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Division of Clinical Pharmacology
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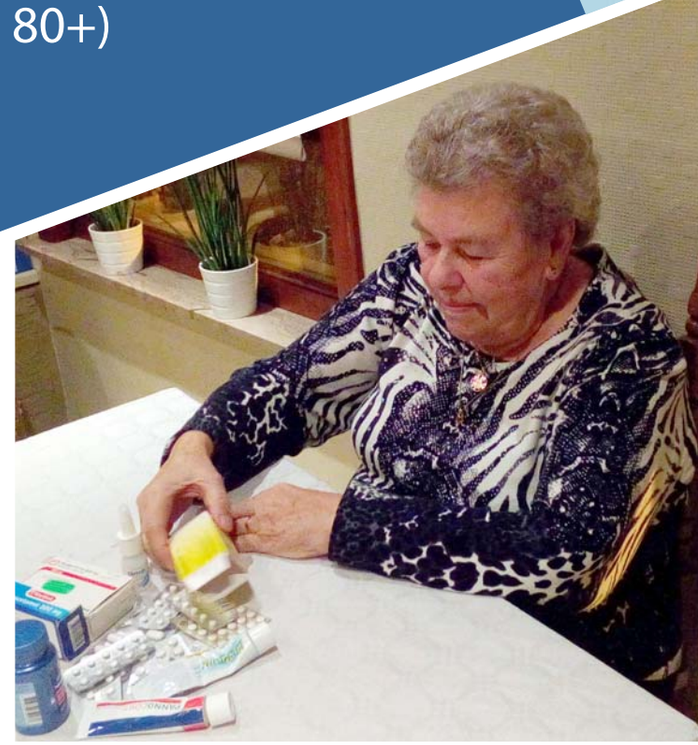
Appraisal of the appropriateness of prescribing in community-dwelling oldest old (aged 80+)



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Appraisal of prescribing in the 80+
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Chapter 4: Contents

4.1 Abstract

Background: High drug use and associated adverse outcomes are common in older adults. This study investigates association of medication use with mortality, hospitalisation, and institutionalisation in a cohort of community-dwelling oldest old (aged 80 and over).

Methods: Baseline data included socio-demographic, clinical, and functional characteristics, and prescribed medications. Medications were coded by the Anatomic Therapeutic Chemical classification. Survival analysis was performed at 18 months after inclusion using Kaplan-Meier, and multivariate analysis with Cox regression to control for covariates.

Results: Patients' (n=503) mean age was 84.4 years (range 80 – 102), and 61.2% was female. The median medication use was 5 (0 – 16). The mortality, hospitalisation, and institutionalisation rate were 8.9%, 31.0%, and 6.4% respectively. The mortality and hospitalisation group had a higher level of multimorbidity and weaker functional profile. Adjusted multivariate models showed an 11% increased hospitalisation rate for every additional medication taken. No association was found between high medication use and mortality, nor with institutionalisation. A higher association for mortality was observed among verapamil/diltiazem users, hospitalisation was higher among users of verapamil/diltiazem, loop diuretics and respiratory agents. Institutionalisation was higher among benzodiazepines users.

Conclusion: In the community-dwelling oldest old (aged 80 and over), high medication use was clearly associated with hospitalisation, independent of multimorbidity. The association with mortality was clear in univariate, but not in multivariate analysis. No association with institutionalisation was found. The appropriateness of the high medication use should be further studied in relation to mortality, hospitalisation, and institutionalisation for this specific age group.

4.2 Introduction

The oldest old (defined as individuals aged 80 and over) are characterised by a high level of multimorbidity, resulting in possible high medication intake [241, 242]. In this age group, medications are prescribed even though the benefit-risk profile is not always fully understood [270, 271]. Age related changes in pharmacokinetics and –dynamics alter the sensitivity for the therapeutic effects and often increase the side effects.

High medication use and polypharmacy (defined as the daily intake of five medications or more [135]), increases the risk of inappropriate prescribing (including overuse, underuse and misuse), drug interactions, and adverse effects in older adults [272, 273]. This can again contribute to drug related problems (DRPs) [274, 275]. DRPs alter the expected bonus of medications on their health into a possible risk. Due to a worsening clinical or functional profile of those aged 80 and more, DRPs will become more prevalent, and potentially impede with the beneficial influence of medications on their health [276].

Both the beneficial and harmful effects of medication on outcomes have been explored in younger populations (aged 65 and over). In this age group, high medication use has been associated with hospitalisation, mortality, and increased health care costs [277, 278]. In Belgium, medication related hospital admissions account for 20.9% of all hospitalisations in adults aged 65 years and over[96].

However, studies exploring the medication use in relation to relevant outcomes in the oldest old (aged 80 and over) are limited, as well as studies exploring the specific role of medications and their effect on outcomes. Studies either failed to disentangle the independent role of medications, due to the strong interrelationship with multimorbidity [279, 280], or studies focussed primarily on the appropriateness of prescribing [281, 282]. Therefore, this study aims to explore the association of medication use (number of medications, polypharmacy, specific medication groups) in the community-dwelling oldest old (aged 80 and over) with mortality, hospitalisation, and institutionalisation during a follow-up period of 18 months, and taking into account the role of multimorbidity, and demographic, clinical, and functional characteristics.

4.3 Methods

This study uses data of the Belfrail-cohort [252], a prospective, observational population-based cohort study. In summary, eligible patients were adults aged 80 years and older, without known dementia, and not in acute or palliative care. Inclusion of patients was done by general practitioners [252]. For this study, all community-dwelling patients with medication records available were selected, yielding the Belfrail-MED cohort (n=503).

Baseline data

General practitioners and clinical research assistants collected the data (structured questionnaire, clinical examination, and standardised tests). Baseline data collection consisted of socio-demographic, clinical, and functional data described in the baseline study of the Belfrail-MED cohort [283].

Socio-demographic data included age, gender, level of education, level of education, whether they lived alone, or received nursing care at home.

Clinical characteristics were collected from the standardised medical history and the list of current clinical problems. Multimorbidity was operationalised using the Cumulative Illness Rating Scale (CIRS) [253]. The CIRS measures the chronic medical illness burden while taking into consideration the severity of chronic diseases (Hudon, Fortin, and Soubhi 2007). The CIRS counts the number of 14 body systems affected with moderate disability, morbidity or extremely severe disease (severity score at least 3) [254] (possible range: 0 to 14) [14].

Functional characteristics included Activities of Daily Living (ADL, derived from the KATZ scale), physical activity (LASA Physical Activity Questionnaire, LAPAQ), cognitive status (Mini Mental State Examination, MMSE, adjusted for age and level of education) [259], and fall risk (Tinetti).

Medication data included all chronic medications at baseline. The brand name, active substance, and the prescribed daily dose were recorded by the general practitioners.

Follow-up data

Follow-up data was collected using standardised questionnaires, filled in by the general practitioners. The original follow-up period was 5

years. For this study, we defined a cut-off at 18 months, because in longer follow-up periods, associations with baseline characteristics are expected to fade away. Patients who died, who were institutionalised, or were hospitalised during the 18 months follow-up period were considered as 'events'.

The data on mortality included date and cause of death. Data on hospitalisation (defined as unplanned hospital stays lasting longer than 1 day) included the date of the first hospital stay. Institutionalisation was defined as entering the nursing home for permanent stay. The date of entering a nursing home was recorded.

Medication handling

All drugs were recorded by brand or compound name. They were entered into a data program based on the official register of medications on the Belgian market (source: https://www.ehealth.fgov.be). The medication was translated into the Anatomical Therapeutic Chemical classification (WHO ATC/DDD 2013) [284].

For the analysis of the medication use in association with the outcomes, we used three models: the number of medications, polypharmacy, and medication subclasses. Polypharmacy was defined as the chronic intake of ≥5 medications [2]. For the medication subclasses, we analysed the first (main anatomical groups) and second ATC level (therapeutical main groups). Subsequently, we analysed medications at the third ATC level (therapeutic subgroup) or lower for medications or medication groups that are specifically mentioned in Potential Inappropriate Medication (PIM) lists (BEERS, STOPP/START)[133, 187]. Additionally, we created a dichotomous variable including all medications with anticholinergic properties, according to the study of Duran et al. (2010) [215].

Functional data handling

The KATZ ADL-scale and the LAPAQ scores were divided into smaller groups to determine those with the highest care dependency, and those with the lowest physical activity respectively.

The KATZ ADL-scale (range 6 – 30) has six domains (bathing, clothing, toileting, transferring, continence, and feeding), and a higher domain or overall score signifies being more care dependent. We identified those care independent (KATZ ADL score 6, scoring 1 at all six domains), the somewhat care dependent (KATZ ADL scores 7 - 12), and those most care dependent (scoring 13 and more).

The raw LAPAQ scores (range 0 - ∞) were divided into quartiles. The lowest quartile was identified as those with the lowest physical activity.

Finally, the MMSE was used for identification of cognitive impairment, with a cut-off adapted to the age and level of education of the respondents [259].

Statistical analysis

SPSS 21.0 (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA) was used for statistical analysis.

For descriptive statistics means, medians or proportions were used. Comparison of continuous data was done using t-tests or non-parametric tests in case of skewed data. Analysis of categorical variables was done using chi^2 tests.

The Kaplan-Meier method was used to estimate survival. For the assessment for the difference of survival between the groups with and without polypharmacy, the log-rank test was used. The censor date was set at 18 months after inclusion, and time to event was calculated for the three outcomes. For the calculation of the observation periods for both hospitalisation, and institutionalisation, censoring was done for deaths. The date of death was then regarded as the end of the observation period. For all others, censoring was set at 18 months after inclusion. The mean time to death, first hospitalisation or institutionalisation was calculated.

A Cox proportional hazard models was used to calculate univariate and adjusted multivariate Hazard Ratios (HRs). Two multivariate models were constructed, one using the number of medications as the continuous independent variable, and the other using therapeutic medication subclasses. To study the specific role of medications, all models were adjusted for multimorbidity, and additional confounding demographic variables.

Ethical considerations

The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université catholique de Louvain (UCL), Brussels (B40320084685, on 27/10/2008) and later by the Ethics Committee of Ghent University Hospital (B670201421408, on 26/06/2014). All patients provided informed consent.

4.4 Results

Description of the study population

An overview of the socio-demographic, functional, and clinical characteristics and the medication use of the participants are provided in Table 4.1. The mean age was 84.4 years (range 80 – 102), 61.2% was female. The median level of multimorbidity (defined by CIRS) was 4 (range 1 – 9), with hypertension as the most prominent clinical problem. The mean number of medications was 5.4 (range 0 – 16) and polypharmacy

Table 4.1. *Demographical, clinical, and functional characteristics, and medication use at baseline (n= 503).*

Demographical	**%**
Mean age in years (range)	*84.4* (80 - 102)
Gender (% female)	61.2
Living alone	43.3
Low education (≤8 years)	69.2
Clinical[1]	**%**
Median multimorbidity[2] (range)	*4* (1 – 9)
Hypertension	70.4
Osteoarthritis	57.1
Hyperlipidaemia	44.1
Heart Failure (NYHA > 0)	38.4
Diabetes	18.9
Post infarct / post stroke	17.7
COPD / asthma	13.1
Chronic renal failure	11.1
Functional	**Median (IQR range)**
Activities of daily living, ADL	6 (6 - 8)
Physical activity, LAPAQ	70 (30 – 102)
Mental status, MMSE	28 (26 – 29)
Medication use[3]	**%**
Median number of medication (range)	*5* (0-16)
Polypharmacy (≥5 drugs daily)	57.7
ATC C - Cardiovascular	86.3
ATC B - Blood and blood forming	56.1
ATC N - Nervous system	54.5
ATC A - Alimentary tract and metabolism	50.1
ATC M - Musculo-skeletal system	23.5
ATC R - Respiratory system	15.9
ATC H - Systemic hormonal preparations	11.7
ATC G - Genito-urinary system and sex hormones	10.3

(≥5 medications) was present in 57.7% of the population. Cardiovascular, haematological, and nervous system drugs were most used.

Mortality

The mortality rate was 8.9% (n=45) at 18 months. Most prominent causes of death were cardiovascular and/or cerebrovascular events (48.9% of deaths), followed by cancer (20.0%), respiratory problems (13.3%), and general deterioration (6.7%).

The deceased patients were older, and received more nursing care at home. They also had a higher mean level of multimorbidity (CIRS). Within the separate clinical problems, only chronic renal failure was significantly associated with higher mortality. All the functional characteristics were associated with higher mortality (see Table 4.2).

The survival rate 18 months after inclusion differed significantly between those with polypharmacy and those without (93% versus 88% respectively, p=0.049).

In univariate analysis, mortality was significantly associated with high medication use. At medication subclass level, mortality was higher in those taking high-ceiling or loop diuretics, selective calcium channel blockers with a direct cardiovascular effect, predominantly verapamil/diltiazem use , antidepressants, and anticholinergics, see Table 4.3.

In multivariate analysis, no association with mortality was found for the number of medications (Hazard Ratio 1.05, 95% CI 0.94 – 1.18), after correction for multimorbidity, age, and gender. At medication subclass level, selective calcium channel blockers, predominantly verapamil/diltiazem, were associated with increased mortality (HR 2.84, 95% CI 1.10 – 7.36), see Table 4.4. The additional introduction of specific clinical problems (heart failure) into the model, yielded similar results.

Hospitalisation

The hospitalisation rate in the Belfrail-MED cohort was 31.0% (n=156). Those hospitalised received more nursing care at home, had a higher level of multimorbidity, and had more clinical problems. They showed a weaker functional profile, were more care dependent, less physically active, more cognitively impaired, and had a higher risk of falling (see Table 4.2).

The hospitalisation rate after 18 months differed significantly between those with polypharmacy and those without (75% vs 63%, p=0.001).

In univariate analysis, hospitalisation was significantly associated with

Table 4.2. *Socio-demographic, clinical, and functional characteristics associated with mortality, first hospitalisation, and institutionalisation after a follow-up of 18 months.*

	Dead?				Hospitalised?				Institutionalised?			
	Yes N=45	No N=458	P value	Hazard Ratio*	Yes N=156	No N=347	P value	Hazard Ratio	Yes N=32	No N=471	P value	Hazard Ratio
Event rate (%)	**8.9**	**91.1**			**31.0**	**69.0**			**6.4**	**93.6**		
Socio-demographic	%	%		HR (95% CI)	%	%		HR (95% CI)	%	%		HR (95% CI)
Mean age	*85.7*	*84.3*	*.016*	*1.09 (1.01 – 1.16)*	*84.9*	*84.2*	*.058*	*1.04 (0.998 – 1.08)*	*86.7*	*84.1*	*<.001*	*1.15 (1.10 – 1.21)*
Female gender	60.0	61.4	.859	0.94 (0.52 – 1.70)	59.0	62.2	.486	0.89 (0.65 – 1.22)	73.2	59.3	.025	1.78 (1.05 – 3.01)
Low education (≤8 years)	65.9	70.4	.533	0.83 (0.45 – 1.55)	70.1	70.0	.971	1.03 (0.73 – 1.45)	70.4	70.0	.936	1.02 (0.62 – 1.70)
Living alone	46.7	43.0	.637	1.15 (0.64 – 2.07)	44.2	42.9	.787	1.06 (0.77 – 1.46)	60.6	40.5	.002	2.06 (1.28 – 3.32)
Clinical												
Mean comorbidity, CIRS	*4.6*	*3.7*	*<.001*	*1.36 (1.15 – 1.59)*	*4.3*	*3.6*	*<.001*	*1.25 (1.14 – 1.36)*	*3.9*	*3.8*	*.496*	*1.08 (0.94 – 1.24)*
Hypertension	73.3	70.2	.664	1.60 (0.60 – 2.24)	71.8	69.9	.674	1.09 (0.77 – 1.54)	73.2	70.1	.587	1.17 (0.69 – 1.98)
Osteoarthritis	61.4	57.9	.657	1.15 (0.63 – 2.10)	59.7	57.5	.644	1.11 (0.81 – 1.53)	58.0	58.3	.965	1.00 (0.62 – 1.61)
Hyperlipidaemia	44.2	45.4	.877	0.95 (0.52 – 1.73)	47.4	44.4	.539	1.08 (0.79 – 1.49)	36.8	46.7	.127	0.68 (0.41 – 1.10)
Heart Failure	46.7	37.6	.230	1.44 (0.80 – 2.58)	46.8	34.6	.009	1.56 (1.14 – 2.14)	42.3	37.7	.468	1.20 (0.75 – 1.92)
Diabetes	29.5	18.0	.062	1.85 (0.97 – 3.54)	24.0	16.8	.056	1.48 (1.02 – 2.14)	5.6	21.2	.002	0.26 (0.10 – 0.73)
Post MI / post CVA	29.3	17.8	.073	1.80 (0.92 – 3.51)	22.8	17.1	.145	1.32 (0.89 – 1.95)	21.7	18.3	.501	1.28 (0.72 – 2.27)
COPD/Asthma	24.4	13.9	.070	1.92 (0.94 – 3.92)	21.4	11.9	.007	1.80 (1.21 – 2.68)	13.0	15.1	.657	0.90 (0.45 – 1.81)
Depression	20.9	12.1	.099	1.88 (0.90 – 3.92)	20.9	9.3	<.001	1.97 (1.34 – 2.91)	18.6	11.9	.125	1.66 (0.91 – 3.03)
Chronic renal failure	25.0	10.1	.003	2.79 (1.41 – 5.53)	16.1	9.4	.031	1.74 (1.12 – 2.69)	13.4	11.1	.574	1.30 (0.65 – 2.63)
Functional												
Most care dependent[1]	25.0	7.8	<.001	3.42 (1.73 – 6.76)	14.6	7.0	.007	2.04 (1.30 – 3.20)	18.8	8.6	.057	1.45 (0.70 – 3.04)
Lowest physical active[2]	44.4	23.2	.002	2.48 (1.38 – 4.49)	31.6	22.3	.028	1.51 (1.07 – 2.12)	36.6	23.2	.016	1.88 (1.16 – 3.05)
Cognitive impairment	30.2	13.8	.004	2.54 (1.32 – 4.86)	22.3	12.2	.004	1.81 (1.23 – 2.67)	24.3	13.7	.023	2.05 (1.19 – 3.54)
Fall risk – Tinetti	45.5	20.0	<.001	3.13 (1.73 – 5.66)	36.0	16.3	<.001	2.45 (1.76 – 3.43)	45.7	18.4	<.001	3.60 (2.25 – 5.76)

[1] Highest care dependency was defined as respondents scoring ≥ 13 (9.1%) on the KATZ ADL scale.

[2] Lowest physical active was defined as the quartile with the lowest raw score on the LAPAQ.

[3] Cognitive impairment was defined using the MMSE, adjusted for age and level of education.

Table 4.3. Medication use associated with mortality, first hospitalisation, and institutionalisation at 18 months.

	Dead				Hospitalised				Institutionalised			
	Yes	No	P	Hazard Ratio*	Yes	No	P	Hazard Ratio	Yes	No	P	Hazard Ratio
	N=45	N=458	value		N=156	N=347	value		N=32	N=471	value	
Event rate (%)	**8.9**	**91.1**			**31.0**	**69.0**			**6.4**	**93.6**		
	%	%		HR (95% CI)	%	%		HR (95% CI)	%	%		HR (95% CI)
Mean number of medications	*6.4*	*5.3*	*0.033*	*1.12 (1.02 – 1.22)*	*6.3*	*5.0*	*<0.001*	*1.14 (1.05 – 1.20)*	*5.5*	*5.4*	*0.842*	*1.02 (0.94 – 1.10)*
Polypharmacy (≥5 drugs)	71.1	56.3	0.056	1.87 (0.98 – 3.56)	67.3	46.7	0.003	1.69 (1.21 – 2.36)	59.2	57.4	0.782	1.11 (0.69 – 1.78)
At least 1 psychotropic drug	55.6	41.0	0.060	1.73 (0.96 – 3.12)	50.0	38.9	0.020	1.44 (1.05 – 1.97)	56.3	40.0	0.010	1.85 (1.16 – 2.96)
At least 3 cardiovascular drugs	20.0	16.4	0.534	1.26 (0.61 – 2.61)	21.8	14.4	0.040	1.56 (1.06 – 2.28)	18.3	16.4	0.695	1.13 (0.62 – 206)
At least 1 anticholinergic drug	38.6	19.8	0.004	2.40 (1.31 – 4.40)	30.3	17.4	0.001	1.82 (1.29 – 2.56)	22.5	21.3	0.809	1.14 (0.65 – 1.98)
A02 – acid related drugs	31.1	23.8	0.276	1.42 (0.76 – 2.67)	28.2	22.8	0.189	1.22 (0.86 – 1.73)	23.9	24.5	0.914	0.98 (0.57 – 1.69)
A10 – antidiabetic drugs	24.4	15.1	0.101	1.76 (0.89 – 3.47)	17.9	15.0	0.401	1.22 (0.81 – 1.84)	4.2	17.8	0.004	0.24 (0.08 – 0.76)
A12 – Mineral supplements	17.8	16.6	0.839	1.10 (0.51 – 2.35)	23.1	13.8	0.010	1.63 (1.13 – 2.37)	16.9	16.7	0.961	1.00 (0.54 – 1.87)
B01 – antithrombotic agents	51.1	54.8	0.635	0.88 (0.49 – 1.58)	53.8	54.8	0.850	0.98 (0.71 – 1.34)	52.1	54.9	0.666	0.90 (0.57 – 1.44)
C01 – cardiac therapy medication	24.4	20.3	0.513	1.25 (0.63 – 2.47)	25.0	18.7	0.108	1.36 (0.95 – 1.96)	19.7	20.8	0.830	0.95 (0.53 – 1.71)
C03 – Diuretics	46.7	30.6	0.027	1.92 (1.07 – 3.50)	44.2	26.5	<0.001	1.96 (1.43 – 2.68)	39.4	30.8	0.148	1.50 (0.93 – 2.42)
C03CA – Loop diuretics	34.1	15.6	0.002	2.61 (1.40 – 4.86)	29.7	11.6	<0.001	2.61 (1.85 – 3.69)	22.5	16.4	0.202	1.57 (0.90 – 2.74)
C07 – Beta Blocking agents	35.6	42.6	0.362	0.75 (0.41 – 1.38)	37.8	43.8	0.208	0.81 (0.58 – 1.11)	39.4	42.4	0.644	0.86 (0.53 – 1.38)
C08 – Calcium Channel blockers	26.7	24.0	0.692	1.14 (0.59 – 2.21)	24.4	24.2	0.971	1.03 (0.71 – 1.48)	23.9	24.3	0.947	0.96 (0.56 – 1.66)
C08D – Selective Ca channel blockers	11.4	3.3	0.009	3.49 (1.38 – 8.86)	7.7	2.3	0.004	2.49 (1.38 – 4.49)	5.6	3.7	0.451	1.66 (0.61 – 4.56)
C09 – agents acting on RAAS	44.4	41.7	0.722	1.12 (0.62 – 2.01)	42.9	41.5	0.760	1.10 (0.80 – 1.51)	32.4	43.5	0.078	0.67 (0.41 – 1.09)
C10 – Lipid modifying agents	28.9	33.6	0.520	0.81 (0.42 – 1.54)	32.7	33.4	0.871	0.97 (0.70 – 1.36)	28.2	36.0	0.331	0.77 (0.46 – 1.30)
Benzodiazepines [1]	40.0	35.2	0.517	1.21 (0.66 – 2.19)	37.8	34.6	0.483	1.11 (0.81 – 1.54)	49.3	33.3	0.009	1.80 (1.13 – 2.87)
Antidepressants [2]	26.7	15.1	0.043	2.00 (1.03 – 3.86)	23.1	13.0	0.004	1.73 (1.19 – 2.51)	14.1	16.4	0.617	0.92 (0.47 – 1.80)
R03 – medication for obstructive airway diseases	17.8	11.8	0.244	1.29 (0.94 – 1.78)	21.8	8.1	<0.001	2.41 (1.64 – 3.52)	15.5	11.8	0.381	1.36 (0.71 – 2.58)

* Hazard Ratios are calculated using Cox regression analysis (univariate analysis)

[1] Benzodiazepines are defined as ATC classes N05BA, N05CD, N05CF.

[2] Antidepressants are defined as ATC classes N06AA, N06AB, N06AG, and N06AX.

high medication use (see Table 4.3). Hospitalisation was significantly associated with the use of mineral supplements, loop diuretics, verapamil/diltiazem, antidepressants, drugs for obstructive airway diseases, and anticholinergic agents, see Table 4.3.

In multivariate analysis, hospitalisation was significantly associated with high medication use (HR 1.11, 95% CI 1.03 – 1.18). For every additional medication taken at baseline, there was an 11% increased hospitalisation rate. At medication subclass level, hospitalisation was also associated with the use of verapamil/diltiazem (HR 2.14, 95% CI 1.10 – 4.16), loop diuretics (HR 2.24, 95% CI 1.48 – 3.40), and medications used in obstructive airway diseases (HR 1.76, 95% CI 1.12 – 2.79), see Table 4.4. The additional introduction of specific clinical problems (heart failure, COPD/Asthma) into the model, yielded similar results.

Institutionalisation

The institutionalisation rate after 18 months was 6.4% (n=32). Those entering a nursing home were older, female, lived alone, and received more nursing care at home. Their level of multimorbidity was equal to those who remained at home. Having diabetes or using medications for diabetes had a negative association with institutionalisation. The institutionalised were less physically active, more cognitively impaired, had a high risk of falling, but were not more care dependent (see Table 4.2).

There was no difference in institutionalisation rate 18 months after inclusion among those with polypharmacy and those without (94% vs 93%, p=0.654, see Figure 4.1).

In univariate analysis, institutionalisation was not associated with high medication use. Increased institutionalisation was associated with the use of at least 1 psychotropic medication, predominantly due to a higher benzodiazepine use, see Table 4.3.

Multivariate analysis showed no associations with high medication use (HR 1.00, 95% CI 0.90 – 1.09). At medication subclass level, institutionalisation was only associated with the use of benzodiazepines (HR 1.62, 95% CI 1.01 – 2.60), see Table 4.4.

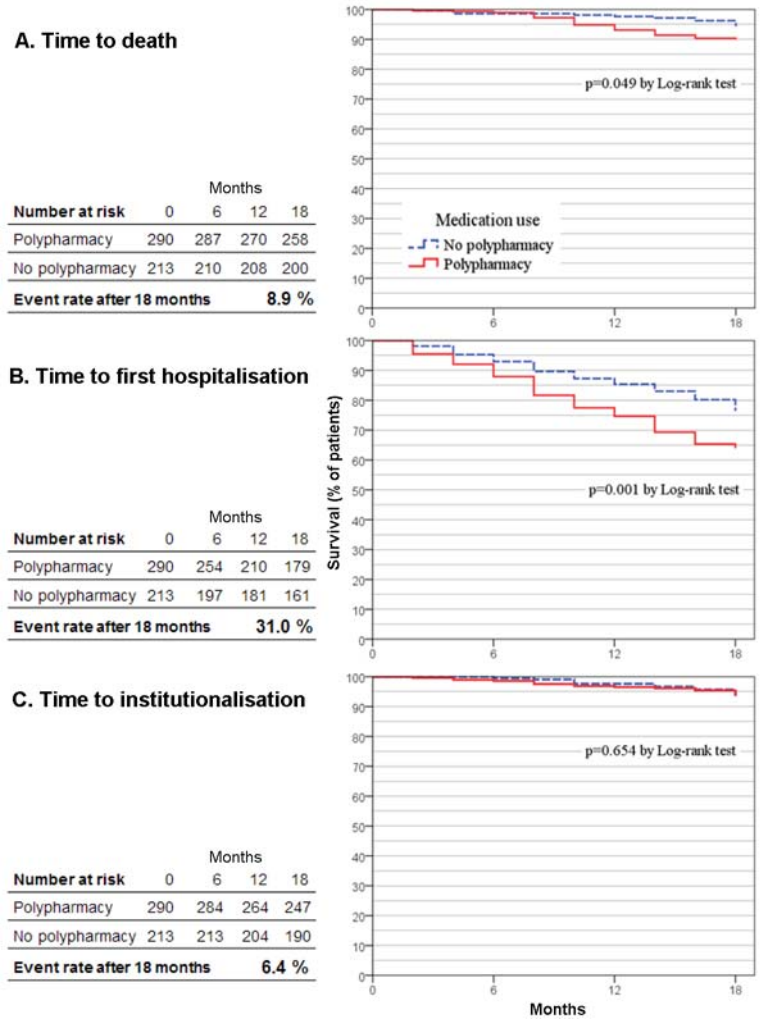

Figure 4.1. *Kaplan-Meier Survival analysis of time to death (**A**), time to the first hospitalisation (**B**), and to institutionalisation (**C**) for patients having polypharmacy (≥5 medications) and patients without polypharmacy.*

Table 4.4. *Multivariate analysis of medication use in association with mortality (9.3%), hospitalisation (31.0%), and institutionalisation (6.4%) after 18 months in a cohort of oldest old, aged 80 and over.*

		Mortality	Hospitalisation	Institutionalisation
Model 1	Number of medications	1.05 (0.94 – 1.18)	1.11 (1.03 – 1.18)	1.00 (0.90 – 1.09)
Model 2	C08D – Selective Calcium channel blockers	2.84 (1.10 – 7.36)	2.14 (1.10 – 4.16)	-
	C03CA - Loop diuretics	-	2.24 (1.48 – 3.40)	-
	R03 - Agents in obstructive airway diseases	-	1.76 (1.12 – 2.79)	-
	Benzodiazepines[1]	-	-	1.62 (1.01 – 2.60)

The models were adjusted for age, gender, and for multimorbidity (using the CIRS).

[1] Benzodiazepines are defined as ATC classes N05BA, N05CD, N05CF.

4.5 Discussion

This study explored association of high chronic medication use with three different outcomes (mortality, hospitalisation, and institutionalisation) during an 18 months observation period in a cohort of community-dwelling oldest old, defined as persons aged 80 years and over.

Main finding of this study

To the best of our knowledge, this is the first longitudinal study investigating these associations in a cohort of community-dwelling oldest old. Our main finding is that in this oldest old cohort, every additional medication used at baseline did increase the rate of hospitalisation with 11% after an observation period of 18 months

At the level of specific medication groups in multivariate analysis, the use of verapamil/diltiazem showed associations with increased mortality. The use of verapamil/diltiazem, loop diuretics and asthma/COPD-medications were independently associated with higher hospitalisation rate. Finally, benzodiazepines were associated with higher institutionalisation rate.

What this study adds

The major strengths of this study are the longitudinal design, and the

exclusive cohort of oldest old (aged 80 and over), and the multivariate analysis, adjusted for multimorbidity. This study provides new information in this specific subpopulation, where little is known on medication related outcomes [285].

Limitations of the study

Limitations are the observational nature, not allowing causal interference. We had data on chronic baseline medication use, but no data on over-the-counter drugs or *pro re nata* drugs (medication that is taken when needed, or if the situation arises).

What is already known

Medication is given to treat or prevent disease, with the aim to lower the risk of mortality, and hospitalisation. The beneficial effect of medications can be jeopardised by the increasing presence of drug related problems with increasing higher medication use. In younger populations (aged 65 and over) the association of polypharmacy with hospitalisation and mortality is more clear [286–288]. In the oldest old (aged 80 and over), the association with hospitalisation remained, but there was no association found with mortality for the number of medications.

One may speculate why in the oldest old (aged 80 and over), high medication use, was not clearly associated with mortality. Only looking at the number of medications may be too crude to address the complex relationship with mortality, as it does not take into account the role of inappropriate medications or the role of not-used medications (either by not prescribing, or by deprescribing). It is possible that patients with high medication use are well treated in a well-balanced therapy with little excess risk of mortality [244], as well as those with a low medication use miss beneficial, necessary medications. In following studies, we will address the role of inappropriate medications, and inappropriate prescribing by both looking at misused and underused medications.

The observed association between institutionalisation and cognitive impairment and use of benzodiazepines suggests that cognitive problems, but not the level of multimorbidity and care dependency, is the dominating reason for older adults to move from home care to the nursing home [289]. The puzzling association with anti-diabetic drugs might be explained by the focused and continuous home care provided for older community-dwelling diabetes patients in Belgium [290].

In our univariate analysis, all aspects of functional profile in the oldest

old were strongly associated with mortality, hospitalisation, and institutionalisation. Other findings also suggest that more functionally active oldest old benefit in terms of reduced mortality or hospitalisation risks [291]. However we could not confirm this association in multivariate analysis, after the introduction of multimorbidity.

4.6 Conclusion

In the community-dwelling oldest old (aged 80 and over), high medication use, independent of multimorbidity, was clearly associated with hospitalisation The association with mortality was present in univariate analysis, but not in multivariate. There was no association with institutionalisation. The appropriateness of the high medication use should be further studied in relation to mortality, hospitalisation, and institutionalisation for this specific age group aged 80 and over.