A computational framework to identify patients with poor adherence to blood pressure lowering medication

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\textbf{Abstract}

Background: Blood pressure (BP) lowering medications have impressive efficacy in reducing cardiovascular and renal events; but low adherence threatens their effectiveness. Analysis of patterns in electronic prescribing from electronic medical records (EMRs) may have the potential to reveal cohorts of patients with significant adherence problems.

Methods: We developed a computational framework to identify patient cohorts with poor adherence to long-term medication through analysis of electronic prescribing patterns. A range of quality reporting criteria can be specified (as an XML document). We illustrate the framework by application to the EMRs of a New Zealand general practice with a focus on adherence to angiotensin-converting enzyme inhibitors (ACE-inhibitors) and/or angiotensin II receptor blockers (ARBs) in patients classified with hypertension and diabetes. We analyse medication supply based on Medication Possession Ratio (MPR) and duration of lapse in ACE-inhibitors/ARBs over a 12-month evaluation period. We describe graphical tools to assist visualisation of prescribing patterns and relationship of the analysis outputs to controlled blood pressure.

Results: Out of a cohort of 16,504 patient EMRs, 192 patients were found classified with both hypertension and diabetes and under active ACE-inhibitor and/or ARB management. Of these, 107 (56%) patients had an ACE-inhibitor/ARB MPR less than 80% together with a lapse in ACE-inhibitors/ARBs for greater than 30 days. We find non-adherent patients (i.e. MPR <80% or lapse >30 days) are three times more likely to have poor BP than adherent patients (odds ratio = 3.055; \( p = 0.012 \)).

Conclusions: We have developed a generic computational framework that can be used to formulate and query criteria around issues of adherence to long-term medication based on practice EMRs. Within the context of the example we have used, the observed adherence levels indicate that a substantial proportion of patients classified with hypertension and diabetes have poor adherence, associated with poorer rates of blood pressure control, that can be detected through analysis of electronic prescribing. Further work is required to identify effective interventions using the reporting information to reduce non-adherence and improve patient outcomes.

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Research has shown impressive efficacy rates of blood pressure (BP) lowering medications for reduction in cardiovascular and renal events. These antihypertensive medications come in a variety of classes and subclasses, with varying indications, as well as used in combination, depending on other characteristics of the patient, such as presence of diabetes or heart failure. For this paper, the reader is referred to the categories of blood pressure lowering medications and their use as per the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC7) [1], as well as New Zealand Heart Foundation guidelines [2]. Notably, we will refer to the medication categories of angiotensin-converting enzyme inhibitors (ACE-inhibitors) and angiotensin II receptor blockers (ARBs), which are indicated for patients with concurrent (‘comorbid’) diabetes and hypertension.

Although these drugs are effective when taken as directed, low adherence (also sometimes called ‘non-compliance’) to prescribed regimens threatens their effectiveness in real-world use. Long-term adherence with medications for chronic diseases is low in general, particularly among lower socioeconomic groups [3]. Based on the international literature, it is thought that poor adherence to antihypertensive medication contributes to inadequate BP control in more than two-thirds of hypertensive patients [4]. A Swedish study found satisfactory refill adherence for thiazide diuretics at 55%, ACE-inhibitors at 59% and selective beta-blocking agents at 66% [5]. The level of adherence has been positively correlated with good BP control and reduction in the complications of hypertension [6]. Low adherence has been cited in the international literature as the primary cause of unsatisfactory control of BP [1], however, studies that are focussed on identifying specific cohorts of patients who are non-adherent are limited.

The reasons for non-adherence are poorly understood and vary with psychosocial factors [7]. Efforts to improve adherence to antihypertensive medication can be divided into behavioural (e.g. phone reminders, packaging, dosing changes, social assistance), educational interventions (written or verbal) or combined approaches. One meta-analysis found no one approach was superior to any other but there was a trend to improved adherence with a combined approach [8]. Reminder packaging for improving adherence to long-term medication was the subject of a Cochrane review where the authors found that this intervention improved the percentage of medications taken [9]. Interventions for improving medical adherence in primary care (specifically) found patient education alone was insufficient and the evidence for complex interventions involving social support, education and reminders was inconclusive [10]. It is difficult to judge the independent effects of individual components (e.g., nurse phone call reminders) of complex interventions. An organised system of recall and regular review may be the most successful and sustainable intervention [11].

In light of the large magnitude of long-term medication adherence issues, and the on-going need to formulate successful adherence improvement strategies, we set forth to develop a computational framework with the aim of successfully identifying patients with poor adherence to their medication, focussing mainly on antihypertensive prescribing. We hypothesise that there is an opportunity for carefully formulated automated analysis of electronic prescribing records to identify medication adherence problems in the context of blood pressure control. We utilise the concepts of Medication Possession Ratio (MPR) and duration of lapse of medication supply as key criteria in the computational framework presented in this paper. Our framework enables analysis of patterns in electronic prescribing from electronic medical records (EMRs). In previous work we have identified that moderately sensitive and specific identification of suboptimal management of hypertension can be derived from the EMRs of Australian [12] and New Zealand [13] general practice EMRs. Moreover, we have found that analysis of electronic prescribing indicates particularly large cohorts of hypertensive patients exhibiting gaps in continuity of therapy suggestive of poor adherence and correlated to poor blood pressure control [14]. The framework presented herein is flexible in terms of the specific criteria of interest with respect to medications, adherence thresholds, time periods of interest and defining characteristics of cohorts of interest. We illustrate the framework in terms of adherence to ACE-inhibitors and ARBs in patients classified with comorbid hypertension and diabetes through analysis of the EMRs of a New Zealand general medical practice.

In this paper we present a novel computational framework that can be used to identify specific patients with medication adherence issues in terms of MPR and medication lapses, as relevant to BP lowering medication. In the following sections we outline our methodology and discuss details related to the framework implementation and demonstrate how our framework has been used to identify patients with the adherence issues using production EMR data. Furthermore, we demonstrate that this cohort has significantly lower odds of having successful controlled BP compared to adherent patients. We introduce a prescription timeline visualisation scheme we have developed to aid clinicians to visualise a selected patient’s antihypertensive prescribing patterns. We conclude with discussion of how our framework can be used in an active patient intervention and/or management effort and possible future directions.

2. Methodology

2.1. Adherence to medication

Andrade et al. in their systematic literature review that investigated different adherence measures concluded that identification, aptness and selection of measures for adherence should be determined by the objectives of the study, and limitations and benefits of the measures should be considered [15]. Adherence refers to the extent to which a patient’s behaviour to take the prescribed medications aligns with the instructions and recommendations from the prescriber [16]. A widely used measure of adherence is defined in terms of a proportion-of-days-covered model, which calculates the proportion of days within a fixed interval that the patient has an available supply of medication [17].
In this paper we employ persistence based adherence measures of proportion-of-days-covered based on the prescribing of the patient's general practice. This is a type of MPR measure, although alternatively the MPR may be computed from dispensing or by direct observation of pill counts at the patient’s home. MPR is often expressed as a percentage and an MPR of less than 80% has been indicated as a threshold upon which clinical effectiveness of a therapy is significantly compromised [15]. Herein we will refer to a patient as ‘non-adherent’ if their MPR is less than 80% and/or they have a medication lapse >30 days for a given medication over a given time period. We will consider scenario (i) in Fig. 1. If definition (2) is used to calculate MPR for this prescribing scenario, only the second prescription (denoted by Pr2) will be included, which is a rather incomplete picture of medication possession for this patient over the EP. In terms of the definition in (1) for scenario (i), failure to account for Pr1 (because it is not ‘obtained during the observation period’) tends to underestimate medication possession; conversely, the medication possession from Pr3 will be overestimated. Moreover, we would get a misleadingly low MPR if we use a denominator of the entire duration of the EP for a scenario such as (iv) where Pr2 is the patient’s very first prescription of that drug after being classified. If a period of considerable duration (such as a year) is considered, there are likely to be many patients who are newly diagnosed during the EP, and, as such, if low MPRs are used as the basis to identify non-adherent patients, cases with a prescribing pattern similar to scenario (iv) will contribute towards false-positives resulting in low specificity. Similar issues arise when definition (1) and/or (2) is applied to other scenarios.

Therefore, for our work we calculated MPR by including the boundary prescriptions such that if we consider scenario (i) in Fig. 1, only those parts of Pr1 and Pr3 coverages that fall within the EP are included in the numerator of the MPR calculation. Furthermore, we defined a period called the run-in period prior to the EP so that prescriptions such as Pr1 (prescribed prior to beginning of EP) can be correctly accounted for.

For our MPR calculations we use the following definition:

If patient was classified before beginning of the EP:

\[
\text{MPR} = \frac{\# \text{ of days in EP} - \text{total gap duration}}{\# \text{ of days in EP}} \times 100
\]  

(3)

Else:

\[
\text{MPR} = \frac{(\# \text{ of days between classification date and end of EP})}{\text{total gap duration}} \times \frac{\# \text{ of days between classification date and end of EP}}{100}
\]  

(4)

where total gap duration refers to the sum of all medication lapses as determined after various temporal considerations shown in Fig. 1.

### 2.2. Patient classifications

Often we want to identify patients with low MPRs who have also been diagnosed with a particular condition. In our present work, we are mainly interested in antihypertensive prescribing, and therefore we require our patients to have a hypertension classification and possibly also some of the commonly comorbid conditions, such as diabetes. The nature of chronic illness is such that once a patient is diagnosed with a chronic condition such as hypertension and/or diabetes, it becomes a life-long condition. In a perfect world...
patients would get classified with a chronic condition only once; we find, however, that a single practice’s EMR may in fact include multiple repeat classifications of the same chronic condition. To calculate MPR only for the period after multiple chronic conditions have all been classified as present for a given patient, we considered only those portions of prescriptions that occurred after the most recent of the classification dates (and if a single chronic condition is classified on multiple occasions, the earliest is used). For example, if a patient was classified with hypertension on 7-August-2000 and 5-January-2001 and with diabetes on 12-May-2003 as well as on 20-August-2005, we would consider the patient was classified with hypertension on 7-August-2000 and with diabetes on 12-May-2003. For all subsequent MPR calculations required ‘after a hypertension and a diabetes classification’, per Fig. 1, all medication lapses need to start on or after 12-May-2003.

Both drugs and disease classifications may use a variety of terms with varying degrees of specificity. New Zealand General Practitioners (GPs) currently employ Read Clinical Codes [18] (a precursor system to that later incorporated into SNOMED CT) for diagnosis classification. The knowledgebase of our computational workbench (Fig. 2) manages the relevant taxonomies.

2.3. Computational workbench

We developed a computational workbench using the C# .NET programming language (we will refer to this simply as C# from here on) to determine patient medication adherence, while taking into account the various temporal considerations shown in Fig. 1. An overview of the components of the workbench is shown in Fig. 2.

We collaborated with a New Zealand general medical practice that has patients from the ethnically diverse West Auckland suburbs (and, in the case of this practice, caters largely to a Pacific Island population). Patient EMR data was extracted from this practice’s commercial practice management system (MedTech32 – http://www.medtechglobal.com/ [cited 25 May 2009]) into a Microsoft SQL Server database, represented by Patient Data in Fig. 2. In New Zealand, GPs and their staff use the practice management system for electronic prescribing (but not dispensing) and maintain lists of patients’ long-term problems; observations such as BP’s are also recorded into the practice EMR. In the case of prescriptions, the duration for a given prescription was computed from the dosage instructions, pack sizes and number of refills as indicated in the prescription record.

The Drug and Classification Knowledge Base consists of the antihypertensive drugs (based on generic names) and their corresponding drug classes, and is based on the information extracted from DrugDigest (http://www.drugdigest.org/ [cited 20 May 2009]). During our data analysis stage, we identified cases where antihypertensive drugs were prescribed using popular brand names, instead of their generic name, and we included several such brand names too into our knowledge base. The drug knowledge base consists of different drug classes such as ACE-inhibitors, ARBs, diuretics and so on that are collectively categorised under the drug class “Antihypertensives”, leading to a drug class hierarchy (therefore a drug hierarchy since each drug belongs to some drug class). Likewise, the classification knowledge base consists of corresponding Read Codes for hypertension, diabetes and some other common comorbidity conditions of hypertension. A key advantage of creating such a knowledge base (in fact, an ontology) is the ability to cluster many transaction-level concepts (such as G2.00 which is a Read Code used to code hypertension) into domain level concepts (such as ‘hypertension’). This improves manageability and reusability of the knowledge bases. To create our knowledge bases we used the Protégé-OWL ontology editor (http://protege.stanford.edu/overview/protege-owl.html [cited 20 May 2009]), which is a widely used, free tool that supports the creation of such (hierarchical) knowledge bases. The ontology-C# parser module in Fig. 2 is used to convert the ontology knowledge from its native format into a C# representation.

The Reporting Criteria and the Reporting Criteria Template together define the content and the structure of the reporting criteria. The former is an XML [19] document containing specifics of the criteria while the latter is an XML-Schema (XML-S) [20] document that specifies the structure of the MPR and/or lapse that patients need to satisfy, along with any prior classifications patients need to have. For example, to define a reporting criterion such as "Patients with hypertension with an MPR less than 80% with a lapse in antihypertensive medication for greater than 30 days with lapse overlapping EP" in the XML document one needs to specify the required patient classifications (i.e. hypertension), MPR thresholds (i.e. less than operator and 80% threshold level), lapse in medication type (i.e. antihypertensive medication) and lapse thresholds (i.e. greater than and 30), as well as specify the evaluation period. This XML document is then validated against the corresponding XML-S by the XML-S Validator module shown in Fig. 2. If validation was successful, the C# XML Criteria Parser module will then create a C# representation of the XML that can be processed by other C# modules. The classification(s) and medication type must match an entry in the Drug and Classification Knowledge Base, or else an informative error message will be displayed to the user.

The main purpose of the Data Preprocessor module is to transform relational data from the database to C# objects, so that other C# modules can process information. The SQL MPR/Lapse Processor is used to retrieve patient data from SQL Server after executing various procedures on the server (primarily User-Defined Functions and Stored Procedures),
depending on the nature of criteria specified in the XML document.

2.4. Framework verification

The SQL MPR/Lapse Processor module in Fig. 2 uses SQL Server stored procedures and various SQL Server functions to determine a cohort of patients that satisfies a given criterion. However, the nature of a SQL query is such that it will almost always return some result, unless there was an obvious syntax error (and is almost certain to return a result via a visual query builder). Therefore, it is required to verify that our SQL based implementation produces the correct results. To assist with our results verification process, we designed the Sequential MPR/Lapse Processor module which is an independent (from the SQL MPR/Lapse Processor) C# based procedural implementation that uses a discrete-event simulation model to determine the patients of interest. This module retrieves the knowledge on the required criteria details (lapse and/or MPR thresholds, type of medication and so on) by communicating with the C# XML Criteria Parser module. The pseudo-code to identifying gaps is:

- For each patient prescription, create two prescription events, one a start-event and the other an end-event denoting the start and end dates of prescription coverage.
- Order the prescription events by (date) ascending order.
- Loop through the prescription events; incrementing a counter by 1 if it is a start event and decrementing the same counter by 1 if it is an end event. If counter equals zero, then it is a lapse in medication.
- If we are interested in lapse durations (i.e. as specified in the XML document) and the lapse satisfies the required temporal constraints and is after the required patient classification(s) (per Fig. 1), then it becomes a valid lapse that we need to report.
- If MPR criteria has been specified in the XML, then add the lapse duration (or the portion of the lapse duration per Fig. 1) to TotGap so that we can calculate MPR later.
- If MPR is required, calculate MPR using Eqs. (3) and (4) now that we know the value of TotGap.
- Consider the special cases (per Fig. 1) where there may be no knowledge of any prescriptions, and therefore will not be picked up above.
- Report on satisfied patient details, tailoring the output to the specifics of MPR and/or lapse criteria required.

Finally, the SQL-Sequential Verifier module verifies the results of the SQL MPR/Lapse Processor and Sequential MPR/Lapse Processor by comparing the outputs of these two modules to ensure that the results using the two different mechanisms remain the same. The Verifier Results module (which reflects a system output) shown in Fig. 2 is representative of the output from the SQL-Sequential Verifier module and contains details of any discrepancies that may have occurred if verification failed. A run with failed verification indicates an error somewhere, either in the SQL or sequential implementation, or a patient case we have not accounted for at all, hence each time verification failed, the issues behind the discrepancies in the results were identified and the relevant implementation was rectified. This was carried out as an iterative process until both implementations resulted in the same number of patients for a given criterion. Furthermore, we have written a number of test cases to perform boundary value analysis, equivalence class testing and all-pairs testing for the various cases shown in Fig. 1. Refer to [21] for details on these software testing techniques.

2.5. Protocol

Our study protocol was approved under University of Auckland Human Participants Ethics Committee protocol number 2007/078 and patient confidentiality was protected by withholding any identifying patient details (including name, address and National Health Index number) from the University based researchers. However, a practice-specific patient identifier was provided to the researchers (e.g., “M004162”) so that the expert panel of clinicians working for the practice could still identify the patients for clinical follow-up on their cases if required. Our protocol was to extract data for 24 months prior (from the date of extraction) with the exception of classifications, which are relevant for an indefinite time with respect to chronic illness and hence were extracted for 10 years back. Out of the 24-month period, we used the initial 6-month period as the run-in period, the next 12-month period as the evaluation period and the final 6 months as a period where any outcome measures of interest (such as BP) should be present for analysis (impact of MPR on BP control for example).

We demonstrate our framework using data extracted from the practice’s EMR for the 24-month period ending 30th November 2008 (with the exception of classifications which were extracted for 10 years back). The data extract involved 16,504 patients, 48,309 prescriptions (~12% for antihypertensive medications), and 80,110 patient classification codes (encoding 2731 hypertension and 2894 diabetes classifications based on Read Clinical Codes [18]—not necessarily the same number of individual patients with hypertension and diabetes however as a single patient can have multiple diagnosis codes).

Our EP was defined as the 1-year period from 1-June-2007 to 31-May-2008 giving a run-in period from 1-December-2006 to 31-May-2007. As discussed previously, our framework can be used to easily determine patients who satisfy certain criteria by creating the corresponding XML document with the required criteria details, and then processing it through the framework shown in Fig. 2. Treating with an ACE-inhibitor/ARB is an important and indicated component of most regimens to control BP in hypertensive patients with diabetes as investigated by other researchers [1,22], and is recommended by the American Diabetes Association as first-line therapy for the treatment of hypertension in persons with diabetes due to the ability of these drugs to slow the development and/or progression of diabetic nephropathy (i.e. kidney disease due to diabetes), and should be considered for every person
Fig. 3 – A snippet of the XML document showing reporting criteria.

3. Results

Out of the cohort of 16,504 patients, 6655 patients were presently funded for this practice, meaning these patients are managed by the New Zealand Primary Health Organisation (PHO) to which this practice belongs. Taking only the funded patients into account, we identified 804 classifications encoding hypertension (582 patients), 823 classifications encoding diabetes (494 patients) and 248 patients who were classified with hypertension and diabetes. There were 8411 prescriptions for antihypertensive drugs prescribed to funded patients.

Out of the 248 patients with hypertension and diabetes, we identified 192 (77%) patients under active ACE-inhibitor and/or ARB management. Processing the XML document in Fig. 3 for the three scenarios of interest: (i) 109 (57%) patients had a non-zero ACE-inhibitor/ARB MPR < 80%, (ii) 174 (91%) patients had a lapse in ACE-inhibitors/ARBs for greater than 30 days, and (iii) 107 (56%) patients had a non-zero ACE-inhibitor/ARB MPR less than 80% with a lapse in ACE-inhibitors/ARBs for greater than 30 days.

3.1. MPR/Lapse reports

A key output of the framework is MPR/Lapse reports that contain a list of patients who satisfy the required criteria,
Fig. 4 – Details of a patient who satisfies criterion “ACE-inhibitor/ARB MPR less than 80% with a lapse greater than 30 days”.

with justification for each patient being included in a particular result set. The system can be configured to produce outputs using the Sequential MPR/Lapse Processor and/or the SQL MPR/Lapse Processor (Fig. 2) with each processor module producing its own output. If both are selected (which should produce the same outputs), the results will be verified by the SQL-Sequential Verifier module. If verification fails (i.e. the number of patients identified by the independent processors is not the same), an informative message is displayed to the user and the program exits. Fig. 4 illustrates the resultant output for one patient who satisfies the criteria (i.e., who has a significant lapse and low MPR). At the top of the report we display the explicit reporting criteria in a more human friendly format (than the original XML document we used to specify criteria details). The Patient Id is the practice-specific patient identifier the researchers were given, as per our ethics protocol. The corresponding Read Codes for the patient diagnoses are shown within the brackets after the Read Terms (i.e. diabetes mellitus and hypertensive disease in this case).

3.2. Patient prescribing charts

The Lapse/MPR report is a text file containing only the specific patient information related to the criteria we are interested in, and at times visualising the temporal sequence of these events may be challenging. To overcome this barrier, as well as to assist a clinician to get a quick visual understanding of the medication a patient has been receiving, we developed a novel prescribing chart visualisation tool in C# .NET using some freely available software written in Visual Basic .NET as a starting point [24]. Once we have identified a patient we are interested in investigating further (as a result of the patient appearing in the MPR/Lapse report, or some other reason), the patient identifier can be entered into the Prescribing Charts module in Fig. 2, which will produce a chart with prescribing details for the selected patient (Fig. 5). In fact, the prescribing chart in Fig. 5 corresponds to the prescriptions issued to the patient identified by Fig. 4 as being non-adherent.

The chart indicates the different medications the patient has been prescribed and also uses a different colour for each drug, to aid following a single drug on the temporal axis. The drop-down option on the top-left provides the various drug classes the prescribed medications belong to (based on the drug ontology), effectively implementing a drug class filter (in Fig. 5 All Drug Classes has been selected, therefore all prescriptions are shown). The prescribing chart also shows the selected evaluation period (1-June-2007 to 31-May-2008 in this case). Shown in Fig. 6 is a filtered version of Fig. 5, which shows only the prescriptions with an ACE-inhibitor (per Fig. 5, this patient has no ARB prescriptions, so the MPR/Lapses are for ACE-inhibitors only). The figure also shows how hovering the mouse over a prescription bar brings up a tooltip that includes prescription duration and the different drug classes it belongs to.

It should be noted that in Fig. 6 there are three lapses in ACE-inhibitors, although in Fig. 4, only two have been reported. The report in Fig. 4 shows ACE-inhibitor/ARB MPR is 67.4% but if we do a simple MPR calculation based on these two lapses, that is [365 – (33 + 75)]/365, we get 70.4%. This is not a discrepancy in results, but is due to the fact that there is a lapse of 11 days from 7-December-2007 to 18-December-2007 (this can be seen if we hover the mouse over the relevant prescriptions) which is not shown in Fig. 4, as we queried only for lapses greater than 30 days. Now if we do the true MPR calculation which is [365 – (33 + 75 + 11)]/365, then we get the same 67.4% which is in fact what is reported in Fig. 4.
Table 1 – Non-adherence vs. having controlled BP (N = 162).

<table>
<thead>
<tr>
<th>Uncontrolled BP (systolic ≥ 130 mmHg or diastolic ≥ 80 mmHg)</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>MPR &lt;80% or lapse &gt;30 days (‘non-adherent’)</td>
<td>82</td>
<td>10</td>
</tr>
<tr>
<td>Yes</td>
<td>51</td>
<td>19</td>
</tr>
</tbody>
</table>

3.3. Impact of MPR on blood pressure control

To determine the relevance of the reporting to patient outcomes, we analysed the relationship of MPR, as yielded by our computational framework, to BP control. JNC7 [1] recommends a goal BP of <130/80 mmHg for patients with hypertension and diabetes, and as such, we define ‘uncontrolled BP’ for the present analysis as having systolic BP ≥ 130 mmHg or diastolic BP ≥ 80 mmHg (the New Zealand Heart Foundation guidelines [2] use a more sophisticated BP target that slides according to overall cardiovascular risk). Out of the 192 patients with hypertension and diabetes under active ACE-inhibitor and/or ARB management, 162 patients had a BP measurement during the 6-month period after the end of EP, that is between 1st June 2008 and 30th November 2008. Using the earliest BP measurement during this period as the outcome BP, we constructed a 2 × 2 table as per Table 1.

4. Discussion

4.1. Significance

In this paper we have presented a novel computational framework that can readily assess patient adherence to prescribed antihypertensive medication. Using a refined definition for medication possession as applied to a specified evaluation period, the framework has been used to identify patients with hypertension and diabetes who show poor adherence to ACE-inhibitors and/or ARBs. We have emphasised flexibility in the parameters of adherence queries to suit the range of guidelines and specific circumstances under which clinical teams may wish to conduct clinical audit, as well as in consideration of how much is yet to be learned about interventions to improve adherence. The XML document format we have created for queries provides a transparent and standards-based interface to the architecture (along with the use of Protégé-OWL to manage relevant concept taxonomies for drugs, problem classifications and other supporting inputs such as BPs). Furthermore, we have demonstrated the use of a new graphical tool that can be used to visualise prescribing patterns across all the prescribed antihypertensive drug classes, as well as a particular drug class the user is interested in (such as ACE-inhibitors and/or ARBs).

Our results (see Table 1) indicate that non-adherent patients with hypertension and diabetes are three times more likely to have uncontrolled BP than adherent patients (odds ratio = 3.055; p = 0.012). The result is unsurprising, per se, and agrees with past findings about the impact of non-adherence on BP control [25]. However, the result validates that we can analyse electronic prescribing (as compared to dispensing, or some other more proximate source of data) to provide a significant indication of poor BP control.

Two main uses for this form of reporting for improvement of chronic disease management are evident.

1. Awareness of immediate cases—identification of those patients that, at a particular moment in time, are out of supply of an indicated medication. In the first instance, the action is to treat the non-adherence as inadvertent and recall the patient and/or simply prescribe as indicated at the next opportunity. This includes not just patients with lapsed medications, but also those whose circumstances have changed (e.g., due to development of a comorbidity) and thus require additions to previous therapy.

2. Opportunity for communication with those with poor supply profiles—at some point it becomes logical to look to a lack of concordance between doctor and patient, and/or to the ability of the patient to achieve adherence for other reasons. Low MPR over an extended time period and repeated lapses in medication supply indicate the need for improved communication between GP and patient; possibly the clinician needs to engage the patient more in a joint “problem-solving” approach in relation to underlying adherence barriers.

As a broader research opportunity, GP EMR data is a promising resource for gaining a more detailed understanding of the
factors that predispose patients to non-adherence risk and thence for development of targeted intervention strategies for specific clusters of patients (e.g., those who are persistently inadvertently non-adherent due to specific lifestyle issues vs. those that are intentionally non-adherent due to disagreeing with the doctor’s recommendations or simply due to cost).

The results of our study indicate that a high proportion of our hypertensive and diabetic population (a particularly high-risk group) have deficiencies in their blood pressure control care process that can be detected from analysis of the electronic prescribing records. Beyond blood pressure, taking prescribed medications is one of the key factors to glycemic control for many patients (especially with type 2 diabetes). A previous study reported that less than 15% of diabetic patients on single-agent therapy maintained good adherence during a 1-year period, while patients on multi-drug therapy for diabetes experienced even lower levels of persistence and adherence [26]. In another study, it was reported that approximately 20% of diabetic patients were non-adherent (i.e. MPR <80%), which correlated with higher systolic and diastolic blood pressure, low-density lipoprotein (LDL) cholesterol, and glycosylated haemoglobin (HbA1C), and was associated with greater risk of all-cause hospitalisation and all-cause mortality; and therefore it was recommended that all patients should be evaluated for medication adherence, and if non-adherence is determined to be a problem, it should be addressed so that patients can receive the full benefit of medications [27,28]. Our framework has much potential to contribute to this adherence assessment function; i.e., to be used as a tool to identify specific patient cohorts to be contacted and address the non-adherence issues.

4.2 Related work

Statistical reporting and retrospective auditing of general practice medicine is not uncommon and there have been many past studies where patient non-adherence to medication has been discussed [29–31]. What we offer is an approach for achieving valuable adherence audit information directly from the EMR. Most practice management systems have ‘query-builder’ reporting functionalities for day-to-day reporting; however, the full consideration of the temporal issues for concepts such as lapse and MPR is non-trivial (refer back to Fig. 1), as is the knowledge-based requirements to produce concepts such as ‘ACE-inhibitors/ARBs’ or ‘diabetes’ from records that code specific drugs and diagnosis codes. Despite the computational challenges to achieving precise measures of chronic disease management activities, we have entered an era where quality auditing (and, in fact, “pay for performance”) are operational realities in some healthcare systems.

The National Health Service (NHS) in the UK has a Quality and Outcomes Framework (QOF) [32] that is part of the General Medical Services contract which encourages GPs to use evidence-based interventions, particularly in the management of chronic diseases (such as diabetes). The QOF is essentially a payment system for the GPs and consists of many quality indicators across five broad areas: clinical, organisational, patient experience, additional services and holistic care. Out of these, the clinical domain consists of indicators for conditions including hypertension and diabetes. The linking of the QOF directly to GP payment and its clinical outcomes has had mixed reviews with [33,34] reporting improvement in certain conditions, while others [35–37] have viewed the whole scheme more sceptically. It is interesting to note that the most valuable item in the QOF is achieving controlled BP (at the level of 150/90 for patients diagnosed with hypertension, and with additional points for tighter management of patients with diabetes and with chronic kidney disease). As per our results, we have found MPR as computed in our framework is associated with improved odds of successful BP control (at the more stringent targets recommended in JNC7). Thus, there may be an opportunity to improve QOF performance using an analysis framework similar to ours.

Our work most closely resembles the IDAN/KNAVE II framework [38,39] for temporal abstraction on clinical data. However, we have taken a much narrower focus that has allowed the majority of the work to be done (after sufficient conditioning of the data in our architecture) through a set of domain specific SQL queries. Moreover, we have explored in greater detail the specific temporal issues around cohorts of individuals over fixed ‘evaluation periods’ while considering the interplay of therapy and indications. Jin et al. [40] propose a novel data mining oriented approach using unexpected temporal association rules (UTARs) where adverse drug reactions that occur within a given time period (somewhat similar to our evaluation period) can be detected directly from healthcare administrative databases. Theirs is an approach where the adverse drug reactions are ‘discovered’ using UTARs automatically, whereas we give a careful quantification of a known issue as compared to discovering a new issue. Hence, there is a parallel of our work to that of Jin et al. in that they have specialised methods for adverse drug reaction detection, while we have specialised methods for adherence assessment.

There has also been an attempt “to develop an explicit tool precisely for measuring guideline adherence” in the context of adherence to the JNC7 guideline where the researchers developed 22 explicit criteria in four domains of care [29]. This tool, however, is focussed on an overall scoring of the adherence of the care process, including quality of documentation, to the guideline, as compared to our focus on quantified targets around medication adherence. Herein we use a refined definition for MPR (as discussed in Section 2.1); following a similar desire to refine MPR for computation, researchers developed a new refill-based adherence algorithm called ReComp [41]. However, ReComp was suggested as a more reliable adherence measure for short evaluation periods of around 90 days.

4.3 Limitations and future work

A limitation of our identification of MPR and/or medication lapses is that it is currently based on general practice prescribing data. As such, the lapses are those implied by the doctor–patient interactions within a particular practice. It is possible that patients receive prescriptions or otherwise achieve medication supply through other means. And conversely, our data provide no guarantee that prescribed medication has been dispensed or subsequently consumed by the patient as directed. In fact, it is interesting to note
that a considerable number of patients have uncontrolled BP despite being ‘adherent’ based on prescribing data. More complete monitoring of the prescribing, dispensing, consumption cycle would be desirable—for instance in New Zealand, linkage of prescribing to dispensing will be greatly facilitated if the New Zealand Health Informatics Standards Organisation (HISO) draft e-pharmacy specification [42] is adopted. However, the present research is based on taking the prescribing record alone as the basis for identification of patients in need of quality improvement action; and we believe this would have some inherent merit, at least from the GP’s perspective, as prescribing is a direct action that has been taken on a patient which is a reflection of GP adherence to evidence-based guidelines. It is interesting that prescribing alone already uncovers such substantial cohorts for intervention and shows significant association to blood pressure control. However, extension to include dispensing, or even home monitoring, would obviously result in superior ‘intelligence’ and is a desirable future direction. Therefore, without dispensing data, we cannot know with certainty if adherence issues presented herein are manifested as a failure of the patient to get a prescription dispensed, or to return to the pharmacy for refills (a typical New Zealand antihypertensive prescription is for 30 days with two refills with a prescription expiry date of 3 months after issue date), or relates to dispensed medication not being taken and thus accumulating at home. Another limitation of our computational framework is that it is tailored to medications that are taken regularly, in discrete, uniform doses. As such, the framework is not presently sufficiently fine-grained to assess adherence to treatments where the patient adjusts the dose in response to conditions, as with adjustment of insulin dosing based on blood sugar.

In this work we have focussed primarily on adherence issues, but the framework can be extended to specify other important chronic condition management criteria as well—e.g., patients with hypertension who have three or more consecutively high BP measurements with the last measurement recorded during EP and the duration between the first and the last high BP greater than 120 days. Such patients indicate cohorts of patients that take ‘too long’ to achieve their therapeutic goal, and therefore indicate a suitable focus group for a possible intervention. In fact, our research on analysis of general practice reporting requirements indicates that there are four broad categories of reporting criteria [13]—persistence of indicated treatment, timely measurement of outcomes, timely achieving of goals/targets, and absence of contraindications to current treatment. The work presented herein focussed primarily on the first category and currently we are looking at extending the framework to include criteria covered by the other categories.

Beyond expansion of the data analysis framework per se, the immediate future work programme is to investigate the issues and motivations associated with those patients whose prescribing patterns indicate a low MPR. Our framework does not inherently provide any solution with respect to how the information is to be used by a practice to improve adherence. However, we are presently engaged in the first phase of a study where patients with low adherence receive follow-up phone calls from practice nurses, providing reminders and offering further assistance. Intuitively, the absence of timely prescri-

5. Conclusions

The computational framework we have developed to identify and visualise specific patient cohorts with poor adherence to prescribed antihypertensive medication shows potential to be used as a tool to improve clinical outcomes. Our framework supports analysis of practice EMRs with consideration of various non-trivial temporal relations between prescriptions and problem classification within the context of a specified evaluation period. We have found the Medication Possession Ratio (MPR) computed with our framework to be significantly associated with odds of successful blood pressure control for patients with diabetes and hypertension. Further work is needed both to expand the EMR-based reporting to other important classes of quality audit criteria for chronic condition management and to determine how to effectively utilise such reporting to improve patient outcomes.
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