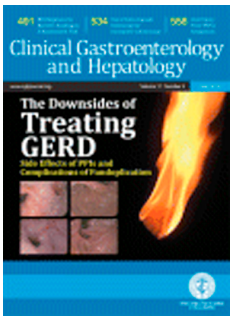

Effects of Metformin Exposure on Survival in a Large National Cohort of Patients with Diabetes and Cirrhosis

David E. Kaplan, Marina Serper, Binu V. John, Kristen M. Tessiatore, Renata Lerer, Rajni Mehta, Rena Fox, Ayse Aytaman, Michelle Baytarian, Kristel Hunt, Jeffrey Albrecht, Tamar H. Taddei, for the VOCAL Study Group

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Authors: David E. Kaplan[1,2], Marina Serper[1,2], Binu V. John[3], Kristen M. Tessiatore[2], Renata Lerer[2], Rajni Mehta[4], Rena Fox[5], Ayse Aytaman[6], Michelle Baytarian[7], Kristel Hunt[8], Jeffrey Albrecht[9], and Tamar H. Taddei[4] for the VOCAL Study Group.

Institutions:

1. Corporal Michael J. Crescenz VA Medical Center, Philadelphia PA
2. Division of Gastroenterology and Hepatology, Hospital of the University of Pennsylvania, Philadelphia, PA
3. Bruce W Carter VA Medical Center, Miami FL
4. VA Connecticut Healthcare System, West Haven, CT
5. San Francisco VA Medical Center, San Francisco, CA
6. VA New York Harbor Health Care System, Brooklyn, NY
7. Boston VA Healthcare System, Boston, MA
8. James J. Peters VA Medical Center, Bronx, NY
9. Minneapolis VA Medical Center, Minneapolis, MN

Corresponding Author:

David E. Kaplan, MD MSc FACP FAASLD

Associate Professor

Division of Gastroenterology and Hepatology

Perelman School of Medicine

University of Pennsylvania

Director of Hepatology

Corporal Michael J. Crescenz VA Medical Center

3900 Woodland Ave,

Philadelphia, PA 19104

T: (215) 823 5800 x 6729

dakaplan@pennmedicine.upenn.edu

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Author Contributions:

MS – analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis

BVJ – critical revision of the manuscript for important intellectual content; statistical analysis

THT - study concept and design; acquisition of data; analysis and interpretation of data; drafting of the manuscript; critical revision of the manuscript for important intellectual content; statistical analysis; obtained funding; technical, or material support; study supervision

KMT - acquisition of data; outcome validation; critical revision of the manuscript for important intellectual content

RL - acquisition of data; outcome validation; critical revision of the manuscript for important intellectual content

RM – acquisition of data; technical, and material support

AA – study concept and design; critical revision of the manuscript for important intellectual content; obtained funding

MB – study concept and design; critical revision of the manuscript for important intellectual content; obtained funding

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Abbreviations:

ALD – alcoholic liver disease

HBV – hepatitis B virus-related disease

HCC – hepatocellular carcinoma

HCV – hepatitis C virus-related disease

MSM – marginal structural model

NAFLD – nonalcoholic fatty liver disease

NASH – nonalcoholic steatohepatitis

LDL – low density lipoprotein cholesterol

HDL – high density lipoprotein cholesterol

TGL – triglycerides

ABSTRACT: 251 words

ABSTRACT

Background & Aims: Type II diabetes mellitus worsens the prognosis of cirrhosis. Multiple medications including metformin and statins are often co-administered to manage patients with diabetes. The aim of this study was to assess the impact of metformin exposure on mortality, hepatic decompensation, and hepatocellular carcinoma in individuals with diabetes and cirrhosis, controlling for multiple concomitant exposures.

Methods: We performed a retrospective cohort study of patients with cirrhosis diagnosed between January 1, 2008, through June 30, 2016, in the Veterans Health administration. Marginal structural models and propensity matching approaches were implemented to quantify the treatment effect of metformin in patients with pre-existing diabetes with or without prior metformin exposure.

Results: Among 74,984 patients with cirrhosis, diabetes mellitus was present prior to the diagnosis of cirrhosis in 53.8% and was diagnosed during follow-up in 4.8%. Prior to the diagnosis of cirrhosis, 11,114 patients had active utilization of metformin. In these patients, metformin, statin, and ACEI/A2RB exposure were independently associated with reduced mortality (metformin HR 0.68 95%CI 0.61-0.75); metformin was not associated with reduced hepatocellular carcinoma (HCC) or hepatic decompensation after adjustment for concomitant statin exposure. For patients with diabetes prior to diagnosis of cirrhosis but no prior metformin exposure, metformin was similarly associated with reduced mortality (HR 0.72 95%CI 0.35-0.97) but not with reduced HCC or hepatic decompensation.

Conclusions: Metformin use in patients with cirrhosis and diabetes appears safe and is independently associated with reduced overall but not liver-related mortality, hepatocellular carcinoma or decompensation after adjusting for concomitant statin and ACEI/A2RB exposure.

KEY WORDS: human, cirrhosis, diabetes, metformin, statin, alcohol, hepatitis, nonalcoholic steatohepatitis, fatty liver, NAFLD

INTRODUCTION

Progressive liver injury predisposes to the development of diabetes mellitus (DM), and DM accelerates liver disease progression.[1-4] While 20-40% of patients diagnosed with cirrhosis already carry a diagnosis of DM,[5, 6] of those not yet diagnosed 60% may exhibit insulin resistance or DM on formal testing.[7] DM is a strong risk factor for hepatocellular carcinoma (HCC) in patients with and without known liver disease,[1] and for liver-related death among patients with cirrhosis.[4, 8]

In retrospective studies, the standard first-line treatment for DM, metformin, has been observed to reduce the risk of HCC,[9-13] either via direct anti-neoplastic effects or by suppressing hyperinsulinemia. However the strength of the data remains low. A recent meta-analysis showed reduced all-cause mortality with metformin use in patients with cirrhosis.[14] However, only 3 studies met inclusion criteria, only one of which was prospective with a total N=432.

Diabetic patients are often co-prescribed multiple other medications, such as aspirin, statins, angiotensinogen-converting enzyme inhibitors (ACEI) or angiotensin-2-receptor blockers (A2RB) that might confound the associations of medication exposure and various outcomes, a bias for which adjustment has not been adequately addressed in prior studies.

To address these limitations, we aimed to investigate the impact of metformin exposure on mortality, hepatic decompensation, and HCC in individuals diagnosed with cirrhosis with a pre-existing diagnosis of DM with and without prior metformin utilization. In observational studies, exposures to medications of interest vary over time. Time-varying covariates, such as concomitant medication exposures, and variables that confound an exposure but also may fall in the causal pathway (such as HBA1c and body mass index) cannot be accounted in fixed

regression models without creating immortal time bias and other biases. Using marginal structural modeling (MSM), an approach to estimate the causal effect of an exposure with time-updating confounding,[15] we observed that metformin was independently associated with reduced mortality, but that associations with reduced hepatocellular carcinoma or decompensation were no longer statistically significant after adjustment for concomitant statin exposure.

METHODS

Data Sources, Regulatory, Subject Identification

Clinical data were obtained from VA Corporate Data Warehouse (CDW). Approval was obtained from the Institutional Review Boards at all participating VA sites. Patients with cirrhosis were identified using a validated methodology as previously described based on International Classification of Diseases, 9th Revision, Clinical Modification (ICD9-CM) or 10th Revision (ICD10) diagnosis codes.[16, 17] from 1/1/2008 to 12/31/2016 with follow-up through 6/30/2019. Cohort entry date was defined as the first date of the cirrhosis diagnosis entered into the electronic medical record (EMR). Patients were excluded for: fewer than 180 days of clinical follow-up, development of HCC in fewer than 180 days from the diagnosis of cirrhosis, fewer than 2 VA outpatient visits in the index year of diagnosis, age less than 18 or greater than 85 years, or a FIB-4 score < 1.45 (indicating lack of significant fibrosis).[18] The diagnosis of diabetes was based upon the validated algorithm of Butt et al,[19] utilizing ICD9/10 codes, fasting glucose, and diabetes-related medication exposures.

Covariates

Baseline laboratory values (see Supplemental Methods) were taken closest to the index date of cirrhosis obtained between 180 days prior to, or 30 days following the diagnosis code. Throughout follow-up , average laboratory values in each quarter of follow-up were used to generate time updating measures of liver disease severity such as the Model for End-Stage Liver Disease-Sodium (MELDNa).[20] Electronic Child-Turcotte-Pugh CTP (eCTP) scores were determined using a validated algorithm.[21] Tobacco use was characterized as current, former, or lifetime non-use using a validated approach.[22] Alcohol use was characterized both by ICD codes as well as Alcohol Use Disorders Identification Test (AUDIT-C);[23] AUDIT-C scores >4 for men and >3 for women were classified as alcohol misuse.[24] Liver disease etiology was assigned per the schema of Beste et al.[25] The Cirrhosis Comorbidity Index was calculated per Jepsen et

al.[26] The presence of hepatic and cardiovascular comorbidities was identified using 1 inpatient or 2 outpatient ICD codes or Common Procedural Terminology (CPT) codes (**Supplemental Table 1**) consistent with published, validated algorithms.[27]

Outcomes

Death was ascertained using the Vital Status Master File (censoring as of 6/30/2019).[28] Cause of death (through 12/31/2017) was obtained from the VA Mortality Data Repository,[29] and classified as likely liver-related, diabetes-related, cardiovascular or other (**Supplemental Table 2**). Secondary outcomes included hepatic decompensation using a previously validated algorithm;[30] and HCC using ICD9/10 codes known to be 80% specific for HCC (**Supplemental Table 1**).[31]

Exposures

Prescriptions for metformin, statins, ACEI/A2RB, sulfonylureas, nonselective beta blockers, and other relevant medications (see Supplemental Methods) were quantified prior to and following the diagnosis of cirrhosis based on dose and days of medication supplied as previously described.[16] Exposure to medications in each 30-day time-window of follow-up was calculated using the tmerge function of the R survival package using a 30-day delay to avoid protopathic bias (reverse causality).[32] Exposure was considered present if a patient received ≥7 days of medication in a 30-day period.

Statistical Analysis

Time-to-event data were compared using the log-rank test and Kaplan-Meier methodology. Marginal structural models (MSM) were fit using inverse probability-of-treatment weighting (IPTW)[15, 33] to correct for time-varying confounding related to the clinical decision to initiate/maintain metformin therapy. Covariates included in the IPTW model were age, gender,

HBA1c (modeled as natural spline with 5 degrees of freedom, **Supplementary Figure 1**), serum albumin, BMI, 10-year cardiovascular risk,[34] prior exposure to metformin, insulin, sulfonylureas, thiazolidinediones, GLP1RAs, and the duration of diabetes. The AUROC for this model was 0.94. Covariate weights were truncated at the 0.01 and 0.99 quantiles (**Supplementary Table 3**). IPTW covariate balance was evaluated in the pseudo-populations generated (**Supplementary Table 4**); covariates for which SMD ≤ 0.1 could not be balanced were included as covariates in outcome models. IPTW weight balance over time are shown in **Supplementary Figure 2**. The associations of metformin exposure and overall mortality, cause-specific mortality, hepatic decompensation (death as competing-risk) and HCC (also competing risk) were estimated in MSM using time-updating Cox proportional hazards models using Fine-Gray estimators for competing risks where relevant. These models were further adjusted for or stratified by Child-Turcotte-Pugh Class and disease etiology, and adjusted for age, gender, race/ethnicity, MELDNa score, tobacco use, AUDIT-C, prior CAD, aspirin, statin, ACEI/A2RB and NSBB exposure (if present), serum cholesterol, and HBA1c. Variables were chosen based on established clinical associations with either liver disease severity or risk of mortality. Covariates for time-varying models were chosen if p was <0.15 in univariable analyses. A two-sided p-value of <0.05 was defined to be statistically significant. To compare effects of different metformin exposures and doses on outcomes, we performed landmark analyses examining the exposure to metformin in terms of days and dose (mg/d) in the first 180 or 360d after cirrhosis diagnosis among patients surviving ≥180 or 360d respectively and assessed subsequent survival and time to HCC in Cox models adjusted for age, etiology, Child-Turcotte-Pugh stage, statin and ACEI/A2RB exposure. Analyses were performed using the Survival and ipw package in R.[32, 33]

Sensitivity Analyses

We tested the effect of varying the exposure time within a time window (7/30, 14/30, 21/30 days) for defining exposure on the association of metformin with overall survival. We also assessed the impact of varying HCC latency exclusions (180, 360, 540, and 720 days) on the association of metformin and statins with hepatocellular carcinoma incidence.

RESULTS

Patient Groups and Characteristics

Of an initial cohort of 129,051 patients with new diagnoses of cirrhosis, after exclusion of subjects with fewer than 2 outpatient encounters in the index year, fewer than 180 days of clinical follow-up, and/or FIB-4 < 1.45, a total of 74,984 were analyzed (**Figure 1)**. Of these, 43,674 (58.2%) were diagnosed with diabetes, 40,368 (53.8%) prior to the diagnosis of cirrhosis and 3,660 (4.8%) following the diagnosis of cirrhosis. Of the patients with diabetes prior to cirrhosis, 18,600 received at least 1 prescription of metformin and 21,768 were metformin naïve. A total of 11,527 patients received a prescription for metformin within 90-days of the diagnosis of cirrhosis; 66.8% of active metformin users received new prescriptions within 90 days of diagnosis of cirrhosis and 85.4% were ever re-prescribed metformin during follow-up for a median exposure of 673 days (IQR 250-1320 days). Patients who never resumed metformin exhibited markedly higher rates of morbidity and mortality (HCC rates 5.9 vs. 2.3 per 100 patient-years; decompensation 17.1 vs 9.1; death rate 18.1 vs. 8.8; all $p < 0.0001$, unadjusted data presented in **Supplemental Table 5**).

Among patients with cirrhosis with pre-existing diabetes, metformin-experienced patients were more likely White, obese with NAFLD/NASH, and to have prior cardiovascular disease (coronary artery disease, MACE), to be on concomitant aspirin (41.0 vs 31.5%), statins (62.7% vs. 35.8%), insulin (45.4% vs 26.2%), sulfonylureas, thiazolidinediones, and ACE inhibitors and/or A2RB. They were less likely to have been diagnosed with a prior hepatic decompensation (17.7 vs 22.0%) or treated with a NSBB (**Table 1 and Supplemental Table 6)**.

Effect of Continuing Metformin in Metformin-experienced Diabetic Patients Diagnosed with Cirrhosis

We first analyzed the effect of ongoing exposure to metformin among 11,571 metformin-experienced patients with active utilization of metformin within 90 days of cirrhosis diagnosis. A relatively stable fraction (>50%) of prior users continued use during 5 years of follow-up (**Figure 2A**). In 2-way ANOVA, there was no observable effect of metformin on BMI (data not shown). As shown in **Table 2**, after adjustment for covariates, as well as relevant prior and concurrent medication exposures (particularly statins), metformin remained significantly associated with reduced mortality with a HR 0.68 (95%CI 0.61-0.75). Statins, ACEI/A2RB and sulfonylurea therapy, but not aspirin use, were also independently associated with reduced mortality in this cohort (statin HR 0.78 95%CI 0.69-0.87). Varying the definition of exposure from 7 to 14 to 21 days per 30-day window had minimal impact on the estimation of effect size (**Supplemental Table 7**). In models to assess for synergy, we found no evidence of anything other than an additive effect of metformin with statins or metformin with ACEI/A2RB on the outcome of overall mortality (for statin S statistic 0.97 95%CI 0.71-1.31 where S = 1 is pure additive effect; the S statistic for ACEI/A2RB was 0.74 95%CI 0.63-0.87, again < 1 showing no synergy). In stratified analysis, the benefit of metformin on mortality was present in patients with CTP A and B cirrhosis due to HCV, alcohol, and/or NAFLD/NASH but not in the subgroup of patients with cirrhosis due to other causes (**Table 2**). The effect of metformin on overall survival appeared dose-related; in Landmark analysis evaluating metformin exposure in either the first 180 or 360 day of cirrhosis, both cumulative days of exposure (**Figure 2B-C**) and dose received (**Figure 2D-E**) was strongly associated with reduced subsequent risk of death.

Liver Cancer, Hepatic Decompensation and Cause-specific Mortality

We next evaluated the effect of metformin, adjusted for concomitant exposures and covariates, on liver-related complications and cause-specific causes of death (**Table 3**). Metformin was not significantly associated with reduced rates of HCC and hepatic decompensation after adjustment for statin exposure and other relevant covariates (**Table 3, Supplemental Table 8-**

89, Supplemental Figure 3). The lack of association of metformin with HCC development was insensitive to changes in HCC latency (**Supplemental Table 10**). In MSM but not Landmark competing-risk models, metformin was associated with a reduction in liver-related death (**Table 4**). In both models, metformin was significantly associated with reduced death from diabetes or cardiovascular causes (HR 0.67 95%CI 0.47-0.95, every 30 days of metformin exposure during year 1 associated with HR 0.95 95%CI 0.93-0.98 for diabetes/cardiovascular death, **Table 4, Supplemental Figure 4**).

Effect of Starting Metformin in Diabetic Patients after Diagnosis with Cirrhosis.

In patients with cirrhosis and diabetes who had not previously been treated with metformin, metformin was initiated in 3,980 individuals (18%) during follow-up (**Figure 2D**). In adjusted MSM models, metformin remained significantly associated with reduced mortality with HR 0.72 (95%CI 0.63-0.82) but similar to previously exposed cirrhotic patients, metformin was not independently associated with reduced HCC or decompensation (**Supplemental Table 11**).

DISCUSSION

The analysis of pharmacological exposure outcomes related to diabetes and cirrhosis is challenging due to the timing of diagnosis of diabetes, the possible impact of the diagnosis of cirrhosis itself or manifestations of cirrhosis on prescribing behavior, and multiple potential concomitant therapies for diabetes or related conditions that could also impact cirrhosis-related outcomes.[16, 35, 36] For example, metformin may affect HBA1c, which may be both a predictor of survival as well as indication to start/continue metformin. A patient previously on metformin is also more likely to remain on metformin, and may be more likely to receive other diabetes-related medications and care. MSM, an approach to estimate the causal effect of an exposure using inverse probability of treatment weighting to adjust for time-dependent covariates that are risk factors for, or predictors of, the outcome and also predictors of the exposure of interest were applied in this study to adjust as much as possible for time-dependent confounding by indication.[15, 37]

In this large cohort of patients with cirrhosis, DM was present at baseline in 53.8% and was diagnosed during follow-up in an additional 4.8%. Fewer than half of patients with known diabetes had any exposure to metformin prior to being diagnosed with cirrhosis. Of those actively using metformin, the diagnosis of cirrhosis was temporally associated with permanent discontinuation of metformin in 14.5%. From administrative data, it is not possible to ascertain the reason for medication discontinuation. Exposure to metformin after cirrhosis diagnosis was associated with reduced mortality even after adjusting for other commonly utilized medications in the diabetic and/or cirrhosis population such as aspirin, statins, ACEI/A2RB, and NSBB. Child-Turcotte-Pugh A and B (but not C) patients appeared to benefit. The magnitude of the hazard ratio of metformin for mortality ranged from 0.65-0.72 for the specific subpopulations evaluated and was dose dependent. This hazard ratio is a more conservative estimate than that found in a non-randomized prospective cohort of 250 diabetic patients with cirrhosis in which

metformin was either continued or not (HR 0.43 95%CI 0.24-0.78)[38], likely due to the nonrandomized nature and effect of confounders incompletely controlled in the prior study. We could not observe an impact of metformin on liver-related outcomes such as HCC, hepatic decompensation, or liver-related death but found a strong association with reduced cardiovascular mortality (HR 0.58 95%CI 0.39-0.87), as has been observed in some but not all meta-analyses of metformin use in non-cirrhosis settings.[39, 40]

In prior observational studies, metformin use has most strongly been associated with reduced rates of liver cancer in patients with cirrhosis,[9-12] chronic hepatitis B,[41] or diabetes[42, 43] with hazard ratios ranging from 0.19-0.49. Metformin directly inhibits the growth of HCC cell lines *in vitro* and in animal models,[44] and may also reduce hepatic fibrogenesis.[45] In a large population-based study from Taiwan, Chen et al.[12] reported a 21% decrease in the risk of HCC in diabetic patients exposed to metformin after multiple adjustments, but not controlling for concomitant statin use. In another study using the Taiwanese national database, after adjustment for statin exposure, an apparent protective effect of metformin in univariable analysis disappeared while statins remained significantly associated with reduced HCC risk.[35, 46] Similarly, we found no demonstrable impact of metformin on HCC or hepatic decompensation events after adjusting for concomitant statin utilization, further supporting the argument that statin co-utilization has confounded the prior evidence for metformin as a chemopreventive agent for HCC in population-level studies.

Discontinuation of medications in patients with liver disease is a common practice due to the perceived threat of altered hepatic metabolism and toxicity. Indeed, the Food and Drug

As with any observational cohort study, unmeasured confounding and residual confounding by indication cannot be excluded. There is no active comparator for metformin use and we did not

formally compare metformin plus statin to metformin without statins. This was a study of mostly male U.S. Veterans who are older, may be more affected by medical comorbidities, and have worse outcomes than the general U.S. population. While we did adjust for aspirin, statins, other diabetes therapies, ACEI/A2RB and NSBB use, there are other medication exposures that could confound the association of metformin with survival outcomes. Finally, we had a small representation of Child-Turcotte-Pugh C patients limiting the strength of inferences related to treatment effect in this subgroup.

CONCLUSIONS:

In this large cohort of patients with cirrhosis, diabetic patients exposed to metformin exhibited dose-dependent reduced mortality (HR 0.57-0.87) even after adjusting for the concomitant use of aspirin, statins, ACEI/A2RB, and NSBBs. Contrasting with some prior studies, no significant effect of metformin was observed on the reduction of HCC, hepatic decompensation, or liver-related death after adjusting for concomitant statin and ACEI/A2RB exposure. Metformin use was generally safe. Similar to the general diabetic population, metformin should be utilized when appropriate in diabetic patients with cirrhosis for improvement of overall, but not necessarily liver-related, survival. .

FIGURE LEGENDS

Figure 1. Cohort identification and grouping for analysis.

Figure 2. Effect of Metformin Continuation in Existing Users. A. Persistence of metformin utilization among metformin-experienced patients with cirrhosis over the course of follow-up. Red line indicates percentage surviving. **B**. Effect of continued metformin exposure in days on relative risk of death in Landmark analysis evaluating first 360 days in metformin-experienced patients. Weighted (gray) and unweighted analysis (black) are shown. **C**. Effect of continued metformin exposure in cumulative dose (mg) on relative risk of death in Landmark analysis evaluating first 360 days in metformin-experienced patients. **D-F.** Parallel analysis to A-C for metformin-naïve diabetic patients with cirrhosis.

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TABLES.

Table 1. Baseline Characteristics of Patients with Cirrhosis and Pre-Existing Diabetes

	Diabetes Preceding Cirrhosis Prior Metformin		
	No	Yes	p
N	23228	19301	
Age, Median (IQR)	62 (57-67)	63 (58-67)	<0.0001
Gender, Male, N (%)	22695 (97.7%)	18715 (97.0%)	<0.0001
Race/Ethnicity, N (%)			<0.0001
White	12863 (55.4%)	11610 (60.2%)	
Black	4830 (20.8%)	3249 (16.8%)	
Hispanic	1928 (8.3%)	1567 (8.1%)	
Other/Unknown	3607 (15.5%)	2875 (14.9%)	
Etiology, N (%)			<0.0001
HCV + Alcohol	6081 (26.2%)	4195 (21.7%)	
HCV	3444 (14.8%)	2445 (12.7%)	
Alcohol	7650 (32.9%)	6448 (33.4%)	
NAFLD/NASH	4614 (19.9%)	5123 (26.5%)	
Other	1439 (6.2%)	1090 (5.6%)	
AUDIT-C > 4 in prior year, N (%)	3327 (14.3%)	2336 (12.1%)	0.013
HIV+, N (%)	460 (2.0%)	258 (1.3%)	<0.0001
Managed at Academic Center, N (%)	13427 (57.8%)	10822 (56.1%)	0.005
Seen by Hepatologist, N (%)	3994 (17.2%)	3480 (18.0%)	<0.0001
Body Mass Index, Median (IQR)	28.2 (24.5-32.5)	30.3 (26.4-34.6)	0.22
Body Mass Class, N (%)			<0.0001
Underweight	760 (3.3%)	308 (1.6%)	
Ideal	5261 (22.6%)	2735 (14.2%)	
Overweight	7856 (33.8%)	5861 (30.4%)	
Obese	9351 (40.3%)	10397 (53.9%)	
Child-Turcotte-Pugh Score, Median (IQR)	6 (5-7)	6 (5-7)	<0.0001
MELDNa Score, Median (IQR)	9 (7-12)	8 (7-11)	<0.0001
Decompensated at Cirrhosis Diagnosis, N (%)	4931 (21.2%)	3393 (17.6%)	<0.0001
Duration of diabetes, Median Days (IQR)	1958 (659-3132)	2706 (1556-3706)	<0.0001
Dyslipidemia, N (%)	21192 (91.2%)	18780 (97.3%)	<0.0001
Hypertension, N (%)	22261 (95.8%)	19135 (99.1%)	<0.0001
Pre-Existing CAD, N (%)	5916 (25.5%)	5782 (30.0%)	<0.0001
Cumulative Metformin Exposure prior to cirrhosis, Median (IQR)	0 (0-0)	670 (248-1316)	<0.0001
Cumulative Metformin Exposure after cirrhosis, Median (IQR)	0 (0-0)	272 (0-876)	<0.0001
Metformin stopped > 90d before Cirrhosis, N (%)	0 (0.0%)	7312 (37.9%)	<0.0001
Metformin filled within 90d after Cirrhosis, N (%)	855 (3.7%)	8751 (45.3%)	<0.0001
Any Metformin after Cirrhosis, N (%)	4740 (20.4%)	12408 (64.3%)	<0.0001
Prior Exposure to Statin, N (%)	8166 (35.2%)	12055 (62.5%)	<0.0001
Prior Exposure to Insulin, N (%)	5910 (25.4%)	8751 (45.3%)	<0.0001
Prior Exposure to Sulfonylurea, N (%)	5098 (21.9%)	11626 (60.2%)	<0.0001
Prior Exposure to TZD, N (%)	503 (2.2%)	1818 (9.4%)	<0.0001
Prior Exposure to DPP4, N (%)	75 (0.3%)	294 (1.5%)	<0.0001
Prior Exposure to GLP1, N (%)	21 (0.1%)	88 (0.5%)	<0.0001
Prior Exposure to Other Anti-Diabetes, N (%)	171 (0.7%)	605 (3.1%)	<0.0001
Follow-up Time, Median (IQR)	1232 (653-2084)	1142 (631-1892)	<0.0001

Table 2. Univariable and Multivariable Cox Proportional Hazards for Death

Model	At-risk/Events 11,527 / 3,885 Variable	Univariate HR (95%CI)	p	Multivariate HR (95%CI)	p
1*	**Exposure to Metformin, Time-Updating**	**0.42 (0.38-0.46)**	**<0.0001**	**0.68 (0.61-0.75)**	**<0.0001**
	Exposure to Statin, Time-Updating	0.53 (0.50-0.56)	<0.0001	0.71 (0.64-0.80)	<0.0001
	Exposure to ACEI/A2RB, Time-Updating	0.40 (0.36-0.43)	<0.0001	0.60 (0.54-0.66)	<0.0001
2‡	**CTP A**			**0.54 (0.48-0.60)**	**<0.0001**
	CTP B			**0.68 (0.57-0.81)**	**<0.0001**
	CTP C			**0.55 (0.30-1.02)**	**0.06**
3°	**HCV + ETOH**			**0.58 (0.46-0.74)**	**0.0004**
	HCV			**0.58 (0.41-0.80)**	**<0.0001**
	ETOH			**0.75 (0.65-0.88)**	**0.0003**
	NAFLD/NASH			**0.58 (0.48-0.68)**	**<0.0001**
	Other Etiology			**0.66 (0.43-1.01)**	**0.053**
4¶	**Cumulative Exposure to Metformin, Time-Updating (per year)**	**0.82 (0.80-0.83)**	**<0.0001**	**0.955 (0.924-0.987)**	**0.007**
1*	Age	1.03 (1.03-1.04)	<0.0001	1.03 (1.02-1.04)	<0.0001
	Etiology				
	HCV+EtOH	REF		REF	
	HCV	1.04 (0.93-1.15)	0.52	1.34 (1.13-1.59)	0.0008
	EtOH	1.30 (1.20-1.41)	<0.0001	1.26 (1.10-1.45)	0.0008
	NAFLD/NASH	1.46 (1.34-1.58)	<0.0001	1.52 (1.30-1.77)	<0.0001
	Other	1.21 (1.07-1.38)	0.004	1.20 (0.95-1.52)	0.10
	HCV DAA after diagnosis, Time-Updating	0.41 (0.36-0.46)	<0.0001	0.73 (0.59-0.90)	0.003
	Child-Turcotte-Pugh Class (Time-Updating)				
	A	REF		REF	
	B	5.01 (4.71-5.32)	<0.0001	2.74 (2.46-3.04)	<0.0001
	C	16.17 (13.96-18.72)	<0.0001	7.03 (5.42-9.12)	<0.0001
	MELDNa, Time-Updating (per unit)	1.14 (1.13-1.15)	<0.0001	1.04 (1.03-1.06)	<0.0001
	Hemoglobin A1c, Time-Updating (per unit)	splined	<0.0001	splined	<0.01
	Tobacco Use Status				
	Never User	REF		REF	
	Former User	1.16 (1.08-1.26)	0.0002	1.21 (1.07-1.36)	0.002
	Current User	1.35 (1.26-1.45)	<0.0001	1.59 (1.40-1.81)	<0.0001
	Unknown	1.54 (1.21-1.95)	0.0004	1.76 (1.31-2.37)	0.0001
	Hypertension				
	No	REF		REF	
	Yes	1.02 (0.79-1.31)	0.91	1.14 (0.98-1.34)	0.10
	Coronary Artery Disease				
	No	REF		REF	
	Yes	1.32 (1.24-1.40)	<0.0001	1.21 (1.09-1.34)	0.0003
	AUDIT-C ≥ 4 in year prior to cirrhosis				
	No	REF		REF	
	Yes	1.17 (1.07-1.27)	0.0003	1.18 (1.01-1.37)	0.02
	Total Cholesterol, mg/dl, Time-Updating (per unit)	0.99 (0.99-0.99)	<0.0001	0.99 (0.99-0.99)	<0.0001
	Cumulative Exposure to Meformin before Cirrhosis (per year)	1.01 (0.99-1.02)	0.30	1.00 (0.99-1.00)	0.33
	Exposure to Insulin, Time-Updating	1.05 (0.99-1.11)	0.10	1.06 (0.95-1.18)	0.25
	Exposure to Sulfonylurea, Time-Updating	0.66 (0.61-0.70)	<0.0001	0.90 (0.80-1.01)	0.08
	Exposure to TZD, Time-Updating	0.53 (0.37-0.74)	<0.0001	0.81 (0.55-1.19)	0.29
	Exposure to GLP1, Time-Updating	0.42 (0.24-0.76)	0.004	0.69 (0.44-1.08)	0.10
	Exposure to DPP4, Time-Updating	0.55 (0.42-0.72)	<0.0001	0.74 (0.41-1.35)	0.33

* Model 1 covariates include gender, race/ethnicity, Cirrhosis comorbidity score, body mass index class, academic affiliation of managing center, frequency of low socioeconomic status at the managing center ‡ Model 1 stratifed by time-updated Child-Turcotte-Pugh class ° Model 1 stratified by disease etiology ¶ Model evaluates cumulative exposure to Metformin (in years) as a time-updating covariate with identical covariates to Model 1.

Table 3. Impact of Metformin and other medications on HCC, decompensation and MACE

HCC[*]	At-risk/ Events	HR	p
Exposure to Metformin, Time-Updating	11,246 /	0.98 (0.81-1.18)	0.86
Exposure to Statin, Time-Updating	856	**0.74 (0.60-0.90)**	**0.003**
Exposure to Insulin, Time-Updating		**1.41 (1.15-1.72)**	**0.001**
Exposure to Sulfonylurea, Time-Updating		1.16 (0.96-1.40)	0.11
Decompensation[*,§]	At-risk/ Events	HR	p
Exposure to Metformin, Time-Updating	8,088 /	1.06 (0.82-1.09)	0.43
Exposure to Statin, Time-Updating	1,545	**0.78 (0.68-0.90)**	**0.0007**
Exposure to Insulin, Time-Updating		**1.19 (1.01-1.41)**	**0.034**
Exposure to Sulfonylurea, Time-Updating		1.07 (0.93-1.23)	0.37
MACE[*,†]	At-risk/ Events	HR	p
Exposure to Metformin, Time-Updating	9,833 /	1.00 (0.83-1.23)	0.93
Exposure to Statin, Time-Updating	663	1.09 (0.89-1.34)	0.39
Exposure to Insulin, Time-Updating		1.18 (0.95-1.45)	0.12
Exposure to Sulfonylurea, Time-Updating		1.15 (0.94-1.41)	0.17

*Models adjutsed for age, gender, race/ethnicity, disease etiology, Child-Turcotte-Pugh stage, MELDNa, platelet count, AST, ALT, academic affiliation of treatment site, socioeconomic indicator, baseline history of CAD § Child-Turcotte-Pugh A patients only † Analysis includes only patients with no previous MACE events.

Table 4. Effect of Metformin on Liver-related and Diabetes/Cardiovascular Death in Landmark Competing Risk and MSM models

Cohort/Outcome	Outcome	At-Risk/Events	Analysis		Exposure	HR (95%CI)	p
Metformin-experienced	Liver-related death or transplant[1]	10,238 / 858	Univariable	Landmark	**Metformin exposure, per 30 days**	**0.98 (0.96-0.99)**	**0.03**
	Liver-related death	11,527 / 637		MSM	**Metformin exposure, time-updating**	**0.34 (0.27-0.43)**	**<0.0001**
	Liver-related death or transplant[1]	10,238 / 858	Multivariable[3]	Landmark	Metformin exposure, per 30 days	0.99 (0.98-1.01)	0.89
					Statin exposure, per 30 days	0.94 (0.93-0.96)	<0.0001
					ACEI exposure, per 30 days	1.00 (0.99-1.02)	0.18
	Liver-related death	11,527 / 637	Multivariable[4]	MSM	**Metformin exposure, time-updating**	**0.65 (0.51-0.84)**	**0.001**
					Statin exposure, time-updating	0.47 (0.35-0.64)	<0.0001
					ACEI/A2RB exposure, time-updating	0.51 (0.40-0.66)	<0.0001
	Diabetes/Cardiovascular death[2]	10,238 / 341	Univariable	Landmark	**Metformin exposure, per 30 days**	**0.96 (0.94-0.98)**	**0.002**
	Diabetes/Cardiovascular death	11,527 / 374		MSM	**Metformin exposure, time-updating**	**0.53 (0.39-0.72)**	**<0.0001**
	Diabetes/Cardiovascular death[2]	10,238 / 341	Multivariable[3]	Landmark	**Metformin exposure, per 30 days**	**0.95 (0.93-0.98)**	**0.0009**
					Statin exposure, per 30 days	1.01 (0.99-1.04)	0.06
					ACEI exposure, per 30 days	1.01 (0.99-1.03)	0.21
	Diabetes/Cardiovascular death	11,527 / 374	Multivariable[4]	MSM	**Metformin exposure, time-updating**	**0.67 (0.47-0.95)**	**0.02**
					Statin exposure, time-updating	0.88 (0.62-1.25)	0.49
					ACEI/A2RB exposure, time-updating	0.89 (0.64-1.25)	0.52

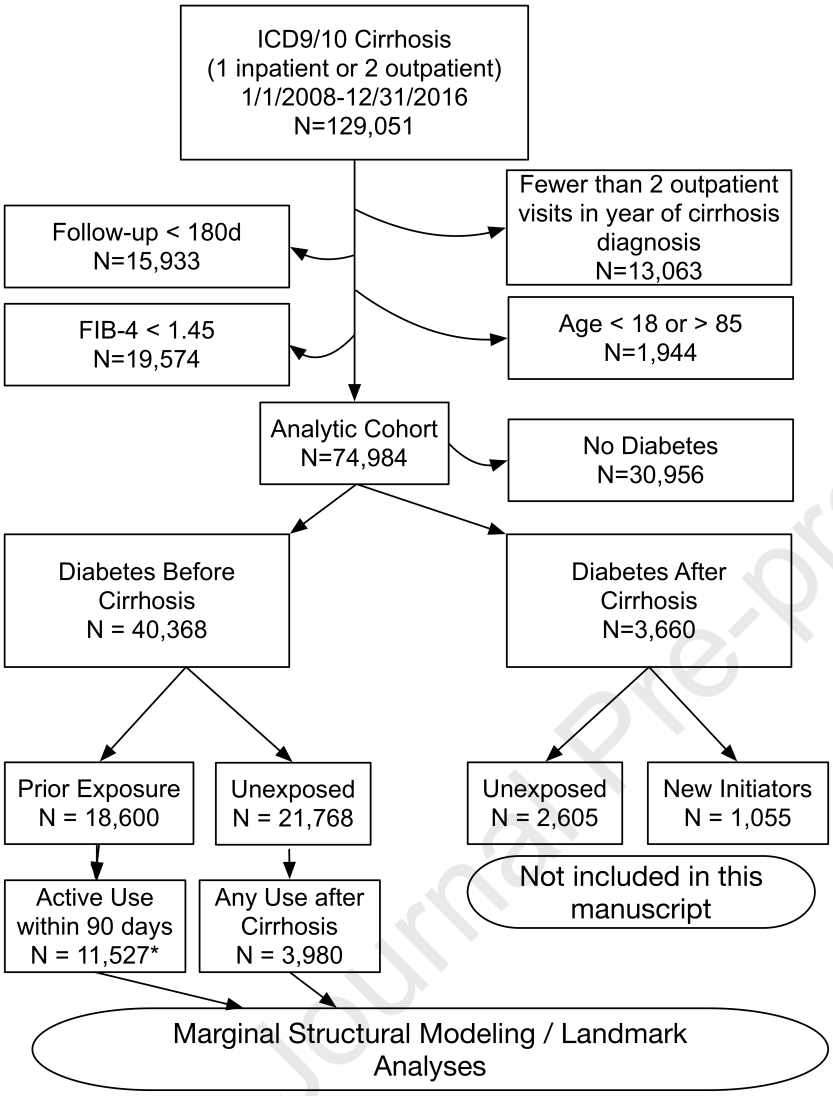
[1] Diabetes/Cardiovascular death as competing-risk

[2] Liver-related death or transplant as competing-risk

[3] Adjusted for age, race/ethnicity, etiology, Child-Turcotte-Pugh Score

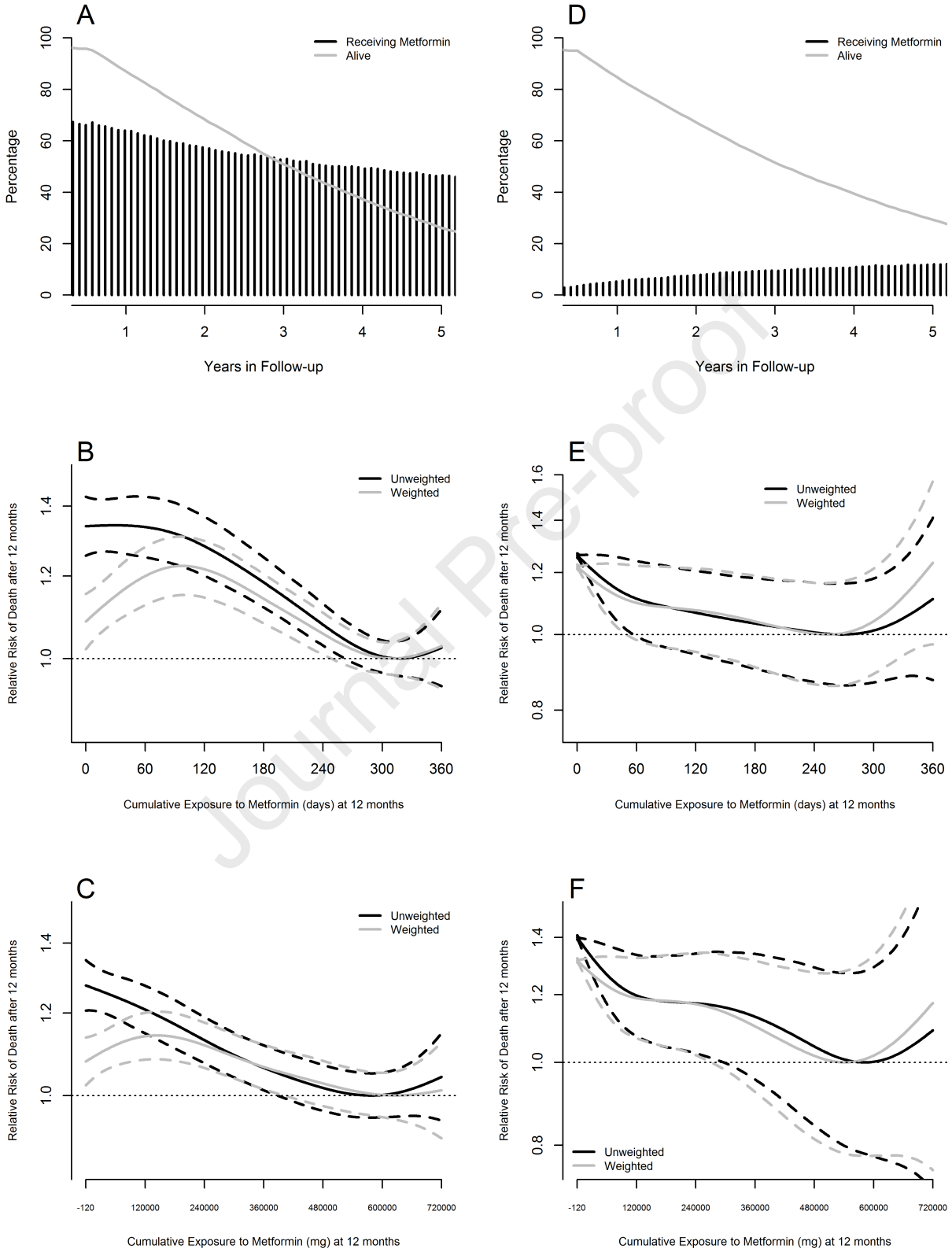
[4] Adjusted for age, race/ethnicity, etiology, Child-Turcotte-Pugh Score, exposure to aspirin, other diabetes therapies, MELDNa, FIB4, Circom, smoking, prior CAD, AUDIT-C, BMI, HCV DAA therapy , HBA1c, Total cholesterol, prior metformin exposure and prior insulin exposure; HR for cardiovascular death alone 0.58 95%CI 0.39-0.87.

Figure 1. Cohort identification and grouping for analysis.



* N = 1,680 (14.5%) had no additional metformin fills

Figure 2. Use of Metformin in Patients with Diabetes Prior to Cirrhosis



Supplemental Methods

Data Sources

The VA Corporate Data Warehouse is a centralized data repository that contains patient demographics, International Classification of Diseases (ICD9-CM/ICD10 (ICD) diagnosis and current procedural terminology (CPT) codes, laboratory data as well as pharmacy prescription records on all patients receiving care within the VA.

Covariates

The following laboratory values were obtained from 2 years prior to cohort entry and throughout follow-up: serum sodium (Na), creatinine (Cr), total bilirubin (TBili), albumin (Alb), alanine aminotransferase (ALT), aspartate aminotransferase (AST), alphafetoprotein (AFP), hepatitis C virus RNA (HCV RNA), hepatitis B DNA (HBV DNA), serum lipids, international normalized ratio (INR), hemoglobin A1c (HBA1c) and platelet count (PLT). Missing laboratory data were imputed in R using the MICE package with a random forest algorithm.[1]

Chart validation of Mortality Death Registry

To validate the accuracy of the VA Mortality Death Registry (MDR) for attribution of cause of death, we performed a retrospective chart review of 321 patient charts between January 1, 2008 and June 30, 2016. Two adjudicators (KMT, RL) separately reviewed 321 charts to determine cause of death and determine liver-relatedness of death. Discrepant results were adjudicated by a third reviewer (DEK, MS). 47 cases were excluded due to insufficient data in the VA chart to determine likely cause of death. The performance characteristics of the MDR for identifying liver-related deaths were as follows: sensitivity 81.3%, specificity 87.9%, positive predictive value 91.3% (95% CI: 86.4% - 96.4%), negative predictive value 75.2% (95% CI: 66.6% - 83.8%). Inter-rater kappa agreement between final adjudication and MDR was k = 0.70 (95% CI: 0.607–0.792).

Exposures

Medication exposures quantified included: Aspirin (ASA); insulin and insulin-sulfonylureas, thiazolidinediones, dipeptidyl-peptidase inhibitors, GLP1 receptor agonists, SLGT2 inhibitors, and other hypoglycemic agents; HMG-coA reductase inhibitors (statins); ACE inhibitors and A2RB (ACEI/A2RB); nonselective beta-blockers (NSBB); and direct acting antivirals (DAAs) for chronic hepatitis B and C

Supplemental Results

Lactic Acidosis

Among 16,649 patients with cirrhosis who received metformin after cirrhosis over 56,237 years of follow-up, 1,250 events were documented where lactic acid levels were ≥ 5 mmol/l. Of these, 588 cases coincided with active metformin utilization at a rate of 1.7 cases per 100 patient-years of exposure. This rate was significantly lower than 3.0 cases of lactic acidosis per 100 patient-years of follow-up for these patients when not exposed to metformin, and 3.3 per 100 patient-years for never metformin-exposed diabetic patients with cirrhosis (HR 0.61 95%CI 0.52-0.72).

Discussion

Administration has a boxed warning for metformin in the setting of impaired hepatic function due to the risk of lactic acidosis. Paradoxically, in exploratory analyses we found that lactic acidosis rates were indeed lower among metformin users than non-users in this population of diabetic cirrhosis patients at high risk for acute kidney injury and sepsis. While selection could bias these results, these data support data from larger population studies that suggest that metformin utilization does not impart a significant excess risk of lactic acidosis.[2]

Supplementary Figure 1. Relationship of HBA1c and all-cause mortality. Effect of HBA1c modeled in MSM as linear predictor or natural spline (df=5) on mortality after adjusting for age, Child-Pugh status, race/ethnicity, gender, disease etiology, alcohol use and platelet count.

Supplementary Figure 2. Inverse probability weights. Balance of IPTW weights over follow up are shown using three different definitions of exposure in metformin-experiences (**A-C**) and metformin-naïve subjects (**D-F**). **A, D** 7d/30d windown. **B, E**. 14d/30d window. **C, F**. 21d/30d window.

Supplementary Figure 3. Effect of Metformin or Statin Exposure on risk of hepatocellular carcinoma in Landmark analysis. A. Metformin Experienced patients. B. Metformin-naïve patients. Hazard ratio for death across exposures ranges in days for metformin (black) and statin (gray) in Landmark analysis at 360 days after diagnosis of cirrhosis.

Supplementary Figure 4. Effect of Metformin Exposure on risk of liver-related or diabetes/cardiovascular-related death in Landmark analysis. A. Metformin Experienced patients. B. Metformin-naïve patients. Hazard ratio for death across exposures ranges in days for metformin for the outcome of liver-related death (black) and diabetes/cardiovascular-related death (gray) in Landmark analysis at 360 days after diagnosis of cirrhosis.

Supplemental Figure 5. Effect of Metformin Exposure Days and Dose on Overall Mortality. Landmark Analysis at 180 days. B. Effect of continued metformin exposure in days on relative risk of death in Landmark analysis evaluating first 180 days in metformin-experienced patients. Weighted (gray) and unweighted analysis (black) are shown. **B**. Effect of continued metformin exposure in cumulative dose (mg) on relative risk of death in Landmark

analysis evaluating first 180 days in metformin-experienced patients. Days exposure to metformin. **C-D** Parallel analysis in metformin-naïve diabetic patients.

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Supplementary Table 1. ICD-9-CM, ICD10, and CPT Codes used for Identification of Morbidities

Diagnosis	ICD9-CM	ICD10	CPT Codes
Atrial Fibrillation	427.31	I48.0-I48.4, I48.91-I48.92	
Acute Myocardial Infarction	410.xx, 411	I21.x - I 24.x	
Ascites	789.5x	R18.0, R18.8	
Coronary Artery Disease	410.xx, 411.xx, 412.xx, 413.xx (except 413.0x, 413.1x), 414.xx (except 414.1x)	I20.x , I25.x	
Cardiac Arrest	427.5	I46.2, I46.8, I46.9	
Congestive Heart Failure	398.91, 402.01, 402.11, 404.01,402.91, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4x - 425.9x, 428.xx	I50.1x - I50.43, I50.9	
Cerebrovascular Accident	430.xx - 436.xx, 438.xx, 997.02	I60.x - I63.x	
Dyslipidemia	272.x	E78.x	
Diabetes mellitus	250.x	E10.x, E11.x, E13.x	
Hepatocellular carcinoma	155.0, 155.2, exclude 155.1	C22.0, C22.8, exclude C22.1	
Hepatorenal Syndrome	572.4	K76.7	
Hypertension	401.x	I10, I12.0, I12.9	
Myositis/Myopathy	359.4, 359.8, 359.9, 729.1	M60.x, G72.x	
Obesity	278.x	E66.x	
Osteopenia	733.9x	M85.8x	
Osteoporosis	733.x	M80.0x, M80.8x	
Pulmonary Embolism	415.1x	I26.x	
Pulmonary Hypertension	572.3	K76.6	
Spontaneous Bacterial Peritonitis	567.2x, 567.8x, 567.9	K65.2	
Varices	456.1x, 456.2x	I85.0x, I85.1x, I86.4	
Percutaneous Cardiac Intervention			99275, 92980-92984, 92995-92996
Coronary Artery Bypass Graft			33510-33545
Hepatic Decompensation	789.5x, 567.2x, 567.8x, 567.9, 456.1x, 456.2x, 572.4	R18.0, K65.2, I85.0x, I85.1x, I86.4, R18.8, K76.7	
Major Acute Cardiovascular Event	410.xx, 411, 430.xx - 436.xx, 438.xx, 997.02	I21.x - I 24.x, I60.x - I63.x	99275, 92980-92984, 92995-92996, 33510-33545

Supplemental Table 2. ICD10 Coding/Classification of Cause of Death in Mortality Data Repository

ICD10 Code	General Class	Probably Liver-related	Probably Diabetes Related	Cardiovascular	Other
A%	Infection				X
B16 - B19	Liver-related infection	X			
B94.2	Liver-related infection	X			
All other B	Infection				X
C22	Liver-related Neoplasm	X			
All other C	Neoplasm				X
D13.4, D37.6	Liver-related Neoplasm	X			
All other D	Neoplasm				X
E1%	Diabetes		X		
E3%	Neoplasm				X
E5%	Substance Abuse				X
E6%	Obesity				X
E7%	Cardiovascular			X	
E84%	Pulmonary				X
E87%	Renal		X		
All other E	Endocrine				X
F%	Psychiatric				X
G0%	Infection				X
All other G	Neurological				X
I%	Cardiovascular			X	
J%	Pulmonary				X
K7%	Liver-related	X			
K9%, K22.6	Gastrointestinal hemorrhage	X			
K4%	Hernia related	X			
K65%	Peritonitis	X			
All other K	Other				X
L%	Other				X
M86.9	Osteomyelitis		X		
M7%	Infection				X
All other M	Other				X
N%	Renal		X		
Q%	Other				X
R04%	Infection				X
R09%	Pulmonary				X
All other R	Cardiovascular			X	
Y83%	Liver-related	X			
All other Y	Other				X

Supplemental Table 3. IPW Weights used in Survival Analyses

Metformin Status	Days required for Exposure = 1	Type	Min.	1st Qu.	Median	Mean	3rd Qu.	Max.
Experienced	7	Raw	0.000	0.582	0.822	1.677	1.189	9920.234
		Truncated	0.033	0.582	0.822	1.029	1.189	6.624
	14	Raw	0.000	0.639	0.854	1.561	1.178	8971.917
		Truncated	0.045	0.639	0.854	1.034	1.178	5.930
	21	Raw	0.000	0.556	0.855	1.049	1.111	614.601
		Truncated	0.030	0.556	0.855	0.916	1.111	4.024
Naïve	7	Raw	0.003	0.901	0.978	1.024	1.033	222.683
		Truncated	0.206	0.901	0.978	0.993	1.033	2.827
	14	Raw	0.036	0.895	0.975	1.029	1.033	260.916
		Truncated	0.198	0.895	0.975	0.998	1.033	3.052
	21	Raw	0.048	0.891	0.973	1.026	1.029	150.963
		Truncated	0.174	0.891	0.973	1.000	1.029	3.338

Supplemental Table 4. Effect of IPTW on balance of covariates

	Unweighted			Weighted		
	Unexposed	Exposed	SMD	Unexposed	Exposed	SMD
N of pseudopopulation	241904	283799		266544.14	274479.16	
Age	64.37 (7.47)	64.11 (6.90)	0.036	64.04 (7.55)	63.71 (6.82)	0.047
Race/Ethnicity			0.042			0.051
W	149568.0 (61.8)	180088.0 (63.5)		164331.1 (61.7)	171987.8 (62.7)	
B	38603.0 (16.0)	42887.0 (15.1)		42837.0 (16.1)	43452.4 (15.8)	
H	21078.0 (8.7)	23412.0 (8.2)		22801.9 (8.6)	22959.1 (8.4)	
API	3763.0 (1.6)	5133.0 (1.8)		3642.6 (1.4)	5065.6 (1.8)	
O/U	28892.0 (11.9)	32279.0 (11.4)		32931.5 (12.4)	31014.3 (11.3)	
Etiology			0.097			0.108
HCV+EtOH	56007.0 (23.2)	58251.0 (20.5)		62108.0 (23.3)	58496.3 (21.3)	
HCV	26609.0 (11.0)	37415.0 (13.2)		28966.6 (10.9)	38098.3 (13.9)	
EtOH	84000.0 (34.7)	93850.0 (33.1)		93272.3 (35.0)	89191.1 (32.5)	
NAFLD/NASH	60945.0 (25.2)	77097.0 (27.2)		67030.5 (25.1)	72899.6 (26.6)	
Other	14343.0 (5.9)	17186.0 (6.1)		15166.7 (5.7)	15793.8 (5.8)	
Child-Turcotte-Pugh class			0.37			0.24
A	177786.0 (73.5)	248965.0 (87.7)		203033.6 (76.2)	234523.9 (85.4)	
B	60939.0 (25.2)	34070.0 (12.0)		60576.1 (22.7)	38799.5 (14.1)	
C	3179.0 (1.3)	764.0 (0.3)		2934.5 (1.1)	1155.7 (0.4)	
WHO ISH Risk			0.058			0.054
<10%	99404.0 (41.1)	121608.0 (42.9)		112690.8 (42.3)	120543.8 (43.9)	
10-19.9%	87594.0 (36.2)	103569.0 (36.5)		95350.4 (35.8)	99053.4 (36.1)	
20-29.9%	33380.0 (13.8)	37038.0 (13.1)		35895.3 (13.5)	34680.1 (12.6)	
30-39.9%	9060.0 (3.7)	9472.0 (3.3)		9542.6 (3.6)	8794.3 (3.2)	
>= 40%	12201.0 (5.0)	11827.0 (4.2)		12782.4 (4.8)	11101.7 (4.0)	
Unknown	265.0 (0.1)	285.0 (0.1)		282.6 (0.1)	305.9 (0.1)	
ASCVD	0.73 (0.44)	0.66 (0.47)	0.149	0.70 (0.46)	0.67 (0.47)	0.066
Hepatic encephalopathy subscore	1.01 (0.10)	1.00 (0.06)	0.072	1.01 (0.10)	1.00 (0.07)	0.05
Ascites subscore	1.04 (0.23)	1.01 (0.13)	0.123	1.03 (0.21)	1.02 (0.15)	0.084
Albumin	3.53 (0.61)	3.77 (0.51)	0.442	3.57 (0.60)	3.73 (0.53)	0.292
Total Bilirubin	1.13 (1.04)	0.94 (0.68)	0.221	1.11 (0.96)	0.96 (0.75)	0.166
HBA1c	7.19 (1.78)	7.20 (1.55)	0.006	7.22 (1.79)	7.24 (1.61)	0.012
Platelet count	125.44 (60.92)	132.81 (59.19)	0.123	126.48 (59.82)	131.95 (59.78)	0.092
Creatinine	1.13 (1.11)	1.02 (0.93)	0.107	1.11 (1.08)	1.06 (1.10)	0.046
Diabetes duration	3901.55 (1500.85)	3706.38 (1390.92)	0.135	3658.15 (1556.94)	3787.76 (1329.43)	0.09
Metformin lag	0.07 (0.26)	0.92 (0.26)	3.264	0.07 (0.25)	0.92 (0.27)	3.259
ACEI/A2RB lag	0.41 (0.49)	0.64 (0.48)	0.481	0.39 (0.49)	0.65 (0.48)	0.553
Statin lag	0.30 (0.46)	0.46 (0.50)	0.333	0.28 (0.45)	0.47 (0.50)	0.4
Sulfonylurea lag	0.20 (0.40)	0.35 (0.48)	0.336	0.18 (0.39)	0.34 (0.47)	0.373
Insulin lag	0.42 (0.49)	0.36 (0.48)	0.135	0.37 (0.48)	0.42 (0.49)	0.091
TZD lag	0.01 (0.10)	0.02 (0.12)	0.058	0.01 (0.10)	0.01 (0.12)	0.042
Other diabetes	0.01 (0.08)	0.01 (0.10)	0.044	0.01 (0.08)	0.01 (0.10)	0.055

Supplemental Table 5. Baseline and Event rates in follow-up of Metformin-experienced patients with or without re-exposure after a diagnosis with cirrhosis

	Event	No Re-exposure	Re-exposed
N		1680	9847
Baseline	Decompensation	48.8%	23.2%
	MACE	20.1%	14.4%
	Ascites	23.3%	7.2%
	Hepatic Encephalopathy	5.6%	2.4%
Event rates	Death	18.1	8.8
	HCC	5.9	2.3
	Decompensation	17.1	9.1
	MACE	3.5	2.4
	Ascites	9.5	4.6
	Hepatic Encephalopathy	8.0	3.6

Supplemental Table 6. Baseline Morbidity and Event Rates during Follow-up

	Diabetes Preceding Cirrhosis Prior Metformin	
	No	Yes
Pre-Existing Comorbidity (%)		
Hepatic Decompensation	39.2%	31.2%
Ascites	19.3%	12.6%
Hepatic Encephalopathy	6.6%	4.2%
TIPSS placement	0.3%	0.2%
Major Adverse Cardiovascular Event	15.4%	16.8%
History of Acute Myocardial Infarction	4.4%	4.6%
Coronary Artery Disease	34.2%	42.8%
History of Cardiac Arrest	0.4%	0.2%
History of Stroke	10.8%	11.6%
Congestive Heart Failure	22.1%	21.5%
History of Cardiac Intervention (CABG or PCI)	1.1%	1.7%
Atrial Fibrillation	11.3%	10.1%
Pulmonary Embolus	1.3%	0.9%
Event Rate (per 100 patient-years)		
Death	12.7	11.4
Death, Child-Pugh A Only	9.7	8.9
Death, Child-Pugh A Only, HCV-infected treated with HCV DAA	2.6	2.4
Death, Child-Pugh A Only, NAFLD/NASH	13.2	11.0
Death, Child-Pugh A Only, Alcohol-related	9.3	8.4
Hepatocellular Carcinoma	3.0	2.8
Hepatic Decompensation	10.9	10.2
Ascites	6.1	5.5
Hepatic Encephalopathy	5.0	4.4
TIPSS placement	0.5	0.6
Major Adverse Cardiovascular Event	2.7	2.7
Acute Myocardial Infarction	0.8	0.8
Coronary Artery Disease	2.9	3.0
Cardiac Arrest	0.3	0.2
Stroke	2.0	1.8
Congestive Heart Failure	3.5	3.7
Cardiac Intervention (CABG or PCI)	0.2	0.2
Atrial Fibrillation	1.8	1.6
Pulmonary Embolus	0.3	0.2

Supplemental Table 7. Estimates of Effect Size varying Exposure threshold

Cohort	Threshold days for Exposure = 1	Univariable HR	p-value	Multivariable HR*	p-value
Metformin-experienced	7	0.42 (0.38-0.46)	<0.0001	0.68 (0.61-0.75)	<0.0001
	14	0.41 (0.37-0.44)	<0.0001	0.66 (0.60-0.73)	<0.0001
	21	0.37 (0.34-0.41)	<0.0001	0.62 (0.57-0.69)	<0.0001
Metformin-naive	7	0.37 (0.24-0.56)	<0.0001	0.69 (0.56-0.85)	0.0006
	14	0.34 (0.20-0.56)	<0.0001	0.44 (0.27-0.73)	0.0016
	21	0.49 (0.31-0.76)	0.002	0.46 (0.27-0.78)	0.004

*Adjusted for age, race, ethnicity, etiology, Child-Turcotte-Pugh stage; statin, ACEI/A2RB, insulin, secretagogue, aspirin, and other diabetes therapy exposures; MELDNa, FIB4, Circom, smoking, prior CAD, AUDIT-C, BMI, HCV DAA therapy , HBA1c, Total cholesterol

Supplemental Table 8. Univariable and Multivariable Marginal Structural Model of Risk of Hepatic Decompensation

At-risk/Events 8,088 /1,545	Univariable		Multivariable	
Variable	HR (95%CI)	p	HR (95%CI)	p
Prior exposure to Metformin, per year	1.00 (1.00-1.00)	0.23	1.00 (1.00-1.00)	1.00
Prior exposure to Insulin, per year	1.00 (1.00-1.00)	**0.06**	1.00 (1.00-1.00)	0.16
Metformin Exposure, time-updating	**0.78 (0.71-0.87)**	**<0.0001**	0.93 (0.79-1.09)	0.36
Statin Exposure, time-updating	**0.74 (0.67-0.82)**	**<0.0001**	**0.80 (0.68-0.96)**	**0.01**
ACEI/A2RB exposure, time-updating	**0.77 (0.69-0.85)**	**<0.0001**	0.80 (0.68-0.95)	0.01
Aspirin exposure, time-updating	**0.77 (0.67-0.87)**	**<0.0001**	1.05 (0.86-1.29)	0.62
Non-selective beta-blocker, time-updating	1.70 (1.49-1.94)	<0.0001	1.33 (1.07-1.66)	0.01
insulin Exposure, time-updating	1.10 (0.99-1.22)	0.07	1.14 (0.93-1.40)	0.2
Sulfonylurea Exposure, time-updating	1.10 (0.99-1.23)	0.07	1.15 (0.96-1.37)	0.13
Age, per year	0.98 (0.98-0.99)	<0.0001	0.98 (0.97-1.00)	0.007
Gender				
Male	REF		REF	
Female	0.99 (0.75-1.30)	0.93	1.26 (0.82-1.94)	0.30
Race/Ethnicity				
White	REF			
Black	0.50 (0.42-0.59)	**<0.0001**	**0.48 (0.37-0.62)**	**<0.0001**
Hispanic	0.97 (0.81-1.16)	0.77	0.92 (0.68-1.25)	0.60
Asian/Pacific Islander	0.82 (0.56-1.22)	**0.33**	0.88 (0.54-1.44)	0.61
Other/Unknown	1.20 (1.04-1.38)	0.01	1.20 (0.96-1.51)	0.11
Etiology				
HCV+Alcohol	REF			
HCV	0.79 (0.66-0.95)	**0.01**	0.81 (0.61-1.07)	0.14
Alcohol	1.22 (1.07-1.39)	**0.004**	0.81 (0.64-1.01)	0.06
NAFLD/NASH	1.03 (0.89-1.19)	**0.68**	**0.76 (0.59-0.97)**	**0.03**
Other/Unknown	1.10 (0.88-1.37)	0.42	**0.56 (0.37-0.87)**	**0.009**
Child-Turcotte-Pugh				
A	REF			
B	2.93 (2.60-3.31)	**<0.0001**	1.93 (1.51-2.46)	**<0.0001**
C	9.54 (5.18-17.58)	**<0.0001**	4.44 (1.68-11.75)	**0.003**
MELDNa, time-updating, per unit	1.08 (1.07-1.09)	**<0.0001**	1.04 (1.02-1.06)	**<0.0001**
FIB-4, time-updating, per unit	1.01 (1.01-1.01)	<0.0001	**1.01 (1.00-1.01)**	**<0.0001**
Cirrhosis Comorbidity Index				
0	REF			
1+0	1.05 (0.93-1.18)	0.45	1.03 (0.85-1.24)	0.8
1+1	0.85 (0.71-1.02)	0.08	0.82 (0.63-1.07)	0.15
3+0	0.89 (0.68-1.17)	0.40	1.10 (0.74-1.65)	0.64
3+1	0.92 (0.75-1.13)	0.42	1.01 (1.00-1.02)	**0.03**
BMI, time-updating, per unit	1.01 (1.01-1.02)	**0.0002**	1.01 (1.00-1.02)	**0.03**
HCVDAA exposure, time-updating	0.26 (0.19-0.34)	**<0.0001**	0.23 (0.14-0.38)	**<0.0001**
HBA1c, natural spline, time-updating) 1	0.23 (0.13-0.40)	<0.0001	0.39 (0.15-1.02)	0.06
HBA1c, natural spline, time-updating) 2	0.24 (0.12-0.45)	**<0.0001**	0.36 (0.12-1.04)	0.06
HBA1c, natural spline, time-updating) 3	0.50 (0.29-0.88)	**0.02**	0.42 (0.18-0.96)	0.04
HBA1c, natural spline, time-updating) 4	0.09 (0.02-0.41)	**0.002**	0.17 (0.02-1.82)	0.14
HBA1c, natural spline, time-updating) 5	0.49 (0.08-2.96)	0.44	1.83 (0.22-15.33)	0.58
Total Cholesterol, time-updating, per 10 mg/dl	0.98 (0.96-0.99)	**0.0005**	1.00 (1.00-1.00)	**0.05**

Supplemental Table 9. Univariable and Multivariable Marginal Structural Model of Risk of Hepatocellular Carcinoma

At-risk/Events 11,246/856	Univariable		Multivariable	
Variable	HR (95%CI)	p	HR (95%CI)	p
Metformin Exposure, time-updating	**0.83 (0.73-0.96)**	**0.009**	0.98 (0.81-1.18)	0.87
Statin Exposure, time-updating	**0.63 (0.54-0.73)**	**<0.0001**	**0.74 (0.60-0.90)**	**0.003**
ACEI/A2RB exposure, time-updating	0.92 (0.80-1.05)	0.20	1.01 (0.85-1.22)	0.83
Aspirin exposure, time-updating			1.05 (0.82-1.34)	0.66
Non-selective beta-blocker, time-updating	**1.48 (1.28-1.71)**	**<0.0001**	1.35 (1.11-1.64)	0.001
Insulin Exposure, time-updating	1.09 (0.95-1.25)	0.21	1.43 (1.17-1.75)	0.0003
Sulfonylurea Exposure, time-updating	1.17 (1.02-1.35)	**0.03**	1.17 (0.97-1.42)	0.09
Age, per year	1.01 (1.00-1.02)	0.13	1.02 (1.01-1.03)	0.0004
Gender				
Male	REF		REF	
Female	0.52 (0.30-0.87)	0.01	0.70 (0.38-1.28)	0.25
Race/Ethnicity				
White	REF			
Black	1.07 (0.88-1.30)	**0.48**	0.95 (0.72-1.24)	0.71
Hispanic	1.31 (1.04-1.64)	0.02	1.74 (1.26-2.41)	0.001
Asian/Pacific Islander	1.38 (0.86-2.21)	**0.19**	1.85 (1.08-3.15)	0.02
Other/Unknown	1.47 (1.21-1.78)	<0.0001	1.44 (1.12-1.85)	0.004
Etiology				
HCV+Alcohol	REF			
HCV	1.30 (1.07-1.59)	**0.009**	1.45 (1.12-1.88)	0.004
Alcohol	0.62 (0.51-0.74)	**<0.0001**	0.58 (0.44-0.77)	0.0001
NAFLD/NASH	0.70 (0.58-0.85)	**0.0003**	0.73 (0.54-0.98)	0.04
Other/Unknown	0.82 (0.61-1.11)	0.19	0.75 (0.51-1.11)	0.16
Child-Turcotte-Pugh				
A	REF			
B	2.00 (1.73-2.32)	**<0.0001**	1.83 (1.48-2.25)	<0.0001
C	3.18 (1.88-5.37)	**<0.0001**	2.43 (1.20-4.89)	0.01
MELDNa, time-updating, per unit	1.04 (1.02-1.06)	**<0.0001**	1.00 (0.98-1.03)	0.55
FIB-4, time-updating, per unit	1.01 (1.00-1.01)	<0.0001	1.00 (1.00-1.00)	<0.0001
Cirrhosis Comorbidity Index				
0	REF			
1+0	1.04 (0.88-1.22)	**0.65**	0.92 (0.74-1.14)	0.48
1+1	0.91 (0.71-1.16)	**0.44**	0.79 (0.57-1.08)	0.14
3+0	1.37 (1.00-1.86)	**0.05**	1.46 (1.01-2.11)	0.04
3+1	0.76 (0.56-1.04)	0.09	0.70 (0.48-1.03)	0.07
Smoking Status				
Never	REF			
Former	1.18 (0.98-1.42)	**0.08**	1.10 (0.86-1.41)	0.43
Current	1.28 (1.08-1.52)	**0.004**	1.30 (1.03-1.63)	0.02
Unknown	1.17 (0.64-2.15)	**0.61**	0.90 (0.42-1.95)	0.80
Prior Coronary Artery Disease				
Yes	0.78 (0.66-0.91)	**0.002**	0.85 (0.68-1.06)	0.17
HCVDAA exposure, time-updating	0.98 (0.78-1.23)	**0.88**	0.92 (0.66-1.28)	0.63
HBA1c, natural spline, time-updating) 1	0.25 (0.10-0.64)	**0.004**	0.61 (0.18-2.01)	0.42
HBA1c, natural spline, time-updating) 2	0.29 (0.10-0.84)	**0.02**	0.60 (0.15-2.31)	0.45
HBA1c, natural spline, time-updating) 3	0.22 (0.10-0.48)	**0.0001**	0.18 (0.07-0.46)	0.0003
HBA1c, natural spline, time-updating) 4	0.11 (0.01-1.11)	**0.06**	0.52 (0.02-9.83)	0.66
HBA1c, natural spline, time-updating) 5	1.15 (0.15-8.97)	**0.89**	2.87 (0.35-23.3)	0.32
Total Cholesterol, time-updating, per 10 mg/dl	0.97 (0.95-0.99)	**0.004**	0.99 (0.99-1.00)	0.78

Supplemental Table 10. Sensitivity Analysis for Various Exclusionary Windows for HCC development

Exclusionary period	Variable	Metformin-experienced N events	Metformin-experienced HR (95% CI)	Metformin-experienced p-value	Metformin-naïve N events	Metformin-naïve HR (95% CI)	Metformin-naïve p-value
180d	Metformin exposure, time-updating	856	0.98 (0.81-1.18)	0.86	2053	1.01 (0.83-1.23)	0.87
	Statin-exposure time-updating		0.74 (0.60-0.90)	0.003		0.60 (0.51-0.70)	<0.0001
360d	Metformin exposure, time-updating	712	0.92 (0.74-1.14)	0.46	1754	1.08 (0.88-1.32)	0.42
	Statin-exposure time-updating		0.74 (0.59-0.93)	0.009		0.58 (0.50-0.69)	<0.0001
540d	Metformin exposure, time-updating	608	0.94 (0.76-1.18)	0.64	1490	1.10 (0.89-1.36)	0.37
	Statin-exposure time-updating		0.79 (0.62-1.01)	0.06		0.56 (0.47-0.67)	<0.0001
720d	Metformin exposure, time-updating	522	1.02 (0.80-1.31)	0.81	1267	1.02 (0.81-1.28)	0.82
	Statin-exposure time-updating		0.83 (0.63-1.09)	0.18		0.57 (0.47-0.69)	<0.0001

Supplemental Table 11. Outcomes related to medication exposure in metformin-naïve diabetic patients with cirrhosis

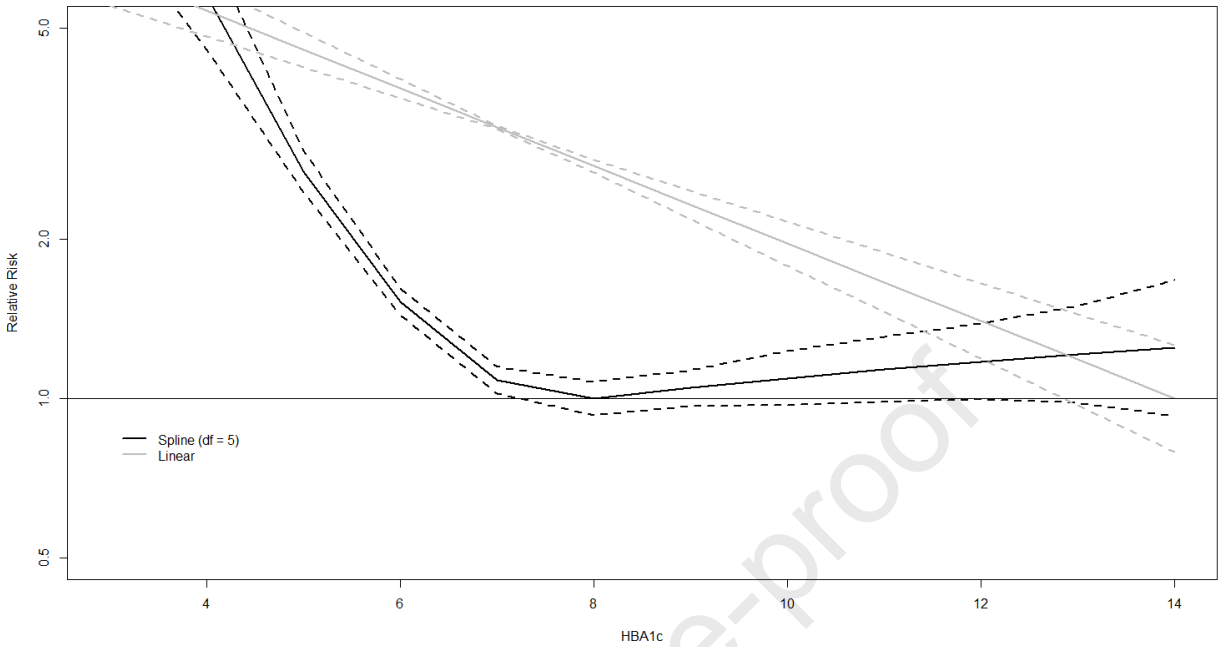
Outcome	At-risk / Events	Medication	HR (95% CI)	p-value
Death[1]	21.768 / 9,848	**Metformin**	**0.72 (0.63-0.82)**	**<0.0001**
At-risk/Events 21,768/1,582		**Statin**	**0.77 (0.66-0.90)**	**0.001**
Decompensation[2]	13,514 / 1,493	Metformin	1.07 (0.53-2.15)	0.84
At-risk/Events 21,768/		**Statin**	**0.66 (0.56-0.77)**	**<0.0001**
Hepatocellular Carcinoma[3]	21,269 / 2,053	Metformin	1.01 (0.83-1.23)	0.87
At-risk/Events 21,269/2		**Statin**	**0.60 (0.51-0.70)**	**<0.0001**

[1] Adjusted for age, gender, race/ethnicity, etiology, Child-Turcotte-Pugh class, MELDNa, FIB-4, CirCom score, tobacco use, prior CAD, AUDIT-C, BMI, exposure to HCV antiviral therapy, HBA1c, total cholesterol, prior insulin exposure, insulin exposure, secretagogue exposure, DPP4 exposure, thiazolidinedione exposure, GLP1RA, ACEI/A2RB, and NSBB exposure

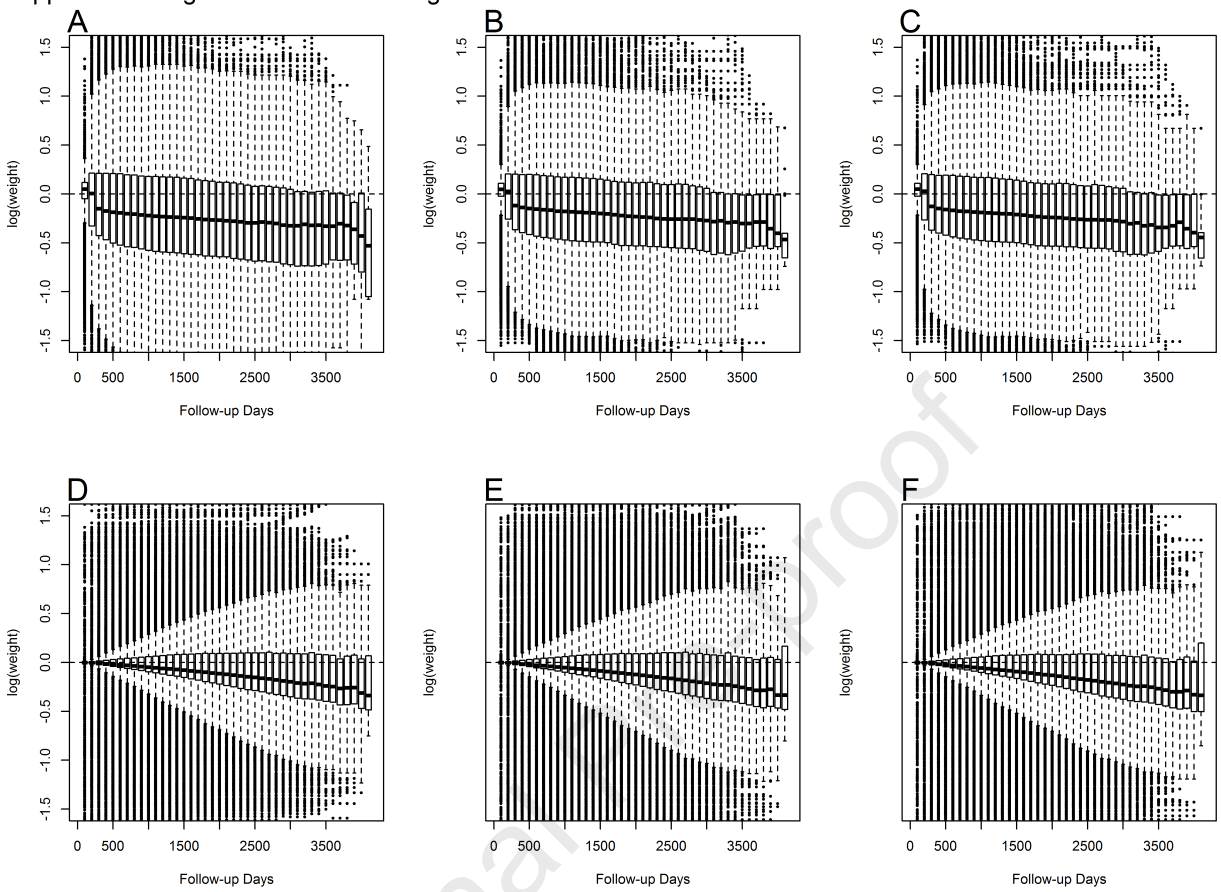
[2] As for death anaylsis, but not including tobacco use

[3] As for death, but not including GLP1RA exposure

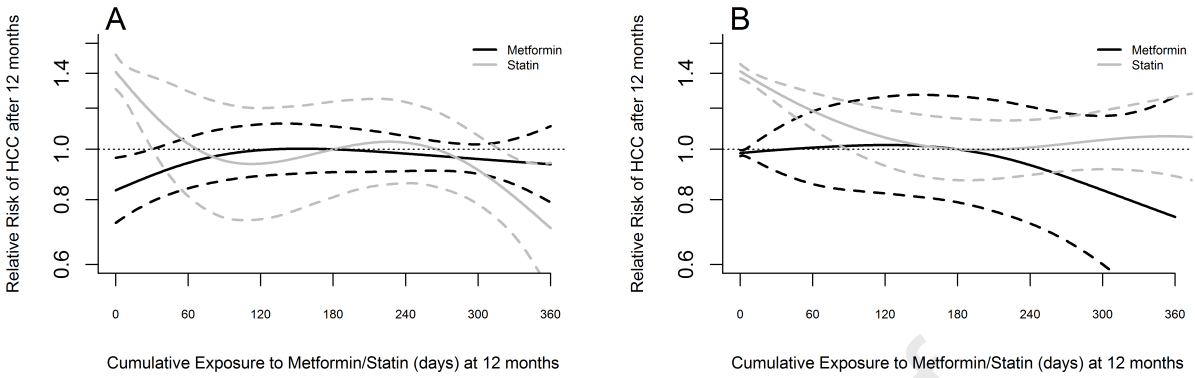
Supplemental Figure 1. Association of HBA1c and Relative Risk of Mortality. Comparison of linear and natural spline (df =5) relationship



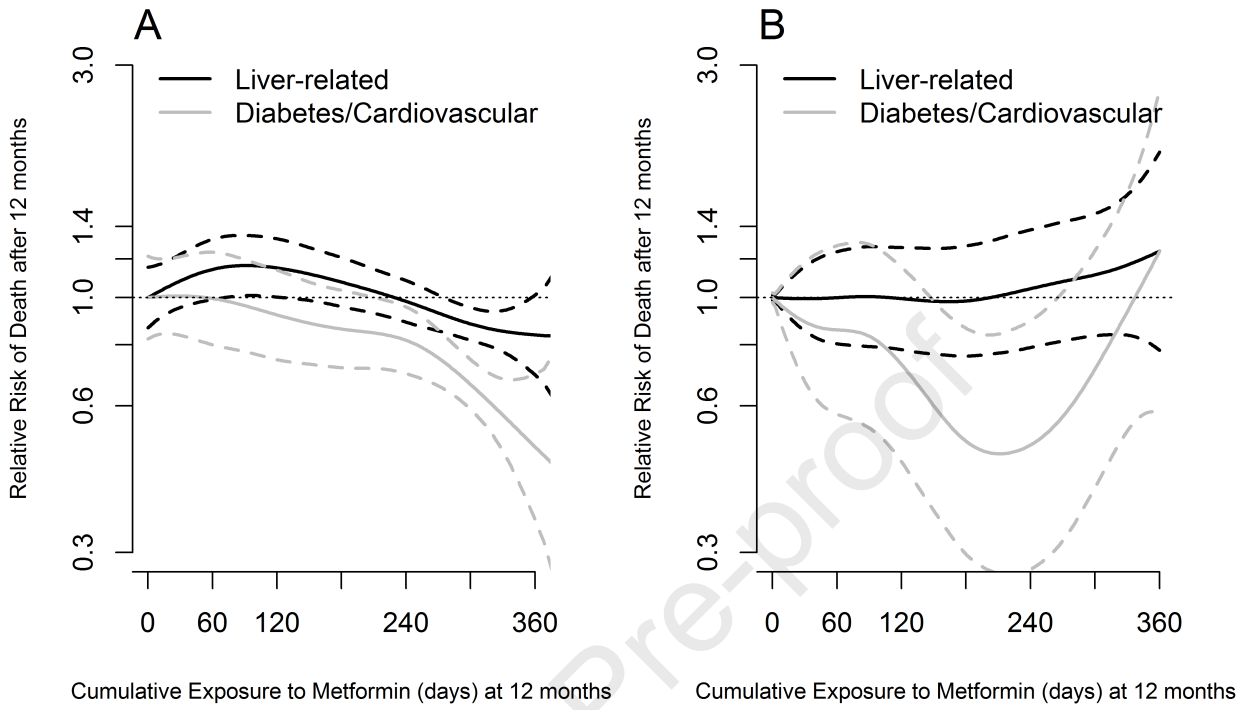
Supplemental Figure 2. Stabilized Weights of IPTW Models



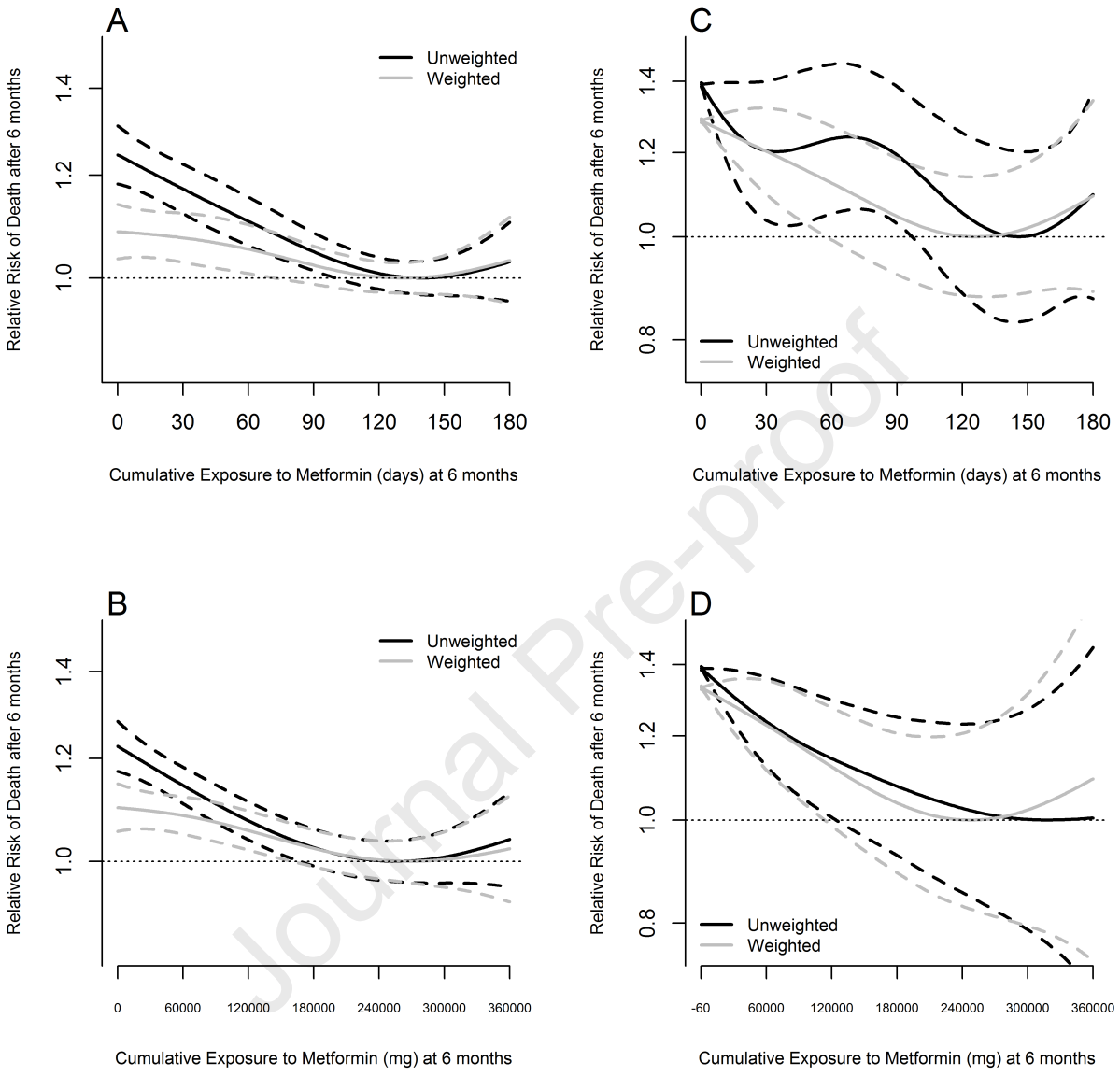
Supplemental Figure 3. Effect on HCC of Exposure to Metformin or Statin in Patients with Diabetes Prior to Cirrhosis



Supplemental Figure 4. Effect of Exposure to Metformin on Liver-related and Diabetes/cardiovascular



Supplemental Figure 5. Use of Metformin in Patients with Diabetes Prior to Cirrhosis



LAY SUMMARY FOR TABLE OF CONTENTS

Among a large, national sample, each year of exposure to metformin therapy was associated with reduced mortality but effects on hepatocellular risk were largely mediated by co-administration of statins.

WHAT YOU NEED TO KNOW

BACKGROUND AND CONTEXT

Multiple studies suggest that metformin reduce the risks of liver cancer in patients with diabetes and cirrhosis but have incompletely controlled for critical confounding by factors such as concomitant administration of statins, ACE inhibitors or angiotensin-2 receptor blockers.

NEW FINDINGS

Adjusting for statin use and other relevant covariates in marginal structural models, metformin was associated with an 30-43% reduction of mortality in patients with cirrhosis and diabetes, but had no significant impact on liver cancer.

LIMITATIONS

Unmeasured residual confounding cannot be excluded. The study included older, mostly male U.S. Veterans who may not completely represent the general U.S. population.

IMPACT

This study supports and refines understanding of the association of metformin therapy with reduced risks of death in diabetic patients with cirrhosis. Statin utilization in diabetic patients appears most impactful for independent reductions in liver cancer and hepatic decompensation.