


How many older adults receive drugs of questionable clinical benefit near the end of life? A cohort study

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Abstract

Background: The high burden of disease-oriented drugs among older adults with limited life expectancy raises important questions about the potential futility of care.

Aim: To describe the use of drugs of questionable clinical benefit during the last 3 months of life of older adults who died from life-limiting conditions.

Design: Longitudinal, retrospective cohort study of decedents. Death certificate data were linked to administrative and healthcare registries with national coverage in Sweden.

Setting: Older adults (≥ 75 years) who died from conditions potentially amenable to palliative care between 1 January and 31 December 2015 in Sweden. We identified drugs of questionable clinical benefit from a set of consensus-based criteria.

Results: A total of 58,415 decedents were included (mean age, 87.0 years). During their last 3 months of life, they received on average 8.9 different drugs. Overall, 32.0% of older adults *continued* and 14.0% *initiated* at least one drug of questionable clinical benefit (e.g. statins, calcium supplements, vitamin D, bisphosphonates, antimentia drugs). These proportions were highest among younger individuals (i.e. aged 75–84 years), among people who died from organ failure and among those with a large number of coexisting chronic conditions. Excluding people who died from acute and potentially unpredictable fatal events had little influence on the results.

Conclusion: A substantial share of older persons with life-limiting diseases receive drugs of questionable clinical benefit during their last months of life. Adequate training, guidance and resources are needed to rationalize and deprescribe drug treatments for older adults near the end of life.

Keywords

Drug utilization, frail elderly, deprescriptions, inappropriate prescribing, drug therapy, geriatrics, palliative care, cohort studies

What is already known about the topic?

- Older adults who approach the end of life are often prescribed an increasing number of drugs.
- Drugs that provide a long-term benefit but no short-term advantage for quality of life are of limited interest for older persons with limited life expectancy.

What this paper adds?

- This study shows that during the last 3 months of life, drugs of questionable clinical benefit are continued in 32% of older adults with life-limiting conditions and initiated in 14% of them.
- Statins and other lipid-lowering drugs are the most common drugs of questionable clinical benefit near the end of life, followed by calcium supplements, antimentia drugs, bisphosphonates and vitamin D.

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Implications for practice, theory or policy

- Many older adults with life-limiting conditions receive drugs that are unlikely to achieve a meaningful health outcome during their remaining lifetime.
- Unnecessary and potentially harmful drugs have a disruptive effect on older persons' life and can lead to serious adverse drug-related events.
- Clinicians caring for older adults need adequate training, guidance and resources to rationalize drug treatments near the end of life.

Introduction

Most older adults die from long-standing and progressive illness accompanied by a multitude of chronic comorbidities and symptoms, which results in complex healthcare needs.¹ Consequently, older adults who approach the end of life are often prescribed an increasing number of drugs.² The concomitant use of many drugs (polypharmacy) comes with a higher risk of adverse drug reactions, drug–drug interactions and drug-related injuries.³ Older persons with serious illness are particularly vulnerable to side effects because of age- and disease-related physiological changes that can modify their metabolism and excretion of drugs.^{4,5}

The burden of drugs in the context of limited life expectancy also raises important questions about the potential futility of care.⁶ When prognosis worsens, it is recommended that physicians progressively shift away from disease-targeted treatments and instead prioritize palliative goals of care. Older persons with serious illness often change preferences regarding therapy as the disease progresses and the prospect of cure becomes unlikely. Ensuring symptoms management and preserving the quality of life may, for instance, become more important than extending survival. In the United States, a recent population-based survey showed that ‘being comfortable and without pain’ (78%) was more often mentioned as an important end-of-life priority than ‘living as long as possible’ (46%).⁷ Medical interventions near the end of life should thus be evaluated according to their ability to achieve goals that are meaningful to the patients.⁸ The expected benefit of the treatment should also be in keeping with the remaining life expectancy.⁹ Drugs that provide a long-term benefit but no short-term advantage in terms of symptoms, function or quality of life may be of limited interest for older persons with only a few months to live. Treatment decisions should also incorporate the anticipated patterns of change in physical functioning, cognition and comorbidities.¹⁰

There is now widespread consensus that overly aggressive anticancer therapy should be avoided during the final months and weeks of life.¹¹ The utilization of invasive mechanical ventilation for patients with advanced chronic obstructive pulmonary disease (COPD) and the use of feeding tubes for patients with severe dementia are also considered as low-value care.^{12–14} However, remarkably

little is known about the use of chronic disease medications near the end of life. Alongside comfort-oriented drugs (e.g. analgesics), some studies have suggested that pharmacological treatments for the long-term prevention of cardiovascular diseases are prescribed until the very end of life and have cast serious doubts regarding their benefit in this context.^{15–17} However, most of these studies have been conducted in selected populations, in small geographical areas or in specific care settings, which limits their generalizability. Moreover, previous approaches to evaluate the appropriateness of prescription drugs in the context of limited life expectancy were often limited to particular diseases, namely, cancer and dementia.^{18,19}

A consensus-based list of drugs of questionable clinical benefit for older adults nearing the end of life was recently published,²⁰ which provides an opportunity to broaden the scope of previous studies by examining drug utilization patterns across diseases and care settings. Also, these criteria make a clear distinction between the *continuation* of previously prescribed drugs and the *initiation* of new drugs during the final months of life, which pose different challenges in clinical practice.²¹ In this study, taking advantage of real-world longitudinal data with national coverage in Sweden, we aimed to describe the use of drugs of questionable clinical benefit during the last 3 months of life of older adults who died from life-limiting conditions.

Methods

Study design and population

This was a cohort study of decedents based on routinely collected administrative and healthcare data in Sweden. Older adults (>75 years) who died between 1 January and 31 December 2015 were identified in the Swedish National Cause of Death register (N = 64,715). Individuals were included in the cohort if at least one condition potentially amenable to palliative care was listed as the underlying or contributing cause of death (Supplementary Table 1). We also excluded decedents who were missing an exact date of death, those whose cause of death was either unknown (International Statistical Classification of Diseases, 10th Revision (ICD-10) code R99) or not reported, as well as individuals for whom information regarding drug prescribing was unavailable (~2.5% of all decedents). These data were linked at the individual level

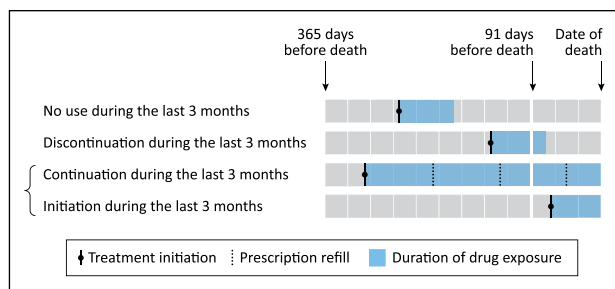


Figure 1. Drug utilization patterns during the last months of life. The ‘continuation’ of drugs of questionable clinical benefit is defined as the dispensing of at least one such drug during the last 3 months before death, among older persons who had not been treated with the same drug during the 9-month period prior (i.e. between 365 and 92 days before death). Individuals who were potentially exposed to drugs of questionable clinical benefit during the last 3 months of life but did not refill their prescription were considered as having discontinued their treatment.

to other national registers by the National Board of Health and Welfare and by Statistics Sweden, with >99.9% completeness of personal identifiers.²² The study was approved by the Regional Ethical Review Board in Stockholm (no. 2016/1001-31/4) and follows the REporting of studies Conducted using Observational Routinely collected health Data (RECORD)²³ guidelines (Supplementary Table 2).

Outcome measurement

The main outcome was twofold and included both the *continuation* and the *initiation* by the prescribers of drugs of questionable clinical benefit during the last 3 months before death (Figure 1). These drugs were defined according to a previously published set of consensus-based criteria, which were developed through a Delphi process that involved 40 experts in geriatrics, clinical pharmacology and palliative medicine from 10 different European countries.²⁰ Although this list also encompasses drugs deemed ‘questionable’ for use among older adults with a remaining life expectancy of <3 months, we restricted our analysis to drugs considered as ‘often inadequate’ in order to increase specificity. We determined drug utilization patterns using dispensing data from the Swedish Prescribed Drug Register, which has been described elsewhere.²⁴ Drugs were classified according to the Anatomical Therapeutic Chemical (ATC) classification system and are listed in detail in Supplementary Table 3.

Decedent characteristics

We ascertained the sociodemographic characteristics of decedents through deterministic patient-level record

linkage with data from the Swedish Total Population Register (sex, date of birth, marital status) and the Swedish Register of Education (highest educational attainment). Living arrangement 3 months before death was defined as either ‘community-dwelling’ or ‘nursing home resident’ based on information retrieved from the National Social Services Register, and the drug dispensing scheme was either ‘ordinary prescriptions’ (i.e. drugs dispensed manually) or ‘multidose’ (i.e. drugs dispensed in machine-packed pouches). Decedents were assigned to one of three distinct illness trajectories according to their cause of death (‘cancer’, ‘organ failure’ and ‘prolonged dwindling’), using an algorithm published elsewhere.²⁵ These trajectories are useful to determine the potential time frame of functional decline at the end of life.²⁶ We also estimated the overall burden of chronic multimorbidity by applying a recently validated list of conditions.²⁷ For this purpose, we considered all diagnoses reported during inpatient and specialized outpatient care admissions that occurred between 5 years and 3 months before death, diagnoses considered as contributing (but not underlying) causes of death on the death certificate, as well as relevant clinical indications mentioned in the Swedish Prescribed Drug Register during the same time period. Finally, the Hospital Frailty Risk Score²⁸ was computed based on inpatient and specialized outpatient care discharge reports from 5 years to 3 months before death. All codes and algorithms used for these purposes are listed in detail in Supplementary Tables 4 and 5.

Statistical analysis

The study outcome was measured as the proportion of decedents who continued or initiated at least one drug of questionable clinical benefit during the last 3 months before death. In sensitivity analyses, older adults whose underlying cause of death suggested an acute and potentially unpredictable fatal event (e.g. sepsis, fall-related injury, suicide, acute myocardial infarction or stroke with no prior history of ischemic heart disease) were excluded. The purpose of this sensitivity analysis was to account for the challenge of estimating the remaining life expectancy by measuring whether the observed patterns of drug utilization near the end of life were substantially different among older adults whose death may not have been anticipated by clinicians despite the presence of an underlying life-limiting disease. The algorithm used to detect these potentially unexpected deaths is available in Supplementary Table 6. Subgroup analyses by age, illness trajectory, and living arrangement were also performed to explore potential variations. Generalized linear models with log link function and binomial distribution (log-binomial regressions) were then fitted to identify factors independently associated with both the *continuation* and the *initiation* of drugs of questionable clinical benefit near the

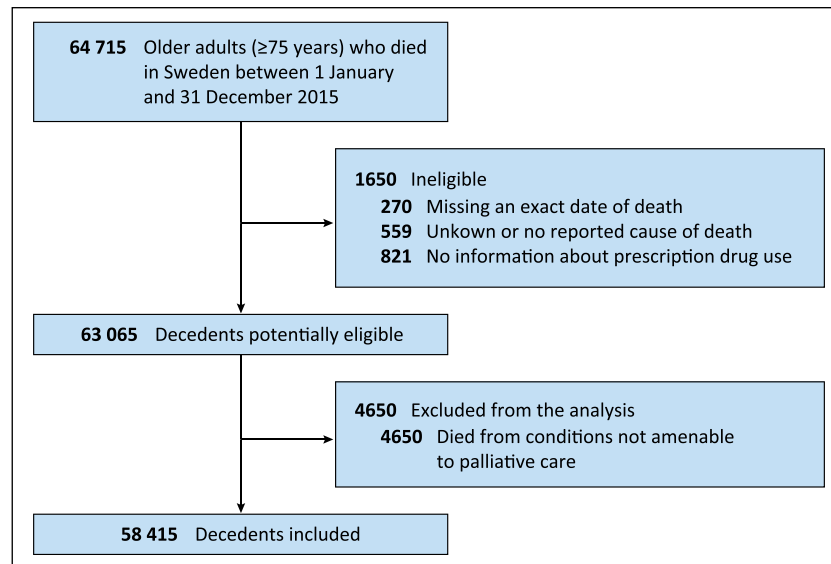


Figure 2. Study population flowchart.

end of life. This modelling strategy was chosen over logistic regression analysis because the latter tends to generate odds ratios that overestimate the underlying risk ratios (RR) in cohort studies, which can lead to misinterpretations of the findings when the outcome is common.²⁹ RR are reported with 95% confidence intervals (CI). Individuals with missing data for education ($n = 1302$, 2.2%) were excluded from the models. Analyses were performed with JMP version 14.1 (SAS Institute) and Stata version 14.1 (StataCorp).

Results

Characteristics of the study population

Out of 64,715 older adults aged 75 years and older who died in Sweden in 2015, 1650 (2.5%) did not meet our inclusion criteria and 4650 (7.2%) died from conditions indicative of a sudden and unexpected dying trajectory (Figure 2). The 58,415 decedents included in the study population included a majority of women (55.9%) and were aged 87.0 years on average (median, 87; interquartile range, 82–92 years). As shown in Table 1, 28% died from cancer, 40% from organ failure, and 32% followed a trajectory of prolonged dwindling. Chronic multimorbidity was highly prevalent, with 60.2% of decedents diagnosed with six or more chronic conditions. Fourteen per cent of them had a high hospital frailty risk score, and nearly half (42%) were living in nursing homes 3 months before death.

Continuation and initiation drugs of questionable clinical benefit

During their last 3 months of life, these older adults received 8.9 (SD = 4.7) different drugs on average, scattered

across 7.2 (SD = 3.5) therapeutic classes. Overall, 32.0% ($n = 18,681$) of patients had at least one prescription drug of questionable clinical benefit *continued*, while the *initiation* of drugs of questionable clinical benefit affected 14.0% ($n = 8180$) of older adults. While 4.5% both continued and initiated drugs of questionable benefit, 58.6% did neither. The proportion of individuals for whom drugs of questionable benefit were continued until the end of life was substantially lower among cancer decedents (25.8%), while the proportion of individuals who initiated such drugs was lowest among people with a trajectory of prolonged dwindling (9.7%). These findings remained after adjusting for potential confounders (Table 2). Chronic multimorbidity was associated with an increase in the probability of both continuing and initiating questionably beneficial drugs near the end of life. In contrast, while older persons with a high risk of frailty were less likely than those with a low frailty risk to initiate drugs of questionable benefit (RR = 0.83, 95% CI = 0.78–0.89), they were substantially more likely to continue these drugs if they had been initiated before (RR = 1.27, 95% CI = 1.23–1.31). Nursing home residents were as likely as community dwellers to continue drugs of questionable benefit during the last 3 months of life (32.9% vs 31.3%, RR = 1.01, 95% CI = 0.98–1.04) but they were noticeably less likely to initiate them (RR = 0.56, 95% CI = 0.53–0.59). In sensitivity analyses, excluding older adults who died from acute and potentially unpredictable fatal events ($n = 9918$, 17%) did not substantially modify these findings (Supplementary Table 7). Subgroup analyses showed that age-specific rates of continuation and initiation of drugs of questionable benefit varied across illness trajectories (Supplementary Figure 1), and that differences between illness trajectories and across frailty risk scores were less pronounced among nursing home residents than among community dwellers (Supplementary Table 8).

Table 1. Characteristics of the study population at time of death (Sweden, 2015).

Decedents in cohort, No.	58,415
Sex, No. (%)	
Men	25,738 (44.1)
Women	32,677 (55.9)
Age at time of death, years	
Mean (SD)	87.0 (6.3)
No. (%)	
75–84	22,270 (38.1)
85–94	30,056 (51.5)
>95	6089 (10.4)
Illness trajectory, No. (%)	
Cancer	16,338 (28.0)
Organ failure	23,379 (40.0)
Prolonged dwindling	18,698 (32.0)
Number of chronic diseases	
Mean (SD)	6.6 (3.2)
No. (%)	
0–1	1711 (2.9)
2–3	8045 (13.8)
4–5	13,519 (23.10)
>6	35,140 (60.2)
Hospital Frailty Risk Score, No. (%)	
Low risk (<5)	27,365 (46.8)
Moderate risk (5–15)	22,847 (39.1)
High risk (>15)	8203 (14.1)
Living arrangement, No. (%)	
Community-dwelling	33,862 (58.0)
Nursing home	24,553 (42.0)
Place of death, No. (%)	
Home	7685 (13.3)
Nursing home	28,580 (49.6)
Hospital	20,989 (36.4)
Other	376 (0.7)
Marital status, No. (%)	
Married	17,527 (30)
Single or divorced	11,807 (20.2)
Widowed	29,081 (49.8)
Level of education, No. (%)	
Primary education	28,807 (50.4)
Secondary education	21,864 (38.3)
Tertiary education	6442 (11.3)

SD: standard deviation.

Missing values: place of death, 785 (1.3%); level of education, 1302 (2.2%).

Most commonly prescribed drugs of questionable clinical benefit

Statins and other lipid-lowering drugs were the most commonly continued drugs of questionable clinical benefit near the end of life, followed by calcium supplements, antidementia drugs, bisphosphonates and vitamin D (Table 3). The most commonly initiated drugs of questionable benefit during the last 3 months of life were

antianaemia drugs (e.g. iron supplements, vitamin B12), angiotensin-converting enzyme inhibitors and angiotensin II receptor antagonists, novel oral anticoagulants, statins and vitamin K antagonists. Detailed lists of drugs continued or initiated near the end of life are available in Supplementary Tables 9 and 10.

Discussion

Main findings

In this nationwide cohort study of decedents, we found that among older adults who died from life-limiting conditions, drugs of questionable clinical benefit were commonly continued (32%) or even initiated (14%) during the last 3 months of life. These proportions were highest among younger individuals (i.e. aged 75–84 years), among people who died from organ failure, and among those with a large number of coexisting chronic conditions. Excluding people with life-limiting conditions who died from acute and potentially unpredictable fatal events had little influence on the prevalence of drugs of questionable clinical benefit.

Interpretation and implications for clinical practice

Our results add weight to the conclusions of previous studies,^{15,30} without being limited to a specific disease or healthcare setting. We found that a large proportion of older adults continue to receive preventive drugs despite their limited life expectancy. Statins are often recognized as being of limited clinical benefit near the end of life because of their long time-until-benefit.^{31–33} It has been demonstrated that the existence of a recognizable life-limiting disease did not change the timing of discontinuation of statins before death (not even for patients without cardiovascular conditions),³⁴ and that people with poor-prognosis cancer often continue to receive statins during the short time between diagnosis and death.³⁵ In a large US cohort, Tjia et al.³⁶ showed that only a third of nursing home residents who were prescribed statins at the time of progression to advanced dementia discontinued their treatment during follow-up and that 61% of them were still using statins at the time of death. These reports are consistent with our own finding that 65% of older adults treated with statins continued therapy during their last 3 months of life. In our opinion, this represents a missed opportunity for deprescribing since a majority of older adults are willing to consider discontinuation,^{37,38} with potential benefits on their quality of life.^{39,40}

The overall burden of unnecessary and potentially harmful prescription drugs near the end of life has come under intense scrutiny. Earlier studies reported a prevalence of hyper-polypharmacy (>10 concomitant drugs) close to 50% during the last month before death.^{2,41} In our

Table 2. Factors associated with the continuation and initiation of drugs of questionable clinical benefit for older adults near the end of life.

	Continuation		Initiation	
	%	RR (95% CI)	%	RR (95% CI)
Total	32.0	-	14.0	-
Sex				
Men	31.8	1	14.8	1
Women	32.1	1.08 (1.05–1.11)	13.4	1.03 (0.98–1.08)
Age at time of death, years				
75–84	36.9	1	15.6	1
85–94	31.3	0.79 (0.77–0.81)	13.6	0.97 (0.93–1.02)
≥95	17.2	0.46 (0.43–0.49)	10.1	0.83 (0.76–0.90)
Illness trajectory				
Cancer	25.8	1	15.0	1
Organ failure	34.9	1.36 (1.32–1.40)	16.8	1.17 (1.12–1.23)
Prolonged dwindling	33.7	1.42 (1.37–1.47)	9.7	0.93 (0.87–0.99)
Number of chronic diseases				
0–1	10.6	1	9.8	1
2–3	20.3	1.78 (1.54–2.05)	10.8	1.02 (0.87–1.20)
4–5	27.7	2.35 (2.04–2.70)	12.8	1.21 (1.04–1.41)
>6	37.3	3.00 (2.62–3.44)	15.4	1.42 (1.23–1.65)
Hospital Frailty Risk Score				
Low risk (<5)	27.0	1	15.1	1
Moderate risk (5–15)	34.0	1.10 (1.07–1.13)	13.6	0.94 (0.90–0.98)
High risk (>15)	43.2	1.27 (1.23–1.31)	11.3	0.83 (0.78–0.89)
Living arrangement				
Community-dwelling	31.3	1	17.7	1
Nursing home	32.9	1.01 (0.98–1.04)	8.8	0.56 (0.53–0.59)
Marital status				
Married	34.2	1	15.7	1
Single or divorced	32.0	0.94 (0.91–0.97)	13.6	0.96 (0.91–1.02)
Widowed	30.6	0.97 (0.94–1.00)	13.2	0.99 (0.94–1.05)
Level of education				
Primary education	31.4	1	13.9	1
Secondary education	33.1	1.01 (0.98–1.03)	14.1	0.99 (0.95–1.04)
Tertiary education	32.0	0.98 (0.94–1.02)	14.0	0.98 (0.91–1.04)

Percentages are calculated as a fraction of the entire cohort of decedents. Risk ratios (RR) and 95% confidence intervals (CI) from log-binomial regression models. Estimates are mutually adjusted.

cohort, 42% of older adults who died from life-limiting conditions were dispensed >10 drugs during their last 3 months of life, distributed across seven different therapeutic classes. This may partly be explained by switches between similar drug classes (e.g. two different antihypertensives) or by the initiation of comfort-oriented drug combinations (e.g. laxatives to counter opioid-induced constipation). Nevertheless, the potential for adverse drug reactions is critical, which can aggravate symptoms and worsen the quality of life.^{42–44} Moreover, severe adverse drug-related events can lead to emergency department visits and unplanned hospital admissions, which contribute to the fragmentation of care and induce an additional layer of emotional distress for the patients and their caregivers. Taking nine different drugs every day

also has a disruptive effect on older people's life: it often leads to a loss of appetite, it necessitates regular general practitioner (GP) visits to monitor physiological parameters and it can result in a reduction in the activities of daily living and social engagement because of side effects (e.g. insomnia, nausea, urinary incontinence, oedema, dyspnoea). In our opinion, the finding that almost one-third of our cohort of older decedents continued to be prescribed drugs considered as inadequate in the context of end-of-life care can be examined from three different perspectives.

First, what was the expected benefit of these (mostly preventive) drugs? As the patient health status gradually deteriorates and life expectancy diminishes, the number needed to treat of medications increases exponentially

Table 3. Prevalence of the most commonly prescribed drugs of questionable clinical benefit for older adults near the end of life.

Drug class (ATC code)	Total	Illness trajectory		
		Cancer	Organ failure	Prolonged dwindling
		No./No. at risk (%)	No./No. at risk (%)	No./No. at risk (%)
Continuation during the last 3 months of life				
Statins and other lipid-lowering agents (C10A)	8394/12,875 (65.2)	2104/4023 (52.3)	4707/6546 (71.9)	1583/2306 (68.6)
Calcium supplements (A12A)	6855/9856 (69.6)	1517/2591 (58.5)	3127/4392 (71.2)	2211/2873 (77.0)
Antidementia drugs (N06D)	4463/5459 (81.8)	633/804 (78.7)	617/751 (82.2)	3213/3904 (82.3)
Drugs for osteoporosis (M05B)	1581/2668 (59.3)	461/855 (53.9)	780/1258 (62.0)	340/555 (61.3)
Vitamin D (A11CC)	1225/1905 (64.3)	245/414 (59.2)	737/1097 (67.2)	243/394 (61.7)
Initiation during the last 3 months of life				
Antianaemia drugs (B03A, B03B, B03XA01)	2090/35,959 (3.6)	675/10,657 (6.3)	909/14,307 (6.4)	506/10,995 (4.6)
ACE inhibitors or angiotensin II antagonists (C09)	1333/35,858 (2.3)	283/10,241 (2.8)	794/12,079 (6.6)	256/13,538 (1.9)
Novel oral anticoagulants (B01AE, B01AF)	848/56,396 (1.5)	155/15,862 (1.0)	510/22,239 (2.3)	183/18,295 (1.0)
Statins and other lipid-lowering agents (C10A)	686/45,540 (1.2)	164/12,315 (1.3)	423/16,833 (2.5)	99/16,392 (0.6)
Vitamin K antagonists (B01AA)	680/51,042 (1.2)	128/14,574 (0.9)	461/19,060 (2.4)	91/17,408 (0.5)

ACE: angiotensin-converting enzyme.

For 'continuation', the number of individuals at risk corresponds to the population already treated with each specific drug class between 12 and 3 months before death. For 'initiation', the number of individuals at risk amounts to the decedents who were not previously treated and had at least one refill during the last 3 months before death. Antidementia drugs include both anticholinesterases (donepezil, rivastigmine and galantamine) and memantine. Antianaemia drugs include iron supplements, vitamin B12, folic acid and erythropoietin.

and the probability of achieving a clinically meaningful endpoint becomes slim.⁶ Rather than the absolute risk reduction over a 5- or 10-year period, physicians trying to rationalize drug treatments should take into consideration the *time-to-benefit* (i.e. the time until a benefit is observed among people receiving therapy compared to those not receiving it).⁹ Moreover, since the benefit of treatments is only meaningful if it meets the patients' personal preferences and priorities, drugs prescribed near the end of life should be concordant with the goals of care. The *American Geriatrics Society* has, for instance, recently emphasized the necessity to incorporate the patients' health priorities into decision-making.⁴⁵ Since the preferences of older adults with advanced diseases often vary over time, keeping the therapeutic target aligned with the goals of care requires continuous communication between the clinicians, the patient and the relatives.^{46,47} Specialist palliative care services could potentially play an important role in facilitating the deprescribing process, for instance, by ensuring that the time-to-benefit of drug treatments is incorporated in advance care planning.

Second, to what extent did the prescribers consider the potential for serious drug–drug interactions, drug-related injuries, and drug-induced symptoms? Balancing the benefits and risks of treatments is particularly challenging when it involves trade-offs between survival and quality of life. Although avoiding harm is a tenet of clinical practice, prescribers may insufficiently integrate the exacerbated vulnerability of older, frail and multimorbid patients to the adverse effects of drugs. The initiation of

beta-blockers after myocardial infarction has, for instance, been found to be associated with a reduction of mortality and also with a worsening of functional outcomes among nursing home residents, especially among those with moderate-to-severe cognitive impairment or severe functional limitations.^{48,49} Our finding that older adults at high risk of frailty were less likely to initiate but more likely to continue drugs of questionable benefit at the end of life should give pause. It illustrates the ability of clinicians to recognize the futility of initiating disease-oriented drugs for these patients, but their difficulty to discontinue these same drugs once they have been initiated – a phenomenon closely related to what is known as the 'endowment bias' in behavioural economics.^{50,51}

Third, could these drugs realistically have been deprescribed? In retrospect, the benefit of long-term preventive treatments near the end of life can be deemed as limited or even non-existent. However, several factors can hinder their discontinuation in routine clinical practice. Prognostic uncertainty is often cited as being one of the drivers of overly aggressive therapy at the end of life.⁵² Despite considerable efforts to develop robust instruments and tools, predictions about the remaining life expectancy of individual patients remain highly inaccurate, and clinicians are most often over-optimistic.^{53–55} It is, therefore, delicate to find the optimal timing of deprescribing strategies.^{56,57} Moreover, aligning drug treatments with the end-of-life goals of care proves to be difficult in real-world care settings, not only because discussing end-of-life-related issues can be personally

challenging and emotionally burdensome for clinicians, patients and family members alike^{58,59} but also because of practical obstacles.⁶⁰ Optimal communication and shared decision-making with seriously ill persons require skills for which physicians are rarely trained⁶¹ and an amount of time that they often cannot afford (in Europe, the average duration of GP consultations ranges from 5 to 20 min).⁶² Clinicians also need time for gradually tapering off drugs that may otherwise cause withdrawal syndromes or have a rebound effect, for closely monitoring patients afterwards in order to detect potential adverse events and for documenting their decision in the medical records.⁶³ Finally, the patient and family expectations may contribute to the decision not to discontinue drug treatments of limited benefit, fuelled by the apprehension of physicians to cause harm, to appear as being neglectful or to take away the patient's hope.⁶⁴ Qualitative research is warranted to better understand the mechanisms that lie behind the provision of preventive drugs at the end of life and to disentangle prescribing practices guided by clinically justified motives from low-value care driven by cognitive biases and irrational decision-making.^{50,65}

Strengths and limitations

To our knowledge, this is the first study investigating the prescribing of drugs of questionable clinical benefit at the end of life in a large population of older adults. Strengths include the nationwide coverage of both community dwellers and nursing home residents, the selection of individuals who died from conditions potentially amenable to palliative care, the possibility to investigate patterns of drug prescribing across different illness trajectories and the inclusion of a rich set of chronic diseases and frailty indicators. These results can be leveraged by palliative care clinicians to target their efforts towards the patients who could benefit the most from individualized deprescribing interventions near the end of life. However, our study should be interpreted in light of several limitations. First, analysing healthcare utilization in a cohort of deceased persons underestimates the prognostic uncertainty that the prescribers experienced. Although the study population consists of older adults who died with life-limiting conditions amenable to palliative care, clinicians may not necessarily have been able to anticipate the exact time of death. We tried to mitigate this risk of bias in sensitivity analyses by excluding individuals whose underlying cause of death suggested an acute and unpredictable fatal event. Second, our definition of drugs of questionable clinical benefit is based on a consensus of European experts, with only little high-quality empirical evidence to support its conclusions. It is possible that for a small number of patients, the use of drugs deemed inadequate was in fact justified by a valid palliative indication. Explicit criteria are useful to describe

prescribing patterns in large populations, but the actual clinical benefit of therapy can only be determined by the prescribing physician caring for a specific individual patient.⁶⁶ Other tools such as STOPPFrail⁶⁷ would offer a more precise assessment of potentially inadequate drugs, but their use in epidemiological studies requires extensive information about the clinical indication of drugs that are typically not available in routinely collected data. It should also be noted that the Swedish Prescribed Drug Register only contains data about prescription drugs dispensed through community pharmacies; over-the-counter drugs and treatments administered in hospitals or from nursing home drug storeroom are not included (~10% of all defined daily doses dispensed in Sweden annually). Finally, our data do not enable us to ascertain whether patients ingested their medications as prescribed: some persons in our cohort may, for example, have refilled drugs of questionable benefit during their last 3 months of life without actually using them.

Conclusion

Many older adults with life-limiting illness receive drugs of questionable clinical benefit during their last 3 months of life. In most cases, these drugs are unlikely to achieve a meaningful health outcome during the patients' remaining lifetime. Clinicians caring for older adults should receive adequate training, guidance and resources to help them reduce the burden of potentially unnecessary and harmful drug treatments near the end of life. Specialist palliative care services could also potentially play an important role in facilitating the deprescribing process.

Author contributions

L.M. conceived and designed the study, created the study population database, performed the statistical analysis, interpreted the data, and drafted and critically revised the manuscript. J.W.W. and M.-L.L. interpreted the data and critically revised the manuscript. J.F. acquired, analysed and interpreted the data, and critically revised the manuscript. K.J. obtained funding, provided supervision, interpreted the data and critically revised the manuscript. All authors approved the final version of the manuscript and agree to be accountable for all aspects of the work. The authors affirm that this manuscript is an honest, accurate and transparent account of the study being reported, and that no important aspects of the study have been omitted.

Availability of data and materials

Clinical data and individual data from the Swedish Prescribed Drug Register cannot be made publicly available.

Declaration of conflicting interests

The author(s) declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Ethical approval

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Supplemental material

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