TITLE PAGE

Title of project:

Measuring adherence trends among patients taking a 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitor

Course title: PHPR 862

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ABSTRACT

Specific Aims: There are three specific aims for this project. 1) Determine if PDC rates in patients taking a statin medication differ between male and female patients. 2) Determine if PDC rates in patients taking a statin medication differ between patients with only one chronic condition versus those with more than one chronic condition. 3) Determine if PDC rates in patients taking a statin medication differ between type of statin therapy. Our working hypothesis for all three hypotheses is that there is a statistically significant difference between groups.

Purpose: How many of your patients are not adherent to their statin regimen? Patients who are nonadherent to their 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitor therapy (statin) are at increased risk of uncontrolled cholesterol levels, cardiovascular events, and mortality. As patients are diagnosed with more disease states they are likely to be prescribed more medications for treatment. The study objective was to evaluate how the number of comorbidities affect medication adherence, measured via the Proportion of Days Covered. Additional analyses were conducted for adherence based on patient gender and by type of HMG-CoA reductase inhibitor.

Methods: Data was originally collected by SinfoníaRx, a medication management technology and service company, as part of an internal quality improvement project. For this retrospective review, the data were deidentified by SinfoníaRx staff prior to providing it to the researchers. Variables in the de-identified data set included patient age, patient gender, Proportion of Days Covered, the number of chronic conditions for each patient, and the specific 3-hydroxy-3-methylglutaryl-coenzyme A reductase drug the patient was taking. Separate data sets were then created from the original data by filtering patients by gender, number of comorbidities, and specific drug. The gender analysis consisted of two groups (male and female) and a t-test was performed to analyze the average Proportion of Days Covered between the groups. An analysis of variance was performed to analyze the average Proportion of Days Covered. A Bonferonni post-hoc analysis was performed to measure significance between the groups.

Results: A total of 55,345 patients were included in the analysis. Patients with multiple comorbidities were significantly more adherent according to their average Proportion of Days Covered (expressed as a percent) as follows: 0- (58.8%, P = <0.01), 1- (63.4%, P = <0.01), and 2-4- comorbidities (68.1%, P = <0.01). Men's adherence rates were 68.13% and women's adherent rates were 67.65%. Atorvastatin and the ezetimibe/simvastatin combination medications had significantly better adherence when compared individually to the other drugs included in the analysis.

Conclusion: This study suggests that patients with more chronic conditions were more adherent to their medications than those with fewer or no chronic conditions. However, even the most adherent patients in this study still had Proportion of Days Covered values well below the recommended threshold. Future research is warranted to facilitate designing adherence program materials to help patients with fewer chronic conditions improve adherence to prescribed regimens.

Measuring adherence trends among patients taking a 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitor

INTRODUCTION

Adherence rates with regards to 3-hydroxy-3-methylglutaryl-coenzyme-A (HMG-CoA) reductase inhibitors, or statins, play an important part in medication therapy management. Statins are integrated in in numerous national guidelines, such as the American Heart Association ST-elevated Myocardial Infarction (STEMI) guidelines.[1]. For their full lipid lowering effect, patients need to be adherent to their prescription. Adherence is commonly calculated as proportion of days covered (PDC). According to the Pharmacy Quality Alliance (PQA), PDC is defined as, "the proportion of days in the measurement period covered by prescription claims for the same medication or another in its therapeutic category".[2]

Medication adherence affects all patients taking prescription medications, however, there is a deficit in literature that demonstrates the relationship between the number of chronic conditions and its effects on PDC rates in patients taking statin medications. Other trends that are lacking in literature include difference in adherence between genders as well as differences between varying statin drugs. If there are significant differences, medication therapy management companies can use this information to develop predictive analytic tools. This study is specifically focusing on adherence with statins. With hundreds of drug classes on the market today, this study could be repeated with anti-hypertensives, diabetes medications, and beyond.

This project will determine which patient populations have statistically significant lower PDC rates. By identifying these trends, it can serve as a predictive analytic tool. The outcome findings can be applied to achieve client specific PDC goals and improve call center efficiencies, all the while improving patient specific outcomes.[3]

METHODS

This study was a retrospective descriptive study looking at adherence trends of patients prescribed 3-hydroxy-3-methylgluatryl-coenzyme A reductase inhibitor medications. Patient data was retrospectively collected by SinfoniaRx as part of an internal quality improvement project. The data set for each patient included their gender (male or female), their number of chronic conditions, the type of 3-hydroxy-3-methylglutaryl-coenzyme-A reductase inhibitor they were taking, and their PDC value.

Data Collection The sample contained primarily patients with Medicare.[3] Although, cash claims were also included.

Data analysis There were three data sets that went through data analysis. The first was the data filtered between the male and female patients. As it was only two group data comparison, the groups were put through a t-Test: Two-Sample Assuming Equal Variances. The second set of data was three groups divided into 0 Chronic Conditions (A), 1 Chronic Condition (B), 2,3, 4 Chronic conditions (C). The three groups in the second set of data were put through ANOVA and then post hoc analysis was completed by Bonferroni, Holm, and Tukey statistical tests. The third data set was divided up by type of statin, there were 10 different groups. At first, they were all put through ANOVA and then post hoc analysis was completed by Bonferroni and Holm statistical tests.

RESULTS

Table 2 shows the results of the gender analysis. Significance was found in the difference between the two gender groups as demonstrated by a p-value > 0.05.

The groups used in the comorbidity analysis are seen described in table 3, where an ANOVA analysis was performed on the three treatment groups. The p-value corresponding to the F-statistic of one-way ANOVA is lower than 0.05, suggesting that the one or more treatments are significantly different. We then moved onto the Tukey HSD and Bonferroni and Holm table post-hoc tests that would identify which of the pairs of treatments are significantly different from each other. We present below color coded table results for the Tukey results (table 5), and Bonferroni and Holm table (table 6) (red for insignificant, green for significant) of evaluating whether $Qi,j>Qcritical$Qi,j>Qcritical for all relevant pairs of treatments. In this first combined Bonferroni and Holm table below, we consider all possible contrasts (pairs) for simultaneous comparison, thus qq=3. In both tests, all outcomes were significant.[3,4]

Table 7 shows the results of the type of drug analysis. The p-value corresponding to the F-statistic of one-way ANOVA is lower than 0.05, suggesting that the one or more treatments are significantly different. We then performed a Bonferroni and Holm multiple comparison test as shown below in table 9. These post-hoc tests would likely identify which of the pairs of treatments are significantly different from each other. In this first combined Bonferroni and Holm table below, we consider all possible contrasts (pairs) for simultaneous comparison, thus qq=45. The Bonferroni and Holm p-values of the observed TT-statistic Ti,jTi,j for all relevant qq=45 pairs of

treatments is shown below, along with color coded Bonferroni and Holm inferences (red for insignificant, green for significant) based on the p-value. As shown on the table many pairs drop out of significance in the post hoc test.

DISCUSSION

Male patients were more adherent than female patients. While the difference in adherence were only slightly above 0.5%, this was a significant difference as confirmed by the paired t-test. There were unlimited possibilities as to why men may be more adherent than women, but for medication management companies this could be an area of interest when directing outreach.[2] Patients with multiple comorbidities were more adherent to their statin medication than patients with fewer comorbidities (0 or 1). Tables 3 through 6 describe the data for these patients and it is shown that patients with two or more chronic conditions are almost 5% more adherent than patients with only one. The main reason for this is potentially that with more chronic conditions patients understand the importance of staying adherent to their medications. When comparing different statin medication adherence there once again was significant differences between groups. Running a Bonferroni post-hoc analysis determined what groups are significant between one another.[6] This data can be seen in Table 9; comparisons highlighted in green are significant while those in red are insignificant. For example, patients on one statin medication may have experienced more myopathy than another Statin and therefore were less adherent to that specific statin. Regardless of the reasons for any of the differences between groups, adherence rates can still be improved. Medication management companies can use the data from this study to determine specific populations that may be more at risk of being non-adherent.

This study was significant in the sense that there are not many other studies of this nature that have been completed. With the significant findings of this study, there is potential to find more significant data in other therapeutic classes. For example, this study could be repeated with different classes of hypertension medications to see if males or females are more adherent. There is still a lot of research to be done to fully analyze these adherence trends.[5,6]

There are some limitations to the study. Primarily, the data (while containing a large sample size) is still only a small fraction of the total number of patients in the U.S. who are taking a statin. The results of the study are therefore a generalization of the entire population. Secondly, the patient sample provided was a convenience sample of community pharmacy data. It was also mostly consisting of Medicare patients, with some cash claims

included as well. Each patient's level of insurance not being provided, as well as the payer type, can be considered limitations of this study.

CONCLUSIONS

This study showed that there were significant differences in adherence rates of patients taking statin medications. Males showed to be more adherent than females, while those with more than one chronic condition showed to be more adherent than those with only one. The type of statin drug was also shown to have significant differences in adherence rates when comparing statins against one another. Future research is warranted to determine if different medication classes show similar trends in adherence or if they differ and in regard to which variable.

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TABLES AND FIGURES

TABLE 1- Descriptive Statistics of the whole set of data

	PDC
Mean	67.8618303
Standard Error	0.08082826
Median	69
Mode	100
Standard Deviation	19.015266
Sample Variance	361.580341
Kurtosis	-0.3625336
Skewness	-0.1985359
Range	92
Minimum	8
Maximum	100
Sum	3755813
Count	55345

Table 2: t-Test: Two-Sample Assuming Equal Variances, a comparison of the two genders

	Male	*Female*
Mean PDC (%)	68.1348366	67.6501684
Variance	356.697156	365.275253
Observations	24170	31175
Pooled Variance	361.529088	
Hypothesized Mean Difference	0	
df	55345	
t Stat	2.9742347	
P(T<=t) one-tail	0.00146923	
t Critical one-tail	1.64488116	
P(T<=t) two-tail	0.00293847	
t Critical two-tail	1.96000685	

Table 3: Descriptive Statistics on Three groups: 0 Chronic Conditions (A), 1 Chronic Condition (B), 2,3, 4 Chronic conditions (C)

Treatment →	A	B	C	Pooled Total
observations N	881	1350	53114	55345
sum ∑*xi*∑xi	51,844.0000	85,572.0000	3,618,397.0000	3,755,813.0000
mean *x*¯x¯ PDC (%)	58.8468	63.3867	68.1251	67.8618
sum of squares ∑*x*2*i*∑xi2	3,449,886.0000	5,934,530.0000	265,503,231.0000	274,887,647.0000
sample variance *s*2s2	453.4481	378.3589	357.7193	361.5803
sample std. dev. *ss*	21.2943	19.4514	18.9135	19.0153
std. dev. of mean *SEx*¯SEx¯	0.7174	0.5294	0.0821	0.0808

Table 4: ANOVA Single Factor on Three groups: 0 Chronic Conditions (A), 1 Chronic Condition (B), 2,3,or 4 Chronic conditions (C)

source	sum of squares SS	degrees of freedom *νν*	mean square MS	F statistic	p-value
treatment	102,318.2877	2	51,159.1438	142.2096	1.1102e-16
error	19,908,984.1289	55342	359.7446		
total	20,011,302.4166	55344			

Table 5: Post Hoc Analysis of Chronic Condition Groups, Tukey HSD results

treatments pair	Tukey HSD Q statistic	Tukey HSD p-value	Tukey HSD inferfence
A vs B	7.8157	0.0010053	** p<0.01

treatments pair	Tukey HSD Q statistic	Tukey HSD p-value	Tukey HSD inferfence
A vs C	20.3659	0.0010053	** p<0.01
B vs C	12.8195	0.0010053	** p<0.01

Table 6: Post Hoc Analysis, Bonferroni and Holm results: all Chronic Condition pairs simultaneously compared

treatments pair	Bonferroni and Holm *T*T-statistic	Bonferroni p-value	Bonferroni inferfence	Holm p-value	Holm inferfence
A vs B	5.5266	9.8415e-08	** p<0.01	3.2805e-08	** p<0.01
A vs C	14.4009	0.0000e+00	** p<0.01	0.0000e+00	** p<0.01
B vs C	9.0647	0.0000e+00	** p<0.01	0.0000e+00	** p<0.01

Table 7: Descriptive Statistics on the 10 different statin groups

Group A: Atorvorvastatin/amlodipine-atorvastatin, **B:** Crestor **C:** Ezetimibe/simvastatin **D:** Fluvastatin, **E:** Livalo, **F:** Lovastatin, **G:** Pravastatin, **H:** Rosuvastatin, **I:** Simvastatin **J:** Vytorin

Treatment →	A	B	C	D	E	F	G	H	I	J	Pooled Total
observations N	25011	55	78	6	153	3286	8504	6846	11372	31	55342
sum ∑*xi*∑xi	1,677,077.0000	3,969.0000	5,962.0000	421.0000	10,218.0000	237,338.0000	579,464.0000	453,355.0000	785,556.0000	2,172.0000	3,755,532.0000
mean $\bar{x}\bar{x}$ PDC (%)	67.0536	72.1636	76.4359	70.1667	66.7843	72.2270	68.1402	66.2219	69.0781	70.0645	67.8604

Treatment →	A	B	C	D	E	F	G	H	I	J	Pooled Total
sum of squares $\sum x2i\sum$ xi2	121,271,191.0000	322,835.0000	488,954.0000	30,549.0000	773,038.0000	18,338,632.0000	42,578,112.0000	32,762,273.0000	58,121,436.0000	174,066.0000	274,861,086.0000
sample variance $s2s2$	352.5462	674.3987	431.7296	201.7667	596.2887	364.2054	363.7936	400.3290	339.1725	729.5290	361.5595
sample std. dev. ss	18.7762	25.9692	20.7781	14.2045	24.4190	19.0842	19.0734	20.0082	18.4166	27.0098	19.0147
std. dev. of mean SEx^- SE x^-	0.1187	3.5017	2.3527	5.7989	1.9742	0.3329	0.2068	0.2418	0.1727	4.8511	0.0808

Table 8: One-way ANOVA of kk=10 independent Statin treatments:

source	sum of squares SS	degrees of freedom $\nu\nu$	mean square MS	F statistic	p-value
treatment	121,958.2921	9	13,550.9213	37.7028	1.1102e-16
error	19,887,105.6808	55332	359.4142		
total	20,009,063.9729	55341			

Table 9: Bonferroni and Holm Post Hoc Analysis:

treatments pair	Bonferroni and Holm *TT* - statistic	Bonferroni p-value	Bonferroni inferfence	Holm p-value	Holm inferfence
A vs B	1.9968	2.0633722	insignificant	1.2838760	insignificant
A vs C	4.3640	0.0005757	** p<0.01	0.0004606	** p<0.01
A vs D	0.4022	30.9399768	insignificant	6.8755504	insignificant
A vs E	0.1751	38.7434532	insignificant	3.4438625	insignificant
A vs F	14.7066	0.0000e+00	** p<0.01	0.0000e+00	** p<0.01
A vs G	4.5659	0.0002243	** p<0.01	0.0001844	** p<0.01
A vs H	3.2162	0.0584812	insignificant	0.0389874	* p<0.05
A vs I	9.4418	0.0000e+00	** p<0.01	0.0000e+00	** p<0.01
A vs J	0.8837	16.9582240	insignificant	7.1601390	insignificant
B vs C	1.2799	9.0269634	insignificant	4.4131821	insignificant
B vs D	0.2450	36.2905835	insignificant	4.0322871	insignificant
B vs E	1.8048	3.2001223	insignificant	1.8489595	insignificant
B vs F	0.0246	44.1171460	insignificant	1.9607620	insignificant
B vs G	1.5689	5.2508786	insignificant	2.8004686	insignificant
B vs H	2.3151	0.9276156	insignificant	0.5977967	insignificant
B vs I	1.2041	10.2847315	insignificant	4.7995414	insignificant
B vs J	0.4930	27.9904467	insignificant	7.4641191	insignificant
C vs D	0.7805	19.5782125	insignificant	6.9611422	insignificant
C vs E	3.6592	0.0113950	* p<0.05	0.0086096	** p<0.01
C vs F	1.9379	2.3690675	insignificant	1.4214405	insignificant
C vs G	3.8470	0.0053869	** p<0.01	0.0041898	** p<0.01

C vs H	4.7314	0.0001006	** p<0.01	8.4956e-05	** p<0.01
C vs I	3.4160	0.0286204	* p<0.05	0.0197163	* p<0.05
C vs J	1.5829	5.1053456	insignificant	2.8363031	insignificant
D vs E	0.4287	30.0667489	insignificant	7.3496497	insignificant
D vs F	0.2660	35.5620244	insignificant	5.5318705	insignificant
D vs G	0.2617	35.7085125	insignificant	4.7611350	insignificant
D vs H	0.5095	27.4693943	insignificant	7.9356028	insignificant
D vs I	0.1406	39.9679468	insignificant	2.6645298	insignificant
D vs J	0.0121	44.5662508	insignificant	0.9903611	insignificant
E vs F	3.4712	0.0233330	* p<0.05	0.0171109	* p<0.05
E vs G	0.8768	17.1275054	insignificant	6.4703909	insignificant
E vs H	0.3629	32.2497485	insignificant	6.4499497	insignificant
E vs I	1.4866	6.1705832	insignificant	3.1538536	insignificant
E vs J	0.8785	17.0864722	insignificant	6.8345889	insignificant
F vs G	10.4949	0.0000e+00	** p<0.01	0.0000e+00	** p<0.01
F vs H	14.9255	0.0000e+00	** p<0.01	0.0000e+00	** p<0.01
F vs I	8.3865	0.0000e+00	** p<0.01	0.0000e+00	** p<0.01
F vs J	0.6321	23.7288960	insignificant	7.9096320	insignificant
G vs H	6.2315	2.0940e-08	** p<0.01	1.8148e-08	** p<0.01
G vs I	3.4509	0.0251611	* p<0.05	0.0178924	* p<0.05
G vs J	0.5641	25.7701671	insignificant	8.0173853	insignificant
H vs I	9.8487	0.0000e+00	** p<0.01	0.0000e+00	** p<0.01
H vs J	1.1260	11.7080193	insignificant	5.2035641	insignificant
I vs J	0.2893	34.7556563	insignificant	6.1787833	insignificant

APPENDICES

Appendix A:

- No IRB was required for this project because no human subjects were used.

Commented [RL1]: I believe Dr. Slack wants us to keep Appendices in the document even though we don't refer to them at all. I could be wrong – easy to delete if unnecessary.

Appendix B:

- Data Dictionary:
    - For the data collection tool, the following variables will be typed into the data collection tool at Sinfonia Rx :
        - Gender
        - # Conditions
        - Statin (type of statin)
        - PDC
        - Age
    - From here an excel spreadsheet will be generated with all these variables listed.