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Value of N-Terminal Pro-Brain Natriuretic Peptide for Embolic Events Risk Prediction in Patients with Atrial Fibrillation; a Systematic Review and Meta-Analysis

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Abstract: **Introduction:** A comprehensive conclusion has yet to be made about the predictive value of serum N-terminal pro-brain natriuretic peptide (NT-proBNP) for stroke/systemic embolic events (SEE) in patients with atrial fibrillation (AF). This study aims to review the evidence for evaluating the value of NT-proBNP in predicting the risk of stroke/SEE in patients with AF through a systematic review and meta-analysis. **Methods:** Two independent reviewers screened all relevant studies that were retrieved from the database of Medline, Embase, Scopus, and Web of Science until December 7th, 2021. The predictive value of NT-proBNP in the prediction of stroke/SEE was recorded as hazard ratio (HR) and 95% confidence interval (95% CI). **Results:** Nine articles (38,093 patients, 3.10% stroke/SEE) were included in our analysis. There was no publication bias in these studies (P=0.320). Our analysis showed that NT-proBNP can be a good predictor of stroke/SEE risk in AF patients, even at different cut-off values (HR=1.76; 95% CI: 1.51, 2.02; P < 0.001). Subgroup analysis showed that diabetes could have a possible effect on the predictive value of NT-proBNP (meta-regression coefficient = 0.042; P = 0.037). **Conclusion:** Measurement of NT-proBNP during the first admission could be used to assess the short- or long-term risk of stroke/SEE in patients with AF. Further studies are needed to evaluate the possible applicability of serum NT-proBNP measurement in the settings in which stroke is the sole outcome of the investigation.

Keywords: Pro-brain natriuretic peptide; Stroke; Embolism, Paradoxical; Atrial fibrillation; Meta-analysis

1. Introduction

Stroke and thromboembolic events are considered as one of the leading causes of death and disability worldwide (1, 2). In the past, stroke was believed to be a disease that mostly affected the elderly population. However, recent studies have shown that the incidence of stroke in the younger population is increasing (3-5). Regardless of the age group, there is a high prevalence of cardiovascular accidents worldwide, which results in lifelong disabilities and death in severe cases (6, 7).

There are many risk factors associated with a higher occurrence of stroke, such as hypertension, diabetes, old age, smoking, and sedentary lifestyle (8, 9). Atrial fibrillation (AF), an irregular rapid beating of the atriums (10), increases the risk of strokes and other thromboembolic events. It is well established that patients with atrial fibrillation are at higher risk for strokes and systemic thromboembolic events compared to patients without AF (11, 12). The identification of

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high-risk patients for stroke is commonly made by using a clinical score such as the CHADS2, a scoring system designed to predict the risk of stroke in patients with atrial fibrillation based on their risk factors (heart failure, hypertension, age > 75, diabetes, prior stroke/ transient ischemic attack (TIA), vascular disease, ages 65-75, and sex category) (13, 14). In addition to the availability of clinical scoring tools, there is still a need for additional simple, accurate, and reliable markers for the identification of patients with a higher risk of stroke in the clinical setting.

In recent years, serum biomarkers such as natriuretic peptides have been mentioned as a suitable marker for predicting stroke and systemic embolic events (SEE) in patients with AF (15, 16). Studies have shown that NT-proBNP levels are often elevated in patients with AF, which can be used as a tool for predicting the risks of adverse outcomes such as strokes (11). There are various isoforms and metabolites of natriuretic peptides, including natriuretic brain peptide, atrial natriuretic peptide, and N-terminal pro-brain natriuretic peptide (NT-proBNP). NT-proBNP is an inactive prohormone secreted primarily by cardiac cells (17). An increase in this prohormone has been reported in patients with AF, and elevated levels of this protein are associated with an increased risk of stroke and mortality (16, 18, 19).

Despite various existing studies, a conclusion has not yet been reached about the possible use of serum NT-proBNP levels for predicting the occurrence of stroke/SEE in patients with AF. This study aims to review the evidence for evaluating the value of N-terminal pro B-type natriuretic peptide in predicting stroke/SEE in patients with atrial fibrillation through a systematic review and meta-analysis study.

2. Methods

2.1. Study design and settings

The present study is a systematic review and meta-analysis designed to evaluate the predictive value of serum NT-proBNP levels for the occurrence of stroke/SEE in patient with AF. In this study, PICO was defined as: Patients (P): Patients with atrial fibrillation, Index test (I): serum NT-proBNP levels, Comparison (C): AF patients who did not develop stroke/SEE Outcome (O): occurrence of stroke/SEE.

2.2. Search strategy

The keywords for our search were extracted with the help of experts in the field and by reviewing the titles of relevant papers. Synonyms and equivalent words were identified using MeSH and Emtree databases. The search strategy was modified based on the standard Boolean operators and standard tags of the Medline, Embase, Scopus, and Web of Science databases. Extensive searches were performed on each of the mentioned databases for papers published until De-

cember 7th, 2021 (Online Resources). Additionally, Google and Google Scholar search engines were used to search for gray literature and non-indexed material. Finally, the citations and bibliography of the eligible articles were reviewed to find any papers that might have been missed.

2.3. Selection criteria

All observational or trial studies investigating the relationship between serum NT-proBNP levels and the occurrence of stroke/SEE in patients with AF were included. Exclusion criteria were: not having a non-stroke/non-SEE group, not having a stroke/SEE as an outcome, not reporting data for NT-proBNP, not having AF as the etiology of stroke/SEE, not reporting a hazard ratio (HR), not reporting original data, not having any valuable data, study protocol publications, editorials, letter to editors, duplicates, and reviews.

2.4. Data collection

Two independent reviewers performed title and abstract screening of the potentially related articles, after which the retrieved full texts were studied, and the applicable studies were included. Finally, the information provided by the included studies was extracted into a checklist. Any dispute in this process was resolved using the opinion of a third reviewer.

The extracted data comprised study characteristics (name of the first author, year of publication, and country), study type, setting of included patients, sample size, age, gender distributions, the prevalence of underlying diseases, follow-up duration, and number of stroke/SEE patients. The predictive value of NT-proBNP in prediction of stroke/SEE was recorded as hazard ratio (HR) and 95% confidence interval (95% CI).

2.5. Risk of bias and certainty of evidence assessment

The included articles were designed as cohort studies and randomized clinical trials (RCTs). All the included articles were considered prognostic studies and thus their quality was evaluated using the Quality in Prognosis Studies (QUIPS) guidelines (20). Grading of Recommendations, Assessment, Development and Evaluations (GRADE) framework was used to evaluate the level of evidence of the included articles (21). All the evaluations were done independently by two researchers and in cases of disagreement, the third reviewer was consulted.

2.6. Statistical analysis

All analyses were performed using STATA 17.0 statistical program. The relationship between NT-proBNP serum values and occurrence of stroke/SEE was evaluated by reporting a pooled HR using the "meta" command. Heterogeneity between the included studies was assessed by using I2 statis-

tics, and while there was no heterogeneity, meta-regression was performed to analyze the data further. The effect of different cut-off values, follow-up duration, prevalence of diabetes, hypertension, heart failure and other underlying diseases of the population on the predictive value of NT-proBNP for stroke/SEE in patients with AF was investigated. A sensitivity analysis was also performed according to the quality of the included studies. Lastly, publication bias was examined using Egger's test.

3. Results

3.1. Study characteristics

The systematic search in four online databases of PubMed, Embase, Scopus and Web of Science resulted in 3,902 articles, from which 2,356 were non-duplicates. Title and abstract screening were performed on the remaining articles, 144 of which were potentially eligible. A total of 8 articles were included in this meta-analysis after the full-text screening. A manual search resulted in an additional article. Therefore, a total of 9 papers were included in our analysis (15, 22-29) (Figure 1).

Four articles had a randomized clinical trial design, and five were designed as prospective cohort studies. The studies compromised data on 38,093 patients, 21,972 of which were male. During the average follow-up time of roughly three years, 3.10% of patients experienced a stroke/SEE. The general characteristics of the included papers are summarized in Table 1.

3.2. Risk of bias and publication bias

The quality of the studies was assessed using the QUIPS assessment tool for the prognostic studies. Two studies were found to have moderate risk of bias in study participation domain due to small sample size, two studies were found to have moderate risk in study attrition domain due to no reports of samples lost to follow-up and in domain of outcome measurement two studies were found to have moderate risk and the risk of one study was classified as unclear, due to unspecific description of outcome assessment method. Risk of bias was low in all the remaining domains of the guideline (Table 2).

As for the publication bias, Egger's test was used, and the results showed that there was no publication bias in the studies regarding the prognostic use of NT-proBNP in prediction of stroke/SEE in AF patients (p= 0.320) (Figure 2).

3.3. Meta-Analysis

Relationship between NT-proBNP serum values and occurrence of stroke/SEE in patients with AF

Our analysis showed that serum levels of NT-proBNP can be a good predictor of stroke/SEE occurrence in patients with AF, even at different cut-off values (HR= 1.76; 95% CI: 1.51, 2.02; P < 0.001). A detailed presentation of the effect size for each study is shown in Figure 3. Also, no heterogeneity was reported between the included studies using the I2 statistic (I2 = 15.2%, P = 0.50)

Meta-regression

Although there was no heterogeneity between the included studies, meta-regression was done to investigate the possible effects of confounders on the predictive value of NT-proBNP (Table 3). The analysis showed that from all the investigated factors, only diabetes could have a possible effect on the predictive value of NT-proBNP (meta-regression coefficient=0.042; P = 0.037). Other factors such as cut-off values (P = 0.970), follow-up duration (P = 0.392), hypertension (P = 0.052), heart failure (P = 0.140), prior myocardial infarction (MI) (P = 0.245), history of stroke or TIA or systemic embolism (P = 0.329), previous peripheral artery disease (P = 0.591), previous coronary artery disease (P = 0.638) and sample size (P = 0.761) did not have any noticeable effect on the predictive value of NT-proBNP for occurrence of stroke/SEE in AF patients (Figure 4).

Certainty of evidence

Level of evidence were evaluated using the GRADE framework. Since the nature of assessments in the included papers were observations of prognostic value of NT-proBNP, despite the RCT design of some of them, the initial level of evidence was considered to be low. Evidence for stroke/SEE was rated to be moderate, one point increase due to the dose-response gradient effect was observed. However, evidence for stroke alone was rated as low, one point increases due to the dose-response gradient effect, and one point decrease due to the small sample size of the studies were observed. (Table 4). Summary of findings is demonstrated in table 5.

Sensitivity analysis

To assess the effects of the overall quality of the included studies on the reported effect size, we divided the studies into 2 groups of "low risk" and "unclear". The analysis showed that the reported effect size for "low risk" articles (HR = 1.774; 95% CI: 1.50, 2.05; I2 = 19.41) did not have a significant difference with the effect size reported for "unclear" articles (HR = 1.731: 95% CI: 1.02, 2.44; I2 = 20.10) (meta-regression coefficient = -0.06; 95% CI: -0.77, 0.65; P = 0.864).

4. Discussion

The current study aimed to review and summarize existing literature regarding the possible predictive applicability of serum NT-proBNP levels for predicting the occurrence of stroke/SEE in patients with AF. Our analysis showed that abnormally high serum levels of NT-proBNP, at any of the cut-off points and at any follow-up duration used by the included studies, had a significant correlation with stroke/SEE occur-

rence in patients with AF.

Although no heterogeneity was observed between the studies, we conducted a meta-regression to evaluate our results further. The value of NT-proBNP in predicting stroke/SEE in patients with AF was shown to be affected by diabetes. Therefore, diabetic patients with AF and high levels of NT-proBNP are at higher risk of stroke/SEE compared to AF patients without diabetes. It has been reported that higher levels of NT-proBNP is associated with higher rates of vascular complications among individuals who developed type 2 diabetes (30). This is a possible explanation for the confounding effect of diabetes on the predictive value of serum NT-proBNP.

Various cut-off points used by the studies did not affect the capability of serum NT-proBNP levels for prediction of stroke/SEE in patients with AF. NT-proBNP levels could be measured even with the lowest cut-off value and still be helpful in stroke/SEE prediction. The lowest cut-off used in the included studies was 169 pg/ml. Appropriately, this cut-off can be used to evaluate the risk of stroke/SEE in patients with AF.

The follow-up duration in the included studies varied between 1 and 5 years. Our results show that serum levels of NT-proBNP is a good predictor of stroke/SEE in patients with AF at any follow-up duration. Therefore, a one-time measurement of serum NT-proBNP levels during the first admission to the hospital can be a good predictor of stroke/SEE even at longer follow-ups. Considering that neither cut-off values nor follow-up duration differences influenced the predicting capabilities of serum NT-proBNP, it can be implied that measurement of NT-proBNP can be a helpful risk assessment tool in clinical settings.

To the best of our knowledge one meta-analysis has studied the association between natriuretic peptides (BNP and NT-proBNP) and atrial fibrillation (31). In their study, Hong et. al, have reported a hazard ratio of 2.53 (95% CI 2.00, 3.19) for the pooled value of BNP and NT-proBNP in prediction of stroke/SEE in AF patients; however, the predictive value of NT-proBNP alone has only been evaluated with four included studies with a reported risk ratio of 2.43 (95% CI 1.90, 3.11). Our study further solidifies the predictive value of NT-proBNP in evaluation of stroke/SEE in AF patients with a larger number of included articles and a larger sample size. Additionally, we have also considered the medical characteristics of the included populations and have provided a possible cut-off for the use of NT-proBNP in the evaluation of the risk of stroke/SEE in patients with AF.

5. Limitation

This systematic review and meta-analysis has its limitations. The primary goal of the study was to investigate the possi-

ble predictive value of serum NT-proBNP for stroke as the sole outcome; but only three studies met this criterion, while other studies had pooled the data of stroke with SEE. As a result, this study should be used cautiously in the setting of stroke alone. Further studies could shed more light on the predictive applicability of NT-proBNP for stroke as the sole outcome. Another limitation of this study was the incomplete report of some of the demographic information and the fact that the full text of one of the included articles could not be found, even after multiple email inquiries to their corresponding authors.

As for the strength of this study, it is worth noting that no heterogeneity and no publication bias were observed in the included studies. Different sample sizes of the included studies did not affect the predictive value reported by the articles; this shows that none of the included articles had insufficient sample size.

6. Conclusion

The results of our study show that there is a significant association between serum levels of NT-proBNP and the risk of stroke/SEE in patients with AF. Measurement of serum NT-proBNP can be used as a clinical tool to assess the short term or long-term risk of stroke/SEE in patients with AF during first the admission to the hospital. Despite our findings, further studies are needed to evaluate the possible applicability of serum NT-proBNP measurement in settings with stroke as the sole outcome of the investigation.

7. Declarations

7.1. Acknowledgments

Not applicable.

7.2. Conflict of interest

The authors declare that there is no conflict of interest.

7.3. Fund

7.4. Authors' contribution

Study design and conception: Yousefifard M, Azizi Y; Data gathering: All authors; Analysis: Yousefifard M; Drafting and revising: All authors.

7.5. Data availability

Data can be shared at the request of any qualified investigator for purposes of replicating procedures and results.

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Table 1: Characteristics of included studies

Study, Year, Registry, Country	Design	Participants	No. cases	Age*	Male	HF	HTN	DM	Stroke/ TIA/SE	MI	CAD	PAD	Follow-up (year)	Outcome	N event
Berg, 2018, ENGAGE AF-TIMI 48, Multinational	RCT	AF and CHADS2 score ≥2.	8705	72 (64-78)	5330	59.4	95.5	37	28	NR	34.8	4.4	2.8	Stroke/ SEE	139
Ha, 2011, NA, Korea	PCS	AF patients	200	68.9 ± 11.7	38	NR	49	18.5	15	NR	NR	NR	1.26	Stroke	14
Hamatani, 2021, FUSHIMI, Japan	PCS	AF patients w/o HF	1159	72.1 ± 10.2	718	NR	69.7	20.2	14.3	NR	13.2	8.2	5	Stroke/ SEE	113
Hijazi, 2012, RELY, Multinational	RCT	AF patients + at least one of the following risk factors: previous stroke or TIA, CHF or reduced LVEF <40%, age > 75, age > 65 with DM or HTN or CAD	6189	72 (67-77)	3944	30	78.4	21.4	19.6	17.4	24.9	NR	2.2	Stroke/ SEE	183
Hijazi, 2013, ARISTOTLE, Multinational	RCT	AF and at least 1 CHADS2 risk factor	14892	69 (62-75)	9590	35.9	87.5	30.9	18.7	12.8	NR	4.9	1.9	Stroke/ SEE	393
Kuronuma, 2020, SAKURA, Japan	PCS	Non-valvular AF, >20 year, receiving oral anticoagulant	2417	72 (66-79)	1777	25.9	72.3	23.5	11.4	NR	NR	NR	3.25	Stroke/ SEE	107
Roldan, 2014, NA, Spain	PCS	Permanent or paroxysmal AF patients, taking OAC with stable INR for > 6 months	1172	76 (71-81)	575	30	82	26	19	NR	19	NR	2.75	Stroke/ SEE	51
Singleton, 2019, REGARDS, USA	PCS	AF patients	175	66 ± 9	NR	NR	NR	NR	NR	NR	NR	NR	5.2	Stroke	81
Tomasdottir, 2021, AVEROES & ACTIVE A, Multinational	RCT	AF patients, receiving aspirin with no oral anticoagulation	3184	NR	NR	NR	NR	NR	NR	NR	NR	NR	2.5	Stroke	NR

* Age was reported as mean ± SD or median (interquartile range). Data of medical history were reported as a percentage of the whole population. RCT: Randomized Clinical Trial, PCS: Prospective Cohort Study, HF: Heart Failure, HTN: Hypertension, DM: Diabetes Mellitus, TIA: Transient Ischemic Attack, SEE: Systemic Embolic Event, MI: Myocardial Infarction, CAD: Coronary Artery Disease, PAD: Peripheral Artery Disease; NR: not reported; AF: atrial fibrillation; CHADS: Congestive heart failure, Hypertension, Age, Diabetes, prior Stroke; CHF: congestive heart failure; LVEF: left ventricular ejection fraction; OAC: oral anticoagulant; INR: international normalized ratio.

Table 2: Risk of bias assessment

| Study	Study Participation	Study Attrition	Prognostic Factor Measurement	Outcome Measurement	Study Confounding	Statistical Analysis/ Reporting
Berg, 2018	Low	Low	Low	Low	Low	Low
Ha, 2011	Moderate	Low	Low	Moderate	Low	Low
Hamatani, 2021	Low	Moderate	Low	Moderate	Low	Low
Hijazi, 2012	Low	Low	Low	Low	Low	Low
Hijazi, 2013	Low	Low	Low	Low	Low	Low
Kuronama, 2020	Low	Moderate	Low	Unclear	Low	Low
Roldan, 2014	Low	Low	Low	Low	Low	Low
Singleton, 2019	Moderate	Low	Low	Low	Low	Low
Tomasdottir, 2021	Low	Low	Low	Low	Low	Low
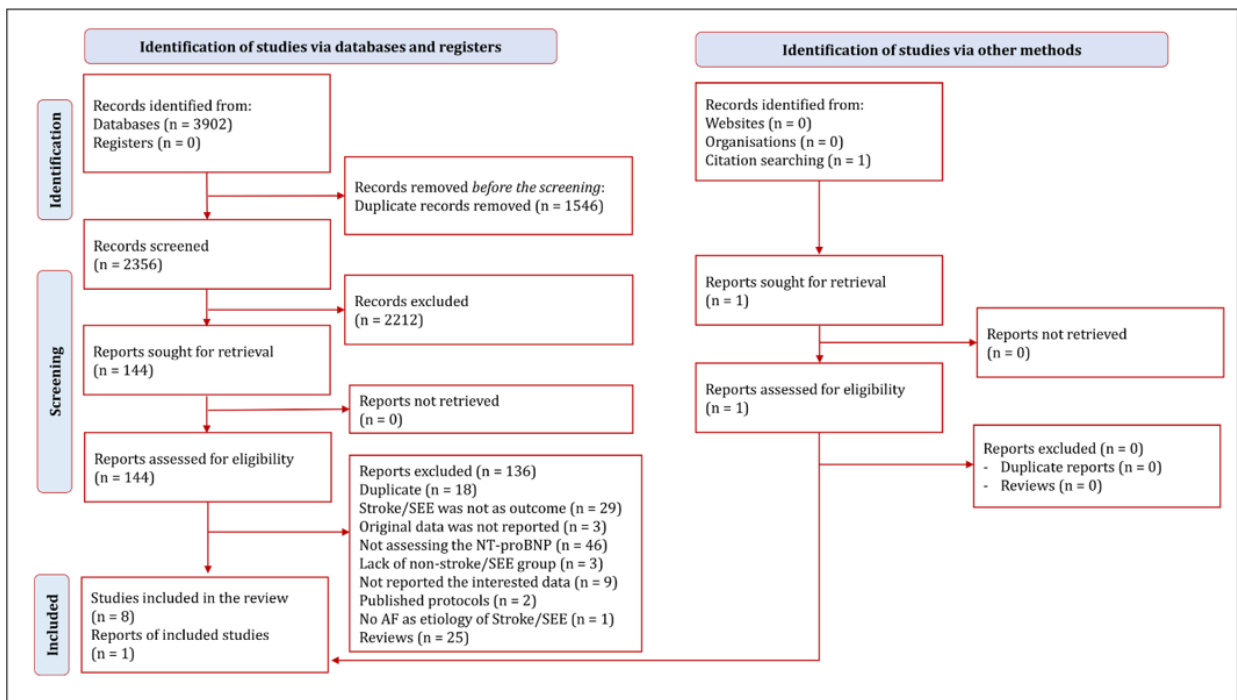
Figure 1: PRISMA flow diagram of the present study. SEE: Systemic Embolic Event; AF: atrial fibrillation.
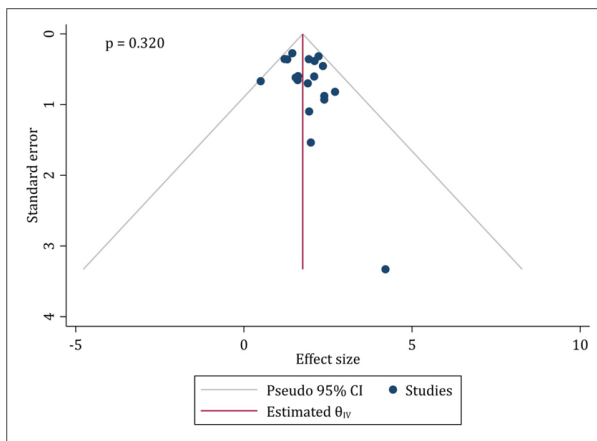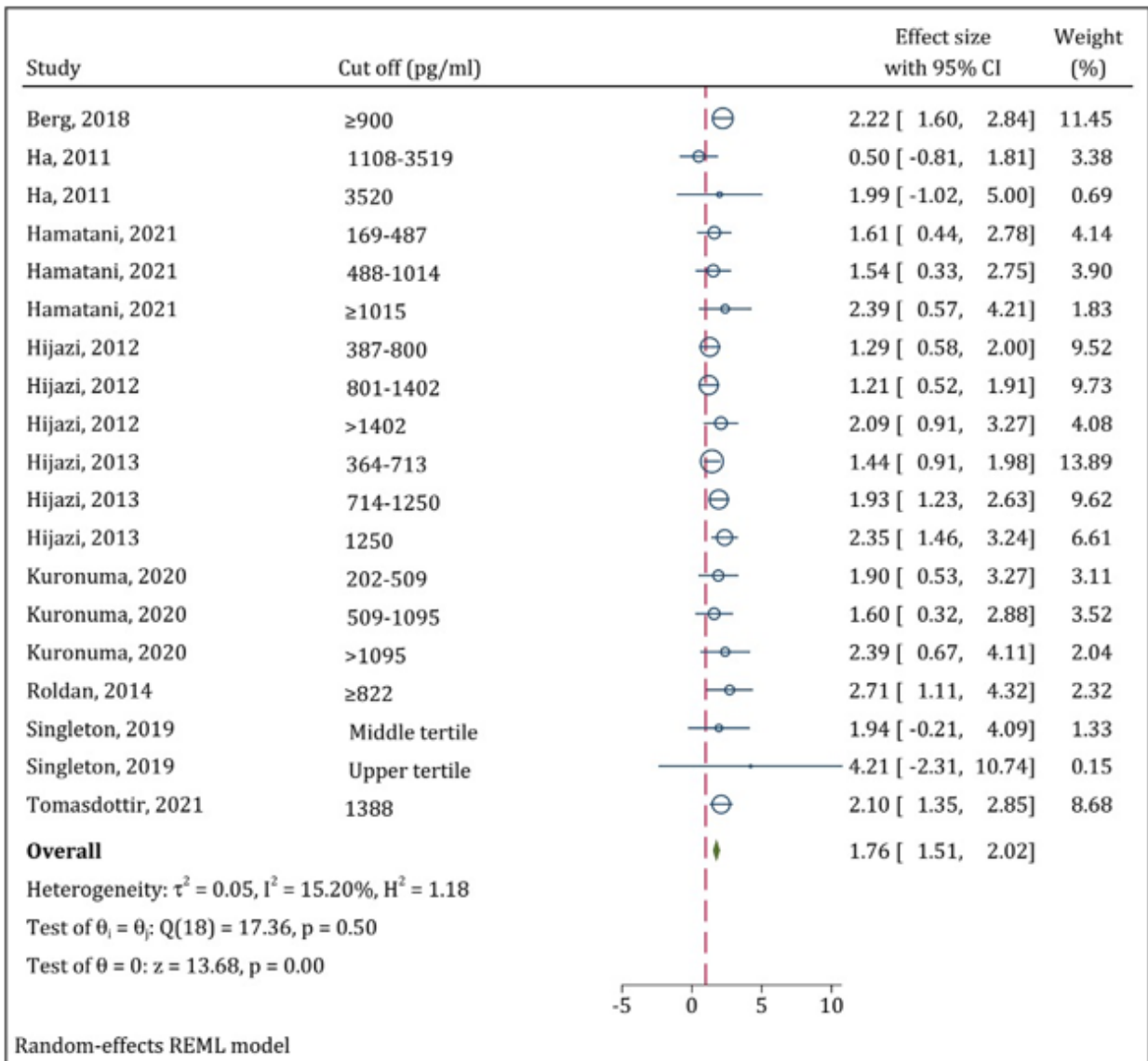

Figure 2: Assessment of publication bias.

Figure 3: Effect size of the predictive effect of NT-proBNP in different cut-off values for the occurrence of stroke/SEE in AF patients.

Table 3: Meta-regression analysis for the effect of confounding factors on the predictive value of NT-proBNP for the occurrence of stroke/Systemic embolic events (SEE) in patients with atrial fibrillation

Variable	Meta-regression coef.	95% CI	P value
Cut-off point	0.00001	-0.00055, 0.00057	0.970
Follow-up duration	0.11156	-0.14374, 0.36687	0.392
Diabetes	0.04203	0.00253, 0.08153	0.037
Hypertension	0.02357	-0.00023, 0.04738	0.052
Heart Failure	0.01932	-0.00635, 0.04500	0.140
Prior MI	-0.08606	-0.23119, 0.05907	0.245
Stroke/TIA/SEE	0.02979	-0.03008, 0.08967	0.329
Peripheral Artery Disease	-0.07108	-0.33050, 0.18833	0.591
Coronary Artery Disease	0.01336	-0.04233, 0.06906	0.638
Sample Size	0.00001	-0.00004, 0.00005	0.761

CI: confidence interval; coef.: coefficient; TIA: Transient Ischemic Attack; MI: Myocardial Infarction.
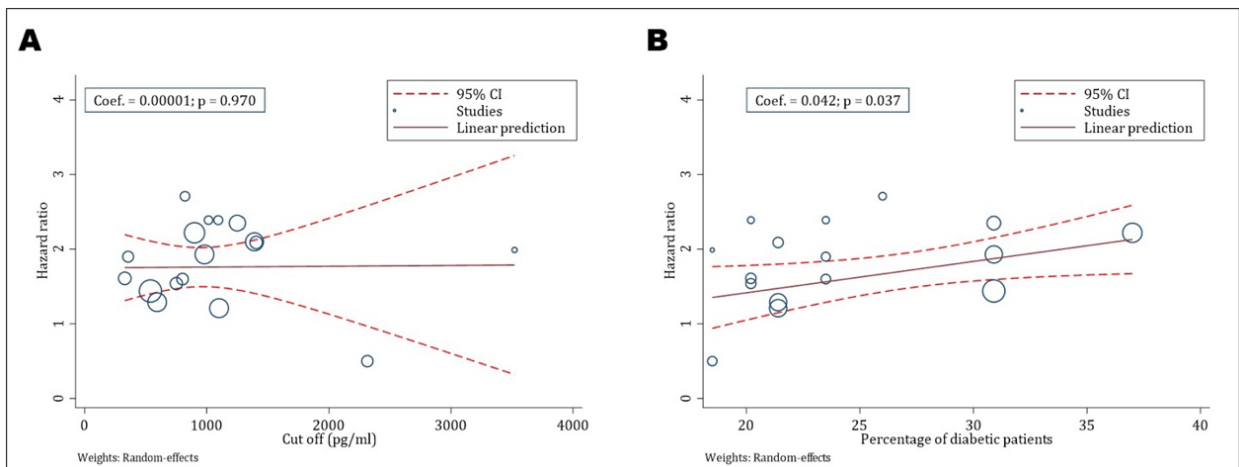
Figure 4: Meta-regression for assessment of the effect of cut-off values (A) and percentage of diabetic patients (B) in included studies on the occurrence of stroke/SEE following atrial fibrillation.

Table 4: Certainty of Evidence

Outcome	Number of studies (analysis)	N	N event	Quality of Evidence
Stroke/SEE	6 (14)	34534	986	Moderate ⊕⊕⊕⊕ + dose-response gradient
Stroke	3 (5)	375 (+3184)	95 (+NR)	Low ⊕⊕⊕⊕⊝ +dose-response gradient - small sample size

SEE: systemic embolic events; NR: Not Reported; N: sample size.