

# Prescription Patterns for Pacific Patients with Poor Cardiovascular Disease Medication Supply

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## Abstract

**Introduction:** The Caring Does Matter (CDM) programme aims to improve medication adherence amongst Pacific patients with high cardiovascular disease (CVD) risk. This paper examines CDM baseline (pre-intervention) data for patterns of poor medication adherence. **Methods:** Electronic medical records from 14 general practices are analysed with respect to prescribing patterns for antihypertensive, cholesterol lowering and oral antidiabetic medications. Patients who recently started treatment and had <80% medication possession in the latest 15 months are grouped into three categories: (1) just one prescription; (2) initial persistence ( $\leq 30$  day lapse between the first and second prescriptions; and (3) other (i.e. multiple lapses, including a lapse immediately after the first prescription). **Results:** Over half of patients recently started on CVD-related medication are non-adherent in the latest 15 months; and the rate is higher than in those patients having started the medications earlier. A lapse after the first prescription is associated with significantly increased odds of non-adherence. Non-adherence is not dominated by a single prescription pattern category. **Discussion:** General practices usually get return visits from patients developing a pattern of poor medication possession, providing a series of signals of non-adherence risk, and offering ample opportunity for adherence promotion intervention.

**Keywords:** Cardiovascular risk management, electronic medical records, medication compliance, pharmaco-epidemiology.

## 1 Introduction

Poor adherence (also known as *compliance*) to long-term medication is a major issue undermining the effective delivery of healthcare (Rodgers and Ruffin, 1998). It is frequently overlooked by prescribing physicians when intensifying treatment (Heisler et al., 2008, Pittman et al., 2012). Statins, as a case in point, are a central element in cardiovascular disease (CVD) risk management as per guidelines in New Zealand (New Zealand Guidelines Group, 2012), Australia (National Vascular Disease Prevention Alliance, 2012) and internationally (Perk et al., 2012). The rate of failure to maintain statin therapy for 12 months after initiation is high (Benner et al., 2002) even when initiated after acute coronary events (Thornley et al., 2012). And poorer levels of statin adherence are associated with higher rates of long-term mortality after acute myocardial infarction (Rasmussen et al., 2007) and in coronary artery disease generally (Ho et al., 2008). New Zealand CVD guidelines place particular emphasis on the role of estimated 5-year risk of a cardiovascular event (e.g. heart attack and stroke) as central in the decision to treat – by prescribing statins or other relevant classes of medication, as well as through lifestyle modifications such as smoking cessation (New Zealand Guidelines Group, 2012).

EMRs related to medication supply (i.e. prescribing and dispensing) enable systematic estimation of medication adherence by indicating the availability of prescription medications to patients. One powerful statistic computable from EMRs is medication possession ratio (MPR), which is a percentage of days covered with

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medication supply in some evaluation period; an MPR<80% is commonly interpreted as indicating non-adherence (i.e. the EMRs showed that the patient would have lacked adequate supply of the medication at least one day in five)(Andrade et al., 2006). EMRs have been successfully used in New Zealand general practices to identify potential intervention targets with poor blood pressure (BP) medication adherence (Mabotuwana et al., 2009b) as well as to identify cases for review who were on unchanged therapy while CVD risk and systolic BP remained high (Patel et al., 2013).

There are 266,000 Pacific people living in New Zealand (NZ), according to the 2006 census data (Statistics New Zealand and Ministry of Pacific Island Affairs, 2010). This population group have higher risk for CVD and higher mortality rate from CVD than the overall New Zealand population (Ministry of Health, 2012), but low adherence to CVD medications (Warren et al., 2012b). The Caring Does Matter (CDM) programme aims to improve Pacific people's adherence to CVD medications by delivering structured primary care to the patients with high CVD risk (5-year event risk  $\geq 10\%$ ) and low medication possession ratio (MPR <80%) (Warren et al., 2012a). The CDM programme uses the general practice EMR to identify gaps in CVD medication supply (indicating poor medication adherence) in Pacific adults with high CVD risk.

This paper examines the CDM baseline data to understand the patterns of poor adherence for CVD medications by examining the medication supply in EMR prescribing records among the Pacific patients who became non-adherent to these medications. The objective is to gain insight into how medication non-adherence presents over time in the EMR data to better inform future interventions aimed at reduction of CVD event risk.

## 2 Methods

The CDM protocol was approved by the Northern X Regional Ethics Committee (NTX/12/EXP/102). The CDM baseline (pre-intervention) data from 14 CDM-participating general practices that use the MedTech EMR system (12 in Auckland and 2 in Northland) were analysed for the present study. This baseline data was extracted between May and September 2012. Data collected was de-identified prior to removal from the practice and included: ethnicity codes (up to three), age, gender, enrolment status and date enrolment commenced, and prescriptions for the previous five years. Three broad classes of CVD-related medication prescriptions – antihypertensive, cholesterol lowering and oral antidiabetic medications – are examined using the prescription records in the EMR by the SAS statistical software package, version 9.2 (SAS Institute Inc., Cary, North Carolina). These three medication classes are central to the CDM programme as each control one of the key risk factors known from epidemiological studies to increase risk of CVD events (Ho et al., 1993, Mannan et al., 2013):

1. *Antihypertensive agents* refer to the class of drugs used in the treatment of acute or chronic vascular hypertension (high blood pressure),

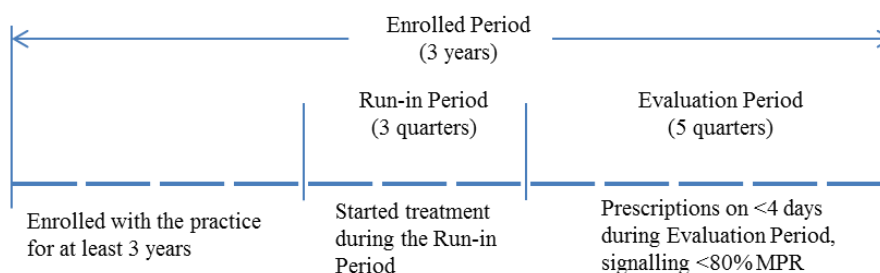
including diuretics, adrenergic beta-antagonists, angiotensin-converting enzyme inhibitors and calcium channel blockers (National Library of Medicine, 2011) – herein treatments for chronic hypertension are the ones of interest.

2. *Cholesterol lowering medications* include statins and fibrates, as well as other drugs to manage hyperlipidemia (high cholesterol), such as ezetimibe (Pahan, 2006).
3. *Oral antidiabetic medications* lower the blood glucose level in patients with type 2 diabetes mellitus; these oral hypoglycaemic agents include sulfonylureas, meglitinides and biguanides (Luna and Feinglos, 2001).

Our primary interest in the present study is to characterise the development of poor adherence from the commencement of therapy in the above three classes of medication. To identify Pacific adults starting therapy, we apply the following inclusion criteria:

1. Self-identified as Pacific: any of the three ethnicity fields in the patient's EMR is identified as Cook Island Maori, Fijian, Niuean, Other Pacific Island, Pacific Islander (Not Further Defined), Samoan, Tokelauan or Tongan.
2. Aged 20 or over at baseline.
3. Currently enrolled (at baseline) in the general practice and have been enrolled for at least three years.
4. In the last five years, the first prescription (for the class of medication being analysed, e.g. antihypertensives) occurred in one of the first three quarters of past two years (the 'Run-in Period' in Figure 1). In other words, the patient has no prescription record in the practice EMR for 3 years prior to the 9-month window of starting treatment.
5. In the last 15 months (the remaining five quarters of past two years, or 'Evaluation Period'), the EMR recorded prescriptions on three or less distinct days, which signals the patient as being significantly undersupplied and having an MPR < 80%. (Given the usual NZ practice of prescribing a 90-day supply for long-term medications, five prescriptions for five quarters of therapy are expected; manual analysis confirms that virtually all prescriptions in these medication classes are for 90 days' supply – e.g. a bottle of 30 with instructions to take one per day and with 2 refills.)

For each class of the CVD medication, we compute the inclusion eligibility and MPR with a SAS algorithm based on our previous work with the ChronoMedIt architecture (Mabotuwana and Warren, 2010). MPR < 80% in the Evaluation Period (most recent five quarters) is interpreted as non-adherence (and conversely MPR  $\geq 80\%$  is termed 'high' adherence). Note that this approach to identification of non-adherence is conservative – e.g. a patient might not choose to get a prescription dispensed, and they might not choose to take the dispensed medication; but without a prescription they are unlikely to



**Figure 1: Illustration of the patient timeline for inclusion as a patient starting CVD-related therapy and having low medication adherence**

be in supply (with some exceptions, e.g. use of a family member’s medication). It is also tolerant, or at least conservative, with respect to changes of dose, changes of medication sub-class due to side-effects and combination therapy (e.g. multiple classes of antihypertensive prescribed concurrently) – in each case, additional prescriptions may cause us to overestimate supply but are unlikely to result in an underestimate.

If there are 120 or more days between two adjacent prescribing dates (essentially >30 day out of supply), we define this out-of-supply period as a ‘lapse.’ This duration of lapse is concerning even taking into account mild stockpiling of medication and transient events such as a brief hospital stay. The calculation of lapses allows us to group the non-adherers into three categories:

1. Just one prescription (i.e. a single prescription in the Run-in with no further prescription in that class during the Run-in or Evaluation Period);
2. Initial persistence (i.e. the first prescription had less than a 30-day lapse before the next prescription);
3. Other (i.e. multiple lapses, including a lapse after the first prescription).

The definition of these three categories is consistent with patterns of non-adherence in antidepressant therapy analysed previously with similar methods (Mabotuwana et al., 2011). Descriptive analysis of the three groups is carried out to compare the characteristics of each group in terms of the number of lapses and ‘final lapse’ duration (how long out of supply patients went at the end of the Evaluation Period if it was >30 days). The odds ratio (OR) and 95% confidence interval (CI) for high adherence for initial persistence status compared to initial lapse status (including both the just-one-prescription and multiple-lapses types) are calculated to test if there is any significant association between initial persistence status and adherence.

For comparison, we also compute adherence for the Pacific adults whose information is recorded in the practice’s EMR as ‘casual’ patients (e.g. enrolled elsewhere). This is to test the assumption that most patients get their long-term medication prescriptions

(such as for CVD) from their usual general practice. Another comparison is undertaken to investigate if there is any difference in adherence rate between the Pacific patients who started on CVD medication in the Run-in Period and patients who started treatment prior to the two recent years (i.e. meeting the first three criteria, but started the first prescription before the Run-in Period). The level of adherence, and its 95% CI range, were calculated for those two groups using SAS Enterprise Guide version 4.3; furthermore, the binomial proportion equivalence test was undertaken to compare the adherence levels in those two groups.

### 3 Results

#### 3.1 Study Participants

The EMR at 14 CDM-participating general practices recorded information for 49,088 Pacific patients, including 31,227 aged 20 or over. Among these Pacific adults, 10,185 (33%) were enrolled and funded at the practices at baseline, including 5,744 (18%) enrolled with the practice for three or more years. Considering only these 5,744 patients, **Error! Reference source not found.** shows their rates of having CVD medication prescriptions in the last five years, with separate tallies for those who started treatment during and before the study Run-in Period.

As per Table 1, 28% (1627 out of 5744) of Pacific adults have had at least one antihypertensive prescription in the last five years; 22% for cholesterol lowering medication, and 15% for oral antidiabetic medications. Due to the high percentage of Pacific adults present in the practice EMRs not enrolled with the practice at baseline (21,042, 67%), we also examined the prescription records of these ‘not enrolled’ patients (e.g. historically enrolled then moved away or currently visiting as ‘casual’). Some of these patients have been prescribed CVD medications from the practices in the last five years. However, the percentage of these ‘not enrolled’ Pacific adult patients having CVD prescriptions in the last five years is only 3% for antihypertensives, 2% for cholesterol lowering medication and 1% for oral antidiabetic medications.

Drug class	Having prescription in last five years	Starting treatment during Run-in Period	Starting treatment before Run-in Period
Antihypertensive medication	1627	109	1382
Cholesterol medication	1285	98	1099
Oral antidiabetic medication	841	60	691

**Table 1: CVD Medications Prescribed to the 5,744 Pacific Adults Enrolled for at least 3 Years**

### 3.2 High Adherence levels

Among all the Pacific adults who fit the study inclusion criteria 1-4 (i.e. enrolled for at least 3 years and with the first prescription in the medication class starting in the Run-in Period), there are more non-adherers (i.e. having <80% MPR in the recent 15 months) than high adherers ( $\geq 80\%$  MPR). Those Pacific adults starting treatment prior to the recent two years have significantly higher rates of adherence than those starting in the Run-in Period for all three medication classes (binomial proportion equivalence test,  $p < 0.001$ ); see Table 2.

To investigate the pattern of how a patient became a high adherer or non-adherer, we examined the MPR level of those meeting the study inclusion criteria 1-4 and if they persisted with the treatment initially (i.e. the first prescription had less than a 30-day lapse before the next prescription). Table 3 shows that those who persisted initially are more likely to adhere to their medications as compared to those who lapsed on first prescription (including those having only one prescription and multiple lapses). The odds ratio for high adherence for initial persistence status compared to initial lapse status is 8.05 for antihypertensives, 4.17 for cholesterol and 2.11 for antidiabetic medications, indicating increasing odds of high adherence for initial persistence. The 95% confidence interval of the OR indicates that the odds of high adherence are significantly higher for the initial persistence group compared to the initial lapse group (for antihypertensive and cholesterol medications, at 0.05 significance level; i.e. neither CI contains 1.00).

### 3.3 Categories of Non-adherers

The medication supply gaps identified in the non-adherers falls into three categories: (1) with just one prescription, (2) having persisted initially, or (3) having had multiple lapses (including a lapse after the first prescription). Table 4 shows that none of the three categories dominates the non-adherence pattern, except for a low rate of just-one-prescription cases for the oral antidiabetic medication class. However, it must be noted that in this fine-grained analysis the sample sizes are becoming quite small.

Figure 2 illustrates the initial persistence type of non-adherence pattern over two years using a case where a patient started Gliclazide (a sulfonylurea) and Metformin Hydrochloride (a biguanides) therapy in the first quarter of the two years. The timeline demonstrates some persistence initially but the lapses between prescriptions are tending to increase over time. However, at the CDM baseline data extraction time, the patient seems to be in supply, but only for Metformin Hydrochloride. The coloured areas indicate the 90-day coverage of each prescription from the date of prescribing.

Figure 3 shows an example of the multiple-lapse type of non-adherence pattern over two years for Simvastatin (a statin). The timeline view on prescription events demonstrates the first >30 day lapse right after the initial prescription as well as significant lapse beginning in Quarter 5, and a final lapse (continuing at the time of CDM baseline).

Drug class	High adherers among those starting treatment during Run-in Period: N (% , CI)	High adherers among those starting treatment before Run-in Period: N (% , CI)
Antihypertensive medication	33 (30%, 22%-40%)	759 (55%, 52%-58%)
Cholesterol medication	27 (28%, 19%-38%)	441 (40%, 37%-43%)
Oral antidiabetic medication	20 (33%, 22%-47%)	339 (49%, 45%-53%)

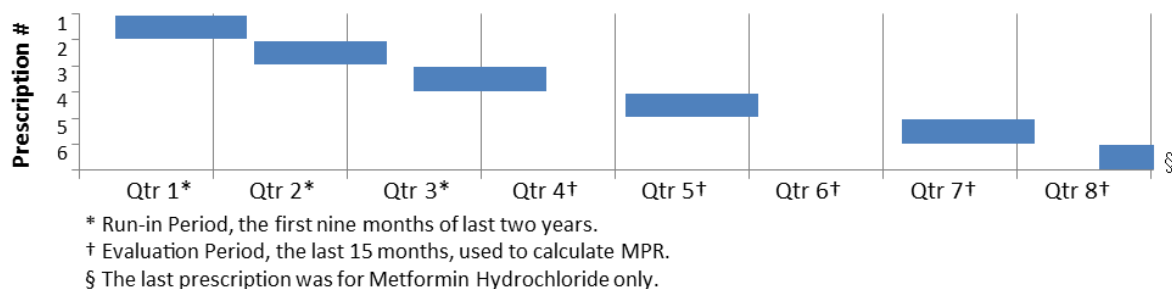
**Table 2: Adherence Rate of Enrolled Pacific Adults who Started Therapy during and before the Run-in Period**

Drug class (number initiating therapy in Run-in)	Persisted or Lapsed Initially	High adherers	Non-adherers	High adherence OR for 'initial persistence' compared to 'initial lapse' (CI)
Antihyper-tensive medication (109)	Persisted initially (50)	26	24	<b>8.05 (3.07, 21.12)</b>
	Lapsed initially (59)	7	52	
Cholesterol medication (98)	Persisted initially (41)	18	23	<b>4.17 (1.63, 10.71)</b>
	Lapsed initially (57)	9	48	
Oral antidiabetic medication (60)	Persisted initially (35)	14	21	2.11 (0.68, 6.60)
	Lapsed initially (25)	6	19	

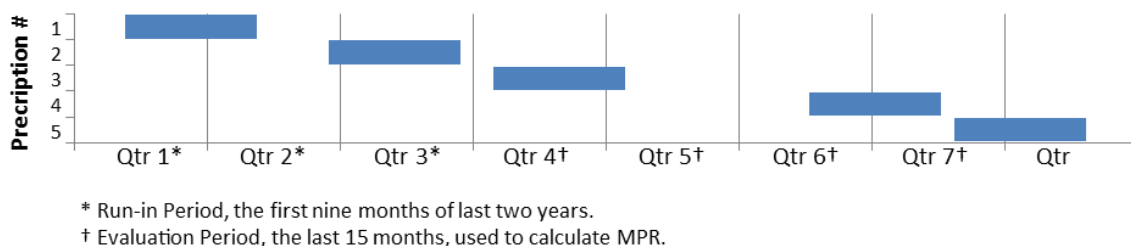
**Table 3: Adherence Status by Persisted or Lapsed Initially**

Drug class	Just one prescription	Initial persistence	Multiple lapses
Antihypertensive medication (76)	25 (33%)	24 (32%)	27 (36%)
Cholesterol medication (71)	19 (27%)	23 (32%)	29 (41%)
Oral antidiabetic medication (40)	3 (8%)	21 (53%)	16 (40%)

**Table 4: Patient Number (%) in Non-adherence Categories**



**Figure 2: A Timeline Example of Prescription Events for Initial Persistence Type of Non-adherence**



**Figure 3: A Timeline Example of Prescription Events for Multiple Lapses Type of Non-adherence**

Note that these timeline graphs are meant purely to be illustrative and were not sampled to represent ‘typical’ cases in any specific way. The next section provides quantitative tabulation to contrast supply patterns among the non-adherence types.

### 3.4 Characteristics of non-adherers

By definition, those in the just-one-prescription category had one lapse continuing through to the CDM baseline date. But between those who persisted initially (<30-day lapse between the first and second prescriptions) and those who did not persist but had multiple lapses for antihypertensive and cholesterol lowering medications, some differences are observed in terms of the mean number of lapses per patient over two years (see Table 5). Note that statistical significance was not tested given the small sample size.

Table 4 illustrates that patients who have come to have a low MPR often do so through multiple lapses – not just going away never to return. Table 6 provides rate and duration of final lapses (cases where the patient has not had a prescription for medication in the given class within 120 days of the end of the Evaluation Period). This shows that, among the non-adherers, a larger proportion of those

who persisted initially than of those who had multiple lapses show long final lapse, and that those final lapses are longer than for the cases with multiple lapses that include a lapse immediately after the first prescription. As with Table 5, we refrain from testing statistical significance due to the small sample size.

### 4 Discussion

Analysis of primary care EMR data allows detailed examination of CVD medication supply and patterns of non-adherence. We found that rates of non-adherence after commencing therapy is high, with more than half of Pacific adults making an initial (as far as we could observe) start to CVD-related medication treatment having gaps in their medication supply consistent with non-adherence in the latter 15 months of treatment. The higher adherence level in those who have been on treatment for more than two years, as compared to those starting in the study Run-in Period, suggests that adherence levels may improve gradually over a period of several years. It could be that this is explained by the patients that started earlier having a greater burden of CVD-related morbidity; for instance, it is known that adherence rates are higher in those who have had a

Drug class	Just one prescription	Initial persistence	Multiple lapses
Antihypertensive medication	1	1.6	2.1
Cholesterol medication	1	1.7	2.1
Oral antidiabetic medication	1	1.9	1.9

**Table 5: Mean Number of Lapses per Patient over Two Years among Non-adherers**

Drug class	Just one prescription	Initial persistence	Multiple lapses
Antihypertensive medication	100%, 498	67%, 253	44%, 178
Cholesterol medication	100%, 519	65%, 264	45%, 180
Oral antidiabetic medication	100%, 440	48%, 268	19%, 176

**Table 6: Non-adherers with Final Lapse by Category (% , Mean Number of Days in Final Lapse)**

myocardial infarction than those who have not (Naderi et al., 2012). Another possibility is that the patients that appear newly started by our inclusion criteria were ones who had lapsed for all of the year before the Run-in Period (and for up to two year before that if they had been with the practice that long), while not being genuinely new to the therapy. Indeed it seems probable that we are observing a mixture of these effects; the degree to which these factors are in play will require further analysis to assess.

The prescription pattern for the patients with low medication possession demonstrates that the adherence gaps are not dominated by 'just-one-script' cases. The presence of subsequent prescriptions of the same class in the majority of low medication possession cases indicates: (a) that the practice GPs are persisting in the belief that therapy in the given medication class is appropriate for that patient (i.e. they have not re-assessed the CVD risk or concluded that it is contraindicated); and (b) that patients are continuing in their relationship with the practice and concur to the therapy insofar as to accept another script (but not sufficiently to achieve high adherence). This means that the practice typically gets the opportunity for 'another look' at patients heading into poor CVD medication adherence, and so has a chance to take some further responsibility and action to promote medication adherence. We observe that the odds of non-adherence in the longer term (the latter 15 months of the two years that include initiation of therapy) are significantly greater if patients lapse after the very first prescription – this should be taken by practices as a 'red flag' to trigger adherence promotion activity.

This study has a number of limitations. The set of practices is a convenience sample based on practices willing to participate in the CDM initiative. Moreover, our analysis is based on patients that were still enrolled with a practice after three years; in day-to-day prescribing, from a practice perspective, non-adherence will be more frequent due to patients that have changed enrolment to a different practice. However, if a practice had a policy of systematic follow-up for poor medication supply, such enrolment changes would be quickly revealed. Moreover, we found that rates of prescribing to 'casual' patients in the CVD-related medication classes analysed in this study were very low (only 1-3% of patients) – thus, a change in CVD medication prescriber appears to track well with a change in enrolment. Supply-based MPR is, of course, an indirect measure of adherence, although widely accepted due to its practical applicability at the population level as compared to direct monitoring, and with less vulnerability to over-estimating adherence as compared to pill counts or self-report (Andrade et al., 2006, Steiner and Prochazka, 1997, Vermeire et al., 2001). While we have based our adherence assessment only on prescriptions, we have found previously that general practice prescriptions for long-term medication match well with national reimbursement data for dispensing (Mabotuwana et al., 2009a) and that – at least for antihypertensive medication – improved MPR based on prescribing translates to improved MPR on dispensing (Warren et al., 2012b). Although we started with a large cohort of Pacific adults,

tracking non-adherence for those starting long-term therapy in a narrow time period led to small sample size for some of the more fine-grained analysis. It may be that linkage to national data is the only method that can build a population model that is robust across enrolment changes; however, the richness of general practice EMRs should not be abandoned in the process.

While there is widespread agreement that medication adherence is a major problem in management of CVD risk (Lemstra et al., 2012), we believe that the temporal dimension of the phenomenon has been under-analysed. Our analysis indicates that a general practice usually makes repeated prescriptions (i.e. subsequent prescriptions in the same broad medication class) to patients developing a pattern of poor medication possession, providing a series of signals and 'red flags' of non-adherence risk, and offering ample opportunity for adherence promotion intervention.

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