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Keywords:	transitions of care, medication reconciliation, continuity of patient care, cohort study

Unintended discontinuation of medication following hospitalisation: a retrospective cohort study

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Abstract

Objectives: Whether unintended discontinuation of common, evidence based, long-term medication occurs after hospitalisation; what factors are associated with unintended discontinuation; and whether the presence of documentation of medication at hospital discharge is associated with continuity of medication in general practice.

Design: Retrospective cohort study between 2012 and 2015.

Setting: Electronic records and hospital supplied discharge notifications in 44 Irish general practices

Participants: 20,488 patients aged 65 years or more prescribed long-term medication for chronic conditions.

Primary and secondary outcomes: Discontinuity of four evidence-based medication drug classes- antithrombotic, lipid-lowering, thyroid replacement drugs and respiratory inhalers in hospitalised versus non-hospitalised patients; patient and health system factors associated with discontinuity; impact of absence of medication in the hospital discharge summary on continuity of medication in a patient's GP prescribing record at six months follow up.

Results: In patients admitted to hospital, medication discontinuity ranged from 6-11% in the six months post-hospitalisation. Discontinuity of medication is significantly lower for hospitalised patients taking respiratory inhalers (adjusted odds ratio (AOR) 0.63, 95% Confidence Interval (CI) (0.49, 0.80), p<0.001) and thyroid medications (AOR 0.62, 95%CI (0.40, 0.96), p=0.03). There is no association between discontinuity of medication and hospitalisation for antithrombotics (AOR 0.95, 95%CI (0.81, 1.11), p=0.49) or lipid lowering medications (AOR 0.92, 95%CI (0.78, 1.08), p=0.29). Older patients and those who paid to see their GP were more likely to experience increased odds of discontinuity in all four medicine groups. Less than half (39% to 47.4%) of patients had medication listed on their hospital discharge summary. Presence of medication on hospital discharge summary is significantly associated with continuity of medication in the GP prescribing record for lipid lowering medications (AOR 1.64, 95%CI (1.15, 2.36), p=0.01) and respiratory inhalers (AOR 2.97, 95%CI (1.68, 5.25), p<0.01).

Conclusion: Discontinuity of evidence-based long-term medication is common. Increasing age and private medical care are independently associated with a higher risk of medication discontinuity. Hospitalisation is not associated with discontinuity but less than half of hospitalised patients have medication recorded on their hospital discharge summary.

Article Summary

Strengths and limitations of this study

1. This study includes prescribing data from a diverse group of general practices that includes non-fee and fee-paying patients.
2. We examined the impact of hospitalisation on continuity of evidence-based, long term medication after discharge.
3. We had no information on reasons for hospitalisation or therapeutic intent in terms of discontinuing medication.
4. We examined a limited number of medication groups and did not report on patient related-outcomes.

Introduction

Older patients are more likely to be prescribed multiple medications, have multiple chronic conditions, and experience increasing number of transitions of care.(1–3) Adherence to clinically appropriate, evidence-based therapies is important for lowering the risk of progression and complications related to their underlying chronic conditions.

Poor coordination of transitions of care is associated with adverse drug events (ADEs), rehospitalisation and discrepancies in medication lists.(4–9) Disruptions in medication continuity following hospitalisation have been reported.(10–13) In particular, omission of medication with known benefit has been noted in prescribing errors at discharge.(14–18) There has been limited assessment of the immediate impact of hospitalisation on medication omission at hospital discharge which in turn, influences general practice repeat prescribing records.(19–23)

Aim and objectives

The aim of this study was to determine whether the potentially unintentional discontinuation of common, evidence-based medications for chronic diseases occurs after hospitalisation among older community dwelling adults. The medicine groups considered are: antithrombotics (antiplatelet or anticoagulants); lipid-lowering medications; thyroid medications; and respiratory inhalers. These medications are commonly prescribed in older populations, have a strong evidence base in terms of efficacy and once started are usually recommended to be continued on a long-term basis. Furthermore, the continuity of these medications in prescribing and dispensing records has been the subject of study internationally – allowing for comparison of results. (11,24–31).

We compare discontinuity of medication for each of the four medicine groups listed above in the GP prescribing record over a six-month period between patients who had been admitted to hospital and a group of patients who had not been admitted to hospital. Second, we examine whether other patient and health-system factors are associated with discontinuity of medication. A third objective is to assess whether

documentation of prescribing of the specific medication in the hospital discharge summary record is associated with the presence of the same medication in the GP's prescribing record in the following six months.

Methods

Study design

We conducted a retrospective cohort study, adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.(32) Anonymous data were gathered using the general practice patient management system which includes prescribing, demographic and clinical records, and hospital supplied hospitalisation records. Project approval was received from the Irish Primary Care Research Network (IPCRN) and ethical approval was granted from the Irish College of General Practitioners.

Practice recruitment

A data extraction tool was developed with Socrates (providers of Electronic Health Record [EHR] software to a majority of GP practices in Ireland). Following piloting of the extraction tool, a convenience sample of practices using Socrates EHR and receiving electronic hospital discharge communication (n=48) were invited to participate. Forty-four GP practices (response rate 91%) provided consent to take part in the study. Thirty practices were in the catchment area of the Dublin hospitals, with one in the North-East of Ireland. Eleven practices were in the catchment area of the Galway hospitals and two in the catchment area of the Cork hospitals. Participating GPs were awarded continuing professional development points for their participation.

Medication classes

Four distinct patient cohorts were created based on the four medication classes: antithrombotics, lipid-lowering medications, thyroid medications, and respiratory inhalers (Figure 1 – Medication classes). These medications are commonly prescribed in older populations and once commenced, are usually continued on a long-term basis.

Study, enrolment and follow-up period criteria

The study period for each patient ranged from the 1st of January 2012 to the date when the data was extracted from the GP practice; this varied between practices, with the median time being one year and 180 days (Figure 2 – Study enrolment and

follow-up). The study period included a one-year enrolment period, and a six-month follow-up period. The enrolment period for each medication class was the earliest one-year period post 1st January 2012 over which a patient was continuously prescribed medication from that medication class. Continuously prescribed was defined as two prescriptions issued at least five months apart. No hospitalisations were allowed during the enrolment period to avoid misclassifying patients according to exposure. Patients could not be enrolled before 65 years of age and could be enrolled into more than one of the medication groups.

The start of the follow-up period, the period of time where discontinuity of medication was estimated, was marked by an index date. For patients who had been hospitalised, this was assigned as the day following discharge from hospital. For those individuals not experiencing hospitalisation, the index date was randomly assigned following the enrolment period. This method of generating a comparison group has been used previously and is in line with assuming the medications are long-term and unlikely to be discontinued.(11)

The follow-up period comprised a six-month period following the index date. For patients who were readmitted to hospital during this six-month period, the start of the follow-up period was reset until after the next discharge until a six-month period free from further hospitalisation was established. For all hospitalised patients the 180-day follow-up period was extended to take account of their length of stay of the relevant admission (reflecting the possibility that patients may have supplies of long-term medication at home). A median length of stay for those hospitalised was added to the unexposed group follow-up period.

Patients who were categorised as deceased/inactive at the extraction date or who had no consultations after each follow-up period were excluded from the analyses. This avoided misclassifying a patient who may, for example, have died in hospital or was discharged to a long-term care facility and were not under the care of their previous general practitioner.

Explanatory variables of interest

Hospitalisation was the main explanatory variable of interest. The electronic messaging system *Healthlink* provided discharge messages in 41 practices to signal a hospitalisation (inpatient stay, not Emergency Department attendances). Hospitalisation was coded manually by research centre trained coders in four practices by examining the clinical records directly (one practice provided both *Healthlink* electronic discharge information and manually-coded discharge information). We examined whether patient and health-system variables might be associated with absence (primary analysis) or presence (secondary analysis) of medication in the GP prescribing - age, gender, public / private status, number of GP consultations, polypharmacy or multi-morbidity. (33–38) Medication burden was calculated using RxRisk (33–39). All covariates were measured during the enrolment period. For the third objective, we were interested in hospitalised patients only and whether or not absence of specific medication on their hospital discharge summary note was associated with subsequent omission on their repeat general practice prescribing record.

Outcomes

The primary outcome was discontinuity of medication (failure to renew medication) in one of the four, pre-specified medication classes in the general practitioner record over the follow-up period. For each medication class, discontinuity of medication was compared between those who had been hospitalised and those who had not. We calculated univariable associations across the four medication classes and adjusted for important confounders and other explanatory variables of interest. The secondary outcome was presence of relevant medication in the patient's general practice prescribing record following discharge from hospital. Again, this was estimated for each medication cohort.

Sample size

The pilot phase and previous international studies in this area informed the calculation (11,12). Sample size calculation was based on 90% power to detect a 3% difference in the proportion of patients experiencing discontinuity. We assumed 11%

of non-hospitalised patients have medications unintentionally discontinued. Additionally, a 4:1 ratio of non-hospitalised to hospitalised patients (based on experience from the pilot phase) with a statistical significance of 5% was used. This gave a total requirement of 8410 participants in any one medication cohort group.

Plan of analysis

The number of patients at each stage of the study is reported, including those potentially eligible for enrolment, those enrolled into each of the four cohorts, and those available for analysis in the follow-up period. Reasons for removal are documented at each stage.

Descriptive statistics for the primary exposure (hospitalisation) and other explanatory variables are reported. For the primary outcome in each medication class, a multilevel multivariable model was fitted to examine the association between hospitalisation and discontinuity of medication at the follow-up period. Multilevel modelling allows for the fact that patients within any given practice could reasonably be expected to have more in common with each other than with those from a different practice- for instance in terms of prescriber patterns. Models were adjusted for patient and health system variables- age, gender, public/private status, Charlson score (comorbidity), number of repeat drug classes (polypharmacy), and number of enrolment period GP consultations. Results are reported as Adjusted Odds Ratios (AOR) with 95% Confidence Intervals (CI). In addition, we assessed the impact of repeated hospital admissions on discontinuity of medication in the GP prescribing record, using the number of hospital admissions (count variable) between the end of the enrolment period and the beginning of the follow-up period.

For the secondary analyses, multilevel logistic regression was used to examine the association between prescribing of the specified medication at discharge from hospital and presence of the medication in the subsequent GP prescribing history over the next six months. All analyses were performed using Stata V14.(40)

Patient and Public Involvement

Patients were not involved in the conception, design, or conduct of this research. We plan to disseminate the findings to the public and patients through our contacts in patient representative bodies, the popular media, and through the participating general practices.

Results

Cohort flow

A total of 92,048 patients had their records extracted from the 44 recruited practices, of which 53,921 (58.6%) were removed immediately due to insufficient data (patients with sociodemographic data only, or who had no prescriptions or consultations with the GP after 1 January 2012). (Figure 3 – Participant flow chart) A further 11,871 patients were removed due to not being prescribed any medications from the four drug groups of interest or having less than 12 months of follow-up data available to enable enrolment. The enrolment criteria were applied to the 26,256 remaining patients, creating four cohorts - antithrombotics (Anatomical Therapeutic Chemical (ATC) classification system, B01) (n=13,684), lipid-lowering medications (ATC C10) (n=14,427), thyroid medications (ATC H03) (n=3,484), and respiratory inhalers (ATC R03) (n=5,227). Out of the whole group of patients, 7,896 (38.5%) were enrolled in one medicine group, 9,184 (44.8%) in two groups, 3,074 (15.0%) in three groups and 334 (1.6%) in all four groups.

Descriptive statistics

The demographics of the participants within the four cohorts of those available at the follow-up period are presented in Table 1 (Participant Descriptives). Patients admitted to hospital tended to be slightly older, have more consultations with their general practitioner and higher levels of polypharmacy and co-morbidity during the enrolment period than patients who remained out of hospital.

Among patients who were not hospitalised, the percentage of participants experiencing discontinuation of medication at follow-up ranged from 8.5% (thyroid medications) to 17.0% (respiratory inhalers); and from 5.9% (thyroid medications) to 11.1% (respiratory inhalers) in those who were hospitalised. Levels of discontinuity were higher among those who had not been hospitalised in three of the four drug classes that were examined (Table 1).

Over two thirds of patients did not experience a hospital admission during follow up across the four medication groups (Table 2 – Hospital admissions). Of those admitted to hospital, the percentage of patients experiencing a single admission

ranged between 20.4% and 23.9% across the four medication groups. A minority of patients experienced multiple medical admissions (Table 2).

Univariable and multivariable associations

There is no difference in terms of likelihood of discontinuity for lipid-lowering and antithrombotic drugs between hospitalised and non-hospitalised patients. Hospitalisation is associated with less odds of discontinuity of long term medication on those prescribed thyroid medications and respiratory inhalers after adjustment for important confounders (Table 3 – Analysis of Primary outcome). For all four medication groups, older patients are more likely to experience discontinuity of medication than younger patients, with the odds of discontinuity increasing by between 3%-6% per year ($p<0.001$). Private patients (those who paid for their own prescriptions and their GP visits out of pocket) have the strongest association with discontinuity across all four medicine groups with adjusted odds ratios (AOR) varying between 3.75, (95% CI 2.84, 4.96) for respiratory inhalers to 11.67, (95% CI 8.02, 16.96) for thyroid medications (Table 3). Number of consultations, multi-morbidity, number of repeat medications and gender are not associated with an increased odds of discontinuity.

Repeated hospital admissions

To assess the impact of repeated hospital admissions, models were re-estimated with the hospital exposure defined as the number of hospital admissions (count) between the end of the enrolment period and the beginning of the follow-up period. For antithrombotics, lipid-lowering medications, and thyroid medications there was no evidence of a statistically significant association between the number of admissions to hospital and discontinuity of medication in the six-month follow up period. However, for respiratory inhalers, the odds of discontinuity of medication fell by an estimated 13% per additional admission to hospital after adjusting for confounders (AOR 0.87, (95%CI 0.76, 0.99), $p=0.03$). For further details see Supplementary Table 1 (Repeated admissions analysis).

Impact of medication specified in patient's hospital discharge summary

Recording of medication on the hospital discharge summary was relatively poor, with only 39.2% to 47.4% of patients having the relevant medication group documented

across the four medication groups. Medication recording had improved at six months post discharge, being present in 89.2% to 94.7% of patient's GP clinical records across medication groups (Table 4 – Documentation of medication at discharge and in the GP record). Having medication listed on hospital discharge summary was independently associated with medication being present on the GP record as six months follow up for both lipid-lowering drugs and respiratory inhalers. Private patients were significantly less likely to have the relevant medication in their GP prescribing record in the six-month period following discharge from hospital than public patients. (Table 5 – Analysis of secondary outcome).

Discussion

Principal findings

Discontinuation of medication in patients who had been recently hospitalised ranged from 6 to 11% for commonly prescribed, evidence-based medicines, compared to 5-17% for non-hospitalised patients. Patients prescribed thyroid medications and respiratory inhalers, who experienced hospitalisation, actually had a lower risk of discontinuity. Public or private care played a significant role in the likelihood of medication being discontinued with the odds of discontinuation significantly higher for private patients than non-private patients in all medication groups. Increasing age is independently associated with an increased odds of discontinuation of medication. Lastly, recording of mediation on hospital discharge summaries is incomplete, being present in less than 50% of discharged patients for all four medication groups. Presence of medication on hospital discharge summaries is associated with continuity on the GP prescribing record at six months for lipid lowering medication and respiratory inhalers.

Previous research

Findings from this observational study differs from similar studies in the US, both in the magnitude of discontinuation: reported to be between 12-19% for thyroid and antithrombotic medications; and in terms of the impact of hospitalisation, with hospitalisation being independently associated with discontinuation, when assessed using pharmacy dispensing data.(8,9,10,41) The impact of hospitalisation appears to be context and health system-specific, with some studies not finding a relationship between discontinuity and hospitalisation.(42–44). We found that increase number of medications was not associated with discontinuation; in the respiratory inhalers group patients were less likely to be discontinued if they had increased numbers of medications.(33,36–38,45–47) Like other studies we found that increasing age was independently associated with an increased discontinuity post discharge.(41)

This study reported a varying discontinuity rate across the four drug classes (lower in antithrombotics and higher in respiratory inhalers). This variation may be explained by disease specific issues: altering doses of thyroxine replacement meaning repeat prescriptions are not required; varying severity of disease – if a patient is

asymptomatic they are less likely to take the medication regularly; evolving diagnoses or clinical considerations to patient beliefs about the effectiveness or benefits of the therapy or their own susceptibility to illness.(48)

A particularly interesting finding in our study is the marked difference between publicly funded and privately funded patients. Private patients were found to have a consistent pattern of discontinuity independent of other patient and health system factors (Table 3). Similarly, in hospitalised patients, being a private patient was associated with discontinuity of medication recording in their GP record and significantly more likely at six months follow up. There are possible explanations for this finding. Private patients are not required to have their hospital discharge prescription transcribed by their GP and may proceed directly to the pharmacy, thereby appearing as if their medication has been discontinued by our method of outcome calculation. Nevertheless, lack of continuity in the GP record raises concerns about completeness of the information a GP in relation to a patient's medication file, monitoring requirements, potential drug-to-drug interactions and other potential prescribing errors.

In keeping with findings from other studies, the quality of prescribing information contained in hospital discharge summaries was incomplete for over half of discharged patients, with the omission of essential medications common.(18,34) Furthermore lack of medication reconciliation upon hospital discharge appeared to persist for at least six months in general practice medication records.(20) The hospital discharge summary used to determine discharge medication in this study is only one element of the information normally provided to patients at discharge from hospital. A supplementary discharge prescription may also be provided.(34) Therefore a discrepancy may arise between the hospital discharge summary and additional discharge prescription, as hospital doctors make judgements about what to include/exclude from discharge prescriptions.(49) These parallel methods of providing post-discharge medication information is a cause for concern and likely enhance risks of medication discontinuity.

Lastly, whilst lack of medication reconciliation following hospital discharge may be one possible explanation for the reported discontinuity, there are other possible

explanations, most commonly poor patient adherence. A recent UK study of statin adherence reported discontinuation rates of 27% at one year in those prescribed statins. Notably this was examining primary non-adherence (failure to fill an initial prescription) as distinct from what may be secondary non-adherence (inadequate medication possession over a defined period of time) in this cohort).(50,51) The factors that influence adherence may be patient, therapy, physician or health system related.(52) While this study was able to control for some of these factors (demographics, comorbidities, public/private care status) others were not recorded (socioeconomic status, side-effects, individual physician behaviour and access to healthcare).

Strengths and limitations of study

This is the largest Irish study to date to examine the effect of hospitalisation on the continuity of evidence-based medication in the GP prescribing record. It is also the first study to systematically use GP prescribing records (as opposed to pharmacy dispensing records) and includes details of both private and public patients, unique features of the mixed public/private health system in Ireland. The recruitment of GP practices was not limited to one geographically area/hospital catchment and the inclusion of multiple hospitals allowed comparison of messaging standards and their impact on prescribing continuity, enhancing the generalisability of the findings.

There are several limitations to this study. The medication groups were specifically chosen to be evidence-based and long-term in their usage and the establishment of an enrolment period of continuous usage over one year further ensures the pattern of ongoing use. However, the primary outcome of discontinuation of medication was applied to a prescribing database and does not contain information about indication or therapeutic intent, for example intentional discontinuation of statins in end-of-life patients.

The nature of data collection and the dataset itself also incur limitations. Hand written prescriptions were not captured by this data collection technique. The follow-up of participants from enrolment through to outcome calculation also required

assumptions to be made in preparing the data for analysis. However, the methods have been used previously, and are in line with the underlying assumption that there should be no difference between groups with both having 100% persistence of the medication in the GP record. Lastly, the recording of hospitalisation is likely to be variable within practices, with the *Healthlink* service employed differently by hospitals with the possibility of misclassification of exposed individuals. These methodological and data issues were explored in the sensitivity analysis with no change in the overall findings.

Clinical and healthcare policy implications

The quality of electronic discharge communication received by general practices and the possible association with inappropriate discontinuation of evidence-based medication suggests more emphasis needs to be placed on improving the quality of discharge communication. The HSE's ePrescribing initiative and eScript pilot projects are efforts to improve the transfer of medication information.(53,54)

Future efforts should focus on identifying high-risk individuals who are receiving medications that would be the best targets for reconciliation studies and interventions. Recent efforts have been made to develop a consensus about high risk medications and methods of assessing the potential severity of medication omission.(55)

Conclusions

Discontinuity of evidence-based long-term medication is common. Increasing age and private medical care are independently associated with a higher risk of medication discontinuity. Hospitalisation was not associated with discontinuity but less than half of hospitalised patients had medication recorded on their hospital discharge summary. System based solutions that include ePrescribing are needed to enhance the transfer of medication information across the primary/secondary care interface.

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Ethics:

Ethical approval was granted from the Irish College of General Practitioners' Research Ethics Committee. GPs as individual practice data controllers gave informed consent to participate.

Conflict of interests:

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Author Contributions:

PR initiated the project, designed data collection tools, monitored data collection, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper.
RMcDowell wrote the statistical analysis plan, cleaned and analysed the data and revised the paper.
TG designed the data collection tools, wrote the statistical analysis plan, and revised the paper.
FB designed the data collection tools, wrote the statistical analysis plan, and revised the paper.
RMcDonnell designed the data collection tools and revised the paper.
CH initiated the project, advised on the statistical analysis plan, and revised the paper.

TF initiated the project, monitored data collection, advised on the analysis plan and revised the paper. He is guarantor.

Data statement

Will individual participant data be available (including data dictionaries)?

No additional data is available. A data sharing provision was not included in the application to the research ethics committee for approval of this study.

What data in particular will be shared?

N/A

What other documents will be available?

N/A

When will data be available (start and end dates)?

N/A

With whom?

N/A

For what types of analyses?

N/A

By what mechanism will data be made available?

N/A

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Table 1

Descriptive statistics for participants in four evidence-based drug classes (ATC code)

Medication Group (No patients enrolled)	Antithrombotics (B01) (n=13,684)		Lipid-lowering (C10) (n=14,427)		Thyroid meds (H03) (n=3,484)		Respiratory inhalers (R03) (n=5,227)	
No. patients at end of follow-up period	Hospitalised (n=2,707)	Non-hospitalised (n=6,152)	Hospitalised (n=2,622)	Non-hospitalised (n=6,944)	Hospitalised (n=586)	Non-hospitalised (n=1,641)	Hospitalised (n=1,067)	Non-hospitalised (n=2,110)
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)
Age (years)	78.38 (7.06)	75.32 (6.95)	77.05 (6.77)	73.78 (6.45)	78.34 (7.25)	74.59 (7.18)	76.88 (7.02)	74.29(6.90)
No of consultations in enrolment period	18.28 (10.40)	14.80 (9.66)	17.50 (10.09)	13.71 (8.79)	18.76 (10.29)	14.81 (9.10)	19.64 (11.09)	16.07 (10.57)
No of repeat drug classes during enrolment period	8.04 (3.72)	7.01 (3.45)	7.77 (3.75)	6.44 (3.41)	8.59 (4.30)	6.67 (3.87)	9.26 (4.24)	7.99 (4.13)
RxRisk during enrolment period	5.07 (2.05)	4.55 (1.89)	4.99 (2.09)	4.26 (1.97)	5.37 (2.42)	4.36 (2.09)	4.79 (2.18)	4.29 (2.12)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Female	1,414 (52.23%)	3,176 (51.63%)	1,423 (54.27%)	3,957 (56.98%)	468 (79.86%)	1,349 (82.21%)	626 (58.67%)	1,276 (60.47%)
Insurance type: GMS/DVC	2,495 (92.17%)	5,495 (89.32%)	2,429 (92.64%)	6,194 (89.20%)	537 (91.64%)	1,445 (88.06%)	998 (93.53%)	1,898 (89.95%)
Charlson index of 1 or more	1,400 (51.72%)	2,638 (42.88%)	1,357 (51.75%)	2,736 (39.40%)	290 (49.49%)	543 (33.09%)	690 (64.67%)	1,120 (53.08%)
Patients experiencing one hospitalisation only during first follow-up period	2,011 (74.29%)	-	1,958 (74.68%)	-	457 (77.99%)	-	761 (71.32%)	-
No. (%) patients discontinued during 1st follow-up period	288 (10.64%)	693 (11.26%)	282 (10.76%)	727 (10.47%)	35 (5.97%)	139 (8.47%)	118 (11.06%)	359 (17.01%)

ATC: Anatomical Therapeutic Chemical classification system

GMS: General Medical Services

DVC: Doctor Visit Card

SD: standard deviation

Table 2

Number of hospital admissions following enrolment for patients assessed for medication discontinuity at follow-up

Medication Group (No patients enrolled)	Antithrombotics (B01) (n=13,684)	Lipid-lowering (C10) (n=14,427)	Thyroid meds (H03) (n=3,484)	Respiratory inhalers (R03) (n=5,227)
No. patients at end of follow-up period				
0	6,152 (69.44%)	6,944 (72.59%)	1,641 (73.69%)	2,110 (66.41%)
1	2,011 (22.70%)	1,958 (20.45%)	457 (20.52%)	761 (23.95%)
2	448 (5.06%)	419 (4.38%)	90 (4.04%)	200 (6.30%)
3	140 (1.58%)	139 (1.45%)	26 (1.17%)	60 (1.89%)
4	25 (0.28%)	50 (5.23%)	5 (0.23%)	27 (0.85%)
5	8 (0.09%)	24 (0.25%)	6 (0.27%)	5 (0.16%)
6	7 (0.08%)	8 (0.09%)	1 (0.04%)	5 (0.16%)
>6	23 (0.26%)	24 (0.25%)	1 (0.04%)	14 (0.44%)

Table 3

Univariable and multivariable associations in four evidence-based drug classes (ATC code)

	Antithrombotics (B01)		Lipid-lowering (C10)		Thyroid meds(H03)		Respiratory inhalers (R03)	
	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)
Hospitalised v non-hospitalised	0.95 (0.82,1.10), p=0.49	0.95 (0.81,1.11), p=0.49	1.04 (0.89,1.20), p=0.64	0.92 (0.78,1.08), p=0.29	0.68 (0.46,1.00), p=0.05	0.62 (0.40,0.96), p=0.03	0.62 (0.49,0.78), p=0.001	0.63 (0.49,0.80), p<0.001
Age (years)	1.02 (1.01,1.03), p<0.001	1.03 (1.02,1.04), p<0.001	1.04 (1.03,1.05), p<0.001	1.05 (1.04,1.06), P<0.001	1.03 (1.01,1.05), p=0.002	1.06 (1.04,1.09), p<0.001	1.02 (1.01,1.03), p=0.004	1.04 (1.02,1.05), p<0.001
Gender: Female v Male	1.02 (0.89,1.17), p=0.79	1.00 (0.87,1.15), p=0.99	0.85 (0.74,0.96), p=0.01	0.82 (0.72,0.95), p=0.01	0.84 (0.57,1.24), p=0.38	0.85 (0.56,1.30), p=0.46	1.04 (0.85,1.28), p=0.68	1.03 (0.83,1.27), p=0.79
Insurance type: Private v GMS/DVC patients	5.10 (4.31,6.04), p<0.001	5.35 (4.50,6.34), p<0.001	4.78 (4.06,5.62), p<0.001	5.68 (4.48,6.73), p<0.001	9.79 (6.90,13.89), p<0.001	11.67 (8.02,16.96), p<0.001	3.66 (2.78,4.82), p<0.001	3.75 (2.84,4.96), p<0.001
Number of repeat drug classes	0.99 (0.98,1.01), p=0.56	0.99 (0.97,1.01), p=0.28	1.01 (1.00,1.04), p=0.04	1.01 (0.99,1.04), p=0.24	0.98 (0.95,1.02), p=0.41	0.98 (0.94,1.03), p=0.44	0.97 (0.94,0.99), p=0.01	0.97 (0.94,0.99), p=0.02
Charlson score (>=1 v0)	0.93 (0.80,1.07), p=0.31	0.94 (0.80,1.09), p=0.41	1.05 (0.91,1.21), p=0.48	0.98 (0.84,1.14), p=0.78	0.78 (0.56,1.08), p=0.15	0.80 (0.54,1.15), p=0.22	0.66 (0.53,0.81), p<0.001	0.71 (0.58,0.88), p=0.002
No of consultations in enrolment period	1.00 (0.99,1.01), p=0.62	1.00 (0.99,1.01), p=0.63	1.00 (0.99,1.01), p=0.69	1.00 (0.99,1.01), p=0.75	0.99 (0.97,1.00), p=0.11	1.00 (0.98,1.02), p=0.83	0.99 (0.98,1.00), p=0.02	1.00 (0.99,1.01), p=0.72

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

DVC: Doctor Visit Card

OR: odds ratio

CI: confidence interval

Table 4

Cross tabulation of patients by presence of medication on hospital discharge summary and in the GP prescribing record at six months following hospitalisation

		GP Record		GP record		GP record		GP record	
Medication Group		Antithrombotics (B01) (n=1,991)†		Lipid-lowering (C10) (n=1,954) †		Thyroid meds(H03) (n=456) †		Respiratory inhalers (R03) (n=757) †	
		Absent	Present	Absent	Present	Absent	Present	Absent	Present
Hospital discharge	Absent	113 (10.55%)	958 (89.45%)	123 (10.35%)	1,065 (89.65%)	16 (6.67%)	224 (93.33%)	65 (14.19%)	393 (85.81%)
Hospital discharge	Present	78 (8.48%)	842 (91.52%)	63 (8.22%0	703 (91.78%)	8 (3.70%)	208 (96.30%)	17 (5.69%)	282 (94.31%)

†patients with medication discontinued at hospital discharge excluded

Table 5

Multivariable association of required medication appearing in GP clinical record following discharge from hospital

	Antithrombotics (B01) (N=1,991)*		Lipid-lowering (C10) (N=1,954)*		Thyroid meds(H03) (N=456)*		Respiratory inhalers (R03) (N=757)*	
	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)
Medication listed on discharge summary	1.29 (0.95,1.76), p=0.11	1.34 (0.97,1.87), p=0.08	1.40 (0.99,1.97), p=0.06	1.64 (1.15,2.36), p=0.01	1.86 (0.77,4.43), p=0.16	1.76 (0.70,4.42), p=0.23	2.74 (1.57,4.78), p<0.001	2.97 (1.68,5.25), p<0.001
Age (years)	0.98 (0.96,1.00), p=0.03	0.98 (0.96,1.00), p=0.08	0.96 (0.94,0.98), p<0.001	0.95 (0.93,0.98), p<0.001	0.96 (0.91,1.02), p=0.16	0.96 (0.91,1.02), p=0.16	0.97 (0.94,1.01), p=0.12	0.96 (0.93,1.00), p=0.03
Female v Male	1.02 (0.76,1.38), p=0.90	0.97 (0.70,1.33), p=0.84	1.14 (0.84,1.56), p=0.39	1.15 (0.83,1.59), p=0.41	1.34 (0.52,3.49), p=0.54	1.35 (0.49,3.73), p=0.57	0.93 (0.58,1.50), p=0.77	0.87 (0.53,1.43), p=0.59
Insurance type: Private v GMS/DVC patients	0.18 (0.13,0.26), p<0.001	0.18 (0.12, 0.27), p<0.001	0.19 (0.12,0.28), p<0.001	0.17 (0.11,0.27), p<0.001	0.10 (0.04,0.26), p<0.001	0.10 (0.04,0.26), p<0.001	0.26 (0.14,0.50), p<0.001	0.26 (0.13,0.49), p<0.001
Number of repeat drug classes	1.04 (1.00,1.09), p=0.06	1.04 (0.99,1.09), p=0.11	0.99 (0.94,1.03), p=0.49	1.00 (0.96,1.06), p=0.86	1.06 (0.95,1.18), p=0.30	1.10 (0.96,1.26), p=0.18	1.07 (10.01,1.13), p=0.03	1.08 (1.00,1.15), p=0.06
Charlson score (>=1 v0)	1.14 (0.84,1.54), p=0.40	1.08 (0.79,1.49), p=0.63	0.76 (0.55,1.04), p=0.09	0.79 (0.56,1.11) p=0.18	1.06 (0.46,2.40), p=0.90	0.82 (0.33,2.03), p=0.67	0.98 (0.61,1.58), p=0.94	0.86 (0.52, 1.45), p=0.55
No of consultations in enrolment period	1.01 (0.99,1.03), p=0.19	1.00 (0.99,1.02), p=0.74	0.99 (0.97,1.01), p=0.22	0.99 (0.97,1.01), p=0.16	1.01 (0.97,1.06), p=0.63	0.99 (0.94, 1.04), p=0.63	1.02 (1.00,1.05), p=0.07	1.02 (0.98,1.04), p=0.41

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

DVC: Doctor Visit Card

OR: odds ratio

CI: confidence interval

World Health Organization Anatomical Therapeutic Chemical (WHO - ATC) Classification System Code*	Drug class/name	Examples
C10	Lipid modifying agents	Statins, ezetimibe etc.
B01 (includes N02BA01)	Antithrombotics (antiplatelet or anticoagulant agents)	Aspirin, clopidogrel, warfarin, novel oral anticoagulants (NOACs) etc.
H03	Thyroid medication	Levothyroxine, carbimazole etc.
R03	Respiratory inhalers	Inhaled anticholinergics, short & long acting beta agonists, inhaled steroids

*ATC code groupings (as above) were used to ensure all component drugs within a class were included (e.g. prasugrel, tecagrelor etc.)
This chapter refers to each cohort by the first three figures of the ATC group.

Figure 1 Medication classes

Figure 1 Medication classes

338x190mm (300 x 300 DPI)

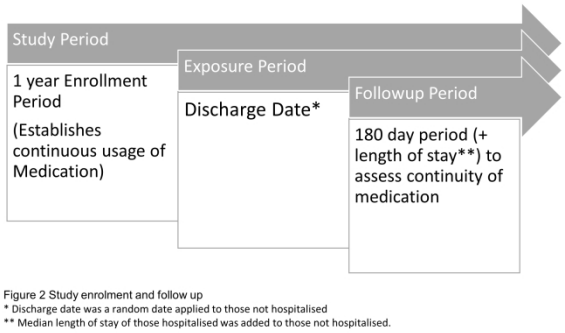

Figure 2 Study enrolment and follow up
* Discharge date was a random date applied to those not hospitalised
** Median length of stay of those hospitalised was added to those not hospitalised.

Figure 2 Study enrolment and follow up

338x190mm (300 x 300 DPI)

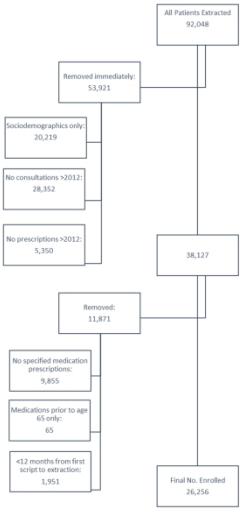

Figure 3 Participant flow chart

Figure 3 Participant flow chart

338x190mm (300 x 300 DPI)

Supplementary Table 1

Association between number of hospital admissions and medication discontinuation at follow-up

	Antithrombotics (B01)		Lipid-lowering (C10)		Thyroid meds(H03)		Respiratory inhalers (R03)	
	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)
Hospitalised v non-hospitalised	1.05 (0.99,1.11), p=0.09	1.06 (0.98,1.12), p=0.49	1.06 (1.00,1.12), p=0.03	1.03 (0.97,1.10), p=0.26	0.84 (0.65,1.08), p=0.18	0.79 (0.59,1.06), p=0.11	0.84 (0.74,0.96), p=0.01	0.87 (0.76,0.99), p=0.03
Age (years)	1.02 (1.01,1.03), p<0.001	1.02 (1.02,1.04), p<0.001	1.04 (1.03,1.05), p<0.001	1.05 (1.04,1.06), P<0.001	1.03 (1.01,1.05), p=0.002	1.06 (1.04,1.08), p<0.001	1.02 (1.01,1.03), p=0.004	1.03 (1.02,1.05), p<0.001
Gender: Female v Male	1.02 (0.89,1.17), p=0.79	1.01 (0.87,1.16), p=0.90	0.85 (0.74,0.96), p=0.01	0.83 (0.72,0.95), p=0.01	0.84 (0.57,1.24), p=0.38	0.85 (0.56,1.30), p=0.46	1.04 (0.85,1.28), p=0.68	1.04 (0.84,1.28), p=0.74
Insurance type: Private v GMS/DVC patients	5.10 (4.31,6.04), p<0.001	5.38 (4.54,6.39), p<0.001	4.78 (4.06,5.62), p<0.001	5.69 (4.80,6.74), p<0.001	9.79 (6.90,13.89), p<0.001	11.69 (8.04,16.96), p<0.001	3.66 (2.78,4.82), p<0.001	3.79 (2.87,5.02), p<0.001
Number of repeat drug classes	0.99 (0.98,1.01), p=0.56	0.99 (0.97,1.01), p=0.25	1.01 (1.00,1.04), p=0.04	1.01 (0.99,1.03) p=0.28	0.98 (0.95,1.02), p=0.41	0.98 (0.93,1.03), p=0.44	0.97 (0.94,0.99), p=0.01	0.97 (0.94,0.99), p=0.02
Charlson score (>=1 v0)	0.93 (0.80,1.07), p=0.31	0.93 (0.80,1.09), p=0.37	1.05 (0.91,1.21), p=0.48	0.97 (0.84,1.13), p=0.70	0.78 (0.56,1.08), p=0.15	0.79 (0.54,1.15), p=0.21	0.66 (0.53,0.81), p<0.001	0.71 (0.57,0.88), p=0.001
No of consultations in enrolment period	1.00 (0.99,1.01), p=0.62	1.00 (0.99,1.01), p=0.78	1.00 (0.99,1.01), p=0.69	1.00 (0.99,1.01), p=0.89	0.99 (0.97,1.00), p=0.11	1.00 (0.98,1.02), p=0.90	0.99 (0.98,1.00), p=0.02	1.00 (0.99,1.01), p=0.64

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

DVC: Doctor Visit Card

OR: odds ratio

CI: confidence interval

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	15-16
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	15
		(*e*) Describe any sensitivity analyses	16
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	See Figures
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	See Figures
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	See tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Unintended discontinuation of medication following hospitalisation: a retrospective cohort study

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Unintended discontinuation of medication following hospitalisation: a retrospective cohort study

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Abstract

Objectives: Whether unintended discontinuation of common, evidence based, long-term medication occurs after hospitalisation; what factors are associated with unintended discontinuation; and whether the presence of documentation of medication at hospital discharge is associated with continuity of medication in general practice.

Design: Retrospective cohort study between 2012 and 2015.

Setting: Electronic records and hospital supplied discharge notifications in 44 Irish general practices

Participants: 20,488 patients aged 65 years or more prescribed long-term medication for chronic conditions.

Primary and secondary outcomes: Discontinuity of four evidence-based medication drug classes- antithrombotic, lipid-lowering, thyroid replacement drugs and respiratory inhalers in hospitalised versus non-hospitalised patients; patient and health system factors associated with discontinuity; impact of the presence of medication in the hospital discharge summary on continuity of medication in a patient's GP prescribing record at six months follow up.

Results: In patients admitted to hospital, medication discontinuity ranged from 6-11% in the six months post-hospitalisation. Discontinuity of medication is significantly lower for hospitalised patients taking respiratory inhalers (adjusted odds ratio (AOR) 0.63, 95% Confidence Interval (CI) (0.49, 0.80), p<0.001) and thyroid medications (AOR 0.62, 95%CI (0.40, 0.96), p=0.03). There is no association between discontinuity of medication and hospitalisation for antithrombotics (AOR 0.95, 95%CI (0.81, 1.11), p=0.49) or lipid lowering medications (AOR 0.92, 95%CI (0.78, 1.08), p=0.29). Older patients and those who paid to see their GP were more likely to experience increased odds of discontinuity in all four medicine groups. Less than half (39% to 47.4%) of patients had medication listed on their hospital discharge summary. Presence of medication on hospital discharge summary is significantly associated with continuity of medication in the GP prescribing record for lipid lowering medications (AOR 1.64,

95%CI (1.15, 2.36), p=0.01) and respiratory inhalers (AOR 2.97, 95%CI (1.68, 5.25), p<0.01).

Conclusion: Discontinuity of evidence-based long-term medication is common. Increasing age and private medical care are independently associated with a higher risk of medication discontinuity. Hospitalisation is not associated with discontinuity but less than half of hospitalised patients have medication recorded on their hospital discharge summary.

Article Summary

Strengths and limitations of this study

1. This study includes prescribing data from a diverse group of general practices that includes non-fee and fee-paying patients.
2. We examined the impact of hospitalisation on continuity of evidence-based, long term medication after discharge using a novel data collection technique accessing GP prescribing records (as opposed to pharmacy dispensing records), codified chronic disease information and hospital provided discharge summary information.
3. We had no information on reasons for hospitalisation or therapeutic intent in terms of discontinuing medication.
4. We examined a limited number of medication groups and did not report on patient related-outcomes.

Introduction

Older patients are more likely to be prescribed multiple medications, have multiple chronic conditions, and experience increasing number of transitions of care.(1–3) Adherence to clinically appropriate, evidence-based therapies is important for lowering the risk of progression and complications related to their underlying chronic conditions.

Poor coordination of transitions of care is associated with adverse drug events (ADEs), rehospitalisation and discrepancies in medication lists.(4–9) Disruptions in medication continuity following hospitalisation have been reported.(10–13) In particular, omission of medication with known benefit has been noted in prescribing errors at discharge.(14–18) Previous studies have primarily examined large dispensing and/or administrative databases post hospitalisation to record the outcome of 'discontinuity'.(10–13,19) Hospitalisation giving rise to discontinuity may be attributable to prescribing errors at discharge (e.g. omissions, communication issues), disruption in the prescribing process at the general practitioner (GP) level, failure or error in dispensing at the pharmacy level or the multitude of reasons for patient non-adherence. It is unclear where and why this discontinuity arises. There has been limited assessment of the immediate impact of hospitalisation on medication omission at hospital discharge which in turn, influences general practice repeat prescribing records.(20–24)

Aim and objectives

The aim of this study was to determine whether the potentially unintentional discontinuation of common, evidence-based medications for chronic diseases occurs after hospitalisation among older community dwelling adults. The medicine groups considered are: antithrombotics (antiplatelet or anticoagulants); lipid-lowering medications; thyroid medications; and respiratory inhalers. These medications are commonly prescribed in older populations, have a strong evidence base in terms of efficacy and once started are usually recommended to be continued on a long-term basis. Furthermore, the continuity of these medications in prescribing and dispensing

records has been the subject of study internationally – allowing for comparison of results. (11,25–32).

We compare discontinuity of medication for each of the four medicine groups listed above in the GP prescribing record over a six-month period between patients who had been admitted to hospital and a group of patients who had not been admitted to hospital. Second, we examine whether other patient and health-system factors are associated with discontinuity of medication. A third objective is to assess whether documentation of prescribing of the specific medication in the hospital discharge summary record is associated with the presence of the same medication in the GP's prescribing record in the following six months.

Methods

Study design

We conducted a retrospective cohort study, adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.(33) Anonymous data were gathered using the general practice patient management system which includes prescribing, demographic and clinical records, and hospital supplied hospitalisation records. Project approval was received from the Irish Primary Care Research Network (IPCRN) and ethical approval was granted from the Irish College of General Practitioners.

Practice recruitment

A data extraction tool was developed with Socrates (providers of Electronic Health Record [EHR] software to a majority of GP practices in Ireland). Following piloting of the extraction tool, a convenience sample of practices using Socrates EHR and receiving electronic hospital discharge communication (n=48) were invited to participate. Forty-four GP practices (response rate 91%) provided consent to take part in the study. Thirty practices were in the catchment area of the Dublin hospitals, with one in the North-East of Ireland. Eleven practices were in the catchment area of the Galway hospitals and two in the catchment area of the Cork hospitals. Participating GPs were awarded continuing professional development points for their participation.

Medication classes

Four distinct patient cohorts were created based on the four medication classes: antithrombotics, lipid-lowering medications, thyroid medications, and respiratory inhalers (Figure 1 – Medication classes). These medications are commonly prescribed in older populations and once commenced, are usually continued on a long-term basis.

Study, enrolment and follow-up period criteria

The study period for each patient ranged from the 1st of January 2012 to the date when the data was extracted from the GP practice; this varied between practices, with the

median time being one year and 180 days (Figure 2 – Study enrolment and follow-up). The study period included a one-year enrolment period, and a six-month follow-up period. The enrolment period for each medication class was the earliest one-year period post 1st January 2012 over which a patient was continuously prescribed medication from that medication class. Continuously prescribed was defined as two prescriptions issued at least five months apart. No hospitalisations were allowed during the enrolment period to avoid misclassifying patients according to exposure. Patients could not be enrolled before 65 years of age and could be enrolled into more than one of the medication groups.

The start of the follow-up period, the period of time where discontinuity of medication was estimated, was marked by an index date. For patients who had been hospitalised, this was assigned as the day following discharge from hospital. For those individuals not experiencing hospitalisation, the index date was randomly assigned following the enrolment period. This method of generating a comparison group has been used previously and is in line with assuming the medications are long-term and unlikely to be discontinued.(11)

The follow-up period comprised a six-month period following the index date. For patients who were readmitted to hospital during this six-month period, the start of the follow-up period was reset until after the next discharge until a six-month period free from further hospitalisation was established. For all hospitalised patients the 180-day follow-up period was extended to take account of their length of stay of the relevant admission (reflecting the possibility that patients may have supplies of long-term medication at home). A median length of stay for those hospitalised was added to the unexposed group follow-up period.

Patients who were categorised as deceased/inactive at the extraction date or who had no consultations after each follow-up period were excluded from the analyses. This avoided misclassifying a patient who may, for example, have died in hospital or was

discharged to a long-term care facility and were not under the care of their previous general practitioner.

Explanatory variables of interest

For the first two objectives, hospitalisation was the main explanatory variable of interest. The electronic messaging system *Healthlink* provided discharge messages in 41 practices to signal a hospitalisation (inpatient stay, not Emergency Department attendances). Hospitalisation was coded manually by research centre trained coders in four practices by examining the clinical records directly (one practice provided both *Healthlink* electronic discharge information and manually-coded discharge information). For the third objective, the main exposure variable was presence of medication in the hospital discharge summary note. This analysis was limited to hospitalised patients only. For all analyses, we examined whether patient and health-system variables might be associated with absence (primary analysis) or presence (secondary analysis) of medication in the GP prescribing - age, gender, public / private status, number of GP consultations, polypharmacy or multi-morbidity. (34–39) Medication burden was calculated using RxRisk (34–40). All covariates were measured during the enrolment period.

Outcomes

The primary outcome was discontinuity of medication (failure to renew medication) in one of the four, pre-specified medication classes in the general practitioner record over the follow-up period. Changes within ATC class were allowed (e.g. between different brands of inhalers). For each medication class, discontinuity of medication was compared between those who had been hospitalised and those who had not. We calculated univariable associations across the four medication classes and adjusted for important confounders and other explanatory variables of interest. The secondary outcome was presence of relevant medication in the patient's general practice

prescribing record following discharge from hospital. Again, this was estimated for each medication cohort.

Sample size

The pilot phase and previous international studies in this area informed the calculation (11,12). Sample size calculation was based on 90% power to detect a 3% difference in the proportion of patients experiencing discontinuity. We assumed 11% of non-hospitalised patients have medications unintentionally discontinued. Additionally, a 4:1 ratio of non-hospitalised to hospitalised patients (based on experience from the pilot phase) with a statistical significance of 5% was used. This gave a total requirement of 8410 participants in any one medication cohort group.

Plan of analysis

The number of patients at each stage of the study is reported, including those potentially eligible for enrolment, those enrolled into each of the four cohorts, and those available for analysis in the follow-up period. Reasons for removal are documented at each stage.

Descriptive statistics for the primary exposure (hospitalisation) and other explanatory variables are reported. For all statistical analyses, multilevel modelling was used to examine the association between each exposure and outcome of interest, adjusting for patient and health-system variables. In these models, individual patient, are nested within GP practices, giving rise to a (two level) multilevel model. Multilevel modelling allows for the fact that patients within any given practice could reasonably be expected to have more in common with each other than with those from a different practice- for instance in terms of prescriber patterns.

For the primary outcome, a multilevel logistic multivariate model was fitted to estimate the association between hospitalisation and discontinuity of medication for each medication class in turn, adjusted for patient and health system variables- age, gender, public/private status, Charlson score (comorbidity), number of repeat drug classes

(polypharmacy), and number of enrolment period GP consultations. Results are reported as Adjusted Odds Ratios (AOR) with 95% Confidence Intervals (CI). These analyses were repeated using the number of hospital admissions (count variable) between the end of the enrolment period and the beginning of the follow-up period as the main exposure, in order to assess the impact of repeated hospital admissions on discontinuity of medication in the GP prescribing record.

For the secondary analyses, multilevel logistic multivariate regression was again used to examine, for each medication group, the association between prescribing of the specified medication at discharge from hospital and presence of the medication in the subsequent GP prescribing history over the next six months. Models were adjusted for the same patient and health-service variables listed above. Unadjusted analyses, examining the association between each explanatory variable and outcome in turn are reported for comparative purposes All analyses were performed using Stata V14.(41)

Patient and Public Involvement

Patients were not involved in the conception, design, or conduct of this research. We plan to disseminate the findings to the public and patients through our contacts in patient representative bodies, the popular media, and through the participating general practices.

Results

Cohort flow

A total of 92,048 patients had their records extracted from the 44 recruited practices, of which 53,921 (58.6%) were removed immediately due to insufficient data (patients with sociodemographic data only, or who had no prescriptions or consultations with the GP after 1 January 2012). (Figure 3 – Participant flow chart) A further 11,871 patients were removed due to not being prescribed any medications from the four drug groups of interest or having less than 12 months of follow-up data available to enable enrolment. The enrolment criteria were applied to the 26,256 remaining patients, creating four cohorts - antithrombotics (Anatomical Therapeutic Chemical (ATC) classification system, B01) (n=13,684), lipid-lowering medications (ATC C10) (n=14,427), thyroid medications (ATC H03) (n=3,484), and respiratory inhalers (ATC R03) (n=5,227). Out of the whole group of patients, 7,896 (38.5%) were enrolled in one medicine group, 9,184 (44.8%) in two groups, 3,074 (15.0%) in three groups and 334 (1.6%) in all four groups.

Descriptive statistics

The demographics of the participants within the four cohorts of those available at the follow-up period are presented in Table 1 (Participant Descriptives). Patients admitted to hospital tended to be slightly older, have more consultations with their general practitioner and higher levels of polypharmacy and co-morbidity during the enrolment period than patients who remained out of hospital.

Among patients who were not hospitalised, the percentage of participants experiencing discontinuation of medication at follow-up ranged from 8.5% (thyroid medications) to 17.0% (respiratory inhalers); and from 5.9% (thyroid medications) to 11.1% (respiratory inhalers) in those who were hospitalised. Levels of discontinuity were higher among those who had not been hospitalised in three of the four drug classes that were examined (Table 1).

Over two thirds of patients did not experience a hospital admission during follow up across the four medication groups (Table 2 – Hospital admissions). Of those admitted to

hospital, the percentage of patients experiencing a single admission ranged between 20.4% and 23.9% across the four medication groups. A minority of patients experienced multiple medical admissions (Table 2).

Univariable and multivariable associations

There is no difference in terms of likelihood of discontinuity for lipid-lowering and antithrombotic drugs between hospitalised and non-hospitalised patients. Hospitalisation is associated with less odds of discontinuity of long term medication on those prescribed thyroid medications and respiratory inhalers after adjustment for important confounders (Table 3 – Analysis of Primary outcome). For all four medication groups, older patients are more likely to experience discontinuity of medication than younger patients, with the odds of discontinuity increasing by between 3%-6% per year ($p<0.001$). Private patients (those who paid for their own prescriptions and their GP visits out of pocket) have the strongest association with discontinuity across all four medicine groups with adjusted odds ratios (AOR) varying between 3.75, (95% CI 2.84, 4.96) for respiratory inhalers to 11.67, (95% CI 8.02, 16.96) for thyroid medications (Table 3). Number of consultations, multi-morbidity, number of repeat medications and gender are not associated with an increased odds of discontinuity.

Repeated hospital admissions

To assess the impact of repeated hospital admissions, models were re-estimated with the hospital exposure defined as the number of hospital admissions (count) between the end of the enrolment period and the beginning of the follow-up period. For antithrombotics, lipid-lowering medications, and thyroid medications there was no evidence of a statistically significant association between the number of admissions to hospital and discontinuity of medication in the six-month follow up period. However, for respiratory inhalers, the odds of discontinuity of medication fell by an estimated 13% per additional admission to hospital after adjusting for confounders (AOR 0.87, (95%CI 0.76, 0.99), p=0.03). For further details see Supplementary Table 1 (Repeated admissions analysis).

Impact of medication specified in patient's hospital discharge summary

Recording of medication on the hospital discharge summary was relatively poor, with only 39.2% to 47.4% of patients having the relevant medication group documented across the four medication groups. Medication recording had improved at six months post discharge, being present in 89.2% to 94.7% of patient's GP clinical records across medication groups (Table 4 – Documentation of medication at discharge and in the GP record). Having medication listed on hospital discharge summary was independently associated with medication being present on the GP record as six months follow up for both lipid-lowering drugs and respiratory inhalers. Private patients were significantly less likely to have the relevant medication in their GP prescribing record in the six-month period following discharge from hospital than public patients. (Table 5 – Analysis of secondary outcome).

Discussion

Principal findings

Discontinuation of medication in patients who had been recently hospitalised ranged from 6 to 11% for commonly prescribed, evidence-based medicines, compared to 5-17% for non-hospitalised patients. Patients prescribed thyroid medications and respiratory inhalers, who experienced hospitalisation, actually had a lower risk of discontinuity. Public or private care played a significant role in the likelihood of medication being discontinued with the odds of discontinuation significantly higher for private patients than non-private patients in all medication groups. Increasing age is independently associated with an increased odds of discontinuation of medication. Lastly, recording of mediation on hospital discharge summaries is incomplete, being present in less than 50% of discharged patients for all four medication groups. Presence of medication on hospital discharge summaries is associated with continuity on the GP prescribing record at six months for lipid lowering medication and respiratory inhalers.

Previous research

Findings from this observational study differs from similar studies in the US, both in the magnitude of discontinuation: reported to be between 12-19% for thyroid and antithrombotic medications; and in terms of the impact of hospitalisation, with hospitalisation being independently associated with discontinuation, when assessed using pharmacy dispensing data.(8,9,10,41) The impact of hospitalisation appears to be context and health system-specific, with some studies not finding a relationship between discontinuity and hospitalisation.(42–44). We found that increased number of medications was not associated with discontinuation; in the respiratory inhalers group patients were less likely to be discontinued if they had increased numbers of medications.(34,37–39,45–47) Like other studies we found that increasing age was independently associated with an increased discontinuity post discharge.(19)

This study reported a varying discontinuity rate across the four drug classes (lower in antithrombotics and higher in respiratory inhalers). This variation may be explained by

disease specific issues: altering doses of thyroxine replacement meaning repeat prescriptions are not required; varying severity of disease – if a patient is asymptomatic they are less likely to take the medication regularly; evolving diagnoses or clinical considerations to patient beliefs about the effectiveness or benefits of the therapy or their own susceptibility to illness.(48)

A particularly interesting finding in our study is the marked difference between publicly funded and privately funded patients. Private patients were found to have a consistent pattern of discontinuity independent of other patient and health system factors (Table 3). Similarly, in hospitalised patients, being a private patient was associated with discontinuity of medication recording in their GP record and significantly more likely at six months follow up. There are possible explanations for this finding. Private patients are not required to have their hospital discharge prescription transcribed by their GP and may proceed directly to the pharmacy, thereby appearing as if their medication has been discontinued by our method of outcome calculation. Nevertheless, lack of continuity in the GP record raises concerns about completeness of the information a GP in relation to a patient's medication file, monitoring requirements, potential drug-to-drug interactions and other potential prescribing errors.

In keeping with findings from other studies, the quality of prescribing information contained in hospital discharge summaries was incomplete for over half of discharged patients, with the omission of essential medications common.(18,35) Furthermore lack of medication reconciliation upon hospital discharge appeared to persist for at least six months in general practice medication records.(21) The hospital discharge summary used to determine discharge medication in this study is only one element of the information normally provided to patients at discharge from hospital. A supplementary discharge prescription may also be provided.(35) Therefore a discrepancy may arise between the hospital discharge summary and additional discharge prescription, as hospital doctors make judgements about what to include/exclude from discharge prescriptions.(49) These parallel methods of providing post-discharge medication information is a cause for concern and likely enhance risks of medication discontinuity.

While lack of medication reconciliation following hospital discharge may be one possible explanation for the reported discontinuity, there are other possible explanations, most commonly poor patient adherence. A recent UK study of statin adherence reported discontinuation rates of 27% at one year in those prescribed statins. Notably this was examining primary non-adherence (failure to fill an initial prescription) as distinct from what may be secondary non-adherence (inadequate medication possession over a defined period of time) in this cohort).(50,51) The factors that influence adherence may be patient, therapy, physician or health system related.(52) While this study was able to control for some of these factors (demographics, comorbidities, public/private care status) others were not recorded (socioeconomic status, side-effects, individual physician behaviour and access to healthcare).

Lastly, inadequate adherence (and the related terms non-compliance and non-concordance) may take many forms e.g. non-filling of prescriptions, altering doses, stopping/starting. This study reported a varying discontinuity rate across the four drug classes (lower in antithrombotics and higher in thyroid medications and respiratory inhalers). This variation may be explained by disease-specific issues; for example, altering doses of thyroxine replacement due to undulating severity of disease meaning repeat prescriptions are not required; asymptomatic asthma patients not needing to take bronchodilator inhalers;), evolving or clinical considerations such as the changing risk benefit profile of an antithrombotic in a patient with a high risk of falls.(48)

Strengths and limitations of study

This is the largest Irish study to date to examine the effect of hospitalisation on the continuity of evidence-based medication in the GP prescribing record. It is also the first study to systematically use GP prescribing records (as opposed to pharmacy dispensing records) and includes details of both private and public patients, unique features of the mixed public/private health system in Ireland. The recruitment of GP practices was not limited to one geographically area/hospital catchment and the inclusion of multiple hospitals allowed comparison of messaging standards and their impact on prescribing continuity, enhancing the generalisability of the findings.

There are several limitations to this study. The medication groups were specifically chosen to be evidence-based and long-term in their usage and the establishment of an enrolment period of continuous usage over one year further ensures the pattern of ongoing use. However, the primary outcome of discontinuation of medication was applied to a prescribing database and does not contain information about indication or therapeutic intent, for example intentional discontinuation of statins in end-of-life patients. In addition, the nuances between different medications (e.g. warfarin and aspirin) is lost by grouping in larger ATC classes.

The nature of data collection and the dataset itself also incur limitations. Hand written prescriptions were not captured by this data collection technique. The follow-up of participants from enrolment through to outcome calculation also required assumptions to be made in preparing the data for analysis. However, the methods have been used previously, and are in line with the underlying assumption that there should be no difference between groups with both having 100% persistence of the medication in the GP record. These findings reflect the Irish healthcare system and may not be applicable in other systems with greater or lesser usage of electronic communication between primary/secondary care or developed reconciliation systems. Lastly, the recording of hospitalisation is likely to be variable within practices, with the *Healthlink* service employed differently by hospitals with the possibility of misclassification of exposed individuals. These methodological and data issues were explored in the sensitivity analysis with no change in the overall findings.

Clinical and healthcare policy implications

Medication reconciliation, the process of creating the most accurate list of medications at transition points, has been advocated by a number of different professional and accrediting bodies internationally. Ensuring the accuracy of medication information at transitions is reliant on good communication. The quality of electronic discharge communication received by general practices and the possible association with

inappropriate discontinuation of evidence-based medication suggests more emphasis needs to be placed on improving the quality of discharge communication. The HSE's ePrescribing initiative and eScript pilot projects are efforts to improve the transfer of medication information.(53,54)

Future efforts should focus on identifying high-risk individuals who are receiving medications that would be the best targets for reconciliation studies and interventions. Recent efforts have been made to develop a consensus about high risk medications and methods of assessing the potential severity of medication omission.(55)

Conclusions

Discontinuity of evidence-based long-term medication is common. Increasing age and private medical care are independently associated with a higher risk of medication discontinuity. Hospitalisation was not associated with discontinuity but less than half of hospitalised patients had medication recorded on their hospital discharge summary. System based solutions that include ePrescribing are needed to enhance the transfer of medication information across the primary/secondary care interface.

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Ethics:

Ethical approval was granted from the Irish College of General Practitioners' Research Ethics Committee. GPs as individual practice data controllers gave informed consent to participate.

Conflict of interests:

We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Author Contributions:

PR initiated the project, designed data collection tools, monitored data collection, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper.
RMcDowell wrote the statistical analysis plan, cleaned and analysed the data and revised the paper.
TG designed the data collection tools, wrote the statistical analysis plan, and revised the paper.
FB designed the data collection tools, wrote the statistical analysis plan, and revised the paper.
RMcDonnell designed the data collection tools and revised the paper.

CH initiated the project, advised on the statistical analysis plan, and revised the paper. TF initiated the project, monitored data collection, advised on the analysis plan and revised the paper. He is guarantor.

Data statement

Will individual participant data be available (including data dictionaries)?

No additional data is available. A data sharing provision was not included in the application to the research ethics committee for approval of this study.

What data in particular will be shared?

N/A

What other documents will be available?

N/A

When will data be available (start and end dates)?

N/A

With whom?

N/A

For what types of analyses?

N/A

By what mechanism will data be made available?

N/A

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Table 1

Descriptive statistics for participants in four evidence-based drug classes (ATC code)

Medication Group (No patients enrolled)	Antithrombotics (B01) (n=13,684)		Lipid-lowering (C10) (n=14,427)		Thyroid meds (H03) (n=3,484)		Respiratory inhalers (R03) (n=5,227)	
No. patients at end of follow-up period	Hospitalised (n=2,707)	Non-hospitalised (n=6,152)	Hospitalised (n=2,622)	Non-hospitalised (n=6,944)	Hospitalised (n=586)	Non-hospitalised (n=1,641)	Hospitalised (n=1,067)	Non-hospitalised (n=2,110)
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)
Age (years)	78.38 (7.06)	75.32 (6.95)	77.05 (6.77)	73.78 (6.45)	78.34 (7.25)	74.59 (7.18)	76.88 (7.02)	74.29(6.90)
No of consultations in enrolment period	18.28 (10.40)	14.80 (9.66)	17.50 (10.09)	13.71 (8.79)	18.76 (10.29)	14.81 (9.10)	19.64 (11.09)	16.07 (10.57)
No of repeat drug classes during enrolment period	8.04 (3.72)	7.01 (3.45)	7.77 (3.75)	6.44 (3.41)	8.59 (4.30)	6.67 (3.87)	9.26 (4.24)	7.99 (4.13)
RxRisk during enrolment period	5.07 (2.05)	4.55 (1.89)	4.99 (2.09)	4.26 (1.97)	5.37 (2.42)	4.36 (2.09)	4.79 (2.18)	4.29 (2.12)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Female	1,414 (52.23%)	3,176 (51.63%)	1,423 (54.27%)	3,957 (56.98%)	468 (79.86%)	1,349 (82.21%)	626 (58.67%)	1,276 (60.47%)
Insurance type: GMS/DVC	2,495 (92.17%)	5,495 (89.32%)	2,429 (92.64%)	6,194 (89.20%)	537 (91.64%)	1,445 (88.06%)	998 (93.53%)	1,898 (89.95%)
Charlson index of 1 or more	1,400 (51.72%)	2,638 (42.88%)	1,357 (51.75%)	2,736 (39.40%)	290 (49.49%)	543 (33.09%)	690 (64.67%)	1,120 (53.08%)
Patients experiencing one hospitalisation only during first follow-up period	2,011 (74.29%)	-	1,958 (74.68%)	-	457 (77.99%)	-	761 (71.32%)	-
No. (%) patients discontinued during 1st follow-up period	288 (10.64%)	693 (11.26%)	282 (10.76%)	727 (10.47%)	35 (5.97%)	139 (8.47%)	118 (11.06%)	359 (17.01%)

ATC: Anatomical Therapeutic Chemical classification system

GMS: General Medical Services

DVC: Doctor Visit Card

SD: standard deviation

Table 2

Number of hospital admissions following enrolment for patients assessed for medication discontinuity at follow-up

Medication Group (No patients enrolled)	Antithrombotics (B01) (n=13,684)	Lipid-lowering (C10) (n=14,427)	Thyroid meds (H03) (n=3,484)	Respiratory inhalers (R03) (n=5,227)
No. patients at end of follow-up period				
0	6,152 (69.44%)	6,944 (72.59%)	1,641 (73.69%)	2,110 (66.41%)
1	2,011 (22.70%)	1,958 (20.45%)	457 (20.52%)	761 (23.95%)
2	448 (5.06%)	419 (4.38%)	90 (4.04%)	200 (6.30%)
3	140 (1.58%)	139 (1.45%)	26 (1.17%)	60 (1.89%)
4	25 (0.28%)	50 (5.23%)	5 (0.23%)	27 (0.85%)
5	8 (0.09%)	24 (0.25%)	6 (0.27%)	5 (0.16%)
6	7 (0.08%)	8 (0.09%)	1 (0.04%)	5 (0.16%)
>6	23 (0.26%)	24 (0.25%)	1 (0.04%)	14 (0.44%)

Table 3

Univariable and multivariable associations in four evidence-based drug classes (ATC code)

	Antithrombotics (B01)		Lipid-lowering (C10)		Thyroid meds(H03)		Respiratory inhalers (R03)	
	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)
Hospitalised v non-hospitalised	0.95 (0.82,1.10), p=0.49	0.95 (0.81,1.11), p=0.49	1.04 (0.89,1.20), p=0.64	0.92 (0.78,1.08), p=0.29	0.68 (0.46,1.00), p=0.05	0.62 (0.40,0.96), p=0.03	0.62 (0.49,0.78), p=0.001	0.63 (0.49,0.80), p<0.001
Age (years)	1.02 (1.01,1.03), p<0.001	1.03 (1.02,1.04), p<0.001	1.04 (1.03,1.05), p<0.001	1.05 (1.04,1.06), P<0.001	1.03 (1.01,1.05), p=0.002	1.06 (1.04,1.09), p<0.001	1.02 (1.01,1.03), p=0.004	1.04 (1.02,1.05), p<0.001
Gender: Female v Male	1.02 (0.89,1.17), p=0.79	1.00 (0.87,1.15), p=0.99	0.85 (0.74,0.96), p=0.01	0.82 (0.72,0.95), p=0.01	0.84 (0.57,1.24), p=0.38	0.85 (0.56,1.30), p=0.46	1.04 (0.85,1.28), p=0.68	1.03 (0.83,1.27), p=0.79
Insurance type: Private v GMS/DVC patients	5.10 (4.31,6.04), p<0.001	5.35 (4.50,6.34), p<0.001	4.78 (4.06,5.62), p<0.001	5.68 (4.48,6.73), p<0.001	9.79 (6.90,13.89), p<0.001	11.67 (8.02,16.96), p<0.001	3.66 (2.78,4.82), p<0.001	3.75 (2.84,4.96), p<0.001
Number of repeat drug classes	0.99 (0.98,1.01), p=0.56	0.99 (0.97,1.01), p=0.28	1.01 (1.00,1.04), p=0.04	1.01 (0.99,1.04), p=0.24	0.98 (0.95,1.02), p=0.41	0.98 (0.94,1.03), p=0.44	0.97 (0.94,0.99), p=0.01	0.97 (0.94,0.99), p=0.02
Charlson score (>=1 v0)	0.93 (0.80,1.07), p=0.31	0.94 (0.80,1.09), p=0.41	1.05 (0.91,1.21), p=0.48	0.98 (0.84,1.14), p=0.78	0.78 (0.56,1.08), p=0.15	0.80 (0.54,1.15), p=0.22	0.66 (0.53,0.81), p<0.001	0.71 (0.58,0.88), p=0.002
No of consultations in enrolment period	1.00 (0.99,1.01), p=0.62	1.00 (0.99,1.01), p=0.63	1.00 (0.99,1.01), p=0.69	1.00 (0.99,1.01), p=0.75	0.99 (0.97,1.00), p=0.11	1.00 (0.98,1.02), p=0.83	0.99 (0.98,1.00), p=0.02	1.00 (0.99,1.01), p=0.72

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

DVC: Doctor Visit Card

OR: odds ratio

CI: confidence interval

Table 4

Cross tabulation of patients by presence of medication on hospital discharge summary and in the GP prescribing record at six months following hospitalisation

		GP Record		GP record		GP record		GP record	
Medication Group		Antithrombotics (B01) (n=1,991)†		Lipid-lowering (C10) (n=1,954) †		Thyroid meds(H03) (n=456) †		Respiratory inhalers (R03) (n=757) †	
		Absent	Present	Absent	Present	Absent	Present	Absent	Present
Hospital discharge	Absent	113 (10.55%)	958 (89.45%)	123 (10.35%)	1,065 (89.65%)	16 (6.67%)	224 (93.33%)	65 (14.19%)	393 (85.81%)
Hospital discharge	Present	78 (8.48%)	842 (91.52%)	63 (8.22%0	703 (91.78%)	8 (3.70%)	208 (96.30%)	17 (5.69%)	282 (94.31%)

†patients with medication discontinued at hospital discharge excluded

Table 5

Multivariable association of required medication appearing in GP clinical record following discharge from hospital

	Antithrombotics (B01) (N=1,991)*		Lipid-lowering (C10) (N=1,954)*		Thyroid meds(H03) (N=456)*		Respiratory inhalers (R03) (N=757)*	
	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)
Medication listed on discharge summary	1.29 (0.95,1.76), p=0.11	1.34 (0.97,1.87), p=0.08	1.40 (0.99,1.97), p=0.06	1.64 (1.15,2.36), p=0.01	1.86 (0.77,4.43), p=0.16	1.76 (0.70,4.42), p=0.23	2.74 (1.57,4.78), p<0.001	2.97 (1.68,5.25), p<0.001
Age (years)	0.98 (0.96,1.00), p=0.03	0.98 (0.96,1.00), p=0.08	0.96 (0.94,0.98), p<0.001	0.95 (0.93,0.98), p<0.001	0.96 (0.91,1.02), p=0.16	0.96 (0.91,1.02), p=0.16	0.97 (0.94,1.01), p=0.12	0.96 (0.93,1.00), p=0.03
Female v Male	1.02 (0.76,1.38), p=0.90	0.97 (0.70,1.33), p=0.84	1.14 (0.84,1.56), p=0.39	1.15 (0.83,1.59), p=0.41	1.34 (0.52,3.49), p=0.54	1.35 (0.49,3.73), p=0.57	0.93 (0.58,1.50), p=0.77	0.87 (0.53,1.43), p=0.59
Insurance type: Private v GMS/DVC patients	0.18 (0.13,0.26), p<0.001	0.18 (0.12, 0.27), p<0.001	0.19 (0.12,0.28), p<0.001	0.17 (0.11,0.27), p<0.001	0.10 (0.04,0.26), p<0.001	0.10 (0.04,0.26), p<0.001	0.26 (0.14,0.50), p<0.001	0.26 (0.13,0.49), p<0.001
Number of repeat drug classes	1.04 (1.00,1.09), p=0.06	1.04 (0.99,1.09), p=0.11	0.99 (0.94,1.03), p=0.49	1.00 (0.96,1.06), p=0.86	1.06 (0.95,1.18), p=0.30	1.10 (0.96,1.26), p=0.18	1.07 (10.01,1.13), p=0.03	1.08 (1.00,1.15), p=0.06
Charlson score (>=1 v0)	1.14 (0.84,1.54), p=0.40	1.08 (0.79,1.49), p=0.63	0.76 (0.55,1.04), p=0.09	0.79 (0.56,1.11) p=0.18	1.06 (0.46,2.40), p=0.90	0.82 (0.33,2.03), p=0.67	0.98 (0.61,1.58), p=0.94	0.86 (0.52, 1.45), p=0.55
No of consultations in enrolment period	1.01 (0.99,1.03), p=0.19	1.00 (0.99,1.02), p=0.74	0.99 (0.97,1.01), p=0.22	0.99 (0.97,1.01), p=0.16	1.01 (0.97,1.06), p=0.63	0.99 (0.94, 1.04), p=0.63	1.02 (1.00,1.05), p=0.07	1.02 (0.98,1.04), p=0.41

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

DVC: Doctor Visit Card

OR: odds ratio

CI: confidence interval

Figure 1 – Medication classes

Figure 2 – Study enrolment and follow-up

Figure 3 – Participant flow chart

World Health Organization Anatomical Therapeutic Chemical (WHO - ATC) Classification System Code*	Drug class/name	Examples
C10	Lipid modifying agents	Statins, ezetimibe etc.
B01 (includes N02BA01)	Antithrombotics (antiplatelet or anticoagulant agents)	Aspirin, clopidogrel, warfarin, novel oral anticoagulants (NOACs) etc.
H03	Thyroid medication	Levothyroxine, carbimazole etc.
R03	Respiratory inhalers	Inhaled anticholinergics, short & long acting beta agonists, inhaled steroids

*ATC code groupings (as above) were used to ensure all component drugs within a class were included (e.g. prasugrel, tecagrelor etc.)

This chapter refers to each cohort by the first three figures of the ATC group.

Figure 1 Medication classes

Figure 1 Medication classes

338x190mm (300 x 300 DPI)

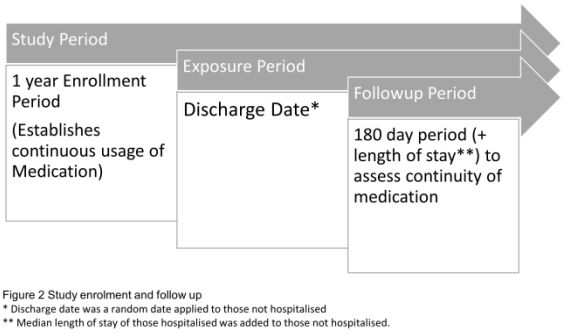

Figure 2 Study enrolment and follow up

338x190mm (300 x 300 DPI)

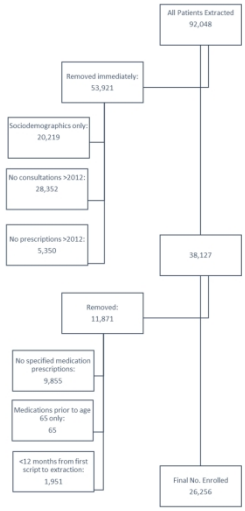

Figure 3 Participant flow chart

Figure 3 Participant flow chart

338x190mm (300 x 300 DPI)

Supplementary Table 1

Association between number of hospital admissions and medication discontinuation at follow-up

	Antithrombotics (B01)		Lipid-lowering (C10)		Thyroid meds(H03)		Respiratory inhalers (R03)	
	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)
Hospitalised v non-hospitalised	1.05 (0.99,1.11), p=0.09	1.06 (0.98,1.12), p=0.49	1.06 (1.00,1.12), p=0.03	1.03 (0.97,1.10), p=0.26	0.84 (0.65,1.08), p=0.18	0.79 (0.59,1.06), p=0.11	0.84 (0.74,0.96), p=0.01	0.87 (0.76,0.99), p=0.03
Age (years)	1.02 (1.01,1.03), p<0.001	1.02 (1.02,1.04), p<0.001	1.04 (1.03,1.05), p<0.001	1.05 (1.04,1.06), P<0.001	1.03 (1.01,1.05), p=0.002	1.06 (1.04,1.08), p<0.001	1.02 (1.01,1.03), p=0.004	1.03 (1.02,1.05), p<0.001
Gender: Female v Male	1.02 (0.89,1.17), p=0.79	1.01 (0.87,1.16), p=0.90	0.85 (0.74,0.96), p=0.01	0.83 (0.72,0.95), p=0.01	0.84 (0.57,1.24), p=0.38	0.85 (0.56,1.30), p=0.46	1.04 (0.85,1.28), p=0.68	1.04 (0.84,1.28), p=0.74
Insurance type: Private v GMS/DVC patients	5.10 (4.31,6.04), p<0.001	5.38 (4.54,6.39), p<0.001	4.78 (4.06,5.62), p<0.001	5.69 (4.80,6.74), p<0.001	9.79 (6.90,13.89), p<0.001	11.69 (8.04,16.96), p<0.001	3.66 (2.78,4.82), p<0.001	3.79 (2.87,5.02), p<0.001
Number of repeat drug classes	0.99 (0.98,1.01), p=0.56	0.99 (0.97,1.01), p=0.25	1.01 (1.00,1.04), p=0.04	1.01 (0.99,1.03) p=0.28	0.98 (0.95,1.02), p=0.41	0.98 (0.93,1.03), p=0.44	0.97 (0.94,0.99), p=0.01	0.97 (0.94,0.99), p=0.02
Charlson score (>=1 v0)	0.93 (0.80,1.07), p=0.31	0.93 (0.80,1.09), p=0.37	1.05 (0.91,1.21), p=0.48	0.97 (0.84,1.13), p=0.70	0.78 (0.56,1.08), p=0.15	0.79 (0.54,1.15), p=0.21	0.66 (0.53,0.81), p<0.001	0.71 (0.57,0.88), p=0.001
No of consultations in enrolment period	1.00 (0.99,1.01), p=0.62	1.00 (0.99,1.01), p=0.78	1.00 (0.99,1.01), p=0.69	1.00 (0.99,1.01), p=0.89	0.99 (0.97,1.00), p=0.11	1.00 (0.98,1.02), p=0.90	0.99 (0.98,1.00), p=0.02	1.00 (0.99,1.01), p=0.64

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

DVC: Doctor Visit Card

OR: odds ratio

CI: confidence interval

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	15-16
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	15
		(*e*) Describe any sensitivity analyses	16
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	See Figures
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	See Figures
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	See tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.

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Unintended discontinuation of medication following hospitalisation: a retrospective cohort study

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Unintended discontinuation of medication following hospitalisation: a retrospective cohort study

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Abstract

Objectives: Whether unintended discontinuation of common, evidence based, long-term medication occurs after hospitalisation; what factors are associated with unintended discontinuation; and whether the presence of documentation of medication at hospital discharge is associated with continuity of medication in general practice.

Design: Retrospective cohort study between 2012 and 2015.

Setting: Electronic records and hospital supplied discharge notifications in 44 Irish general practices

Participants: 20,488 patients aged 65 years or more prescribed long-term medication for chronic conditions.

Primary and secondary outcomes: Discontinuity of four evidence-based medication drug classes- antithrombotic, lipid-lowering, thyroid replacement drugs and respiratory inhalers in hospitalised versus non-hospitalised patients; patient and health system factors associated with discontinuity; impact of the presence of medication in the hospital discharge summary on continuity of medication in a patient's GP prescribing record at six months follow up.

Results: In patients admitted to hospital, medication discontinuity ranged from 6-11% in the six months post-hospitalisation. Discontinuity of medication is significantly lower for hospitalised patients taking respiratory inhalers (adjusted odds ratio (AOR) 0.63, 95% Confidence Interval (CI) (0.49, 0.80), p<0.001) and thyroid medications (AOR 0.62, 95%CI (0.40, 0.96), p=0.03). There is no association between discontinuity of medication and hospitalisation for antithrombotics (AOR 0.95, 95%CI (0.81, 1.11), p=0.49) or lipid lowering medications (AOR 0.92, 95%CI (0.78, 1.08), p=0.29). Older patients and those who paid to see their GP were more likely to experience increased odds of discontinuity in all four medicine groups. Less than half (39% to 47.4%) of patients had medication listed on their hospital discharge summary. Presence of medication on hospital discharge summary is significantly associated with continuity of medication in the GP prescribing record for lipid lowering medications (AOR 1.64, 95%CI (1.15, 2.36), p=0.01) and respiratory inhalers (AOR 2.97, 95%CI (1.68, 5.25), p<0.01).

Conclusion: Discontinuity of evidence-based long-term medication is common. Increasing age and private medical care are independently associated with a higher risk of medication discontinuity. Hospitalisation is not associated with discontinuity but less than half of hospitalised patients have medication recorded on their hospital discharge summary.

Article Summary

Strengths and limitations of this study

1. This study includes prescribing data from a diverse group of general practices that includes non-fee and fee-paying patients.
2. We examined the impact of hospitalisation on continuity of evidence-based, long term medication after discharge using a novel data collection technique accessing GP prescribing records (as opposed to pharmacy dispensing records), codified chronic disease information and hospital provided discharge summary information.
3. We had no information on reasons for hospitalisation or therapeutic intent in terms of discontinuing medication.
4. We examined a limited number of medication groups and did not report on patient related-outcomes.

Introduction

Older patients are more likely to be prescribed multiple medications, have multiple chronic conditions, and experience increasing number of transitions of care.(1–3) Adherence to clinically appropriate, evidence-based therapies is important for lowering the risk of progression and complications related to their underlying chronic conditions.

Poor coordination of transitions of care is associated with adverse drug events (ADEs), rehospitalisation and discrepancies in medication lists.(4–9) Disruptions in medication continuity following hospitalisation have been reported.(10–13) In particular, omission of medication with known benefit has been noted in prescribing errors at discharge.(14–18) Previous studies have primarily examined large dispensing and/or administrative databases post hospitalisation to record the outcome of 'discontinuity'.(10–13,19) Hospitalisation giving rise to discontinuity may be attributable to prescribing errors at discharge (e.g. omissions, communication issues), disruption in the prescribing process at the general practitioner (GP) level, failure or error in dispensing at the pharmacy level or the multitude of reasons for patient non-adherence. It is unclear where and why this discontinuity arises. There has been limited assessment of the immediate impact of hospitalisation on medication omission at hospital discharge which in turn, influences general practice repeat prescribing records.(20–24)

Aim and objectives

The aim of this study was to determine whether the potentially unintentional discontinuation of common, evidence-based medications for chronic diseases occurs after hospitalisation among older community dwelling adults. The medicine groups considered are: antithrombotics (antiplatelet or anticoagulants); lipid-lowering medications; thyroid medications; and respiratory inhalers. These medications are commonly prescribed in older populations, have a strong evidence base in terms of efficacy and once started are usually recommended to be continued on a long-term basis. Furthermore, the continuity of these medications in prescribing and dispensing

records has been the subject of study internationally – allowing for comparison of results. (11,25–32).

We compare discontinuity of medication for each of the four medicine groups listed above in the GP prescribing record over a six-month period between patients who had been admitted to hospital and a group of patients who had not been admitted to hospital. Second, we examine whether other patient and health-system factors are associated with discontinuity of medication. A third objective is to assess whether documentation of prescribing of the specific medication in the hospital discharge summary record is associated with the presence of the same medication in the GP's prescribing record in the following six months.

Methods

Study design

We conducted a retrospective cohort study, adhering to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) statement.(33) Anonymous data were gathered using the general practice patient management system which includes prescribing, demographic and clinical records, and hospital supplied hospitalisation records. Project approval was received from the Irish Primary Care Research Network (IPCRN) and ethical approval was granted from the Irish College of General Practitioners.

Practice recruitment

A data extraction tool was developed with Socrates (providers of Electronic Health Record [EHR] software to a majority of GP practices in Ireland). Following piloting of the extraction tool, a convenience sample of practices using Socrates EHR and receiving electronic hospital discharge communication (n=48) were invited to participate. Forty-four GP practices (response rate 91%) provided consent to take part in the study. Thirty practices were in the catchment area of the Dublin hospitals, with one in the North-East of Ireland. Eleven practices were in the catchment area of the Galway hospitals and two in the catchment area of the Cork hospitals. Participating GPs were awarded continuing professional development points for their participation.

Medication classes

Four distinct patient cohorts were created based on the four medication classes: antithrombotics, lipid-lowering medications, thyroid medications, and respiratory inhalers (Figure 1 – Medication classes). These medications are commonly prescribed in older populations and once commenced, are usually continued on a long-term basis.

Study, enrolment and follow-up period criteria

The study period for each patient ranged from the 1st of January 2012 to the date when the data was extracted from the GP practice; this varied between practices, with the median time being one year and 180 days (Figure 2 – Study enrolment and

follow-up). The study period included a one-year enrolment period, and a six-month follow-up period. The enrolment period for each medication class was the earliest one-year period post 1st January 2012 over which a patient was continuously prescribed medication from that medication class. Continuously prescribed was defined as two prescriptions issued at least five months apart. No hospitalisations were allowed during the enrolment period to avoid misclassifying patients according to exposure. Patients could not be enrolled before 65 years of age and could be enrolled into more than one of the medication groups.

The start of the follow-up period, the period of time where discontinuity of medication was estimated, was marked by an index date. For patients who had been hospitalised, this was assigned as the day following discharge from hospital. For those individuals not experiencing hospitalisation, the index date was randomly assigned following the enrolment period. This method of generating a comparison group has been used previously and is in line with assuming the medications are long-term and unlikely to be discontinued.(11)

The follow-up period comprised a six-month period following the index date. For patients who were readmitted to hospital during this six-month period, the start of the follow-up period was reset until after the next discharge until a six-month period free from further hospitalisation was established. For all hospitalised patients the 180-day follow-up period was extended to take account of their length of stay of the relevant admission (reflecting the possibility that patients may have supplies of long-term medication at home). A median length of stay for those hospitalised was added to the unexposed group follow-up period.

Patients who were categorised as deceased/inactive at the extraction date or who had no consultations after each follow-up period were excluded from the analyses. This avoided misclassifying a patient who may, for example, have died in hospital or was discharged to a long-term care facility and were not under the care of their previous general practitioner.

Explanatory variables of interest

For the first two objectives, hospitalisation was the main explanatory variable of interest. The electronic messaging system *Healthlink* provided discharge messages in 41 practices to signal a hospitalisation (inpatient stay, not Emergency Department attendances). Hospitalisation was coded manually by research centre trained coders in four practices by examining the clinical records directly (one practice provided both *Healthlink* electronic discharge information and manually-coded discharge information). For the third objective, the main exposure variable was presence of medication in the hospital discharge summary note. This analysis was limited to hospitalised patients only. For all analyses, we examined whether patient and health-system variables might be associated with absence (primary analysis) or presence (secondary analysis) of medication in the GP prescribing - age, gender, public / private status, number of GP consultations, polypharmacy or multi-morbidity. (34–39) Medication burden was calculated using RxRisk (34–40). All covariates were measured during the enrolment period.

Outcomes

The primary outcome was discontinuity of medication (failure to renew medication) in one of the four, pre-specified medication classes in the general practitioner record over the follow-up period. Changes within ATC class were allowed (e.g. between different brands of inhalers). For each medication class, discontinuity of medication was compared between those who had been hospitalised and those who had not. We calculated univariable associations across the four medication classes and adjusted for important confounders and other explanatory variables of interest. The secondary outcome was presence of relevant medication in the patient's general practice prescribing record following discharge from hospital. Again, this was estimated for each medication cohort.

Sample size

The pilot phase and previous international studies in this area informed the calculation (11,12). Sample size calculation was based on 90% power to detect a 3% difference in the proportion of patients experiencing discontinuity. We assumed 11%

of non-hospitalised patients have medications unintentionally discontinued. Additionally, a 4:1 ratio of non-hospitalised to hospitalised patients (based on experience from the pilot phase) with a statistical significance of 5% was used. This gave a total requirement of 8410 participants in any one medication cohort group.

Plan of analysis

The number of patients at each stage of the study is reported, including those potentially eligible for enrolment, those enrolled into each of the four cohorts, and those available for analysis in the follow-up period. Reasons for removal are documented at each stage.

Descriptive statistics for the primary exposure (hospitalisation) and other explanatory variables are reported. For all statistical analyses, multilevel modelling was used to examine the association between each exposure and outcome of interest, adjusting for patient and health-system variables. In these models, individual patient, are nested within GP practices, giving rise to a (two level) multilevel model. Multilevel modelling allows for the fact that patients within any given practice could reasonably be expected to have more in common with each other than with those from a different practice- for instance in terms of prescriber patterns.

For the primary outcome, a multilevel logistic multivariate model was fitted to estimate the association between hospitalisation and discontinuity of medication for each medication class in turn, adjusted for patient and health system variables- age, gender, public/private status, Charlson score (comorbidity), number of repeat drug classes (polypharmacy), and number of enrolment period GP consultations. Results are reported as Adjusted Odds Ratios (AOR) with 95% Confidence Intervals (CI). These analyses were repeated using the number of hospital admissions (count variable) between the end of the enrolment period and the beginning of the follow-up period as the main exposure, in order to assess the impact of repeated hospital admissions on discontinuity of medication in the GP prescribing record.

For the secondary analyses, multilevel logistic multivariate regression was again used to examine, for each medication group, the association between prescribing of

the specified medication at discharge from hospital and presence of the medication in the subsequent GP prescribing history over the next six months. Models were adjusted for the same patient and health-service variables listed above. Unadjusted analyses, examining the association between each explanatory variable and outcome in turn are reported for comparative purposes All analyses were performed using Stata V14.(41)

Patient and Public Involvement

Patients were not involved in the conception, design, or conduct of this research. We plan to disseminate the findings to the public and patients through our contacts in patient representative bodies, the popular media, and through the participating general practices.

Results

Cohort flow

A total of 92,048 patients had their records extracted from the 44 recruited practices, of which 53,921 (58.6%) were removed immediately due to insufficient data (patients with sociodemographic data only, or who had no prescriptions or consultations with the GP after 1 January 2012). (Figure 3 – Participant flow chart) A further 11,871 patients were removed due to not being prescribed any medications from the four drug groups of interest or having less than 12 months of follow-up data available to enable enrolment. The enrolment criteria were applied to the 26,256 remaining patients, creating four cohorts - antithrombotics (Anatomical Therapeutic Chemical (ATC) classification system, B01) (n=13,684), lipid-lowering medications (ATC C10) (n=14,427), thyroid medications (ATC H03) (n=3,484), and respiratory inhalers (ATC R03) (n=5,227). Out of the whole group of patients, 7,896 (38.5%) were enrolled in one medicine group, 9,184 (44.8%) in two groups, 3,074 (15.0%) in three groups and 334 (1.6%) in all four groups.

Descriptive statistics

The demographics of the participants within the four cohorts of those available at the follow-up period are presented in Table 1 (Participant Descriptives). Patients admitted to hospital tended to be slightly older, have more consultations with their general practitioner and higher levels of polypharmacy and co-morbidity during the enrolment period than patients who remained out of hospital.

Among patients who were not hospitalised, the percentage of participants experiencing discontinuation of medication at follow-up ranged from 8.5% (thyroid medications) to 17.0% (respiratory inhalers); and from 5.9% (thyroid medications) to 11.1% (respiratory inhalers) in those who were hospitalised. Levels of discontinuity were higher among those who had not been hospitalised in three of the four drug classes that were examined (Table 1).

Over two thirds of patients did not experience a hospital admission during follow up across the four medication groups (Table 2 – Hospital admissions). Of those admitted to hospital, the percentage of patients experiencing a single admission

ranged between 20.4% and 23.9% across the four medication groups. A minority of patients experienced multiple medical admissions (Table 2).

Univariable and multivariable associations

There is no difference in terms of likelihood of discontinuity for lipid-lowering and antithrombotic drugs between hospitalised and non-hospitalised patients. Hospitalisation is associated with less odds of discontinuity of long term medication on those prescribed thyroid medications and respiratory inhalers after adjustment for important confounders (Table 3 – Analysis of Primary outcome). For all four medication groups, older patients are more likely to experience discontinuity of medication than younger patients, with the odds of discontinuity increasing by between 3%-6% per year ($p<0.001$). Private patients (those who paid for their own prescriptions and their GP visits out of pocket) have the strongest association with discontinuity across all four medicine groups with adjusted odds ratios (AOR) varying between 3.75, (95% CI 2.84, 4.96) for respiratory inhalers to 11.67, (95% CI 8.02, 16.96) for thyroid medications (Table 3). Number of consultations, multi-morbidity, number of repeat medications and gender are not associated with an increased odds of discontinuity.

In a sub-group analysis of the antithrombotics (B01) category, we found that antiplatelets were independently associated with increased discontinuation after hospitalisation (adjusted odds ratio 1.30, 95 % CI 1.12, 1.52), whilst for warfarin and New Oral Anticoagulants (NOACs), no association between hospitalisation and discontinuation was observed (adjusted odds ratio 0.97, 95% CI 0.68, 1.39). For both antiplatelets and NOACs older age and private patients were independently associated with discontinuation (Supplementary Table 1).

Repeated hospital admissions

To assess the impact of repeated hospital admissions, models were re-estimated with the hospital exposure defined as the number of hospital admissions (count) between the end of the enrolment period and the beginning of the follow-up period. For antithrombotics, lipid-lowering medications, and thyroid medications there was no evidence of a statistically significant association between the number of admissions to hospital and discontinuity of medication in the six-month follow up period. However, for respiratory inhalers, the odds of discontinuity of medication fell

by an estimated 13% per additional admission to hospital after adjusting for confounders (AOR 0.87, (95%CI 0.76, 0.99), p=0.03). For further details see Supplementary Table 2 (Repeated admissions analysis).

Impact of medication specified in patient's hospital discharge summary

Recording of medication on the hospital discharge summary was relatively poor, with only 39.2% to 47.4% of patients having the relevant medication group documented across the four medication groups. Medication recording had improved at six months post discharge, being present in 89.2% to 94.7% of patient's GP clinical records across medication groups (Table 4 – Documentation of medication at discharge and in the GP record). Having medication listed on hospital discharge summary was independently associated with medication being present on the GP record as six months follow up for both lipid-lowering drugs and respiratory inhalers. Private patients were significantly less likely to have the relevant medication in their GP prescribing record in the six-month period following discharge from hospital than public patients. (Table 5 – Analysis of secondary outcome).

Discussion

Principal findings

Discontinuation of medication in patients who had been recently hospitalised ranged from 6 to 11% for commonly prescribed, evidence-based medicines, compared to 5-17% for non-hospitalised patients. Patients prescribed thyroid medications and respiratory inhalers, who experienced hospitalisation, actually had a lower risk of discontinuity. Public or private care played a significant role in the likelihood of medication being discontinued with the odds of discontinuation significantly higher for private patients than non-private patients in all medication groups. Increasing age is independently associated with an increased odds of discontinuation of medication. Lastly, recording of mediation on hospital discharge summaries is incomplete, being present in less than 50% of discharged patients for all four medication groups. Presence of medication on hospital discharge summaries is associated with continuity on the GP prescribing record at six months for lipid lowering medication and respiratory inhalers.

Previous research

Findings from this observational study differs from similar studies in the US, both in the magnitude of discontinuation: reported to be between 12-19% for thyroid and antithrombotic medications; and in terms of the impact of hospitalisation, with hospitalisation being independently associated with discontinuation, when assessed using pharmacy dispensing data.(8,9,10,41) The impact of hospitalisation appears to be context and health system-specific, with some studies not finding a relationship between discontinuity and hospitalisation.(42–44). We found that increased number of medications was not associated with discontinuation; in the respiratory inhalers group patients were less likely to be discontinued if they had increased numbers of medications.(34,37–39,45–47) Like other studies we found that increasing age was independently associated with an increased discontinuity post discharge.(19)

A particularly interesting finding in our study is the marked difference between publicly funded and privately funded patients. Private patients were found to have a

consistent pattern of discontinuity independent of other patient and health system factors (Table 3). Similarly, in hospitalised patients, being a private patient was associated with discontinuity of medication recording in their GP record and significantly more likely at six months follow up. There are possible explanations for this finding. Private patients are not required to have their hospital discharge prescription transcribed by their GP and may proceed directly to the pharmacy, thereby appearing as if their medication has been discontinued by our method of outcome calculation. Nevertheless, lack of continuity in the GP record raises concerns about completeness of the information a GP in relation to a patient's medication file, monitoring requirements, potential drug-to-drug interactions and other potential prescribing errors.

In keeping with findings from other studies, the quality of prescribing information contained in hospital discharge summaries was incomplete for over half of discharged patients, with the omission of essential medications common.(18,35) Furthermore lack of medication reconciliation upon hospital discharge appeared to persist for at least six months in general practice medication records.(21) The hospital discharge summary used to determine discharge medication in this study is only one element of the information normally provided to patients at discharge from hospital. A supplementary discharge prescription may also be provided.(35) Therefore a discrepancy may arise between the hospital discharge summary and additional discharge prescription, as hospital doctors make judgements about what to include/exclude from discharge prescriptions.(48) These parallel methods of providing post-discharge medication information is a cause for concern and likely enhance risks of medication discontinuity.

While lack of medication reconciliation following hospital discharge may be one possible explanation for the reported discontinuity, there are other possible explanations, most commonly poor patient adherence. A recent UK study of statin adherence reported discontinuation rates of 27% at one year in those prescribed statins. Notably this was examining primary non-adherence (failure to fill an initial prescription) as distinct from what may be secondary non-adherence (inadequate medication possession over a defined period of time) in this cohort).(49,50) The factors that influence adherence may be patient, therapy, physician or health system

related.(51) While this study was able to control for some of these factors (demographics, comorbidities, public/private care status) others were not recorded (socioeconomic status, side-effects, individual physician behaviour and access to healthcare).

Lastly, inadequate adherence (and the related terms non-compliance and non-concordance) may take many forms e.g. non-filling of prescriptions, altering doses, stopping/starting. This study reported a varying discontinuity rate across the four drug classes (lower in antithrombotics and higher in respiratory inhalers). The variation between medication classes observed here may be explained by disease-specific issues; for example, altering doses of thyroxine replacement due to undulating severity of disease meaning repeat prescriptions are not required; asymptomatic asthma patients not needing to take bronchodilator inhalers;), evolving or clinical considerations such as the changing risk benefit profile of an antithrombotic in a patient with a high risk of falls.(52)

Strengths and limitations of study

This is the largest Irish study to date to examine the effect of hospitalisation on the continuity of evidence-based medication in the GP prescribing record. It is also the first study to systematically use GP prescribing records (as opposed to pharmacy dispensing records) and includes details of both private and public patients, unique features of the mixed public/private health system in Ireland. The recruitment of GP practices was not limited to one geographically area/hospital catchment and the inclusion of multiple hospitals allowed comparison of messaging standards and their impact on prescribing continuity, enhancing the generalisability of the findings.

There are several limitations to this study. The medication groups were specifically chosen to be evidence-based and long-term in their usage and the establishment of an enrolment period of continuous usage over one year further ensures the pattern of ongoing use. However, the primary outcome of discontinuation of medication was applied to a prescribing database and does not contain information about indication or therapeutic intent, for example intentional discontinuation of statins in end-of-life patients. In addition, the nuances between different medications (e.g. warfarin and

aspirin) is lost by grouping in larger ATC classes. Differential discontinuation within the antithrombotic (B01) class of drugs was observed in a sub-group analysis, with antiplatelet discontinuation associated with hospitalisation, whilst for NOACs hospitalisation was not associated with discontinuation. These findings need to be treated with caution, as they were not pre-specified and the magnitude of association with antiplatelets is relatively modest.

The nature of data collection and the dataset itself also incur limitations. Hand written prescriptions were not captured by this data collection technique. The follow-up of participants from enrolment through to outcome calculation also required assumptions to be made in preparing the data for analysis. However, the methods have been used previously, and are in line with the underlying assumption that there should be no difference between groups with both having 100% persistence of the medication in the GP record. These findings reflect the Irish healthcare system and may not be applicable in other systems with greater or lesser usage of electronic communication between primary/secondary care or developed reconciliation systems. Lastly, the recording of hospitalisation is likely to be variable within practices, with the *Healthlink* service employed differently by hospitals with the possibility of misclassification of exposed individuals. These methodological and data issues were explored in the sensitivity analysis with no change in the overall findings.

Clinical and healthcare policy implications

Medication reconciliation, the process of creating the most accurate list of medications at transition points, has been advocated by a number of different professional and accrediting bodies internationally. Ensuring the accuracy of medication information at transitions is reliant on good communication. The quality of electronic discharge communication received by general practices and the possible association with inappropriate discontinuation of evidence-based medication suggests more emphasis needs to be placed on improving the quality of discharge communication. The HSE's ePrescribing initiative and eScript pilot projects are efforts to improve the transfer of medication information.(53,54)

Future efforts should focus on identifying high-risk individuals who are receiving medications that would be the best targets for reconciliation studies and interventions. Recent efforts have been made to develop a consensus about high risk medications and methods of assessing the potential severity of medication omission.(55)

Conclusions

Discontinuity of evidence-based long-term medication is common. Increasing age and private medical care are independently associated with a higher risk of medication discontinuity. Hospitalisation was not associated with discontinuity but less than half of hospitalised patients had medication recorded on their hospital discharge summary. System based solutions that include ePrescribing are needed to enhance the transfer of medication information across the primary/secondary care interface.

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Ethics:
Ethical approval was granted from the Irish College of General Practitioners' Research Ethics Committee. GPs as individual practice data controllers gave informed consent to participate.

Conflict of interests:
We have read and understood BMJ policy on declaration of interests and declare that we have no competing interests.

Author Contributions:
PR initiated the project, designed data collection tools, monitored data collection, wrote the statistical analysis plan, cleaned and analysed the data, and drafted and revised the paper.
RMcDowell wrote the statistical analysis plan, cleaned and analysed the data and revised the paper.
TG designed the data collection tools, wrote the statistical analysis plan, and revised the paper.
FB designed the data collection tools, wrote the statistical analysis plan, and revised the paper.
RMcDonnell designed the data collection tools and revised the paper.
CH initiated the project, advised on the statistical analysis plan, and revised the paper.

TF initiated the project, monitored data collection, advised on the analysis plan and revised the paper. He is guarantor.

Data statement

No additional data is available. A data sharing provision was not included in the application to the research ethics committee for approval of this study.

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Table 1

Descriptive statistics for participants in four evidence-based drug classes (ATC code)

Medication Group (No patients enrolled)	Antithrombotics (B01) (n=13,684)		Lipid-lowering (C10) (n=14,427)		Thyroid meds (H03) (n=3,484)		Respiratory inhalers (R03) (n=5,227)	
No. patients at end of follow-up period	Hospitalised (n=2,707)	Non-hospitalised (n=6,152)	Hospitalised (n=2,622)	Non-hospitalised (n=6,944)	Hospitalised (n=586)	Non-hospitalised (n=1,641)	Hospitalised (n=1,067)	Non-hospitalised (n=2,110)
	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)	Mean(SD)
Age (years)	78.38 (7.06)	75.32 (6.95)	77.05 (6.77)	73.78 (6.45)	78.34 (7.25)	74.59 (7.18)	76.88 (7.02)	74.29(6.90)
No of consultations in enrolment period	18.28 (10.40)	14.80 (9.66)	17.50 (10.09)	13.71 (8.79)	18.76 (10.29)	14.81 (9.10)	19.64 (11.09)	16.07 (10.57)
No of repeat drug classes during enrolment period	8.04 (3.72)	7.01 (3.45)	7.77 (3.75)	6.44 (3.41)	8.59 (4.30)	6.67 (3.87)	9.26 (4.24)	7.99 (4.13)
RxRisk during enrolment period	5.07 (2.05)	4.55 (1.89)	4.99 (2.09)	4.26 (1.97)	5.37 (2.42)	4.36 (2.09)	4.79 (2.18)	4.29 (2.12)
	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)	N (%)
Female	1,414 (52.23%)	3,176 (51.63%)	1,423 (54.27%)	3,957 (56.98%)	468 (79.86%)	1,349 (82.21%)	626 (58.67%)	1,276 (60.47%)
Insurance type: GMS/DVC	2,495 (92.17%)	5,495 (89.32%)	2,429 (92.64%)	6,194 (89.20%)	537 (91.64%)	1,445 (88.06%)	998 (93.53%)	1,898 (89.95%)
Charlson index of 1 or more	1,400 (51.72%)	2,638 (42.88%)	1,357 (51.75%)	2,736 (39.40%)	290 (49.49%)	543 (33.09%)	690 (64.67%)	1,120 (53.08%)
Patients experiencing one hospitalisation only during first follow-up period	2,011 (74.29%)	-	1,958 (74.68%)	-	457 (77.99%)	-	761 (71.32%)	-
No. (%) patients discontinued during 1st follow-up period	288 (10.64%)	693 (11.26%)	282 (10.76%)	727 (10.47%)	35 (5.97%)	139 (8.47%)	118 (11.06%)	359 (17.01%)

ATC: Anatomical Therapeutic Chemical classification system

GMS: General Medical Services

DVC: Doctor Visit Card

SD: standard deviation

Table 2

Number of hospital admissions following enrolment for patients assessed for medication discontinuity at follow-up

Medication Group (No patients enrolled)	Antithrombotics (B01) (n=13,684)	Lipid-lowering (C10) (n=14,427)	Thyroid meds (H03) (n=3,484)	Respiratory inhalers (R03) (n=5,227)
No. patients at end of follow-up period				
0	6,152 (69.44%)	6,944 (72.59%)	1,641 (73.69%)	2,110 (66.41%)
1	2,011 (22.70%)	1,958 (20.45%)	457 (20.52%)	761 (23.95%)
2	448 (5.06%)	419 (4.38%)	90 (4.04%)	200 (6.30%)
3	140 (1.58%)	139 (1.45%)	26 (1.17%)	60 (1.89%)
4	25 (0.28%)	50 (5.23%)	5 (0.23%)	27 (0.85%)
5	8 (0.09%)	24 (0.25%)	6 (0.27%)	5 (0.16%)
6	7 (0.08%)	8 (0.09%)	1 (0.04%)	5 (0.16%)
>6	23 (0.26%)	24 (0.25%)	1 (0.04%)	14 (0.44%)

Table 3

Univariable and multivariable associations in four evidence-based drug classes (ATC code)

	Antithrombotics (B01)		Lipid-lowering (C10)		Thyroid meds(H03)		Respiratory inhalers (R03)	
	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)
Hospitalised v non-hospitalised	0.95 (0.82,1.10), p=0.49	0.95 (0.81,1.11), p=0.49	1.04 (0.89,1.20), p=0.64	0.92 (0.78,1.08), p=0.29	0.68 (0.46,1.00), p=0.05	0.62 (0.40,0.96), p=0.03	0.62 (0.49,0.78), p=0.001	0.63 (0.49,0.80), p<0.001
Age (years)	1.02 (1.01,1.03), p<0.001	1.03 (1.02,1.04), p<0.001	1.04 (1.03,1.05), p<0.001	1.05 (1.04,1.06), P<0.001	1.03 (1.01,1.05), p=0.002	1.06 (1.04,1.09), p<0.001	1.02 (1.01,1.03), p=0.004	1.04 (1.02,1.05), p<0.001
Gender: Female v Male	1.02 (0.89,1.17), p=0.79	1.00 (0.87,1.15), p=0.99	0.85 (0.74,0.96), p=0.01	0.82 (0.72,0.95), p=0.01	0.84 (0.57,1.24), p=0.38	0.85 (0.56,1.30), p=0.46	1.04 (0.85,1.28), p=0.68	1.03 (0.83,1.27), p=0.79
Insurance type: Private v GMS/DVC patients	5.10 (4.31,6.04), p<0.001	5.35 (4.50,6.34), p<0.001	4.78 (4.06,5.62), p<0.001	5.68 (4.48,6.73), p<0.001	9.79 (6.90,13.89) , p<0.001	11.67 (8.02,16.96) , p<0.001	3.66 (2.78,4.82), p<0.001	3.75 (2.84,4.96), p<0.001
Number of repeat drug classes	0.99 (0.98,1.01), p=0.56	0.99 (0.97,1.01), p=0.28	1.01 (1.00,1.04), p=0.04	1.01 (0.99,1.04), p=0.24	0.98 (0.95,1.02), p=0.41	0.98 (0.94,1.03), p=0.44	0.97 (0.94,0.99), p=0.01	0.97 (0.94,0.99), p=0.02
Charlson score (>=1 v0)	0.93 (0.80,1.07), p=0.31	0.94 (0.80,1.09), p=0.41	1.05 (0.91,1.21), p=0.48	0.98 (0.84,1.14), p=0.78	0.78 (0.56,1.08), p=0.15	0.80 (0.54,1.15), p=0.22	0.66 (0.53,0.81), p<0.001	0.71 (0.58,0.88), p=0.002
No of consultations in enrolment period	1.00 (0.99,1.01), p=0.62	1.00 (0.99,1.01), p=0.63	1.00 (0.99,1.01), p=0.69	1.00 (0.99,1.01), p=0.75	0.99 (0.97,1.00), p=0.11	1.00 (0.98,1.02), p=0.83	0.99 (0.98,1.00), p=0.02	1.00 (0.99,1.01), p=0.72

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

DVC: Doctor Visit Card

OR: odds ratio

CI: confidence interval

Table 4

Cross tabulation of patients by presence of medication on hospital discharge summary and in the GP prescribing record at six months following hospitalisation

		GP Record		GP record		GP record		GP record	
Medication Group		Antithrombotics (B01) (n=1,991)†		Lipid-lowering (C10) (n=1,954) †		Thyroid meds(H03) (n=456) †		Respiratory inhalers (R03) (n=757) †	
		Absent	Present	Absent	Present	Absent	Present	Absent	Present
Hospital discharge	Absent	113 (10.55%)	958 (89.45%)	123 (10.35%)	1,065 (89.65%)	16 (6.67%)	224 (93.33%)	65 (14.19%)	393 (85.81%)
Hospital discharge	Present	78 (8.48%)	842 (91.52%)	63 (8.22%0	703 (91.78%)	8 (3.70%)	208 (96.30%)	17 (5.69%)	282 (94.31%)

†patients with medication discontinued at hospital discharge excluded

Table 5

Multivariable association of required medication appearing in GP clinical record following discharge from hospital

	Antithrombotics (B01) (N=1,991)*		Lipid-lowering (C10) (N=1,954)*		Thyroid meds(H03) (N=456)*		Respiratory inhalers (R03) (N=757)*	
	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)
Medication listed on discharge summary	1.29 (0.95,1.76), p=0.11	1.34 (0.97,1.87), p=0.08	1.40 (0.99,1.97), p=0.06	1.64 (1.15,2.36), p=0.01	1.86 (0.77,4.43), p=0.16	1.76 (0.70,4.42), p=0.23	2.74 (1.57,4.78), p<0.001	2.97 (1.68,5.25), p<0.001
Age (years)	0.98 (0.96,1.00), p=0.03	0.98 (0.96,1.00), p=0.08	0.96 (0.94,0.98), p<0.001	0.95 (0.93,0.98), p<0.001	0.96 (0.91,1.02), p=0.16	0.96 (0.91,1.02), p=0.16	0.97 (0.94,1.01), p=0.12	0.96 (0.93,1.00), p=0.03
Female v Male	1.02 (0.76,1.38), p=0.90	0.97 (0.70,1.33), p=0.84	1.14 (0.84,1.56), p=0.39	1.15 (0.83,1.59), p=0.41	1.34 (0.52,3.49), p=0.54	1.35 (0.49,3.73), p=0.57	0.93 (0.58,1.50), p=0.77	0.87 (0.53,1.43), p=0.59
Insurance type: Private v GMS/DVC patients	0.18 (0.13,0.26), p<0.001	0.18 (0.12, 0.27), p<0.001	0.19 (0.12,0.28), p<0.001	0.17 (0.11,0.27), p<0.001	0.10 (0.04,0.26), p<0.001	0.10 (0.04,0.26), p<0.001	0.26 (0.14,0.50), p<0.001	0.26 (0.13,0.49), p<0.001
Number of repeat drug classes	1.04 (1.00,1.09), p=0.06	1.04 (0.99,1.09), p=0.11	0.99 (0.94,1.03), p=0.49	1.00 (0.96,1.06), p=0.86	1.06 (0.95,1.18), p=0.30	1.10 (0.96,1.26), p=0.18	1.07 (10.01,1.13) , p=0.03	1.08 (1.00,1.15), p=0.06
Charlson score (>=1 v0)	1.14 (0.84,1.54), p=0.40	1.08 (0.79,1.49), p=0.63	0.76 (0.55,1.04), p=0.09	0.79 (0.56,1.11) p=0.18	1.06 (0.46,2.40), p=0.90	0.82 (0.33,2.03), p=0.67	0.98 (0.61,1.58), p=0.94	0.86 (0.52, 1.45), p=0.55
No of consultations in enrolment period	1.01 (0.99,1.03), p=0.19	1.00 (0.99,1.02), p=0.74	0.99 (0.97,1.01), p=0.22	0.99 (0.97,1.01), p=0.16	1.01 (0.97,1.06), p=0.63	0.99 (0.94, 1.04), p=0.63	1.02 (1.00,1.05), p=0.07	1.02 (0.98,1.04), p=0.41

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

DVC: Doctor Visit Card

OR: odds ratio

CI: confidence interval

Figure 1 – Medication classes

Figure 2 – Study enrolment and follow-up

Figure 3 – Participant flow chart

World Health Organization Anatomical Therapeutic Chemical (WHO - ATC) Classification System Code*	Drug class/name	Examples
C10	Lipid modifying agents	Statins, ezetimibe etc.
B01 (includes N02BA01)	Antithrombotics (antiplatelet or anticoagulant agents)	Aspirin, clopidogrel, warfarin, novel oral anticoagulants (NOACs) etc.
H03	Thyroid medication	Levothyroxine, carbimazole etc.
R03	Respiratory inhalers	Inhaled anticholinergics, short & long acting beta agonists, inhaled steroids

*ATC code groupings (as above) were used to ensure all component drugs within a class were included (e.g. prasugrel, tecagrelor etc.)

This chapter refers to each cohort by the first three figures of the ATC group.

Figure 1 Medication classes

Figure 1 Medication classes

338x190mm (300 x 300 DPI)

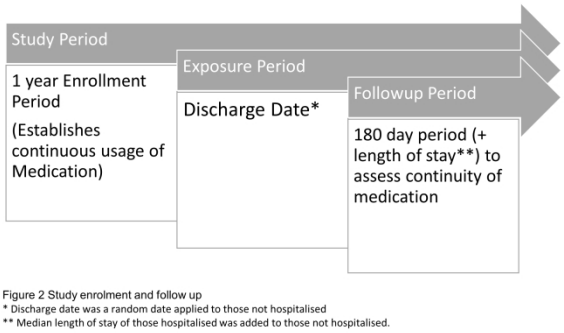

Figure 2 Study enrolment and follow up

338x190mm (300 x 300 DPI)

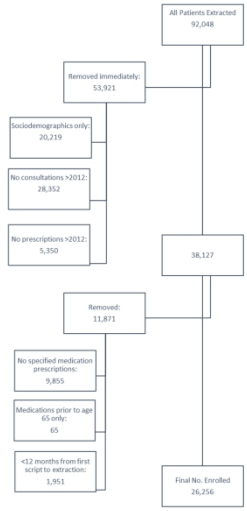

Figure 3 Participant flow chart

Figure 3 Participant flow chart

338x190mm (300 x 300 DPI)

Supplementary Table 1

Subgroup analysis of B01 subgroups and primary outcome of discontinuity

Unadjusted OR (95%CI, p-value)						Adjusted OR (95%CI, p-value)					
	Antithrombotics (B01) (n=13,684)	Aspirin and other antiplatelet agents: N02BA 01 B01AC (n=7613)	Warfarin: B01 AA (n=1267)	NOACs: B01AE B01AF (n=235)	Warfarin + NOACs: B01AA B01AE B01AF (n=1475)		Antithrombotics (B01) (n=13,684)	Aspirin and other antiplatelet agents: N02BA 01 B01AC (n=7613)	Warfarin: B01 AA (n=1267)	NOACs: B01AE B01AF (n=235)	Warfarin + NOACs: B01AA B01AE B01AF (n=1475)
Hospitalised v non-hospitalised	0.95 (0.82,1.10), p=0.49	1.33 (1.15,1.53) p<0.001	1.11 (0.82,1.50) p=0.49	1.05 (0.47,2.35) p=0.90	1.09 (0.78,1.53) p=0.61	Hospitalised v non-hospitalised	0.95 (0.81,1.11), p=0.49	1.30 (1.12,1.52) p<0.001	0.95 (0.69,1.30) p=0.74	1.01 (0.43,2.34) p=0.99	0.97 (0.68,1.39) p=0.88
Age (years)	**1.02 (1.01,1.03), p<0.001**	1.03 (1.02,1.04) p<0.001	1.04 (1.01,1.06) p<0.001	1.00 (0.94,1.05) p=0.91	1.04 (1.01,1.06) p<0.001	Age (years)	**1.03 (1.02,1.04), p<0.001**	1.03 (1.02,1.04) p<0.001	1.05 (1.02,1.07) p<0.001	1.00 (0.94,1.06) p=0.96	1.04 (1.02,1.07) p<0.001
Gender: Female v Male	1.02 (0.89,1.17), p=0.79	0.94 (0.83,1.08) p=0.39	0.91 (0.68,1.23) p=0.55	1.10 (0.53,2.31) p=0.80	1.22 (0.88,1.69) p=0.23	Gender: Female v Male	1.00 (0.87,1.15), p=0.99	0.88 (0.76,1.01) p=0.07	0.81 (0.58,1.11) p=0.19	1.24 (0.56,2.73) p=0.59	1.18 (0.83,1.67) p=0.36
Private v Public (GMS/DVC) patients	5.10 (4.31,6.04), p<0.001	3.89 (3.28,4.63) p<0.001	3.87 (2.55,5.87) p<0.001	3.72 (1.44,9.58) p=0.01	4.05 (2.64,6.23) p<0.001	Private v Public (GMS/DVC) patients	5.35 (4.50,6.34), p<0.001	4.26 (3.57,5.08) p<0.001	4.33 (2.81,6.67) p<0.001	4.42 (1.62,12.02) p<0.001	4.38 (2.81,6.82) p<0.001
Number of repeat drug classes	0.99 (0.98,1.01), p=0.56	1.01 (0.99,1.03) p=0.26	1.01 (0.97,1.05) p=0.67	0.99 (0.90,1.10) p=0.87	0.98 (0.93,1.02) p=0.27	Number of repeat drug classes	0.99 (0.97,1.01), p=0.28	1.00 (0.98,1.02) p=0.86	1.01 (0.97,1.06) p=0.52	0.95 (0.85,1.07) p=0.38	0.97 (0.92,1.02) p=0.23
Charlson score (>=1 v0)	0.93 (0.80,1.07), p=0.31	0.84 (0.73,0.97) p=0.02	0.93 (0.69,1.26) p=0.65	0.96 (0.46,2.00) p=0.91	1.04 (0.74,1.46) p=0.81	Charlson score (>=1 v0)	0.94 (0.80,1.09), p=0.41	0.81 (0.70,0.95) p=0.01	0.84 (0.61,1.16) p=0.29	1.07 (0.50,2.31) p=0.87	1.00 (0.70,1.43) p=1.00
No of consultations in enrolment period	1.00 (0.99,1.01), p=0.62	1.01 (1.00,1.01) p=0.11	1.00 (0.99,1.02) p=0.52	1.02 (0.98,1.06) p=0.35	1.00 (0.98,1.01) p=0.68	No of consultations in enrolment period	1.00 (0.99,1.01), p=0.63	1.01 (1.00,1.01) p=0.23	1.00 (0.99,1.02) p=0.48	1.03 (0.99,1.07) p=0.15	1.00 (0.98,1.02) p=0.98

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

DVC: Doctor Visit Card

OR: odds ratio

CI: confidence interval

Supplementary Table 2

Association between number of hospital admissions and medication discontinuation at follow-up

	Antithrombotics (B01)		Lipid-lowering (C10)		Thyroid meds(H03)		Respiratory inhalers (R03)	
	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)	Unadjusted OR (95%CI, p-value)	Adjusted OR (95%CI, p-value)
Hospitalised v non-hospitalised	1.05 (0.99,1.11), p=0.09	1.06 (0.98,1.12), p=0.49	1.06 (1.00,1.12), p=0.03	1.03 (0.97,1.10), p=0.26	0.84 (0.65,1.08), p=0.18	0.79 (0.59,1.06), p=0.11	0.84 (0.74,0.96), p=0.01	0.87 (0.76,0.99), p=0.03
Age (years)	1.02 (1.01,1.03), p<0.001	1.02 (1.02,1.04), p<0.001	1.04 (1.03,1.05), p<0.001	1.05 (1.04,1.06), P<0.001	1.03 (1.01,1.05), p=0.002	1.06 (1.04,1.08), p<0.001	1.02 (1.01,1.03), p=0.004	1.03 (1.02,1.05), p<0.001
Gender: Female v Male	1.02 (0.89,1.17), p=0.79	1.01 (0.87,1.16), p=0.90	0.85 (0.74,0.96), p=0.01	0.83 (0.72,0.95), p=0.01	0.84 (0.57,1.24), p=0.38	0.85 (0.56,1.30), p=0.46	1.04 (0.85,1.28), p=0.68	1.04 (0.84,1.28), p=0.74
Insurance type: Private v GMS/DVC patients	5.10 (4.31,6.04), p<0.001	5.38 (4.54,6.39), p<0.001	4.78 (4.06,5.62), p<0.001	5.69 (4.80,6.74), p<0.001	9.79 (6.90,13.89), p<0.001	11.69 (8.04,16.96), p<0.001	3.66 (2.78,4.82), p<0.001	3.79 (2.87,5.02), p<0.001
Number of repeat drug classes	0.99 (0.98,1.01), p=0.56	0.99 (0.97,1.01), p=0.25	1.01 (1.00,1.04), p=0.04	1.01 (0.99,1.03) p=0.28	0.98 (0.95,1.02), p=0.41	0.98 (0.93,1.03), p=0.44	0.97 (0.94,0.99), p=0.01	0.97 (0.94,0.99), p=0.02
Charlson score (>=1 v0)	0.93 (0.80,1.07), p=0.31	0.93 (0.80,1.09), p=0.37	1.05 (0.91,1.21), p=0.48	0.97 (0.84,1.13), p=0.70	0.78 (0.56,1.08), p=0.15	0.79 (0.54,1.15), p=0.21	0.66 (0.53,0.81), p<0.001	0.71 (0.57,0.88), p=0.001
No of consultations in enrolment period	1.00 (0.99,1.01), p=0.62	1.00 (0.99,1.01), p=0.78	1.00 (0.99,1.01), p=0.69	1.00 (0.99,1.01), p=0.89	0.99 (0.97,1.00), p=0.11	1.00 (0.98,1.02), p=0.90	0.99 (0.98,1.00), p=0.02	1.00 (0.99,1.01), p=0.64

Adjusted model includes gender, age, insurance type, Charlson Index, number of repeat drugs, number of consultations in the enrolment period

GMS: General Medical Services

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OR: odds ratio

CI: confidence interval

STROBE 2007 (v4) Statement—Checklist of items that should be included in reports of *cohort studies*

Section/Topic	Item #	Recommendation	Reported on page #
Title and abstract	1	(*a*) Indicate the study's design with a commonly used term in the title or the abstract	1
		(*b*) Provide in the abstract an informative and balanced summary of what was done and what was found	2
Introduction			
Background/rationale	2	Explain the scientific background and rationale for the investigation being reported	3
Objectives	3	State specific objectives, including any prespecified hypotheses	3-4
Methods			
Study design	4	Present key elements of study design early in the paper	6
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	6-7
Participants	6	(*a*) Give the eligibility criteria, and the sources and methods of selection of participants. Describe methods of follow-up	6-7
		(*b*) For matched studies, give matching criteria and number of exposed and unexposed	
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable	7-8
Data sources/ measurement	8*	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	*7-8*
Bias	9	Describe any efforts to address potential sources of bias	15-16
Study size	10	Explain how the study size was arrived at	8
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen and why	8-9
Statistical methods	12	(*a*) Describe all statistical methods, including those used to control for confounding	8-9
		(*b*) Describe any methods used to examine subgroups and interactions	N/A
		(*c*) Explain how missing data were addressed	9
		(*d*) If applicable, explain how loss to follow-up was addressed	15
		(*e*) Describe any sensitivity analyses	16
Results			

Participants	13*	(a) Report numbers of individuals at each stage of study—eg numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed	10
		(b) Give reasons for non-participation at each stage	N/A
		(c) Consider use of a flow diagram	See Figures
Descriptive data	14*	(a) Give characteristics of study participants (eg demographic, clinical, social) and information on exposures and potential confounders	See Figures
		(b) Indicate number of participants with missing data for each variable of interest	N/A
		(c) Summarise follow-up time (eg, average and total amount)	7
Outcome data	15*	Report numbers of outcome events or summary measures over time	10
Main results	16	(*a*) Give unadjusted estimates and, if applicable, confounder-adjusted estimates and their precision (eg, 95% confidence interval). Make clear which confounders were adjusted for and why they were included	11
		(*b*) Report category boundaries when continuous variables were categorized	See tables
		(*c*) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period	N/A
Other analyses	17	Report other analyses done—eg analyses of subgroups and interactions, and sensitivity analyses	16
Discussion			
Key results	18	Summarise key results with reference to study objectives	13
Limitations			
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	13-16
Generalisability	21	Discuss the generalisability (external validity) of the study results	13-16
Other information			
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	17

*Give information separately for cases and controls in case-control studies and, if applicable, for exposed and unexposed groups in cohort and cross-sectional studies.

Note: An Explanation and Elaboration article discusses each checklist item and gives methodological background and published examples of transparent reporting. The STROBE checklist is best used in conjunction with this article (freely available on the Web sites of PLoS Medicine at http://www.plosmedicine.org/, Annals of Internal Medicine at http://www.annals.org/, and Epidemiology at http://www.epidem.com/). Information on the STROBE Initiative is available at www.strobe-statement.org.