Evaluation of Proton Pump Inhibitor Use on Treatment Outcomes with Ledipasvir and Sofosbuvir in a Real-World Cohort Study

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Abstract

Many patients with chronic hepatitis C (HCV) are on prolonged proton-pump inhibitor (PPI) therapy, and wish to remain on PPI therapy once treatment for HCV starts. A preliminary report recently suggested decrease rates of sustained virologic response (SVR) for patients taking concomitant PPI and Ledipasvir/Sofosbuvir (LDV/SOF). We sought to determine the effect of PPI use on the rate of SVR in a real-world cohort of 1,979 patients with chronic HCV treated with LDV/SOF. We collected clinical data and pharmacy dispensing records on patients taking 8, 12 or 24 weeks of LDV/SOF±Ribavirin. The primary outcome was SVR12 in a per-protocol analysis in order to determine the effect of PPI use adjusted for confounders. Statistical adjustment was performed in propensity-matched analysis. In the per-protocol analysis, SVR12 was achieved in 441 (97.1%) of PPI recipients compared with 1497 (98.2%) in PPI non-recipients (p = 0.19). Neither low nor high dose PPI was associated with decreased SVR. Although, patients taking twice daily PPI achieved a lower SVR12 rate: 91.2%, CI (77.0 – 97.0, p = 0.046). After propensity-matching for PPI use, there were no significant associations between SVR12 and any dose or frequency of PPI use. However, in a sensitivity analysis focusing on patients with cirrhosis, twice daily PPI use was associated with lower odds ratio for SVR12 0.11 95% CI (0.02 – 0.59).

Conclusion

These data from a cohort of real-world patients receiving anti-HCV therapy with LDF/SOF±Ribavirin support the prescription labeling suggesting that patients take no more than low dose (20 mg omeprazole equivalents) PPI daily.

Introduction

Cures for chronic hepatitis C (HCV) infection are within reach for the vast majority of patients treated with direct-acting antiviral therapies.(1-6) Furthermore, eradication of HCV is associated with measurable benefits, including decreased overall morbidity and mortality as well as increased quality of life and reduced healthcare utilization. (6-9) For these reasons, medical therapy for HCV is cost-effective even though direct wholesale medication costs are high.(7, 8, 10, 11) As healthcare stewards wishing to maximize access to treatment for all patients with chronic HCV, clinicians should work to contain costs where possible. In part this can be achieved by providing patients with adequate medication management education in order to avoid adverse drug interactions.

Teaching regarding proton-pump inhibitor (PPI) use is one of the principle components of pre-treatment education for patients prescribed ledipasvir/sofosbuvir (LDV/SOF). LDV has a pH dependent solubility whereby it is essentially insoluble when pH $\geq$ 4. In phase 1 pharmacokinetic studies (GS-US-248-0104), an interaction between PPI and LDV was noted in healthy volunteers suggesting decreased LDV absorption. The package insert, therefore, recommends a maximum of 20 mg of omeprazole taken simultaneously with the drug.(12) In a preliminary retrospective evaluation of the effect PPI use on HCV treatment results, the HCV-TARGET investigators reported that any PPI use was independently associated with lower sustained virologic response (SVR) rates.(13) These data appear to suggest that PPI use could be a modifiable factor determining the success of treatment with LDV/SOF. However, there was no data provided on specific PPIs used including type, dose, duration and frequency. Although preliminary, these data have increased focus on the management of patients taking PPIs prior to

initiation of treatment. Caution is warranted before excluding PPI use while on HCV therapy. Many of our patients with chronic HCV take and have legitimate indications for the use of PPIs. Herein, we determine the effect of PPI use on the rate of SVR in a real-world cohort of 1,979 patients with chronic HCV treated with LDV/SOF.

Methods

Data were collected through Trio Health's Innervation Platform, a proprietary platform designed as a portal for specialty pharmacies (SP) and physicians to collaborate, communicate and manage patient information for the purpose of improving patient care. Baseline information as well as outcomes data were collected through both the specialty pharmacies (SPs) and clinicians that work with Trio Health Advisory Group and were entered into the portal via a combination of nightly file feeds and manual user entry. Following the input of clinical data, the portal applied proprietary logic to identify errors and prompted SPs and clinicians to input data to ensure all data were complete and accurate. Where mandated by State law, patients signed an electronic informed consent allowing the SP to collect the data. Each clinician and SP enrolled in the portal signed agreements attesting to complying with all rules and regulations regarding the disclosure of patient information to a shared prescription database. Trio Health Analytics was provided with de-identified, HIPAA-compliant patient information from the platform for multiple purposes, including license of de-identified data. At the time of abstraction, all patient identifiers, treating physician and practice names were scrubbed and replaced with generic codes (e.g. Patient 001, Physician 001, Practice 001). This process and the following study plan was approved as an IRB exemption under category 45 CFR 46 without waivers from specific institutions (Western Institutional Review Board #1-921115-1).

This retrospective cohort study is based on data from all patients who were treated using any duration of LDV/SOF +/- ribavirin (RBV) between October 2014 and March 2015. SVR data was collected from the MD provider at week 12 post-treatment. The primary endpoint was

SVR12, defined by a negative hepatitis C viral load by polymerase chain reaction assessed at 12 weeks following the completion of therapy. Treatment start and end dates were defined by pharmacy dispensing records.

The primary exposure variable was PPI use during HCV treatment as defined by a filled PPI prescription during therapy. The duration (number of refills), dose (high and low), frequency (times taken daily) and type of PPI use was further delineated based on pharmacy dispensing records. Low dose was defined as any dose equivalent to 20 mg omeprazole; high dose was any dose equal to $\geq$ 2 20mg-omeprazole equivalents. A PPI patient is defined as a hepatitis C patient taking a PPI at any point during the HCV treatment and represents 23% (n=454 patients). The vast majority (n = 439, 96.7%) of PPI patients were on PPI treatment throughout the course of HCV treatment and a minority either started after initiation, used intermittently or discontinued prior to completion of HCV treatment which was tracked throughout therapy. Additional clinical characteristics were recorded, including age, sex, ethnicity, physician-reported fibrosis burden, transplant status, comorbidities (Human Immunodeficiency Virus (HIV), hepatitis B (HBV), and diabetes), prior treatment experience, intended treatment and practice type. Collected laboratory values include HCV genotype, initial viral load, alanine and aspartate aminotransferase (ALT, AST), hemoglobin, and platelet count.

Data Analysis

As the focus of this study was to determine the effect of PPI use on treatment efficacy, while the results of therapy are displayed for the 'intention to treat' population in Figure 1, endpoints were evaluated for the main analysis for those who completed therapy. In this case, the denominator excluded those who died, were lost-to-follow-up, or discontinued therapy during treatment. Statistical Analysis System (SAS) version 9.3 (SAS Institute, Cary, NC, USA) was used to analyze the data. Univariate comparisons were performed using chi-squared testing for proportions, Student's T testing for Gaussian continuous variables or Wilcoxon rank-sums testing for non-Gaussian continuous variables. Significant p-values were two-tailed and < 0.05.

Propensity Score Matching

Patients were not randomized to PPI use. In the context of this retrospective analysis, we sought to account for selection bias by conducting propensity score matching conditioned on PPI use during HCV therapy. To estimate the propensity score, a logistic regression model was used in which use of PPI (yes vs. no) was regressed on the potential baseline confounders including age, gender, cirrhosis, platelet count, treatment naive, and actual duration of treatment .Missing data was rare (<2% per variable), thus no imputation was performed. Thereafter, PPI treated and untreated patients were matched on the propensity score using a 1:1 matching algorithm. Two sensitivity analyses entailed matching the cohort after excluding patients without cirrhosis and those who were inconsistent PPI prescription refillers. Matching was later repeated for a separate analysis with a propensity score conditioned on high dose PPI use. A similar matching procedure was not possible for a score conditioned on twice daily PPI use given the size that subset (n = 39).

Logistic Regression

Multiple logistic regression analysis was conducted on the matched sample to determine the association between SVR12 and PPI use (yes vs. no) adjusting for age, gender (male vs. female), ethnicity (African American vs. Non-African American), practice type (academic vs. community), treatment naïve vs experienced, genotype group (1a, 1b, mixed, unspecified), baseline viral load, the presence of cirrhosis, platelet count (<100 vs. ≥ 100), and duration of treatment (8 , 12 , and 24 weeks). As failure to achieve SVR was a rare outcome, we employed a penalized logistic regression (Firth method)(14) to assess the prognostic factors of SVR. All adjusted effect sizes for PPI use were compared to the SVR12 of PPI nonusers as a reference. A significance level of 0.05 was required to allow a variable into the model and also to stay in the model. Model fit was tested using the Hosmer and Lemeshow goodness-of-fit test. Logistic regression was again performed for the sensitivity analyses described above.

Results

The pretreatment demographics and clinical characteristics of the patients who completed therapy are described in Table 1. In general the population was aged 59.7± 9.4 years, 58% male and 57% Caucasian. The majority of patients were treatment naïve (58%), 34% were cirrhotic, 2.1% decompensated and 2.7% post-transplant. With respect to baseline viral characteristics, 1343 (67.9%) were genotype 1a and the median viral load was 1.87 million IU/L (IQR 0.70 -4.69 million). Among the patients prescribed histamine receptor 2 blockers, 34 (4.3%) were not taking PPI while 9 (4.1%) were taking concomitant PPI (p = 1.0). Numerous clinical characteristics differed significantly at baseline between those taking and not taking PPI: body mass index, race, diabetes status, transplant status, platelet count, the presence of cirrhosis (decompensated or not), type of clinical practice and duration of therapy.

Overall, the treatments were highly effective, irrespective of PPI use.(Figure 1) There were no between-group differences in the proportion of on-treatment deaths, discontinuation or lost-to-follow-up; 2 in each arm died, 8 in the PPI group (1.7%) vs 25 (1.6%) were lost-to-follow-up and 4 in the PPI group (0.9%) vs 14 (0.9%) discontinued therapy. Among patients who completed therapy, SVR12 was achieved in 441 (97.1%) of PPI recipients compared with 1497 (98.2%) in PPI non-recipients (p = 0.19).

Subgroup analyses were performed to determine whether particular features of PPI therapy were associated with SVR12 (Figure 2). Only one PPI therapy group was associated with

a lower SVR rate. Patients taking their PPI twice daily achieved SVR 91.2% 95% CI (77.0 – 97.0%) of the time compared to 98.2% 95% CI (97.4% - 98.7%) among non-users, a statistically significant difference (p = 0.042) despite wide confidence intervals.

A propensity-matched analysis was performed to assess the independent effect of PPI use on SVR across therapeutic regimens. Table 2 delineates the balancing of clinical characteristics following the matching procedures. Overall, the propensity score yielded PPI and Non-PPI cohorts that were well balanced. However, among PPI recipients there were more patients seen at academic practices (57.6% vs 49.4%) and patients with decompensated cirrhosis (4.5% vs 1.3%). After propensity score matching, SVR12 rates were no different as a function of PPI use, irrespective of treatment duration. In the matched cohort, patients receiving daily PPI (n = 410) experienced SVR12 97.8% (96.4 – 99.2) of the time while those receiving PPI twice daily (n = 34) experienced an SVR12 rate of 91.1% (81.5 – 100.0). Patients not taking PPI (n = 443) experienced SVR 97.2% (95.7 – 98.7). of the time.

Multiple logistic regressions were performed to ascertain the effect of PPI use on SVR in cohorts matched based on propensity scores for any PPI use (see Table 2). The results of the adjusted regression analyses are detailed in Table 3. Among patients matched on their propensity to receive any PPI, neither PPI use overall, nor high dose or twice daily PPI was associated with SVR12. Sensitivity analyses were performed by restricting the matched cohort to patients with cirrhosis and PPI users who refilled their PPI prescriptions throughout treatment. (Table 3) When restricted to patients with cirrhosis, it appears that twice daily PPI use may be associated with lower SVR12 rates, OR 0.11 95% CI (0.02 – 0.59), albeit with p = 0.05. A separate sensitivity

analysis was performed by matching the cohort using a propensity scores conditioned on high dose PPI use instead of any daily PPI use. After matching based on the propensity to receive high dose PPI use, there were no significant effects on SVR12 from any PPI use, high dose PPI use or twice daily PPI use, with respective SVR12 rates of 98.7% 95% CI (97.5% - 100%), 100% 95% CI (100% - 100%), and 97.8% 95% CI (93.6% - 100%). After multivariable regression, no significant differences in SVR12 rates were detected.

Discussion

We sought to determine the effect of PPI therapy on LDV/SOF effectiveness given the biological plausibility – decreased absorption of ledipasvir at higher gastric pH – and the decreased SVR rate attributed to PPI therapy in a report from the HCV-TARGET. This study of 1,979 patients from a real-world cohort with chronic HCV treated with LDV/SOF clarifies the relationship between PPI and SVR. First, we show that PPI usage overall is not associated with SVR, irrespective of treatment duration. Second, we demonstrate an unadjusted association between twice daily PPI use and decreased SVR that is no longer significant after adjustment for propensity to receive PPIs.

These data extend the prior literature on the real-world outcomes of HCV with highly effective direct-acting antivirals (DAA) in multiple ways. First, the SVR rates observed in this study (> 94% intention to treat, > 97% for those who completed therapy) mirror those of the LDV/SOF controlled registration trials (ION-1,2,3,4), where PPI use was specifically prohibited.(1, 2, 15, 16) The replicable success with LDV/SOF in a real-world cohort suggests the closing of the 'chasm between efficacy and effectiveness' observed when first generation DAA's failed to translate successes in the trial setting to the clinic.(17)

Second, these data confirm the therapeutic efficacy of LDV/SOF-based on package labeling that allows for daily PPI. Our propensity-score adjusted analyses demonstrate no

statistical association between PPI use and SVR. Although statistically insignificant, the numerically lower SVR rate associated with twice daily PPI use gives us pause. This is particularly true for patients with cirrhosis where the adjusted odds ratio for SVR12 associated with twice daily PPI was 0.11 95% CI (0.02 – 0.59, p = 0.05). Given that the population taking twice daily PPI was small, this study was not powered to detect differences on the basis of PPI frequency. These data therefore provide reassurance that the labeled recommendation for PPI use is acceptable. Namely, PPI doses comparable to omeprazole 20 mg can be administered with LDV-SOF.

One prior study has examined the effect of PPI use on treatment success for patients taking LDV-SOF containing regimens. from the effect of PPI use on SVR observed during the HCV-TARGET study by Terrault and colleagues has been presented in abstract form.(13) Among 1,074 patients receiving LDV/SOF±Ribavirin , these investigators found decreased SVR rates associated with baseline PPI use. Specifically, using statistical techniques to adjust for confounding with respect to PPI use, they found an odds ratio (OR) of 2.48 95% CI (1.57 – 3.93, p <0.001) for SVR in patients not on PPI at baseline. Multiple differences in methodology help reconcile the differences. First, we used pharmacy records to confirm which patients filled their PPI prescriptions throughout therapy as well as the dose and quantity of pills dispensed to delineate frequency. Whereas HCV-TARGET examined only PPI use at baseline, we provide data on the dose and frequency of PPI use and analyze the effect on SVR of FDA labeling recommended PPI dose equivalents. These data with respect to PPI use are essential to support (or contradict) the FDA label. Second, the number of PPI users included in our cohort was much larger (454 versus 255), potentially minimizing the risk of confounding.

These findings must be interpreted in the context of the study design. First, propensity matching seeks to balance the cohort in order to yield similar groups for comparison. This process involves discarding patients from analysis who were extremely likely to receive or not receive PPI. Furthermore, despite most variables achieving balance, some were not (academic practice, decompensated cirrhosis). There are two reasons why these factors should not affect the assessment of our data. One, the unmatched analyses on the treatment completers failed to yield differences based on PPI use save for twice daily usage. Two, the misbalancing after matching favored patients not taking PPI, yet no difference was observed. Second, despite observed refill rates, we cannot be certain that patients were taking their PPI as prescribed. Third, we cannot be certain whether non-PPI users were using over-the-counter PPI unless recorded by the specialty pharmacy and, admittedly, over the counter use is not infrequent. Fourth, we lack data on the patients' specific timing of PPI use relative to LDV-SOF dosing. This could be important as the raised pH of any dose PPI may raise the gastric pH > 4 for 10-14 hours.(18)

In conclusion, these data confirm the effectiveness of LDV/SOF±Ribavirin in a large real-world cohort and affirm the package labeling with respect to PPI use. Despite the lack of statistical association observed, we recommend that PPIs be prescribed no more frequently than once daily for patients receiving anti-HCV therapy with LDV/SOF.

Table1: Demographics and Clinical Characteristics

	Overall (N = 1979)	PPI (n= 454)	No PPI (n= 1525)	P value
Male sex (n, %)	1143 (57.8%)	262 (57.7%)	881 (57.7%)	1.0
Age (mean ± SD)	59.7 ± 9.4	60.1 ± 8.7	59.6 ± 9.6	0.35
BMI (median IQR)	27.6 (24.3 – 31.5)	28.2 (25.0 – 32.0)	27.5 (24.2 – 31.4)	0.02
Caucasian (n, %)	1124 (56.8%)	290 (63.9%)	834 (54.7%)	0.003
Treatment naïve (n, %)	1143 (57.8%)	231 (50.9%)	912 (60.0%)	0.0008
Diabetes (n, %)	302 (16.9%)	86 (20.3%)	216 (15.8%)	0.04
HIV (n, %)	133 (6.7%)	23 (5.1%)	110 (7.2%)	0.13
HBV (n, %)	15 (0.8%)	4 (0.9%)	11 (0.8%)	0.76
Post-transplant (n, %)	54 (2.7%)	24 (5.3%)	30 (2.0%)	0.0004
Platelets < 100K (n, %)	249 (14.2%)	82 (20.0%)	167 (12.5%)	0.0003
Cirrhosis (n, %)	679 (34.3%)	190 (41.9%)	489 (32.1%)	0.0002
Decompensated (n, %)	36 (2.1%)	18 (4.8%)	18 (1.4%)	0.0003
Academic practice (n, %)	971 (49.1%)	262 (57.7%)	709 (46.5%)	< 0.0001
8 week regimen (n, %)	275 (13.9%)	41 (9.0%)	234 (15.3%)	< 0.0001
12 week regimen(n, %)	1342 (67.8%)	297 (65.4%)	1045 (68.5%)	
24 week regimen (n, %)	362 (18.3%)	116 (25.6%)	246 (16.1%)	

BMI = Body mass index, HBV = hepatitis B virus coinfection, HIV = human immunodeficiency virus coinfection, IQR = interquartile range, PPI = proton pump inhibitor, SD = standard deviation

Table 2: Clinical Characteristics of the Propensity-Matched Cohorts

	PPI (n = 444)	No PPI (n = 443)	P value
Male sex (n, %)	254 (57.2%)	273 (61.6%)	0.18
Age (mean ± SD)	60.1 (8.5)	60.0 (9.8)	0.09
BMI mean (median IQR)	28.2 (25 – 32.1)	27.5 (24.2-31.4)	0.37
Caucasian (n, %)	373 (84.0%)	353 (79.6%)	0.09
Treatment naïve (n, %)	229 (51.5%)	244 (55.0%)	0.30
Diabetes (n, %)	84 (20.1%)	67 (16.5%)	0.17
HIV (n, %)	22 (4.9%)	26 (5.8%)	0.55
HBV (n, %)	4 (0.9%)	3 (0.7%)	0.18
Post-transplant (n, %)	24 (5.4%)	13 (2.9%)	0.07
Platelets < 100K (n, %)	83 (18.6%)	82 (18.5%)	0.94
Cirrhosis (n, %)	180 (40.5%)	155 (35.0%)	0.09
Decompensated (n, %)	17 (4.5%)	5 (1.3%)	0.009
Academic practice (n, %)	256 (57.6%)	219 (49.4%)	0.01
8 week regimen(n, %)	41 (9.2%)	41 (9.2%)	1.0
12 week regimen (n, %)	294 (66.2%)	294 (66.3%)	
24 week regimen (n, %)	109 (24.5%)	108 (24.3%)	

Patients were matched 1:1 based on a propensity score conditioned on the receipt of PPIs. BMI = Body mass index, HBV = hepatitis B virus coinfection, HIV = human immunodeficiency virus coinfection, IQR = interquartile range, PPI = proton pump inhibitor, SD = standard deviation

Table 3: Effect of Proton Pump Inhibitor (PPI) Dosing on Sustained Virologic Response (SVR12) After Propensity Score Matching

	No PPI use SVR12 rate (95% CI)	PPI use category	Unadjusted SVR12 rate (95% CI)	Adjusted Odds ratio for SVR12 (95% CI)	P value
Propensity matching based on any daily PPI use (N = 887)	97.2% (95.7 – 98.7)	Any PPI use (n = 351)	97.8% (96.4 – 99.2)	0.34 (0.05 – 2.29)	0.27
		High dose PPI use (n = 149)	98.0% (95.7 - 100)	0.95 (0.37 – 2.47)	0.98
		Twice daily PPI use (n = 32)	91.1% (81.5 – 100.0)	0.33 (0.09 – 1.19)	0.36
Sensitivity Analyses:					
Restricting matched cohort to patients with cirrhosis (N = 343)	96.3% (93.5 – 99.2)	Any PPI use (n = 179)	95.5% (92.5 – 98.6%)	0.67 (0.25 – 1.78)	0.42
		High dose PPI use (n = 75)	96.0 (91.6 - 100)	0.71 (0.20 – 2.50)	0.73
		Twice daily PPI use (n =13)	76.9% (54.0 - 99.8)	0.11 (0.02 – 0.59)	0.05
Restricting matched cohort to either non PPI users or consistent PPI prescription refillers (N =720)	97.0% (95.3 – 98.8)	Any PPI use (n = 351)	97.2% (95.4 - 98.9)	0.978 (0.44 – 2.19)	0.98
		High dose PPI (n = 149)	97.3% (95.7 - 100)	0.73 (0.24 – 2.28)	0.44
		Twice daily PPI (n = 32)	90.6% (80.5 - 100)	0.29 (0.07 – 1.11)	0.28

Adjusted odds ratios were obtained from multiple logistic regression analysis conducted after propensity score matching to determine the association between SVR12 and PPI use adjusting for age, gender, ethnicity, practice type, treatment experience, genotype group, baseline viral load, the presence of cirrhosis, platelet count (<100) and duration of treatment (8 , 12 , and 24 weeks). As failure to achieve SVR12 was a rare outcome, we employed a penalized logistic regression (Firth method). SVR12 = sustained virologic response at 12 weeks after treatment completion. PPI users had consistent refills throughout therapy.

Figure Legends

Figure 1: Outcomes by Proton Pump Inhibitor Use

DC = discontinued, LTFU = lost to follow up, PPI = proton pump inhibitor SVR = sustained virologic response.

Figure 2: Predictors of Sustained Virologic Response – Univariate Associations

The dotted line indicates the overall sustained virologic response rate (97.9%) in the per-protocol analysis. PPI = proton pump inhibitor

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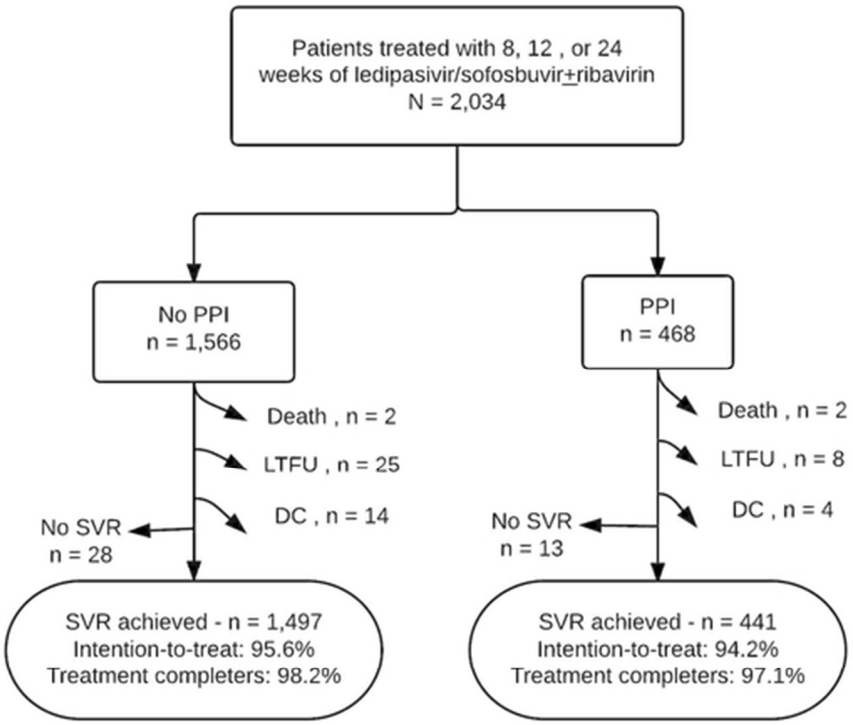

Figure 1: Outcomes by Proton Pump Inhibitor Use

DC = discontinued, LTFU = lost to follow up, PPI = proton pump inhibitor SVR = sustained virologic response.

50x40mm (300 x 300 DPI)

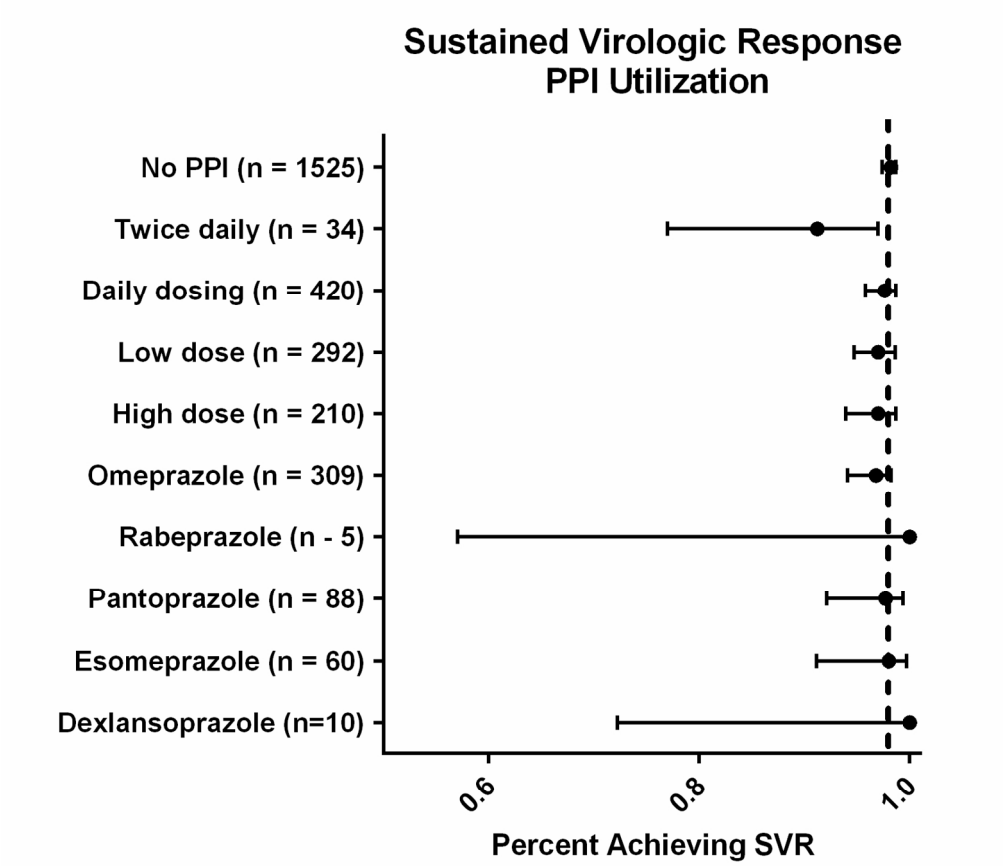

Figure 2: Predictors of Sustained Virologic Response – Univariate Associations

The dotted line indicates the overall sustained virologic response rate (97.9%) in the per-protocol analysis. PPI = proton pump inhibitor

142x126mm (300 x 300 DPI)