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# Cardiovascular drug use among people with cognitive impairment living in nursing homes in northern Sweden

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## Abstract

**Purpose** The aim of this study was to describe changes in the pattern of cardiovascular agents used in elderly people living in nursing homes between 2007 and 2013. Further, the aim was to analyse the use of cardiovascular drugs in relation to cognitive impairment and associated factors within the same population, where prescription of loop diuretics was used as a proxy for heart failure.

**Methods** Two questionnaire surveys were performed including 2494 people in 2007 and 1654 people in 2013 living in nursing homes in northern Sweden. Data were collected concerning drug use, functioning in activities of daily living (ADL) and cognition, using the Multi-Dimensional Dementia Assessment Scale (MDDAS). The use of different drugs and drug classes among people at four different levels of cognitive function in 2007 and 2013 were compared.

**Results** The proportion of people prescribed ASA and diuretics was significantly lower at all four levels of cognitive function in 2013 compared to 2007. Among people prescribed loop diuretics, the use of angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARBs) increased from 37.8 to 45.6%,  $\beta$ -blockers from 36.0 to 41.8% and warfarin from 4.4 to 11.4%. The use of warfarin, ACEI/ARBs,  $\beta$ -blockers and mineralocorticoid receptor antagonists (MRAs) were less common among individuals with more severe cognitive impairment.

**Conclusion** The results indicate that cardiovascular drug treatment has improved between 2007 and 2013, but there is room for further improvement, especially regarding adherence to guidelines for heart failure. Increasing cognitive impairment had an effect on treatment patterns for heart failure and atrial fibrillation.

**Keywords** Major neurocognitive disorders · Nursing home · Cardiovascular drugs · Heart failure · Drug use

## Introduction

Cardiovascular disease, leading to about one-third of all deaths globally, is the most common cause of mortality [1].

Untreated hypertension is an important risk factor in developing heart failure, ischaemic heart disease, stroke, atrial fibrillation, chronic kidney disease and peripheral arterial disease, and it has also been associated with a higher risk of cognitive decline [2]. Hypertension is a common condition with more than one billion people affected worldwide. The number of people with hypertension has increased significantly in recent decades, partly due to the growing and ageing population [3]. The prevalence of systolic hypertension increases with age [4], but might be declining again in very advanced age [5].

As mentioned above, untreated hypertension can cause heart failure. Typical symptoms of heart failure are fatigue, tiredness, shortness of breath and ankle swelling [6]. The prognosis for people with heart failure is poor, and the rates of hospital admissions and mortality are high [7]. A majority of these people are elderly [8]. Even though heart failure is a disease with high prevalence in the elderly, these people are often

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excluded or underrepresented in clinical studies [9–11]. Underrepresentation in studies and less contact with specialist care are possible reasons for the sparse evidence for disease management of heart failure in elderly people [9]. These people often have multiple comorbidities, polypharmacy [12–14] and a worse prognosis than do younger people [9, 14].

Untreated hypertension is also a risk factor for atrial fibrillation and is increasingly common as people age. In Europe, the estimated prevalence of atrial fibrillation in adults is 1–4%. This number is rising to > 13% among individuals over 80 years [15]. Also, there is an association between prevalent atrial fibrillation and development of vascular cognitive impairment [16].

Major neurocognitive disorders are age-related, progressive disorders that affect cognitive, emotional, behavioural and neurological functions [17, 18]. Today, a high proportion of people living in nursing homes have cognitive impairment [19]. With an ageing population, and as the prevalence of cardiovascular diseases and cognitive impairment increases with age, people in the future will be more likely to suffer from both these conditions [20]. Also, today multiple medical comorbid conditions are common in older adults with major neurocognitive disorders. Schubert et al. reported that people with major neurocognitive disorders attending primary care had on average 2.4 chronic conditions and received 5.1 medications. Cardiovascular diseases such as hypertension, coronary artery disease, chronic heart failure and stroke were common and required the use of multiple drugs [21]. Furthermore, the presence of chronic diseases such as chronic heart failure and hypertension in people with major neurocognitive disorders is associated with higher rates of hospitalisation compared with those who do not have cognitive impairment [22].

Many studies have described drug use as being specifically inappropriate for people with cognitive impairment, for example, antipsychotic drugs [23], anticholinergic drugs [24] and potentially inappropriate drugs (PIMs) [25] according to different criteria. Much less is known about how major neurocognitive disorders affect treatment patterns regarding chronic conditions such as cardiovascular diseases. Previous studies have shown that there is an undertreatment of some cardiovascular diseases for people with cognitive impairment [26, 27]. The aim of this study was, therefore, to describe changes in the pattern of cardiovascular agents used in elderly people living in Swedish nursing homes between 2007 and 2013. Furthermore, the aim was to analyse the use of cardiovascular drugs in relation to cognitive impairment and associated factors within the same population where prescription of loop diuretics is used as a proxy for heart failure.

## Methods

### Material

A questionnaire was distributed in 2007 and 2013, including all those living in nursing homes in the County of Västerbotten in northern Sweden (see Figs. 1 and 2). In 2007, but not in 2013, geriatric and psychogeriatric hospital wards were included in the survey. These were excluded (99 persons). In total 2494 people from 2007 and 1654 people from 2013 were selected for the current analyses.

### Ethical approval and consent to participate

An opt-out consent procedure was used in this study. Nursing home staff completed the survey form without direct involvement of the residents. All participants were provided written information, and there were information posters by the entrances to the nursing homes. Residents and their relatives could decline participation if they did not want to be included. The Regional Ethical Review Board in Umeå, Sweden, approved the study (registration number 07-028M [2007] and 2012-646-31M [2013]).

### Procedures

The questionnaires were sent out to all nursing homes in the County of Västerbotten. The questionnaires included written instructions on how to carry out the assessments, and the member of staff who had the best knowledge about each resident was asked to fill in the questionnaires based on observations of the resident's condition during the preceding week. Further, the staff was informed about the possibility of contacting the research team in case of questions.

### Assessments

The Multi-Dimensional Dementia Assessment Scale (MDDAS) [28] was used to make the assessments. The scale measures, for example, cognition, motor functions, vision, hearing, speech, level of functioning in the activities of daily living (ADL) and behavioural and psychological symptoms. The present study included assessments of ADL, cognition and also registration of current drug prescriptions. The MDDAS has good inter- and intra-rater reliability [28].

Cognitive impairment was measured using a scale developed by Gottfries and Gottfries consisting of 27 items that measure a person's level of cognitive function [29, 30]. A score of less than 24 is considered to indicate cognitive impairment, which correlates with a sensitivity of 90% and a specificity of 91% [28] to the usual 24/30 Mini-Mental State Examination (MMSE) cut-off [31]. The ADL score (0–24) was calculated based on the resident's ability to cope with

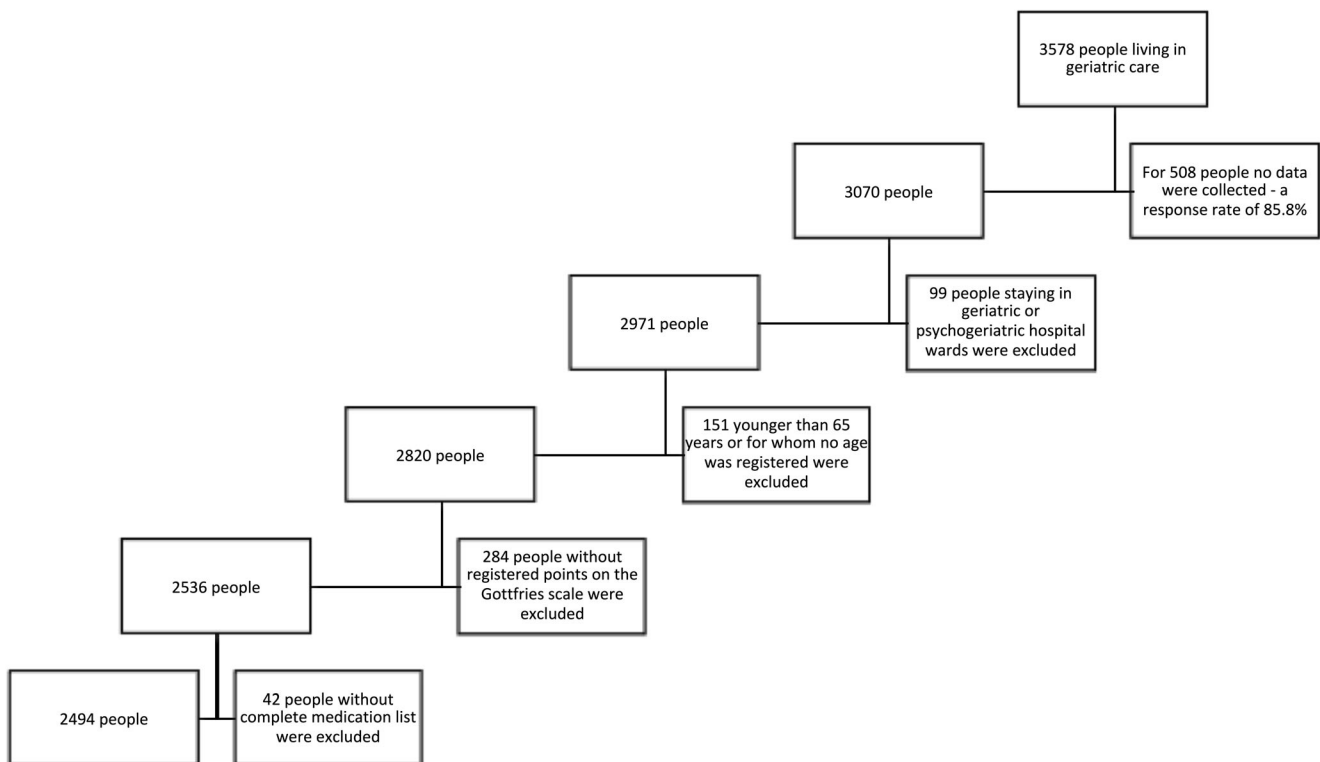


Fig. 1 Flow chart of participants in 2007

dressing, hygiene, eating and bladder and bowel control [30]. A higher score indicates greater ADL independence. The residents were divided into four groups based on Gottfries' cognitive score: severe (0–7), moderate (8–15), mild (16–23) and no (24–27) cognitive impairment [32, 33]. Information regarding drug use was collected as part of the MDDAS, and the drug data were then grouped and coded by members of the research team. The WHO ATC (Anatomical Therapeutic Chemical Index) classification system was used in order to group the drugs. The following drugs and drug classes were included in this analysis: Antithrombotic agents (B01A), warfarin (B01AA), heparin group (B01AB), platelet aggregation inhibitors excluding heparin (B01AC), aspirin/acetylsalicylic acid (B01AC06), direct thrombin inhibitors (B01AE) and other antithrombotic agents (B01AX). Cardiovascular drugs (C) and the sub-groups digitalis glycosides (C01AA), diuretics (C03),  $\beta$ -blockers (C07), calcium channel blockers (C08), angiotensin-converting enzyme inhibitor/angiotensin II receptor blockers (ACEI/ARBs) (C09) and lipid modifying agents (C10) were also included. Aliskiren (C09XA) was also included in the analysis, but no participants were prescribed this drug. Drugs were initially entered into the data file based on the first word in the drug name, and subsequently combination products, e.g. ACEI/ARB in combination with thiazides were categorised as C09. Information regarding doses and *pro re nata* medication was not coded.

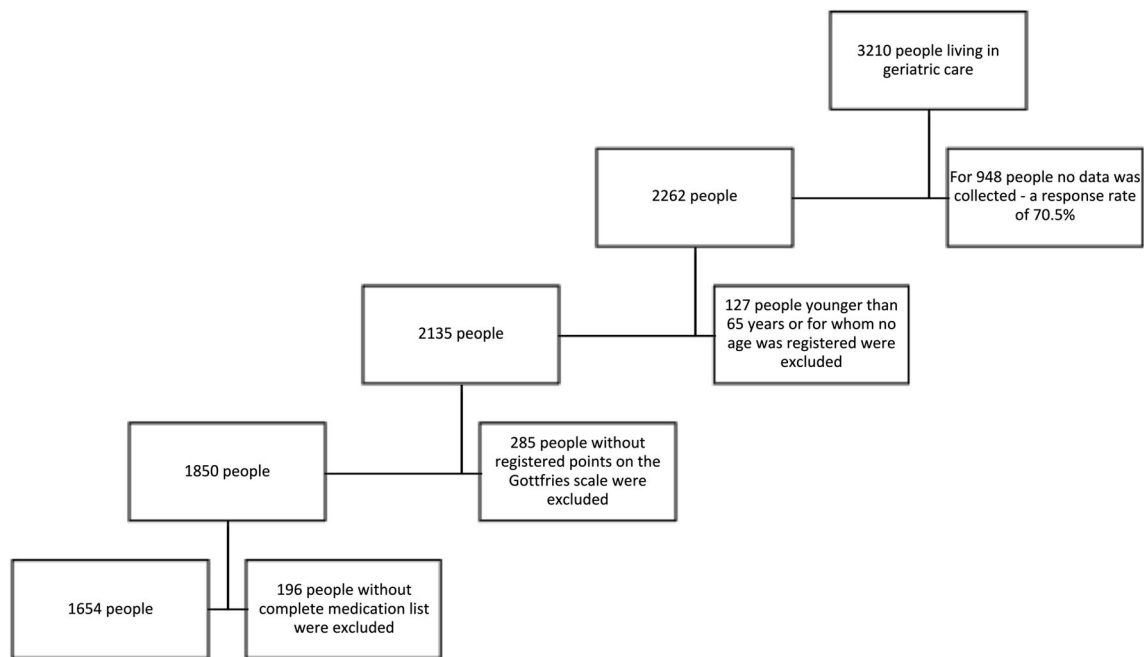
## Identification of patients with heart failure

In this study, prescription of loop diuretic was used as a proxy for heart failure. Using prescription data has been suggested as a method to identify people with heart failure [34], and since loop diuretics is the group of diuretics which is most commonly prescribed to relieve congestion in heart failure patients [35], prescription of this medication was used as a proxy.

## Statistics

Dichotomous variables were analysed using the Pearson chi-square test and continuous variables using the independent sample *t* test. The use of different drugs and drug classes were compared among people in four different levels of cognitive function (see above) in 2007 and 2013. A logistic regression model was constructed so as to control for demographic differences between the two samples.

To find factors associated with the use of different drugs and drug classes among people prescribed loop diuretics, a multiple logistic regression model was constructed. The model had the drug or drug class as the dependent variable and included sex, age, level of ADL dependency, cognitive function and year of investigation (2007 or 2013) as independent variables. Drugs and drug classes (dependent variables) included in this analysis were warfarin (B01AA), ASA



**Fig. 2** Flow chart of participants in 2013

(B01AC06), digitalis glycosides (C01AA), mineralocorticoid receptor antagonists (MRAs) (C03DA),  $\beta$ -blockers (C07), ACEI/ARBs (C09) and lipid modifying agents (C10).

In order to investigate the relationship between different drug classes and cognitive impairment, the prevalence of each drug class was plotted in relation to Gottfries' cognitive score. Polynomial regression curves were fitted to the data. First-, second- and third-degree terms were entered into a multiple linear regression model for each drug class. Significant coefficients ( $p < 0.05$ ) were used in the final regression model. A  $p$  value of  $< 0.05$  was considered to be statistically significant. Statistical calculations were performed using the SPSS Statistics 24.

## Results

The basic characteristics of the study population in the years 2007 and 2013 are presented in Table 1. The group with severe cognitive impairment was significantly larger in 2007 (21.5%) than in 2013 (18.7%) ( $p = 0.031$ ). Also, the mean age in 2007 was lower ( $84.6 \pm 6.8$ ) compared to 2013 ( $85.1 \pm 7.0$ ,  $p = 0.016$ ). There were no other significant differences between the years.

### Differences in drug treatment between 2007 and 2013 in all people and in four groups of different cognitive status

The prevalence of selected drugs and drug classes, in 2007 and 2013, in all people and in the four groups with different

levels of cognitive impairment is presented in Table 2. Among all people, the use of warfarin increased and the use of ASA was reduced between 2007 and 2013. Furthermore, the use of digitalis glycosides and diuretics decreased while the use of calcium channel blockers, ACEI/ARBs and lipid-modifying agents increased between the years.

The use of ASA and diuretics had declined significantly in all groups of different cognitive status in 2013 compared to 2007. The prevalence of digitalis glycosides in 2013 was reduced in all groups except for mild cognitive impairment (however, the same trend could be seen, but it was not statistically significant) in comparison with 2007. From 2007 to 2013, the use of ACEI/ARBs increased in the groups with severe, mild and no cognitive impairment. The prescribing of warfarin and calcium channel blockers increased between 2007 and 2013 in the groups with mild or no cognitive impairment. The use of antithrombotic agents was significantly lower in the group with severe cognitive impairment in 2013 compared to 2007. In the group with moderate cognitive impairment, the prescribing of cardiovascular drugs decreased between 2007 and 2013.

### Drug use and associated factors for people with loop diuretics

When investigating people prescribed loop diuretics as a proxy for heart failure, the proportion of people using warfarin,  $\beta$ -blockers and ACEI/ARBs had increased significantly in 2013 compared to 2007 (see Table 3). The use of ASA and digitalis glycosides declined from 2007 to 2013. No

**Table 1** Basic characteristics of the studied samples

	2007	2013	<i>p</i> value
Total number of people <i>n</i>	2494	1654	
Women <i>n</i> (%)	1707/2489 (68.6)	1119/1645 (68.0)	0.706
Age mean ± SD	84.6 ± 6.8	85.1 ± 7.0	0.016
Severe cognitive impairment <sup>a</sup>	536 (21.5)	310 (18.7)	0.031
Moderate cognitive impairment <sup>b</sup>	604 (24.2)	423 (25.6)	0.322
Mild cognitive impairment <sup>c</sup>	609 (24.4)	445 (26.9)	0.072
No cognitive impairment <sup>d</sup>	745 (29.9)	476 (28.8)	0.449
ADL score (4–24) mean ± SD	15.4 ± 6.3	15.6 ± 6.2	0.277

ADL activities of daily living, SD standard deviation

<sup>a</sup> Gottfries scale 0–7

<sup>b</sup> Gottfries scale 8–15

<sup>c</sup> Gottfries scale 16–23

<sup>d</sup> Gottfries scale 24–27

statistically significant changes were seen for the use of MRAs or lipid-lowering drugs.

Table 4 shows the results of the multiple logistic regression analysis for factors associated with different drugs or drug classes within the group of people treated with loop-diuretics. The year 2013 was associated with a higher proportion of people using warfarin,  $\beta$ -blockers and ACEI/ARBs. For ASA and digitalis, the year 2013 was associated with a decreased proportion of people prescribed the drugs. People with a higher ADL score were more likely to be prescribed ACEI/ARBs,  $\beta$ -blockers and lipid modifying agents. Furthermore, female sex was associated with a higher use of MRAs, but lower use of ASA and lipid-modifying agents. Increasing age made it more unlikely to be prescribed warfarin, ACEI/ARBs and lipid-modifying agents. Finally, people with a higher cognitive score were associated with an increased use of ACEI/ARBs,  $\beta$ -blockers and warfarin.

### Associations between prescribed drug classes and cognitive impairment in people with loop diuretics

The prevalence of drugs or drug classes in relation to cognitive function is presented in Fig. 3, where polynomial regression curves were fitted to the data. The prescription of warfarin, ACEI/ARBs,  $\beta$ -blockers and MRAs showed a linear correlation with the cognitive score. The use of these drugs declined with increasing cognitive impairment. There was a nonlinear association for lipid-modifying agents related to cognitive score. No statistically significant trends were seen for digitalis glycosides and ASA.

## Discussion

This study found an overall decline in the use of diuretics, and an increased use of ACEI/ARBs,  $\beta$ -blockers and calcium channel blockers at some of the different levels of cognitive function between 2007 and 2013. This might be interpreted as an increased treatment of hypertension among the study population, but, since no medical diagnoses are available, conclusions are difficult to draw. It can still be an undertreatment, which has been seen in previous studies among people with major neurocognitive disorders [26, 27]. There has been a debate regarding overall benefits from antihypertensive treatment in people with established cognitive impairment [36]. Avoiding adverse drug events such as hypotension and electrolyte disturbances that can cause hospitalisation might be more important than preventing cardiovascular events [37]. Extrapolating the positive results of antihypertensive treatment in people without cognitive impairment to those who have major neurocognitive disorders is controversial [38]. There are indications that antihypertensive therapy may accelerate cognitive decline [39–41], but there are also studies where antihypertensive treatment was associated with a protective effect against cognitive impairment [42].

More can be said about the treatment of heart failure. We found an overall decline in the use of diuretics, and increased use of ACEI/ARBs in three of four groups of different levels of cognitive function between the years in the whole sample. Furthermore, among people prescribed loop diuretics, ACEI/ARBs and  $\beta$ -blockers increased between the years. Although there was no significant increase in MRAs, these results suggest that treatment for heart failure has improved over the years. The overall decrease in diuretics might, however, indicate a more restrictive use of diuretics in people with heart failure in 2013 compared to 2007, and suggest that those who were prescribed diuretics in 2013 had more symptoms and

**Table 2** Drug use in 2007 and 2013

	2007	2013	Odds ratio <sup>a</sup>	95% confidence interval <sup>a</sup>	<i>p</i> value <sup>a</sup>
All people, <i>n</i>	2494	1654			
Antithrombotic agents (B01A), <i>n</i> (%)	1218 (48.8)	757 (45.8)	0.894	0.785–1.018	0.091
Warfarin (B01AA), <i>n</i> (%)	69 (2.8)	92 (5.6)	2.114	1.524–2.930	< 0.001
Heparin group (B01AB), <i>n</i> (%)	7 (0.3)	25 (1.5)	6.421	2.615–15.768	< 0.001
Platelet aggregation inhibitors excluding heparin (B01AC), <i>n</i> (%)	1147 (46.0)	646 (39.1)	0.759	0.666–0.866	< 0.001
ASA (B01AC06), <i>n</i> (%)	1089 (43.7)	558 (33.7)	0.663	0.581–0.758	< 0.001
Direct thrombin inhibitors (B01AE)	0 (0.0)	2 (0.1)			
Other antithrombotic agents (B01AX)	0 (0.0)	2 (0.1)			
Cardiovascular drugs (C), <i>n</i> (%)	1579 (63.3)	1048 (63.4)	0.959	0.836–1.000	0.548
Digitalis glycosides (C01AA), <i>n</i> (%)	157 (6.3)	54 (3.3)	0.490	0.353–0.680	< 0.001
Diuretics (C03), <i>n</i> (%)	1137 (45.6)	596 (36.0)	0.636	0.556–0.728	< 0.001
β-blockers (C07), <i>n</i> (%)	653 (26.2)	468 (28.3)	1.111	0.959–1.287	0.160
Calcium channel blockers (C08), <i>n</i> (%)	244 (9.8)	230 (13.9)	1.447	1.185–1.766	< 0.001
ACEI/ARBs (C09), <i>n</i> (%)	581 (23.3)	516 (31.2)	1.486	1.284–1.719	< 0.001
Lipid-modifying agents (C10), <i>n</i> (%)	148 (5.9)	125 (7.6)	1.382	1.063–1.798	0.016
People with severe cognitive impairment, <i>n</i>	536	310			
Antithrombotic agents (B01A), <i>n</i> (%)	195 (36.4)	88 (28.4)	0.675	0.493–0.924	0.014
Warfarin (B01AA), <i>n</i> (%)	5 (0.9)	4 (1.3)	1.370	0.357–5.253	0.646
Heparin group (B01AB), <i>n</i> (%)	1 (0.2)	2 (0.6)	3.387	0.301–38.085	0.323
Platelet aggregation inhibitors excluding heparin (B01AC), <i>n</i> (%)	190 (35.4)	79 (25.5)	0.604	0.438–0.834	0.002
ASA (B01AC06), <i>n</i> (%)	186 (34.7)	70 (22.6)	0.529	0.380–0.737	< 0.001
Direct thrombin inhibitors (B01AE)	0 (0.0)	1 (0.3)			
Other antithrombotic agents (B01AX)	0 (0.0)	2 (0.6)			
Cardiovascular drugs (C), <i>n</i> (%)	224 (41.8)	129 (41.6)	0.926	0.688–1.247	0.613
Digitalis glycosides (C01AA), <i>n</i> (%)	23 (4.3)	4 (1.3)	0.296	0.101–0.866	0.026
Diuretics (C03), <i>n</i> (%)	164 (30.6)	65 (21.0)	0.546	0.386–0.772	0.001
β-blockers (C07), <i>n</i> (%)	50 (9.3)	46 (14.8)	1.700	1.094–2.640	0.018
Calcium channel blockers (C08), <i>n</i> (%)	23 (4.3)	18 (5.8)	1.228	0.634–2.378	0.542
ACEI/ARBs (C09), <i>n</i> (%)	50 (9.3)	56 (18.1)	2.080	1.372–3.155	0.001
Lipid-modifying agents (C10), <i>n</i> (%)	11 (2.1)	13 (4.2)	1.884	0.813–4.365	0.140
People with moderate cognitive impairment, <i>n</i>	604	423			
Antithrombotic agents (B01A), <i>n</i> (%)	275 (45.5)	180 (42.6)	0.915	0.706–1.184	0.499
Warfarin (B01AA), <i>n</i> (%)	11 (1.8)	9 (2.1)	1.090	0.433–2.747	0.854
Heparin group (B01AB), <i>n</i> (%)	3 (0.5)	6 (1.4)	4.105	0.817–20.617	0.086
Platelet aggregation inhibitors excluding heparin (B01AC), <i>n</i> (%)	262 (43.4)	167 (39.5)	0.884	0.681–1.147	0.352
ASA (B01AC06), <i>n</i> (%)	253 (41.9)	143 (33.8)	0.738	0.566–0.962	0.025
Direct thrombin inhibitors (B01AE)	0 (0.0)	0 (0.0)			
Other antithrombotic agents (B01AX)	0 (0.0)	0 (0.0)			
Cardiovascular drugs (C), <i>n</i> (%)	376 (62.3)	230 (54.4)	0.732	0.565–0.948	0.018
Digitalis glycosides (C01AA), <i>n</i> (%)	40 (6.6)	13 (3.1)	0.472	0.248–0.899	0.022
Diuretics (C03), <i>n</i> (%)	260 (43.0)	116 (27.4)	0.486	0.368–0.642	< 0.001
β-blockers (C07), <i>n</i> (%)	155 (25.7)	92 (21.7)	0.778	0.575–1.054	0.105
Calcium channel blockers (C08), <i>n</i> (%)	74 (12.3)	43 (10.2)	0.814	0.542–1.221	0.319
ACEI/ARBs (C09), <i>n</i> (%)	131 (21.7)	108 (25.5)	1.332	0.987–1.797	0.061
Lipid-modifying agents (C10), <i>n</i> (%)	25 (4.1)	18 (4.3)	1.096	0.581–2.067	0.777
People with mild cognitive impairment, <i>n</i>	609	445			
Antithrombotic agents (B01A), <i>n</i> (%)	326 (53.5)	214 (48.1)	0.824	0.640–1.060	0.131
Warfarin (B01AA), <i>n</i> (%)	21 (3.4)	36 (8.1)	2.561	1.462–4.486	0.001

**Table 2** (continued)

	2007	2013	Odds ratio <sup>a</sup>	95% confidence interval <sup>a</sup>	<i>p</i> value <sup>a</sup>
Heparin group (B01AB), <i>n</i> (%)	1 (0.2)	5 (1.1)	6.648	0.767–57.642	0.086
Platelet aggregation inhibitors excluding heparin (B01AC), <i>n</i> (%)	305 (50.1)	176 (39.6)	0.659	0.511–0.851	0.001
ASA (B01AC06), <i>n</i> (%)	286 (47.0)	153 (34.4)	0.595	0.458–0.771	< 0.001
Direct thrombin inhibitors (B01AE)	0 (0.0)	0 (0.0)			
Other antithrombotic agents (B01AX)	0 (0.0)	0 (0.0)			
Cardiovascular drugs (C), <i>n</i> (%)	410 (67.3)	322 (72.4)	1.196	0.908–1.576	0.204
Digitalis glycosides (C01AA), <i>n</i> (%)	47 (7.7)	25 (5.6)	0.653	0.388–1.099	0.108
Diuretics (C03), <i>n</i> (%)	294 (48.3)	188 (42.2)	0.730	0.565–0.944	0.016
β-blockers (C07), <i>n</i> (%)	170 (27.9)	143 (32.1)	1.182	0.898–1.554	0.233
Calcium channel blockers (C08), <i>n</i> (%)	60 (9.9)	72 (16.2)	1.680	1.148–2.457	0.008
ACEI/ARBs (C09), <i>n</i> (%)	156 (25.6)	157 (35.3)	1.453	1.105–1.910	0.007
Lipid-modifying agents (C10), <i>n</i> (%)	22 (3.6)	34 (7.6)	1.242	1.255–4.007	0.006
People with no cognitive impairment, <i>n</i>	745	476			
Antithrombotic agents (B01A), <i>n</i> (%)	422 (56.6)	275 (57.8)	1.093	0.859–1.392	0.469
Warfarin (B01AA), <i>n</i> (%)	32 (4.3)	43 (9.0)	2.500	1.532–4.080	< 0.001
Heparin group (B01AB), <i>n</i> (%)	2 (0.3)	12 (2.5)	11.011	2.376–51.021	0.002
Platelet aggregation inhibitors excluding heparin (B01AC), <i>n</i> (%)	390 (52.3)	224 (47.1)	0.822	0.647–1.045	0.109
ASA (B01AC06), <i>n</i> (%)	364 (48.9)	192 (40.3)	0.728	0.571–0.927	0.010
Direct thrombin inhibitors (B01AE)	0 (0.0)	1 (0.2)			
Other antithrombotic agents (B01AX)	0 (0.0)	0 (0.0)			
Cardiovascular drugs (C), <i>n</i> (%)	569 (76.4)	367 (77.1)	1.033	0.781–1.367	0.821
Digitalis glycosides (C01AA), <i>n</i> (%)	47 (6.3)	12 (2.5)	0.351	0.174–0.708	0.003
Diuretics (C03), <i>n</i> (%)	419 (56.2)	227 (47.7)	0.718	0.564–0.914	0.007
β-blockers (C07), <i>n</i> (%)	278 (37.3)	187 (39.3)	1.170	0.914–1.496	0.212
Calcium channel blockers (C08), <i>n</i> (%)	87 (11.7)	97 (20.4)	1.995	1.432–2.780	< 0.001
ACEI/ARBs (C09), <i>n</i> (%)	244 (32.8)	195 (41.0)	1.457	1.137–1.868	0.003
Lipid-modifying agents (C10), <i>n</i> (%)	90 (12.1)	60 (12.6)	1.154	0.795–1.675	0.452

ACEI angiotensin-converting enzyme inhibitor, ARBs angiotensin receptor blockers

<sup>a</sup> Corrected for sex, age, ADL performance and level of cognitive impairment

needed more treatment. The recommended treatment with ACEIs, MRAs and β-blockers has shown improved survival in people with heart failure with reduced ejection fraction (HFrEF) [6]. In the guidelines from the Swedish Medical Products Agency from 2006 [43], as well as the guidelines from the Swedish National Board of Health and Welfare from 2008 [44], ACEIs were recommended for NYHA I–IV and β-blockers for NYHA II–IV. Spironolactone was recommended for NYHA III–IV if the treatment outcome was not good enough with ACEIs and β-blockers. In the ESC guidelines from 2012, the recommendation of using MRAs widened also for this to be given to people with NYHA II [45]. If these people still showed symptoms in NYHA III–IV, the recommendation was to try digoxin to alleviate symptoms. However, it is stated that the main indication for digoxin is atrial fibrillation. The lower use of digitalis glycosides in three groups and the overall decrease among people prescribed loop diuretics can also be interpreted as better “base” drug therapy.

A decreased use of digitalis is positive, because of the risk of side effects in elderly people [46]. Even though the overall

**Table 3** Drug use in 2007 and 2013 among people prescribed loop-diuretics

<i>n</i>	2007	2013	<i>p</i> value
Warfarin (B01AA), <i>n</i> (%)	41 (4.4)	56 (11.4)	< 0.001
ASA (B01AC06), <i>n</i> (%)	483 (52.0)	210 (42.6)	0.001
Digitalis glycosides (C01AA), <i>n</i> (%)	101 (10.9)	34 (6.9)	0.015
MRAs (C03DA), <i>n</i> (%)	97 (10.5)	48 (9.7)	0.671
β-blockers (C07), <i>n</i> (%)	334 (36.0)	206 (41.8)	0.032
ACEI/ARBs (C09), <i>n</i> (%)	351 (37.8)	225 (45.6)	0.004
Lipid-modifying agents (C10), <i>n</i> (%)	64 (6.9)	35 (7.1)	0.886

MRAs mineral corticosteroid antagonists, ACEI angiotensin-converting enzyme inhibitor, ARBs angiotensin receptor blockers

**Table 4** Multiple logistic regression analysis of factors associated with different drugs/drug classes among people with loop-diuretics

	Odds ratio	95% confidence interval	<i>p</i> value
<b>Warfarin</b>			
Year 2013 <sup>a</sup>	2.841	1.849–4.365	<0.001
ADL	1.040	0.993–1.089	0.098
Female sex	0.683	0.438–1.065	0.093
Higher age	0.960	0.931–0.989	0.007
Higher cognitive score	1.040	1.002–1.078	0.037
<b>ASA</b>			
Year 2013 <sup>a</sup>	0.689	0.549–0.865	0.001
ADL	1.005	0.982–1.028	0.673
Female sex	0.759	0.600–0.961	0.022
Higher age	1.015	0.998–1.032	0.076
Higher cognitive score	1.010	0.993–1.027	0.256
<b>Digitalis glycosides</b>			
Year 2013 <sup>a</sup>	0.576	0.375–0.885	0.012
ADL	1.040	0.999–1.083	0.058
Female sex	1.382	0.899–2.126	0.141
Higher age	1.003	0.975–1.032	0.836
Higher cognitive score	0.973	0.945–1.001	0.058
<b>MRAs</b>			
Year 2013 <sup>a</sup>	0.933	0.636–1.368	0.722
ADL	1.016	0.977–1.056	0.429
Female sex	1.947	1.246–3.042	0.003
Higher age	0.984	0.958–1.011	0.236
Higher cognitive score	1.020	0.991–1.050	0.172
<b>β-blockers</b>			
Year 2013 <sup>a</sup>	1.289	1.018–1.632	0.035
ADL	1.047	1.022–1.072	<0.001
Female sex	1.010	0.789–1.294	0.936
Higher age	0.983	0.966–0.999	0.044
Higher cognitive score	1.032	1.014–1.050	0.001
<b>ACEI/ARBs</b>			
Year 2013 <sup>a</sup>	1.393	1.104–1.758	0.005
ADL	1.042	1.017–1.067	0.001
Female sex	1.052	0.825–1.343	0.681
Higher age	0.973	0.956–0.989	0.001
Higher cognitive score	1.024	1.006–1.042	0.008
<b>Lipid-modifying agents</b>			
Year 2013 <sup>a</sup>	1.105	0.697–1.752	0.671
ADL	1.065	1.015–1.117	0.010
Female sex	0.620	0.395–0.973	0.038
Higher age	0.894	0.867–0.922	<0.001
Higher cognitive score	1.037	0.999–1.077	0.055

ACEI angiotensin-converting enzyme inhibitor, ARBs angiotensin receptor blockers, MRAs mineralocorticoid receptor antagonists

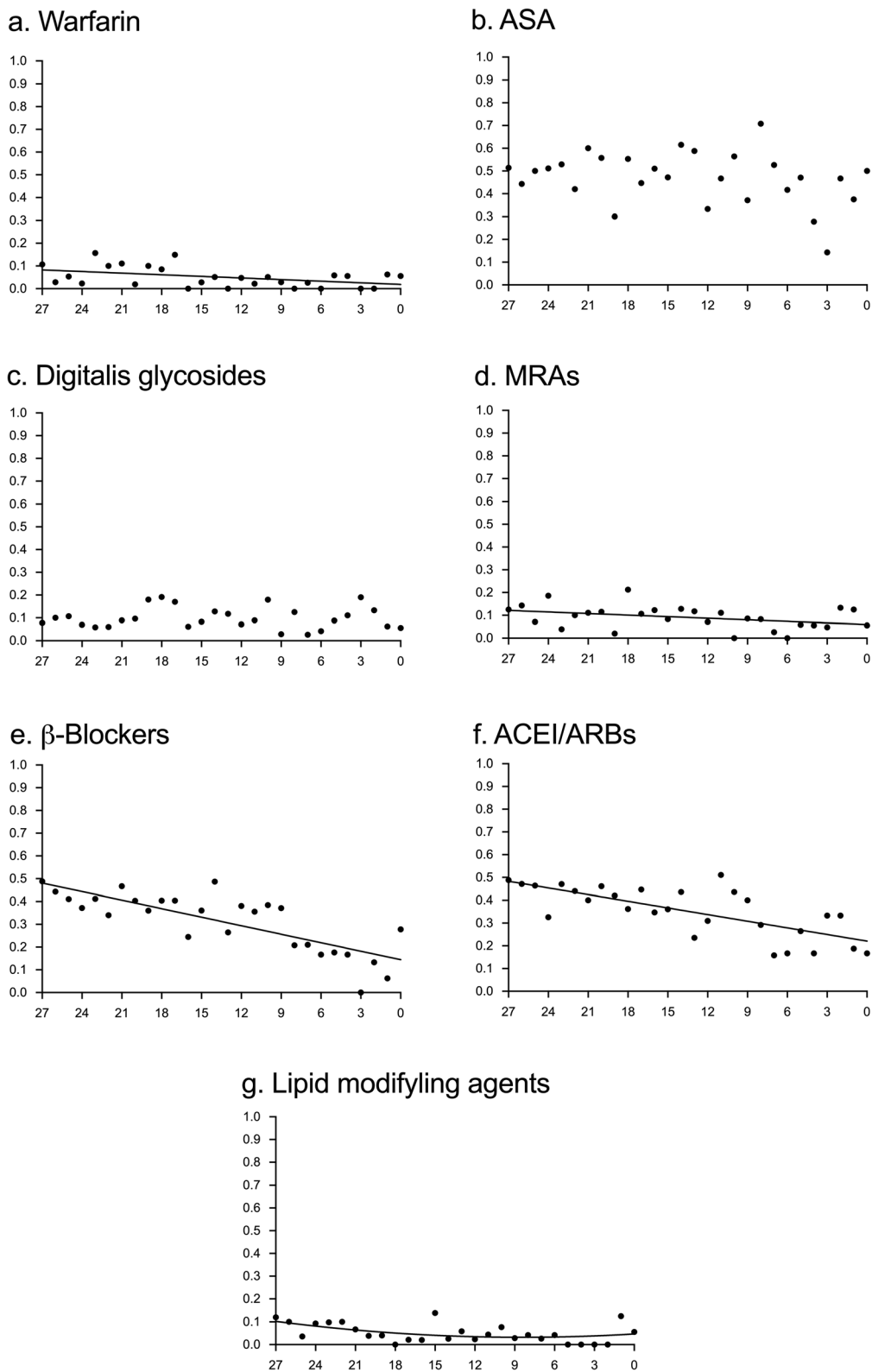
<sup>a</sup> Reference category year 2007

results in our study imply that the prescribing pattern has improved in regard to heart failure guidelines, not even half of the people prescribed loop diuretics received treatment with ACEI/ARBs (45.6%) and β-blockers (41.8%) in 2013.

However, it should be noted that elderly people are more likely to have heart failure with preserved ejection fraction (HFpEF) [47, 48]. In the Swedish guidelines for treatment of heart failure from 2006, HFpEF is mentioned [43]. At that time, knowledge about treatment for this group was limited. The main purpose of the drug therapy was to improve function and alleviate symptoms. Based on results from a few small studies, these people were recommended treatment with ARBs in high doses, β-blockers, ACEIs, diuretics and/or verapamil. In the guidelines from the Swedish National Board of Health and Welfare from 2008, only ARBs were mentioned in the recommendation for people with HFpEF [44].

Although the results in the present study indicate that treatment of heart failure has improved overall over the years, it was also found that the use of ACEI/ARBs, β-blockers and MRAs declined with increasing cognitive impairment among people prescribed loop diuretics. The regression analysis performed revealed two other factors besides higher cognitive score associated with the use of ACEI/ARBs and β-blockers, namely lower age and higher ADL score. Similar results have been found in a study performed in the USA, where people with Alzheimer's disease and concomitant heart failure were less likely to receive evidence-based medications (ACEI/ARBs, selective β-blockers and MRAs) than people with heart failure without comorbid Alzheimer's disease [49]. Another study performed in Sweden found that people with cognitive impairment were treated to a lesser extent with ACEIs and β-blockers compared with people with MMSE > 23, indicating under-treatment of some cardiovascular diseases among the elderly with cognitive impairment. Possible reasons—discussed by Klarin et al. [27]—are that the people with cognitive impairment might have problems in communicating symptoms to the doctor, or that doctors are doubtful regarding life-prolonging or preventive treatment of these people.

Another finding in this study was that the use of ASA decreased significantly in all groups between 2007 and 2013. It cannot be ruled out that this decline is due to decreased ischaemic heart disease among the population. However, since the prescribing of warfarin increased in two out of four groups of different cognitive level, it is more likely to be connected to better treatment of atrial fibrillation in 2013 compared to 2007. Prophylactic treatment with aspirin was considered as an option for low-risk patients in the ACC/AHA/ESC guidelines for atrial fibrillation from 2006 [50]. This recommendation was changed in the ESC updated guidelines from 2012, where it said that the use of aspirin should be restricted only to those who refused to take oral anticoagulants or did not tolerate them [51]. In the guidelines from the Swedish National Board of Health and Welfare in 2008, it was stated that there were signs of under-treatment with warfarin of people with atrial fibrillation [52]. According to these



**Fig. 3** The prevalence of different drugs in relation to cognitive impairment. The x-axis represents Gottfrides' cognitive scale (0–27 points, <24 points = cognitive impairment) (a–g). The y-axis represents the proportion of participants prescribed the drug or at least one of the different drugs in each drug class. Polynomial regression curves were fitted to

the data. The associations were statistically significant in (a, d–g), but not statistically significant in (b, c). *MRAs* mineralocorticoid receptor antagonists, *ACEI* angiotensin-converting enzyme inhibitor, *ARBs* angiotensin receptor blockers

guidelines, many people received ASA, which is less efficient than warfarin, or no treatment at all. The guidelines recommend that people with atrial fibrillation with one major risk factor or two non-major risk factors should be treated with warfarin. Heart failure and age > 65 years are both considered non-major risk factors [53]. In the present study, most people who were selected based on being prescribed loop diuretics, with concomitant atrial fibrillation should, therefore, be prescribed warfarin. The increase of warfarin between the two years among this subgroup might indicate an improved treatment overall in the population.

However, while there was a reduction of ASA at all levels of cognitive impairment, the use of warfarin only increased among people with no or mild cognitive impairment. This might indicate that the treatment with ASA among people with atrial fibrillation in the population as a whole has been withdrawn, but there is a hesitation to prescribe warfarin among those with more pronounced cognitive impairment. In line with this is our finding that the use of warfarin declined with increasing cognitive impairment among people prescribed loop diuretics. It is possible that prescribing of anticoagulants was lower for these people due to higher risks of side effects and/or falls. Major neurocognitive disorder has in a previous study been found to be one of two decisive factors for whether people were prescribed anticoagulants [54].

In the analysis of factors associated with different drug classes, higher prescribing of MRA was seen in women. This could be due to hormonal side effects. Gynecomastia in men is a known side effect of spironolactone [55]. In the Swedish guidelines, spironolactone was the first line drug in the MRA group [43]. Female sex was also connected to lower prescribing of ASA and lipid-modifying agents. Lower use of statins has been seen in several other studies where women generally receive less statins than men [56, 57]. The use of lipid-modifying agents was also associated with lower age, results in line with other research [58]. In a previous study, it was found that major neurocognitive disorders were associated with a lower likelihood of taking a lipid-lowering drug, possibly reflecting different prescribing patterns for people with major neurocognitive disorders and people without major neurocognitive disorders [59]. Our study found an association between lipid-modifying agents and higher ADL score, and in the polynomial regression as shown in Fig. 3, it was found that these drugs were associated with cognitive score.

The strengths of the present study include a large number of participants and the unselected sample of people living in nursing homes, and the fact that drug registration was generally of high quality. However, there are also some limitations of this study that have to be taken into account when interpreting the results. Most importantly, we do not know the background of the participants or any diseases. That also accounts for hypertension, atrial fibrillation and heart failure. To

identify people with heart failure, using International Classification of Disease (ICD) codes would have been preferred. However, the present data collection did not contain information about diagnoses, and due to this, loop diuretics was used instead as a proxy for heart failure in this study. This gives only an estimation and is therefore a potential source of error as compared to recorded diagnoses. Using prescription data alone has been suggested as a method to identify people with heart failure, although the specificity and sensitivity are lower compared to ICD codes [34]. Another drawback is a potential change in sensitivity/specificity of the proxy between 2007 and 2013, as a result of the decreased use of loop diuretics among people with heart failure over the years [60]. Furthermore, the reasons for drug prescription were not recorded in this study, and the doses of the drugs were not registered. There was also a lack of information about specific reasons for the non-use of certain drugs (e.g. patient refusal or history of adverse effects). There is a potential risk for under-reported use of thiazides in both 2007 and 2013 due to the categorising of ATC-code for combination products, and a possibility that an increased use of fixed combinations containing thiazides between 2007 and 2013 could explain some of the reported overall decrease in use of diuretics. Another drawback is that we had no information about *pro re nata* medication that might lead to the exclusion of some people with heart failure. The results should also be interpreted taking into account that several statistical tests were performed. The results of single significant *p* values should therefore be interpreted with proper caution with regards to the risk of type 1 errors. No adjustment of *p* values were performed due to expected dependency among the outcome measures in the different analyses, which make adjustment of *p* values overly conservative.

## Conclusion

The results indicate that cardiovascular drug treatment has improved between 2007 and 2013, but there is room for further improvement, especially when it comes to adherence to guidelines for heart failure. Increasing cognitive impairment had an effect on treatment patterns for heart failure and atrial fibrillation.

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**Authors' contribution** S. Svahn, M. Gustafsson and H. Lövhelm analysed and interpreted the data. S. Svahn and M. Gustafsson prepared the manuscript. P.O. Sandman and U. Isaksson were responsible for the study concept, design, and acquisition of subjects. All authors carried out a critical revision of the manuscript, contributed with comments and approved the final version.

## Compliance with ethical standards

**Conflict of interest** The authors declare that they have no conflict of interest.

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## References

- WHO. World health organization (2017) Cardiovascular diseases (CVDs). Available from [https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-\(cvds\)](https://www.who.int/news-room/fact-sheets/detail/cardiovascular-diseases-(cvds)) Accessed 31 March 2019
- Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement D, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen S, Kreutz R, Laurent S, Lip GYH, McManus R, Narkiewicz K, Ruschitzka F, Schmieder R, Shlyakhto E, Tsioufis K, Aboyans V, Desormais I, List of authors/Task Force members (2018) Practice guidelines for the management of arterial hypertension of the European Society of Hypertension and the European Society of Cardiology: ESH/ESC Task Force for the Management of Arterial Hypertension. *J Hypertens* 36:2284–2309. <https://doi.org/10.1097/hjh.0000000000001961>
- Zhou B, Bentham J, Di Cesare M et al (2017) Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. *Lancet* 389:37–55. [https://doi.org/10.1016/s0140-6736\(16\)31919-5](https://doi.org/10.1016/s0140-6736(16)31919-5)
- Duprez DA (2008) Systolic hypertension in the elderly: addressing an unmet need. *Am J Med* 121:179–184.e173. <https://doi.org/10.1016/j.amjmed.2007.10.027>
- Molander L, Lovheim H (2013) Blood pressure change and antihypertensive treatment in old and very old people: evidence of age, sex and cohort effects. *J Hum Hypertens* 27:197–203. <https://doi.org/10.1038/jhh.2012.14>
- Ponikowski P, Voors AA, Anker SD, Bueno H, Cleland JG, Coats AJ, Falk V, González-Juanatey JR, Harjola VP, Jankowska EA, Jessup M, Linde C, Nihoyannopoulos P, Parissis JT, Pieske B, Riley JP, Rosano GM, Ruilope LM, Ruschitzka F, Rutten FH, van der Meer P, Authors/Task Force Members, Document Reviewers (2016) ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Developed with the special contribution of the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 18: 891–975. <https://doi.org/10.1002/ejhf.592>
- Metra M, Teerlink JR (2017) Heart failure. *Lancet* 390:1981–1995. [https://doi.org/10.1016/s0140-6736\(17\)31071-1](https://doi.org/10.1016/s0140-6736(17)31071-1)
- Bui AL, Horwich TB, Fonarow GC (2011) Epidemiology and risk profile of heart failure. *Nat Rev Cardiol* 8:30–41. <https://doi.org/10.1038/nrcardio.2010.165>
- Lazzarini V, Mentz RJ, Fiuzat M, Metra M, O'Connor CM (2013) Heart failure in elderly patients: distinctive features and unresolved issues. *Eur J Heart Fail* 15:717–723. <https://doi.org/10.1093/eurjhf/hft028>
- Screever EM, Meijers WC, van Veldhuisen DJ, de Boer RA (2017) New developments in the pharmacotherapeutic management of heart failure in elderly patients: concerns and considerations. *Expert Opin Pharmacother* 18:645–655. <https://doi.org/10.1080/14656566.2017.1316377>
- Vitale C, Rosano G, Fini M (2016) Are elderly and women under-represented in cardiovascular clinical trials? Implication for treatment. *Wien Klin Wochenschr* 128:433–438. <https://doi.org/10.1007/s00508-016-1082-x>
- Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, Wu AW (2003) Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. *J Am Coll Cardiol* 42:1226–1233
- Wong CY, Chaudhry SI, Desai MM, Krumholz HM (2011) Trends in comorbidity, disability, and polypharmacy in heart failure. *Am J Med* 124:136–143. <https://doi.org/10.1016/j.amjmed.2010.08.017>
- Cvetinovic N, Loncar G, Farkas J (2016) Heart failure management in the elderly - a public health challenge. *Wien Klin Wochenschr* 128:466–473. <https://doi.org/10.1007/s00508-016-1138-y>
- Rahman F, Kwan GF, Benjamin EJ (2014) Global epidemiology of atrial fibrillation. *Nat Rev Cardiol* 11:639–654. <https://doi.org/10.1038/nrcardio.2014.118>
- Ding M, Fratiglioni L, Johnell K, Santoni G, Fastbom J, Ljungman P, Marengoni A, Qiu C (2018) Atrial fibrillation, antithrombotic treatment, and cognitive aging: A population-based study. *Neurology* 91:e1732–e1740. <https://doi.org/10.1212/wnl.0000000000006456>
- Prince M, Bryce R, Albanese E, Wimo A, Ribeiro W, Ferri CP (2013) The global prevalence of dementia: a systematic review and metaanalysis. *Alzheimers Dement* 9:63–75.e62. <https://doi.org/10.1016/j.jalz.2012.11.007>
- Finkel SI, Costa e Silva J, Cohen G, Miller S, Sartorius N (1996) Behavioral and psychological signs and symptoms of dementia: a consensus statement on current knowledge and implications for research and treatment. *Int Psychogeriatr* 8:497–500
- Gustafsson M, Sandman P-O, Karlsson S, Isaksson U, Schneede J, Sjölander M, Lövhelm H (2015) Reduction in the use of potentially inappropriate drugs among old people living in geriatric care units between 2007 and 2013. *Eur J Clin Pharmacol* 71:507–515. <https://doi.org/10.1007/s00228-015-1825-z>
- Heckman GA, Patterson CJ, Demers C, St Onge J, Turpie ID, McKelvie RS (2007) Heart failure and cognitive impairment: challenges and opportunities. *Clin Interv Aging* 2:209–218
- Schubert CC, Boustani M, Callahan CM, Perkins AJ, Carney CP, Fox C, Unverzagt F, Hui S, Hendrie HC (2006) Comorbidity profile of dementia patients in primary care: are they sicker? *J Am Geriatr Soc* 54:104–109. <https://doi.org/10.1111/j.1532-5415.2005.00543.x>
- Bynum JP, Rabins PV, Weller W, Niefeld M, Anderson GF, Wu AW (2004) The relationship between a dementia diagnosis, chronic illness, medicare expenditures, and hospital use. *J Am Geriatr Soc* 52: 187–194
- Drummond N, McCleary L, Freiheit E, Molnar F, Dalziel W, Cohen C, Turner D, Miyagishima R, Silvius J (2018) Antidepressant and antipsychotic prescribing in primary care for people with dementia. *Can Fam Physician* 64:e488–e497
- Cross AJ, George J, Woodward MC, Ames D, Brodaty H, Wolfe R, Connors MH, Elliott RA (2017) Potentially Inappropriate

- Medication, Anticholinergic Burden, and Mortality in People Attending Memory Clinics. *J Alzheimers Dis* 60:349–358. <https://doi.org/10.3233/jad-170265>
25. Sonnerstam E, Sjolander M, Gustafsson M (2017) An evaluation of the prevalence of potentially inappropriate medications in older people with cognitive impairment living in Northern Sweden using the EU(7)-PIM list. *Eur J Clin Pharmacol* 73:735–742. <https://doi.org/10.1007/s00228-017-2218-2>
  26. Lopponen M, Raiha I, Isoaho R, Vahlberg T, Puolijoki H, Kivela SL (2006) Dementia associates with undermedication of cardiovascular diseases in the elderly: a population-based study. *Dement Geriatr Cogn Disord* 22:132–141. <https://doi.org/10.1159/000093739>
  27. Klarin I, Fastbom J, Wimo A (2003) A population-based study of drug use in the very old living in a rural district of Sweden, with focus on cardiovascular drug consumption: comparison with an urban cohort. *Pharmacoepidemiol Drug Saf* 12:669–678. <https://doi.org/10.1002/pds.878>
  28. Sandman PO, Adolfsson R, Norberg A, Nystrom L, Winblad B (1988) Long-term care of the elderly. A descriptive study of 3600 institutionalized patients in the county of Vasterbotten, Sweden. *Compr Gerontol A* 2:120–132
  29. Adolfsson R, Gottfries CG, Nystrom L, Winblad B (1981) Prevalence of dementia disorders in institutionalized Swedish old people. The work load imposed by caring for these patients. *Acta Psychiatr Scand* 63:225–244
  30. Gustafsson M, Isaksson U, Karlsson S, Sandman PO, Lovheim H (2016) Behavioral and psychological symptoms and psychotropic drugs among people with cognitive impairment in nursing homes in 2007 and 2013. *Eur J Clin Pharmacol* 72:987–994. <https://doi.org/10.1007/s00228-016-2058-5>
  31. Folstein MF, Folstein SE, McHugh PR (1975) "Mini-mental state". A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12:189–198
  32. Lovheim H, Bergdahl E, Sandman PO, Karlsson S, Gustafsson Y (2010) One-week prevalence of depressive symptoms and psychotropic drug treatments among old people with different levels of cognitive impairment living in institutional care: changes between 1982 and 2000. *Int Psychogeriatr* 22:1154–1160. <https://doi.org/10.1017/s104161021000061x>
  33. Skottheim A, Lovheim H, Isaksson U, Sandman PO, Gustafsson M (2018) Insomnia symptoms among old people in nursing homes. *Int Psychogeriatr* 30:77–85. <https://doi.org/10.1017/s1041610217001703>
  34. McCormick N, Laccaille D, Bhole V, Avina-Zubieta JA (2014) Validity of heart failure diagnoses in administrative databases: a systematic review and meta-analysis. *PLoS One* 9:e104519. <https://doi.org/10.1371/journal.pone.0104519>
  35. Pellicori P, Kaur K, Clark AL (2015) Fluid management in patients with chronic heart failure. *Card Fail Rev* 1(2):90–95. <https://doi.org/10.15420/cfr.2015.1.2.90>
  36. Beishon LC, Harrison JK, Harwood RH, Robinson TG, Gladman JR, Conroy SP (2014) The evidence for treating hypertension in older people with dementia: a systematic review. *J Hum Hypertens* 28:283–287. <https://doi.org/10.1038/jhh.2013.107>
  37. Salvi F, Marchetti A, D'Angelo F, Boemi M, Lattanzio F, Cherubini A (2012) Adverse drug events as a cause of hospitalization in older adults. *Drug Saf* 35:29–45. <https://doi.org/10.1007/bf03319101>
  38. van der Wardt V, Logan P, Conroy S, Harwood R, Gladman J (2014) Antihypertensive treatment in people with dementia. *J Am Med Dir Assoc* 15:620–629. <https://doi.org/10.1016/j.jamda.2014.03.005>
  39. Birkenhager WH, Forette F, Staessen JA (2004) Dementia and antihypertensive treatment. *Curr Opin Nephrol Hypertens* 13:225–230
  40. Qiu C, von Strauss E, Fastbom J, Winblad B, Fratiglioni L (2003) Low blood pressure and risk of dementia in the Kungsholmen project: a 6-year follow-up study. *Arch Neurol* 60:223–228
  41. van Beek AH, Sijbesma JC, Jansen RW, Rikkert MG, Claassen JA (2010) Cortical oxygen supply during postural hypotension is further decreased in Alzheimer's disease, but unrelated to cholinesterase-inhibitor use. *J Alzheimers Dis* 21:519–526. <https://doi.org/10.3233/jad-2010-100288>
  42. Rouch L, Cestac P, Hanon O, Cool C, Helmer C, Bouhanick B, Chamontin B, Dartigues JF, Vellas B, Andrieu S (2015) Antihypertensive drugs, prevention of cognitive decline and dementia: a systematic review of observational studies, randomized controlled trials and meta-analyses, with discussion of potential mechanisms. *CNS Drugs* 29:113–130. <https://doi.org/10.1007/s40263-015-0230-6>
  43. Swedish Medical Products Agency (2006) Hjärtsvikt. [Eng Heart failure] Available from <https://lakemedelsverket/malgrupp/Hals%2D%2Dsjukvard/Behandlings%2D%2Drekommendationer/Behandlingsrekommendation%2D%2Dlistan/Hjartsvikt/> Accessed 31 March 2019
  44. The National Board of Health and Welfare (2008) Hjärtsvikt - Vetenskapligt underlag för Nationella riktlinjer för hjärtsjukvård 2008. [Eng. Heart failure - Scientific grounds for National guidelines for Cardiac Care 2008]
  45. McMurray JJ, Adamopoulos S, Anker SD, Auricchio A, Böhm M, Dickstein K, Falk V, Filippatos G, Fonseca G, Gomez-Sanchez MA, Jaarsma T, Køber L, Lip GY, Maggioni AP, Parkhomenko A, Pieske BM, Popescu BA, Rønnevik PK, Rutten FH, Schwitzer J, Seferovic P, Stepinska J, Trindade PT, Voors AA, Zannad F, Zeiher A, Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology, Bax JJ, Baumgartner H, Ceconi C, Dean V, Deaton C, Fagard R, Funck-Brentano C, Hasdai D, Hoes A, Kirchhof P, Knuuti J, Kolh P, McDonagh T, Moulin C, Popescu BA, Reiner Z, Sechtem U, Sirnes PA, Tendera M, Torbicki A, Vahanian A, Windecker S, McDonagh T, Sechtem U, Bonnet LA, Avraamides P, Ben Lamin HA, Brignole M, Coca A, Cowburn P, Dargie H, Elliott P, Flachskampf FA, Guida GF, Hardman S, Jung B, Merkely B, Mueller C, Nanas JN, Nielsen OW, Orn S, Parissis JT, Ponikowski P, ESC Committee for Practice Guidelines (2012) ESC guidelines for the diagnosis and treatment of acute and chronic heart failure 2012: The Task Force for the Diagnosis and Treatment of Acute and Chronic Heart Failure 2012 of the European Society of Cardiology. Developed in collaboration with the Heart Failure Association (HFA) of the ESC. *Eur J Heart Fail* 14:803–869. <https://doi.org/10.1093/eurjhf/hfs105>
  46. Currie GM, Wheat JM, Kiat H (2011) Pharmacokinetic considerations for digoxin in older people. *Open Cardiovasc Med J* 5:130–135. <https://doi.org/10.2174/1874192401105010130>
  47. Ather S, Chan W, Bozkurt B, Aguilar D, Ramasubbu K, Zachariah AA, Wehrens XH, Deswal A (2012) Impact of noncardiac comorbidities on morbidity and mortality in a predominantly male population with heart failure and preserved versus reduced ejection fraction. *J Am Coll Cardiol* 59:998–1005. <https://doi.org/10.1016/j.jacc.2011.11.040>
  48. Yancy CW, Jessup M, Bozkurt B et al (2013) ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 62:e147–e239. <https://doi.org/10.1016/j.jacc.2013.05.019>
  49. Rattinger GB, Dutcher SK, Chhabra PT, Franey CS, Simoni-Wastila L, Gottlieb SS, Stuart B, Zuckerman IH (2012) The effect of dementia on medication use and adherence among Medicare beneficiaries with chronic heart failure. *Am J Geriatr Pharmacother* 10:69–80. <https://doi.org/10.1016/j.amjopharm.2011.11.003>

50. Fuster V, Ryden LE, Cannom DS et al (2006) ACC/AHA/ESC 2006 Guidelines for the management of patients with atrial fibrillation: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines and the European Society of Cardiology Committee for Practice Guidelines (Writing Committee to Revise the 2001 Guidelines for the Management of Patients With Atrial Fibrillation): developed in collaboration with the European Heart Rhythm Association and the Heart Rhythm Society. *Circulation* 114:e257–e354. <https://doi.org/10.1161/circulationaha.106.177292>
51. Camm AJ, Lip GY, De Caterina R, Savelieva I, Atar D, Hohnloser SH, Hindricks G, Kirchhof P (2012) 2012 focused update of the ESC Guidelines for the management of atrial fibrillation: an update of the 2010 ESC Guidelines for the management of atrial fibrillation. Developed with the special contribution of the European Heart Rhythm Association. *Eur Heart J* 33(21):2719–2747. <https://doi.org/10.1093/eurheartj/ehs253>
52. The National Board of Health and Welfare (2008) Nationella riktlinjer för hjärtsjukvård 2008 - beslutsstöd för prioriteringar. [Eng. National guidelines for Cardiac Care 2008 - decision support for priorities]
53. Camm AJ, Kirchhof P, Lip GY, Schotten U, Savelieva I, Ernst S, van Gelder I, al-Attar N, Hindricks G, Prendergast B, Heidbuchel H, Alfieri O, Angelini A, Atar D, Colonna P, de Caterina R, de Sutter J, Goette A, Gorenek B, Heldal M, Hohloser SH, Kolh P, le Heuzey JY, Ponikowski P, Rutten FH, ESC Committee for Practice Guidelines (2010) Guidelines for the management of atrial fibrillation: the Task Force for the Management of Atrial Fibrillation of the European Society of Cardiology (ESC). *Europace* 12:1360–1420. <https://doi.org/10.1093/europace/euq350>
54. Appelros P, Farahmand B, Terent A, Asberg S (2017) To treat or not to treat: anticoagulants as secondary preventives to the oldest old with atrial fibrillation. *Stroke* 48:1617–1623. <https://doi.org/10.1161/strokeaha.117.016902>
55. Deepinder F, Braunstein GD (2012) Drug-induced gynecomastia: an evidence-based review. *Expert Opin Drug Saf* 11:779–795. <https://doi.org/10.1517/14740338.2012.712109>
56. Zhang H, Plutzky J, Shubina M, Turchin A (2016) Drivers of the sex disparity in statin therapy in patients with coronary artery disease: a cohort study. *PLoS One* 11:e0155228. <https://doi.org/10.1371/journal.pone.0155228>
57. Victor BM, Teal V, Ahedor L, Karalis DG (2014) Gender differences in achieving optimal lipid goals in patients with coronary artery disease. *Am J Cardiol* 113:1611–1615. <https://doi.org/10.1016/j.amjcard.2014.02.018>
58. Zhang H, Plutzky J, Shubina M, Turchin A (2016) Risk factors for lack of statin therapy in patients with diabetes and coronary artery disease. *J Clin Lipidol* 10:1406–1413. <https://doi.org/10.1016/j.jacl.2016.09.010>
59. Rodriguez EG, Dodge HH, Birzescu MA, Stoehr GP, Ganguli M (2002) Use of lipid-lowering drugs in older adults with and without dementia: a community-based epidemiological study. *J Am Geriatr Soc* 50:1852–1856
60. Paren P, Rosengren A, Zverkova Sandstrom T, Schaufelberger M (2019) Decrease in loop diuretic treatment from 2005 to 2014 in Swedish real-life patients with chronic heart failure. *Eur J Clin Pharmacol* 75:247–254. <https://doi.org/10.1007/s00228-018-2574-6>

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