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Use of renal risk drugs in hospitalized patients with impaired renal function—an underestimated problem?

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Abstract

Background. Inappropriate use of drugs in patients with renal impairment (RI) may be harmful and may have deleterious effects. We aimed to investigate the use of renal risk drugs in such patients in general hospitals and to analyse the relationship to demographic factors, risk factors and occurrence of drug-related problems (DRPs).

Methods. Patients admitted to departments of internal medicine and rheumatology in five general hospitals were included. We recorded demographic data, drugs used, drugs described to be a risk in RI (renal risk drugs), relevant medical history, laboratory data and clinical/pharmacological risk factors. We used levels of glomerular filtration rates, calculated by the Modification of Diet in Renal Disease formula to classify patients into five stages of renal function. DRPs were recorded and assessed in multidisciplinary hospital team discussions.

Results. Of the 808 included patients, 293 (36%) had normal renal function (stage 1), 314 (39%) had mild RI (stage 2), 160 (20%) had moderate RI (stage 3), 35 (4%) had severe RI (stage 4) and six (0.7%) had kidney failure (stage 5). Mean number of drugs used per patient in patients with RI (stages 3, 4 and 5) and patients evaluated to have adequate renal function relative to drug therapy (stages 1 and 2): on admission 6.2 *vs* 4.1; started in hospital 4.3 *vs* 3.9 and total number of renal risk drugs 6.1 *vs* 4.5. All but six patients with RI stages 3, 4 and 5 used two or more renal risk drugs. 124 (62%) of the patients with RI stages 3, 4 and 5 had DRPs linked to the renal risk drugs, and 26% of the renal risk drugs were associated with DRPs. The most common drug classes associated with DRPs were antibacterials, antithrombotic agents, angiotensin-converting enzyme (ACE) inhibitors, opioids and non-steroidal anti-inflammatory drugs (NSAIDs).

Conclusions. Among patients admitted to general hospitals, a considerable proportion had renal impairment. In patients with reduced renal function, renal risk drugs were widely used and often in combination. DRPs were frequently associated with the use of renal risk drugs.

Keywords: drugs; drug-related problems; kidney disease; renal impairment; renal risk drugs

Introduction

Kidney disease is increasingly recognized as a significant health issue in the population. The incidence and prevalence of kidney failure are rising, the outcomes are poor and the costs are high [1,2]. Early detection and treatment may prevent or delay renal events [3]. Many drugs and their metabolites are eliminated through the kidney. Inappropriate use of drugs in patients with renal impairment (RI) may therefore be harmful and have deleterious effects [4–6].

Patients diagnosed with severe RI and patients in dialysis are followed closely by nephrologists in specialized nephrology departments. However, the spectrum of chronic kidney disease (CKD) extends from slight kidney damage to severe renal damage needing renal transplant or renal replacement therapy. Often comorbidity, implying concomitant use of many drugs, makes the management of these patients particularly challenging. Studies have suggested that care provided by multidisciplinary nephrology teams may improve patient outcome [7]. However, in most patients with mild to moderate RI, the reduced function may not have been diagnosed and these patients are managed in general practice and in general hospitals.

The necessity of dose adjustment or drug avoidance is probably underestimated in clinical practice. We found only three studies which evaluated the appropriateness of drug use for patients with mild to severe

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RI in hospitals [8–10]. To our knowledge no study has been performed in general hospitals applying a prospective bedside approach.

The aim of the study was to assess drug therapy in patients with mild to severe RI in a general hospital setting and to investigate the extent of inappropriate drug use. Further, to obtain an understanding of the relationship to demographic factors, types of drugs used and other risk factors for the occurrence of drug-related problems (DRPs).

Subjects and methods

Patients and design

A prospective multicentre design was applied. The study was approved by The Regional Committee for Medical Research Ethics. From May to December 2002, patients admitted to eight departments, i.e. six internal medicine—represented by cardiac, respiratory and geriatric wards—and two rheumatology wards, at five general hospitals in Norway were enrolled in the study. Emergency departments were not included. None of the wards had engaged nephrologists or received routine service from nephrologists. The patients were consecutively included in the study. Readmissions of eligible patients were excluded. The following data were recorded for each patient: age, gender, drugs on admission, drugs introduced at the ward, reason for admission, relevant medical history and results of routine laboratory tests. We recorded clinical/pharmacological risk factors for DRPs to occur. These factors, which are the most often acknowledged as such in the literature, were: reduced renal function [glomerular filtration rate (GFR) under 50 ml/min or serum creatinine over normal range], reduced liver function (aspartate aminotransferase or alanine aminotransferase three times over normal values), polypharmacy (≥ 5 drugs on admission), confirmed diabetes mellitus, confirmed cardiac failure, history of allergy or adverse events to drugs, non-compliance, use of drugs with a small therapeutic index and others, e.g. alcohol abuse or problems with swallowing, which could hamper intake of the drugs prescribed.

Data collection

A bedside approach was used and data were collected from medical records, laboratory records and from information received at the morning multidisciplinary meeting where each patient was discussed with regard to diagnosis and therapy. Participants at these meetings were physicians, nurses, clinical pharmacists and occasionally physiotherapists and other health professionals.

Grading of renal impairment

The patients were divided into groups according to the grade of RI. The grading into five stages of RI was made in harmonization with the definition of the National Kidney Foundation [11]: stage 1 (normal kidney function), GFR ≥ 90 ml/min/1.73 m^2; stage 2 (mild reduction of GFR), GFR 60–89 ml/min/1.73 m^2; stage 3 (moderate reduction of GFR), GFR 30–59 ml/min/1.73 m^2; stage 4 (severe reduction of GFR), GFR 15–29 ml/min/1.73 m^2 and stage 5 (kidney failure), GFR ≤ 15 ml/min/1.73 m^2.

We used the Modification of Diet in Renal Disease (MDRD) formula to calculate GFR in all the patients and applied the National Kidney Foundation's GFR calculator [12]. We considered patients in stages 1 and 2 to have adequate kidney function in relation to drug therapy, while patients with stages 3, 4 and 5 had impaired renal function and were in need of special attention with regard to drug therapy.

Drugs categorized as renal risk drugs

Precautions are recommended for several drugs and drug classes eliminated through renal excretion when they are to be used in patients with RI. These drugs are named here as renal risk drugs. We used recommendation lists in the Norwegian National Therapy Guidelines [13] and similar lists in the British National Formulary [14] to assign drugs to the renal risk drug group. Further, we classified renal risk drugs into three main categories: drugs for which *dose adjustments* are recommended; drugs to be used with *caution* and drugs to be *avoided* in RI. Some renal risk drugs were classified into more than one category, for example, with regard to the benzodiazepines, *caution* is advised due to cerebral sensitivity in patients with RI, and it is recommended that in this condition, therapy should be started in small doses, i.e. *dose adjustment*.

Some drugs included in the lists of renal risk drugs may also have renoprotective properties. These—with recommendations for handling in RI—are: ACE inhibitors (caution: reduce dose); angiotensin II antagonists (caution: reduce dose); calcium channel blockers (caution when initiating therapy); some statins (simvastatin: dose above 10 mg to be used with caution, pravastatin: start with small doses, fluvastatin: avoid in severe RI). These drugs were included in the total number of renal risk drugs, but were also depicted separately as renoprotective drugs.

We introduced the proportion of renal risk drugs in relation to the total number of drugs used in order to identify the 'proportion of drugs at risk' for each patient.

Classification of drug-related problems (DRPs)

DRPs were defined in accordance with the definition of Pharmaceutical Care Network Europe: *a drug related problem is an event or circumstance involving drug therapy that actually or potentially interferes with desired health outcomes* [15]. The pharmacist assessed if the patient had DRPs by using national and local guidelines and the Norwegian Drug Catalogue. Thereafter the DRPs were evaluated further in the multidisciplinary team. Twelve categories were used for the classification of DRPs: *need for an additional drug* i.e. according to evidence-based guidelines, *unnecessary drug, non-optimal drug, non-optimal dose, no further need of drug, drug interaction, need for monitoring, adverse drug reaction (ADR), medical chart error, compliance problems, therapy discussions* and *counselling to* patients in need of drug information. For the DRP *drug interaction*, a generally accepted grading according to clinical significance was used. Only those regarded to be clinically important, were included.

One medication may introduce more than one DRP, some of them dependent on each other. For example, a given drug may have caused an interaction, a dose reduction may be needed and monitoring of the drug by laboratory tests may also be required. Thus, three DRPs could be related to the drug. However, the patient might perceive only one DRP—the actual drug itself. In this study, the former approach was applied and the reported frequencies of DRPs are based on the counting of all recorded DRPs. We have previously reported further details concerning the classification and occurrence of DRPs [16].

Statistical analysis

The data were analysed in SPSS 12.0 for Windows. Descriptive statistics are shown as means and frequencies with standard deviations. *P*-values <0.05 ($P < 0.05$) were accepted as statistically significant. To test for differences between patients with RI, stages 3, 4 and 5, and patients with adequate function, stages 1 and 2, independent samples *t*-test are used for continuous variables, while chi-square tests are used for categorical variables. For each category of DRP, the Kruskal–Wallis test was used to test for differences in the mean number of DRPs per patient between patients with different stages of RI, as these data showed strong deviations from the normal distribution.

Results

Patient characteristics

The study included 827 patients, 19 of whom were excluded due to lack of exact information on renal function. We analysed the data on the remaining 808 patients, 59% female and 41% male, with a mean age of 70.9, SD 17.2 (range 15–98). A total of 515 patients (64%) were found to have GFR<90 ml/min/1.73 m^2. The stage distribution was as follows: 293 (36%) had normal renal function; 314 patients (39%) had mild

RI (stage 2); 160 patients (20%) had moderate RI (stage 3); 35 patients (4%) had severe RI (stage 4) and six patients (0.1%) had kidney failure (stage 5). Patients with stages 1 and 2 (adequate renal function) constituted 607 patients (75%) while 201 patients (25%) had stages 3, 4 and 5. RI of stages 2, 3, 4 and 5 were most frequently found among patients in the cardiac ward (79%) while the corresponding figures for the patients in geriatric, respiratory or rheumatic wards were 71, 63 and 43%, respectively.

The mean serum creatinine (SCr) values for patients grouped in stages 1, 2, 3, 4 and 5 were 59, 80, 119, 210 and 408 μmol/l, respectively.

The patients in the group with RI stages 3, 4 and 5 were older, used more drugs and had more clinical/pharmacological risk factors than the group of patients with adequate renal function (stages 1 and 2) (Table 1).

Renal risk drugs

The 201 patients with RI stages 3, 4 and 5, used a total of 2110 drugs. On admission, 1209 drugs were used on a regular basis while 901 drugs were introduced at the hospital; of the latter, 676 drugs were for regular use and 225 drugs to be used as required. Table 2 shows the pattern of drug use for the different patient groups.

Generally, in the patients with RI stages 3, 4 and 5, more than a third of the drugs used on admission were renal risk drugs with the label *caution* (Table 3). Two-fifths of the drugs prescribed in hospital were drugs to be used with *caution*. In patients with stages 3, 4 and 5, drugs needing *dose adjustment* constituted 17% of the drugs on admission and 34% of the drugs started in hospital. Drugs recommended to be *avoided* in RI were used by 49 patients with stage 3; eight patients with stage 4 and three patients with stage 5. Drugs to be avoided constituted 5% of the drugs used on admission and 1% of the drugs started in hospitals.

Table 1. Comparison of patients with adequate renal function (stages 1 and 2) and patients with reduced renal function (stages 3, 4 and 5) with regard to demographic and other characteristics

	Patients with adequate renal function $n = 607$	Patients with reduced renal function $n = 201$	Difference between groups 95% CI	*P*-values
Gender				
Females% (No.)	57 (343)	65 (130)	8 (0.005−0.16)	0.05
	Mean (SD)	Mean (SD)		
Age	68 (18.1)	79.7 (9.7)	11.8 (9.2−14.4)	<0.001
No. of drugs on admission	4.1 (3.1)	6.2 (3.0)	2.10 (1.61−2.59)	<0.001
No. of drugs started in hospital	3.9 (2.9)	4.3 (3.0)	0.46 (-0.01−0.93)	0.06
Total no. of renal risk drugs[a]	4.5 (2.6)	6.1 (2.8)	1.60 (1.17−2.02)	<0.001
No. of DRP[b] per patient	2.4 (2.4)	3.3 (2.7)	0.90 (0.50−1.29)	<0.001
No. of other risk factors (than RI)				
	% (No.) of patients	% (No.) of patients		
Polypharmacy	41 (248)	69 (138)	0.28 (0.20−0.35)	<0.001
Narrow therapeutic index	25 (154)	43 (87)	0.18 (0.10−0.26)	<0.001
Cardiac failure	15 (92)	28 (56)	0.13 (0.06−0.20)	<0.001
Diabetes mellitus	9 (57)	18 (36)	0.09 (0.03−0.14)	0.02

[a]Drugs for which dose adjustment is recommended, drugs to be used with caution or drugs recommended to be avoided in patients with renal impairment (RI), see Subjects and methods section.
[b]Drug-related problems (DRP), definition is given in Subjects and methods section.

Table 2. Renal risk drugs as proportions of all drugs used by patients with various degrees of renal impairment (RI) and by patients with normal renal function

Renal function	Patients	Drugs on admission		Drugs started in hospital, regularly used		Drugs started in hospital, used as required		Ratio per patient (mean)
	No.	No. of drugs (No. of drugs per patient)	Renal risk drugs (%)	No. of drugs (No. of drugs per patient)	Renal risk drugs (%)	No. of drugs (No. of drugs per patient)	Renal risk drugs (%)	Renal risk drugs/all drugs
Stage 1 GFR $\geq$90 ml/min/1.73 m^2	293	1038 (3.5)	51	882 (3.0)	57	306 (1.0)	82	0.59
Stage 2 GFR 60–89 ml/min/1.73 m^2	314	1384 (4.4)	48	895 (2.9)	60	296 (0.9)	75	0.59
Stage 3 GFR 30–59 ml/min/1.73 m^2	160	950 (5.9)	51	496 (3.1)	61	179 (1.1)	77	0.59
Stage 4 GFR 15–29 ml/min/1.73 m^2	35	225 (6.4)	58	147 (4.2)	61	38 (1.1)	79	0.61
Stage 5 GFR $\leq$15 ml/min/1.73 m^2	6	34 (5.7)	59	33 (5.5)	45	8 (1.3)	88	0.57

Renal risk drugs that may also be renoprotective were used by 133 (66%) of the patients with RI stages 3, 4 and 5, compared with 251 users (41%) among those with stages 1 and 2. Among the drugs with potential dual functions, ACE inhibitors and angiotensin II inhibitors were the most frequently prescribed and used by 110 (55%) of the patients with RI stages 3, 4 and 5. A total of 210 renoprotective drugs were used by patients with RI stages 3, 4 and 5, that is 17% of all the renal risk drugs used by the patients belonging to these stages.

Loop diuretics (furosemide and bumetanide) were used by 127 (63%) patients with RI stages 3, 4 and 5, compared with 187 users (31%) in the patient group with renal function of stages 1 or 2 ($P < 0.001$).

All but 6 patients with RI stages 3, 4 and 5 used two or more renal risk drugs. Some combinations are regarded as hazardous in renal impairment, for example, the combination of ACE inhibitors/angiotensin II antagonists and NSAIDs. Altogether, 4% (32 patients) of the total hospital population had this combination; namely 21, three and one patients had RI stages 3, 4 and 5, respectively. Furthermore, this combination was introduced at the hospital in seven patients belonging to stages 3, 4 or 5.

Drug-related problems (DRPs)

Of the 201 patients with RI stages 3, 4 and 5, 124 (62%) had DRPs linked to renal risk drugs. Around 26% of the renal risk drugs were associated with at least one DRP and altogether 20% of renal risk drugs were associated with the DRPs that were particularly relevant with regard to renal function: *need for an additional drug, non-optimal drug, non-optimal dose, no further need of drug, drug interaction, need for monitoring and adverse drug reaction*. For drugs on admission, the DRPs were most often related to drugs to '*avoid*': 27% of renal risk drugs with this caution rule were linked to DRPs. For drugs started in hospital, DRPs were most often associated with drugs needing *dose adjustment*: 19% of the renal risk drugs with this caution were found to be associated with DRPs (Table 3).

The most common DRP for all patients was *non-optimal dose*. In patients with RI (stages 3, 4 and 5) compared with patients with adequate renal function (stages 1 and 2), the mean number of DRPs per patient was significantly higher for the DRPs *non-optimal drug* 0.35 *vs* 0.24 ($P = 0.03$), *non-optimal dose* 0.69 *vs* 0.42 ($P < 0.001$), *drug interaction* 0.33 *vs* 0.18 ($P = 0.02$), *adverse drug reaction* 0.15 *vs* 0.07 ($P = 0.002$) and *need for monitoring* 0.44 *vs* 0.22 ($P < 0.001$). Also, the mean number of DRPs per patient varied with the severity of renal impairment. Generally there was a trend towards an increasing number of DRPs with deteriorating renal function (Figure 1).

The commonest drug classes used in patients with RI stages 3, 4 and 5, and linked to DRPs were antibacterials (52 occurrences), antithrombotic

Table 3. Use of renal risk drugs in 201 patients with renal impairment (RI) stages 3, 4 and 5 and frequency of drug-related problems (DRPs) in relation to risk rules in RI

Risk rule for drugs in RI	Drugs on admission (n = 1209)					Drugs started in hospital (n = 901)				
	No. of patients[a]	No. of renal risk drugs (% of drugs on admission)	No. of renal risk drugs with DRPs[b] (% of renal risk drugs)	DRPs[b] acted upon (% of renal risk drugs with DRP)	Most frequent substances with DRP[b]	No. of patients[a]	No. of renal risk drugs (% of drugs started in hospital)	No. of renal risk drugs with DRPs[b] (% of renal risk drugs)	DRPs[b] acted upon (% of renal risk drugs with DRP)	Most frequent substances with DRP[b]
Dose adjustment	126	207 (17%)	34 (16%)			146	303 (34%)	57 (19%)		
Caution, reduce dose in mild to moderate RI	50	58	19 (33%)	15 (79%)	NSAIDs, atenolol, ranitidin	68	81	21 (26%)	18 (86%)	NSAIDs ciprofloxacin
Reduce dose in severe RI	22	22	10 (45%)	10 (100%)	allopurinol, pivmecillinam	80	111	31 (28%)	20 (65%)	Allopurinol, benzylpenicillin
Start with small doses	93	127	5 (4%)	1 (20%)	benzodiazepines	83	111	5 (5%)	2 (40%)	diazepam
Caution	178	459 (38%)	84 (18%)			160	365 (41%)	52 (14%)		
Caution	143	227	53 (23%)	33 (62%)	enalapril, lisinopril, metoprolol	82	109	22 (20%)	18 (82%)	potassium, simvastatin, paracetamol, metoprolol
Caution, monitor serum concentration	10	12	4 (33%)	4 (100%)	carbamazepine, lithium	10	12	6 (50%)	5 (83%)	aminoglycosides
Increased bleeding tendency	113	120	14 (12%)	10 (71%)	warfarin, acetylsalicylic acid	70	89	14 (16%)	7 (50%)	warfarin, acetylsalicylic acid, dalteparin
Increased cerebral sensitivity	65	100	13 (13%)	8 (62%)	tramadol, codeine/paracetamol	99	155	10 (6%)	5 (50%)	codeine/paracetamol
Avoid	52	66 (5%)	18 (27%)			12	12 (1%)	2 (17%)		
Avoid in mild to moderate renal impairment	31	38	12 (32%)	12 (100%)	metformin, spironolactone	9	9	1 (11%)	1 (100%)	colchicine
Avoid in severe RI	27	28	6 (21%)	4 (67%)	glibenclamide, alendronate	3	3	1 (33%)	0 (0%)	glibenclamide

[a]The number of patients in each main risk rule category is lower than the sum of patients in subgroups. The reason is that each patient may belong to more than one of the subgroups, see Subjects and methods section.
[b]DRPs included: need for an additional drug, non-optimal drug, non-optimal dose, no further need of drug, drug interaction, need for monitoring and adverse drug reaction.
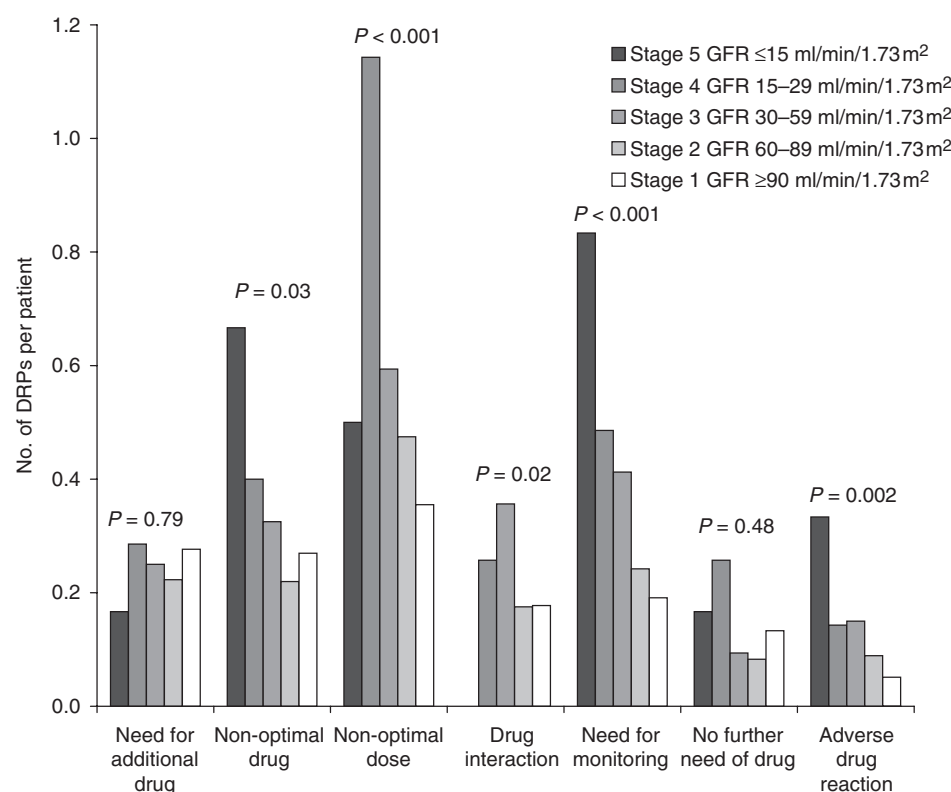
Fig. 1. Distribution of the most relevant drug-related problems (DRP) per patient in hospitalized patients with different stages of renal function. *P*-values analysed by Kruskal–Wallis test are given for differences between the group of patients with stages 3, 4 and 5 and the patient group with adequate renal function (stages 1 and 2).

agents (44), followed by ACE inhibitors (32), opioids (20), NSAIDs (20) and allopurinol (14).

Discussion

Drugs recommended to be used with caution, avoided or given with dose adjustment (renal risk drugs) in the case of reduced renal function were commonly used in patients with RI. Apparently, the recommendations were only followed to a limited degree, as the utilization rates of renal risk drugs were equally high in patients with moderate to severe RI and in patients with adequate renal function. Explanations for the high rates in patients with definite RI might be that the physicians underestimate the harmful consequences of such drugs in this condition or have inadequate knowledge of medications requiring adjustments [4].

It should, be kept in mind that some of these drugs are needed in patients with renal impairment and are in fact renoprotective in many patients. ACE inhibitors, angiotensin II antagonists, calcium channel blockers and the statins are considered to be such renoprotective drugs. These drugs are often used with the objective of preventing cardiovascular events. Used long-term they are renoprotective through positive effects on renal arteries and renal microcirculation. The renal adverse effects associated with these drugs are most often presented acutely at the start of the treatment or when other renal risk drugs, for example NSAIDs, are added to these basically protective drugs. Thus, the fine line between risk and benefit should be recognized and considered when dealing with some drug classes that are on the lists of potential renal risk drugs.

The present study included patients in general hospitals, and therefore the results are assumed to be representative of a general patient population. Although early referral to a nephrologist is recommended in patients with declining renal function, patients with mild to moderate RI will most often be admitted to general hospitals for treatment of non-renal conditions, for example, pneumonia and heart diseases. Then, specialists other than nephrologists will be in charge of the management. Our results show that the scale of the problem concerning use of renal risk drugs in RI is considerable, and hence extensive knowledge about this issue is required among all physicians.

We found that more drugs were prescribed per patient in the patient group with impaired renal function (stages 3, 4 and 5) than in patients with adequate function (stages 1 and 2). The main reason for this was that the patients in the former group were older and had more accompanying comorbidities; for example, diabetes, hypertension and cardiac diseases, which evoke decline of renal function in addition to the genuine age-related decline. Thus, the pharmacotherapy of the elderly becomes more abundant and

more complex, contributing to the high proportion of renal risk drugs being used in patients with non-adequate renal function. We did, however, find a lower ratio of renal risk drugs in the patients with the most severe RI, indicating somewhat heightened awareness directed towards this group. The identification of high numbers of DRPs in patients with renal impairment is probably a result of special awareness of DRPs within the multidisciplinary team, particularly so among the clinical pharmacists who, among other tasks, were specifically screening for DRPs.

Attention to the occurrence of DRPs is a valuable way of monitoring drug therapy, helping physicians and other health care workers to act and adjust drug regimens before adverse events arise. Although an international standard for the classification of DRPs does not exist, we applied a generally well-acknowledged classification containing twelve DRP categories. Our results show that among these, particular attention should be paid to the DRPs such as *non-optimal dose*, *need for monitoring*, *non-optimal drug*, *drug interactions* and *adverse drug reactions*, since these occurred more frequently in patients with non-adequate renal function, and besides, with a trend of more frequent occurrence with increased severity of renal impairment. Other researchers have not used this broad spectrum of DRPs in studies concerning RI, bedside methods have not been used. However, relatively high frequency of inappropriate drug use has been reported in patients with RI, observations that largely are in line with our findings [8–10,17].

Renal function is more frequently assessed by laboratory samples in hospitals than in primary care. Inadequate estimation of the patient's renal function may lead to ignorance of medications needing dose adjustment or drugs inappropriate in RI. However, although SCr is included in a mandatory laboratory test panel on admission to most hospitals, this test is regarded as an imperfect screening test for renal function. The Kidney Disease Outcomes Quality Initiative (K/DOQI) [11] recommends GFR to be estimated from calibrated SCr and estimating equations, such as the MDRD equation or the Cockcroft–Gault formula. Furthermore, it is recommended that drug dosing should be based on GFR estimates. Until a few years ago the Cockcroft–Gault formula has been recommended in Norway. However, in clinical practice, few patients have their weight taken regularly—in our study only two-fifths of the patients. This limits the value of using the Cockcroft–Gault formula in attempts to obtain more detailed information about the renal function. Since the MDRD equation is based on more easily available information—gender, age, race and SCr—this is a more practically useful method and accordingly, has recently been recommended as the preferred method in our country. Of note, though, is our finding (data not shown) that when applying the Cockcroft-Gault equation on those patients who had their weight taken, the proportion of patients with RI turned out to be of the same magnitude as that which was recorded with the MDRD formula.

In the evaluation of drug therapy, mild reduction of renal function, that is to say, GFR in the range of 60–90 ml/min/1.73 m^2, could be considered together with definitely normal function. This is so, because most often, mildly reduced function does not affect drug metabolism and elimination in a clinically significant way. Such considerations are consistent with the way one defines renal function reduction when this factor is assessed to be a risk factor for developing DRPs. We and others have used GFR below 50–60 ml/min/1.73 m^2 to identify and describe patients at increased risk [17,18].

The recommendation lists for renal risk drugs are long and include many drugs in common use, also drugs which are important and beneficial for patients with certain renal diseases, for example, ACE inhibitors [18]. Usually such substances do not create problems. However, since they are included in the list of renal risk drugs, prescribers may get the impression that the list presents an overcautious approach to drug therapy. This may lead to ignorance and also undeservingly bring the list into disrepute. Moreover, the drug recommendation lists address only single substances and do not give any guidance on how to handle the combination of several renal risk drugs. Combinations of renal risk drugs may increase the hazards for patients with reduced renal function. We found that most patients received not only one renal risk drug but a combination of two or more. The question of how to combine renal risk drugs has not been addressed in the literature. Some combinations of renal risk drugs are mentioned in lists outlining interactions, emphasising that attention to possible renal adverse effects should be given. However, cross-reference to recommendation lists for drug dosage in RI does not exist. This lack of guidance leaves general practitioners on their own to judge the risks. Our analysis on patients with impaired renal function demonstrates the value of having drug experts as a part of the multidisciplinary team in general health care.

Conflict of interest statement. None declared.

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