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Role of N-terminal pro-B type natriuretic peptide as a predictor of poor outcomes in patients with HFrEF receiving primary prevention implantable cardioverter-defibrillator therapy: a systematic review and dose–response meta-analysis

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ABSTRACT

Introduction Several studies have demonstrated that combining left ventricular ejection fraction and New York Heart Association functional class is insufficient for predicting risk of appropriate implantable cardioverter-defibrillator (ICD) shock in primary prevention candidates. Hence, our aim was to assess the relationship between N-terminal pro-B type natriuretic peptide (NT-pro BNP) along with appropriate ICD shock and all-cause mortality in order to improve the stratification process of patients with heart failure with reduced ejection fraction (HFrEF) being considered for primary preventive ICD therapy.

Methods A systematic literature search from several databases was conducted up until 9 June 2022. Studies were eligible if they investigated the relationship of NT-pro BNP with all-cause mortality and appropriate ICD shock.

Results This meta-analysis comprised nine studies with a total of 5117 participants. Our study revealed that high levels of NT-pro BNP were associated with all-cause mortality (HR=2.12 (95% CI=1.53 to 2.93); p<0.001, I^2=78.1%, p<0.001 for heterogeneity) and appropriate ICD shock (HR=1.71 (95% CI=1.18 to 2.49); p<0.001, I^2=43.4%, p=0.102 for heterogeneity). The adjusted HR for all-cause mortality and appropriate ICD shock increased by approximately 3% and 5%, respectively per 100 pg/mL increment pursuant to concentration–response model ($P_{non\text{-}linearity}$ <0.001). The curves became steeper after NT-pro BNP reached its inflection point (3000 pg/mL).

Conclusion A positive concentration-dependent association between elevated NT-pro BNP levels along with the risk of all-cause mortality and appropriate ICD shock was found in patients with HFrEF with ICD.

PROSPERO registration number CRD42022339285.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ According to several studies, NYHA functional class and LVEF are insufficient for independently stratifying HFrEF patients who are candidates for primary preventive ICD placement. Additionally, the prognostic significance of NT-pro BNP remains unexplored in HFrEF patients with ICD.

WHAT THIS STUDY ADDS

⇒ High NT-pro BNP levels in HFrEF patients with ICD significantly increased the risk of all-cause mortality and appropriate ICD shock by nearly twofold compared to those with lower NT-pro BNP levels. Furthermore, we discovered a concentration-response relationship between NT-pro BNP and outcomes of interest.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ NT-pro BNP should be used as an additional stratification criterion alongside LVEF and NYHA in identifying the most qualified patients with HFrEF in terms of ICD therapy for primary prevention.

INTRODUCTION

According to the most recent European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines of heart failure (HF), implantable cardioverter-defibrillator (ICD) implantation remains the mainstay therapy to avert sudden cardiac death (SCD) in symptomatic patients with HF (NYHA (New York Heart Association) functional class II–III) with severely reduced left

ventricular ejection fraction (LVEF ≤35%), despite more than 3 months of optimal medical treatment.[1 2]

Interestingly, several shreds of evidence have emphasised that LVEF and NYHA criteria are insufficient for independently stratifying patients with heart failure with reduced ejection fraction (HFrEF) who are candidates for primary preventive ICD placement. Zeitler *et al* perform the prospective study by recruiting a combination study population from the Multicenter Automatic Defibrillator Implantation Trial-II trial and the Sudden Cardiac Death-Heart Failure Trial. It revealed that only 19.5% of patients with HF received at least one appropriate ICD shocks during a median follow-up of 2.59 years.[3] Similarly, in 2020, the EUropean Comparative Effectiveness Research to Assess the Use of Primary ProphylacTic Implantable Cardioverter-Defibrillators, a multicentre cohort study that recruited 1516 patients with HF being investigated for primary prevention ICD treatment, discovered that only 7% of patients with HF received at least one appropriate ICD shock during a median period of 2.5 years.[4] Consistently, a prospective cohort study conducted by Rosenkaimer *et al* found that only 13% of primary prevention candidates received appropriate ICD shocks during approximately 36 months of follow-up.[5] Hence, due to the sheer poor sensitivity and specificity of using the LVEF and NYHA criteria as the preferred means of SCD risk stratification, many people who undergo ICD receive minimal benefit while also possibly failing to detect those who are truly at high risk of SCD.

Not to mention, there are a number of concerns associated with ICD implantation (eg, thrombosis, infection, inappropriate shocks and so on) that might affect the patients' quality of life.[6] Furthermore, not all regions have offered insurance coverage for ICD implantation in this group, particularly in Indonesia. It implies that further risk stratification for SCD in patients with HFrEF is urgently needed to assist clinicians in selecting the primary prevention candidates who may benefit the most from ICD implantation, thereby lowering the cost burden and diminishing the occurrence of complications related to ICD implantation in patients who benefit less from primary prevention ICD therapy.

It has been demonstrated that N-terminal pro-B type natriuretic peptide (NT-pro BNP) is playing a pivotal role in diagnosing, determining disease severity, treatment planning and therapeutic monitoring in HF.[1 7] This biomarker's use has grown significantly as it was previously only capable of predicting all-cause mortality and HF hospitalisation in patients with HF. According to two studies, an increase in natriuretic peptide levels is also related to an increased risk of SCD in patients with HFrEF.[8–10] As a result, NT-pro BNP might theoretically be used for risk classification in patients with HFrEF who are eligible for primary preventive ICD treatment. Accordingly, several cohort studies have shown that measuring NT-pro BNP is effective in predicting the likelihood of appropriate ICD shock and all-cause mortality in primary prevention candidates, despite the ambiguous relationship between these two entities.[11–18] Thus, this meta-analysis aims to evaluate the association between NT-pro BNP along with appropriate ICD shock and all-cause mortality in patients with HFrEF who received ICD implantation as primary prevention of SCD.

MATERIALS AND METHODS

Protocol and registration

This meta-analysis was registered to the PROSPERO database and conformed to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines.[19]

Search strategy

Two authors independently conducted a systematic literature search in different electronic databases (PubMed, Europe PMC and ScienceDirect) from conception to 9 June 2022) using the keywords ("BNP" [all fields] OR "B-type Natriuretic Peptide" [all fields]) AND ("implantable cardioverter defibrillator" [all fields] OR "ICD" [all fields] OR ("cardiac resynchronization therapy defibrillator" [all fields] OR "CRT-D" [all fields]). We proceed with duplication elimination using Mendeley software V.1.19.8 after assembling records from the initial search. Following that, the remaining papers were manually evaluated for eligibility based on their titles and abstracts, and relevance was determined based on full-text eligibility. We did not include words relevant to our outcomes of interest to acquire the greatest number of search results. Disagreement between two independent authors was resolved through discussion. Our search followed the PRISMA guidelines, and the search and screening processes are depicted in figure 1.

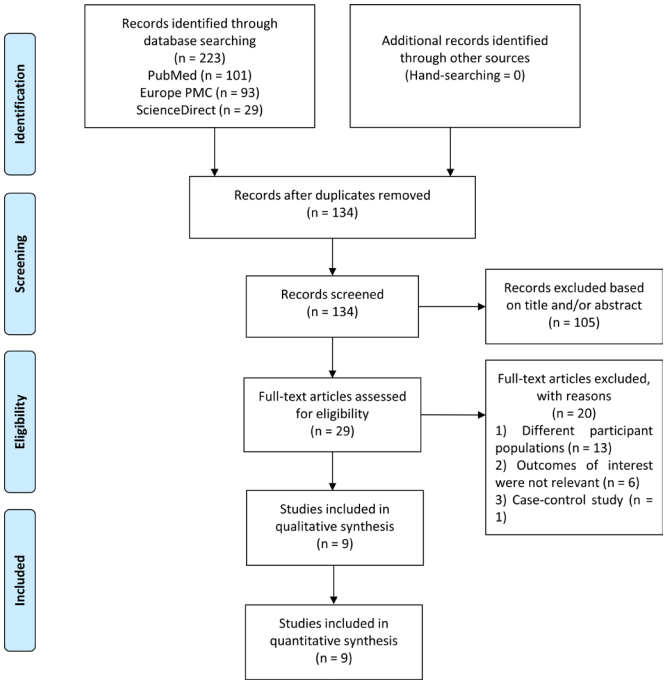

Figure 1 Flow chart of study selection.

Eligibility criteria

Included studies were restricted to relevant articles concerning the relationship of NT-pro BNP with all-cause mortality and appropriate ICD shock in patients with HFrEF with ICD. The articles had to be either prospective or retrospective observational studies, and they had to disclose risk estimates with the corresponding 95% CI or adequate data to generate the effect size. For a dose–response meta-analysis, the study must provide risk estimates at three or more quantitative categorised levels. Studies that did not report sufficient of the aforementioned data were omitted from our analysis. Review papers, editorials, comments, case reports/series, meta-analysis, conference abstracts and studies written in languages other than English were excluded from our meta-analysis.

Data extraction and quality assessment

The pertinent data from the selected studies were then retrieved by two separate authors using a predesigned table. Extracted data comprised baseline and methodological features of the studies involving first author's name, publication year, the country in which study was conducted, study design, total participants, study population, ICD implantation criteria, age, sex and study outcomes.

Our study population included any patients with HFrEF who had an ICD implanted for primary prevention purpose (patients who had not been resuscitated for SCD owing to documented ventricular tachycardia (VT) or ventricular fibrillation (VF)). All-cause mortality, defined as clinically validated death or non-survivor in patients with HF with ICD due to any underlying causes, was of our outcomes of interest. Furthermore, the secondary endpoint of our study was appropriate ICD shock, which was defined as shock delivered for true ventricular tachyarrhythmias (VT/VF).[11]

Two independent authors assessed the risk of bias using the Newcastle-Ottawa Scale (NOS). NOS has eight questions, each with its own score, divided into three sections: selection, comparability and result. If an included study has a total score of seven or higher, it is considered to have a low risk of bias. Those who had a total score of six or less were considered to have a considerable risk of bias. Any discrepancies among the authors were addressed through discussion.[20]

Statistical analysis

All statistical analyses were performed using STATA (Software for Statistics and Data Science) software V.17.0. A comparison between the highest versus lowest NT-pro BNP categories in terms of all-cause mortality and appropriate ICD shock event was performed using restricted-likelihood random-effects meta-analysis regardless of its heterogeneity.[21 22] The effect size in the current analysis was calculated as HR with 95% CIs. All statistical analyses were two-sided, with a p value of <0.05 indicating statistical significance. Moreover, the I^2 method was used to examine inter-study heterogeneity, and an I^2 statistic >50% or p value <0.10 indicated significant heterogeneity.[23] When significant heterogeneity was observed, a sensitivity analysis was carried out using the leave-one-out or leave-two-out procedures to determine the cause of heterogeneity. The leave-one-out and leave-two-out strategies were used to determine which study was responsible for increased heterogeneity by eliminating each included study and two included studies one at a time.[24] A dose–response meta-analysis includes studies with at least three NT-pro BNP values observed. We used the lowest category of circulating NT-pro BNP concentration as a reference concentration in each study. We used generalised least-squares regression to analyse the trend estimate across categories for NT-pro BNP. Each HR in every study was generated using restricted cubic splines with three knots per 500 pg/mL increment in NT-pro BNP concentration.[25] Eventually, Begg's funnel plot analysis and Egger's test were employed to investigate the publication bias in both qualitative and quantitative ways throughout our study. Begg's funnel plot analysis, on the other hand, should be used only when there are at least 10 studies included in the meta-analysis, because the power of the tests is too low to distinguish chance from true asymmetry when there are fewer studies.[23]

RESULTS

Study selection and baseline characteristics

The preliminary search revealed 223 studies in total. Following a screening of abstracts, titles and duplicates, 89 irrelevant studies were excluded, leaving 134 acceptable studies for a screening procedure based on the predetermined inclusion criteria. Conclusively, after detailed consideration, nine studies were chosen for final inclusion, with a total of 5117 participants incorporated in this meta-analysis (figure 1).[11–18 26] The participant in this research had a mean age of 62.4 years, whereas 76.4% of the participants were men. Amid the overall patients, the aetiology of 48.5% patients was ischaemic and the mean duration of follow-up was 3.6 years. Baseline characteristics of the included studies were provided in online supplemental table 1.

NT-pro BNP and all-cause mortality

In patients with HF with ICD, greater NT-pro BNP levels were generally linked with all-cause mortality (HR=2.12 (95% CI=1.53 to 2.93); p<0.001), but with considerable heterogeneity (I^2=78.1%, p<0.001 for heterogeneity) (figure 2A). Succeeding a leave-one-out analysis, however, revealed that two studies[14 15] markedly increased heterogeneity within the included studies. Following the withdrawal of the aforementioned studies, heterogeneity fell substantially (I^2=0%, p=0.587 for heterogeneity), and the pooled effect size remained statistically significant (HR=1.57 (95% CI=1.40 to 1.76); p<0.001).

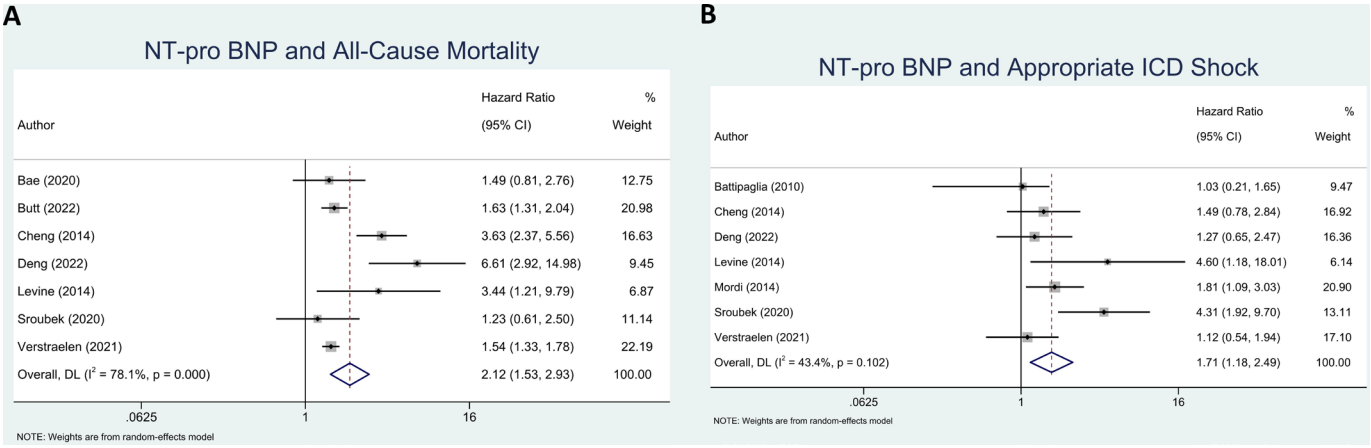

Figure 2 Forest plot showing an association between high NT-pro BNP with all-cause mortality (A) and appropriate ICD shock (B). ICD, implantable cardioverter-defibrillator; NT-pro BNP, N-terminal pro-B type natriuretic peptide.

NT-pro BNP and appropriate ICD shock

Compared with participants within the lower group of NT-pro BNP, individuals with higher NT-pro BNP levels had a significantly increased risk of appropriate ICD shock (HR=1.71 (95% CI=1.18 to 2.49); p<0.001), with a low degree of heterogeneity observed across the included studies (I^2=43.4%, p=0.102 for heterogeneity) (figure 2B).

Dose–response meta-analysis

Every included study that fitted our outcomes of interest was eligible for inclusion in the dose–response meta-analysis. The total HR of all-cause mortality risk per 500 pg/mL increment in NT-pro BNP was (HR=1.22 (95% CI=1.10 to 1.33)) and (HR=1.34 (95% CI=1.22 to 1.45)) for risk of appropriate ICD shock. Apart from linearity occurring at NT-pro BNP of 3000 pg/mL and the curves becoming steeper, a non-linear connection ($P_{non\text{-}linearity}$<0.001) was detected between NT-pro BNP and both of our outcomes of interest in our research population. Using NT-pro BNP of 500 pg/mL as the increment value, the HR for patients with NT-pro BNP of 1000, 1500, 2000 and 2500 pg/mL were 1.22 (1.10 to 1.33), 1.43 (1.21 to 1.64), 1.62 (1.31 to 1.94), 1.80 (1.40 to 2.20) for all-cause mortality (figure 3A) and 1.34 (1.22 to 1.45), 1.66 (1.44 to 1.88), 1.94 (1.62 to 2.25), 2.15 (1.78 to 2.52) for appropriate ICD shock (figure 3B), respectively.

Risk of bias assessment

The NOS, with an average NOS score of 8.9±0.4, suggests a low likelihood of bias (online supplemental table 2). Finally, since the number of studies in each outcome was rather small (<10 studies), Begg's funnel plot could not be used to establish publication bias across the included research. Hence, Egger's test was used and revealed no evidence of small study effects across all outcomes in this meta-analysis (p=0.538 for all-cause mortality and p=0.555 for appropriate ICD shock).

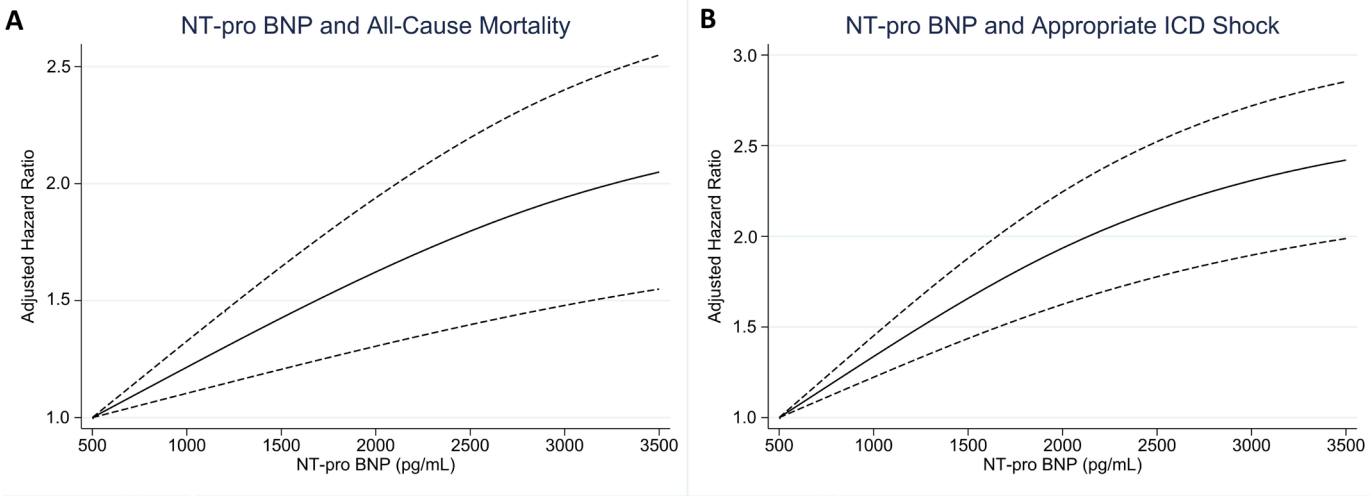

Figure 3 Dose–response meta-analysis of NT-pro BNP and all-cause mortality (A) and appropriate ICD shock (B) in a random-effects concentration–response model using restricted cubic splines. The relation of the NT-pro BNP with the risk of our outcomes of interest is represented by a HR (solid line) with a 95% CI (long-dashed lines). ICD, implantable cardioverter-defibrillator; NT-pro BNP, N-terminal pro-B type natriuretic peptide.

DISCUSSION

The prognostic significance of NT-pro BNP in patients with HFrEF has been thoroughly established, however, it remains mainly unexplored in patients with HFrEF with ICD. Thus, we performed a meta-analysis evaluating the use of NT-pro BNP to predict all-cause mortality and appropriate ICD shock, which included data from approximately 5000 patients with HFrEF treated with ICD. Several key findings arose from this meta-analysis. To begin, in patients with HFrEF with ICD, a raised NT-pro BNP levels had a nearly twofold increase in the risk of all-cause mortality and appropriate ICD shock as compared with those with a lower NT-pro BNP levels, with a mean duration of follow-up 3.6 years. Second, we discovered a concentration–response relationship between NT-pro BNP and appropriate ICD shock as well as all-cause mortality. However, given its stagnant trends when NT-pro BNP levels reach above the inflection point (3000 pg/mL in both outcomes of interest), it appears that NT-pro BNP has a ceiling effect, which means that an exceedingly high NT-pro BNP value does not necessarily translate into an extremely high risk of composite poor outcomes. Therefore, it justifies the convention that NT-pro BNP should be used as an additional stratification criterion alongside LVEF and NYHA in identifying the most qualified patients with HFrEF in terms of ICD therapy for primary prevention.

The pathophysiological relationship between NT-pro BNP increases and ventricular tachyarrhythmia in HF is poorly understood, but biologically plausible. NT-pro BNP is mostly released from the ventricles in response to increases in intraventricular pressure induced by pooling of the blood inside the ventricle due to left ventricular dysfunction, triggering myocardial stretch. Alterations in ventricular pressure and shape also trigger depolarising cation channels in cardiomyocytes, resulting in electrophysiological changes that may contribute to enhanced arrhythmogenesis, such as dispersed refractoriness and early after depolarisations, which may lead to lethal arrhythmic events.[27 28] As the amount of myocardial expansion directly affects the level of NT-pro BNP, and arrhythmogenesis is initiated due to the myocardial dilatation process, measurement of this peptide might conceivably predict the risk of ventricular tachyarrhythmia in patients with HFrEF.[29]

Despite presenting with satisfying results, it should be emphasised that NT-pro BNP is not only increased with the severity of HFrEF condition, but other cardiac (eg, valvular heart disease, myocarditis, atrial fibrillation and so on) and non-cardiac factors (eg, age, female gender, renal dysfunction, pulmonary embolism, sepsis, severe burns, haemodynamic profile and so on) may also play a role in elevating natriuretic peptide levels.[30 31] Regarding these numerous factors that may affect the NT-pro BNP levels, it seems impossible to rule them all out. Moreover, compared with patients with HFrEF with low NT-pro BNP levels, those with high NT-pro BNP levels were older, and tended to have more comorbidities (hypertension, diabetes mellitus, atrial fibrillation, valvular heart disease and kidney dysfunction), as well as presented with lower LVEF, higher NYHA functional class and more HF hospitalisation.[12 14 15 18] Fortunately, as most of the included studies were adjusted for several confounding variables and only adjusted HRs were incorporated into the analysis, we can fairly infer that NT-pro BNP was independently correlated with all-cause mortality, thereby reducing the confounding bias.

To the best of our knowledge, no prior study has particularly investigated the predictive value of NT-pro BNP in prognosticating all-cause mortality and appropriate ICD shock in patients with HFrEF eligible for primary prevention therapy of ICD. The fact that a single NT-pro BNP determination was an independent predictor of these composite poor outcomes, the association between NT-pro BNP and all-cause mortality, however, exhibits a moderate-high heterogeneity (figure 2A). Exploration of heterogeneity should ideally be undertaken using meta-regression and subgroup analysis, although this is implausible due to a paucity of research. Hence, the leave-one-out sensitivity analysis was carried out, and it was discovered that two studies[14 15] were deemed as the primary contributors to the high inter-study heterogeneity. This can be explained by the fact that Cheng *et al* and Deng *et al* investigations have an increased prevalence of hypertension and diabetes, which are conceded as substantial independent risk factors for mortality.[32] Though being adjusted in their multivariate analyses, this should be emphasised that hypertension in both studies and diabetes in Deng *et al* study disclose statistically significant differences amid their interquartile populations, unlike other included studies, by such means contributing to a considerable heterogeneity within the analysis. Nonetheless, the result of our meta-analysis was fairly robust in the leave-one-out sensitivity analysis; removal of any single study did not alter the statistical significance of the pooled estimate, indicating that our results were stable and reliable.

As a matter of concern, various HF aetiologies within our study population also warrant a further discussion. In contrast to ischaemic cardiomyopathy (ICM), primary preventive ICD therapy in patients with non-ischaemic cardiomyopathy (NICM) is still in a moot point. The AHA and the ESC were unable to reach an agreement regarding this matter. According to the AHA guideline, patients with NICM still receive recommendation class I for ICD treatment for primary prevention.[2] In contrast, the recent ESC guideline has degraded its recommendation to class IIa.[1] The basis for this contentious issue is that the recent The Danish Study to Assess the Efficacy of Implantable Cardioverter-Defibrillators in Patients with Non-ischemic Systolic Heart Failure on Mortality trial revealed that ICD implantation for primary prevention did not substantially reduce all-cause mortality risk in patients with NICM after a median follow-up of 9.5 years.[33] Aside from the previously stated stretch-induced

arrhythmia mechanism, scar formation resulting from a prior myocardial infarction can also result in ventricular tachyarrhythmias in patients with HF, implying that NT-pro BNP as a parameter of ventricular dilatation may not be solely correlated with appropriate ICD shock in patients with ICM.[34] Hence, it is reasonable to discriminate the study population into two distinct HF entities (ICM and NICM) to ascertain whether NT-pro BNP can assist LVEF in stratifying for primary SCD prevention, especially in NICM population. However, a large cohort study conducted by Deng *et al* suggests that HF aetiology (ICM and NICM) had no effect on the significant correlation between NT-pro BNP and appropriate ICD shock in patients with HF based on their multivariate analysis.[15] Unfortunately, since the majority of our included studies recruited the whole HF population, subgroup analysis was not possible in this meta-analysis.[11 13–18]

In regard to addressing the aforementioned dispute, Mirelis *et al* conducted a cohort study in which they demonstrated that the combination of late gadolinium enhancement from cardiac magnetic resonance (CMR) and positive genotype was useful in predicting SCD risk in patients with NICM and thus capable of stratifying the most qualified patients who benefit the most from primary prevention ICD therapy in this population. However, because CMR and genetic laboratories are time-consuming and hardly available in most healthcare institutions, as well as the restricted usage of gadolinium contrast in patients with end-stage renal disease, NT-pro BNP is still preferable to be used.[17 35] Thus, more cohort studies evaluating the predictive efficacy of NT-pro BNP in ICM and NICM are highly needed to better understand the role of NT-pro BNP in stratifying patients with HFrEF who would benefit the most from ICD implantation for primary prevention.

Additionally, as ventricular arrhythmias were deemed as the primary mode of death in patients with HFrEF, several studies are being pursued with fervour to identify a pharmaceutical strategy for lowering the incidence of SCD in such population. Therefore, several novel HF drugs, namely sodium-glucose cotransporter 2 inhibitor (SGLT2i) and angiotensin receptor neprilysin inhibitor (ARNI) were proposed into various tenable hypotheses to likely reduce the risk of this lethal arrhythmic events.[1 2 36 37] Although ARNI usage was opted in Deng *et al* study,[15] the association between these two variables failed to reach statistical significance, despite the fact that none of our included studies involved SGLT2i into their analysis given to the novelty of this drug. Thus, we also recommend further large cohort studies addressing patients with HFrEF who receive these state-of-the-art medications to thoroughly evaluate the relationship between NT-pro BNP and SCD in patients with HFrEF with ICD implantation under the influence of these treatments.

Several limitations still warrant consideration in this meta-analysis. First, four of nine included studies were retrospective cohorts; hence, it increases the likelihood of recall and selection bias. Second, several confounding factors that alter NT-pro BNP levels are not entirely excluded by all included studies, thereby increasing the possibility of bias. Third, the dynamic variations in NT-pro BNP caused by several aforementioned factors, which represent the variability of ventricular dilatation degree, might increase the risk of ventricular arrhythmic events over time. However, our analysis was confined to investigating the prognostic value of baseline NT-pro BNP. As a result, it may overestimate or underestimate the likelihood of our outcomes of interest. Lastly, several observational studies that studied the connection between NT-pro BNP along with all-cause mortality and appropriate ICD shock in patients with ICM and NICM separately are utmost important in light of this debatable subject about the indication of primary preventive ICD treatment in NICM population.

CONCLUSION

In conclusion, this meta-analysis found that all-cause mortality rates and appropriate ICD shock rose as baseline NT-pro BNP levels increased, indicating a concentration–response interconnection. Therefore, we propose that NT-pro BNP should be included into future studies as a factor that may be helpful in diagnosing those who might benefit from ICD therapy. Finally, more cohort studies evaluating the predictive value of NT-pro BNP in ICM and NICM separately are utmost needed to increase the utility of NT-pro BNP as a prognosticator of poorer outcomes in patients with HFrEF who underwent ICD implantation as the main prevention for SCD.

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Contributors HSP and ICSP conceived and design the study. ICSP, WK and RP performed study selection, data extraction and interpreted the data. HSP, ICSP, WK and RP performed extensive search of relevant topics. ICSP, WK and RP performed statistical analysis. MI, GK, MP, NYK, CA, JWM and MRA performed review and extensive editing of the manuscript. All authors contributed significantly to the writing of the manuscript. All authors approved the final manuscript. All authors accept full responsibility for the work and/or the conduct of the study, had access to the data, and controlled the decision to publish.

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