom (UK). Patients were eligible if they met the following criteria:

- Histologically confirmed cancer
- Receiving ongoing treatment for cancer (chemotherapy and or radiotherapy)
- Radiologically confirmed symptomatic deep vein thrombosis (DVT) and/or pulmonary embolus (PE)
- Receiving anticoagulation for their diagnosed DVT and/or PE
- Receiving anticoagulation for no more than six months.

Qualitative module

Nine CAT patients (5 from Germany, 4 from the UK) were interviewed about their anticoagulation experiences in order to establish a framework for the generation of attributes within the main CBC module. These are discussed in the results section.
Interviews were conducted at home, and lasted an average of 45 minutes.

Quantitative module

One hundred patients (Germany n=50, UK n=50) participated. Tasks were completed independently, following an initial introduction by the interviewer.

The attributes and attribute levels used (Table 1) were developed by the study steering committee based on the results of the qualitative module and available clinical trial data for currently used anticoagulants. The conjoint part of the interviews took no more than 15 minutes to ensure reliable answering behavior without overloading the respondent.[21] Choice tasks were computer-generated following the guidelines of the Sawtooth Software Technical Paper.[22] Based on sample size, number of attributes and attribute levels, 15 scenarios were developed. Ten different computer-generated versions of the conjoint exercise (each containing the 15 scenarios) were used to guarantee the CBC design was well balanced across all respondents.

In each scenario, the patient was asked to choose their preferred treatment option: scenarios consisted of 3 treatment options (Table 2). Patients were asked: "Imagine now that you have received the diagnosis of a blood clot. Your physician offers you treatment option A, B, or C. Which of the treatment options would you choose?" Estimates to determine the part-worth utilities were derived by a hierarchic Bayes regression based on a mixed multinomial logit model.[23] Considerations on sample size were based on measures of convergence of estimations: overall sample size was approached to allow preferences to be estimated with a precision of ± 2%, recommending an overall sample size of n=100, thus the final analysis was based on 100 patients.

Table 1. Attributes and levels of the CBC design.

Attributes	Levels
Efficacy (risk of new / recurring blood clot)	
1	New blood clot in 9 out of 100 patients
2	New blood clot in 13 out of 100 patients
3	New blood clot in 17 out of 100 patients
Risk of minor bleeding (e.g. bruising, nose bleeds)	
1	Minor bleeding every day
2	Minor bleeding once a week
3	Minor bleeding less than once a month
Risk of major bleeding (e.g. requiring transfusion, hospitalization)	
1	Major bleeding in 2 out of 100 patients
2	Major bleeding in 4 out of 100 patients
3	Major bleeding in 7 out of 100 patients
Administration form	
1	Injection under the skin
2	Tablet
Interference with cancer treatment (e.g. requiring postponement of surgery)	
1	No interference
2	Interference with cancer treatment in 4 out of 100 patients
3	Interference with cancer treatment in 8 out of 100 patients
4	Interference with cancer treatment in 15 out of 100 patients
Frequency of administration	
1	Once daily
2	Twice daily
3	Change from twice daily to once daily after 3 weeks of treatment initiation
Monitoring through blood tests (with potential dose adjustment)	
1	No monitoring
2	Monitoring required once a week
3	Monitoring required only once after 3 weeks of treatment initiation

Additional data were elicited from patients regarding their cancer/VTE history, the importance placed on doctor recommendations for type of anticoagulants and issues around food restrictions during medical treatment.

Results

Patients' characteristics

The characteristics of participants are summarized in Table 3. The patient population studied was predominantly female, with an average age of 57 years (the UK study population was significantly older than that in Germany). It is noteworthy that 41% of patients had stage IV cancer disease (in the UK significantly more stage IV patients were included than in Germany, 52% *vs.* 30%, respectively). Time from diagnosis of VTE varied from 1 month prior to the study (or more recent) to up to 12 months prior to the study, with an even distribution over time in the patient sample. Almost half of the patients (46%) were diagnosed up to 3 months prior to the study. Interestingly, in Germany significantly more patients (32%) were diagnosed between 6 and 12 months prior to the study, compared to the UK (16%). Almost two thirds of patients (61%) had been diagnosed with a deep vein thrombosis (DVT), with pulmonary embolism (PE) being relatively more frequent in the UK patient sample. The majority of patients were taking injected anticoagulants (70%), with a significantly higher proportion in the UK (90%) than in Germany (50%).

Qualitative component

The main finding of the qualitative research was that, whilst patients consider the efficacy and safety of the anticoagulant as a prerequisite, they were more concerned about interactions between the anticoagulant and other medications (particularly the cancer therapies), resulting in anxiety regarding drug-drug interactions. The results of this research served well as a framework for the design of the CBC to be used in the main quantitative phase.

Choice Based Conjoint (CBC) analysis and patient preferences

Based upon the qualitative exercise, the following attributes were considered:

1. Efficacy (risk of new / recurring blood clot)
2. Risk of minor bleeding (e.g. bruising, nose bleeds)
3. Risk of major bleeding (e.g. requiring transfusion, hospitalization)
4. Administration form
5. Interference with cancer treatment (e.g. requiring postponement of surgery)
6. Frequency of administration
7. Monitoring through blood tests (with potential dose adjustment)

Table 2. Example of a choice task.

	Treatment A	Treatment B	Treatment C
Please imagine now that you have received the diagnosis of a blood clot. Your physician offers you treatment options A, B, or C. Which of the treatment options would you choose?			
Efficacy (risk of new / recurring blood clot)	New blood clot in 9 out of 100 patients	New blood clot in 13 out of 100 patients	New blood clot in 17 out of 100 patients
Risk of minor bleeding (e.g. bruising, nose bleeds)	Minor bleeding once a week	Minor bleeding everyday	Minor bleeding less than once a month
Risk of major bleeding (e.g. requiring transfusion, hospitalization)	Major bleeding in 2 out of 100 patients	Major bleeding in 7 out of 100 patients	Major bleeding in 4 out of 100 patients
Administration form	Injection under the skin	Tablet	Tablet
Interference with cancer treatment (e.g. requiring postponement of surgery)	No interference	Interference with cancer treatment in 15 out of 100 patients	Interference with cancer treatment in 8 out of 100 patients
Frequency of administration	Once daily	Twice daily	Change from twice daily to once daily after 3 weeks of treatment initiation
Monitoring through blood tests (with potential dose adjustment)	Monitoring required once a week	No monitoring required	Monitoring required only once after 3 weeks of treatment initiation

Table 3. Patients' characteristics.

	Total	Country Germany	UK
N. of respondents	100	50	50
Age (average)			
Age	57	53*	61
Gender			
Female	55	52	58
Male	45	48	42
Stage of cancer disease			
Stage I-III	57	66	48
Stage IV	41	30*	52
Don't know	2	4	0
Time since VTE diagnosis			
1 month ago or more recent	20	14	26
More than 1 month to 3 months ago	26	26	26
More than 3 months to 6 months ago	30	28	32
More than 6 months to 1 year ago	24	32*	16
Location of blood clot			
In the leg (DVT)	61	68	54
In the lung (PE)	35	28	42
In the leg and in the lung	4	4	4
Administration form of current VTE medication			
Tablet	30	50*	10
Injection under the skin	70	50*	90

*Data expressed in percentage (%) of respondents. *Significance difference between countries (two-tailed t-test, 90% confidence interval).*

The relative importance of attributes is presented in Table 4. The attribute with the highest relative importance for patients was the interference with cancer treatment (39%), followed by efficacy of the VTE treatment (24%), and the risk of major bleeding (19%). The administration form of the VTE treatment seems to have moderate importance (13%), whereas risk of minor bleeds (2%), monitoring through blood tests (2%), and frequency of administration of the VTE drug (1%) are of minor relevance.

In the current conjoint analysis, the part-worth utility values (Figure 1) are important indicators of the effect of the attribute levels on the preference for VTE treatment. Results show that no interference with cancer treatment is by far the most desirable level, but that a minor interference of 4 in 100 patients might still be accepted. Higher rates of interference with cancer treatment have a negative effect on patient preference. As for efficacy, the lowest rate of recurrence of VTE is the most acceptable (9 in 100 patients at risk of a new blood clot), but also 13 patients out of 100 might be accepted, even with a major drop in utility. The lowest risk of a major bleeding (2 in 100 patients) has the highest utility for patients, but a risk of 4 in 100 patients might also be accepted, again with a major drop in utility.

Regarding administration form (the fourth most important attribute), a clear preference for tablet over injection can be observed. The frequency of administration plays a minor role in influencing patient preference, with once daily, or a change from twice daily to once daily after 3 weeks having a small positive impact on patient preference.

Minor bleeds have a minor impact on patient preference, with a frequency of less than once a month being the most acceptable. Also, the need for monitoring through blood tests is of minor relevance for patients: although no monitoring at all was the preferred option for patients.

After completion of the conjoint exercise, two further aspects related to the medical treatment of VTE (the importance of doctor's recommendation for a specific VTE medication, and the importance of having no food restrictions due to the medical treatment) were ranked by importance on a 5-point scale (Table 5). 58% of patients reported that a doctor's recommendation for a specific VTE medication is very important for them. This was especially important in the UK (74%). On the other hand, food restrictions resulting from VTE treatment did not appear to be highly rated, with only 7% of patients considering a lack of treatment related food restrictions to be very important (12% in the UK *vs.* 2% in Germany).

Discussion

Clinical guidelines have recommended LMWH as the first-line treatment of CAT for over ten years. Despite this, 30% of our study participants were prescribed oral (VKA or NOACs) anticoagulants, suggesting that treatment decisions are not based on clinical guidelines or efficacy and safety data alone. Whilst poor compliance with VTE clinical guidelines is not a new phenomenon, the reasons are not fully understood.[24,25] Specific to CAT, and despite qualitative data to the contrary, there is an ongoing perception that LMWH is unacceptable or burdensome to patients.[16,26,27] Whilst it is important to offer patients a choice in their anticoagulation treatment, it must be with the caveat that such a choice is informed by data and that preferences for certain

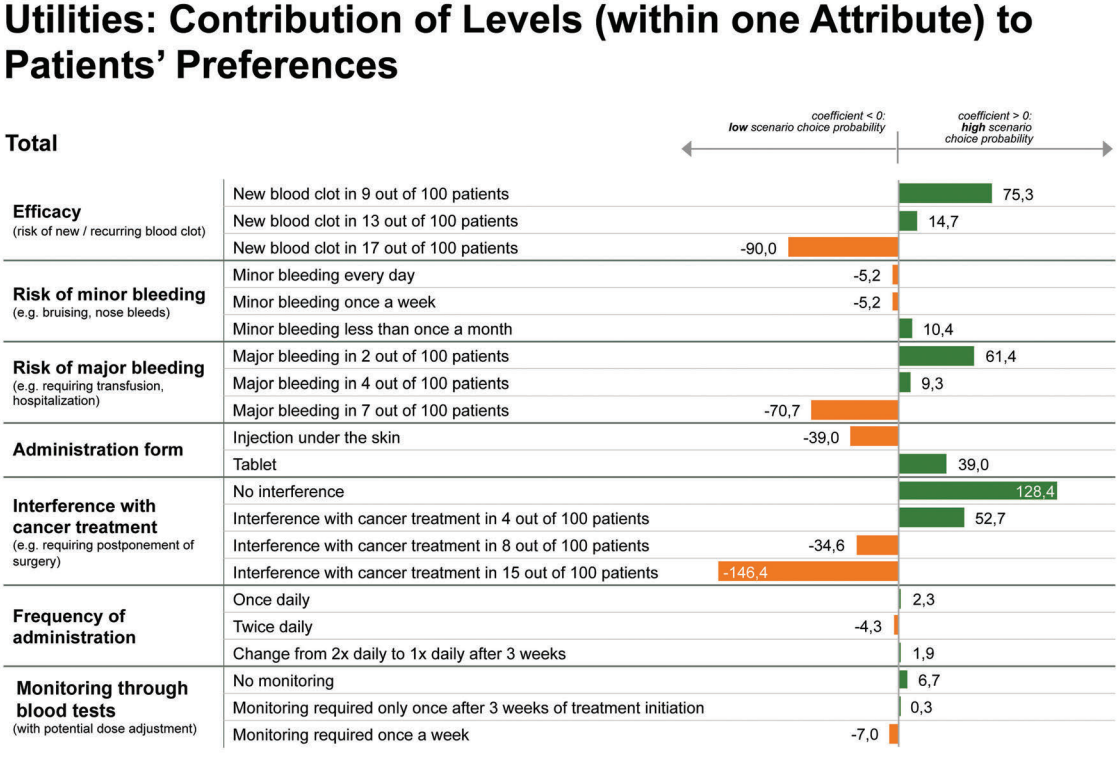

Figure 1. Effect of attribute levels on preference for VTE treatment: part-worth utilities.

attributes may confer a degree of trade-off.

In this study we not only explored which attributes of VTE treatment are most relevant to cancer patients, but also identified the degree of comparative importance which patients place on each therapy attribute. Patients reported that the three most important features of their anticoagulation were, in order of preference: that it did not interfere with or delay their cancer treatment; that it had a low VTE recurrence and a low major bleeding rate. Administration form was the fourth most important attribute, with a clear preference for oral administration over injection, as shown by the part-worth utilities. This gives a valuable insight into patient priorities at this stage of their cancer journey and has several implications for the treatment of CAT. Firstly, it highlights that the diagnosis of VTE must be considered holistically in the context of a patient's overall cancer journey. As such, anticoagulation needs to be managed in close communication with the patient's oncology team. Secondly, it strongly implies that patients perceive themselves as cancer patients first and VTE patients second, and therefore prioritize the absence of interruption of their cancer treatment above any other attribute. Finally, as suggested in previous qualitative research, participants strongly favored efficacy and safety over convenience of anticoagulation administration. Whilst, at face value, patients would prefer a tablet to an injection, this rests on the premise that both options had a minimal impact on the patient's cancer treatment whilst exhibiting similar efficacy and safety profiles.

In considering how these results inform the clinician, one needs to consider the published data on each of the anticoagulants. With respect to interference with cancer treatments, LWMHs have very few interactions with commonly used chemotherapies and supportive drugs. VKA/warfarin has many drug-drug interactions and, as it takes 3 days or more to start/stop, it may also delay surgery. Of the NOACs, rivaroxaban, dabigatran and apixaban interact with inhibitors of P-glycoprotein such as cyclosporine, lapatinib, nilotinib, sunitinib, imatinib, tamoxifen, and taxol. In addition, rivaroxaban and apixaban may interact with CYP3A4 inducers such as dexamethasone, adriamycin and vinblastine.[28] There have been no clinical trials comparing any of the NOACs with the

Table 4. Relative importance of VTE treatment attributes in % (obtained from the CBC).

Attribute	Relative importance in % (Total n=100)
Interference with cancer treatment (e.g. requiring postponement of surgery)	39
Efficacy (risk of new / recurring blood clot)	24
Risk of major bleeding (e.g. requiring transfusion, hospitalization)	19
Administration form	13
Monitoring through blood tests (with potential dose adjustment)	2
Risk of minor bleeding (e.g. bruising, nose bleeds)	2
Frequency of administration	1

Table 5. Importance of further aspects related to treatment of VTE.

My doctor's recommendation for a specific medication to treat my blood clot is...

Percentage (%) of respondents

	Total	Germany	UK
N. of patients	100	50	50
Very important	58	42	74
Important	36	50	22
Neutral	5	8	2
Not important	1	–	2
Not important at all	–	–	–

To have no food restrictions (i.e. not being allowed to eat certain food) due to the medical treatment of my blood clot is…

Percentage (%) of respondents

	Total	Germany	UK
N. of patients	100	50	50
Very important	7	2	12
Important	19	16	22
Neutral	29	38	20
Not important	25	22	28
Not important at all	20	22	18

LMWHs in the treatment of CAT. Whilst the emerging data from cancer subgroup analyses favor NOACs over warfarin, it would be premature to consider NOACs to be as effective as LMWHs until a direct comparison in a representative cancer population has been reported.

It is of interest to note that 30% of participants, by receiving oral anticoagulants, were thereby being treated suboptimally and contrary to the attribute values expressed in the study. The reasons for this are not clear. However, with 94% of participants stating their doctor's specific recommendation of anticoagulant to be "important" or "very important," it would be reasonable to assume the prescribing decision was strongly influenced by the doctors. A recent German study exploring physicians' preferences for anticoagulation in CAT suggested oncologists believed the requirement for a patient or carer to administer a LMWH was an important factor in reducing adherence to this drug.[25] Our data directly challenges this perception and supports the assertion that the views of patients should not only be considered, but actively sought out in planning therapies.[26] Moreover, rather than relying on intuition on which to base expectations of patient preferences, the evidence base should be given due consideration. As such, familiarity with clinical guidelines must coincide with a consideration of preferences as expressed by patients.

There are limitations in this study. Ideally an evaluation of patient preferences would have best taken place as an embedded study within a randomized trial comparing LMWH with an oral anticoagulant. Since participants were recruited having already commenced anticoagulation, it is possible that their experiences with their own treatment may impact on their preferences. With the majority of participants receiving LMWH, it is possible that this introduced selection bias which down-valued the importance attributed to the administration form of treatment. However, it could equally be argued that if injections were unacceptable, a greater sample of patients receiving LMWH would disproportionately bias the results in favor of orals. Nevertheless, there was a consistency of views on LMWH and orals across patients with early or late stage cancers and in those who have been treated for more or less than a month. Furthermore, there was no association between participant views and severity of the experienced VTE. The populations were well matched for sex and represented a breadth of disease stages, VTE type and length of anticoagulation therapy. However, the average participant age was considerably lower than the average age of the cancer population and it is possible that some of the views may not represent issues specific to the elderly.[27] Despite the described limitations, the strength of importance attributed to "interference with cancer treatment" and "efficacy of the VTE treatment" is sufficiently greater than "administration form of the VTE treatment" in order to assure the wider validity of the results.

The importance of patient preference should not be underestimated and, in complex clinical situations such as CAT, the views of the cancer patient regarding their treatment are essential. Our study has identified that what patients value most is an anticoagulant that interferes as little as possible with their cancer treatment. It also clearly demonstrates that they rate efficacy and then safety over convenience, whether it be the route of delivery, administration frequency or the need for monitoring. In addition to international guidelines that recommend LMWHs as a first-line treatment of CAT, our data strongly suggests this class of drugs possess the attributes most valued by patients within the context of their cancer journey. Until such time that NOACs demonstrate non-inferiority to LMWHs in the cancer setting, it would be incorrect to use these drugs on the basis of patient preference or quality of life. Even if that is demonstrated, considering the potential for drug-drug interactions with some chemotherapeutic and supportive medicines, it is unlikely that NOACs could fully replace LMWHs if patients' views are to be given the due consideration they deserve.

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