Detecting Associations between Major Depressive Disorder Treatment and Essential Hypertension using Electronic Health Records

Jyotishman Pathak, PhD 1 Gyorgy Simon, PhD 2 Dingcheng Li, PhD 1 Joanna M. Biernacka, PhD 1 Gregory J. Jenkins, MS 1 Christopher G. Chute, MD,DrPH 1 Daniel K. Hall-Flavin, MD 1 Richard M. Weinshilboum, MD 1

1Mayo Clinic, Rochester, MN 2University of Minnesota, Twin Cities, MN

Abstract
In this observational study, we investigate the correlation between depression and hypertension on a cohort of patients treated for major depressive disorder using Selective Serotonin Reuptake Inhibitors (SSRIs) and assess the effect of depression treatment on the diagnoses and treatment for essential hypertension. Our results indicate that the positive effect of successful depression treatment can be discovered and estimated from electronic health record (EHR) data even for a small sample size. We have also successfully detected differences in the effect of depression treatment in hypertensive patients between the two phenotypes representing successful treatment outcomes—response and remission—concluding that achieving remission has a longer lasting effect than response.

1. Introduction
It is well known that among high utilizers of medical care, a process for systematic identification and treatment of depression is often regarded as the cornerstone to significant and sustained improvements in clinical outcomes, and potentially reducing healthcare related costs. Several efforts 1,2 have explored this within the context of collaborative care management for patients with depression and chronic illnesses, and the early results demonstrate promise in the integration of interventions in real-world practices. However, these studies have been conducted in a controlled clinical trial environment, and the evidence remains preliminary with regard to the effectiveness of collaborative care in primary care settings and the bi-directional impact on treatment for depression and cardiovascular diseases 3.

To address this critical gap, we conducted an electronic health record (EHR) data-driven observational study on patients who had essential hypertension and major depressive disorder (MDD), and subsequently treated with selective serotonin reuptake inhibitors (SSRIs) to analyze the effect of treated hypertension on treatment response to MDD. In particular, we included the patient cohort (N=794) that was enrolled as part of an 8-week outpatient SSRI clinical trial within the Mayo Clinic Pharmacogenomics Research Network Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS; ClinicalTrials.gov number: NCT00613470), and applied structured data as well as natural language processing (NLP) queries to retrospectively extract vital signs, medications, diagnoses, smoking status and other co-morbidities for hypertension from the patient EHRs. We developed a linear mixed effect model to associate the success of depression treatment with improvement in hypertension control, and our results indicate that the positive effect of successful depression treatment can be discovered and estimated from EHR data even for a small patient cohort (N=135 with hypertension out of 794 depressed patients). We have also successfully detected differences in the effect of depression treatment in hypertensive patients between the two phenotypes representing successful treatment outcomes—response and remission—arriving at the conclusion that achieving remission has a longer lasting positive effect on treated hypertension than response. We acknowledge these findings are preliminary and provide an early insight in associating MDD treatment response with essential hypertension, but nonetheless demonstrate the applicability of secondary use of EHR data for answering an important question that has significant implications in improved patient outcomes and reducing the healthcare burden.

2. Background
2.1 Major Depressive Disorder and Hypertension
Depression is a risk factor for hypertension 4,5, and studies have shown an association with poor compliance with anti-hypertensive treatment regimens. However, studies investigating the association between high blood pressure (BP) and psychopathology have not produced consistent results, primarily for two major classes of psychiatric ailments: MDD and anxiety. Some have shown increased BP among patients with depression 6, whereas others have found no association 7, and even in some cases, a decrease in the BP measurements for depressed patients 8. A possible explanation for this lack of consensus could be that antidepressant use confounds the relationship between psychopathology and BP. For example, antidepressants such as Venlafaxine increase adrenergic activity which leads to higher BP. Similarly, Serotonin (5HT) can cause constriction or dilatation in various vascular systems. In a prospective study of patients treated with antidepressants 9, those who took an SSRI had a 78% increased chance of being prescribed blood pressure medication compared with those who did not. In addition, several clinical trials 10,11 have tried to shed more light on the effect of SSRIs on hypertension. While the findings are still inconclusive and inconsistent—few show an increase in BP and others demonstrate the converse.
Further, apart from the TrueBlue study by Morgan and colleagues, to our knowledge, none of them have investigated this within a primary care setting either prospectively or retrospectively leveraging patient data from EHR systems. The focus of our study is the latter, and in particular, investigating the correlation between essential hypertension and treatment response to SSRIs for patients diagnosed with MDD using data from EHRs.

2.2 Mayo Clinic Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS)

The Mayo Clinic Pharmacogenomic Research Network Antidepressant Medication Pharmacogenomic Study (PGRN-AMPS) is an NIH funded study that is investigating the pharmacogenetics of SSRI treatment response to MDD. The study was designed as an 8-week outpatient SSRI clinical trial performed at the Mayo Clinic in Rochester, MN, USA. Patients enrolled in the study met diagnostic criteria for MDD without psychosis or mania and had a 17-item Hamilton Depression Rating Scale (HAMD-17) score &ge;14. The study was designed with inclusion and exclusion criteria similar to those used in the Sequenced Treatment Alternatives to Relieve Depression study (STAR*D). Specifically, potential study subjects taking an antidepressant, antipsychotic or mood-stabilizing medication were excluded. Patients with MDD initially received either 10 mg of escitalopram or 20 mg of citalopram. SSRI efficacy and treatment response was determined using the 16-item Quick Inventory of Depressive Symptomatology (QIDS-C16) scores after 4-weeks and then 8-weeks of SSRI therapy. The patients were further followed up by the study team at 24 weeks. At 4-weeks after the initiation of treatment, the dose could be increased to 20 mg of escitalopram or 40 mg of citalopram after a clinical assessment of the subject. All patients provided written informed consent. The study protocol was approved by the Mayo Clinic Institutional Review Board. The two primary outcomes that we investigate in this study are “response” (defined as ≥ 50% reduction in QIDS-C16 score from baseline to the last visit) and “remission” (defined as a QIDS-C16 score of ≤ 5 at the last visit). For both outcomes, we do separate analysis using linear mixed modelling for building predictive classifiers.

3. Materials and Methods

3.1 Cohort and dataset description

The PGRN-AMPS cohort is comprised of 794 Mayo Clinic patients (see Table 1). The study population contained more females (62%) than males (38%), and was overall younger with only 21% above the age of 51 at the time of enrollment. For all study participants, baseline, 4-weeks, and 8-weeks HAMD-17 and QIDS-C16 scores were recorded. At each visit, if the QIDS-C16 score was ≤5, indicating remission, the dose would be maintained. If the score was between 6 and 8, a clinical decision was made to either maintain or increase the dose. A QIDS-C16 score of ≥9 would lead to a dose increase unless contraindicated. The specific dosing information along with the depression scores were adequately captured in the PGRN-AMPS dataset. In addition to the information collected as part of the trial, we retrospectively applied structured data and NLP queries using cTAKES for extracting vital signs (including systolic and diastolic BP measurements), medications, diagnoses, signs and symptoms, and smoking status from the patients’ EHR at Mayo Clinic.

3.2 Predictive modeling and classification

The data studies the longitudinal trends (defined as an increase or decrease over time) in BP measurements in essential hypertension for a number of patients (N=135) treated for depression whose antidepressant treatment outcomes can be grouped into either remission or response. In our EHR data, multiple observations exist for these patients both “before” and “after” the trial. We assume that trends before the trial (“pre-trial trends”) are common across all patients regardless of depression outcome, but after the beginning of the trial, the trends (“post-trial trends”) may change. We capture the patient’s pre-trial trends in a predictive model that we call the “pre-trial trend model”. The pre-trial trend model is a linear mixed effect model clustered by patient (random effect) that predicts the BP measurements based on two fixed effects: time (relative to the beginning of the trial) and depression outcome for treatment response. With hypertension being a chronic disease (most likely under control), we consider 3 years as a relatively short period of time. We built our pre-trial model on data observed during the 1.5 year period preceding the beginning of the trial and make predictions using the model for time periods ranging between 6 months and 3 years after the beginning of the trial. Since the mechanism underlying the depression outcome can also affect the BP measurements, we included the depression outcome as a fixed effect. This setup allows for each patient to have his own baseline BP measurement and an effect based on his depression treatment outcome.
Once the pre-trial trend model is developed, we use it to make a prediction for BP measurements within a certain window (of at most 3 years after the beginning of the trial). We compare this predicted measurement with the observed result from patient’s EHR data. The residual (difference) is in part noise, and in part, a systematic bias that stems from the pre-trial trend model’s inability to correctly model the post-trial trend. Since we attribute the change in the trends (from pre- to post-trial) to the depression treatment, the systematic bias quantifies the effect of the depression treatment on the BP measurements. For patients, who did not see any improvement in their depression status, this bias should be close to 0. But for patients, who saw improvement in their depression status and this improvement in depression was accompanied by an improvement in hypertension, the bias is positive. To assess the significance of the bias, we applied bootstrapping with the sampling unit being a patient (rather than the observation). In other words, we created bootstrap samples of the data set by sampling the patients with replacement and including all observations pertaining to the selected patient (possibly multiple times). We used 2000 bootstrap iterations to estimate p-values and confidence intervals.

4. Results and analysis

From the PGRN-AMPS study, we identified 135 patients with depression and essential hypertension. For these patients, we collected relevant covariates including age, gender, race, marital status, smoking status and history of obesity from the EHR data along with all blood pressure measurements. We also had these patients’ QIDS-C16 scores at baseline (beginning of the trial), 4 and 8 weeks into the trial at our disposal. As the treatment regimen could be adjusted at 4 weeks, we decided to only use the scores at baseline and at 8 weeks. We used the QIDS-C16 scores to define our depression treatment phenotypes following the PGRN study. The population is divided into three groups: patients whose depression remitted, patients who showed response (improvement) but whose depression did not remit, and patients with effectively no response. Formally, patients with a QIDS-C16 score of less than 5 at week 8 form the “remission” phenotype, patients whose QIDS-C16 score dropped by half between baseline (beginning of the trial) and 8 weeks form the “response” phenotype and the remaining patients who did not experience significant improvement are the “controls”. Based on this definition, out of 135 patients, 83 remitted, 17 responded and 35 were control patients. The remission and response phenotypes both indicate (at least partially) successful depression treatment, but we consider them separately.

Our primary clinical interest lies in the effect of depression on essential hypertension. Specifically, we aim to assess whether the SBP for patients who underwent successful treatment is lower than it would be if the treatment had been unsuccessful. To achieve this, we applied the pre-trial trend model to predict the SBP level at 180 days and also at 3 years (1080 days). The importance for these time points is as follows: At 180 days, the non-linear trends that likely exist in the data still have only negligible effect on the predictions from the pre-trial model, and hence, we can relatively accurately quantify the effect of successful depression treatment. However, 180 days is indeed a short time period and it may not be sufficient for the successful treatment to significantly impact blood pressure. At 3 years, we have sufficient time to realize any gains that the successful depression treatment may have conferred on the blood pressure. This effect may be diluted (i.e., depression may have recurred) and the pre-trial trend model may get increasingly inaccurate the further we move away from (with respect to time-periods) the beginning of the trial.

Figure 1 depicts the residuals of the control, response and remission patients for all observations obtained during a window of 180 days (in the left pane) and 1080 days (in the right pane). A time window of 180 days starts 8 weeks after the beginning of the trial and ends 180 days later. Recall that the residual is the (signed) difference between the observed SBP and the expected SBP under the assumption that the pre-trial trend continued after the beginning of the trial. This assumption is tantamount to saying that the treatment had no effect. The residuals are signed, such that they reflect improvements: positive residuals indicate that the observed SBP was lower than what we expected. There is a residual for each observation, and thus the figure presents the residuals summarized into boxplots, one boxplot for each depression treatment phenotype: control, response and remission. Comparing the median residuals (the tick horizontal lines in the middle of the three boxes) there is a substantial difference between control and response patients reflected in the window size at 180 days after the beginning of the trial, and remission is “catching up” by day 1080. This tendency may continue for beyond 1100 days (i.e., beyond 3 years from the beginning of the trial), however, we cannot ascertain this because the pre-trial model becomes increasingly invalid resulting in excessive estimation errors.

Our results in Figure 1 suggest not only that successful depression treatment affects blood pressure (and thus hypertension) beneficially, but also that a difference exists between the two phenotypes representing successful depression treatment. To further illustrate this difference, we depict the mean improvement (reduction in SBP) for the two phenotypes.
over increasingly long time windows between 180 and 1100 days (at 30 day increments). All time windows start 8 weeks after the beginning of the trial. Figure 2 depicts the mean of the residuals and their confidence interval (vertical axis) as a function of time window size (horizontal axis). For example, in case of the 180-day window, the mean of the residuals is approximately 13, meaning that on average, response patients saw SBP levels of approximately 13 mmHg less than expected. The mean as well as the confidence interval was obtained through bootstrap estimation from 2000 replications.

The left pane presents the results for response patients (Figure 2). Recall that depression treatment successfully reduced the QIDS-C16 score by half for response patients; these patients are still clinically depressed (their QIDS-C16 score still exceeds 5). Figure 2 also shows that this substantial reduction in QIDS-C16 score was accompanied with an almost immediate improvement in SBP with a lasting effect: their SBP is lower than what we would expect without successful depression treatment as long as three years after the trial. The effect is significant throughout the 1100 days. Remission patients had a baseline QIDS-C16 score of at least 7 and by week 8, it reduced to a score of 5 or below. Relative to the response patients, the reduction in QIDS-C16 score can be more modest. However, these patients are no longer clinically depressed. The effect of depression treatment in this phenotype can only be seen later. It is only after 2.5 years where the effect of this phenotype is significant. It is interesting to point out the difference between the response and remission phenotypes: for response, the effect of depression treatment on SBP is immediately noticeable, but decreases

Figure 1: The residuals (reduction in SBP) over 180 days (left pane) and 1080 days (right pane) after the beginning of the trial summarized as boxplots. Significant reduction in SBP has been achieved through successful depression treatment.

Figure 2: The mean improvement (reduction in SBP) in the Response and Remission phenotypes during windows of 180, 210, …1100 days after the beginning of the trial. This illustrates the difference in SBP response between the Response and Remission phenotypes.
over time. However, for remission, the effect of depression treatment on SBP slowly builds up over time. This could suggest that remission has a more lasting effect on SBP than response.

5. Discussion

5.1 Summary
Acknowledging that factors associated with depression such as sedentary activity or unhealthy nutrition may predispose an individual to hypertension underscores more fully the relationship between depression and hypertension and will assist in the management of both conditions. While several clinical trials in the recent past have attempted to evaluate the bidirectional relationship between depression and hypertension with appropriate real-world interventions, in this study, we illustrate the feasibility of studying such a relationship retrospectively using an ambulatory EHR on out-patients who were diagnosed with MDD, and were subsequently treated with SSRIs. We found that the positive effect of successful depression treatment can be discovered and estimated from EHR data even for a small sample size (N=135 patients diagnosed for MDD and essential hypertension). We have also successfully detected differences in the effect of depression treatment in hypertensive patients between the two phenotypes representing successful treatment (response and remission) arriving at the suggestion that achieving remission has a longer lasting effect than response.

5.2 Limitations
We took great precaution in estimating the significance of the treatment effects. We performed simulations to estimate probabilities and confidence intervals, which was necessary due to the clustered nature of the data set. However, we need to point out, that with only 7 “response” patients for hypertension, the subpopulations we worked with are very small and may not be representative of the general population. The modeling approach we took effectively eliminates (or reduces) individual variability of the patients, but we did not have sufficient sample size to estimated additional fixed effects such as age, gender, and ethnicity. Besides, contributing to the individual variability (which we largely accounted for) these factors may also influence the pre-trial trend. When the proposed approach is applied to an entire EHR, rather than a small subset of the cohort that was used in a clinical trial, these limitations are virtually eliminated. In fact, the sheer number of patients in an EHR may allow for non-linear modeling of the trends—a topic that we plan to explore in future.

5.3 Future work
As mentioned above, one of the major limitations of our work is the smaller cohort size. Hence, our immediate plans are to experiment with the linear mixed model in a larger cohort of patients diagnosed with MDD at Mayo Clinic. Further, we intend to investigate EHR data-driven analysis for understanding the association for treatment response to MDD with multiple chronic illness as well as specialty care, including surgeries. The objective here would be to ascertain the bi-directionality of the relationship with respect to treatment response to these conditions. In collaboration with the Mayo Clinic PGRN, our eventual goal is to understand better the pharmacogenomics of antidepressant treatment response and its impact on differing health care outcomes.

5.4 Conclusion
In this retrospective study, we investigate the correlation between depression and hypertension on a cohort of patients treated for MDD using SSRIs and assess the effect of depression treatment on the diagnoses and treatment for essential hypertension. While limited by the size of our cohort, our preliminary results provide positive evidence on the impact of response to antidepressant therapy for patients with hypertension.

Acknowledgment. This research is supported in part by the Mayo Clinic Early Career Development Award (FP00058504), PheMA (R01-GM105688), SHARP (90TR002), PHONT and PGRN (U19-GM061388) networks.

References
1. Bogner HR, de Vries HF. Integration of Depression and Hypertension Treatment: A Pilot, Randomized Controlled Trial. The Annals of Family Medicine. 2008;6(4):295-301.
2. Katon WJ, Lin EHB, Von Korff M, et al. Collaborative Care for Patients with Depression and Chronic Illnesses. New England Journal of Medicine. 2010/12/30 2010;363(27):2611-2620.
3. Morgan MAJ, Coates MJ, Dunbar JA, Reddy P, Schlicht K, Fuller J. The TrueBlue model of collaborative care using practice nurses as case managers for depression alongside diabetes or heart disease: a randomised trial. BMJ Open. 2013;3(1).
4. Michal M, Wiltink J, Lackner K, et al. Association of hypertension with depression in the community: results from the Gutenberg Health Study. Journal of Hypertension. 2013;Publish Ahead of Print.
5. Wu E-L, Chien IC, Lin C-H, Chou Y-J, Chou P. Increased risk of hypertension in patients with major depressive disorder: A population-based study. Journal of Psychosomatic Research. 9// 2012;73(3):169-174.
6. Rutledge T, Hogan BE. A Quantitative Review of Prospective Evidence Linking Psychological Factors With Hypertension Development. *Psychosomatic Medicine.* 2002;64(5):758-766.

7. Shinn EH, Poston WSC, Kimball KT, St. Jeor ST, Foreyt JP. Blood pressure and symptoms of depression and anxiety: a prospective study*. *American Journal of Hypertension.* 2001;14(7):660-664.

8. Hildrum B, Mykletun A, Stordal E, Bjelland I, Dahl AA, Holmen J. Association of low blood pressure with anxiety and depression: the Nord-Trøndelag Health Study. *Journal of Epidemiology and Community Health.* 2007;61(1):53-58.

9. Monte S, Macchia A, Romero M, D’Ettorre A, Giuliani R, Tognoni G. Antidepressants and cardiovascular outcomes in patients without known cardiovascular risk. *Eur J Clin Pharmacol.* 2009/11/01 2009;65(11):1131-1138.

10. Ji Y, Biernacka JM, Hebbring S, et al. Pharmacogenomics of selective serotonin reuptake inhibitor treatment for major depressive disorder: genome-wide associations and functional genomics. *Pharmacogenomics J.* 08/21/online 2012.

11. Hamilton M. Development of a rating scale for primary depressive illness. *Brit. J. Soc. Clin. Psychol.* 1967;6(1):278-296.

12. Rush AJ, Fava M, Wisniewski SR, et al. Sequenced treatment alternatives to relieve depression (STAR*D): rationale and design. *Controlled Clinical Trials.* 2/2004;25(1):119-142.

13. Doraiswamy PM, Bernstein IH, Rush AJ, et al. Diagnostic utility of the Quick Inventory of Depressive Symptomatology (QIDS-C16 and QIDS-SR16) in the elderly. *Acta Psychiatrica Scandinavica.* 2010;122(3):226-234.