New Medicine Service at Readmission to Primary Care:

Drug Related Problems, Patient Satisfaction and Self-Efficacy in Cardiovascular Disease

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Abstract

Background Patients starting new medicines for chronic cardiovascular disease may experience practical problems, concerns or questions about necessity, all possibly contributing to the risk of non-adherence. These problems may be more pronounced upon readmission to primary care, when patients must resume self-management. Achieving a successful start in medical treatment is crucial and may be improved by the New Medicine Service (NMS), a counselling intervention for patients starting new medicines intended for long-term use.

Objective The aim of this study was to evaluate NMS during implementation in a real-life setting on Drug Related Problems (DRPs), patient satisfaction and self-efficacy in patients who initiate cardiovascular medicines intended for long term use at readmission to primary care. Secondary objectives were identifying risk factors for DRPs and evaluating first-fill discontinuation.

Methods An observational living-lab study was conducted in 14 pharmacies in Almere, the Netherlands. Eligible patients were aged 18 or over and received a first prescription by an in-hospital physician for a cardiovascular medicine intended for long-term use. NMS consisted of telephone counselling guided by a semi-structured conversation protocol and was performed two weeks after the first prescription. The control group received usual care. Patients reported on Satisfaction with Information about Medicines and Medication Understanding and Use Self-Efficacy. First-fill discontinuation was measured with dispensing data from the pharmacy information system.

Results 2165 patients were selected for NMS, 1647 were eligible and 743 received the intervention. In the control group, 96 patients were included. 72.5% of all patients that received the service had at least one identified DRP. Factors affecting drug related problems were outpatient visits (adj. OR 0.64 (95% CI 0.42-0.94)), current usage of cardiovascular medicine (adj. OR 0.65 (0.43-1.00)) and usage of medicine for other chronic diseases (adj. OR 1.71 (1.01-2.67)). NMS improved satisfaction with information about medicines and medication understanding and use self-efficacy ($p<0.001$). No difference in first-fill discontinuation was seen after NMS (12.5% and 13.3%, $p=0.822$). Patients with an identified DRP had a higher first-fill discontinuation than patients without a DRP (14.8% and 8.6%, $p=0.030$).

Conclusion NMS resulted in the identification of drug-related problems in the majority of patients. Since satisfaction with information and self-efficacy improved, it can be a valuable tool to address needs, concerns and other DRPs for all patients with new cardiovascular medicine in a transitional care setting. The living-lab setting illustrated the time restraints pharmacists' experienced in everyday practice force a sustainable selection of patients who benefit most from NMS with identified risk factors.

Samenvatting in het Nederlands

Achtergrond Patiënten die starten met nieuwe geneesmiddelen voor chronische hart- en vaatziekten, kunnen praktische problemen, zorgen of andere medicatie-gerelateerde problemen ondervinden, die mogelijkerwijs bijdragen aan het risico op therapieontrouw. Bij transitiezorg van de tweede lijn naar eerstelijnszorg, waarbij patiënten afhankelijk zijn van zelfredzaamheid, zijn patiënten extra kwetsbaar voor dit soort barrières. Een succesvolle start van de behandeling is cruciaal en kan worden verbeterd door telefonische start begeleiding (New Medicine Service, NMS), een begeleidingsinterventie voor patiënten die nieuwe chronische geneesmiddelen starten.

Doelstelling Het doel van deze studie was om NMS tijdens implementatie in een real-life omgeving te evalueren op medicatie-gerelateerde problemen (Drug Related Problems, DRP's), patiënttevredenheid en zelfredzaamheid bij patiënten die starten met chronische cardiovasculaire geneesmiddelen tijdens transitie van tweedelijnszorg naar de eerste lijn. Secundaire doelstellingen waren het identificeren van risicofactoren voor DRP's en het evalueren van medicatiestakingen na de eerste uitgifte.

Methode Een observationele proeftuinstudie werd uitgevoerd in 14 apotheken in Almere, Nederland. Patiënten van 18 jaar of ouder kwamen in aanmerking wanneer ze een eerste uitgifte ontvingen voor een chronisch cardiovasculair middel voorgeschreven door een ziekenhuisarts. NMS bestond uit telefonische begeleiding aan de hand van een gespreksprotocol en werd twee weken na het eerste uitgifte uitgevoerd. De controlegroep ontving gebruikelijke zorg. Tevredenheid met informatie over geneesmiddelen en zelfredzaamheid werden uitgevraagd aan patiënten en medicatiestakingen na de eerste uitgifte werden ingewonnen uit het apotheekinformatiesysteem.

Resultaten 2165 patiënten werden geselecteerd voor NMS, 1647 kwamen in aanmerking en 743 ontvingen de interventie. De controlegroep bevatte 96 patiënten. 72,5% van alle patiënten die de interventie ontvingen, had ten minste één vastgesteld DRP. Factoren die een effect hadden op DRPs waren polikliniekbezoeken (adj. OR 0,64 (95% CI 0,42-0,94)), bestaande gebruikers van cardiovasculaire geneesmiddelen (adj. OR 0,65 (0,43-1,00)) en gebruikers van geneesmiddelen voor andere chronische ziekten (adj. OR 1,71 (1,01-2,67)). NMS verbeterde de tevredenheid met informatie en de zelfredzaamheid bij het begrijpen en gebruiken van geneesmiddelen ($p<0,001$). Tussen de controlegroep en de interventiegroep werd geen verschil in medicatiestaking na de eerste uitgifte gezien (12,5% en 13,3%, $p=0,822$). Patiënten met een DRP staakten vaker hun medicatie na de eerste uitgifte dan patiënten zonder DRP (14,8% en 8,6%, $p=0,030$).

Conclusie NMS resulteerde in de identificatie van medicatie-gerelateerde problemen in de meerderheid van de patiënten. Aangezien de tevredenheid met de informatie en de zelfredzaamheid verbeterden, kan het een waardevol instrument zijn om behoeften, zorgen en andere DRP's aan te pakken voor alle patiënten met nieuwe cardiovasculaire geneesmiddelen in transitiezorg. De realistische setting van de studie toonde aan dat tijdsbeperkingen in de dagelijkse praktijk apothekers dwingen patiënten te selecteren voor NMS, waarvoor de geïdentificeerde risicofactoren voor DRP's gebruikt kunnen worden.

Introduction

Medicines are the most widely used therapeutic option for patients after receiving their diagnosis. In cardiovascular disease, medicines are often prescribed to prevent onset and decline of disease.(1,2) These prevention-oriented therapies mostly lack an immediate noticeable effect and are prone to increase in complexity over time.(1) Furthermore, patients initiating these medicines can encounter a myriad of practical and perceptual barriers at the start that could influence their medicine intake behaviour.(3-6) In transitional care settings these initial barriers for non-adherence to medicine might be even more prominent. Due to the involvement of multiple healthcare providers, the risk of poor communication and loss of important information is increased.(7,8) Moreover, patients need to incorporate their new medicines into their daily routine and resume self-management.(7) This may result in patients feeling forlorn and unknowing who they should contact for appropriate guidance or with questions concerning their new medicine.(5) Patients' perspective on the necessity of their treatment may be negatively impacted and result in patients deviating either intentionally or non-intentionally from their newly prescribed regimen.(2,3,9,10) Studies on cardiovascular medicines have shown that up to 50% of the patients discontinue within the first six months after initiation and even up to 19% discontinue their antihypertensive medication after the first fill.(11-14)

This illustrates the importance of focusing on patients' adherence to medicines at the initiation of therapy; the first component of the adherence process.(3) Providing a good start is a crucial step in addressing patients' needs and supporting their self-management. An intervention to facilitate a better start for patients is the New Medicine Service (NMS). NMS is a pharmacist-led patient-centred counselling intervention for patients starting new medicines intended for long-term use. It aims to identify problems regarding the treatment (such as adverse effects), as well as give information and advice based on identified needs.(15-17) Studies have shown that NMS increased patient satisfaction and their perceived knowledge of medication, identified more drug related problems (DRPs) and improved medication adherence.(15,17) Since NMS has also been shown to be cost-effective, broader implementation is rational.(18) During implementation of a service in a real-life setting, barriers related to involvement of health care providers (HCP) and patients may arise.(19) A living-lab approach in research is meant to enhance development and implementation of an innovation and has been adopted in healthcare settings in the past decade. Living-labs have demonstrated to contribute to successful implementation outcomes by fostering collaboration, co-creation and participation. (19)

In the Netherlands, NMS has been studied in a randomised controlled trial in a primary care setting with specific medicines intended for long term use. This trial showed an improvement in adherence and satisfaction with the information patients received.(16,20) However, a perspective on this service in a transitional care setting involving the unique challenge for patients to resume self-management, is lacking. Furthermore, a controlled study environment is difficult to compare with a real-life setting, where time constraints in the pharmacy may play an important role.(21) Therefore, this study was conducted within a living-lab setting that focuses on a sustainable implementation of NMS in community pharmacies. The objective of this study was to evaluate NMS during implementation in a real-life setting on patient reported outcome measures (PROMs) in patients who initiate cardiovascular medicines intended for long term use at readmission to primary care. The PROMs measured are identified Drug Related Problems (DRPs), satisfaction with information and self-efficacy. Secondary objectives were identifying risk factors for DRPs and evaluating first-fill discontinuation.

Methods

Study design and setting

A observational living-lab study was conducted between April 2021 and August 2022. The study primarily focused on implementing NMS in participating community pharmacies. A secondary objective was to evaluate the intervention on patient reported outcome measures and first-fill discontinuation. As a result, a more pragmatic living-lab study was designed to ensure the most sustainable implementation of NMS. This approach allowed for unique participation by performing pharmacists in the form of regular meetings to facilitate implementation progress, as well as apply further adjustments to the service, such as additional selection criteria.

The study was performed in the outpatient and 14 community pharmacies of Zorggroep Almere (ZGA). ZGA is a large multidisciplinary primary healthcare organization that employs, amongst others, general practitioners and pharmacists. The community pharmacies were divided in three clusters. To facilitate implementation, the service was gradually introduced in pharmacies within one cluster before introducing the next cluster. In Almere, a city with around 200,000 inhabitants, all community pharmacists share the same pharmacy information system.(22,23) Their interlinked healthcare information system encourages collaboration and research that surpasses the current standard of care in the Netherlands.(24,25) The outpatient pharmacy is based within and closely collaborates with a general non-teaching hospital (Flevoziekenhuis).

Patient selection

Patients ≥ 18 years of age were eligible to receive NMS if they were living at home and filled a first-time prescription for a cardiovascular medicine intended for long term use at the outpatient pharmacy. Under Dutch healthcare law, first time prescriptions are defined as having no dispensings in the previous year for that specific medicine. The medicine had to be prescribed by an in-hospital physician either at hospital discharge or at the outpatient clinic. Included medicines were as follows: antithrombotic agents (ATC3-code: B01), cardiac therapy (C01), diuretics (C03), beta blocking agents (C07), calcium channel blockers (C08), agents acting on the renin-angiotensin system (C09) and lipid modifying agents (C10). Patients who only received a PRN prescription were excluded. After feedback from performing pharmacists, prescriptions from gynaecology were excluded. Furthermore, pharmacists were allowed to exclude eligible participants based on their professional opinion. These reasons for exclusion were recorded and further evaluated during implementation meetings.

New Medicine Service and usual pharmacy care

Usual care started with a patient filling a first prescription at the outpatient pharmacy. In the Netherlands, professional guidelines emphasize the importance of counselling at the start of a new medicine, which is mainly performed by a pharmacy technician (PT) (Figure 2).(26) Furthermore, all community and outpatient pharmacies keep electronic dispensing data and perform clinical risk management at time of dispensing.(26) Additionally, the outpatient pharmacy sent an animated medication information tool to the patient via email (Watchyourmeds).(27) Watchyourmeds provides information in an accessible manner through animated videos and is therefore especially suitable for people with limited health literacy.(27) In this study, usual care was complemented with the New Medicine Service (NMS), consisting of:

- **Medicine Information Transfer:** After visiting the outpatient pharmacy, patients' medicine information was transferred to patients' own primary healthcare providers. Their community pharmacist consulted a weekly generated list to select potential patients eligible for NMS.
- **Telephone counselling (NMS)**: Eligible patients received a telephone call by their community pharmacist in the second week after initiating their new cardiovascular

medicine. The counselling was guided by a semi-structured interview protocol consisting of five open-ended questions and possible follow-up questions (Appendix A). The protocol was based on the study of Kooij *et al*.(28) Together with Kooij the original protocol was updated to current professional standards and comprised of two instruments: (1) TRIAGE practical questions set and trigger list for identification of possible DRPs and (2) professional guideline for consultation in pharmacies (Royal Dutch Pharmacy Association, KNMP).(20,29) The latter is a guideline for pharmacy consultations based on the Calgary-Cambridge-model. The NMS protocol focused on both practical and perceptual barriers to taking medicine, including possible side effects. When a DRP was identified, the pharmacist provided information, reassurance, possible solutions or referred the patient to their prescriber (either GP or medical specialist). The protocol was finalized by an expert panel, consisting of four local community pharmacists and a community communication expert. They commented on the applicability of the protocol in practice, incorporating an open-ended communication style and ensuring all adherence themes were covered. All participating community pharmacists had experience performing patient counselling interviews. To ensure further generalizability and robustness in conducting NMS, pharmacists received a training course on patient-centred communication and adherence provided by the same communication expert. Furthermore, they received protocol-specific training on applying the NMS protocol in everyday pharmacy practice by the research team.

To continue the medication regimen, patients sent in a repeat prescription request to their general practitioner after approximately one month. The community pharmacy dispensed the repeat prescription, after which a patient entered the usual primary-care circuit and continued their medicine as prescribed.

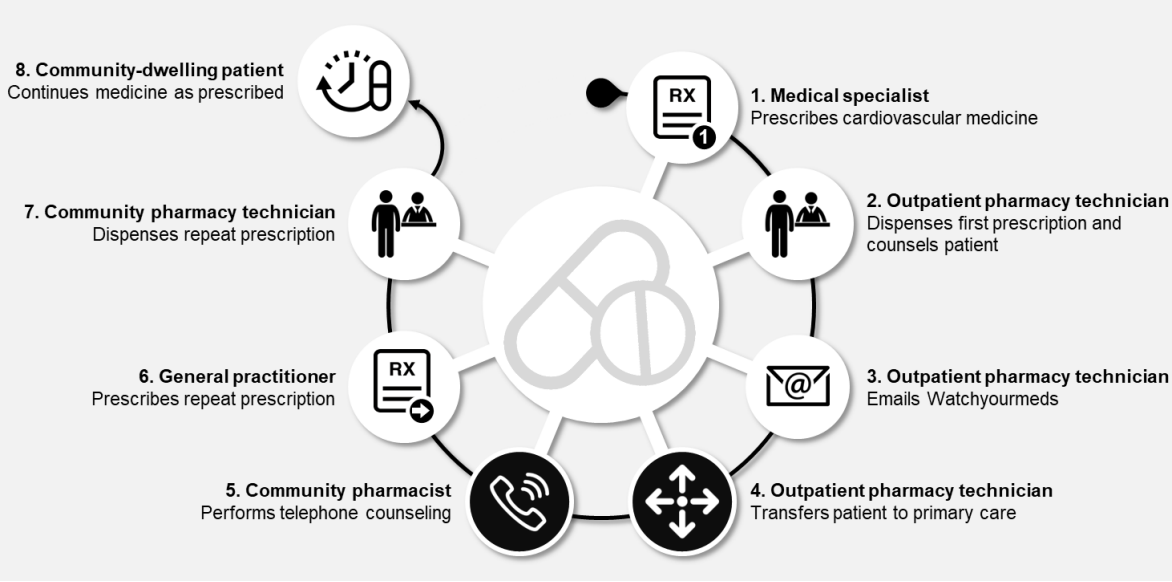

Figure 1. Usual care after a first prescription from an in-hospital physician, with the New Medicine Service intervention integrated in steps 4 and 5.

Definition of outcomes and data collection

The primary patient-reported outcome measures (PROMs) of this study were: (1) Drug Related Problems (DRPs) patients experienced at the start of their medicine, (2) satisfaction about the information received by the pharmacist and (3) medicine understanding and self-efficacy. The secondary outcomes were risk factors for DRPs and first-fill discontinuation.

Drug-related problems

During the NMS interviews, pharmacists filled in a data collection sheet with possible DRPs and follow-up actions (appendix B), based on the main problem domains in the TRIAGE

protocol to identify DRPs (29). These domains were: practical intake problems, problems with incorporating intake in daily routine, complex medicine regimens, self-reported side effects, perceived low necessity, concerns, knowledge barriers, vulnerable patients and problems with costs. The follow-up actions were: giving practical advice or help, verbal explanations and reassurances, consulting with the prescriber, referring to additional information, making changes in the medicine, assessing a patients environment, and communication techniques, including assessing the risk of discontinuation. The actions were organised in the same problem domains as the DRPs for easy comparison.

Satisfaction and understanding

The next workday, a follow-up questionnaire was conducted by telephone by a PT. The questionnaire consisted of the *Satisfaction with Information about Medicines Scale (SIMS)* with 15 out of the original 17 questions, and the *Medication Understanding and Use Self-Efficacy Scale (MUSE)* with 7 out of 8 questions, both translated to Dutch (appendix C). The SIMS scale consisted of an overall score (0-15), an *action and usage*- (0-7) and a *potential problems* subscore (0-8).(30) The MUSE scale consisted of an overall score (7-28), a *taking medication*- (3-12) and a *learning about medication* subscore (4-16).(31) One question was removed from the original MUSE scale, as translation of this question to Dutch resulted in two almost identical questions.

During the first phase of the study, patients from the other pharmacy clusters that met inclusion criteria received a telephone call by a PT for the SIMS/MUSE questionnaire. These patients had not received NMS and were therefore considered the control group. Data collection was aimed at 100 interviews to reduce unnecessary burden on pharmacy employees.

Baseline characteristics and first-fill discontinuation

Finally, patient characteristics and prescription data were extracted from pharmacy and hospital information systems, as well as information about possible reasons for discontinuing medicines or switching to different medicines. The proportion of subjects who discontinued after the first dispensing of their new CV medicine (first-fill discontinuation) was a secondary outcome. A medicine was considered discontinued if there were no refills for that specific CV medicine in the three months after the first dispensing.(13) Late refills were defined as being collected between 14 and 60 days after the expected date for starting the refill prescription.

Ethics approval

The trial protocol by Kooy *et al*. for NMS intervention has been previously approved by the Institutional Review Board (IRB) of the division of Pharmacoepidemiology and Clinical Pharmacology of Utrecht University (UPPER).(28) In continuation of this previous protocol, the study protocol was approved by the IRB at UPPER (registration number UPF 2009). All data-collection sheets and patient characteristics were encrypted under unique patient identification codes. Complete datasets were only available to the researchers.

Data analysis

Baseline characteristics of the intervention group and control group were compared using Mann-Whitney tests for numerical characteristics and Chi-square tests for categorical variables. Statistical tests were performed using Chi-square tests for categorical variables and Mann-Whitney U-tests for non-normal numerical data. Univariate and multivariable logistic regression was performed for patient characteristics as possible risk factors of DRPs. Akaike's Information Criterion (AIC) and Hosmer and Lemeshow goodness-of-fit test were used to determine the best-fitting model. All data were analysed using SPSS statistics 28.0.1.1. A p-value of 0.05 was considered statistically significant.

Results

General characteristics

A total of 2165 patients filled a first prescription for the selected medicines in the outpatient pharmacy and were selected for NMS. After exclusion, 1647 were eligible. Most excluded patients only received temporary or PRN medicine (n=208). Of all eligible patients, 743 received NMS (34.3% of all selected patients), which corresponded to 12.3 ± 4.3 a week on average for all 14 pharmacies. The main reasons a patient did not receive NMS counselling were scheduling challenges of the pharmacists, which included sickness (of the pharmacist), shortage of staff and holiday leave. NMS was performed 13.5 ± 2.6 days (range 3-27) after first dispensing. The telephone call lasted for approximately 6 minutes (06:18 ± 03:30, range 1-24 minutes).

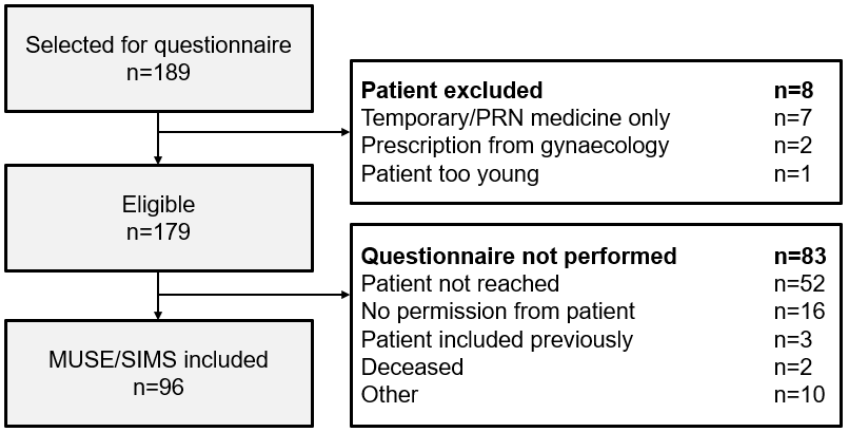

Figure 2: Patient selection figure for the control group receiving usual care. MUSE=Medication Understanding and use Self-Efficacy scale. SIMS=Satisfaction with Information about Medicines Scale. PRN=Pro Re Nata.

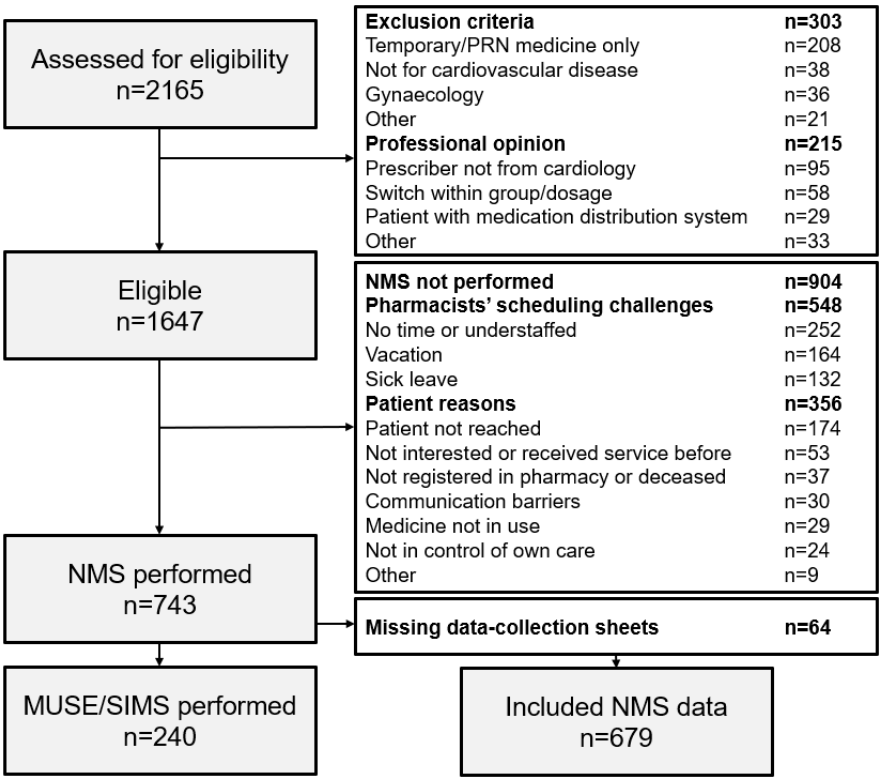

Figure 3: Patient selection figure for the intervention group receiving NMS. NMS=New Medicine Service. MUSE=Medication Understanding and use Self-Efficacy scale. SIMS=Satisfaction with Information about Medicines Scale. PRN=Pro Re Nata.

The mean age of patients who received NMS (intervention group) was 63.6 ± 12.6 years and 44.0% (n=327) were female, compared to 61.4 ± 13.5 and 47.9% (n=46) in the control group (Table 1). A minority received the prescription after hospital discharge, 43.9% (n=326) and 46.9% (n=45), respectively. The remaining prescriptions originated from outpatient hospital visits. Approximately a third of the of the patients in both groups had no cardiovascular medicine in use at the time of the new prescription. The majority of patients had prescription medicines in use for other comorbidities at the time of the new prescription, 78.6% (n=584) and 72.9% (n=70), respectively.

Table 1: Patient characteristics of the intervention group and control group

Baseline characteristic	**Intervention group (n=743)**	**Control group (n=96)**	**P-value**
Age, year, *mean (SD, range)*	63.6 (12.6, 20-96)	61.4 (13.5, 24-91)	0.180[M]
Sex female, *% (n)*	44.0 (327)	47.9 (46)	0.469[X]
Hospital discharge*, *% (n)*	43.9 (326)	46.9 (45)	0.578[M]
Hospital department *% (n)*			
Cardiology	54.5 (405)	37.5 (36)	0.109[X]
Internal medicine	16.4 (122)	21.9 (21)	
Neurology	11.7 (87)	17.7 (17)	
Emergency	8.6 (64)	10.4 (10)	
Surgery	4.7 (35)	6.3 (6)	
Pulmonary	3.5 (26)	5.2 (5)	
Other[#]	0.5 (4)	1.0 (1)	
Cardiovascular medicine			
Current CV medicine user, *% (n)*	67.0 (498)	66.7 (64)	0.944[X]
Number of CV medicines in use, *mean (SD, range)*	1.9 (1.9, 0-9)	1.9 (1.8, 0-7)	0.850[M]
Number of CV medicine started**, *mean (SD, range)*	1.8 (1.1, 1-6)	1.7 (1.2, 1-6)	0.318[M]
Other medicines in use			
Current other medicine users[##], *% (n)*	78.6 (584)	72.9 (70)	0.206[X]
Number of other prescription medicines in use*** *mean (SD, range)*	2.4 (2.4, 0-16)	2.4 (2.6, 0-17)	0.696[M]

: % of patients that received a first prescription after hospital discharge, instead of after outpatient hospital visit. [#]:Rheumatology, paediatrics, ophthalmology. **: Number of new cardiovascular medicines dispensed at first fill in the outpatient pharmacy that fit inclusion criteria. [##]: % of patients that are current users of medicines intended for long-term use, for comorbidities except CV disease. *: Number of prescription medicines in use, except temporary medicine and topical treatments, for comorbidities except CV disease. M: Mann-Whitney test used, X: Chi-squared test used. SD=standard deviation, CV=cardiovascular.*

DRPs and follow-up actions

In total, 1043 DRPs were identified in 679 patients. The number of DRPs that were identified in a patient ranged from 0 to 9 (Figure 4). For 72.5% (n=492) of the patients who received NMS, at least one DRP was identified and 42.9% (n=291) of patients had more than one DRP. The highest number of patients had a DRP in the domains self-reported side effects (33.9%, n=230) and problems with complexity of the medicine regimen (31.7%, n=215). Regarding the total number of DRPs, unclarity in the repeat prescription process was the most identified DRP, which was identified 135 times (12.9%). Detailed results on specific DRPs and follow-up actions can be found in Appendix D.

In total, 1711 follow-up actions were performed in the 679 telephone calls. The number of actions ranged from 0 to 11 (Figure 4). For 77.5% (n=526) of patients, at least one follow-up action was performed. Pharmacists performed the most follow-up actions in the domains of self-reported side effects, perceived low necessity of the medication (both 34.2%, n=232) and complexity of medication regimen (33.7%, n=229). For 9.0% of patients, the prescribing physician was contacted. Looking at the total number of actions, the most performed actions

by pharmacists were verbal explanations and reassurances (56.2%, n=961), e.g. reassuring after a known side effect (11.7%, n=200) and explaining the purpose of the medicine (9.7%, n=166), practical advice or help (19.5%, n=334), e.g. explaining repeat prescription process (8.1%, n=138) and assessing possible risks for discontinuation (13.1%, n=224).

More actions were performed than DRPs identified (1711 compared to 1043 in total). Pharmacists frequently performed several follow-up actions after one DRP was identified. In the self-reported side effects domain, this difference was seen most prominently (34.2% of patients (n=232) received 418 actions in total). In the perceived necessity domain, a difference was seen in the number of patients in which a DRP was identified (13.7%, n=93), compared to the number of patients that received a follow-up action in this domain (34.2%, n=232). Explaining the purpose of the medicine and emphasizing the importance of regular use of a medicine were the most performed actions in this domain (n=166 and n=151). In 7.4% (n=39) of patients, actions were performed by the pharmacist, despite no DRP being identified. For these patients, the most frequently performed actions were explanations of the purpose of the medicine (46.2%, n=18) and emphasizing the importance of regular use of the medicine (51.3%, n=20).

Table 2: Number of patients with identified DRPs and follow-up actions performed, divided by category of problem

Category of DRP	**Patients with DRP** n=679, % (n)	**Patients with follow-up action** n=679, % (n)
Practical intake problems	7.8 (53)	9.3 (63)
Problems with incorporating intake in daily routine	7.1 (48)	7.4 (50)
Complexity of medicine (regimen)	31.7 (215)	33.7 (229)
Self-reported side effects	33.9 (230)	34.2 (232)
Perceived low necessity of the medicine	13.7 (93)	34.2 (232)
Concerns about the medicine	13.0 (88)	16.6 (113)
Knowledge barriers	15.2 (103)	15.6 (106)
Vulnerable patients	6.8 (46)	7.4 (50)
Costs	0.4 (3)	0.4 (3)

DRP=Drug Related Problem.

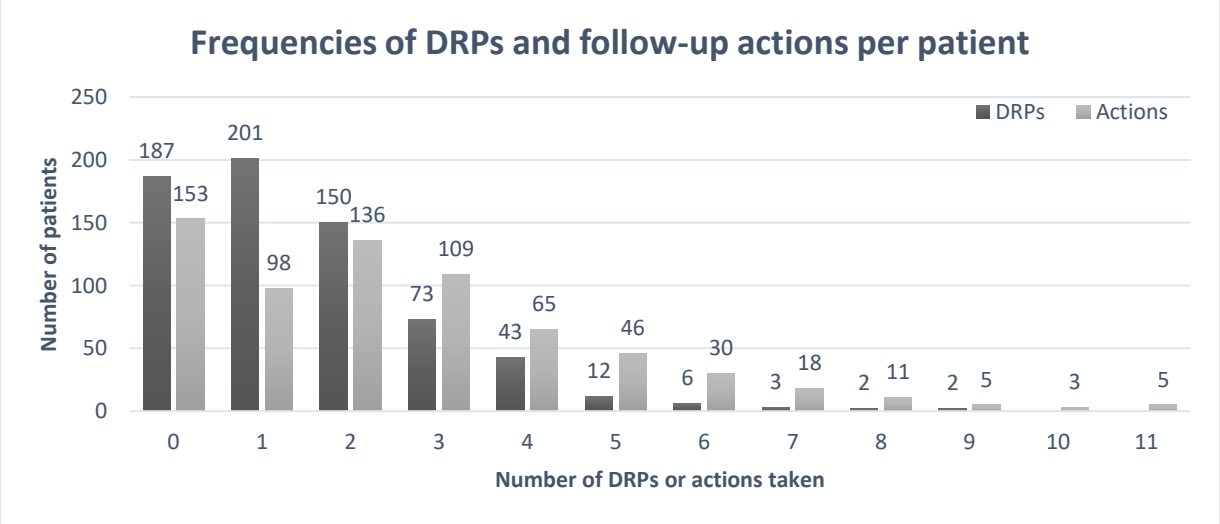

Figure 4: Frequencies of the number of DRPs and follow-up actions taken per patient receiving NMS. DRP= Drug related problem.

Baseline characteristics that resulted in a significant difference in the number of patients with an identified DRP were: (1) discharge from the hospital compared to outpatient visit (78.3%, n=238 and 67.7%, n=254, p=0.002) and (2) naivety to CV medicine compared to previous users of CV medicine (77.9%, n=173 and 69.8%, n=319, p=0.026).

After multivariate regression analysis, the adjusted OR for prescriptions from outpatient visits was 0.64 (95%-CI 0.43-0.94, p=0.024), compared to prescriptions received after discharge. The OR of users of CV medicine was 0.65 (95%-CI 0.42-1.00, p=0.048) compared to patients with naivety to CV medicine. A patient using prescription medicine for other comorbidities had an odds of 1.71 (95%-CI 1.10-2.66, p=0.018) compared to a patient without other medicine in use of having a DRP. The odds of having a DRP also decreased significantly for a patient being a year older, albeit the effect size being small (OR 0.98 (95%-CI 0.97-1.00), p=0.029). The multivariate logistic regression with the best fit included all characteristics with statistically significant differences in the overall multivariable logistic regression in table 3, which were hospital setting, previous usage of CV medicines, using prescription medicines for other comorbidities and age.

Table 3: Univariate and multivariable logistic regression analysis for patient characteristics and their effect on having a DRP.

Characteristic		**OR unadjusted (95% CI)**	**p-value unadjusted**	**OR adjusted (95% CI)**	**p-value adjusted**
Age (years)		0.99 (0.97-1.00)	0.060	0.98 (0.97-1.00)	**0.025**
Cardiology prescription	Yes	1.18 (0.84-1.66)	0.332	1.21 (0.84-1.74)	0.298
CV medicine in use	Yes	0.66 (0.45-0.95)	**0.027**	0.65 (0.42-1.00)	**0.048**
Hospital setting	Outpatient visit	0.58 (0.41-0.83)	**0.002**	0.64 (0.43-0.94)	**0.024**
Number of new CV medicines started	>1	1.40 (0.99-1.98)	0.054	1.11 (0.76-1.63)	0.298
Other prescription medicine in use	Yes	1.52 (1.02-2.27)	**0.039**	1.71 (1.10-2.66)	**0.018**
Sex	Female	0.93 (0.66-1.30)	0.654	0.97 (0.69-1.38)	0.875

OR=Odds Ratio, CV=cardiovascular. Statistically significant p-values (p<0.05) are depicted in bold text.

SIMS and MUSE scales

The intervention group was more satisfied with the information received overall (median (IQR)= 13 (10-15), p<0.001) and also scored higher on both subscales (Action and Usage and Potential Problems) (p<0.001) (table 4). The intervention group also scored higher on the MUSE scale overall, as well as for both the taking medication and learning about medication subscales (p<0.001). The median only increased in the overall score (21 to 22). However, the frequency of patients reporting the highest score (28) increased after NMS (35.4%, n=85 and 8.3%, n=8). Whether DRPs were identified during NMS did not have a significant effect on the SIMS and MUSE scores.

Table 4: SIMS and MUSE scores and subscores for the intervention and control group.

	Intervention group (n=240), median [IQR]	**Control group (n=96)**, median [IQR]	P-value
SIMS score (0-15)	**13 [10-15]**	**10 [7-12]**	**<0,001**
Action and Usage subscore (0-7)	7 [6-7]	5.5 [4-6.75]	<0,001
Potential problems subscore (0-8)	7 [4-8]	4.5 [2-6.75]	<0,001
MUSE score (7-28)	**22 [21-28]**	**21 [20-21]**	**<0,001**

Taking medication subscore (3-12)	9 [9-12]	9 [9-9]	<0,001
Learning about medication subscore (4-16)	12 [12-16]	12 [12-12]	<0,001

The range of each scale is displayed between parentheses. IQR= Interquartile range, SIMS= Satisfaction with Information about Medicines Scale, MUSE= Medication Understanding and Self-Efficacy Scale.

First-fill discontinuation

Overall, no differences were found between the control group and the intervention group in first-fill discontinuation (12.5% and 13.3%, p=0.822). Furthermore, no differences were found for late collection of the first refill (4.2% of the control group, 3.0% of the intervention group, p=0.521).

A significant difference in the number of patients with first-fill discontinuation was found between patients with DRPs (14.8%, n=73) and patients with no DRPs (8.6%, n=16, p=0.030). No difference was seen in late refills between patients with DRPs (3.9%, n=19) and patients with no DRPs (1.1%, n=2, p=0.060). No difference was seen in the SIMS and MUSE scores between patients with first-fill discontinuations and without (p=0.293 and p=0.373 respectively).

Discussion

The aim of this study was to evaluate New Medicine Service (NMS) on patient reported outcome measures and first-fill discontinuation in a living-lab setting in patients initiating long-term cardiovascular medicines at readmission to primary care. Overall, 743 patients received NMS throughout the duration of the study. Scheduling problems from the pharmacist were the cause of NMS not being performed for around 25% of all selected patients. In 72.5% of patients who received NMS at least one drug-related problem (DRP) was identified. Patients who received a prescription at hospital discharge, had no CV medicine in use, were using other medicine intended for long term use and of lower age, were more at risk for a DRP. After NMS, patients were more satisfied with the received information about medicines and reported a higher self-perceived medicine understanding and use self-efficacy. Overall, first-fill discontinuations and late refills did not differ between groups, but patients with a DRP discontinued more often after the first fill.

In this study, over 70% of patients had at least one DRP, which was a high prevalence of DRPs compared to a Danish study on NMS.(15) This may be a result of the use of an extensive trigger list of DRPs and follow-up actions, enabling an extensive assessment of the pharmacist counselling performed during NMS. At the same time, the co-creation aspect of the living-lab approach ensured the list was not an unrealistic burden for performing pharmacists. In accordance with the present results, previous studies have demonstrated that a majority of patients had problems caused by medicines, of which potential side effects were the most common one, as well as a substantial need for further information.(8,25,32) Although not all identified DRPs may have a clinical impact, DRPs have been linked to adverse outcomes such as hospital readmission (33), and as shown in this study, a higher first-fill discontinuation rate. This finding is in line with previous studies on adherence problems, which show that a negative balance in concerns-benefits, insufficient knowledge and problems with forgetting medicines are factors associated with cardiovascular medicine non-adherence.(10,34) These problems were also frequently identified within this study. Furthermore, a difference was seen in the number of patients with a DRP and the number of patients with follow-up actions. This difference might be explained by pharmacists giving unsolicited advice based on gut-feeling rather than an identified DRP. Research has shown that pharmacists include gut-feeling and non-verbal cues in problem identification and may therefore give unsolicited advice.(35) Although satisfaction with unsolicited advice has not been explored in literature, the need for further information has been described (8) and the high satisfaction with information found in this study highlights patients' openness to counselling.

Since first-fill discontinuation was increased in patients with identified DRPs, identifying risk-factors for DRPs is especially relevant. The possibility of multivariate regression analysis with patient characteristics potentially affecting DRPs was also one of the results of the extensive data collection on DRPs. Hospital discharge, no use of CV medicine and use of medicine for other comorbidities were found to increase the odds of DRPs. These are all easily accessible patient characteristics for pharmacists in the Netherlands, and therefore useful after implementation. Lower age, albeit resulting in a statistically significant difference, is unlikely to be clinically relevant due to its small effect size, and conflicting evidence of the effect of age on DRPs in literature.(32,36,37) While the number of medicines in use has been previously named as a risk factor for DRPs, naivety to CV medicine and a prescription after hospital discharge were not, which may be a result of previous studies mostly using medication reviews as input.(14,32,37)

An important finding was that patients reported higher satisfaction with information about medicine and scored higher on understanding of medicine and use self-efficacy after receiving NMS. This effect may be due to the high number of pharmacists actions that were related to providing reassurance and in-depth explanations. The needs and concerns patients in transitional care may experience (7,8) were reflected in the concerns about side effects and

unclarities that were frequently identified in this study, and are still often omitted during counselling in usual care.(6,38) These findings suggests NMS can be a useful tool in addressing patients' needs and concerns after starting a new cardiovascular medicine. Some studies also reported high satisfaction with the counselling received in NMS, which is in line with the results from this study, as well as increased understanding of medication.(15,20) However, none of these focused on transitional care, thus making this the first study to report on patients experiences of self-management after additional counselling in the form of NMS, which is especially relevant at readmission to primary care.(10,25)

Contrary to the observed increase in medication adherence in other studies on NMS, this study was unable to demonstrate that first-fill discontinuations decreased after NMS.(15-17) The relatively short follow-up period in this study resulted in only looking at first-fill discontinuations, in the first three months. This is shorter than several studies describing discontinuations, which usually include six to twelve months of follow-up.(13,14,39) Furthermore, the overall rate of first-fill discontinuations was already low, around 13%, making decreasing first-fill discontinuations even further less plausible. Other studies have found rates of first-fill discontinuations ranging from 8% to 20% for several cardiovascular therapies, but more importantly concluded that first-fill discontinuations play an important role in long-term non-adherence.(13,14) Finally, since this was a secondary outcome measure, it is possible that the living-lab setting of this study and focus on the PROMs resulted in not enough power to observe a difference in first-fill discontinuations.

Strengths and limitations

The living-lab approach that was chosen in this study resulted in several strengths. Firstly, the setting allowed for co-creation by performing pharmacists throughout the duration of the study. Furthermore, this approach resulted in a setting where real-life challenges such as time restraints were visible in the percentage of patients that did not receive NMS. Pharmacists were free to exclude patients based on professional opinion, thus securing the possibility to prioritise patients most likely to be helped by the service. These characteristics may have helped to create a realistic scenario as well, as these patients most likely would have been excluded in the same manner in a real-life setting. Consequently, the resemblance to a real-life setting makes extrapolation to general patients populations and primary care settings more realistic, especially combined with findings on broader patients groups.(15-17,20) Another strength was that pharmacists did not perform the MUSE/SIMS questionnaire after NMS. The second questionnaire was performed by a PT and therefore was not influenced by a pharmacist selecting patients that may be more likely to participate.

One limitation related to the living-lab setting was that the pragmatic approach resulted in a less structured study. Pharmacists making decisions on which patients were included could result in selection bias. To reduce this risk of bias, the patient selection list only included names, dates of birth and names of the new medicines. Additionally, reasons for exclusion were evaluated in the expert panel throughout the study. An interesting comparison would be to include patients that did not receive NMS in an intention to treat analysis, as done in other NMS studies (16,17), but this was deemed not feasible in this study due to time limitations in data-extraction. Furthermore, this study used dispensing data, which may overestimate medication adherence.(40) Although this data is an approximation of medication adherence, its use is in line with the realistic setting of this study, because of its availability to pharmacists.

Another limitation could be the representability of the control group for the standard of care. By performing the questionnaire, patients were contacted more often than they would without the questionnaire, which might serve as a reminder for their refill prescription, impacting the actual difference in first-fill discontinuation between usual care and NMS. No differences were observed between the control group and intervention group in these outcome measures, so it is possible that the telephone questionnaire influenced this outcome. Lastly, the control group

was relatively small compared to the group that received NMS, since the living-lab setting favoured a realistic situation, in which performing pharmacists and PTs were not burdened with a disproportionate amount of questionnaires. This resulted in less statistical power, especially for subgroup analyses with less patients. Still, significant differences were found for several main outcome measures, so this limitation did not impact the overall study disproportionally.

Implications for practice

- The pragmatic characteristics of this living-lab study are exceptionally useful to evaluate the actual effect implementation of NMS would have, since patients were included and excluded in a manner that mimics a real-life scenario.
- Due to the high prevalence of DRPs in the included patient group, it would be advisable to offer NMS to all patients with new cardiovascular medicines for long term use at readmission to primary care.
- Since time constraints were one of the most common reasons for patients not receiving NMS, pharmacists may want to select patients that may benefit the most from NMS. Hospital discharge, use of prescription medicines for other comorbidities and naivety to CV medicine were factors that increased the odds of having an identified DRP for patients with newly started medicines for chronic cardiovascular disease.

Conclusion

New Medicine Service can be a valuable tool to address needs, concerns and other drug-related problems for all patients who initiate a cardiovascular medicine in a transitional care setting. After NMS, patients were more satisfied with the received information about medicines and reported a higher self-perceived medicine understanding and self-efficacy. Furthermore, the living-lab setting illustrated the time restraints pharmacists' experienced in everyday practice force a sustainable selection of patients who benefit most from NMS. Factors that increased the risk of DRP and can be used in daily practice are: (1) patients who received a prescription at hospital discharge, (2) had no CV medicine in use and (3) were using other medicine intended for long term use.

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Appendix A: Interview guideline telephone start consultation

The telephone start-up counselling is the conversation with the patient in which care questions about a recently started treatment with a prescription medicine are discussed. The consultation is in line with the KNMP guideline on consultation and uses the Calgary-Cambridge structure for patient conversations: (1) beginning of the conversation, (2) obtaining information, (3) explanation and advice and (4) closing the conversation (see next page).

In addition, the general communication techniques below should be continuously applied during the consultation:

1. **Bringing structure.** Or, enabling an orderly but flexible conversation, using time efficiently, promoting patient engagement. You do this by:
    - Summarising in between subjects, give the patient opportunity to correct/give additions
    - "I would like to discuss [number] of things with you, namely…"
    - "If I understand correctly then … "/ "Is it true that you …"/ "You say that …"
2. **Building the relationship.** In other words, establish and maintain good contact with patient, create a bond of trust and promote mutual satisfaction. You do this by:
    - Engaging attitude and showing genuine interest.
    - Deploying a friendly voice.
    - Explaining what you are doing, going to do and how long it will take approximately.

IMPORTANT
Each consultation should always ask **the 5 starting** questions so that **all adherence themes** are discussed. These themes are: - intake problems and resistances, - side effects, - views and motivation, - other questions/concerns.

If the patient does not share on their own, you can then use the suggestions for follow-up questions that you can ask the patient during the different stages of the consultation. You will gradually discover which questions suit you. Focus your questions as much as possible on the patient and his/her answers and situation.

Note: *Tick identified problems on the menu.*

Note: *Use the menu for suggestions for follow-up actions in line with the identified problems.*

Beginning of conversation
Purpose: Ensure that healthcare provider and patient know with whom consultation is conducted. Discuss reason for consultation.
"Good day. You are speaking to [*name + position*] from pharmacy [*name*]. Around [*date*] you received [*name of medicine*] from the outpatient pharmacy for the first time. As an additional **pharmacy service** we call clients who have recently started a heart/vascular medicine to hear how they are doing. Am I calling conveniently?"

Gather information			
Starting questions	Target	Note!	Follow-up question suggestions
1. "Before I start, do you already have a question or a concern about your new medicine?"	This is the opening question so the patient can **immediately ask questions/express concerns.**		
2. "Have you started taking your medicine yet? I am curious about your experiences, how have been doing using this medicine recently?"	This question is designed to find out **intake problems** and **resistances.**	If the patient does not clarify on his own or answers very generally with "good", then ask follow-up questions about intake.	"Can you tell a bit more about how you use this medicine?" "What do you find difficult in using this medicine?" "Has there been any change in how you use the medicine? Can you tell a bit more about that?" "To what extent do you manage to take the medicine every day?" "What do you do if you forget this medicine?"
3. "Any medicine may have side effects. What is that like for you? Which side effects do you think you may have experienced?"	This question is intended to find out **possible side effects**.	Make sure you have the main side effects at hand. If the patient hesitates, ask specifically about these possible side effects.	"Would this side effect be a reason for you to stop taking this medicine?" "We know that this medicine can give … as a side effect, have you experienced that?"
4. "How do you feel about having to take this medicine (long-term)?"	This question is designed to assess **views** (need/concern) about the drug and **motivation** for use.	If the patient replies with "I have no choice" or "I just have to", ask further about their views on the medicine and their motivation to take the medicine.	"How important do you think it is to take this medicine every day?" "Do you ever worry about having to take this medicine?" (be careful this does not cause the patient to worry!) "What do you notice about the effect of the drug?" "What do you expect from this medicine?"

			"What would be a reason for you to stop taking this medicine?"
5. "What other questions do you have?"	This is the concluding questions to find out **other questions/concerns.**		"What questions, concerns or uncertainties would you like to discuss further?"

EXPLANATION AND ADVICE
Purpose: To provide explanations and advice in line with the identified problems, check that the explanations have been understood, come to a decision with the patient on how to take the medicine.
Example sentences: - "You indicated that you had a question and/or concern about …"/ "I will now address the questions/concerns you have …" - "I will walk you through the main points in using this medicine." / "I am now going to explain [*the effect*] [*the usage*] [*etc.*] to you." - "What you need to watch out for with this medicine is …" / "If you forget this medicine, then …" - "I would like to know if I have explained it correctly. Can you tell me how you will take the medicine later?" (feedback method)

CONCLUSION OF THE INTERVIEW
Purpose: Confirm policy discussed, discuss steps patient can take if policy does not go according to plan, note consultation in the patient record.
- "We discussed the following: …" "If you have any questions or complaints from your medication later, please come by or call." - "We are also studying the effectiveness of this service. Soon you will be called to briefly answer some questions. You can, of course, always refuse."

Appendix B: Data collection sheet used during NMS for DRPs and follow-up actions

Date of phone call: _____ Patient code: _____

Identified problem & causes	Suggestions for follow-up actions
A. Practical intake problems ❑ Forgetfulness ❑ Intake schedule unclear (how often/when) ❑ Problem with opening packaging/ blister ❑ Problem with preparing medicine (e.g. breaking a tablet) ❑ Problem with taste or shape of the medicine ❑ Technical problem, e.g. with lancing pen, inhaler ❑ NONE	❑ Provide reminder before intake (e.g. medicine alarm clock, alarm on phone) ❑ Link intake moment to place/moment (e.g. next to toothbrush, during dinner) ❑ Recommend medication distribution system to organise different medicines ❑ Provide intake schedule showing when (time of day) and how often the medicine should be used ❑ Recommend tool to eliminate packaging or processing problems ❑ Assess whether someone close to patient can support medicine intake ❑ Provide swallowing advice ❑ Check device for defects, give instructions for use (again)
B. Problems with daily routine ❑ Unable to fit medicine in routine (e.g. irregular work, busy ❑ social life, Ramadan) ❑ Unable to cope with interruptions in daily routine ❑ Medicine not properly stocked at home ❑ NONE	❑ Increase awareness of routine interrupting events ❑ Find recurring moments with patient to which intake moment(s) can be linked ❑ Make intake plan with patient for times that interrupt routine ❑ Assess whether someone close to patient can support medicine use ❑ Explain and recommend repeat prescription process
C. Complexity of medicine (regimen) ❑ Many different medicines ❑ Many intake moments per day ❑ Uncertainty due to changes after hospitalisation ❑ Uncertainty about duration of use (chronic or temporary) ❑ Unclear repeat prescription process ❑ Lack of clarity on dosage forms ❑ Uncertainty about storage conditions ❑ NONE	❑ Provide verbal explanation of dosage forms, changes, duration of use and/or storage conditions ❑ Provide intake schedule showing when (time) and how often the medicine should be used ❑ Advise medication distribution system to organise different medicines ❑ Reduce number of intake moments: merge times ❑ Reduce number of intake moments in consultation with prescriber: adjust dosage

	❑ Reduce number of intake moments in consultation with prescriber: switch medicine ❑ Refer patient to additional sources of information ❑ Explain repeat prescription process
D. Experienced side effects ❑ Which side effects: _____ ❑ NONE	❑ Reassure patient in case of a known side effect and discuss the course of the side effect ❑ Assess the extent to which the perceived side effects pose a problem for the patient (risk of discontinuation) ❑ If patient experiences great discomfort (risk of discontinuation is high), consult with prescriber about alternatives
E. Perceived low necessity of medicine (discontinuation risk) ❑ Low necessity: lack of noticeable effect ❑ Low necessity: not experiencing symptoms of illness (anymore) ❑ Not motivated to follow treatment ❑ Doubts about accuracy of diagnosis ❑ NONE	❑ Verbally explain purpose of medicine (ask about indication if necessary) ❑ Emphasise importance of regular use for optimal effect (e.g. prevention of complications, new infarct) ❑ Emphasise not to discontinue on own accord, only in consultation with prescriber ❑ Refer patient to additional sources of information
F. Concerns about medicine ❑ Concerns about side effects ❑ Concerns about long-term effects of medicine ❑ Concerns about dependence on medicine ❑ Patient is afraid of stopping (e.g. with temporary drug) ❑ NONE	❑ Listen to concerns ❑ Explain the risk of side effects (or recurrence) and reassure the patient ❑ Assess whether (unjustified) concerns have been addressed with your explanation! ❑ Refer patient to additional sources of information
G. Knowledge barriers ❑ Lack of knowledge about medicine/disease/body ❑ Lack of knowledge about change in packaging ❑ Received conflicting information about medicine ❑ Lack of insight in own medicine regimen ❑ Lack of confidence to take medicine as prescribed ❑ NONE	❑ Provide verbal explanation of mechanism of action, side effects and use of medicine ❑ Provide verbal explanation of reason for packaging change and possible consequences ❑ Emphasise (again) importance of regular use of the medicine ❑ Refer patient to additional sources of information ❑ Provide intake schedule showing when (time) and how often the medicine should be used ❑ Assess whether someone close to patient can support medicine use (give self-confidence)
H. Vulnerable patients ❑ Limited health literacy/low literacy	❑ Use short sentences, avoid difficult words, build in pauses in the conversation

❑ Language barrier/cultural differences ❑ Memory problems ❑ Problems with hearing/vision/mobility ❑ NONE	❑ Repeat key information ❑ Check regularly that the patient has understood the information ❑ Ask patient to repeat in own words ❑ Search for 'simple information material' ❑ Assess whether someone close to patient can support in medicine use
I. Not being able to take certain substances ❑ Religious beliefs, e.g. alcohol ❑ Vegetarian/vegan beliefs, e.g. gelatine, food colouring ❑ NONE	❑ Check whether there is an alternative that does not contain substance(s) ❑ Consult with prescriber for alternatives
J. Costs ❑ Own contribution/co-pay problem ❑ Uncertainty about costs ❑ NONE	❑ Explain medicine costs/ co-payment ❑ Assess the extent to which co-payment is a problem (risk of discontinuation) ❑ Check whether there is an alternative where the co-payment is lower or non-existent ❑ Consult with prescriber for alternatives
K. Other problems, causes and follow-up actions _____	

Call duration: ____ minutes

Appendix C: SIMS and MUSE questionnaire

Satisfaction with Information About Medicines Scale (SIMS) (30)

Action and usage

1. What your medicine is called.

2. What your medicine is for.

3. What it does.

4. How it works.

5. How long you will need to be on your medicine.

6. How to use your medicine.

7. How to get a further supply.

Potential problems of medication

8. Whether the medicine has any unwanted effects (side effects).

9. What are the risks of you getting side effects.

10. What you should do if you experience unwanted side effects.

11. Whether you can drink alcohol whilst taking this medicine.

12. Whether the medicine interferes with other medicines.

13. Whether the medication will make you feel drowsy.

14. Whether the medication will affect your sex life.

15. What you should do if you forget to take a dose.

Medication Understanding and Use Self-Efficacy (MUSE) scale. (31)

Taking medication

1. It is easy for me to take my medicine on time.
2. It is easy to remember to take all my medicines.
3. It is easy for me to set a schedule to take my medicines each day

Learning about medication

4. It is easy for me to ask my pharmacist questions about my medicine.
5. It is easy for me to understand my pharmacist's instructions for my medicine.
6. It is easy for me to understand instructions on medicine bottles.
7. It is easy for me to get all the information I need about my medicine.

Appendix D: Extended table of number of DRPs and follow-up actions.

DRP identified n=1043, % (n)		**Follow-up actions performed** n=1711, % (n)	
Practical intake problems	**5.5% (57)**	**Total**	**4.4% (76)**
Unclear regimen	2.4% (25)	Recommend medication distribution system	1.7% (29)
Forgetfulness	1.6% (17)	Provide intake schedule	1.1% (19)
Other (e.g. problems with opening or preparing medicine)	1.4% (15)	Other (e.g. advise medication reminder or tool)	1.6% (28)
Problems with incorporating intake in daily routine	**4.6% (48)**	**Total**	**3.2% (54)**
Unable to keep stock at home	3.7% (39)	Explain or advise repeat prescription service	2.4% (41)
Other (e.g. problems with interruptions in routine)	0.9% (9)	Other (e.g. provide intake schedule)	0.8% (13)
Complexity of medication (regimen)	**25.7% (268)**	**Total**	**16.6% (284)**
Unclear repeat prescription process	12.9% (135)	Explain repeat prescription process	8.1% (138)
Unclear usage period	4.5% (47)	Provide explanation on dosage forms, changes, etc.	3.5% (60)
Multiple different medicines	4.2% (44)	Other (e.g. advise medication distribution system)	5.0% (86)
Other (e.g. complex intake regimen)	4.0% (42)		
Self-reported side effects	**28.7% (299)**	**Total**	**24.4% (418)**
Central or other side effects	11.7% (122)	Reassure patient in case of a known possible side effect	11.7% (200)
Gastro-enteric side effects	5.9% (62)	Assess the risk of discontinuation	9.2% (157)
Cardiovascular side effects	3.0% (31)	Contact prescriber	3.6% (61)
Other (e.g. side effects of the muscles or skin)	8.1% (84)		
Perceived low necessity of the medicine	**9.8% (102)**	**Total**	**25.9% (443)**
Lack of noticeable effect	5.4% (56)	Explain purpose of medicine	9.7% (166)
Other (e.g. doubt about diagnosis)	4.4% (46)	Emphasize importance of regular use of medicine	8.8% (151)
		Other (e.g. emphasize to not discontinue on own accord)	7.4% (126)
Concerns about the medication	**9.1% (95)**	**Total**	**12.0% (206)**
Concerns about side effects	6.6% (69)	Listen to concerns	5.9% (101)
Other (e.g. concerns about long-term use)	2.5% (26)	Explain risk of side effects and reassure	3.9% (66)
		Other (e.g. assess whether concerns have been addressed)	2.3% (39)
Knowledge barriers	**11.3% (118)**	**Total**	**9.1% (156)**
Lack of knowledge about medicine/disease/body	8.1% (84)	Explain mechanism of action, side effects or how to use medicine	5.0% (86)
Contradictory information received from HCP	2.1% (22)	Emphasise (again) importance of regular use of the medicine	1.6% (28)
Other (e.g. lack of insight in medicine regimen)	1.2% (12)	Other (e.g. refer patient to additional information)	2.5% (42)
Vulnerable patients	**5.1% (53)**	**Total**	**4.1% (70)**
Language barrier or cultural differences	2.2% (23)	Assess patients' support system	1.9% (33)
Limited (health) literacy	1.9% (20)	Other (e.g. conversational skills)	2.2% (37)

Other	1.0% (10)		
Costs	**0.3% (3)**	**Total (e.g. explain cost of medicine)**	**0.2% (4)**

Problems and actions are displayed as percentages of the total number of DRPs and follow-up actions, respectively. HCP=Health Care Provider.