Electronic Medical Records and Quality of Prescriptions in General Practice

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"In God we trust. All others must bring data"
W. Edwards Deming

Electronic Medical Records and Quality of Prescriptions in General Practice
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About the cover: The cover is inspired by an art design of a labyrinth. This design demonstrates the nature of pursuit for truth and quality.

Electronic Medical Records and Quality of Prescriptions in General Practice

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Chapter 1

Introduction

General introduction

Health care is costly and needs constant improvement. In order to improve it we should be able to measure its quality. Quality indicators (QIs) form an instrument to measure quality.

QIs come in various forms. A common form states 1) a ratio with a nominator a denominator, and 2) a minimal or maximal percentage that the ratio should have. For example, in the QI "*At least 80% of diabetic patients should have an annual glycated hemoglobin measurement*" the nominator is the number of diabetic patients with an annual glycated hemoglobin measurement, the denominator is the number of diabetic patients in that year, and the 80% is the minimal percentage that ought to be achieved in order to render care as having good quality. Sometimes the percentage is not explicitly mentioned, only the nominator and denominator, hence only providing the performance unit.

In other times, QIs are implicitly formulated as clinical rules. An example of such a QI reads as follows: *"IF a vulnerable elder has diabetes, THEN glycated hemoglobin should be measured at least annually"*. This form of QIs, which we will adopt in this thesis, indicates what should be done under which circumstance, but can also be used to measure quality of care. Concretely, we can measure the *adherence* to this rule in terms of the ratio of the number of diabetic patients with at least one glycated hemoglobin measurement in a year, and the number of diabetic patients in that year. This adherence measurement can be fed back as quality assessment to the care providers in order to enable them to improve care. Alternatively, we could directly use these clinical rules to provide decision support in the form of alerts or reminders to healthcare professionals to comply with the rule. The computer has an important role to play in both of these scenarios of providing feedback and decision support. The swift advent of electronic patient records and the increasing availability of digital data underline this role.

The ultimate goal of this PhD thesis is the improvement of quality of prescribing to elderly patients in general practice. In particular, we sought to investigate the amenability of computerized assessment of quality of care based on quality indicators, and the opportunities they offer for clinical decision support. The context of investigation is defined by the primary care setting, the elderly patient population, and the prescription phase in the health care process.

Below, we provide preliminaries on quality of elderly care; prescriptions for elderly patients in general practice, and clinical decision support.

Quality of care for the elderly patient

Quality of care for elderly patients has become an increasingly important area of research especially due to the rapid increase in the number and share of this population. Elderly patients have longer lives than elderly patients of previous generations. The longer life expectancy is accompanied by an increase in healthcare expenditure [1] due to an increase in the prevalence of chronic illness and disability [2]. In addition, health policy makers are encouraging elderly persons to stay in their own homes instead of nursing homes or other centers offering institutionalized care. Many of these community dwelling elders seek health services from the general practices. There is thus an increase in the burden of care at the general practice level with a simultaneous increase in risk of lower quality of care. The importance of primary care for the elderly patients is therefore increasing.

Previous studies have shown that there are gaps in quality of care received by elderly persons. For instance, studies commissioned by the RAND Corporation in the USA found that the overall quality of care for elderly persons was lower than that of the general population[3,4]. In addition, these studies showed that physicians often fail to prescribe recommended medications to older adults. Moreover, other studies revealed that substantial variation existed in adherence to recommended care [5].

Quality of prescribing

In this thesis, we address quality of prescribing in general practice with focus on elderly patients. Many elderly persons suffer from multiple medical conditions that necessitate prescription of multiple chronic medications (polypharmacy) [6,7]. The elderly patients are thus vulnerable to adverse drug events [8,9]. Several factors increase the risk of adverse events to elderly persons, including physiological changes like reduction in renal and hepatic function, both of which are detrimental to drug metabolism. Furthermore, elderly persons are more prone to adverse events such as falls and delirium due to age related visual and cognitive decline.

One cause of preventable adverse drug events is the prescription of inappropriate medications. Inappropriate medication prescription (IMP) is defined as prescription that introduces a significant risk of an adverse drug related event when there is evidence for an equally or more effective alternative medication [10]. Previous studies have shown that inappropriate prescription to elderly patients is common.

In an attempt to improve quality of prescribing, various organizations have proposed different sets of prescription related quality indicators [10]. The quality indicators are meant to provide feedback to physicians to enable them change their prescribing behaviors. Studies have shown that quality indicators and guidelines result in improvement of care [11].

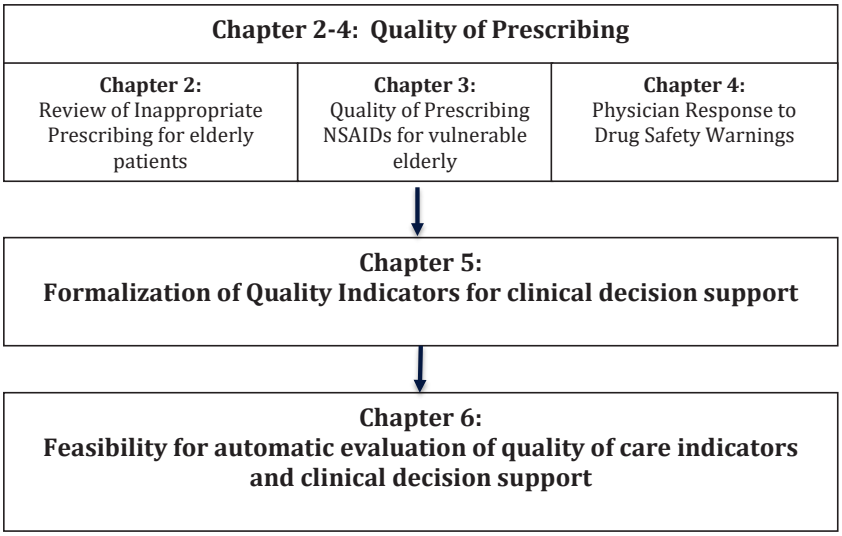
Clinical Decision Support

As mentioned earlier, quality indicators can be presented as clinical rules to physicians for the purposes of guiding decisions around patient care**.** Embedding such clinical rules in electronic medical records (EMRs) in the form of clinical decision support (CDS) is one method of improving quality of prescribing [12,13]. Most clinical rules are presented in a natural language. Conversion of the clinical rules into computer interpretable formats is thus required to allow

for computerized CDS. Unfortunately, there is lack of standard methodologies for formalizing clinical rules for use in clinical decision support.

Figure 1 summarizes the scope of the studies investigating the quality of prescribing and potential use of clinical decision support in EMRs for quality improvement.

Figure1. Thesis outline showing assessment of the state of quality of prescription and moving to formalization of quality indicators and, finally, to amenability of automatic evaluation of quality of care indicators.



Research Questions and outline of thesis

In this thesis, we sought to understand quality of prescribing and the applicability of the quality indicators for the evaluation of quality of care among the elderly in general practice using existing electronic medical records systems.

We formulated the following research questions:

1. What is the quality of prescribing to elderly patients in general practice?
2. How can quality indicators be formalised and used in computerised decision support for prescribing?
3. To what extent can clinical rules be automatically evaluated in general practice for assessing quality of care?

The thesis includes the following chapters:

Chapter 2 presents a review of the quality of prescriptions to elderly patients who attend primary care. In this chapter, we present results of a systematic review which we conducted to assess the overall quality of prescribing to elderly persons. The review included primary studies from several countries. Each primary study used a predefined set of quality indicators to assess the appropriateness of prescriptions to elderly patients. Quality of prescribing was reported as the rate of inappropriate medication prescription (IMP). The review is linked to research question 1.

Chapter 3 focuses on the quality of co-prescription of NSAIDs and gastroprotective medications for elders. Co-prescription of gastroprotective medications reduces the incidence of complications of NSAID use. We limited this study to general practices in the Netherlands. Furthermore, we explored epidemiological association of quality of prescribing and brands of EMRs used in general practice. This study is linked to the first research question, namely, what is the quality of prescribing to elderly patients in general practice?

Chapter 4 reports response of Dutch physicians to drug safety warnings and further explores the potential impact of electronic medical records in modifying the response. Drug safety warnings are issued by regulatory authorities such as the Federal Drug Agency (FDA). Physicians are expected to promptly change practice after the warnings. This study investigated the reaction of physicians to one such warning aimed at prescribing for the elderly diabetic patient group. It also addresses the first research question.

Chapter 5 presents the development of a method for assessing and formalising clinical rules for decision support. The motivation for this study was the lack of

standard methodology for formalizing clinical rules. We therefore developed the Logical Elements Rules Method (LERM) which is a method for assessing the extent to which clinical rules can be formalised for computerized decision support. The study answers the second research question: how can quality indicators be formalised and used in computerised clinical decision support?

Chapter 6 presents the analysis of feasibility of automatic evaluation of quality of care indicators in general practice. Using the LERM method we went further to assess the extent to which automatic evaluation of quality of care and clinical decision support can be implemented in Dutch general practices. Chapter six answers the third research question.

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Chapter 2

Inappropriateness of medication prescriptions to elderly patients in the primary care setting: a systematic review

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PLoS One; 2012; 7(8):e43617

Abstract:

Background

Inappropriate medication prescription is a common cause of preventable adverse drug events among elderly persons in the primary care setting.

Purposes

The aim of this systematic review is to quantify the extent of inappropriate prescription to elderly persons in the primary care setting.

Data Sources

Ovid-Medline and Ovid-EMBASE from 1950 and 1980 respectively to March 2012.

Study Selection

Two independent reviewers screened and selected primary studies published in English that measured (in) appropriate medication prescription among elderly persons (>65years) in the primary care setting.

Data extraction

We extracted data sources, instruments for assessing medication prescription appropriateness, and the rate of inappropriate medication prescriptions. We grouped the reported individual medications according to the Anatomical Therapeutic and Chemical (ATC) classification and compared the median rate of inappropriate medication prescription and its range within each therapeutic class.

Data Synthesis

We included 19 studies, 14 of which used the Beers criteria as the instrument for assessing appropriateness of prescriptions. The median rate of inappropriate medication prescriptions (IMP) was 20.5% [IQR: 18.1 to 25.6%.]. Medications with largest median rate of inappropriate medication prescriptions were

propoxyphene 4.31(0.10 - 23.30) %, doxazocin 3.96(0.32 - 15.70) %, diphenhydramine 3.30(0.02 - 4.40) % and amitriptiline 3.20(0.05 - 20.5) % in a decreasing order of IMP rate.

Limitations

Available studies described unequal sets of medications and different measurement tools to estimate the overall prevalence of inappropriate prescription.

Conclusions

Approximately one in five prescriptions to elderly persons in primary care is inappropropriate despite the attention that has been directed to quality of prescription. Diphenhydramine and amitriptiline are the most common inappropriately prescribed medications with high risk adverse events while propoxyphene and doxazoxin are the most commonly prescribed medications with low risk adverse events. These medications are good candidates for being targeted for improvement e.g. by computerized clinical decision support.

2.1 Introduction

The elderly population is increasing, resulting in a concomitant increase in chronic diseases and functional impairment (1). Moreover many of the elderly persons suffer from co-morbid conditions and disabilities that necessitate multiple medications or polypharmacy (2;3).

Adverse drug events are common in ambulatory care settings (4) and up to 35% of high risk older outpatients develop preventable adverse drug events (5). One cause of preventable adverse drug events is the prescription of inappropriate medications. Inappropriate medication prescription (IMP) has been defined as the prescription(s) that introduce(s) a significant risk of an adverse drug related event when there is evidence for an equally or more effective alternative medication(6). It can also be described as the failure to achieve the optimal quality of medication use (7). IMP has been classified as underprescribing, misprescribing or overprescribing (8). Several factors increase the risk of IMP to elderly persons, including physiological changes like reduction in renal and hepatic function, both of which are detrimental of drug metabolism and disabilities like visual and cognitive decline.

Aparasu *et al*. (9) and Gallagher *et al*. (10) reviewed, in 2000 and 2006 respectively, the incidence of IMP in elderly persons. Both reviews included studies with elderly persons in any healthcare setting from community dwelling elders to nursing home residents. Since then the criteria of assessing IMP have been revised and new medication list based tools have been developed (11-14). In addition, there is lack of a detailed review that compared the incidences of IMP within specific pharmacotherapeutic classes. Such a review is necessary to allow for the development of interventions that target the improvement of prescription of specific medications.

The aim of this systematic review is to identify and summarize published studies on IMP in elderly in primary care in order to quantify its extent in elderly

persons, and to identify medications for which interventions may be implemented to improve medication prescription quality.

2.2 Methods

Data Sources and Searches

We searched for relevant English articles using MeSH terms and keywords in title and abstract in the Ovid EMBASE (1980 – 8th March 2012), Ovid-Medline and Ovid Medline In-Process (1950 to 8th March 2012). The final literature search was performed on 8th March 2012. Figure 1 shows the search strategy and its corresponding flow chart. The search included terms related to elderly or geriatric persons, medications, prescription, appropriate prescription, primary care, ambulatory care, general practice, office practice or outpatient care as shown in box 1. Duplicate articles found in both two databases were removed. We screened the references of the identified papers as supplementary search.

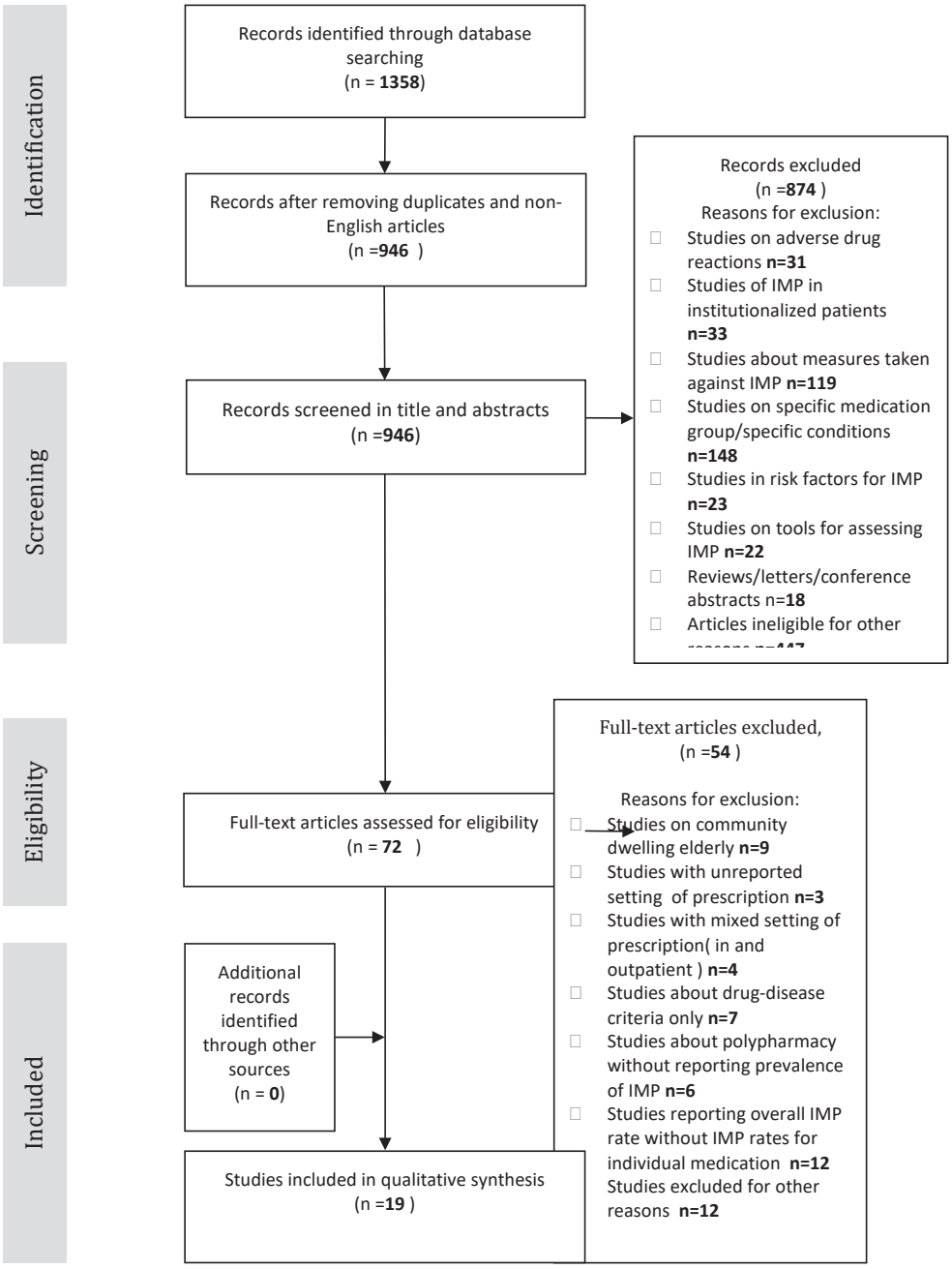
Box 1: Full search strategy

1. (elder* or senior* or geriatr* or (old* and adult*)).af.
2. (medication and error*).af.
3. (prescr* and error*).af.
4. (medication and safety).af.
5. (prescr* and safety).af.
6. (inappropriate* and prescr*).af.
7. (inappropriate* and medication).af.
8. 2 or 3 or 4 or 5 or 6 or 7
9. ((primary and care) or (office and practice) or (ambulat* and care) or (general and practice) or (outpatient* and care)).mp. [mp=ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, ps, rs, ui]
10. 1 and 8 and 9
11. remove duplicates from 10
12. limit 11 to english language

Study Selection

Two reviewers independently screened the titles and abstracts of the retrieved articles. Inclusion was limited to studies that defined the elderly as persons of 65 years and older who received prescriptions in the primary care setting.

Figure 1: Article selection flow diagram.



In this review, we only included papers that explicitly defined the setting of prescription as outpatient clinics, office practice, and general practice and primary health care clinics. Studies that included institutionalized patients and community dwelling elderly without indicating the specific setting in which the prescriptions were prescribed were excluded. In addition, studies which did not report the clinical setting of the study were also excluded.

Our analysis was limited to studies that reported IMP using drug-age criteria, which belong to the *unconditionally inappropriate medication prescription (IMP)* for persons 65 years old or older. Studies that reported IMP based on *drug-disease criteria* alone were not included due to heterogeneity of reporting in literature. For studies that evaluated IMP using the Beers criteria, we only included data indicating the rate of IMP measured independent of existing medical conditions and without any restrictions concerning dosage or duration of use, to allow for comparability of IMP with studies that did not use the Beers criteria. The principle of unconditionally inappropropriate prescription holds true for most of the list based criteria used for assessing IMP. Studies that reported only a single medication were excluded as well as studies that only described medication prescription for a specific disease group of elderly persons such as dementia patients.

To be included, studies must also report the rate of IMP for individual medications. This requirement allows for comparability of IMP rates of individual medication across different studies. Studies that reported rate of IMP after aggregating prescription by pharmacological classes, for example cardiovascular drugs, were excluded since it was impossible to find out which individual medications were included. Discrepancies between the two reviewers were resolved by consensus involving a third reviewer.

Data Extraction

The two reviewers extracted data from the selected articles on the following items: country; source of data used and instrument of assessing the

appropriateness of medication prescription. Additional data extracted included the number of patients involved in each study and data on the rate of IMP. In the studies where more than one instrument was used to measure the rate of IMP, the rate estimated by the latest Beers criteria was used to compare studies. When repeated measurements were reported, we used the most recent rate of IMP. We calculated weighted rates of IMP for individual medications in studies that reported rates of IMP in males and females separately. Discrepancies between these two reviewers were again resolved by consensus involving the third reviewer.

Data Synthesis and Analysis

We calculated the median and ranges of the overall rates of IMP for all medications reported in a study. We compared the overall rates of IMP per country and source of data. For each study that assessed IMP with more than one instrument, we compared the incidences of IMP among them.

Subsequently, we grouped all individual medications reported in the studies into their Anatomical Therapeutic and Chemical (ATC) class. The ATC is a World Health Organisation (WHO) hierarchical standard for classifying medications based on the anatomical organ or system on which they act, therapeutic group, pharmacological and chemical composition of the active ingredient (15). We classified medications at the therapeutic (T) level of the ATC classification. We considered the following eight major therapeutic classes: analgesics and non-steroidal anti-inflammatory drugs (NSAIDs), sedative hypnotics, anticholinergics(6) and antihistamines, antihypertensives, muscle relaxants, antidepressants, antiarrhythmics and anticlotting medications. Medications which do not belong to the above 8 therapeutic classes were not included for practical purposes.

For each medication in a therapeutic class, we calculated the median and range its IMP rate among all studies reporting on it. Additionally, each medication was labelled as high risk (H) or low risk (L) for adverse events to allow analysis at the

level of a medication's adverse event risk profile. This risk categorization was derived from the Beers criteria that distinguish between IMP with potentially low and high severity of adverse outcomes(6).

2.3 Results

Out of 946 articles screened 19 met the inclusion criteria for detailed analysis. Table 1 lists the included articles. The studies were conducted in 11 different countries. Seven studies were performed in the United States of America and eight in Europe. Two studies were conducted in Italy while one study was conducted in each of the following EU countries: Germany, The Netherlands, Ireland, Norway, Portugal, and the United Kingdom.

Table 1: List of included studies.

No	Author	Year	Country	Data Source	No. Patients	Criteria	Overall IMP rate
1	Goltz(16)	2012	Germany	Insurance data	12513584	Beers 2003	2.90
2	Ghadimi(17)	2011	Iran	Insurance data	2041	Beers 2003	30.0
3	Zaveri(18)	2010	India	Prospective data	407	Beers 2003	23.6
4	Maio(19)	2010	Italy	Others	91741	Modified Beers 2003	25.8
5	Ryan(20)	2009	Ireland	Practice data	1329	Beers 2003	18.3
6	Lai (21)	2009	Taiwan	Insurance data	2133864	Beers 2003	19.1
7	Lin (22)	2008	Taiwan	Insurance data	5741	Beers 2003	23.7
8	Wilde(23)	2007	UK	National health data	162000	Beers 2003	32.2
9	Bierman(24)	2007	USA	National health data	965756	Zhan	15.6
10	Maio (25)	2006	USA	Prospective data	100	Beers 2003	25.0
11	De Oliveira(26)	2006	Portugal	Prospective data	213	Beers 2003	38.5
12	Maio(27)	2006	Italy	Insurance data	849425	Beers 2003	18.0
13	Pugh(28)	2006	USA	National health data	1096361	HEDIS HRME	19.6
14	Van der Hooft (29)	2005	Holland	National health data	25258	Beers 2003	20.0
15	Pugh(30)	2005	USA	National health data	1265434	Others	33.0
16	Curtis (31)	2004	USA	Insurance data	765423	Beers 1997	21.0
17	Aparasu(32)	1999	USA	National health data	NA	Beers 1997	4.45
18	Straand (33)	1999	Norway	Prospective data	16874	MRPS List	13.5
19	Aparasu(34)	1997	USA	National Health data	NA	Beers 1991	5.04

Study description:

Eight different tools were used to assess the IMP rates. Beers based criteria were used in 15 of 19 studies: one study used Beers 1991, 2 studies used its 1997 version (Beers 1997), 11 used its 2003 version, (Beers 2003) and one study used modifications of Beers 2003. Other instruments used for assessing medication prescription included: Zhan's criteria (1 studies)(35), More & Romsdal Prescription Study (MRPS) list (1 study)(33). One study utilised the Health Plan Employer Data and Information Set (HEDIS) criteria (36). One study did not explicitly mention the instrument used for assessing the quality of prescription(30).

Four studies used more than one instrument for assessing the appropriateness of medication use. Two studies (26;29) that used the Beers 1997 and 2003 versions found consistently lower IMP percentages for the 1997 version: 27.7 vs. 38.5% and 18.5 vs. 20.0%. Pugh *et al*. found that Zhan's criteria had had a low rate of IMP (0.8%) when compared to unidentified reporting criteria (33.3%)(30). Ryan *et al*. compared Beers 2003 and the Screening Tool for Older Persons Prescriptions (STOPP) and found IMP rates of 18.3% and 21.4% respectively(20).

Six of the 18 studies (33.3%) used health insurance data, while 4 (22.2%) used prospectively collected data. Six studies (33.3%) used national health surveys and databases, and one study (5.6%) used general practice data. One study did not explicitly report the data sources used.

Overall inappropriate medication prescription measures

The overall median rate of IMP among the elderly was 20.0% with an absolute range of 2.9 to 38.5% and interquartile range of 16.8 to 25.4%. In the seven studies from the United States of America, the median was 19.6% with a range from 4.5 to 33.3%. In the European Union the median rate of inappropriate prescription was 19.1% with a range of 2.9 to 38.5%.

Results for grouping prescriptions by the type of prescription quality assessment instrument were: for Beers 1997 the median IMP rate was 12.7% (range: 4.5 to 21.0%); for Beers 2003 the median was 23.6% (range: 2.9 to 38.5%); and for Zhan's criteria, the only study reported a rate of IMP of 15.6%.

Inappropriate prescription within therapeutic classes

IMP rates markedly varied across and within individual therapeutic medication classes as shown in Table 2. The four most commonly inappropriately prescribed medications were, in a decreasing order of IMP rate, were propoxyphene 4.31(0.10-23.30) %, doxazosin 3.96 (0.32 15.70) %, diphenhydramine 3.30(0.02 -4.40) % and amitriptiline 3.20 (0.05 -20.5) %.

Non-steroidal anti-inflammatory drugs (NSAIDS)

Within the class of analgesic/NSAIDS, propoxyphene, which is a low risk analgesic medication, had the highest IMP median of 4.52% with range of 0.10 to 23.30%, while meperidine and pentozacine, which are high risk medications, had the lowest median of 0.1% and 0.03% (with range of 0.01 to 0.10% and of 0.00 to 0.44%, respectively).

Antiarrhythmics

Dysopyramide had the lowest median rate of IMP 0.08(0.01-0.4) % among the antiarrhythmic medications while the digoxin was the most inappropropriately prescribed antiarrhythmic medication 3.10(0.01-21.1)%. Disopyramide is classified as a high risk medication while digoxin in a low risk medication.

Anticholinergics

Diphenhydramine was the most inappropriately prescribed anticholinergic medication 3.30(0.02-4.40)% while belladonna alkaloids were the least inappropriate prescribed anticholinergic 0.04(0.0-0.50)%. Both diphenhydramine and belladonna alkaloids are high risk anticholinergic medications.

Table 2: Rate of inappropriate prescription of individual medications grouped by pharmacological classes divided according to the WHO ATC classification.

		Beers 1991	Beers 1997		Beers 2003											HD	MB	MR	OT	ZN		
MEDICATIONS	**No of studies**	Aparasu 1997(34)	Curtis 2004(31)	Aparasu 1999(32)	Goltz 2012(16)	Ghadimi 2011(17)	Zaveri 2010(18)	Ryan 2009(20)	Lai 2009(21)	Lin 2008(22)	Wilde 2007(23)	Maio 2006(25)	De Oliveira 2006(26)	Maio 2006(27)	Van der Hooft 2005(28)	Pugh 2006(36)	Maio 2010(19)	Straand 1999(33)	Pugh 2005(30)	Biermann 2007(24)	**Median**	**Range (LL-UL)**
Analgesics																						
Indomethacin	**15**	7.0	6.5	3.86	0.40	6.2			6.5	0.2	0.55		0.9	3.9	0.5		1	0.2	1.4	2.04	1.40	0.20-7.00
Ketorolac	**6**								2.2		0			20.5	0.2	0.5	2.3				1.35	0.00-20.5
Meperidine	**6**				0.01				0.1		0.04					0.1			0.1	0.09	0.10	0.01-0.10
Naproxen	**5**							0.45		0.1	0.63	13	0.9								0.63	0.10-13.0
Pentazocine	**10**	0.96		0.44	0.01						0.01				0.1	0	0	0.04	0.1	0.02	0.03	0.00-0.96
Piroxicam	**2**										0.12		2.3								1.21	0.12-2.30
Propoxyphene	**9**	23.3		23.3			0.57				9.37				0.1	4.52		0.3	4.1	4.81	4.52	0.10-23.3
Antarrhythmic																						
Amiodarone	**11**				0.08	0.1	0.05	0.67	1.9	10.9	1.2	4	6.1	12.6	0.7						1.20	0.05-12.6
Digoxin	**4**									3	0.01		2.8				21.1		3.4		3.10	0.01-21.1
Disopyramide	**6**				0.01						0.05			0.4	0.1				0.1	0.05	0.08	0.01-0.40
Anticholinergics																						
Belladona alkaloids	**8**				0.03	0.05					0		0.5		0.3	0			0.1	0.02	0.04	0.00-0.50

Chlorpheniramine	**9**					0.7	1.09	0.07		0.7	1.21				0.1	2.11			1.8	2.26	1.09	0.07-2.26
Clidinium	**1**					3.1															3.10	3.01-3.10
Cyproheptadine	**7**				0.01	0.4					0.02				0.1	0.3			0.2	0.31	0.20	0.01-0.40
Dicyclomine	**7**		4.2			0.5	0.74					13				0.51			0.4	0.49	0.51	0.40-13.0
Diphenhydramine	**7**				0.03	4.4				0.5	0.02					3.52			3.3	3.8	3.30	0.02-4.40
Hydroxyzine	**11**		6.9		0.08	2.0		0.07			0.51	4	0.9		0.3	3.2			2.7	3.43	2.00	0.07-6.90
Hyoscamine	**3**															0.1			0.1	0.15	0.10	0.10-0.15
Oxybutinin	**9**		6.8		0.09	1.2		0.52		0.6	0.96	8.0			0.7				1.6	2.39	0.96	0.09-6.80
Propantheline	**3**															0			0.1	0.05	0.05	0.00-0.10
Promethazine	**6**				0.24	0.8									0.9	0.71			0.2	0.71	0.71	0.20-0.90
Anticlotting																						
Dipyridamole	**10**	18.6		12.56		0.7			0.1	36.1	0.24		1.4			0.6		0		0.58	0.65	0.00-36.1
Ticlopidine	**6**				0.03				2.6	1.2			8	18.3					0.4	0.51	0.86	0.03-18.3
Antidepressants																						
Amitriptiline	**16**	20.5	16.3	10.46	0.25	1.0	0.05	1.12	1.7	3.8	4.5		1.4	6.7	2		6.2	0.7	2.6	3.98	2.60	0.05-16.3
Doxepin	**7**		3.1						0.8	0.3	0.12				0.1				0.6	0.84	0.60	0.10-3.10
Fluoxetine	**7**					1.6			1.5	1.8	1.49	17	2.3		0.4						1.60	0.40-17.0
Antihypertensives																						
Clonidine	**8**				0.06		0.05	0.07			0.15	8		9.5	0.1		0.9				0.12	0.05-9.5
Doxazosin	**6**				0.32			6.47		15.7	3.91	4		23	0.5						3.96	0.32-15.7
Guanethidine	**2**								0.1		0										0.05	0.00-0.10
Methyldopa	**11**				0.07	1.4		0.07	0.2		0.2			0.5	0.1		0.6	1.23	0.1	0.1	0.20	0.07-1.40
Nifedipine	**8**				0.19	0.7		0.15	12.9	6	0.22		1.9			0.1	0.1				0.20	0.10-12.90

Reserpine	**3**									0								0.1	0.06	0.06	0.00-0.10
Musclerelaxants																					
Carisoprodol	**7**	0.50	3.6	1.49						0					0.2			0.1	0.16	0.20	0.00-3.60
Chlorzoxazone	**3**								6.1									0.1	0.2	0.20	0.10-6.10
Cyclobenzaprine	**5**	2.7	9.7	1.95											1.91			1.2	2	1.95	1.20-9.70
Metaxalone	**2**														0			0.1	0	0.05	0.00-0.10
Methocarbamol	**8**	1.0		0.42	0.01	4.0				0.7					2.21			1.6	2.41	1.30	0.01-4.00
Orphenadrine	**7**	1.8		0.99	0.01				3.1	0.05			1.6	0.1	0	0.7				0.70	0.00-3.10
Sedatives																					
Alprazolam	**2**									0								0.1		0.05	0.00-0.10
Chlorazepate	**4**				0.01					0.02		3.8		0.4						0.21	0.01-3.80
Chlordiazepoxide	**13**	6.0	2.4	8.7	0.07	3.0		0.3		1.6	0.24		0.9		0.2	0.4		0.4	0.44	0.44	0.07-8.70
Diazepam	**15**	11.6	10.6	30.05	0.43	1.6	0.05	2.7	21.3	2	2.74	13	11.7		2.8	1.5		1.2	1.57	2.74	0.05-30.0
Flurazepam	**10**	2.7		1.26	0.01	0.1			0.7		0.05				0.5	0.1		0.1	0.06	0.10	0.01-2.70
lorazepam	**4**					0.1		0.82			0.2							0.1		0.15	0.10-0.82
Meprobamate	**8**	3.5		0.93					0.1		0.1				0.1	0		0.1	0.01	0.10	0.00-3.50
Oxazepam	**2**										0							0.1		0.05	0.00-0.10
Temazepam	**3**							0.6			0.74	4						1		0.74	0.60-4.00
Triazolam	**3**							0.22			0							0.1		0.10	0.00-0.22

HD: Health Plan Employer Data and Information Set (HEDIS) criteria
MB: Modified beers 2003
MR: More & Romsdal Prescription Study (MRPS) list
OT: Other unspecified criteria
ZN: Zhan's Criteria
ATC: World Health Organisation's Anatomic Therapeutic and Chemical Classification

Anticlotting medications

IMP was reported for two anticlotting medication as follows dipyridamole 0.65(0.00- 36.1) % and ticlopidine 0.86 (0.03- 18.3)%. Dipyridamole is a low risk medication while toclopidine is a high risk anticlotting agent.

Antidepressants

Doxepin was the least inappropriately 0.6(0.10 - 3.1) % prescribed antidepressant medication while amitryptiline 3.2(0.05-20.5)% was the most inappropriately prescribed. Both antidepressants are high risk medications.

Antihypertensives

The median rate of IMP among the antihypertensive medication was lowest with guanethidine, 0.05 (0.00-0.1) %. Doxazosin 3.96 (0.32-15.7) % was reported to be the most inappropriately prescribed antihypertensive medication. Guanethidine is a high risk antihypertensive medication while doxazosin is a low risk medication.

Muscle relaxants

Among the muscle relaxants, metaxalone 0.05(0.00-0.1) % had the lowest IMP rates while cyclobenzaprine 1.95 (1.20-9.7) % had the highest. Both muscle relaxants are high risk medications.

Sedative hypnotics

Diazepam 2.74 (0.05-30.05) % had the highest rates of IMP while alprazolam 0.05 (0.00-0.10) % had the lowest rate of IMP among the sedative hypnotic medications. All sedative hypnotics investigated are considered to be high-risk medications.

2.4 Discussion

In spite of increasing attention to the quality of medication prescription among elderly persons presenting to the primary care setting, there are still high overall rates of inappropriate medication prescription in primary care. This review found that one in five (20.0%) prescriptions to elderly persons is inappropriate with marked variation of rates of IMP within individual therapeutic classes.

The overall prevalence of inappropriate prescription showed wide variations between 2.9 and 38.5%. Several factors may contribute to this variation. Different countries use different sets of medications due to registration issues. There is hence no universal list of medications and criteria for assessing the overall medication use by older patients. Even within the United States inappropriate medication use markedly differed, suggesting that there some systematic differences between practices may exist. The differences in the quality of prescribing across geographical regions have recently been highlighted (37). Cost and purchasing system of medication is another probable reason for the medication choices made in prescription (37). Moreover, local drug procurement policies and the structure of financing of medication are among the probable factors that may contribute to the differences in prescription patterns.

Consistent with our review, the review of Aparasu *et al*. in 2000 estimated that between 14.2% and 25% of elderly patients were exposed to IMP(9). Our review found an IMP rate of 20.0%. Of note, 16 out 19 studies included in our review were published after the year 2000 and the overall rate of IMP seems to not have decreased considerably over the last 11 years despite the attention that has been directed on the subject of IMP among elderly patients. While Aparasu *et al*. included studies that were based only on Beers criteria, our study included also non-Beers criteria based studies which reported IMP based on individual medications. Gallagher *et al.* found IMP rates of 12% among community dwelling elderly and 40% among patients in nursing homes(10). Patients who stay in nursing homes are likely to be exposed to higher rates of IMP, as shown by Gallagher *et al* than those patients who receive prescription in the primary care setting. Unlike Gallagher *et al.* who reviewed studies that evaluated IMP in all clinical settings, our review was limited to studies that included patients who received their prescription in a primary care setting. The overall rate of IMP (20.0%) that we report in this review falls within the range (12 - 40%) reported by Gallagher *et al*. A more recent review of IMP among the elderly, which was based on studies that utilised administrative database, reported an IMP rate ranging from 11.5-62.5%. This finding is consistent with our overall IMP rate

(20.0%) given that 12 out of 18 studies that we included were performed using retrospective databases(38).

Unlike the three reviews described above, our study compared the rate of IMP within therapeutic classes of medication. The patterns of inappropriate prescriptions vary considerably within therapeutic classes. Some medications with high risk for adverse events such as diazepam and nifedipine have high prevalence of inappropriate prescription compared to medications in the same therapeutic class. Prescription of high-risk medication exposes the elderly to frequent and severe adverse drug events. Alternative low risk medications should be prescribed when available. There is therefore a need to move towards interventions that can improve the quality of medication prescriptions among the elderly in primary care such as employing clinical decision support systems (CDSS). These systems can provide alerts during prescription based on medication prescription guidelines such as the Beers criteria. Good alert design by focusing on the relevant alert can improve the effectiveness of these systems(39).

This review included various list based criteria for the measurement of IMP which are comparable to each other given that they report individual medications. Modifications that were made in the various versions of the Beers criteria involved inclusion and exclusion of individual medications on the list of medications inappropriate for elderly patients. It was therefore possible for us to compare the rates of IMP for individual medications between studies even if they used different versions of the Beers criteria. However, the overall rate of IMP was not comparable between studies that used different versions of the Beers criteria or other instruments to measure the rates of IMP.

We regard classification of medications as unconditionally appropriate for elderly patients over 65 years as suggested by the Beers criteria is an over simplification of real clinical practice. Some medications such digoxin or doxazocin may still be used safely in patients who are older than 65 depending on their clinical conditions. Improvements in the definition of inappropriate

medication prescription have been made based on drug-disease combination in the elderly.

Twelve studies (12 of 19) relied on secondary analysis of existing database sources such as National Health Service databases, general practice and insurance databases, which were developed for other purposes. Although previous studies have shown that insurance databases do not necessary have high quality clinical notes documentation, they do generally have high quality of medication documentation due to their use for reimbursement purposes (40). An outstanding drawback of insurance health databases is, however, that only insured patients are enrolled. There is patient selection bias in countries or regions where insurance companies do not have universal coverage. Furthermore, we speculate that quality assurance and incentive programs by some insurers may lead to better quality of care.

Strengths and weaknesses

A strength of our study is the analysis of medication prescription appropriateness within therapeutic classes based on an international standard. This classification mitigates the difficulty in comparing inappropriate medication prescription measures originating from studies with different sets of medication that is influenced by the availability of medications and local prescription practices. This analysis is useful to policy makers and clinicians when making choices between medications from the same therapeutic class. We also compared IMP in studies which utilised multiple instruments to measure quality of prescription.

We used extensive search criteria to capture the different ways inappropriate prescription and elderly are referred to in the published literature. Nevertheless our study may be limited by publication bias of studies on inappropriate medication prescription. In addition, some of the excluded articles may be relevant but due to uncertainty about or lack of reporting about the setting of the prescription, they have been excluded.

Furthermore, our study was limited by the heterogeneity of the included studies. The number of patients included in the studies varied widely, which makes it difficult to estimate the overall prevalence of IMP. Heterogeneity in reporting of the rates of IMP limited our ability to completely compare rates of IMP for individual medication in all studies. Some studies reported fewer drugs than others. We believe that unavailability of some medications in some countries may have resulted in the differences in the sets of medications which were reported.

Although our study was limited to quantifying the extent of IMP among elderly patients, it would be important to understand the factors that predispose these patients to IMP. In addition, understanding the relationship between IMP and the incidence of adverse events to the patients will provide better guidance to the prescribing physician. Demonstration of the relationship between IMP and adverse events require the validation of the tools used to define IMP in the first place.

Future studies that investigate therapeutic intents and choices of medication among physicians may help further understanding of their prescribing behaviour. This may particularly aid in understanding how choices can be presented to physicians in primary care. Such studies can result in improvement strategies by computerized decision support.

Conclusion

Despite intensified efforts to scrutinize and improve the quality of medication prescription among elderly persons living in community, inappropriate medication prescriptions are still common. Approximately one in five prescriptions to elderly persons is inappropriate. Diphenhydramine diazepam are the most common inappropriately prescribed medications with high risk adverse events. These medications are good candidates for being targeted for improvement e.g. by computerized clinical decision support. Focused and systematic interventions are needed to improve the quality of medication prescription in this patient group.

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Chapter 3

Quality of co-prescribing NSAIDs and gastroprotective medications for elders in the Netherlands and its association with electronic medical record

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ABSTRACT

Objective

To assess guideline adherence of co-prescribing NSAID and gastroprotective medications for elders in general practice over time, and investigate its potential association with the electronic medical record (EMR) system brand used.

Methods

We included patients 65 years and older who received NSAIDs between 2005 and 2010. Prescription data were extracted from EMR systems of GP practices participating in the Dutch NIVEL Primary Care Database. We calculated the proportion of NSAID prescriptions with co-prescription of gastroprotective medication for each GP practice at intervals of three months. Association between proportion of gastroprotection, brand of electronic medical record (EMR), and type of GP practice were explored. Temporal trends in proportion of gastroprotection between electronic medical records systems were analyzed using a random effects linear regression model.

Results

We included 91,521 patient visits with NSAID prescriptions from 77 general practices between 2005 and 2010. Overall proportion of NSAID prescriptions to the elderly with co-prescription of gastroprotective medication was 43%. Mean proportion of gastroprotection increased from 27% (CI 25 - 29%) in the first quarter of 2005 with a rate of 1.2% every 3 months to 55%(CI 52 – 58%) at the end of 2010. Brand of EMR and type of GP practice were independently associated with co-prescription of gastroprotection.

Conclusion

Although prescription of gastroprotective medications to elderly patients who receive NSAIDs increased in The Netherlands, they are not co-prescribed in about half of the indicated cases. Brand of EMR system is associated with differences in prescription of gastroprotective medication. Optimal design and utilization of EMRs is a potential area of intervention to improve quality of prescription.

Introduction

Pain is a common problem among elderly persons living in the community as well as in institutions of organized care such as nursing homes[1][2]. Tsai *et al.* reported a 50% prevalence of pain among community dwelling elderly patients[3] and a 65% prevalence among nursing home residents in Taiwan[4]. Therefore the consumption of pain medication among the elderly is high. Population studies in the US have shown that 70% of people older than 65 years use non-steroidal antiinflammatory drugs (NSAIDs) at least once per week while about 34% use the drugs at least once a day[5].

Many studies have shown an increased risk of gastrointestinal complications among NSAID users, particularly peptic ulcers and its attendant complications such as upper gastrointestinal bleeding and perforations[6]. Laine *et al.* reported a prevalence of 15-30% of peptic ulcers and an annual prevalence of 1.0-1.5% of upper gastrointestinal bleeding among NSAID users[7].

Adherence to safe NSAID prescribing practices as proposed by clinical guidelines has been shown to reduce upper gastrointestinal toxicities[8]. For example, patients using NSAIDs and gastroprotection with proton pump inhibitors have a lower risk of upper gastrointestinal toxicities compared to patients without gastroprotective medication risk of 1.8 versus 1.1[9].

Clinical guidelines on safe NSAID prescribing include the Assessing Care of Vulnerable Elders (ACOVE) clinical rule recommending a concomitant gastroprotective medication, proton pump inhibitors or misoprostol, to elderly patients at high risk of upper gastrointestinal bleeding[10,11]. This clinical rule has been adopted by a team of experts in geriatric care for use in general practice in the Netherlands[12]. Similarly, the Dutch College of General Practitioners also recommends the prescription of gastroprotective medication to elderly patients at high risk for upper gastrointestinal events. In 2009, this has been corroborated by a report in The Netherlands, from an expert group with a focus on optimizing extramural medication safety, with specific recommendations for prescribing PPIs in regular NSAID users with an increased risk of GI complications[13]. Previous studies have indicated that sub-optimal and inappropriate prescription of medications exist in primary care settings despite various interventions which have been implemented to improve the quality of prescribing[14].

Safe prescription practices in primary care may be affected by factors including the electronic medical record (EMR) system in use. EMR system types, with six main types in the Netherlands, may use different approaches, such as reminders and alerts, to support medication prescription. We hypothesize that differences in EMR systems used in the Netherlands contribute to difference in co-prescription of NSAID with gastroprotective medications.

In this study, we assessed the proportion of co-prescribing NSAIDs and gastroprotective medications, and investigated its association with the EMR

system type in general practice in the Netherlands between 2005 and 2010 based on the Dutch translation of the ACOVE clinical indicators[12].

Methods

We extracted prescription data for all NSAIDs and gastroprotective medications between 1-1-2005 and 31-12-2010 from EMR systems of GP practices participating in the Dutch NIVEL Primary Care Database. The NIVEL Primary Care Database started in 1992 as the Netherlands Information Network of General practice (LINH) and developed into a multidisciplinary primary care database in recent years, encompassing not only data from GP practices but also from out of hours services, psychologists and other primary care disciplines. In the Netherlands, all citizens are registered with a GP practice and GPs act as a gatekeeper for further access to specialized care. During the study period about 90 general practices participated, with a total practice population of 350,000 patients. The database encompasses consultation claims data, health problems, lab test results, prescriptions and referrals, patient age and gender, practice type and EMR system brand.

We note that all EMRs are designed according to standards developed by the Dutch College of General Practitioners. By design any brand of EMR can be used in any type of GP practice. The EMRs are web-based and a doctor within a practice has his or her separate log in credentials. Prescriptions are recorded in general practice using the Anatomical Therapeutic Classification (ATC) developed by the World Health Organization (WHO). Topical preparations of NSAIDs were excluded from the data because they have limited adverse effects

on the gastrointestinal system. Gastroprotective agents (GPAs) included all proton pump inhibitors and misoprostol containing preparations. **Table 1** shows the non-steroidal anti-inflammatory medications which we included in the analysis.

Table 1: List of Non Steroidal Anti-inflammatory Drugs (NSAIDs) included in the study grouped by pharmacological class.

Pharmacological class	ATC class code	Name	ATC code
Acetic acid derivative	M01AB	Indomethacin	M01AB01
		Aceclofenac	M01AB16
		Diclofenac combinations	M01AB55
		Sulindac	M01AB02
		Diclofenac	M01AB05
Butylpyrazolidine	M01AA	Phenylbutazone	M01AA01
Coxibs	M01AH	Valdecoxib	M01AH03
		Rofecoxib	M01AH02
		Celecoxib	M01AH01
		Etoricoxib	M01AH05
Fenamate	M01AG	Tolfenamic	M01AG02
Oxicam	M01AC	Tenoxicam	M01AC02
		Meloxicam	M01AC06
		Piroxicam	M01AC01
Propionic acid derivatives	M01AE	Dexibuprofen	M01AE14
		Tiaprofenic acid	M01AE11
		Flurbiprofen	M01AE09
		Ketoprofen	M01AE03
		Naproxen	M01AE02
		Ibuprofen	M01AE01
Others	M01AX01	Nabumetone	M01AX01

Measurements and outcome variable

The primary outcome variable was the proportion of NSAIDs prescriptions with concomitant co-prescription of gastroprotective medication. Co-prescription was measured as the concurrence of records of NSAID and gastroprotective medication within a 24 hours time frame This proportion was calculated by dividing the number of NSAID prescriptions with a concomitant gastroprotective medication by the total number of NSAID prescriptions. Proportion of gastroprotection was aggregated for every general practice per quarter of a year, i.e. 3 months. The first quarter was the period from 1st January 2005 to 31st March 2005 while the 24th quarter was the period from 1st October 2010 to 31st December 2010.

The following variables were included in the analysis: type of practice and brand of Electronic Medical Record system used in the general practice. All six EMR systems brands were included in the study. Four practice types were distinguished, single handed, duo practice (2 GPs), group practice and health centers. Type of general practice and brand of Electronic Medical Record system were treated as categorical data while the proportion of gastroprotection was treated as a continuous variable.

In the Netherlands, there is no need to obtain consent when only registry data obtained from routine care and without patient identifying information are used, as is stated in the selection criteria for the Medical Research Involving Human Subjects Act (WMO)[15].

Analysis

Univariate and multivariate linear regression analysis was performed to explore associations between gastroprotection and the variables brand of EMR and type of practice.

Random effects linear regression analysis was used to model trends in prescription of gastroprotective medications from 2005 to 2010 based on the six brands of EMR systems. The random intercept was modeled to represent each brand of EMR at the beginning of the study period while the random slope represented the rate of change of gastroprotection for each brand of EMR. This means that prescriptions were clustered by the brand of electronic medical record system. Temporal profiles of gastroprotection for each brand of EMR system were estimated from the model and presented graphically.

Results

A total of 91,521 patient visits with NSAID prescriptions from 77 general practices between January 2005 and December 2010 were included. **Table 2** shows the description of the general practices contributing data to this study. Forty three out of the 77 practices (56%) had a single practitioner while 7 (9%) were organized as health centers. Six different brands of electronic medical record (EMR) systems were used by the GP practices during the study period. None of the GPs changed EMR brand during the study period. **Table 3** shows the distribution of EMRs within the different types of GP practices. A chi-square test of the association between practice type and distribution of EMR was statistically insignificant with a p-value of 0.117

Table 2: Characteristics of general practices and determinants of co-prescription of gastroprotective medication with NSAIDS.

Brand of Electronic Medical Record system	**Number of practices**
EMR 1	11
EMR 2	8
EMR 3	18
EMR 4	13
EMR 5	21
EMR 6	6
Type of practice	
Single handed	43
Duo (Two GPs)	16
Group	11
Health Center	7

The overall proportion of gastroprotection co-prescription with NSAIDS during this five year period was 43.0%. The overall rate of gastroprotection in all the practices increased from 26.6% (CI 24.6 - 28.7) in the first quarter of 2005 with 1.2% (CI 1.03 - 1.3) every 3 months to 54.7%(CI 51.9 – 57.5%) at the end of 2010.

Table 3: Distribution of electronic medical records (EMR) system according to type of general practices in the Netherlands.

	Solo	Duo	Group	Health Centre	**TOTAL**
EMR 1	2	4	3	2	**11**
EMR 2	6	2	0	0	**8**
EMR 3	11	3	2	2	**18**
EMR 4	11	2	0	0	**13**
EMR 5	11	4	3	3	**21**
EMR 6	2	1	3	0	**6**
TOTAL	**43**	**16**	**11**	**7**	**77**

Figure 1 shows the mean proportion of concomitant gastroprotection with NSAIDS comparing the brand of EMR system and type of general practice. General practices that used EMR brand 4 and EMR brand 6 had statistically significant higher proportions of prescription of gastroprotective medications compared to EMR brands 1, 2, 3 and 5.

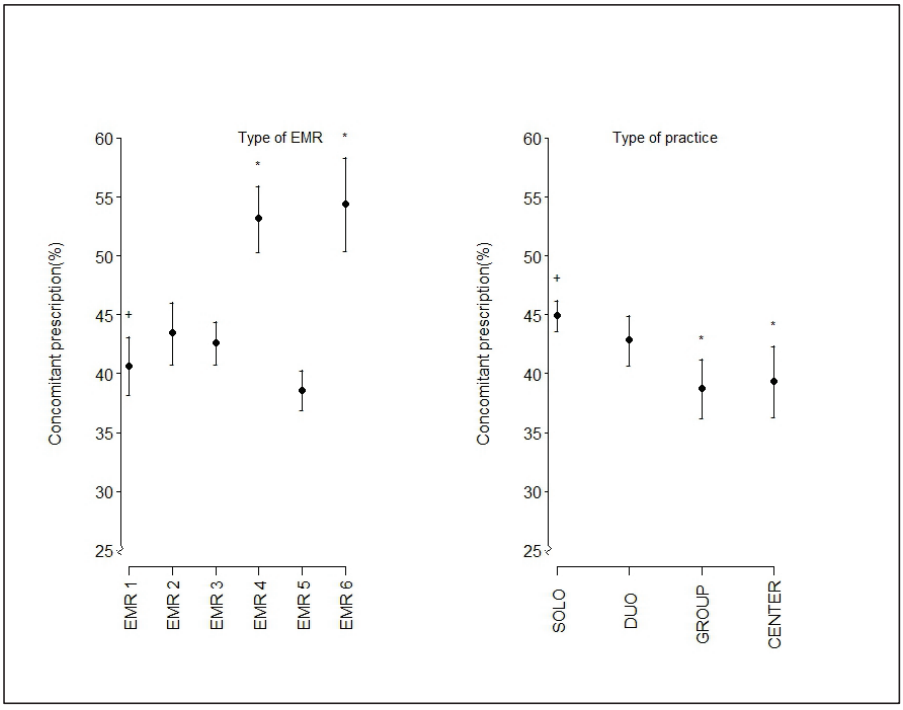

Figure 1: Univariate analysis of proportions of concomitant gastroprotection with NSAIDS based on brand of electronic medical record system and type of general practice. + - reference group in univariate analysis, * - statistically significant different from the reference group. SOLO – a single practitioner practice, DUO – a two practitioners practice, GROUP – a more than two practitioner's practice, CENTER – a health center, usually with more primary health care services, EMR – Electronic Medical Record System.

Multivariate linear regression analysis of time, brand of EMR system and type of GP practice showed significant differences in the rate of concomitant gastroprotection as shown in **Table 4**. Statistically significant differences in proportions of gastroprotection were observed with EMR brand 4 and EMR brand 6 compared to EMR brand 1 while the difference in gastroprotection was not significant between EMR brands 2, 3 and 5 as compared to EMR brand 1.

Group practices had lower rates of gastroprotection compared to single practitioner practices (p-value <0.001). The differences between dual practitioner and group practices, and single practitioner practices were not statistically significant.

Table 4: Regression analysis of determinants of rate of concomitant co-prescription of gastroprotective medications with NSAIDs.

	Univariate analysis			**Multivariate analysis**		
Factors	**Coefficient (%)**	**95% CI**	**P value**	**Coefficient (%)**	**95% CI**	**P value**
Time (quarter)	1.2	1.0-1.3	<0.001*	1.0	0.9-1.1	<0.001*
Brand of EMR						
EMR 1– reference	-	-	-	-	-	-
EMR 2	2.8	-0.8-6.3	0.156	1.82	5.1-12.9	0.306
EMR 3	2.0	-1.1-5.0	0.222	1.31	0.1-6.3	0.372
EMR 4	12.5	8.8-16.2	<0.001*	7.15	12.1-20.4	<0.001*
EMR 5	-2.1	-5.0-0.9	0.198	-2.42	-2.6-3.6	0.087
EMR 6	13.7	9.1-18.4	<0.001*	10.32	8.2-17.4	<0.001*
Type of practice						
Solo practice-reference	-	-		-	-	-
Duo practice	-2.1	-4.6-0.4	0.125	-1.7	-3.3-1.1	0.133
Group practice	-6.2	-9.0-(-3.4)	<0.001*	-5.4	-4.8-1.0	<0.001*
Health Center	-5.6	-8.8-(-2.3)	<0.001*	-2.71	-10.5-(-4.4)	0.084

LL- Lower limit of confidence interval.

UL-Upper limit of confidence interval.

Figure 2 shows the differences in the rates of prescription of gastroprotective medication over time. EMR brand 4 and brand 6 have a higher mean rate of prescription of gastroprotective medication compared to EMR brands 2, 3 1 and 5 respectively having adjusted for the effect of time. EMR brand 6 showed the highest increase in gastroprotection rates over time.

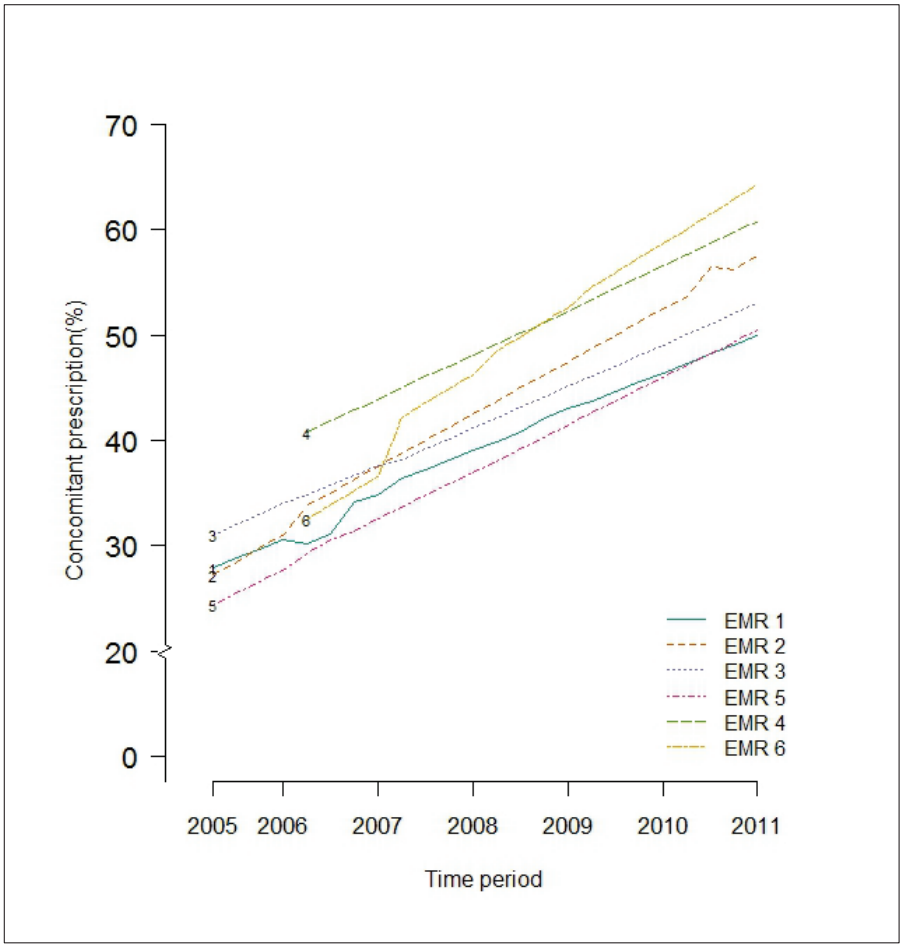

Figure 2: Time trends of the rate of concomitant prescription of gastroprotective medication with NSAIDs between various electronic medical record (EMR) systems.

Discussion

The mean proportion of concomitant gastroprotection for elderly persons who received NSAIDs in the Netherlands between 2005 and 2010 was 43.0%. Despite the increase of this proportion from 26.6% with a rate of 1.2% every 3 months to 54.7%, gastroprotection is not co-prescribed in about half of the indicated cases. Finally, the Electronic Medical Record system used was associated with the proportion of the concomitant gastroprotection prescription.

Thiefin *et al.* observed that 39% of elderly patients received gastroprotection in a study conducted between June and August 2006 France [12] while a study conducted in Sweden by Fastbom *et al.* found a gastroprotection rate of 22% [13]. Sturkenboom *et al* showed that a majority of patients with one or more gastrointestinal risk factors do not receive appropriate prescription of NSAID and gastroprotective medication or COX-2 selective NSAID[16]. Hartnell et al also found underutilization of gastroprotection for seniors[17]. Similar to our finding of the increase in proportion of concomitant gastroprotection for elderly persons receiving NSAIDs, Valkhoff *et al.* showed an increase from 6.9% to 39.4% over a 10 year period in a study that examined the quality of prescription of gastroprotective medications in one region of the Netherlands from 1996 to 2006 [14]. Lana et al found a 75.8% rate of gastroprotection in primary care centers in Spain[18]. The increase in co-prescription of gastroprotective medication is perhaps due to increasing awareness among physicians about the risk of upper GI bleeding among the elderly patients.

To the best of our knowledge the association between the Electronic Medical Record system with the concomitant prescription of gastroprotection identified in our study is new. Differences in EMR system design may confer advantages

to users leading to better quality of prescription. Computerized order entry systems (CPOEs) with inbuilt decision support systems have been shown to improve the quality of medication prescription [15]. All the six EMRs included in this study could generate decision support for prescription of NSAIDs and gastroprotective medications. The six systems allow the GPs to adjust the settings of decision support delivered. Unfortunately, we do not have data that shows the status of decision support for each prescription that was made via the EMRs. Additional insight into the specific functionalities and implementation of the EMRs at the point of care is necessary to fully interpret the differences observed in our study. Unfortunately, a detailed examination of the EMRs as implemented and used during the period of this study is not possible since we conducted a retrospective study. Our identified association is not necessarily causal, and since we did not consider all potential confounders. Future studies should investigate this relationship by appropriately designed trials

Our study has different strengths. First is the large sample with a good representation of the Dutch population. Second, we measured quality of prescribing and explored the variation in the quality of gastroprotection according to the brand of EMR used to issue the prescription. Studies that describe only the overall prescription proportions or trends of care alone do not identify factors that are associated with quality of care. Third, our study also explores the effect of time in the improvement of the quality of prescription. Of note are the gains in quality with time in comparison to the baseline performance. A new intervention would be deemed beneficial only if it can confer benefits that are more than those benefits accruable to time alone.

There are some limitations of our study. First, the ACOVE guidelines are not exactly the same as the current Dutch guidelines. The ACOVE guideline uses 65 years to identify elderly patients who require gastroprotection while the Dutch guidelines suggest that gastroprotection should be initiated at the age of 70 years for all elderly persons and only for high risk elderly persons between 65-70 years. Nevertheless we believe that our study captures the general patterns of co-prescription of gastroprotective agents for high risk elderly persons. Second, the estimate of gastroprotection study was based on the presence or absence of appropriate proton pump inhibitor or misoprostol on the day of NSAID prescription, which is a limited definition of concomitant prescription. Some patients may be carrying current prescription of gastroprotective medication thereby contributing to apparent under prescribing. Similarly some patients may receive refills of gastroprotective medications because they still have stock of NSAIDs at home. The ideal estimate of gastroprotection would be obtained by calculating the dosages and duration of both NSAIDs and gastroprotective medications administered. Third, our dataset did not capture all confounders to correct for relationship between specific EMR and co-prescription of gastroprotective medication. For instance, we did not have data which would indicate whether a specific prescription was made with or without the facilitation of decision support in the EMR.

Future studies need to explore the duration of coverage of gastroprotective agents by investigating the medication dosage duration of treatment and different definitions of elders at "high risk" of gastrointestinal complications.

Furthermore, changes in the prevalence of upper gastrointestinal complications related to NSAIDs among the elderly population merit investigation. Finally, future trials should be conducted to explore the design characteristics and utilization of EMR systems that may be associated with higher or lower quality of prescription of gastroprotective medications.

This study demonstrates differences in the percentage of gastroprotection between brands of EMR in the Netherlands. The differences observed suggest the need for interventions to reduce the disparities in the quality of gastroprotection prescription among these systems. Specific policies need to be formulated to identify areas of need for targeted interventions. Developers of GP information systems have a potential opportunity for leveraging the use of clinical decision support systems to contribute to the improvement of quality of prescription to the elderly.

CONCLUSION

The proportion of prescription of gastroprotective medications to elderly who receive NSAIDs steadily improved in the Netherlands between 2005 and 2010, but gastroprotection is still not co-prescribed in about half of the indicated cases. The type of GP information system is a modifiable factor associated with concomitant medication. Optimal design and utilization of GP information systems is a potential area of intervention to improve the proportion of gastroprotection prescription in combination with NSAIDs in the elderly.

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Chapter 4

Response of physicians to rosiglitazone drug safety warnings in the Netherlands

Dedan Opondo, Saeid Eslami, Stefan Visscher, Robert Verheij, Joke Korevaar and Ameen Abu-Hanna

(under review)

Abstract

Purpose

To investigate the effect of drug safety warnings on the duration of exposure of patients to medications with high risk for adverse events

Methods

We included 8168 patients who received prescriptions of oral antidiabetics medications in the Netherlands between 2001 and 2010. Data were extracted from the Netherlands information network for general practice (LINH) database. Food and Drug Administration (FDA) issued safety warnings for rosiglitazone in 2007 which were also adopted by the Dutch national Medicines Evaluation Board (CBG). We thus divided patients who received rosiglitazone prescriptions into two groups based on the year of their first rosiglitazone prescription: 2001-2007 group and 2007 - 2010 group. Duration of rosiglitazone use was calculated per patient. Kaplan Meier analysis was done to compare the two groups.

Results

Out of 8168 patients on oral antidiabetics, 498(5%) received rosiglitazone prescriptions. Peak initial prescription of rosiglitazone was in the year 2004. The mean (sd) duration of rosiglitazone use was 723.1(691) days versus 309.6(385) days for the 2001-2007 group and 2007-2010 group respectively. The two-year probability of using rosiglitazone was 0.53[0.48 - 0.58] for patients in the 2001-2007 group versus 0.32[0.19 - 0.52] for 2007-2010 group. These differences in these probabilities were statistically significant with a p-value of $p < 0.001$

Conclusion

Drug safety warnings are effective in reducing the chance and duration of exposure to high-risk medication.

Introduction

Regulatory authorities such as the Food and Drug Administration (FDA) issue drug safety warnings to physicians for specific medications. The warnings come with instructions about appropriate use or even withdrawal of a particular medication. The safety warnings advice physicians and pharmacists to be more cautious with prescription of particular drug or to avoid the drug for a specific patient group[1]. Safety warnings are based on post marketing surveillance and studies on medications. Uptake of the warnings in clinical practice may vary due to the different methods, which are used to communicate the warning to physicians. Some of the approaches used to ensure uptake of safety warnings include change of product information and labels, education programs, prescriber mail outs, or restriction of authorized prescribers[2].

Rosiglitazone is a second line oral antidiabetic. It was introduced in Europe in the year 2000. Studies conducted after market authorization showed that rosiglitazone increased the risk of cardiovascular accidents[3–6]. In response to these studies, Federal Drug Agency (FDA) issued warnings in 2007, which advised physicians to be cautious when prescribing rosiglitazone to patients at risk of cardiac complications or with existing cardiovascular disease.

In this study, we aim to investigate the effect of the FDA safety warnings on the duration of exposure of diabetic patients to rosiglitazone prescription. Furthermore, we evaluate the effect of the warnings on discontinuation of rosiglitazone prescription.

Methods

Prescription data for all oral antidiabetic medications between 1-1-2001 and 31-12-2010 were collected from 37 general practices in the Netherlands Information Network of General Practice.

Data source

General practitioners (GPs) in the Netherlands universally use electronic medical records (EMR) to document patient information. Data from GP practices are collected into a central research database of the Netherlands Information Network of General Practice (LINH) (4) . The LINH database is maintained by the Netherlands Institute for Health Services Research (NIVEL). Routine quality checks are performed on the data to ensure good data quality.

The LINH database contains prescription data. Each prescription is a single record. Details about each prescription include date and time, code name of drug, amount and frequency. The anatomical and therapeutic chemical (ATC) classification system is used for the coding the name of the medication[7] .

Analysis

For each patient, the first and the last rosiglitazone prescriptions were identified. Duration of rosiglitazone prescription was defined as the time interval between the first and last prescription. Rosiglitazone prescriptions were considered as discontinued, if a patient remained actively receiving other antidiabetic prescriptions for at least 120 days from the GP practice after the last documented rosiglitazone prescription. Patients who received rosiglitazone prescriptions were divided into two groups based on the year of their first rosiglitazone prescription i.e 2001- 2007 group and 2007 - 2010 group. Kaplan Meier analysis was done to compare the two groups. The difference between the two groups was tested using log rank test.

All statistical analysis was performed using R-statistical programming software version 2.15.3 and the level of statistical significance was set at 0.05.

Results

We included prescription data from 8,221 patients who received a total of 225,851 prescriptions of oral antidiabetic medications from 37 general practices

between 2001 and 2010 as shown in Table 1. Rosiglitazone was prescribed in 498 (6.1%) patients during the period constituting 2.1% of all oral antidiabetic prescriptions.

Table 1 shows prescription of oral antidiabetic prescriptions between the years 2001 and 2010 in 37 general practices.

Characteristics	Patients N=**8221**	Prescriptions N=**225851**
Age mean (sd)	63.7(14.1)	66.6(12.7)
Gender		
Male n(%)	4116 (50.4)	112281 (50.2)
Female n(%)	4052 (49.6)	111224 (49.8)
Oral antidiabetic medications		
Metformin n(%)	7077 (86.6)	120836 (54.1)
Toltbutamide n(%)	2149 (26.3)	34390 (15.4)
Glimepiride n(%)	1758 (21.5)	27077 (12.1)
Gliclazide n(%)	1299 (15.9)	18014 (8.1)
Glibenclamide n(%)	825 (10.1)	12328 (5.5)
Rosiglitazone n(%)	498 (6.1)	4736 (2.1)
Pioglitazone n(%)	386 (4.7)	3696 (1.7)
Acarbose n(%)	155 (1.9)	1420 (0.6)
Others n(%)	179 (2.2)	1008 (0.5)

Figure 2 shows the number of diabetic patients who received initiation and discontinuation prescription of rosiglitazone every year. More patients were initiated on rosiglitazone every year from year 2001 to year 2006. Initiation prescriptions reduced in year 2007 following the drug safety warnings. Highest discontinuations were recorded in year 2007.

Figure 2: Bar graph showing the number of patients who were initiated and discontinued on rosiglitazone prescription each year between January 2001 and December 2010.

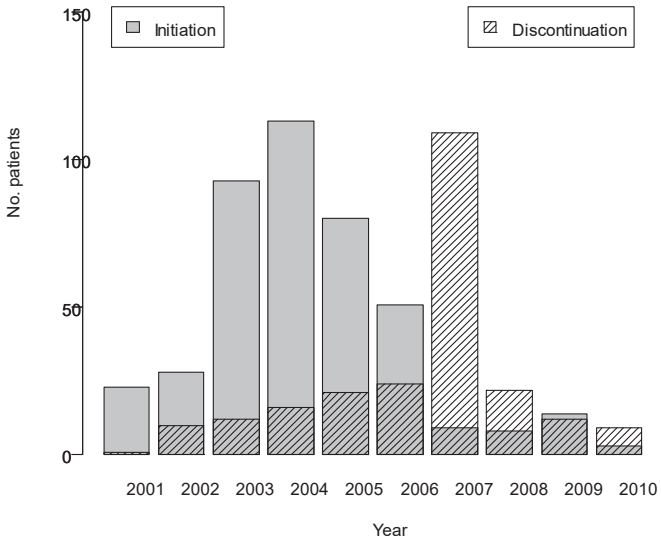
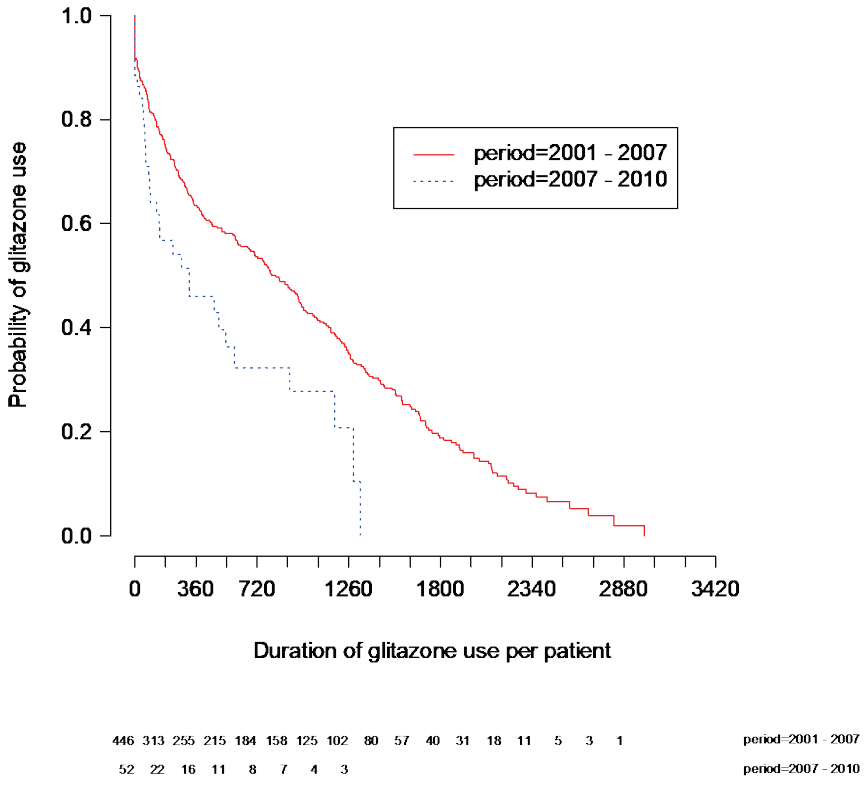


Table 2: Differences between patients who started using rosiglitazone prescriptions before and after FDA drug safety warning

Characteristics	2001-2007 Group n=446	2007 -2010 Group n=52	p-value
Age mean (sd)	59.4(12.1)	56.2(15.5)	0.152
Gender			
Male n(%)	226 (50.7)	23 (44.2)	0.46
Female n(%)	220 (49.3)	29 (55.7)	
Rosiglitazone use			
Duration in days mean(sd)	723.1(691)	309.6(385)	<0.001
1-year probability of rosiglitazone use	0.63[0.58-0.68]	0.45[0.33-0.63]	<0.001
2-year probability of rosiglitazone use	0.53[0.48-0.58]	0.32[0.19-0.52]	<0.001
3-year probability of rosiglitazone use	0.40[0.36-0.46]	0.27[0.15-0.48]	<0.001

Figure 3 shows the differences in probability continuing with a prescription of rosiglitazone plotted against the duration of use of rosiglitazone categorized by the period when the individual patient was initiated on rosiglitazone. The two-year probability of using rosiglitazone was 0.53[0.48 - 0.58] for the 2001-2007 group while the two-year probability of using rosiglitazone was 0.32[0.19 - 0.52] the 2007-2010 group. These differences in these probabilities were statistically significant with a p-value of p <0.001.

Figure 3: Kaplan meier curve showing the effect of drug safety warning on duration of rosiglitazone use.



Discussion

Our study shows that the probability of receiving rosiglitazone prescription for one year reduced from 63% to 45% in the period after the FDA drug warnings. In addition, we noted that the average duration for which a patient received rosiglitazone prescription was shorter after the drug warnings compared to the period before.

The shorter duration of use of rosiglitazone and lower chance of receiving rosiglitazone prescription attest to the effectiveness of drug safety warnings in protecting patients. The cumulative period during which a patient receives prescriptions of medications with high risk for adverse events determines the proportion of patients who are likely to develop adverse events.

Cohen *et al.* found that the combined effect of scientific publications, advisories and media exposure was associated with a remarkable decrease in the prescription of rosiglitazone by office based physicians in the United States of America[8]. Similarly drug utilization studies demonstrated a reduction of more than 50% decline pharmacy claims of rosiglitazone in USA after the FDA safety warnings[9].

Unlike the study of Startner *et al*, our study explores the effect of safety warnings on duration of exposure to rosiglitazone in addition to the reduction in utilization. We are not aware of any other study that investigated the relationship of drug safety warning to duration of medication use. Duration of prescription is a closer proxy of actual dose consumed since it longitudinally measures the period of drug utilization.

Our study was limited by lack of information about the cardiovascular health status of the individuals. The cardiovascular data would allow us to compare the rate of discontinuation of patients at the highest risk for adverse events from rosiglitazone. Notably, the average age and gender were comparable between the group before and after the drug safety warnings. Age, gender and diabetes are cardiovascular risk factors.

Furthermore our study showed that the probability of receiving refill prescriptions of rosiglitazone reduced to 4 and 2.7% in the groups before and after the safety warning respectively. These observations suggest that physicians discontinued more patients even after 2 years on rosiglitazone use. Whether the later discontinuations were due to observed adverse events or due to a late identification of a patient at risk is not known. Reasons of discontinuation of medications are not documented in the LINH prescription database. Similarly, the database does not capture adverse drug events.

CONCLUSION

Drug safety warnings are effective in reducing the chance and duration of exposure to high-risk medication.

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Chapter 5

LERM (Logical Elements Rule Method): a method for assessing and formalizing clinical rules for decision support

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ABSTRACT

Purpose: The aim of this study was to create a step-by-step method for transforming clinical rules for use in decision support, and to validate this method for usability and reliability.

Methods: A sample set of clinical rules was identified from the relevant literature. Using an iterative approach with a focus group of mixed clinical and informatics experts, a method was developed for assessing and formalizing clinical rules. Two assessors then independently applied the method to a separate validation set of rules. Usability was assessed in terms of the time required and the error rate, and reliability was assessed by comparing the results of the two assessors.

Results: The resulting method, called the Logical Elements Rule Method, consists of 7 steps: (1) restating the rule proactively; (2) restating the rule as a logical statement (preserving key phrases); (3) assess for conflict between rules; (4) identifying concepts which are not needed; (5) classify concepts as crisp or fuzzy, find crisp definitions corresponding to fuzzy concepts, and extract data elements from crisp concepts; (6) identify rules which are related by sharing patients, actions, etc.; (7) determine availability of data in local systems. Validation showed that the method was usable with rules from various sources and clinical conditions, and reliable between users provided that the users agree on a terminology and agree on when the rule will be evaluated.

Conclusions: A method is presented to assist in assessing clinical rules for their amenability to decision support, and formalizing the rules for implementation. Validation shows that the method is usable and reliable between users. The method is useful for future developers of systems which offer decision support based on clinical rules.

1. Introduction

A clinical guideline is a systematically developed document to assist practitioner and patient decisions about appropriate care [1]. Use of guidelines has the potential to improve patient care, especially if guideline recommendations are provided in the form of clinical decision support [2]. Clinical decision support can be broadly defined as any computer-based system designed to help people make clinical decisions [1].

Much work in clinical decision support in the last decade has been devoted to developing computer-interpretable clinical guidelines [3]. In order to build decision support based on a guideline, the guideline is formalized (transformed from natural language to a logical algorithm) and implemented (using the algorithm to program decision support software which is used in practice). Recent work on formalization has focused on narrative guidelines, which describe a process of care with branching decisions unfolding over time [3].

In recent years, a demand for quality assurance and accountability has led to increased interest in performance indicators and other quality measures. In order for the quality of care to improve as a result of these measures, they must be linked to a process of care [4]. For example, a rule such as "80% of diabetic patients should have an HbA1c below 7.0" could be linked to processes such as: "All diabetic patients should have an annual HbA1c test" and "Patients with values over 7.0 should be rechecked within 2 months." When quality measures are linked to processes of care, the resulting statements closely resemble what Shiffman [5] called *condition-action rules*. Condition action rules specify one or at most a few conditions which are linked to a specific action [5], in contrast to narrative guidelines which describe a series of branching or iterative decisions unfolding over time [3]. These quality measures and condition-action rules are hereafter referred to as "clinical rules."

As a case in point, at our institution a set of 87 clinical rules based on the ACOVE (Assessing Care of Vulnerable Elders) [6] set were used to determine areas for

improvement in quality of care [7]. We planned on assessing the rules to determine whether they could be evaluated (that is, determining whether the computer can determine when the condition applies and whether the action should be taken), and formalizing the rules for a proactive clinical decision support system to help clinicians to adhere to these rules. To our knowledge, there is no systematic method described in the literature for assessing and formalizing clinical rules for decision support implementation. Although decision support systems based on clinical rules have been studied, [8, 9, 10, 11, 12, 13, 14, 15] these studies do not provide much concrete guidance for the process of rule formalization. Williams *et. al*. afford the most detailed description: (1) identifying the data elements needed to evaluate each rule, (2) determining if these are explicitly defined in the local computer systems, and (3) for those which are not explicitly defined, determining whether they can be acquired [15].

Systematic methods for guideline formalization have been described in the literature, however. These methods suggest that a domain ontology (a formal specification of concepts and relationships) and a control-flow structure (determination of what will execute and in what order) [16] must be specified. Shahar et.al. describe a process of semantic mark-up of the guideline by expert physicians (identifying the domain concepts), cooperative addition of control-flow structure, and then formalization by an expert in knowledge modelling (specification of the ontology) [17]. Svátek and R ožička describe a similar process: (1) input text format (2) course-grained mark-up (mark parts of the document which describe actions to be taken) (3) fine-grained mark-up (replace linguistic expressions with formal structures, and resolve ambiguity) (4) modularize the knowledge paths (encapsulate context, abandoning the narrative structure) (5) map to the specific knowledge base, and (6) encode [18].

However, clinical rules differ from narrative guidelines in that they describe a discrete condition-action recommendation rather than a process which unfolds over time. Each rule describes one or a few actions to be taken. Narrative guidelines are complex and need to be decomposed into independent paths of

action. By contrast, clinical rules are presented as discrete units and need to be composed into unified paths of action (for example, identifying rules which will apply to the same patients or result in the same recommended action). Disambiguating the domain concepts presents a significant barrier [15]. A method which draws on previous work with guidelines, and addresses the problems particular to clinical rules, could structure this task of assessing and formalizing rules.

The aim of our investigation was to create a step-by-step method for assessing and formalizing clinical rules, and to validate this method to assess its usability and reliability. The method we propose is referred to as LERM, the Logical Elements Rule Method.

2. Methods

In order to create a robust method which could be used with diverse clinical rules, we chose to develop LERM using a sampling of rules from multiple sources. We turned to the literature for studies of decision support systems based on quality measures which were linked to processes or condition-action rules: such as quality indicators, performance indicators, performance measures, standards of care, or clinical rules. We sought studies which implemented decision support systems based on published sets of clinical rules (thus excluding rules which were created specifically for a decision support system). The clinical rules used in these studies, together with the rules which we planned to use in our institution, formed our sample set of clinical rules (listed in Table 1). These rules fit our requirements of representing diverse areas of clinical care, from several sources, and in different formats.

Tabel 1 - Sources of rules

Source	Clinical area	Implementation study
Rand Health	Vulnerable elderly [7]	
Cooperative cardiovascular project	Acute myocardial infarction [20]	Sauaia et al. [9]
Joint Commission	Acute myocardial infarction [21]	Butler et al. [10]
Joint Commission	Heart failure [21]	Butler et al. [10]
Joint Commission	Pneumonia [21]	Niemi et al. [11]

National Kidney Foundation	Dialysis [22]	Diamond and Daly [12]
Arthritis Foundation/Rand Health	Rheumatology [23]	Williams et al. [16]
American Diabetes Association(ADA)	Diabetes [24]	Club Diabete Sicili [13]

The sets of rules varied widely in size: from 392 rules in the ACOVE set [6] to only 4 rules in the Joint Commission heart failure set [20]. In order to maintain a good mix of rule sources and clinical conditions in our validation set, 2 rules from each set were randomly selected and reserved.

To develop LERM, a focus group was recruited consisting of the primary researchers (SM and DO), two clinical experts (SdR and PW), and one expert in medical informatics (AA). LERM was developed in an iterative process, with the starting assumption that, like guideline formalization, the new method would need to delineate a domain ontology and a control-flow structure [16]. In addition, the requirements of LERM were defined as: (1) assessing clinical rules to determine if the rules can be implemented as proactive computerized decision support, (2) formalizing rules for implementation of decision support using data from existing clinical information systems (identifying the specific data which are needed so that access to these systems can be prioritized), and (3) a process which can be applied consistently over a large set of rules.

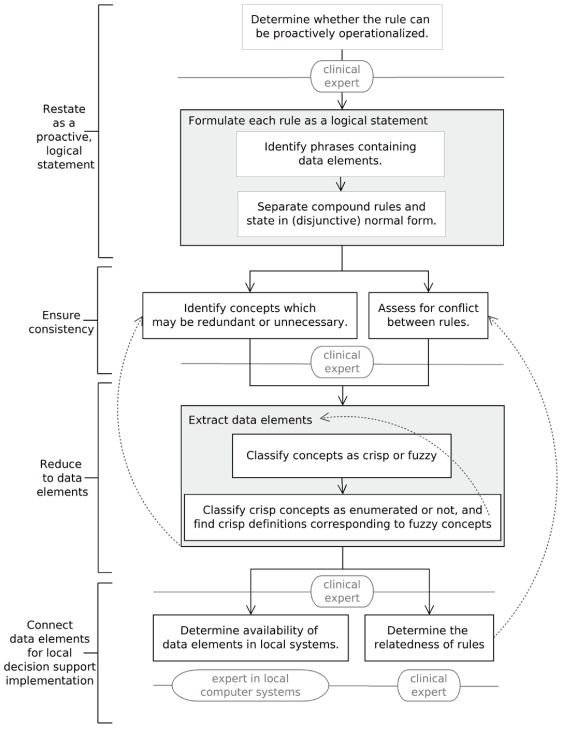
Each successive version of LERM was tested with a sample of rules from the development set, and the results discussed at the focus group meetings. The questions discussed in the focus group meetings were: (1) Is the clinical intent of the rules in that iteration maintained? (2) Is the mapping of phrases from one terminology to another correct? (3) Are there inconsistencies between or within rules or other problems which were revealed? (4) Could these problems be identified earlier, and would it be useful to do so? The method was revised on the basis of these results and the process repeated. Validation was performed to assess both the inter-user reliability and usability of the method. Usability was assessed in terms of the time required to assess the rules and the error rate. Errors were defined as any inconsistency between the formalized rule and the original rule (for example, omitting a concept), or between the identified data elements and the terminology (for example, failure to locate a concept in the

terminology which maps to the concept in the rule). Errors were located by comparing the results from the two assessors. Reliability was measured by assessing agreement between the two sets of results for each step of the method, and noting points of divergence and re-convergence. Each assessor independently formalized the rules, then the results were discussed together. Agreement and Cohen's κ were calculated in R. It was anticipated that use of a standard terminology would affect agreement, thus the assessment was performed first without a standard terminology, and then the relevant steps repeated using SNOMED-CT (Systematized Nomenclature of Medicine - Clinical Terms) [24] as the target terminology.

3. Results

LERM was created as a step-by-step method in order to systematize rule transformation and facilitate its contemporaneous application to many clinical rules. Although the process is presented linearly, there are several places where steps may be carried out in parallel. In the illustration of the method in Figure 1, these places are indicated by branches.

Figure 1: LERM: the Logical Elements Rule Method. Although the method is presented linearly in the



text, in practice some steps may be done in parallel, as shown here. Some steps, such as extracting data elements or checking for conflicts between rules, may need to be repeated with the results of later steps as input

Clinical rules are formulated for a particular purpose, and a clinical expert is needed to ensure that this intent is maintained as the rule is formalized. Side-by-side cooperation of a clinical expert and an informatics knowledge expert may be the best approach [17], but points are noted where clinical expert involvement is essential.

LERM is best described by illustrating its steps using concrete examples. Table 2 gives examples of clinical rules from the various rule sets, including the rules used in the examples below.

Tabel 2: Examples of clinical rules. Clinical rules are independent statements which link one or a few conditions to a conclusion.

ACOVE [6] (Assessing Care of Vulnerable Elders): IF a vulnerable elder is prescribed an ongoing medication for a chronic medical condition, THEN there should be a documentation of response to therapy
ACOVE [6]: IF a vulnerable elder requires analgesia, THEN meperidine should not be prescribed
Cooperative Cardiovascular Project [19]: Criterion: Received aspirin during hospitalization. Eligible: All patients with confirmed AMI (acute myocardial infarction). Exclusions: [list of exclusions].
Joint Commission AMI [20]: Description: Acute myocardial infarction (AMI) patients who are prescribed aspirin at hospital discharge. Numerator Statement: AMI patients who are prescribed aspirin at hospital discharge. Denominator Statement: AMI patients. Excluded Populations:[list of exclusions]
Joint Commission pneumonia [20]: Description: Pneumonia patients transferred or admitted to the ICU (intensive care unit) within 24 hours of hospital arrival, who had blood cultures performed within 24 hoursprior to or 24 hours after hospital arrival. Numerator Statement: Number of pneumonia patients transferred or admitted to the ICU within 24 hours of hospital arrival who had blood cultures performed within 24 hours prior to or 24 hours after arrival at the hospital. Denominator Statement: Pneumonia ICU patients 18 years of age and older. Excluded Populations: none.
National Kidney Foundation [21]: The delivered dose of hemodialysis should be measured at regular intervals no less than monthly.
Arthritis Foundation Quality Indicators [22]: If a patient has RA (rheumatoid arthritis) and is being treated with a DMARD (disease-modifying antirheumatic drug) and reports worsening of symptoms over a 6-month period of time and there is evidence of active disease, then one of the following should be done: increase DMARD dose, change DMARD, add an additional DMARD or, start or increase dose of glucocorticoids.

ADA (American Diabetes Association) Standards of Medical Care in Diabetes [23]: Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients with overt CVD (cardiovascular disease) or without CVD who are over the age of 40 and have one or more other CVD risk factors.

1. Determine whether the rule can be proactively operationalized.

In order to provide proactive decision support for a rule, the rule must be stated such that it can be proactively operationalized. That is, it must be possible to use the rule to make a decision for an individual patient before it is too late to carry out the recommended care. For example, outcome-oriented indicators will need to be restated in terms of a care process which can be improved [4].

Example 1.1: (from the Joint Commission AMI set) [19].
Eligible [patients]: All patients with confirmed AMI. Criterion [for adherence]: Received aspirin during hospitalization. Exclusions: [list of exclusions]. As it is stated, this rule can only be evaluated after the patient has been discharged. A proactive restatement of this rule might be: "All patients with confirmed AMI should receive aspirin within 1 day of admission, and daily long-term, except [list of exclusions]."

The rule may need to be made more explicit in order to be actionable, but the intent of the rule should be preserved. Since a clinical understanding of the rule is required, a clinical expert should be involved in this step.

2. Formulate each rule as a logical statement.

Like guidelines, rules need to be transformed from natural to formal language. This step combines elements of steps 2 and 3 from Svátek and Rožička (markup and replacing linguistic structures with formal structures) [18]. A potential caveat of this transformation is that the formal version must be medically valid, but clinicians may have difficulty understanding formal restatements of the rules. Thus this is broken into smaller steps, and the original vocabulary and structures such as negations and chronological relationships are kept intact.

(a) Identify phrases containing data elements.

Williams *et. al.* [15] use the term data elements to describe the units of clinical information used by the decision support system. In some cases a single phrase may later be broken down into multiple data elements, but the goal at this stage

is to identify domain concepts (shown in the example as underlined phrases) without changing the language used.

Example 2.1: (from the ADA set) [23].
Statin therapy should be added to lifestyle therapy, regardless of baseline lipid levels, for diabetic patients with overt CVD or without CVD who are over the age of 40 and have one or more other CVD risk factors.

(b) Separate compound rules. Restate the rules in disjunctive (or conjunctive) normal form.
Here the basic control-flow structure is defined by defining which condition will trigger which action. Rules often contain compound statements (joined by "and", "or", etc.). There are two reasons to break the rules down into their simplest parts. One is that it makes it easier to later program the rules. The other is that if only part of the data is available, part of the rule may be able to be implemented, which may still provide useful decision support.

Example 2.2: The rule in Example 2.1 can be broken into independent parts:
(1) diabetes AND overt CVD → statin therapy AND lifestyle therapy (2) diabetes AND (NOT CVD) AND over age 40 AND CVD risk factor [other than diabetes] → statin therapy AND lifestyle therapy

3. Assess for conflict between rules.
Simply restating the rules in a uniform grammar may reveal inconsistencies within a set of rules which were not noticed by the developers of the rule set, or inconsistencies between sets of rules. Although it is mentioned as an early step in the process, further formalization may reveal other conflicts. Conflicts within and between guidelines are well recognized, [16] and clinical rules are susceptible to this problem as well.

4. Identify concepts which may be redundant or otherwise unnecessary.
As electronic patient data is often incomplete or stored in proprietary databases, it is useful to determine the minimum data needed to provide decision support

for the rule. If all data are available, redundant concepts can be used to check one another. There are two categories of phrases which are dealt with in this step: phrases which can be excluded without changing the meaning of the rule Example 4.1); and phrases which are not redundant, but are not needed to interpret the rule in current clinical practice (Example 4.2).

Example 4.1: (from the ACOVE set) [6]
IF a vulnerable elder is prescribed an ongoing medication for a chronic medical condition, THEN there should be a documentation of response to therapy.
The vast majority of ongoing medications are prescribed for an ongoing (chronic) condition. The phrase "for a chronic medical condition" can probably be omitted without changing the meaning of the rule, and would greatly simplify use of this rule for decision support.

Example 4.2: (from the ACOVE set) [6]
IF a vulnerable elder requires analgesia, THEN meperidine should not be prescribed.
There are no indications for meperidine other than analgesia (pain relief). However, the indications for meperidine could change as practice changes. The rule can be implemented by assuming that meperidine is always contraindicated in elderly patients, but this implementation should be checked regularly to ensure that there are no new indications for meperidine which would justify its use.

At this stage, the rules have been broken into their simplest parts and restated in a consistent logical grammar, and apparent redundancies and conflicts annotated. The following steps entail translating the phrases used by the authors of the clinical rules to the language which will be used inside the decision support system. Thus it is important at this stage to consult with a clinical expert to ensure that the rules, as stated in their new form, are medically valid and retain the intent of the original rules.

5. **Extract data elements.**

Data elements are the units of clinical information which will be used by the software which provides decision support. The level of granularity which is "elemental" for a particular set of rules will depend on the clinical context where

it is deployed. The decision support system may use its own terminology [17], in which case the data elements are the units of information at the level of granularity of this terminology.

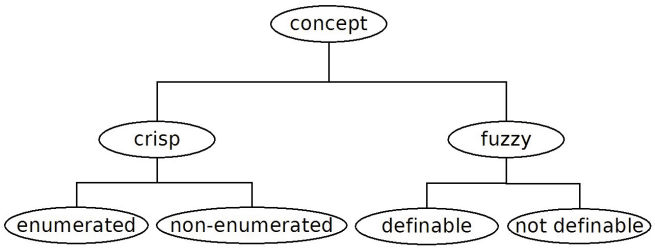
(a) Classify phrases as crisp or fuzzy.

In order to use a rule for decision support, all terms must be clearly defined. This can present a significant barrier to implementation [15]. The terms crisp and fuzzy are drawn from set theory. A set of objects is a fuzzy set if it is possible to have degrees of membership in that set. Likewise, a set is crisp if it is possible to unambiguously determine whether something is or is not a member of the set. [25] For the purposes of evaluating a clinical rule, the concepts in the rule are crisp if it is possible to unambiguously determine whether the rule applies and has been followed, based on mapping patient data to the concepts in the rule. Using the same rule as in Example 2.1 and 2.2:

Example 5.1:

crisp: diabetes, statin therapy, age > 40

fuzzy: overt CVD, CVD risk factor, lifestyle therapy



(b) Classify crisp concepts as enumerated or not enumerated, and where possible, find crisp definitions corresponding to fuzzy concepts. (see Figure 2).

Figure 2: Classification of crisp and fuzzy concepts: A concept is crisp if it can be unambiguously determined whether something is included in the concept or not. A concept is enumerated if all relevant examples are listed. A concept is fuzzy if it is possible to have degrees of membership in that concept. It may or may not be possible to agree on a crisp definition of a fuzzy concept for the limited purpose of evaluating the rule.

A crisp concept is enumerated if all known examples are listed [25]. In this case, concept is considered enumerated if all examples which are relevant to

evaluation of the rule are listed. If a terminology is used, a concept is enumerated if it maps to exactly one concept in the target terminology.

Example 5.2: Diabetes may be considered enumerated if, in the logic of the decision support system, it is a single concept. More typically, the crisp term "diabetes" would be enumerated as "diabetes type I" and "diabetes type II." For some rules it may need to be further enumerated into clinical stage and etiological subtypes.

In order to create a domain ontology, crisp definitions will need to be found which correspond to fuzzy concepts. The crisp definition may not encompass the whole of the fuzzy concept, but should encompass the part of the concept needed to evaluate the rule correctly. The same phrase may be defined differently for different rules. In the simplest case, the supplementary material of the rule set may provide a crisp definition. In other cases, the concept may be redefined for the limited domain of the rule. Ambiguity can represent a lack of evidence or consensus [16] and thus it may not be possible to agree on an unambiguous definition. A working definition may be reached by local consensus, but this should be updated regularly as new evidence emerges, and reassessed if the software is deployed in a new clinical setting.

Example 5.3: "CVD risk factors" are listed in the supplementary text: dyslipidemia, hypertension, smoking, a positive family history of premature coronary disease, and the presence of micro- or macroalbuminuria. These terms will in turn need to be classified as crisp or fuzzy and defined as necessary. By contrast, "lifestyle therapy" is not defined in the text. A review of the evidence or expert consensus may be needed to agree on a definition of "lifestyle therapy" for the purpose of evaluating this rule. The result of these steps is a restatement of the rule in terms of data elements:

Example 5.4: diabetes [diabetes type I, diabetes type II] AND overt CVD [AMI, peripheral artery occlusive disease...] → statin therapy [atorvastatin, fluvastatin, lovastatin...]

A clinical expert will need to advise on the definition of fuzzy concepts, and confirm that the rules are valid and maintain the intent of the original rule with

their new vocabulary. A clinical expert can also advise on whether there are exceptions to the rule or other revisions needed in order to accurately evaluate the rule. These exceptions may also need to be specified in terms of data elements. If the clinical experts cannot agree on a crisp definition for all concepts in the rule, then it may not be possible to implement decision support based on the rule.

6. **Determine relatedness of rules.**

By this stage the rules are defined in a crisp language and uniform grammar. The relationships between the domain concepts can now be mapped. Rules may be related if they share data elements, share a patient population, or require the same action from the clinician. It is important to recognize these convergence points to specify a control flow structure which will create a good workflow and user experience for the clinician. If multiple rules apply at the same time, the clinician should be guided through them to create a good workflow. If multiple rules result in the same recommendation, the clinician should still receive only one message with an appropriate explanation. Example 6.1: It can now be seen that the AMI rule from Example 1.1 overlaps with the diabetes rule from example 2.1, in that they will both apply to patients with AMI. Other rules in the Joint Commission AMI set suggest discharge medications for the AMI patient, including aspirin. The rules should be linked to ensure that the patient gets a continuous, appropriate aspirin prescription, and that the clinician gets a single list of recommended discharge medications.

7. **Determine availability of data elements.**

To this point, analysis has been independent of the local data systems. In this step, the results of the above analysis are applied to the local setting. The analysis described above allows quantification of the importance of a particular data element to the interpretation of the rule set. Thus, if that data element is not recorded, there can be a discussion with the clinicians as to whether separate entry of that data item is worth their time (Example 7.1).

Example 7.1: In a hypothetical hospital, all data elements for the diabetes rule in the example above are available except lifestyle therapy. It is decided to add a tab to the electronic patient record which allows documentation of lifestyle therapy so that decision support can be provided for this rule.

Results of validation

LERM was validated with a set of 16 rules which were reserved for validation prior to developing the method. The results of this assessment are summarized in Table 3.

Tabel 3: Results of the validation of LERM

Step	Result	Agreement
Determine whether rule can be proactively operationalised	12/16 rules need to be rephrased	Agreement on which rules need to be changed, differences in how they were operationalized in 5/12 rules.
Phrases containing data elements		Minor variations, except those caused by step 1
Separate compound rules and state in normal form	4/16 rules were compound	Minor variation, except those caused by step 1
Assess conflict between rules	Potential conflict between 4/16 rules	Same conflicts noted by both assesors
Check for unnecessary phrases	No unnecessary phrases	Assessors agreed
Data elements	100 data elements according to one assessor, 83 elements according to the other	13/100 and 2/83 represented unique concepts, the others were the same or minor variations
Crisp/fuzzy concepts	Without terminology: of 67 classified the same: 60 crisp and 7 fuzzy. With terminology: of 82 classified the same: 72 crisp, 10 fuzzy.	Without terminology: 77.0% agreement ($K=0.315$, $p<0.001$) With terminology: 87.4% agreement ($K=0.76$, $p<0.01$)
Crisp-enumerated/fuzzy-definedd concepts	Without terminology:52 classified the same:37 enumerated, 8 non-enumerated, 3 defined, 4 fuzzy-undefined. With terminology: of 76 classified the same: 14 enumerated, 52 non-enumerated, 3 defined, 7 fuzzy-undefined.	Without terminology:58.6% agreement ($K=0.322$, $p<0.001$) With terminology: 87.4% agreement ($k=0.763$, $p<0.001$)

Relatedness of rules	Each rule related to at least 1 other rule by sharing data; 4 share patients, 4 share recommendations	Agreed on which rules shared data, populations, and recommendations.

Without use of a terminology, the process took about 4 hours for one participant and about 6 for the other. Variation was noted in the proactive rephrasing of the rule. Upon discussion, the differences in results stemmed from different visions of when a rule would be evaluated. For example, one of the rules states that AMI patients should receive aspirin within 24 hours of arrival. One assessor envisioned a consulting system (suggests aspirin in the list of orders upon arrival), the other envisioned a critiquing system (issues a reminder if there is no aspirin after 24 hours). Other than differences resulting from this early departure, there was little divergence in the subsequent steps, except as anticipated in step 5. Errors were rare, with 7 errors noted (although one error was systematic, with the same concept omitted 3 times by each assessor). In all cases the source of error was omission of a phrase in a complex rule while restating it in conjunctive normal form. This experience suggests that the results of this step should be carefully checked for errors, or performed by two persons and the results compared.

Step 5 (concerning crisp and fuzzy concepts) was repeated using SNOMED-CT. For this purpose, a concept was considered crisp if it could be completely represented using SNOMED-CT concepts, and enumerated if it was represented in SNOMED-CT by a concept or a composition of concepts which had no child-concepts. The 87 phrases were represented by a minimum of 114 SNOMED-CT concepts. (SNOMED-CT concepts are not disjoint, [26] thus there can be more than one way to represent a concept. The simplest representation was preferred.) As predicted, inter-user reliability improved considerably. However, this came at the cost of more time (about 4 additional hours) and an increased error rate: 17 errors were noted in this step, including 3 systematic errors. Most were due to the difficulty of determining whether a concept was truly absent from SNOMED-CT. The assessors noted concepts which seemed to be as crisp as other SNOMED-CT concepts, but were omitted by chance from the terminology.

For example, SNOMED-CT contains the concept "on admission" but not "at discharge." In total 15 such concepts were noted by both assessors as possible omissions, and subsequently classified as crisp concepts.

Discussion

To our knowledge, LERM is the first method for formalizing clinical rules for use in decision support, focusing on condition-action clinical recommendations rather than time-oriented guidelines. We present a step-by-step method for formalizing clinical rules, which has been validated with a sample of rules from diverse sources and clinical domains.

The most important limitation of this investigation is the inherent subjective nature of development through inductive methods. It is possible that a different team, using the same or different rules, would arrive at a different set of steps. That said, each step in the method can be linked to a potential caveat in developing the decision support system. Another limitation is the relatively small number of rules which were reserved for validation, leaving open the possibility that the randomly selected rules are not representative of all the rules in that set. Even so, validation allowed an assessment of patterns in the reliability, error rate, and time cost of formalization using the method. Formalization is recognized as a time- and labor-intensive process, [16] but most studies do not report the time required for formalization, though one group reported a total implementation time of 7 weeks per rule [14].

Another well-recognized problem is disambiguation of natural language text [16]. Ultimately, concepts are sufficiently defined when they can be mapped to elements of the patient record and the resulting electronic representation of the rule generates correct results. However, directly mapping to a specific patient record would be detrimental to another important goal for decision support systems: interoperability [27, 28]. Thus LERM does not bind the formalization to a particular set of patient data until the last step, using the terms crisp and fuzzy to help define ambiguity for the intermediate steps.

The terms crisp and fuzzy are borrowed from set theory. The sets in this context are the set of conditions in which the rule should be evaluated, and then dividing those into disjoint sets where support should be offered or not (meaning the rule is decidable" [29]). Thus "diabetes" in this context refers not to the disease, but to patients to which rules about diabetes should be applied. The onset of a disease such as diabetes is gradual, and the diagnosis is not always clear, but it is the task of doctors to disambiguate the patient's state. While there is no defined moment when a patient becomes diabetic, there is a defined moment when the patient is diagnosed with diabetes, and this is when rules about diabetes apply. Thus, although "diabetes" is fuzzy, the diagnosis of diabetes is a crisp concept.

In order to implement a decision support system, knowledge of medicine and its intricacies must be combined with knowledge of computer reasoning to create a program which is formally valid and medically useful. This requires the cooperation of both clinical experts and experts in medical informatics [17]. To facilitate this cooperation, we chose to separate the steps of changing the grammar to a logical form and changing the vocabulary to data elements. Tools such as DeGEL (Digital electronic Guideline Library), [17] GEM (Guideline Elements Model) [30] or DELT/A (Document Exploration and Linking Tool / Add-ons) [31] could assist in maintenance and tracking of these changes.

After transformation, clinical rules are suitable for implementation as Medical Logic Modules (MLMs) [27], with data elements in the data slot (which are mapped to a local database). Rules which have been recomposed into clinical paths can be implemented using guideline implementation software such as Asbru, GLIF (GuideLine Interchange Format), PROforma, and Gaston [3, 16]. Composing the rules into paths is reserved as a final step, as connections between rules may not be apparent until the rules are fully specified.

The primary audience for LERM are others who wish to implement decision support based on clinical rules. We have developed an approach which has proven robust and reliable. Although intended for human users, a systematic

approach such as LERM may also be informative for development of automated formalization [32]. In addition to its primary audience, LERM may also prove useful for improving the rules themselves. Guidelines are easier to follow when they are clearly specified [16, 5]. Similarly, clinical rules which use crisp terms, or acknowledge candidly when the evidence is not sufficient and clinical judgment is required, would likely be easier for clinicians to follow as well as easier to formalize. Often, clinical rules are developed in order to audit quality and provide performance feedback. Automated evaluation of rules to assess adherence could allow for continuous auditing and more frequent feedback. By omitting the first step of the method, LERM could also be applied to this task.

Thus far, this method has only been tested in vitro. Its use in developing decision support for use in a clinical trial is currently under investigation. The steps described here end with assessing the availability of data. As many hospitals are in transition from paper to electronic records, the result of this assessment will often be that key data elements are not available or are incomplete. Others have leveraged existing data to infer more information about the patient than is directly recorded in the system, [10] but the impact of such inferences on the quality of decision support which can be offered is not yet known. Adapting the type of support offered to the quality of underlying data may affect the quality of support which is offered, and, in turn, the quality of care.

In summary, the Logical Elements Rule Method (LERM) is presented to assist in assessing clinical rules for their amenability to decision support, and formalizing the rules for implementation. The method was validated with a sample of clinical rules from diverse sources pertaining to a variety of clinical conditions. Validation showed that the method was robust and reliable between assessors, provided that it is agreed in advance what terminology will be used and when the rule will be evaluated. We envision an important role for LERM in this era of increasing attention to performance indicators and quality assurance. LERM can assist in transforming an indicator into an improvement in the everyday practice of medicine.

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Chapter 6

Feasibility of automatic evaluation of clinical rules in general practice

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ABSTRACT

Purpose

To assess the extent to which clinical rules (CRs) can be implemented for automatic evaluation of quality of care in general practice.

Methods

We assessed 81 clinical rules (CRs) adapted from a subset of Assessing Care of Vulnerable Elders (ACOVE) clinical rules, against Dutch College of General Practitioners(NHG) data model. Each CR was analyzed using the Logical Elements Rule Method (LERM). LERM is a stepwise method of assessing and formalizing clinical rules for decision support. Clinical rules that satisfied the criteria outlined in the LERM method were judged to be implementable in automatic evaluation in general practice.

Results

Thirty-three out of 81 (40.7%) Dutch-translated ACOVE clinical rules can be automatically evaluated in electronic medical record systems. Seven out of 7 CRs (100%) in the domain of diabetes can be automatically evaluated, 9/17 (52.9%) in medication use, 5/10 (50%) in depression care, 3/6 (50%) in nutrition care, 6/13 (46.1%) in dementia care, 1/6 (16.6%) in end of life care, 2/13 (15.3%) in continuity of care, and 0/9 (0%) in the fall-related care. Lack of documentation of transmural activities and ambiguous formulation of clinical rules were the main reasons for the inability to automate the clinical rules.

Conclusion

Approximately two-fifths of the primary care Dutch ACOVE-based clinical rules can be automatically evaluated. Clear definition of clinical rules, improved GP database design and electronic linkage of primary and secondary healthcare facilities can improve prospects of automatic assessment of quality of care. These findings are relevant especially because the Netherlands has very high automation of primary care.

INTRODUCTION

Quantification of quality of care is critical for quality management in general practice. Specifically, measurement of quality of care allows general practitioners to appraise the current status of quality and to identify opportunities for improvement.

Evaluation of quality of care utilizes predefined sets of quality of care indicators against which data collected from electronic medical record (EMR) are evaluated (1). These evaluation activities are often performed retrospectively. This approach is tedious, time consuming and presents performance results months after the target clinical process activities have occurred. Opportunities for timely intervention are thus lost. Increasing demand for adherence to several clinical guidelines and quality indicators make it even more difficult to perform quality of care assessment manually.

Automatic evaluation of care can be used to solve the problem of large amounts of data collected in general practices. Automatic evaluation of quality of care requires compatibility of quality indicators and clinical databases in terms of definition of concepts. Unfortunately most quality indicators are formulated in natural language without considering that they can be represented in a computer interpretable format.

In this study, we investigated the extent to which the quality of care provided to elderly persons can be automatically evaluated using EMR data that is routinely

recorded by general practices that participate in the Netherlands Information network of General Practice. We use Assessing Care of Vulnerable Elders (ACOVE) quality indicators to evaluate the feasibility of automatic evaluation of quality of care of elderly persons at the general practice level (2). Automation is important because it allows for applications such as quality assessment and real time decision support. Automation provides timely feedback to general practitioners that enable them to change their practice and thus improve quality of care.

METHODS

ACOVE Quality indicators

Assessing Care of Vulnerable Elders (ACOVE) clinical rules were developed by the RAND foundation in the USA to assess quality of care of elderly persons (2). A subset containing 81 clinical rules (CRs) were translated for evaluating quality of care in general practice by a panel of Dutch geriatric care experts (3). The CRs are divided into eight domains of care namely: *organization of continuity of care*, *dementia care*, *depression care*, *diabetes care*, *end of life care*, *prevention and management of falls, appropriate medication use and, diagnosis and management of under nutrition.* The CRs are formulated as ***IF .....THEN statements***. A given clinical condition or state in the **IF** segment of the CR prompts an action in the **THEN** segment of the CR. An example of the CRs reads as follows*: **IF** a vulnerable elder has diabetes, **THEN** glycated hemoglobin should be measured at least annually*.

Data source

General practitioners (GPs) in the Netherlands universally use electronic medical records (EMR) to document patient information.

Description of Standard Reference Model of EMRs in Dutch General Practice

The Dutch College of General Practitioners publishes a reference model which describes a minimum dataset that all EMRs in Dutch general practice must collect. EMR databases are derived from the same reference model to facilitate data exchange and aggregation. In this study, we used the NHG database model to establish the data variables that are collected from the EMR databases.

Patient contacts are classified as consultations, home visits or drug prescriptions. General practitioners link each contact to specific clinical episodes of care. An episode is defined as a medical problem for which a patient seeks medical assistance, for example hypertension or diabetes. Patient diagnosis (es) in each contact is coded using the International Classification for Primary Care (4).

Patient characteristics in the EMR databases include age and gender.

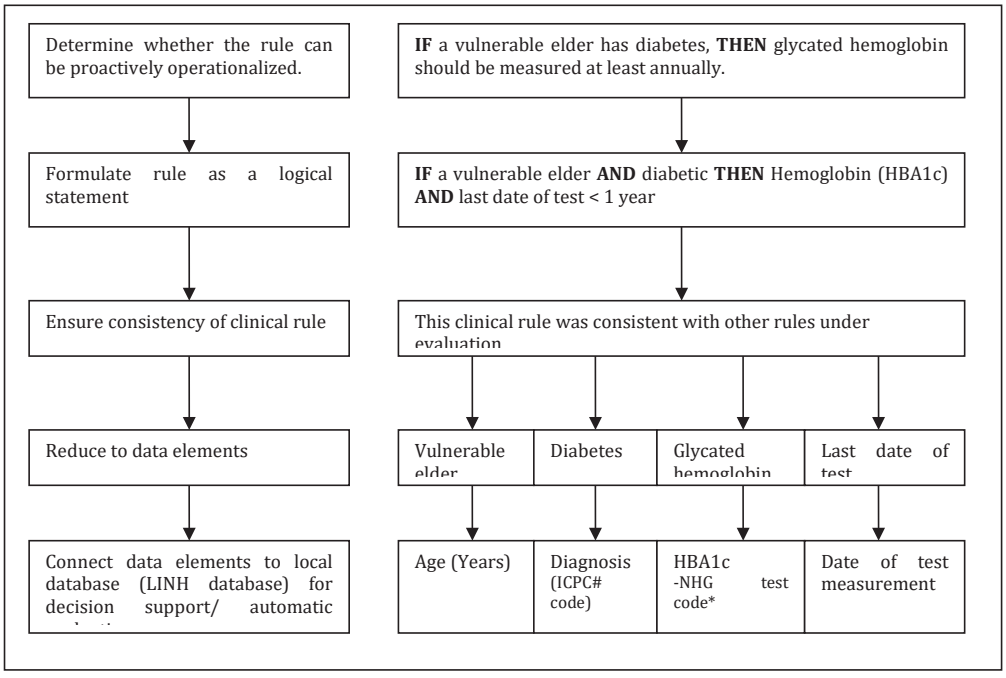
Data collected about the general practices include: type of practice, geographical location and urbanization level of the locality of the practice. The brand of EMR used in each practice is also documented. Findings of diagnostic procedures such as physical examinations and laboratory tests are coded and documented using a terminology developed by the Dutch College of General Practitioners.

The EMR databases also contain prescription data. Each prescription is a single record. Details about each prescription include date and time, code name of drug, amount and frequency. The anatomical and therapeutic chemical (ATC) classification system used for coding the name of the medication (5).

LERM Analysis

We analyzed 81 ACOVE clinical rules using the Logical Elements Rule Method (see supplementary table for a list of the clinical rules). LERM analyses a clinical rule to establish if the terms and concepts that constitute it can be represented in a computer interpretable form (6,7). Each clinical rule was analyzed separately. **Figure 1** illustrates the steps in the analysis of the quality indicators using a clinical rule.

Figure 1: An illustration of the steps in the LERM analysis of a sample clinical rule.



The first step involved analyzing whether the CR could be proactively operationalized. A proactively stated CR is one which can be used to make a decision for a clinical intervention when its condition is fulfilled. A non-proactive CR is one whose condition and recommendation is temporally invalid. Non proactive CR do not give the physician no opportunity to change practice because it is aimed at foregone events. For example: ***IF*** *a vulnerable elder who had dyspnea in the last 7 days of life died an expected death,* ***THEN*** *the general practitioners record should document a dyspnea policy.* In this clinical rule, no intervention can be implemented because the patient has already died. Non-proactive CRs are thus limited to assessing past performance. The sample CR about diabetes is proactive, because the GP has an opportunity to test the

Secondly, each CR was formulated into a logical statement. During this process phrases containing concepts were extracted from the statement of the indicator. In the illustration, the following concepts phrases were extracted from the logical statement: *Vulnerable elder, diabetes, glycated hemoglobin and date of last laboratory test* .

Thirdly, concepts extracted from the clinical rule are converted to data variables, as they would be represented in EMR databases. We then assess if all data variables that constitute each clinical rule are documented in the EMR databases in sufficient detail to allow for development of electronic feedback to the general practitioners. Clinical rules whose data variables are captured in the EMR databases were considered to be amenable for automatic evaluation at the point of care.

These steps were repeated for each of the 81 clinical rules.

RESULTS

Table 1 shows clinical rules which can be used for automatic assessment of quality of care. Overall 33 out of 81 clinical rules were found to be evaluable with the current data available in the EMR databases. The following paragraphs explain the results of the analysis for each domain of care.

Table 1: Number of ACOVE based clinical rules that can be evaluated in Dutch General Practice per domain of care.

ACOVE Domain of care	No of clinical rules (n)	Proactive Clinical rules (n)	Clinical rules reducible to data elements (n)	Clinical rules with data in GP database (n)
Continuity of care	13	13	4	2
Depression	10	10	8	5
Dementia	13	13	8	6
Diabetes	7	7	7	7
Medication use	17	16	9	9
Nutrition care	6	6	4	3
Falls and mobility care	9	9	8	0
End of life care	6	3	2	1
TOTAL	**81**	**77(95.0%)**	**50(61.7%)**	**33(40.7%)**

Continuity of Care

Two of thirteen CRs associated with continuity of care were found to be amenable for automation. The two clinical rules involve the follow up of diagnostic laboratory results and scheduled preventive care such as vaccinations. Three CRs were found to be ambiguous in their definitions. These CRs would be evaluable if they are redefined. Four CRs that involve

documentation of information that is generated at hospital discharge and two CRs that involve information sharing between the nursing home and GP practice cannot be automated since there is not electronic data linkage between nursing homes and GP practices. Two CRs regarding information sharing when a patient migrates from one GP practice to another or when a patient receives medication from another GP practice to is not automatable. There existed no electronic linkage between GP practices at the time of this analysis.

Depression Care

Five out of ten CRs in the domain of depression care can be automated. Three of the six CRs involve documentation of co morbidities at the time of diagnosis of dementia. Two deal with prescription of treatment for depressed patients. On the contrary, one CR that deals with providing patient information is not evaluable since the patient information is not documented. Similarly, two CRs regarding assessment of response to treatment and judgment of suicidal ideation by a depressed patient cannot be automated since responses to treatment are not documented in this database.

Dementia Care

Six out of thirteen CRs about dementia care can be automated. Five of the six deal with documentation required at the time of diagnosis of dementia such as cognitive function, use of medication and laboratory investigations. Five CRs were not sufficiently defined to allow for the mapping of their data concepts. Two are however well defined but cannot be automated because their data

concepts are not captured in the EMR databases.

Diabetes Care

All seven CRs associated with diabetes can be automated. They involve schedules of follow up laboratory examination or indication for initiating additional treatment for diabetic patients.

Medication Use

Nine out of seventeen CRs associated with medication use can be automated. Three CRs involve regular review of the current and previous medications that the patient has been taking. Another three (3) CRs deal with laboratory follows up of patients on medication. One CR deals with co-prescription of gastroprotective medication with NSAIDs. Two CRs involve duration of treatment with benzodiazepines and prescription of alternative medication to strong anticholinergic medications. Seven clinical rules could not be automated because their data elements are not captured by the NHG data model. The CRs deal with patient counselling about medication use and justification of specific medication use. One clinical rule required data from both the GP EMR and Dutch Thrombosis Service. Such data was not contemplated in the NHG data model.

Nutritional care

Three out of six CRs associated with nutritional care can be automated. One CR involves prescription of Vitamin D use to the elderly. Two CRs deal with diagnosis of nutritional disorders by monitoring weight of the patient and documenting causes of weight loss and documenting weight of patients suffering

from chronic obstructive airway disease. A CR regarding referral of patients with decubitus to a dietitian cannot be automated.

Falls and morbidity

None of the nine CRs in the domain of prevention of fall can be automated. There is no standardized coding for falls in the terminology systems that were used in the GP practice, and were therefore not available in the EMR databases.

End of life Care

One out of six CRs associated with end of life care can be automated. The CR concerns prescription of opioid analgesic to patients with metastatic cancer or terminal pulmonary disease. Four of the CRs are not proactive because that they are meant to review the quality of palliative care provided around the time death. They can only be evaluated in retrospect, postmortem. One CR was insufficiently defined to allow for assessment using currently available data.

DISCUSSION

Main findings

Thirty three (40.7%) out of eighty one Dutch translated ACOVE clinical rules can be automatically evaluated based on the current data collected by the Dutch general practices. Majority of clinical processes that can be automatically evaluated deal with specific well coded diagnosis such as diabetes or depression and medication use. However, the number of CRs regarding continuity of care that can be automatically evaluated is low. This is mainly because information sharing between hospitals, nursing homes, and general practices is mainly not

electronic. Clinical letters and other paper-based media are used between GP practices and other health service providers. These materials contain unstructured clinical information and are not stored in the EMR databases. Flink *et al*. have previous highlighted the lack of patient-centered documentation between hospital and primary health care and how it impairs continuity of care (8).

Moreover, CRs that were less specifically defined were found to be inappropriate for automatic evaluation. Lack of detail in the formulation of quality indicators offsets the ability to evaluate them effectively (9). Use of implementability appraisal frameworks by authors of clinical rules may reduce ambiguity and improve their implementation and subsequent evaluation (10). Likewise future revisions of CRs may consider redefinition of concepts to make them more specific. Two approaches are therefore necessary to increase the ability of quality indicators to be automatically assessed using existing clinical data. The first is to try and re-formulate the concepts in the quality indicators clearly to allow for easy mapping to the target source of clinical data (11). This can be done by using guideline representation languages (12). Secondly, standardization of documentation is necessary to improve data sharing between general practices, nursing homes and hospitals. Standardization potentially improves the quality of data generated from transmural care activities.

Our study demonstrates the potential of the EMRs in automated monitoring of quality of care in general practice. Automation provides an opportunity for

timely feedback to the general practitioners. Prompt feedback can be in the form of real-time measurement of quality indicators. The GP compares his/her performance against quality benchmarks. Alternatively, automation can be implemented in the form of real time clinical decision support, for example in the form of alerts or reminders, available at the point of care.

Quality evaluation research in such a case is a secondary application for the clinical data (13). Re-use of clinical databases is widely accepted in several research domains such as clinical epidemiology and decision analysis among others (14). Re-use is often motivated by the fact that primary data collection for quality assurance is expensive (15). Re-use of data nevertheless has its weaknesses such as incomplete data, inappropriate terminology for the secondary use and undocumented observations.

We used a structured method that not only examines the data source but also examines the inherent features of a clinical rules that determine if it can be electronically evaluated. The benefit of this approach is the ability to identify CRs that can be transmuted into clinical rules for clinical decision support. By selecting CRs that can be automatically assessed one is able to measure the level of performance and simultaneous implement decision support. Automated monitoring of quality of cares supports the dual goals of measurement as well as improving care. Interventions can be instituted promptly in cases where the quality of care is suboptimal.

Future studies

Our study has analyzed the possibility of automatic evaluation quality of care-based data collected by EMRs at GP practices. Individual studies involving each of the CRs can be performed to evaluate the impact of automatic assessment of quality of care on patient's outcomes in general practice. Furthermore it is possible to conduct studies on clinical decision support based on the quality indicators identified in this study. Such studies would give more insight on how quality the twin aspects of quality measurement and improvement can be simultaneously implemented.

CONCLUSION

Approximately two-fifths of the ACOVE based clinical rules relevant for general practice can be automatically evaluated. Clear definition of clinical rules, improved GP database design and electronic linkage of transmural care activities can improve prospects of automatic assessment of quality of care.

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Chapter 7

Summary and discussion

Summary and Discussion

In this PhD thesis, we set out to improve quality of prescribing to elderly patients in general practice. Our focus was on the use of computer technology in quality improvement. We formulated three main research questions pertaining to the following studies. First, we studied the current quality of prescribing for elderly patients in general practice. Subsequently, we studied the possibility of formalizing quality indicators for use in electronic medical record systems. Finally, we studied the feasibility for automatic evaluation of quality of prescribing and clinical decision support.

Below, we restate the research questions and summarize the findings of their corresponding studies.

General Research Question 1: What is the current quality of prescribing to elderly patients in general practice?

Previous studies have reported that elderly patients receive sub-optimal care compared to the rest of the general population. These studies were conducted in different settings of care such as nursing homes, in-patient departments, ambulatory care centers, community surveys, and general practice.

We therefore decided to establish the quality of prescribing to elderly patients with focus on general practice. Our focus on general practice was based on the observation that much of the care to elderly patients is currently provided in this setting.

Three specific research questions were derived from the general first research question and studies were conducted for each question. The respective results of the studies are reported in Chapters 2-4.

Specific research Questions

Chapter 2: What is the extent of inappropriate medication prescription to elderly patients?

Context and aim of Study

The aim of the systematic review presented in Chapter 2 was to quantify the extent of inappropriate medication prescription (IMP) to elderly patients in primary care. IMP increases risk of adverse events such as falls, urine retention and gastric ulcers. Avoidance of IMP thus contributes to lowering morbidity and mortality.

In this systematic review, we isolated primary studies which were performed in general practice. The studies were conducted in 11 different countries including the Netherlands. The primary studies assessed (in)appropriateness of medication prescriptions to elderly patients. Appropriateness of prescription was evaluated in these studies mainly by using the Beers criteria.

Findings and meaning of study

The systematic review found that one out of five prescriptions to elderly patients is inappropriate. Our study also compared the rate of IMP within therapeutic classes. We found that variations in rates of IMP exist both within and across therapeutic classes of medication. This finding is important because we could now identify specific classes of medications that warranted more attention. With our findings, interventions can target a specific therapeutic class of high priority to improve quality of prescription.

Weaknesses and Further studies

Our systematic review was limited by the heterogeneity of the studies included. For example, the time periods across which the primary studies were conducted varied, and rate of IMP is prone to change over time. For example, some studies reported an average rate of IMP over a period of 5 years. Such summaries assume that there was no change in the incidence of IMP in the study population.

Ideally, individual studies need to stipulate the specific time period when IMP is evaluated and also report on a year by year basis instead of longer time periods. This allows for appropriate comparison between different clinical settings.

Moreover, different studies included different sets of medications. Future studies of IMP should group medications in specific therapeutic classes because prescription decisions are often confined to choices of medication within the same class. Assessing IMP of a specific medication and comparing to IMP of other medications in the same therapeutic class will help to establish whether there is a medication specific or class specific IMP. Interventions can then be instituted to focus on the individual medication or the whole class of medications.

Chapter 3: What is the extent of adherence of co-prescribing NSAID and gastroprotective medications for elders in general practice.

Context and aim of study

Chapter 3 demonstrates our focus on one of the therapeutic classes, namely Non-steroidal anti-inflammatory drugs (NSAIDs). The aim of the study presented in this chapter was to quantify rate of co-prescription of NSAIDs and gastroprotective medications for elders in general practice. This study was motivated by the association between lack of prescription of gastroprotective medications in vulnerable elderly patients who receive NSAIDs and the risk of upper gastrointestinal events such as gastric ulcers, bleeding and perforation of stomach. These events impair quality of life and can lead to preventable morbidity and mortality. Besides, NSAIDs are some of the most commonly prescribed medication to older persons.

Findings and meaning of study

Using prescription data in the NIVEL Primary Care database between 2005 and 2010, we found that the proportion of NSAIDs with co-prescription of gastroprotective medications was 43%. Improvement in the proportion of gastroprotective medication was observed from 27% in 2005 to 55% in 2010.

This finding demonstrates that improvement in quality of prescribing was achievable.

Nevertheless, at the end of the study period in 2010, still about 1 in 2 patients did not receive co-prescription of gastroprotective medication. Furthermore, we noted that the brand of EMR used to make prescription was associated with differences in co-prescription of gastroprotective medication.

Weakness and further studies

We believe that detailed review of the sub-group of patients who did not receive co-prescription of gastroprotective medications would guide further refinement of interventions. Unfortunately, the NIVEL Primary Care database used in the study did not contain all data elements required for a detailed risk stratification of patients at risk of adverse events associated with lack of prescription of gastroprotective medications. We further state that optimal design and utilization of EMRs is a potential area of interventions to improve quality of prescription.

Chapter 4: What is the extent of drug safety warnings on the duration of exposure of patients to medications with high risk for adverse events?

Context and aim of study

The aim of the study presented in chapter 4 was to estimate the response of General Practitioners (GPs) to Food and Drug Administration (FDA) drug safety warning against use of rosiglitazone. The FDA warnings were adopted by the Dutch national Medicines Evaluation Board (CBG). Rosiglitazone is an oral antidiabetic medication which is associated with a high risk of cardiovascular events in some patients.

We measured the duration when patients continued to receive rosiglitazone after the FDA safety warning in 2007. The incidence of adverse events associated with a medication, increases with duration when a patient is exposed to it. The study included patients who received oral antidiabetic medications from Dutch GPs.

Findings and meaning of study

Our study found that patients received prescriptions for a shorter duration after the safety warning, compared to the period before. For instance, the probability of receiving rosiglitazone prescription for 1 year reduced from 63% to 45% after the drug safety warning. However, in a 3-year follow-up, 27% of patients who received prescriptions of rosiglitazone before the FDA warning continued to receive its prescription. This study showed that safety warnings result in reduced prescription of high risk medication and estimated the effect of time on this reduction.

Weakness and Future studies

Unfortunately, our study was limited by lack of clinical data that could help to classify patients as either low or high risk for adverse events from rosiglitazone use. It is thus difficult to know exactly if the patients who continued on rosiglitazone were at low risk of adverse events.

Detailing clinical data and design of electronic medical records (EMRs) with generic decision support tools for delivering drug safety warnings at the point of care is a potential intervention that can increase the rate of implementation of drug safety advice by physicians. Future studies should investigate the role of safety warnings with and without electronic clinical decision support in reducing exposure to high risk medications.

General Research Question 2: How can quality indicators be formalized and used in computerized decision support?

We conducted one study to answer the second general research question which is stated above. The results of this study are presented in chapter 5.

Context and aim of study

In Chapter 5, we aimed to develop a method for formalizing quality indicators for use in computerized decision support. This effort was motivated by the fact that there is a persistent gap in quality of prescribing in general practice as compared to clinical guidelines as shown by the studies outlined in Chapters 2-4. This gap exists despite the plethora of quality indicators (QIs) on the one hand and the ubiquitous existence of EMRs in many general practices on the other hand.

Unfortunately, there is no standardized methodology for translating QIs to computerized decision support systems. QIs have to be formulated in a clear format that does not lead to ambiguity. Ambiguity makes it difficult for physicians to make the right decisions. It also makes it even more difficult to use QIs in computerized decision support. In addition, the EMR platform on which clinical decision support is to be implemented must also have minimal data elements to enable clinical decision support (CDS).

Findings and meaning of study

We describe the development of the Logical Elements Rule Method (LERM) which is a stepwise method for analyzing clinical rules for implementation in clinical decision support. This is a structured and practical method that developers of clinical decision support can use to evaluate clinical rules for implementability in existing EMR platforms. In addition, it can be used to elucidate modifications which are necessary to make in EMRs to allow for automatic assessment of quality of care.

Weakness and Future studies

The main limitation of the LERM is the subjective nature of interpretation of concepts which exist in statements of clinical guideline. Subjectivity is primarily a problem of disambiguation of natural language text which is the commonest way that clinical guidelines are presented. Further validation studies of the LERM method can help improve it as a tool for formalizing condition-action type of clinical rules for decision support.

General Research Question 3: To what extent can clinical rules be automatically evaluated in general practice?

We conducted one study to answer the third general research question stated above. The results of this study are presented in chapter 6.

Context and aim of study

Following the development of the LERM in the previous chapter, we aimed to assess the extent to which quality indicators (QIs) formulated as clinical rules can be implemented for automatic evaluation of quality of care in general practice. The goal of this study which we reported in Chapter 6 is to increase the extent to which quality indicators are translated in computerized decision support.

Findings and meaning of study

Using a sample of the Assessing Care of Vulnerable Elders (ACOVE) QIs, we found that two fifths of the indicators could be implemented for automatic evaluation of care. Automatic evaluation of quality is beneficial to the physician and patients. Prompt feedback to the physician should result in timely change in behavior. In addition, the automatic evaluation of care can be incorporated into clinical decision support. This results in a proactive approach to quality improvement in contrast to performance initiatives based on post hoc quality reports.

Weakness and Future studies

Our study was limited by lack of access to the databases of the various EMR brands used in the general practice. We assume that individual EMR implementations may facilitate or hinder the possibility of implementing clinical decision support. Further studies should be conducted to evaluate actual EMRs as implemented in GP practice against various sets of clinical rules.

FUTURE STUDIES

Further to the foregoing discussion, three key areas of further research highlighted by the work presented in this thesis include:

Refining the assessment of quality of care.

Detailed clinical data is required to make precise measurements of quality of care. Many studies investigating quality of care use broad inclusion criteria e.g *vulnerable elderly patients receiving NSAIDs.* In practice, physicians often make exemptions from recommendations of a guideline based on clinical judgement. Such exemptions are specific to a particular patient's clinical profile. Exemptions are inadequately captured in studies that assess quality of care. Such exemptions are thus likely wrongly categorized as inappropriate or sub-optimal care. Detailed documentation of clinical data such as co-morbid conditions, severity of illnesses, and functional status of patient as well as prescription data e.g dose, frequency and duration are needed to make more precise estimates of quality of care.

Improved definition of quality indicators

Collaboration of clinical experts and knowledge representation experts (KREs) should be encouraged in the process of developing quality indicators and clinical guidelines. For example, clinical experts would aim to optimize the definition of clinical scenarios when a particular recommendation of a guideline should be applicable. At the same time the clinical experts would clarify definition of sub-groups of patients who are exempted from a recommendation of a guideline. On the other hand, knowledge representation experts would ensure that standardized terminology is used in the text of clinical guidelines. Standardized terminology is necessary to enhance translation of clinical guideline statements to computer interpretable format that can be used in CDS.

Integration of drug warning systems with clinical decision support

Clinical decision support systems should be designed to allow for integration with electronic drug safety warning systems (DSWS). For instance, drug regulatory authorities such as the FDA or the European Medicines Agency (EMA)

would develop drug safety warning systems and maintain the knowledge base with drug safety warning statements. We believe that an electronic integration would result in faster dissemination of safety warning to the physicians at the point of care. The impact of electronic DSWS would then be compared with the current methods of dissemination of drug safety warnings.

Concluding remarks

There is a gap in the quality of care provided to the elderly patients in general practice as compared to recommendation of clinical guidelines. Several reasons contribute to the difference between actual practice and clinical standards like guidelines and clinical rules. A simple method for formalizing clinical rules for implementation in electronic medical records systems such as the LERM can improve adherence to clinical guidelines in general practice. Future EMRs should be designed to serve the role of optimizing the care process, and improving quality and safety.

Samenvatting en discussie

Samenvatting en discussie

Dit proefschrift gaat over de kwaliteit van voorschrijven van geneesmiddelen aan oudere patiënten in de huisartsenpraktijk. Onze aandacht gaat specifiek uit naar de mogelijkheden van computertechnologie om verbeteringen in het voorschrijven te bewerkstelligen.

Aan de hand van de drie hoofdvragen vatten we de bevindingen samen.

- Vraag 1: Wat is de huidige kwaliteit van voorschrijven aan oudere patiënten in de huisartsenpraktijk?
- Vraag 2: Hoe kunnen richtlijnen, die geformuleerd zijn als klinische regels, worden gebruikt in geautomatiseerde beslissingsondersteunende systemen?
- Vraag 3: In hoeverre is het mogelijk het naleven van klinische regels in de huisartsenpraktijk automatisch te bepalen?

Vraag 1: Wat is de kwaliteit van voorschrijven aan oudere patiënten in de huisartsenpraktijk?

Uit eerdere studies komt naar voren dat oudere patiënten, in vergelijking met de rest van de bevolking, niet altijd optimale zorg krijgen. Deze studies werden uitgevoerd in verschillende settings, zoals verpleeghuizen, ziekenhuizen, gezondheidscentra, en huisartsenpraktijken.

In dit proefschrift richten we ons op de huisartsenpraktijk. In de huisartsenpraktijk wordt een belangrijk deel van de zorg aan oudere patiënten geleverd. Doordat ouderen langer zelfstandig blijven wonen, groeit bovendien het belang van de huisarts in de zorg voor ouderen.

De eerste onderzoeksvraag is vertaald in drie meer specifieke onderzoeksvragen. Deze vragen worden beantwoord in de hoofdstukken 2-4.

Hoofdstuk 2: In hoeverre is er sprake van suboptimaal voorschrijven bij oudere patiënten?

Context en doel van de studie

Het doel van deze studie, een systematische review, was het kwantificeren van de mate waarin sprake is van suboptimaal voorschrijven van geneesmiddelen (in het Engels: inappropriate medication prescription (IMP)) bij oudere patiënten in de huisartsenpraktijk. IMP verhoogt het risico op bijwerkingen zoals urineretentie, maagzweren of valincidenten. Het vermijden van IMP draagt bij tot het verlagen van morbiditeit en sterfte.

De gevonden studies zijn uitgevoerd in 11 verschillende landen, waaronder Nederland. In de meeste studies werd de kwaliteit van het voorschrijven beoordeeld op basis van de zogenaamde Beers criteria.

Bevindingen en betekenis van onze studie

Eén op de vijf recepten bij oudere patiënten blijkt suboptimaal te zijn. We hebben vastgesteld dat variaties in IMP-voorschriften zowel binnen als tussen therapeutische klassen van medicatie voorkomen. Deze bevinding is belangrijk omdat we op basis hiervan specifieke geneesmiddelengroepen kunnen identificeren die meer aandacht behoeven. Hiernaast bepalen we op basis hiervan welke groepen het meest baat hebben bij specifieke interventies.

Beperkingen van de studie en aanbevelingen voor toekomstige studies

Onze systematische review was beperkt door de heterogeniteit van de onderzochte studies. De duur van de meetperiode verschilde tussen studies. Uitkomsten waren daardoor niet vergelijkbaar, omdat de mate en hoeveelheid

IMP verandert over de tijd. Toekomstige studies zouden de IMP op jaarbasis moeten melden om vergelijking tussen studies mogelijk te maken.

Bovendien gaan de studies over verschillende medicijnen met verschillende klassen, die niet altijd in de studies vermeld zijn. In toekomstig onderzoek naar IMP zouden de therapeutische klassen vermeld moeten worden, om te helpen beoordelen of er sprake is van een medicijn-specifieke of klasse-specifieke IMP. Met deze informatie zal het gemakkelijker zijn om gerichte interventies te plegen.

Hoofdstuk 3: In hoeverre worden NSAIDs en maagbeschermende middelen gelijktijdig voorgeschreven voor ouderen in de huisartsenpraktijk

Context en doel van studie

In hoofdstuk 3 gaan we in op een specifieke therapeutische klasse, namelijk niet-steroïdale anti-inflammatoire geneesmiddelen (NSAID's). NSAID's horen bij de meest voorgeschreven geneesmiddelen bij ouderen. We onderzochten in hoeverre NSAID's gelijktijdig worden voorgeschreven met maagbeschermende middelen. NSAIDs zorgen voor een verhoogd risico op de bovenste gastro-intestinale aandoeningen zoals maagzweren, bloedingen en perforatie van de maag en maagbeschermende middelen verlagen dit risico. Deze aandoeningen beperken de kwaliteit van leven en kunnen leiden tot sterfte.

Bevindingen en betekenis van de studie

Gegevens uit elektronische patiëntendossiers, beschikbaar gesteld via "NIVEL Zorgregistraties eerste lijn" uit 2005 tot en met 2010, lieten zien dat 43% van de NSAIDrecepten werd vergezeld van een recept voor maagbeschermende medicatie. Dit percentage verbeterde van 27% in 2005 tot 55% in 2010. Dit laat zien dat verbetering van de kwaliteit van het voorschrijven goed mogelijk is.

Niettemin kreeg aan het einde van de studieperiode in 2010 nog steeds één derde van de patiënten met een NSAID geen maagbeschermende medicatie voorgeschreven. Daarnaast zagen we dat het voorschrijven van maagbeschermende medicatie bij NSAIDs verschilt tussen de huisartsinformatiesystemen.

Beperkingen van de studie en aanbevelingen voor toekomstige studies

Met gedetailleerde kennis over de subgroep patiënten, die geen maagbeschermende geneesmiddelen kreeg voorgeschreven, zou het mogelijk zijn om verfijndere interventies toe te passen. We konden echter niet beschikken over de daarvoor benodigde gedetailleerde gegevens. Dit kwam doordat de elektronische patiëntendossiers, waaruit onze data afkomstig was, niet alle data-elementen bevatten voor een gedetailleerde risicostratificatie van patiënten op mogelijke bijwerkingen. Hierdoor was het moeilijk te bepalen bij wie het risico op bijwerkingen groot was zonder maagbeschermende medicatie. Verder veronderstellen wij dat verbeteringen in ontwerp en gebruik van elektronische patiëntendossiers aandacht verdient. Deze kunnen bijdragen aan een verbeterde kwaliteit van het voorschrijven en het vaststellen van relevante risicofactoren.

Hoofdstuk 4: In hoeverre hebben waarschuwingen bij het voorschrijven van een bepaald geneesmiddel effect op de duur van het voorschrijven bij patiënten met een hoog risico op bijwerkingen?

Context en doel van de studie

Doel van de studie in hoofdstuk 4 was het beoordelen van de effecten van waarschuwingen van het College Beoordeling Geneesmiddelen (CBG) bij het voorschrijven van het middel rosiglitazon. Rosiglitazon is een oraal middel tegen diabetes, dat bij sommige patiënten geassocieerd is met een vergroot risico op hart- en vaatziekten.

We hebben gemeten hoe lang patiënten rosiglitazon kregen voorgeschreven vóór en na de veiligheidswaarschuwing van het CBG in 2007. Dit is van belang omdat het risico op bijwerkingen toeneemt met de duur van de blootstelling aan rosiglitazon.

Bevindingen en betekenis van de studie

Uit onze studie bleek dat het geneesmiddel vaker voor een kortere periode werd voorgeschreven ná de waarschuwing van het CBG dan daarvoor. Bijvoorbeeld het percentage recepten van rosiglitazon met een duur van 1 jaar nam af van 63% tot 45%. Echter 27% van de patiënten, die vóór de waarschuwing rosiglitazon kregen voorgeschreven, kreeg dat middel drie jaar later nog steeds. De studie laat zien dat, en hoe, waarschuwingen van het CBG tot minder recepten van hoog risico geneesmiddelen kunnen leiden.

Beperkingen van de studie en aanbevelingen voor toekomstige studies

Binnen de context van deze studie was het niet mogelijk patiënten in te delen op het risico op bijwerkingen van rosiglitazon. Het was daardoor niet vast te stellen of patiënten waarbij rosiglitazon gecontinueerd werd, wellicht een laag risico liepen op bijwerkingen.

Het gebruik van gedetailleerde klinische gegevens als basis voor beslissingsondersteunende systemen op het gebied van medicatieveiligheid kan de naleving van geneesmiddelenveiligheidsadviezen verbeteren. Daarom is onderzoek naar het effect van waarschuwingen met en zonder gebruik van geautomatiseerde beslissingsondersteunende systemen een belangrijk onderwerp voor toekomstige studies.

Vraag 2: Hoe kunnen richtlijnen die geformuleerd zijn als klinische regels worden gebruikt in geautomatiseerde beslissingsondersteunende systemen?

In het kader van de tweede algemene onderzoeksvraag hebben we één studie uitgevoerd. De resultaten van deze studie worden in hoofdstuk 5 weergegeven.

Context en doel van de studie

In hoofdstuk 5 beoogden we een methode te ontwikkelen voor het formaliseren van klinische regels voor gebruik bij geautomatiseerde beslissingsondersteunende systemen. Deze regels zijn simpele richtlijnen in de vorm van "Als voorwaarde Dan actie". Klinische regels kunnen worden gebruikt als kwaliteitsindicatoren: de mate waarin artsen deze regels naleven, zegt iets over de kwaliteit van zorg. Achtergrond van deze studie was het verschil in de mate van voorschrijven volgens de klinische richtlijnen tussen huisartsenpraktijken, zoals naar voren kwam in de studies beschreven in hoofdstukken 2-4. Het verschil in voorschrijven bestaat ondanks de overvloed aan kwaliteitsindicatoren (QI's) die explicit beschreven zijn in de vorm van klinische regels.

Helaas bestaat er geen gestandaardiseerde methode voor het vertalen van klinische regels naar een vorm die gebruikt kan worden door geautomatiseerde beslissingsondersteunende systemen. QI's zijn daarnaast vaak niet geformuleerd in een duidelijke en ondubbelzinnige wijze. Ambiguïteit maakt het moeilijk voor artsen om de juiste beslissingen te nemen. Het maakt het ook moeilijker om QI's in geautomatiseerde beslissingsondersteunende systemen te gebruiken.

Bevindingen en betekenis van de studie

We beschreven de ontwikkeling van de Logical Elements Rule Method (LERM) en haar toepassing in de eerste lijn. LERM is een gestructureerde stapsgewijze en praktische methode die ontwikkelaars van beslissingsondersteunende systemen kunnen gebruiken om QI's die in de vorm van klinische regels zijn geformuleerd (Als voorwaarde Dan actie) om te zetten in een format dat de computer kan gebruiken. Geautomatiseerde beslissingsondersteunende systemen die gebruik maken van de geformaliseerde regels kunnen bijvoorbeeld een signaal geven

wanneer een arts een actie die aanbevolen wordt door de regel is vergeten uit te voeren. Daarnaast kan LERM gebruikt worden om aan te geven welke gegevens die voor de klinische regels nodig zijn ontbreken in het (huisarts)informatiesysteem of op een andere manier horen vastgesteld te worden.

Beperkingen van de studie en aanbevelingen voor toekomstige studies

De belangrijkste beperking van LERM is dat de vertaling van concepten naar klinische richtlijnen of regels subjectief van aard is. Twee verschillende formalisatiepogingen kunnen tot twee verschillende regels leiden. De belangrijkste reden hiervoor is dat regels en richtlijnen, die in natuurlijke taal geschreven zijn, ambigue kunnen zijn. Verdere validatiestudies van LERM zijn nodig om de methode te verbeteren.

Vraag 3: In hoeverre is het mogelijk de naleving van klinische regels in de huisartsenpraktijk automatisch te bepalen?

Deze hoofdvraag wordt beantwoord in hoofdstuk 6.

Context en doel van de studie

Na de ontwikkeling van de LERM in het vorige hoofdstuk, waarin we hebben gekeken naar vertaling van QI's in klinische regels die begrijpelijk zijn voor de computer, bekijken we in hoofdstuk 6 in hoeverre het naleven van deze regels automatisch kan worden bepaald in de huisartsenpraktijk. De mate van naleving geeft aan in hoeverre aan een regel wordt voldaan door de zorgverlener, en is een indicatie voor de kwaliteit van de zorg waarop de regel betrekking heeft.

Bevindingen en betekenis van studie

In een steekproef van de Assessing Care of Vulnerable Elders (ACOVE) QI's vonden we dat 40% van de indicatoren vertaald kan worden naar een klinische

regel. Met behulp van deze vertaling kan de naleving van deze indicatoren automatisch bepaald worden. Hierdoor kan men achteraf feedback aan de arts geven over de kwaliteit van de geleverde zorg of direct tijdens het voorschrijven waarschuwingen en herinneringen geven via een beslissingsondersteunend systeem. Dit systeem kan het voorschrijfgedrag van de arts beïnvloeden en indien nodig corrigeren.

Beperkingen en toekomstige studies

We hebben het onderzoek uitgevoerd met gegevens van "NIVEL Zorgregistraties eerste lijn" op basis van gegevensextracties uit huisartsinformatiesystemen. Helaas konden wij geen gebruik maken van de uitgebreidere oorspronkelijke databases in de huisartsenpraktijken zelf, en konden we het ontwerp van het huisartsinformatiesysteem niet in het onderzoek betrekken. Het ontwerp van een huisartsinformatiesysteem kan namelijk het voorschrijven sterk beïnvloeden. Verdere studies zijn nodig om te onderzoeken in hoeverre de verschillende soorten huisartseninformatiesystemen het naleven van klinische regels ondersteunen en wat daarvan dan de effecten zijn.

TOEKOMSTIGE STUDIES

Naast de punten genoemd in bovenstaande discussies van de studies in dit proefschrift, zijn er drie belangrijke gebieden die verder onderzoek behoeven:

Verbeteren van de beoordeling van de kwaliteit van zorg

Gedetailleerde klinische gegevens zijn nodig om de kwaliteit van de geleverde zorg te meten. Veel studies naar de kwaliteit van zorg gebruiken brede inclusiecriteria, bijvoorbeeld "kwetsbare oudere patiënten die NSAID's voorgeschreven krijgen". In de praktijk vinden artsen vaak dat een richtlijn niet van toepassing is op een individuele patiënt vanwege het specifieke klinische profiel van die patiënt. De arts wijkt dan terecht af van de richtlijn. Veel studies over de kwaliteit van zorg houden niet voldoende rekening met dit soort

terechte afwijkingen. Dit kan leiden tot onderschatting van de kwaliteit van zorg. Gedetailleerde klinische gegevens, zoals co-morbiditeit, ernst van de ziekte, en functionele status van de patiënt, evenals dosering, frequentie en duur van geneesmiddelengebruik zijn nodig om de kwaliteit van zorg goed te kunnen beoordelen.

Verbeterde definitie van kwaliteitsindicatoren

Klinische deskundigen en deskundigen op het gebied van ICT moeten samenwerken bij de ontwikkeling van kwaliteitsindicatoren en klinische richtlijnen. Klinische deskundigen zouden kunnen aanscherpen *in welke gevallen* en omstandigheden een specifieke aanbeveling van een richtlijn van toepassing is en in welke gevallen niet. Aan de andere kant kunnen ICT-deskundigen er voor zorgen dat gestandaardiseerde terminologie wordt gebruikt in de beschrijving van klinische richtlijnen. Gestandaardiseerde terminologie is nodig voor de vertaling naar een format dat geschikt is voor geautomatiseerde beslissingsondersteuning.

Integratie van waarschuwingen tegen onveilig voorschrijven in beslissingsondersteunende systemen

Elektronische waarschuwingen tegen onveilig voorschrijven (electronic drug safety warning systems, DSWS), moeten geïntegreerd worden in klinische beslissingsondersteunende systemen. Regelgevende instanties, zoals het CBG, zouden mee moeten werken aan de ontwikkeling van DSWS. Uitkomsten van die systemen zouden zij weer kunnen gebruiken voor het onderhouden van de kennis omtrent de waarschuwingen. Zo'n integratie van beslissingsondersteunende systemen en DSWS resulteert in een snellere verspreiding van waarschuwingen aan artsen, zelfs al op het moment van voorschrijven.

Algemene conclusie

De kwaliteit van zorg aan oudere patiënten in de eerste lijn laat te wensen over als deze beoordeeld wordt op basis van de huidige kwaliteitsindicatoren. Deels ligt dit aan de geleverde zorg, maar deels ook aan het feit dat de beschrijving van de doelgroep van de kwaliteitsindicatoren niet specifiek genoeg geformuleerd is. Een eenvoudige methode, zoals de LERM, voor het formaliseren van klinische regels draagt bij aan de implementatie van deze regels in elektronische patiëntendossiers en aan de naleving van de klinische regels. Huisartsinformatiesystemen kunnen meer bijdragen aan het veilig voorschrijven van geneesmiddelen en de kwaliteit van zorg dan nu het geval is.

PhD Profile

PhD Profile

Name PhD supervisor:	Prof. dr. Ameen Abu-Hanna	
Name of PhD Student:	Dedan Opondo	
PhD period:	01/02/2011-31/12/2017	
1. PhD training		
	Year	Workload (Hrs/ECTS)
General courses		
Entrepreneurship in Health and Life Sciences	2012	(42/1.5)
NIHES courses		
Missing values in Clinical Research	2012	(28/1)
Repeated measurements in clinical studies	2012	(12/0.4)
Advanced Topics in Clinical Epidemiology	2011	(32/1.1)
Seminars, workshops, masterclasses, Conferences		
Workshops		
HIMMSS 2012, Las Vegas	2012	-
IPHEA master class, Seattle	2010	-
Protege Workshop, Amsterdam	2009	-
		-

Publications

Peer reviewed articles related to this thesis	**Year**
Feasibility of automatic evaluation of clinical rules in general practice. ***Opondo D***, *Visscher S, Eslami S, Medlock S, Verheij R, Korevaar JC, Abu- Hanna A.* Int J Med Inform. 2017 Apr;100:90-94.	2017
Quality of co-prescribing NSAID and gastroprotective medications for elders in the Netherlands and its association with electronic medical record. ***Opondo D***, *Visscher S, Eslami S, Verheij RA, Korevaar JC, Abu-Hanna A.* PLoS One. 2015 Jun 25;10(6).	2015
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Curriculum Vitae

Dedan Opondo was born on 29th April 1981 in Nairobi, Kenya. He went to Ulowa Primary School and thereafter proceeded to the Maseno School for his secondary education. In school, he excelled in academia and field hockey. After his secondary school examination, Dedan was admitted to the school of Medicine at the University of Nairobi on 15th October 2001.

He attended the Amsterdam Summer School in 2005 at the Department of Medical Informatics. On the completion of his medical school training, he pursued a pre-master course in medical informatics from the Academic Medical Center between 2007 and 2008.

In 2009, he was awarded Amsterdam Merit Scholarship and Boumeester Foundation Grant to pursue masters in medical informatics at the Academic Medical Center. He completed his masters with a cum laude in 2011. Thereafter, he started his PhD project as a part-time candidate.

He joined the department of urology at the academic medical center as a clinical research medical officer. In 2017, he completed his residency and fellowship training in urology at the University of Stellenbosch in Cape Town South Africa. He currently works as a consultant urologist and lecturer at Tygerberg Hospital in Cape Town.

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