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Association of chocolate consumption with neurological and cardiovascular outcomes in atrial fibrillation: data from two Swiss atrial fibrillation cohort studies (Swiss-AF and BEAT-AF)

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Summary

AIM: To assess the associations of chocolate consumption with neurocognitive function, brain lesions on magnetic resonance imaging (MRI), and cardiovascular outcome in patients with atrial fibrillation (AF).

METHODS: We analysed data from patients of two prospective multicentre Swiss atrial fibrillation cohort studies (Swiss-AF) and (BEAT-AF). Assessments of MRI findings and neurocognitive function were performed only in the Swiss-AF population (in 1727 of 2415 patients [71.5%] with a complete data set), as patients enrolled in BEAT-AF were not systematically evaluated for these outcomes. Otherwise, the two cohorts had an equivalent set of clinical assessments. Clinical outcome analysis was performed in 3931 patients of both cohorts. Chocolate consumption was assessed by questionnaire. Patients were cate-gorised as no/low chocolate consumption (No/Low-Ch) ≤1 servings/week, moderate chocolate consumption (Mod-Ch) >1–6 servings/week, and high chocolate consumption (High-Ch) >6 servings/week, respectively. Brain lesions were evaluated by MRI. Assessment of cognitive function was performed by neurocognitive functional testing and in-cluded global cognition measurement with a cognitive con-struct score. Cerebral MRI and cognition were evaluated at baseline. Cross-sectional associations between choco-late consumption and MRI findings were analysed by multivariate logistic regression models and associations with neurocognitive function by multivariate linear regression models. Clinical outcome events during follow-up were recorded and assessed by a clinical event committee. The associations between chocolate consumption and clinical outcomes were evaluated by Cox regression models. The median follow-up time was 6 years.

RESULTS: Chocolate consumption was not associated with prevalence or volume of vascular brain lesions on MRI, nor major adverse cardiac events (ischaemic stroke, myocardial infarction, cardiovascular death). However, No/Low-Ch was independently associated with a lower cognitive construct score compared to Mod-Ch (No/Low-Ch vs. Mod-Ch: coeff. -0.05, 95% CI -0.10-0), whereas other neurocognitive function tests were not independently associated with chocolate consumption categories. In addition, there was a higher risk of heart failure hospitalisation (No/Low-Ch vs. Mod-Ch: HR 1.24, 95% CI 1.01-1.52) and of all-cause mortality (No/Low-Ch vs. Mod-Ch: HR 1.29, 95% CI 1.06-1.58) in No/Low-Ch compared to Mod-Ch. No significant associations with the evaluated outcomes were observed when High-Ch was compared to Mod-Ch.

CONCLUSION: While chocolate consumption was not associated with MRI findings and major adverse cardiac events in an atrial fibrillation population, No/Low-Ch was associated with a lower cognitive construct score, higher risk of heart failure hospitalisation and increased all-cause mortality compared to Mod-Ch.

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Introduction

Atrial fibrillation (AF) is the most common arrhythmia in European countries. In view of an ageing population, its prevalence is expected to increase further [1]. Atrial fibrillation has been associated with an increased risk of cardiovascular morbidity and death [2]. According to previous investigations, chocolate consumption is linked to a decreased risk of cardiovascular and cerebrovascular disease [3–5] and may affect cognitive function [6–9].

The most important components of chocolate are cocoa flavonoids and methylxanthines [6]. A number of beneficial systemic effects have been attributed to flavonoids, including increased nitric oxide bioavailability [10], antioxidant properties [10, 11], antithrombotic mechanisms and anti-inflammatory effects [12]. Both flavonoids and methylxanthines may permeate the blood-brain barrier. Whereas flavonoids may affect brain function via mechanisms such as increased cerebral blood flow [8, 13], promotion of cerebral angiogenesis [9, 13], or inhibition of neuronal death by apoptosis [9], methylxanthines may act as mild central nervous system stimulants [6].

Chocolate may have the most favourable effect when consumed in moderation [3, 4]. Moderate chocolate intake may also be inversely related to the risk of clinically apparent atrial fibrillation [14]. However, data regarding this association are conflicting [15, 16]. To date, the effect of chocolate consumption on neurocognitive function, cerebral and cardiovascular outcomes in patients diagnosed with atrial fibrillation has not been studied. With a per capita consumption of 9.9 kg/year, the Swiss population has the highest consumption of this aliment in Europe [17]. The prevalence of atrial fibrillation in Switzerland is 600–699/100,000 persons [18]. The widespread consumption of chocolate in a country with a high prevalence of atrial fibrillation gave rise to searching for associations between chocolate intake and clinical outcomes in a Swiss AF population.

Based on the above-mentioned considerations, the aim of the present study was to evaluate the association between chocolate consumption and 1) neurocognitive function, 2) brain lesions on MRI, and 3) cardiovascular events in patients with atrial fibrillation.

Methods

Study design, data sources and participants

Data from two ongoing prospective, observational multicentre cohort studies from Switzerland – the Swiss Atrial Fibrillation Cohort study (Swiss-AF) and the Basel Atrial Fibrillation Cohort study (BEAT-AF) – were included in this study [19, 20]. Patients were eligible for participation in Swiss-AF if they had a history of documented atrial fibrillation and if they were aged 65 years or older. An additional 10–15% of patients between 45–65 years of age were aimed to be enrolled to assess atrial fibrillation in individuals who are potentially in the active workforce [19]. In BEAT-AF, patients with atrial fibrillation documented on electrocardiogram were asked to participate [20]. In both cohort studies, patients could be recruited from in- and outpatient clinics. Enrolment of patients with acute illnesses was postponed until stabilisation. More detailed information on the underlying cohorts is described elsewhere [19, 20]. Both cohort studies use an equivalent set of clinical assessments, including chocolate consumption, patient demographic characteristics, medical history, and medication. During the course of the study, information on clinical events is collected yearly.

For data derived from brain magnetic resonance imaging (MRI) as well as from cognitive functional testing, only data from the Swiss-AF cohort were included. In BEAT-AF, these outcomes were not systematically evaluated. For the analyses regarding brain lesions and cognitive function testing, we used the baseline data (= data of the first visit) from all enrolled Swiss-AF patients with a full data set, i.e., patients that had a baseline MRI as well neurocognitive function testing performed at the initiation visit. The association between chocolate consumption and clinical events was assessed using the data of all Swiss-AF and BEAT-AF patients with available information on baseline chocolate consumption.

The local Ethics Committees approved the study protocols of both registries. All patients gave written informed consent.

Categorisation of chocolate consumption

Chocolate consumption was reported by the patients on a yearly basis via a multiple-choice question with the following nine answer options: never or less than one bar (German: “Riegel”) per month, 1–3 bars per month, 1 bar per week, 2–4 bars per week, 5–6 bars per week, 1 bar per day, 2–3 bars per day, 4–5 bars per day, and 6+ bars per day, respectively.

One serving is considered to correspond to approximately 30 g of chocolate [21]. As the size and composition of a chocolate bar is variable and the chocolate content is therefore difficult to determine, we chose to equate a bar of chocolate to one serving. According to two meta-analyses, the quantity of chocolate intake potentially associated with a reduction in the risk of cardiovascular disease ranges from 45g to 180 g/week, which is considered to represent moderate consumption [3, 4]. Consequently, we defined three groups of chocolate consumption. Patients were stratified into the no/low chocolate consumption group (No/Low-Ch) if they stated they ate ≤1 servings (corresponding to ≤30 g/week) of chocolate per week. In the moderate chocolate consumption group (Mod-Ch), the weekly chocolate intake ranged from >1 to 6 servings (>30 g to 180 g per week), and in the high chocolate consumption group (High-Ch), chocolate consumption exceeded 6 servings per week (>180 g per week).

Clinical measures

Weight and height were directly measured and body mass index (BMI) calculated. Patient history was assessed at baseline. Educational status, smoking status, medical history, and history of oral anticoagulation medication were obtained by questionnaire. Atrial fibrillation type was classified as paroxysmal, persistent, or permanent atrial fibrillation [18].

Outcome measures

The primary interest of our study was to evaluate the association between chocolate consumption and neurocognitive function in a real-world atrial fibrillation population. Given the unique data set on cerebral MRI performed and systematically analysed in a large number of Swiss-AF participants, we additionally intended to search for associations between chocolate intake and brain lesions. Moreover, the assembly of data from both the Swiss-AF and the BEAT-AF cohorts enabled us to evaluate the association between chocolate consumption and clinical outcome measures in a large population of patients suffering from atrial fibrillation. The study was exploratory in nature and aimed to be hypothesis-generating rather than confirmatory. Therefore, no distinct primary endpoint was defined prior to analysis of data.

Cognitive testing

Centrally trained study personnel performed standardised neurocognitive assessments. The tests were provided in paper format in the main national languages of Switzerland (i.e., German, French and Italian) [22]. Neurocognitive testing included the Montreal Cognitive Assessment (MoCA) which is a screening test to detect mild cognitive impairment. Patients can obtain a score from 0 to 30 points [23]. The Trail Making Test (TMT) parts A and B and the Semantic Fluency Test (SF) were included for detection of dementia [24, 25]. In the TMT, patients connect circled numbers in ascending order by drawing a continuous line (trail) between them. Trails A and B are of different lengths. The test score is defined as the time used divided by the total number of circles correctly connected in that time [22, 24]. In the SF test, patients are asked to name as many animals as possible within 60 seconds [25].

The Digit Symbol Substitution Test (DSST) was used to evaluate psychomotor performance [26]. In this test, patients receive a key grid of numbers and matching symbols. The score is the number of correct number-symbol matches achieved within 120 seconds [22, 26]. Additionally, we used the cognitive construct score, a factor score developed for the Swiss-AF study that allows for quantification of cognitive function. The test is composed of 17 differently weighted combined items from all of the above-mentioned individual neurocognitive tests [22].

Brain MRI

Brain MRI was performed on 1.5 or 3 Tesla MRI scanners. A standardised protocol was used in all participating centres. The standard protocol did not demand the administration of contrast agent. Brain lesions were assessed as small non-cortical infarcts (SNCIs), large non-cortical or cortical infarcts (LNCCIs), microbleeds (Mb), and white matter lesions (WML) [19]. As 99% of patients presented with WML, we used the Fazekas score as a binary endpoint for WML in the analysis. At least moderate disease was defined as a score ≥2 [27].

Main clinical outcome measures

Main clinical outcome measures were prespecified and included major adverse cardiac events (combined end-point of ischaemic stroke, myocardial infarction and cardiovascular death), stroke, major bleeding, myocardial infarction, hospitalisation for heart failure, cardiovascular death, and all-cause death, respectively. If a clinical outcome measure was reported or found in the medical records, additional information was collected from involved hospitals and/or treating physicians. All events were adjudicated by a blinded clinical event committee [19].

Statistical analysis

Baseline patient characteristics by categories of chocolate consumption were described by mean and standard deviation, or absolute and relative frequency, as appropriate. Prevalence of lesions on baseline MRI were presented as absolute and relative frequency, lesion volume and lesion count as median and interquartile range. Results from neurocognitive tests were described by mean and standard deviation. Group comparisons were performed by ANOVA tests (one-way, three groups) for continuous variables and by chi-squared tests for categorical variables.

In all analyses, we considered available data from both the BEAT-AF and Swiss-AF cohort until 13 May 2022.

In all the analyses evaluating the association between chocolate consumption and outcomes, Mod-Ch was used as the reference category and the two other categories were compared to this reference category.

The association between chocolate consumption and cerebral lesions on MRI was examined using multivariable-adjusted mixed-effects logistic regression models, including study centre as a random intercept. In this analysis, we included all patients with a brain MRI reading available at baseline (n = 1727). In patients that presented with cerebral lesions, we also analysed the association between chocolate consumption and lesion volume using multivariable-adjusted mixed-effects linear regression models with the lesion volumes (log-transformed due to the skewed distribution and mean-centred) as the dependent variable. LNCCIs, SNCI, WML and Mb were analysed. These models also included study centre as a random intercept.

In all patients with a brain MRI reading available at baseline, we also assessed the cross-sectional association between chocolate consumption and cognitive function using linear mixed-effects models with study centre as a random intercept. The test scores of the performed neurocognitive tests as well as the calculated cognitive construct factor score were used as continuous outcome variables. Given the previous association between the neurocognitive test scores and the presence as well as the volume of neurological lesions [28], we additionally adjusted the models for neurocognitive outcomes for the presence and volume of LNCCI, the presence of white matter lesions with Fazekas scale ≥2, as well as the volume of white matter lesions. The volumes were set to 0 for patients who did not present with the particular lesions. Given the very low proportion of missing data at baseline, we performed an available case analysis.

We investigated the association between chocolate consumption and clinical events using Cox proportional hazard models with study centre as a stratification factor. All variables in the model were time-updated to account for variations in chocolate consumption and other covariates over time (information updated with each patient visit). In

case of missing data occurring at follow-up visits or of missed visits, we performed a simple imputation with the patient's last observation carried forward until the next visit or censoring. In potentially recurring events, only the first event was considered.

For each outcome, two models were constructed: (1) a model adjusted for age and gender, and (2) a model adjusted for age, gender, and additional clinical covariates (the lists of covariates are displayed in the corresponding tables). For each model, the estimates (odds ratio for logistic regression models, coefficient for linear models, and hazard ratios for Cox models) for the fixed effects of the different levels of chocolate consumption along with their corresponding 95% confidence interval (CI) are reported.

As a sensitivity analysis, we investigated the potential effect of the two different cohorts by adding an interaction term of cohort with chocolate consumption. This did not result in a better model fit and therefore it was not considered in the analysis.

All analyses were performed using the statistical software R version 4.2.2. The analytical code is provided as supplementary material (appendix 1).

Ethics statement

The studies involving human participants were reviewed and approved by the Ethics Committee Nordwest- und Zentralschweiz, Switzerland and all local Ethics Committees at the study sites. The project numbers were 2021-00701 for Swiss-AF and EK 331/09 for BEAT-AF (both numbers from the lead Ethics Committee).

Results

Brain MRI and neurocognitive function analysis

Baseline characteristics

Of the 2415 patients enrolled in the Swiss-AF cohort, 1727 (71.5%) patients were included in the analysis for brain lesions on brain MRI and for neurocognitive function testing. 672 (27.8%) patients did not undergo brain MRI; the main reason for this was an implanted cardiac device (n = 461; [68.6%]). Other reasons were contraindications for MRI and claustrophobia. 11 (0.5%) patients were excluded from the analysis due to missing MoCA assessment during the baseline visit and in 5 (0.2%) patients we did not have information on chocolate consumption at baseline.

Baseline characteristics of the 1727 included patients are displayed in table 1. 1127 (65.3%) patients were in the No/Low Ch, 375 (21.7%) in the Mod-Ch, and 225 (13.0%) in the High-Ch group.

Prevalence and volume of brain lesions on MRI

Analysis of brain MRI showed LNCCI in 387 (22.4%) patients, SNCI in 367 (21.3 %), Mb in 371 (21.5 %), and WML in 1710 (99.0%) patients. Of the patients with WML, 926 (53.7%) presented with a Fazekas score ≥2 (table 2).

The association between chocolate consumption and the prevalence of lesions detected by brain MRI is presented in table 3. In the simple model adjusted for age and gender, as well as in the full model adjusted for additional clinical variables, there was no association found for prevalence of brain lesions on brain MRI and the different groups of chocolate consumption (table 3). Moreover, no significant associations were found between the volume of brain lesions and chocolate consumption (table 3).

Neurocognitive function tests

The results of neurocognitive function tests are shown in table 4. Whereas MoCA and cognitive construct varied between groups, the remaining neurocognitive test results were similar. The association between chocolate consumption and neurocognitive function in multivariate analysis is shown in table 5. In the simple model adjusting for age and gender, Mod-Ch was associated with better TMT-B, DSST, and cognitive construct results compared to No/Low-Ch. However, in the full model of the multivariate analysis, only the association between Mod-Ch and a better cognitive construct score remained significant. Evaluation of neu-

Table 1:
Baseline characteristics of patients in the brain MRI and neurocognitive function analyses.

Chocolate consumption groups	Overall	No/Low-Ch	Mod-Ch	High-Ch	p
n	1727	1127	375	225	
Age (y), mean (SD)	72.55 (8.39)	72.49 (8.51)	72.42 (8.21)	73.09 (8.06)	0.58
Female, n (%)	474 (27.4)	292 (25.9)	109 (29.1)	73 (32.4)	0.098
BMI (kg/m^2), mean (SD)	27.66 (4.75)	27.96 (4.83)	27.39 (4.68)	26.61 (4.32)	<0.001
Active smoker, n (%)	130 (7.5)	83 (7.4)	26 (6.9)	21 (9.3)	0.53
Arterial hypertension, n (%)	1196 (69.3)	793 (70.4)	258 (68.8)	145 (64.4)	0.21
Education level, n (%)					0.44
− basic	203 (11.8)	140 (12.4)	34 (9.1)	29 (12.9)	
− middle	843 (48.8)	551 (48.9)	184 (49.1)	108 (48.0)	
− advanced	681 (39.4)	436 (38.7)	157 (41.9)	88 (39.1)	
AF-type (non-paroxysmal), n (%)	936 (54.2)	648 (57.5)	175 (46.7)	113 (50.2)	0.001
History of diabetes mellitus, n (%)	270 (15.6)	203 (18.0)	48 (12.8)	19 (8.4)	<0.001
History of stroke, n (%)	228 (13.2)	138 (12.2)	57 (15.2)	33 (14.7)	0.27
History of heart failure, n (%)	373 (21.6)	250 (22.2)	76 (20.3)	47 (20.9)	0.7
History of renal failure, n (%)	312 (18.1)	225 (20.0)	60 (16.0)	27 (12.0)	0.009
Oral anticoagulation, n (%)	1555 (90.0)	1015 (90.1)	341 (90.9)	199 (88.4)	0.62

Continuous variables are presented as mean with standard deviation, categorical variables are presented as numbers and percentages. Group comparisons were performed by ANOVA tests for continuous variables and by chi-squared tests for categorical variables.

No/Low-Ch: no or low chocolate consumption; Mod-Ch: moderate chocolate consumption; High-Ch: high chocolate consumption; BMI: body mass index; AF: atrial fibrillation

rocognitive test results in High-Ch versus Mod-Ch exhibited no significant associations in the two statistical models (table 5).

Clinical outcome analysis

Baseline characteristics of patients included in the clinical outcome analysis

Of the 4039 patients in the Swiss-AF and the BEAT-AF cohorts, 3931 (97.2%) were included in the analysis. 108 pa-

Table 2:
Lesions detected by brain MRI at baseline.

Chocolate consumption groups		Overall	No/Low-Ch	Mod-Ch	High-Ch
	n	1727	1127	375	225
LNCCI	Prevalence	387 (22.4)	258 (22.9)	78 (20.8)	51 (22.7)
	Volume	1623 [255, 7314]	1337 [229, 6824]	2340 [399, 6107]	1656 [227, 8805]
	Count	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 3.0]
SNCI	Prevalence	367 (21.3)	238 (21.1)	83 (22.1)	46 (20.4)
	Volume	63 [30.0, 160.5]	66 [30.0, 167.2]	57 [30.0, 159.0]	57 [33.0, 107.3]
	Count	1.0 [1.0, 3.0]	2.0 [1.0, 3.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]
Microbleeds	Prevalence	371 (22.2)	248 (22.8)	71 (19.4)	52 (24.0)
	Number	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]	1.0 [1.0, 2.0]
WML	Prevalence	1710 (99.0)	1121 (99.5)	371 (98.9)	218 (96.9)
	Volume	3921 [1446, 9786]	3792 [1395, 9705]	3738 [1476, 8954]	5334 [1700, 11770]
	Count	23 [11.0, 41.0]	22 [11.0, 40.0]	23 [11.0, 41.0]	25 [14.0, 44.8]
Fazekas scale ≥2		926 (53.7)	591 (52.5)	202 (53.9)	133 (59.1)

Categorical variables are presented as numbers and percentages, non-normally distributed variables as median with interquartile range.

No/Low-Ch: no or low chocolate consumption; Mod-Ch: moderate chocolate consumption; High-Ch: high chocolate consumption; LNCCI: large non-cortical or cortical infarcts; SNCI: small non-cortical infarcts; WML: white matter lesions

Table 3:
Association between chocolate consumption and the prevalence of brain lesions.

	Simple model				Full model			
	No/Low-Ch vs Mod-Ch		High-Ch vs Mod-Ch		No/Low-Ch vs Mod-Ch		High-Ch vs Mod-Ch	
Outcome	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**	**OR (95% CI)**	**p**
LNCCI	1.12 (0.84, 1.49)	0.46	1.10 (0.73, 1.65)	0.65	1.22 (0.88, 1.68)	0.23	1.14 (0.72, 1.79)	0.56
SNCI	0.93 (0.69, 1.24)	0.61	0.87 (0.57, 1.33)	0.52	0.96 (0.71, 1.29)	0.79	0.87 (0.57, 1.34)	0.53
Microbleeds	1.20 (0.89, 1.62)	0.23	1.28 (0.85, 1.93)	0.22	1.22 (0.90, 1.66)	0.20	1.31 (0.86, 2.00)	0.20
Fazekas ≥2	0.93 (0.72, 1.21)	0.59	1.20 (0.83, 1.73)	0.334	0.91 (0.70, 1.18)	0.48	1.17 (0.81, 1.70)	0.40
Outcome	**coeff (95% CI)**	**p**	**coeff (95% CI)**	**p**	**coeff (95% CI)**	**p**	**coeff (95% CI)**	**p**
LNCCI volume	−0.29 (−0.81, 0.22)	0.27	−0.06 (−0.78, 0.66)	0.87	−0.24 (−0.71, 0.23)	0.31	−0.01 (−0.67, 0.64)	0.97
SNCI volume	0.07 (−0.23, 0.36)	0.66	−0.09 (−0.52, 0.33)	0.66	0.1 (−0.20, 0.40)	0.50	−0.06 (−0.49, 0.37)	0.80
WML volume	−0.02 (−0.16, 0.12)	0.80	0.14 (−0.07, 0.34)	0.19	−0.04 (−0.18, 0.10)	0.59	0.13 (−0.07, 0.33)	0.20

Cross-sectional analysis from data assessed at baseline. Moderate chocolate consumption (Mod-Ch) was used as the reference category and the two other categories, no or low chocolate consumption (No/Low-Ch) and high chocolate consumption (High-Ch), were compared to this reference category. The simple model is adjusted for age and gender, the full model is additionally adjusted for educational status, BMI, smoking status, arterial hypertension, history of diabetes, history of stroke, history of heart failure, history of kidney failure, atrial fibrillation type, and oral anticoagulation.

OR: odds ratio; CI: confidence interval; coeff: coefficient; LNCCI: large non-cortical or cortical infarcts; SNCI: small non-cortical infarct

Table 4:
Results of neurocognitive function tests.

Chocolate consumption group	Overall	No/Low-C	Mod-Ch	High-Ch	p
n	1727	1127	375	225	
MoCA	25.53 (3.03)	25.38 (3.05)	25.78 (2.98)	25.81 (2.98)	0.03
TMT-A	0.54 (0.22)	0.54 (0.22)	0.55 (0.20)	0.53 (0.21)	0.6
TMT-B	0.22 (0.11)	0.21 (0.11)	0.23 (0.11)	0.21 (0.10)	0.13
DSST	44.54 (14.19)	44.02 (14.70)	45.97 (13.03)	44.72 (13.31)	0.07
SF	19.04 (5.36)	18.96 (5.46)	19.35 (5.13)	18.92 (5.18)	0.45
CoCo	0.03 (0.53)	0.01 (0.54)	0.09 (0.49)	0.03 (0.50)	0.05

Variables are presented as mean with standard deviation. Comparisons were performed by ANOVA tests.

No/Low-Ch: no or low chocolate consumption; Mod-Ch: moderate chocolate consumption; High-Ch: high chocolate consumption; MoCA: Montreal Cognitive Assessment; TMA-A: Trail Making Test-A; TMA-B: Trail Making Test-B; DSST: Digit Symbol Substitution Test; SF: Semantic Fluency Test; CoCo: Cognitive Construct Score

tients were excluded due to missing data at baseline. The median observation time was 6.05 years. The total person-years of follow-up added up to 21,726 years. The baseline characteristics of the patients stratified by the level of chocolate consumption are shown in table 6.

Association between chocolate consumption and clinical outcomes

During follow-up, a total of 1358 (34.5%) patients experienced one or more clinical events. Major adverse cardiac events occurred in 560, stroke in 210, major bleeding in 392, hospitalisation for heart failure in 632, myocardial infarction in 150, cardiovascular death in 446, and all-cause death in 726 patients, respectively. The association between chocolate consumption and clinical outcomes in multivariate analysis is shown in Table 7. No independent association of chocolate consumption with major adverse cardiac events was found. In the simple model adjusting for age and gender as well as following adjustment for various additional clinical parameters, the risk of hospitalisation for heart failure and of all-cause death was higher in No/Low-Ch compared to Mod-Ch (table 7). For the comparison between High-Ch vs. Mod-Ch no corresponding associations were seen. The Kaplan-Meier curves for the end-points hospitalisation for heart failure and all-cause death in the three groups of chocolate consumption are presented in figure 1.

Discussion

In this large cohort study of patients with atrial fibrillation, we observed no association between chocolate consumption and the prevalence or volume of vascular brain lesions on brain MRI. On the other hand, No/Low-Ch, when compared to Mod-Ch, was independently associated with low-

Table 5:
Association between chocolate consumption and neurocognitive function.

	Simple model				Full model			
	No/Low-Ch vs. Mod-Ch		High-Ch vs. Mod-Ch		No/Low-Ch vs. Mod-Ch		High-Ch vs. Mod-Ch	
Outcome	**coeff (95% CI)**	**p**	**coeff (95% CI)**	**p**	**coeff (95% CI)**	**p**	**coeff (95% CI)**	**p**
MoCA	−0.41 (−0.74, −0.08)	0.14	0.07 (−0.39, 0.54)	0.76	−0.27 (−0.59, 0.06)	0.11	0.07 (−0.38, 0.53)	0.76
TMT−A	−0.01 (−0.03, 0.01)	0.36	−0.01 (−0.04, 0.02)	0.63	−0.004 (−0.03, 0.02)	0.72	−0.01 (−0.04, 0.02)	0.65
TMT−B	−0.01 (−0.02, −0.00)	0.02	−0.01 (−0.02, 0.01)	0.36	−0.01 (−0.02, 0.003)	0.14	−0.01 (−0.02, 0.01)	0.33
DSST	−1.81 (−3.26, −0.36)	0.01	−0.60 (−2.65, 1.46)	0.57	−1.09 (−2.46, 0.28)	0.12	−0.53 (−2.46, 1.40)	0.59
SF	−0.37 (−0.97, 0.22)	0.22	−0.28 (−1.1, 0.56)	0.51	−0.22 (−0.81, 0.37)	0.47	−0.27 (−1.09, 0.56)	0.53
CoCo	−0.08 (−0.13, −0.03)	0.003	−0.03 (−0.10, 0.05)	0.44	−0.05 (−0.10, 0)	0.049	−0.03 (−0.10, 0.04)	0.43

Cross-sectional analysis from data assessed at baseline. Moderate chocolate consumption (Mod-Ch) was used as the reference category and the two other categories, no or low chocolate consumption (No/Low-Ch) and high chocolate consumption (High-Ch), were compared to this reference category. The simple model is adjusted for age, gender, the presence and volume of large noncortical or cortical infarcts, and the presence of white matter lesions Fazekas score ≥2, as well as the volume of white matter lesions. The full model is additionally adjusted for educational status, BMI, smoking status, arterial hypertension, history of diabetes, history of stroke, history of heart failure, history of kidney failure, atrial fibrillation type, and oral anticoagulation.

Coeff: coefficient; CI: confidence interval; MoCA: Montreal Cognitive Assessment; TMA-A: Trail Making Test-A; TMA-B: Trail Making Test-B; DSST: Digit Symbol Substitution Test; SF: Semantic Fluency Test; CoCo: Cognitive Construct Score

Table 6:
Baseline characteristics of patients in the clinical outcome analysis.

Chocolate consumption g roup	Overall	No/Low-Ch	Mod-Ch	High-Ch	p
n	3.931	2.548	836	547	
Age (y), mean (SD)	71.42 (10.07)	71.48 (9.79)	71.38 (10.56)	71.68 (10.35)	0.86
Female, n (%)	1117 (28.2)	678 (26.6)	249 (29.8)	178 (32.5)	0.9
BMI (kg/m^2), mean (SD)	27.46 (4.76)	27.74 (4.80)	27.18 (4.64)	26.54 (4.51)	<0.001
Active smoker, n (%)	313 (7.9)	212 (8.3)	59 (7.1)	38 (6.9)	0.35
Arterial hypertension, n (%)	2736 (69.1)	1790 (70.3)	571 (68.3)	356 (65.1)	0.49
Highest education level, n (%)					0.4
− basic	483 (12.3)	324 (12.8)	77 (9.2)	75 (13.7)	
− middle	1936 (49.1)	1256 (49.4)	421 (50.5)	254 (46.5)	
− advanced	1520 (38.6)	961 (37.8)	336 (40.3)	217 (39.7)	
AF type non-paroxysmal, n (%)	2020 (51.0)	1355 (53.2)	397 (47.5)	253 (46.3)	0.1
History of diabetes, n (%)	635 (16.0)	469 (18.4)	106 (12.7)	54 (9.9) 106 (19.4)	<0.001
History of stroke / TIA, n (%)	676 (17.1)	418 (16.4)	151 (18.1)		0.18
History of heart failure, n (%)	942 (23.8)	621 (24.4)	187 (22.4)	126 (23.0)	0.44
History of renal failure, n (%)	741 (18.7)	521 (20.5)	144 (17.3)	75 (13.7)	0.1
History of MI, n (%)	582 (14.7)	398 (15.6)	110 (13.2)	71 (13.0)	0.1
History of CAD, n (%)	1059 (26.7)	730 (28.7)	206 (24.6)	117 (21.4)	0.1
History of major bleeding, n (%)	152 (3.8)	95 (3.7)	30 (3.6)	27 (4.9)	0.37
Oral anticoagulation, n (%)	3333 (84.2)	2141 (84.1)	703 (84.1)	464 (85.0)	0.87
Antithrombotic medication, n (%)	189 (4.8)	133 (5.3)	33 (4.0)	22 (4.0)	0.21

Continuous variables are presented as mean with standard deviation, categorical variables are presented as numbers and percentages. Group comparisons were performed by ANOVA tests for continuous variables and by chi-squared tests for categorical variables.

No/Low-Ch: no or low chocolate consumption; Mod-Ch: moderate chocolate consumption; High-Ch: high chocolate consumption; BMI: body mass index; AF: atrial fibrillation; TIA: transient ischaemic attack; MI: myocardial infarction; CAD: coronary artery disease

er neurocognitive function as assessed by the cognitive construct score. Moreover, whereas major adverse cardiac events, comprising ischaemic stroke, myocardial infarction and cardiovascular death, appeared to be unrelated to chocolate consumption, No/Low-Ch was associated with an increased risk of hospitalisation for heart failure and all-cause mortality when compared to Mod-Ch.

It is generally accepted that a healthy lifestyle has a positive effect on health in patients with atrial fibrillation and lifestyle modification is considered an important therapeutic intervention in these patients according to current atrial fibrillation guidelines [18]. Chocolate, when consumed in moderation, may potentially represent a nutritional contribution to the well-being of atrial fibrillation patients.

Of note, in our study, BMI was lower in patients with higher chocolate consumption, a finding that has previously been observed by others [14]. This association is somewhat counter-intuitive. Potentially, it might indicate a generally healthier lifestyle in patients consuming more chocolate. Alternatively, the finding may have been influenced by disease, as obese patients, particularly those with diabetes mellitus, are generally advised to reduce their consumption of high-sugar foods, including chocolate. Moreover, as chocolate intakes were self-reported by patients, underreporting by obese subjects due to social desirability bias could have added to this finding. Interestingly, according to a previous study in a population with no history of cardiovascular disease, frequent chocolate consumption may independently be linked to lower BMI. The observed

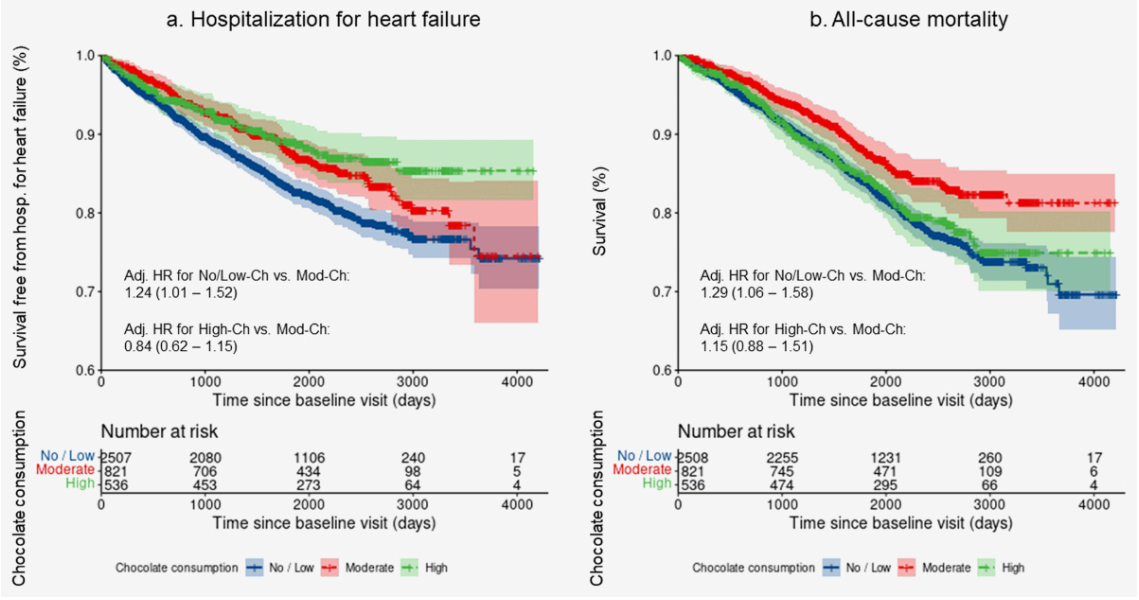
Table 7:
Association between chocolate consumption and clinical outcomes.

		Simple model		Full model	
		HR	**95% CI**	**HR**	**95% CI**
MACE	No/Low-Ch vs. Mod-Ch	1.21	[0.98, 1.50]	1.12	[0.90, 1.39]
	High-Ch vs Mod-Ch	1.02	[0.76, 1.38]	0.98	[0.72, 1.32]
Stroke	No/Low-Ch vs. Mod-Ch	0.99	[0.71, 1.39]	0.99	[0.70, 1.38]
	High-Ch vs Mod-Ch	0.94	[0.59, 1.51]	0.88	[0.54, 1.42]
Major bleeding	No/Low-Ch vs. Mod-Ch	1.25	[0.97, 1.61]	1.23	[0.95, 1.59]
	High-Ch vs. Mod-Ch	1.06	[0.74, 1.51]	1.08	[0.75, 1.54]
Hospitalisation for acute heart failure	No/Low-Ch vs. Mod-Ch	1.36	[1.11, 1.67]	1.24	[1.01, 1.52]
	High-Ch vs Mod-Ch	0.82	[0.60, 1.11]	0.84	[0.62, 1.15]
Myocardial infarction	No/Low-Ch vs. Mod-Ch	1.36	[0.89, 2.07]	1.26	[0.82, 1.92]
	High-Ch vs Mod-Ch	1.10	[0.61, 2.00]	1.14	[0.63, 2.07]
Cardiac death	No/Low-Ch vs. Mod-Ch	1.19	[0.94, 1.52]	1.08	[0.85, 1.39]
	High-Ch vs Mod-Ch	1.04	[0.75, 1.45]	0.92	[0.66, 1.30]
All-cause death	No/Low-Ch vs. Mod-Ch	1.42	[1.16, 1.73]	1.29	[1.06, 1.58]
	High-Ch vs Mod-Ch	1.24	[0.95, 1.62]	1.15	[0.88, 1.51]

The simple model is adjusted for age and gender. The full model is additionally adjusted for educational status, BMI, smoking status, arterial hypertension, history of diabetes, history of myocardial infarction, history of hospitalisation for acute heart failure, history of renal failure, atrial fibrillation type, oral anticoagulant medication, antithrombotic medication, history of coronary artery disease, history of major bleeding, and history of stroke or transient ischaemic attack.

No/Low-Ch: no or low chocolate consumption; Mod-Ch: moderate chocolate consumption; High-Ch: high chocolate consumption; HR: hazard ratio; CI: confidence interval; MACE: major adverse cardiovascular events

Figure 1: Kaplan-Meier curves with confidence bands showing: (a) the probability of survival free from hospitalisation for heart failure and (b) the survival probability for all-cause mortality for each group of chocolate consumption.
Hosp.: hospitalisation; adj.: adjusted; HR: hazard ratio; No/Low-Ch: no or low chocolate consumption; Mod-Ch: moderate chocolate consumption; High-Ch: high chocolate consumption



association was not explained by calorie intake, activity, or other potential confounders [29]. These results are intriguing, but in line with preclinical data in animals [30]. To account for the differences in baseline characteristics observed among the three groups of chocolate consumption, we corrected for these potential confounders in multivariate analyses.

The beneficial systemic effects of chocolate are thought to be primarily mediated by cocoa flavonoids, a group of polyphenols that may improve endothelial function, decrease platelet reactivity, decrease sympathetic tone and lower blood pressure [10, 31]. Additionally, oxidative stress reduction and anti-inflammatory effects have been attributed to chocolate intake [11, 12, 14].

Cardiovascular health is closely linked to cognitive performance [8]. Moreover, components of chocolate such as flavonoids and methylxanthines may cross the blood-brain barrier and therefore exhibit direct cerebral effects [6, 9]. Flavonoids may increase central blood flow, promote angiogenesis, inhibit neuronal cell destruction by neurotoxicants, and interact with cellular and molecular signalling cascades in regions involved in learning and memory [8, 9, 13]. Methylxanthines may act as mild central nervous system stimulants and lead to expression of neurotrophins that influence neurocognitive function [6].

Published data indicate that moderate consumption of chocolate may have a positive effect on cardiovascular health [3, 4]. However, the link between chocolate consumption and atrial fibrillation is less well-established. To date, research in the field has mainly focused on the risk of atrial fibrillation and results have been inconsistent. Although in the Danish Diet, Cancer and Health Study, an inverse association between moderate chocolate intake and the incidence of atrial fibrillation was observed [14], other studies did not find a similar link between chocolate consumption and the risk of atrial fibrillation occurrence [15, 16].

To the best of our knowledge, our study is the first to evaluate the potential associations between chocolate consumption and neurocognitive function, vascular brain lesions, and clinical outcome in patients with an established diagnosis of atrial fibrillation.

Whereas findings on brain MRI appeared to be unrelated to chocolate intake, better neurocognitive function as assessed by the cognitive construct score was independently associated with moderate chocolate consumption. The cognitive construct score, as a summary measure of the common aspects of the four neurocognitive tests used in our study, has previously been shown to reveal good psychometric properties and to increase measurement sensitivity when applied to the Swiss-AF population [22]. This may explain the fact that a significant independent association between neurocognitive function and chocolate consumption was only found when the cognitive construct score was used. However, the absence of independent associations between chocolate intake and any of the four tests performed with the patients may call into question the clinical relevance of our finding.

In line with the observed link between the cognitive construct score and moderate chocolate consumption, a positive association between cognitive performance and improved memory has previously been attributed to habitual chocolate intake in patients without atrial fibrillation [6–9]. Interestingly, it has also been recognised that the highest number of Nobel Prize winners can be found in countries with the highest chocolate consumption [32]. However, this potential link is rather speculative and has not been elaborated in detail. It cannot be excluded that the association might simply be due to the fact that in highly developed countries, where the luxury good chocolate is more frequently consumed, more research can be afforded and conducted and with this, the likelihood of citizens receiving Nobel Prizes may rise.

In our study, a decreased risk of hospitalisation for heart failure could be seen for Mod-Ch compared to No/Low-Ch, when assessed in multivariate analysis. This observation is in accordance with a previously found association between moderate chocolate consumption and a lower risk of heart failure [5]. Improvement of endothelial function with activation of nitric oxide, reduction in sympathetic tone, lowering of blood pressure and anti-inflammatory properties are potential effects of flavonoids that may contribute to a positive influence on heart failure [10, 12, 31, 33].

Unlike for heart failure hospitalisation, we did not find a link between chocolate consumption and the risk of myocardial infarction or cardiovascular death. This contrasts with previously published data implying a beneficial effect of chocolate consumption on the risk of cardiac events, including myocardial infarction and cardiac death [3, 4, 34, 35]. The discrepancy in findings regarding cardiovascular outcomes is difficult to explain. A potential factor might be a variability in the consumed concentration of plant-derived flavonoids. Whereas protective effects on the cardiovascular system have been attributed to high amounts of flavonoids ingested either directly via daily cocoa consumption or by intake of dark chocolate [10, 33, 34], we had no information on the type of chocolate consumed in our study.

In contrast to the lack of an association with cardiovascular mortality, moderate chocolate consumption was independently related to a decreased risk of all-cause mortality in our study. Given the large difference in event rates of the two endpoints, this disparity in findings, at least in part, may have been related to a statistical power issue. A true dissociation between cardiovascular and all-cause mortality would imply the presence of relevant effects of chocolate consumption on extra-cardiovascular systems. For example, this might be mediated by anti-inflammatory actions or decreased genotoxicity due to antioxidant properties [11, 12, 36, 37].

Limitations

In the present study, we did not have information on the type of chocolate or the cocoa concentration consumed. However, it cannot be assumed that patients only ever eat the same type of chocolate and our data may represent a real-life setting in this regard. In Switzerland, the most frequently consumed chocolate is milk chocolate. Therefore, the amount of flavonoids consumed in our study may have been lower than if patients had eaten only dark chocolate. Despite this limitation, we observed significant associations between chocolate consumption and important clin-

ical endpoints in multivariate analyses. Whether the associations would have been more pronounced if only dark chocolate was used remains speculative.

Our study was exploratory in nature. Therefore, a high number of tests on associations between chocolate consumption and outcome measures were performed, no clear primary endpoint was defined, and no adjustment for multiple comparisons was done. Consequently, given an alpha level of 5%, we cannot exclude that some of the findings may have resulted by chance and therefore, the data should be interpreted with caution. However, as discussed above, similar associations were found in other studies investigating different populations.

Another limitation of our study is adherent to its non-randomised, observational design. Although we performed multivariate analyses adjusting for multiple co-variables, the possibility of residual confounding due to selection bias, including Berkson's bias, or due to unmeasured potentially influencing factors, as well as the possibility of reverse causality, cannot be excluded. This must be taken into account when interpreting the results. Due to its exploratory nature, our work is hypothesis-generating rather than confirmatory.

Conclusion

Based on our findings, Mod-Ch consumption may potentially be beneficial in patients with atrial fibrillation. No/Low-Ch, when compared to Mod-Ch, was associated with lower cognitive function as assessed by the cognitive construct factor score, higher risk of heart failure hospitalisation and increased all-cause mortality, while there were no associations of chocolate consumption with MRI findings and major adverse cardiac events in a real-world atrial fibrillation population.

Data availability statement

Due to restrictions by the Ethical Committee, data is not publicly available. Requests to access the datasets should be directed to the corresponding author.

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Potential competing interests

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Appendix

CROSS-SECTIONAL ANALYSIS

DATA PREPARATION

The Swiss-AF data base is stored in the data-frame df.saf which is prepared using standardized processes

by the Data-Science team of the department of clinical research, University of Basel, Switzerland.

Load required R libraries:

```
library(lme4)

library(nlme)

library(survival)

library(survminer)
```

```
# Extract baseline visit

df.saf.bl <- df.saf[which(df.saf$visit.name == 'Baseline'),]
```

```
# Create variable chocolate consumption in 3 categories according to analysis plan

df.saf.bl <- mutate(df.saf.bl,

                    chocolate = ifelse(grepl("Monat", koffein.schokolade), 1,

                                       ifelse(koffein.schokolade == "1 pro Woche", 1,

                                              ifelse(koffein.schokolade == "2-4 pro Woche", 2,

                                                     ifelse(koffein.schokolade == "5-6 pro Woche", 2,3)))))
```

Analysis set: all patients with MRI measurement of Large non-cortical or cortical infarcts (lncci.yn) and MoCA score at baseline measurement (bl)

```
df.saf.bl <- df.saf.bl[which(!is.na(df.saf.bl$lncci.yn) & !is.na(df.saf.bl$moca) &
!is.na(df.saf.bl$chocolate)),]


# Log transform volume variables

df.saf.bl$lncci.vol.log <- log(df.saf.bl$lncci.vol)

df.saf.bl$snci.vol.log <- log(df.saf.bl$snci.vol)

df.saf.bl$wml.vol.log <- log(df.saf.bl$wml.vol)


## ANALYSIS

# Simple model for lesion presence

model_lncci.yn <- glmer(lncci.yn ~ chocolate + age.bl + pat.sex + (1 | center), data = df.saf.bl,
nAGQ = 0, family = binomial)



# Full model presence lesions (model for 1 outcome is shown, other outcomes follow the same
structure)

model_lncci.yn <- glmer(lncci.yn ~ chocolate + age.bl + pat.sex + education.groups + bmi +
active.smoker + prev.diabetes + prev.stroke

        + prev.heart.failure + prev.niereninsuff + af.type + med.oak.yn + prev.hypertonie + (1 |
center), data = df.saf.bl, nAGQ = 0, family = binomial)


# Simple model lesion volume (model for 1 outcome is shown, other outcomes follow the same
structure)

model_lncci <- lme(lncci ~ chocolate + age.bl + pat.sex, random=~1|center, data =
df.saf.bl[which(df.saf.bl$lncci.yn == 1),], na.action = na.omit)


# Full model lesion volume (model for 1 outcome is shown, other outcomes follow the same
structure)

model_lncci <- lme(lncci.vol.log ~ chocolate + age.bl + pat.sex education.groups + bmi +
active.smoker + prev.diabetes + prev.stroke

            + prev.heart.failure + prev.niereninsuff + af.type + med.oak.yn + prev.hypertonie,
random=~1|center, data = df.saf.bl[which(df.saf.bl$lncci.yn == 1),], na.action = na.omit)
```

```
# Simple model cognition (model for 1 outcome is shown, other outcomes follow the same structure)

model_moca <- lme(moca ~ chocolate + age.bl + pat.sex, random=~1|center, data = df.saf.bl, na.action = na.omit)


# Full model lesion volume (model for 1 outcome is shown, other outcomes follow the same structure)

model_moca <- lme(moca ~ chocolate + age.bl + pat.sex education.groups + bmi + active.smoker + prev.diabetes + prev.stroke

                  + prev.heart.failure + prev.niereninsuff + af.type + med.oak.yn + prev.hypertonie, random=~1|center, data = df.saf.bl, na.action = na.omit)


#=====================================================================


### EVENT ANALYSIS


## DATA PREPARATION


# Chocolate (as predictor, 3 levels)

df$chocolate <- ifelse(grepl("Monat", df$koffein.schokolade), 1,

                       ifelse(df$koffein.schokolade == "1 pro Woche", 1,

                              ifelse(df$koffein.schokolade == "2-4 pro Woche", 2,

                                     ifelse(df$koffein.schokolade == "5-6 pro Woche", 2,3))))

df$chocolate <- factor(df$chocolate,

                       levels = c(2, 1, 3),

                       labels = c("Moderate", "No / Low", "High"))


# collect variables covariates

pred.fix <- c("age.bl", "pat.sex", "highest.education.level.groups")
```

```
pred.time.update <- c("bmi", "smoking", "prev.diabetes", "prev.hypertonie", "prev.niereninsuff",
"med.oak.yn", "med.tca.yn", "prev.heart.failure",

                      "prev.major.bleed", "prev.mi", "prev.stroke.tia", "prev.coronary.heart.disease",
"rr.sys.liegend", "chocolate", "af.type", "choc.per.week", "choc.per.week.log")


# Fixed variables needed for checking and building time to event database

vars.fix <- c("pat.id", "visit.name", "visit.nr", "visit.date", "center", "eintritts.datum", "source.df")


# Create one data set with all variables needed of Swiss-AF and BEAT-AF

df.ana <- rbind(df[which(names(df) %in% c(pred.fix, pred.time.update, vars.fix))])


## Perpare for time to event analysis

# Total follow up time starting from baseline

df.start <- df.ana[df.ana$visit.name == "Baseline", c(var.fix, "total.fup.time")]


# define tmerge structure

df.start <- tmerge(df.start, df.start, id = pat.id, tstop = total.fup.time)


# data frame with time update variables + pat.id + visit.time for merging

df.tdc.vars <- df.ana %>% select(pred.time.update, main.predictor, pat.id, visit.time)


# merge the time dependent covars into the starting df by time (visit.time) -> same procedure for
all time-updated veriables

df.updated.vars <- tmerge(df.start, df.tdc.vars, id = pat.id,

                          bmi = tdc(visit.time, bmi))


# Add events according to time (multiple events possible for some events) -> shown for MACE,
same procedure for all events

df.ana <- tmerge(df.updated.vars, events, id = pat.id,

                         mace = event(time.end.mace, mace),
```

```
                cum.mace = cumtdc(time.end.mace, mace))



#=====================================================================

## ANALYSIS


# Simple model (model for 1 outcome is shown, other outcomes follow the same structure)

cox.mace.simple <-  coxph(Surv(tstart, tstop, mace) ~ age.bl + pat.sex + chocolate +
strata(center), subset = is.na(cum.mace), data = df.ana)


# Full model (model for 1 outcome is shown, other outcomes follow the same structure)

cox.mace.full <-  coxph(Surv(tstart, tstop, mace) ~ age.bl + pat.sex + chocolate + strata(center)
+ highest.education.level.groups + bmi + smoking + prev.diabetes + prev.mi + prev.hypertonie +

                 prev.heart.failure + prev.niereninsuff + af.type + med.oak.yn + med.tca.yn +
prev.coronary.heart.disease + prev.major.bleed + prev.stroke.tia,

                subset = is.na(cum.mace), data = df.ana)


# Kaplan Maier Plots

outcomes <- c("mace", "stroke", "major.bleed", "heart.failure", "mi")


for(out in outcomes){

fit <- survfit(Surv(tstop, out) ~ chocolate, subset = is.na(get(paste0("cum.", out))), data =
df.surv.choc)

km <- ggsurvplot(fit, data = df.surv.choc,

                    conf.int=TRUE,

                    risk.table = FALSE,

                    break.time.by = 1000,

                    xlab = "Time since baseline visit (days)",

                    ylab = "Survival probability (%)",

                    ylim = c(0.80,1),
```

```
                    xlim = c(0,4300),
                    linetype = "strata",
                    axes.offset = FALSE,
                    palette = "lancet",
                    legend = "bottom",
                    legend.title = "Chocolate consumption",
                    legend.labs = c("No / Low", "Moderate", "High"))
print(km)
}

outcomes.death <- c("death.any", "death.cardiac")
for(out in outcomes.death){
  fit <- survfit(Surv(tstop, out) ~ chocolate, data = df.surv.choc)
  km <- ggsurvplot(fit, data = df.surv.choc,
                   conf.int=TRUE,
                   risk.table = FALSE,
                   break.time.by = 1000,
                   xlab = "Time since baseline visit (days)",
                   ylab = "Survival probability (%)",
                   ylim = c(0.80,1),
                   xlim = c(0,4300),
                   linetype = "strata",
                   axes.offset = FALSE,
                   palette = "lancet",
                   legend = "bottom",
                   legend.title = "Chocolate consumption",
                   legend.labs = c("No / Low", "Moderate", "High"))
  print(km)
}
```