Natriuretic Peptides as Predictors of Atrial Fibrillation Recurrences Following Electrical Cardioversion

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Abstract

Electrical cardioversion (ECV) can be effective in restoring sinus rhythm (SR) in the majority of patients with atrial fibrillation (AF). Several factors that predispose to AF recurrences, such as age, AF duration and left atrial size have been used to guide a decision for cardioversion, but increasing evidence suggests that they may be rather poor markers of left atrial structural remodeling that determines the long-term success of a rhythm control strategy. In this context, the use of easily obtainable biomarkers, such as the levels of atrial natriuretic peptide (ANP) and B-type natriuretic peptide (BNP), to predict AF recurrences may be preferable. Since ANP production is associated with the extent of functional atrial myocardium, and both ANP and BNP reflect atrial pressure and mechanical stretching, these peptides are good candidate biomarkers to assess predisposition to AF recurrences. In this review we focus on the pathophysiological mechanisms and the available clinical evidence regarding the prediction of AF recurrences following successful ECV from pre-procedural ANP and BNP levels.

Keywords

Atrial fibrillation, electrical cardioversion, atrial natriuretic peptide, B-type natriuretic peptide

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Atrial fibrillation (AF) affects 1–2 % of the population, and its prevalence is expected to increase in the next 50 years.^{1,2} The treatment of these patients includes either restoration and maintenance of sinus rhythm (SR) or control of the ventricular rate.³

Electrical cardioversion (ECV) can be effective in restoring SR in the majority of patients; however, it is associated with several risks and complications, including thromboembolic events, post-cardioversion arrhythmias and the risks of anaesthesia.³ Furthermore, ECV is effective in less than half of the patients, since AF recurrences are common, with a 40 % rate of AF recurrences within the month.⁴ Factors that predispose to AF recurrence are age, AF duration before cardioversion, number of previous recurrences, increased left atrial (LA) size or reduced LA function, and the presence of coronary heart disease or, pulmonary or mitral valve disease.⁵ Nevertheless, increasing evidence suggests that the above-mentioned factors may be poor markers of LA structural remodeling, which determines the propensity to AF recurrences. In fact, the extent of atrial fibrosis appears to be highly variable between patients with the same risk factors for AF.⁶ The extent of fibrosis can be determined using delayed enhancement magnetic resonance imaging; however, it could be adequately assessed by the secretory function of the remaining atrial myocardium.

A method to choose patients for whom ECV would be more successful based on easily obtainable biomarkers, such as natriuretic peptides (NPs), may improve clinical outcomes and cost-efficiency. In this review, we focus on the pathophysiological mechanisms and the available clinical evidence regarding the prediction of AF recurrences following successful ECV from pre-procedural NP levels.

Natriuretic Peptide System

The NP system consists of three different NPs sharing a common 17-amino acid ring, namely – atrial NP (ANP), B-type or brain NP (BNP) and C-type NP (CNP) (see *Figure 1*). Their biological actions are mediated through membrane-bound NP receptors (NPRs) – NPR-A, NPR-B and NPR-C.

Atrial Natriuretic Peptide

Mammalian atrial myocytes have been found to contain specific granules, with characteristics compatible with a secretory function.⁷ The importance of these granules was demonstrated by de Bold et al., who reported the occurrence of a natriuretic response following cross-animal injection of atrial myocardium extract.⁸ This natriuretic effect was later ascribed to a 28-amino acid peptide, which was simultaneously isolated and sequenced by several research groups, and was found to be strictly localised within the specific granules.^{9–11} In cardiac myocytes, ANP is synthesised and stored as a 126-amino acid precursor, pro-ANP, which is cleaved to biologically active ANP and the N-terminal portion of pro-ANP (NT-proANP) by a transmembrane cardiac serine protease, corin, during the secretion process.¹²

ANP secretion is primarily regulated by mechanical stretching of the atria, secondary to increased loading, but an increase in the rate of contraction also causes an increase in ANP. Equally potent stimuli for ANP release are hypoxia and myocardial ischaemia.¹³ Several other factors have been associated with ANP regulation, such as angiotensin II, vasopressin and adrenergic agonists, which seem to induce ANP secretion; nevertheless, there is some controversy as to whether this

Figure 1: Natriuretic Peptides and their Respective Receptors

Binding of NPR-A with its ligand (ANP or BNP) increases production of cyclic guanosine monophosphate. NPR-C binds with high affinity to all three NPs and facilitates their clearance from the circulation through receptor-mediated internalisation and degradation. ANP = atrial natriuretic peptide; BNP = B-type natriuretic peptide; cGMP = cyclic guanosine monophosphate; CNP = C-type natriuretic peptide; NPR-A = natriuretic peptide receptor-A; NPR-B = natriuretic peptide receptor-B; NPR-C = natriuretic peptide receptor-C; GTP = guanosine triphosphate.

is due to a direct effect or due to affecting venous return or cardiac afterload.¹³ Paracrine factors derived from endothelial cells modulate ANP secretion as well. Endothelin, a potent vasoconstrictor, stimulates ANP secretion and enhances stretch-induced ANP secretion, whereas nitric oxide (NO), an important vasodilator, inhibits ANP secretion.¹³

ANP in plasma is characterised by a short half-life, which ranges between 2 and 4 minutes and rapid metabolic clearance.^{14,15} In contrast to BNP and NT-proBNP, ANP has much higher renal extraction, with a renal fractional extraction of approximately 50 %.¹⁶ In accordance with BNP, ANP is inactivated by two pathways; enzymatic degradation by neutral endopeptidase and lysosomal degradation after binding to NPR-C. ANP binds with greater affinity to NPR-C compared with BNP, which contributes significantly to its shorter plasma half-life.¹⁷

Brain Natriuretic Peptide

Even though BNP was initially isolated from porcine brain, and was therefore named 'brain natriuretic peptide',¹⁸ it was later found that in humans BNP is highly synthesised and secreted in the ventricles, in contrast to ANP, which is preferentially secreted from the atria.¹⁹ Nevertheless, both peptides can be synthesised in either chamber under pathological conditions.²⁰ The BNP messenger RNA (mRNA) expression is more than twofold higher in atria than in ventricles, but the BNP production in the ventricles is considered more important for the contribution to BNP plasma concentrations due to the larger mass of the ventricles.²¹ In patients with AF, Inoue et al. have suggested that BNP is predominantly produced in the atrium.²²

In contrast to ANP, which seems to be well conserved in mammals, BNP and NT-proBNP differ among mammalian species. Another significant difference is that, unlike ANP, BNP has minimal storage in granules and most of BNP regulation is done during gene expression, with most BNP synthesised in bursts of activation from physiological and pathophysiological stimuli when peptide secretion occurs.²³

In response to left ventricular stretch and wall tension, natriuretic peptide precursor (NPPB) gene is translated into a 134-amino acid precursor, which undergoes rapid removal of a 26-amino acid signal peptide, resulting in the formation of proBNP1-108. Upon cleavage from prohormone convertases, furin and corin, an active BNP hormone comprising 32-amino acid residues (BNP1-32), along with a physiologically inactive N-terminal fragment (NT-proBNP1-76) are formed from proBNP.²⁴

Even though BNP and NT-proBNP are produced in equimolar proportions, circulating NT-proBNP levels are approximately sixfold higher compared with BNP levels, due to a difference in half-life times.²⁵ BNP has a half-life of approximately 20 minutes, whereas NT-proBNP has a longer half-life of approximately 120 minutes.²⁶ Due to its longer half-life, NT-proBNP levels are more stable and less sensitive to acute stress. These differences in plasma half-lives can be ascribed to different clearance mechanisms. Even though evidence suggests that renal extraction of BNP is comparable to that of NT-proBNP and consistent with the renal extraction of other bio-active peptides,²⁷ glomerular filtration plays only a minor role in the elimination of BNP, which is primarily eliminated by binding to NPR-C and through enzymatic degradation by neutral endopeptidases. In contrast, NT-proBNP is thought to be largely cleared by renal excretion.²⁶

BNP exerts more potent natriuretic and blood pressure-lowering effects compared with ANP, whereas both NPs suppress the renin-angiotensin-aldosterone system to the same extent.²⁸ Furthermore, there is evidence that BNP has a direct anti-fibrotic effect on cardiac fibroblasts, by opposing transforming growth factor-beta (TGF-beta) regulated genes related to fibrosis (such as collagen 1, fibronectin, connective tissue growth factor [CTGF], plasminogen activator inhibitor-1 [PAI-1] and tissue inhibitor of metalloproteinase-3 [TIMP3]), myofibroblast conversion and proliferation (alpha-smooth muscle actin 2 and non-muscle myosin heavy chain, platelet-derived growth factor [PDGFA], insulin-like growth factor 1 [IGF-1], fibroblast growth factor-18 [FGF18] and IGF binding protein-10 [IGFBP10]) and inflammation (cyclooxygenase-2 [COX2], Interleukin 6 [IL6], tumor necrosis factor [TNF] alpha-induced protein 6 and TNF superfamily, member 4).²⁹

Natriuretic Peptide Receptors

The biological actions of NPs are mediated by the membrane-bound NPRs. The basic topology of NPR-A, which preferentially binds ANP and BNP, consists of an extracellular ligand-binding domain (a short hydrophobic membrane-spanning region) and an intracellular domain, which contains a guanylyl cyclase catalytic domain in its C-terminus.³⁰ Association of NPR-A with its cognate ligand (ANP or BNP) causes a conformational change that relaxes tonic inhibition of guanylyl cyclase activity and increases production of cyclic guanosine monophosphate (cGMP).³¹ NPR-B, which preferentially binds CNP, shares a similar structure with NPR-A. As mentioned, NP clearance from the blood is mediated by NPR-C, which has an extracellular domain that is structurally homologous to that of the other NPRs. NPR-C binds with high affinity to all three NPs and facilitates their clearance from the circulation through receptor-mediated internalisation and degradation.³¹

Brain Natriuretic Peptide as a Predictor of Atrial Fibrillation Recurrences Post-electrical Cardioversion

Elevated levels of BNP and NT-proBNP in patients with AF compared with patients in SR have long been described.³²⁻³⁴ Upon restoration of SR, levels of BNP rapidly normalise.^{35,36} Furthermore, BNP and NT-proBNP levels have been shown to predict the risk of AF occurrence in various

Table 1: Observational Studies of the Association of Preprocedural BNP or NT-proBNP Levels and AF Recurrences Following Successful ECV

Study	Study Characteristics	AF Duration	n	AF Recurrence Rate	Follow-up Period	AF Detection	BNP in SR Group	SR Group n	BNP in AF Group	AF Group n
BNP										
Ari et al.	Preserved LVEF (55.50 ± 2.98)	23.2 ± 6.5 months	58	34.5 %	6 months	ECG	210.89 ± 35.80 pg/mL	38	340.60 ± 42.74 pg/mL	20
Beck da Silva et al.	NYHA class I or II, preserved LVEF	6 (4–9) months	14	36 %	2 weeks	ECG	163 ± 122 pg/mL	9	293 ± 106 pg/mL	5
Falcone et al.	NYHA I or II	–	93	28 %	6 months	24h ambulatory ECG	91 ± 24 pg/mL	67	188.00 ± 30.75 pg/mL	26
Kawamura et al.	Preserved LVEF (61.1 ± 9.6)	37 ± 26 days	142	38 %	24 months	ECG	140 ± 98 pg/mL	88	120 ± 92 pg/mL	54
Leclouche et al.	NYHA I or II, preserved LVEF (63 ± 12)	3.7 months	66	45 %	1 year	ECG	177 ± 140 pg/mL	36	358 ± 339 pg/mL	30
Mabuchi et al.	NYHA II or III, LVEF: 40.7 ± 2.2	4.5 ± 1.7 months	65	45 %	553 days	Physical, ECG	121.6 ± 15.7 pg/mL	36	182.2 ± 25.9 pg/mL	29
Watanabe et al.	NYHA I–III, LVEF: 0.59 ± 0.10	37 (1–350) days	84	76 %	140 ± 144 days	24h Holter, ECGs at follow-up	137 ± 123 pg/mL	20	119 ± 113 pg/mL	64
Wozakowska et al.	NYHA I, LVEF: 58.1 ± 6.4	101.3 ± 92.6 days	77	41 % *	6 months	ECG, Holter ECG monitoring	71.3 ± 26.1 pg/mL	47	99.6 ± 35.5 pg/mL	30
NT-proBNP										
Govindan et al.	Preserved LVEF (56.7 ± 10.4)	<18 months	53	62 %	12 months	24h Holter, monthly ECG	848 ± 522 ng/mL	21	953 ± 456 ng/mL	32
Barassi et al.	NYHA I or II, LVEF: 0.58 (0.44–0.71)	3 months (0–15)	57	33 %	3 weeks	ECG	717 ± 449 pg/mL	38	664 ± 349 pg/mL	19
Buob et al.	No clinical CHF, LVEF 0.57 ± 0.11	90 ± 75 days	25	44 %	4 weeks	Physical, ECG	1647 ± 1,272 pg/mL	14	2996 ± 3,965 pg/mL	11
Freynhofer et al.	Persistent AF	NA	86	49 %	340 ± 81 days	ECG	741 (514–1,401) pg/mL	44	973 (474–1,533) pg/mL	42
Kallergis et al.	Lone AF, LVEF: 57.1 ± 8.5	>3 months	40	29 %	1 month	Weekly visits, ECG	398 ± 268 pg/mL	31	1,362 ± 862 pg/mL	9
Lombardi et al.	NYHA I, LVEF: 58.7 ± 5.8	3 months (1 month–1 year)	53	34 %	3 weeks	Weekly phone interviews, ECG	638 ± 329 pg/mL	35	735 ± 370 pg/mL	18
Mollmann et al.	Lone AF, LVEF: 0.57 ± 0.06	181.5 ± 32.7 days	49	39 %	4 weeks	Ambulatory ECG	759 (618–1,139) pg/mL	30	1,124 (925–1,542) pg/mL	19
Shin et al.	Persistent AF, normal LVEF	10.9 ± 8.3 weeks	34	29.4 %	11 days	ECG	973.6 (541.5–1,191.3) pg/mL	24	1570.5 (397.1–2,202.1) pg/mL	10
Tveit et al.	Persistent AF, NYHA I, FS: 29.9 ± 7.3	Median 10.5 weeks	129	69 %	6 months	ECG at follow-up	746.2 (500.8–1,262.6) pg/mL	40	761.4 (467.8–1,170.9) pg/mL	89

*Four patients failed the initial cardioversion. AF = atrial fibrillation; BNP = B-type natriuretic peptide; CHF = congestive heart failure; ECG = electrocardiogram; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal portion of proBNP; NYHA = New York Heart Association; SR = sinus rhythm.

Table 2: Observational Studies of the Association of Preprocedural ANP or NT-proANP Levels and AF Recurrences Following Successful ECV

Study	Study Characteristics	AF Duration	n	AF Recurrence Rate	Follow-up Period	ANP in SR Group	SR Group n	ANP in AF Group	AF Group n
ANP									
van den Berg et al. 1995	CHF, NYHA II or III	20 months median	18	9/18	6 weeks	63 ± 50 pmol/L	9	70 ± 48 pmol/L	9
Theodorakis et al. 1996	Non-valvular AF, NYHA I or II	6 ± 5 months (2–13 months)	19	11/19	3 months	129 ± 58 fmol/mL	8	112 ± 58 fmol/mL	11
Mabuchi et al. 2000	CHF, NYHA II or III	20.4 months	65	29/65	2 months	67.4 ± 10.0 pg/mL	36	65.8 ± 12.3 pg/mL	29
Wozakowska et al. 2004	Broad spectrum of underlying disease, NYHA I, II or III	7.1 ± 7.1 months	35	6/35	1 month	58.1 ± 13.0 pg/mL	29	60.2 ± 11.2 pg/mL	6
Thomas et al. 2005	NYHA I or II	>1 month and <1 year	23	9/23	1 month	150 ± 34 pg/mL	14	250 ± 62 pg/mL	9
NT-proANP									
Kim et al. 2009	Broad spectrum of underlying disease	>1 month	74	48/74	13.2 ± 11.0 months	6.68 ± 4.09 nmol/L	26	4.92 ± 4.36 nmol/L	48
Bartkowiak et al. 2010	Preserved LV systolic function	12.3 ± 15.3 weeks	43	19/43	1 month	5.1 ± 3.5 nmol/L	24	4.4 ± 2.0 nmol/L	19
Govindan et al. 2012	Non-valvular AF, preserved LV systolic function	<18 months	54	33/54	12 month	5.9 ± 2.4 nmol/L	21	7.3 ± 1.9 nmol/L	33

AF = atrial fibrillation; ANP = atrial natriuretic peptide; CHF = congestive heart failure; LV = left ventricular; NT-proBNP = N-terminal portion of proBNP; SR = sinus rhythm.

clinical settings. Elevated pre-operative levels of BNP or NT-proBNP have been associated with increased risk of new-onset AF following coronary artery bypass grafting surgery.^{37,38} The association of pre-operative BNP levels with the post-operative development of AF has also been documented in patients undergoing general thoracic surgery and major non-cardiac surgery.^{39,40}

Similar findings are reported in several studies assessing the recurrence of AF following catheter ablation. Patients with higher baseline levels of BNP and NT-proBNP have higher rates of AF recurrence.^{41,42} Whereas, both BNP and NT-proBNP have been recognised as independent predictors of AF recurrence in the majority of studies, there are reports that failed to identify such an association.^{43,44}

In the context of the above mentioned data, several observational studies have assessed the value of BNP and NT-proBNP levels in predicting AF recurrences following ECV (see Table 1). Evidence from the majority of these studies supports an association between BNP or NT-proBNP levels before ECV and the risk of AF recurrence.^{45–54} Nevertheless, other studies have failed to observe a relationship.^{55–58} In fact, in the three most recent studies, a statistically significant association between baseline BNP or NT-proBNP levels and SR maintenance was not observed.^{59–61} A meta-analysis that included ten of the above-mentioned studies concluded that higher BNP levels before ECV were associated with an increased risk of AF recurrence following successful ECV, suggesting that the measurement of BNP levels could improve the initial selection of suitable patients for ECV.⁶²

In the patients included in the above-mentioned studies, which mainly have preserved ejection fraction, high BNP/NT-proBNP levels may be the consequence of several pathogenic mechanisms. BNP levels may reflect a higher degree of systematic inflammation, which is consistently associated with AF.⁶³ *In vitro* studies suggest that BNP may be selectively up-regulated at the transcriptional and translational level by pro-inflammatory cytokines, and that plasma BNP levels may increase as a response to systemic inflammation in the absence of haemodynamic changes.^{64,65} The frequent occurrence of AF in patients with inflammatory conditions, such as myocarditis and pericarditis, and the finding of marked inflammatory infiltrates, myocyte necrosis and fibrosis in atrial biopsies from patients with lone AF, support an association between AF and inflammation.⁶⁶ Further evidence of a pro-inflammatory state in patients with AF comes from an observed increase in inflammatory markers, such as C-reactive protein (CRP) and interleukin-6 in patients with persistent and permanent AF compared with controls.^{67,68} Consequently, patients with a higher degree of inflammation observed by higher BNP levels may have greater and more active atrial structural remodeling, thereby hindering SR maintenance.⁶⁹

Furthermore, high BNP or NT-proBNP levels may predict a greater predisposition to AF recurrences by reflecting increased LA pressure. Atrial arrhythmias frequently occur under conditions associated with atrial dilation.⁷⁰ The effect of atrial pressure in atrial refractoriness was evaluated in several animal models as well as in humans. Increased atrial pressure results in increased susceptibility to AF that is associated with shortening of the atrial effective refractory period (AERP),^{71,72} possibly by opening of stretch-activated ion channels.⁷³ Furthermore, atrial conduction delay in patients with paroxysmal AF or patients with diabetes and hypertension was associated with increased LA pressure and impaired left ventricular (LV) relaxation.⁷⁴ An association between BNP and myocardial stretch, as well as intra-atrial pressures has been well established. In patients

with preserved ejection fraction (EF) a significant correlation between NT-proBNP and LA appendage emptying velocity was observed reflecting atrial strain.⁵⁶ Moreover, in patients with diastolic dysfunction, increased BNP levels have been associated with higher left ventricular end-diastolic pressure (LVEDP) and have been proposed as a diagnostic marker for diastolic dysfunction.⁷⁵ Elevated LVEDP results in excessive tension in ventricular and also atrial walls, which may stimulate ventricular and atrial BNP production. Therefore, elevated BNP levels in patients with AF may reflect diastolic dysfunction, which is an independent predictor of AF, especially in the elderly.⁷⁶ The presence and severity of diastolic dysfunction has been repeatedly demonstrated to predict AF development in patients with risk factors for cardiac disease, such as diabetes, and in patients after myocardial infarction.^{77–79}

Atrial Natriuretic Peptide as a Predictor of Atrial Fibrillation Recurrences Post-electrical Cardioversion

The link between ANP or NT-proANP and AF has been equally well established. Patients with AF have higher ANP levels compared with patients in SR,^{80,81} which usually decrease following ECV and SR restoration.^{82,83} Elevated ANP levels can predict the development of paroxysmal AF in patients with congestive heart failure⁸⁴ or following cardiac surgery.⁸⁵

In accordance with these studies, there is accumulating evidence regarding the role of an assay detecting mid-regional proANP (MR-proANP). Given that NT-proANP has a much longer half-life than mature ANP and is more stable under laboratory conditions,^{86,87} NT-proANP seems as a more reliable analyte to measure. Available assays for the detection of NT-proANP used an antibody against the N-terminal region combined with a second antibody against either the mid-region or the C-terminal region.^{88–90} Since under certain conditions, the N-terminal region may be minimally accessible for antibody binding, an immunoassay for the mid-region of proANP was developed in 2004.⁹¹ Improvement in analytical performance by MR-proANP assays could improve their ability in identifying patients at increased risk for AF. In the Malmö Diet and Cancer Study, higher MR-proANP levels predicted incident AF, whereas in the Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico - Atrial Fibrillation (GISSI-AF) study, higher MR-proANP levels independently predicted a higher risk for AF recurrence.^{92,93} Finally, MR-proANP concentration has recently been shown to reliably identify the time from onset of AF to presentation.⁹⁴

Several studies have examined the association of SR maintenance post-ECV with ANP and NT-proANP levels before the procedure (see

Table 2).^{51,60,95–100} In half of the existing studies, ANP levels were higher in patients who succeeded in maintaining SR,^{51,96,99,100} whereas in the other half, ANP levels were lower.^{60,95,97,98} According to the available evidence, an association between AF recurrences after successful ECV and ANP levels before the procedure cannot be established.

The discrepancies observed in the available studies can be explained considering the mechanism of ANP production in patients with AF. As mentioned, ANP secretion is mainly regulated by mechanical stretching of the atria. This can be reflected in the positive correlation between ANP levels and LA volume, which has been established in several studies using echocardiography and cardiac magnetic resonance.^{101–104} In accordance with BNP levels, higher ANP levels have been associated with LV diastolic dysfunction and increased filling pressures,^{105–107} hence patients with higher ANP levels during the acute phase of an episode of persistent AF may be predisposed to an increased risk of AF recurrences.

Apart from between-patient differences, increased ANP levels during an AF episode are probably an acute physiological response to increased atrial pressure.¹⁰⁸ Following restoration of SR, plasma ANP concentration is rapidly decreased in conjunction with filling pressures.⁸³ Thereafter, a gradual normalisation of ANP levels is observed concomitantly with atrial mechanical function improvement.¹⁰⁹

When SR is not restored and AF becomes long-standing, several morphological changes, termed structural remodeling, ensue in the atrial myocardium. The main changes include interstitial fibrosis and cellular dedifferentiation and apoptosis,^{110–112} resulting in functional cell loss and reduced ANP production. This inverse association between atrial structural damage and ANP production has been observed in a histopathological study of patients with mitral valve disease,¹¹³ and is considered the basis of the inverse association between AF duration and ANP levels.^{114,115} Hence, in patients with long-standing AF, lower ANP levels reflect pronounced atrial remodeling and would predict a difficulty in maintaining SR following cardioversion.

In conclusion, according to the evidence provided, the use of BNP or NT-proBNP for prediction of long-term response to ECV appears to be useful. Therefore, further research should be done to investigate a cut-off value indicating that SR maintenance is feasible following ECV. Conversely, since ANP concentration can be influenced in an opposing manner by both filling pressure and the extent of structural remodeling, its use as a predictor of AF recurrences is not reasonable, which is also reflected in the relevant studies. ■

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