Among Patients With NAFLD, Treatment of Dyslipidemia Does Not Reduce Cardiovascular Mortality

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Dyslipidemia is one of the common risk factors for NAFLD and is associated with cardiovascular (CV) mortality, which is the most common cause of death in NAFLD. Lipid-lowering agents (LLAs) are used to reduce CV events in the general population. Our aim was to assess whether the use of LLAs in patients with NAFLD can reduce the risk of CV mortality. We used the third National Health and Nutrition Examination Survey mortality linked files. Mortality was determined from the National Death Index records through 2011. NAFLD was diagnosed by ultrasound after exclusion of other causes of liver disease. After inclusion and exclusion, the cohort consisted of 2,566 patients with NAFLD (45.8% < 45 years of age, 52.8% male, 75.4% white). Those who were taking LLAs were more likely to be older, non-Hispanic white, and had significantly higher rates of diabetes mellitus (DM), hyperlipidemia, hypertension, metabolic syndrome, and history of CV disease (CVD) (all $P < 0.01$). In our multivariate analysis, DM was an independent predictor of overall mortality (adjusted hazard ratio [aHR]: 1.79 [95% confidence interval (CI): 1.40-2.30]) and CV mortality (aHR: 1.89 [95% CI: 1.08-3.30]). History of CVD was associated with both overall (aHR: 2.03 [95% CI: 1.57-2.63]) and CV mortality (aHR: 3.69 [95% CI: 2.23-6.08]). In contrast, the use of statins and other LLAs was not associated with reduction in overall (aHR = 0.95 [95% CI: 0.37-2.44] and aHR = 1.43 [95% CI: 0.99-2.07]) and CV mortality (aHR = 1.20 [95% CI: 0.26-5.54] and aHR = 1.63 [95% CI: 0.70-3.76]). *Conclusion:* The use of statins and other LLAs did not reduce the increased risk of overall or CV mortality in NAFLD. (*Hepatology Communications* 2018;2:1227-1234).

NAFLD is poised to soon become the most common cause of liver disease in the world.[1-3] The persistent increase in rates of obesity, diabetes mellitus (DM), and metabolic syndrome (MS) are major contributing factors to the rapid increase in the prevalence of NAFLD. Dyslipidemia is an important comorbidity that is frequently observed in these patients.[4] In fact, patients with NAFLD have a proatherogenic lipid profile characterized by high triglycerides, increased very-low density lipoprotein (LDL), and high apolipoprotein B to apolipoprotein A-1 ratio, as well as a higher concentration of small dense LDL coupled with low high-density lipoprotein concentration.[5-7] In this context, cardiovascular disease (CVD) is also very common among patients with NAFLD, and cardiovascular (CV) mortality is the most common cause of death in these patients.[1-5]

Current treatments for patients with NAFLD include lifestyle modification with the aim of weight loss, the use of pioglitazone, and vitamin E

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; CKD, chronic kidney disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; HL, hyperlipidemia; HTN, hypertension; LLAs, lipid-lowering agents; MS, metabolic syndrome; NCHS, National Center for Health Statistics; and NHANES III, Third National Health and Nutrition Examination Survey.

Received March 20, 2018; accepted July 12, 2018.

Additional Supporting Information may be found at onlinelibrary.wiley.com/doi/10.1002/hep4.1241/suppinfo.

View this article online at wileyonlinelibrary.com.

DOI 10.1002/hep4.1241

Potential conflict of interest: Dr. Younossi is a consultant to BMS, Gilead, AbbVie, Intercept, and GSK.

supplementation.[8-10] Many of these patients also take statins or other lipid-lowering agents (LLAs), as they often have many of the components of metabolic syndrome including diabetes, insulin resistance, dyslipidemia, and obesity.[1-10] In this context, impaired cholesterol metabolism may play a part in the development of NAFLD and its CV complications. The hepatic lipotoxicity hypothesis implies that exposure to, or accumulation of, certain lipid species within hepatic cells may directly cause cellular toxicity or act in a pro-inflammatory or pro-fibrotic manner.[7,11] Potentially lipotoxic molecules include cholesterol, free fatty acids, and their derivatives, as well as diacylglycerol or ceramides. Extensive dysregulation of cholesterol homeostasis has been documented in NAFLD, causing both increased synthesis and uptake of cholesterol as well as decreased removal of cholesterol, leading to increased hepatic cholesterol levels.[12-14]

There has been some concern over the use of LLAs such as statins and their potential to cause hepatotoxicity in NAFLD patients.[15-20] The 2014 Statin Liver Safety Taskforce recommendations further expresses the opinion that discontinuation of statin therapy is a major concern among patients with mildly elevated transaminase without elevation in serum bilirubin.[21] However, a population-based study showed that there is no increase in mortality of NAFLD patients who use statins.[22] Mild to moderate elevation in transaminases (less than 2-3 times the upper limit of normal) without increase in serum bilirubin likely does not represent true hepatotoxicity, but can result in discontinuation of therapy in the clinical setting.

From the literature, there is a general consensus that statins reduce overall mortality, combined fatal and nonfatal CVD, coronary heart disease, and fatal and nonfatal stroke in both primary and secondary prevention.[23-25] Evidence has shown that the treatment of atherogenic dyslipidemia in patients with DM or MS does reduce the risk of CVD and favorably affects mortality.[5] Furthermore, due to their anti-inflammatory, anti-oxidant, and antithrombotic effects, some believe statins may be beneficial for the treatment for NAFLD.[17] Interestingly, recent data have suggested that the association between NAFLD and CVD cannot be solely attributable to the common risk factors among these diseases and there is an independent association between NAFLD and CVD in the US population.[25] In contrast to the data about the positive impact of statins on mortality in the general population, there are little data to suggest that treating dyslipidemia in NAFLD with statins or other LLAs can be effective in reducing CV or overall mortality. With these concepts in mind, we aimed to examine whether the use of LLAs can affect CV and overall mortality in patients with NAFLD.

Materials and Methods

We conducted a retrospective study using data from the National Health and Nutrition Examination Survey (NHANES) III collected by the National Center for Health Statistics (NCHS) with the public-use linked mortality file. The survey includes an interview at home for demographic, socioeconomic, dietary, and health-related questions, a subsequent physical examination at a mobile examination center, as well as laboratory tests and radiologic test with ultrasound of the gallbladder and liver. The descriptions of NHANES data have been reported in detail elsewhere.[26]

STUDY DEFINITIONS

Obesity was defined as body mass index ≥ 30 kg/m^2 or a waist circumference ≥ 102 cm in men and ≥ 88 cm in women. DM was defined as a fasting glucose value

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≥ 126 mg/dL or current use of hypoglycemic and/or insulin. Insulin resistance was defined as a homeostasis of model assessment score ≥ 3.0. Hypertension (HTN) was defined as mean systolic blood pressure ≥ 140 mmHg, mean diastolic blood pressure ≥ 90 mmHg, or current use of antihypertensive medications. Hyperlipidemia (HL) was defined as a total serum cholesterol ≥ 240 mg/dL. Excessive alcohol consumption was defined as ≥ 20 g per day in men and ≥ 10 g per day in women. Iron overload (IO) is defined as serum transferrin saturation ≥ 50%. Elevated liver enzymes were defined as increased cholesterol level ≥ 40 U/L in men and ≥ 31 U/L in women or aspartate aminotransferase level ≥ 37 U/L in men and ≥ 31 U/L in women. Alcoholic liver disease (ALD) was defined by excessive alcohol use and elevated liver enzyme. Chronic hepatitis C (CH-C) was defined as positive hepatitis C virus RNA. Chronic hepatitis B (CH-B) was defined as positive Hepatitis B surface antigen. We defined CVD as a history of congestive heart failure, heart attack, or stroke obtained by individual self-report. Chronic kidney disease (CKD) was defined by either the presence of albuminuria or an estimated glomerular filtration rate (GFR) of ≤ 60 mL/min/1.73m^2. Serum creatinine measurements were standardized by the NHANES recommendation.[27] Albuminuria was defined as a urinary albumin-creatinine ratio ≥ 30 mg/g. GFR was estimated by using the 2012 CKD Epidemiology Collaboration creatinine equation.[28] Participants' age, race/ethnicity (non-Hispanic white, non-Hispanic black, Mexican-American, or other, which included other Hispanics, Asians, and Native Americans), sex, and current smoking status are gathered from self-reported data from the NHANES in-home interview.

USE OF LLAS

Current use of LLAs was determined by the use of statins, HMG-CoA (3-hydroxy-3-methylglutaryl-CoA) reductase inhibitors, (simvastatin, lovastatin, or pravastatin) or other LLAs (cholestyramine, clofibrate, colestipol, gemfibrozil, niacin, or probucol) in the prescription medication file and niacin in the vitamin and mineral file.[27] In the household adult questionnaire, participants taking LLAs were also included.

PRESENCE OF NAFLD

For NHANES III adults aged 20 to 74 years, the presence of fat within the hepatic parenchyma (hepatic steatosis) was assessed by reviewing the archived hepatobiliary ultrasound video images between 2009 and 2010. The assessment was reported as normal, mild, moderate, or severe hepatic steatosis.[29] For the purpose of this study, NAFLD was defined as moderate or severe hepatic steatosis in the absence of any other evidence of chronic liver diseases such as ALD, CH-B, CH-C, or IO and erythema annulare centrifugum.[30]

MORTALITY

NCHS linked NHANES III participants aged 20 years and older to the National Death Index to December 31, 2011, using probabilistic matching. Cause of death was obtained from the underlying cause listed on the death certificate by using codes from the International Classification of Diseases ninth version (ICD-9 code; 1988-1998) or tenth version (ICD-10 code; 1999-2006). From the public-use linked mortality files, we identified deaths from overall and CV (ICD-9: 390-459 and 410-414; ICD-10: I00-I90, I11, I13, and I20-I51),[31] such as ischemic heart diseases, heart failure, atherosclerosis, aortic aneurysm, and other diseases of arteries, arterioles, and capillaries.

STUDY POPULATION

Of the 20,050 adult participants from NHANES III, we excluded 1,261 participants who were younger than 20 years and not followed for mortality. Of these 18,789 participants, we excluded 4,918 participants due to missing information on hepatic ultrasound data. For the purpose of the study, we excluded 10,143 participants without NAFLD. The final cohort included 2,566 participants who had NAFLD based on ultrasonographic findings. Compared with participants in the final cohort, participants who were excluded due to not having NAFLD were more likely to be younger (41.8 versus 47.8 years, $P < 0.001$), non-Hispanic black (11.34% versus 8.67%, $P = 0.003$), and female (53.6% versus 47.2%, $P < 0.001$). Those without NAFLD also had a lower prevalence of comorbidities (obesity, DM, HL, HTN, MS, CKD, and CVD, $P < 0.001$), and lower risk for overall or CV mortality (16.8% versus 25.5% or 3.6% versus 6.1%, respectively).

STATISTICAL ANALYSIS

The complex survey design elements (clusters, strata, and sampling weights) provided by the NCHS were used to account for the survey design, survey

nonresponse, and oversampling of older persons, black persons, and Mexican-Americans.[32] Sampling errors were estimated by the Taylor series linearization, a design-based method using subpopulation (domain) analysis. Variables were expressed as weighted means or percentages with standard error. Various characteristics were compared by LLA users in NAFLD patients using the stratum-specific chi-square test for categorical variables and a t-statistic for continuous variables at the $P < 0.05$ significance level. Cox proportional-hazards models were used to evaluate the association of statin use with overall or CV mortality in NAFLD patients after adjustment for demographics and comorbidities. The proportional hazards assumption of the Cox models were examined by testing time-dependent covariates.[33] All analyses were performed with SAS software, version 9.4 (SAS Institute, Cary, NC).

Results

CHARACTERISTICS OF STUDY POPULATION

In our study, we included 2,566 patients with NAFLD (52.8% male, 75.4% non-Hispanic white, 8.7% non-Hispanic black, 7.6% Mexican-American, and 8.3% of other racial backgrounds). The mean age of all patients was 47.8 years (Table 1). The prevalence of comorbid chronic conditions among those with NAFLD included obesity (47.6%), DM (15.2%), HL (28.1%), HTN (35.3%), MS (58.1%), CKD (13.5%), history of cancer (7.1%), and history of CVD (7.8%) (Table 1).

There were significant differences in statin and other LLA use by NAFLD status (1.2% versus 1.9% and 2.1% versus 3.8%, $P < 0.05$) (Supporting Table S1). Approximately 28% of patients with NAFLD

TABLE 1. CHARACTERISTICS OF NAFLD, BY LLA USE, NHANES III (1988-1994)

Characteristics	All (n = 2,566)	No Medication Use (n = 2,450)	LLA Use		
			Other Use (n = 81)	Statin Use (n = 35)	All (n = 116)
Age, SEM	47.78 (0.56)	47.18 (0.59)	58.09 (0.77)*	56.89 (2.31)*	57.68 (0.99)*
Age, years					
20-44	45.81 (2.06)	47.66 (2.16)	11.61 (6.25)	22.57 (12.35)	15.30 (5.50)*
45-54	20.07 (1.18)	19.77 (1.29)	29.03 (6.20)	17.18 (7.60)	25.04 (4.72)
55-64	18.62 (1.37)	17.63 (1.41)	29.72 (6.22)*	45.63 (10.19)*	35.07 (5.40)*
65-74	15.50 (0.96)	14.95 (0.98)	29.64 (6.02)*	14.63 (5.24)†	24.58 (4.47)*
Male	52.76 (1.29)	52.46 (1.33)	53.74 (6.92)	65.48 (9.52)	57.69 (5.46)
Race					
non-Hispanic white	75.36 (1.76)	74.42 (1.82)	90.15 (3.04)*	92.46 (3.22)*	90.93 (2.39)*
non-Hispanic black	8.67 (0.83)	8.88 (0.87)	5.72 (2.27)	4.41 (2.42)	5.28 (1.77)
Mexican American	7.64 (0.81)	7.93 (0.85)	3.10 (1.18)*	2.45 (1.59)	2.88 (0.86)*
Other	8.32 (1.32)	8.77 (1.38)	1.03 (0.77)*	0.68 (0.71)*	0.91 (0.70)*
Active smoker	22.83 (1.16)	23.66 (1.25)	10.00 (3.21)*	7.61 (5.55)	9.20 (2.90)*
Comorbidities					
Obese	47.57 (1.97)	47.50 (1.99)	46.45 (7.26)	52.89 (8.69)	48.62 (5.15)
DM	15.24 (0.90)	14.45 (0.99)	24.57 (5.82)	36.66 (10.79)*	28.80 (5.23)*
HL	28.12 (1.61)	24.40 (1.59)	88.84 (4.25)*	91.07 (7.10)*	89.59 (3.69)*
HTN	35.29 (1.73)	34.02 (1.72)	60.44 (7.65)*	48.32 (9.74)	56.36 (5.77)*
MS	58.08 (1.85)	56.69 (2.01)	80.77 (7.35)*	81.60 (7.50)*	81.06 (6.31)*
CKD	13.37 (1.09)	13.23 (1.13)	17.89 (4.88)	12.22 (5.12)	15.93 (3.45)
History of cancer	7.14 (0.73)	6.70 (0.72)	13.45 (5.18)	16.40 (6.24)*	14.44 (4.44)*
History of CVD	7.80 (0.72)	6.51 (0.69)	21.89 (5.72)*	43.46 (11.44)*	29.16 (5.36)*
Overall mortality, %	25.49 (1.51)	24.29 (1.58)	49.15 (6.69)*	38.05 (9.84)*	45.41 (5.38)*
CV mortality, %	6.12 (0.64)	5.44 (0.61)	17.92 (6.11)*	16.37 (7.54)*	17.40 (4.60)*

Note: Data are presented as the weighted percentage/SEM.
*$P < 0.05$ compared with no medication use.
†$P < 0.05$ compared with other medication use.

had hyperlipidemia (Table 1). Only 18.2% of NAFLD with hyperlipidemia used LLAs (data not shown).

Compared with NAFLD patients who were not on LLAs, those who did were more likely to be older, non-Hispanic white, have DM, HL, HTN, MS, history of cancer, and history of CVD (all *P* values < 0.01). There were no significant differences in comorbidities of obesity and CKD.

MORTALITY

The median follow-up was 225 months for the entire NAFLD cohort and 199 months for NAFLD patients using LLAs. The weighted unadjusted overall mortality was significantly higher in statin and other LLA users than in nonmedication users (38.1% and 49.2% versus 24.3%, $P < 0.001$). An analogous pattern was observed with CV mortality rates (16.4% and 17.9% versus 5.44%, $P < 0.001$). There were also no significant differences in overall and CV mortality rates between those who used statins versus those who used other LLAs.

OVERALL MORTALITY

The unadjusted hazard ratios of overall mortality were 2.01 (95% confidence interval [CI]: 0.96-4.21) for statin and 2.41 (95% CI: 1.63-3.56) for other LLA users compared with nonmedication users. After adjusting for demographic, metabolic components, and important comorbidities, the use of statin (aHR = 0.95 [95% CI: 0.37-2.44]) and other LLAs (aHR = 1.43 [95% CI: 0.99-2.07]) was not significantly associated with risk for overall mortality. In contrast, older age, male, smoking, presence of DM, CKD, and history of CVD were statistically associated with increased mortality (Table 2).

CARDIOVASCULAR MORTALITY

The unadjusted hazard ratios of CV mortality were 3.80 (95% CI: 1.26-11.46) for statin and 3.87 (95% CI: 1.79-8.33) for other LLA users compared with nonmedication users. After adjusting for demographic, metabolic components, and important comorbidities, the use of statin (aHR = 1.20 [95% CI: 0.26-5.54]) and other LLAs (aHR = 1.63 [95% CI: 0.70-3.76]) were

TABLE 2. INDEPENDENT PREDICTORS OF OVERALL AND CV MORTALITY IN NAFLD, NHANES III (1988-1994)

Covariate	Overall Mortality aHR (95% CI)	*P*	Cardiovascular Mortality aHR (95% CI)	*P*
Group by medication use		0.1512		0.409
No medication use	Reference		Reference	
Statin use	0.95 (0.37-2.44)	0.9143	1.20 (0.26-5.54)	0.8092
Other LLA use	1.43 (0.99-2.07)	0.0544	1.63 (0.70-3.76)	0.2488
Age, years		< 0.0001		< 0.0001
20-44	Reference		Reference	
45-54	2.74 (1.68-4.48)	0.0001	2.81 (1.49-5.29)	0.0019
55-64	7.31 (4.92-10.85)	< 0.0001	8.85 (3.61-21.68)	< 0.0001
65-74	15.58 (10.72-22.63)	< 0.0001	21.49 (11.04-41.84)	< 0.0001
Male	1.20 (0.99-1.47)	0.0681	1.48 (0.86-2.57)	0.1557
Race		0.0011		0.0882
non-Hispanic white	Reference		Reference	
non-Hispanic black	1.11 (0.92-1.35)	0.2700	0.93 (0.56-1.56)	0.7863
Mexican American	0.91 (0.72-1.16)	0.4368	0.85 (0.55-1.32)	0.4691
Other	0.40 (0.25-0.65)	0.0004	0.14 (0.03-0.65)	0.0133
Active smoker	1.94 (1.48-2.55)	< 0.0001	2.65 (1.76-3.97)	< 0.0001
Obese	0.96 (0.77-1.20)	0.7112	1.03 (0.64-1.66)	0.9030
DM	1.79 (1.40-2.30)	< 0.0001	1.89 (1.08-3.30)	0.0260
HL	1.10 (0.84-1.45)	0.4687	1.23 (0.78-1.94)	0.3631
HTN	1.13 (0.84-1.54)	0.4121	1.17 (0.75-1.82)	0.4834
CKD	1.89 (1.48-2.41)	< 0.0001	1.82 (0.92-3.62)	0.0860
History of cancer	1.21 (0.87-1.67)	0.2502	0.75 (0.45-1.24)	0.2578
History of CVD	2.03 (1.57-2.63)	< 0.0001	3.69 (2.23-6.08)	< 0.0001

not significantly associated with risk for CV mortality. Note that there were 228 CV deaths in NAFLD, 6 of which occurred among statin users and 17 among other LLA users. Because of the small number of events, the aHR for statin had a wide confidence interval. In contrast, older age, male gender, active smoking, DM, and history of CVD were statistically associated with increased CV mortality (Table 2).

Discussion

In this study, we used a population-based database in the United States to assess the link between the use of LLAs and CV mortality among individuals with NAFLD. Consistent with previous report, our study suggests that after adjustment for important confounders, the use of LLAs did not have a positive effect on overall or CV mortality in patients with NAFLD. Similar findings were observed when the data were analyzed for statin use instead of all LLAs.[23] There are multiple potential explanations for this observation. First, the effect of other risk factors for CV mortality (DM, smoking, history of CVD) was greater in NAFLD patients who are also candidates for LLA or statin treatment. In fact, our data show that DM, CKD, and a history of CVD were the strongest predictors of CV mortality in NAFLD. In this context, the effect of LLA and statin use on overall mortality or CV mortality in NAFLD patients can negate any potential benefit of these drugs on mortality. Another explanation is a related to the significant underuse of LLAs and statins in NAFLD subjects with HL who would otherwise be a candidate for treatment and are also at risk for CV mortality. Given that most of these NAFLD patients were not receiving LLAs and statins, the effect on mortality could have been minimized. These findings are in contrast to the results of the *post hoc* analyses of clinical trials and studies targeting multiple components of MS.[34–36] In this context, it is reasonable to conclude that the effect of LLAs or statin therapy on the mortality of patients with NAFLD has not been firmly established. Nevertheless, it is also important that our data support the safety of statin and LLAs in NAFLD subjects. In fact, the use of statin or LLAs did not lead to any excess mortality in NAFLD. This is important because of substantial fear in clinical practice about the side effects of LLAs, and especially statins, in patients with NAFLD. Our data do not support any negative effect of these medications on the long-term mortality of NAFLD patients. In this context, our data provide an important message: The use of these drugs to treat dyslipidemia of patients with NAFLD is not associated with adverse effects on long-term outcomes. However, if treatment of dyslipidemia in patients with NAFLD is undertaken to reduce CV mortality, our data do not provide evidence to support this premise. These data suggest that the pathogenic abnormalities that increase mortality in patients with NAFLD may not be targeted by solely treating dyslipidemia. Current literature suggests that other mechanisms such as gut microbiome dysbiosis in NAFLD may lead to the disruption of intestinal barrier and translocation of pro-inflammatory substances to the liver through portal circulation, leading to increased CV and cancer risks.[38,39]

In fact, it is also important to note that statins have been linked to a decrease in cancer-related mortality, suggesting that their use may have additional benefits.[37] Future studies are needed to assess the effect of statins on the cancer risks in patients with NAFLD.

An important strength of our study is that it evaluates a large cohort of the US general population with in-depth clinical and laboratory data, as well as long duration of mortality follow-up, which makes the study quite unique. Our study contributes to the understanding of the long-term effects of LLAs on mortality in patients with NAFLD. Conversely, our limitations include using the self-reported LLA use history, which may not be reliable in all cases. Furthermore, the NHANES data set did not have any information about the efficacy of LLAs in patients with NAFLD. Finally, even though hepatic ultrasound data were broadly used for the population-based studies for the diagnosis of NAFLD, the true prevalence of NAFLD might still be underestimated in this population due to measurement error. In addition, given that hepatic ultrasound examinations were performed on adults aged 20 to 74, it is unlikely that these data re completely representative of the entire US population.

In summary, although LLAs are often used to treat dyslipidemia in patients with NAFLD, our data show that they do not necessarily decrease CV or all-cause mortality in these patients when adjusting for other risk factors. As described previously, the reasons for this may be multifactorial. However, our findings suggest that the presence of NAFLD is in itself an independent risk factor for CVD. In contrast, our study does support previous literature that statin use does

not cause harm or increase mortality in patients with liver disease. These findings highlight the need for further investigation on the association between the use of LLAs and mortality, as well as the pathophysiological mechanisms that increase CV and overall mortality in NAFLD patients.

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