# Inappropriate continuation of stress ulcer prophylaxis beyond the intensive care setting

KJ Farley, Kerryn L Barned and Tim M Crozier


## ABSTRACT

**Objective:** To determine how frequently stress ulcer prophylaxis (SUP) medications prescribed in the intensive care unit are inappropriately continued on the ward and on hospital discharge.

**Design:** Retrospective cohort study; chart review.

**Setting:** Two Australian ICUs: one tertiary centre and one metropolitan centre.

**Participants:** We included 387 adult, non-pregnant patients who were admitted to the ICU between 1 February 2011 and 31 March 2011 and who survived to hospital discharge.

**Main outcome measures:** Rate of unnecessary continuation of ICU-prescribed SUP medications on the ward and on discharge from hospital.

**Results:** While in the ICU, 329 of the 387 patients (85%) were prescribed SUP medications. Of the 233 patients who had not been taking acid-suppressive medications before admission to the ICU, 190 were prescribed SUP medications in the ICU. Of these 190 patients, most (63%) had their SUP continued in the ward without any obvious indication, and many (39%) had their SUP medications inappropriately continued on discharge from hospital.

**Conclusions:** SUP medications commenced in ICU are frequently continued unnecessarily, both in the wards and on hospital discharge.


Crit Care Resusc 2013; 15: 147–151

Stress ulceration describes injury of the gastrointestinal (GI) mucosa in response to stressors such as hypoperfusion, hypoxia, reperfusion, and imbalance between gastric acid production and mucosal defence mechanisms.[1] Endoscopic evidence of stress ulceration is seen in most patients soon after admission to the intensive care unit,[2] with clinical severity ranging from endoscopic findings only to life-threatening haemorrhage. Certain subgroups of critically ill patients have increased risk of clinically significant GI bleeding (Table 1),[3,4] with rates of 3.7% in those with coagulopathy and those needing > 48 hours of mechanical ventilation, compared with 0.1% in patients without these risk factors.[5] Clinically significant GI bleeding should be prevented where possible as it is associated with a significant attributable morbidity, mortality[6,7] and increased length of stay in the ICU.[7]

Non-pharmacologic methods for preventing stress ulceration include rapid reversal of shock, providing enteral nutrition and avoiding gastrotoxic medications.[2] Additionally, stress ulcer prophylaxis (SUP) medications are commonly prescribed to ICU patients, frequently as part of "bundles" of general care such as the FASTHUG (feeding, analgesia, sedation, thromboembolic prophylaxis, head-of-bed elevation, stress ulcer prevention, and glucose control) mnemonic.[8] We are unaware of any Australian SUP prescribing guidelines for critically ill patients. Knowledge of Australian SUP prescribing practices has previously been limited to snapshot surveys[9] showing that proton pump inhibitors (PPIs) are increasingly used as first-line SUP agents, histamine-2 receptor blockers (H2RBs) are sometimes used, while sucralfate and antacids are used infrequently — similar to studies in other regions.[10] Apart from evidence showing superiority of H2RBs over sucralfate or antacids,[4,11,12] there is insufficient evidence to make a definitive recommendation on a particular type of SUP at this time.[13-15]

Studies in the United States have shown a high incidence of SUP prescribing to critically ill patients who do not have current evidence-based indications for SUP medication,[16-18] and that ICU-prescribed SUP medications are frequently continued when patients are discharged to the ward, and not ceased on hospital discharge.[16,17,19,20] We are unaware of any published data showing an Australian perspective on this. We investigated the hypothesis that many Australian patients who were prescribed SUP medication while critically ill have this inappropriately continued beyond the ICU setting.

## Methods

This was an Australian retrospective observational study, conducted at one tertiary and one metropolitan ICU. The Southern Health Human Research Ethics Committee approved the study as a quality assurance exercise; hence, the requirement for informed consent was waived.

The files of all non-pregnant patients aged over 18 years who were admitted to the ICU from 1 February 2011 to 31 March 2011 and who survived to hospital discharge were hand searched by two of us (KJF or KLB). Demographic data collected included age, sex, ICU length of stay, admission source (elective v emergency) and ICU campus (tertiary v metropolitan).

**Table 1. Risk factors for upper gastrointestinal (GI) bleeding from stress ulceration in the intensive care unit**

- coagulopathy
- > 48 hours of mechanical ventilation
- acute spinal cord injury
- burns to > 35% of body surface area
- sepsis
- renal or hepatic failure or transplantation
- severe trauma
- head injury with Glasgow Coma Score < 11
- partial hepatectomy

**Table 2. Appropriate indications for continuing acid suppressive medications beyond the intensive care unit**

- gastrointestinal bleeding within the preceding year
- patient taking > 25 mg/day prednisolone or equivalent
- renal or hepatic failure or transplantation
- odynophagia
- *Helicobacter pylori* eradication
- caustic substance ingestion
- patient taking more than one antiplatelet or anticoagulant medication

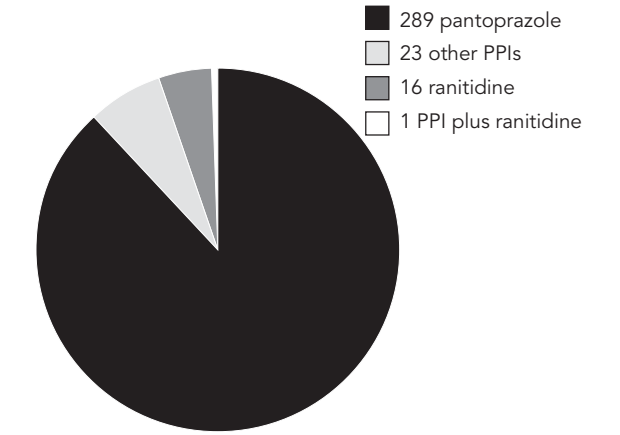
Data were collected for all acid-suppressive medications (ASMs) (PPIs, H2RBs, sucralfate and antacids), including dose, frequency and route of administration, location of commencement and cessation (pre-ICU, ICU, ward or hospital discharge), and indications (Table 2). Patients without one of these indications were considered to have continued receiving their SUP medication inappropriately. Patients who were taking ASMs before ICU admission were considered separately. Data were collected on the initial ASM used, and whether this was changed or ceased during hospital admission.

Prespecified subgroups for analysis included:

- cardiac surgical v other surgical patients
- surgical v medical patients
- elective v emergency ICU admissions
- age ⩽ 65 years v > 65 years
- metropolitan v tertiary centre
- male v female patients.

Statistical analysis was performed by a Southern Health biostatistician, using Excel 2010 (Microsoft). Proportions were compared with $\chi^2$ analysis using Yates correction for $2 \times 2$ tables.

**Figure 1. Type of stress ulcer prophylaxis medication prescribed to 329 patients while in the intensive care unit**




PPI = proton pump inhibitors

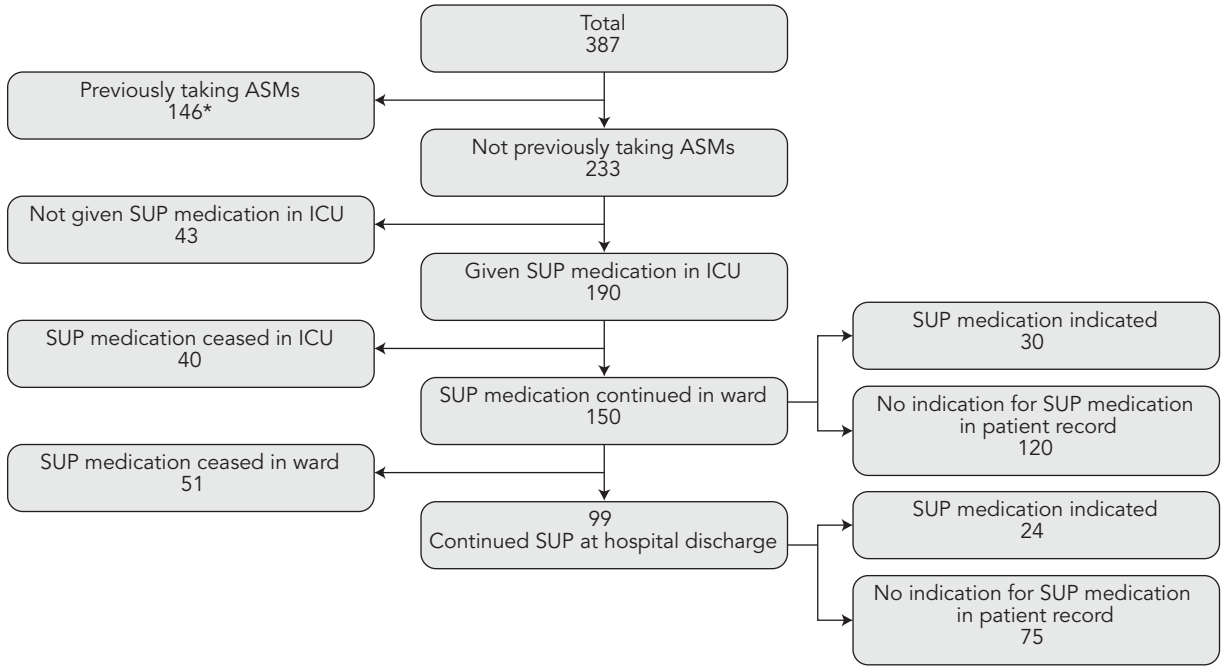
**Table 3. Demographic data of 387 patients admitted to the intensive care unit from 1 February 2011 to 31 March 2011**

| | |
|---|---|
| Mean age | 67.7 years |
| Sex | |
| Male | 226 (58%) |
| Female | 161 (42%) |
| Age | |
| > 65 years | 205 (53%) |
| ⩽ 65 years | 182 (47%) |
| ICU campus | |
| Metropolitan | 187 (48%) |
| Tertiary | 200 (52%) |
| Admission type | |
| Elective | 126 (33%) |
| Emergency | 247 (64%) |
| Unknown | 14 (4%) |
| Medical patients | 179 (46%) |
| Surgical patients | 208 (54%) |
| Cardiac surgical patients | 84 (22%) |
| Average ICU length of stay | 3.27 days |
| Taking acid-suppressive medications before ICU admission | |
| Yes | 146 (38%) |
| No | 233 (60%) |
| Unknown | 8 (2%) |

## Results

This study included 387 patients, of whom 85% received SUP medication in the ICU (Figure 1). Demographic data are summarised in Table 3.

**Figure 2. Prescription of stress ulcer prophylaxis (SUP) medications in 387 patients in the intensive care unit, and continuation of these medications on the ward and at hospital discharge**




ASM = acid-suppressive medication.

* Seven patients had no data available on previous ASM medication, and one patient was transferred from another ICU.

There were 233 patients who had not been taking ASMs before ICU admission. Most (63%) of the 190 patients who had newly received SUP medications in the ICU continued receiving these medications in the ward without any obvious indication, and 75 patients (39%) had these medications continued at discharge from hospital, despite having no indication for SUP medication on record (Figure 2).

By the time they were discharged from hospital, 29 of the 146 patients who were known to be taking ASMs before ICU admission (20%) had their prescription changed to a different drug, and 11 (8%) had their ASM ceased. Only two patients had a documented indication for these changes.

Of the prespecified subgroups, the tertiary ICU prescribed significantly more SUP medications than the metropolitan centre (92% v 69% of patients, respectively). The high number of cardiac surgical patients at the tertiary centre may explain this, as cardiac surgical patients were prescribed significantly more SUP medications than other surgical patients. Significantly more elective than emergency patients (89% v 74%) inappropriately continued receiving SUP medications in the ward, although this difference became insignificant by the time of discharge from hospital. No other statistically significant differences were noted (Table 4).

## Discussion

Our study showed that SUP medications commenced in the ICU are often unnecessarily continued beyond the ICU setting. Most (63%) of the patients who were prescribed new SUP medications while critically ill had these medications continued in the ward without any obvious indication, and 39% had SUP medications inappropriately continued at hospital discharge. This is particularly significant, as recent evidence suggests that SUP may not benefit critically ill patients as much as previously suggested.[21-23] This may be due to changes in overall ICU care which have decreased the baseline risk of stress ulceration — particularly early enteral nutrition and improved resuscitation from shock, which decrease the baseline risk of stress ulceration in the ICU. Despite this emerging evidence, but consistent with a 2005 Australian survey,[9] 85% of our study population received SUP medications while in the ICU.

Studies from the US show similar rates (24.4%[20] to 31%[17]) of inappropriate continuation of ICU-prescribed SUP medication on hospital discharge. Inadequate understanding of appropriate indications for SUP and perceived lack of harm from these medications may be contributing to these medication errors. Similar factors may have played a role for the 38 of our patients who had their pre-ICU ASM ceased or changed without an obvious reason during their hospital

**Table 4. Stress ulcer prophylaxis (SUP) treatment in 233 patients *not* taking acid-suppressive medications before admission to the intensive care unit**

| Patient subgroup | Received SUP in the ICU | SUP continued inappropriately in the ward ($n = 150$) | SUP continued inappropriately on discharge ($n = 99$) |
|---|---|---|---|
| Cardiac surgical | 55/58 (95%)* | 46/49 (94%) | 19/22 (86%) |
| Other surgical | 47/64 (73%)* | 33/41 (80%) | 23/29 (79%) |
| > 65 years old | 86/106 (81%) | 61/72 (85%) | 37/44 (84%) |
| ⩽65 years old | 104/127 (82%) | 59/78 (76%) | 38/55 (69%) |
| Male | 124/147 (84%) | 81/97 (84%) | 53/68 (78%) |
| Female | 66/86 (77%) | 39/53 (74%) | 22/31 (71%) |
| Elective admission† | 66/79 (84%) | 50/56 (89%)* | 26/31 (84%) |
| Emergency admission† | 122/150 (81%) | 68/92 (74%)* | 48/67 (72%) |
| Metropolitan ICU | 75/108 (69%)* | 40/49 (82%) | 28/36 (78%) |
| Tertiary ICU | 115/125 (92%)* | 80/101 (79%) | 47/63 (75%) |
| Surgical | 102/122 (84%) | 79/90 (88%)* | 42/51 (82%) |
| Medical | 88/111 (79%) | 41/60 (68%)* | 33/48 (69%) |

* Indicates a statistically significant result. † Eight patients did not have admission source data available.

admission. Additionally, almost all of our patients (95%) who received SUP medication were prescribed PPIs — compared with the 45% reported previously,[9] despite no clear data to suggest superiority of PPIs over H2RBs in reducing mortality in ICU patients.[10,23]

The difference in SUP prescription between the two ICU campuses may reflect a different unit casemix, varying policies or guidelines, different medical staff or other factors such as pharmacist presence on ward rounds. Subgroup differences in ward-based inappropriate continuation of ICU-prescribed SUP became statistically insignificant at hospital discharge, suggesting that interventions to reduce unnecessary SUP prescription should be hospital-wide rather than targeted at particular groups.

The sequelae of unnecessary ASMs in this patient group are unknown; however, there are many documented adverse reactions to the short- and long-term use of H2RBs and PPIs, including increased incidence of community- and hospital-acquired pneumonia[24,25] (including ventilator-associated pneumonia), *Clostridium difficile* disease,[26-28] interstitial nephritis and allergic reactions,[29] osteoporosis and fractures,[30] vitamin $B_{12}$ deficiency,[31] and potential interactions with other medications such as those that require an acidic environment for absorption. The adverse effects of polypharmacy in elderly patients are well documented,[32,33] and most of our patients were elderly. Evidence from interventions reducing polypharmacy in the elderly[34,35] could perhaps be used to plan similar studies in post-ICU patients; however, interventional studies attempting to decrease unnecessary SUP prescription overseas have had varying degrees of success.[18,36,37]

This study has important limitations. It looked at a relatively small number of patients in only two ICUs; therefore, the findings may represent a local problem only, rather than overall Australian practice, although anecdotally this seems unlikely. The study's retrospective nature may have led to missed indications for prescribed ASMs due to poor documentation in the clinical record or missing data. We have not adjusted for multiple comparisons; hence, some findings may be due to chance alone. We have not studied outpatient changes in medication, and may be unaware of cases where ASMs are appropriately ceased after hospital discharge.

This study raises several important questions that deserve further research. Although most of our ICU patients receive SUP medication, is this practice evidence-based? What are the sequelae of unnecessary SUP prescription for the post-ICU patient? Perhaps most importantly, how can the unnecessary prescription of SUP medication be decreased? Should intensivists be responsible for stopping SUP medications on ICU discharge, or perhaps, for providing a "stop date" for the ward, analogous to that for antibiotics commenced in the ICU? Quantifying the financial cost of inappropriate SUP prescribing to the health care system and to individuals would also be important for future studies.

## Conclusion

This study showed a high rate of inappropriate continuation of SUP medication beyond the ICU setting. Clinicians should give more consideration to stopping SUP (and other) medications that are no longer required, to prevent possible patient harm, as well as unnecessary costs for individuals and the health care system. Further studies are needed to quantify these outcomes in more detail.

## Acknowledgements

We thank Wendy Ewing for assistance with data collection, Craig Noonan for statistical analysis and Stuart Wilson for assistance with the original concept design.

## Competing interests

None declared.

## Author details

**KJ Farley,** Intensive Care Fellow[1]
**Kerryn L Barned,** Acute Medical Services Pharmacist[2]
**Tim M Crozier,** Intensive Care Specialist[3]
1 Alfred Hospital, Melbourne, VIC, Australia.
2 Royal Melbourne Hospital, Melbourne, VIC, Australia.
3 Monash Medical Centre, Melbourne, VIC, Australia.
***Correspondence:*** k.farley@alfred.org.au

## References

1 Stollman N, Metz DC. Pathophysiology and prophylaxis of stress ulcer in intensive care unit patients. *J Crit Care* 2005; 20: 35-45.
2 Ali T, Harty RF. Stress-induced ulcer bleeding in critically ill patients. *Gastroenterol Clin North Am* 2009; 38: 245-65.
3 American Society of Health-System Pharmacists. ASHP therapeutic guidelines on stress ulcer prophylaxis. *Am J Health Syst Pharm* 1999; 56: 347-79.
4 Cook D, Heyland D, Griffith L, et al. Risk factors for clinically important upper gastrointestinal bleeding in patients requiring mechanical ventilation. *Crit Care Med* 1999; 27: 2812-7.
5 Cook DJ, Fuller HD, Guyatt GH, et al. Risk factors for gastrointestinal bleeding in critically ill patients. *N Engl J Med* 1994; 330: 377-81.
6 Ellison RT, Perez-Perez G, Welsh CH, et al. Risk factors for upper gastrointestinal bleeding in intensive care unit patients: role of *Helicobacter pylori*. *Crit Care Med* 1996; 24: 1974-81.
7 Cook DJ, Griffith LE, Walter SD, et al. The attributable mortality and length of intensive care unit stay of clinically important gastrointestinal bleeding in critically ill patients. *Crit Care* 2001; 5: 368-75.
8 Vincent JL. Give your patient a fast hug (at least) once a day. *Crit Care Med* 2005; 33: 1225-9.
9 Robertson MS, Wilson SJ, Cade JF. Acute stress ulceration prophylaxis: point prevalence surveys in intensive care units in Victoria, 1997 and 2005. *Crit Care Resusc* 2008; 10: 18.
10 Lin PC, Chang CH, Hsu PI, et al. The efficacy and safety of proton pump inhibitors vs histamine-2 receptor antagonists for stress ulcer bleeding prophylaxis among critical care patients: a meta-analysis. *Crit Care Med* 2010; 38: 1197-205.
11 Cook D, Guyatt G, Marshall J, et al. A comparison of sucralfate and ranitidine for the prevention of upper gastrointestinal bleeding in patients requiring mechanical ventilation. *N Engl J Med* 1998; 338: 791-7.
12 Cook DJ, Reeve BK, Guyatt GH, et al. Stress ulcer prophylaxis in critically ill patients. Resolving discordant meta-analyses. *JAMA* 1996; 275: 308-14.
13 Barkun AN, Bardou M, Pham CQ, Martel M. Proton pump inhibitors vs. histamine 2 receptor antagonists for stress-related mucosal bleeding prophylaxis in critically ill patients: a meta-analysis. *Am J Gastroenterol* 2012; 107: 507-20.
14 Brett S. Science review: the use of proton pump inhibitors for gastric acid suppression in critical illness. *Crit Care* 2005; 9: 45-50.
15 Schupp KN, Schrand LM, Mutnick AH. A cost-effectiveness analysis of stress ulcer prophylaxis. *Ann Pharmacother* 2003; 37: 631-5.
16 Thomas L, Culley EJ, Gladowski P, et al. Longitudinal analysis of the costs associated with inpatient initiation and subsequent outpatient continuation of proton pump inhibitor therapy for stress ulcer prophylaxis in a large managed care organization. *J Manag Care Pharm* 2010; 16: 122-9.
17 Farrell CP, Mercogliano G, Kuntz CL. Overuse of stress ulcer prophylaxis in the critical care setting and beyond. *J Crit Care* 2010; 25: 214-20.
18 Pitimana-aree S, Forrest D, Brown G, et al. Implementation of a clinical practice guideline for stress ulcer prophylaxis increases appropriateness and decreases cost of care. *Intensive Care Med* 1998; 24: 217-23.
19 Zeigler AJ, McAllen KJ, Slot MG, Barletta JF. Medication reconciliation effect on prolonged inpatient stress ulcer prophylaxis. *Ann Pharmacother* 2008; 42: 940-6.
20 Wohlt PD, Hansen LA, Fish JT. Inappropriate continuation of stress ulcer prophylactic therapy after discharge. *Ann Pharmacother* 2007; 41: 1611-6.
21 Marik PE, Vasu T, Hirani A, Pachinburavan M. Stress ulcer prophylaxis in the new millennium: a systematic review and meta-analysis. *Crit Care Med* 2010; 38: 2222-8.
22 Faisy C, Guerot E, Diehl JL, et al. Clinically significant gastrointestinal bleeding in critically ill patients with and without stress-ulcer prophylaxis. *Intensive Care Med* 2003; 29: 1306-13.
23 Pilkington KB, Wagstaff MJ, Greenwood JE. Prevention of gastrointestinal bleeding due to stress ulceration: a review of current literature. *Anaesth Intensive Care* 2012; 40: 253-9.
24 Laheij RJ, Sturkenboom MC, Hassing RJ, et al. Risk of community-acquired pneumonia and use of gastric acid-suppressive drugs. *JAMA* 2004; 292: 1955-60.
25 Miano TA, Reichert MG, Houle TT, et al. Nosocomial pneumonia risk and stress ulcer prophylaxis: a comparison of pantoprazole vs ranitidine in cardiothoracic surgery patients. *Chest* 2009; 136: 440-7.
26 Howell MD, Novack V, Grgurich P, et al. Iatrogenic gastric acid suppression and the risk of nosocomial *Clostridium difficile* infection. *Arch Intern Med* 2010; 170: 784-90.
27 Dial S, Delaney JA, Barkun AN, Suissa S. Use of gastric acid-suppressive agents and the risk of community-acquired *Clostridium difficile*-associated disease. *JAMA* 2005; 294: 2989-95.
28 Leonard J, Marshall JK, Moayyedi P. Systematic review of the risk of enteric infection in patients taking acid suppression. *Am J Gastroenterol* 2007; 102: 2047-56.
29 Coté GA, Howden CW. Potential adverse effects of proton pump inhibitors. *Curr Gastroenterol Rep* 2008; 10: 208-14.
30 Thomson AB, Suave MD, Kassam N, Kamitakahara H. Safety of the long-term use of proton pump inhibitors. *World J Gastroenterol* 2010; 16: 2323-30.
31 Heidelbaugh JJ, Goldberg KL, Inadomi JM. Overutilization of proton pump inhibitors: a review of cost-effectiveness and risk [corrected]. *Am J Gastroenterol* 2009; 104 Suppl 2: S27-32.
32 Hajjar ER, Cafiero AC, Hanlon JT. Polypharmacy in elderly patients. *Am J Geriatr Pharmacother* 2007; 5: 345-51.
33 Lindley CM, Tully MP, Paramsothy V, Tallis RC. Inappropriate medication is a major cause of adverse drug reactions in elderly patients. *Age Ageing* 1992; 21: 294-300.
34 Rollason V, Vogt N. Reduction of polypharmacy in the elderly: a systematic review of the role of the pharmacist. *Drugs Aging* 2003; 20: 817-32.
35 Hanlon JT, Weinberger M, Samsa GP, et al. A randomized, controlled trial of a clinical pharmacist intervention to improve inappropriate prescribing in elderly outpatients with polypharmacy. *Am J Med* 1996; 100: 428-37.
36 Erstad BL, Camamo JM, Miller MJ, et al. Impacting cost and appropriateness of stress ulcer prophylaxis at a university medical center. *Crit Care Med* 1997; 25: 1678-84.
37 Hatch JB, Schulz L, Fish JT. Stress ulcer prophylaxis: reducing non-indicated prescribing after hospital discharge. *Ann Pharmacother* 2010; 44: 1565-71. ❑