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Effects of Systematic Atrial Fibrillation Screening According to N-Terminal Pro-B-Type Natriuretic Peptide: a Secondary Analysis of the randomized LOOP Study

Running title: *Xing et al.; NT-proBNP and AF screening*

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Abstract

Background: Research suggests N-terminal pro-B-type natriuretic peptide (NT-proBNP) to be a strong predictor of incident atrial fibrillation (AF) and stroke. However, its utility in AF screening remains unknown. This study aimed to investigate NT-proBNP as a potential marker for screening efficacy with respect to AF yield and stroke prevention.
Methods: In the LOOP Study, 6004 AF-naïve individuals aged 70-90 years with additional stroke risk factors were randomized 1:3 to either continuous screening with implantable loop recorder (ILR) and anticoagulation initiation upon detection of AF episodes ≥6 minutes, or usual care (Control). This post-hoc analysis included the study participants with available NT-proBNP measurement at baseline.
Results: A total of 5819 participants were included (mean age 74.7 years (standard deviation, 4.1), 47.5% females). The median NT-proBNP level was 15 pmol/L [interquartile range: 9-28], corresponding to 125 pg/mL [interquartile range: 76-233]. NT-proBNP above median was associated with an increased risk of AF diagnosis both in the ILR group (hazard ratio (HR) 1.84 [95% confidence interval (CI): 1.51-2.25]) and the Control group (HR 2.79 [95% CI: 2.30-3.40]). Participants with NT-proBNP above median were also at higher risk of clinical events compared with those having lower levels (HR 1.21 [95% CI: 0.96-1.54] for stroke or systemic embolism (SE), 1.60 [95% CI: 1.32-1.95] for stroke/SE/cardiovascular death, and 1.91 [95% CI: 1.61-2.26] for all-cause death). Compared with usual care, ILR screening was associated with significant reductions in stroke/SE and stroke/SE/cardiovascular death among participants with NT-proBNP above median (HR 0.60 [95% CI: 0.40-0.90] and 0.70 [95% CI: 0.53-0.94], respectively), but not among those with lower levels ($p_{interaction}$=0.029 for stroke/SE and 0.045 for stroke/SE/cardiovascular death). No risk reduction in all-cause death was observed in either NT-proBNP subgroup for ILR versus Control ($p_{interaction}$=0.68). Analyzing NT-proBNP as a continuous variable yielded similar findings.
Conclusions: In an elderly population with additional stroke risk factors, ILR screening for AF was associated with a significant reduction in stroke risk among individuals with higher NT-proBNP levels, but not among those with lower levels. These findings should be considered hypothesis-generating and warrant further study before clinical implementation.
Clinical Trial Registration: The LOOP Study (https://www.clinicaltrials.gov; identifier NCT02036450)

Keywords: atrial fibrillation; stroke; B-type natriuretic peptide; screening.

Non-standard Abbreviations and Acronyms

AF	Atrial fibrillation
CI	Confidence interval
HR	Hazard ratio
ILR	Implantable loop recorder
IQR	Interquartile range
NNS	Number needed to screen
NT-proBNP	N-terminal pro-B-type natriuretic peptide
OAC	Oral anticoagulation
SBP	Systolic blood pressure
SD	Standard deviation
SE	Systemic embolism

Clinical Perspective

What is new?

- In an elderly population with additional stroke risk factors but without known atrial fibrillation (AF), a higher N-terminal pro-B-type natriuretic peptide (NT-proBNP) level at baseline was associated with increased risks of AF, stroke, and death.
- The screening yield on AF detection using implantable loop recorder (ILR) compared to usual care was greater among participants with lower NT-proBNP levels than those with higher levels.
- Compared with usual care, ILR screening was associated with a significantly reduced stroke risk among participants with higher NT-proBNP levels, but not among those with lower levels.

What are the clinical implications?

- Higher NT-proBNP may identify high-risk individuals who would benefit from AF screening.
- Using NT-proBNP for risk stratification may improve the cost-effectiveness of AF screening.

Introduction

It is well known that atrial fibrillation (AF) contributes to a substantially increased risk of stroke.[1,2] As the majority of AF episodes remain asymptomatic,[2,3] the timely diagnosis of AF seems to be a major challenge in clinical practice. The LOOP Study (*Atrial Fibrillation detected by Continuous ECG Monitoring using Implantable Loop Recorder to prevent Stroke in High-risk Individuals*) was a randomized trial to assess systematic AF screening with implantable loop recorder (ILR) in an elderly population with high stroke risk based on the CHA_2DS_2-VASc score. However, the study reported only a non-significant reduction in stroke,[4] suggesting that not all subclinical AF is worth screening for. Further insights into risk stratification of subclinical AF are therefore warranted to refine future screening strategies. N-terminal pro-B-type natriuretic peptide (NT-proBNP) is a cardiac biomarker that has been linked to incident AF and stroke in previous research.[5–11] Data from several randomized anticoagulation trials also showed that adding NT-proBNP to the CHA_2DS_2-VASc score significantly improved the prediction of cardiovascular outcomes including stroke, in anticoagulated AF patients.[9–11] However, data on the relationship between NT-proBNP and AF screening effects are lacking. To fill this knowledge gap, we conducted a secondary analysis of the LOOP Study to examine the effects of ILR screening versus usual care on stroke prevention according to NT-proBNP.

Methods

The study data underlying this article cannot be shared publicly for ethical reasons, but the methodology will be shared upon reasonable request to the corresponding author (JHS), who has full access to all the data in the study and takes responsibility for its integrity and the data analysis.

The LOOP Study

The LOOP Study was a randomized, controlled, multicenter trial to investigate long-term continuous AF screening in individuals aged 70-90 years and with ≥1 additional stroke risk factor (arterial hypertension, diabetes mellitus, heart failure, or prior stroke). A total of 6004 participants were enrolled at four centers in Denmark (from January 31st, 2014 to May 17th, 2016) and randomized to either ILR screening or usual care (the Control group) in a ratio 1:3. During ILR monitoring, oral anticoagulation (OAC) was recommended when any new-onset ILR-detected AF episode ≥6 minutes was confirmed by ≥2 senior cardiologists. The trial design and the primary reporting of the LOOP Study have been published previously.[4,12] The LOOP Study (Clinical-Trials.gov identifier: NCT02036450) was approved by the Regional Scientific Ethics Committee for the Capital Region of Denmark (H-4-2013-025) and conducted in accordance with the Declaration of Helsinki. Oral and written informed consents were obtained from all study participants at inclusion.

NT-proBNP levels

In the LOOP Study, whole blood samples were taken from the study participants at the local centers upon randomization. NT-proBNP levels were measured in two central hospital laboratories using the sandwich electrochemiluminescence-immunoassay (Roche Diagnostics GmbH, Germany) and the Cobas 8000 analyzer system (Roche Diagnostics) in accordance with the manufacturer's instructions.

In the present study, we included the participants with available NT-proBNP measurement at baseline and further divided them into two subgroups based on the median NT-proBNP level, which was also identical to the clinically reasonable cutoff for AF screening as previously proposed and currently used in ongoing trials.[13,14] Supplementary analyses were further conducted to assess NT-proBNP as a continuous variable. NT-proBNP levels are reported as pmol/L. The conversion factor for NT-proBNP expressed as pg/mL is 1 pg/mL = 0.12 pmol/L (see **Table S1**).[15]

Study outcomes and follow-up

All study participants in the LOOP Study were followed up from randomization until death or January 28th, 2021, with zero participants lost to follow-up. As in the primary reporting of the LOOP Study, the primary outcome for this secondary analysis was a composite endpoint of stroke or systemic embolism (SE). Secondary outcomes were 1) the composite endpoint of stroke, SE, or cardiovascular death, and 2) the endpoint of all-cause death. Other outcomes of interest included diagnosis of AF, ILR-detected AF episode ≥24 hours, and OAC initiation. The primary and secondary outcomes were adjudicated by a clinical endpoint committee blinded to randomization assignment in accordance with pre-specified criteria,[12] whereas the endpoint of AF episode ≥24 hours was evaluated by ≥1 experienced physician.

Statistical analysis

Baseline characteristics were summarized as frequency with percentage for categorical variables and the distributions were compared using χ^2 test. For continuous variables, the characteristics were summarized as mean with standard deviation (SD) or median with interquartile range (IQR) where appropriate, and further compared using t-test and Kruskal-Wallis test, respectively.

All outcomes were analyzed as time-to-first-event. Crude event rates (expressed as events per 100 person-years) were calculated with Poisson regression, whereas cumulative incidences were determined using the Kaplan-Meier estimator for all-cause death and using the Aalen-Johansen estimator with death as competing risk for all other outcomes. The relative risks of outcomes between NT-proBNP subgroups were estimated in the entire study cohort using multivariable cause-specific Cox regression models adjusted for sex, age, body-mass index, weekly alcohol consumption, smoking pack years, estimated glomerular filtration rate, total cholesterol concentration, hypertension, diabetes, prior stroke, heart failure, valvular heart disease, ischemic heart disease, and peripheral artery disease. For

primary and secondary outcomes, NT-proBNP was also analyzed as a continuous variable with restricted cubic spline regression (knots located at the 5th, 35th, 65th, and 95th percentiles) in the multivariable Cox models.

The relative risks of study outcomes for ILR screening versus usual care were examined according to NT-proBNP subgroups in cause-specific Cox regression models, with the potential interaction tested by further adding an interaction term to the models. The intention-to-treat principle was applied in the analyses of screening effects. Additionally, linear and spline-based models were employed to assess the associations between continuous NT-proBNP and the relative risks of primary and secondary outcomes for ILR versus Control, where we used Akaike Information Criterion to find the model with an optimal balance between fit and parsimony.[16,17] Finally, a model assuming a linear relationship between log-transformed NT-proBNP and log hazards of primary and secondary outcomes in each randomization group was selected due to the lowest Akaike Information Criterion score (**Table S2**). Furthermore, as risk factor management is an important part of guideline-directed AF treatment and particularly high systolic blood pressure (SBP) constitutes a predominant stroke risk factor,[2,18,19] it was explored by determining blood pressure changes over the first three years of follow-up according to randomization assignment in each NT-proBNP subgroup. The analysis was performed using a constrained linear mixed model with unstructured covariance pattern to account for repeated measurements in the same subject.

The Cox proportional-hazard assumption was tested with scaled Schoenfeld residuals and any variables violating this were treated with stratification to allow different baseline hazards. All data analyses were performed using R (version 4.1.0, R Core Team). Two-sided p-values ≤0.05 set the statistical significance.

Results

Of the 6004 participants enrolled in the LOOP Study, 5819 (96.9%) had available NT-proBNP measurement at baseline and were included in this secondary analysis, with a mean age of 74.7 years (SD, 4.1) and with 47.5% being female. The median level of NT-proBNP was 15 pmol/L [IQR: 9-28] at baseline (**Figure S1**). **Table 1** summarizes the baseline characteristics according to NT-proBNP subgroups. Participants with baseline NT-proBNP >15 pmol/L were older, more likely female, and had higher tobacco consumption and systolic blood pressure, but lower body-mass index and weekly alcohol consumption, compared with those having lower NT-proBNP levels. Cardiovascular comorbidities such as heart failure, previous stroke, ischemic heart disease, valvular heart disease, and peripheral artery disease were also more prevalent among participants with NT-proBNP above median.

Primary and secondary outcomes according to NT-proBNP

Among 5819 participants included, 310 had stroke/SE (307 stroke and three SE) and 669 died during a median follow-up duration of 5.4 years [IQR: 4.9-5.8]. For the entire study cohort, the event rate of the primary outcome of stroke/SE was numerically higher among participants with NT-proBNP >15 pmol/L (1.21 [95% confidence interval (CI): 1.04-1.40] per 100 person-years) than those with lower levels (0.89 [95% CI: 0.74-1.05] per 100 person-years), as indicated by a hazard ratio (HR) of 1.21 [95% CI: 0.96-1.54]. For secondary outcomes, participants with NT-proBNP >15 pmol/L were at significantly increased risks of both stroke/SE/cardiovascular death and all-cause death compared with those having lower levels (HR 1.60 [95% CI: 1.32-1.95] and 1.91 [95% CI: 1.61-2.26], respectively). The cumulative incidences and crude event rates of primary and secondary outcomes according to NT-proBNP subgroups are presented in **Figure 1** and **Table S3**. When assessed as a continuous variable, elevating NT-proBNP levels were significantly associated with

increasing risks of stroke/SE, stroke/SE/cardiovascular death, and all-cause death (p-value 0.0026, <0.0001, and <0.0001, respectively; **Figure S2**).

ILR screening effects on primary and secondary outcomes according to NT-proBNP

Figure 2 illustrates the relative risks of primary and secondary outcomes for ILR screening versus usual care according to NT-proBNP subgroups. The risk of stroke/SE was not statistically different across the randomization groups among participants with NT-proBNP ≤15 pmol/L at baseline (HR 1.11 [95% CI: 0.76-1.62]), whereas a significant risk reduction by ILR screening compared with usual care was observed among participants having higher NT-proBNP levels (HR 0.60 [95% CI: 0.40-0.90]); $p_{interaction}$=0.029. The 6-year cumulative incidence was estimated to 4.28% [95% CI: 2.71-5.86] in the ILR group and 7.51% [95% CI: 6.26-8.76] in the Control group among participants with NT-proBNP >15 pmol/L (**Figure S3**), corresponding to an absolute risk reduction of 3.23% and a number needed to screen (NNS) to avoid one stroke/SE of 31 (i.e. 100 divided by 3.23). Likewise, ILR screening was associated with a significant risk reduction of stroke/SE/cardiovascular death only among participants with NT-proBNP >15 pmol/L (HR 0.70 [95% CI: 0.53-0.94]), but not among those with lower levels (HR 1.11 [95% CI: 0.79-1.55]); $p_{interaction}$=0.045. For all-cause death, no significant risk difference between the randomization groups was found in either NT-proBNP subgroups. With NT-proBNP analyzed as a continuous variable, similar effect patterns were observed on stroke/SE ($p_{interaction}$=0.084), stroke/SE/cardiovascular death ($p_{interaction}$=0.11), and all-cause death ($p_{interaction}$=0.98); **Figure 3**. Both for stroke/SE and stroke/SE/cardiovascular death, the risk reduction for ILR screening versus usual care appeared to increase with higher NT-proBNP levels and the trend curves crossed the reference line (HR = 1) at a NT-proBNP level of 9 pmol/L. With further exploration using NT-proBNP cutoffs corresponding to the 75th (i.e. >28 pmol/L) and 95th (i.e. >76 pmol/L) percentiles, the absolute risk differences in stroke/SE were estimated to 3.26% (6-year

cumulative incidence of 8.61% [95% CI: 6.77-10.45] for Control versus 5.35% [95% CI: 2.83-7.88] for ILR) and 4.68% (6-year cumulative incidence of 11.55% [95% CI: 7.04-16.06] for Control versus 6.87 [95% CI: 1.06-12.69] for ILR), respectively. The NNS to avoid one stroke/SE after six years was 31 for participants with NT-proBNP >28 pmol/L and 21 for participants with NT-proBNP >76 pmol/L.

AF outcomes and OAC initiation

In total, 1014 (17.4%) of 5819 participants were diagnosed with AF during follow-up: 544 (12.5%) of 4356 participants in the Control group versus 470 (32.1%) of 1463 participants in the ILR group. **Figure 4** depicts cumulative incidences of AF diagnosis according to NT-proBNP subgroups. A baseline NT-proBNP >15 pmol/L was associated with an increased risk of AF diagnosis in both the Control group (HR 2.79 [95% CI: 2.30-3.40]) and the ILR group (HR 1.84 [95% CI: 1.51-2.25]). Similarly, during ILR monitoring with a median duration of 3.27 years [IQR: 3.06-3.45], participants with NT-proBNP >15 pmol/L were also more likely to experience ILR-detected AF episodes lasting ≥24 hours compared with those having lower levels in the ILR group (HR 2.45 [95% CI: 1.46-4.10]; **Figure S4**). For ILR screening versus usual care (**Table S4**), the screening yield on AF diagnosis was significantly greater among participants with NT-proBNP ≤15 pmol/L (HR 4.06 [95% CI: 3.27-5.04]) than those with higher NT-proBNP levels (HR 2.89 [95% CI: 2.49-3.37]); $p_{interaction}$=0.012.

Among the 1014 participants diagnosed with AF, 898 (88.6%) were initiated OAC: 471 (86.6%) of 544 in the Control group versus 427 (90.9%) of 470 in the ILR group. During follow-up, the event rate of OAC initiation was 1.63 [95% CI: 1.40-1.89] per 100 person-years in the Control group and 5.37 [95% CI: 4.60-6.23] per 100 person-years in the ILR group among participants with NT-proBNP ≤15 pmol/L (HR 3.25 [95% CI: 2.64-4.00]). For participants with higher NT-proBNP levels, OAC initiation occurred at a rate of 3.92 [95%

CI: 3.54-4.32] and 10.14 [95% CI: 8.96-11.45] per 100 person-years in the Control group and the ILR group, respectively, corresponding to a HR of 2.55 [95% CI: 2.18-2.98].

Blood pressure management

Among the 5819 participants included, 5813 had available SBP measurements at baseline. For 3-year follow-up versus baseline, SBP was reduced by 2.8 [95% CI: 2.2-3.4] mmHg in the Control group and 3.9 [95% CI: 2.9-4.9] mmHg in the ILR group (p-value 0.049; **Figure S5**). When further stratified by NT-proBNP subgroups, the mean SBP reduction was 3.8 [95% CI: 2.8-4.8] mmHg in the Control group and 4.6 [95% CI: 3.1-6.2] mmHg in the ILR group among participants with NT-proBNP >15 pmol/L (p-value 0.35). For those having lower NT-proBNP levels, SBP was reduced by 1.8 [95% CI: 1.0-2.6] mmHg and 3.1 [95% CI: 1.9-4.4] mmHg in the Control group and the ILR group, respectively (p-value 0.059).

Discussion

This is the first study to assess the effects of AF screening on clinical outcomes according to NT-proBNP levels. In the present post-hoc analysis of 5819 elderly individuals with additional stroke risk factors enrolled in a large AF screening trial, we reported the following major findings: 1) participants with higher levels of NT-proBNP were at higher risks of AF, stroke, and death; and 2) compared with usual care, ILR screening was associated with a significant reduction in stroke risk among participants with baseline NT-proBNP above median (>15 pmol/L), but not among those having lower levels.

NT-proBNP is a well-established biomarker for the diagnostics and risk stratification of heart failure,[20,21] but its utility in the setting of AF is less clarified. Mounting evidence from large epidemiological cohort studies has indicated NT-proBNP to be a strong, independent predictor of incident AF.[5–8] Furthermore, the secondary analyses of the RE-LY trial, the ARISTOTLE trial, and the ENGAGE AF-TIMI 48 trial consistently demonstrated a

positive correlation between NT-proBNP and stroke risk in AF patients.[9–11] In line herewith, our study also confirms that participants with higher baseline levels of NT-proBNP were at increased risks of AF and stroke. This could indeed explain the favorable effects of ILR screening among participants with NT-proBNP >15 pmol/L and the absence of screening benefits for those with lower levels. In addition, the observed stroke risk reduction for ILR screening versus usual care in the participant group with NT-proBNP >15 pmol/L seems to be mainly attributable to OAC initiation upon AF detection rather than risk factor management, as no statistically significant difference in SBP reduction during follow-up was found across the randomization groups among these participants. Another interesting observation from our study is the relatively smaller screening yield on AF detection among participants with NT-proBNP >15 pmol/L despite a greater stroke risk reduction for ILR versus Control. Compared with usual care, ILR screening appeared to increase the rate of AF diagnosis by less than 3-fold among participants with NT-proBNP >15 pmol/L versus more than 4-fold among those with NT-proBNP ≤15 pmol/L. The discrepancy between screening effects on AF detection and on stroke prevention may well translate into the potential of NT-proBNP to identify those more likely to develop clinically relevant AF that indeed merit anticoagulation treatment. This notion is further supported by our finding of a higher risk of ILR-detected AF ≥24 hours among participants with NT-proBNP >15 pmol/L than those with lower levels, as a secondary analysis of the ASSERT study already revealed that the increased stroke risk of device-detected AF was primarily related to long-lasting episodes exceeding 24 hours.[22] Still, it could also be speculated that high NT-proBNP merely acts as a risk marker of cardiovascular comorbidities and thereby mediates the potential linkage between higher comorbidity burden and greater screening benefits. Countering this argument is a prior LOOP sub-study that found the ILR screening effects to be upheld by the more healthy participants, not those with established cardiovascular disease.[23] Additionally,

previous research suggests that NT-proBNP may serve as an etiological indicator of ischemic stroke. A meta-analysis of 23 stroke studies pointed towards an association between elevated NT-proBNP and cardioembolic stroke,[24] whereas a Japanese study of AF patients with acute ischemic stroke reported a higher prevalence of co-existing small vessel occlusion and/or large artery atherosclerosis among those having lower levels of B-type natriuretic peptide.[25] Indeed, increased wall tension in the atria has been proposed to stimulate atrial secretion of B-type natriuretic peptides and thus, elevated NT-proBNP may reflect atrial dysfunction.[26–28] Given the documented correlation between atrial function and atrial thrombus formation,[29] the observed differential effect of ILR screening according to NT-proBNP levels is therefore biologically plausible.

The latest guidelines from European Society of Cardiology recommend considering systematic electrocardiogram screening in individuals aged ≥75 years or those at high stroke risk as assessed by the CHA_2DS_2-VASc score.[2] However, the present study suggests that NT-proBNP may modify AF screening effects on stroke prevention and thereby be useful for identifying the appropriate subpopulation who would benefit the most from AF screening and subsequent management. Besides, when applying NT-proBNP >15 pmol/L as a cutoff, the NNS to avoid one stroke after six years would be reduced from 62 in the entire population,[4] to 31. NT-proBNP is now also available as point-of-care test, with expected decreasing cost over time. Hence, it may constitute an easily accessible and decisive tool for risk stratification that has the potential to improve the cost-effectiveness of AF screening.

Of note, although the arbitrary cutoff of NT-proBNP >15 pmol/L appeared useful in the present exploratory analysis, the optimal cutoff to implement for AF screening in clinical practice has yet to be defined and validated. Indeed, according to our analyses of continuous NT-proBNP, a stroke risk reduction for ILR screening versus usual care already emerged at a NT-proBNP level from 9 pmol/L. However, it is worth mentioning that both European and

American guidelines recommend using 125 pg/mL (i.e. 15 pmol/L) as the threshold to rule out ventricular dysfunction in non-acute settings.[20,21] The same cutoff has also been proposed for systematic AF screening in a sub-analysis of the STROKESTOP I trial and is currently tested in the ongoing STROKESTOP II trial.[13,14] Importantly, further studies are warranted to investigate potential harms from various thresholds for screening implementation, such as anticoagulation-related bleeding risks and overdiagnosis of impaired ventricular dysfunction and the related downstream testing.

Limitations

Several study limitations should be acknowledged. First, this was not a pre-specified analysis of the LOOP Study, and our findings should therefore be considered exploratory and hypothesis-generating only. Second, echocardiographic data are lacking, although multivariable adjustments were performed as an attempt to accommodate confounders mediating the link between ventricular function and NT-proBNP. Third, due to the inclusion criteria of the LOOP Study, our study population solely comprised of elderly individuals aged 70-90 years, which would limit the generalizability of our results to other age groups. Finally, values for NT-proBNP expressed as pg/mL instead of pmol/L may differ slightly depending on the number of significant figures in the conversion factor.

Conclusions

In this exploratory post-hoc analysis of a large, randomized trial of elderly individuals with additional stroke risk factors, higher NT-proBNP levels at baseline were associated with increased risks of AF diagnosis, stroke, and death. Compared with usual care, long-term continuous screening with ILR and subsequent OAC initiation upon AF detection was associated with a significant reduction in stroke risk among individuals with higher NT-proBNP levels, but not among those with lower levels. These findings should be considered

hypothesis-generating and future studies are warranted to assess net benefits of AF screening according to NT-proBNP.

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Disclosures

JHS reports to be a member of Medtronic advisory boards and to have received speaker honoraria and research grants from Medtronic in relation to this work and outside this work. SZD reports to be a part-time employee of VitalBeats and advisor at Bristol-Myers

Squibb/Pfizer, not related to this work. DWK reports to be a Medtronic Focus Group member. RFS reports speaker honorarium and consultant fees from Novo Nordisk. AB reports research grants from The Region of Zealand, The Canadian Institutes of Health Research, The Danish Heart Foundation, and Theravance, and speaker honoraria from Boehringer Ingelheim and Bristol-Myers Squibb not related to this work. LK reports speaker honoraria from Novo Nordisk, AstraZeneca, Novartis, and Boehringer, not related to this work. Other authors have no conflicts of interest to report.

Supplemental Materials

Tables S1-S4

Figures S1-S5

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Figure Legends

Figure 1. Cumulative Incidences of Primary and Secondary Outcomes According to NT-proBNP Subgroups

The figure shows the absolute risks of stroke/SE, stroke/SE/cardiovascular death, and all-cause death in the entire study cohort according to NT-proBNP subgroups. Cumulative incidences were plotted using the Kaplan-Meier estimator for all-cause death and the Aalen-Johansen estimator for other outcomes with death as competing risk. HRs and p-values were determined in cause-specific Cox models adjusted for sex, age, body mass index, weekly alcohol consumption, smoking pack years, estimated glomerular filtration rate, total cholesterol concentration, hypertension, diabetes, prior stroke, heart failure, valvular heart disease, ischemic heart disease, and peripheral artery disease.

The conversion factor for NT-proBNP expressed as pg/mL is 1 pg/mL = 0.12 pmol/L. Hence, 15 pmol/L corresponds to 125 pg/mL.

Abbreviations: Cl, confidence interval; HR, hazard ratio; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SE, systemic embolism.

Figure 2. ILR Screening Effects on Primary and Secondary Outcomes According to NT-proBNP Subgroups

The figure shows event rates and hazard ratios of stroke/SE, stroke/SE/cardiovascular death, and all-cause death for ILR screening versus usual care, according to NT-proBNP subgroups. Crude event rates are presented as number of events per 100 person-years and were estimated using Poisson regression. Hazard ratios and p-values for interaction were determined in cause-specific Cox models.

The conversion factor for NT-proBNP expressed as pg/mL is 1 pg/mL = 0.12 pmol/L. Hence, 15 pmol/L corresponds to 125 pg/mL.

Abbreviations: Cl, confidence interval; ILR, implantable loop recorder; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SE, systemic embolism.

Figure 3: The Associations of ILR Screening Effects on Primary and Secondary Outcomes With NT-proBNP as a Continuous Variable

The figure shows the effects of ILR screening versus usual care on stroke/SE, stroke/SE/cardiovascular death, and all-cause death, according to NT-proBNP as a continuous variable. Hazard ratios were estimated in cause-specific Cox models, with the Control group as reference. The colored areas represent 95% confidence intervals.

The conversion factor for NT-proBNP expressed as pg/mL is 1 pg/mL = 0.12 pmol/L.

Abbreviations: ILR, implantable loop recorder; NT-proBNP, N-terminal pro-B-type natriuretic peptide; SE, systemic embolism.

Figure 4: Cumulative Incidences of AF Diagnosis According to NT-proBNP Subgroups

The figure shows the absolute risk of AF diagnosis in the Control group and in the ILR group, according to NT-proBNP subgroups. Cumulative incidences were plotted using the Aalen-Johansen estimator with death as competing risk. HRs and p-values were determined in cause-specific Cox models adjusted for sex, age, body mass index, weekly alcohol consumption, smoking pack years, estimated glomerular filtration rate, total cholesterol concentration, hypertension, diabetes, prior stroke, heart failure, valvular heart disease, ischemic heart disease, and peripheral artery disease.

The conversion factor for NT-proBNP expressed as pg/mL is 1 pg/mL = 0.12 pmol/L. Hence, 15 pmol/L corresponds to 125 pg/mL.

Abbreviations: AF, atrial fibrillation; Cl, confidence interval; HR, hazard ratio; ILR, implantable loop recorder; NT-proBNP, N-terminal pro-B-type natriuretic peptide.

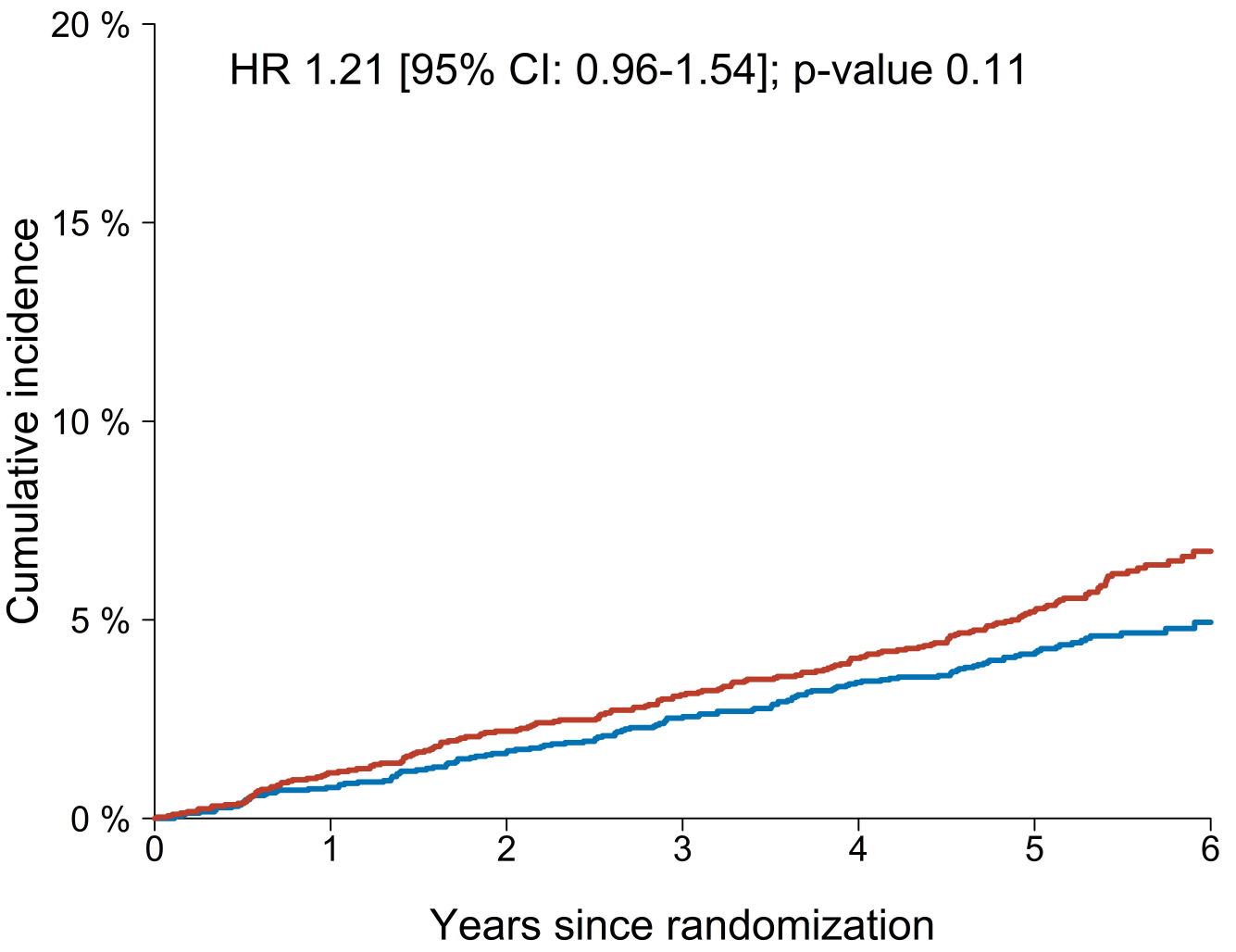
Table 1. Baseline Characteristics According to NT-proBNP Subgroups

	Total (n=5819)	NT-proBNP ≤15 pmol/L (n=2940)	NT-proBNP >15 pmol/L (n=2879)	p-value
ILR assignment (%)	1463 (25.1)	752 (25.6)	711 (24.7)	0.46
Male sex (%)	3054 (52.5)	1607 (54.7)	1447 (50.3)	0.00086
Age, years (SD)	74.7 (4.1)	73.8 (3.5)	75.7 (4.5)	<0.0001
Alcohol consumption, standard units per week [IQR]	5 [1-10]	5 [1-10]	4 [1-10]	0.0064
Smoking pack years [IQR]	6 [0-28]	5.5 [0-26]	8 [0-30]	0.022
Blood pressure, mmHg (SD)				
Systolic	149.9 (19.5)	148.6 (18)	151.3 (20.8)	<0.0001
Diastolic	84.1 (11.2)	84.8 (10.6)	83.5 (11.8)	<0.0001
Pulse rate, beats per min (SD)	71.3 (12.4)	73.2 (12.3)	69.4 (12.2)	<0.0001
Body-mass index, kg/m2 (SD)	27.6 (4.6)	28 (4.5)	27.3 (4.6)	<0.0001
Estimated glomerular filtration rate, mL/min (SD)	75.5 (19.5)	78.8 (18)	72.2 (20.3)	<0.0001
Total cholesterol, mmol/L (SD)	4.8 (1.1)	4.8 (1.1)	4.7 (1.1)	<0.0001
CHA_2DS_2-VASc score (SD)	3.8 (1.2)	3.5 (1.1)	4 (1.2)	<0.0001
Comorbidities (%)				
Hypertension	5275 (90.7)	2646 (90.0)	2629 (91.3)	0.093
Diabetes mellitus	1653 (28.4)	892 (30.3)	761 (26.4)	0.0011
Heart failure	265 (4.6)	59 (2.0)	206 (7.2)	<0.0001
Previous stroke	1028 (17.7)	488 (16.6)	540 (18.8)	0.034
Chronic ischemic heart disease	781 (13.4)	228 (7.8)	553 (19.2)	<0.0001
Valvular heart disease	236 (4.1)	85 (2.9)	151 (5.2)	<0.0001
Peripheral artery disease	157 (2.7)	62 (2.1)	95 (3.3)	0.0065
Concomitant medications (%)				
Beta-blockers	1501 (25.8)	464 (15.8)	1037 (36.0)	<0.0001
Calcium channel blockers	2179 (37.4)	1133 (38.5)	1046 (36.3)	0.087

Renin-angiotensin inhibitors	3863 (66.4)	1992 (67.8)	1871 (65.0)	0.027
Diuretics	1946 (33.4)	893 (30.4)	1053 (36.6)	<0.0001
Platelet inhibitors	2838 (48.8)	1313 (44.7)	1525 (53.0)	<0.0001
Statins	3374 (58.0)	1690 (57.5)	1684 (58.5)	0.45
Insulins	465 (8.0)	245 (8.3)	220 (7.6)	0.36
Other antidiabetic drugs	1240 (21.3)	694 (23.6)	546 (19.0)	<0.0001

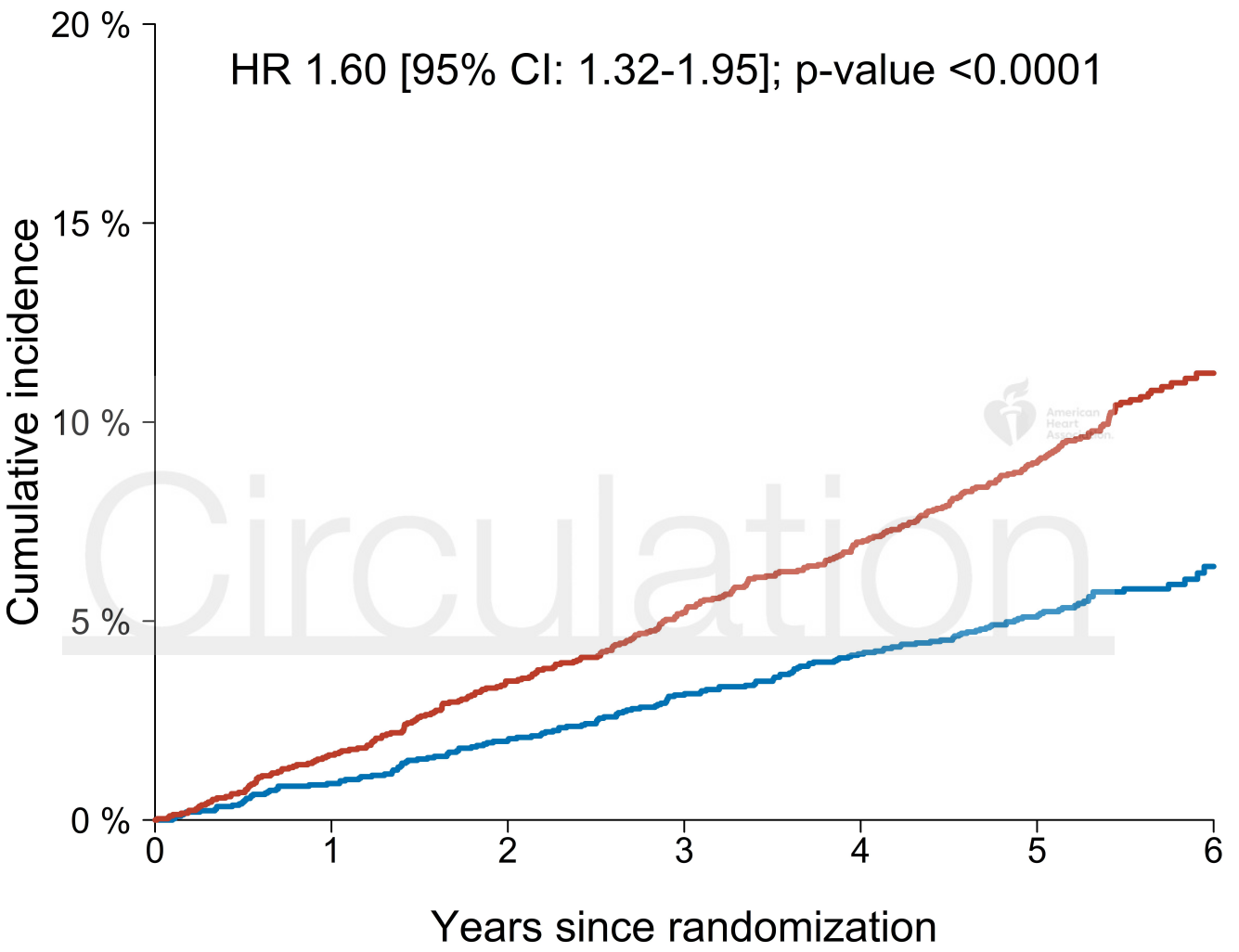
Values are presented as n (%), mean (SD), or median [IQR].
The conversion factor for NT-proBNP expressed as pg/mL is 1 pg/mL = 0.12 pmol/L. Hence, 15 pmol/L corresponds to 125 pg/mL.
Missing observations: alcohol consumption n=3; blood pressure n=6; pulse rate n=20; estimated glomerular filtration rate, n=13; total cholesterol, n=1.
Abbreviations: NT-proBNP, N-terminal pro-B-type natriuretic peptide; ILR, implantable loop recorder; SD, standard deviation; IQR, interquartile range.

Stroke or SE



NT-proBNP							
≤ 15 pmol/L	2940	2894	2828	2761	2680	2025	488
> 15 pmol/L	2879	2799	2687	2575	2456	2002	486

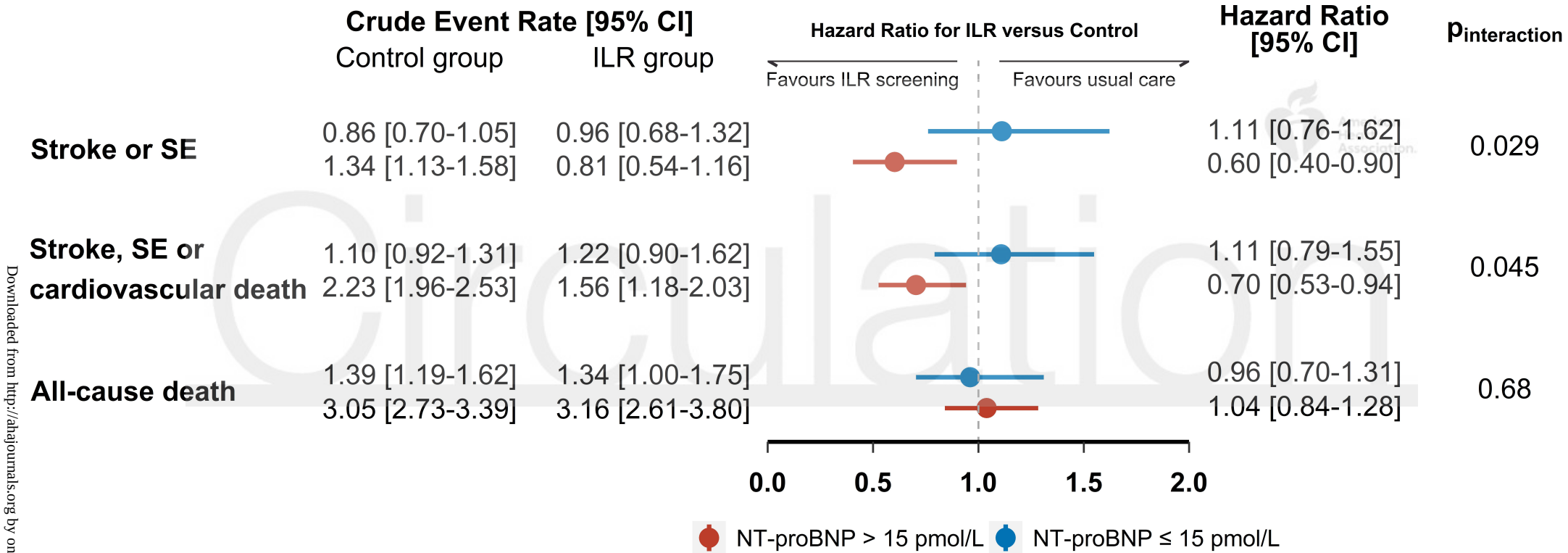
Stroke, SE or cardiovascular death

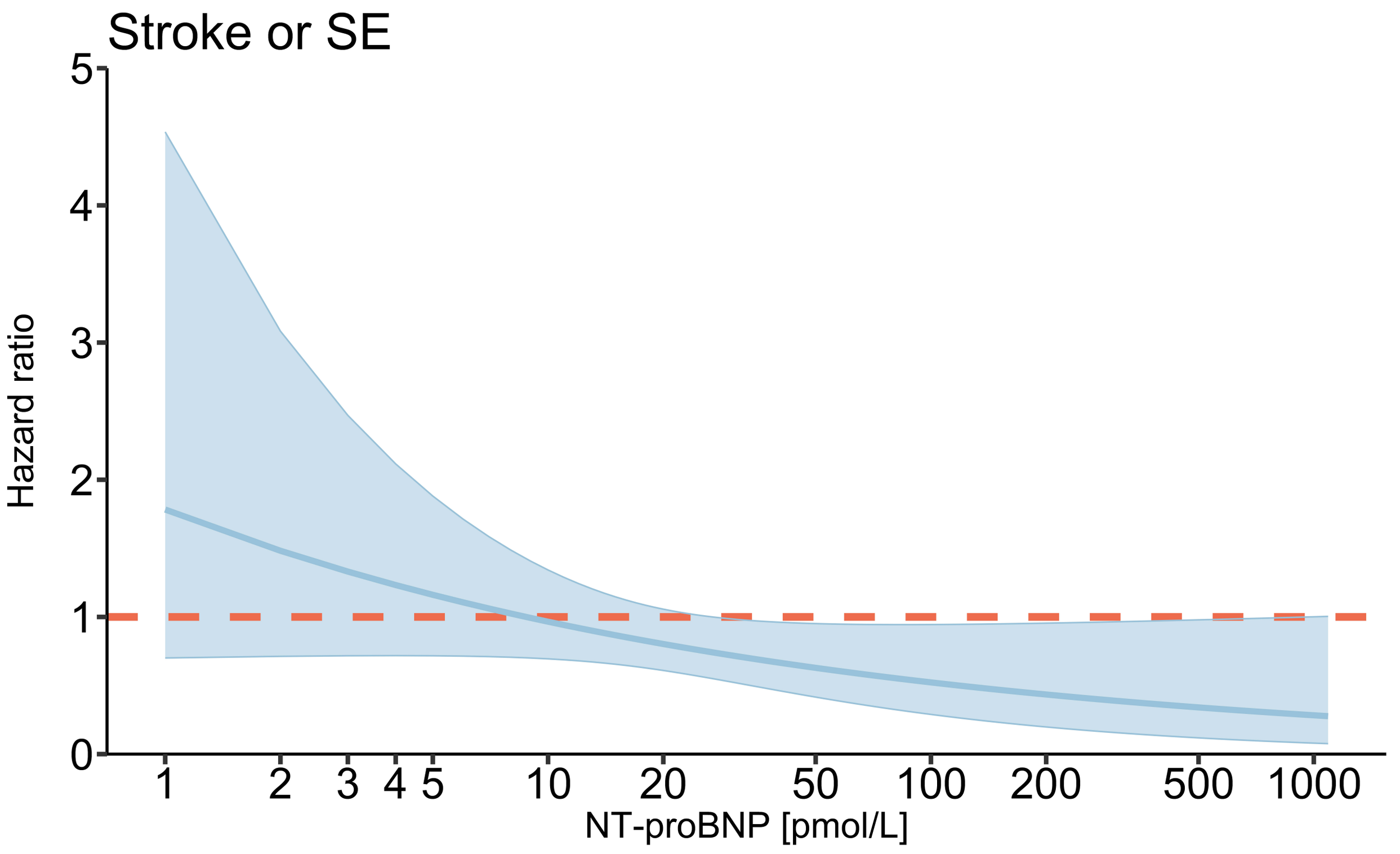


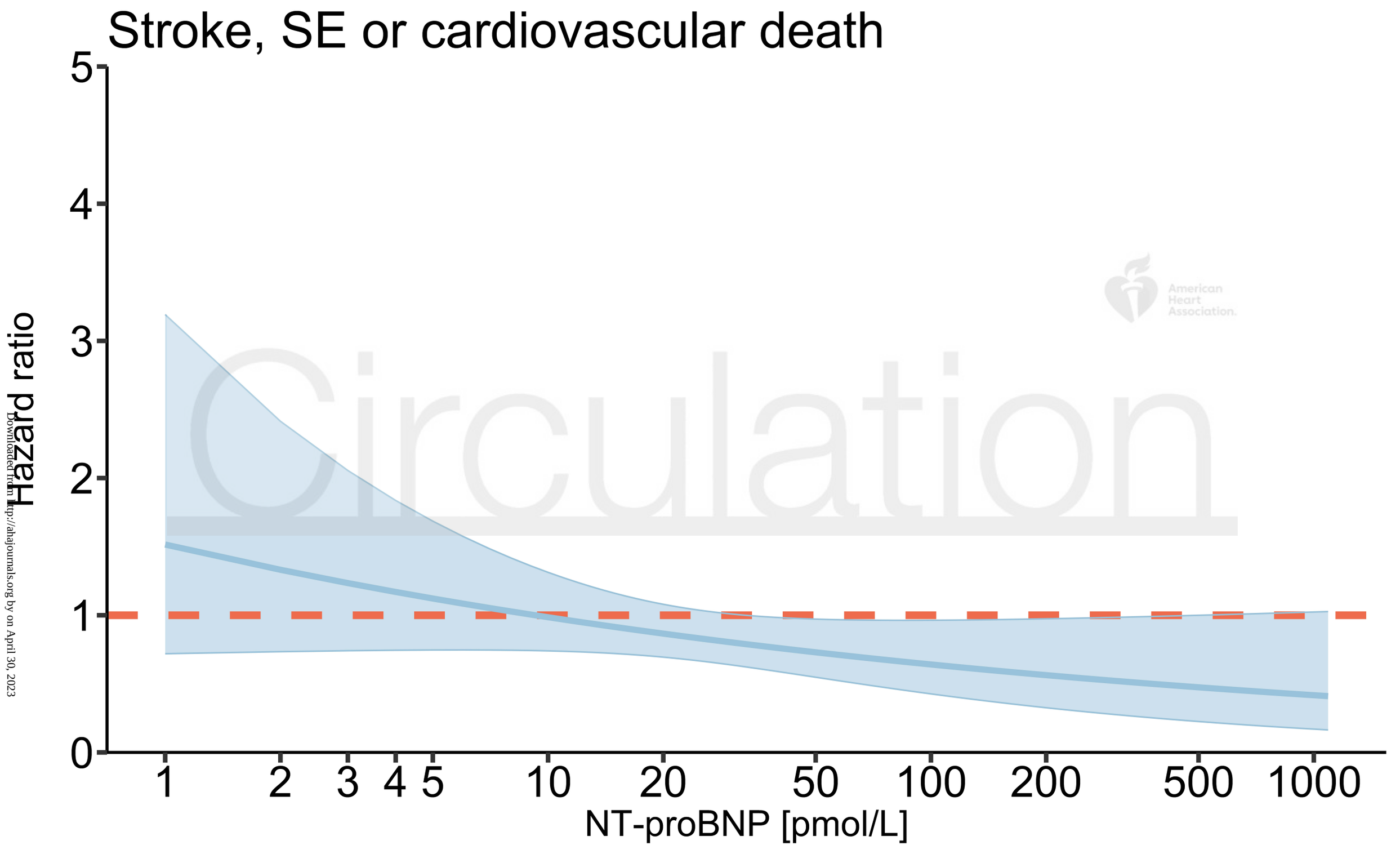
NT-proBNP							
≤ 15 pmol/L	2940	2894	2828	2761	2680	2025	488
> 15 pmol/L	2879	2799	2687	2575	2456	2002	486

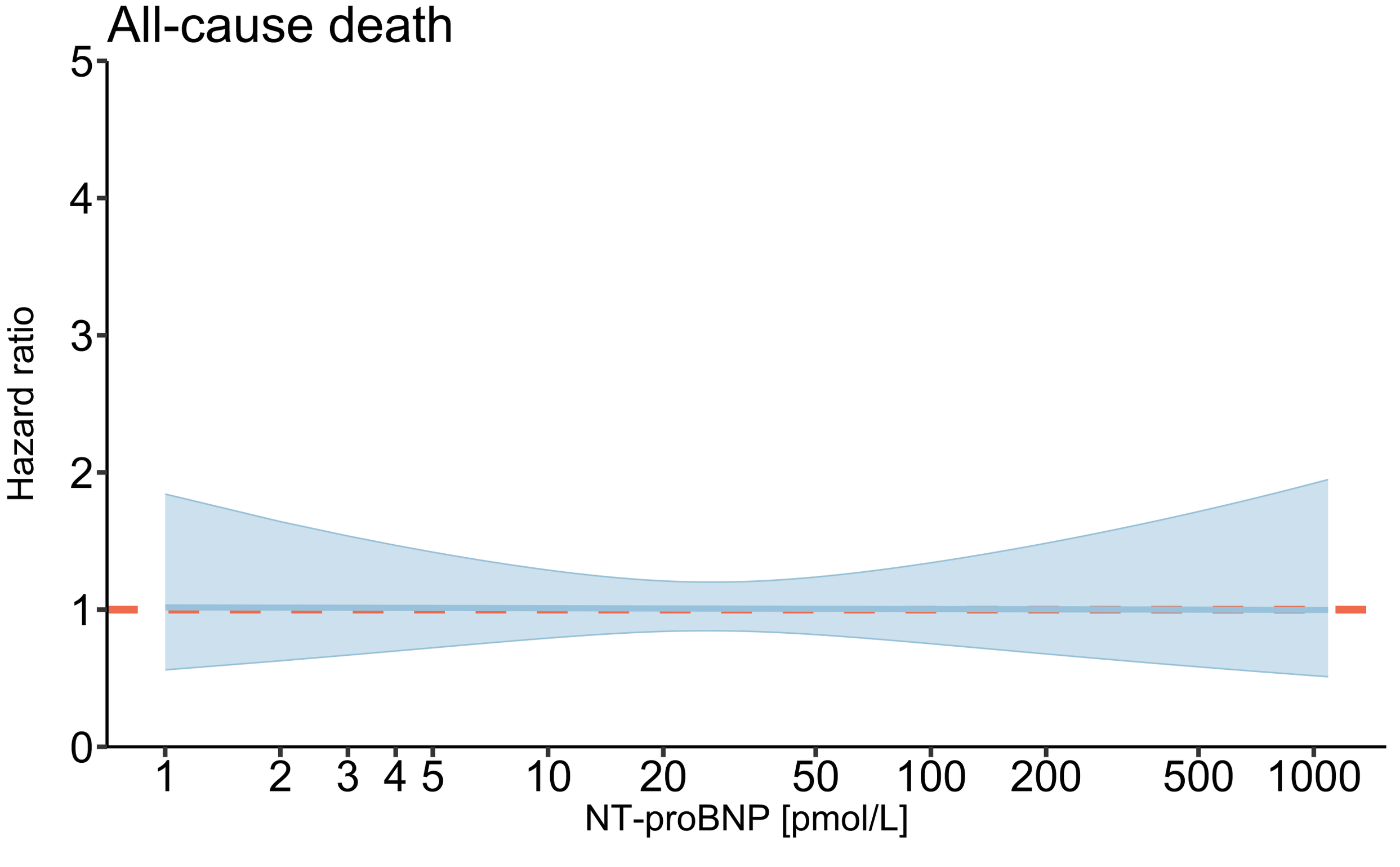
All-cause death

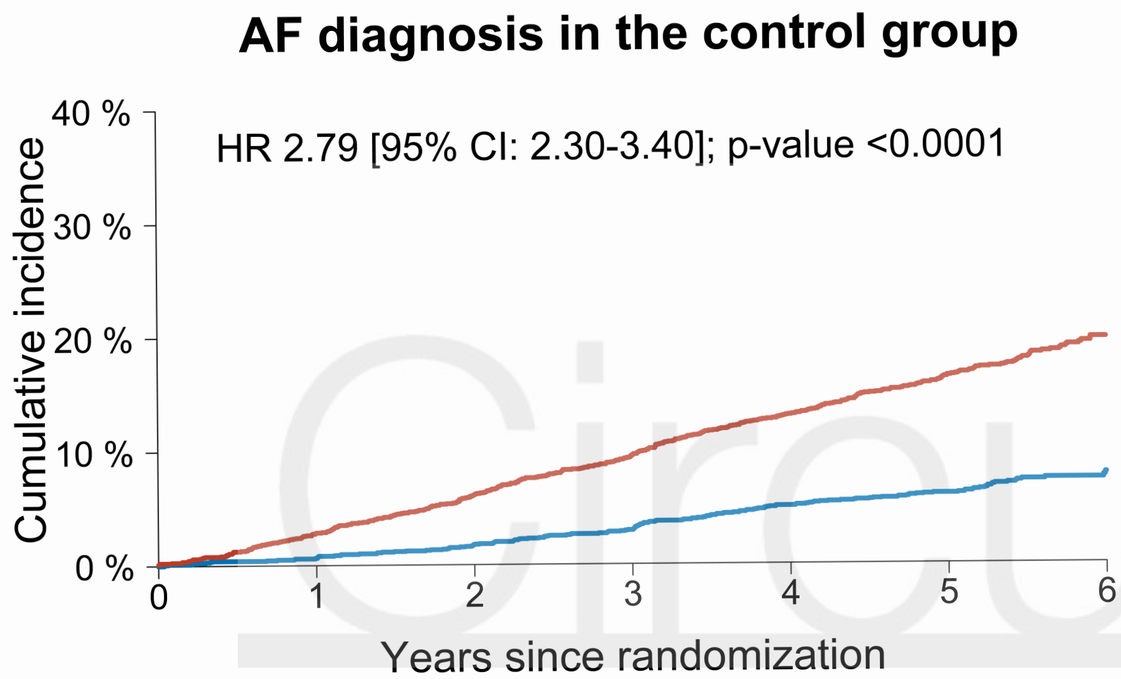
NT-proBNP							
≤ 15 pmol/L	2940	2916	2875	2829	2770	2111	509
> 15 pmol/L	2879	2829	2740	2643	2540	2091	513

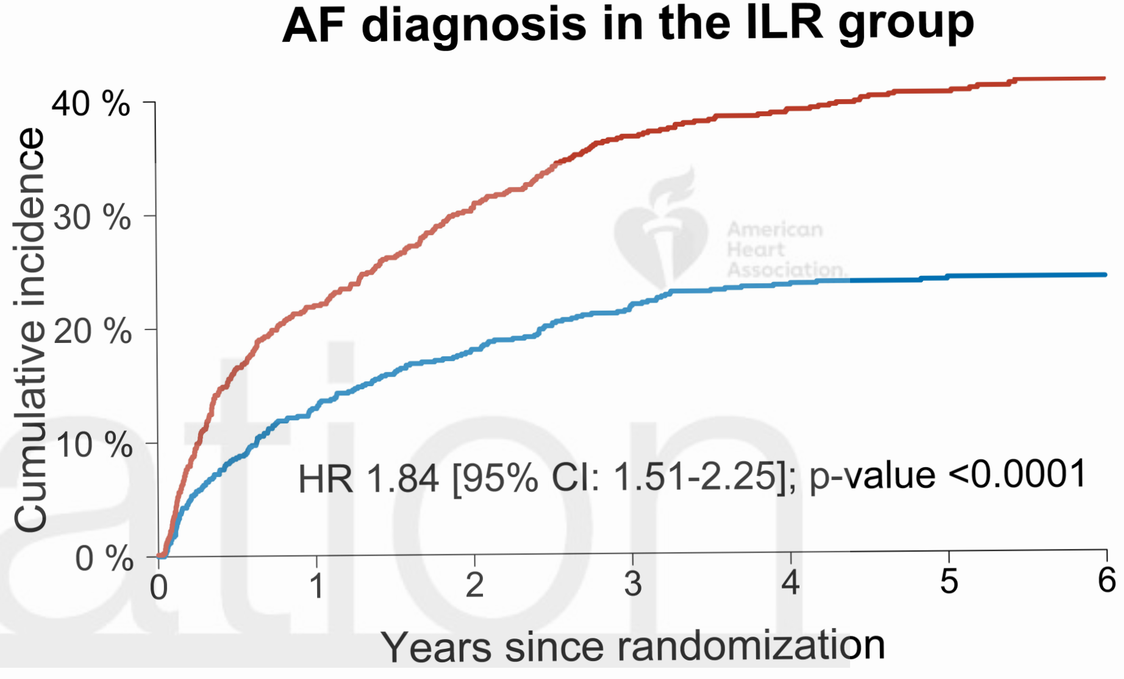












NT-proBNP							
≤ 15 pmol/L	2188	2160	2105	2044	1959	1482	355
> 15 pmol/L	2168	2077	1947	1813	1669	1319	326

NT-proBNP							
≤ 15 pmol/L	752	646	601	569	548	402	93
> 15 pmol/L	711	542	474	421	397	311	55