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RESEARCH ARTICLE

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Use of benzodiazepine and Z-drugs and mortality in older adults after myocardial infarction

Shengxin Liu[1] | Sabita S. Soedamah-Muthu[2,3] | Seia C. van Meerten[4] | Daan Kromhout[5] | Johanna M. Geleijnse[6] | Erik J. Giltay[4]

[1]Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Solna, Sweden

[2]Center of Research on Psychological Disorders and Somatic Diseases (CoRPS), Department of Medical and Clinical Psychology, Tilburg University, Tilburg, The Netherlands

[3]Institute for Food, Nutrition and Health (IFNH), University of Reading, Reading, UK

[4]Department of Psychiatry, Leiden University Medical Centre, Leiden, The Netherlands

[5]Department of Epidemiology, University Medical Centre Groningen, University of Groningen, Groningen, The Netherlands

[6]Division of Human Nutrition and Health, Wageningen University, Wageningen, The Netherlands

Correspondence

Erik J. Giltay, Department of Psychiatry, Leiden University Medical Centre, Postalzone B-1 P, P.O. Box 9600, 2300 RC Leiden, The Netherlands.
Email: E.J.Giltay@LUMC.nl

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Abstract

Background: The adverse cardiovascular effects of benzodiazepines and Z-drugs (jointly referred as BZDRs) have been of concern. Yet, little is known about the use of BZDRs in relation to mortality risk among older adults with myocardial infarction history (post-MI).

Methods: This study is a secondary analysis of the Alpha Omega Cohort study, comprising post-MI patients aged 40–60 years. Self-reported information on the use of BZDRs, including types and dose, was collected at baseline. Four categories of mortality were examined, namely all-cause mortality, cardiovascular (CVD) mortality, cancer mortality, and non-CVD/non-cancer mortality. Associations between BZDRs use, by types and doses, and mortality were estimated with Cox regression models, adjusted for demographic and classic cardiovascular risk factors.

Results: A total of 433 (8.9%) out of 4837 (21.8% females) patients reported BZDRs use at baseline. During a median follow-up of 12.4 years, 2287 deaths were documented, of which 825 (36.1%) were due to CVD. BZDRs use was related to a statistically significantly higher risk of all-cause and CVD mortality; adjusted hazard ratios [95% CI] were (1.31 [1.41, 1.52]) and (1.43 [1.14, 1.81]), respectively. These relationships were dose-dependent—patients using BZDRs on an as-needed basis had similar risks compared to the non-uses, whereas patients with a daily use schedule and increasing doses had higher risks (*p*-value for trend: <0.001).

Conclusion: BZDRs use was independently associated with a higher risk of all-cause and cardiovascular mortality in older post-MI patients, and there was evidence for a dose-dependent relationship.

Clinical trial registration: NCT00127452 (www.ClinicalTrials.gov).

KEYWORDS

all-cause mortality, benzodiazepine, cardiovascular mortality, dose-dependent

Key points

- Use of benzodiazepine and Z-drugs was associated with a higher risk of all-cause and cardiovascular mortality in post-myocardial infarction patients independent of classic CVD risk factors.
- There was a dose-dependent relationship—patients with a daily use schedule and with higher doses compared to those using benzodiazepine and Z-drugs (more sporadically) on an as-needed basis and non-users.
- In older patients with a history of CVD events, benzodiazepine and Z-drugs should be prescribed cautiously.

1 | INTRODUCTION

Benzodiazepine and drugs related to benzodiazepine (i.e., Z-drugs) (jointly referred as BZDRs) are a group of psychoactive drugs commonly used for anxiety, insomnia, seizures, and mania and are among the most frequently prescribed medications globally. In recent decades, despite the policy to discourage prescriptions, the prevalence of BZDRs use remains worryingly high in the elderly population, ranging from 10%–30% across countries.[1–4]

Several concerns have been claimed about the extensive use of BZDRs in the elderly, such as drug dependence, withdrawal symptoms, cognitive decline, and prolonged reaction times, which can increase the risk of traffic accidents and falls, resulting in hip fractures.[5] However, a critical controversy remains regarding BZDRs use and mortality risk. So far, findings from previous longitudinal studies remain discrepant and yielded no conclusive evidence, ranging from null association[6–8] to a potentially elevated risk of mortality[9–13] in the general elderly population.

Moreover, since cardiovascular disease (CVD) poses as the leading cause of mortality in the elderly, the cardiovascular effects of BZDRs have been of concern. Although the underlying biological mechanisms are unknown, several aspects are worth noting. On the one hand, their sedative-hypnotic effects can be helpful for relieving insomnia, anxiety, and other stress symptoms, which are known risk factors for cardiac morbidity and mortality.[14,15] On the other hand, their sedative and respiratory depression effects can worsen existing sleep-related breathing disorders, especially in those with heart failure[16]; effects on peripheral gamma-aminobutyric acid (GABA) binding sites may affect cholesterol transport, immune response, and eventually trigger cardiac arrhythmias and other events.[17] Nevertheless, whether BZDRs can be linked to cardiovascular mortality remains far from elucidated; a better understanding, especially by types and doses of used benzodiazepines, is essential to understand this potential relationship.

Furthermore, little is known about the use of BZDRs in relation to mortality among older adults who have had a history of myocardial infarction (MI), a condition caused by atherosclerotic plaques, arrhythmias, and subsequent ischemic heart disease. Only one study has investigated the association between used BZDRs dose and CVD outcomes among post-MI patients aged above 30.[18] During an average of 4.8 years of follow-up, a statistically significant 'J'-shape relationship between the BZDRs used and the risk of sudden death was observed among 7419 post-MI patients. However, the study did not account for potential confounding by classic CVD risk factors, such as elevated blood pressure and low-density lipoprotein cholesterol (LDL-cholesterol). Since post-MI psychological experience has been considered essential in secondary prevention,[19] more information on the putative harmful effects of BZDRs use among post-MI patients would assist practice guidelines.

This study aimed to investigate the association between the use of BZDRs and all-cause and cause-specific mortality in Dutch post-MI older adults, and to assess whether the association is dose-dependent. We also examined whether the associations differ across specific types of BZDRs used.

2 | MATERIALS AND METHODS

2.1 | Study design

The present analysis was performed in the Alpha Omega Cohort (AOC, ClinicalTrials.gov number, NCT03192410) in the Netherlands. In brief, 4837 Dutch adults aged 60–80 years (21.8% female), who had a MI within the previous 10 years, were recruited through their cardiologists from 32 hospitals from 2002 to 2006. During the first 40 months of follow-up, patients participated in an intervention study of low doses of omega-3 fatty acids (ClinicalTrials.gov number, NCT00127452), which did not affect major CVD events.[20] At the baseline (2002–2006) and the end of the trial period (median length of 40.8 months), patients filled in questionnaires and were physically examined by trained research nurses at home or in the hospital, which included blood sampling. After the trial period, the AOC continued as a prospective cohort study for risk prediction after MI, and patients were continuously followed for cause-specific mortality.

The study was approved by a central medical ethics committee (Haga Hospital, Leyenburg, The Hague, the Netherlands) and by the ethics committees of participating hospitals, and written informed consent was obtained from all patients.

2.2 | Exposure: Benzodiazepine and Z-drugs

Data on the use of BZDRs, doses, and specific types of used BZDRs was obtained from the structured questionnaires filled by the

patients at baseline. Three questions were asked, including (1) the name of used medications, (2) the dosage and/or the number of tablets used on a daily basis, and (3) whether that medication was consumed every day. Patient-reported doses, frequencies, and types of used BZDRs were first checked by trained research nurses in accordance with the packages of patients' used medications and then coded by an independent pharmaco-epidemiologist based on the Anatomical Therapeutic Chemical (ATC) Classification System and the defined daily dose (DDD) by the WHO Collaborating Centre for Drug Statistics Methodology guideline.[21,22] Used benzodiazepine included benzodiazepine derivatives used as clonazepam (N03AE01), anxiolytics (N05BA), hypnotics and sedatives (N05CD), and benzodiazepine-related drugs (N05CF) (detailed ATC codes presented in Supplemental Table 1). Based on the used doses, patients were grouped into four categories: no use, use on an as-needed basis, a fixed schedule (i.e., on a daily basis), with <0.75 DDD, and a fixed schedule with ≥0.75 DDD. The 0.75 DDD cut-off was selected in accordance with previous studies.[23,24] Specific types of used BZDRs included oxazepam, temazepam, diazepam, lorazepam, nitrazepam, other benzodiazepines, and Z-drugs. According to the plasma half-life, benzodiazepines were also classified into two groups: short-acting (half-life <20 h) and intermediate-to-long-acting (half-life ≥20 h) (Supplemental Table 1).

2.3 | Mortality endpoints

Follow-up for cause-specific mortality occurred in three phases. From 2002 to 2009 (trial period),[20,22] information was obtained from the national mortality registry (Statistics Netherlands [CBS]), treating physicians and close family members. Primary and contributing causes of death were coded by an independent Endpoint Adjudication Committee, as described previously.[20,22] From 2010 to 2012 (AOC period), data on vital status was first obtained from municipal registers, and the primary and contributing causes of death were obtained through CBS. From 2013 onwards, CBS provided data on the primary cause of death only, and treating physicians were asked to fill out an additional cause-of-death questionnaire (response rate: 67%), which was coded by independent study physicians. The endpoint CVD was allocated to all patients for whom it was a primary or contributing cause of death, based on any of the data sources. Mortality coding was performed according to the International Classification of Diseases, tenth revision (ICD-10)[25] (detailed ICD codes presented in Supplemental Table 1). Person-years were calculated from April 2002 to the date of death or 31 December 2018, whichever came first. One patient was lost to follow-up and censored after 2.9 years.

2.4 | Covariates

Information on the general characteristics, diet and lifestyle factors, medical history, and medication use was collected at baseline and month-40.8, using questionnaires completed by trained research nurses or self-completed by the patients at their homes. The detailed measurement process has been described in previous publications.[20,22] Marital status was dichotomized as married/cohabiting or not. The highest education level was dichotomized into low (primary education) or high (at least upper secondary education). Smoking status was dichotomized into the current user or not. Alcohol use was divided into four categories: never, less than one glass per week or past drinker, 1–13 glasses per week, and 14 or more glasses per week. Physical activity was assessed using the self-report Physical Activity Scale for the Elderly[26] and was dichotomized into physically active (≥5 days per week for physical activity >3 metabolic equivalents of task [MET]), or less active (1–4 days per week for physical activity >3 MET, light activity [≤3 MET] or no activity). Self-rated health was assessed by the question 'How do you rate your overall health at this moment?' using a 5-point scale and was categorized into poor or moderate, good, or very good or excellent. Prevalent diabetes mellitus was considered if self-reported physician diagnosis, use of medication for diabetes, or elevated plasma glucose (≥7.0 mmol/L if fasted >4 h or ≥11.1 mmol/L if nonfasted). Self-reported other medication usage was ascertained by trained research nurses and coded by ATC, and was grouped into anti-hypertensive medication, anti-diabetic medication, lipid-lowering drugs, and other psychotropic drugs, including antidepressants, antipsychotics, and lithium, which are not benzodiazepine derivatives. Information on LDL-cholesterol, body mass index (BMI), and systolic blood pressure (SBP) was acquired from blood sampling and physical examinations at baseline and 40-month follow-up for 2531 (52.3%) patients.[20,22]

2.5 | Statistical analysis

Baseline characteristics were compared between BZDRs users and non-users, using *t*-test for continuous variables and chi-square test for categorical variables. The Kaplan-Meier (KM) method was used to present crude mortality rates according to categories of BZDRs doses. Cox proportional hazards models were used to estimate the association between baseline benzodiazepine use and four mortality outcomes (i.e., all-cause mortality, CVD, cancer-related, and non-CVD/non-cancer mortality), with risk estimates presented as hazard ratios (HR) with 95% confidence intervals (95% CI). The proportional hazard assumption was tested for all variables dichotomized using the log-minus-log graphical method, and this assumption was met.

Model 1 was the crude (unadjusted) model. Model 2 was adjusted for socio-demographic risk factors: sex, age, level of education, and marital status. Model 3 was additionally adjusted for baseline overall self-rated health and classic CVD risk factors: smoking status, alcohol use, physical activity level, BMI, SBP, LDL, and presence of diabetes mellitus. All adjusted covariates were selected as a priori based on previous literature. All models were repeated for the pre-defined four dose categories with testing for a

dose-dependent relationship, specific types of BZDRs, and short-acting and long-acting benzodiazepines.

Since cause-specific mortality may be overestimated in the setting of competing events,[27] we repeated the analyses for cause-specific mortality after accounting for other causes of death as competing risks. To eliminate the imbalance of baseline characteristics between BZDRs users and non-users, we used the inverse probability of treatment weighting (IPTW) method, where the propensity score was calculated with a logistic regression model that estimated the probability of using BZDRs, condition on the same risk factors that we adjusted for in Model 3. In addition, to minimize the influence of other pre-existing mental health problems on the assessed association, we performed sensitivity analyses by excluding patients who reported using other types of psychotropic medication. In consideration of exploring the difference between males and females, we tested the interaction of benzodiazepine use with sex, which was not statistically significant (p-value for interaction = 0.06), and therefore we did not perform sex-stratified analyses.

A two-tailed $p < 0.05$ was considered statistically significant. Data management was performed using SAS 9.4, and data analyses were performed using RStudio (R version 4.0.5), with main packages 'survival' (version 2.44) and 'survminer' (version 0.4.4).

3 | RESULTS

Out of a total of 4837 patients, 433 (8.9%) reported using BZDRs at baseline, among whom 39.5% were females and 60.5% were males. Compared to the BZDRs non-users, the BZDRs users were more likely to be female and current smokers but less likely to use alcohol and have lower SBP (Table 1). They were also more likely to have diabetes and use other psychotropic drugs.

TABLE 1 Baseline characteristics of 4837 post-myocardial infarction patients according to benzodiazepine use

	Data available for (*n*)	No benzodiazepine use (*n* = 4404)	Benzodiazepine use (*n* = 433)	*p*-value
Age, mean (SD), years	4837	69.0 (5.6)	69.3 (5.8)	0.30
Male, *n* (%)	4837	3521 (80.0)	262 (60.5)	<0.001
High education level,[a] *n* (%)	4804	1920 (43.6)	169 (39.0)	0.07
Married or cohabiting, *n* (%)	4830	3649 (82.9)	310 (71.6)	<0.001
Current smoker, *n* (%)	4836	714 (16.2)	98 (22.6)	<0.001
Alcohol use, *n* (%)	4827			<0.001
Never		448 (10.2)	59 (13.6)	
<1 glass/week or past drinker		635 (14.5)	114 (26.3)	
1–13 glasses/week		2361 (53.7)	189 (43.6)	
≥14 glasses/week		950 (21.6)	71 (16.4)	
Physically active,[b] *n* (%)	4808	935 (21.2)	78 (18.0)	0.14
BMI, kg/m^2, mean (SD)	4828	27.74 (3.80)	28.14 (4.30)	0.06
LDL-cholesterol, mmol/l, mean (SD)	4492	2.58 (0.83)	2.63 (0.87)	0.25
Systolic blood pressure, mmHg, mean (SD)	4831	142 (21.6)	139 (22.2)	0.002
Self-rated health, *n* (%)	4817			<0.001
Very good or excellent		538 (12.2)	16 (3.7)	
Good		2871 (65.2)	227 (52.4)	
Moderate or poor		978 (22.1)	187 (43.2)	
Diabetes mellitus, *n* (%)	4837	907 (20.6)	107 (24.7)	0.05
Medication use, *n* (%)				
Anti-hypertensive drugs	4837	3940 (89.5)	400 (92.4)	0.06
Glucose-lowering drugs	4837	661 (15.0)	79 (18.2)	0.08
Lipid-lowering drugs	4837	3800 (86.3)	361 (83.4)	0.10
Other psychotropic drugs[c]	4837	120 (2.7)	65 (15.0)	<0.001

[a]High education level was defined as having at least completed secondary education.

[b]Physically active was defined as ≥5 days/week of physical activity >3 MET.

[c]Other psychotropic drugs included antidepressants, antipsychotics, and lithium, which are not benzodiazepine derivatives.

During a median follow-up period of 12.4 years, we documented 2287 (47.3%) deaths, of whom 825 (36.1%) were ascertained to be due to CVD, 653 (28.6%) to cancer, and 809 (35.4%) to non-CVD/non-cancer causes. After multivariate adjustment, BZDRs users had a 1.31-fold higher risk of all-cause mortality compared to the non-users (95% CI: 1.14, 1.52) (Table 2). Further analyses with cause-specific mortality endpoints showed that BZDRs users had a significantly higher risk of CVD mortality (1.43 [1.14, 1.81]), which remained statistically significant after accounting for potential competing events (i.e., other causes of death) (1.27 [1.01, 1.60], Supplemental Table 2). BZDRs users also appeared to be at higher risk of cancer-related mortality (1.39 [1.08, 1.81]) and non-CVD/non-cancer mortality (1.37 [1.09, 1.73]). However, these elevated risks were no longer statistically significant after adjusting for classic CVD risk factors (1.27 [0.96, 1.68], and 1.24 [0.97, 1.59], respectively).

KM plots demonstrated dose-dependent relationships between using BZDRs and mortality (Figure 1). When modeled by Cox regression analyses, statistically significant dose-dependent relationships were observed for all-cause and CVD mortality (Table 3, all *p*-value for trend <0.001). Compared to the non-users, patients who used BZDRs on an as-needed basis showed no difference in risk (0.97 [0.73, 1.30]), whereas patients who used benzodiazepine on a daily basis had significantly higher risks of all-cause mortality (<0.75 DDD: 1.37 [1.09, 1.71]; ≥0.75 DDD: 1.67 [1.30, 2.14]) and CVD mortality (<0.75 DDD: 1.63 [1.15, 2.29]; ≥0.75 DDD: 1.84 [1.24, 2.73]). After accounting for potential competing events, the observed significant associations persisted with the results in Table 3 (Supplemental Table 2).

Among the six specific types of BZDRs, after multivariate adjustment, baseline usage of temazepam ($n = 111$) and nitrazepam ($n = 22$) were found to be statistically significantly associated with a higher risk of all-cause mortality (1.52 [1.17, 1.97], and 2.03 [1.19, 3.48], respectively) and of CVD mortality (1.69 [1.12, 2.54], and 2.65 [1.23, 5.69], respectively), with wide 95%CI due to relatively low numbers (Supplemental Figure 1). When examining short-acting and long-acting benzodiazepines separately, after multivariate adjustment, the statistically significantly elevated risk was observed for short-acting benzodiazepines for all-cause mortality (1.34 [1.14,

TABLE 2 Associations between benzodiazepine use and mortality, estimated by hazard ratio (HR) and 95% confidence interval (95% CI)

	N	No benzodiazepine use	Benzodiazepine use	*p*-value
Patients, *n*	4837	4404	433	
All-cause mortality				
Casus, *n* (%)	2287 (47.3)	2032 (46.1)	255 (58.9)	
Model 1		1.0 (ref)	1.49 (1.30, 1.69)	<0.001
Model 2[a]		1.0 (ref)	1.49 (1.31, 1.70)	<0.001
Model 3[b]		1.0 (ref)	1.31 (1.14, 1.52)	<0.001
CVD mortality				
Casus, *n* (%)	825 (17.1)	721 (16.4)	104 (24.0)	
Model 1		1.0 (ref)	1.70 (1.38, 2.09)	0.02
Model 2[a]		1.0 (ref)	1.69 (1.37, 2.09)	0.01
Model 3[b]		1.0 (ref)	1.43 (1.14, 1.81)	0.002
Cancer-related mortality				
Casus, *n* (%)	653 (13.5)	586 (13.3)	67 (15.5)	
Model 1		1.0 (ref)	1.33 (1.03, 1.72)	0.003
Model 2[a]		1.0 (ref)	1.39 (1.08, 1.81)	0.01
Model 3[b]		1.0 (ref)	1.27 (0.96, 1.68)	0.10
Non-cardiovascular/non-cancer mortality				
Casus, *n* (%)	809 (16.7)	725 (16.5)	84 (19.4)	
Model 1		1.0 (ref)	1.40 (1.11, 1.75)	0.004
Model 2[a]		1.0 (ref)	1.37 (1.09, 1.73)	0.008
Model 3[b]		1.0 (ref)	1.24 (0.97, 1.59)	0.08

[a]Model 2: Adjusted for socio-demographic risk factors: sex, age, level of education, and marital status.

[b]Model 3: Additionally adjusted for classic CVD risk factors: smoking status, alcohol use, physical activity level, BMI, SBP, LDL-cholesterol levels, presence of diabetes mellitus, and overall self-rated health.

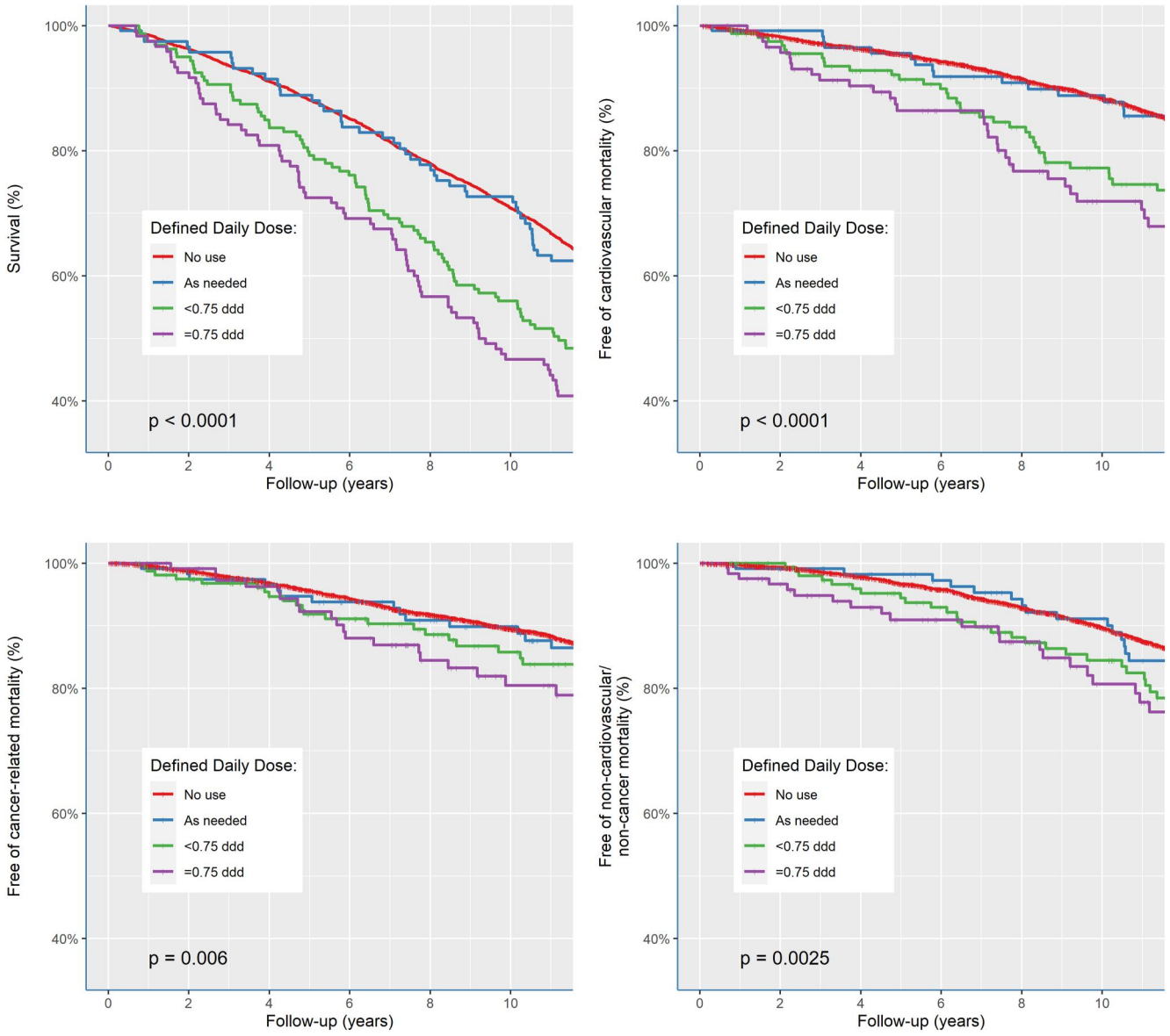

FIGURE 1 Unadjusted Kaplan–Meier curves of mortality according to the doses of used benzodiazepines.

1.59]), CVD mortality (1.48 [1.13, 1.93]) and non-CVD/non-cancer mortality (1.35 [1.01, 1.79]), compared to the non-users (Supplemental Table 3). Whereas, no statistically significant association was observed for intermediate-to-long-acting benzodiazepines.

After applying IPTW methods, all of the baseline characteristics were well balanced between BZDRs users and non-users, as indicated by the absolute standardized differences being <0.1 (Supplemental Table 4).[28] Effect estimates from IPTW methods were largely comparable (and somewhat stronger) to those estimated associations after multivariate adjustment (Supplemental Table 5). BZDRs user had statistically significant elevated risks of all-cause mortality (1.51 [1.31, 1.75]), CVD mortality (1.46 [1.10, 1.94]) and non-CVD/non-cancer mortality (1.46 [1.07, 2.00]). The dose-dependent analyses remained statistically significant for BZDRs with all-cause, CVD-related and cancer-related mortality. The sensitivity analysis of excluding patients using other types of psychotropic (n = 185) yielded similar results with slight attenuations: patients who use benzodiazepines showed statistically significantly higher risks of all-cause and CVD mortality after adjustment (1.23 [1.06, 1.45], and 1.29 [1.00, 1.66], respectively), with evidence suggesting these associations being dose-dependent (p-value for trend <0.001, detailed data not shown).

4 | DISCUSSION

In post-MI patients, we observed that self-reported BZDRs usage was related to a higher risk of both all-cause and CVD mortality after adjustments for socio-demographic and classic CVD risk factors. These relationships were dose-dependent—where the risk was not statistically different when used on an as-needed basis, but thereafter gradually increased with higher daily doses of BZDRs.

TABLE 3 Associations between doses of used benzodiazepine and mortality, estimated by hazard ratio (HR) and 95% confidence interval (95% CI)

	N	No benzodiazepine use	Use as-needed	<0.75 DDD	≥0.75 DDD	*p*-value for trend
Patients, *n*	4800	4404	117	159	120	
All-cause mortality						
Casus, *n* (%)	2264 (47.2)	2032 (46.1)	51 (43.6)	98 (61.6)	83 (69.2)	
Model 1		1.0 (ref)	0.92 (0.70, 1.22)	1.59 (1.30, 1.95)	2.04 (1.64, 2.54)	<0.001
Model 2[a]		1.0 (ref)	0.98 (0.74, 1.30)	1.53 (1.25, 1.88)	2.26 (1.81, 2.83)	<0.001
Model 3[b]		1.0 (ref)	0.97 (0.73, 1.30)	1.37 (1.09, 1.71)	1.67 (1.30, 2.14)	<0.001
CVD mortality						
Casus, *n* (%)	814 (17.0)	721 (16.4)	18 (15.4)	40 (25.2)	35 (29.2)	
Model 1		1.0 (ref)	0.92 (0.58, 1.47)	1.82 (1.33, 2.51)	2.40 (1.71, 3.37)	<0.001
Model 2[a]		1.0 (ref)	0.96 (0.60, 1.54)	1.74 (1.26, 2.41)	2.68 (1.90, 3.77)	<0.001
Model 3[b]		1.0 (ref)	0.85 (0.51, 1.43)	1.63 (1.15, 2.29)	1.84 (1.24, 2.73)	<0.001
Cancer-related mortality						
Casus, *n* (%)	650 (13.5)	586 (13.3)	16 (13.7)	24 (15.1)	24 (20.0)	
Model 1		1.0 (ref)	1.01 (0.62, 1.67)	1.33 (0.89, 2.00)	1.96 (1.31, 2.95)	0.05
Model 2[a]		1.0 (ref)	1.11 (0.67, 1.83)	1.38 (0.91, 2.08)	2.11 (1.39, 3.21)	0.04
Model 3[b]		1.0 (ref)	1.15 (0.69, 1.93)	1.24 (0.80, 1.94)	1.68 (1.05, 2.68)	0.15
Non-cardiovascular/non-cancer mortality						
Casus, *n* (%)	800 (16.7)	725 (16.5)	27 (14.5)	34 (21.4)	24 (20.0)	
Model 1		1.0 (ref)	0.86 (0.53, 1.39)	1.58 (1.12, 2.23)	1.74 (1.16, 2.61)	0.12
Model 2[a]		1.0 (ref)	0.89 (0.55, 1.45)	1.45 (1.02, 2.07)	1.97 (1.31, 2.96)	0.23
Model 3[b]		1.0 (ref)	0.97 (0.60, 1.57)	1.22 (0.83, 1.81)	1.52 (0.98, 2.37)	0.57

Note: Information on the dose of used benzodiazepine was not reported by 37 patients.

[a]Model 2: Adjusted for socio-demographic risk factors: sex, age, level of education, and marital status.

[b]Model 3: Additionally adjusted for classic CVD risk factors: smoking status, alcohol use, physical activity level, BMI, SBP, LDL-cholesterol levels, presence of diabetes mellitus, and overall self-rated health.

Only a few studies, including the present one, have focused on the elderly population with CVD history but observed inconsistent associations between BZDRs use and mortality.[29,30] A large Danish population-based study (n = 136,068), similar to ours, has estimated a 1.3–1.6-fold significantly higher risk of all-cause mortality concerning benzodiazepine and related drugs among older patients with stroke.[29] In contrast, a Spanish study consisting of older patients with heart failure history (n = 1017) observed that benzodiazepine users had lower all-cause mortality (0.70 [0.57–0.87]) but comparable CVD mortality[30] than non-users. Regardless of these discrepancies in CVD patients, our findings remained broadly consistent with previously published studies among the general elderly that also found higher mortality rates in BZDRs users.[9–13] These and our findings further support current guidelines that argue that BZDRs should be prescribed cautiously and not continuously for more than several weeks, and that its use be especially discouraged among the elderly.[31]

Several possible rationalizations have been proposed linking benzodiazepine use to modified CVD risks. BZDRs, targeting GABA type A ($GABA_A$) receptors, can allosterically increase the $GABA_A$ receptor's affinity for GABA and consequently express inhibitory effects in the central nerve system. Though such $GABA_A$ receptor blockade function can be beneficial in terms of sedative and hypnotic effects, it has been linked to abnormal blood flow related to stroke.[29,32] Also, the respiratory depression effects of benzodiazepine may result in sleep disruptions and exacerbate obstructive sleep apnea and chronic obstructive pulmonary disease,[33] which can further contribute to increased risks of CVD events, including atrial fibrillation, non-sustained ventricular tachycardia,[17] and heart failure.[34] In addition, the changes in liver and renal functions due to aging increase the time needed for drug metabolism and clearance, which can subsequently prolong the benzodiazepine-mediated responses and the duration of benzodiazepine-mediated effects.[35] Finally, its chronic use in the elderly may cause lethargy, daytime sleepiness, and physical inactivity (especially when combined with opioids and alcohol use), while rebound and withdrawal symptoms may activate the autonomic nervous system resulting in physiological

symptoms like sleep disturbances, irritability, anxiety, tremors, sweating, and palpitations. These features pose the elderly population, especially those with a history of CVD events, with an even higher hazard of experiencing adverse effects on the cardiovascular system.

Another question that often comes up in clinical practice is whether to dose BZDRs standing, that is, with a fixed schedule, or on an as-needed basis. Our study supports the idea that using BZDRs on an as-needed basis is safer in terms of mortality risk among older post-MI patients, whereas our findings suggest that using a fixed schedule and higher doses was harmful. This finding is generally in line with previous studies conducted on post-MI patients[18] and the general (elderly) population.[36–39] Wu et al. observed that no risk increases in post-MI patients using benzodiazepine with a low or moderate dose (equivalent to diazepam ≤1.2 and 1.2–5.0 mg/day), but a statistically significantly higher risk (HR: 1.96 [1.02, 3.74]) among those use >5.0 mg/day. Although we used DDD to indicate the dose of used BZDRs, our demonstrated dose-dependent relationships were in line with their findings. One explanation may be that when BZDRs were used as-needed, the patients may benefit more from its rapid and efficacious relieving effects, with less hazard of experiencing dependence and other adverse drug effects. It is also possible that compared to patients on a lower dose, those on higher doses might react less well to the initial dose and/or may have experienced more psychological symptoms, which subsequently add to the mortality risks.[40,41]

Disentangling associations between specific types of BZDRs with mortality risk is also of clinical interest. Although nitrazepam and temazepine were to be associated with the risk of all-cause and CVD mortality in our study sample, these findings need to be interpreted cautiously due to the small proportion of patients using each type of BZDRs. Similar to previous studies,[42,43] short-acting benzodiazepines were found to be associated with a higher mortality risk. It should be reiterated that we must interpret these findings with caution because of our limited statistical power (reflected by the wide 95%CI) and the potential for channeling bias and residual confounding. Future studies with larger sample sizes, longer follow-up periods, and detailed assessments of indications and use patterns of benzodiazepine are warranted to provide deeper insights into this matter. The strengths of the present study include a well-defined and large cohort of post-MI patients, with an extensive follow-up of the vital status and validated cause of death of the patients. Also, the wide range of risk factors that were adjusted for, especially the classic CVD-related factors, facilitates the accuracy of the estimated effect.

Several potential limitations need to be addressed. Firstly, our study sample only included patients who were willing to participate in the Alpha Omega Trial, who might have a higher health awareness, and thus may not be a good representation of all post-MI patients in the Netherlands and may not be necessarily generalizable to other settings. Secondly, despite the large sample size of our study cohort, we still have limited statistical power in estimating associations, as reflected by the relatively wide 95% CI, and evaluating specific types of BZDRs. Thus, the observed associations should be interpreted with caution and require further exploration in different and larger samples with more sophisticated pharmaco-epidemiological designs, for example, active comparators or new-user designs. This calls for caution when interpreting the observed associations into clinical significance. Thirdly, the information on benzodiazepine use, including types and doses, was self-reported at baseline. Thus, we were not able to take into account changes in benzodiazepine use during follow-up. Although baseline BZDRs use has been found to be a good predictor of long-term BZDRs use in older adults,[44] the observed associations might be diluted as we were not able to ascertain long-term BZDRs users. Fourthly, although we have accounted for many potential confounders, residual confounding and reverse causation nonetheless cannot be ruled out. All participants have had a MI, and this may have resulted in poor sleep quality, for which BZDRs may have been prescribed. Moreover, we lacked information on the severity of anxiety and insomnia symptoms and thus cannot fully eliminate possible confounding by indication bias. To address this issue, we have adjusted for self-rated health, which could be regarded as a proxy of general well-being, including mental health status.[45,46] If the observed higher mortality risk was mainly driven by indications of benzodiazepines, such as symptoms of anxiety or insomnia, we would not expect the association to persist after adjusting for self-rated health. In addition, we excluded patients using other psychotropic medications in the sensitivity analyses to minimize potential contributions from these psychotropic medications and their indicating conditions. Nevertheless, it is worth repeating that confounding by indication is complex and cannot be ruled out in the present study. The observed associations should be further investigated with studies of different study samples with in-depth information on the indications for the prescription of BZDRs.

In summary, this study showed a dose-dependent relationship between the use of benzodiazepine and Z-drug and an elevated risk of all-cause and CVD mortality in post-MI older adults, with estimates consistent with previous literature among the general elderly population. In light of the current therapeutic dilemma on prescribing benzodiazepines to the elderly, clinicians are encouraged, as proposed by Matthew Hirschtritt and colleagues, to "seek a balance between overprescribing of benzodiazepines to patients at risk and underuse of these effective medications when indicated".[47] To conclude, our findings supported the current guidelines that benzodiazepine and Z-drugs should be prescribed cautiously in elderly individuals with a history of CVD events. Future research remains needed to illuminate further whether there is any causal relationship between benzodiazepine and Z-drug use and mortality in the elderly population in order to ameliorate current guidelines on clinical practice and elderly care.

AUTHOR CONTRIBUTIONS

Shengxin Liu, Sabita S. Soedamah-Muthu, Seia C. van Meerten, and Erik J. Giltay concept and designed the study. Shengxin Liu, Sabita S. Soedamah-Muthu, and Erik J. Giltay analyzed and interpreted data. Shengxin Liu, Sabita S. Soedamah-Muthu, and Erik J. Giltay wrote the first draft of the paper. All authors interpreted the data, contributed

to the writing of the paper, and approved the final version. Each author participated sufficiently in work to take public responsibility for appropriate portions of the content.

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CONFLICT OF INTEREST

None of the authors has any financial or personal conflict of interest to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

ETHICS STATEMENT

The study was approved by a central medical ethics committee (Haga Hospital, Leyenburg, The Hague, The Netherlands) and by the ethics committees of participating hospitals.

PATIENT CONSENT STATEMENT

Written informed consent was obtained from all patients.

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