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REVIEW

Natriuretic peptides: biomarkers for atrial fibrillation management

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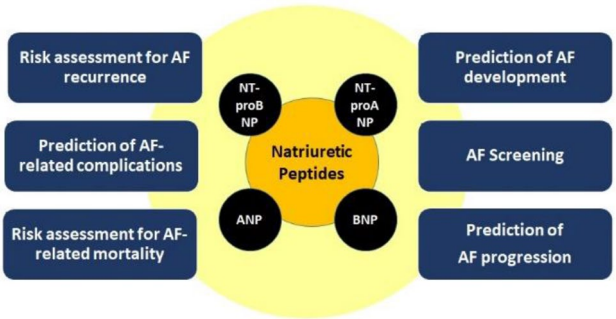
Abstract

In clinical practice, atrial fibrillation (AF) is known as the most common sustained arrhythmia. Therefore, identification of individuals at risk of AF development/recurrence or its associated complications has emerged as a hot topic in the field of cardiology. Recently, several biomarkers have been introduced to predict AF and its consequences; however, use of biomarkers in AF management has not been highly recommended by guidelines yet. While utilization of natriuretic peptides (NPs) including brain (B-type) NPs (BNPs) in heart failure management has been well established, their use in relation to AF has not been fully understood. Accordingly, this review article aimed at presenting an overview of the role of NPs in predicting AF development/recurrence as well as its complications and making suggestions for their use in management of patients with AF in clinical settings.

Graphic abstract



Keywords Atrial fibrillation · Natriuretic peptide · BNP · NT-ProBNP · B-Type natriuretic peptide · Biomarker

Introduction

Atrial fibrillation (AF) is known as the most common sustained arrhythmia in clinical practice; estimated to have a prevalence rate of around 18 million people in Europe by 2060 [1]. AF is associated with serious complications including strokes, thromboembolism, and cognitive impairments that can influence patients' quality of life and impose higher medical care costs [2–5]. Nowadays, identification of individuals at risk of AF development or its associated complications as well as prediction of AF recurrence has emerged as a hot topic in the field of cardiac electrophysiology [6, 7].

Biomarkers, as indicators of biological or pathological states and even therapeutic responses, are frequently employed in the management of various cardiovascular diseases (CVDs) [8, 9]. In recent years, several biomarkers have also been identified with their own substantial importance in prediction of AF and its consequences [10]. However, routine use of biomarkers to manage patients with AF has not

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been highly recommended by available guidelines; limited only to refining risk of stroke and bleeding with Class IIb of recommendations [11, 12]. Nevertheless, biomarkers can play not only a substantial role in identifying patients with increased risk of AF occurrence/recurrence or complications but also in understanding causes and mechanisms of these scenarios.

Natriuretic peptides (NPs) refer to a class of cardiac neurohormones secreted from myocardium cells mostly in response to increased wall tension due to pressure or volume overload [13]. The value of NPs as biomarkers useful for CVDs was first described in patients with heart failure and continued in those with acute coronary syndrome (ACS) presentations [14]. Over the past decade, there has also been growing evidence on use of atrial NPs (ANPs), brain (B-type) NPs (BNPs), and N-terminal pro-B-type NP (NT-proBNP) in AF [15–18]. Although utilization of NPs in heart failure management has been well established, importance of these biomarkers in relation to AF has not been fully understood yet. Accordingly, better understanding of the role of NPs in AF management may thus facilitate integration of these widely available biomarkers in clinical applications. Therefore, this review article aimed at presenting an overview of the role of NPs in predicting AF development/recurrence as well as complications and making suggestions for their use in management of patients with AF in clinical settings.

AF development

General population

An association between high NP levels and an increased risk of AF incidence has been shown in different community-based cohorts (Table 1). Moreover, most of the conducted studies revealed that increased levels of these peptides, mainly NT-proBNPs, could remarkably improve the AF risk prediction beyond clinical factors (Table 1). NT-proBNPs have also been introduced as the only predictors of incident AF in two cohorts among the variety of other biomarkers including high-sensitivity cardiac troponin, cystatin-C, growth differentiation factor-15, and high-sensitivity C-reactive protein; once adjusted for cardiovascular risk factors and other biomarkers [18]. An association between longitudinal changes in concentrations and AF development was correspondingly investigated for the first time in a recently published study on 9705 individuals without AF during a median follow-up period of 16 years. This study showed that greater increases in NT-proBNP levels could be correlated with more growth in incident AF (hazard ratio (HR) 2.82), and NT-proBNP addition could change into a predictive model leading to an improvement in AF prediction [19].

However, there are still many doubts about the practical use of NPs for AF prediction in a population-based setting. We believe that the risk prediction model resulted from the CHARGE-AF consortium of community-based cohort studies which is one example of the efforts made to address these doubts [20]. This belief is based on the facts that: (1) this risk prediction model is based on a research with a sample size of over 18,500; (2) it allows the physicians to measure the risk of AF in their patients at any time and from any place using information such as age, sex, height, weight, blood pressure, history of heart disease and diabetes, and BNP level; (3) this risk prediction model is available online in a simplified environment (access link: supplementary material online); and (4) BNP is the only blood marker used in this model, and since it can be rapidly measured in many centers, it is feasible to use a BNP-based risk score. The importance of such models lies in the fact that physicians can use the obtained risk scores alongside clinical evidence to nominate patients for ECG screening, which is a costly and burdensome process. Nevertheless, it seems that more studies should evaluate the role of NT-proBNP concentration monitoring among individuals at high risk of incident AF.

AF screening

Nowadays, more evidence is being generated regarding the value of NPs in population-based AF screening [21]. In a recently conducted screening study recruiting 7173 Swedish residents, NT-proBNP > 125 ng/L (pg/mL) showed 75% sensitivity and 92% negative predictive value in terms of detection of new-onset AF, highlighting the value of NPs as useful screening markers for AF detection [22]. In another screening study, utilization of an NT-proBNP cut-off of 124 ng/L (pg/mL) yielded a negative predictive value of 86% [23]. Although an NT-proBNP cut-off of 124–125 ng/L (pg/mL) was introduced by these two studies, the external validity of this cut-off should be confirmed in other larger cohorts.

Postoperative AF

Blood level of NPs has been assumed to be valuable for postoperative AF prediction. In this respect, a meta-analysis of ten studies including 1844 patients estimated 75% sensitivity and 80% specificity of elevated NP levels for postoperative AF prediction [24]. Further results also demonstrated that postoperative NT-proBNP assessment had appeared to have better predictive value than preoperative BNP assessment [24]. Similar findings had been further reported in another meta-analysis on patients undergoing cardiothoracic surgery, confirming an association between elevated preoperative NP levels and increased risks of postoperative AF [25]. A recently conducted study had similarly revealed that factors

Table 1 Summary of main studies investigating association between natriuretic peptides and atrial fibrillation incidence in general population

Study	Year of publication	Design	Participants, no	Follow-up	Assay type	Setting	Main result
Wang et al. [81]	2004	Prospective	3346	Mean of 5.2 years	BNP and NT-proBNP	Community-based study	↑ BNP or/and NT-proBNP levels were associated with ↑ risk of AF
Patton et al. [17]	2009	Prospective (Cardiovascular Health Study)	5445	Median of 10 years	NT-proBNP	Community-based study	NT-proBNP was a remarkable predictor of incident AF
Schnabel et al. [82]	2010	Prospective (Framingham Offspring Study)	3120	Median of 9.7 years	BNP	Community-based study	BNP was the strongest predictor of incident AF
Patton et al. [83]	2013	Prospective (MESA Study)	5518	Median of 7.6 years	NT-proBNP	Community-based study	NT-proBNP was a remarkable predictor of incident AF
Sinner et al. [20]	2014	Prospective (CHARGE-AF Consortium of community-based cohort studies)	18,556	Patients were followed for 5 years	BNP	Community-based study	BNP remarkably improved AF risk prediction beyond clinical factors
Svennberg et al. [18]	2016	Prospective (Uppsala Longitudinal Study of Adult Men)	883	Median of 12.6 years	NT-proBNP	Community-based study	NT-proBNP was the strongest predictor of incident AF
Kumarathurai et al. [84]	2017	Prospective (Copenhagen Holter Study)	646	Median of 14.4 years	NT-proBNP	Community-based study	Addition of NT-proBNP did not improve AF risk discrimination
Li et al. [19]	2018	Prospective (Atherosclerosis Risk in Communities Study)	9705	Median of 16 years	NT-proBNP	Community-based study	Positive NT-proBNP change was associated with ↑ AF incidence Addition of NT-proBNP modestly improved incident AF prediction

AF Atrial fibrillation, *BNP* B-type natriuretic peptide, *NT-proBNP* N-terminal pro B-type natriuretic peptide

including male gender, open-heart surgery, and elevated preoperative BNP level > 59 pg/mL could be associated with postoperative AF occurrence in patients undergoing non-cardiothoracic surgery [26]. Based on current evidence, perioperative evaluation of NPs seems to be a valuable diagnostic strategy for identifying patients at high risk of postoperative AF development, mainly those undergoing major cardiothoracic surgeries. Also, it appears that with further research, the NP level can be turned into a supplementary criterion to decide whether it is necessary to take preventive measures such as prescribing beta-blocker or antiarrhythmic drugs like amiodarone to deal with postoperative AF. Nevertheless, appropriate thresholds, blood assessment times, along with management based on elevated levels of NPs are still among remaining issues to be addressed in this field.

Intensive Care Unit (ICU)

Incident AF in patients admitted to ICUs has shown to reach a high rate of 5–15% [27]; however, data relating to biomarkers for AF occurrence in such populations are scarce. In a study on patients admitted to a non-cardiac

ICU, a multivariable model could identify increased NT-proBNP values (odds ratio (OR) 1.28 for each 1000 pg/mL increase) as an independent predictor of new-onset AF [28]. In this study, using an NT-proBNP cut-off of 5.6 pg/mL presented 65.2% sensitivity and 82% specificity in the detection [28]. In another investigation conducted on patients admitted to ICUs, it was demonstrated that NT-proBNP ≥ 600 ng/L (pg/mL) (OR 4.3), age ≥ 70 years (OR 3.7), and history of AF (OR 25.3) were among the most important independent predictors for new-onset AF on the first 3 days of admission to ICU [29]. The currently available evidence for use of NP levels in AF prediction in ICU settings is also poor and requires further studies.

Hypertrophic cardiomyopathy

Elevated BNP levels have been shown to be associated with AF presence in patients with hypertrophic cardiomyopathy (HCM), but evidence on its role in predicting AF occurrence is sparse [30]. In an investigation on 70 patients affected with HCM, the value of different parameters including left atrial phasic functions, P wave dispersion, and NT-proBNP levels in predicting AF development had been assessed. The results had revealed that NT-proBNP > 720 pg/mL could predict incident AF with 60% sensitivity and 70% specificity during a follow-up of 53.09 ± 1.87 months, [31]. However, in another report, NT-proBNP level was not associated with well-known AF predictors including P wave dispersion and intra and inter-atrial electromechanical dys-synchrony in patients suffering from HCM [32]. Based on these data, regular assessment of serum NP levels has not been still suggested to identify at-risk patients and further studies need to be conducted to evaluate this approach.

Acute coronary syndrome

An association between NPs and AF development in patients with ACS has been investigated in different studies. Although the results seem contradictory, the findings of a new meta-analysis of six studies, comprised of around 6000 patients with ACS, suggested that higher levels of NT-proBNP could be correlated with greater risk of new-onset AF in patients with ACS [33]. In a recent study, NT-proBNP level > 1774 pg/ml was also considered to be associated with risk of new AF on ACS history [14]. These results indicate that NPs may be useful biomarkers in predicting new-onset AF in patients with ACS; however, considering the observed heterogeneity across the available studies, more research is still needed to confirm this association.

The importance of pretest probability

This section discussed the use of NPs in the prediction of AF in different clinical settings, but it should be noted that for individuals at the risk of AF, diagnostic and therapeutic measures are usually planned based on pretest probability. The experience of the treating physician, the prevalence of AF, and the clinical decision-making criteria are the three most important determinants of pretest probability for every disease, including AF. We know that a high enough pretest probability justifies the initiation of more diagnostic measures and a low enough pretest probability rules out the possibility of AF and, therefore, we can reassure the patient. Therefore, using NPs for AF risk prediction is useful mainly in subjects with an intermediate pretest probability, when we in daily practice want to decide whether to perform further diagnostic procedures.

AF progression

AF progression is often defined by a transition from paroxysmal to persistent or permanent AF, increased left atrial diameter, or periprocedural evidence of low voltage areas [34, 35]; which might be associated with a decrease in quality of life [36]. Recently, the value of NPs in predicting different AF progression phenotypes was delineated in a pilot cohort [37]. This cohort study demonstrated that NT-proANP levels were significantly higher in AF patients with increased left atrial diameter (LAD) and those with low voltage areas. It was also shown that patients with higher AF progression—as defined by AF type and low voltage areas have higher NT-proANP levels [37]. This study also reported that patients with paroxysmal AF without low voltage areas have significantly lower NT-proANP levels, but those with persistent AF and low voltage areas have higher NT-proANP levels [37].

Another cohort study showed that patients with elevated BNP levels are at greater risk of progression to persistent or permanent forms of AF [38]. However, while this study revealed that increasing BNP levels up to 800 ng/L (pg/mL) were associated with increased risk of AF progression, BNP values greater than 800 ng/L (pg/mL) were associated with decreased risk of AF progression. Although the findings of this study were generally consistent with other reports, suggesting that elevated BNP is associated with increased risk of AF progression; interestingly, this study indicated that despite the association of elevated BNP with increased risk of major adverse cardiovascular or neurological events, it has no association with the risk of bleeding [38]. As the author of this cohort has explained, this can perhaps be attributed to the following reasons: (1) patients with higher levels of BNP are

more likely to have symptomatic heart failure, and since in patients with heart failure, BNP is secreted more from ventricular myocytes than from atrial ones, the absence of an association between increased BNP and AF progression appears to be related to the non-atrial origin of BNP. (2) Patients with higher levels of BNP have a higher rate of mortality and serious cardiovascular/neurological complications, which means the majority of these patients may have died before undergoing AF progression. Therefore, although BNP values greater than 800 ng/L (pg/mL) were not associated with an increased risk of AF progression, it was followed by worse outcomes such as death. Moreover, another study revealed an association between AF development and an increase in NT-proBNP and other inflammatory factors [39]. Although the relatively small sample size could be regarded as a limitation to these studies, they raised the hypothesis that "NT-proANP can have a clinical impact on refining individualized therapy", which should be evaluated in further research.

AF recurrence

Pulmonary vein isolation

Pulmonary vein isolation is taken into account as one of the best strategies to maintain sinus rhythm in AF patients [40, 41]. However, AF recurrence is still regarded as a big challenge in the field of cardiac electrophysiology; since the efficacy of early AF ablation is estimated to be 50–80% [35, 42–45]. So far, various clinical scores including the ALARMEC risk score, the APPLE score, the MB-LATER score, and ATLAS have been introduced for risk assessment of recurrence in patients undergoing AF ablation [46–49]. Despite the great body of data whose interesting predictive values have been confirmed, routine use of blood biomarkers is still limited [50, 51].

Associations between NPs and post-ablation AF recurrence have also been examined thoroughly in the past. While some studies have shown relatively controversial results regarding the role of NPs, mainly ANPs, in recurrence prediction [52, 53]; majority of investigations have confirmed a close relationship between NP status and therapeutic success. Two different meta-analyses had also revealed that increased pre-ablation levels of NPs including ANPs, BNPs, and NT-proBNPs could be significantly associated with a higher risk of AF recurrence after catheter ablation [50, 54]. A more recently conducted study correspondingly showed a higher level of baseline BNP in patients with AF recurrence in comparison with those without it; whereas there were no significant differences in the CHADS2, CHA2DS2–VASc, and APPLE scores during a 2-year follow-up period [51].

Electrical cardioversion

Electrical cardioversion (ECV) is frequently used to restore sinus rhythm in AF patients; however, post-ECV recurrence rate of AF seems undesirable [55, 56]. Moreover, factors predicting AF recurrence after successful ECV have not been quiet understood [57]. While most of studies have demonstrated an association between higher levels of NPs and higher recurrence rates after ECV, other groups have not confirmed it [58]. Recently published meta-analyses of around 20 publications also showed that higher levels of pre-intervention BNP and NT-proBNP could be associated with AF recurrence after successful ECV, regardless of long or short-term follow-up periods [59, 60]. In summary, recent evidence implies that elevated BNP values after ECV seem to be an independent predictor for sinus rhythm after ECV and AF recurrence [61]. Moreover, decreased BNP and NT-proBNP values are mostly recorded after successful ECVs [62]. Although a BNP cut-off of 700 fmol/ml (≈591.99 pg/mL) on day seven after ECV has been established as a predictor of AF recurrence (with 71% specificity and 78% sensitivity) [63]; more studies are still required to determine validated cut-offs for NP levels before/after direct ECV to predict AF recurrence.

Mechanisms

A likely explanation for the role of NPs in predicting AF recurrence may be a direct association between these peptides and larger left atrial size, which might lead to a higher risk of post-ablation AF recurrence due to atrial fibrosis and remodeling [50]. However, it seems that the role of heart rhythm at the time of blood collection for BNP assessment as well as possible interaction of BNP with other factors including age, left ventricle ejection fraction, and left atrial diameter may define heterogeneity between studies investigating the association between BNP and post-therapy AF recurrence [51].

Further steps

Although current evidence has still failed to guide therapeutic interventions via NP levels, importance of ANPs, BNPs, and NT-proBNPs as possible markers of AF recurrence prediction seems undeniable. However, the exact time point of NP evaluation, frequency, as well as methods of evaluation and justification require further investigations to achieve a suitable patient selection strategy for ablation or ECV, based on NP levels.

AF complications

Stroke, systemic embolism, and bleeding

Thromboembolic events are among serious complications of AF, leading to impaired quality of life as well as increased medical costs [64]. AF also increases risks of stroke development by 5–7 times, so stroke incidence in AF may correspondingly reach 15–20% [65, 66]. In addition to existing risk stratification scores, there is currently an interest in further optimization of identifying patients at risk of thromboembolic events using biomarkers [67, 68]. NPs are also likely to represent myocytic stress and, therefore, atrial dysfunction in AF patients [69]. Since atrial dysfunction is a risk factor for thrombogenesis in AF, a relationship between NPs and thromboembolic complications seems reasonable.

Besides, NPs have shown to be effective in improving functionality of biomarker-based scores over clinical ones in terms of prediction of stroke and bleeding [70]. In the apixaban for reduction in stroke and other thromboembolic events in atrial fibrillation (ARISTOTLE) trial, higher levels of NT-proBNP in AF had been thus significantly associated with an increased risk of stroke/systemic embolism (HR 2.35) [16]. Moreover, they had reported that NT-proBNP could improve risk stratification beyond CHA_2DS_2–VASc in a significant manner [16]. Similar results were also found in the REGARDS cohort, wherein higher levels of NT-proBNP in patients with AF had yielded a higher risk of stroke (HR 2.9) during 5.4 year follow-up among around 30,000 black and white participants [71]. In another study, stroke rates had been approximately twice higher (HR 2.4) in patients with increased NT-proBNP (> 1402 ng/L (pg/mL)) in comparison with the lowest NT-proBNP quartile groups (< 387 ng/L (pg/mL)) [72].

NT-proBNP is used in new ABC scoring systems for assessment of AF-related bleeding and stroke risks, indicating the importance of NPs in prognosis estimation of patients affected with AF [73]. According to the latest publications, the novel biomarker-based ABC scores (age, biomarkers, and clinical characteristics) may perform better than presently used clinical risk scores for bleeding and thromboembolic prediction in patients with AF [73]. However, use of ABC risk scores for routine clinical practices need more validation studies. The results of the large ENGAGE AF-TIMI 48 randomized trial further revealed that higher levels of NT-proBNP (≥ 900 vs. < 450 pg/mL) could be independently associated with a higher incidence of stroke/systemic embolic events (HR 2.2) [74]. Overall, most of the clinical studies in this domain have confirmed the role of NP as an independent predictor of development of thromboembolic events [75]; however, BNPs or NT-proBNPs, the best time points, as well as optimal cut-off points for thromboembolic event prediction are the remaining issues to be addressed by future multicenter prospective studies.

Mortality

In a study on older patients affected with AF, all-cause mortality was associated with elevated levels of NT-proBNPs in both univariate (HR 1.84) and multivariate (HR 1.37) Cox regression for survival analyses [76]. Interestingly, the ability of NT-proBNP in evaluating all-cause mortality was confirmed to be even higher in comparison with CHADS2 and CHA2DS2–VASc scores [76]. In a real-world cohort of anticoagulated AF patients, higher baseline NT-proBNP was also introduced as a predictor for ACS or acute heart failure (HR 1.85) and all-cause mortality (HR 1.66) [77]. Moreover, another study indicated that persistent elevation of NT-proBNP at baseline and 3 months would increase risks of cardiovascular mortality by around four times [78]. In the ARISTOTLE trial, annual rates of cardiac death were reportedly higher in patients with NT-proBNP > 1250 than ≤ 363 ng/L (pg/mL) (HR 2.5) [16].

Patients with AF admitted to emergency department (ED)

Considering the importance of ED in management of patients affected with AF, use of risk stratification biomarkers for proper and timely treatment seems to be of utmost importance. However, a limited number of studies have been performed to investigate the role of NPs in management of patients suffering from symptomatic AF and admitted to EDs. One study in this regard showed that a high baseline NT-proBNP (> 500 pmol/L ≈ > 4228.5 pg/mL) was independently associated with increased mortality rate (HR 2.26) and major adverse cardiac events (HR 1.67) during a 2-year follow-up period [79]. Similar findings were correspondingly reported in another study, wherein mortality hazard increased with every quintile of NT-proBNP by 1.5 [80]. Although the primary results have shown that NT-proBNPs may assist in achieving this goal, more studies are still needed.

Conclusion

The current clinical applications of NPs in AF management are summarised in Fig. 1. Even though some studies have revealed relatively controversial results on the role of NPs in AF management, majority of such investigations have confirmed a close association between NP status and AF

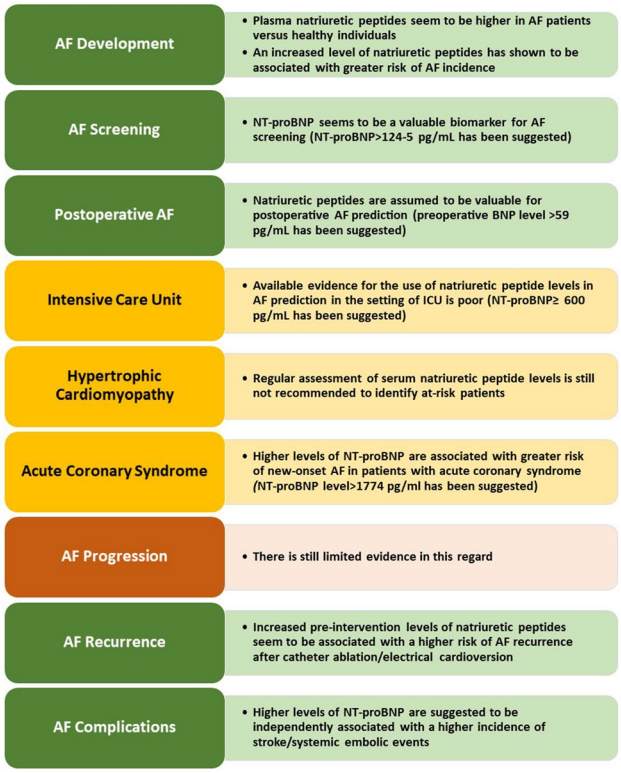

Fig. 1 Summary of available evidence regarding role of natriuretic peptides in atrial fibrillation management

incidence/recurrence. It seems that measurement of plasma levels in NPs before interventions, such as pulmonary vein isolation and electrical cardioversion, may help in predicting risks of AF recurrence, thus aiding in initial selection of suitable patients for AF treatment. Moreover, NPs seem to play an important role in AF-related morbidity and mortality risk assessment. However, the most optimal cut-offs and the corresponding managements based on elevated levels of NPs for AF development/recurrence prediction as well as complication formation are still not fully clear. Besides, the exact time point of NP assessment as well as frequency and methods of evaluation of these biomarkers need further studies to be validated in different populations.

Compliance with ethical standards

Conflict of interest Drs Bollmann, Dagres and Hindricks report research grants from Abbott and Boston Scientific to the institution without personal financial benefits. Other authors do not declare any conflict of interest.

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