Optimizing drug prescribing and dispensing in subjects at risk for drug errors due to renal impairment: a survey on improving drug safety in primary health care by low eGFR alerts.

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Optimizing drug prescribing and dispensing in subjects at risk for drug errors due to renal impairment:

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Article summary

Objectives- (defined as an estimated glomerular filtration (eGFR) ≤40 ml/min/1.73 m^2)

Article focus

- To evaluate the number of subjects with at risk for drug errors due to renal impairment (eGFR≤40 ml/min/m^2) in a primary care setting.
- To assess the risk of medication errors in subjects with renal impairment.
- To evaluate the effectiveness of automatic eGFR≤40-alerts and drug reviews involving community pharmacists.

Key messages

- Extending renal laboratory data towards pharmacists in primary care revealed a considerable number of subjects at increased risk for ADEs due to renal impairment
- The introduction of eGFR alerts resulted in valuable drug adjustment proposals of community pharmacists towards prescribing physicians, with good acceptance rate
- Implementation of this simple protocol could identify many pADEs and thus substantially reduce the risks of unnecessary iatrogenic damage in subjects with impaired renal function

Strenghts/limitations

- Implementation in clinical practice possible in various health care settings
- Increased collaboration with community pharmacists improved health care safety and awareness on drug errors related to renal function impairment in primary care
- Extending the availability of laboratory renal data which were not shared formerly is relatively easy to achieve with low costs
- Effect of eGFR alerts on the incidence of adverse drug events could not be not measured
- Study design does not allow determining individual health care effects, nor overall cost-benefits of this health care safety strategy

Abstract

Objectives- To assess the risk of medication errors in subjects with renal impairment (defined as an estimated glomerular filtration (eGFR) ≤40 ml/min/1.73 m^2) and the effectiveness of automatic eGFR≤40-alerts relayed to community pharmacists.

Design- Clinical survey.

Setting- The city of Zwolle, The Netherlands with a primary care setting including 22 community pharmacists and 65 general practitioners.

Participants- All adults who underwent creatinine measurement triggering an eGFR≤40-alert.

Primary and secondary outcome measures- Total number of subjects with an eGFR≤40-alert within a year and amount of medication errors related to renal impairment. Type and number of proposed drug adjustments by the community pharmacist and subsequent physician's acceptance rate. Classification of all medication errors on the potential to cause an ADE and the occurrence of ADEs one year after the introduction of eGFR≤40-alerts.

Results- Creatinine measurements were performed in 25929 adults and in 5.3% (n=1369) of these subjects an eGFR ≤40-alert was identified. This group had a median [IQR] age of 78 [69,84] years and in 73% polypharmacy (≥5 drugs) was present. In 15% (n=211) of these subjects a medication error was detected. The proportion of errors increased with age. Pharmacists proposed 342 drug adjustments; mainly concerning diuretics (22%) and antibiotics (21%). Physicians' acceptance rate was 66%. Of all medication errors 88% was regarded as potential ADE, mainly classified as significant or serious. At follow-up, ADE risk (n=40) appeared highest when proposed adjustments in drug regimen were not implemented (38% versus 6%).

Conclusions- The introduction of automatic eGFR-alerts identified a considerable amount of subjects at risk for ADEs due to renal impairment. Nationwide implementation of this simple protocol could identify many potential ADEs and thus substantially reduce the risks of unnecessary iatrogenic damage in subjects with impaired renal function.

Introduction

Safe medication management is an important health-care topic. Medication errors are a significant source of iatrogenic patient harm.[1-7] Adverse drug events (ADEs) are injuries secondary to medication errors (Figure 1). Various factors are associated with ADEs, including patient characteristics, lack of medication monitoring and prescription errors.[4-6,8] Studies on medication-related hospital admissions estimated that 21-91% of admissions were potentially preventable.[1,6,9,10] Important patient determinants for ADEs are increasing age, female gender, polypharmacy, noncompliance and co-morbidities like cognitive dysfunction or renal impairment.[1-4,7,8,10]

Renal impairment is a well-known risk factor for ADEs, but often remains unrecognized for prescribing physicians and pharmacists.[11-14] Even in high-risk patients like diabetics and elderly health care workers are not always alert.[15-17] Various studies reported considerable dosing difficulties and subsequent medication errors in patients with renal impairment.[10,12,17-19] Therefore, intensified collaboration between health care workers (like general practitioners, pharmacists, nephrologists and other hospital-based physicians) is recommended with exchange of relevant patient information (medical history and co-morbidities) and more effective use of routinely collected data from electronic patient records (e.g. like laboratory results related to renal function).[2,6,20-23]

In this 1-year observational study, we aimed to evaluate the number of subjects at risk for medication errors due to renal impairment (defined as an estimated glomerular filtration rate (eGFR) ≤40 ml/min/1.73 m^2) and the effectiveness of automatic eGFR ≤40-alerts towards community pharmacists in a shared pharmaceutical care model. In addition, we classified all medication errors on the potential to cause an ADE and evaluated after 1 year the number of ADEs in those with a medication error.

Materials and methods

Setting

This study was conducted in a city in the Netherlands (Zwolle) with over 89.000 adult inhabitants.[24] All primary care pharmacies (n=11) and general practitioners' (GP) practices (n=24) in the city agreed to participate. Their characteristics are shown in Table 1. Dutch patients are generally registered at one single pharmacy and GP practice, which promotes continuity of care and reliable information regarding individuals' drug use. Secondary care in this region is delivered by the Isala Clinics, a 1000+ bed teaching-hospital in Zwolle. In this city all standard laboratory investigations requested from both primary and secondary care are performed in one laboratory, using a single electronic system for data handling.

Design and case-finding

This prospective observational study was conducted between February 1st 2009 and January 31st 2010. During this period, all consecutive adult inhabitants of Zwolle in whom a serum creatinine was measured and had an eGFR at or below the cut-off point of 40 ml/min/1.73 m^2 were identified, irrespective of the reason for laboratory testing. This threshold was based on guidelines advising dosage adjustment in renal impairment.[25,26] Each week the laboratory automatically reported on patients with an eGFR ≤40 ml/min/1.73 m^2 to the pharmacists.

Study protocol

A predefined protocol was followed after the pharmacist received a report on an eGFR ≤40 ml/min/1.73 m^2 (Figure 2). First, the patients' pharmacist checked the actual drug regimen for current medication errors related to renal impairment. Numbers and types of errors were registered. Medication errors were based on Dutch Pharmacists guidelines including 'the National Formulary on drug prescribing in renal impairment' and the 'National Shared Care Guidelines on Chronic Kidney Disease (CKD)'.[25,26] Second, the pharmacist alerted the prescribing physician (GP or clinician) on the low eGFR and, if appropriate, an adjusted drug regimen was proposed. Pharmacists contacted prescribing physicians by telephone or (if unreachable) by email. Finally, an alert warning for a low eGFR (eGFR≤40-alert) was activated in the patient's pharmacy record. This eGFR≤40-alert then appeared after that with every new prescription. After this first laboratory notification, follow-up eGFR results were also reported to the pharmacists. When an eGFR

recovered well beyond the cut-off value during follow-up (specified as an eGFR >50 ml/min/1.73m^2), the eGFR≤40-alert was removed from the pharmacy record.

The study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the Declaration of Helsinki. All pharmacists and GPs informed their patients about the study through flyers, issued both at the pharmacies and at the GP practices. The patient-folder and website of the Isala Clinics also contained information about the stepwise eGFR≤40-alert protocol, sharing of laboratory data and medication monitoring. Because the protocol was designed to improve medication safety, the study had an opt-out policy. Thus, subjects who expressed not to participate in this pharmacovigilance study were excluded from the weekly reporting. It should also be emphasized that the final decision about (not) changing the drug regimen after an alert (and informing the patient) was considered to be the responsibility of the prescribing physician.

Definitions and calculations

Serum creatinine was measured with an enzymatic essay (Modular, Roche, Mannheim, Germany) and eGFR was calculated with the enzymatic MDRD formula.[27] Drug inclusion was restricted to drugs prescribed by health care professionals, excluding topical or over the counter (OTC) medicines. Actual drug use was assessed by documenting all current prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification system[28] at the moment of the first eGFR≤40-alert. Polypharmacy was defined as chronic (>1 year) use of ≥5 drugs.

Data collection

For all identified subjects with an eGFR ≤40-alert, demographics and information on drug use were collected. All proposed drug adjustments were recorded including the patient's medical record number, pharmacist, type and daily dose of drugs, prescribing physician (GP or clinician). Also the physician's response to the proposed adjustment was recorded. Finally, the pharmacists' time spent on every eGFR≤40-alert was documented.

Classification and tracking of (potential) adverse drug events

To evaluate the impact of eGFR≤40-alerts two pharmacists (EP and KB) independently evaluated all medication errors on the potential to cause an ADE (defined as a potential ADE (pADE)) using a methodology developed for classification of medication errors and (p)ADEs.[29] Figure 1 clarifies the

relationship between these terms. They judged and classified the theoretical severity of the medication error, yielding a score of 0-4 (0=drug error without significant harm, 1=potentially significant, 2=potentially serious, 3=potentially life threatening, 4=potentially fatal) (Table 2). To reach consensus, all discrepant ratings were discussed with two nephrologists (HB and HJ). Examples of pADE classification are listed in Table 2. The best assessment of the number of ADEs proved to be from documentation on ADEs in the hospital records.[30] Therefore, one year after the end of the study, we checked hospital-records of all subjects in whom a medication error was detected in order to track whether ADEs had occurred.

Data analysis

The main outcome measures were the incidence of eGFR≤40-alerts, the number and type of medication errors and the amount and type of drug adjustments proposals. Secondary outcome measures were the time required for pharmacists to process the eGFR<40-alerts, the adherence of physicians towards the proposed drug adjustments, risk factors for medication errors and the severity of medication errors. In addition, after one year follow-up, we checked the incidence of ADEs in subjects in whom a medication error was detected. Statistical analysis was performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA.) Data are presented as mean and standard deviation (SD) when normally distributed. Otherwise, median and interquartile range [IQR] were used. For normally distributed data, differences in baseline characteristics were evaluated with the independent samples *t*-test. For nonparametric data Mann-Whitney *U* test was used. Differences in distribution were calculated by chi-square tests.

Results

Incidence of eGFR<40-alert and characteristics of the study population

During the study period 46781 creatinine measurements were performed in 25929 adult inhabitants of Zwolle. In 5.3% (n=1369) of these subjects an eGFR ≤40-alert was identified. One patient indicated no willingness to participate for privacy reasons, leaving 1368 subjects for analysis (Figure 2). Characteristics are summarized in Table 3. Overall, 56% was female, median age was 78 [69,84] years (age distribution is shown in Figure 3) and median eGFR was 34 [27,38] ml/min/1.73m^2. Overall, polypharmacy was present in 73% (n=993) with a mean number of drugs per patient of 7 (range 0-21). An overview of the actual medication use in the study population (which reflects comorbidities) according to the ATC classification is given in *appendix 1*.

Number and type of medication errors

Overall, 342 medication errors were detected in 211 patients with an eGFR ≤40-alert (15% of the study population) (Figure 2). The proportion of errors increased with higher age (Figure 3). Figure 4 summarizes the drug groups associated with medication errors. Most errors concerned diuretics (22%) and antibiotics (21%), followed by anti-gout medication (15%). The majority of these drugs (77%) were prescribed by GPs.

Proposed drug adjustments and physicians' adherence

Figure 5 gives an overview of the frequency and types of proposed drug adjustments. The most common advices were 'change drug dosage' (55%), followed by 'stop drug' (24%). In 31% (n=105) the proposal concerned a new prescription. Physicians complied with the proposal in 66% (n=226). In 28% (n=96) the pharmacists' advice was rejected and the medication regimen remained unchanged. The main reasons for rejection were already increased alertness with intensive monitoring by the prescribing physician (often being an internist or nephrologist deliberately prescribing the concerning drug) and an insufficient response to lower dosages in the past. In some cases recovery of acute renal impairment was expected or underestimation of renal function (both generally checked with a 24-hour creatinine clearance) was presumed. Notably, in 22 out of the 96 cases drug regimen was changed a short time later due to further decrease of eGFR or an ADE. Thus, from the latter it seems plausible that with the eGFR <40-alert the

physician's awareness on ADE risks was triggered. Data on rejection or agreement lacked in 6% (n=20) of the proposals.

Potential risk factors for medication errors in patients with eGFR<40 alerts

Compared to the subjects without medication errors (n=1157), subjects with drug adjustments proposals (n=211) were more often female (59% versus 41%, p=0.04) and had a lower eGFR (median 34 [28,38] versus 29 [2,34] ml/min/1.73m^2, p<0.001, respectively). Notably, the latter had higher rates of polypharmacy (70 versus 89%, p<0.001, mean number of drugs 6.6 (3.8) versus 8.2 (3.5), p<0.001).

Effectiveness: potential ADEs and occurrence of ADEs after follow up

Overall, 88% (n=299) of the medication errors were regarded as relevant pADEs (score>0). These were mainly judged to be either significant or serious. An overview of the number and potential severity of pADEs in the study population is given in Figure 2.

Overall, 40 ADEs were tracked within one year in the group of subjects with a medication error, including two life-threatening ADEs (bradycardia due to digoxin intoxication and acute kidney injury with lactic acidosis associated with persistent metformin use). The number and severity of ADEs are shown in Figure 2. Importantly, the ADE risk was higher in subjects whose drug regimen remained unchanged (n=60) as compared to subjects whose drug regimen was adjusted as proposed by the pharmacist (n=139); 38% versus 6%, respectively (Table 4).

Effectiveness: workload and time investment of pharmacists

After receiving an eGFR≤40-alert, the pharmacist needed on average 11 minutes (range 5-13 minutes) to check an individual's drug regimen on medication errors. When taking into account the time needed for consultation of the prescribing physician, pharmacists required on average 20 minutes processing one eGFR≤40-alert triggering a drug adjustment. All pharmacists judged the time investment as feasible in daily practice, mainly because on average every pharmacy received only one alert per week.

Overall, 904 eGFR≤40-alerts were activated in the records of the participating pharmacies after one year, as 16% (n=214) of the population died during the study period and in 250 subjects the most recent eGFR was at least twice >50 ml/min/1.73m^2. Thus, on average, every primary care

pharmacy had 82 patients with an activated eGFR≤40-alert. If we translate this to a standard Dutch GP practice (±2300 patients), simple laboratory data sharing identified approximately 23 patients per practice who need drug adjustment(s) or extra alertness in medication management.

Discussion

The main findings of this study were that an eGFR ≤40-alert was identified in 5.3% of the adult population of a Dutch city in whom a creatinine measurement was performed and that in these subjects 342 medication errors (mainly involving antibiotics and diuretics) were detected one year after the introduction of an automatic eGFR≤40-alert system. The majority of medication errors was regarded as a relevant pADE, necessitating drug adjustment according to pharmacists' protocols. Physicians complied with 66% of these proposals. ADE risk seems to increase with age, polypharmacy and when proposed drug adjustments are rejected initially. Overall, automatically generated low eGFR-alerts in primary care seemed effective, easy to implement and, importantly, improves pharmacists' and physicians' awareness on drug safety.

Comparison with other studies

Despite the fact that primary care settings account for the majority of drug prescribing and dispensing, most studies on (p)ADEs are hospital-based.[3,9,10] We aimed to study the incidence of (p)ADEs in a shared pharmaceutical care model with a central role for community pharmacists. Three primary health care studies on this topic reported lower pharmacist drug proposal rates (0.7-1.9%) than the reported 15% in our study.[31-33] These studies were performed in a general population, while we selected a high-risk population of subjects with renal impairment. In line with our results, primary and ambulatory care studies evaluating pharmacists' drug proposals in vulnerable subgroups like elderly or subjects with cardiovascular risk factors also reported higher rates.[12,17,34,35] One recent study, also concerning subjects with renal impairment, identified drug-related problems due to inappropriate prescriptions in 20% of the patients.[18]

Patients with renal impairment are especially vulnerable to medication errors.[12,13,18] Various strategies to improve drug safety in these patients have been studied, like educational wards rounds, immediate clinician-pharmacist feedback or dose adjustment according to renal function at hospital discharge.[12,18,36-41] But despite the fact that the majority of drug prescriptions take place in primary health care, most strategies so far were tailored to hospital settings and therefore not suitable for primary care settings. Others have demonstrated the effectiveness of 'computerized physician order entry' and 'clinical decision support' in reducing medication errors in renal impairment.[38-40] However, computerized drug prescribing alerts do not always guarantee a

reduction of prescribing errors,[42] partly because such alerts are often overridden or ignored by prescribing physicians.[40,43-45] This phenomenon is also reflected in our data, as in 28% drug proposals were rejected by the prescribing physicians.

A central role for community pharmacists in improving medication safety in primary care has been recognized. Many pharmacists are gradually extending their role as an integral part of the medical team around the patient, thus taking an important position in a shared care environment.[21,46,47] This is not only induced by legislative issues,[21,25] but also recommended in different guidelines and studies to counteract problems associated with multiple (drug) prescribers.[20,26,32,47] This is also important in view of our ageing population in which complex drug therapy will only increase, polypharmacy is common and renal impairment omnipresent.[48,49] A recent review showed notable differences in ADE prevalence by age groups increasing from 5% for adults up to 16% for elderly.[7] Thus, in case of complex drug prescriptions (like in renal impairment) close collaboration of community pharmacists and physicians seems essential to prevent ADEs and our method could be a simple initiative for this.

Our strategy included three steps to reduce medication errors in patients with renal impairment. First, automatic laboratory alerts were generated, second these laboratory alerts were linked to pharmacy data to judge the need for drug adjustments and third pharmacists discussed drug proposals with physicians. Several studies investigated the impact of any the above steps. The introduction of automatically recorded laboratory alerts on renal impairment directly towards prescribing physicians had varied impact.[40,50,51] Authors suggested that passive alerts were not directive enough for physicians. Data on extending alerts towards community pharmacists are however limited. Others showed that drug dosage could benefit from the linkage of pharmacy data with laboratory renal data.[12,41,52] We aimed to optimize medication safety in renal impairment by combining these above steps and tailored our strategy to primary care.

Implications for clinical practice

The estimated prevalence of both moderate (30-59 ml/min/1.73m^2) and severe (15-29 ml/min/1.73m^2) renal insufficiency in the adult American and Dutch population is 4.5% and 5.3% respectively.[26,53] Thus, the number of subjects potentially susceptible to renal drug errors is substantial. If we compile our pADE-rate towards nationwide figures (based on 12,500,000 adults in the Netherlands), our type of data sharing could intercept more than 40,000 potential ADEs

related to renal impairment each year. This would undoubtedly increase health care safety with already available data and decrease costs of ADE related morbidities. Drug safety management might be further improved by extending patient data exchange towards other important parameters, like drug allergies, platelet count, electrolyte concentrations, INR, liver enzymes and plasma drug levels.

Strenghts and weaknesses of the study

Some limitations of this study have to be noted. First, our study design does not allow determining individual health care effects, nor overall cost-benefits. However, participating GPs and pharmacists indicated that the protocol improved their awareness on drug errors related to renal function impairment. Second, data on the incidence of ADEs before start of the study project were not available in our region; therefore a possible change in ADEs incidence as a result of our interventions cannot be determined. Besides, the incidence of ADEs is likely underestimated due to underreporting, missed recognition and lack of recording in daily clinical practice.

Our study also has several strengths. First, our intervention is easily implementable in various health care settings. We simply extended the availability of laboratory renal data which were not shared formerly. Second, physicians valued the pharmacists' involvement in improving health care delivery. Acceptance of recommendations was fairly good (67%), as compared to previous studies (24-82%)[17,32,34,38,50] and our prescription ratio between GPs and hospital-based physicians (77:23%) reflects the normal distribution of prescriptions in the Netherlands (82:18%).[54] Third, time investment was acceptable and costs were low. Finally, we chose for a safe, but also feasible threshold for kidney function alerts. Some guidelines advice a higher cut-off point for dose adjustments (creatinine clearance 50-60 ml/min),[11,55] but this was expected to result in an amount of alerts exceeding an acceptable workload. Moreover, as the MDRD tends to underestimate true GFR and we presumably already included subjects with true GFR >40ml/min.[56]

Conclusions and policy implications

In conclusion, the introduction of automatic renal function alerts towards pharmacists in primary care revealed that a considerable number of subjects is at risk for ADEs due to renal impairment. Extending the availability of renal laboratory data towards community pharmacists resulted in a considerable amount of drug adjustment proposals to prescribing physicians. In our opinion nationwide implementation of this simple protocol could identify many pADEs and thus

substantially reduce the risks of unnecessary iatrogenic damage in subjects with impaired renal function.

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Table 1 | Characteristics of participating pharmacists and GPs, and their practices

	Characteristics	Pharmacists	GPs
Participants			
	Number (%)	22 (100)	65 (100)
	Sex, n (%)		
	male	9 (40)	42 (65)
	female	13 (60)	23 (35)
	Years in practice, n (%)		
	0-10	10 (45)	25 (39)
	11-20	9 (41)	15 (23)
	21-30	0 (0)	21 (32)
	>30	3 (14)	4 (6)
	Position in practice, n (%)		
	(joint) owner	6 (27)	45 (70)
	employee	16 (73)	20 (30)
Practice			
	Number (%)	11 (100)	24 (100)
	Practice type, n (%)		
	independent	9 (80)	-
	chain	2 (20)	-
	Overall number of patients, n	114.033	117.147
	Practice size, median [IQR]	10.000 [7.000, 14.000]	3426 [2691, 6586]
	Prescription system, n (%)		
	computer-based	11 (100)	24 (100)

IQR=Interquartile Range; GP=general practitioner

Table 2 | **Categories of potential adverse drug events (pADEs) according to severity**

Score	Potential severity	Examples
0	*Drug error without potential harm*	• *Not applicable*
1	*Significant*	• Gastro-intestinal complaints • Therapeutically ineffective dose according to eGFR • Mild neurological effects (e.g. motoric dysfunction) • Hepatic dysfunction • Any significant event identified by patient which does not require change in therapy
2	*Serious*	• Hypoglycemia • Nephrotoxicity or increased risk nephrolithiasis • Electrolyte disturbances (e.g. hyperpotassiemia) • Altered mental status due to sedation • Myopathy or rhabdomyolysis • Gastrointestinal bleed
3	*Life threatening*	• Lactic acidosis • Cardiac arrhythmia • Decline in mental status with risk of falling • Respiratory failure requiring intubation (e.g. bronchospasms)
4	*Fatal*	• Death

Table 3 | Characteristics of the study population

Variable	
Number of subjects, n (%)	1368 (100)
Demographics	
Age (years), median [IQR]	78 [69,84]
Male, n (%)	601 (44)
Diabetes, n (%)	346 (25)
Renal variables	
eGFR (ml/min/1.73m^2), median [IQR]	34 [27,38]
Serum creatinine (µmol/ml), median [IQR]	152 [128,186]
Actual drug regimen	
Number of drugs, median [IQR]	7 [4,9]
Polypharmacy, n (%)	993 (73)

IQR=interquartile range; eGFR=estimated glomerular filtration rate

Table 4 | Adverse drug event (ADE) risk in subjects with a medication error. Comparison of ADE risk in subjects whose drug regimen was adjusted as proposed by the pharmacist versus subjects in whom drug regimen remained unchanged.

Subjects with medication error	Potential ADE (n=211)	ADE (n=34)	ADE Risk
Drug regimen adjusted *(number of subjects)*	139	9	*With intervention:* **6%**
Drug regimen unchanged *(number of subjects)*	60	23	*Without intervention:* **38%**
Unknown *(number of subjects)*	12	2	-

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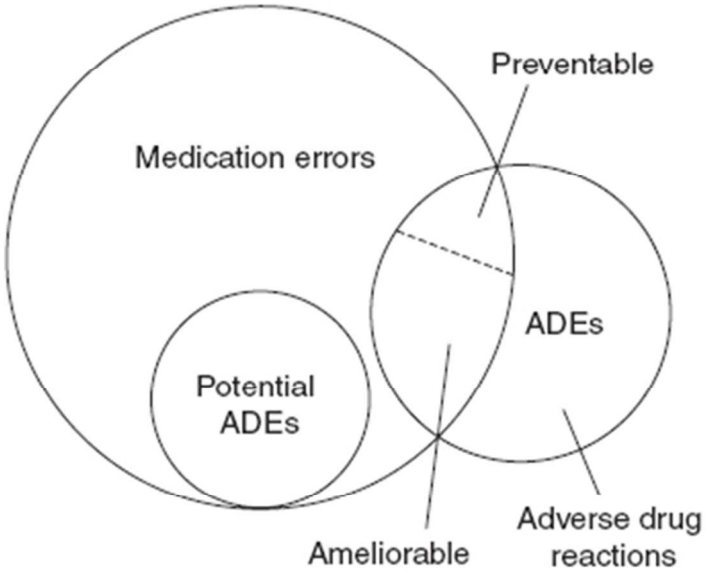
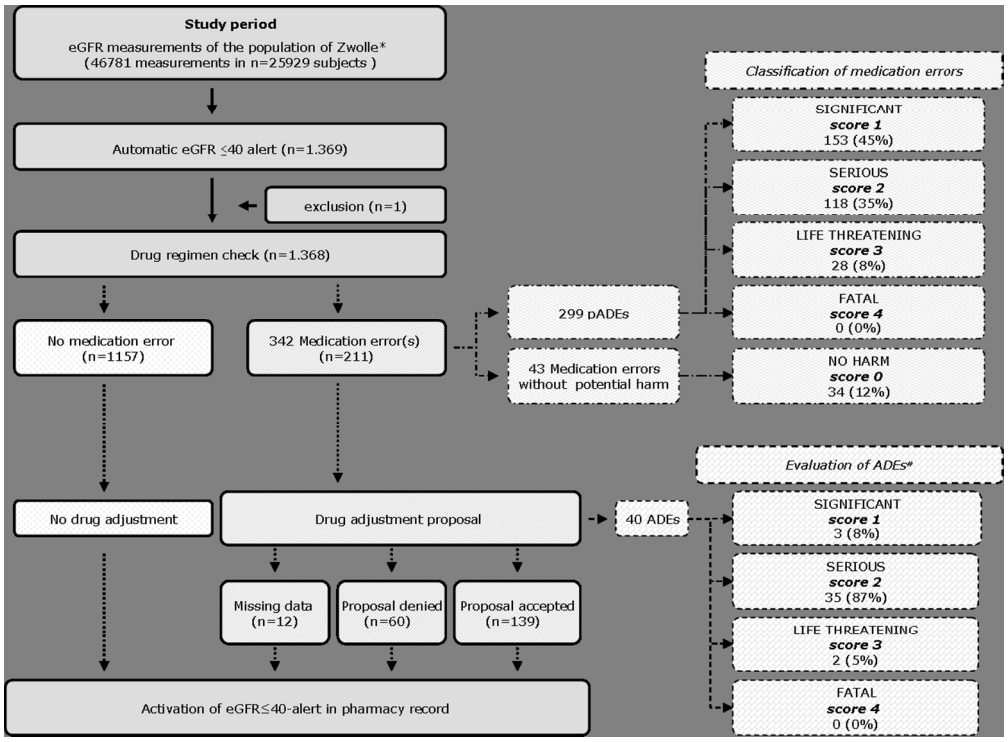
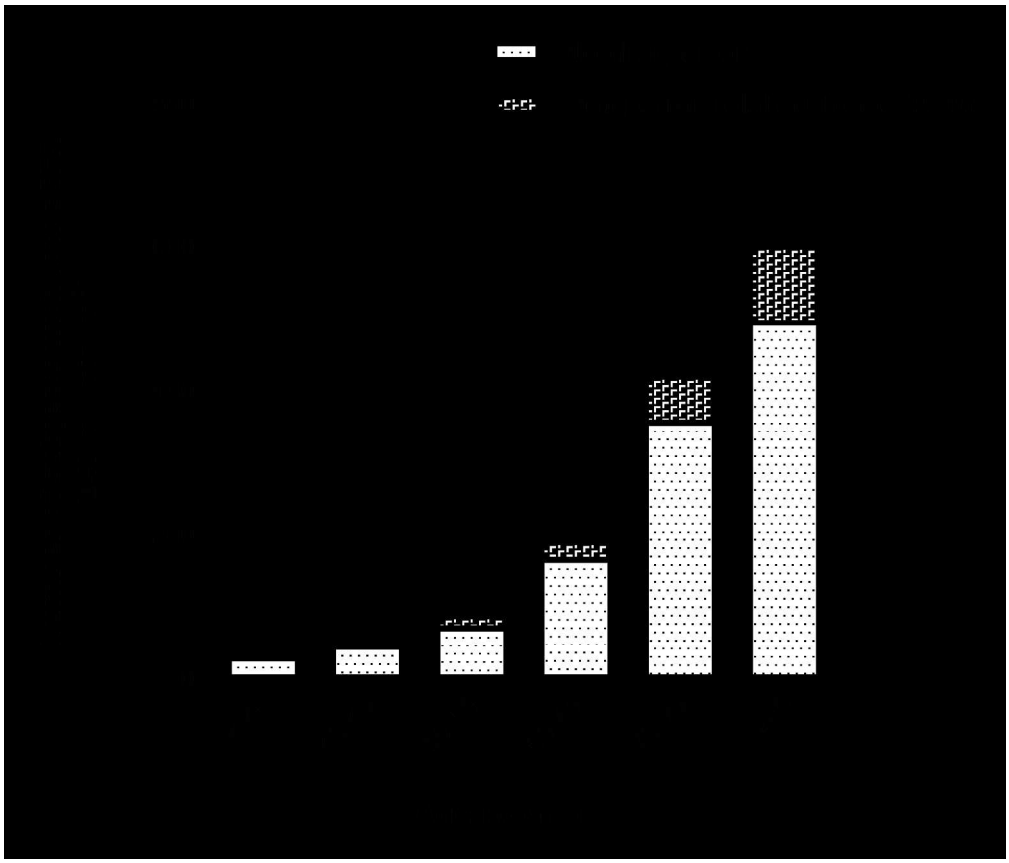


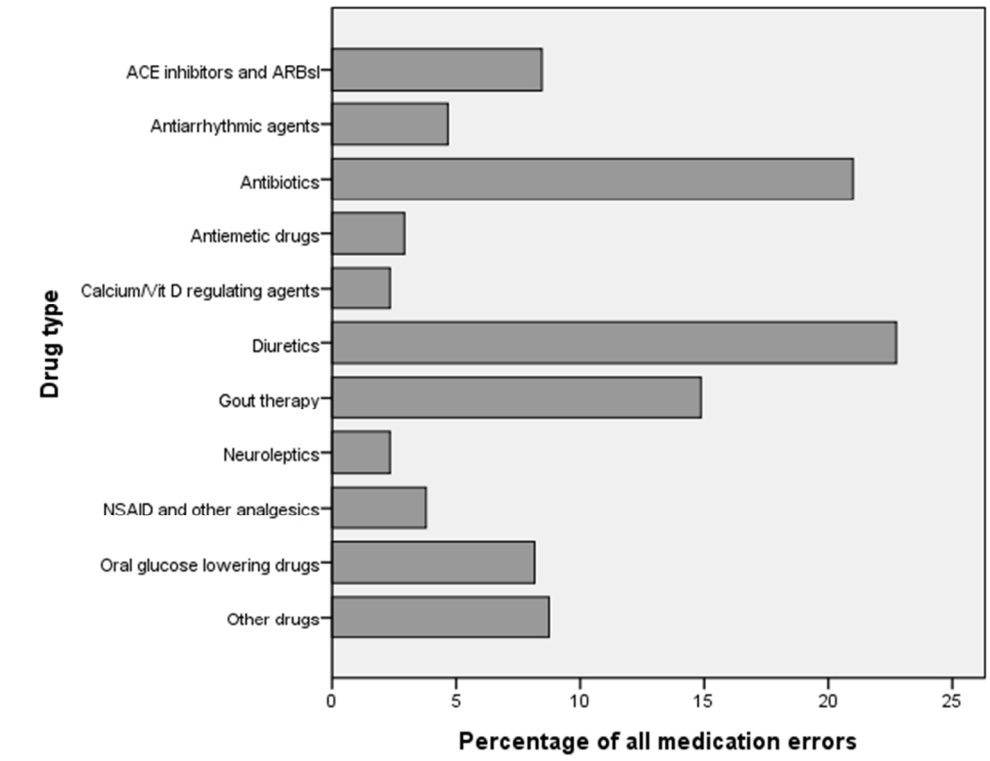
Relationship between adverse drug events (ADEs), potential ADEs (pADEs) and medication errors.[29]



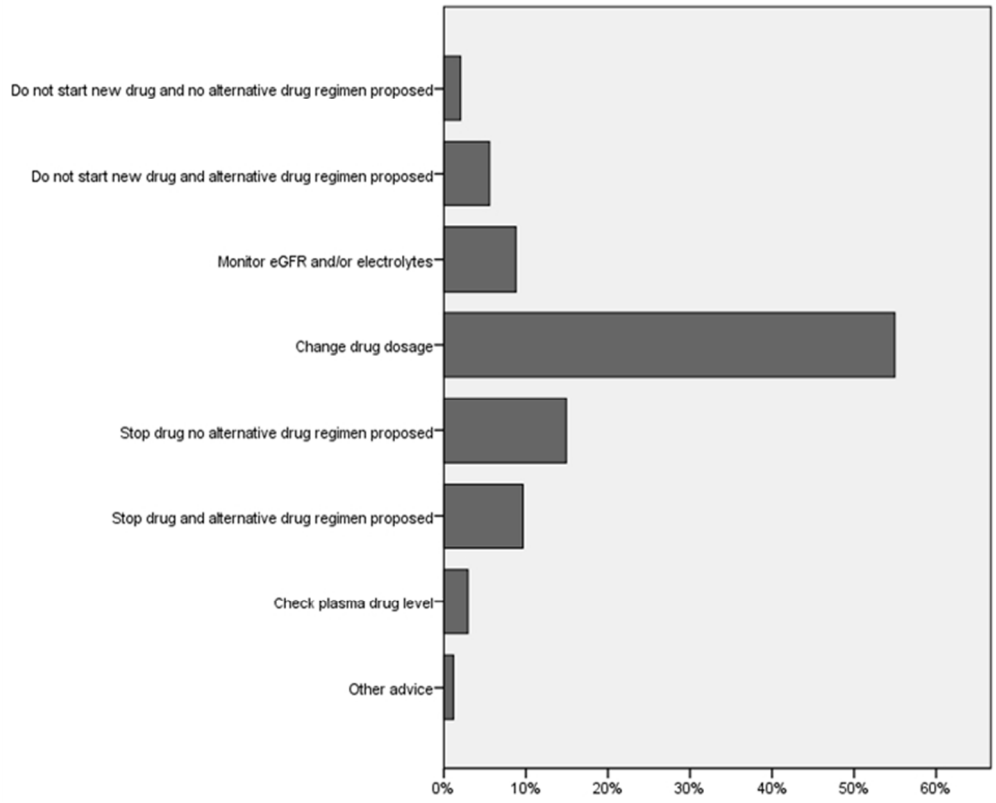
Flow chart summarizing study method and selection of study population



Age distribution of study population and risk of medication error per age category



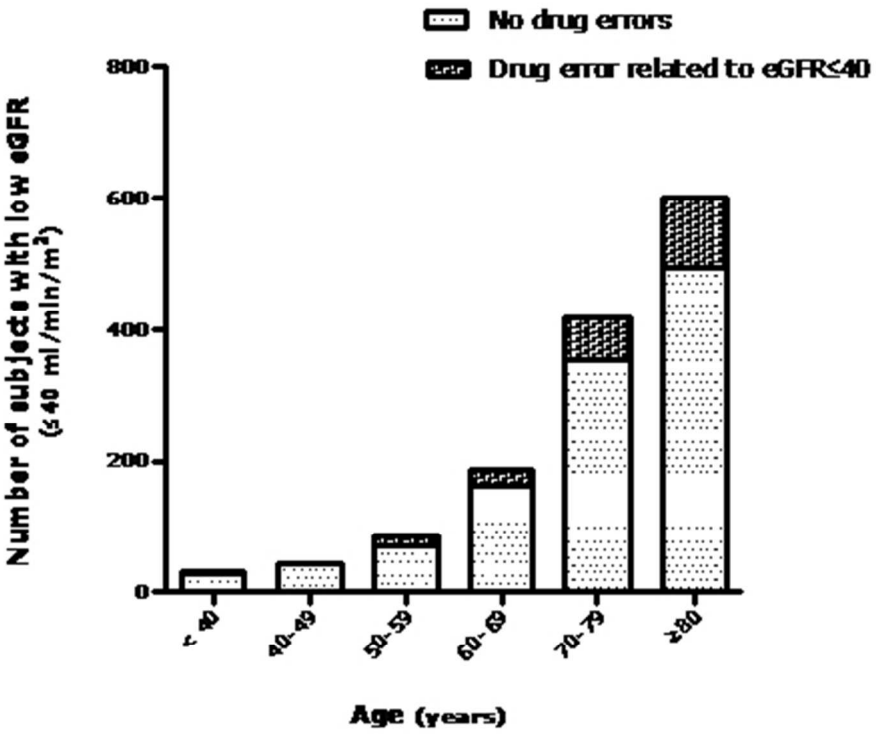
Drug groups associated with medication errors related to renal impairment



Type and frequency of drug adjustment proposals by community pharmacists
192x120mm (102 x 131 DPI)

Appendix 1 | **Overview of drug use according to the ATC classification in the study**

ATC CLASSIFICATION		Number (%)
A	**ALIMENTARY TRACT AND METABOLISM**	**1764 (19.1)**
A01	STOMATOLOGICAL PREPARATIONS	4
A02	DRUGS FOR ACID RELATED DISORDERS	556
A03	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	27
A04	ANTIEMETICS AND ANTINAUSEANTS	15
A05	BILE AND LIVER THERAPY	7
A06	LAXATIVES	194
A07	ANTIDIARRHEALS, ANTIINFLAMMATORY/ANTIINFECTIVE	30
A09	DIGESTIVES, INCL. ENZYMES	6
A10	DRUGS USED IN DIABETES	558
A11	VITAMINS	179
A12	MINERAL SUPPLEMENTS	185
A15	APPETITE STIMULANTS	1
A16	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	2
B	**BLOOD AND BLOOD FORMING ORGANS**	**1107 (11.9)**
B01	ANTITHROMBOTIC AGENTS	902
B02	ANTIHEMORRHAGICS	2
B03	ANTIANEMIC PREPARATIONS	203
C	**CARDIOVASCULAR SYSTEM**	**4064 (43.8)**
C01	CARDIAC THERAPY	400
C02	ANTIHYPERTENSIVES	28
C03	DIURETICS	1145
C04	PERIPHERAL VASODILATORS	1
C07	BETA BLOCKING AGENTS	767
C08	CALCIUM CHANNEL BLOCKERS	316
C09	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	830
C10	LIPID MODIFYING AGENTS	577
D	**DERMATOLOGICALS**	**3 (0.03)**
G	**GENITO URINARY SYSTEM AND SEX HORMONES**	**147 (1.6)**
H	**SYSTEMIC HORMONAL PREPARATIONS**	**254 (2.8)**
J	**ANTIINFECTIVES FOR SYSTEMIC USE**	**165 (1.9)**
L	**ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**	**100 (1.0)**
M	**MUSCULO-SKELETAL SYSTEM**	**312 (3.4)**
N	**NERVOUS SYSTEM**	**846 (9.2)**
P	**ANTIPARASITIC PRODUCTS, INSECTICIDES.REPELLENTS**	**6 (0.06)**
R	**RESPIRATORY SYSTEM**	**417 (4.6)**
S	**SENSORY ORGANS**	**6 (0.06)**
V	**VARIOUS**	**36 (0.5)**
OVERALL		**9227 (100)**



Optimizing drug prescribing and dispensing in subjects at risk for drug errors due to renal impairment: a survey on improving drug safety in primary health care by low eGFR alerts.

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Optimizing drug prescribing and dispensing in subjects at risk for drug errors due to renal impairment:

improving drug safety in primary health care by low eGFR alerts.

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Iefke Drion; authorship included collection of the data and revising the manuscript

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Kees J. Boogerd; authorship included the design and conceptualisation of the study, interpretation of the data and revising the manuscript. No disclosures.

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Article focus

- To evaluate the number of subjects with at risk for medication errors due to renal impairment (defined as eGFR≤40 ml/min/m^2) in a primary care setting.
- To assess the risk of medication errors in subjects with renal impairment.
- To evaluate the effectiveness of generating automatic eGFR≤40-alerts and medication reviews involving community pharmacists.

Key messages

- Providing renal laboratory data to pharmacists in a primary care setting revealed that there were a considerable number of subjects at increased risk for adverse drug events (ADEs) due to renal impairment
- The issuance of eGFR alerts allowed community pharmacists to provide valuable medication adjustment recommendations to the prescribing physicians, with good acceptance rate
- The implementation of this simple protocol could identify many potential ADEs (pADEs), thereby substantially reducing the risks of unnecessary iatrogenic damage in subjects with impaired renal function

Strenghts/limitations

- Implementation of this protocol in clinical practice is possible in various health care settings
- Increased collaboration with community pharmacists improved health care safety and awareness on medication errors related to renal function impairment in primary care
- Extending the availability of laboratory renal data which were not formerly shared is relatively straightforward with minimal expense
- Effect of eGFR alerts on the incidence of ADEs could not be not measured
- Study design does not allow determining individual health care effects, nor an overall cost-benefit analysis of this health care safety strategy

Abstract

Objectives- To assess the risk of medication errors in subjects with renal impairment (defined as an estimated glomerular filtration (eGFR) ≤40 ml/min/1.73 m^2) and the effectiveness of automatic eGFR≤40-alerts relayed to community pharmacists.

Design- Clinical survey.

Setting- The city of Zwolle, The Netherlands, in a primary care setting including 22 community pharmacists and 65 general practitioners.

Participants- All adults who underwent ambulatory creatinine measurements which triggered an eGFR≤40-alert.

Primary and secondary outcome measures- The total number of ambulatory subjects with an eGFR≤40-alert during the study period of one year and the number of medication errors related to renal impairment. The type and number of proposed drug adjustments recommended by the community pharmacist and acceptance rate by the prescribing physicians. Classification of all medication errors on their potential to cause an adverse drug event (ADE) and the actual occurrence of ADEs (limited to those identified through hospital record review) one year after the introduction of the alerts.

Results- Creatinine measurements were performed in 25929 adults. An eGFR ≤40-alert was indicated for 5.3% (n=1369). This group had a median [IQR] age of 78 [69,84] years, and in 73% polypharmacy (≥5 drugs) was present. In 15% (n=211) of these subjects, a medication error was detected. The proportion of errors increased with age. Pharmacists recommended 342 medication adjustments; mainly concerning diuretics (22%) and antibiotics (21%). The physicians' acceptance rate was 66%. Of all the medication errors, 88% were regarded as potential ADEs, with most classified as significant or serious. At follow-up, the ADE risk (n=40) appeared highest when the proposed medication adjustments were not implemented (38% versus 6%).

Conclusions- The introduction of automatic eGFR-alerts identified a considerable number of subjects who are at risk for ADEs due to renal impairment in an ambulatory setting. The nationwide implementation of this simple protocol could identify many potential ADEs thereby substantially reducing iatrogenic complications in subjects with impaired renal function.

Introduction

Safe medication management is an important health-care topic, as medication errors are a significant source of iatrogenic injury to patients.[1-7] Injuries resulting from such errors are known as adverse drug events (ADEs) . Various factors are associated with ADEs, including patient characteristics, lack of medication monitoring, and prescription errors.[4-6,8] Studies on medication related hospital admissions estimate that 21-91% of admissions were potentially preventable.[1,6,9,10] Important patient determinants for ADEs are increasing age, female gender, polypharmacy, noncompliance and co-morbidities such as cognitive dysfunction or renal impairment.[1-4,7,8,10]

Renal impairment is a well-known risk factor for ADEs, but often remains unrecognized by physicians and pharmacists.[11-14] Even in high-risk patients such as elderly and those with diabetics, health care workers are not always sufficiently alert.[15-17] Various studies reported considerable dosing difficulties and subsequent medication errors in patients with renal impairment.[10,12,17-19] Therefore, intensified collaboration between health care workers (such as general practitioners (GPs), pharmacists, and nephrologists) is recommended with exchange of relevant patient information (medical history and co-morbidities) and more effective use of routinely collected data from electronic patient records such as laboratory results relating to renal function).[2,6,20-23]

In this 1-year observational study, we aimed to evaluate the number of subjects at risk for medication errors due to renal impairment (defined as an estimated glomerular filtration rate (eGFR) ≤40 ml/min/1.73 m^2) and the effectiveness of providing automatically generated eGFR ≤40-alerts towards community pharmacists in a shared pharmaceutical care model. In addition, we classified all medication errors for their potential to cause ADEs and evaluated the actual number of ADEs in those with a medication error after a period of one year.

Materials and methods

Setting

This study was conducted in Zwolle, which is a city in the north of the Netherlands with a population of more than 89.000 adults.[24] All of the primary care pharmacies (n=11) and the general practices (n=24) participated in this study. Their characteristics are shown in Table 1. Dutch patients are generally registered at one single pharmacy and GP practice, which promotes continuity of care and reliable information regarding each individuals' medication use. Secondary care in this region is delivered by the Isala Clinics, a 1000+ bed teaching-hospital in Zwolle. All standard laboratory investigations requested in both primary and secondary care are performed in one laboratory, which uses a single electronic system for data handling.

Design and case-finding

This prospective observational study was conducted between February 1st 2009 and January 31st 2010. During this period, all consecutive adults in whom a serum creatinine was measured in the ambulatory setting who had an eGFR at or below the cut-off point of 40 ml/min/1.73 m^2 were identified, irrespective of the reason for laboratory testing. This threshold was based on guidelines advising dosage adjustment in renal impairment[25,26] and also chosen from a practical point of view. A higher cut-off-point of 50-60 ml/min/1.73m^2 was expected to exceed an acceptable workload, and the generation of many alarms induces the risk of ignoring and overriding alerts. Each week the laboratory automatically generated a report for any ambulatory patients with an eGFR ≤40 ml/min/1.73 m^2 for the pharmacists.

Study protocol

A predefined protocol was followed after the pharmacist received a report on an eGFR ≤40 ml/min/1.73 m^2 (Figure 1). First, the patients' pharmacist checked the actual medication regimen for current errors related to renal impairment. Numbers and types of errors were registered. Medication errors were based on Dutch Pharmacists guidelines including 'the National Formulary on drug prescribing in renal impairment' and the 'National Shared Care Guidelines on Chronic Kidney Disease (CKD)'.[25,26] Second, the pharmacist alerted the prescribing physician (GP or clinician) on the low eGFR and, if appropriate, an adjusted medication regimen was recommended. Pharmacists

contacted prescribing physicians by telephone or (if unreachable) by email. Finally, an alert warning for a low eGFR (eGFR≤40-alert) was activated in the patient's pharmacy record. This eGFR≤40-alert then appeared with every future new prescription. After this first laboratory notification, follow-up eGFR results were also reported to the pharmacists. When an eGFR recovered well beyond the cut-off value during follow-up (specified as an eGFR >50 ml/min/1.73m^2), the eGFR≤40-alert was removed from the pharmacy record.

The study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the Declaration of Helsinki. All pharmacists and GPs informed their patients about the study through flyers, issued both at the pharmacies and at the GP practices. The patient folder and the Isala Clinics website also contained information about the stepwise eGFR≤40-alert protocol, the sharing of laboratory data, and medication monitoring. The study had an opt-out policy, therefore, subjects who did not wish to participate in this pharmacovigilance study were excluded from the weekly reporting. It should be emphasized that the final decision about making any medication changes after an alert (and informing the patient) was considered to be the responsibility of the prescribing physician.

Definitions and calculations

Serum creatinine was measured with an enzymatic essay (Modular, Roche, Mannheim, Germany) and eGFR was calculated with the enzymatic MDRD formula.[27] to the only medications included were those prescribed by health care professionals, and topical or over the counter (OTC) products were excluded. Actual medication use was assessed by documenting all current prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification system[28] at the moment of the first eGFR≤40-alert. Polypharmacy was defined as chronic (>1 year) use of ≥5 drugs.

Data collection

For all identified subjects with an eGFR ≤40-alert, demographics and medication information were collected. Any medication adjustment recommendations were recorded, which included the patient's medical record number, the pharmacist, the type and daily dose of the medication, and the prescribing physician (GP or clinician). The physician's response to the pharmacist's recommendation was also recorded. Finally, the amount of time the pharmacists spent on every eGFR≤40-alert was documented.

Classification and tracking of (potential) adverse drug events

To evaluate the impact of eGFR≤40-alerts two pharmacists (EP and KB) independently evaluated all medication errors on the potential to cause an ADE (defined as a potential ADE (pADE)). They received a database that was anonymized by an investigator not involved in the eGFR-alert processing (HJ). A methodology developed for classification of medication errors and (p)ADEs.[29] They judged and classified the theoretical severity of the medication error, yielding a score of 0-4 (0=drug error without significant harm, 1=potentially significant, 2=potentially serious, 3=potentially life threatening, 4=potentially fatal) (Table 2). To reach a consensus, all discrepant ratings were discussed with both pharmacists and two nephrologists (HB and HJ). Examples of pADE classifications are listed in Table 2. The best assessment of the number of ADEs proved to be from the documentation on ADEs in the hospital records.[30] Therefore, one year after the end of the study, the hospital records of all subjects in whom a medication error was detected, were reviewed. This review was performed by two nephrologists (HJ and HB) who independently checked the occurrence of ADEs. ADEs were based on admission and discharge diagnosis in the patients' medical records. The relationship of the ADE with the 'suspected' agent was double checked by evaluating whether the medication regimen at admission in the hospital record matched with the pharmacy record at the date of admission. After review of the hospital records HJ and HB discussed their findings for reaching consensus.

Data analysis

The main outcome measures were the incidence of eGFR≤40-alerts, the number and types of medication errors, and the number and types of medication adjustment proposals. Secondary outcome measures were the time required for pharmacists to process the eGFR<40-alerts, the adherence of physicians to the proposed adjustments, risk factors for medication errors, and the severity of medication errors. In addition, after one year of follow-up, we checked the incidence of ADEs in subjects in whom a medication error was detected. Statistical analysis was performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA.) Data are presented as mean and standard deviation (SD) when normally distributed. Otherwise, median and interquartile range [IQR] were used. For normally distributed data, the differences in baseline characteristics were evaluated with the independent samples *t*-test. For nonparametric data Mann-Whitney *U* test was used. Differences in distribution were calculated using the chi-square tests.

Results

Incidence of eGFR<40-alert and characteristics of the study population

During the study period 46781 creatinine measurements were performed in 25,929 subjects. In 5.3% (n=1369) of cases, an eGFR ≤40-alert was indicated. One patient indicated no willingness to participate for privacy reasons, leaving 1368 subjects for analysis (Figure 1). Their characteristics are summarized in Table 3. Overall, 56% was female, the median age was 78 [69,84] years (distribution is shown in Figure 2) and the median eGFR was 34 [27,38] ml/min/1.73m^2. Overall, polypharmacy was present in 73% (n=993) with a mean number of medications per patient of 7 (range 0-21). An overview of the actual medication use in the study population (which reflects comorbidities) according to the ATC classification is given in *Appendix A*.

Number and type of medication errors

Overall, 342 medication errors were detected in 211 patients with an eGFR ≤40-alert (15% of the study population) (Figure 1). The proportion of errors increased with increasing age (Figure 2). The types of medication most commonly associated with errors were diuretics (22%), antibiotics (21%), and anti-gout medications (15%) (Figure 3).The majority of these medications (77%) were prescribed by GPs. An overview of the type of medication errors that were identified by the pharmacists is given in figure 4.

Physicians' compliance with medication adjustment recommendations

Figure 5 gives an overview of the frequency and types of medication adjustment recommendations. The most common recommendations were 'change dosage' (55%), followed by 'stop medication (24%). In 31% (n=105) the proposal concerned a new prescription. Physicians complied with the recommendation in 66% (n=226) of cases. In 28% (n=96) of cases, the pharmacists' advice was rejected and the medication regimen remained unchanged. The main reasons for rejection included already increased alertness with intensive monitoring by the prescribing physician (often being an internist or nephrologist) and an inadequate response to lower dosages in the past. The majority of rejected recommendations included diuretics and renin-angiotensin-aldosterone system (RAAS) blockers like ACE inhibitors and ARB drugs. In some cases, the recovery of renal function was expected or underestimation of renal function was presumed, both of which

were generally checked with a 24-hour creatinine clearance. Overall, acutely reduced eGFR did not account for an important subset of the eGFR<40 alerts towards the community pharmacists (n=3). Notably, in 22 of the 96 cases , the medication was soon changed anyway, due to a further decrease in the eGFR or the occurrence of an ADE. Therefore, from the latter it seems plausible that with the eGFR ≤40-alert the physician's awareness of the risk for an ADE was triggered. Data on rejection or agreement lacked in 6% (n=20) of cases.

Potential risk factors for medication errors in patients with eGFR≤40 alerts

Compared to the subjects without medication errors (n=1157), subjects for whom medication adjustments were recommended (n=211) were more often female (59% versus 41%, p=0.04) and had a lower eGFR (median 34 [28,38] versus 29 [2,34] ml/min/1.73m^2, p<0.001, respectively). Notably, the latter had higher rates of polypharmacy (70 versus 89%, p<0.001, mean number of medications 6.6 (3.8) versus 8.2 (3.5), p<0.001).

Effectiveness: potential ADEs and occurrence of ADEs after follow up

Overall, 88% (n=299) of the medication errors were regarded as relevant pADEs (score>0). These were mainly judged to be either significant or serious. An overview of the number and potential severity of pADEs in the study population is given in Figure 1.

Overall, 40 ADEs were identified in hospital records within one year after the study period in the group of subjects with medication errors, including two life-threatening ADEs (bradycardia due to digoxin intoxication and acute kidney injury with lactic acidosis associated with persistent metformin use). The number and severity of ADEs are shown in Figure 1. Importantly, the ADE risk was higher in subjects whose medication regimen remained unchanged (n=60) as compared to subjects whose medication regimen was adjusted as recommended by the pharmacist (n=139); 38% versus 6%, respectively.

Effectiveness: workload and time investment of the pharmacists

After receiving an eGFR≤40-alert, the pharmacist needed an average of 11 minutes (range 5-13 minutes) to check an individual's medication regimen for errors. When taking into account the time needed for consultation with the prescribing physician, pharmacists required an average of 20 minutes to process one eGFR≤40-alert triggering a medication adjustment. All pharmacists judged the time investment as feasible, particularly considering the fact that each pharmacy received an

average of only one alert per week. Retrospectively we evaluated the feasibility of different thresholds for kidney function alerts by calculating the number of low eGFR-alerts that would have been generated during the study period using different cut-offs for renal impairment (<30, <50 and <60 ml/min/1.73m^2, respectively, see Appendix B).

Overall, 904 eGFR≤40-alerts were activated in the records of the participating pharmacies at the end of the study period, as 16% (n=214) of the population died and in 250 subjects, the most recent eGFR was at least twice >50 ml/min/1.73m^2. Therefore, on average, every primary care pharmacy had 82 patients with an activated eGFR≤40-alert. If we translate this to a standard Dutch GP practice (±2300 patients), simple laboratory data sharing identified approximately 23 patients per practice who need drug adjustment(s) or extra alertness in medication management.

Discussion

The main findings of this study were that an eGFR ≤40-alert was indicated in 5.3% of the adult population of a Dutch city in whom a creatinine measurement was performed in an ambulatory setting and that in these subjects 342 medication errors (mainly involving antibiotics and diuretics) were detected during the year following the introduction of an automatic eGFR≤40-alert system. The majority of the medication errors was regarded as relevant pADEs, necessitating medication adjustments as recommended by pharmacists. Physicians complied in 66% of cases. ADE risk increases with age, polypharmacy, and in instances when the proposed medication adjustments were initially rejected. Overall, automatically generated low eGFR-alerts in primary care seemed effective, easy to implement, and, importantly, improve both the pharmacists' and the physicians' awareness of medication safety.

Comparison with other studies

Despite the fact that medications are usually both prescribed and dispensed in the primary care setting, most studies on (p)ADEs have been hospital-based.[3,9,10] We aimed to study the incidence of (p)ADEs in a shared pharmaceutical care model with a central role for community pharmacists. Three primary health care studies on this topic reported lower pharmacist drug proposal rates (0.7-1.9%) than the 15% we found.[31-33] These studies were performed in a general population, while we selected a high-risk population of subjects with renal impairment. In line with our results, primary and ambulatory care studies evaluating pharmacists' drug proposals in vulnerable subgroups like the elderly or subjects with cardiovascular risk factors also reported higher rates.[12,17,34,35] Two recent studies, also concerning subjects with renal impairment, identified problems related to inappropriate prescribing in over 20% of patients.[18,36]

Patients with renal impairment are especially vulnerable to medication errors.[12,13,18] Various strategies to improve drug safety in these patients have been studied, such as educational wards rounds, immediate clinician-pharmacist feedback, or dose adjustment according to renal function at hospital discharge.[12,18,37-42] However, despite the fact that most prescribing takes place in the primary health care setting, the majority of the strategies implemented so far have been tailored to hospital settings and are therefore not suitable for primary care. Others have demonstrated the effectiveness of 'computerized physician order entry' and 'clinical decision support' in reducing

medication errors in case of renal impairment.[39-41] However, computerized drug prescribing alerts do not always guarantee a reduction of prescribing errors,[43] partly because such alerts are often overridden or ignored by prescribing physicians.[41,44-46] This phenomenon is also reflected in our data, as in 28% of cases pharmacist recommendations were rejected by the prescribing physician. A central role for community pharmacists in improving medication safety in primary care has been recognized. Many pharmacists are gradually extending their role as integral members of the medical team around the patient, thereby taking an important position in a shared care environment.[21,47,48] This has not only been induced by legislative issues,[21,25] but also recommended in various guidelines and studies to counteract problems associated with multiple medication prescribers.[20,26,32,48] This is important in view of our ageing population in which complex drug therapy will only increase, polypharmacy is common and renal impairment widespread.[49,50] A recent review showed notable differences in ADE prevalence rates by age groups increasing from 5% for adults up to 16% for the elderly.[7] Therefore, in complex cases (as with renal impairment) the close collaboration between community pharmacists and physicians is essential to prevent ADEs.

The alert method we have investigated here could be a simple solution to address this.

Our strategy included three steps to reduce medication errors in patients with renal impairment. First, automatic laboratory alerts were generated, second these alerts were linked to pharmacy data to judge the need for drug adjustments, and third, pharmacists discussed recommended changes with physicians. Several studies investigated the impact of the above steps. The introduction of automatically generated laboratory alerts had varied effects on the prescribing physician.[41,51,52] Authors suggested that such passive alerts did not have enough of an impact. There is limited data on the effect of extending the alerts so that the community pharmacist was also involved.. Other studies showed that when the pharmacy data were linked with the laboratory renal data, the medication dosage could be beneficially adjusted..[12,42,53] We aimed to optimize medication safety in cases of renal impairment by combining the aforementioned steps and tailored our strategy for application in the primary care setting. .

Implications for clinical practice

The estimated prevalence of both moderate (30-59 ml/min/1.73m^2) and severe (15-29 ml/min/1.73m^2) renal insufficiency in the adult American and Dutch population is 4.5% and 5.3%

respectively.[26,54] Therefore, the number of subjects potentially susceptible to related medication errors is substantial. If we compile our pADE-rate towards nationwide figures (based on 12,500,000 adults in the Netherlands), our type of data sharing could intercept more than 40,000 potential ADEs related to renal impairment each year. This would undoubtedly increase health care safety with already available data and (hopefully) decrease the costs of ADE related morbidities. Drug safety management might be further improved by extending patient data exchange towards other important parameters, such as medication allergies, platelet counts, electrolyte concentrations, INR, liver enzymes, and plasma drug levels.

Strenghts and weaknesses of the study

Some limitations of this study have to be noted. First, our study design does not allow determining individual health care effects, nor overall cost-benefits. This would necessitate a more complex study design as was for example used in the population-based randomized controlled renal drug alert effectiveness trial of Bhardwaja et al, or a 'before and after' design.[36] However, participating GPs and pharmacists indicated that the protocol improved their awareness of medication errors related to renal function impairment. Second, data on the incidence of ADEs before start of the study project were not available in our region; therefore a possible change in ADE incidence as a result of our interventions cannot be determined. Besides, the incidence of ADEs is likely underestimated due to underreporting, missed recognition, and lack of recording in daily clinical practice. Our study also has several strengths. First, our intervention can be easily implemented in various health care settings. We simply extended the availability of laboratory renal data which were not shared formerly. Second, physicians valued the pharmacists' involvement in improving health care delivery. The acceptance percentage of the pharmacists' was fairly good (67%), as compared to previous studies (24-82%)[17,32,34,37,51] and our prescription ratio between GPs and hospital-based physicians (77:23%) reflects the normal distribution of prescriptions in the Netherlands (82:18%).[55] However, to improve the overall efficiency of the eGFR-alerts, also variables influencing physicians' (non) adherence towards pharmacists' recommendations (like type and duration of medication use) should be further studied. Third, the time investment was acceptable and costs were low. Finally, we chose for a safe, but also feasible threshold for renal function alerts. However, as thresholds for dosage adjustment vary between different guidelines, a higher cut-off of ≤50 or 60 ml/min/1.73m^2, or drug specific thresholds could be discussed.[25,26,36,56] Besides, as the Cockcroft-Gault (CG) formula is often used in pharmacokinetic studies and for drug

dosing recommendations, the implications of the use of renal function estimates like the MDRD equations for drug dosing, is under debate. Several studies have compared drug dosing recommendations based on the CG with those based on the MDRD.[57-59] In summary, the accuracy of the MDRD seems comparable to the CG.[57-59] Based on these studies, in our opinion, the MDRD is a reasonable alternative to the CG for drug dosing. This is of importance especially since there is an increasing trend of clinical laboratories reporting the MDRD along with serum creatinine, which is also recommended by national and international organizations. [26,60] Some guidelines advise a higher cut-off point for dose adjustments (creatinine clearance 50-60 ml/min),[11,61] but this was expected to result in an amount of alerts exceeding an acceptable workload. Moreover, as the MDRD tends to underestimate true GFR, we presumably already included subjects with true GFR >40ml/min.[62]

Conclusions and policy implications

The introduction of automatic renal function alerts in the ambulatory care setting, with the involvement of both GPs and community pharmacists, revealed that a considerable part of the population is at risk for ADEs due to impaired renal function.. Extending the availability of renal laboratory data to community pharmacists resulted in their presenting the prescribing physicians with a considerable number of medication adjustment recommendations. We feel that nationwide implementation of this simple protocol could potentially identify many pADEs and substantially reduce the risks of iatrogenic damage in persons with decreased renal function.

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Table 1 | Characteristics of participating pharmacists and GPs, and their practices

	Characteristics	Pharmacists	GPs
Participants			
	Number (%)	22 (100)	65 (100)
	Sex, n (%)		
	male	9 (40)	42 (65)
	female	13 (60)	23 (35)
	Years in practice, n (%)		
	0-10	10 (45)	25 (39)
	11-20	9 (41)	15 (23)
	21-30	0 (0)	21 (32)
	>30	3 (14)	4 (6)
	Position in practice, n (%)		
	(joint) owner	6 (27)	45 (70)
	employee	16 (73)	20 (30)
Practice			
	Number (%)	11 (100)	24 (100)
	Practice type, n (%)		
	independent	9 (80)	-
	chain	2 (20)	-
	Overall number of patients, n	114.033	117.147
	Practice size, median [IQR]	10.000 [7.000, 14.000]	3426 [2691, 6586]
	Prescription system, n (%)		
	computer-based	11 (100)	24 (100)

IQR=Interquartile Range; GP=general practitioner

Table 2 | **Categories of potential adverse drug events (pADEs) according to severity**

Score	Potential severity	Examples
0	*Drug error without potential harm*	• *Not applicable*
1	*Significant*	• Gastro-intestinal complaints • Therapeutically ineffective dose according to eGFR • Mild neurological effects (e.g. motoric dysfunction) • Hepatic dysfunction • Any significant event identified by patient which does not require change in therapy
2	*Serious*	• Hypoglycemia • Nephrotoxicity or increased risk nephrolithiasis • Electrolyte disturbances (e.g. hyperpotassiemia) • Altered mental status due to sedation • Myopathy or rhabdomyolysis • Gastrointestinal bleed
3	*Life threatening*	• Lactic acidosis • Cardiac arrhythmia • Decline in mental status with risk of falling • Respiratory failure requiring intubation (e.g. bronchospasms)
4	*Fatal*	• Death

Table 3 | Characteristics of the study population

Variable	
Number of subjects, n (%)	1368 (100)
Demographics	
Age (years), median [IQR]	78 [69,84]
Male, n (%)	601 (44)
Diabetes, n (%)	346 (25)
Renal variables	
eGFR (ml/min/1.73m^2), median [IQR]	34 [27,38]
Serum creatinine (µmol/ml), median [IQR]	152 [128,186]
Actual drug regimen	
Number of drugs, median [IQR]	7 [4,9]
Polypharmacy, n (%)	993 (73)

IQR=interquartile range; eGFR=estimated glomerular filtration rate

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Optimizing drug prescribing and dispensing

in subjects at risk for drug errors due to renal impairment:

improving drug safety in primary health care by low eGFR alerts.

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Article focus

- To evaluate the number of subjects with at risk for medication errors due to renal impairment (defined as eGFR≤40 ml/min/m^2) in a primary care setting.
- To assess the risk of medication errors in subjects with renal impairment.
- To evaluate the effectiveness of generating automatic eGFR≤40-alerts and ~~drug~~ medication reviews involving community pharmacists.

Key messages

- Providing ~~Extending~~ renal laboratory data to~~wards~~ pharmacists in a primary care setting revealed that there were a considerable number of subjects at increased risk for adverse drug events (ADEs) due to renal impairment
- The ~~introduction~~ issuance of eGFR alerts ~~resulted in valuable drug adjustment proposals of~~allowed community pharmacists to provide valuable medication adjustment recommendations to ~~wards~~the prescribing physicians, with good acceptance rate
- The im~~Im~~plementation of this simple protocol could identify many potential ADEs (pADEs), thereby ~~and thus~~ substantially reduc~~e~~inge the risks of unnecessary iatrogenic damage in subjects with impaired renal function

Strenghts/limitations

- Implementation of this protocol in clinical practice is possible in various health care settings
- Increased collaboration with community pharmacists improved health care safety and awareness on ~~drug~~ medication errors related to renal function impairment in primary care
- Extending the availability of laboratory renal data which were not formerly shared ~~formerly~~ is relatively ~~easy~~ straightforward with minimal expense~~to achieve with low costs~~
- Effect of eGFR alerts on the incidence of ~~adverse drug events~~ADEs could not be not measured
- Study design does not allow determining individual health care effects, nor an overall cost-benefit~~s~~ analysis of this health care safety strategy

Abstract

Objectives- To assess the risk of medication errors in subjects with renal impairment (defined as an estimated glomerular filtration (eGFR) ≤40 ml/min/1.73 m^2) and the effectiveness of automatic eGFR≤40-alerts relayed to community pharmacists.

Design- Clinical survey.

Setting- The city of Zwolle, The Netherlands, ~~with~~ in a primary care setting including 22 community pharmacists and 65 general practitioners.

Participants- All adults who underwent ambulatory creatinine measurements which triggered~~ring~~ an eGFR≤40-alert.

Primary and secondary outcome measures- The total number of ambulatory subjects with an eGFR≤40-alert ~~within~~ during the study period of one~~a~~ year and ~~amount~~ the number of medication errors related to renal impairment. ~~T~~the type and number of proposed drug adjustments recommended by the community pharmacist and ~~subsequent physician's~~ acceptance rate by the prescribing physicians. Classification of all medication errors on their potential to cause an adverse drug event (ADE) and the actual occurrence of ADEs (limited to those identified through hospital record review) one year after the introduction of ~~eGFR≤40~~the alerts ~~alerts~~ were measured.

Results- Creatinine measurements were performed in 25929 adults. An eGFR ≤40-alert was indicated for~~and in~~ 5.3% (n=1369) ~~of these subjects an eGFR ≤40-alert was identified~~. This group had a median [IQR] age of 78 [69,84] years, and in 73% polypharmacy (≥5 drugs) was present. In 15% (n=211) of these subjects, a medication error was detected. The proportion of errors increased with age. Pharmacists ~~proposed~~ recommended 342 ~~drug~~ medication adjustments; mainly concerning diuretics (22%) and antibiotics (21%). The p~~P~~hysicians' acceptance rate was 66%. Of all the medication errors, 88% ~~was~~ were regarded as potential ADEs, ~~mainly~~ with most classified as significant or serious. At follow-up, the ADE risk (n=40) appeared highest when the proposed medication adjustments ~~adjustments in drug regimen~~ were not implemented (38% versus 6%).

Conclusions- The introduction of automatic eGFR-alerts identified a considerable ~~amount~~ number of subjects who are at risk for ADEs due to renal impairment in an ambulatory setting. The ~~N~~nationwide implementation of this simple protocol could identify many potential ADEs ~~and thus~~thereby substantially reduce~~inge~~ ~~the risks of unnecessary~~ iatrogenic complications~~damage~~ in subjects with impaired renal function.

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Introduction

Safe medication management is an important health-care topic, as ~~. M~~medication errors are a significant source of iatrogenic injury to patient~~s harm~~.[1-7] Injuries resulting from such errors are known as ~~A~~adverse drug events (ADEs) ~~are injuries secondary to medication errors (Figure 1).~~ Various factors are associated with ADEs, including patient characteristics, lack of medication monitoring, and prescription errors.[4-6,8] Studies on medication -related hospital admissions ~~estimated~~ estimate that 21-91% of admissions were potentially preventable.[1,6,9,10] Important patient determinants for ADEs are increasing age, female gender, polypharmacy, noncompliance and co-morbidities ~~like~~ such as cognitive dysfunction or renal impairment.[1-4,7,8,10]

Renal impairment is a well-known risk factor for ADEs, but often remains unrecognized ~~for prescribing~~by physicians and pharmacists.[11-14] Even in high-risk patients ~~like~~ such as elderly and those with ~~diabetics~~diabetics, ~~and elderly~~ health care workers are not always sufficiently alert.[15-17] Various studies reported considerable dosing difficulties and subsequent medication errors in patients with renal impairment.[10,12,17-19] Therefore, intensified collaboration between health care workers (~~like~~ such as general practitioners (GPs), pharmacists, and nephrologists ~~and other hospital-based physicians~~) is recommended with exchange of relevant patient information (medical history and co-morbidities) and more effective use of routinely collected data from electronic patient records ~~(e.g.~~such as ~~like~~ laboratory results ~~related~~ relating to renal function).[2,6,20-23]

In this 1-year observational study, we aimed to evaluate the number of subjects at risk for medication errors due to renal impairment (defined as an estimated glomerular filtration rate (eGFR) ≤40 ml/min/1.73 m^2) and the effectiveness of providing automatically generated eGFR ≤40-alerts towards community pharmacists in a shared pharmaceutical care model. In addition, we classified all medication errors ~~on the~~for their potential to cause ~~an~~ ADEs and evaluated the actual number of ADEs in those with a medication error after a period of ~~1~~one year.

Materials and methods

Setting

This study was conducted in Zwolle, which is a city in the north of the Netherlands ~~(Zwolle)~~ with a population of more than ~~over~~ 89.000 adult~~s inhabitants~~.[24] All of the primary care pharmacies (n=11) and the general ~~practitioners' (GP)~~ practices (n=24) ~~in the city agreed to~~ participate~~d~~ in this study. Their characteristics are shown in Table 1. Dutch patients are generally registered at one single ~~community~~ pharmacy and GP practice, which promotes continuity of care and reliable information regarding each individuals' ~~drug~~ medication use. Secondary care in this region is delivered by the Isala Clinics, a 1000+ bed teaching-hospital in Zwolle. ~~In this city all~~All standard laboratory investigations requested ~~from~~ in both primary and secondary care are performed in one laboratory, which uses ~~using~~ a single electronic system for data handling.

Design and case-finding

This prospective observational study was conducted between February 1st 2009 and January 31st 2010. During this period, all consecutive adult~~s inhabitants of Zwolle~~ in whom a serum creatinine was measured in the ambulatory setting ~~and~~ who had an eGFR at or below the cut-off point of 40 ml/min/1.73 m^2 were identified, irrespective of the reason for laboratory testing. This threshold was based on guidelines advising dosage adjustment in renal impairment~~.~~[25,26] and also chosen from a practical point of view. A higher cut-off-point of 50-60 ml/min/1.73m^2 was expected to exceed an acceptable workload, and the generation of many alarms induces the risk of ignoring and overriding alerts. Each week the laboratory automatically ~~reported~~ generated a report for ~~on~~any ambulatory patients with an eGFR ≤40 ml/min/1.73 m^2 ~~to~~ for the pharmacists.

Study protocol

A predefined protocol was followed after the pharmacist received a report on an eGFR ≤40 ml/min/1.73 m^2 (Figure ~~2~~1). First, the patients' pharmacist checked the actual ~~drug~~ medication regimen for current ~~medication~~ errors related to renal impairment. Numbers and types of errors were registered. Medication errors were based on Dutch Pharmacists guidelines including 'the National Formulary on drug prescribing in renal impairment' and the 'National Shared Care

Guidelines on Chronic Kidney Disease (CKD)'.[25,26] Second, the pharmacist alerted the prescribing physician (GP or clinician) on the low eGFR and, if appropriate, an adjusted ~~drug~~ medication regimen was ~~proposed~~recommended. Pharmacists contacted prescribing physicians by telephone or (if unreachable) by email. Finally, an alert warning for a low eGFR (eGFR≤40-alert) was activated in the patient's pharmacy record. This eGFR≤40-alert then appeared ~~after that~~ with every future new prescription. After this first laboratory notification, follow-up eGFR results were also reported to the pharmacists. When an eGFR recovered well beyond the cut-off value during follow-up (specified as an eGFR >50 ml/min/1.73m^2), the eGFR≤40-alert was removed from the pharmacy record.

The study was approved by the local medical ethics committee and conducted in accordance with the guidelines of the Declaration of Helsinki. All pharmacists and GPs informed their patients about the study through flyers, issued both at the pharmacies and at the GP practices. The patient~~–~~ folder and ~~website of~~ the Isala Clinics website ~~–~~also contained information about the stepwise eGFR≤40-alert protocol, the sharing of laboratory data, and medication monitoring. ~~Because t~~The study had an opt-out policy, therefore, ~~protocol was designed to improve medication safety, the study had an opt-out policy. Thus,~~ subjects who did not wish ~~expressed not~~ to participate in this pharmacovigilance study were excluded from the weekly reporting. It should ~~also~~ be emphasized that the final decision about making any medication changes ~~(not) changing the drug regimen~~ after an alert (and informing the patient) was considered to be the responsibility of the prescribing physician.

Definitions and calculations

Serum creatinine was measured with an enzymatic essay (Modular, Roche, Mannheim, Germany) and eGFR was calculated with the enzymatic MDRD formula.[27] ~~Drug inclusion was restricted to~~to the only medications included were those ~~drugs~~ prescribed by health care professionals, ~~excluding~~ and topical or over the counter (OTC) ~~medicines~~products were excluded. Actual ~~drug~~ medication use was assessed by documenting all current prescriptions according to the Anatomical Therapeutic Chemical (ATC) classification system[28] at the moment of the first eGFR≤40-alert. Polypharmacy was defined as chronic (>1 year) use of ≥5 drugs.

Data collection

For all identified subjects with an eGFR ≤40-alert, demographics and medication information ~~on drug use~~ were collected. ~~All~~ Any ~~proposed~~ ~~drug~~ medication adjustment recommendations were recorded, ~~which included~~ ~~including~~ the patient's medical record number, the pharmacist, the type and daily dose of ~~drugs~~the medication, and the prescribing physician (GP or clinician). ~~Also t~~The physician's response to the ~~proposed adjustment~~pharmacist's recommendation was also recorded. Finally, the amount of time the pharmacists' ~~time~~ spent on every eGFR≤40-alert was documented.

Classification and tracking of (potential) adverse drug events

To evaluate the impact of eGFR≤40-alerts two pharmacists (EP and KB) independently evaluated all medication errors on the potential to cause an ADE (defined as a potential ADE (pADE)). They received a database that was anonymized by an investigator not involved in the eGFR-alert processing (HJ). ~~using a~~ A methodology developed for classification of medication errors and (p)ADEs.[29] ~~Figure 1 clarifies the relationship between these terms.~~ They judged and classified the theoretical severity of the medication error, yielding a score of 0-4 (0=drug error without significant harm, 1=potentially significant, 2=potentially serious, 3=potentially life threatening, 4=potentially fatal) (Table 2). To reach a consensus, all discrepant ratings were discussed with both pharmacists and two nephrologists (HB and HJ). Examples of pADE classifications are listed in Table 2. The best assessment of the number of ADEs proved to be from the documentation on ADEs in the hospital records.[30] Therefore, one year after the end of the study, the hospital records of all subjects in whom a medication error was detected, were reviewed. This review was performed by two nephrologists (HJ and HB) who independently checked the occurrence of ADEs. ADEs were based on admission and discharge diagnosis in the patients' medical records. The relationship of the ADE with the 'suspected' agent was double checked by evaluating whether the medication regimen at admission in the hospital record matched with the pharmacy record at the date of admission. After review of the hospital records HJ and HB discussed their findings for reaching consensus.~~The best assessment of the number of ADEs proved to be from documentation on ADEs in the hospital records.[30] Therefore, one year after the end of the study, we checked hospital records of all subjects in whom a medication error was detected in order to track whether ADEs had occurred.~~

Data analysis

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The main outcome measures were the incidence of eGFR≤40-alerts, the number and types of medication errors, and the ~~amount~~ number and types of ~~drug~~ medication ~~adjustments~~ adjustment proposals. Secondary outcome measures were the time required for pharmacists to process the eGFR<40-alerts, the adherence of physicians ~~towards~~ to the proposed ~~drug~~ adjustments, risk factors for medication errors, and the severity of medication errors. In addition, after one year of follow-up, we checked the incidence of ADEs in subjects in whom a medication error was detected. Statistical analysis was performed with SPSS version 16.0 (SPSS Inc., Chicago, IL, USA.) Data are presented as mean and standard deviation (SD) when normally distributed. Otherwise, median and interquartile range [IQR] were used. For normally distributed data, the differences in baseline characteristics were evaluated with the independent samples *t*-test. For nonparametric data Mann-Whitney *U* test was used. Differences in distribution were calculated ~~by~~ using the chi-square tests.

Results

Incidence of eGFR<40-alert and characteristics of the study population

During the study period 46781 creatinine measurements were performed in 25,929 ~~adult inhabitants of Zwolle~~subjects. In 5.3% (n=1369) of ~~these subjects~~cases, an eGFR ≤40-alert was ~~identified~~indicated. One patient indicated no willingness to participate for privacy reasons, leaving 1368 subjects for analysis (Figure ~~2~~1). Their ~~C~~characteristics are summarized in Table 3. Overall, 56% was female, the median age was 78 [69,84] years (~~age~~ distribution is shown in Figure ~~3~~2) and the median eGFR was 34 [27,38] ml/min/1.73m^2. Overall, polypharmacy was present in 73% (n=993) with a mean number of ~~drugs~~ medications per patient of 7 (range 0-21). An overview of the actual medication use in the study population (which reflects comorbidities) according to the ATC classification is given in ~~a~~*Appendix* ~~1~~A.

Number and type of medication errors

Overall, 342 medication errors were detected in 211 patients with an eGFR ≤40-alert (15% of the study population) (Figure ~~2~~1). The proportion of errors increased with ~~higher~~ increasing age (Figure ~~3~~2). The types of medication most commonly associated with errors were diuretics (22%), antibiotics (21%), and anti-gout medications (15%) (Figure 3).~~Figure summarizes the drug groups associated with medication errors. Most errors concerned diuretics (22%) and antibiotics (21%), followed by anti-gout medication (15%).~~ The majority of these ~~drugs~~ medications (77%) were prescribed by GPs. An overview of the type of medication errors that were identified by the pharmacists is given in figure 4.

Physicians' compliance with medication adjustment recommendations

~~**Proposed drug adjustments and physicians' adherence**~~

Figure 5 gives an overview of the frequency and types of medication adjustment recommendations~~proposed drug adjustments~~. The most common ~~advices~~ recommendations were 'change ~~drug~~ dosage' (55%), followed by 'stop ~~drug~~' medication (24%). In 31% (n=105) the proposal concerned a new prescription. Physicians complied with the ~~proposal~~ recommendation in 66% (n=226) of cases. In 28% (n=96) of cases, the pharmacists' advice was rejected and the medication regimen remained unchanged. The main reasons for rejection ~~were~~ included already increased alertness with intensive monitoring by the prescribing physician (often being an internist

or nephrologist ~~deliberately prescribing the concerning drug~~) and an ~~insufficient~~ inadequate response to lower dosages in the past. The majority of rejected recommendations included diuretics and renin-angiotensin-aldosterone system (RAAS) blockers like ACE inhibitors and ARB drugs. In some cases, the recovery of renal function~~acute renal impairment~~ was expected or underestimation of renal function ~~(both generally checked with a 24-hour creatinine clearance)~~ was presumed, both of which were generally checked with a 24-hour creatinine clearance. Overall, acutely reduced eGFR did not account for an important subset of the eGFR<40 alerts towards the community pharmacists (n=3). Notably, in 22 ~~out~~ of the 96 cases , the medication was soon changed anyway,~~drug regimen was changed a short time later~~ due to a further decrease ~~of~~ in the eGFR or the occurrence of an ADE. ~~Thus~~Therefore, from the latter it seems plausible that with the eGFR ≤40-alert the physician's awareness ~~on~~ of the risk for an ADE ~~risks~~ was triggered. Data on rejection or agreement lacked in 6% (n=20) of ~~the proposals~~cases.

Potential risk factors for medication errors in patients with eGFR≤40 alerts

Compared to the subjects without medication errors (n=1157), subjects ~~with~~ for whom medication~~drug~~ adjustments ~~proposals~~ were recommended (n=211) were more often female (59% versus 41%, p=0.04) and had a lower eGFR (median 34 [28,38] versus 29 [2,34] ml/min/1.73m^2, p<0.001, respectively). Notably, the latter had higher rates of polypharmacy (70 versus 89%, p<0.001, mean number of ~~drugs~~ medications 6.6 (3.8) versus 8.2 (3.5), p<0.001).

Effectiveness: potential ADEs and occurrence of ADEs after follow up

Overall, 88% (n=299) of the medication errors were regarded as relevant pADEs (score>0). These were mainly judged to be either significant or serious. An overview of the number and potential severity of pADEs in the study population is given in Figure ~~2~~1.

Overall, 40 ADEs were identified in hospital records ~~were tracked~~ within one year after the study period in the group of subjects with ~~a~~ medication errors, including two life-threatening ADEs (bradycardia due to digoxin intoxication and acute kidney injury with lactic acidosis associated with persistent metformin use). The number and severity of ADEs are shown in Figure ~~2~~1. Importantly, the ADE risk was higher in subjects whose ~~drug~~ medication regimen remained unchanged (n=60)

as compared to subjects whose ~~drug~~ medication regimen was adjusted as ~~proposed~~ recommended by the pharmacist (n=139); 38% versus 6%, respectively ~~(Table 4)~~.

Effectiveness: workload and time investment of the pharmacists

After receiving an eGFR≤40-alert, the pharmacist needed ~~on~~ an average of 11 minutes (range 5-13 minutes) to check an individual's ~~drug~~ medication regimen ~~on medication~~for errors. When taking into account the time needed for consultation ~~of~~ with the prescribing physician, pharmacists required ~~on~~ an average of 20 minutes ~~processing~~ to process one eGFR≤40-alert triggering a ~~drug~~ medication adjustment. All pharmacists judged the time investment as feasible ~~in daily practice~~, particularly considering the fact that each pharmacy received an average of only one alert per week~~mainly because on average every pharmacy received only one alert per week~~.

Retrospectively we evaluated the feasibility of different thresholds for kidney function alerts by calculating the number of low eGFR-alerts that would have been generated during the study period using different cut-offs for renal impairment (<30, <50 and <60 ml/min/1.73m^2, respectively, see Appendix B).

Overall, 904 eGFR≤40-alerts were activated in the records of the participating pharmacies ~~after one year~~at the end of the study period, as 16% (n=214) of the population died ~~during the study period~~ and in 250 subjects, the most recent eGFR was at least twice >50 ml/min/1.73m^2. ~~Thus~~Therefore, on average, every primary care pharmacy had 82 patients with an activated eGFR≤40-alert. If we translate this to a standard Dutch GP practice (±2300 patients), simple laboratory data sharing identified approximately 23 patients per practice who need drug adjustment(s) or extra alertness in medication management.

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Discussion

The main findings of this study were that an eGFR ≤40-alert was ~~identified~~ indicated in 5.3% of the adult population of a Dutch city in whom a creatinine measurement was performed in an ambulatory setting and that in these subjects 342 medication errors (mainly involving antibiotics and diuretics) were detected during the year following ~~one year after~~ the introduction of an automatic eGFR≤40-alert system. The majority of the medication errors was regarded as ~~a~~ relevant pADEs, necessitating ~~drug~~ medication adjustments as recommended by pharmacists~~according to pharmacists' protocols~~. Physicians complied ~~with~~ in 66% of ~~these proposals~~cases. ADE risk ~~seems to~~ increases with age, polypharmacy~~-~~, and in instances when the proposed medication adjustments were initially rejected~~and when proposed drug adjustments are rejected initially~~. Overall, automatically generated low eGFR-alerts in primary care seemed effective, easy to implement, and, importantly, improves both the pharmacists' and the physicians' awareness ~~on drug~~of medication safety.

Comparison with other studies

Despite the fact that medications are usually both prescribed and dispensed in the primary care setting, most studies on (p)ADEs have been hospital-based~~Despite the fact that primary care settings account for the majority of drug prescribing and dispensing, most studies on (p)ADEs are hospital-based~~.[3,9,10] We aimed to study the incidence of (p)ADEs in a shared pharmaceutical care model with a central role for community pharmacists. Three primary health care studies on this topic reported lower pharmacist drug proposal rates (0.7-1.9%) than the ~~reported~~ 15% ~~in our study~~we found.[31-33] These studies were performed in a general population, while we selected a high-risk population of subjects with renal impairment. In line with our results, primary and ambulatory care studies evaluating pharmacists' drug proposals in vulnerable subgroups like the elderly or subjects with cardiovascular risk factors also reported higher rates.[12,17,34,35] ~~One~~ Two recent studies~~y~~, also concerning subjects with renal impairment, identified ~~drug-related~~ problems ~~due~~ related to inappropriate ~~prescriptions~~ prescribing in over 20% of ~~the~~ patients.[18,36]

Patients with renal impairment are especially vulnerable to medication errors.[12,13,18] Various strategies to improve drug safety in these patients have been studied, ~~like~~ such as educational wards rounds, immediate clinician-pharmacist feedback, or dose adjustment according to renal

function at hospital discharge.[12,18,37-42] ~~But~~ However, despite the fact that most prescribing takes place in the primary health care setting~~the majority of drug prescriptions take place in primary health care~~, the majority of the strategies implemented so far have been tailored to hospital settings and are therefore not suitable for primary care~~most strategies so far were tailored to hospital settings and therefore not suitable for primary care settings~~. Others have demonstrated the effectiveness of 'computerized physician order entry' and 'clinical decision support' in reducing medication errors in case of renal impairment.[39-41] However, computerized drug prescribing alerts do not always guarantee a reduction of prescribing errors,[43] partly because such alerts are often overridden or ignored by prescribing physicians.[41,44-46] This phenomenon is also reflected in our data, as in 28% ~~of cases~~ pharmacist recommendations ~~drug proposals~~ were rejected by the prescribing physician~~s~~.

A central role for community pharmacists in improving medication safety in primary care has been recognized. Many pharmacists are gradually extending their role as integral members ~~an integral part~~ of the medical team around the patient, ~~thus~~ thereby taking an important position in a shared care environment.[21,47,48] This ha~~i~~s not only been induced by legislative issues,[21,25] but also recommended in ~~different~~ various guidelines and studies to counteract problems associated with multiple medication~~(drug)~~ prescribers.[20,26,32,48] This is ~~also~~ important in view of our ageing population in which complex drug therapy will only increase, polypharmacy is common and renal impairment widespread~~omnipresent~~.[49,50] A recent review showed notable differences in ADE prevalence rates by age groups increasing from 5% for adults up to 16% for the elderly.[7] ~~Thus~~Therefore, in ~~case of~~ complex ~~drug prescriptions~~cases (~~like in~~as with renal impairment) the close collaboration ~~of~~ between community pharmacists and physicians ~~seems~~ is essential to prevent ADEs.

The alert method we have investigated here could be a simple solution to address this.

~~and our method could be a simple initiative for this.~~

Our strategy included three steps to reduce medication errors in patients with renal impairment. First, automatic laboratory alerts were generated, second these ~~laboratory~~ alerts were linked to pharmacy data to judge the need for drug adjustments, and third, pharmacists discussed recommended changes~~drug proposals~~ with physicians. Several studies investigated the impact of ~~any~~ the above steps. The introduction of automatically ~~recorded~~ generated laboratory alerts had varied effects on the prescribing physician.[41,51,52] Authors suggested that such passive alerts did

not have enough of an impact. There is limited data on the effect of extending the alerts so that the community pharmacist was also involved.~~on renal impairment directly towards prescribing physicians had varied impact.[40,50,51] Authors suggested that passive alerts were not directive enough for physicians. Data on extending alerts towards community pharmacists are however limited~~. Other studies showed that when the pharmacy data were linked with the laboratory renal data, the medication dosage could be beneficially adjusted.~~Others showed that drug dosage could benefit from the linkage of pharmacy data with laboratory renal data~~.[12,42,53] We aimed to optimize medication safety in cases of renal impairment by combining the aforementioned steps and tailored our strategy for application in the primary care setting. ~~in renal impairment by combining these above steps and tailored our strategy to primary care~~.

Implications for clinical practice

The estimated prevalence of both moderate (30-59 ml/min/1.73m^2) and severe (15-29 ml/min/1.73m^2) renal insufficiency in the adult American and Dutch population is 4.5% and 5.3% respectively.[26,54] ~~Thus~~Therefore, the number of subjects potentially susceptible to related medication~~renal drug~~ errors is substantial. If we compile our pADE-rate towards nationwide figures (based on 12,500,000 adults in the Netherlands), our type of data sharing could intercept more than 40,000 potential ADEs related to renal impairment each year. This would undoubtedly increase health care safety with already available data and (hopefully) decrease the costs of ADE related morbidities. Drug safety management might be further improved by extending patient data exchange towards other important parameters, ~~like~~ such as ~~drug~~ medication allergies, platelet counts, electrolyte concentrations, INR, liver enzymes, and plasma drug levels.

Strenghts and weaknesses of the study

Some limitations of this study have to be noted. First, our study design does not allow determining individual health care effects, nor overall cost-benefits. This would necessitate a more complex study design as was for example used in the population-based randomized controlled renal drug alert effectiveness trial of Bhardwaja et al, or a 'before and after' design.[36] However, participating GPs and pharmacists indicated that the protocol improved their awareness ~~on~~ of ~~drug~~ medication errors related to renal function impairment. Second, data on the incidence of ADEs before start of the study project were not available in our region; therefore a possible change in ADE~~s~~ incidence as a result of our interventions cannot be determined. Besides, the incidence of ADEs is likely

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underestimated due to underreporting, missed recognition, and lack of recording in daily clinical practice.

Our study also has several strengths. First, our intervention can beis easily implementedable in various health care settings. We simply extended the availability of laboratory renal data which were not shared formerly. Second, physicians valued the pharmacists' involvement in improving health care delivery. The acceptance percentage of the pharmacists' ~~Acceptance of recommendations~~ was fairly good (67%), as compared to previous studies (24-82%)[17,32,34,37,51] and our prescription ratio between GPs and hospital-based physicians (77:23%) reflects the normal distribution of prescriptions in the Netherlands (82:18%).[55] However, to improve the overall efficiency of the eGFR-alerts, also variables influencing physicians' (non) adherence towards pharmacists' recommendations (like type and duration of medication use) should be further studied. Third, the time investment was acceptable and costs were low. Finally, we chose for a safe, but also feasible threshold for renal function alerts. However, as thresholds for dosage adjustment vary between different guidelines, a higher cut-off of ≤50 or 60 ml/min/1.73m^2, or drug specific thresholds could be discussed.[25,26,36,56] Besides, as the Cockcroft-Gault (CG) formula is often used in pharmacokinetic studies and for drug dosing recommendations, the implications of the use of renal function estimates like the MDRD equations for drug dosing, is under debate. Several studies have compared drug dosing recommendations based on the CG with those based on the MDRD.[57-59] In summary, the accuracy of the MDRD seems comparable to the CG.[57-59] Based on these studies, in our opinion, the MDRD is a reasonable alternative to the CG for drug dosing. This is of importance especially since there is an increasing trend of clinical laboratories reporting the MDRD along with serum creatinine, which is also recommended by national and international organizations.[26,60]

Some guidelines advisce a higher cut-off point for dose adjustments (creatinine clearance 50-60 ml/min),[11,61] but this was expected to result in an amount of alerts exceeding an acceptable workload. Moreover, as the MDRD tends to underestimate true GFR, ~~and~~ we presumably already included subjects with true GFR >40ml/min.[62]

Conclusions and policy implications

The introduction of automatic renal function alerts in the ambulatory care setting, with the involvement of both GPs and community pharmacists, revealed that a considerable part of the population is at risk for ADEs due to impaired renal function. ~~In conclusion, the introduction of~~

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~~automatic renal function alerts towards pharmacists in primary care revealed that a considerable number of subjects is at risk for ADEs due to renal impairment~~. Extending the availability of renal laboratory data to~~wards~~ community pharmacists resulted in their presenting the prescribing physicians with a considerable number of medication adjustment recommendations~~in a considerable amount of drug adjustment proposals to prescribing physicians~~. ~~In our opinion~~We feel that nationwide implementation of this simple protocol could potentially identify many pADEs and ~~thus~~ substantially reduce the risks of ~~unnecessary~~ iatrogenic damage in ~~subjects~~ persons with ~~impaired~~ decreased renal function.

Acknowledgments

We would like to thank ~~all~~ the community pharmacists, the dispensary employees, and ~~all~~ the general practitioners in Zwolle for their participation in this study. We would also like to acknowledge Anton Huisman (laboratory staff) and Ellen Witteveen (medical student) who both took care of data collection and Marcel Ariës (neurologist) for his careful comments on the manuscript.

Table 1 | **Characteristics of participating pharmacists and GPs, and their practices**

Characteristics		Pharmacists	GPs
Participants			
	Number (%)	22 (100)	65 (100)
	Sex, n (%)		
	male	9 (40)	42 (65)
	female	13 (60)	23 (35)
	Years in practice, n (%)		
	0-10	10 (45)	25 (39)
	11-20	9 (41)	15 (23)
	21-30	0 (0)	21 (32)
	>30	3 (14)	4 (6)
	Position in practice, n (%)		
	(joint) owner	6 (27)	45 (70)
	employee	16 (73)	20 (30)
Practice			
	Number (%)	11 (100)	24 (100)
	Practice type, n (%)		
	independent	9 (80)	-
	chain	2 (20)	-
	Overall number of patients, n	114.033	117.147
	Practice size, median [IQR]	10.000 [7.000, 14.000]	3426 [2691, 6586]
	Prescription system, n (%)		
	computer-based	11 (100)	24 (100)

IQR=Interquartile Range; GP=general practitioner

Table 2 | **Categories of potential adverse drug events (pADEs) according to severity**

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Score	Potential severity	Examples
0	*Drug error without potential harm*	• *Not applicable*
1	*Significant*	• Gastro-intestinal complaints • Therapeutically ineffective dose according to eGFR • Mild neurological effects (e.g. motoric dysfunction) • Hepatic dysfunction • Any significant event identified by patient which does not require change in therapy
2	*Serious*	• Hypoglycemia • Nephrotoxicity or increased risk nephrolithiasis • Electrolyte disturbances (e.g. hyperpotassiemia) • Altered mental status due to sedation • Myopathy or rhabdomyolysis • Gastrointestinal bleed
3	*Life threatening*	• Lactic acidosis • Cardiac arrhythmia • Decline in mental status with risk of falling • Respiratory failure requiring intubation (e.g. bronchospasms)
4	*Fatal*	• Death

Table 3 | Characteristics of the study population

Variable	
Number of subjects, n (%)	1368 (100)
Demographics	
Age (years), median [IQR]	78 [69,84]
Male, n (%)	601 (44)
Diabetes, n (%)	346 (25)
Renal variables	
eGFR (ml/min/1.73m^2), median [IQR]	34 [27,38]
Serum creatinine (µmol/ml), median [IQR]	152 [128,186]
Actual drug regimen	
Number of drugs, median [IQR]	7 [4,9]
Polypharmacy, n (%)	993 (73)

IQR=interquartile range; eGFR=estimated glomerular filtration rate

Table 4 | Adverse drug event (ADE) risk in subjects with a medication error.
Comparison of ADE risk in subjects whose drug regimen was adjusted as proposed by the pharmacist versus subjects in whom drug regimen remained unchanged.

Subjects with medication error	Potential ADE (n=211)	ADE (n=34)	ADE Risk
Drug regimen adjusted *(number of subjects)*	139	9	*With intervention:* **6%**
Drug regimen unchanged *(number of subjects)*	60	23	*Without intervention:* **38%**
Unknown *(number of subjects)*	12	2	-

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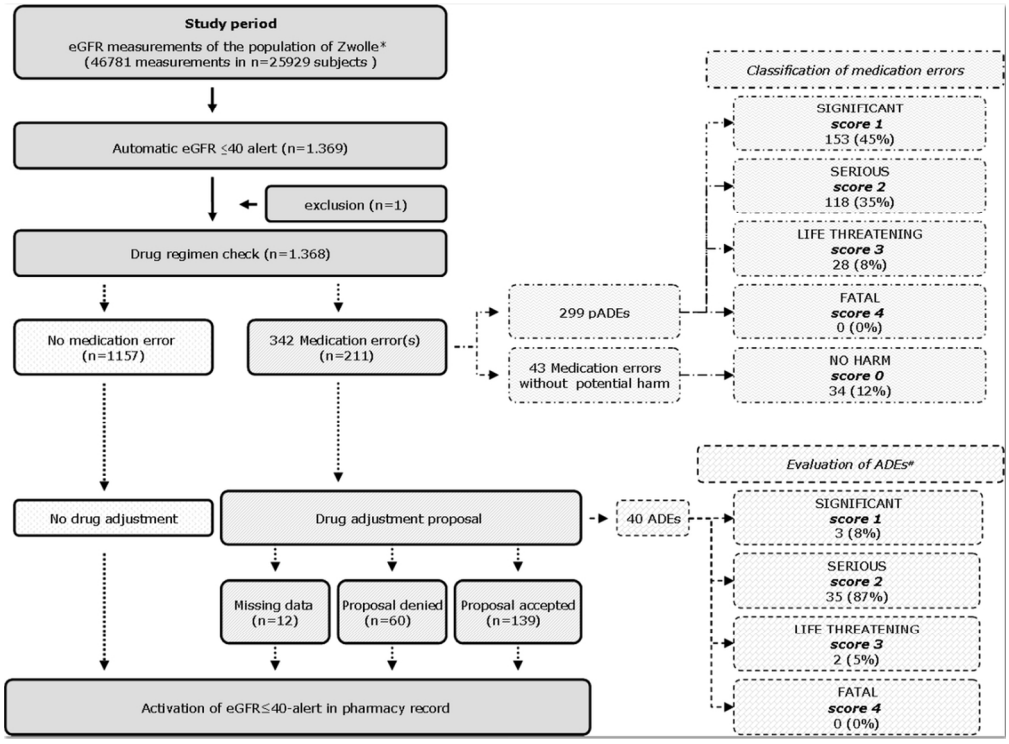
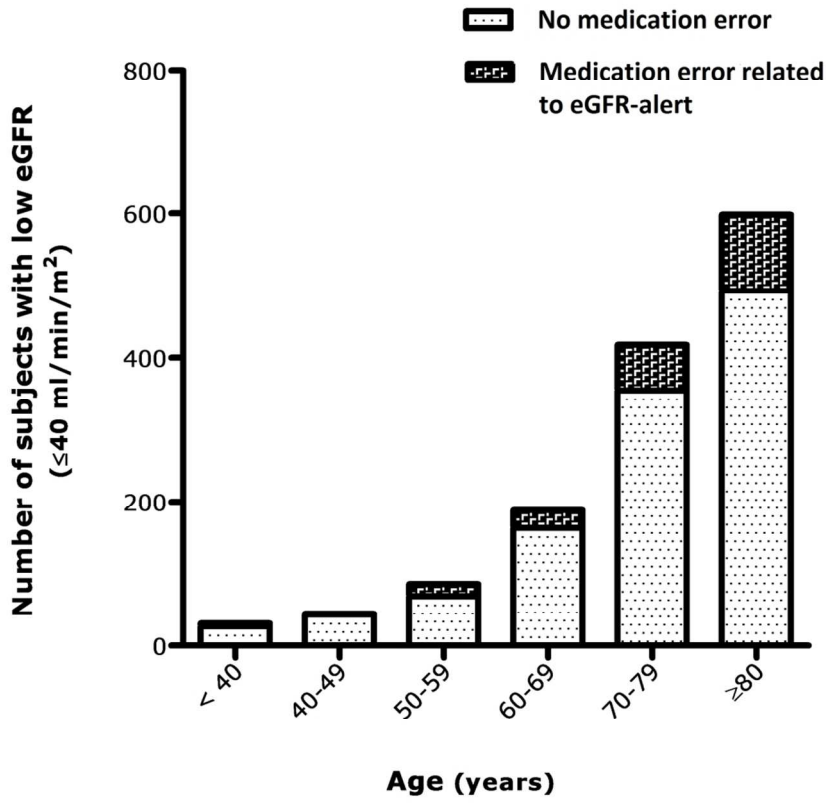
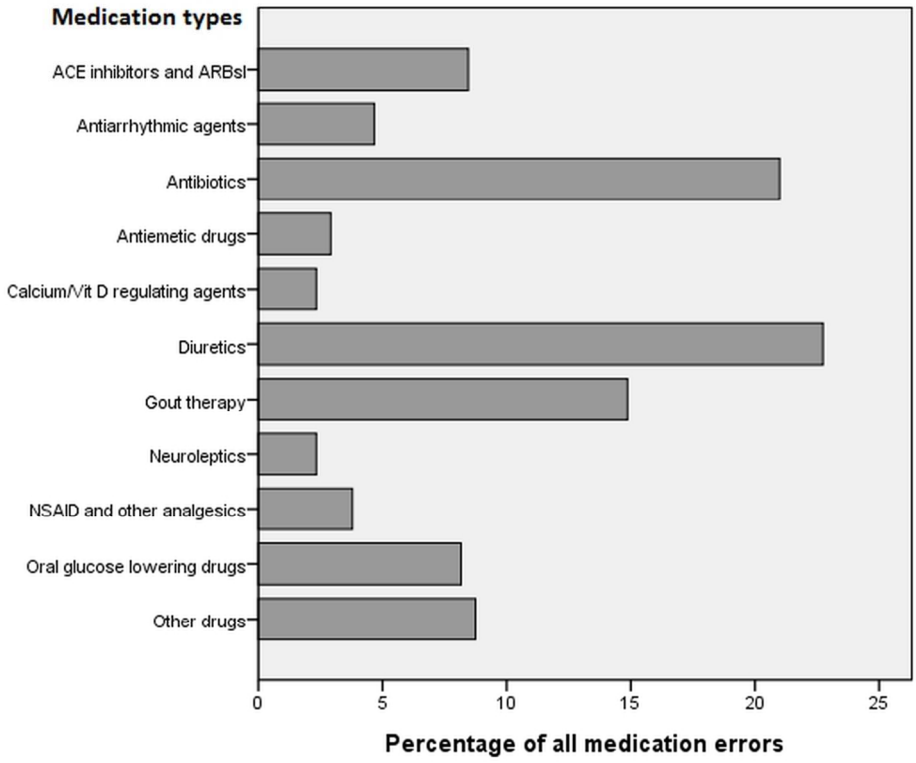


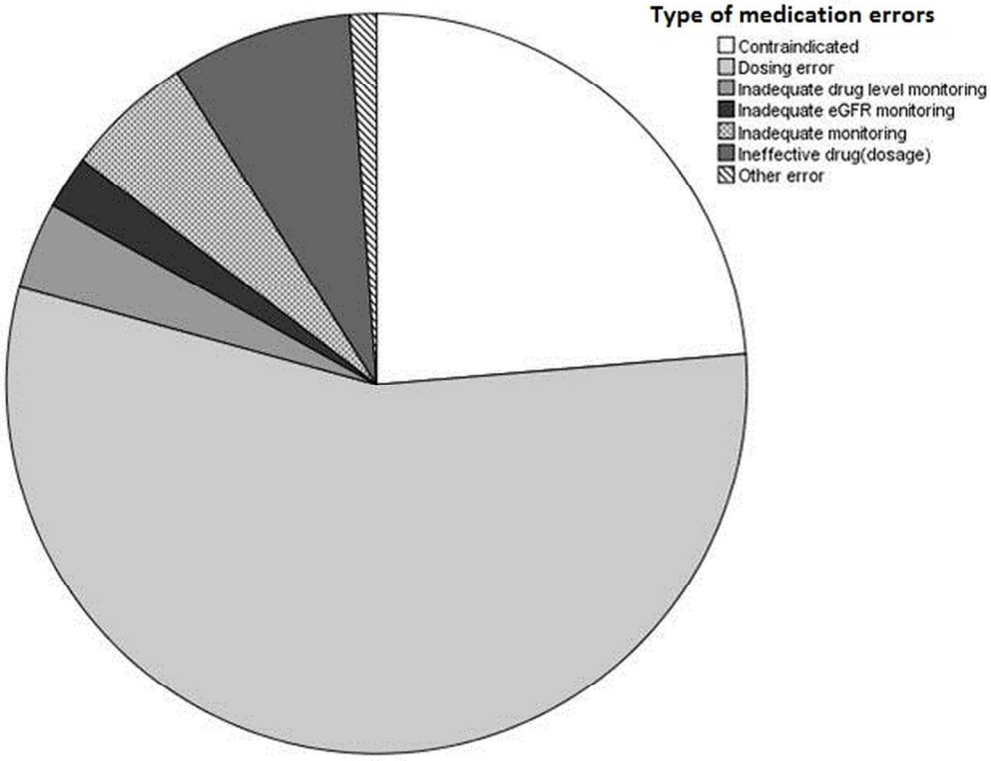
Flow chart summarizing study method and selection of study population.
122x90mm (300 x 300 DPI)



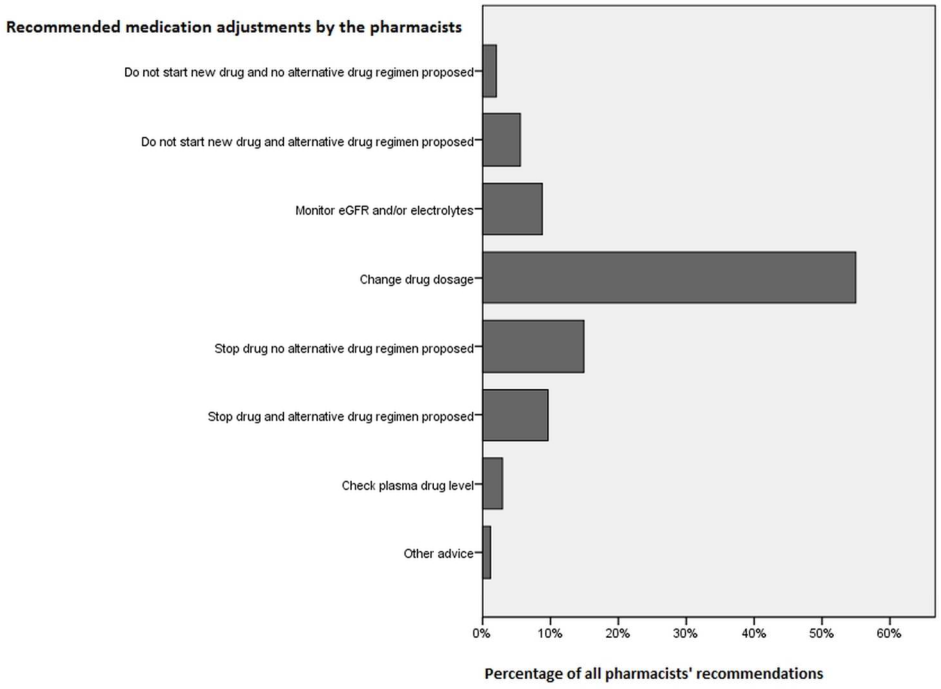
Age distribution of study population and risk of medication error per age category.
105x90mm (300 x 300 DPI)



Medication groups associated with medication errors related to renal impairment.
106x90mm (300 x 300 DPI)



Type of medication errors identified by the pharmacists.
112x90mm (300 x 300 DPI)



Type and frequency of recommended medication adjustments by community pharmacists.
129x90mm (300 x 300 DPI)

SUPPLEMENTAL DATA

Supplemental table A | Overview of medication use according to the ATC classification in the study

ATC CLASSIFICATION		Number (%)
A	**ALIMENTARY TRACT AND METABOLISM**	**1764 (19.1)**
A01	STOMATOLOGICAL PREPARATIONS	4
A02	DRUGS FOR ACID RELATED DISORDERS	556
A03	DRUGS FOR FUNCTIONAL GASTROINTESTINAL DISORDERS	27
A04	ANTIEMETICS AND ANTINAUSEANTS	15
A05	BILE AND LIVER THERAPY	7
A06	LAXATIVES	194
A07	ANTIDIARRHEALS, ANTIINFLAMMATORY/ANTIINFECTIVE	30
A09	DIGESTIVES, INCL. ENZYMES	6
A10	DRUGS USED IN DIABETES	558
A11	VITAMINS	179
A12	MINERAL SUPPLEMENTS	185
A15	APPETITE STIMULANTS	1
A16	OTHER ALIMENTARY TRACT AND METABOLISM PRODUCTS	2
B	**BLOOD AND BLOOD FORMING ORGANS**	**1107 (11.9)**
B01	ANTITHROMBOTIC AGENTS	902
B02	ANTIHEMORRHAGICS	2
B03	ANTIANEMIC PREPARATIONS	203
C	**CARDIOVASCULAR SYSTEM**	**4064 (43.8)**
C01	CARDIAC THERAPY	400
C02	ANTIHYPERTENSIVES	28
C03	DIURETICS	1145
C04	PERIPHERAL VASODILATORS	1
C07	BETA BLOCKING AGENTS	767
C08	CALCIUM CHANNEL BLOCKERS	316
C09	AGENTS ACTING ON THE RENIN-ANGIOTENSIN SYSTEM	830
C10	LIPID MODIFYING AGENTS	577
D	**DERMATOLOGICALS**	**3 (0.03)**
G	**GENITO URINARY SYSTEM AND SEX HORMONES**	**147 (1.6)**
H	**SYSTEMIC HORMONAL PREPARATIONS**	**254 (2.8)**
J	**ANTIINFECTIVES FOR SYSTEMIC USE**	**165 (1.9)**
L	**ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS**	**100 (1.0)**
M	**MUSCULO-SKELETAL SYSTEM**	**312 (3.4)**
N	**NERVOUS SYSTEM**	**846 (9.2)**
P	**ANTIPARASITIC PRODUCTS, INSECTICIDES,REPELLENTS**	**6 (0.06)**
R	**RESPIRATORY SYSTEM**	**417 (4.6)**
S	**SENSORY ORGANS**	**6 (0.06)**
V	**VARIOUS**	**36 (0.5)**
OVERALL		**9227 (100)**

Supplemental table B | The calculated number of patients in the study setting and the change in amount of patients (workload) when applying different thresholds for eGFR-alerts

eGFR threshold (ml/min/1.73m^2)	Number of patients	Change in workload (%)
<30	647	-47%
<40 (current study design)	1369	*reference*
<50	2696	*+196%*
<60	5041	*+368%*

Supplemental table C. Technical details of automatic laboratory alerts

In the management database system of our laboratory the relationship and indexes of different types of data are embedded. We defined a query in this database to select our study population. This query included: test code (eGFR), ambulatory laboratory requests (excluding clinical eGFR data), and data were filtered on age ≥18, eGFR ≤45 and zip codes of the city of Zwolle. The query was run periodically (weekly). A module matching the patients' unique Citizens Service Number (CSN) with the patient's pharmacy code was developed for this project, which enabled us to address the eGFR-alerts to the right community pharmacy. The fact that in The Netherlands patients are generally registered at one single community pharmacy (en thus have a one personal pharmacy code) facilitates this method.