Medication-related interventions delivered both in hospital and following discharge: a systematic review and meta-analysis

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ABSTRACT

Background Harm due to medications is common during the transition from hospital to home. Approaches that seek to prevent harm often involve isolated medication-related interventions and show conflicting results. However, until now, no review has focused on the effect of intervention components delivered both in hospital and following discharge from hospital to home.

Objective To examine effects of medication-related interventions on hospital readmissions, medication-related problems (MRPs), medication adherence and mortality.

Methods For this systematic review and meta-analysis, we searched the PubMed, Embase, CINAHL and CENTRAL databases without language restrictions. Citations of included articles were checked through Web of Science and Scopus from inception to 20 June 2019. We included prospective studies that examined effects of medication-related interventions delivered both in hospital and following discharge from hospital to home compared with usual care. Three authors independently extracted data and assessed study quality in pairs.

Results Fourteen original studies were included, comprising 8182 patients. Interventions consisted mainly of patient education and medication reconciliation in the hospital, and patient education following discharge. Nine studies were included in the meta-analysis; compared with usual care (n=3376 patients), medication-related interventions (n=1820 patients) reduced hospital readmissions by 3.8 percentage points within 30 days of discharge (number needed to treat=27, risk ratio (RR) 0.79 (95% CI 0.65 to 0.96)). Meta-regression analysis suggested that readmission rates were reduced by 17% per additional intervention component (RR 0.83 (95% CI 0.75 to 0.91)). Medication adherence and MRPs may be improved. Effects on mortality were unclear.

Conclusions Studied medication-related interventions reduce all-cause hospital readmissions within 30 days. The treatment effect appears to increase with higher intervention intensities. More evidence is needed for recommendations on adherence, mortality and MRPs.

INTRODUCTION

Up to 18% of patients are readmitted within 30 days after discharge from the hospital.[1] Of all hospital readmissions, approximately 20% are caused by medication-related problems (MRPs).[2–5] MRPs occur in at least half of patients either during admission, discharge or in the first month after discharge.[6–9] Another key contributor to early hospital readmission and mortality is treatment failures due to medication non-adherence.[10–12] In the USA, of all medication-related hospital admissions, 33%–69% are caused by medication non-adherence.[13]

Optimising the treatment benefit of medications while minimising their potential for harm is therefore crucial during the transition from hospital to home. Studies hypothesise that effective transitional care (ie, continuity of healthcare during a move from one healthcare setting to another) is most likely to be achieved by combining in-hospital and out-of-hospital interventions, as single component interventions appear not to work.[14–16]

To date, limited evidence is available on medication-related interventions (eg, medication reconciliation) delivered both in hospital and following discharge; systematic reviews either focused on medication-related interventions that were performed in hospital or out of hospital[14 17–21] or on transitional care studies in general, which did not focus explicitly on medications. Furthermore, these systematic reviews report the effects on hospital readmissions or MRPs and evidence on other important outcomes, such as medication adherence and mortality, are missing.

The current review expands on earlier findings and aims to examine the effects

on hospital readmissions, MRPs, medication adherence and mortality of medication-related interventions delivered both in hospital and following discharge from hospital to home.

METHOD

This systematic review and meta-analysis was conducted according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[22] The protocol for this review was registered in the International Prospective Register of Systematic Reviews (ID: CRD42019125411).

Data sources and searches

A search strategy was developed with the assistance of an information specialist. The following databases were searched for relevant studies without language restrictions: PubMed, Embase, CINAHL and Cochrane Central Register of Controlled Trials (CENTRAL). In addition to database searching, cited reference searching was performed through Web of Science and Scopus, both forwards (by checking each of the articles citing the included article) and backwards (by checking all the references in the included article). The databases were searched from inception to 20 June 2019. The search strategy consisted of four search blocks with terms related to patient discharge, medication, the possible interventions and the outcomes.

We used a methodological filter based on the Cochrane Highly Sensitive Search Strategy for identifying randomised trials.[23] We adapted and expanded this filter with terms for controlled clinical trials, prospective studies, before-after studies and studies with a control group. The connector NOT was used to exclude terms related to mental health problems and children. Full search strategies for all databases are available in online supplementary appendix table 1. Endnote was used to manage all the search results and used to remove any duplicate articles.

Study selection

Studies were included if they were prospective studies, examined the effect of medication-related interventions delivered both in hospital and following discharge from hospital to home (from now on this term is shortened to medication-related interventions) compared with usual care. Studies needed to include either all-cause unplanned hospital readmissions, MRPs, medication (non-)adherence (direct and indirect measurement methods) or all-cause mortality as outcome measure(s) and include adults (aged ≥18 years) who had been admitted to the hospital for at least 24 hours.

For the purpose of this study, medication-related interventions were defined as interventions that focused explicitly on medications (eg, medication reconciliation or education on a medication combined with lifestyle advice) and were performed by any healthcare provider in the hospital and within 1 month following hospital discharge. Previous studies have shown that within 1 month following discharge, most harm occurs due to medications and interventions are most effective.[4 24–26] Definitions of medication-related interventions and the outcome measures are presented in online supplementary appendix table 2.

Studies were excluded if they examined only a specific medication group, as they provide limited insight into a patient's complete medication regimen. Due to the ageing population and a rising prevalence of patients with multimorbidity,[27] patients often use more than one medication.[28] Taking a holistic view on patient medications is therefore needed to gain insight into the effects of interventions to prevent potential adverse outcomes.

Furthermore, non-peer reviewed articles (eg, abstracts, posters, presentations and case reports) and literature reviews were excluded due to concerns regarding the quality. These exclusions may increase the risk of publication bias. However, the number of non-peer reviewed sources that can be retrieved may be an unrepresentative sample of all non-peer reviewed sources. Therefore, including data from these sources may also introduce publication bias.[29] Furthermore, studies including patients with psychiatric disorders, patients that were cognitively impaired or patients discharged to another institution (eg, nursing home) were excluded, as we expected that different and more complex interventions are needed for these patient groups. Finally, studies were excluded if the outcomes could not be extracted from the results after consulting the authors (eg, reporting a composite outcome of readmissions or mortality without the event rates of readmissions alone).[30]

Three authors worked in pairs and independently screened all titles and abstracts for eligibility, and subsequently, the full version of studies of the included abstracts against the agreed inclusion and exclusion criteria. Any disagreements were resolved by consensus or via consultation with a fourth expert.

Data extraction and quality assessment

Three authors worked in pairs and independently extracted data and assessed study quality, using the revised Cochrane risk-of-bias tool for randomised trials and the Risk Of Bias In Non-randomized Studies of Interventions tool for non-randomised studies.[31 32] Disagreements were resolved by consensus or via consultation with a fourth expert. The following data were extracted for each study:

- Characteristics of the study (design, setting, country, objective, primary and secondary outcomes and inclusion and exclusion criteria).
- Study methods (usual care, type and timing of medication-related interventions (online supplementary appendix table 2), professionals involved (eg, pharmacist, general practitioner or nurse)),

- Patient characteristics (study population, number of patients allocated to treatment group and analysed and mean age).
- Outcome measures (hospital readmissions, postdischarge MRPs, postdischarge medication adherence and mortality and follow-up periods of measurements (online supplementary appendix table 2).

Data synthesis and analysis

We categorised the medication-related interventions on the basis of the prespecified intervention subcategories: *education* by a healthcare provider to a patient (written information or oral consultation), *pharmacotherapy* (medication reconciliation with a focus on eliminating unintentional discrepancies in medication use or medication review with a focus on optimising the pharmacotherapy based on guidelines) and *information transfer* between healthcare providers (eg, on medication changes initiated during hospitalisation or following discharge (written information or oral consultation)) (online supplementary appendix table 2). Furthermore, for each intervention subcategory, we presented when it was delivered (in the hospital or following discharge).

Meta-analyses was performed using a random-effects model to estimate pooled risk ratios (RRs) and 95% CIs. Where measured outcomes were too different for meta-analysis due to large differences in definitions for the same outcome, assessment methods and follow-up time, only narrative synthesis was used. This was expected for the outcome measures of MRPs and medication adherence based on previous systematic reviews[14 33 34]; however, this also appeared to be the case for mortality, as limited studies have reported on this outcome and all had varying follow-up times, ranging from 1 month to 12 months. Therefore, meta-analyses was performed only for hospital readmissions.

Besides visual inspection of forest plots, statistical heterogeneity across studies was tested using Cochran's Q test and quantified with the I^2 index. We planned to assess for small study effects (ie, publication bias). However, as there were fewer than 10 studies included in the meta-analysis, the potential power of the tests was too low to distinguish chance from real asymmetry. Consequently, the tests were not performed.[29 35]

Furthermore, we planned to examine whether the treatment effect on hospital readmissions differed among several prespecified subgroups of patients and study characteristics. Subgroup analysis was only carried out for the number of different professions involved in the delivery of the intervention (one vs more than one). There were too few studies to carry out the previously planned subgroup analyses for methodological quality of included studies (high risk of bias vs non-high) and the primary hospital admission diagnosis (cardiac vs other).[29] The intensity of medication-related interventions was scored as the total number of interventions and the repetition of delivered intervention components (one intervention=1 point, one intervention delivered two to three times=2 points, one intervention delivered four to five times=3 points and one intervention delivered six or more times=4 points). This method to calculate intensity has been used before.[36] To investigate whether the intensity of the delivered medication-related interventions was associated with the magnitude of the treatment effect on hospital readmissions, we regressed the logarithms of the RRs against the intensity score (meta-regression).

Finally, post hoc sensitivity analyses were performed for the outcome hospital readmissions to examine to which extent the meta-analytic findings changed when restricted only to studies without a high risk of bias or when the intensity of medication-related interventions was expressed as the sum of interventions components only (without repetitions).

The software Review Manager (RevMan) VV.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014) was used to perform the meta-analyses and subgroup analyses, and R, V.3.5.2, Mixed-Effects Model (tau^2 estimator: Sidik-Jonkman) was used to perform the meta-regression analyses.

RESULTS

The search strategy identified 11 741 records; 8773 from the database searching and 2968 from the cited reference searching (figure 1). Following removal of duplicates, 7800 records remained. After screening of title and abstract, 242 records remained for full-text review (exclusion reasons for non-included full-text articles are presented in online supplementary appendix table 3). Fifteen records met the eligibility criteria and were included in the systematic review and nine in the meta-analysis. These 15 records related to 14 studies. Two records[37 38] were from the same study but presented different outcomes.

Study characteristics

All 14 studies had a prospective design (table 1). Nine studies were randomised trials,[30 37 39–44] of which three were performed in a multicentre setting[37 40 42]

Two studies had a before–after design,[45 46] two studies had a controlled clinical design[47 48] and one study had a matched case–control design.[49] Eleven studies reported on hospital readmissions,[30 37 41–44 46–50] three on MRPs,[38 45 50] four on medication adherence[39 40 44 47] and four on mortality.[30 40 44 49]

The 14 studies involved 8182 patients; 4881 studies were assigned to usual care and 3301 to the medication-related interventions. The majority of studies included patients admitted either to the internal medicine, pulmonology, neurology or cardiology ward. The mean study-specific patient age ranged from 48 to 77 years (weighted mean for age by number in study, 59 years) in usual care and from 47 to 75 years in the

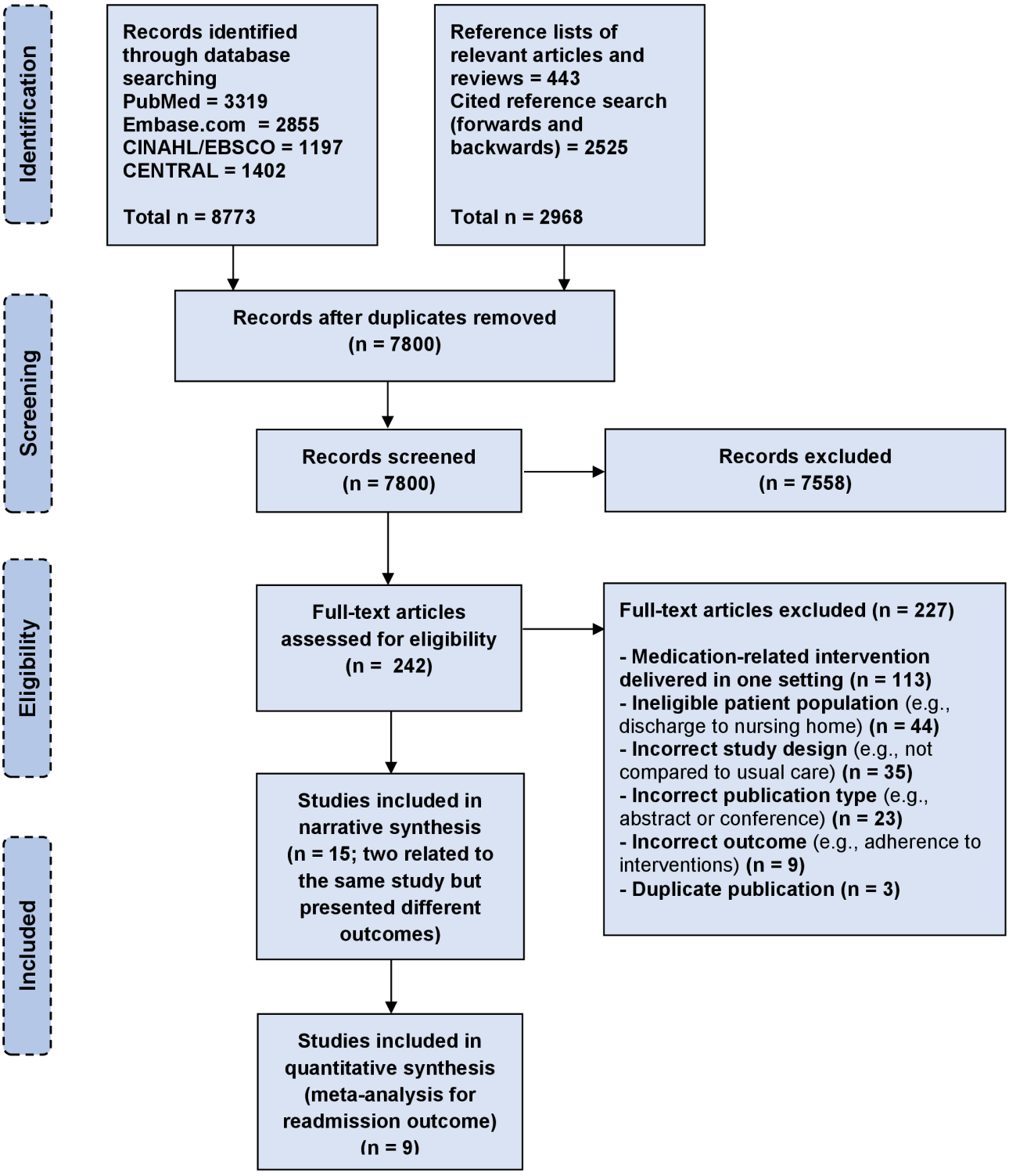

Figure 1 Summary of evidence search and selection. PRISMA flow diagram. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

intervention group (weighted mean for age by number in study, 60 years).

Usual care

Usual care varied among the studies. Two studies did not specify usual care delivered in the hospital[41] or following discharge,[39] and one did not report on usual care at all.[46] In nine studies, discharge instructions, including follow-up appointments and prescriptions, were provided as part of usual care either through written information[43] or oral consultation.[30 37 39 40 45 47–49] Five studies performed medication reconciliation in the hospital,[37 45 48–50] three studies provided patients with medication supplies at

Table 1 Study characteristics

Study, Year	Study design	Study setting	Population	U, n	I, n	U mean age (SD), unless otherwise noted	I mean age (SD), unless otherwise noted	Medication-related intervention in-hospital						Medication-related intervention following discharge						Outcomes postdischarge	Risk of bias
								Education		Pharmacotherapy	Information Transfer			Education		Pharmacotherapy	Information Transfer				
Balaban 2008 (43)	RCT	US, monocenter	DM II, decompensated HF coronary artery disease, COPD, depression	49	47	54.1*	58.0*		W			W		O				W		Readmission 30 days	Moderate
Bell 2016 (37)/ Kripalani(38)*	RCT	US, multicenter	ACS, acute decompensated HF	428	423	59.0 (14.0)	61.0 (14.0)	O	W	MRec				O						Readmission 30 days/MRPs	Low/Low
Calvert 2012 (39)	RCT	US, monocenter	Any non-surgical cardiology service, coronary artery disease	72	71	62.0 (IQR: 52–70)	63.0 (IQR: 54–71)	O	W		O	W		O		MRec	O			Adherence 6 months	Low
Daliri 2019 (45)	Before-after study	The Netherlands, multicenter	Internal medicine, cardiology pulmonology, neurology	234	222	70.8 (11.9)	70.2 (12.8)	O	W		O			O		MRec	O	W		MRPs	Moderate
Goldman 2014 (30)	RCT	US, monocenter	Internal or family medicine, cardiology, neurology	352	347	66.0 (9.0)	66.5 (9.0)	O	W	MRec	O			O				W		Mortality	Low
Ho 2013 (40)	RCT	US, multicenter	ACS	119	122	64.0 (8.6)	63.8 (9.3)	O				W		O		MRec				Adherence 12 months; Mortality	Low
Hoover 2017 (48)	Controlled clinical trial	US, monocenter	HF	36	30	77.5*	75.4*	O	W	MRec				O						Readmission 30 days	High
Jack 2009 (41)	RCT	US, monocenter	Medical/surgical	376	373	49.6 (15.3)	50.1 (15.1)	O	W	MRec		W		O			O			Readmission 30 days	Moderate
Nguyen 2018 (44)	RCT	Vietnam, monocenter	ACS	87	79	59.8 (8.8)	62.0 (8.4)	O	W					O						Readmission 30 days; Adherence 1 and 3 months; Mortality	Moderate
Phatak, 2016 (50)	RCT	US, monocenter	Internal medicine	141	137	55.8*	55.4*	O	W	MRec				O			O			Readmission 30 days; MRPs	Moderate
Sarangarm, 2013 (47)	Controlled clinical trial	US, monocenter	Internal medicine	139	140	50.4 (16.5)	49.0 (15.8)	O		MRec				O						Readmission 30 days; Adherence 30 days	High
Simorangkir 2017 (46)	Before-after study	Indonesia, monocenter	Internal medicine, pulmonology, neurology, cardiology	1212	428	47.8 (17.9)	47.0 (18.2)	O	W	MRec		W		O						Readmission 30 days	Low
Weinberger 1996 (42)	RCT	US, multicenter	DM II, COPD, decompensated HF	701	695	62.6 (10.9)	63.0 (11.1)	O	W	MRec	O			O	W					Readmission 180 days	Moderate

Continued

Table 1 Continued

Study, Year	Study design	Study setting	Population	U, n	I, n	U mean age (SD), unless otherwise noted	I mean age (SD), unless otherwise noted	Medication-related intervention in-hospital				Medication-related intervention following discharge				Outcomes postdischarge	Risk of bias
								Education	Pharmacotherapy	Information Transfer		Education		Pharmacotherapy	Information Transfer		
Wright 2019 (49)	Matched case-control study	US, multicenter	HF, acute myocardial infarction, COPD, pneumonia, DM II	935	187	67.0 (14.0)	69.0 (12.0)		MRec		W	O	W	MRev		Readmission 30 days; Mortality	High
Delivered intervention sub-category by studies, n(%)								13 (93)	9 (64)	9 (64)		14 (100)		4 (29)	6 (43)		

*SD or CI is not reported in study.
ACS, acute coronary syndrome; COPD, chronic obstructive pulmonary disease; DM, diabetes mellitus; HF, heart failure; I, intervention; MRec, medication reconciliation; MRev, medication review; MRPs, medication-related problems; O, oral consultation; RCT, randomised controlled trial; U, usual care; W, written information.

discharge,[30 47 48] three studies communicated discharge instructions to primary care providers and two studies handed patients a discharge medication list.[40 45] Four studies provided routine follow-up appointments after 1–12 months in the hospital,[40 42 44 48] and two an occasional telephone call following discharge.[37 49]

Medication-related interventions

The 14 studies delivered similar types of medication-related interventions (table 1; online supplementary appendix table 4); however, they varied in the timing and intensity of delivered intervention components (online supplementary appendix table 5). Medication-related interventions in the hospital were delivered at admission in three studies,[37 48 50] before hospital discharge in eight studies[30 42 44–49] and/or at hospital discharge in nine studies.[37 39–41 43 46 47 49 50] Medication-related interventions following discharge predominantly took place through telephone calls, followed by additional visits to the primary care clinic or community pharmacy[40 42 49] or patients' homes.[45 48] In all studies, the medication-related interventions were initiated within the first week after hospital discharge. Except one,[49] all studies provided education interventions both in hospital and following discharge. Oral communication techniques, such as teach-back and motivational interviewing, were used to instruct patients on medications (eg, reasons for medication changes). In addition, 11 studies additionally provided written information to patients to improve medication use following discharge, such as daily medication schedules.[30 37 39 41–46 48 50] Nearly all studies provided pharmacotherapy interventions to address unintended discrepancies between a patient's actual medication use and what was prescribed and to optimise medication use (table 1). One study performed a medication review.[49] Finally, 10 studies also incorporated information transfer interventions[30 39–43 45 46 49 50] to inform healthcare providers (community pharmacists, general practitioners or community care nurses) on, for example, medication use.

Ten studies used interprofessional collaborations, either between pharmacists and nurses,[41 48] nurses and physicians,[30 42 43] pharmacists and physicians,[37 40 45 50] or pharmacists, nurses and physicians.[39] The remaining four studies were either pharmacy[44 47 49] or nurse initiated.[46]

Risk of bias

We deemed six studies to be at low, six at moderate and three at high risk of bias (online supplementary appendix table 6). Studies with a high risk of bias were non-randomised and were so categorised due to one or more of the following reasons: unblinded outcome assessors, potential baseline incomparability and possible deviations from the intended interventions due to lack of blinding of patients or professionals delivering the interventions.

Effects of medication-related interventions

Hospital readmissions

In total, 10 studies reported on hospital readmissions, one study within 180 days of discharge[42] and nine studies within 30 days of discharge.[37 41 43 44 46–50]

A reduction in hospital readmissions was seen in the intervention group compared with usual care in three studies: (RR 0.30 (95% CI 0.11 to 0.80))[48] ; RR 0.72 (95% CI 0.52 to 0.99))[41];RR 0.58 (95% CI 0.35 to 0.95)).[49] These studies provided medication-related interventions with a minimum intensity score of six points (online supplementary appendix table 5). All three studies delivered a pharmacotherapy intervention in the hospital and education following discharge. One study additionally delivered a pharmacotherapy intervention,[49] and one study an intervention to enhance information transfer.[41] In three studies, the proportion of readmitted patients was lower in the intervention group compared with usual care; however, it is not statistically significant.[37 46 50] These studies had intervention intensity scores of 4–6 points. All studies provided a pharmacotherapy intervention in the hospital and education interventions following discharge. One study additionally delivered an information transfer intervention.[50] In four studies, the proportion of readmitted patients was higher in the intervention group compared with usual care; however, it is not statistically significant.[42–44 47] These studies had an intensity score of 3–6 points. Two studies provided a pharmacotherapy intervention in the hospital.[42 47] Following discharge, all four studies delivered a single education session. One study additionally delivered an information transfer intervention.[42]

All nine studies reporting on hospital readmissions within 30 days of discharge were included in the meta-analysis. The meta-analysis results showed that medication-related interventions (n=1820 patients) reduced the proportion of patients readmitted to the hospital within 30 days from 17.1% to 13.3% (number needed to treat=27; RR 0.79 (95% CI 0.65 to 0.96, I^2=23%)) as compared with usual care (n=3376 patients) (figure 2).

Medication-related problems

Three studies reported on MRPs within 30 days of discharge.[38 45 50] All three studies used a different definition of MRPs: overall MRPs,[45] adverse drug events[38] or a combination of adverse drug events and medication errors[50] (online supplementary appendix table 2).

One study delivered all three subcategories of medication-related interventions (education, pharmacotherapy and information transfer) in the hospital and following discharge and showed a reduction in MRPs (OR 0.57 (95% CI 0.38 to 0.86)) as compared with usual care.[45] Another study delivered education and pharmacotherapy interventions in the hospital, followed by multiple education interventions and an information transfer intervention following discharge (OR 0.57 (95% CI 0.25 to 1.29)).[50] No clear difference was seen in the other study between the intervention group and usual care (OR 0.97 (95% CI 0.74 to 1.27)).[38] This study delivered education and pharmacotherapy interventions in the hospital and a single education session following discharge.

Medication adherence

Medication adherence was assessed in four studies.[39 40 44 47] In three studies, adherence to cardioprotective medications (eg, statins) was measured,[39 40 44] and in one study, all regularly scheduled medications (eg, cardiovascular agents) were measured.[47] All four studies used indirect measurement methods to assess the proportions of patients that were adherent to their medications. Three studies used prescription refill records to measure adherence[39 40 47] of which one also measured adherence using a self-reported adherence questionnaire (four-item Morisky Medication Adherence Scale).[39] One study measured adherence using

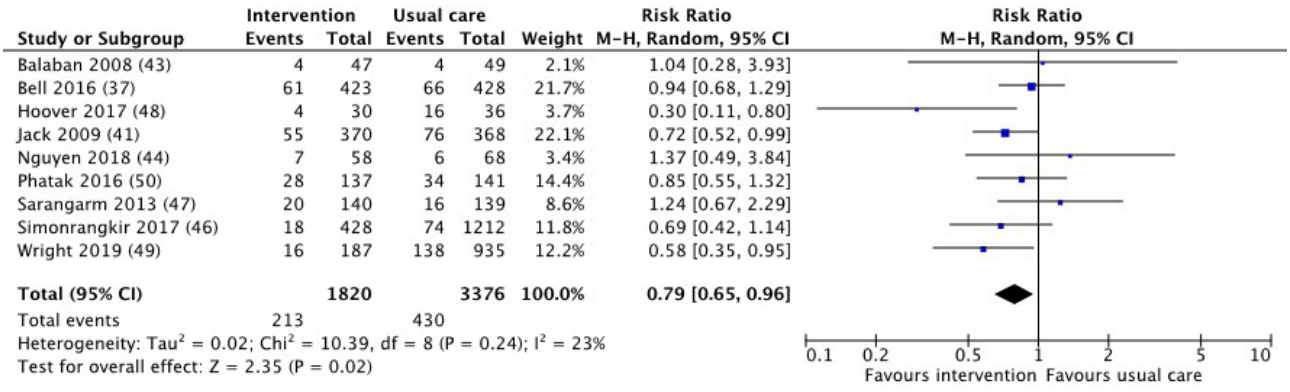

Figure 2 Effect of medication-related interventions delivered both in hospital and following discharge, as compared with usual care, on hospital readmissions within 30 days of hospital discharge. Forest plot of medication-related interventions delivered both in hospital and following discharge on hospital readmissions within 30 days of hospital discharge.[37 41 43 44 46–50] The squares represent the individual study weights, and horizontal lines represent 95% CIs. The diamond represents the overall pooled risk ratio, provided by the Mantel-Haenszel (M–H) random-effects method and 95% CI.

a combination measure of the eight-item Morisky Medication Adherence Scale and whether follow-up prescriptions were obtained on time.[44]

Medication adherence was measured at 1,[44 47] 3,[44 39]6 and 12 months[40] (**table 1**). The intensity of medication-related interventions varied (online supplementary appendix table 4); two studies had an intensity score of three points[44 47] and delivered education interventions in the hospital and following discharge. In addition, one also delivered a pharmacotherapy intervention in the hospital.[47]The other two studies had [40]7 and 10 points[39] and delivered the three subcategories of medication-related interventions either in the hospital or following discharge.[39 40]

Two studies showed improved medication adherence in the intervention group as compared with usual care, at 1 (RR 1.18 (95% CI 1.01 to 1.38)), 3 (RR 1.17 (95% CI 0.99 to 1.38))[44] and 12 months (RR 1.21 (95% CI 1.07 to 1.37)).[40] The effect on adherence was uncertain in the two other studies, both at 3 (RR 1.30 (95% CI 0.91 to 1.85))[47] and 6 months using the prescription refill records (RR 1.39 (95% CI 0.92 to 2.09)) or the self-reported questionnaire (RR 0.96 (95% CI 0.87 to 1.07)).[39]

Mortality

All-cause mortality was studied in four studies,[30 40 44 49] within 1,[49] 3,[44 30]6 and 12 months[40] of discharge. The intensity score ranged from 3[44] to 7 points.[30 40 49] All studies delivered education interventions, and three studies additionally delivered a pharmacotherapy intervention[30 40 49] of which one combined medication reconciliation in the hospital with a medication review following discharge.[49] This study showed a reduction in mortality; however, it is not statistically significant (RR 0.43 (95% CI 0.16 to 1.19)). No clear difference was seen for mortality rates in the other studies (RR 1.56 (95% CI 0.86 to 2.82)[30]; RR 0.39 (95% CI 0.02 to 9.39)[44]; RR 1.19 (95% CI 0.51 to 2.77)[40]).

Additional analyses on hospital readmissions within 30-day postdischarge

The subgroup analysis did not show a different effect on hospital readmissions within 30 days of discharge for the number of professions involved (one vs more than one) in delivering medication-related interventions. Nine studies (n=5196 patients) were included in the meta-regression analysis. The results showed a stronger treatment effect on hospital readmissions within 30 days when a higher intensity of medication-related interventions was delivered (RR 0.83 (95% CI 0.75 to 0.91, I^2=0%)) (figure 3).[51]

A sensitivity analysis showed that without counting the repetition of provided intervention components, both the point estimate for the relative effect and the

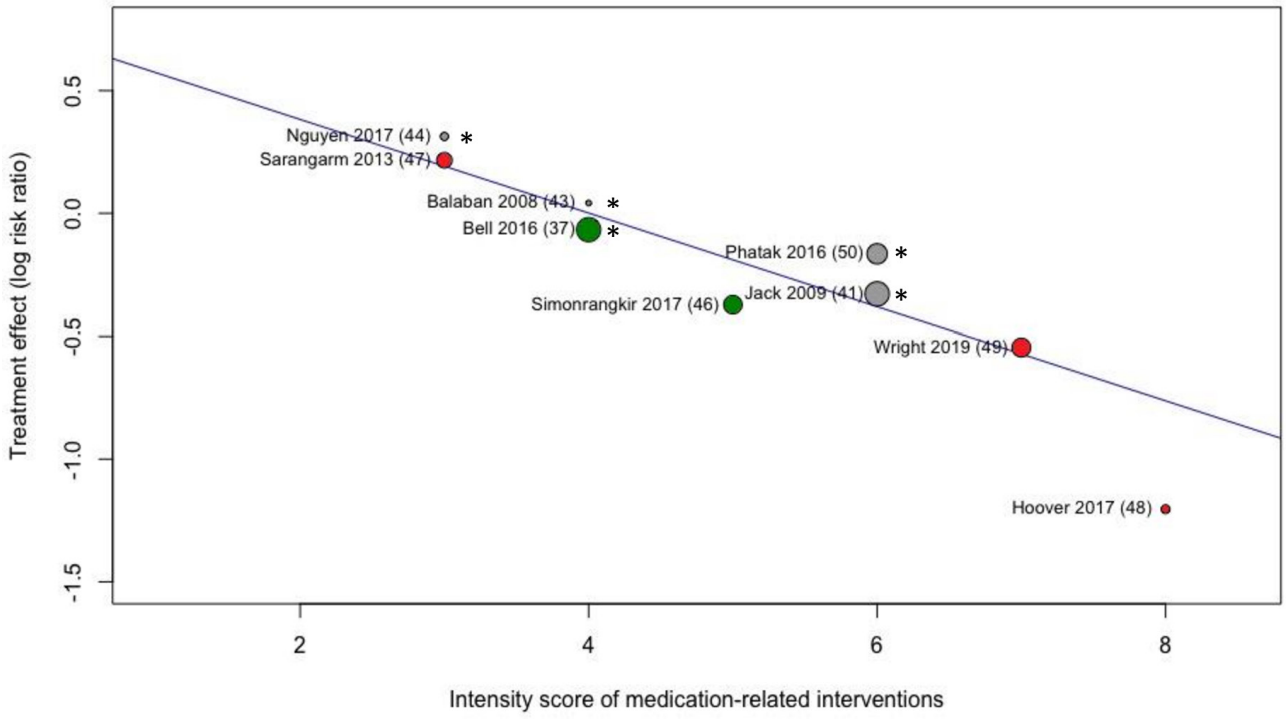

Figure 3 Meta-regression plot of the (log) risk ratio reduction in hospital readmissions within 30 days of hospital discharge regressed against the intensity score of the intervention between treatment arms. Meta-regression bubble plot R (mixed-effects model, k=9): tau^2: 0.0209 (SE=0.0461), intercept (log Rr estimate): 0.7640 (SE=0.2140), intensity covariate (log Rr estimate): −0.1908 (SE=0.0395). Circles represent the estimates from each study.[37 41 43 44 46–50] The area of each circle is inversely proportional to the variance of the estimated treatment effect weights (precision of each estimate)[51]; green circles represent studies with a low risk of bias (n=2); grey circles represent studies with a moderate risk of bias (n=4); red circles represent studies with a high risk of bias (n=3); circles with an asterisk represent the randomised controlled trials (n=5).

SE of that effect estimate increase (RR 0.78 (95% CI 0.65 to 0.93, I^2=33%)).

Finally, the meta-analytic findings did not change when restricted only to studies without a high risk of bias (RR 0.82 (95% CI 0.69 to 0.99, I^2=0%)).

DISCUSSION

This systematic review shows evidence that the studied medication-related interventions delivered both in hospital and following discharge reduce hospital readmission rates within 30 days of discharge compared with usual care. The results persisted across several sensitivity analyses. Medication adherence and MRPs may be improved. We found no consistent evidence on mortality.

The current review expands on earlier findings in several ways. Previous systematic reviews show conflicting results of medication-related interventions on hospital readmissions within 30 days of discharge.[20 52 53] The reviews that did not find an effect studied isolated interventions, either in the hospital or following discharge. As previously stated by Hansen *et al*[16] and showed by Ravn-Nielsen *et al*,[15] isolated interventions are less successful as compared with interventions that are initiated in the hospital and continued following discharge. Nevertheless, it is possible that the key to success is not the combination of medication-related interventions (in hospital and following discharge) but rather the content that is provided. Our meta-regression results suggest that the magnitude of the treatment effect increases with the intensity of delivered medication-related interventions. In fact, our findings suggest that readmission rates are reduced by 9%–25% with every component added to the intervention bundle. Another study, although not focusing exclusively on medication-related interventions, found similar results on hospital readmissions rates within 30 days of discharge.[36] Nevertheless, our results should be interpreted with caution, as fewer than 10 studies were included in the meta-regression. Moreover, the intensity gives limited insight into synergies between components, the quality or content of delivered components.

Previous systematic reviews[18 19 54] showed evidence that medication-related interventions delivered in one setting only, for example, following hospital discharge, reduce MRPs.[55–57] In the current systematic review, studies were included that delivered medication-related interventions both in hospital and following discharge. Only three studies were eligible for inclusion. Two of the three studies showed a reduction in MRPs.[45 50] The study that did not show an effect[38] delivered a single intervention component following discharge only; a research coordinator screened for MRPs during a telephone call and involved pharmacists as needed. We can be fairly confident that MRPs are reduced by medication-related interventions delivered in both settings (estimated pooled OR 0.80 (95% CI 0.65 to 0.99)). Nevertheless, given the limited number of included studies, and the substantial methodological diversity among the studies due to the different ways that MRPs are measured or defined,[14 33 34] it is difficult to draw firm conclusions. As expected, this also appeared to be the case for adherence[58]; substantial methodological diversity was observed among the included studies due to different included medications, measurement methods, follow-up periods and calculations.

Our study has several strengths. To our knowledge, this is the first study to systematically review the effects of medication-related interventions delivered both in hospital and following discharge on a variety of important outcomes. Furthermore, we performed a meta-analysis on the 30-day readmission outcome and performed subgroup and sensitivity analyses.

These strengths should be weighed against the review's limitations. One-third of the studies included in the meta-analyses were classified as high risk of bias (mostly due to a lack of blinding of patients or professionals) and may have caused conscious or unconscious bias in the design or execution of the intervention. These studies may be responsible for the statistical heterogeneity in the meta-analysis for hospital readmissions. As stated by Cornell *et al*,[59] pooling studies in the face of heterogeneity can cause uncertainty of evidence. Therefore, we performed sensitivity analyses and excluded studies with a high risk of bias, which resulted in the disappearance of statistical heterogeneity. To control for qualitative heterogeneity (study characteristics), we stratified for interventions using predefined subcategories (education, pharmacotherapy and information transfer). Nonetheless, still other sources of heterogeneity may be present, for example, differences in intervention content or studied patient populations. Second, although we had intended to include mortality in our meta-analysis, this was not possible because of the limited number of studies that reported on mortality. All four studies on mortality had different follow-up periods, and we had no individual patient data. Third, the components of usual care were not always (adequately) specified and where they were specified, differed among studies. The heterogeneity of usual care may therefore hamper generalisability of these study results. However, our aim was to estimate the effect of the medication-related interventions that were not provided by any of the usual care practices in the included studies.

Finally, as we did not want to miss any relevant studies in this review and there is still no specific search strategy to identify medication-related interventions, the search identified many records that were ineligible. Despite the thorough search strategy, we may still have missed relevant studies. Authors and coordinating centres of bibliographies should incorporate a term that describes (medication-related) interventions delivered both in hospital and following discharge, as they

show a lot of potential, and more research is needed on these interventions.

CONCLUSIONS

The evidence presented in this systematic review and meta-analysis is compatible with the idea that the studied medication-related interventions, delivered both in hospital and following discharge from hospital to home, reduce all-cause hospital readmissions within 30 days of hospital discharge. Specifically, high-intensity interventions that incorporate pharmacotherapy interventions should receive the greatest consideration by systems or providers seeking to reduce harm due to medications for patients during the transition from hospital to home. However, more evidence through the performance of well-controlled, prospective and adequately powered studies is needed for recommendations on adherence, mortality and MRPs.

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