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## Original Article

# Drug prescriptions unadapted to the renal function in patients aged 80 years and older[a]

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KEY MESSAGE:

- Analysing drug prescription in a representative cohort of older subjects with and without chronic kidney disease (CKD) showed that, despite automatic eGFR reporting, many of these prescriptions are unadapted to the renal function.

ABSTRACT

**Background:** Drug-related problems are common in older people. Often they are related to low estimated glomerular filtration rate (eGFR), which has a high prevalence among older adults.

**Objectives:** The aim of this study was to investigate inappropriate drug prescriptions and dose adaptations in a very old population and their relationship with the eGFR.

**Methods:** Design: A cross-sectional study within a Belgian prospective population-based cohort study (the BELFRAIL study) of 539 participants aged 80 years and older (mean age 85 years). Drug prescriptions at inclusion were reported by the participant's responsible general practitioner. The eGFR was estimated using the MDRD equation. Based on their eGFR, the participants were divided in three groups: $>50$, 30–50 and $<30$ ml/min/1.73 m², respectively. Drug prescriptions were analysed in different eGFR groups. The prevalence and odds ratios of inappropriate drugs and the unadjusted defined daily doses (DDD) of the participant eGFRs were calculated.

**Results:** Thirty-six (of 111) and eight (of 31) of the participants with an eGFR between 30–50 and $<30$ ml/min/1.73 m², respectively, had at least one inappropriate drug prescribed. No decrease in mean DDD, was observed in any prescribed drug in both lower eGFR groups. Participants with a lower eGFR were at higher risk of receiving gliclazide (OR: 4.51; 95% CI: 1.45–14.02) or unadjusted doses of allopurinol (OR: 3.48; 95% CI: 1.26–9.61).

**Conclusion:** Drug prescriptions inappropriate for patient eGFR are common in subjects aged 80 years and older, despite automatic eGFR reporting.

**Keywords:** Drug use, elderly, renal function, eGFR, inappropriate prescriptions

## INTRODUCTION

Drug-related problems among older individuals are common. The prevalence of severe events related to drug use is estimated at 50 per 1000 person-years in the US and Europe (1–3). Approximately half of all drugs and their metabolites are excreted by the kidneys. Therefore, it is not surprising that many drug-related problems have a renal cause (4). The Three City Study demonstrated a 40% higher mortality over a six-year period in community-dwelling older individuals with an impaired estimated glomerular filtration rate (eGFR) receiving drugs or drug doses that were considered to be inappropriate given the participant's renal function (5). Furthermore, it has been shown that many drug-related problems caused by these inappropriate prescriptions are preventable (1).

[a]Prior oral presentation at EUGMS congress, 26–28 September 2012, Brussels, Belgium.

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In older persons, the risk of drug-related problems is high given the high prevalence of impaired renal function in this population group. Various studies have indicated that approximately 30 to 35% of all persons aged 70 or older and 50% of persons aged 80 or older have an impaired eGFR (< 60 ml/min/1.73 m²) (6–8). Moreover, older persons using multiple drugs often see an increase of multi-morbidity with age. This makes the older population a high-risk group for drug prescriptions inappropriate for their eGFR.

As studied previously (4), one of the reasons for adverse drug reactions is concealed renal insufficiency. This problem could be solved by calculating the eGFR instead of only looking at the serum creatinine value. In Belgium, laboratories started to report automatically the eGFR calculated by the MDRD formula in approximately 2007. Before implementing known or new strategies to lower the number of prescriptions inappropriate for the eGFR in older patients, we wanted to study the prevalence of inappropriate prescriptions after the introduction of automatically reported eGFRs. To study this, we used the cross-sectional baseline data from the BELFRAIL study, a prospective cohort study of participants aged 80 years and older in Belgium (9).

## METHODS

The BELFRAIL study is a prospective, observational, population-based cohort study of subjects aged 80 years and older in three well-circumscribed areas in Belgium (Table 1). The full study design, including the power calculation, has been described in detail previously (9). Briefly, between 2 November 2008 and 15 September 2009, 29 GP centres were asked to recruit consecutive consulting patients aged 80 years and older with only three exclusion criteria: severe dementia, palliative care status and medical urgency. In Belgium, more than 90% of all octogenarians consult their GP regularly (10). The GPs reported current drug prescriptions, relevant events or diseases in the medical history and current diseases and medical problems. Drug prescriptions were analysed after coding all the medication using the ATC (Anatomical Therapeutical classification) system.

The BELFRAIL study population has proven to be representative for the Belgian octogenarians (9). The prevalence of the different stages of CKD in this study population is comparable with other population-based studies in Western countries (6,11).

The study protocol was approved by the Biomedical Ethics Committee of the Medical School of the Université Catholique de Louvain, Belgium (B40320084685), and all participants provided informed consent.

### *Laboratory analyses*

Blood samples were collected in the morning. Serum samples obtained after centrifugation less than four hours from collection were stored at −80°C until analysis. The serum concentration of creatinine was measured using a Unicel D × C 800 Synchron instrument (Beckman Coulter, Inc., Brea, CA, USA). We calibrated the creatinine assays against an isotope dilution mass spectrometry (IDMS) traceable method.

We used the Modification of Diet in Renal Disease study equation (MDRD) equation to estimate the eGFR (12). Although the currently used CKD classification (13) uses cut-offs of 60, 45, 30 and 15 ml/min/1.73 m² to classify CKD, other cut-offs are used traditionally in literature for medication adjustment (14–16). These cut-offs of 50 and 30 ml/min/1.73 m² are used in this article (15).

Table 1. Baseline characteristics of whole BELFRAIL study population ($n = 539$) and the study population divided into three categories based on the eGFR of the participants (percentages).

| | eGFR (MDRD equation) | | | | |
|---|---|---|---|---|---|
| *n* % | All participants ($n = 539$) | > 50 ml/min/1.73 m² ($n = 397$) | 30–50 ml/min/1.73m² ($n = 111$) | < 30 ml/min/1.73m² ($n = 31$) | *P* for trend |
| ≥ 85 years | 41 | 38 | 46 | 59 | < 0.01 |
| Male | 37 | 28 | 33 | 45 | 0.45 |
| Reported hypertension | 71 | 68 | 78 | 84 | 0.07 |
| Diabetes mellitus | 19 | 17 | 22 | 36 | 0.10 |
| Myocardial infarction in history | 11 | 11 | 14 | 10 | 0.85 |
| Cerebrovascular event in history | 9 | 9 | 6 | 7 | 0.53 |
| Peripheral arterial disease in history | 9 | 7 | 12 | 16 | 0.05 |
| Reported osteoarthritis | 5 | 4 | 7 | 3 | 0.17 |
| Reported arthrosis | 58 | 55 | 66 | 67 | 0.19 |
| Reported arrhythmia | 11 | 13 | 11 | 16 | 0.72 |
| Chronic atrial fibrillation | 9 | 9 | 11 | 12 | 0.54 |
| Reported peripheral oedema | 34 | 32 | 39 | 42 | 0.15 |
| History of decompensated heart failure | 11 | 7 | 21 | 29 | < 0.01 |

*Inappropriate drug prescriptions*

Medline, PubMed and the Cochrane database were searched for guidelines concerning drug use in persons with impaired eGFR. In addition, the recommendations of different guidelines (a Dutch guideline and a Belgian drug database (http://www.BCFI.BE)) and manuals (drugs prescribing in renal failure (http://www.kdpnet.louisville.edu/renalbook), manual of Belgian nephrology society (http://www.bvn-sbn.be) and a pharmacotherpeutical manual were consulted. Out of all these recommendations a draft list was constructed, and a consensus was searched. These conclusions were checked by an experienced professor of nephrology and an experienced professor of pharmacology. Since we wanted to analyse the inappropriateness of the prescription at individual drug level we selected the drugs that were prescribed to at least 10 participants of the BELFRAIL cohort. Out of the long list of drugs with contraindications or the need of adjusted DDD in patients with impaired renal function. This resulted in a selection of eight (Table 2) frequently used drugs with relative and/or absolute contraindications and/or adjusted maximum DDD in participants with impaired eGFR.

*Statistical analysis*

The significance of the observed differences in demographic factors, co-morbidity, drugs prescribed and DDD between the three eGFR categories was analysed using Chi-square and ANOVA trend tests. The odds ratios (OR) and 95% confidence intervals (CI) for the three eGFR categories (participants with an eGFR $>$ 50 ml/min/1.73 m$^2$ were used as the reference category) for the risk of receiving an inappropriate prescription were calculated using logistic regression analyses. The ORs were corrected for comorbidities with a prevalence that was significantly different in the different eGFR subcategories. We corrected for differences that could explain the differences in drug use or DDD in the prevalence of relevant comorbidities in the three eGFR subcategories.

## RESULTS

*Associations of the eGFR with clinical problems*

Drug prescriptions and eGFR at baseline were available for 539 (mean age 85 years) of the 567 subjects aged 80 years and older participating in the BELFRAIL study. In Table 1, the frequency of comorbidities and the relation with eGFR subcategories is reported. The full characteristics of the BELFRAIL population have been reported elsewhere (7). Participants with lower eGFRs were older, had a higher prevalence of an earlier episode of decompensated heart failure and a trend towards more hypertension, diabetes mellitus and peripheral arterial disease. In total, 21% of the participants had an eGFR of 30–50 ml/min/1.73 m$^2$, and 6% had an eGFR $<$ 30 ml/min/1.73 m$^2$.

*Associations of the eGFR with inappropriate drug prescriptions*

Table 2 reports the general drug prescriptions in the study population. The mean number of different daily used drugs was 3.6 with a standard deviation of 2.2 and a maximum of 13 drugs. Participants with a low eGFR took more drugs influencing their alimentary tract, metabolism and cardiovascular system.

The prescription of the nine drugs under investigation that need adjustment to patient's eGFR is shown in Table 3. Gliclazide, spironolactone and allopurinol were used more often in participants with a low eGFR. The DDD of the drugs under investigation were also analysed according to the different eGFR categories (Table 3). No differences were found for any of these drugs.

The frequency of inappropriate drug use or inappropriate DDD is reported in Table 4 for the eight drugs

Table 2. Overall drug use in the BELFRAIL population ($n$ = 539) by ATC classification.

| | eGFR 4 (MDRD equation) | | | | |
|---|---|---|---|---|---|
| ATC classification | All participants ($n$ = 539) | $>$50ml/min/1.73 m$^2$ ($n$ = 397) | 30–50ml/min/1.73 m$^2$ ($n$ = 111) | $<$30ml/min/1.73 m$^2$ ($n$ = 31) | $P$ |
| Alimentary tract and metabolism | 50% | 46% | 64% | 65% | $<$0.01 |
| Blood and blood forming organs | 55% | 52% | 59% | 61% | 0.37 |
| Cardiovascular system | | | | | |
| 0 drugs | 14% | 17% | 6% | 7% | $<$0.01 |
| 1 drug | 23% | 25% | 20% | 10% | |
| 2 different drugs | 31% | 31% | 28% | 32% | |
| $\geq$3 different drugs | 32% | 28% | 46% | 52% | |
| Musculo-skeletal system | 14% | 14% | 18% | 19% | 0.39 |
| Nervous system | 34% | 35% | 39% | 39% | 0.76 |
| Respiratory system | 5% | 6% | 5% | 7% | 0.97 |

Table 3. Intake and mean DDD of drugs requiring adaptation to the renal function in the BELFRAIL study population ($n = 539$).

| | eGFR 4 variable MDRD equation | | | | |
|---|---|---|---|---|---|
| | All participants ($n = 539$) | $>$50ml/min/1.73 m$^2$ ($n = 397$) | 30–50 ml/min/1.73 m$^2$ ($n = 111$) | $<$30ml/min/1.73 m$^2$ ($n = 31$) | *P* |
| Metformin | 46 (9%) | 31 (8%) | 13 (12%) | 2 (7%) | 0.45 |
| Mean DDD metformin (min–max) | 1259 | 1243 (425–2550) | 1320 (500–2550) | 1063 (850–1275) | 0.83 |
| Gliclazide | 15 (3%) | 7 (2%) | 7 (6%) | 1 (3%) | 0.04 |
| Mean DDD gliclazide (min–max) | 72.5 | 63 (30–160) | 86 (15–320) | 30 (30) | 0.79 |
| Tramadol | 34 (7%) | 25 (6%) | 8 (7%) | 1 (3%) | 0.77 |
| Mean DDD tramadol (min–max) | 106 | 109 (15–300) | 102 (8–300) | 100 (50–150) | 0.95 |
| Spironolactone | 22 (4%) | 12 (3%) | 10 (9%) | 0 | 0.01 |
| Mean DDD spironolactone (min–max) | 1.71 | 54 (25–200) | 27 (12–50) | No cases | 0.14 |
| Sotalol | 17 (3%) | 14 (4%) | 2 (2%) | 1 (3%) | 0.63 |
| Mean DDD sotalol (min–max) | 113 | 120 (40–160) | 80 (80) | 80 (80) | 0.44 |
| Atenolol | 30 (6%) | 22 (6%) | 6 (5%) | 2 (7%) | 0.96 |
| Mean DDD atenolol (min–max) | 59.2 | 63 (25–150) | 67 (50–100) | 63 (25–100) | 0.83 |
| Ranitidine | 35 (7%) | 24 (6%) | 8 (7%) | 3 (10%) | 0.69 |
| Mean DDD ranitidine (min–max) | 262 | 269 (150–300) | 244 (150–300) | 300 (300) | 0.25 |
| Allopurinol | 37 (7%) | 21 (6%) | 10 (9%) | 6 (21%) | 0.01 |
| Mean DDD allopurinol (min–max) | 250 | 260 (100–300) | 260 (100–300) | 200 (100–300) | 0.29 |

under investigation. Of the participants with an eGFR between 30 and 50 ml/min/1.73 m²; 26% received an inappropriate drug or unadjusted DDD (19 (17%) received 1; 8 (7%) received 2; 1 (1%) received 3; and 1 (1%) received 4). Of the participants with an eGFR $<$ 30 ml/min/1.73 m², eight (26%) received one inappropriate drug or unadjusted DDD.

In Table 5, these inappropriate drugs and unadjusted DDDs are further analysed. After correction for comorbidities related to the eGFR (Table 1), participants with an eGFR $<$ 30 ml/min/1.73 m² had a higher risk (OR: 4.51; 95% CI: 1.45–14.02) to receive gliclazide and a higher risk (OR: 3.48; 95% CI: 1.26–9.61) to receive a DDD of allopurinol $>$ 100 mg compared with participants with an eGFR $>$ 50 ml/min/1.73 m². No significant lower risk of receiving one of these drugs was observed.

## DISCUSSION

### *Main findings*

Analysing drug prescriptions in a representative cohort of very elderly indicated that one of four subjects with an eGFR between 30 and 50 ml/ min/ 1.73 m² and one of four subjects with an eGFR $<$ 30 ml/min/ 1.73 m² received at least one inappropriate drug or unadjusted DDD. Moreover, none of these drugs were given in lower doses to the participants with a low eGFR. Furthermore, gliclazide and excessive DDDs of allopurinol were more often given to participants with an eGFR $<$ 30 ml/min/1.73 m² compared with participants with a better eGFR. In contrast, drugs such as tramadol were not used in excessive doses in participants with an eGFR $<$ 30 ml/min/1.73 m², despite a 67% prevalence of osteoarthritis.

Table 4. Frequency of the drug use or inappropriate daily doses based on the renal function in the BELFRAIL cohort ($n = 539$).

| | eGFR (MDRD) (ml/min/1.73 m²) | Possible effect(s) | Participants with inappropriate drug use |
|---|---|---|---|
| Metformine ($n = 46$) | 30–50 | Increased risk for lactate acidosis | 13 |
| | $<$30 | Strongly increased risk for lactate acidosis | 2 |
| Gliclazide ($n = 15$) | $<$50 | Increased risk for hypoglycaemia | 8 |
| Tramadol ($n = 34$) | $<$30 | More side-effects when DD $>$ 200 mg/d | 0 |
| Spironolactone ($n = 22$) | $<$50 | Increased risk for hyperkalaemia | 10 |
| Sotalol ($n = 17$) | 30–50 | More side effects when DD $>$ 160 mg/d | 0 |
| | $<$30 | More side effects when DD $>$ 80 mg/d | 0 |
| Atenolol ($n = 30$) | $<$30 | More side effects | 2 |
| Ranitidine ($n = 35$) | $<$30 | More side effects | 3 |
| Allopurinol ($n = 37$) | 30–50 | More toxic side effects when DD $>$ 200 mg | 8 |
| | $<$30 | More toxic side effects when DD $>$ 100 mg | 3 |

Table 5. Chance of receiving an inappropriate drug or inappropriate daily dose based on renal function.

| Drug with low eGFR contra-indication | eGFR (ml/ min/ 1.73 m²) | Adjusted[a] OR (CI) for receiving drug |
|---|---|---|
| Metformine | > 50 ml/min | 1 (ref) |
| | 30–50 ml/min | 1.58 (0.77–3.24) |
| | < 30 ml/min | 0.76 (0.16–3.51) |
| Gliclazide | > 50 ml/min | 1 (ref) |
| | < 50 ml/min | 4.51 (1.45–14.02) |
| Spironolactone | > 50 ml/min | 1 (ref) |
| | < 50 ml/min | 1.87 (0.74–4.71) |
| Atenolol | > 30 ml/min | 1 (ref) |
| | < 30 ml/min | 1.53 (0.33–7.05) |
| Ranitidine | > 30 ml/min | 1 (ref) |
| | < 30 ml/min | 2.00 (0.53–7.53) |
| **Drug with maximum DDD when eGFR low** | **eGFR (ml/min/1.73 m²)** | **Adjusted[a] OR (CI) for receiving higher dose** |
| Tramadol (DD > 200 mg) | > 50 ml/min | No cases in low eGFR group |
| | < 50 ml/min | |
| Sotalol (DD > 160 mg) | > 50 ml/min | No cases in low eGFR group |
| | < 50 ml/min | |
| Sotalol (DD > 80 mg) | > 30 ml/min | No cases in low eGFR group |
| | < 30 ml/min | |
| Allopurinol (DD > 200 mg) | > 50 ml/min | 1 (ref) |
| | < 50 ml/min | 1.67 (0.75–3.75) |
| Allopurinol (DD > 100 mg) | > 30 ml/min | 1 (ref) |
| | < 30 ml/min | 3.48 (1.26–9.61) |

[a]Adjusted for age and comorbidities reported by the GP who are related to the eGFR (Table 1): reported hypertension, peripheral arterial disease in history episode of decompensated heart failure and diabetes mellitus.

*Strengths and weaknesses*

This study's strength is that it uses the data of a representative cohort of non-hospitalized very elderly subjects. The prescription of drugs was reported by the patient's responsible general practitioner. A weakness of this study is the fact that we selected only frequently used drugs to analyse them individually. Only eight 'chronic' drugs met the inclusion criteria. It may have been interesting to analyse the use for acute illnesses as well (like antibiotics) but due to the cross-sectional data-collection these drugs could not be analysed. In addition, the use of the MDRD equation has only received limited validation in very old persons (17). Recently, there have been new GFR estimations published for very old subjects (18). However, in this article, the MDRD equation was used because it was the equation used to calculate the eGFR reported to the general practitioners in Belgium in the period prior to the data collection.

*Other studies*

The Three City Study analysed drug use in participants aged 65 years and older in 1999–2001 (before the introduction of automatic eGFR reporting), and found an exposure to inappropriate drug in 52.5% (4.5% real contra-indications) of the participants with an eGFR between 30 and 50 ml/min/1.73 m² and in 96% (4.8% real contra-indications) of the participants with an eGFR < 30 ml/min/1.73 m² (5). They also found that 13% of the study population aged 65 years or older received one or more potentially inappropriate drugs, and only 1% of the study population had absolute contra-indications. In a US study population of 1304 participants aged 65 years or older, 6% of the total study participants received inappropriate drugs (19). In our BELFRAIL study of participants aged 80 years and older, 8% of the total study population received an inappropriate drug prescription given the participant's eGFR, but we checked only a limited number of frequently used drugs.

*Implications for research*

Our study demonstrates that even after automatic eGFR reporting, inappropriate drug prescriptions remain common in older subjects, although this problem has already been well documented and many solutions have been proposed (20–23). Further research should focus on preventive strategies to lower these inappropriate prescriptions. A first step could be to study the origin of these inappropriate prescriptions (lack of knowledge regarding drug use of the eGFR, insufficient support by the electronic medical file system and other related factors). For example, is there a reason for the use of allopurinol in older persons with low eGFR despite that it is contra-indicated? Is it because the alternatives that can be used in these older persons with low eGFR (like febuxostat) are insufficiently known or are there other reasons?

*Conclusion*

Despite the automatic reporting by laboratories of patient eGFR, inappropriate drug prescriptions remain common in older subjects. Further research should focus on preventive strategies to assist older community-dwelling persons.

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