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Occurence of implantable cardioverter-defibrillator therapy in clinical practice

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SOUHRN

Průlomové studie MADIT II, SCD-HeFT a COMPANION v letech 2002–2005 prokázaly pozitivní výsledky ve snížení výskytu náhlé srdeční smrti. Od té doby došlo k podstatnému rozšíření indikací pro použití implantabilních kardioverterů-defibrilátorů (ICD). Výskyt vhodné terapie ICD se v jednotlivých studiích liší. Retrospektivně jsme analyzovali výskyt komorové tachykardie / komorové fibrilace (KT/KF) z databáze vzdáleného monitorování ICD (Biotronik Home Monitoring TM, www.biotronik-homemonitoring.com). Nebyl zjištěn žádný významný rozdíl mezi podskupinami rozdělenými na základě indikace implantace, programované stimulace komor, agresivity protokolu programované stimulace komor, ejekční frakce levé komory, typu ICD, procenta stimulace pravé komory, diabetes mellitus, renální dysfunkce a pohlaví. Komorové tachykardie / komorové fibrilace se statisticky významně častěji vyskytovaly u pacientů se záchytem nesetrvalé KT během preimplantační holterovské monitorace EKG, a to u pacientů s ischemickou chorobou srdeční z primárně preventivní indikace, ale ne u pacientů s neischemickou dilatační kardiomyopatií z primárně preventivní indikace. U pacientů s preimplantační synkopou nebo presynkopou jsme pozorovali vyšší výskyt KT/KF, a to vyšší než u pacientů po kardiopulmonální resuscitaci. Trend pro vyšší výskyt KT/KF byl patrný u pacientů s pozitivní programovanou stimulací komor, zvláště u málo agresivního protokolu a u pacientů s ejekční frakcí levé komory 30 % a méně. Autoři shledali preimplantační nesetrvalé komorové tachykardie (NSKT) na holterovské monitoraci EKG jako jediný nezávislý prediktor výskytu KT/KF.

ABSTRACT

The landmark trials MADIT II, SCD-HeFT, and COMPANION in 2002–2005 years have reported their positive results to sudden cardiac death reduction. Since that time the indications for the use of implantable cardioverter-defibrillators (ICDs) have substantially broadened. The occurrence of appropriate ICD therapy differs in the individual trials. We were retrospectively analyzing the occurrence of ventricular tachycardia/ventricular fibrillation (VT/VF) from ICD remote monitoring database (Biotronik Home Monitoring TM, www.biotronik-homemonitoring.com). No significant difference was found between subgroups divided by the implantation indication, the programmed ventricular stimulation, the aggressivity of programmed ventricular stimulation protocol, left ventricular ejection fraction, ICD types, percentage of right ventricular pacing, diabetes mellitus, renal dysfunction and gender. VT/VF occurred statistically significantly more often

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in patients with non-sustained VT on the preimplant Holter monitoring report in patients with primary preventive indication for postinfarction coronary artery disease but not in primary preventive indication for non-ischemic dilated cardiomyopathy. We observed higher VT/VF occurrence in patients with preimplant syncope or presyncope even higher than in patients after cardiopulmonary resuscitation. There was a visible trend for higher VT/VF occurrence in patients with positive programmed ventricular stimulation especially with less aggressive protocol and in patients with left ventricular ejection fraction of 30% and less. Authors found the preimplant nonsustained ventricular tachycardia (NSVT) on Holter monitoring as the only independent predictor of VT/VF occurrence.

Introduction

The landmark trials MADIT II, SCD-HeFT, and COMPANION in 2002–2005 years have reported their positive results to sudden cardiac death reduction [1–3]. Since that time the indications for the use of implantable cardioverter-defibrillators (ICDs) have substantially broadened.

Implantable cardioverter-defibrillators implantation rate varies very much between different countries and continents. There is a stabile trans-Atlantic difference over 10 years. The average implantation rate in Western Europe is 155 per million people [4], in contrary to the US, where it ranges up to 833 per million people [5]. It is still suggested that ICDs are underutilized at both sides of the Atlantic when compared to guidelines.

The ICD implantation rate in the Czech Republic reached around 335 per million people in 2014 [6].

The occurrence of appropriate ICD therapy differs in the individual trials. ICD remote monitoring database enables a user-friendly data system for ICD therapy analysis in the clinical practice.

Methods

Data from ICD remote monitoring database (Biotronik Home Monitoring TM, www. biotronik-homemonitoring. com) were retrospectively analyzed. Only data of ICDs monitored for 2 years after the first implantation were utilized for the analysis. ICDs deactivated from any reason within the analyzed period were discarded. The occurrence of appropriate ICD therapy was described. Possible predictors of the ICD therapy occurrence were analyzed.

Subgroups

For the analysis, the patients were divided into several groups:

1. By the implantation indication: SP (secondary preventive, that means patients after documented hemodynamically significant ventricular tachycardia [VT] or fibrillation [VF]), PP (primary preventive with coronary artery disease, that means patients after myocardial infarction with low left ventricular ejection fraction LVEF ≤ 35 %), DC (primary preventive in patients with non-ischemic dilated cardiomyopathy with LVEF ≤ 35 %). Primary preventive implants from other reasons were discarded.
2. By the programmed ventricular stimulation (PVS) (as a part of electrophysiological study) result: PVS+ (inducible VT/VF during PVS, performed by maximum 3 extrastimuli into paced rhythm 120–160 per minute), PVS– (non-inducible VT/VF). In PVS+ subgroup, divided by the PVS aggressivity: PVSagg (aggressive protocol, defined as the inducibility in 140 ppm and 2 extrastimuli or 160 ppm and 1–3 extrastimuli), PVSnonagg (nonaggressive protocol, defined as the inducibility in 120 ppm or in 140 ppm and 1 extrastimuli). The extrastimuli coupling interval was not lower than 200 ms.
3. By the Holter monitoring result (in PP and DC indication subgroups only): NSVT+ (patients with non-sustained ventricular tachycardia of 4 and more premature beats, NSVT, in Holter monitoring), NSVT– (patients without NSVT), in all primary preventive patients and separately for PP and DC indication: PP-NSVT+, PP-NSVT– (patients with resp. without NSVT in PP indication subgroup), DC-NSVT+, DC-NSVT- (patients with resp. without NSVT in DC indication subgroup).
4. By the LVEF: EF30 (patients with LVEF ≤ 30%), EF31 (patients with LVEF ≥ 31%).
5. By the ICD type: VR (single-chamber ICD), DR (dual-chamber ICD, including biventricular ICDs without functional left ventricular lead), HF (biventricular ICD). In VR and DR subgroups, the average right ventricular pacing percentage (VP%) was compared between ICDs with resp. without ICD therapy. In the same subgroups, VT/VF therapy occurrence was compared between ICDs with VP% of 40% and higher (VP%40 subgroup) versus VP% below 40 % (VP%39 subgroup).
6. By the concomitant diseases: by the diabetes mellitus presence: DM+ (patients with diabetes mellitus DM), DM– (patients without DM), by the renal insufficiency defined by serum creatinine level above 150 μmol/l = 2 mg/dl: CRI+ (patients with high serum creatinine level), CRI– (patients with low creatinine level).
7. By the gender: M (males), F (females).
8. According to the preimplant symptomatology: ASYMP (without pre/syncope), SYNC (syncope or presyncope), CPCR (patient after cardiopulmonary resuscitation).

Statistics

All data are presented as mean values ± standard deviation for continuous variables and as percentages for categorical variables. The Kaplan-Meier analysis with a log-rank test was used to compare the occurrence of ICD therapy. The association between potential risk factors and ICD therapy was analyzed via a univariate logistic regression model. For the parameters with the potential predictive power (providing at least $p < 0.10$ in univari-

ate logistic regression), a multivariate model was used. Results with p-value < 0.05 are considered statistically significant. The statistical package used was SAS Software.

Results

Since April 2008 till June 2015, 187 ICDs after first implantation were activated for remote monitoring (Biotronik Home Monitoring system). The 2-year monitoring period was available for 147 ICDs. Reasons for deactivation during first two years were: death (23), heart transplantation (10), non-compliance (5), premature reimplantation (1) and transmission problems (1). Demographic and preimplant data of analyzed ICDs are mentioned in the Table 1. There was no statistical difference in the demographic data.

At least one episode of detection of VT/VF occurred in 57 (38.8%) of ICDs during 24-month follow-up. VT/VF occurrence in the individual subgroups is displayed in Table 2.

Difference between indication subgroups

VT/VF was detected in 32.8–44.8% in individual subgroups. ICDs in secondary preventive indication had non-significantly higher occurrence of VT/VF (p = 0.3278), see Table 2 and Fig. 1.

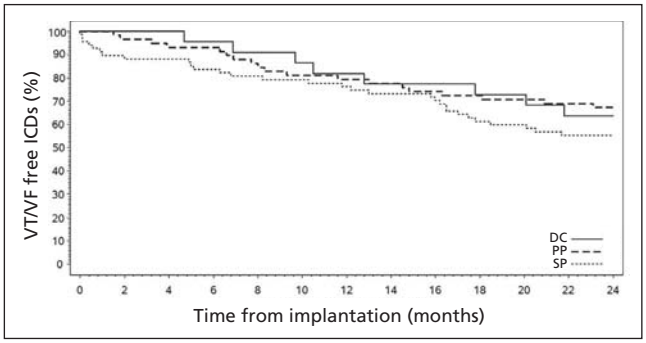

Fig. 1 – Percentage of ICDs without VT/VF detection during 24 months in SP (secondary preventive), PP (primary preventive in coronary artery disease) and DC (primary preventive in dilated cardiomyopathy) subgroups.

Difference between subgroups with regard to programmed ventricular stimulation result

Positive programmed ventricular stimulation was associated with 54.2% possibility of VT/VF occurrence during 24 months. On contrary, negative results were associated with only 33.3%. Due to low numbers (antiarrhythmic drug testing by PVS is not a part of the indication process since 2009) the difference did not reached the 5% significance level, see Table 2.

Positive programmed ventricular stimulation in less aggressive step was associated with 64.3% probability of VT/VF occurrence during 24 months. Aggressive protocol leads to 44.4% of VT/VF occurrence. The result was not statistically significant probably due to low numbers. See Table 2.

Difference between Holter monitoring subgroups

Occurrence of non-sustained VT/VF was analyzed only for PP and DC subgroups as majority of SP patients had Holter monitoring data missing. Positive result was associated with 42.9% occurrence of VT/VF in 24-month follow-up, negative result only with 23.7%. The difference reached significant level of p = 0.05. See Table 2 and Fig. 2A.

In PP indication subgroup, occurrence of NSVT resp. non-occurrence of NSVT in Holter monitoring was associated with 44.1% resp. 16.7% probability of VT/VF occurrence during 24-month follow-up. The difference was highly statistically significant with p = 0.0251, see Fig. 2B.

In DC indication subgroup, the NSVT occurrence in Holter monitoring did not predict VT/VF occurrence in 24-month follow-up, see Table 2 and Fig. 2C.

Difference between LVEF subgroups

Left ventricular ejection fraction of 30% and lower was associated with non-significant (p = 0.54) higher probability of VT/VF occurrence compared to LVEF of 31% and higher, see Table 2.

Difference between ICD types

We observed non-significantly higher VT/VF occurrence in DR subgroup and lower VT/VF occurrence in HF subgroup.

Table 1 – Demographic and preimplant data of analyzed ICDs (N = 147), of ICD with VT/VF occurrence (N = 57) and of ICDs without VT/VF occurrence (N = 90).

Parameter	All (N = 147)	VT/VF occurred (N = 57)	No VT/VF occurred (N = 90)
Gender (N [%] males)	129 (88%)	52 (91%)	77 (86%)
Age at implantation (years)	64.3 ± 11.1	63.3 ± 10.6	64.9 ± 11.2
Left ventricular ejection fraction (%)	29.5 ± 12.3	29.9 ± 13.2	29.2 ± 11.7
Implantation indication SP/PP/DK (%)	46/39/15	53/33/14	41/43/16
Holter results VT/VF/NSVT/non-significant finding/unavailable	35/35/6/23	42/36/2/19	31/34/8/25
Programmed ventricular stimulation results Positive/negative/not done (%)	16/6/78	23/5/72	12/7/81
Diabetes mellitus (%)	25	28	23
Renal insufficiency (%)	10	11	10

DK – primary preventive indication in dilated cardiomyopathy; NS – non-significant; PP – primary preventive indication in coronary artery disease; SP – secondary preventive indication.

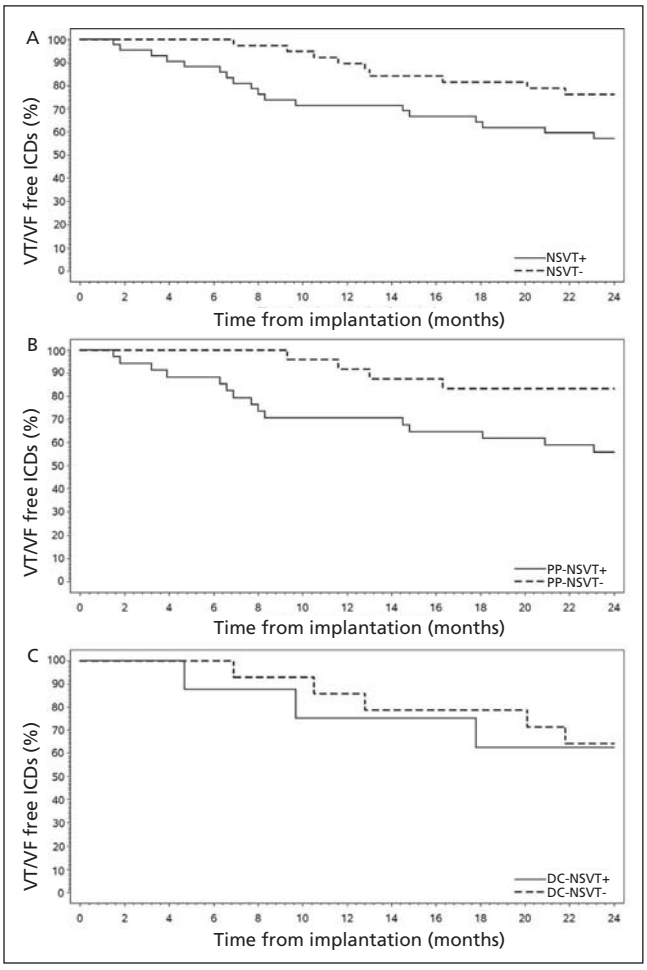

Fig. 2 – Percentage of ICDs without VT/VF detection during 24 months in NSVT+ (non-sustained VT in Holter monitoring) and NSVT– (without non-sustained VT in Holter monitoring) subgroups, (A) all primary preventive patients, (B) primary preventive patients with coronary artery disease, (C) primary preventive patients with non-ischemic dilated cardiomyopathy.

The influence of right ventricular pacing percentage was analyzed for VR and DR subgroups. VP% in ICDs with VT/VF occurrence was 19.1 ± 28.7% (median 1.4) and in ICDs without VT/VF occurrence 16.4 ± 30.9% (median 0.22). The difference was not statistically significant.

The VP% was 39.3% in DR and 11.7% in VR subgroups. No difference was found between ICDs in subgroups VP%40 and VP%39. See Table 2.

Difference in concomitant disease presence

We did not observed any significant difference in VT/VF occurrence between patients with resp. without diabetes.

Creatinine serum levels above 150 μmol/l were not associated with significantly higher occurrence of VT/VF compared to lower level. See Table 2.

Difference by gender

Males were affected by VT/VF more often than females, 40.3 % vs. 27.8 %. Due to low numbers of females the statistical significance was not reached. See Table 2.

Difference between preimplant symptomatology subgroups

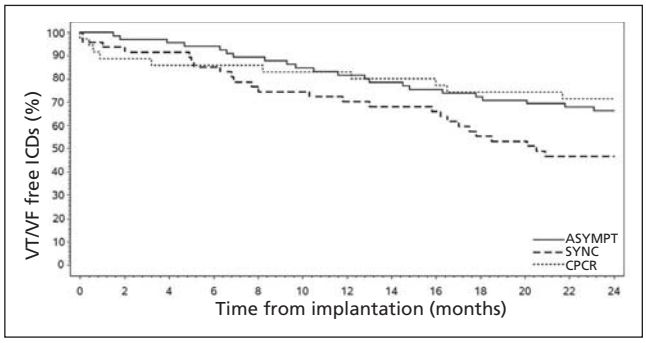

Fig. 3 – Percentage of ICDs without VT/VF detection during 24 months in ASYMP (without pre/syncope), SYNC (presyncope or syncope) and CPCR (after cardiopulmonary resuscitation) subgroups.

Table 2 – VT/VF occurrence in subgroups.

Criterion	Subgroups (N)	VT/VF occurrence (%)	*p*-value
Indication	SP (67)/PP (58)/DK (22)	30 (44.8%)/19 (32.8%)/8 (36.4%)	0.33
PVS positivity	PVS+ (24)/PVS– (9)	13 (54.2%)/3 (33.3%)	0.44
PVS aggressivity	PVSagg (9)/PVSnonagg (14)	4 (44.4%)/9 (64.3%)	0.62
NSVT	NSVT+ (42)/NSVT– (38)	18 (42.9%)/9 (23.7%)	<0.05
NSVT in PP indication	PP-NSVT+ (34)/PP-NSVT– (24)	15 (44.1%)/4 (16.7%)	0.03
NSVT in DK indication	DK-NSVT+ (8)/DK-NSVT– (14)	3 (37.5%)/5 (35.7%)	0.82
LVEF	EF30 (45)/EF31 (102)	19 (42.2%)/38 (37.3%)	0.54
ICD type	VR (74)/DR (30)/HF (43)	29 (39%)/15 (50%)/13 (35%)	0.15
VP%	VP%39 (83)/VP%40 (21)	34 (41.0%)/10 (47.6%)	0.36
Diabetes	DM+ (37)/DM– (109)	16 (43.2%)/41 (37.6%)	0.75
CRI	CRI+ (16)/CRI– (130)	7 (43.8%)/50 (38.5%)	0.98
Gender	M (129)/F (18)	52 (40.3%)/5 (27.8%)	0.30
Symptomatology	ASYMP (65)/SYNC (47)/CPCR (35)	22 (33.8%)/25 (53.2%)/10 (28.6%)	<0.05

CRI – chronic renal insufficiency; DK – primary preventive indication in non-ischemic dilated cardiomyopathy; LVEF – left ventricular ejection fraction; NSVT – non-sustained ventricular tachycardia; PP – primary preventive indication in coronary artery disease; PVS – programmed ventricular stimulation; SP – secondary preventive indication; VP% – right ventricular pacing percentage, see the text for subgroups definition.

The VT/VF has occurred significantly more often in patients with presyncope or syncope in the history, compared to asymptomatic and post-resuscitation patients. See Table 2 and Fig. 3.

Analysis of possible risk factors for VT/VF occurrence

These parameters were analyzed: DM, CHRI, EF ≤ 30%, NSVT, gender. In the multivariate logistic regression, only one parameter, NSVT, appears as a possible independent predictor of VT/VF.

Discussion

We observe very similar incidence of VT/VF in all implantation indication reaching over 32%. On the contrary, the MADIT II Trial showed only 24% incidence of appropriate therapy during mean follow-up of 20 months [7]. Other studies show much higher VT/VF occurrence in secondary preventive compared to primary preventive indication [8–9]. As mentioned above, even in our center the primary preventive implantations are underutilized due to economic barriers. More risky primary preventive patients are preferred for implantation causing higher rate of VT/VF occurrence compared to sponsored clinical trials.

PVS was not suitable to predict an appropriate ICD therapy in patients in our study. But there is a visible trend for higher VT/VF occurrence in patients with positive PVS. For low numbers, the statistical significance was not reached. In spite of the fact that many studies have documented that the inducibility of VT/VF in PVS is a risk factor for appropriate ICD therapy, all concordantly show that patients without an inducibility of VT/VF also have a high incidence of ventricular arrhythmias [10–17]. Several studies including Cardiac Arrest Study Hamburg (CASH) Study did not observe any difference between inducible and non-inducible patients [18].

Subanalysis of MADIT-II Trial showed that the predictive value of EP testing is specific to the protocol of programmed ventricular stimulation used [19]. Belhassen et al. even observed that the mortality rate in patients without inducible VT using an aggressive PVS protocol and who did not undergo subsequent ICD implantation is not different from that of patients with inducible arrhythmias who received an ICD [20].

We observed NSVT in preimplant Holter monitoring as the only independent risk factor for subsequent VT/VF occurrence. This result corresponds to SCD-HeFT observation [21]. In our study, it is a strong predictor in the primary prevention with coronary artery disease subgroup. But we did not find the association of VT/VF therapy and NSVT in preimplant Holter monitoring in non-ischemic dilated cardiomyopathy subgroup. That observation can be explained by the fact that NSVT is suggested to be more prevalent in non-ischemic dilated cardiomyopathy perhaps making it less potent as a predictor of SCD [22]. In spite of that, many studies observed NSVT in dilated cardiomyopathy as a good predictor especially when combined with low LVEF [22,23].

It is generally accepted that LVEF alone is for VT/VF prediction insufficient [24,25]. The same is observed by the authors. On contrary, Lelakowski et al. in analysis of 376 patients found even 20times higher incidence of VT/VF in patients with LVEF below 31% [26].

We observed non-significantly higher occurrence of ICD therapy in dual-chamber and non-significantly lower in biventricular ICDs. There was only small difference between single-chamber and dual-chamber ICDs. It is concordant with substudy of MADIT II Trial which shows no statistically significant difference in VT/VF occurrence between single-chamber and dual-chamber ICDs [27]. We observed a trend to lower VT/VF occurrence in biventricular devices. The reason could be found in the much discussed topic whether the right ventricular pacing is deleterious for ICD recipients or not. The DAVID Trial showed that right ventricular pacing above 40% is associated with worse outcome (death or hospitalization for congestive heart failure) [28]. In the INTRINSIC RV study the dual-chamber pacing has similar outcome as single--chamber backup pacing [29]. We compared ICD with the right ventricular pacing percentage of 40% and higher versus below 40% in single-chamber and dual-chamber devices but found no statistical difference. Very few authors compared dual-chamber and biventricular devices. Single-center studies shows that biventricular pacing reduces arrhythmogenicity [30,31].

Diabetes and renal dysfunction were associated with higher mortality but did not predict ICD therapy in majority observations [32,33]. The only exception was the just published MADIT-RIT Trial where DM was associated with significantly higher risk of VT/VF [34].

Gender difference is similar worldwide. Women are less likely to receive an ICD for primary or secondary prevention of SCD [35,36]. Only 20–30% of ICD recipients are women [37]. Women receive fewer appropriate ICD shock then men in majority studies [38,39] including SCD-HeFT, MADIT II, DEFINITE and COMPANION [1–3]. Only few authors did not find any difference between males and females in ICD therapy occurrence [40,41]. It is suggested that women have different susceptibilities to arrhythmia due to hormonal differences. But the mortality rate for males and females with severe heart failure is the same [42].

We observed higher VT/VF occurrence in patients with preimplant syncope. The reason is that syncope in structural heart disease is associated usually with ventricular arrhythmia causing a higher risk for ICD therapy. Pires et al. observed the same ICD therapy rate in patients with unexplained syncope versus in patients after documented VT/VF [43].

Conclusion

Authors analyzed data from 147 patients who underwent remote monitoring for 2 years after first ICD implantation. VT/VF therapy occurrence was analyzed. No significant difference was found between subgroups divided by the implantation indication, the programmed ventricular stimulation, the aggressivity of programmed ventricular stimulation protocol, left ventricular ejection fraction, ICD types, percentage of right ventricular pacing, diabetes mellitus, renal dysfunction and gender. VT/VF occurred statistically significantly more often in patients with non-sustained VT on the preimplant Holter monitoring

report in patients with primary preventive indication for postinfarction coronary artery disease but not in primary preventive indication for non-ischemic dilated cardiomyopathy. We observed higher VT/VF occurrence in patients with preimplant syncope or presyncope even higher than in patients after cardiopulmonary resuscitation. There was a visible trend for higher VT/VF occurrence in patients with positive programmed ventricular stimulation especially with less aggressive protocol and in patients with left ventricular ejection fraction of 30% and less. Authors found the preimplant NSVT on Holter monitoring as the only independent predictor of VT/VF occurrence.

Conflict of interest
None declared.

Funding body
None.

Ethical statement
Authors state that the research was conducted according to ethical standards.

Informed consent
I declare, that informed consent requirements do not apply to this manuscript.

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