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Heavy drinking habits are associated with worse in-hospital outcomes in patients with acute coronary syndrome: an insight from the AMIS plus registry

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Abstract: Background: The association between alcohol consumption and the occurrence of coronary heart disease is well described in the literature, while data regarding the impact of regular alcohol consumption on in-hospital outcomes in the setting of acute coronary syndrome (ACS) are lacking. We aimed to evaluate the impact of self-reported alcohol consumption on in-hospital outcomes in patients with ACS. Methods: Data derived from patients enrolled between 2007 and 2019 in the Acute Myocardial Infarction in Switzerland (AMIS) Plus registry were retrospectively analyzed. Patients were stratified based on alcohol drinking pattern. Primary outcome was all-cause in-hospital mortality, while secondary outcomes were set as incidence of major adverse cardiac and cerebrovascular events (MACCEs). Outcome comparisons according to quantity of daily alcohol intake were also performed. Results: Records concerning alcohol consumption were available in 25,707 patients; 5,298 of them (21%) fulfilled the criteria of regular alcohol consumption. Regular drinkers were predominantly male, younger, smokers, more comorbid and with a worse clinical presentation as compared with abstainers/occasional drinkers. Daily alcohol intake was reported in 4,059 (77%) of these patients (regular drinkers). Among them, 2,640 were light drinkers (2 drinks/day) and 1,419 heavy drinkers (>2 drinks/day). In-hospital mortality and MACCEs of heavy drinkers were significantly higher compared with those of light drinkers (5.4 vs. 3.3% and 7.0 vs. 4.4%, both $p = 0.001$). When tested together with Global Registry of Acute Coronary Events risk score parameters, heavy alcohol consumption was independently associated with in-hospital mortality ($p = 0.004$). Conclusions: Our results support that heavy alcohol consumption is an independent predictor of in-hospital mortality in patients presenting with ACS.

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Heavy Drinking Habits Are Associated with Worse In-Hospital Outcomes in Patients with Acute Coronary Syndrome: An Insight from the AMIS Plus Registry

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Keywords

Alcohol · Acute coronary syndrome · ST segment elevation myocardial infarction · Non-ST segment elevation myocardial infarction · In-hospital mortality · Global Registry of Acute Coronary Events score

Abstract

Background: The association between alcohol consumption and the occurrence of coronary heart disease is well described in the literature, while data regarding the impact of regular alcohol consumption on in-hospital outcomes in the setting of acute coronary syndrome (ACS) are lacking. We aimed to evaluate the impact of self-reported alcohol consumption on in-hospital outcomes in patients with ACS. **Methods:** Data derived from patients enrolled between 2007 and 2019 in the Acute Myocardial Infarction in Switzerland (AMIS) Plus registry were retrospectively analyzed. Patients were stratified based on alcohol drinking pattern. Pri-

mary outcome was all-cause in-hospital mortality, while secondary outcomes were set as incidence of major adverse cardiac and cerebrovascular events (MACCEs). Outcome comparisons according to quantity of daily alcohol intake were also performed. **Results:** Records concerning alcohol consumption were available in 25,707 patients; 5,298 of them (21%) fulfilled the criteria of regular alcohol consumption. Regular drinkers were predominantly male, younger, smokers, more comorbid and with a worse clinical presentation as compared with abstainers/occasional drinkers. Daily alcohol intake was reported in 4,059 (77%) of these patients (regular drinkers). Among them, 2,640 were light drinkers (≤ 2 drinks/day) and 1,419 heavy drinkers (> 2 drinks/day). In-hospital mortality and MACCEs of heavy drinkers were significantly higher compared with those of light drinkers (5.4 vs. 3.3% and 7.0 vs. 4.4%, both $p = 0.001$). When tested together with Global Registry of Acute Coronary Events risk score parameters, heavy alcohol consumption was independently associated with in-hospital mortality ($p = 0.004$). **Conclusions:** Our results support that heavy alcohol consumption is an independent predictor of in-hospital mortality in patients presenting with ACS.

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G.T. and L.B. contributed equally to the paper.

Introduction

Alcohol use is one of the most common modifiable causes of major noncommunicable diseases. It is estimated that alcohol excess may cause more than 5% of the global disease burden [1]. Recent data from the 2017 Swiss national health survey showed that 1 in 7 men and 1 in 14 women over 15 years of age drink alcohol on a daily basis [2].

Alcohol abuse induces widespread arterial damage in coronary, brain and peripheral limb arteries, potentiates individual cardiovascular risk factors and increases cardiovascular mortality [3]. Observational and prospective studies have consistently shown a lower risk of all-cause and cardiovascular mortality in people with low levels of alcohol consumption when compared with abstainers, and an increase of the risk with high levels of consumption (the so-called “J-shaped” curve effect) [3–6]. Compared with abstainers, drinkers showed a higher coronary heart disease-related mortality [7, 8]. As postulated by a dose-response analysis, the lowest risk of coronary heart disease mortality occurs with 0.5–2 drinks/day [9, 10].

Despite this well-known association, paucity of data is available regarding in-hospital outcomes of alcohol consumers after an acute coronary syndrome (ACS) [11].

Thus, the aim of the present study is to evaluate the impact of self-reported alcohol consumption on in-hospital mortality and major adverse cardiac and cerebrovascular events (MACCEs) in patients presenting with ACS enrolled in the Acute Myocardial Infarction in Switzerland (AMIS) Plus registry.

Materials and Methods

Patient Population

The AMIS Plus is a nationwide prospective registry founded in 1997, enrolling patients with ST elevation myocardial infarction, non-ST segment elevation myocardial infarction and unstable angina (since 2000) in more than 80 Swiss hospitals. Participating centers provide data for each patient through a standardized questionnaire including 260 items. Data collection is centralized at the Epidemiology, Biostatistics and Prevention Institute of the University of Zurich. All data are checked for completeness, plausibility and consistency by the AMIS Plus Data Center, querying treating physicians if the data are incomplete. Since 2010, external monitoring has been regularly performed in randomly selected hospitals. The registry was approved by the Swiss Federal Ethics Committee for Clinical Studies, the Swiss Board for Data Security and the appropriate Cantonal Ethics Commissions. The Ethics Committees waived the requirement to obtain the patients' informed consent. The study protocol adheres to the ethics guidelines of the Declaration of Helsinki. Details about the AMIS Plus registry have been previously described [12, 13].

For all patients, detailed clinical history, in-hospital medical/interventional treatments and complications, therapy and vital status at discharge were available. Data from patients evaluated with coronary angiography were also reported. The Charlson comorbidity index, a quantitative estimate of associated comorbidities, was calculated [14].

Data about self-reported alcohol consumption have been collected since 2007. Each patient was questioned about alcohol use. Alcohol consumption was defined as regular alcohol intake ≥ 1 drink/day at least 4 days per week. In this analysis, patients enrolled between August 2007 and July 2019 were considered.

Baseline and in-hospital data of patients with ACS and regular alcohol consumption (RAC+) were compared with the remaining AMIS Plus population (abstainers or occasional drinkers, RAC-). Among regular alcohol consumers, light drinkers (≤ 2 drinks/day) and heavy drinkers (> 2 drinks/day) were compared.

Cardiovascular risk factors were defined as follows: smoking habit at the time of the cardiovascular event, diabetes, hypertension and dyslipidemia if treated or previously diagnosed by a physician, obesity if body mass index ≥ 30 , positive family history if a patient's first-degree relative was diagnosed with coronary heart disease when < 60 years of age.

The following in-hospital events were considered in the present analysis: (a) all-cause mortality; (b) cardiogenic shock, defined as persistent hypotension (systolic blood pressure < 90 mm Hg) with clinical signs of severe reduction in cardiac index; (c) stroke or transient ischemic attack, defined as any event due to ischemic, thrombotic or hemorrhagic disturbances confirmed by a neurologist or imaging modality; (d) reinfarction, defined as clinical signs or symptoms of ischemia with electrocardiogram changes indicative of new ischemia (new ST changes or new left bundle branch block) and/or at least a new twofold increase in cardiac biomarkers above the upper reference limit (based on the current available assay and its upper reference limits) following the initial infarction; (e) bleedings: recorded if deemed clinically relevant by the individual physician caring for the patient; after publication of the Bleeding Academic Research Consortium (BARC) criteria [15], this classification was used, and major bleeding defined as BARC type 3–5 bleeding.

The primary outcome was set as all-cause in-hospital mortality.

The secondary outcome was considered incidence of in-hospital MACCEs, defined as the combined outcome of in-hospital reinfarction, stroke and/or death by any cause. Outcomes were also compared according to the degree of alcohol consumption.

Statistical Analysis

Data are presented as the proportion of valid cases for discrete variables and as means $\pm$ SD and/or medians with interquartile ranges for continuous variables. Differences in baseline characteristics were compared using the unpaired *t* test or Mann-Whitney U test if appropriate and the Pearson χ^2 test. Bonferroni correction for multiple comparisons was adopted. Statistics for each table are based on all cases with valid data in the specified ranges for all variables in each table.

Univariate and multivariate tests using logistic regression analysis with a stepwise approach to identify predictors of in-hospital mortality in the whole population were performed. For predictors of in-hospital mortality, RAC- patients were used as reference. A multivariate analysis including all variables of the Global Registry of Acute Coronary Events (GRACE) risk predictor model [16] as

Fig. 1. Study flow chart. AMIS, Acute Myocardial Infarction in Switzerland. ¹ Defined as ≥ 1 drink/day at least 4 days/week. ² Defined as ≤ 2 drinks/day. ³ Defined as > 2 drinks/day.

well as heavy alcohol consumption (> 2 drinks/day) was performed. The validity of logistic regression was assessed using the Hosmer-Lemeshow test. The results of logistic regression are reported as odds ratios (OR) with a 95% confidence interval (95% CI). A probability value of $p < 0.05$ was considered significant. The IBM SPSS Statistics version 25 (IBM Corp., Armonk, NY, USA) was used for all statistical analyses.

Results

Overall, 37,327 patients were enrolled in the AMIS Plus registry from August 2007 to July 2019. Data regarding alcohol consumption were available in 25,707 patients; 5,298 of them (21%) reported regular alcohol consumption (regular drinkers). Daily alcohol intake was known in 4,059 (77%) with 2,640 light drinkers and 1,419 heavy drinkers. The patient inclusion flow chart is shown in Figure 1.

Baseline Characteristics

Baseline characteristics are reported in Table 1. Patients with regular alcohol consumption were younger and predominantly males as compared with RAC- patients. Smoking habit, peripheral vascular disease, previous known coronary artery disease (CAD) and liver diseases were more frequent in RAC+ patients, whereas diabetes had a lower incidence.

Heavy drinkers were younger, more often male, smokers, and affected by heart failure (HF), peripheral vascular disease, liver disease with a higher burden of comorbidities than light drinkers. Notably, heavy drinkers had a significantly lower rate of previously known CAD.

Home medication prior to hospital admission is reported in online supplementary Table 1 (see www.karger.com/doi/10.1159/000508928 for all online supplementary material).

Clinical Characteristics

Compared with RAC-, a higher percentage of RAC+ patients had Killip class > 2 at admission (7.1 vs. 5.5%, $p < 0.001$) and a higher incidence of out-of-hospital cardiac arrest (CA, 5.9 vs. 4.4%, $p < 0.001$). Similarly, heavy drinkers presented with a higher Killip class and higher incidence of out-of-hospital CA than light drinkers (8.9 vs. 5.6% and 8.0 vs. 5.0%, respectively).

Acute Treatment

Acute medical treatment in all groups is reported in Table 2. Notably, vasopressors were more frequently administered in RAC+ patients compared with RAC- (9.6 vs. 6.7%, $p < 0.001$), and in heavy compared with light drinkers (12.3 vs. 7.9%, $p < 0.001$).

Percutaneous coronary intervention was performed in 86.7% of RAC+ and in 83.3% of RAC- patients ($p < 0.001$). Among RAC+ patients, percutaneous coronary interven-

Table 1. Baseline characteristics

	Abstainers/ occasional drinkers	Regular drinkers	<i>p</i> value	Light drinkers	Heavy drinkers	<i>p</i> value
Number	20,409	5,298		2,640	1,419	
Mean age (SD), years	66.0 (13.3)	64.8 (12.0)	<0.001	65.7 (12.2)	63.5 (11.7)	<0.001
Sex, female, <i>n</i> (%)	5,964 (29.2)	665 (12.6)	<0.001	399 (15.1)	126 (8.9)	<0.001
Risk factors, <i>n</i> (%)						
Current smokers	6,646 (34.9)	2,509 (48.8)	<0.001	1,092 (42.3)	850 (62.5)	<0.001
Former smokers	4,889 (25.7)	1,615 (31.4)	<0.001	892 (34.6)	340 (25.4)	<0.001
Never smokers	7,507 (39.4)	1,017 (19.8)	<0.001	596 (23.1)	169 (12.4)	<0.001
Dyslipidemia	11,279 (60.6)	3,040 (62.6)	0.010	1,493 (61.7)	780 (60.9)	0.64
Hypertension	12,248 (62.0)	3,199 (63.0)	0.21	1,608 (63.6)	852 (63.1)	0.78
Diabetes	4,009 (20.1)	899 (17.5)	<0.001	442 (17.1)	265 (19.5)	0.067
Obesity	4,057 (22.0)	1,054 (21.6)	0.64	522 (21.9)	271 (20.7)	0.45
Comorbidities, <i>n</i> (%)						
Heart failure	567 (3.0)	122 (2.7)	0.28	52 (2.0)	47 (3.4)	0.010
CAD	5,577 (29.3)	1,509 (32.3)	<0.001	890 (34.3)	407 (29.6)	0.003
CVD	1,028 (5.1)	285 (5.5)	0.31	151 (5.8)	80 (5.8)	1.00
PVD	899 (4.5)	322 (6.2)	<0.001	106 (4.1)	109 (7.8)	<0.001
Renal disease	1,439 (7.1)	277 (5.3)	<0.001	181 (6.9)	58 (4.2)	<0.001
Mild liver disease	93 (0.5)	77 (1.7)	<0.001	14 (0.5)	51 (3.7)	<0.001
Moderate-severe liver disease	71 (0.4)	70 (1.3)	<0.001	9 (0.3)	49 (3.5)	<0.001
Cancer	1,098 (5.4)	349 (6.7)	0.001	161 (6.2)	91 (6.5)	0.68
CCI >1	4,145 (22.0)	1,084 (23.9)	0.006	584 (22.4)	358 (25.7)	0.019
Presentation, <i>n</i> (%)						
STEMI	11,057 (54.2)	2,887 (54.5)	0.69	1,442 (54.6)	779 (54.9)	0.87
Out-of-hospital CA	906 (4.4)	313 (5.9)	<0.001	131 (5.0)	114 (8.0)	<0.001
Killip class, <i>n</i> (%)			<0.001			<0.001
Class I	17,352 (85.3)	4,441 (84.3)		2,271 (86.3)	1,156 (81.7)	
Class II	1,864 (9.2)	453 (8.6)		212 (8.1)	133 (9.4)	
Class III	518 (2.6)	157 (3.0)		64 (2.4)	49 (3.5)	
Class IV	596 (2.9)	214 (4.1)		83 (3.2)	77 (5.4)	
Median pain-to-door time (IQR), min	205 (102, 570)	196 (100, 530)	0.18	210 (102, 565)	194 (96, 520)	0.17
AFib at admission	839 (4.4)	231 (5.0)	0.068	132 (5.0)	66 (4.7)	0.65
Median GRACE score at admission (IQR)	137 (115, 163)	137 (115, 162)	0.62	137 (116, 161)	137 (113, 162)	0.98
GRACE score risk stratification, <i>n</i> (%)			0.26			0.27
Low	6,012 (36.3)	1,485 (36.9)		845 (36.2)	459 (36.8)	
Intermediate	5,079 (30.6)	1,245 (30.9)		758 (32.5)	373 (29.9)	
High	5,489 (33.1)	1,299 (32.2)		730 (31.3)	414 (33.2)	
Mean vital signs at admission (SD)						
Systolic BP, mm Hg	138 (28)	137 (28)	0.008	138 (28)	137 (29)	0.11
Diastolic BP, mm Hg	80 (17)	80 (17)	0.28	81 (17)	80 (18)	0.31
Heart rate, beats/min	78 (19)	79 (20)	<0.001	78 (20)	82 (21)	<0.001

AFib, atrial fibrillation; BP, blood pressure; CA, cardiac arrest; CAD, coronary artery disease; CCI, Charlson comorbidity index; CVD, cerebrovascular disease; IQR, interquartile range; PVD, peripheral vascular disease; SD, standard deviation; STEMI, ST elevation myocardial infarction. Italics indicate statistically significant *p* values.

tion was less frequently performed in heavy drinkers as compared with light drinkers (83.3 vs. 87.4%, $p = 0.001$).

In-Hospital Outcomes

Data regarding in-hospital outcomes are presented in Table 2. The incidence of bleedings and MACCEs was

significantly higher in RAC+ than RAC- patients ($p < 0.001$ and $p = 0.041$, respectively). Notably, heavy drinkers registered a higher rate of cardiogenic shock (4.4 vs. 2.2%, $p < 0.001$), in-hospital mortality (5.4 vs. 3.3%, $p = 0.001$) and MACCEs (7.0 vs. 4.4%, $p = 0.001$) as compared with light drinkers. A comparison between in-hos-

Table 2. Acute treatment and in-hospital outcomes

	Abstainers/ occasional drinkers	Regular drinkers	<i>p</i> value	Light drinkers	Heavy drinkers	<i>p</i> value
Invasive evaluation, <i>n</i> (%)						
Coronary angiography	17,105 (83.9)	4,617 (87.1)	<i><0.001</i>	2,317 (87.8)	1,192 (84.0)	<i><0.001</i>
PCI performed	16,523 (83.3)	4,442 (86.7)	<i><0.001</i>	2,231 (87.4)	1,130 (83.3)	<i>0.001</i>
Treated vessels, <i>n</i> (%)						
One vessel	14,055 (87.3)	3,695 (86.0)	<i>0.029</i>	1,830 (85.4)	960 (87.8)	<i>0.059</i>
Multivessel	2,046 (12.7)	600 (14.0)		314 (14.6)	133 (12.2)	
LVEF, <i>n</i> (%)			<i><0.001</i>			<i>0.025</i>
<30%	558 (5.7)	168 (7.2)		79 (6.3)	67 (8.5)	
30–40%	1,560 (16.0)	416 (17.8)		209 (16.6)	155 (19.6)	
>40%	7,633 (78.3)	1,754 (75.0)		970 (77.1)	569 (71.9)	
Acute medical treatment, <i>n</i> (%)						
Aspirin	19,650 (96.6)	5,063 (95.8)	<i>0.003</i>	2,530 (95.9)	1,347 (95.1)	<i>0.30</i>
P2Y12 inhibitors	18,132 (89.2)	4,661 (88.3)	<i>0.063</i>	2,311 (87.8)	1,228 (87.0)	<i>0.43</i>
β-Blockers	10,946 (58.0)	2,412 (52.9)	<i><0.001</i>	1,394 (53.3)	738 (52.4)	<i>0.62</i>
Nitrates	8,774 (46.8)	2,240 (49.6)	<i>0.001</i>	1,307 (50.6)	679 (48.4)	<i>0.20</i>
ACEI/ARB	11,198 (59.2)	2,576 (56.4)	<i>0.001</i>	1,506 (57.5)	777 (55.1)	<i>0.13</i>
Ca ²⁺ channel blockers	2,324 (12.4)	609 (13.5)	<i>0.048</i>	361 (14.0)	194 (13.9)	<i>0.96</i>
Diuretics	3,701 (19.7)	930 (20.6)	<i>0.19</i>	511 (19.7)	299 (21.5)	<i>0.19</i>
Statins	15,005 (79.3)	3,543 (77.4)	<i>0.004</i>	2,053 (78.1)	1,086 (77.1)	<i>0.50</i>
Vasopressors	1,243 (6.7)	433 (9.6)	<i><0.001</i>	204 (7.9)	171 (12.3)	<i><0.001</i>
In-hospital outcomes, <i>n</i> (%)						
Median LOS (IQR), days	4 (2–7)	4 (2–7)	<i>0.14</i>	4 (2–7)	4 (2–7)	<i>0.01</i>
Cardiogenic shock	515/19,064 (2.7)	141/4,602 (3.1)	<i>0.18</i>	58/2,640 (2.2)	62/1,419 (4.4)	<i><0.001</i>
Reinfarction	164/20,407 (0.8)	42/5,298 (0.8)	<i>0.99</i>	20/2,640 (0.8)	10/1,419 (0.7)	<i>1.00</i>
Bleeding	695/20,407 (3.4)	239/5,298 (4.5)	<i><0.001</i>	126/2,640 (4.8)	65/1,419 (4.6)	<i>0.82</i>
BARC >2 bleeding	86/434 (19.8)	37/174 (21.3)	<i>0.74</i>	13/82 (15.9)	11/54 (20.4)	<i>0.50</i>
Cerebrovascular event	127/20,407 (0.6)	44/5,298 (0.8)	<i>0.10</i>	17/2,640 (0.6)	18/1,419 (1.3)	<i>0.049</i>
MACCE	938/20,407 (4.6)	279/5,298 (5.3)	<i>0.041</i>	116/2,640 (4.4)	99/1,499 (7.0)	<i>0.001</i>
Mortality	723/20,409 (3.5)	209/5,298 (3.9)	<i>0.16</i>	87/2,640 (3.3)	77/1,419 (5.4)	<i>0.001</i>

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BARC, Bleeding Academic Research Consortium; IQR, interquartile range; LOS, length of stay; LVEF, left ventricular ejection fraction; MACCE, major adverse cardiac and cerebrovascular event; PCI, percutaneous coronary intervention. Italics indicate statistically significant *p* values.

pital outcomes in different patient groups is shown in Figure 2.

Outcome Predictors

In the multivariate analysis including all variables of the GRACE risk predictor model, heavy alcohol consumption was an independent predictor of in-hospital mortality (OR 1.98, 95% CI 1.24–3.18, *p* = 0.004; Table 3).

Furthermore, we evaluated the correlation between GRACE score, in-hospital mortality and MACCE in the heavy drinkers' group. The OR for in-hospital mortality of heavy drinkers adjusted for only GRACE score was 1.57 (95% CI 1.08–2.26; *p* = 0.017); the OR for in-hospital MACCE of heavy drinkers adjusted for only GRACE score was 1.62 (95% CI 1.18–2.23; *p* = 0.003).

Discussion

We conducted a 12-year cohort study on the impact of alcohol consumption on in-hospital outcomes in patients with ACS. We showed that patients with regular alcohol consumption, and heavy alcohol consumption in particular, had more comorbidities at baseline and a worse clinical presentation. We also showed that heavy drinkers have worse in-hospital outcomes. Finally, we found that heavy alcohol consumption was an independent predictor of in-hospital mortality when tested against GRACE risk score parameters, highlighting its importance as an additional prognostic parameter.

Our data offer several important insights into the peculiar clinical pattern of alcohol consumers.

Fig. 2. Comparison between in-hospital outcomes in different patient groups. MACCE, major adverse cardiac and cerebrovascular event.

Table 3. Independent predictors of in-hospital mortality of ACS patients

Variables	OR	95% CI	<i>p</i> value
Heavy alcohol consumption	1.98	1.24–3.18	<i>0.004</i>
Age, per additional year	1.05	1.03–1.07	<i><0.001</i>
Heart rate, beats/min	1.08	1.03–1.08	<i><0.001</i>
Systolic blood pressure, mm Hg	0.98	0.98–0.99	<i><0.001</i>
Killip classes	1.87	1.53–2.30	<i><0.001</i>
Creatinine, $\mu\text{mol/L}$	1.007	1.00–1.01	<i><0.001</i>
Cardiac arrest prior to admission	6.43	3.51–11.79	<i><0.001</i>
Elevated troponin	0.70	0.20–2.45	0.58
ST segment deviation	0.64	0.39–1.06	0.082

ACS, acute coronary syndrome; OR, odds ratio; CI, confidence interval. *Italics indicate statistically significant *p* values.*

Comorbidities

First, drinkers have already a greater comorbidity burden at baseline.

The most common alcohol-induced heart disease is cardiomyopathy, which is characterized by depressed cardiac output, reduced myocardial contractility and di-

lation of the heart chambers [3, 17, 18]. The influence of alcohol on left-ventricular function usually occurs after several years of alcohol misuse, and it is dose dependent [17–19]. In addition, moderate alcohol use seems to protect from HF enhancing myocardial contractility [20, 21]. As a result, it does not surprise that, in our study, preexisting HF was more common in heavy drinkers, and that light drinkers had an even lower rate of HF than abstainers.

While RAC+ patients had a higher prevalence of previously known CAD than RAC– patients, heavy drinkers had a significantly lower rate of previously known CAD than light drinkers. A possible explanation of this finding could be that heavy drinkers might ignore CAD-related symptoms like stable angina or dyspnea, neglecting health issues and leading to lower referral rates to the general practitioner or cardiologist. As a result, CAD may be underdiagnosed in these patients. This is supported in the literature, as alcohol consumption has been shown to be associated with lower adherence to self-care behaviors in cardiovascular prevention [22], in other chronic diseases such as diabetes [23] and generally in the elderly population [24].

Clinical Presentation

In our study, regular drinkers, and especially heavy drinkers, had a worse clinical presentation on admission. They presented on average with a higher Killip class, a higher rate of in-hospital cardiogenic shock and more need for vasopressors during hospitalization. Consistently, left ventricular ejection fraction during the hospitalization was significantly reduced in RAC+ compared with RAC- patients, and in heavy compared with light drinkers. This is only partially explained by the higher prevalence of preexisting HF in drinkers, since approximately 20–30% of regular drinkers had a reduced left ventricular ejection fraction during hospitalization. There are multiple possible explanations. One aspect is that acute ischemia may exacerbate alcohol-induced disruption of myocardial contractility, which develops subclinically for many years especially in heavy drinkers. This is well in agreement with a previous study on rats [25], which showed that chronic alcohol consumption reduced the ability of the myocardium to recover pump function after ischemia and reperfusion injury.

On the other hand, several studies linked chronic alcohol intake to protective ischemic preconditioning [26]. Although the exact mechanisms are still unclear, alcohol may influence the activity of protein kinase C isozymes, which are involved in cardioprotection [27]. However, ethanol quantity and intake pattern influence the way ethanol modulates protein kinase C activity [27], thus varying the degree of cardioprotection. Another possible mechanism by which moderate alcohol consumption may attenuate ischemic damage is by modulating angiogenesis. Moderate alcohol consumption was found to activate vascular endothelial growth factor [28, 29] and lower the antiangiogenic protein endostatin, resulting in enhanced angiogenesis, whilst heavy alcohol consumption did not change vascular endothelial growth factor and increased endostatin [29], thereby inhibiting angiogenesis.

An interesting finding of our study is that drinkers have a higher rate of out-of-hospital CA. Heavy drinking is known to be associated with greater risk of sudden cardiac death in patients with preexisting CAD [30, 31], and there is solid evidence on the association between alcohol consumption and arrhythmias [3]. The most common arrhythmias described in the setting of acute drinking are supraventricular, especially atrial extrasystoles and atrial fibrillation [32].

Ventricular extrasystoles and tachycardia have also been described and are more dangerous and can result in sudden death [33]. The acute arrhythmogenic effect of ethanol is uncommon in individuals with normal left ventricular function but is associated with established al-

coholic dilated cardiomyopathy [9]. In chronic alcoholics, acute abstinence is associated with electrolyte deficiencies and higher levels of catecholamines, potential triggers of arrhythmias [3, 33].

Going beyond vascular pathophysiology, drinkers may have a worse status at presentation also because of social and behavioral factors. However, the hypothesis that heavy drinkers' social isolation might cause a delay in hospital admission in our study was confuted by the lack of significant differences regarding the pain-to-door time between the groups.

We have observed that diabetes and renal diseases were less present in regular drinkers. This is in agreement with a well-known confounder represented by individuals that ceased drinking due to other comorbidities: the so-called "sick quitters" [34, 35]. A recent cohort analysis on 97,852 patients confirmed that 15.4% of participants with newly diagnosed diabetes quit drinking [36]. Thus, low-volume drinkers may appear healthier than abstainers in epidemiological studies [35].

Outcomes

Finally, the finding that heavy alcohol consumption is associated with a worse in-hospital prognosis in ACS is consistent with the previous literature in other fields of medicine. In surgery, heavy drinking was found to increase in-hospital mortality in patients undergoing general surgery procedures [37, 38]. In the intensive care unit, alcohol abuse was associated with higher risk of sepsis, septic shock and in-hospital mortality [39], increased in-hospital mortality in patients with ventilator-associated pneumonia [40] and acute respiratory distress syndrome [41]. As already mentioned, a cross-sectional analysis of the 2011 Nationwide Inpatient Sample showed an association between chronic alcohol-related diagnoses (e.g., alcoholic cardiomyopathy, alcoholic liver disease) and in-hospital mortality in patients presenting with acute myocardial infarction [11]. However, this study did not stratify patients by their drinking habits. Our data confirmed the association between alcohol consumption and in-hospital mortality in ACS, though independently of the presence of chronic alcohol-related diagnoses and recognized heavy alcohol consumption as an independent predictor of in-hospital mortality.

Limitations

Our findings must be interpreted in the context of the following limitations. First, data about alcohol consumption were based on the patients' self-reporting. No toxic

cological screening or carbohydrate-deficient transferrin assays were routinely used in our cohort. Physicians were instructed to actively ask for drinking habits, but we cannot exclude some patients' neglect that may have underestimated the percentage of regular drinkers, resulting in selection and reporting biases. Second, our analysis of heavy versus light drinkers only refers to a smaller cohort in which alcohol consumption was quantifiable, since data regarding the exact amount of alcohol consumption were often missing. Third, as the definition of alcohol consumption was based on regular use, binge drinkers may have been underestimated. Fourth, due to the retrospective nature of the study, we cannot exclude confounding factors as an explanation for our results. However, we adjusted as appropriately as possible for conventionally recognized confounders. Fifth, as an intrinsic limitation of our registry, bleedings were recorded if deemed clinically relevant by the individual physician. The BARC classification of bleeding events was introduced after its validation in 2012, therefore it is not available for the whole population. Finally, "sick quitters" may have been present in the RAC- group, increasing morbidity-related outcome such as in-hospital mortality and MACCEs and attenuating between-group differences.

Conclusions

In conclusion, our study shows that regular alcohol consumers admitted with ACS more frequently present with higher Killip class and out-of-hospital CA, and heavy drinkers have worse in-hospital outcomes compared with light drinkers. Moreover, heavy alcohol intake represents an independent predictor of in-hospital mortality when tested against GRACE risk score parameters. Our results emphasize the importance of considering regular alcohol consumption as a possible determinant of worse in-hospital prognosis in patients with ACS.

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Statement of Ethics

The AMIS Plus registry was approved by the Swiss Federal Ethics Committee for Clinical Studies, the Swiss Board for Data Security and the appropriate Cantonal Ethics Commissions. The study protocol adheres to the ethics guidelines of the Declaration of Helsinki.

Disclosure Statement

We hereby declare that all authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation. All authors have no conflict of interest to disclose.

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Author Contributions

G.T., L.B. and G.P. analyzed the data and drafted the manuscript. G.T. and L.B. equally contributed to the present manuscript and should be considered as first co-authors. D.R. acquired and analyzed the data, performed the statistical analysis and critically reviewed the manuscript. H.R., M.R., F.E., M.M., R.J., T.M. and P.E. critically reviewed the manuscript. All authors have read and approved the submission of the paper.

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