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Effects of stratified medication review in high-risk patients at admission to hospital: a randomised controlled trial

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Abstract

Background: Patients at high risk of medication errors will potentially benefit most from medication reviews. An algorithm, MERIS, can identify the patients who are at highest risk of medication errors. The aim of this study was to examine the effects of performing stratified medication reviews on patients who according to MERIS were at highest risk of medication errors.

Methods: A randomised controlled trial was performed at the Acute Admissions Unit, Aarhus University Hospital, Denmark. Patients were included at admission to the hospital and were randomised to control or intervention. The intervention consisted of stratified medication review at admission on patients with a high MERIS score. Clinical pharmacists and clinical pharmacologists performed the medication reviews; the clinical pharmacologists performed the reviews on patients with the highest MERIS score. The primary outcome measure was the number of prescribing errors during the hospitalisation. Secondary outcomes included self-experienced quality of life, health-care utilisation and mortality measured at follow-up 90 days after discharge.

Results: A total of 375 patients were included, of which medication reviews were performed in 64 patients. The medication reviews addressed 63 prescribing errors in 37 patients and 60 other drug-related problems. No difference in the number of prescribing errors during hospitalisation between the intervention group ($n = 165$) and control group ($n = 153$) was found, corresponding to 0.11 prescribing errors per drug (95% confidence interval (CI): 0.08–0.14) *versus* 0.13 per drug (95% CI: 0.09–0.16), respectively. No differences in secondary outcomes were observed.

Conclusion: A stratified medication review approach based on the individual patient's risk of medication errors did not show impact on the chosen outcomes.

Plain language summary

How does a medication review at admission affect patients who are in high risk of medication errors?

Patients are at risk of medication errors at admission to hospital. Medication reviews aim to detect and solve these. Yet, due to limited resources in healthcare, it would be beneficial to detect the patients who are most at risk of medication errors and perform medication reviews on those patients.

In this study we investigated whether an algorithm, MERIS, could detect patients who are at highest risk of medication errors; we also studied whether performing medication reviews on patients at highest risk of medication errors would have an effect on, for example, the number of medication errors during hospitalisation, qualify of life and number of readmissions. We included 375 patients in a Danish acute admission unit and

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they were divided into control group and intervention group. Patients in the intervention group received a medication review at admission if they were considered at high risk of medication errors, assessed with the aid of MERIS. In summary, 64 patients in the intervention group were most at risk of medication errors and therefore received a medication review.
We conclude in the study that MERIS was useful in identifying relevant patients for medication reviews. Yet, the medication reviews performed at admission did not impact on the chosen outcomes.

Keywords: medication errors, medication review, randomised controlled trial

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Introduction

Medication reviews aim to detect and solve drug-related problems (DRPs).[1] DRPs are found in the majority of hospitalised patients.[2] The effects of medication reviews in hospitalised patients have generally shown a positive effect on medication use and costs,[1,3,4] yet a Cochrane review found no effect on hospitalised patients regarding all-cause mortality and all-cause readmissions.[5] This leads to questioning whether all hospitalised patients should receive a comprehensive and structured medication review when admitted to hospital. Based on limited resources in healthcare and the existing evidence, it might be reasonable to prioritise and focus on patients who are assumed would benefit the most. These patients might be those most at risk of DRPs. Risk factors for DRPs have been reported to include age, gender, comorbidities, polypharmacy and inappropriate use of medication, as well as poor cognitive function.[6] In addition, a study concluded that increased focus on seven high-risk medications could potentially reduce the number of hospitalisations, length of hospitalisation, disability, life threatening conditions or deaths by almost 50%.[7] However, the predictive risk factors and their interrelation have been poorly examined. A few studies have solely aimed at identifying patients who are at risk of experiencing adverse drug events[8–11] and tried to explore the predictors' interrelation. The studies were performed in geriatric, emergency, medical and surgical settings and the resulting predictors are different due to the variation in settings and different ways of collecting and analysing data. A more generic algorithm, MERIS, for identifying patients at risk of medication errors has been invented, validated and pilot tested.[12,13] MERIS provides an estimate of the individual patient's risk of medication errors.[12] MERIS consists of drug- and patient-related variables, that is, the drugs' toxicity and potential for drug–drug interactions, the number of drugs and the patient's renal function. Each of these variables leads to separate scores based on the drug and patient characteristics. Finally, the scores are weighted and summed up to result in a final score.[12] DRPs include medication errors and a relevant intervention on patients at high risk of medication errors might therefore be medication reviews. In this study we aim to examine the effects of performing a differentiated intervention consisting of stratified medication reviews on patients who according to MERIS are at highest risk of medication errors and additionally to test the algorithm MERIS on a large patient population.

Methods

Setting and participants

This randomised controlled trial compared standard care with a stratified medication review approach. By stratified medication review approach we meant that patients at low risk of medication errors received the normal procedure at the unit whereas patients at high risk received a medication review. The study was conducted at the Acute Admissions Unit at Aarhus University Hospital from April 2013 to November 2013. The unit was a 16-bed unit receiving patients from several different medical specialties. Approximately 50% of the patients were discharged to home directly from the unit and the in-hospital stay was usually limited to a maximum of 48 h. Patients requiring longer hospitalisation were transferred to departments of internal medicine.

Patients were eligible for inclusion if receiving at least one drug on a regular basis prior to admission and being 18 years or older. Patients were included on weekdays from 08:00 h to 15:00 h. Patients who were considered suicidal, terminal or intoxicated were excluded. Patients eligible for inclusion were informed about the study by a clinical pharmacist (DB, AGP) and written consent was obtained.

After inclusion patients were assigned usual care or the intervention described in the next section in a 1:1 ratio. The randomisation was generated by a computer program on the hospital pharmacy in random blocks of a maximum of 20. Sequentially numbered, opaque and sealed envelopes containing the randomisation codes were delivered to the study pharmacists. Patients were subsequently risk assessed with MERIS by a clinical pharmacist and thus assigned a numerical risk score. Information required in calculating the risk scores was obtained from the electronic medical records. Patients were, according to MERIS, divided into low-risk and high-risk patients, respectively.

MERIS is a simple and robust algorithm or risk score with the ability to detect patients and divide them according to low and high risk of medication errors.[12] It has been developed based on systematic literature reviews and validated on information from both surgical and medical patients.[12] With the aid of MERIS, it is possible to calculate a numerical risk score for each patient, that is, the higher the score, the higher the risk of experiencing a prescribing error. The specificity and sensitivity of the algorithm have been found to be 0.75 and 0.64, respectively. MERIS includes drug- and patient-related factors. The drug-related factors are based on the drugs patients are taking on admission to hospital (excluding cytotoxics); subsequently, every drug's potential for toxicity and drug–drug interaction is assessed with MERIS. The patient-related factors include the number of drugs on admission to hospital and the patient's renal function.[12]

Intervention

Patients in the intervention group received stratified interventions. The low-risk group (MERIS score <14) received the usual routine at the unit whereas high-risk patients (MERIS score $\geqslant 14$) received a medication review. Patients presenting with a risk score between 14 and 26 received a medication review by a clinical pharmacist, whereas patients with a risk score $\geqslant 26$ received a medication review by a clinical pharmacologist. The reason for choosing 14 as the cut-off level was that it has been shown in validating MERIS that the highest precision was generated using the detection limit of 13.[12] However, we chose 14 due to yielding a higher specificity. We knew *a priori* that the patients presenting with the highest risk scores were the patients who had more comorbidities and were considered sicker. Clinical pharmacologists are medical doctors and due to their focus on diagnoses we considered this appropriate. The cut-off at exactly 26 was a pragmatic choice made on the number of patients a clinical pharmacologist, hence a clinical pharmacist, should review.

The medication reviews were performed immediately after the risk assessment, that is, on the day of hospitalisation. The procedure for conducting the medication reviews followed the method described by Graabæk *et al.*[14] Briefly, the medication reviews consisted of: (1) collecting information concerning the patient's drug treatment and the clinical status of the patient, (2) a patient-interview and (3) a critical examination of the patient's overall drug treatment. Clinical pharmacologists and clinical pharmacists both forwarded results of their reviews to the clinician in charge of the patient. Recommendations or information arising from the medication reviews were delivered to the hospital-physicians in a note in the electronic medical record. If fast response was needed, for example, if the patient was about to be discharged or urgent action was required, the note was accompanied by direct contact with a physician. After discharge it was registered whether the hospital-physicians had accepted the recommendations and accordingly changed the patients' prescriptions.

Control group

The usual care regarding medication consisted of medication history and reconciliation of the medications by a ward physician. The ward physician prescribed the drugs in the electronic medical record. Patients in both the intervention group and the control group received the usual care. In addition, patients in the control group were risk assessed with MERIS to assess whether MERIS was found useful in categorising patients at low and high risk, respectively.

Outcomes

The primary outcome was the number of prescribing errors during the patients' hospitalisation (excluding errors in discharge summaries). The definition of prescribing errors used in this study was adapted from a definition of medication errors[14] and was defined as 'an error in the ordering process causing harm or implying a risk of harming the patient'.

We used a two-stage process to determine the primary outcome: first, DRPs were identified and, second, all of these were assessed for prescribing errors. The DRPs were identified retrospectively by clinical pharmacists (CAS, TT) by screening the electronic medical records, which included clinical notes, prescriptions and laboratory test results for the full hospitalisation. The pharmacists were instructed to report all possible DRPs apart from generic substitution. The DRPs were categorised into pre-specified categories, for example, contraindications and dose-related issues.[15] Two clinical pharmacologists (ES, LPN) independently examined the DRPs and determined whether they could be considered prescribing errors according to the definition. In the case of disagreement between the clinical pharmacologists consensus was reached face-to-face. All the reviewers were blinded to the patients' risk scores.

Secondary outcomes were healthcare utilisation, health-related quality of life and mortality 90 days after hospital discharge. Healthcare utilisation was divided into contacts with general practitioners and visits to emergency departments. Data were retrieved from three registries: the Danish National Registry of Patients, the Danish National Health Service Registry and the Civil Registration System.

Health-related quality of life was assessed using EQ-5D, which is a short, validated and accurate instrument to measure patients' experience of quality of life.[16] Five dimensions are covered by EQ-5D: mobility, personal care, usual activities, pain/discomfort and mental health, as well as self-experienced health status (EQ VAS). Data on health-related quality of life were obtained at enrolment to the study and at 90 day follow-up telephone interviews.

Ethical considerations

The Regional Committee on Health Research Ethics in Central Denmark Region reviewed the study protocol and claimed that permission was not required since it did not comply as a biomedical study. The study was registered at the Danish Health and Medicines Authorities and permission was granted to seek information in the included patients' medical records. The permission also included patients who were unable to give written consent due to acute illness or cognitive state since these vulnerable patients were considered to benefit from the intervention. Written informed content was obtained from patients who were not cognitively impaired or too ill to be informed. The study was approved by the Danish Data Protection Agency and registered in ClinicalTrials.gov (identifier: NCT01819974).

Statistical analysis

Sample size calculations were based on the prevalence of prescribing errors (10.4% of prescribed drugs) found in a pilot study.[13] *A priori*, a reduction of 40% on the number of prescribing errors was considered clinically relevant, and to detect this difference with 90% power and a significance level of 0.05, 972 prescriptions should be included in each group. This corresponded to 119 patients when applying the mean number of drugs from a pilot study (8.2 drugs).[13] Physicians accepted approximately 50% of the recommendations and to minimise the risk of potential clustering a total of 375 patients was needed.

Patient characteristics were described and compared between study groups using Wilcoxon rank-sum test for continuous and non-parametric data, while parametric data were analysed with Student's *t*-tests. Pearson chi square test and Fishers' exact tests were used for categorical variables, as appropriate.

Data from EQ-5D were analysed by using the Danish EQ-5D weights.[17] Statistical significance was defined at a level of 0.05 (two-sided). All data were analysed in Stata version 13 (StatCorp, 4905 Lakeway Drive, TX, USA).

Results

A total of 375 patients were enrolled in the study, yet six patients were excluded after randomisation. In summary, 187 patients were analysed from the intervention group and 182 from the usual care group. Patient characteristics are presented in Table 1. Significantly more patients in

Table 1. Characteristics of included patients.

	Intervention ***n*** **= 187**	**Control** ***n*** **= 182**
Age, years, mean (95% CI)	72.4 (70.1–74.5)	72.8 (70.3–75.4)
Gender, male, *n* %	86 (46.0)	81 (44.5)
eGFR, ml/min, *n* (%)		
>60	115 (61.5)	120 (65.9)
30–60	59 (31.5)	42 (23.1)
<30	13 (6.9)	20 (11.0)
Number of drugs at admission, mean (95% CI)	8.6 (7.9–9.3)	8.1 (7.4–8.8)
MERIS score, *n* (%)		
<14 (low risk)	123 (65.7)	122 (67.0)
⩾14–25 (high risk)	57 (30.5)	52 (28.6)
⩾26 (high risk)	7 (3.7)	8 (4.4)
Co-morbidities, *n* (%)*		
Respiratory disease	46 (24.5)	44 (24.2)
Endocrine disease	57 (30.3)	50 (27.5)
Cardiovascular disease	101 (53.7)	97 (53.3)
Musculoskeletal disease	32 (17.0)	32 (17.6)
Cancer	11 (5.9)	23 (12.6)
Psychiatric disorders	31 (16.5)	33 (18.1)
Number of comorbidities, *n* (%)		
0	31 (16.6)	20 (10.9)
1	72 (38.5)	76 (41.8)
2	56 (29.9)	61 (33.5)
⩾3	28 (14.9)	25 (13.7)
Length of hospital stay, days, mean (95% CI)	4.4 (3.6–5.3)	4.4 (3.6–5.2)
Length of stay at the Acute Admissions Unit, h, mean (95% CI)	27.6 (25.2–30.2)	24.5 (22.3–26.6)
Discharged directly from the Acute Admissions Unit, *n* (%)	88 (48.1)	97 (53.3)

The only statistically significant difference between study groups was observed for the co-morbidity cancer ($p = 0.03$).
*Classified according to the International Classification of Diseases (ICD-10).
CI, confidence interval; eGFR, estimated glomerular filtration rate.

the control group had cancer (12.6% *versus* 5.9%), whereas no other differences in baseline characteristics were found. The most frequent cause of admission was respiratory disease, for example, chronic obstructive pulmonary disease and pneumonia (28% of patients in the

Table 2. Primary outcome. Number of prescribing errors during hospitalisation.

Outcome	Events, *n*		Events per patient, mean (95% CI)			Events per drug, mean (95% CI)		
	Intervention	Control	Intervention	Control	*p* value	Intervention	Control	*p* value
Prescribing errors, low-risk patients	84	81	0.68 (0.50–0.86)	0.66 (0.49–0.83)	0.86	0.11 (0.08–0.14)	0.15 (0.10–0.19)	0.66
Prescribing errors, high-risk patients	81	72	1.26 (0.75–1.79)	1.20 (0.82–1.58)	0.86	0.11 (0.05–0.17)	0.09 (0.06–0.13)	0.81
Prescribing errors, all patients	165	153	0.88 (0.67–1.09)	0.84 (0.67–1.01)	0.86	0.11 (0.08–0.14)	0.13 (0.09–0.16)	0.65

CI, confidence interval.

intervention group and 25% of patients in the usual care group).

Interventions

In total 64 patients in the intervention group (34%) had a MERIS score of 14 or greater and accordingly received a medication review. The reviews were performed by a clinical pharmacist for 57 patients and by a clinical pharmacologist for seven patients (MERIS score ⩾26). The medication reviews resulted in 123 recommendations concerning 44 patients, of which 80 recommendations (65%) were accepted by the hospital-physicians. In total, 63 of the 123 recommendations concerned prescribing errors, of which 47 recommendations (75%) were accepted by the hospital-physicians. The most frequent recommendation was terminating a drug treatment.

Primary outcome

The retrospective assessment of prescribing errors detected 165 prescribing errors in the intervention group and 153 in the control group, corresponding to a mean of 0.11 (95% confidence interval (CI): 0.08–0.14) errors per drug in the intervention group and 0.13 (95% CI: 0.09–0.16) errors per drug in the control group. In the intervention group 52% of patients had at least one prescribing error compared with 50% in the control group. More information is provided in Table 2.

A total of 81 prescribing errors in the 46 high-risk patients receiving medication review were not addressed in the medication reviews. Thirty of these were not possible to address as they occurred after completion of the medication reviews, leaving 51 prescribing errors in 24 patients not being addressed in the medication reviews.

Secondary outcomes

In Tables 3 and 4 results from the secondary outcomes are shown; no differences between study groups were observed. Regarding health-related quality of life 265 patients (69% in the control group and 75% in the intervention group) were able to answer the EQ-5D survey at admission. At follow-up only patients who participated at admission were contacted by phone. Of these we were able to contact 177 patients (66% of patients included in EQ-5D in the control group and 67% of patients in the intervention group). Respondents lost to follow-up included 62 patients whom we were not able to reach by phone, 20 patients who had died and six who were too ill to respond properly.

Subgroup analysis

Subgroup analyses of high-risk patients (MERIS score ⩾14) were performed. No statistically significant differences between intervention and control groups were observed.

MERIS' ability to risk stratify the patients in the control group

Significantly more prescribing errors were found in the high-risk group; 0.66 (0.49–0.84) prescribing errors per patient in the low risk group *versus* 1.2 (0.82–1.58) errors per patient in the high-risk group.

Table 3. Secondary outcomes. Health service utilisation within 90 days after discharge.

Outcome	Intervention *n* = 187	Control *n* = 182	*p* value
Emergency department visits, *n*, mean (95% CI)	36, 0.19 (0.12–0.27)	35, 0.19 (0.09–0.28)	0.38
Contacts with general practitioners, *n*, mean (95% CI)	2210, 11.8 (10.3–13.3)	1884, 10.3 (8.9–11.8)	0.19
Time to first contact with emergency departments, days, mean (95% CI)	40.0 (29.2–50.9)	35.3 (25.1–45.5)	0.53
Mortality, *n* (%)	25 (13.4)	35 (19.2)	0.16

Table 4. Health-related quality of life at 90 day follow-up and difference between baseline and follow-up.

	Intervention	Control	*p* value
EQ-5D summarised index			
- 90 day follow-up	0.69 (0.65–0.75)	0.71 (0.66–0.76)	0.73
- Difference between baseline and follow-up	0.031 (–0.019 to 0.080)	0.012 (–0.048 to 0.074)	0.65
EQ VAS			
- 90 day follow-up	66.4 (62.0–70.7)	63.4 (58.1–68.7)	0.39
- Difference between baseline and follow-up*	8.47 (0.98–12.78)	6.89 (2.32–14.62)	0.72

Values are expressed as mean (95% CI).
*Missing: 10 intervention patients and 12 control patients.
CI, confidence interval.

In addition, the patients were older and suffered from more co-morbidity. We found that MERIS had a sensitivity of 0.57 and a specificity of 0.77 in the control group patients. More results are presented in the Supplemental Material online.

Discussion

In this randomised controlled trial comparing standard treatment with treatment including medication reviews on patients assessed as high risk for medication errors, we found that MERIS was useful in risk stratifying and identifying the patients who were most vulnerable to prescribing errors and those who had most prescribing errors. Yet, differentiated medication reviews did not result in a significant reduction in prescribing errors compared with the control group; neither did we observe any significant differences in secondary outcomes.

We hypothesised that the intervention would impact on the number of prescribing errors and we also found that 63 prescribing errors were addressed in the medication reviews. Yet, the medication reviews were performed at admission, meaning that prescribing errors could occur after the intervention; in addition, the retrospective assessment revealed prescribing errors that the medication reviews did not address. Reasons for this might be human oversight, different perspectives and different sources available for the persons performing medication reviews.

The intervention did not impact on secondary outcomes. The intervention was a simple and short medication review performed at admission, thus many drug changes could happen later in patients' admission. In comparison, a recent study found that a comprehensive intervention consisting of medication review, motivational interview and follow-up with the primary care could impact on the number of readmissions, whereas a single medication review did not show any significant impact.[18]

We used the algorithm MERIS as a guide to which patients should receive a medication review. Other risk assessment tools for assessing risk of adverse drug events have been invented.[8–10] In addition, tools have been developed to identify patients in need of intervention regarding medical treatment. A patient prioritisation tool, 'the Assessment of Risk Tool', relates both patient- and drug-related factors in an algorithm suggesting which patients should receive medication reconciliation.[19] In addition, a study has invented a clinical decision rule in the emergency setting suggesting patients for medication reviews.[11] The Hohl study reached a sensitivity of 96.7% and a specificity of 40.3% in relation to experiencing an adverse drug reaction. The study was invented and validated in 1491 patients in an emergency setting in Canada. Contrarily, MERIS has been invented as a generic algorithm based on systematic literature reviews and developed on information from both surgical and medical patients. MERIS includes only a few variables and thus seems realistic to implement in a clinical setting, since the information is accessible in the medical records.

The prevalence of prescribing errors in the study (12% of prescriptions) is higher than the prevalence reported in a review which reported a median of 7% of prescriptions.[20] It is known that the prevalence varies due to different definitions and methods of collecting data.[21] Subjectivity in determining prescribing errors is expected, which has been shown in previous studies.[22,23] The definition in the present study of prescribing errors included both prescribing errors that could potentially harm the patients and those that could lead to actual harm. Assessing potential harm is known to increase subjectivity.[22,23]

Strengths and limitations

There are some limitations of our study. We were unable to conceal whether patients had received a medication review from the pharmacists identifying DRPs, since recommendations from medication reviews were documented in the medical records. We speculate that pharmacists, when examining the records, would be more alert and eager to find errors when recognising that somebody had performed a medication review.

The allocation of patients from the same unit to either control or intervention group may have entailed contamination bias. The physicians treated patients from both the intervention and control group and it is likely that they have adopted some of the principles and applied these to the control group patients and may have focused more on drug treatment. This would bias the estimate of an effect towards the null hypothesis of no difference. A recent study indicated that contamination bias was a major concern in a randomised controlled trial evaluating a pharmacist intervention in an acute setting.[24] Instead of the randomised controlled design, a historical control group could have been used or cluster-randomisation by unit. However, these initiatives could introduce new biases, for example, selection bias and differences in usual care.

Only two clinical pharmacists and two clinical pharmacologists were involved in performing medication reviews, which could limit the generalisability of the present study; however, the procedure for conducting the medication reviews was well-described, making reproducibility more likely.

A major strength of our study is the risk assessment tool guiding whether to perform medication reviews or not. We found that MERIS was useful in assessing patients' risk of medication errors. Many studies on medication reviews focus on elderly[25–29] and polypharmacy patients.[26,30] However, to prioritise patients for medication reviews by assessing each individual's risk of medication errors with an algorithm is a new and rational approach. Despite not being able to show a significant impact of the medication reviews, it would still be relevant to study interventions on high-risk patients in order to prevent and eliminate errors. Furthermore, it would be relevant to investigate and study MERIS and its potential in more detail before wider application.

Conflict of interest statement
The authors declare that there is no conflict of interest.

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