SPECIAL ARTICLE

Safer Prescribing — A Trial of Education, Informatics, and Financial Incentives

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ABSTRACT

BACKGROUND

High-risk prescribing and preventable drug-related complications are common in primary care. We evaluated whether the rates of high-risk prescribing by primary care clinicians and the related clinical outcomes would be reduced by a complex intervention.

METHODS

In this cluster-randomized, stepped-wedge trial conducted in Tayside, Scotland, we randomly assigned participating primary care practices to various start dates for a 48-week intervention comprising professional education, informatics to facilitate review, and financial incentives for practices to review patients' charts to assess appropriateness. The primary outcome was patient-level exposure to any of nine measures of high-risk prescribing of nonsteroidal antiinflammatory drugs (NSAIDs) or selected antiplatelet agents (e.g., NSAID prescription in a patient with chronic kidney disease or coprescription of an NSAID and an oral anticoagulant without gastroprotection). Prespecified secondary outcomes included the incidence of related hospital admissions. Analyses were performed according to the intention-to-treat principle, with the use of mixed-effect models to account for clustering in the data.

RESULTS

A total of 34 practices underwent randomization, 33 of which completed the study. Data were analyzed for 33,334 patients at risk at one or more points in the preintervention period and for 33,060 at risk at one or more points in the intervention period. Targeted high-risk prescribing was significantly reduced, from a rate of 3.7% (1102 of 29,537 patients at risk) immediately before the intervention to 2.2% (674 of 30,187) at the end of the intervention (adjusted odds ratio, 0.63; 95% confidence interval [CI], 0.57 to 0.68; P<0.001). The rate of hospital admissions for gastrointestinal ulcer or bleeding was significantly reduced from the preintervention period to the intervention period (from 55.7 to 37.0 admissions per 10,000 person-years; rate ratio, 0.66; 95% CI, 0.51 to 0.86; P=0.002), as was the rate of admissions for heart failure (from 707.7 to 513.5 admissions per 10,000 person-years; rate ratio, 0.73; 95% CI, 0.56 to 0.95; P=0.02), but admissions for acute kidney injury were not (101.9 and 86.0 admissions per 10,000 person-years, respectively; rate ratio, 0.84; 95% CI, 0.68 to 1.09; P=0.19).

CONCLUSIONS

A complex intervention combining professional education, informatics, and financial incentives reduced the rate of high-risk prescribing of antiplatelet medications and NSAIDs and may have improved clinical outcomes. (Funded by the Scottish Government Chief Scientist Office; ClinicalTrials.gov number, NCT01425502.)

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High-risk prescribing and preventable drug-related complications in primary care are major concerns for health care systems internationally.[1-7] Up to 4% of emergency hospital admissions are caused by preventable adverse drug events,[8-10] and in the United States, the cost of avoidable drug-related hospital admissions, emergency department attendances, and outpatient visits was estimated at $19.6 billion in 2013.[11] The majority of drug-related emergency admissions are caused by commonly prescribed drugs, with substantial contributions from nonsteroidal antiinflammatory drugs (NSAIDs) and antiplatelet medications because of gastrointestinal, cardiovascular, and renal adverse drug events.[4,5,7,8] Despite routine public reporting of a number of indicators of high-risk prescribing, variation among providers[12] and among Medicare hospital-referral regions[13] is large and reductions in high-risk prescribing are minimal or slow.[14,15]

Decisions about prescribing often involve balancing benefits and risks as well as the preferences of the patient, and high-risk prescribing is therefore sometimes appropriate, since benefits may be judged to outweigh the risk of harm to a person.[12,16-19] Nevertheless, the observed high prevalence of and large variation in high-risk prescribing patterns are consistent with the hypothesis that the safety of prescribing in primary care can be improved,[13-17] and at a minimum, regular review to assess appropriateness is required.

However, persuading primary care practices to allocate scarce staff resources to improving the safety of prescribing is challenging, particularly when practices are independent, physician-owned small businesses that provide primary medical care under contract to an external payer, as is the case in many countries, including in the United Kingdom, where this trial was performed.[18] Therefore, the Data-Driven Quality Improvement in Primary Care (DQIP) program systematically developed a multifaceted intervention for the improvement of prescribing safety in primary care practice.[12,19-21] This intervention comprised professional education about the risks of NSAIDs and antiplatelet medications, access to a Web-based tool to identify patients at the highest risk for adverse drug events related to NSAIDs and antiplatelet agents (aspirin or clopidogrel, as defined in Table S1 in the Supplementary Appendix, available with the full text of this article at NEJM.org), and structured financial incentives to review these patients.

We developed and refined this intervention in four pilot practices in which participating physicians judged that approximately 40% of the targeted high-risk prescribing involving NSAIDs and antiplatelet agents required corrective action.[21] We evaluated the intervention in a cluster-randomized trial that examined the effect of the intervention on high-risk prescribing of NSAIDs and antiplatelet medications and related emergency hospital admissions.

Methods

Study Design

In brief, the DQIP trial was a pragmatic, cluster-randomized trial that used a stepped-wedge design, in which all the participating practices received the DQIP intervention but were randomly assigned to 1 of 10 designated start dates between October 30, 2011, and September 2, 2012. Each practice received the intervention for a 48-week period, with continued data collection for 48 weeks after the active intervention ceased. Figure S1 in the Supplementary Appendix shows the stepped-wedge design of the study. The methods of the study are described in detail in the Supplementary Appendix. The study was approved by the National Health Service (NHS) Scotland Fife and Forth Valley research ethics committee. The study was conducted and reported with fidelity to the study protocol, which is available at NEJM.org. The authors vouch for the accuracy and completeness of the data presented.

Participants

Physician-owned practices with contracts to provide NHS primary medical care in the Tayside region of Scotland were eligible to participate if they used an electronic medical record (EMR) system that was compatible with data extraction to the DQIP informatics tool.[19] In the United Kingdom, patients are registered with one primary care practice that is responsible for all prescription of drugs in the community, including any prescribing that is initiated on the recommendation of a specialist. In each practice, patients were included at each data-measure-

ment point if they were alive, were permanently registered with the practice on that date, and had one or more risk factors that made them particularly vulnerable to adverse drug events related to NSAIDs or antiplatelet agents.

INTERVENTION

The development and detailed design of the intervention have been described in previous reports[19-21] and are summarized in the Supplementary Appendix. The intervention comprised three components. First, practices received professional education, with each practice receiving a 1-hour educational outreach visit by a pharmacist at the start of the intervention (see Section 4 in the Supplementary Appendix for the presentation used), additional written material, and newsletters (sent every 8 weeks) tailored to the progress of the practice.

Second, practices received financial incentives in the form of an initial fixed payment of £350 ($600 U.S.) and a payment of £15 ($25 U.S.) for every patient for whom the targeted high-risk prescribing was reviewed during the intervention period (with only one claim allowed for each patient). The average expected payment per full-time physician was approximately £550 ($910 U.S.), or approximately 0.6% of the average physician income.

Third, an informatics tool extracted data from the EMR system of each practice, identified individual patients who needed review, facilitated reviews of patients by graphically displaying relevant drug histories, and provided weekly updates on the rates of high-risk prescribing and progress in reviewing. Physicians accessed the tool by means of a password-protected Web-based portal. Identified patients were flagged by the tool as needing review. Physicians could clear the flag by recording an explicit decision that the prescribing was appropriate, by stopping prescription of the offending drugs, or by adding a gastroprotective drug (proton-pump inhibitor or histamine$_2$-receptor antagonist) for measures targeting the risk of gastrointestinal bleeding.

OUTCOME MEASURES

The primary outcome measure was a composite of nine measures of high-risk prescribing of NSAIDs and antiplatelet agents in people with risk factors for adverse drug events related to these drugs (Table S1 in the Supplementary Appendix). The individual measures were related to three types of adverse drug events: gastrointestinal events (six measures; e.g., aspirin or clopidogrel prescription for a patient taking an oral anticoagulant without coprescription of a gastroprotective drug), renal events (two measures; e.g., NSAID prescription for a patient with chronic kidney disease), and heart failure (NSAID prescription for a patient with heart failure).[20,22-27] The composite primary outcome was defined as the percentage of patients with any risk factor (e.g., taking an anticoagulant, having chronic kidney disease, or having heart failure) who were currently receiving an antiplatelet agent, an NSAID, or both in a way that was defined as "high risk" by one or more individual measures. Prespecified secondary prescribing outcomes included ongoing (prescribed within the previous year) and new (not prescribed within the previous year) high-risk prescribing and the rates of the nine prescribing outcome measures individually. In each practice, all prescribing indicators were measured every 8 weeks before and after the practice started the intervention, with the patients considered to be currently receiving a high-risk prescription if it had been issued at any point in the preceding 8 weeks.

Other prespecified secondary outcomes were emergency hospital admissions for gastrointestinal bleeding, acute kidney injury, or heart failure; we considered admissions that were preceded by targeted high-risk prescribing as well as all such admissions in patients with risk factors for adverse drug events related to NSAIDs and antiplatelet agents, regardless of high-risk prescribing. We also conducted a post hoc analysis involving these same patients to examine changes in the rates of unrelated hospital admissions for hip fracture, cancer, and surgical emergencies (appendicitis, cholecystitis, or pancreatitis) and in the rates of unrelated ambulatory care sensitive admissions (defined as angina, asthma, cellulitis, convulsions and epilepsy, chronic obstructive pulmonary disease, dehydration and gastroenteritis, dental conditions, diabetes complications, infection of the ear, nose, or throat, gangrene, hypertension, influenza and pneumonia, nutritional deficiency, other vaccine-preventable disease, pelvic inflammatory disease, or pyelonephritis) (Table S2 in the Supplementary Appendix).[28] All the outcomes were mea-

sured with the use of routine data that were extracted from practice EMRs (for prescribing) or from linked administrative data sets (for hospital admissions).

RANDOMIZATION AND START-DATE CONCEALMENT

Practices were assigned to 1 of 10 start dates by an independent statistician who was unaware of the identity of the practices, with randomization stratified by thirds of the number of registered patients. Concealment of the start-date assignment from practices and from the research team was not possible, but prescribing measures were calculated at a remote site by the data provider independently of the research team before the data were transferred to the research team, with the use of the same algorithms that were used to provide feedback to practices.

STATISTICAL ANALYSIS

On the basis of data from the pilot practices[19] and the Pharmacist-led Information Technology Intervention for Medication Errors (PINCER) trial,[29] we estimated that the study would have 83% power to detect a 25% reduction in the primary outcome, at an alpha level of 0.05, in 10 practices randomly assigned to 10 start dates.[19,30] We report the prespecified primary patient-level analysis, as well as a secondary practice-level analysis (see the Supplementary Appendix).

The analyses were performed according to the intention-to-treat principle; we analyzed data from all the eligible patients regardless of whether they actually received a review. Multilevel logistic regression was used to estimate odds ratios and 95% confidence intervals for exposure to high-risk prescribing across data points during the intervention period as compared with the preintervention period (Fig. S1 in the Supplementary Appendix), with adjustment for clustering within practices and over time. In prespecified analyses of hospital admissions, we summed events across all the practices during the preintervention period and the intervention period and calculated rates by dividing the sums by the total person-time during which patients had risk factors for adverse drug events related to NSAIDs and antiplatelet agents. The incidence in the intervention period versus the preintervention period was compared with the use of the conditional maximum-likelihood estimate of the rate ratio.[31]

Finally, in a post hoc analysis, we examined whether the effect of the DQIP intervention was sustained after the end of the intervention. We compared the rate of high-risk prescribing in the last 24 weeks of the intervention period with that in the last 24 weeks of the postintervention period using the same model as that used for the primary outcome (Fig. S1 in the Supplementary Appendix).

RESULTS

PARTICIPATING PRACTICES

Of 66 Tayside practices we approached, 34 (52%) agreed to participate, but 1 withdrew before its randomized start date. The intervention was therefore implemented in 33 practices, with a pooled list size of 202,262 patients on the date that the practices started the intervention. A total of 33,334 patients with risk factors for adverse drug events related to NSAIDs and antiplatelet agents were included in the analysis at one or more time points during the preintervention period, and 33,060 patients were included in the intervention period (Fig. S2 in the Supplementary Appendix). There was a significant but clinically small rising trend in the rate of high-risk prescribing during the preintervention period (mean absolute increase, 0.07 percentage points for every 8 weeks elapsed; 95% confidence interval [CI], 0.02 to 0.12).

PREINTERVENTION DATA

Table 1 shows the preintervention characteristics of the participating practices according to their randomly assigned start date. The numbers of patients with risk factors for adverse drug events related to NSAIDs and antiplatelet agents at the start of the intervention ranged from 1894 to 4857 patients across the 10 randomly assigned start dates, with 2.0 to 4.6% of the patients having prescriptions for a high-risk NSAID, an antiplatelet medication, or both at the start of the intervention. Although there were significant differences in the mean age and sex of the patients across start dates, absolute differences were small (range of mean age, 72 to 76 years; range of percentage of men, 45 to 48%). There were no significant differences in mean practice-list sizes and quality of care as measured by performance on the U.K. Quality and Outcomes Framework,[32] but the percentages of patients living in the most

Table 1. Preintervention Characteristics of the Patients and Practices, According to Randomized Start Date.*

Characteristic	Study Group									
	1	2	3	4	5	6	7	8	9	10
Patients†										
No. with risk factors for high-risk prescribing	2236	3253	2384	4857	2849	2532	2631	3968	1894	2933
Exposure to high-risk prescribing in previous 8 wk — no. (%)	90 (4.0)	151 (4.6)	71 (3.0)	184 (3.8)	115 (4.0)	96 (3.8)	108 (4.1)	168 (4.2)	59 (3.1)	60 (2.0)
Age — yr	74±12	74±11	72±13	74±12	76±11	74±13	75±12	75±12	74±12	76±12
Male sex — no. (%)	1009 (45.1)	1466 (45.1)	1143 (47.9)	2308 (47.5)	1340 (47.0)	1141 (45.1)	1226 (46.6)	1833 (46.2)	889 (46.9)	1404 (47.9)
Residence in most deprived quintile of Scottish postal codes — no. (%)‡	312 (14.0)	416 (12.8)	913 (38.3)	246 (5.1)	205 (7.2)	757 (29.9)	10 (0.4)	263 (6.6)	106 (5.6)	48 (1.6)
Practices										
Total no.	3	3	3	4	3	3	3	4	3	4
Training practices — no.§	1	1	0	0	1	1	1	3	0	1
Urban practices — no.¶	2	3	3	1	3	3	2	2	1	1
Mean no. of registered patients (range)	6128 (3680–8621)	6097 (2621–9804)	5323 (1367–7596)	759 (3205–10,052)	5769 (3224–7392)	6535 (3643–9738)	5418 (2738–8888)	7183 (2980–11,643)	5102 (2685–9358)	5171 (1962–8506)
QOF points achieved — mean (range)‖	979 (968–986)	966 (961–1000)	971 (948–1000)	968 (960–980)	970 (954–988)	968 (927–996)	985 (965–997)	982 (972–996)	983 (966–995)	987 (977–996)

* Plus–minus values are means ±SD. The 33 participating practices were divided into 10 study groups, according to the randomized start date of the intervention. The randomized start dates all occurred between October 30, 2011, and September 2, 2012, with 1 indicating the earliest group to start and 10 the latest. There were significant between-group differences in the following characteristics: patients who had high-risk prescribing in the previous 8 weeks, age of the patients, sex, and patients living in most socioeconomically deprived quintile of Scottish postal codes (all $P<0.001$). Analyses were performed with the use of one-way analysis of variance for means and the chi-square test for proportions. The proportions of training and urban practices in each group were not formally compared owing to small numbers.

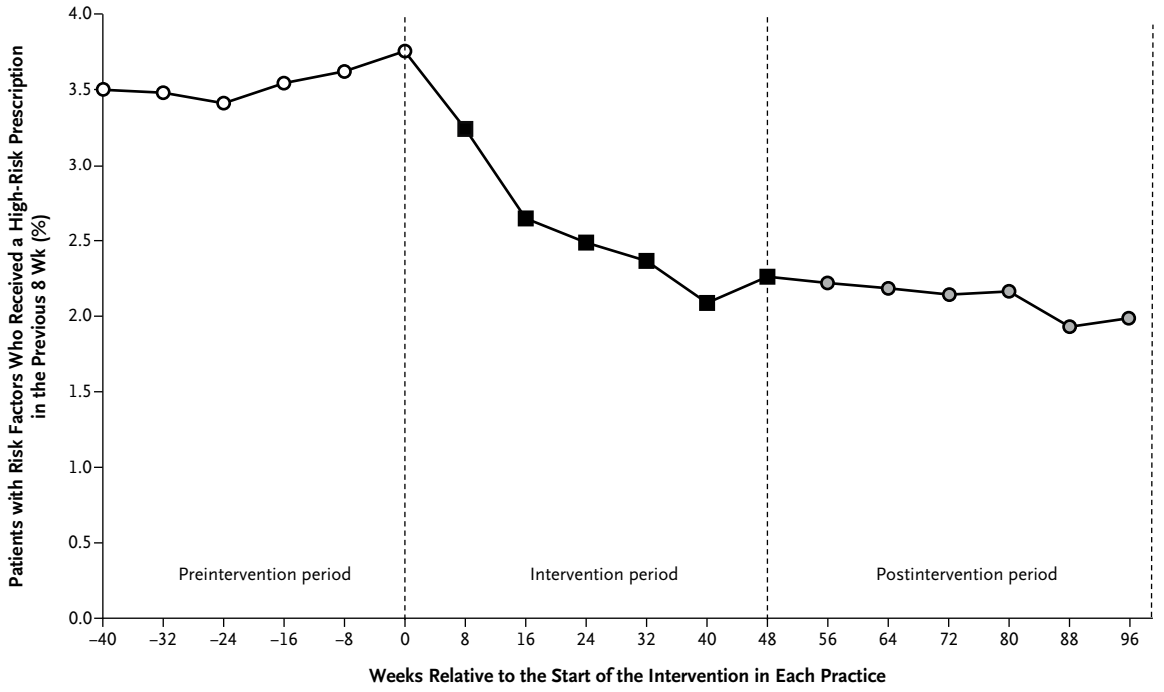
† Data are the total number of patients (defined as people registered to practices) across practices randomly assigned to each start date.

‡ Deprivation was defined as residence in the most socioeconomically deprived fifth of Scottish postal codes and was measured with the use of the Scottish Index of Multiple Deprivation, which is a measure that is applied to areas with a mean of approximately 750 residents.

§ Training practices were defined as practices that were registered for providing general practitioner training.

¶ Urban practices were defined as practices that were based in towns or cities with more than 10,000 residents.

‖ The Quality and Outcomes Framework (QOF) financially rewards primary care practices according to their performance on a range of clinical and organizational indicators, each of which is associated with a number of maximum achievable points, with each point corresponding to a defined payment. QOF scores range from 0 to 1000, with higher scores indicating better performance.[32]



No. of Patients with High-Risk Prescription	965	955	933	977	1036	1102	970	792	744	707	622	674	662	652	630	628	552	560
No. of Patients Particularly Vulnerable to Adverse Drug Events	27,775	27,642	27,565	27,766	28,801	29,537	30,166	30,224	30,246	30,242	30,204	30,187	30,213	30,245	29,804	29,416	29,053	28,616

Figure 1. Overall Trends in the Primary Outcome of High-Risk Prescribing across the Preintervention, Intervention, and Postintervention Periods.

Each data point represents the percentage of patients with risk factors who received a high-risk prescription during the 8 weeks previous to the stated time point. Time point 0 is the randomized intervention start date in each practice.

socioeconomically deprived areas varied significantly (range, 0.4 to 38.3%).

REVIEWS CONDUCTED BY PRACTICES

During the intervention period, 2905 patients with risk factors received at least one high-risk prescription. Approximately half of all patients who needed review during the 48-week intervention period were flagged for review at the first log-in. The remaining patients were flagged later during the intervention period; these patients had a mixture of prior intermittent use and true new use of high-risk prescriptions. Of these patients, 1598 (55.0%) underwent a total of 1858 reviews. At review, follow-up was judged to be required for 1296 of these cases (69.8%). Follow-up involved contacting patients to discuss appropriateness (515 patients [27.7% of all reviews]), planning discussion at future routine contact (409 [22.0%]), changing prescriptions and informing the patient by letter (163 [8.8%]), or other actions (209 [11.2%]).

PRESCRIBING OUTCOMES

Figure 1 shows trends in the primary outcome of high-risk prescribing, relative to the intervention start date in each practice (data for the 10 individual groups, according to the randomly assigned start dates, are shown in Figs. S3 and S4 in the Supplementary Appendix). In the

Table 2. Effect of the Intervention on Primary and Secondary High-Risk Prescribing Outcomes.*

Outcome Measure	Prevalence†		Multilevel Adjusted Odds Ratio of Intervention Effect (95% CI)‡	P Value	Intracluster Correlation Coefficient
	At Start of Intervention	At End of Intervention			
	no./total no. (%)				
Primary outcome: any high-risk prescribing in patient with any risk factor	1102/29,537 (3.7)	674/30,187 (2.2)	0.63 (0.57–0.68)	<0.001	0.036§
Secondary prescribing outcomes					
High-risk prescribing in patient with any risk factor¶					
Ongoing	766/29,537 (2.6)	463/30,187 (1.5)	0.60 (0.53–0.67)	<0.001	0.053
New	336/29,537 (1.1)	211/30,187 (0.7)	0.77 (0.68–0.87)	<0.001	0.027
Gastrointestinal composite	639/24,734 (2.6)	308/25,100 (1.2)	0.55 (0.50–0.62)	<0.001	0.033
NSAID or aspirin without gastroprotection in patient with prior peptic ulcer	252/3973 (6.3)	102/4026 (2.5)	0.27 (0.21–0.34)	<0.001	0.014
NSAID without gastroprotection in patient ≥75 yr of age	214/17,310 (1.2)	109/17,694 (0.6)	0.46 (0.38–0.57)	<0.001	0.084
NSAID without gastroprotection in patient ≥65 yr of age taking aspirin	119/8799 (1.4)	53/8206 (0.6)	0.39 (0.29–0.51)	<0.001	0.021
Clopidogrel without gastroprotection in patient ≥65 yr of age taking aspirin	61/8799 (0.7)	38/8206 (0.5)	0.44 (0.29–0.67)	<0.001	0.021
NSAID without gastroprotection in patient taking an oral anticoagulant	12/2483 (0.5)	3/2970 (0.1)	0.31 (0.10–0.94)	0.04	<0.001
Aspirin or clopidogrel without gastroprotection in patient taking an oral anticoagulant	50/2483 (2.0)	35/2970 (1.2)	0.32 (0.18–0.55)	<0.001	<0.001
Renal composite	533/12,166 (4.4)	381/12,612 (3.0)	0.78 (0.69–0.90)	<0.001	0.040
NSAID in patient taking both renin–angiotensin system blocker and diuretic	391/8033 (4.9)	283/8347 (3.4)	0.77 (0.65–0.91)	<0.001	0.039
NSAID in patient with chronic kidney disease	205/5841 (3.5)	145/6004 (2.4)	0.76 (0.62–0.94)	0.01	0.040
NSAID in patient with history of heart failure	33/1593 (2.1)	37/1784 (2.1)	0.78 (0.49–1.23)	0.29	0.015

* NSAID denotes nonsteroidal antiinflammatory drug.
† Data are the total number of patients across practices, at the start and end of the intervention period in each practice, who had risk factors for high-risk prescribing and who received a high-risk prescription in the previous 8 weeks.
‡ Multilevel adjusted odds ratios account for the clustering of patients within practices and the repeated measurement within patients over time. Under the stepped-wedge design, the adjusted odds ratios are calculated with the use of all data points in the intervention period versus the preintervention period and so represent the average odds of exposure to high-risk prescribing over the entire intervention period versus the preintervention period.
§ The intracluster correlation coefficient is the proportion of variation in outcome that is due to variation between practices.
¶ Ongoing high-risk prescribing was defined as the patient receiving a high-risk prescription during the measurement period and having been prescribed the same drug during the previous 48 weeks. New high-risk prescribing was defined as the patient receiving a high-risk prescription and not having had it during the previous 48 weeks.

Table 3. Secondary Outcome Measures Regarding Emergency Hospital Admission in Patients with Risk Factors for Adverse Drug Events from NSAIDs or Antiplatelet Medications.*

Outcome Measure	Preintervention Period†	Intervention Period†	Absolute Difference (95% CI)	Rate Ratio (95% CI)	P Value
Potentially drug-related hospital admission with relevant high-risk prescribing in the 8 wk before admission					
Gastrointestinal ulcer or bleeding admission preceded by high-risk prescribing in patients with gastrointestinal risk factors					
No. of events/person-yr	15/32,687	1/23,228			
Incidence — no. of events/10,000 person-yr (95% CI)	4.6 (25.7 to 75.7)	0.4 (0.0 to 2.4)	−4.2 (−6.6 to −1.7)	0.09 (0.00 to 0.52)	0.004
Acute kidney injury admission preceded by high-risk prescribing in patients with renal risk factors					
No. of events/person-yr	51/14,720	13/11,740			
Incidence — no. of events/10,000 person-yr (95% CI)	34.6 (25.8 to 45.6)	11.1 (5.9 to 18.9)	−23.6 (−34.8 to −12.3)	0.32 (0.17 to 0.58)	<0.001
Heart failure admission preceded by high-risk prescribing in patients with heart failure					
No. of events/person-yr	14/2374	5/1558			
Incidence — no. of events/10,000 person-yr (95% CI)	59.0 (33.6 to 96.6)	32.1 (11.8 to 71.1)	−26.9 (−68.7 to 14.9)	0.54 (0.20 to 1.51)	0.34
Potentially drug-related hospital admission regardless of preceding high-risk prescribing					
Gastrointestinal ulcer or bleeding admission in patients with gastrointestinal risk factors					
No. of events/person-yr	182/32,687	86/23,228			
Incidence — no. of events/10,000 person-yr (95% CI)	55.7 (48.2 to 64.4)	37.0 (30.0 to 45.7)	−18.7 (−7.4 to −29.9)	0.66 (0.51 to 0.86)	0.002
Acute kidney injury admission in patients with renal risk factors					
No. of events/person-yr	150/14,720	101/11740			
Incidence — no. of events/10,000 person-yr (95% CI)	101.9 (86.5 to 119.2)	86.0 (70.8 to 104.6)	−15.9 (−39.3 to 7.5)	0.84 (0.68 to 1.09)	0.19
Heart failure admission in patients with heart failure					
No. of events/person-yr	168/2374	80/1558			
Incidence — no. of events/10,000 person-yr (95% CI)	707.7 (608.4 to 823.2)	513.5 (412.4 to 639.3)	−194.2 (−349.5 to −38.9)	0.73 (0.56 to 0.95)	0.02
Unrelated hospital admission					
Hip fracture admission in patients with any risk factor					
No. of events/person-yr	465/38,505	377/27,878			
Incidence — no. of events/10,000 person-yr (95% CI)	120.8 (110.0 to 132.3)	135.2 (121.9 to 149.6)	14.5 (−3.0 to 32.0)	1.12 (0.98 to 1.28)	0.10

Any cancer admission in patients with any risk factor					
No. of events/person-yr	706/38,505	516/27,878			
Incidence — no. of events/10,000 person-yr (95% CI)	183.4 (170.1 to 197.4)	185.1 (169.5 to 200.8)	1.7 (−19.2 to 22.7)	1.01 (0.90 to 1.13)	0.87
Appendicitis, cholecystitis, or pancreatitis admission in patients with any risk factor					
No. of events/person-yr	54/38,505	38/27,878			
Incidence — no. of events/10,000 person-yr (95% CI)	14.0 (10.5 to 18.3)	13.6 (9.6 to 18.7)	0.4 (−6.1 to 5.3)	0.97 (0.64 to 1.47)	0.90
Any ambulatory care–sensitive admission in patients with any risk factor‡					
No. of events/person-yr	1926/38,505	1426/27,878			
Incidence — no. of events/10,000 person-yr (95% CI)	500.2 (478.1 to 523.0)	511.5 (485.3 to 538.8)	11.3 (−23.4 to 46.0)	1.02 (0.95 to 1.10)	0.52

* Data are the number of outcome events over the preintervention and intervention periods, during which patients had risk factors for high-risk prescribing. The analyses of potentially drug-related hospital admission with relevant high-risk prescribing in the 8 weeks before admission and potentially drug-related hospital admission regardless of preceding high-risk prescribing were prespecified. The analysis of hospital admission that was considered by the investigators to be unrelated to the specified high-risk prescribing patterns targeted by the intervention was post hoc.

† The differences in person-time are due to longer preintervention periods in practices randomly assigned to later start dates under the stepped-wedge design.

‡ Ambulatory care–sensitive admissions were as defined by Purdy et al.[28] for hospital admissions data in the United Kingdom, but admissions for heart failure, perforated peptic ulcer or bleeding, and iron-deficiency anemia were excluded because the investigators considered them to be potentially related to the targeted prescribing. Ambulatory care–sensitive conditions included were angina, asthma, cellulitis, convulsions and epilepsy, chronic obstructive pulmonary disease, dehydration and gastroenteritis, dental conditions, diabetes complications, infection of the ear, nose, or throat, gangrene, hypertension, influenza and pneumonia, nutritional deficiency, other vaccine-preventable disease, pelvic inflammatory disease, and pyelonephritis.

analysis of the primary outcome, 674 of 30,187 patients (2.2%) with risk factors for related adverse drug events had prescriptions for NSAIDs, antiplatelet agents, or both at the end of the intervention, as compared with 1102 of 29,537 (3.7%) who had prescriptions immediately before the intervention (adjusted odds ratio, 0.63; 95% CI, 0.57 to 0.68; P<0.001).

There were significant reductions in the rates of ongoing high-risk prescribing (from 2.6% immediately before the intervention to 1.5% at the end of the intervention; adjusted odds ratio, 0.60; 95% CI, 0.53 to 0.67; P<0.001) and new high-risk prescribing (from 1.1% to 0.7%; adjusted odds ratio, 0.77; 95% CI, 0.68 to 0.87; P<0.001). There were significant reductions in eight of the nine individual measures of high-risk prescribing (range of adjusted odds ratios, 0.27 to 0.78), but there was no significant reduction in the rate of NSAID prescribing for people with heart failure (Table 2).

Reductions in the rates of high-risk prescribing were sustained after financial incentives ceased. In an analysis of the primary outcome, 674 of 30,187 patients (2.2%) with risk factors for related adverse drug events had prescriptions for NSAIDs, antiplatelet agents, or both at the end of the intervention, and 560 of 28,616 (2.0%) had such prescriptions at 48 weeks after incentives ceased (adjusted odds ratio, 1.14; 95% CI, 0.85 to 1.53; P=0.38).

HOSPITAL ADMISSION OUTCOMES

Table 3 shows that among patients with risk factors for adverse drug events related to NSAIDs and antiplatelet agents, the incidence of admissions preceded by a high-risk prescription (received in the previous 8 weeks) was significantly reduced from the preintervention period to the intervention period; admissions for gastrointestinal bleeding were reduced from 4.6 per 10,000 person-years to 0.4 per 10,000 person-years (rate ratio, 0.09; 95% CI, 0.00 to 0.52), and admissions for acute kidney injury were reduced from 34.6 per 10,000 person-years to 11.1 per 10,000 person-years (rate ratio, 0.32; 95% CI, 0.17 to 0.58). The incidence of admissions for heart failure that were preceded by an NSAID prescription was not significantly reduced from the preintervention period to the intervention period (59.0 and 32.1 admissions per 10,000 person-years, respectively; rate ratio, 0.54; 95% CI, 0.20 to 1.51).

Among patients with risk factors for adverse drug events related to NSAIDs and antiplatelet agents, regardless of preceding high-risk prescribing, the incidence of total hospital admissions for gastrointestinal ulcer or bleeding was significantly reduced (from 55.7 to 37.0 admissions per 10,000 person-years; rate ratio, 0.66; 95% CI, 0.51 to 0.86), as was the incidence of heart failure (from 707.7 to 513.5 admissions per 10,000 person-years; rate ratio, 0.73; 95% CI, 0.56 to 0.95). The incidence of total admissions for acute kidney injury was not significantly reduced from the preintervention period to the intervention period (101.9 and 86.0 admissions per 10,000 person-years, respectively; rate ratio, 0.84; 95% CI, 0.68 to 1.09).

Among patients with risk factors for adverse drug events related to NSAIDs and antiplatelet agents, there was no significant change between the preintervention period and the intervention period in the incidence of admissions for hip fracture (120.8 and 135.2 admissions per 10,000 person-years, respectively; rate ratio, 1.12; 95% CI, 0.98 to 1.28), cancer (183.4 and 185.1 admissions per 10,000 person-years; rate ratio, 1.01; 95% CI, 0.90 to 1.13), or appendicitis, cholecystitis, or pancreatitis (14.0 and 13.6 admissions per 10,000 person-years; rate ratio, 0.97; 95% CI, 0.64 to 1.47), or in the incidence of unrelated ambulatory care sensitive admissions (500.2 and 511.5 admissions per 10,000 person-years; rate ratio, 1.02; 95% CI, 0.95 to 1.10).

DISCUSSION

We found that a complex intervention that combined professional education, informatics to identify high-risk patients, and financial incentives to primary care clinicians significantly reduced the rate of high-risk prescribing of NSAIDs and antiplatelet medications, which is a common cause of drug-related emergency hospital admissions internationally.[4,5,7,8] The effect on ongoing high-risk prescribing was somewhat larger than the effect on new high-risk prescribing — a finding that was consistent with the fact that the intervention prompted review of patients who were already exposed to high-risk prescribing — although both rates fell significantly, and a lower rate of initiation of prescribing contributed to the sustained effect in the year after financial incentives ceased. There was evidence that the intervention led to reductions in the rates of related emergency hospital admissions, with no change observed in the rate of unrelated admissions.

The strengths of the study include the careful intervention design,[12,19-21] evaluation in routine primary care practice, and examination of sustainability after financial incentives ceased. The study also has some important limitations. First, although half the eligible practices took part, participating practices may have been more motivated or had greater capacity to change than nonparticipating practices. Second, the stepped-wedge design can be vulnerable to secular trends if outcomes are already improving.[30] The rate of targeted high-risk prescribing was rising slowly during the preintervention period and there were no other relevant nontrial interventions during the period of implementation, which indicates that secular trends are unlikely to have affected the prescribing outcomes. However, we were unable to reliably examine prior time trends for the hospital admission outcomes examined, since they are relatively rare events, but the rates of four different types of unrelated admission did not fall significantly, which increases confidence in the observed findings.

It should be noted that the reductions in the total rates of admissions due to gastrointestinal bleeding and heart failure were larger than can be explained by reductions in the rates of such admissions that were actually preceded by the targeted high-risk prescribing. A recent study of a large pay-for-performance program in primary care that was conducted in the United Kingdom also showed larger reductions in the rates of emergency admission than could be explained by changes in targeted process measures.[33] Although such halo effects are conceivable (e.g., owing to safer use of other medicines that cause the same adverse effects or recommendations to patients to avoid over-the-counter NSAIDs and aspirin), confirmation in larger studies that are powered to robustly examine hospital admission outcomes is required.

Finally, although it is likely that this intervention would be effective for similar prescribing decisions (those based on an assessment of benefit and harm to the individual patient), common adverse drug events that are associated with other mechanisms will require different approaches. For example, reducing warfarin-related

harm is likely to require improvements in the reliability of monitoring and patient education.

This trial showed that a blend of education, financial incentives to review high-risk patients, and informatics to support review was effective, but we cannot identify which aspect of the intervention mattered most. Financial incentives to stop high-risk prescribing are potentially problematic because there may be a risk of inappropriate cessation to obtain payment in a subgroup of patients in whom the balance of benefit and harm favors continuation of the drug. We therefore chose to provide incentives to review. Since this approach could lead to "tick-box review" simply to obtain payment, we sought to ensure the delivery of meaningful review through the use of education and informatics, because an understanding of risk and an awareness that current practice is suboptimal are likely to be prerequisites for changing prescribing behavior, and there was good evidence from previous studies that both educational outreach visits and audit and feedback practices can lead to small improvements in prescribing.[34,35]

Feedback was one element of the informatics; the other was a reduction in barriers to efficient structured review. Education and minimization of the barriers to change were also elements in the successful PINCER intervention (based in the United Kingdom), in which external pharmacists reviewed patients who were exposed to high-risk prescribing and worked with primary care physicians to implement change. The PINCER trial showed reductions in the rates of high-risk prescribing that were similar to those observed with the DQIP intervention at 6 months, but the effect of pharmacist-led review partly waned by 12 months.[29] In contrast, the DQIP intervention had a sustained effect over the year after the financial incentives ceased, which is important to allow the focus of quality-improvement activity to move to other areas of care.

The three components of this intervention are feasible in any system in which primary care is delivered by physician-owned practices that use EMRs and are under contract with third-party payers, which is a common model internationally. However, complex interventions of this type inevitably require tailoring to context. For example, the size of the incentives that are required to prompt review is likely to vary according to primary care physician payment structures and incomes. Similarly, in some contexts, it may be easier to embed the informatics functionality directly in the EMR (e.g., if all targeted providers use one EMR system and the EMR supplier is willing to cooperate). Although we think that it is likely that interventions that blend education, incentives to review, and informatics will be effective in other health care systems, any implementation should be tailored to context and evaluated for effect.

In conclusion, we found that a complex intervention that combined professional education, informatics to support patient identification and review, and financial incentives to review patients who have been exposed to high-risk prescribing led to substantial and sustained reductions in targeted high-risk prescribing and was associated with reductions in the rates of related emergency admissions.

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