Understanding Adherence and Prescription Patterns Using Large Scale Claims Data

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Abstract

Purpose:
Advanced computing capabilities and novel visual analytics tools now allow us to move beyond the traditional cross-sectional summaries to analyze longitudinal prescription patterns and the impact of study design decisions. For example, design decisions regarding gaps and overlaps in prescription fill data are necessary for measuring adherence using prescription claims data. However, little is known regarding the impact of these decisions on measures of medication possession (e.g., medication possession ratio). The goal of the study is to demonstrate the use of visualization tools for pattern discovery, hypothesis generation and study design.

Method:
We utilize EventFlow, a novel discrete event sequence visualization software, to investigate patterns of prescription fills, including gaps and overlaps, utilizing large scale healthcare claims data. The study analyzes data of individuals who had at least two prescriptions for one of five hypertension medication classes: ACE inhibitors (ACE-I), Angiotensin II receptor blockers (ARB), Beta blockers (Beta), Calcium channel blockers (CCB) and Diuretics (Diur).

We focus on those members initiating therapy with Diuretics (19.2%) who may concurrently or subsequently take drugs in other classes as well. We identify longitudinal patterns in prescription fills for antihypertensive medications, investigate the implications of decisions regarding gap length and overlaps, and examine the impact on the average cost and adherence of the initial treatment episode.

Results:
A total of 790,609 individuals are included in the study sample, 19.2% (N=151,566) of whom started on diuretics first during the study period. The average age is 52.4 years and 53.1% of the population is female. When the allowable gap is zero, 34% of the population has continuous coverage and the average length of continuous coverage is 2 months. In contrast, when the allowable gap is 30 days, 69% of the population shows a single continuous prescription period with an average length of 5 months. The average prescription cost of the period of continuous coverage ranges from $3.44 (when the maximum gap is 0 days) to $9.08 (when the maximum gap is 30 days). Results were less impactful when considering overlaps.

Conclusions:
This proof-of-concept study illustrates the use of visual analytics tools in characterizing longitudinal medication possession. We find that prescription patterns and associated prescription costs are more influenced by allowable gap lengths than by definitions and treatment of overlap. Research using medication gaps and overlaps to define medication possession in prescription claims data should pay particular attention to the definition and use of gap lengths.

Key points for decision makers

- Big data provides an unprecedented level of detail regarding prescribing patterns among large cohorts.
- Visual analytics tools can harness the rich information in big data to provide unique insight into health services utilization among large cohorts as well as generate hypotheses involving the use and cost of health services.
- Study parameters such as allowable gaps can significantly affect the medication coverage period and associated prescription costs; it is important for both researchers and decision makers to be aware of the impact of these parameters.

1. Introduction

Since poor adherence to medication therapy is a major contributor to poor health outcomes [1,2] and higher costs of care [3], it is essential that researchers are able to understand and measure adherence at the population level. The most common, extensively used measurements of drug adherence have historically been medication possession ratio (MPR), proportion of days covered (PDC) and fraction compliant [4-7]. However, big data, combined with new computing technology such as information visualization software, allow us to move beyond cross-sectional investigations of prescription drug utilization and the associated descriptive statistics in order to analyze and describe population adherence over time. This study evaluates the utility of EventFlow for the investigation of longitudinal fill patterns for antihypertensive medications. EventFlow is an interactive visualization software with a graphical user interface that enables users to analyze temporal patterns, to visually inspect and search the prescription patterns of individual patients [8,9]. The software also provides a visual overview of population wide patterns by automatically grouping patients based on their prescriptions patterns (which drug they start on, their subsequent use of drugs of interests and gaps in coverage) and presents the results in a visually comprehensible display that includes information about the timing between prescriptions and duration of coverage gaps.

The study of prescription fill patterns is not new. Studies have investigated trends in antihypertensive prescribing [10] and evaluated the concordance between observed prescription patterns and the guidelines of the seventh report of the joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure [11]. Medication adherence has been investigated in prior studies using direct and indirect measures, which include drug assays or markers, self-reporting, pill counts, electronic monitoring systems, and reviews of pharmacy records or administrative data [12]. Researchers have often used administrative (i.e., claims) data, which offer advantages over other data sources: they are inexpensive, convenient, and can be used for large patient populations [13]. Further, administrative data are non-invasive and objective [12], and estimates derived from pharmacy databases are also more likely than those obtained from clinical trial populations to reflect real-world settings [5]. However, one well-known limitation of using administrative data to measure adherence is the inability to confirm that filled prescriptions correlate to medication usage. Yet, studies have found a high concordance between prescription claims data and pill counts, suggesting that the rate at which patients refill their medications is usually consistent with the rate at which they consume them [13,14].

When processing longitudinal refill data, it is necessary to consider the fact that specific study design decisions can impact the measure of medication possession and, consequently, any summary statistic. For example, one study demonstrated that the choice of gap measurement affects the calculated rate of adherence [15]. Specifically, decisions regarding gaps and overlaps in prescription fill data can materially influence our measures of medication possession. Despite the fact that these decisions are commonly made with input from clinical and statistical experts, information about their impact is limited. It is important, then, to understand how extensively and in what ways these measurement decisions influence study findings on medication possession and associated costs. Visual information about fill patterns may be useful in helping researchers determine appropriate thresholds for gap length or overlap length, particularly when novel software facilitates investigation of variation over time and across individuals.

In this study, we focus on refill patterns, gaps and overlaps for antihypertensive medications. We work within the context of hypertension due to its prevalence [16,17], long-term medication use, and poor adherence [18]. An estimated 50-70% of patients are non-adherent to their antihypertensive medications, with variations in this range due to differences in study groups, duration of follow-up, methods of adherence assessment and different drug regimens [3]. Using a combination of summary statistics and results from EventFlow, we characterize longitudinal patterns in prescription fills for antihypertensive medications and investigate ways in which study design decisions regarding gap length and overlaps can affect a study's findings about prescription fill patterns and costs.

2. Methods

2.1 Data and Study Parameters

In this study we use a cohort of commercially insured members who each fill at least two prescriptions for hypertensive medications. Each prescription in the data consists of a de-identified memberid, drug code, service date, and days-supply, as well as other descriptive columns. We include five drug classes: ACE inhibitors (ACE-I), Angiotensin II receptor blockers (ARB), Beta blockers (Beta), Calcium channel blockers (CCB) and Diuretics (Diur). Each class has been shown to be effective in randomized clinical trials, and during the study period all but ARB were available as generics and in single daily dose formulations. The study period extended from October 1, 2008 to September 30, 2010. The study excluded members taking combined dosage forms (i.e., fixed dose drug/drug combinations like beta blocker plus diuretic), as well as members with any negative costs or claims reflecting data entry errors.

Since patients rarely collect a follow-up prescription on the same day that they consume the last dose of their previous prescription, drug treatment patterns constructed from prescribing or dispensing events in administrative databases often show an overlap or a gap between two prescriptions [19]. These gaps and overlaps are typically processed by defining an allowable length of time or minimum period of time for grouping or separating prescription fills. The 'allowable gap' (i.e., the length of time a patient can be without medication before being considered non-adherent) has been defined in multiple ways in the literature. One study considered gaps as small as 7 days to be an indicator of non-adherence [20], while another study used a gap of 30 days [21]. In a study of patients using Liraglutide, discontinuation was defined as a gap of at least 90 days, which researchers interpreted as non-persistence [22]. Overlaps are defined as instances in which a patient is in possession of two or more filled prescriptions at once. In a single-drug case, the second prescription is often shifted forward [20]. In the case of multi-drug overlap, researchers must be able to distinguish between instances of concurrent use and instances where a patient is switching medication. However, there is limited guidance available for handling overlaps in the case of multi-drug regimens.

2.2 Graphical Interface and Data Modeling in EventFlow

In this section, we introduce EventFlow[9] and discuss the interpretation of the program's data output. We start with a small data sample for clarity of presentation (see Figure 1, representing 10 patients prescribed two different drugs A and B.)

In Figure 1, the timeline on the right shows details of prescription fills data for individual patients, including the sequencing and timing of prescriptions. Each horizontal bar represents a prescription interval, color-coded by the drug (with small vertical lines at both ends of prescription intervals, to make overlaps more apparent). In the center, we see an overview of all the records. It aggregates groups of records with the same sequence of prescriptions into horizontal stripes comprised of colored bars representing each interval. The height of each bar is proportional to the number of records in the group, and the width of the bar is the average duration of the interval (i.e. prescription(s)). When prescriptions overlap the colors are merged. Reading from the left, we can see that all records start with a prescription for Drug A (red). We then identify three different patterns (i.e. groups of records). The largest group is at the top (7 out of 10 patients) . Patients in this group completed the Drug A prescription and did not start another prescription either before or at the time that the prescription for Drug A ended. Six of these patients continue to a prescription for Drug B (blue), while one patient discontinues treatment. The next group (2 patients) is starting a prescription for Drug B before the end of Drug A. The overlap is identified by the purple bar. Lastly, one patient refills a prescription for Drug A before the first prescription is complete, and the duration of the prescription overlap is shown by the darker red bar. In addition EventFlow's interactive features provide summary statistics and distributions of durations of different events.

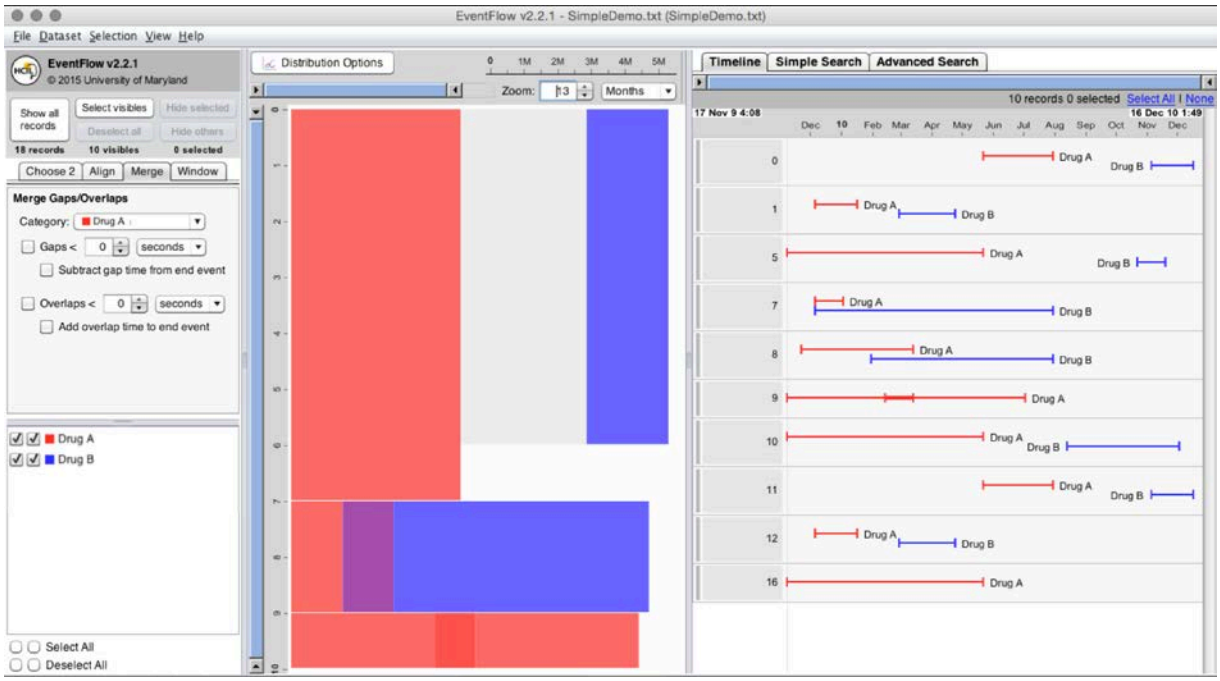


Figure 1. Sample dataset in EventFlow. On the right we see the individuals' prescriptions on a timeline. In the center is an aggregate summary of all the patterns found in the records.

EventFlow has an interactive search panel that makes it possible for users to graphically specify complex queries involving temporal constraints and the absence of events (e.g., which patients used both Drug A and Drug B for at least 30 days?) or search and replace operations (see Figure 2). The combination of these techniques allows users to sharpen the focus of an analysis to records that exhibit particular event sequences. (For detailed explanations of EventFlow's capabilities and how the overview is constructed please see [23]).

EventFlow provides a simple interface that allows multiple interval events (prescriptions) in the same category to be merged into a single interval event (detail view in Figure 2). This can be done in two ways: allowing gaps of certain duration or eliminating overlaps of certain duration. In Figure 2 b), we eliminate a gap that is smaller than the allowable gap parameter. In Figure 2c), the overlap is smaller than the single-drug overlap parameter and as a result, EventFlow will take the length of the overlap and extend the interval by that amount. For example, if a patient refills his or her prescription four days early, the second prescription will be shifted four days and the two prescriptions will be merged into a single, longer interval. The interactive user interface allows users to investigate the impact of different merging parameters on the grouping of the prescription patterns.

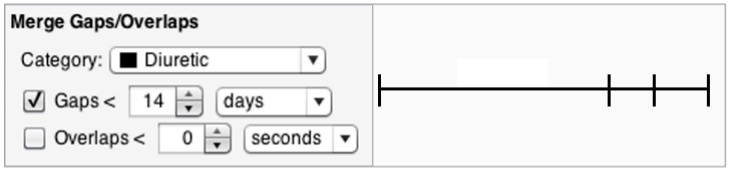
In this study we use the search and replace features to analyze the effects of different parameter values for allowable gaps and for single- and multi-drug overlaps. In Figure 3 we demonstrate how we applied the search and replace feature twice to distinguish between two cases of overlap: when the multi-drug overlap period is less than our parameter and when the multi-drug overlap period is greater than our parameter.

In defining our base parameters, we first set the allowable gap to 15 days, the single-drug overlap parameter to 15 days and the multi-drug overlap parameter to 0 days. EventFlow's interactive features make it very easy to change the value of those parameters and visually inspect the results. This allowed us to rapidly explore the parameter space, which in turn guided the sensitivity analysis.

Finally we set the observation window to two years following the first prescription in the data set for an antihypertensive agent. This is also easily done interactively within EventFlow by aligning all records by their first event, then setting a temporal window parameter.

While EventFlow's overviews can be reproduced as figures in the paper, many other interactive features allow the researchers to gain a more detailed understanding of the data. For example the overview shows only the average durations between events, but the temporal distributions, exact values of counts and percentages are revealed by bringing the cursor on elements of the display.

(a) The merge panel allows users to merge many prescriptions within a period of time into one continuous prescription.Above, we have three Diuretic prescriptions: the first two have a gap of 7 days and the second two overlap by 4 days.



(b) First we merge all gaps less than 14 days, so the first two prescriptions are joined into one.

(c) When merging overlapping intervals, we add the length of the overlap to the end of prescription and extend it. So, if a patient refills their prescription early, the period after the prescription is considered.

Figure 2. On the left: detail of the EventFlow interval merging interface. On the right: illustration of its effect, with (a) original data, (b) first merging, (c) second merging. The vertical bars indicate the start and end of a prescription.

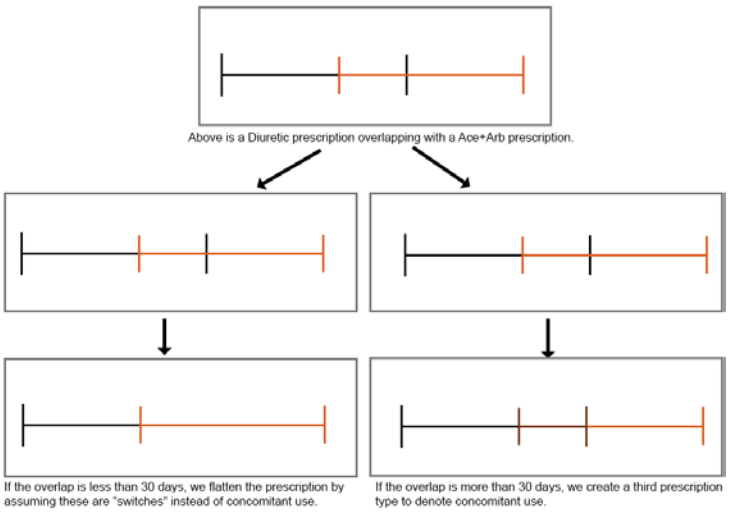


Figure 3. Illustration of how we distinguished between switching pattern and concurrent use pattern. In this example the multi-drug overlap parameter is set to 30. If the overlap is greater than 30 days, the visual display represents concurrent use. Otherwise, it is considered a switch. The EventFlow Search and Replace feature was used to specify the data transformation.

3. Results

3.1 Population Statistics

Our overall population comprises 790,609 members. The majority, 61.8%, only take medications from one drug class, while 25.4% have at least one prescription for two drug classes, 9.8% have a prescription for three drug classes and 2.7% and 0.3% have prescriptions for four and all five drug classes, respectively. The average age is 52.4 years (calculated at the time of individual's first prescription) and 53.1% of the sample is female. Overall, females are more likely to use fewer drug classes, and members using fewer drug classes are on average younger than members with claims for multiple classes. Table 1 summarizes the study population and breaks it down in more detail based on drug class. For example, we note that 37,612 members filled a prescription for both ACE-I and Diuretics, and that those two drug classes are the second most common combination of classes (the more common combination is ACE-I and Beta).

3.2 Members Starting on Diuretics

In clinical practice, newly diagnosed hypertensive patients are typically prescribed a diuretic, either alone or in combination with other antihypertensive agents. The JNC 7 (The seventh report of the joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) [24] recommended thiazide diuretics as initial therapy, for most patients diagnosed with stage one hypertension without compelling indications. The guideline also recommends ACE-I, ARBs, Beta and CCB, alone or in combination. The recent JNC 8 (The eight report of the joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure) [25] recommends thiazide Diuretics, ACE-I, ARBs and CCBs, alone or in combination, as first-line agents for patients who are nonblack without Chronic Kidney Disease.

In order to investigate prescription patterns among patients on multi-drug regimens, in this paper we focus on individuals who begin treatment with Diuretics (Figure A-1 in the Appendix gives an overview of population analysis in EventFlow and Figure A-2 analyzes the population that have their first prescription for Diuretics, alone or in combination with other drug classes). The analysis of all 151,566 members that started on thiazide Diuretics, possibly together with additional drug classes all 151,566 members that started on thiazide Diuretics, possibly together with additional drug classes, reveals that 54% of the population, initiates therapy in our data with Diuretics only (average duration of initial period is 4 months 27 days), followed by at least one gap. There are also large groups that either start on Diuretics and then initiate a second drug class without a gap, or who immediately begin dual medication therapy. Table 2 summarizes the number of members on dual therapy: the most common second class is ACE-I, followed by Beta, CCBs and finally ARBs.

Sub-population	Drug Class(es)	Average Age	%Female	Count	% of the Population	% of Sub-population
Sinlge drug class	ACE-I	51.1	38%	146,956	18.6%	30.1%
	ARB	53.3	44%	43,080	5.4%	8.8%
	Beta	49.0	57%	135,717	17.2%	27.8%
	CCB	50.1	57%	49,414	6.3%	10.1%
	Diur	47.9	78%	113,401	14.3%	23.2%
Two Drug classes	ACE-I, ARB	52.4	45%	7,670	1.0%	3.8%
	ACE-I, Beta	55.8	32%	43,525	5.5%	21.6%
	ACE-I, CCB	55.0	39%	17,674	2.2%	8.8%
	ACE-I, Diur	54.3	57%	37,612	4.8%	18.7%
	ARB, Beta	57.3	43%	10,947	1.4%	5.4%
	ARB, CCB	57.1	46%	6,174	0.8%	3.1%
	ARB, Diur	56.9	67%	9,994	1.3%	5.0%
	Beta, CCB	54.2	53%	15,504	2.0%	7.7%
	Beta, Diur	55.2	67%	34,903	4.4%	17.4%
	CCB, Diur	54.8	66%	17,063	2.2%	8.5%
Three Drug Classes	ACE-I, ARB, Beta	56.1	41.7%	2,639	0.3%	3.4%
	ACE-I, ARB, CCB	55.1	42.3%	1,458	0.2%	1.9%
	ACE-I, ARB, Diur	54.8	61.7%	2,228	0.3%	2.9%
	ACE-I, Beta, CCB	57.8	36.7%	9,491	1.2%	12.2%
	ACE-I, Beta, Diur	58.8	45.0%	25,691	3.2%	33.1%
	ACE-I, CCB, Diur	57.1	49.7%	11,843	1.5%	15.3%
	ARB, Beta, CCB	60.1	43.5%	3,180	0.4%	4.1%
	ARB, Beta, Diur	60.9	55.1%	7,255	0.9%	9.3%
	ARB, CCB, Diur	59.8	59.5%	4,156	0.5%	5.4%
	Beta, CCB, Diur	58.4	59.3%	9,678	1.2%	12.5%
Four Drug Classes	All except ACE-I	62.2	52.8%	4,430	0.6%	20.9%
	All except ARB	60.0	42.9%	12,102	1.5%	57.2%
	All except Beta	57.7	53.7%	1,349	0.2%	6.4%
	All except CCB	59.3	50.4%	2,253	0.3%	10.7%
	All except Diur	58.4	41.7%	1,013	0.1%	4.8%
	All five drug classes	61.1	46.9%	2,209	0.3%	100%

Table 1: Summary statistic of the population broken down by the drug classes that members have filled prescriptions for. ACE-I refers to ACE inhibitors, ARB to Angiotensin II receptor blockers, Beta to Beta blockers, CCB to Calcium channel blockers and Diur to Diuretics.

	# of members starting on two (and only two) classes at the same time	# of members starting with Diur, then adding another class
ACE-I	11,119	8,620 (average duration 1 month 28 days)
ARB	2,150	2,142 (average duration 1 month 10 days)
Beta	8,201	7,035 (average duration 1 month 19 days)
CCB	6,905	3,594 (average duration 1 month 20 days)

Table 2: Number of members initiating dual therapy or adding another drug after starting Diuretics. ACE-I refers to ACE inhibitors, ARB to Angiotensin II receptor blockers, Beta to Beta blockers, and CCB to Calcium channel blockers.

In certain patient subgroups (e.g. diabetes, chronic kidney disease), ACE-I and ARB are the drugs recommended for use with diuretics. In our data 26,747 members that start on Diuretics and also have at least one prescription for ACE-I or ARB (but no prescriptions for Beta or CCB) during the study period. When the patterns of these members are analyzed, the majority (56.6%) start on both diuretics and ACE-I/ARB, and their usage patterns vary greatly and very few or 1.7% have continuous use of both classes for the duration of the two-year study period. Of all other members who start on both, about 13% of them only have a single 30-day prescription, close to 20% have an initial usage duration between 31 and 90 days, and close to 67% have an initial duration longer than 90 days. However, a significant proportion of the population starts out on diuretics alone (for about 2 months on average), then the members either add the second medication class without a gap, have a gap or switch medications: they initiate ACE-I and/or ARB therapy immediately after diuretic use. Overall, we observe that switching (with or without a gap in between drugs) is not a common pattern among these members. The Appendix discusses these patterns in more details, and the visualization is included in Figure A-3.

3.3 Sensitivity Analysis

In this section, we consider the implications of decisions regarding gaps and overlaps for analyzing fill patterns among patients who initiate on diuretics. We investigate the effects of three parameters – the allowable gap, the single-drug overlap and the multi-drug overlap – on the duration of the initial treatment and the first treatment gap, and on prescription costs and adherence.

An increase in the allowable gap parameter will merge more prescriptions together, therefore increasing the length of a continuous coverage period, we will demonstrate this fact using data from members who take diuretics only (Please refer to Appendix B.1 for visual analytics of the effects of the allowable gap parameter). The allowable gap parameter affects any measure of the number of gaps, average duration and distributions of gap length. Table 3 summarizes some population statistics as a function of the allowable gap. For example, when the allowable gap is zero, only 34.4% of the population has continuous coverage – and the average length of continuous coverage is 2 months, 8 days (median 1 month). In contrast, when the allowable gap is 30 days, 68.7% of the population shows a single continuous prescription period with an average length of 5 months and 25 days (median 3 months). We also note, as we increase the allowable gap, that the average length of the observable gaps increases (as shorter gaps have been eliminated). Table 3 reports the average cost (the paid amount by the insurer) for the antihypertensive therapy for the initial period across various gap lengths. We find that the average prescription cost of the initial on-study treatment episode ranges from $3.44 (when the maximum gap is 0

days) to $9.08 (when the maximum gap is 30 days). This is due to the fact, as the allowable gap increases, more prescriptions become a part of the initial treatment episode, its duration is extended and as a result the cost increases. Further, if we calculate the average capped MPR during the initial on-study treatment episode, we note that the average MPR is 1 when the allowable gap is zero. This is due to the fact that when the allowable gap is zero, no gaps are a part of the initial episode. As the allowable gap parameter increases the average MPR slowly decreases, as more and more small gaps are considered a part of the initial episode.

Allowable Gap	**Statistic**	**0 days**	**7 days**	**15 days**	**30 days**
Initial coverage period	average	2 months 8 days	3 months 21 days	4 months 23 days	5 months 25 days
	median	1 month	2 months	3 months	3 months
	st.dev	2 months 12 days	4 months 15 days	5 months 17 days	6 months 12 days
% without a gap		34.4%	46.4%	57.0%	68.7%
Initial gap	average	1 month 5 days	1 month 21 days	2 months 8 days	3 months 6 days
	median	10 days	22 days	1 month 5 days	2 months
	st.dev	2 months 9 days	2 months 17 days	2 months 24 days	3 months 3 days
Paid amount	average	$3.44	$5.80	$7.44	$9.08
	st. dev	$14.80	$26.73	$34.05	$41.77
Adherence (MPR) in initial coverage period	average	1	0.993	0.982	0.964
	fraction above .8	1	1	0.997	0.947

Table 3: Statistics of the Diuretics-only population as a function of the allowable gap length. The initial gap refers to members' first gap in treatment.

We now assess the effects of changing the overlap parameter for a single drug class. Our base parameter is 15 days – that is, if a prescription overlap was less than or equal to 15 days, the overlap was appended to the duration of the drug, otherwise the second drug was considered a replacement and the overlap was merged without appending. The short overlaps affect very few members and as a result the effects are minimal as is summarized in Table 4, which reports the average prescription cost for the initial period across various lengths for single-drug overlap. The average cost of the initial treatment episode ranges from $7.29 (when the maximum overlap is 0 days) to $7.61 (when the maximum overlap is 30 days). The increase in costs is small, reflecting the small changes to the initial coverage period. Similarly we only observe a minimal change in the average capped MPR.

Single-Drug Overlap	**Statistic**	**0 days**	**7 days**	**15 days**	**30 days**
Initial coverage period	average	4 months 21 days	4 months 21 days	4 months 23 days	4 months 26 days
	median	2 months 26 days	3 months	3 months	3 months
	st.dev	5 months 14	5 months 15	5 months 17	5 months 20

		days	days	days	days
% without a gap		55.9%	56.3%	57.0%	58.1%
Initial gap	average	2 months 7 days	2 months 7 days	2months 8days	2 months 9 days
	median	1 month 4 days	1 month 5 days	1 month 5 days	1 month 5 days
	st.dev	2 months 24 days	2 months 24 days	2 months 24 days	2 months 25 days
Paid Amount	average	$7.29	$7.35	$7.44	$7.61
	st.dev	$33.83	$34.02	$34.05	$35.07
Adherence (MPR) in initial coverage period	average	0.983	0.982	0.982	0.981
	fraction above .8	0.997	0.997	0.997	0.997

Table 4: Statistics of the Diuretics-only population as a function of the single-drug overlap parameter. The initial gap refers to members' first gap in treatment.

The last parameter is multi-drug overlap. Adjusting this parameter affects how we distinguish between those switching medications and those with concurrent use. When the parameter is set at zero, any overlap in medication is considered concurrent use; in contrast, when the parameter is set at 30 days, only overlap of more than 30 days is considered concurrent use.

We study this parameter using the data on the 26,747 members that start on Diuretics and also have at least one prescription for ACE-I or ARB (but no prescriptions for Beta or CCB) during the study period. Overall when the parameter changes from zero to 30 days, it only affects only the patterns of 17% of the population, there is a reduction in concurrent use and increase in the number of switchers and single class use (for details please refer to Appendix B.3). Smaller changes to this parameter have marginal effects. For example, changing the parameter from 0 to 15 only affects 122 members (0.5%), and changing it from 0 to 29 affects 157 members (0.6%). In each of these cases, the majority of the patterns change from Diuretic only use to concurrent use followed by ACE/ARB use, to Diuretic only use followed immediately by use of ACE-I/ARB only. Therefore, the critical setting for this parameter is whether or not investigators require more than 30 days of concurrent use to establish simultaneous use. From a payer's cost perspective there is no change in cost. Whether a member's claim is considered a switch or concurrent use does not change the fact that a prescription was filled and paid for.

4. Discussion

Medication non-adherence has significant effects on health care expenditures, as it increases physician visits, emergency incidents, re-hospitalizations, and nursing home re-admissions [26]. Therefore, adherence studies examining outcomes and associated costs can inform important pharmacoeconomic decisions. However, as documented in a systematic review of randomized controlled trials, there is no consensus on how medication adherence is defined, analyzed or reported, and in fact, the literature shows substantial heterogeneity [27].

Traditionally, descriptive summary statistics have been used to report prescription drug usage and adherence. However, these statistics do not provide an intuitive, interactive way to investigate the implications of changes in gap lengths and overlaps across patient groups or on the associated cost effects, and research in this area has been limited. In this paper we have illustrated the use of EventFlow for visualizing large scale prescription claims data. EventFlow revealed the diversity of those patterns and informed the description of the longitudinal patterns in prescription fills for antihypertensive medications. The software also helped us investigate the implications of decisions regarding the merging of gaps and

overlaps, and examine the impact on the average cost of the initial episode. We have found that EventFlow is a useful tool for analyzing high level patterns, but it also allows for a drill down to the patient level data, for example to investigate adverse events in the context of drug patterns.

The literature does not currently offer a 'best standard' for assessing medication adherence nor guidance in identifying the important parameters for measuring medication possession. We show how key study parameters affect the observed prescription patterns, which has direct implications for adherence studies. Studies have shown that changing measures will change the rate of adherence [15], and this in turn has a direct effect on cost evaluation. A study by Jonsson et al. [15] highlights the importance of choosing an adherence measure most appropriate for specific study factors and drug properties. This is vital, since depending on the pharmacokinetic property of the medications under consideration, one method of measuring adherence may be of greater clinical value than another. For example, occasional missed doses may be less important than long gaps in treatment, for drugs that have a long half-life. It is reasonable to consider that in addition to pharmacokinetic properties, other factors (disease-related and patient group characteristics, for instance) may also affect the suitability of an adherence measure. Our sensitivity analysis highlights this point: that it is not only the method of adherence evaluation that is important, but the study design parameters as well. EventFlow's interactive features made it easy to vary those parameters and develop hypotheses about their effect on the overall patterns – which could be later quantified.

EventFlow can be used to explore the implications of alternative design decisions, for example, lengths for a washout (i.e., 'prescription-free') period. For each member, one can define the start date of his/her eligibility as an event. It is then easy to apply a filter, to only show those members with at least six months (or any time period) between their first (the start of their eligibility) and second event (their *first* hypertension prescription). EventFlow also can be used to inform the statistical analysis: 1) to visually inspect the patterns of prescription drug use in clinically important strata (e.g., patients grouped according to the Charlson Comorbidity Index, disease severity, performance status, mental health status, etc.); 2) to understand how the timing and length of medication possession varies over time for patients; 3) to investigate the use of medications and the periods of medication possession in their relationship to a health outcome of interest (e.g., a hospitalization or length of stay of the hospitalization). Findings from EventFlow could help determine how to measure medication possession, whether it is the medication use or interval length of medication possession that is more relevant for predicting a hospitalization, and whether specific subgroups are important to examine separately. These insights can help determine how a covariate enters a regression model built to test the relationship between medication use/adherence and health outcomes. Current analytical tools do not provide this nuanced information, which can be important for study design and statistical model specification.

Since pharmacoeconomic evaluations assess the cost and effect tradeoff, the impact of poor compliance and persistence on medication effectiveness is as important as the impact on costs [28]. Although here again, no single measure can be deemed the 'best' [5], it would be useful in future studies to understand the extent to which design decisions regarding prescription patterns will affect the cost outcomes of a study.

5. Conclusions

This proof-of-concept study illustrated the use of visual analytics tools in characterizing longitudinal medication possession. Given the limited information regarding their impact on measures of medication possession, we investigated the role of decisions regarding gaps and overlaps in prescription fill data. We found that decisions regarding gap length have a stronger effect on the average prescription cost of the initial period compared to decisions regarding single-drug overlaps. Information regarding the cost implications of decisions regarding gap length and overlaps is lacking, and this will be an important area for future research. There is also a need for consensus guidance regarding evaluation of complex fill patterns among individuals on multiple drugs. We have shown that complex patterns can be investigated using a visual analytics tool like EventFlow, and future research can build on these findings to investigate

the implications of these patterns for adherence and associated cost studies. In particular, future research using medication gaps and overlaps to define medication possession in prescription claims data should pay particular attention to the definition and use of gap lengths.

Compliance with Ethical Standards

1. Funding: This study was partially funded by The University of Maryland/Mpowering the State through the Center for Health-related Informatics and Bioimaging.

2. Conflicts of Interest: Dr. Onukwugha reports consulting income from AstraZeneca and Janssen Analytics. Dr. Bjarnadottir has no conflicts of interest to declare. Sana Malik has no conflicts of interest to declare. Tanisha Gooden has no conflicts of interest to declare. Dr. Plaisant reports being a stake-holder in EventFlow through indirect benefit from commercial use of the software. The EventFlow software has been disclosed as an invention with the University of Maryland Office of Technology Commercialization (OTC) so that the OTC can negotiate commercial licenses with companies interested in licensing the software. The IP is owned by the campus and the income is distributed among different entities on campus (OTC, Colleges and departments of the inventors) with a small percentage of the income from those licenses returned to the inventors and used to support further research. The OTC website specifies the availability of the software and the policy of distributing a portion of the income to inventors.

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1. Author contributions: The interpretation and reporting of the results are the sole responsibility of the authors. Dr. Bjarnadottir will act as the guarantor of the work presented in this paper. Dr. Bjarnadottir contributed to the study design, data collection, conduct and interpretation of the analysis, and drafted and revised the manuscript with input from all co-authors. Sana Malik created all figures in the paper, and contributed to the study design, the application of EventFlow to the data, interpretation of the analysis, and commented on/edited all drafts of the manuscript. Dr. Onukwugha contributed to the study design, interpretation of the analysis, drafted and revised the manuscript. Dr. Plaisant contributed to the study design, the application of EventFlow and the interpretation of the analysis, reviewed and commented on/edited all drafts of the manuscript. Tanisha Gooden contributed to the interpretation of the analysis, drafted and/or reviewed and commented on/edited all drafts of the manuscript.

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Appendix A – Visual Analytics and Prescription Patterns

A.1 Example of Population Analysis

When a large subset of the population is analyzed, complex patterns emerge. Figure A-1 summarizes the data from all members who have at least one prescription for each of the five drug classes during the study period (2,209 members total). The center panel in Figure A-1 demonstrates that these members start out on any of the drugs, then continue to add or switch drugs and take break(s) from antihypertensive therapy. We highlight in the figure the members whose first prescription in our dataset is Diuretics, on their own or in combination with another drug class. We further note that these members commonly switch and/or add a second class quickly, most often CCB and to a lesser extent ACE-I and Beta. Interestingly, a significant proportion of the Diuretics initiators in our dataset start on Diuretics, Beta and CCBs.

The timeline view on the right in Figure A-1 provides additional details of members' fill patterns. From the top, the first member shows a clear pattern of gaps and switches and an inconsistent prescription pattern, including a single prescription for ARB and Beta. In contrast, the second patient uses all five drug classes consistently but drops the ACE-I halfway through the period. Finally, the third patient starts out on Beta, and soon Diur is added to the regime. A single prescription of ACE-I appears, followed by a single longer prescription of ARB, which is finally replaced by a series of prescriptions for CCB. This patient's prescription usage appears to stabilize in a concurrent use of Diur, CCB and Beta.

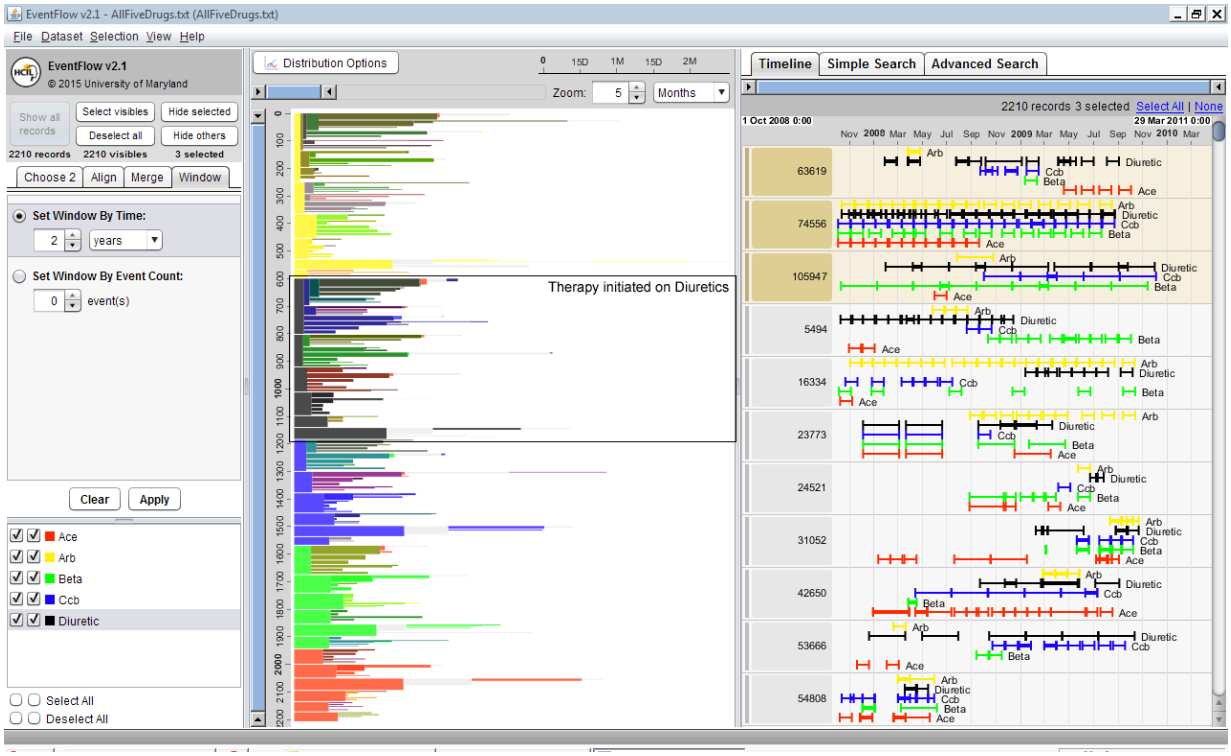

Figure A-1: A screen shot of the EventFlow visualization, showing data from members filling at least one prescription for each of the five drug classes over the study period. On the right side we can see the records of individual patients (one per row), showing each prescription as a color interval. Users would have to scroll down to see the records of all individuals. In the center we see the overview of all prescription patterns found in the 2210 records. Control panels and color legend are in the left panel. Due to size limitations, the printed figure doesn't reveal all the pattern details within small groups of

patients, but more detail is visible when displayed on the analyst's screen. Ace refers to ACE inhibitors, Arb to Angiotensin II receptor blockers, Beta to Beta blockers, and Ccb to Calcium channel blockers.

A.2 Visual Analytics for the Diuretic Population

Figure A-2 shows an overview of all 151,566 members that started on thiazide Diuretics, possibly together with additional drug classes. In this figure, Diuretics are dark grey, and ACE-I, ARB, Beta and CCB are red, yellow, blue and green, respectively. As a result, a darker primary color or green indicates a Diuretic in concurrent use with one of the other drug classes, while darker blended colors (such as purple and orange) indicate three drug classes (with one of them being Diuretics) in concurrent use. The light grey color indicates a gap.

The strongest pattern in the figure, followed by 54% of the population, is to initiate therapy with Diuretics only (average duration of initial period is 4 months 27 days), noted by (a) in the figure, often followed by at least one gap, noted by (b) in the figure, and then one or more additional periods of Diuretic use, noted by (c) in the figure. Of these 82,471 members, 3,200 have a treatment duration of 30 days or less. There are also large groups that either start on Diuretics and then initiate a second drug class without a gap, or who immediately begin dual medication therapy. For example, in members who start on Diuretics and then add CCB, concurrent use is noted by (d) in the figure, and those members who start both Diuretics and ACE-I are noted by (e).

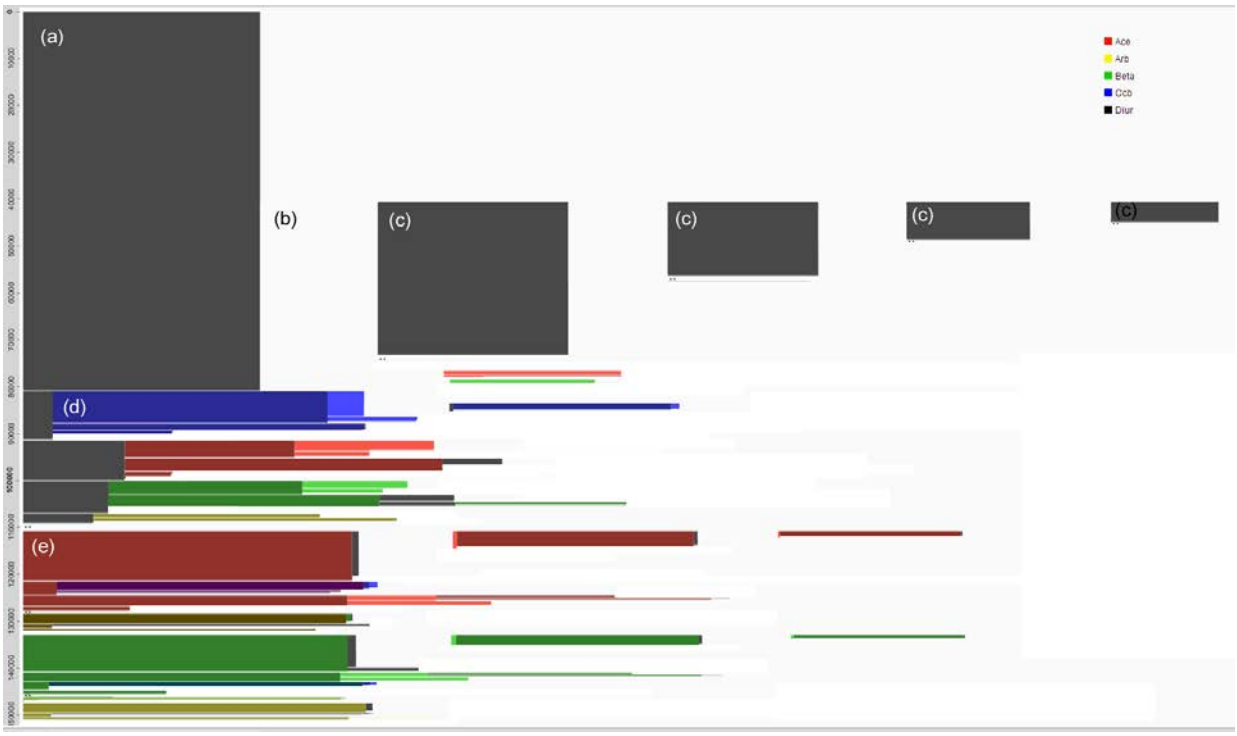

Figure A-2: Overview of the population that starts on Diuretics. The figure shows the details of all the summarized patterns. Ace refers to ACE inhibitors, Arb to Angiotensin II receptor blockers, Beta to Beta blockers, Ccb to Calcium channel blockers, and Diur to Diuretics.

A.2.1 Visual Analytics for the Diuretic and ACE-I and/or ARB population

In certain patient subgroups (e.g. diabetes, chronic kidney disease), ACE-I and ARB are recommended for use with Diuretics. In Figure A-3 we display the patterns of the 26,747 members that

start on Diuretics and also have at least one prescription for ACE-I or ARB (but no prescriptions for Beta or CCB) during the study period.

Of these members, the majority (56.6%) start on both Diuretics and ACE/ARB (the upper part of Figure A-3). Among the 15,138 members who start out on both drugs, usage patterns vary greatly. Out of those members, 457 or 1.7% show continuous use of both classes for the duration of the two-year study period. But of all other members who start on both, about 13% of them only have a single 30-day prescription, close to 20% have an initial usage duration between 31 and 90 days, and close to 67% have an initial duration longer than 90 days. We also observe a repeating pattern of concurrent use with gaps (pattern (a) in Figure A-3), as well as concurrent use leading to a period of single-drug use (either Diuretics or ACE-I/ARB) followed by concurrent use again (pattern (b) in Figure A-3).

A significant proportion of the population starts out on Diuretics alone (the lower part of Figure A-3). About 53% of these Diuretics-only starters add the second medication class without a gap (after, on average, only 2 months and 2 days on Diuretics), about 33% have a gap (following, on average, 2 months and 26 days of Diuretic use) and then most commonly start again on a single drug regimen, and close to 14% are switchers: they initiate ACE-I and/or ARB therapy immediately after Diuretic use (2 months later on average). These patterns are indicated by (c), (d) and (e), respectively, in Figure A-3. Overall, switching (with or without a gap in between drugs) is not a common pattern; members are more likely to start on one drug, add a second, and then perhaps drop to one drug class again.

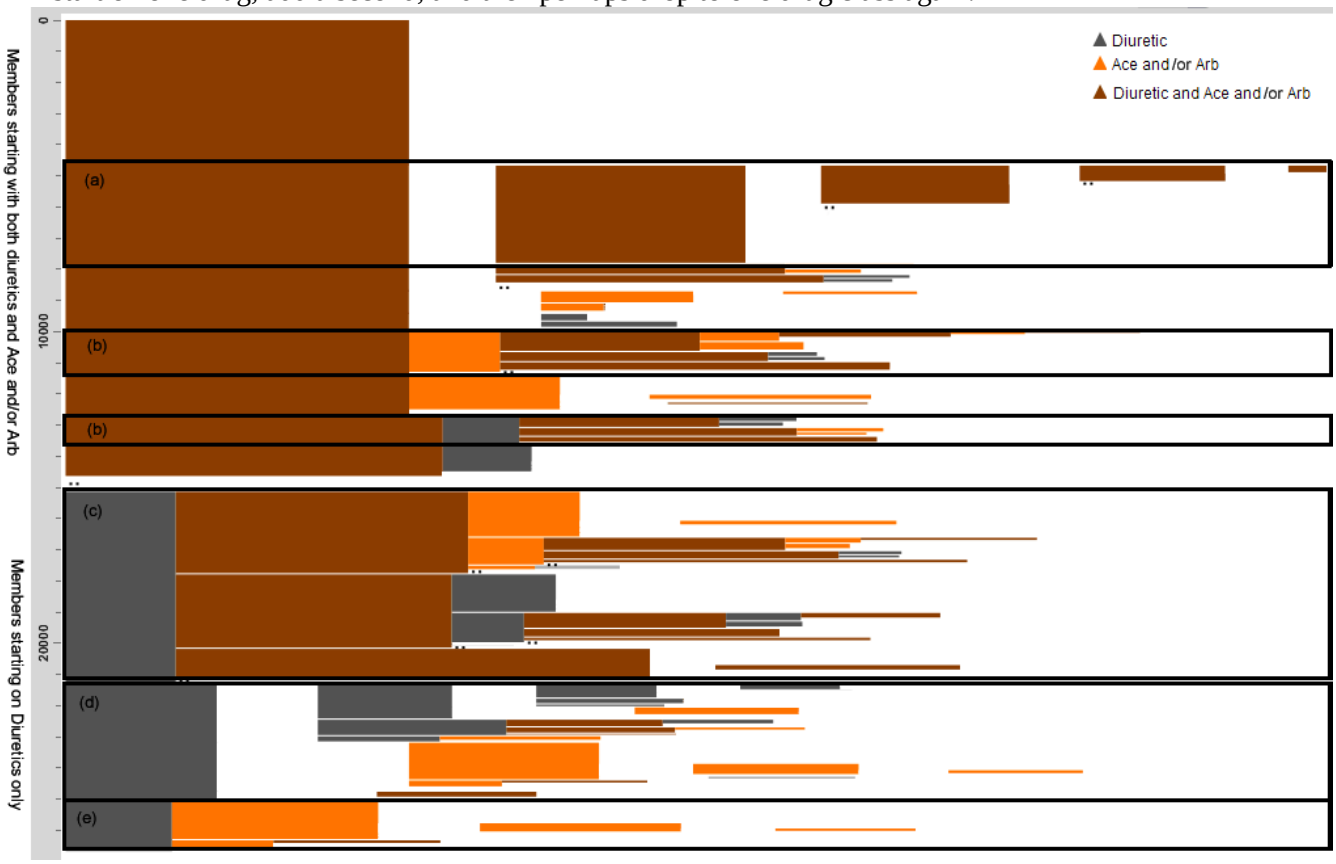

Figure A-3: Members who start on Diuretics and also take Angiotensin II receptor blockers and/or ACE inhibitors. We note five prescription patterns in the figure. Pattern (a) indicates repeating concurrent use of Diuretics; pattern (b) indicates concurrent use followed by a period of single-drug use followed by concurrent use again. Patterns (c)–(e) indicate the use of Diuretics only, followed by concurrent use (c), followed by a gap (d), or followed by a switch to ACE-I/ARB. In the figure, Ace refers to ACE inhibitors and Arb to Angiotensin II receptor blockers.

Appendix B – Visual Analytics and Sensitivity Analysis

B.1 The Allowable Gap

As the allowable gap parameter increases, we ignore short gaps in coverage and more prescriptions are merged together, therefore increasing the length of a continuous coverage period.

Figure B-1 demonstrates the effect of the allowable gap parameter using data from members who take Diuretics only. In the Figure the black bars refer to Diuretics use, while the light grey color represents gaps in treatment. In each panel of the figure, the width of black bars refers to the average length of each treatment episode (continuous coverage); the width of the light grey bars represents the average duration of gaps. The y-axis represents the number of members. As an example we have identified two patterns in the lower left panel. The rectangle labeled (a) identifies members who only have a single treatment episode. From the height of the rectangle we note that this applies to more than half the members. The rectangle labeled (b) in the lower left panel identifies members who have two treatment episodes with a gap in between.

As we compare the panel corresponding to an allowable gap of 0 days with the panels corresponding to longer allowable gaps, we note that the width of the bars increases as a function of the allowable gap parameter, indicating the increase in the length of the continuous coverage period. We also note that as the allowable gap increases, the overall patterns simplify as an increasing number of small coverage gaps are merged with drug use, and patterns of multiple gaps common when the allowable gap is 0 become uncommon. We observe fewer gaps and an increasing number of members with continuous coverage.

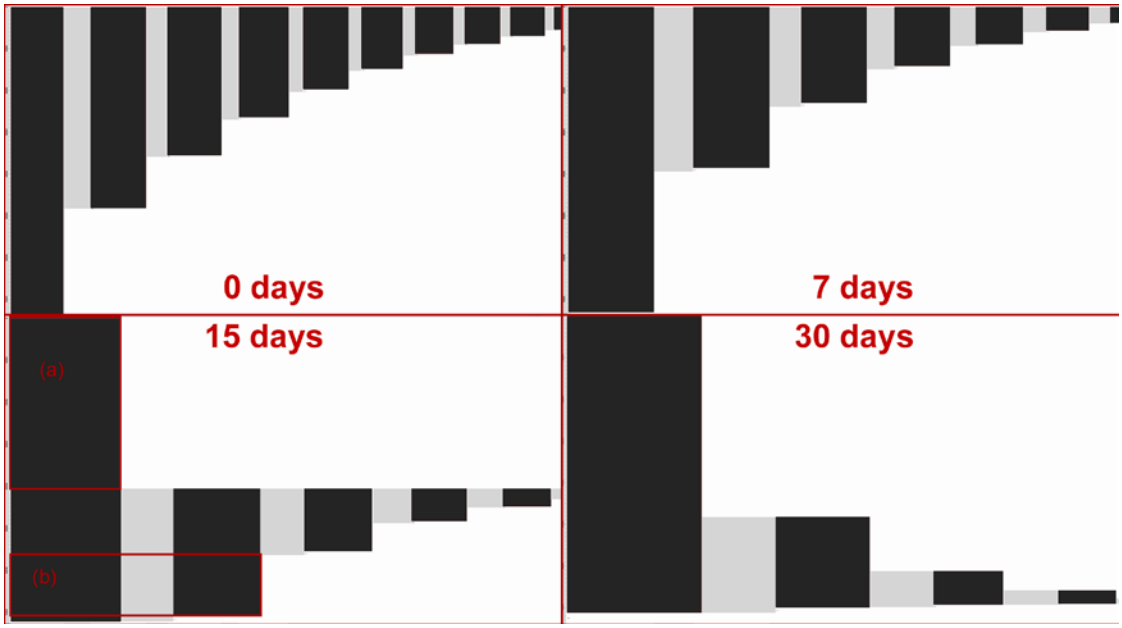

Figure B-1: Sensitivity analysis of the allowable gap for members on Diuretics only. Top: no gap replacement (left), 7-day gaps removed (right). Bottom: 15 days (left), 30 days (right). Even a simple visual comparison reveals the strong effect of gap removal on the overall patterns

B.2 The Single-Drug Overlap

The single-drug overlap parameter defines how overlapping prescriptions of the same drug class are treated. If a prescription overlap is less than or equal to the single-drug overlap parameter, the overlap

was appended to the duration of the drug, otherwise the second prescription is considered a replacement and the overlap was merged without appending.

Figure B-2 demonstrates the effect on members that only have prescriptions for Diuretics when this parameter varies between 0 and 30 days. In the Figure the black bars refer to Diuretics use, while the light grey color represents gaps in treatment. For each panel, the y-axis represents the number of members. As an example, in the upper left panel, representing the single-drug overlap parameter at 0 days, we note that more than half of the members only have a single treatment episode (noted as pattern (a) in the figure). The second most common pattern is a treatment episode, followed by a gap, then followed by a second and last treatment episode (noted as pattern (b) in the figure).

As is evident from the figure, the effects of varying the single-drug overlap parameter are minimal, as all the panels look (almost) identical.

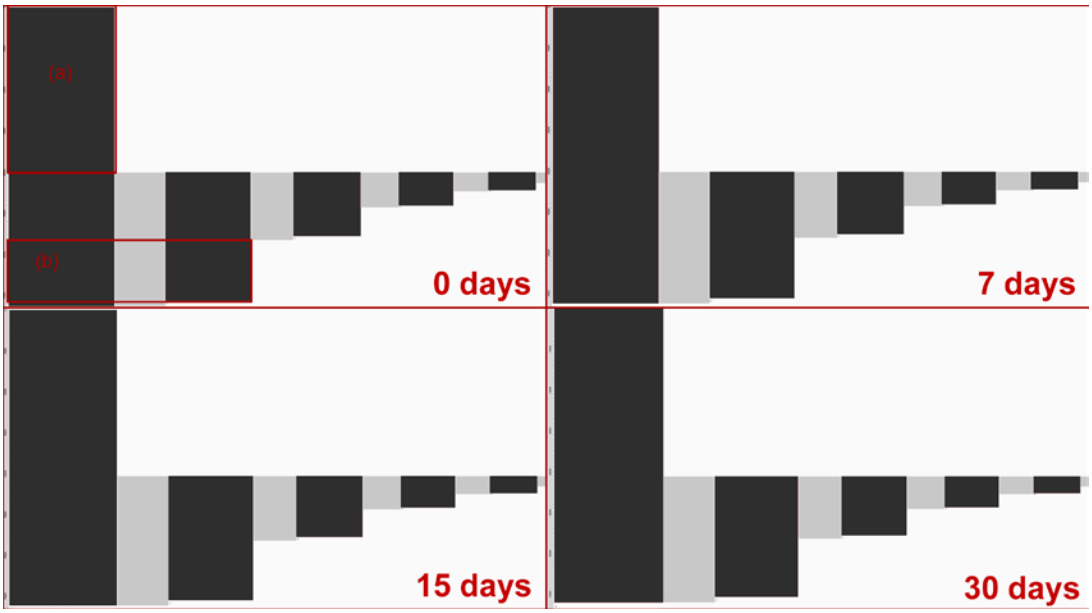

Figure B-2: Sensitivity analysis of single-drug overlap for members on Diuretics only. Top: the single-drug overlap set to 0 days (left), 7 days (right). Bottom: the single-drug overlap set to 15 days (left), 30 days (right). The allowable gap is kept constant at 15 days. Pattern (a) in the top left panel identifies members who have a single treatment episode. Pattern (b) in the top left panel identifies members who have two treatment episodes with a gap in between.

B.3 The Multi-Drug Overlap

The multi-drug parameter affects how we distinguish between those switching medications and those with concurrent use. When the parameter is set at 0, any overlap in medication is considered concurrent use; in contrast, when the parameter is set at 30 days, only overlap of more than 30 days is considered concurrent use. We analyze the multi-drug overlap parameter using the population whose first prescription in our dataset is for Diuretics, alone or in combination with ACE-I and/or ARB. All members have at least one prescription for a Diuretic and one prescription for ACE-I and/or ARB (and no prescriptions for either Beta or CCB).

Figure B-3 contrasts the patterns of the same population when the multi-drug overlap is set at 0 days and when it is set at 30 days. In the Figure, the brown color represents concurrent use, the dark grey represents Diuretics only and the orange color represents ACE-I/ARB use only. We note that the number of members identified who start with concurrent use is smaller when the multi-drug overlap is 30 days, as indicated by the height of the brown bar identified as the rectangle labeled (a). We further note the

difference in the height of the concurrent use bar following an initial treatment with Diuretics only, identified by the rectangle labeled (b). The difference in the height of the rectangles represents members who are identified as switchers when the multi-drug overlap is set to 30 days, as opposed to members who start on Diuretics, then have concurrent use for a short period of time followed by treatment with ACE-I/ARB only. As we increase the multi-drug overlap parameter, we observe an increase in switchers and in members who have an initial episode of one drug class followed by use of the same drug class (identified by the rectangle labeled (c) in the Figure).

More specifically, varying the parameter for multi-drug overlap affects the patterns of 17% of the population. Of those, close to 20% become switchers: that is, instead of (part of) their pattern appearing as a period of Diuretic use, followed by concurrent use of both Diuretics and ACE/ARB, finally followed by use of ACE/ARB only, their pattern appears as a period of Diuretics only followed by a period of ACE/ARB only. Close to 30% become continuous Diuretic users: their patterns change from a period of Diuretics only, followed by a short period of concurrent use, followed by another period of Diuretics only, to a single continuous use of Diuretics. Finally, close to 50% of those whose first pattern is affected by the change are those with a single concurrent prescription of 30 days or less, either as their last event or followed by a gap, which is then followed by a single prescription of one of drug class.

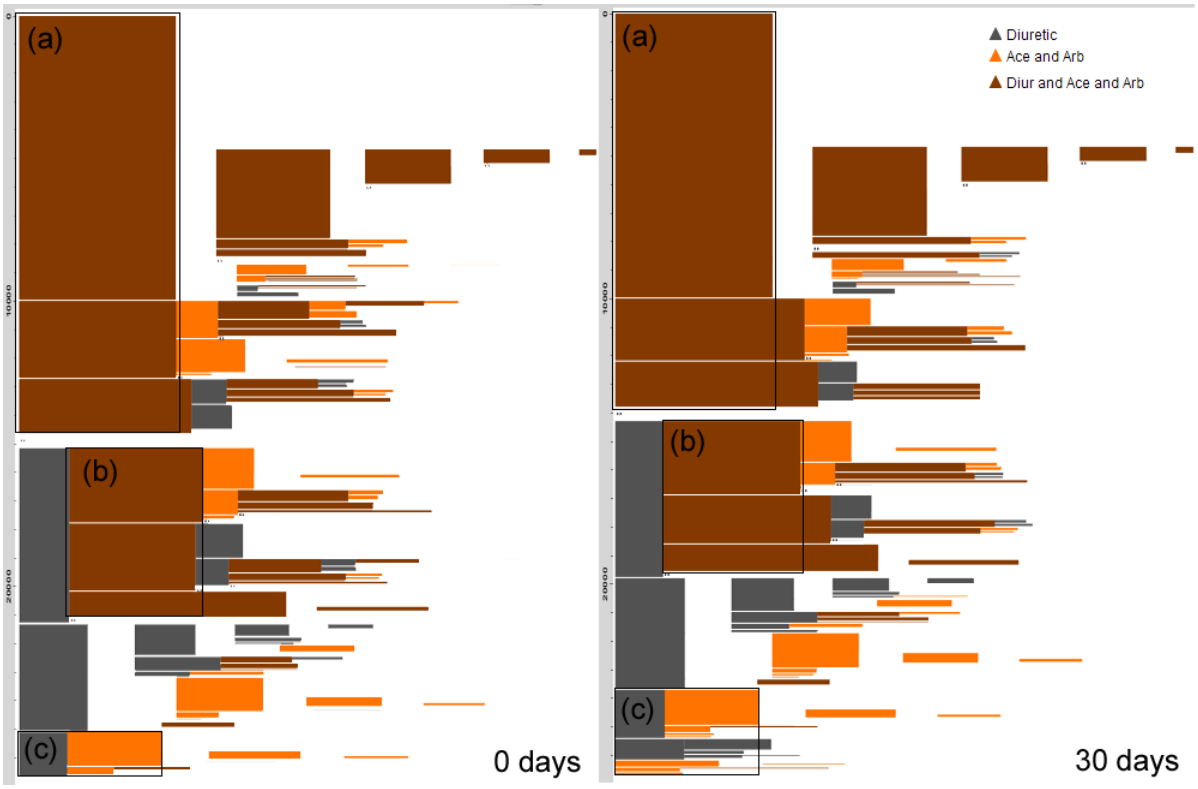

Figure B-3: Sensitivity analysis of multi-drug overlap. The allowable gap is kept constant at 15 days and the single-drug overlap at 0 days. The panel on the left is the case when the multi-drug overlap is set at 0, and the panel on the right is the case when the multi-drug overlap is set at 30 days. Ace refers to ACE inhibitors, Arb to Angiotensin II receptor blockers, and Diur to Diuretics. The height of pattern (a) represents the number of members identified to start with concurrent use, the height of the pattern identified by (b) represents the number of members who start on Diuretics followed by concurrent use, and the height of the pattern identified by (c) represents the number of members who are identified as switchers, or who, after applying the multi-drug overlap of 30 days, are identified as starting and staying on a single class.