'Recommendations for deprescribing of medication in the last phase of life: an international Delphi study'

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Title: 'Recommendations for deprescribing of medication in the last phase of life: an international Delphi study'

Running title: deprescribing in the last phase of life

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ABSTRACT

Context: Medications may become inappropriate for patients in the last phase of life and may even compromise their quality of life.

Objective: To find consensus on recommendations regarding deprescribing of medications for adult patients with a life expectancy of six months or less.

Methods: Experts working in palliative care or other relevant disciplines were asked to participate in this international Delphi study. Existing tools for deprescribing of medication in the last phase of life were integrated in a list of 42 recommendations regarding potential deprescription of various medication types. In two Delphi rounds, experts were asked to rate their agreement with each recommendation on a 5-point Likert-scale (strongly agree – strongly

disagree). Recommendations were accepted, if at least 70% of the experts (strongly) agreed, the interquartile range (IQR) was one or less, and less than 10% strongly disagreed.

Results: 47 experts from 10 countries participated (response rate 53%). In most cases (76%), consensus was reached on deprescribing recommendations for patients with a life expectancy of six months or less. The highest level of consensus was reached for recommendations on the deprescription of diuretics in case of decreasing fluid intake or increasing fluid loss, lipid modifying agents if prescribed for primary prevention, and vitamin K antagonists and direct oral anticoagulants in case of high bleeding risk.

Conclusion: A high level of consensus was reached on recommendations on potential deprescription of several medications for patients with a life expectancy of six months or less.

KEY MESSAGE

An international Delphi study resulted in high levels of agreement among experts on recommendations on potential deprescription of several medications for patients with a life expectancy of six months or less. These results can be helpful for physicians in medication management for patients in the last phase of life.

KEYWORDS

Delphi technique, deprescribing, medication discontinuation, last phase of life, palliative care

INTRODUCTION

For patients with a life-threatening disease, goals of care may change during the disease trajectory, from preventing or curing the disease to optimizing quality of life.[1] In the last phase of life, some interventions may become redundant or even harmful, as may be the case for various medications. These so-called potentially inappropriate medications (PIMs) are nevertheless frequently prescribed and continued in patients in the last phase of life.[2-5] Medications can become inappropriate for a number of reasons. For instance, patients' life expectancy may be shorter than the time needed for preventive medications to have their effect.[6] As a result, patients will only experience the potential burdens and side effects of the medications without any benefits. Such side effects may also involve increased healthcare related costs.[7, 8] In addition, medications can become contra-indicated as organ functions may change in the last phase of life.[9]

Until now, robust evidence to support medication discontinuation for patients in the last phase of life is largely lacking. One randomized clinical trial (RCT) found that it is safe and beneficial for patients' quality of life to stop statins in patients with advanced disease and a life expectancy of one year or less [10]. To support physicians in deprescribing, several guidelines and recommendations based on expert opinion have been published.[11-15] However, most of these recommendations focus on a specific disease or condition, such as cancer or frailty in elderly, without considering comorbidities and without defining the life expectancy for which deprescribing may be considered. In addition, guidance is lacking on the order of deprescribing when various medications are used for the same indication. Therefore, more guidance on deprescribing of medications in adult patients in the last phase of life is needed.

The primary aim of this Delphi study was to reach consensus on recommendations on deprescribing of medications for patients with a life expectancy of six months or less, involving an international and multidisciplinary panel of experts in palliative care and other medical disciplines, such as internal medicine and cardiology. The secondary aims were to develop recommendations on the monitoring of symptoms that may occur after deprescribing specific types of medication and, in the case of diabetes mellitus and hypertension, to prioritize which medications should be deprescribed first when several types of medication are used concurrently.

METHODS

Study design

A two-round Delphi study was conducted using the CREDES guidelines in palliative care: guidance on conducting and reporting Delphi studies.[16] Ethical approval was waived by the medical ethical review committee of the Erasmus MC (MEC-2019-0832).

Context

This Delphi study was conducted within the iLIVE project and its embedded iLIVE medication study.[17] The iLIVE medication study evaluates the effect of personalized medication alerts in the last phase of life. This Delphi study is aimed at substantiating these alerts.

Selection of experts

Experts for this Delphi study were recruited via the professional network of the research team of the iLIVE medication study. The inclusion criteria for the expert panel were:

1. physician or pharmacist specialized and working in palliative care and/or physician or pharmacist with expertise in deprescribing of medication based on their clinical experience or involvement in research,

OR

2. physician working in a relevant specific medical discipline and involved in the treatment of patients in the last phase of life (pain specialists, elderly care/geriatrics, endocrinology, cardiology/cardiovascular medicine, general practice, hematology, intensive care, nephrology, pulmonology).

Participating experts could indicate if they knew another expert who would be interested in filling out the questionnaire by providing the email address of the expert in an open text box at the end of the first questionnaire.

Delphi questionnaire

A systematic review (unpublished) on deprescribing of medication in the last phase of life was conducted [18], identifying eight relevant articles (appendix 1).[10-15, 19-20] Based on these articles, a list of 27 potentially inappropriate medication types was developed, resulting in 42 recommendations on deprescribing.

Experts participating in the Delphi study could rate to what extent they agreed with a recommendation on a 5-point Likert-scale (strongly agree – agree – undecided – disagree – strongly disagree).[21] Each recommendation was substantiated with relevant and corresponding literature.(Appendix 1) If experts disagreed with a recommendation for patients with a life expectancy of six months or less, they were asked to reassess their agreement for patients with a shorter life expectancy, i.e. a life expectancy of three months or less. In case they also disagreed with the recommendation in case of a life expectancy of three months or less, it was asked for a life expectancy of one month or less. If experts disagreed with a recommendation for patients with a life expectancy of one month or less, they could specify the reason for their disagreement in an open text box.

Furthermore, experts could also indicate if necessary information was not available for them to give their opinion on the recommendation or if they had insufficient experience to assess a recommendation. In case they answered 'I miss something', they could specify what they missed in an open text box.

In addition to the list of 27 recommendations on deprescribing, five recommendations were formulated about the monitoring of symptoms after deprescribing antihypertensive medication, antiplatelet therapy and anticoagulants, blood glucose-lowering medication, and medication for digestive problems. Furthermore, participants were asked to prioritize deprescription of different medication types for the treatment of hypertension, type 1 diabetes mellitus and type 2 diabetes mellitus.

The questionnaires were presented to the experts using the online survey software LimeSurvey and GemsTracker.[22, 23]

Study procedures

A pilot test was performed in December 2019 among six physicians from different countries (Sweden, Switzerland and the Netherlands). These physicians were not further involved in this Delphi study or in the iLIVE project. No adaptations were made of the original questionnaire after the pilot test. The experts participating in the Delphi study were asked to sign for informed consent to participate before the first round of the Delphi study commenced.

The first questionnaire was sent out in January 2020, and the second in April 2020. Both questionnaires were online accessible during one month via a link and a password. A maximum of two reminders were sent when the questionnaires were not completed. Each question had to be answered before the following question became available, except for the optional questions about the order in which antihypertensive medications or blood glucose lowering drugs could be deprescribed. Only experts who completed the questionnaire in the first round, were asked to participate in the second round. The questionnaire for the second round included

recommendations that were adapted based on the comments of the experts in the first round. The original recommendation and the anonymized open feedback of experts in the first round were also presented in the second round. Experts could provide feedback on removed recommendations from the first round in an open text box.

Open comments from the experts were analyzed by E.E. and E.G and discussed within the research team. Recommendations from the first Delphi round were revised, if necessary, based on the comments with respect to their wording, ordering and content. Proposals for adaptations were discussed within the research team before the second Delphi questionnaire was sent out.

Analysis

Consensus was considered to be reached if at least 70% of the participating physicians (strongly) agreed, the interquartile range (IQR) was one or less, and less than 10% of the experts strongly disagreed.[24, 25] The answers 'I miss something' or 'I have insufficient expertise to answer this question' were not used for the analysis of consensus.

Ratings of the order of deprescription of medications for hypertension and diabetes mellitus were assessed by calculating the mean and median rank of each type of medication. To assess the level of agreement, Kendall's coefficient of concordance (Kendall's W) was calculated.[26] Data were analyzed using IBM SPSS Statistics.[27]

RESULTS

In total, 98 experts were asked to participate for the first round of this Delphi study. Seventy professionals were approached via the professional network of the researchers and 28 were proposed by the experts participating in the first Delphi round. Nine experts were excluded due to different reasons (Figure 1). In total, 89 experts received the questionnaire. A flowchart of the

inclusion process is shown in Figure 1. A full overview of the Delphi process can be found in Figure 2.

Experts

Forty-seven experts from ten countries completed the questionnaire of the first round of the study (response rate 53%), 44 filled out the second questionnaire (response rate 96%) (Figure 1). Experts from ten different countries participated: 18 of the experts came from the Netherlands). In total, eleven medical specialties were represented. The small majority of the experts (n=28) had a background as palliative care consultant and worked in a single setting (n=28). Hospital (n=30) was the most common working setting (Table 1).

Recommendations about deprescribing of medication

In the first Delphi round, the experts agreed on 28 of the 42 recommendations (67%) for patients with a life expectancy of less than six months. Experts agreed on nine other recommendations, however, for patients with a shorter life expectancy. Five recommendations were removed after the first round based on the feedback of experts (Appendix 2). Eight recommendations from the first round on which there was no agreement for either life expectation, were adapted and included in the second round: for six of these experts agreed for patients with a life expectancy of 6 months or less (Figure 2). Experts agreed for one recommendation only for patients with a life expectancy of less than 3 months and another recommendation for patients with a life expectancy of less than 1 month. An overview of the recommendations and the percentages of consensus are listed in table 2.

Recommendations about monitoring

In the first Delphi round, consensus was reached on two recommendations regarding the monitoring of symptoms after deprescribing. The three remaining recommendations were

revised based on the experts' feedback and included in the second Delphi round, where all three reached consensus (Figure 2).

Experts advised to consider monitoring symptoms and biomarkers after deprescribing blood glucose lowering medications, antihypertensive medications, anticoagulants or medications for the digestive system. Active monitoring after the discontinuation of platelet aggregation inhibitors, does not have to be considered according to the experts (Table 3).

Recommendations on ranking deprescribing of medications

For antihypertensive medications, most experts (89%) agreed to first consider deprescribing central acting antihypertensive medication before considering the deprescription of the ACE-inhibitors / Angiotensin II blockers. For the peripheral alpha blockers, diuretics, beta-blocking agents and calcium channel blockers, the results were less conclusive. For patients with diabetes mellitus type 1, the majority of the experts (79%) agreed on considering to deprescribe short-acting insulins before long-acting insulins. When patients with diabetes mellitus type 2 use oral glucose lowering medications, experts agreed to first consider deprescribing these medications before deprescribing insulins (Table 4).

DISCUSSION

In this Delphi study, we developed recommendations on potential deprescription of various medications for patients in the last phase of life. The included medications were cardiovascular medication types and antithrombotic agents, especially those started to prevent long-term complications, blood glucose lowering medication types, medications for the digestive system,

medications for osteoporosis and the lower urinary tract. An international group of experts reached consensus on the majority of the developed recommendations for patients with a life expectancy of six months or less. The consensus-based set of recommendations presented and developed in this study may inform and support physicians in the process of deprescribing of medications in the patients' last phase of life.

Physicians are often reluctant to deprescribe medications for patients in the last phase of life, partly because of limited evidence on appropriate medication management in the last phase of life.[28] Research has already been conducted on medication management in elderly in the last phase of life. The innovative aspect of this Delphi study is that the medication recommendations are created focused on patients in the last phase of life, regardless of frailty or age.[13-15] The high degree of consensus reached in our study provides solid ground for deprescription policy, supporting physicians in considering the deprescription of PIMs and avoiding unnecessary and potentially harmful polypharmacy in the last phase of life. In the end, patients' quality of life may be improved as a result of adequate deprescription.[29]

Some recommendations on deprescription may seem obvious, such as 'consider deprescribing diuretics in case of decreasing fluid intake or increasing fluid loss' and 'consider deprescribing anticoagulants in case of uncontrolled bleeding'. In clinical practice, however, such medications are often continued, possibly due to physicians who are, probably, insufficiently aware of the need to reconsider the use of medication in case of such events.[30] Increasing physicians' awareness to discontinue medications in patients in the last phase of life, e.g. by means of automatic alerts of a clinical decision support system is therefore warranted, also for non-controversial deprescriptions.

This Delphi study has some limitations. Firstly, the recommendations presented to the panel were largely based on other Delphi studies and not on clinical evidence for empirical research. Secondly, a Delphi study cannot provide empirical evidence on the effects of deprescription. Further study is therefore needed. Thirdly, the recommendations were developed for general use and did not take potential frailty and comorbidities of patients into account. However, it is the responsibility of the attending physician to determine whether a specific recommendation is appropriate for an individual patient, taking their health condition into account. Fourthly, participants came from 10 different countries; however, eight of these countries were European, making the study less representative of the rest of the world. For future research it would be interesting to include more experts from different continents. Fifthly, we did not apply specific criteria to determine participants' level of expertise in deprescribing medication for patients in the last phase of life. Additionally, we did not include the perspectives of patients and their relatives in developing our recommendations. Lastly, this Delphi study gives some guidance on the monitoring of symptoms after deprescribing of medications; details about the duration, intensity and type of symptoms to monitor in the last phase of life have not been investigated. Monitoring of symptoms in patients might be of great importance since little research is available on the clinical impact of deprescribing in the last phase of life. Such monitoring may be even more important as in patients in the last phase of life, many events such as thrombosis or hypotension may already occur [31-33], related to the progression of disease and its additional factors, such as immobility.

CONCLUSION

This Delphi study reached a high level of agreement on deprescribing of medication recommendations for patients with a life expectancy of six months or less. The consensus-based deprescribing recommendations developed in this study may help creating awareness among physicians in deprescribing PIMs and may serve as a tool for clinical intervention studies

on medication deprescription. An example of such a study is the iLIVE medication study, an intervention study to examine the effects of personalized medication recommendations from an automated clinical decision support system, on the quality of life of patients with a life expectancy of six months or less.[17]

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Conflict of Interest Statement

The authors of this manuscript declare no conflicts of interest.

Ethical approval

This study was approved by the Medical Ethical Review Committee of the Erasmus Medical Center in Rotterdam, Netherlands, number MEC-2019-0832.

APPENDIX

Appendix 1. Medications and the literature where the information was extracted. The full information on all the extracted information is available upon request.

Medication	Literature / Indications	Beers criteria	End of Life Diabetes Care	Kutner	OncPal	Menten	Morin	StoppFrail	StoppStart
ACE-inhibitor / ARB	Primary prevention, Hypertension	X			X	X	X	X	
Alpha-adrenoreceptor	Hypertension	X				X	X	X	

antagonists									
Anticholinesterase	Alzheimer's disease	X				X	X	X	
Antiplatelet therapy	Primary prevention, secondary prevention, high risk at bleeding, thrombocytopenia	X			X	X	X	X	X
Beta blocking agent	Hypertension, heart failure and bradycardia, without atrial fibrillation, stable coronary artery disease				X	X	X		X
Biguanides	Secondary prevention		X		X	X	X		
Calcium Channel blocker	Hypertension	X			X	X	X		
Central acting antihypertensive medication	Hypertension	X				X	X		
Digoxin	Asymptomatic atrial fibrillation	X				X	X		X
Diuretics	Decreasing fluid intake/fluid loss, hypertension	X			X	X	X		X
DOAC	High risk at bleeding	X				X	X		X
DPP4	Secondary prevention		X		X		X	X	
Drugs affecting bone structure and mineralization	Osteopororis				X	X	X	X	
Estrogens	Minimal/none climacteric complaints	X						X	X
Fast acting insulin	Few or unregular intake, deterioration, clinical condition	X	X		X	X			
GLP-1 analogues	Secondary prevention		X		X		X	X	
H2 antagonists	No clear medical history, uncomplicated gastric ulcer/ peptic esophagitis and no symptoms				X	X	X	X	
Heparins	High risk at bleeding					X	X		
Lipid modifying agents	Primary prevention Secondary prevention			X	X	X	X	X	
Long acting	Few or unregular		X		X	X			

insulins	intake, deterioration, clinical condition								
LUTS medications	LUTS and risk at falling	X				X	X	X	X
Organic nitrates	Asymptomatic angina without recent complaints					X			
Proton Pump Inhibitor	No clear medical history, uncomplicated gastric ulcer/ peptic esophagitis and no symptoms	X			X	X		X	X
Sulphonyl urea group	Secondary prevention	X	X		X	X	X	X	X
Supplements	Prophylaxis				X	X	X	X	
Vitamin K antagonist	Uncomplicated deep venous thrombosis/pulmonary embolism, High risk at bleeding	X				X	X		X

Appendix 2. Removed alerts

Alerts removed based on the feedback of experts after round 1

Alert 1. Consider deprescribing ACE-inhibitor / Angiotensin-II-receptor blocker if prescribed for the management of stable coronary artery disease (defined as history of angina pectoris in the presence of either risk factors for or known atherosclerotic cardiovascular disease)

Consideration to remove this alert → ACE-inhibitors/ARB's are only prescribed to reduce the cardiovascular risk factors for the management of stable coronary artery disease and not the coronary artery disease per se. Alerts on specific cardiovascular risk factors are already included.

Alert 2. Consider deprescribing amiodarone if prescribed for substantial left ventricular hypertrophy (repolarization abnormalities on electrocardiogram / abnormalities on echocardiogram)

Consideration to remove this alert → Although we have consensus and agreement for this alert at 1 month life expectancy, we would like to remove this alert. We received the open comment that left ventricular hypertrophy is officially no indication to prescribe amiodarone. This is true, although amiodarone is often prescribed for left ventricular hypertrophy with atrial fibrillation as a result. Because left ventricular hypertrophy is not an official indication alone, we would like to remove this alert.

Alert 3. Consider deprescribing amiodarone if prescribed for atrial fibrillation in the first line without concomitant heart failure (NYHA 1-4)

Consideration to remove this alert → In the Netherlands, amiodarone is not prescribed in first line, only in second line by the cardiologist. We would like to remove this alert because of wrong information.

Alert 4. Consider deprescribing digoxin if prescribed for heart failure in case of first line therapy (NYHA class 1 or 2)

Consideration to remove this alert → We received the open comment that heart failure is officially no indication to prescribe digoxin. This is true, although digoxin is often prescribed for heart failure with atrial fibrillation as a result. Because heart failure is not an official indication alone to prescribe digoxin, we would like to remove this alert.

Alert 5. Consider deprescribing diuretics if prescribed for ankle edema and no signs of heart failure (no heart failure or NYHA class 1)

Consideration to remove this alert → We received the open comment that ankle edema is officially no indication to prescribe diuretics. This is true, although diuretics are often prescribed off-label for ankle edema without heart failure, for example by general practitioners. Because this is not an official indication, we would like to remove this alert.

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Figure 1. Inclusion consort diagram

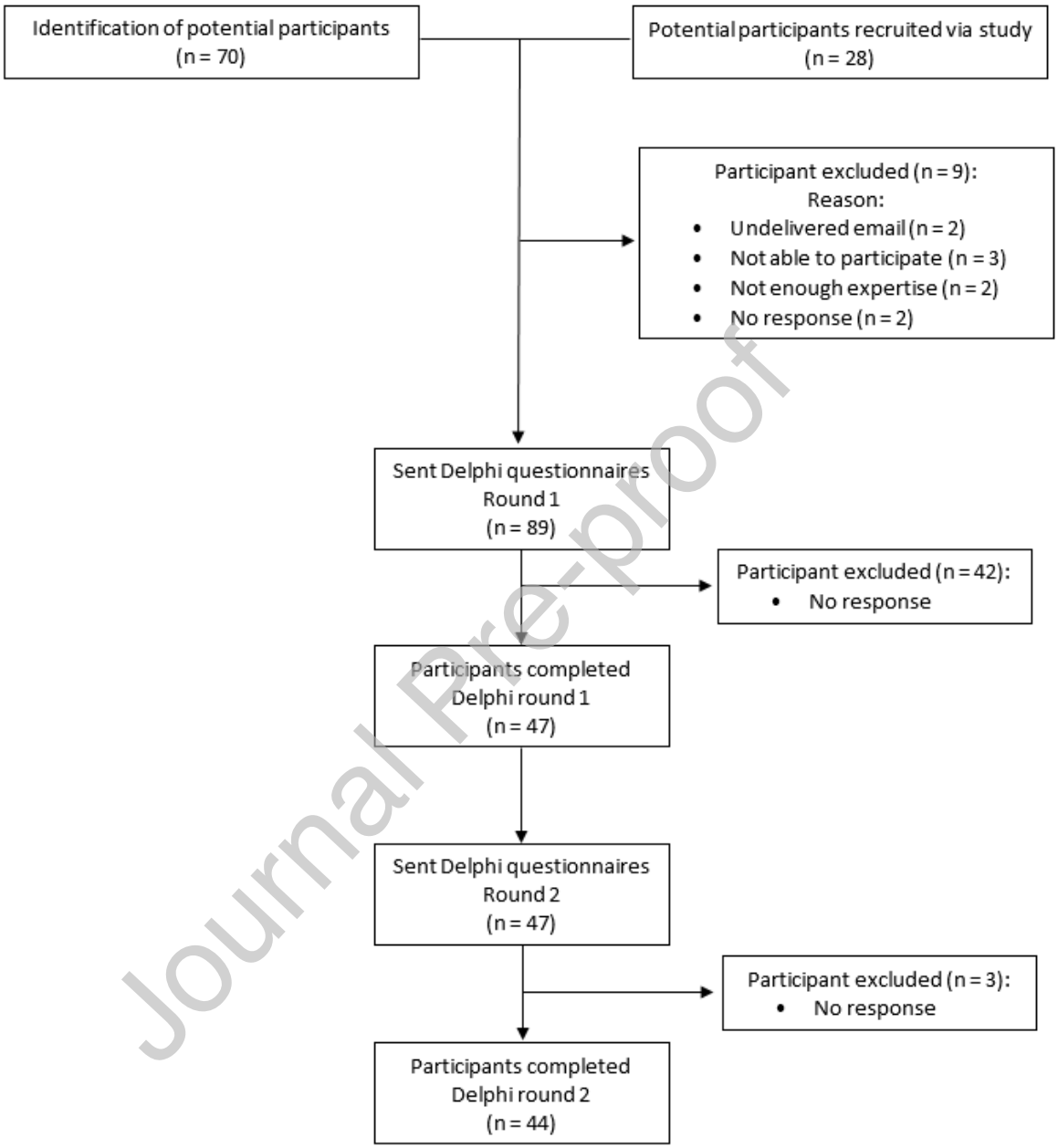
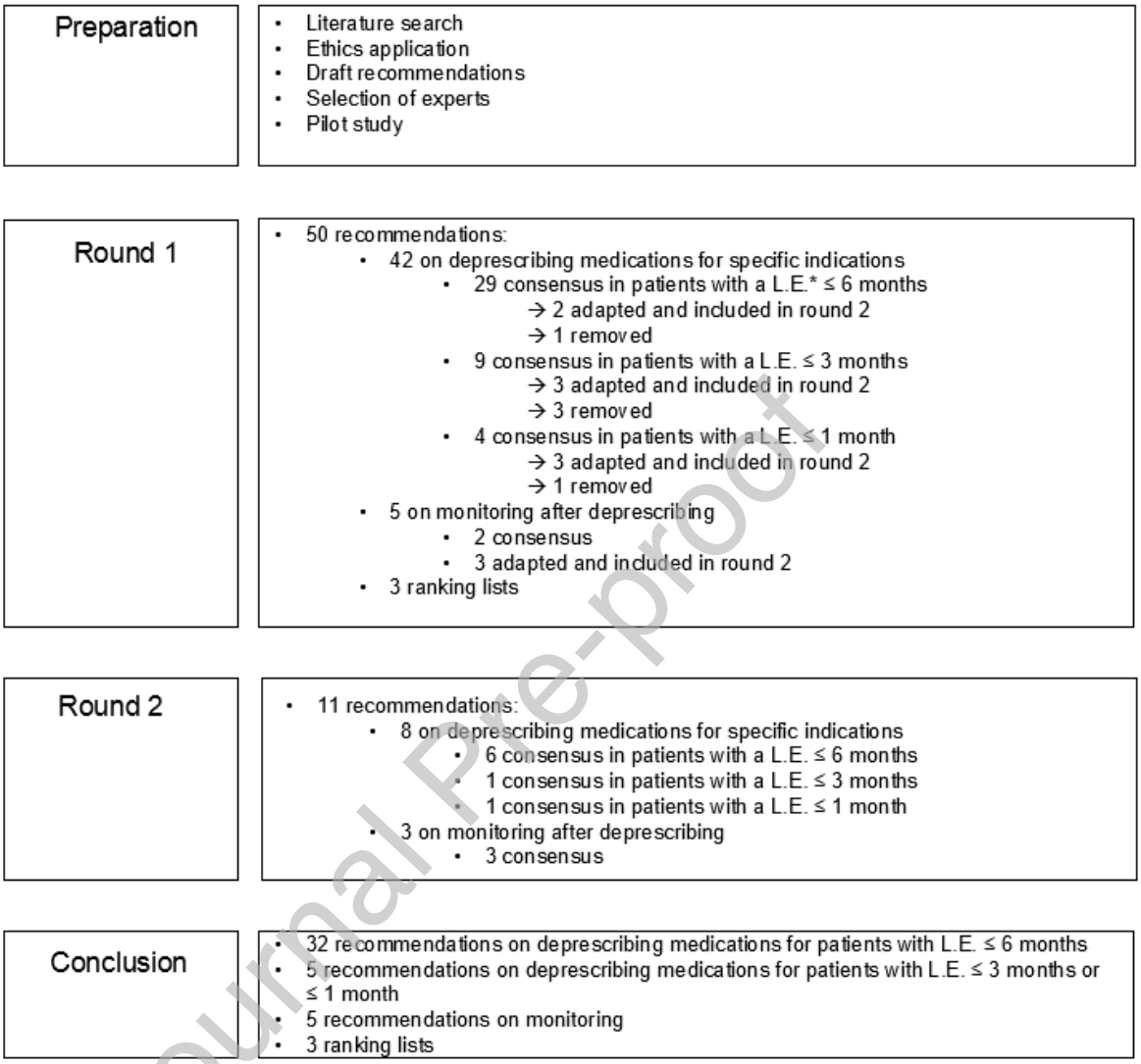


Figure 2. The Delphi process



*Abbrevation L.E.: Life expectancy

Table 1. Characteristics of 47 participating experts

Working country	**Absolute number**	**Percentage**
Netherlands	18	38,3
Sweden	11	23,4
Switzerland	3	6,4
United Kingdom	3	6,4
Belgium	3	6,4
Argentina	3	6,4
New Zealand	2	4,3
Norway	2	4,3
Iceland	1	2,1
Germany	1	2,1
Total	47	100
Area of expertise	**Absolute number**	**Percentage**
Palliative care consultant	28	38,9
Pharmacist	7	9,7
Medical oncologist	6	8,3
General practitioner	6	8,3
Elderly care physician / nursing home physician	5	6,9
Internist for elderly care / geriatrician	4	5,6
Clinical pharmacologist	4	5,6
Endocrinologist	2	2,8
Anesthesiologist	1	1,4
Cardiologist	1	1,4
Intensivist	1	1,4
Other Surgeon Radiation-oncologist Pain medicine Internal and pulmonary medicine	 2 2 1 1	 2,8 2,8 1,4 1,4
Total	71*	100
Working environment	**Absolute number**	**Percentage**
Hospital	30	42,3
Palliative inpatient care	14	19,7
Specialized palliative home care	8	11,3
Hospice	5	7,0
Nursing home	4	5,6
General practice	3	4,2
Hospice at home	3	4,2
Other	4	5,6
Total	71**	100

* n=21 had >1 area of expertise, of which n=3 had >2 areas of expertise
**n=15 worked in 2 settings, n=4 worked in 3 or 4 settings

Table 2. Recommendations about deprescribing of medication

Life-expectancy: Six months or less						
Medication Class	**Medication**	**ATC code**	**Recommendation**	**Agreement**	**IQR**	**Strongly disagree**
Cardiovascular medication	ACE-inhibitor / Angiotensin II receptor blockers	C09	Consider deprescribing ACE-inhibitor / Angiotensin-II-receptor blocker if prescribed for primary prevention of diabetic nephropathy	93,6%	1	0%
	Beta-blocking agents	C07	Consider tapering and if possible stopping beta blocking agents if prescribed for mild-moderate hypertension (systolic blood pressure ≤ 179, diastolic blood pressure ≤ 110 mmHg i.e. stage 1-2-3 hypertension)	90,0%	1	2,3%
		C02A	Consider tapering and if possible stopping beta blocking agents in case of heart failure (NYHA class 1 to 4) without atrial fibrillation in combination with bradycardia (<50 beats/min)	83,7%	1	2,3%
	Centrally acting antiadrenergic agents	C02CA	Consider deprescribing centrally acting antiadrenergic agents if prescribed for hypertension (systolic blood pressure < 179, diastolic blood pressure < 110 mmHg i.e. stage 1-2-3 hypertension)	88,4%	1	2,3%
	Alpha-adrenoreceptor antagonists	C08	Consider deprescribing alpha-adrenoreceptor antagonists (prazosin, doxazosin, urapidil, terazosin) if prescribed for hypertension (all stages, i.e. systolic blood pressure >140 mmHg, diastolic blood pressure >90 mmHg)	90,9%	1	2,3%
	Calcium Channel blockers	C03	Consider deprescribing calcium channel blockers if prescribed for mild-moderate hypertension (systolic blood pressure < 179, diastolic blood pressure < 110 mmHg i.e. stage 1-2-3 hypertension)	77,8%	1	2,2%
	Diuretics	C01DA	Consider deprescribing diuretics in case of decreasing fluid intake or increasing fluid loss (diarrhea, vomiting, excessive sweating)	100%	0	0%
	Organic Nitrates	C01AA	Consider deprescribing organic nitrates if prescribed for asymptomatic angina (angina complaints in past history without recent (<1 yr) complaints)	88,6%	1	0%
	Digoxin	C10	Consider deprescribing digoxin if prescribed for asymptomatic atrial fibrillation (atrial fibrillation in past history without complaints now)	76,2%	1	0%
	Lipid modifying agents		Consider deprescribing lipid modifying agents if prescribed for primary prevention (hypercholesterolemia) of cardiovascular disease	100%	0	0%
			Consider deprescribing lipid modifying agents if prescribed for secondary prevention of cardiovascular disease (> 12 months since last incident, complaints or intervention such as stenting)	97,9%	1	0%
Antiplatelet therapy	Platelet aggregation inhibitor	B01AC	Consider deprescribing platelet aggregation inhibitor (e.g. aspirin > 100 milligram per day, P2Y12-inhibitors) if prescribed for primary prevention of cardiovascular accident	87,2%	1	0%
			Consider deprescribing platelet aggregation inhibitor (e.g. aspirin > 100 milligram per day, P2Y12-inhibitors) in case of an increased bleeding risk and if prescribed for secondary prevention of cardiovascular accident (e.g. > 12 months after incidents, complaints or interventions such as	88,4% 97,8%	1 0	0% 0%

			vascular stenting) Consider deprescribing platelet aggregation inhibitor (e.g. aspirin, P2Y12-inhibitors) in case of a high risk at bleeding: - uncontrolled hypertension (systolic pressure >179 mmHg) - uncontrolled bleeding - relevant recent spontaneous bleeding - clinically relevant bleeding: medical intervention or (prolonged) hospital admission, unscheduled contact physician, discomfort, impairment of activities, multiple source bleeding, hemoglobin drop > 3 g/dL. - HASBLED >3 - kidney of liver failure: Consider deprescribing platelet aggregation inhibitor (e.g. aspirin, P2Y12-inhibitors) in case of thrombocytopenia (<150000 platelets per microliter of blood)	84,1%	1	2,3%
Anticoagulants	Vitamin K antagonist	B01AA	Consider deprescribing vitamin K antagonist (acenocoumarol, fenprocoumon, warfarin) if prescribed for uncomplicated deep venous thrombosis or uncomplicated pulmonary embolism >6 months ago in patients without cancer Consider deprescribing vitamin K antagonist (acenocoumarol, fenprocoumon, warfarin) in case of high risk at bleeding: - uncontrolled hypertension (systolic pressure >179 mmHg) - uncontrolled bleeding - relevant recent spontaneous bleeding - clinically relevant bleeding: medical intervention or (prolonged) hospital admission, unscheduled contact physician, discomfort, impairment of activities, multiple source bleeding, hemoglobin drop > 3 g/dL. - HASBLED >3 - kidney of liver failure	88,6% 100% 95,5%	1 0 1	0% 0% 0%
	Heparins	B01AB				
	Direct Oral Anticoagulants (DOAC)	B01AF	Consider deprescribing heparins in case of high risk at bleeding: - uncontrolled hypertension (systolic pressure >179 mmHg) - uncontrolled bleeding - relevant recent spontaneous bleeding - clinically relevant bleeding: medical intervention or (prolonged) hospital admission, unscheduled contact physician, discomfort, impairment of activities, multiple source bleeding, hemoglobin drop > 3 g/dL. - HASBLED >3 - kidney of liver failure Consider deprescribing Direct Oral Anticoagulants (DOAC) in case of high risk at bleeding: - uncontrolled hypertension (systolic pressure >179 mmHg) - uncontrolled bleeding - relevant recent spontaneous bleeding - clinically relevant bleeding: medical intervention or (prolonged) hospital admission, unscheduled contact physician, discomfort, impairment of activities, multiple source bleeding, hemoglobin drop > 3 g/dL. - HASBLED >3 - kidney of liver failure	100%	1	0%
Blood glucose-lowering medication	Fast-acting insulins	A10AB	Consider changing fast-acting insulins to a simpler regimen; using longer acting insulin in DM type 1 and 2 and deprescribing short or rapid acting insulins to few times a day in patients with few or unregular intake, deterioration of clinical condition	86,7%	1	2,2%
	Long-acting insulins	A10AE	Consider lowering long-acting insulin if prescribed for DM type 1 and 2 with few or unregular intake, deterioration of clinical condition. OF note: in case of DM type 1: do not lower the dose to <10E/day	90,9% 89,1%	1 1	2,3% 0%
	Biguanides	A10BA	Consider deprescribing biguanides (i.e. metformin) if prescribed for mild hyperglycemia for secondary prevention of diabetic associated events	91,3%	1	0%
	Sulphonylureas	A10BB	Consider deprescribing Sulphonylureas (i.e.	81,6%	1	0%

	Dipeptyl peptidase 4 (DPP4) inhibitor Glucagon-like Peptide-1 (GLP-1) analogues	A10BH A10BJ	glibenclamide /gliclazide/ tolbutamide/chlorpropamide) if prescribed for DM type 2 and prevention of diabetic associated events Consider deprescribing Dipeptyl peptidase 4 (DPP-4) inhibitor (Linagliptin, saxagliptin, sitagliptin, vildagliptin) if prescribed for DM type 2 and secondary prevention of diabetic associated events Consider deprescribing Glucacon-like Peptide-1 (GLP-1) analogues (Dulaglutide/exenatide/liraglutide/lixisenatide/semaglutide) if prescribed for DM type 2 and secondary prevention of diabetic associated events	94,3%	1	0%
Digestive system medication	H2-receptor antagonists Proton Pump Inhibitor (PPI)	A02BA A02BC	Consider deprescribing H2-receptor antagonist if prescribed without a clear medical history of gastrointestinal bleeding, peptic ulcer, gastritis, gastro-esophageal reflux disease or use of NSAIDs and steroids Consider deprescribing H2-receptor antagonist if prescribed for uncomplicated gastric ulcer/erosive peptic esophagitis more than 8 weeks ago and no persistent symptoms Consider tapering and if possible stopping Proton Pump Inhibitor (PPI) if prescribed without a clear medical history of gastrointestinal bleeding, peptic ulcer, gastritis, gastro-esophageal reflux disease or use of NSAIDs and steroids	91,5% 78,3% 88,6%	0 1 1	0% 4,3% 0%
Osteoporosis medication	Drugs affecting bone structure and mineralization	M05B	Consider deprescribing drugs affecting bone structure and mineralization (i.e. bisphosponates, denosumab) if prescribed for osteoporosis	91,5%	1	0%
Lower urinary tract medication	Urologicals	G04	Consider deprescribing urologicals (alpha adrenoreceptor antagonists and testosterone-5 alpha reductase inhibitors) if prescribed for lower urinary tract symptoms (LUTS) (e.g. urinary incontinence, nocturnal polyuria, benign prostate hypertrophy, long-term urinary catheter) and risk at falling	86,4%	0	2,3%
Miscellaneous medication	Supplements Systemic estrogens	A11+A12 G03C	Consider deprescribing supplements (vitamins and mineral supplements) when prescribed for prophylaxis Consider deprescribing systemic estrogens if not prescribed for moderate-severe climacteric complaints	100% 82,9%	0 1	0% 0%
Life-expectancy: Three months or less						
Medication Class	**Medication**		**Recommendation**	**% Agreement**		
Cardiovascular medication	ACE-inhibitor / Angiotensin II receptor blockers (C09) Beta-blocking agent Diuretics	C09 C07 C03	Consider deprescribing ACE-inhibitor / Angiotensin-II-receptor blocker if prescribed for mild-moderate hypertension (stage 1-2-3- hypertension, systolic blood pressure < 179, diastolic blood pressure < 110 mmHg i.e. stage 1-2-3 hypertension) Consider tapering and if possible stopping beta blocking agents if prescribed for management of stable coronary artery disease (defined as history of angina pectoris in the presence of either risk factors for or known atherosclerotic cardiovascular disease) Consider deprescribing diuretics if prescribed for mild-moderate hypertension(systolic blood pressure < 179, diastolic blood pressure < 110 mmHg i.e. stage 1-2-3 hypertension)	89,4% 74,4% 78,8%	1 1 1	0% 2,3% 0%
Miscellaneou	Anticholinestera	N07A	Consider deprescribing anticholinesterase if	91,1%	1	2,2%

s	se	A	prescribed for Alzheimer's disease/dementia			
Life-expectancy: One month or less						
Medication Class	**Medication**		**Recommendation**			
Digestive system medication	Proton Pump Inhibitor (PPI)	A02BC	Consider tapering and if possible stopping Proton Pump Inhibitor (PPI) if prescribed for uncomplicated gastric ulcer/erosive peptic esophagitis more than 8 weeks ago and no persistent symptoms	81,8%	1	2,3%

Table 3. Recommendations about monitoring after deprescribing of medication

Monitoring				
Medication Class	**Recommendation**	**Agreement**	**IQR**	**Strongly disagree**
Blood glucose-lowering-medications	Actively monitor blood glucose after deprescribing blood glucose lowering medications in patients with a life-expectancy of 6 months or less. Monitor the blood glucose daily in the first week after deprescribing, monitor the blood glucose after the first week once a week or in case of symptoms	73,9%	1	8,7%
Antihypertensive medication	Consider measuring blood-pressure and heart rate after deprescribing antihypertensives in patients with a life expectancy of 6 months or less once a week in the first month after deprescribing. Hereafter monthly OR in case of symptoms (i.e. headache, dyspnea, palpitations, dizziness, nausea/vomiting, tinnitus, impaired vision).	70,5%	1	2,3%
Anticoagulants	Consider to educate patient to alarm physician in case of symptoms after deprescribing anticoagulants in patients with a life expectancy of 6 months or less; painful and/or swollen calf, dyspnea.	81,8%	1	2,3%
Digestive system medication	Consider to educate patient to alarm physician in case of symptoms after deprescribing of medications for the digestive tract; stomach pain, reflux. Ask the patient actively for stomach pain symptoms after 1 month.	88,6%	1	0%
Platelet aggregation inhibitor	Do not actively monitor symptoms (i.e. thrombo-embolic event) after deprescribing platelet aggregation inhibitors in patients with a life-expectancy of 6 months or less	70,2%*	1	0%*

* for platelet aggregation inhibitors, >70% of the experts disagreed to actively monitor symptoms and none of the experts did strongly agree

Table 4. Order of deprescribing of medication

Medication class	Indication	Medication	Rank order	Mean rank (standard deviation)	Median (standard deviation)
Antihypertensive agents	Hypertension	Central acting antihypertensive medication	1	1,64 (0,962)	1 (0.954)
		Peripheral alpha blocker	2	2,48 (1,302)	2 (1.285)
		Diuretics	3	3,85 (1,544)	4 (1.587)
		Beta-blocking agents	4	4,09 (1,646)	4 (1.632)
		Calcium channel blocker	5	4,27 (1,281)	4 (1,317)
		ACE-inhibitor/Angiotensin II blocker	6	4,67 (1,242)	5 (1,215)
Kendall's coefficient of concordance (W)				0,396	
Chi-square				65,364	
p-value				<0,0001	
Glucose-lowering medication	Diabetes mellitus type 1	Short-acting insulin	1	1,29 (0,461)	1 (0.435)
		Long-acting insulin	2	1,71 (0,461)	2 (0.461)
Kendall's coefficient of concordance (W)				0,176	
Chi-square				5,452	
p-value				0,020	
Glucose-lowering medication	Diabetes mellitus type 2	Oral glucose-lowering medications: - DPP-4 inhibitor - GLP-1 analogues - Sulphonyl-urea group - Metformin	1	 2,67 (1.080) 2,73 (1,306) 2,85 (1,912) 3,30 (1,912)	 3 (1.070) 3 (1.286) 3 (1.298) 3 (1.883)
		Short-acting insulin	2	4,42 (1,714)	5 (1.714)
		Long-acting insulin	3	5,03 (1,357)	5 (1.483)
Kendall's coefficient of concordance (W)				0,283	
Chi-square				46,680	
p-value				<0.001	