PHARMACOEPIDEMIOLOGY AND DRUG SAFETY 2013; **22**: 1054–1060
Published online 30 August 2013 in Wiley Online Library (wileyonlinelibrary.com) **DOI**: 10.1002/pds.3510

ORIGINAL REPORT

Drug–drug interactions in a cohort of hospitalized elderly patients†

Luca Pasina[1]*, Codjo D. Djade[1], Alessandro Nobili[1], Mauro Tettamanti[1], Carlotta Franchi[1], Francesco Salerno[2], Salvatore Corrao[3], Alessandra Marengoni[4], Alfonso Iorio[5], Maura Marcucci[5] and Pier Mannuccio Mannucci[6]

[1] *Laboratory for Quality Assessment of Geriatric Therapies and Services, Drug Information Service for the Elderly, Istituto di Ricerche Farmacologiche Mario Negri (IRCCS), Milan, Italy*
[2] *Internal Medicine I, Policlinico IRCCS San Donato, University of Milan, Milan, Italy*
[3] *Dipartimento Biomedico di Medicina Interna e Specialistica, University of Palermo, Palermo, Italy*
[4] *Geriatric Unit, Spedali Civili, Department of Medical and Surgery Sciences, University of Brescia, Brescia, Italy*
[5] *Department of Internal Medicine, University of Perugia, Perugia, Italy*
[6] *Scientific Direction, IRCCS Maggiore Hospital Foundation, Milan, Italy*

ABSTRACT

Purpose The aim of this study is to assess the prevalence of patients exposed to potentially severe drug–drug interactions (DDIs) at hospital admission and discharge and the related risk of in-hospital mortality and adverse clinical events, readmission, and all-cause mortality at 3 months.

Methods This cross-sectional, prospective study was held in 70 Italian internal medicine and geriatric wards. Potentially severe DDIs at hospital admission and discharge; risk of in-hospital mortality and of adverse clinical events, readmission, and all-cause mortality at 3-month follow-up.

Results Among 2712 patients aged 65 years or older recruited at hospital admission, 1642 (60.5%) were exposed to at least one potential DDI and 512 (18.9%) to at least one potentially severe DDI. Among 2314 patients discharged, 1598 (69.1%) were exposed to at least one potential DDI and 1561 (24.2%) to at least one potentially severe DDI. Multivariate analysis found a significant association with an increased risk of mortality at 3 months in patients exposed to at least two potentially severe DDIs (Odds ratio 2.62; 95% confidence interval, 1.00–6.68; $p = 0.05$). Adverse clinical events were potentially related to severe DDIs in two patients who died in the hospital, in five readmitted, and one who died at 3 months after discharge.

Conclusions Hospitalization was associated with an increase in potentially severe DDIs. A significant association was found for mortality at 3 months after discharge in patients with at least two potentially severe DDIs. Careful monitoring for potentially severe DDIs, especially those created at discharge or recently generated, is important to minimize the risk of harm. Copyright © 2013 John Wiley & Sons, Ltd.

KEY WORDS—drug interactions; hospitalization; mortality; aged; pharmacoepidemiology

Received 11 April 2013; Revised 26 July 2013; Accepted 30 July 2013

INTRODUCTION

Polypharmacy is very common among older adults and is often associated with inappropriate prescribing, poor adherence to therapies, adverse drug events, and higher than usual prevalence of potential drug–drug interactions (DDIs).[1–11] Aging is also an independent risk factor for an increase in potential DDIs,[12] which may even have life-threatening consequences in older adults,[13] because of age-related physiological changes affecting the pharmacokinetics and pharmacodynamics of various medications.[14] The main age-related changes affecting drug excretion is the decrease in renal and hepatic drug clearance.[15–17]

The prevalence of potential DDIs and the related risk of adverse clinical outcomes in the elderly hospital patients are not well defined. Estimates vary considerably in published reports, reflecting variability in patient populations and settings, DDIs considered, and databases and information sources used.[18–21] Studies of the prevalence rates of potential DDI may

*Correspondence to: L. Pasina, Laboratory for Quality Assessment of Geriatric Therapies and Services, Drug Information Service for the Elderly, Istituto di Ricerche Farmacologiche Mario Negri (IRCCS), Via Giuseppe La Masa, 19, 20156 Milan, Italy. E-mail: luca.pasina@marionegri.it

†On behalf of Registry of Polytherapies SIMI (Società Italiana di Medicina Interna).

have overestimated their clinical significance because exposure to a DDI does not always result in adverse reactions.[17] Studies of DDIs that led to adverse outcomes may provide more accurate estimates of the risks. According to a large prospective observational study, 1% of all hospital admissions are due to DDIs,[22] but the risk of adverse outcomes could be particularly serious in the elderly. A review of the literature found that in the elderly, DDIs were responsible for 4.8% of the admissions.[23] The higher prevalence of DDIs in elderly patients is also supported by another recent review, which showed that prevalence of DDIs was between 15% and 45% in hospital and that it was higher in patients with heart diseases and elderly people.[24] We examined Registry of Polytherapies SIMI (Società Italiana di Medicina Interna) (REPOSI), a network of internal medicine and geriatric wards created to investigate the prevalence and correlates of polymorbidity and polypharmacy in elderly hospital patients, to assess the prevalence of those exposed to potentially severe DDIs and possible associations with in-hospital mortality and the related risk of adverse clinical events, readmission, and all-cause mortality at 3 months after hospital discharge. We also checked whether adverse clinical events were associated with the potential DDI.

METHODS

Data collection

The Registry of Polytherapies SIMI (REPOSI) is a collaborative, independent, voluntary initiative of SIMI and the Istituto di Ricerche Farmacologiche Mario Negri. The registry was set up in 2008 from a network of internal medicine and geriatric wards to collect information on an Italian cohort of elderly hospital patients with multimorbidities often receiving polytherapy. The first wave of data collection was between January and December 2008 and the second between January and December 2010. Participation was voluntary, and all patients gave signed informed consent. Data collection complied fully with Italian laws on personal data protection and required no ethical committee approval under the applicable legal principles on patient registries. The attending physicians completed a standardized web-based case report form including diagnosis at hospital admission, sociodemographic details, and drug treatment at hospital admission, during hospital stay, and at discharge.

In the second wave of REPOSI, it was decided to collect additional information and follow-up to improve the quality of data: main laboratory parameters, comorbidity according to the Cumulative Illness Rating Scale (CIRS),[25] basic activities of daily living according to the Barthel Index,[26] cognitive impairment according to the Short Blessed Test,[27] depression according to the Geriatric Depression Scale,[28] and clinical events during hospital stay and outcomes. Patients were also followed for 3 months after discharge with a telephone interview that collected information on new diagnoses, new hospital admission, drug regimens, adverse events, and Barthel Index.

To establish the prevalence of potential DDIs, we considered all patients recruited in both waves of REPOSI. To evaluate the related risk of adverse clinical events, readmission, and all-cause mortality, we considered only patients recruited in the second wave with a complete 3-month follow-up. Of the1380 in-patients recruited in the second wave, follow-up data were not available for 536 (38%) because of death before discharge, transfer to another ward, refusal of the 3-month telephone follow-up, or logistic reasons.

We anticipated, on the basis of the literature, that approximately 20% of the discharged patients would have at least one potentially severe DDI. Because follow-up data were available on about 800 patients, we calculated that we had an approximately 80% power to declare significant, with criterion of significance set at 0.05, an (univariate) odds ratio (OR) with a magnitude of at least 2.5 relative to the association between DDIs and death.

Potential drug–drug interactions

Potential DDIs were analyzed by a computerized system, using the Italian interaction database developed by the Istituto di Ricerche Farmacologiche Mario Negri, previously validated and described in details.[29] Each potential DDI was classified by clinical impact as severe (drug combination should usually be avoided as it may lead to serious clinical consequences, such as severe adverse effects or lack of clinical effects; close monitoring is required), moderate (drugs can be combined; the precipitant drug may modify the effect of the object drug, but the effect can be controlled by individual dose adjustment and/ or on the basis of drug plasma concentration), and minor (drug combination probably has no clinical impact or has not been completely assessed).

Outcomes

To assess the risk of in-hospital mortality, we considered all patients exposed to at least one potentially severe DDI at admission. To evaluate the risk of adverse clinical events from discharge to follow-up date, readmission, and all-cause mortality at follow-up

DOI: 10.1002/pds

associated with potentially severe DDIs, we considered only patients with complete follow-up data eligible for the analyses. Information on readmission and survival of the patients was obtained after 3 months. To check whether adverse clinical events were associated with potentially severe DDIs, we investigated, for each patient, the cause of death, readmission, or adverse clinical event.

Statistical analysis

Analysis of variance was used for the relationship between potentially severe DDIs and length of hospital stay and logistic regression between potentially severe DDIs and incidence of adverse clinical events, readmission, and mortality. Multivariate analyses were adjusted for age, sex, and CIRS comorbidity index as possible confounders for adverse clinical outcomes. Analyses were carried out with JMP PRO 10 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Prevalence of patients with potential drug–drug interactions

The study sample included 2712 patients recruited in 70 internal medicine and geriatric wards (Table 1). In all, 1642 patients (60.5%) were exposed at hospital admission to at least one potential DDI. Among patients admitted, 989 (36.5%) were exposed to at least one potentially moderate DDI and 512 (18.9%) to at least one potentially severe DDI. Of the 4938 potential DDIs, 675 (13.7%) were severe and 3207 (64.9%) were moderate. The median number of potential DDIs per patient with DDIs was two (range 1–16). Among 2314 patients discharged from the hospital, 1598 (69.1%) were exposed to at least one potential DDI, 927 (40.1%) to at least one potentially moderate DDI, and 561 (24.2%) to at least one potentially severe DDI. Of the 5244 potential DDIs, 802 (15.3%) were severe and 3353 (63.9%) were moderate. In all, 2505 potential DDIs were created at hospital discharge, and 464 of them were severe. At discharge, the median number of potential DDIs per patients with DDIs was two (range 1–18). The number of potential DDIs rose from hospital admission to discharge, as did the prevalence of patients exposed to potentially severe DDIs ($p < 0.0001$). The most frequent potentially severe DDIs at admission and discharge are listed in Table 2. Multivariate analysis (adjusted for age, sex, and CIRS comorbidity index) found no significant differences in length of stay between patients exposed to potentially severe DDIs at admission (mean days 10.8; 95% confidence interval (CI), 9.3–12.1) and those with no potential DDIs (11.5; 95% CI, 10.2–11.9; $p = 0.53$).

Table 1. Main sociodemographic characteristics of patients recruited in Registry of Polytherapies SIMI

	At admission	At discharge
Number of patients	2712	2314
Age (mean ± SD)	79.1 (7.4)	79.0 (7.5)
Female (%)	1419 (52.3)	1221 (52.8)
Number of drugs (mean ± SD)	5.1 (2.8)	6.1 (2.9)
Number of diagnoses (mean ± SD)	5.0 (2.7)	6.2 (2.7)

SD = standard deviation.

Potentially severe drug–drug interactions and in-hospital mortality

Of the 64 patients who died during hospitalization, 25 were exposed to at least one potentially severe DDI. Univariate and multivariate analyses (adjusted for age and sex) found no association between exposure to potentially severe DDIs and in-hospital mortality (OR 1.25; 95% CI, 0.74–2.09; $p = 0.40$). The cause of mortality for two patients was potentially related to a severe DDI: one treated with alfuzosin, clarithromycin, and fluconazole and one with flecainide and clarithromycin died of cardiac arrest.

Potentially severe drug–drug interactions and adverse clinical outcome at 3 months

Follow-up data were available for 844 participants (61.2%) (Table 3). Their sociodemographic characteristics were very similar to patients with no follow-up data ($n = 536$; mean age 79.3 years; female 49.4%; CIRS severity index (mean ± standard deviation (SD)) 1.7 ± 0.3; CIRS comorbidity index (mean ± SD) 3.0 ± 1.8). Among 844 patients with follow-up, 622 (73.7%) were discharged with at least one potential DDI and 223 with at least one potentially severe DDI. The median number of potential DDIs per patient was three (range 1–18), and one for those with potentially severe DDIs (range 1–7). Overall, 2158 potential DDIs were detected, and 321 of them (14.9%) were potentially severe. Of the patients with at least one potentially severe DDI, 27 (12.1%) reported an adverse clinical event at follow-up, 45 (20.2%) were readmitted, and 16 (1.9%) died within 3 months of discharge. Exposure to potentially severe DDIs was associated with no increase in the risk of adverse clinical events, readmission, and all-cause mortality at 3 months after hospital discharge in both univariate and multivariate analysis, after adjusting for potential confounders (Table 4). To check whether potentially severe DDIs were associated with adverse clinical

DOI: 10.1002/pds

Table 2. Prevalence of the first 10 potentially severe drug–drug interactions (DDIs) at hospital admission and discharge among patients with at least one potentially severe DDI

Drug combination	Potential adverse events	Patients (*n* (%))	
		At admission (512)	At discharge (561)
Digoxin + furosemide	Increased risk of digoxin toxicity	149 (29.1)	147 (26.2)
Potassium-sparing diuretics + ACEi	Increased risk of hyperkalemia	78 (15.2)	74 (13.2)
Aspirin (low dose) + clopidogrel or ticlopidine	Increased risk of bleeding	51 (10.0)	43 (7.7)
Statin* + calcium antagonist†	Increased risk of myopathy including rhabdomyolysis	44 (8.6)	40 (7.1)
Amiodarone + beta-blocker	Hypotension, bradycardia, or cardiac arrest	35 (6.8)	33 (5.9)
Digoxin + spironolactone	Increased risk of digoxin toxicity	27 (5.3)	34 (6.1)
Clopidogrel + proton pump inhibitor‡	Reduction in clinical efficacy of clopidogrel and increased risk for thrombosis	27 (5.3)	40 (7.1)
Allopurinol + enalapril	Hypersensitivity reactions (Stevens–Johnson syndrome and skin eruptions)	23 (4.5)	26 (4.6)
Simvastatin + amiodarone	Increased risk of myopathy including rhabdomyolysis	12 (2.3)	9 (1.6)
Digoxin + hydrochlorothiazide	Increased risk of digoxin toxicity	11 (2.1)	6 (1.1)
Potassium + potassium-sparing diuretics	Increased risk hyperkalemia	6 (1.2)	16 (2.9)

ACEi = angiotensin-converting enzymes inhibitors.
*Statin: simvastatin and atorvastatin.
†Calcium antagonist: amlodipine, verapamil, or diltiazem.
‡Excluding pantoprazole.

Table 3. Main sociodemographic characteristics of patients with 3-month follow-up data

	Patients with follow-up (844)
Age (mean ± SD)	78.8 (7.4)
Female (%)	432 (51.2)
Number of drugs (mean ± SD)	6.3 (2.8)
Adverse clinical events (%)	82 (9.7)
Readmission (%)	145 (17.2)
Died (%)	66 (7.8)
Cumulative Illness Rating Scale	
Diagnosis (mean ± SD)	6.7 (3.0)
Severity index (mean ± SD)	1.7 (0.3)
Comorbidity index (mean ± SD)	3.0 (1.8)
Number of patients with at least one potential DDI at hospital discharge	
Overall	622 (73.7)
Patients with new DDI at discharge	423 (50.1)
Severe	223 (26.4)
Patients with new DDI at discharge	133 (15.8)

SD = standard deviation; DDI = drug–drug interaction.

Table 4. Association between potentially severe drug–drug interactions and adverse clinical outcomes at 3-month follow-up

	Univariate analysis	
	OR (95% CI)	*p*-value
Adverse clinical events	1.25 (0.69–2.27)	0.46
Readmission	1.56 (0.94–2.57)	0.08
All-cause mortality	1.35 (0.62–2.93)	0.44
Multivariate analysis*		
Adverse clinical events	1.31 (0.68–2.54)	0.41
Readmission	1.37 (0.79–2.38)	0.26
All-cause mortality	1.14 (0.48–2.72)	0.76

*Adjusted for age, sex, and Cumulative Illness Rating Scale comorbidity index.

events in patients with higher comorbidity, we considered different cut offs for the CIRS comorbidity index, obtaining similar results. However, a significant association with an increased risk of mortality was observed for patients exposed to at least two potentially severe DDIs ($n = 62$) in univariate (OR 2.97; 95% CI, 1.16–7.39; $p = 0.02$) and multivariate analyses (OR 2.62; 95% CI, 1.00–6.68; $p = 0.05$).

For five patients, the cause of readmission was classified as related to their potentially severe DDI at discharge: two patients given clopidogrel and proton pump inhibitors at discharge were readmitted for transient ischemic attacks; one with the combination of aspirin and methotrexate was readmitted for anemia; one with digoxin and furosemide, sertraline and trazodone, and ramipril and canrenoate was readmitted for arrhythmias; and one patient receiving simvastatin and amlodipine was readmitted for a muscular adverse reaction. Finally, in one patient, the cause of death might have been related to a severe DDI: one receiving amiodarone and bisoprolol died for cardiac arrest. Four cases had potentially severe DDIs created at hospital discharge (Table 5).

DISCUSSION

In the present study, hospital discharge was associated with a small increase in overall and potentially severe DDIs, raising concerns of avoidable harm to elderly patients. Despite different methods used to classify DDIs, which makes it difficult to compare reports,

DOI: 10.1002/pds

Table 5. Adverse events reported at follow-up and potentially severe drug–drug interactions after hospital discharge

Drug combination	Adverse events reported at follow-up	Time from discharge
Digoxin + furosemide	Readmission for cardiac arrhythmias	2 months
Ramipril + spironolactone		
Simvastatin + amlodipine	Readmission for myopathy	1 month
Clopidogrel + esomeprazole	Readmission for TIA	2 months
Clopidogrel + lansoprazole	Readmission for TIA	19 days

TIA = transient ischemic attack.

these findings are similar to other hospital-based studies.[3,21,30] Among 851 adults in an internal medicine ward, the prevalence of those with at least one potentially moderate or severe DDI at admission and discharge was 30% and 31% using Pharmavista® and 48% and 60% using Drug-Reax®, suggesting that, like in our study, about 50% of these potential DDIs were created by medication changes during the hospital stay.[21] Another retrospective study on 500 adults consecutively discharged from four general medical wards found that 48% at admission and 60% at discharge had a potentially interacting drug combination.[30]

Our finding of a slightly higher prevalence of potential DDIs may be because of the design of REPOSI that focus on elderly patients, because an increase in the prevalence of potential DDIs is associated with aging and an increasing number of prescribed drugs.[12] We found that the most frequent potentially severe DDI at admission and discharge was the combination of digoxin and diuretics. Combinations with furosemide or thiazide diuretics can result in digitalis toxicity secondary to hypokalemia and hypomagnesemia and may precipitate or contribute to the development of arrhythmias, especially in patients with cardiac abnormalities. Similarly, the combination with a potassium-sparing diuretic may precipitate digoxin toxicity because of reduced renal clearance of digoxin. Low-dose aspirin and clopidogrel or ticlopidine are increasingly prescribed in combinations to the elderly to prevent atherothrombotic events (ischemic heart disease, ischemic stroke, and peripheral arterial disease). A study using an Italian database of spontaneously reported drug adverse reactions found that over 17 years, the combination of anticoagulant and antiplatelet agents was responsible for the greatest number of serious adverse reactions and deaths.[31] Because elderly patients treated with antithrombotic drugs have an increased risk of complications,[32] careful monitoring of blood counts and signs and symptoms of bleeding is essential when coadministration is required.

The clinical outcome of a potential DDI is often not known, and epidemiological data dealing with this problem are rare. However, exposure to potential DDI is associated with an increased risk of hospitalization.[33] Egger *et al.* evaluated the potential clinical significance of DDIs in 500 consecutively discharged medical patients and found that of 44 with a potentially severe DDI, only one was readmitted within 2 months after discharge because of adverse consequences of the possible DDI, giving the impression that the clinical impact of the potential DDIs with the highest degree of severity is limited. However, only rehospitalizations were analyzed as an outcome resulting from a potentially severe DDI, and other relevant adverse effects may have been missed.[30] As outcomes, we analyzed the association with in-hospital mortality and any adverse clinical outcomes 3 months after discharge and found a significant association with mortality at 3 months in patients exposed to at least two potentially severe DDIs. Because of the REPOSI design, we could not assess whether patients were monitored for clinical responses or laboratory tests were performed, such as serum potassium or digoxin levels, but particular attention should be paid to the recently created potentially severe DDIs. For those of the 64 patients who died in the hospital potentially related to severe DDIs, one patient treated with alfuzosin, clarithromycin, and fluconazole and one with flecainide and clarithromycin died for cardiac arrest. All these drugs are known to be associated with an increased risk of cardiotoxicity (QT prolongation, torsades de pointes, and cardiac arrest), so monitoring for QT prolongation is required. Although in both cases the starting date of antimicrobial therapy was not available, we suspect that these drugs were recently prescribed (for acute respiratory tract infections) so the potentially severe DDIs had been created recently. At follow-up of 223 patients with a potential severe DDI, five were readmitted within 3 months, and the cause was considered potentially related to their DDI. Two patients prescribed the combination of clopidogrel and proton pump inhibitors at discharge were readmitted for transient ischemic attacks, potentially because of a loss of clinical efficacy of clopidogrel.[34] In one case, the proton pump inhibitor was not given at admission and was added at discharge, and in the other case, this drug replaced ranitidine, which has no risk of interaction with clopidogrel. Although the clinical impact of interaction between proton pump inhibitors and clopidogrel is currently debated, if one of the latter drugs is required, pantoprazole should be preferred, because the platelet response was better than with omeprazole

DOI: 10.1002/pds

when platelet reactivity was measured,[35] and no risk of recurrent myocardial infarction was found in elderly patients treated with clopidogrel and proton pump inhibitors.[34] One patient given aspirin and methotrexate was readmitted for anemia: concomitant aspirin has been reported to increase methotrexate toxicity, reducing its clearance, and inducing severe hematologic toxicity. In general, salicylates should not be administered within 10 days of high-dose methotrexate (the doses used in cancer therapy), and if concomitant treatment is necessary, myelosuppression and renal toxicity should be closely checked. One patient receiving simvastatin and discharged with a new prescription of amlodipine was readmitted for adverse muscle reaction: this combination is associated with an increased risk of myopathy including rhabdomyolysis because of competition with cytochrome P450 3A4-mediated simvastatin metabolism. Limiting the simvastatin dose to no more than 20 mg/day and monitoring serum creatine phosphokinase and muscular symptoms are generally recommended when this combination cannot be avoided (our patient was taking 40 mg/day of simvastatin). One patient readmitted for arrhythmias was exposed to three different potentially severe DDIs associated with an increased risk of arrhythmias, that is, the combination of digoxin and furosemide, sertraline and trazodone, and ramipril and canrenoate. Two of these potentially severe DDIs were created at hospital discharge. Close check of serum potassium and digoxin levels should be considered and of QT prolongation induced by coadministration of sertraline and trazodone. Finally, one patient receiving amiodarone and bisoprolol died of cardiac arrest, a potential consequence of this combination because of their additive cardiac effects and possible CYP2C9 inhibition by amiodarone of beta-adrenergic blocker metabolism. Administration of amiodarone and beta-blockers calls for close attention to cardiac function.

Limitations of the present study include a small number of patients with 3-month follow-up data, which were not available for about 38% of patients recruited in the second wave of REPOSI and may introduce a bias in the results, and the lack of information about adverse clinical events or readmission for those patients who died after discharge, which, however, tends to underestimate the real relevance of DDIs. Again, we could not assess whether or not the patient's clinical responses, laboratory tests, or clinical management were used to reduce the risk of adverse outcomes associated with potentially severe DDIs, especially those commonly seen in practice (e.g., furosemide and digoxin) that can be easily managed clinically with appropriate monitoring. To better quantify the clinical relevance of potentially interacting drug combinations at discharge, a prospective design would be necessary, including longer follow-up after discharge and specific collection of drug-related problems. Lack of information about adherence to drug therapy or changes in drug regimen after discharge is another limit.

CONCLUSION

This study shows that the prevalence of potential DDIs among the elderly is high both at hospital admission and discharge and that hospitalization is associated with increases in potential and potentially severe DDIs. A significant association was found for mortality 3 months after discharge in patients with at least two potentially severe DDIs. Careful monitoring for these severe DDIs, especially for those created at discharge or recently generated, is important to minimize the risk of harm. When we examined whether adverse clinical events were associated with the potential DDI, we saw that in the two patients who died in the hospital, the potentially severe DDIs were probably created shortly before admission, and in four readmitted, they were created at discharge. Because multiple drug treatment is common in hospitals, greater attention should be paid to the DDIs and particularly in elderly patients, who are at higher risk of adverse drug reactions. Built-in software with electronic prescribing databases and the involvement of a clinical pharmacist within multidisciplinary teams may help to highlight DDIs and minimize the occurrence of related risk.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

KEY POINTS
- Hospitalization is associated with increases in potential and potentially severe DDIs and more than half of potentially severe DDIs are created at discharge.
- A significant association was found for mortality 3 months after discharge in patients with at least two potentially severe DDIs.
- Careful monitoring for severe DDIs, especially for those created at discharge or recently generated, is important to minimize the risk of harm.

DOI: 10.1002/pds

ACKNOWLEDGEMENTS

REPOSI is a network of Italian internal medicine hospital wards, which voluntarily and without any financial support, agreed to participate in data collection during the 4 index weeks. The sponsor did not participate in any role. We are grateful to J. D. Baggott for the editorial assistance.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of this article:

Appendix. Investigators and co-authors of the REPOSI (REgistro POliterapie Societá Italiana medicina interna) Study Group

REFERENCES

1. Moura CS, Acurcio FA, Belo NO. Drug–drug interactions associated with length of stay and cost of hospitalization. *J Pharm Pharm Sci* 2009; **12**(3): 266–272
2. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. *N Engl J Med* 2011; **365** (21): 2002–2012.
3. Hilmer SN, Gnjidic D. The effects of polypharmacy in older adults. *Clin Pharmacol Ther* 2009; **85**: 86–98.
4. Steinman MA, Landefeld CS, Rosenthal GE, *et al*. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006; **54**: 1516–1523.
5. Koh Y, Kutty FBM, Li SC. Drug-related problems in hospitalized patients on polypharmacy: the influence of age and gender. *Ther Clin Risk Manag* 2005; **1**: 39–48.
6. Lund BC, Carnahan RM, Egge JA, Chrischilles EA, Kaboli PJ. Inappropriate prescribing predicts adverse drug events in older adults. *Ann Pharmacother* 2010; **44**(6): 957–963.
7. Nobili A, Garattini S, Mannucci PM. Multiple diseases and polypharmacy in the elderly: challenges for the internist of the third millennium. *Journal of Comorbidity* 2011; **1**: 28–44.
8. Cruciol-Souza JM, Thomson, JC. Prevalence of potential drug-drug interactions and its associated factors in a Brazilian teaching hospital. *J Pharm Pharm Sci* 2006; **9**: 427–433.
9. Egger SS, Ratz AE, Bravo AE, Hess L, Schlienger RG, Krahenbuhl S. Age-related differences in the prevalence of potential drug-drug interactions in ambulatory dyslipidaemic patients treated with statins. *Drugs Aging*, 2007; **24**: 429–440.
10. Gagne JJ, Maio V, Rabinowitz C. Prevalence and predictors of potential drug-drug interactions in Regione Emilia-Romagna, Italy. *J Clin Pharm Ther* 2008; **33**: 141–151.
11. Radosevic N, Gantumur M, Vlahovic-Palcevski V. Potentially inappropriate prescribing to hospitalised patients. *Pharmacoepidemiol Drug Saf* 2008; **17**: 733–737.
12. Lin CF, Wang CY, Bai, CH. Polypharmacy, aging and potential drug-drug interactions in outpatients in Taiwan. *Drugs Aging* 2011; **28**(3): 219–225.
13. Hines LE, Murphy JE. Potentially harmful drug-drug interactions in the elderly: a review. *Am J Geriatr Pharmacother* 2011; **9**(6): 364–377
14. Klotz U Pharmacokinetics and drug metabolism in the elderly. *Drug Metab Rev* 2009; **41**: 67–76.
15. Bowie MW, Slattum PW. Pharmacodynamics in older adults: a review. *Am J Geriatr Pharmacother* 2007; **5**: 263–303.
16. Cusack BJ. Pharmacokinetics in older persons. *Am J Geriatr Pharmacother* 2004; (**4**): 274–302. Review.
17. Kinirons MT, O'Mahony MS. Drug metabolism and ageing. *Br J Clin Pharmacol* 2004; **57**(5): 540–544. Review
18. Hastings SN, Schmader KE, Sloane RJ, *et al*. Quality of pharmacotherapy and outcomes for older veterans discharged from the emergency department. *J Am Geriatr Soc* 2008; **56**: 875–880.
19. Johnell K, Klarin I. The relationship between number of drugs and potential drug-drug interactions in the elderly: a study of over 600,000 elderly patients from the Swedish Prescribed Drug Register. *Drug Saf*. 2007; **30** (10): 911–918.
20. Qato DM, Alexander GC, Conti RM, Johnson M, Schumm P, Lindau ST. Use of prescription and over-the-counter medications and dietary supplements among older adults in the United States. *JAMA* 2008;**300**:2867–2878.
21. Vonbach P, Dubied A, Krahenbuhl S, Beer JH. Prevalence of drug-drug interactions at hospital entry and during hospital stay of patients in internal medicine. *Eur J Intern Med* 2008; **19**: 413–420.
22. Pirmohamed M, James S, Meakin S, Green C, Scott AK, Walley TJ, Farrar K, Park BK, Breckenridge AM. Adverse drug reactions as cause of admission to hospital: prospective analysis of 18 820 patients. *BMJ* 2004; **329** (7456): 15–19.
23. Becker ML, Kallewaard M, Caspers PW, Visser LE, Leufkens HG, Stricker BH. Hospitalisations and emergency department visits due to drug–drug interactions: a literature review. *Pharmacoepidemiol Drug Saf* 2007; **16**: 641–651.
24. Espinosa-Bosch M, Santos-Ramos B, Gil-Navarro MV, Santos-Rubio MD, Marín-Gil R, Villacorta-Linaza P. Prevalence of drug interactions in hospital healthcare. *Int J Clin Pharm* 2012; **34**(6): 807–817.
25. Parmelee PA, Thuras PD, Katz IR, Lawton MP. Validation of the Cumulative Illness Rating Scale in a geriatric residential population. *J Am Geriatr Soc* 1995; **43**(2): 130–137.
26. Shah S, Vanclay F, Cooper B. Improving the sensitivity of the Barthel Index for stroke rehabilitation. *J Clin Epidemiol* 1989; **42**(8): 703–709.
27. Katzman R, Brown T, Fuld P, Peck A, Schechter R, Schimmel H. Validation of a short orientation-memory-concentration test of cognitive impairment. *Am J Psychiatry* 1983; **140**(6): 734–739.
28. Hickie C, Snowdon J. Depression scales for the elderly: GDS, Gilleard, Zung. *Clin. Gerontologist* 1987; **6**(3): 51–53.
29. Nobili A, Pasina L, Tettamanti M, Lucca U, Riva E, Marzona I, Monesi L, Cucchiani R, Bortolotti A, Fortino I, Merlino L, Walter Locatelli G, Giuliani G. Potentially severe drug interactions in elderly outpatients: results of an observational study of an administrative prescription database. *J Clin Pharm Ther* 2009; **34**(4): 377–386.
30. Egger SS, Drewe J, Schlienger RG. Potential drug–drug interactions in the medication of medical patients at hospital discharge. *Eur J Clin Pharmacol* 2003; **58**(11): 773–778.
31. Leone R, Magro L, Moretti U, *et al*. Identifying adverse drug reactions associated with drug–drug interactions: data mining of a spontaneous reporting database in Italy. *Drug Saf* 2010; **1;33**(8): 667–675.
32. Kalyanasundaram A, Lincoff AM. Managing adverse effects and drug–drug interactions of antiplatelet agents. *Nat Rev Cardiol* 2011; **8**(10): 592–600.
33. Juurlink DN, Mamdani M, Kopp A, Laupacis A, Redelmeier DA. Drug–drug interactions among elderly patients hospitalized for drug toxicity. *JAMA* 2003; **289**(13): 1652–1658.
34. Juurlink DN, Gomes T, Ko DT, *et al*. A population-based study of the drug interaction between proton pump inhibitors and clopidogrel. *CMAJ* 2009 **31;180** (7): 713–718.
35. Cuisset T, Frere C, Quilici J, *et al*. Comparison of omeprazole and pantoprazole influence on a high 150-mg clopidogrel maintenance dose the PACA (proton pump inhibitors and clopidogrel association) prospective randomized study. *J Am Coll Cardiol* 2009; **22;54**(13): 1149–1153.