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Analysis from a Population-Based Cohort Study

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ABSTRACT

Aims: Data on the impact of liver disease (LD) in patients with atrial fibrillation (AF) and the role of oral anticoagulant (OAC) drugs for stroke prevention, are limited.

Methods: A retrospective observational population-based cohort study on the administrative health databases of Lombardy region Italy. All AF patients ≥40 years admitted to hospital from 2000 to 2018 were considered. AF and LD diagnosis were established using ICD9-CM codes. Use of OAC was determined with Anatomical Therapeutic Chemical (ATC) codes. Primary study outcomes were stroke, major bleeding and all-cause death.

Results: Among 393,507 AF patients, 16,168 (4.1%) had concomitant LD. LD AF patients were significantly less treated with OAC. Concomitant LD was associated with an increased risk in all the study outcomes (HR: 1.18, 95% CI: 1.11-1.25 for stroke; HR: 1.57, 95% CI: 1.47-1.66 for major bleeding; HR: 1.41, 95% CI: 1.39-1.44 for all-cause death). Use of OAC in patients with AF and LD resulted in a reduction in stroke (HR: 0.80, 95% CI: 0.70-0.92), major bleeding (HR: 0.86, 95% CI: 0.74-0.99) and all-cause death (HR: 0.77, 95% CI: 0.73-0.80), with similar results according to subgroups. A net clinical benefit (NCB) analysis suggested a positive benefit/risk ratio in using OAC in AF patients with LD (NCB: 0.408, 95% CI: 0.375-0.472).

Conclusions: In AF patients, concomitant LD carries a significantly higher risk for all clinical outcomes. Use of OAC in AF patients with LD was associated with a significant benefit/risk ratio, even in high-risk patient subgroups.

Keywords: Liver disease; Atrial fibrillation; Oral anticoagulant treatment.

INTRODUCTION

Chronic liver disease (LD), particularly in its advanced stages, has been associated with an increased risk of bleeding[1]. Over time, this belief has taken the form of an actual “dogma”, based on the clinical evidence that many pro-coagulant factors levels are decreased and major and fatal bleeding occur frequently in LD patients[1]. In recent years, accumulating new data have replaced this paradigm with a new concept suggesting that the natural equilibrium between pro-coagulant factors and anti-coagulant factors is globally unbalanced, leading to an increased thrombotic and bleeding risk[1–7].

In the context of subjects with atrial fibrillation (AF), the presence of concomitant LD has often led to undertreatment with oral anticoagulant (OAC) drugs[8,9]. This may be due to the fear of a life-threatening bleeding and to the limited data regarding OAC benefit or harm in LD patients, excluded from randomized controlled trials on OAC in AF[4]. LD has also been reported as being associated with an increased risk of both thromboembolic and bleeding events in AF patients[10]. Further, LD is a risk factor considered in bleeding risk scores[11,12]. Recent observational data on the role of OAC in AF with LD, although limited in terms of sample size, methodology and temporal horizon, suggest how OAC appears beneficial for stroke risk reduction, although conferring greater risk of bleeding events[13].

The aim of this paper was to study the impact of concomitant LD on AF patients, in terms of OAC prescription patterns and major adverse events. Second, we examined the impact of OAC treatment on major adverse events, focused on specific patient subgroups and evaluating its net clinical benefit in these patients.

METHODS

Study Setting and Data Source

This paper relies on a population-based analysis on linked claims data in the Lombardy Region. To date, with a population of more than 10 million inhabitants, Lombardy is the largest Italian region, comprising highly populated urban areas, as well as industrial and rural ones.

The Italian healthcare system is based on a public National Health System (NHS), which provides free assistance to anyone on the National territory. Italian residents have a registration code which allows individual linkage of the administrative database (including demographic data, drug prescription archive, the regional inpatient register, archive of co-payment exemptions and dates of death). The database of residents includes information on vital and emigration status. The drug prescription database comprises all the prescriptions reimbursed by the NHS, as actually picked up at the pharmacy by the patients, and holds information on purchase data, Anatomical Therapeutic Chemical (ATC) classification and forms of dispensing. The regional inpatient register includes hospital admissions, concomitant diagnoses, discharge dates and diagnosis or death and procedures performed according to the 'International Classification Disease, 9th Revision, Clinical Modification' (ICD9-CM).

All databases are linked anonymously using unique encrypted patient codes, in accordance with privacy regulations. By a specific agreement between the Mario Negri Institute and the Lombardy Region, for the use of the anonymous

administrative data, it was not necessary to obtain an ethic approval. Data were available for nineteen consecutive years, from 2000 to 2018.

Study Cohort

People 40 years and older were included in this analysis if they had a hospital admission or access to emergency department for AF (or atrial flutter) among the discharge diagnoses, irrespective of whether was primary or any secondary diagnosis, according to the ICD9-CM codes 427.31 and 427.32 from 1st January 2002 to 31st December 2017. If during this period, patients had more than one hospital admission for AF, the first one was considered as the index date for diagnosis. Patients who had a LD diagnosis in the two years before AF hospital admission were excluded.

Patients with AF were recorded as having LD according to the presence of codes 070.xx, 570-573.xx in the ICD9-CM classification. Patients included in the LD group were classified as mild liver disease (571.xx, 573.xx) and moderate/severe liver disease (070.xx, 570.xx, 572.xx), as described previously[14,15]. All patients diagnosed with LD from 2002 and 2017 were included in the analysis. All patients with hepatic carcinoma (ICD9-CM 155.xx codes) were excluded from the analysis.

All patients entered in the cohort at the index hospitalization for AF diagnosis, contributing to the AF without LD cohort until/whether a hospitalization reporting LD diagnosis occurred. From that moment on, patients who developed LD contributed to the AF with LD cohort. Baseline characteristics for the two cohorts were evaluated at the time of the relative index hospitalization.

Comorbidities and Pharmacological Treatments at Baseline

Comorbidities as listed in Table 1 were recorded in the previous two years before the entry date in study cohort according to ICD9-CM codes, as reported in Supplementary Materials (eTable 1). Hypertension was identified on the basis of prescription of at least one antihypertensive drug, as actually picked up at the pharmacy by the patients, in the six months after entering the study cohort (see Supplementary Materials). Accordingly, the CHA_2DS_2-VASc score was computed following the original definition[16]. A modified version of HAS-BLED score, calculated excluding the 'L' criterion about quality of oral anticoagulation control, was computed similar to previous studies[17]. Pharmacological treatments were recorded if at least one prescription was available in the 6 months after entering the study cohort.

Study Outcomes

Main outcomes of interest were stroke, major bleeding and all-cause death. Additionally, we examined the occurrence of intracranial, gastrointestinal and any bleeding. Follow-up for outcomes started at the date of discharge for the index hospitalization. All patients were followed up until one of the outcomes occurred or when the follow-up was censored (emigration, admission to a nursing home, 31st December 2018). All patients had a minimum allowable follow-up period of one year. All patients whom did not contribute follow-up for at least 1 day were not considered in the two cohorts and excluded from analysis.

Study outcomes for the AF without LD cohort were registered starting from the time of AF diagnosis up until one of the censoring conditions was encountered or whether

they developed LD. Study outcomes for the AF with LD cohort were registered starting from the time of LD diagnosis up until one of the censoring conditions was encountered.

Exposure to OAC

Prescription of OAC in patients with and without LD was analysed. Since we do not have information on prescription at discharge we considered patients as treated with an OAC if they had at least one prescription within 6 month following the index hospitalization. For the comparison between AF LD treated or not treated with OAC, the observation of outcomes started at the date of treatment initiation. Thus, all those patients whom reported events occurred between LD index hospitalization and OAC initiation were excluded from this analysis.

Statistical Analysis

Continuous variables were presented as mean ± standard deviation (SD) and compared using student's t test. Follow-up times were expressed as median and interquartile range [IQR]. Categorical variables were presented as numbers and percentages and compared using Chi-squared test. Logistic and Cox regression analysis were used to evaluate association between clinical characteristics, treatments and outcomes. Number-needed-to-treat (NNT), number-needed-to-harm (NNH) and weighted net clinical benefit (NCB) were also computed. All methodological specifications are reported in Supplementary Materials.

RESULTS

A total of 377,339 patients with AF without LD and 16,168 patients with AF with LD were studied (Table 1). AF patients with LD were younger and less likely female than those without LD. Despite reporting a higher prevalence of diabetes mellitus, patients with AF and LD had a clinical history less burdened with previous myocardial infarction and stroke/transient ischemic attack. Patients with LD reported a higher prevalence of most of the other comorbidities. Baseline thromboembolic risk, evaluated according to CHA_2DS_2-VASc score, was similar between the two groups, but bleeding risk, evaluated according to HAS-BLED score, was higher in patients with LD. AF patients with LD were generally less likely to be treated with any concomitant drugs than those without LD (Table 1).

Prescription of OAC according to Liver Disease Status

At baseline, patients with AF and LD were less likely prescribed with OAC than those without (34.2% vs. 47.2%, respectively; p<0.001). Multivariable adjusted logistic regression analysis confirmed that AF patients with LD were less likely to be treated with OAC, independent of other clinical characteristics (OR: 0.96, 95% CI: 0.92-0.98).

Follow-Up Analysis

Study outcomes were recorded over a median [IQR] follow-up time of 3.81 [1.30-7.90] years. Accordingly, the incidence rate for all the study outcomes considered was higher in AF with LD patients than in those without LD (Table 2). Kaplan-Meier curves showed that cumulative risk for stroke, major bleeding, all cause death and other secondary outcomes was significantly higher in AF with LD patients [Figure 1; eFigure 1-3]. Multivariable adjusted Cox regression analyses (Table 2)

demonstrated that in AF patients, LD is independently associated with an increased risk for all the study outcomes.

OAC in AF Patients with Liver Disease

Differences in baseline characteristics between AF patients with LD treated with OAC and those not treated with OAC are reported in Table 3. Among 5,539 LD patients treated with OAC, there were 5151 (93.0%) treated with vitamin K antagonists (VKAs) and 388 (7.0%) were treated with non-vitamin K antagonist oral anticoagulants (NOACs). Patients treated with OAC were younger ($p<0.001$) compared to those not treated and less likely female (41.4% vs. 44.9%, respectively; $p<0.001$) (Table 3). Thromboembolic risk, evaluated according to CHA_2DS_2-VASc score, was no different in patients treated with OAC than those not treated, while bleeding risk, evaluated according to HAS-BLED score, was lower in patients treated with OAC compared to those not treated ($p<0.001$) (Table 3). Over a median [IQR] follow-up time of 2.85 [0.81- 6.33] years, AF patients with LD treated with OAC reported a lower IR of stroke, gastrointestinal bleeding, any bleeding and all-cause death compared to those not treated. Conversely, these patients reported a slightly higher IR of intracranial bleeding (Table 4).

On univariate Cox regression analysis, use of OAC in LD patients was associated with a reduced risk of stroke, major bleeding, gastrointestinal bleeding, any bleeding and all-cause death occurrence (Table 4). These results were corroborated by the multivariable analysis, confirming an independent association with a lower risk for stroke, major bleeding, gastrointestinal bleeding and all-cause death (Table 4).
No difference was found regarding the risk of intracranial bleeding and any bleeding.

Number Needed to Treat and Net Clinical Benefit

According to the Cox regression model adjusted for all baseline covariates, an NNT of 256 patients to prevent a stroke occurrence was found over the entire study period , while NNT=31 to prevent the occurrence of one all-cause death event over the entire study period (16.5 years). Conversely, an NNH of 450 patients was found for one major bleeding, while 1860 patients would need to be treated with OAC to cause one intracranial bleeding and 345 patients treated for one gastrointestinal bleeding.

In Model 1 of NCB analysis, restricted to the weighting of stroke and intracranial bleeding, showed a significant clinical advantage for OAC treatment compared to non-OAC treatment for AF patients with LD (NCB: 0.575, 95% CI: 0.545-0.590). In Model 2, considering additionally the occurrence of gastrointestinal bleeding, the NCB was found still consistently in favor of OAC treatment (NCB: 0.408, 95% CI: 0.375-0.472).

Subgroup Analysis

For stroke no significant difference was found according to age strata and severity of LD. No difference was found in male patients, while use of OAC was still independently associated with a non-significant reduced risk in female ones. The association with a reduced risk of stroke was statistically significant in patients with high thromboembolic risk (CHA_2DS_2-VASc ≥2, HR: 0.73, 95% CI: 0.65-0.84) and in those with high bleeding risk (HAS-BLED ≥3, HR: 0.80, 95% CI: 0.69-0.91) [Figure 2, Panel A]. We found no differences across the subgroups considered for major bleeding associated to the use of OAC [Figure 2, Panel B].

Lastly, the association with a lower risk of all-cause death was consistent across all the subgroups. A larger risk reduction in patients with age ≥75 years compared to those <75 years (HR: 0.75, 95% CI: 0.69-0.81 vs. HR: 0.87, 95% CI: 0.76-0.99; p<0.001) and in female patients compared to male ones (HR: 0.78, 95% CI: 0.73-0.85 vs. HR: 0.83, 95% CI: 0.77-0.86; p=0.009) [Figure 2, Panel C].

DISCUSSION

In a large population-based Italian cohort study, we show that AF patients with concomitant LD have an increased risk of any clinical event compared to those without LD, but such patients with LD had a lower chance to be prescribed with an OAC. Use of OAC in AF patients with LD was associated with a significant reduction in stroke, major bleeding, gastrointestinal bleeding and all-cause death.

This evidence is further strengthened by the modest number of patients that are needed to be treated to prevent a stroke, which is even lower for the prevention of all-cause death. Conversely, the NNH was higher for the bleeding outcomes. Overall, NCB confirms the clinical advantage obtained by prescribing OAC to AF patients with LD, rather than not treating them.

Lastly, stroke risk reduction did not significantly differ between the subgroups, including female patients and those with a high baseline thromboembolic or bleeding risk. No difference was found in terms of residual bleeding risk for any of the subgroups but there was a greater risk reduction for all-cause death in the elderly (≥75 years) and female patients.

Patients with LD had a higher prevalence of diabetes mellitus however they reported less likely a previous myocardial infarction and stroke/transient ischemic attack than those without LD. This finding is possibly related to the younger age of patients with LD. Indeed, these patients were probably exposed for less time to risk factors, entailing a lower incidence of major cardiovascular events before the occurrence of LD.

In the general population the presence of LD, particularly in advanced stages, is associated with an increased risk of bleeding[1]. LD is also associated with an increased risk of major cardiovascular events and all-cause death[18–21]. In particular, a significant association between liver cirrhosis and non-alcoholic fatty-liver disease with stroke and cerebrovascular events risk has been demonstrated[2,22]. Our data confirm that in AF patients, the concomitant presence of LD significantly increases the risk of stroke, after taking account for all the clinically meaningful covariates, and the other adverse events. Indeed, while the presence of LD is associated with the occurrence of bleeding events also in AF patients, it can also be a significant risk factor for stroke[10]. The results presented confirmed and strengthen this concept in a large population-based cohort with a long follow-up. Thus, LD is a significant comorbidity influencing the natural history of AF patients[23].

Despite the high-risk profile shown by patients with AF and LD, we found that these patients are less likely to be treated with OAC than those without LD. This confirms prior observations showing that ‘liver impairment’ was associated with a lower chance of OAC to be prescribed[24].

Thus far, clinical evidence supporting the use of OAC in AF patients with LD has been limited. In a recent meta-analysis, AF patients with LD treated with OAC had a 42% relative risk reduction in stroke but with a non-significant increase in bleeding[13]. Compared to our study, the meta-analysis had a smaller cohort of patients with AF and significant LD (N= 10637), a small proportion of OAC treated patients (~15%) and a low number of events in the OAC treated group. Furthermore, most of the patients considered (>96%) were Asian, reducing the generalizability of those findings[13] and the 'any bleeding' outcome was used in the analysis, reducing the clinical significance of this information. In the paper by Kuo and colleagues, with a similar design to our study and a large sample of AF patients with LD at high thromboembolic risk, there was no significant difference in stroke and intracranial bleeding in OAC treated patients[25]. Our findings suggest that the use of OAC in AF patients with LD grants a significant advantage in terms of stroke risk reduction with a reduction in terms of bleeding risk as well (which was shown to be neutral in the context of a 'high bleeding risk' group of patients). Lastly, the significantly reduced risk in all-cause death associated with OAC use is another novel observation.

Our findings are further substantiated by the low NNT to prevent stroke and all-cause death, compared to the higher NNH for a major bleeding or intracranial bleeding event. Also, the NCB analysis clearly demonstrated that OAC treatment was associated to a significant clinical usefulness in AF patients with LD. In the paper by Kuo and colleagues, NCB was computed according to three different models[25]. While there was a significant NCB using the higher weighting factors, in their model computed using the same weighting factor than in our NCB Model 1, they did not find a clinical utility in treating LD patients[25].

Even though we did not expect to observe an increase in the risk of major and gastrointestinal bleeding in AF with LD treated with OAC (on the basis of the above-mentioned background), we found a significant reduction in major and gastrointestinal bleeding. Actually, similar data were also reported in the context of LD patients with portal vein thrombosis (PVT). Indeed, both meta-analysis and RCT showed a significant reduction in terms of risk of bleeding in patients treated with low-molecular weight heparin compared to those not treated[26,27]. In these cohorts, the reduction of pressure in the portal vein and the consequential reduced flow in the esophageal and gastric circulation due to the anticoagulant effect, was advocated as a possible explanation of this reduced risk[26,27]. Conversely, in the meta-analysis presented by Chokesuwattanaskul and colleagues, the use of OAC in patients with liver disease showed a non-significant trend in association with increased risk of any bleeding (HR: 1.446, 95% CI: 0.963-2.172), even though the outcome definition was largely heterogenous[13]. Similarly to our paper, in the study by Lee et al., which considered only the occurrence of intracranial bleedings, no difference was found between OAC treated and not-treated patients[25].

Since in our study the reduced risk of major bleeding appears to be related in particular to the reduced risk of gastrointestinal bleeding, we can hypothesize that an effect similar to what described in the PVT cohorts could be entailed even in the AF LD patients. Furthermore, despite the association with reduced risk persisted after the multivariable adjustments, we can theorize that a certain selection bias has occurred, as highlighted by the lower HAS-BLED score at baseline in OAC treated patients, compared to those not treated.

Our subgroup analysis provides additional information in further higher risk subgroups. While no difference was found for the three main outcomes according to LD severity, even amongst patients with moderate/severe LD, no excess in bleeding risk was found. These data contradict previous reports about a significant increase in the risk of bleeding for patients with more advanced LD[28]. Furthermore, the stroke risk reduction was consistent even in patients with high thromboembolic and bleeding risk, with no difference in major bleeding. Also, the greater benefit in terms of reducing all-cause death in elderly patients, gives further reassurance about OAC use in AF and LD disease in this specific subgroup of patients, who are at a higher risk for adverse events[29]. The evidence that also female patients showed a lower risk for all-cause death, further underline the effectiveness of OAC therapy in the LD subgroup even in high-risk patients[30,31].

One recent paper demonstrated that treating AF patients with LD with a NOAC rather than with a VKA was associated with a significant reduction in adverse outcomes[32]. In the subgroup of patients with significant active LD, some of the beneficial effect was attenuated, particularly for all-cause death occurrence[32]. However, there was a broad definition of 'significant active' LD and only a small proportion of patients was considered having a significant active LD compared to the overall LD cohort (~13%)[23]. In our study, we had a limited number of patients treated with NOACs, but our data do support use of OAC even in patients with moderate/severe LD given the significant clinical impact on adverse outcomes.

Limitations

The main limitation of this study is the use of ICD9-CM codes, that although largely validated, cannot completely exclude some risk of bias related to inaccuracies, coding mistakes or some residual confounding. Use of administrative data, limits the generalizability of our results to the overall AF population and could result in underestimation of the patients with concomitant AF and LD. Given the more advanced clinical status and the particularly increased risk for thrombotic complications and death, we excluded patients with hepatocellular carcinoma (HCC), in order to avoid an overestimation of adverse events in the LD group. Hence, our results cannot be applied to LD patients with HCC, which represents a different disease model. The limited number of patients treated with NOACs did not allow insights regarding the possible differences in outcomes according to the various antithrombotic management strategies. Moreover, in this analysis we did not consider treatment switching from VKA to NOAC. Lastly, the absence of specific clinical and laboratory data does not allow us to provide an accurate evaluation and stratification of LD patients clinical status and severity. Taking into account ICD9 codes to estimate disease severity could be considered not highly robust. However, we believe that this categorization is the best available to date, also considering the difficulty of obtaining data to calculate a reliable and accurate proxy tool for disease assessment.

CONCLUSIONS

In AF patients, concomitant LD carries a significantly higher risk for all clinical outcomes. Use of OAC in AF patients with LD was associated with a significant favorable benefit/risk ratio and an overall positive net clinical benefit, even in high-

risk patient subgroups. Our data support the use of OAC in AF patients with LD, even in those with a particularly higher risk profile for major adverse events.

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AUTHORS’ CONTRIBUTION

Study concept and design: Irene Marzona, Marco Proietti, Mauro Tettamanti, Maria Carla Roncaglioni.

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Analysis of data: Pierluca Colacioppo, Tommaso Vannini, Mauro Tettamanti.

Interpretation of data: Irene Marzona, Marco Proietti, Maria Carla Roncaglioni.

Drafting of manuscript: Irene Marzona, Andreana Foresta, Marco Proietti.

Critical revision of the manuscript for important intellectual content: Irene Marzona, Marco Proietti, Maria Carla Roncaglion, Gregory Y.H. Lip.

All authors approved the last version of the manuscript.

Conflict of interest

GYHL has served as consultant for Bayer/Janssen, BMS/Pfizer, Medtronic, Boehringer Ingelheim, Novartis, Verseon, and Daiichi-Sankyo, and as speaker for Bayer, BMS/Pfizer, Medtronic, Boehringer Ingelheim, and Daiichi-Sankyo. No fees are received personally. The other authors have no relevant interests to disclose.

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FIGURE LEGENDS

Figure 1: Kaplan-Meier Curves for Main Study Outcomes according to Liver Diseases Status

Figure 2: Subgroups Analysis for Impact of OAC on Main Study Outcomes in Patients with Liver Disease

Legend: IR is expressed as per 100 patient-years; CI= Confidence Interval; IR= Incidence Rate; OAC= Oral Anticoagulant.

Table 1: Baseline Characteristics according to History of Liver Disease

	AF w/o LD N= 377,339	AF w/ LD N= 16,168	p
Age, *years* mean±SD	76.4 ± 10.5	75.3 ± 9.8	<0.001
Age Classes, n (%)			<0.001
40-64	48,737 (12.9)	2,212 (13.6)	
65-74	94,664 (25.1)	4,484 (27.7)	
≥75	233,938 (62.0)	9,472 (58.6)	
Female Sex, n (%)	185.834 (49.2)	7,077 (43.7)	<0.001
History of Comorbidities			
Hypertension, n (%)	264,035 (70.0)	11,354 (70.2)	0.4932
Diabetes Mellitus, n (%)	77,231 (20.5)	4,715 (29.1)	<0.001
Myocardial Infarction, n (%)	32,048 (8.5)	1,028 (6.3)	<0.001
Stroke/TIA, n (%)	27,126 (7.2)	754 (4.6)	<0.001
Heart Failure, n (%)	94,572 (25.0)	5,297 (32.7)	<0.001
PAD, n (%)	9,975 (2.6)	520 (3.2)	<0.001
Major Bleeding, n (%)	19,820 (5.2)	1,818 (11.2)	<0.001
COPD, n (%)	36,802 (9.7)	2,382 (14.7)	<0.001
Chronic Kidney Disease, n (%)	18,279 (4.8)	1,425 (9.5)	<0.001
Dementia, n (%)	12,530 (3.3)	553 (3.4)	0.0034
Gastrointestinal Disease, n (%)	11,915 (3.1)	1,438 (8.9)	<0.001
Neoplasm, n (%)	43,015 (11.4)	2,527 (15.6)	<0.001
CHA_2DS_2-VASc, mean±SD	3.4±1.5	3.4±1.5	0.09
HAS-BLED, mean±SD	2.2±0.9	3.1±1.0	<0.001
Pharmacological Therapy			

Oral Anticoagulant Drugs, n (%)	178,330 (47.2)	5,539 (34.2)	<0.001
Anti-Arrhythmic Drugs, n (%)	136,628 (36.2)	3,960 (24.5)	<0.001
Beta-Blockers, n (%)	164,074 (43.5)	6,435 (39.8)	<0.001
Calcium-Channel Blockers, n (%)	31,758 (8.4)	1,247 (7.7)	<0.001
ACE Inhibitors/ARBs, n (%)	221,470 (58.7)	7,976 (44.3)	<0.001
Antiplatelet Drugs, n (%)	141,456 (37.5)	5,064 (31.3)	<0.001
Lipid-Lowering Drugs, n (%)	97,446 (25.8)	2,617 (16.2)	<0.001
Concomitant Drugs, *n* mean±SD	2.8 ± 1.5	2.1 ± 1.6	<0.001

Legend: ACE= Angiotensin Converting Enzyme; AF= Atrial Fibrillation; ARBs= Angiotensin Receptor Blockers; COPD= Chronic Obstructive Pulmonary Disease; LD= Liver Disease; PAD= Peripheral Artery Disease; SD= Standard Deviation; TIA= Transient Ischemic Attack.

Table 2: Major Adverse Events according to History of Liver Disease

N ([a]IR)	AF w/o LD	AF w/ LD	LD vs. No LD[b]
	N= 377,339	**N= 16,168**	**HR [95% CI]**
Stroke	29,242 (1.58)	1,213 (1.80)	**1.18 [1.11-1.25]**
Major Bleeding	17,347(0.92)	1,079 (1.59)	**1.57 [1.47-1.66]**
Intracranial Bleeding	7,682 (0.40)	379 (0.56)	**1.37 [1.23-1.51]**
GI Bleeding	9,894 (0.52)	712 (1.03)	**1.71 [1.58-1.85]**
Any Bleeding	39,866 (2.17)	2,407 (3.60)	**1.55 [1.49-1.62]**
All-Cause Death	213,296 (10.9)	11,923 (14.8)	**1.41 [1.39-1.44]**

Legend: [a]IR is expressed as per 100 patient-years; [b]Adjusted for age, sex, hypertension, diabetes mellitus, myocardial infarction, stroke/TIA, heart failure, PAD, major bleeding, COPD, chronic kidney disease, dementia, gastrointestinal disease, neoplasm, pharmacological treatments and index year; GI= Gastrointestinal; RR= Risk Ratio; HR= Hazard Ratio; CI= Confidence interval

For other acronyms please see Table 1.

1 **Table 3: Baseline Characteristics according to Use of OAC in LD patients**

	LD w/o OAC (N=10,629)	LD w OAC (N=5,539)	p
Age, *years* mean±SD	76.2 ± 10.0	73.6 ± 9.2	<0.001
Female Sex, n (%)	4783 (44.9)	2137 (41.4)	<0.001
History of Comorbidities			
Hypertension, n (%)	7160 (67.3)	4194 (75.7)	<0.001
Diabetes Mellitus, n (%)	3040 (28.6)	1675 (30.2)	0.003
Myocardial Infarction, n (%)	796 (7.5)	322 (5.8)	0.040
Stroke/TIA, n (%)	435 (4.1)	319 (5.7)	<0.001
Heart Failure, n (%)	3236 (30.4)	2061 (37.2)	<0.001
PAD, n (%)	363 (3.4)	157 (2.8)	0.0470
Major Bleeding, n (%)	1396 (13.1)	422 (7.6)	<0.001
COPD, n (%)	1610 (15.1)	772 (13.9)	0.0394
Chronic Kidney Disease, n (%)	1000 (9.4)	425 (7.6)	<0.001
Dementia, n (%)	454 (4.3)	86 (1.8)	<0.001
Gastrointestinal Disease, n (%)	1074 (10.1)	364 (6.6)	<0.001
Neoplasm, n (%)	1884 (17.7)	643 (11.6)	<0.001
CHA_2DS_2-VASc, mean±SD	3.4 ± 1.5	3.4 ± 1.5	<0.09
HAS-BLED, mean±SD	3.2 ± 1.0	3.0 ± 0.9	<0.001
Pharmacological Therapy			
Anti-Arrhythmic Drugs, n (%)	2323 (21.8)	1637 (29.5)	<0.001
Beta-Blockers, n (%)	3491 (32.8)	2744 (53.1)	<0.001
Calcium-Channel Blockers, n (%)	667 (6.3)	580 (10.5)	<0.001
ACE Inhibitors/ARBs, n (%)	4454 (41.9)	3522 (63.6)	<0.001

Antiplatelet Drugs, n (%)	4319 (40.6)	745 (13.4)	<0.001
Lipid-Lowering Drugs, n (%)	1367 (12.8)	1250 (22.6)	<0.001
Concomitant Drugs, *n* mean±SD	1.9 ± 1.4	3.3 ± 1.2	<0.001

Legend: For acronyms please see Table 1.

Table 4: Major Adverse Events according to use of OAC in Patients with History of Liver Disease

N (IR[a])	No OAC	OAC	OAC vs. No OAC	
	N= 7,837	N= 5,236	HR [95% CI][b]	HR [95% CI][c]
Stroke	713 (1.97)	413(1.50)	**0.72 [0.63- 0.81]**	**0.80 [0.70- 0.92]**
Major Bleeding	589 (1.60)	396 (1.42)	**0.84 [0.73- 0.95]**	**0.86 [0.74- 0.99]**
Intracranial Bleeding	184 (0.49)	159 (0.58)	1.07 [0.87- 1.33]	1.11 [0.87- 1.41]
GI Bleeding	418 (1.12)	242 (0.87)	**0.72 [0.61- 0.84]**	**0.74 [0.62- 0.88]**
Any Bleeding	1,307 (3.74)	921 (3.52)	**0.87 [0.80- 0.94]**	0.91 [0.83- 1.00]
All-Cause Death	5,688(15.0)	3,148(10.80)	**0.73 [0.69- 0.75]**	**0.77 [0.73-0.80]**

Legend: [a]IR is expressed as per 100 patient-years; [b]Unadjusted; [c]Adjusted for age, sex, hypertension, diabetes mellitus, myocardial infarction, stroke/TIA, heart failure, PAD, major bleeding, COPD, chronic kidney disease, dementia, gastrointestinal disease, neoplasm, pharmacological treatments and index year; CI= Confidence Interval; GI= Gastrointestinal; RR= Risk Ratio; HR= Hazard Ratio; IR= Incidence Rate; for other acronyms please see Table 1.

Figure 1

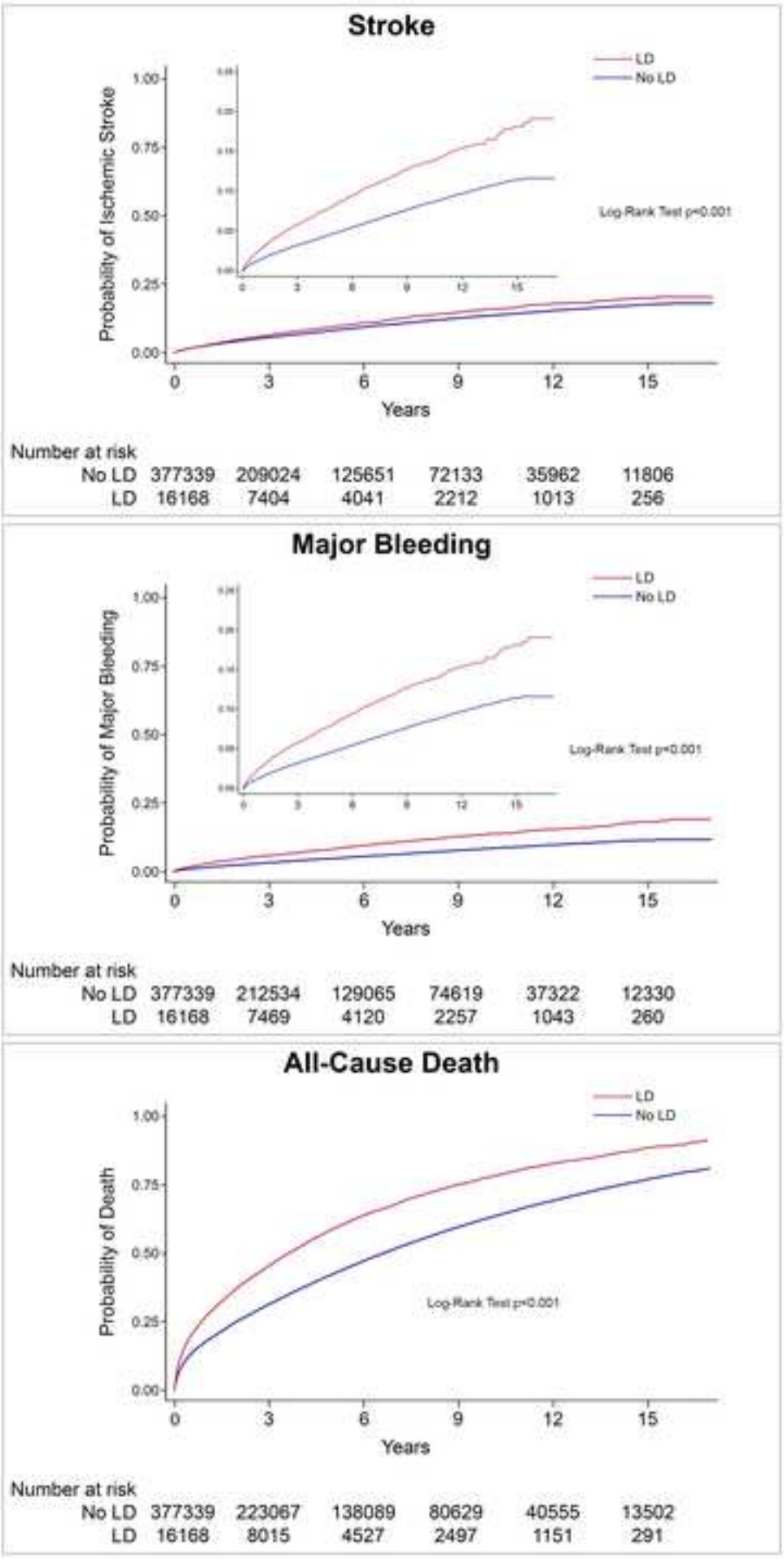

Figure 2