RESEARCH PROTOCOL

Towards cancer patient empowerment for optimal use of antithrombotic therapy at the end of life (SERENITY Physician Survey)

Understanding European patterns of deprescribing antithrombotic medication during end-of-life care in cancer patients

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Coordinating Investigator: Prof. Stavros Konstantinides, MD, PhD

Center for Thrombosis and Haemostasis

University Medical Center Mainz

Langenbeckstraße 1, 55131 Mainz, Germany

Email: stavros.konstantinides@unimedizin-mainz.de

Phone: +49 (0)6131 17-8382

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Abbreviations

ATT	Antithrombotic therapy
DCE	Discrete choice experiment
DOAC	Direct oral anticoagulant
ECOG-PS	Eastern Clinical Oncology Group performance status
eCRF	electronic case report form
FMR	Flash mob research
GDPR	European General Data Protection Regulation
LMWH	Low-molecular-weight heparin
VKA	Vitamin-K antagonist
VTE	Venous thromboembolism

1. Coordinating Investigator and sponsor representative

The Coordinating Investigator of this study is Prof. Stavros Konstantinides, MD, PhD, Center for Thrombosis and Hemostasis (CTH) of the University Medical Center of the Johannes Gutenberg University Mainz (UMCM), Germany, which acts as representative of the sponsor (Leiden University Medical Center, The Netherlands).

2. Definitions

2.1 Active cancer

Cancer diagnosed within the previous six months; recurrent, regionally advanced or metastatic cancer; cancer for which treatment has been administered within the past six months; or haematological cancer that is not in complete remission. Basal cell or squamous cell carcinoma of the skin are excluded from this definition.

2.2 End-of-life care

A patient is considered in end-of-life care in case of a confirmatory negative response of the healthcare professional to the question "Would you be surprised if this patient died in the next 6-12 months?", which is an accurate and widely used trigger for referring a patient to specialist palliative care.[1,2]

3. Background

Deprescribing (i.e., discontinuing medication) is an important part of palliative care to prevent polypharmacy, which is associated with increased risk of adverse drug events, drug-drug and drug-disease interactions, reduced functional capacity, multiple geriatric syndromes, medication nonadherence, and higher healthcare costs. One of the most widely used cardiovascular drug classes in cancer patients in a palliative setting are antithrombotics, including anticoagulant and anti-platelet agents. Antithrombotic drugs, e.g., (DOACs), low-molecular-weight heparins (LMWH), vitamin-K antagonists (VKA) and so-called antiplatelet agents (such as acetyl salicylic acid and P2Y12 inhibitors), are indicated in patients with prosthetic heart valves, in those with venous thromboembolism (VTE), for stroke prevention in atrial fibrillation as well as in patients with established atherosclerotic cardiovascular disease (such as myocardial infarction, stroke, or peripheral artery disease). Most patients have been receiving these drugs chronically before their cancer was diagnosed, whilst others are being prescribed them in order to treat or prevent cancer-associated thrombosis. Obviously, decisions on deprescribing antithrombotics heavily depend on the indication of the antithrombotic drug in addition to patient and healthcare professional preferences and experience, and on the estimated life expectancy of the patient.

Understanding current patterns of management of antithrombotic therapy (ATT) as well as the rationale and preferences behind these patterns is crucial for improving clinical practice. Since deprescribing patterns and rationale may largely differ across countries, relevant data at a large scale is needed to fully understand and appreciate the relevant decision processes.
The insights gained in this study are a first step towards the development of a clinical decision tool supporting decisions on ATT in cancer patients.

4. STUDY OBJECTIVE(S)

- To explore and describe current European practice patterns with regard to the use of ATT in end-of-life care of cancer patients following 'flash mob research (FMR)' methodology.
- To evaluate and understand the processes and factors that inform decisions concerning the deprescription of ATT in the last year of life of cancer patients receiving ATT via a discrete choice experiment (DCE) among healthcare professionals, who deal with end-of-life care in cancer patients, or prescribe such medication to cancer patients.

5. STUDY DESIGN

International cross-sectional qualitative (flash mob research) study conducted as survey among healthcare professionals across Europe.

6. STUDY POPULATION

SERENITY aims to enrol healthcare professionals from various institutions across Europe, who deal with end-of-life care in cancer patients, or prescribe ATT to cancer patients.

These will involve general practitioners, palliative care specialists, nursing home physicians, geriatrists, vascular medicine specialists, oncologists, haematologists, pulmonologists, cardiologists, neurologists, and vascular surgeons with equal gender representation and distribution of experienced versus less experienced (young professionals) physicians.

7. COUNTRIES INVOLVED

The survey will be conducted among healthcare professionals mainly from the eight European countries represented in the SERENITY consortium:

- Denmark
- France
- Germany
- Italy
- The Netherlands
- Poland
- Spain
- United Kingdom

Due to promotion of the project via international networks and social media (s. section 10), we also expect participants from other countries and regions. Depending on the number or proportion of participants from outside Europe, these will be evaluated separately.

8. (TARGETED) NUMBER OF SUBJECTS

The study aims to generate data from a total of at least 800 healthcare professionals (i.e., either 100 each from the countries listed in section 7 or corresponding participant numbers from additional countries) and up to 2400 anonymised patients, considering that each healthcare professional will be asked to describe actual decisions and anonymous data obtained from medical charts in one to three consecutive patients meeting the definitions below at the time of consideration.

9. SAMPLE SIZE CONSIDERATIONS

In view of the FMR design, there is no formal predetermined sample size. In principle, a successful FMR should include a large sample size for reliable and generalizable conclusions.[3]
For DCE, the required sample size (N) depends on the number of choice tasks (t), the number of alternatives (a), and the number of analysis cells (c) according to the following equation: $N > 500c/(t \times a)$. Where DCE studies usually require only 100 responses, the minimum sample size to show that deprescribing ATT in a certain setting is preferred over continuing the ATT with a statistical power β of 80% and a 2-sided significance level α of 0.05 is 190. This is well below the planned number of 800 observations.[4]
We will monitor the number of preregistered participants and adjust the recruitment plan based on the actual accrual.

10. DESCRIPTION OF STUDY PROCEDURES

The study will be divided into three phases: the recruitment phase, the FMR-phase and the data analysis phase.
In the **recruitment phase**, the national coordinators of the project group will advertise the study through traditional professional networks as well as their social media channels. Information about the study will be distributed via personal communication, relevant scientific organisations and journals, and via social media. The healthcare professionals of interest will be invited to pre-register for study participation so they can be assigned a unique link to the electronic case report forms (eCRF). During the preregistration, characteristics of the pre-registrants will be checked (i.e., sex, age, profession, years of experience, the country where they are practicing, and the number of cancer patients in palliative care whom they care for on a yearly basis).

In the **FMR phase**, all preregistered participants will be asked simultaneously to complete the survey using the *Castor electronic data capture platform* within seven days.

The survey will be divided into the following sections:

a) **General questions** regarding end-of-life care (*e.g.*, "When do you consider a patient in end-of-life care?") and (de)prescription of antithrombotic medication to cancer patients during end-of-life care (e.g., "Have you ever considered deprescribing antithrombotic medicine?").

b) A sequence of **choice scenarios** *i.e.*, hypothetical scenarios that vary with regard to several characteristics (**attributes**; e.g., bleeding risk, thrombotic risk). Attributes will be further specified by varying choice levels (**attribute levels**; e.g., low or high bleeding risk), which are considered relevant for the decision on continuation or stopping antithrombotic medication in the patient population studied. In accordance with the discrete choice experiment (DCE) methodology, participants will be asked to select the healthcare intervention (i.e., either continuation or discontinuation of the antithrombotic therapy) that in their opinion would benefit the patient the most within each choice set.

c) Participants will be asked to share **actual case decisions** they made in a maximum of three consecutive cases involving patients with active cancer, who were considered to receive end-of-life care. Fully anonymised data of the patients (sex, age category, primary tumour, tumour

stage, time point in the course of the disease when the conversation about discontinuation of ATT took place, type and indication of ATT) will be collected via multiple-choice questions.

11. Regulatory and legal requirements

As confirmed by the responsible ethics committee, due to the non-interventional nature of this study and since no personal data of patients will be recorded or processed, professional advice and/or submission of this protocol to the ethics committee before commencement of the survey is not required.

Data privacy of participating healthcare professionals will be taken into account in accordance with the European General Data Protection Regulation (GDPR). With the exception of the e-mail addresses of survey participants for the purpose of forwarding the survey link and information on survey launch and completion, no personal data will be stored or processed. As detailed in the information for prospective participants, participants implicitly consent to the use of their e-mail addresses for said purposes by pre-registering.

Data on patients will be sufficiently coarsened such that no identification will be possible. As an additional security measure, this part of the survey will be exported and analyzed separately from the other two sections (s. section 9 above).

12. Study duration and timelines

The total duration of this study is expected to be twelve months.
The recruitment phase, in which the healthcare professionals will be asked to preregister for study participation, will start in March 2023. One week before the study is open for data entry, preregistered healthcare professionals will receive an email with details on the study launch. Data collection (i.e., the FMR phase) will start in the first week of May 2023 and take seven days. Data analysis and publication of results will be conducted from June to October 2023.

13. Statistical analysis

The main analysis of the FMR will be descriptive. Results will be presented for all predefined subgroups and with corresponding 95% confidence intervals. Responses to the DCE will be used to generate preference coefficients for each level of each attribute using random parameters logit regressions, where preference weights represent the relative contribution of the attribute level to the value that participants assigned to an alternative management decision.
The attribute-level coefficients will be expressed as mean preference weights and standard deviations of the mean preference weights, each with appropriate 95% confidence interval. The relative importance of each attribute will be expressed using the within-attribute difference in preference weights as a percentage of the total difference in preference weights across all attributes. For the coefficients, the algebraic sign (positive or negative) of a coefficient reflects whether respondents feel positive or negative with regard to deprescribing. The value of a coefficient indicates the relative importance of the corresponding attribute. The statistical significance of a coefficient ($p \leq 0.05$) indicates that the respondents underline the importance of the attribute within the options in the DCE.

14. REFERENCES

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4. de Bekker-Grob EW, Donkers B, Jonker MF, et al. Sample Size Requirements for Discrete-Choice Experiments in Healthcare: a Practical Guide. *Patient.* 2015;8(5):373-384.

15. APPENDICES

15.1 Survey: Questions for pre-registration

1. Please select your country (*Denmark; France; Germany; Italy; The Netherlands; Poland; Spain; United Kingdom*)
2. Please select your age category (*25-34; 35-44; 45-54; 55-64; 65 or older*)
3. Please select your sex (*male; female; other*)
4. Please select your profession (*general practitioner; palliative care specialist; nursing home physician; geriatrist; vascular medicine specialist; oncologist; haematologist; pulmonologist; cardiologist; neurologists; vascular surgeon*)
5. Please select the professional experience group that matches your years of experience (*< 5 years; 5-10 years; 11-15 years; 16-20 years; 21 or more*)
6. Please provide an estimate on the number of patients you see/treat with active cancer each year, who are considered to be in end-of-life care.
   This number is important for the upcoming data collection.

15.2 Survey: General questions

1. When do you consider a patient in end-of-life care? If the life expectancy is:

A. < 1 year B. < 6 months C. < 3 months D. < 2 weeks

2. When a patient is considered to be in end-of-life care, I **XXX** prescribe antithrombotic medication upon the diagnosis of a thrombotic complication.

A. never B. sometimes C. often D. always

3. Have you ever deprescribed (i.e., terminated) antithrombotic medication in end-of-life care of cancer patients?

A. no B yes

In case of no, the participant will not be redirected to certain questions.

4. When a patient is considered to be in end-of-life care, I **XXX** deprescribe antithrombotic medication.

A. never B. sometimes C. often D. always

5. Give an estimate of the frequency per year that you <u>consider</u> deprescribing antithrombotic medication in patients, considered to be in end-of-life care:
XXX /year

6. Give an estimate of the frequency per year that you <u>actually</u> deprescribed antithrombotic medication in patients considered to be in end-of-life care:

XXX /year

7. Do you discuss deprescription of antithrombotic medication in patients at the end of life with colleagues?
   A. never B. sometimes C. frequently D. always

8. Please indicate what factors determine whether you prescribe antithrombotic medication in patients considered to be in end-of-life care.

9. Please indicate what factors determine whether you deprescribe antithrombotic medication in patients considered to be in end-of-life care.

15.2.1 Examples of factors relevant to questions 8 and 9

1. Antithrombotic medication:
   - DOAC or VKA
   - LMWH (therapeutic)
   - Antiplatelet agent
2. Indication for antithrombotic medication:
   - Atrial fibrillation
   - Treatment of acute VTE event or prevention of (recurrent) VTE
   - Mechanical heart valves
   - Other indication
3. Bleeding risk:
   - Low
   - High
4. Thrombotic risk:
   - Low
   - High
5. Sex:
   - Female
   - Male
   - Other
6. Age:
   - < 40 years
   - 40-75 years
   - > 75 years
7. Patient's performance status:
   - Eastern Clinical Oncology Group performance status (ECOG-PS) grade 0-2 [*Oken MM et al. Am J Clin Oncol. 1982*]
   - ECOG-PS grade ≥ 3
8. Patient prognosis:
   - < 6 months
   - < 3 months
   - < 2 weeks

9. Patient preference:
- Stop antithrombotic treatment
- Continue antithrombotic treatment

10. Other
Free text

15.3 Survey: Examples of potential scenarios for the DCE

a) Variable ATT – High thrombotic risk – High bleeding risk – ECOG-PS Grade ≥ 3

Attributes	Scenario 1	Scenario 2	Scenario 3
ECOG-PS	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3
Thrombotic risk	High	High	High
Bleeding risk	High	High	High
Antithrombotic medication	DOAC or VKA	LMWH (therapeutic)	Antiplatelet agent

b) Variable ATT – high thrombotic risk – low bleeding risk – ECOG-PS Grade ≥ 3

Attributes	Scenario 1	Scenario 2	Scenario 3
ECOG-PS	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3
Thrombotic risk	High	High	High
Bleeding risk	Low	Low	Low
Antithrombotic medication	DOAC or VKA	LMWH (therapeutic)	Antiplatelet agent

c) Variable ATT – low thrombotic risk – high bleeding risk – ECOG-PS Grade ≥ 3

Attributes	Scenario 1	Scenario 2	Scenario 3
ECOG-PS	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3
Thrombotic risk	Low	Low	Low
Bleeding risk	High	High	High
Antithrombotic medication	DOAC or VKA	LMWH (therapeutic)	Antiplatelet agent

d) Variable ATT – low thrombotic risk – low bleeding risk – ECOG-PS Grade ≥ 3

Attributes	Scenario 1	Scenario 2	Scenario 3
ECOG-PS	Grade ≥ 3	Grade ≥ 3	Grade ≥ 3
Thrombotic risk	Low	Low	Low
Bleeding risk	Low	Low	Low
Antithrombotic medication	DOAC or VKA	LMWH (therapeutic)	Antiplatelet agent

e) Variable ATT – high thrombotic risk – high bleeding risk – ECOG-PS Grade 0-2

Attributes	Scenario 1	Scenario 2	Scenario 3
ECOG-PS	Grade 0-2	Grade 0-2	Grade 0-2
Thrombotic risk	High	High	High
Bleeding risk	High	High	High
Antithrombotic medication	DOAC or VKA	LMWH (therapeutic)	Antiplatelet agent

f) Variable ATT – high thrombotic risk – low bleeding risk – ECOG-PS Grade 0-2

Attributes	Scenario 1	Scenario 2	Scenario 3
ECOG-PS	Grade 0-2	Grade 0-2	Grade 0-2
Thrombotic risk	High	High	High
Bleeding risk	Low	Low	Low
Antithrombotic medication	DOAC or VKA	LMWH (therapeutic)	Antiplatelet agent

g) Variable ATT – low thrombotic risk – high bleeding risk – ECOG-PS Grade 0-2

Attributes	Scenario 1	Scenario 2	Scenario 3
ECOG-PS	Grade 0-2	Grade 0-2	Grade 0-2
Thrombotic risk	Low	Low	Low
Bleeding risk	High	High	High
Antithrombotic medication	DOAC or VKA	LMWH (therapeutic)	Antiplatelet agent

h) Variable ATT – low thrombotic risk – low bleeding risk – ECOG-PS Grade 0-2

Attributes	Scenario 1	Scenario 2	Scenario 3
ECOG-PS	Grade 0-2	Grade 0-2	Grade 0-2
Thrombotic risk	Low	Low	Low
Bleeding risk	Low	Low	Low
Antithrombotic medication	DOAC or VKA	LMWH (therapeutic)	Antiplatelet agent

15.4 Survey: Questions on actual case decisions

In the following (multiple choice) questions, you will be asked to describe one to three actual cases of patients with active cancer, who were considered to receive end-of-life care, in which you considered deprescription of antithrombotic medication.

1. Please select the age category of the patient (*< 40 years; 40-75 years; 75 years or older*)
2. Please indicate the type of antithrombotic medication involved (*DOAC; VKA; LMWH (therapeutic); antiplatelet agent*)
3. Please select the indication of the antithrombotic medication (*atrial fibrillation; treatment of acute VTE-event, prevention of (recurrent) VTE; mechanical heart valves; other indication (free text)*)
4. Please indicate the patient's performance status (*ECOG-PS grade 0-2, ECOG-PS ≥ 3*)
5. Please indicate the estimated prognosis of the patient at the time of consideration (*< 6 months; < 3 months; < 2 weeks*)
6. Please specify the setting of the patient at the time of consideration (*at home without palliative care; at home with palliative care; at rehabilitation facility; at nursing facility; at hospice facility; in 'acute care' setting; other (free text)*).
7. Please select one or more of the attributes that played a role in your consideration of deprescribing the antithrombotic medication; multiple answers are possible (*type of antithrombotic* medication*; indication of the antithrombotic* medication*; bleeding risk; thrombotic risk; sex; age; patient's performance status; patient's preference; other (free text)).*
8. Did you decide to deprescribe the antithrombotic treatment? (*yes; no*)

9. If no:
   Which of the following attributes made you decide not to deprescribe the antithrombotic drugs? Multiple choices are possible.
   Experience with deprescribing: not enough; enough
   Symptom burden: high
   Burden of medication (administration): low
   Thrombotic risk: high
   Bleeding risk: low
   Antithrombotic medication indication: atrial fibrillation; acute VTE-event, prevention of (recurrent) VTE; mechanical heart valves; other indication (free text)
   Sex: male; female, other (selection to be made)
   Age: (< 40 years; 40-64 years; 65-74 years; 75 years or older)
   Patient's performance status: ECOG-PS 0-2
   Patient's prognosis: < 2 weeks; < 3 months; < 6 months (selection to be made)
   Patient's preference: continue antithrombotic treatment
   Other (free text)
10. If yes:
    Which of the following attributes made you decide to deprescribe the antithrombotic drugs? Multiple choices are possible.
    Experience with deprescribing: enough
    Symptom burden: low
    Burden of medication (administration): high
    Thrombotic risk: low
    Bleeding risk: high
    Antithrombotic medication indication: atrial fibrillation; acute VTE-event, prevention of (recurrent) VTE; mechanical heart valves; other indication (free text)
    Sex: male; female, other (selection to be made)
    Age: (< 40 years; 40-64 years; 65-74 years; 75 years or older)
    Patient's performance status: ECOG-PS grade ≥ 3
    Patient's prognosis: < 2 weeks; < 3 months; < 6 months (selection to be made)
    Patient's preference: stop antithrombotic treatment
    Other (free text)

    <u>Tumour-specific</u>

11. Please select the type of cancer (*breast; lung; upper gastro-intestinal (GI); lower GI; endocrine; genito-urinary tract; brain; haematological; skin (excluding squamous/basal cell carcinoma); combination (select more than one); other (free text)*
12. Please select the stage of cancer (*localized; regional; distant metastasis; not applicable*)
13. Please select the cancer treatment at the time of consideration/decision – multiple options possible (*none; surgery (in the previous 3 months); radiation therapy (in the previous month); chemotherapy (in the previous month); immunotherapy (in the previous month)*
14. Please select the line of cancer treatment (*first-line, second-line, third-line, fourth-line, not applicable*