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Evaluation of betablockers and digoxin in black African heart failure patients based on a non-interventional cohort study at Abidjan Heart Institute

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The aim was to determine the benefit of betablockers and/or digoxin on mortality in heart failure in black Africans using a comparative study. This was a prospective, non-interventional, comparative, four-arm follow-up cohort study using the Abidjan Heart Institute database. Patients were divided into four arms: betablocker alone, betablocker plus digoxin, digoxin alone, and a control group with conventional treatment without betablocker or digoxin followed for 2 years. The four groups compared were initially comparable for sociodemographic data for a total follow-up of 730.5 days, including 37 deaths at the end of this study (5.70%). In multivariate analysis, after adjustment, treatment with betablocker alone (RR 0.77, p=0.62) or combined with digoxin compared with control (RR 1.13, p=0.84) was not significantly associated with death, nor was treatment with betablocker vs non-betablocker (RR 0.58, p=0.14). On the other hand, treatment with digoxin alone compared with control (RR 3.13, p=0.0388) was significantly associated with death. Male sex, high natraemia and use of anticoagulants were the necessary factors for mortality in the digoxin group. Compared with betablockers, digoxin does not appear to have a beneficial effect on mortality in black African patients with heart failure. However, these patients on digoxin appear to be more severe. These results could be confirmed by a large, long-term study of black subjects.

Key words: Clinical trial, betablocker, digoxin, heart failure, Africa, mortality.

INTRODUCTION

Heart failure is the end stage of many cardiovascular and extracardiac diseases. Although its prevalence is underestimated in the Côte d'Ivoire, it accounts for 60% of cardiology hospitalizations in young patients aged around 54 (Kouamé, 2018), with a very poor prognosis, especially for those admitted to emergency departments in stages III and IV. The 1 and 2-year survival rates in Côte d'Ivoire were 28.7 and 15%, respectively, compared

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with a 5-year survival rate of 50% in Europe (Kouamé, 2018; Nassiet, 2015).

Beta-blockers and digoxin have demonstrated significant benefits in stable chronic heart failure

Clinical trials and scientific studies have reported the benefits of betablockers and/or digoxin in stable chronic heart failure in terms of reducing mortality, improving quality of life, symptoms and the number of rehospitalisations (Adams et al., 1997; Ahmed et al., 2009; Andrey et al., 2011; Digitalis Investigation Group, 1997; Gheorghiade et al., 2013; Katz et al., 2016; Ziff et al., 2015), but also their possible ineffectiveness (Al-Khateeb et al., 2017; Fauchier et al., 2009; Freeman et al., 2013; Katz et al., 2016; Madelaire et al., 2016; Migaj et al., 2018). However, the level of evidence is still insufficient for these compounds, especially digoxin (Martin et al., 2018).

The combination of digoxin and beta-blockers is particularly interesting as it could offer additional benefits in terms of therapeutic synergy. Studies have shown that this combination can potentially optimize symptom control and further reduce the risk of rehospitalization (Ponikowski et al., 2016). However, the data on this combination are still limited and require further investigation, especially in black African subjects.

The prevalence of the use of betablockers in heart failure in our context evolved from 0 to 19% between 2000 and 2012 (Bamba-Kamagate et al., 2016). Given the limited number of studies examining the effect of the accepted combination of digoxin and betablockers (Ponikowski et al., 2016), and with a view to improving patient management, we considered this study in our database of heart failure patients.

The aim was to determine the benefit of betablockers and digoxin on mortality at two years follow-up in heart failure in black African patients, based on a comparative study.

MATERIALS AND METHODS

This was a prospective 4-arm non-interventional comparative follow-up cohort study conducted in the Abidjan Heart Institute database over a three-month period from 11 September to 15 December 2019. It focused on data from black African heart failure patients recruited from 1 January to 31 December 2015 and followed up over 2 years. The betablockers studied were: bisoprolol, carvedilol, nebivolol and metoprolol. These medications were all in tablet form taken orally.

Sampling was exhaustive, with the population divided into four groups according to their treatment regimen: the betablocker group (β-blocker), patients who were treated with betablockers; the digoxin group (Digoxin), patients who were treated with digoxin; the betablocker and digoxin group (β-blocker + digoxin), patients who were treated with both betablockers and digoxin; and the control group, patients who were treated with standard therapy without betablockers or digoxin (neither β-blocker nor digoxin). Patients exposed to the treatment of interest were those treated with betablockers and/or digoxin compared with those not exposed.

Statistical analysis

Data were analyzed using R software version 4.0.2. The main approach of this study was similar to an intention-to-treat analysis. The association of treatments of interest with all-cause mortality during follow-up was developed using a multiple logistic regression model with adjustment for identified confounders. The adequacy of the models was verified using the Hosmer and Lemeshow test after a step-by-step selection technique. Patient confidentiality and anonymity were respected. The outcome was death during the 2-year follow-up period.

Ethics and deontology

Anonymity and confidentiality of data were ensured. This study adheres to the ethical recommendations of the Helsinki Declaration. It was approved by the Ethics and Hygiene Committee of the Cardiology Institute of Abidjan. Informed consent was required. Participation in the study was voluntary and free of charge.

RESULTS

In this study, 649 heart failure patients treated in the database were extracted. These were patients treated with betablockers alone (40.1%), betablockers plus digoxin (17.7%), digoxin alone (15.6%) and standard or conventional treatment without betablockers or digoxin (26.6%). The last group was considered to be the control group. Approximately 375 betablockers were used, including 92.0% bisoprolol, 5.6% carvedilol, 1.6% nebivolol and 0.8% metoprolol. The groups were comparable in socio-demographic terms (Table 1).

There were significant differences between the groups according to the treatment used: patients treated with a betablocker had a higher mean arterial pressure and had received more nitrates, oral anticoagulants and vasodilators. Those treated with digoxin alone had more conduction problems and took more antiaggregants, statins and diuretics. Those who took both betablockers and digoxin had more cardiovascular risk factors, were more sedentary, and had a higher average heart rate, overall heart failure and more rhythm disorders. As for the control group, they were more diabetic than the others, with a history of previous LVEF and hospitalization for heart failure, and had more hypernatremia and hyperkalaemia. During the 730.5-day follow-up, 37 of the patients died (5.70%) (Table 1).

The results of the univariate analysis of predictors of mortality are shown in Table 2. Compared with the group not taking betablockers, treatment with betablockers was associated with a lower risk of death (RR [Relative Risk] 0.42, p=0.014). Compared with the control group, treatment with betablockers alone was also associated with a lower but non-significant risk of death (RR 0.75, p=0.59). Compared with the control group, treatment with

Table 1. Initial and progressive characteristics of patients receiving or not digoxin and/or beta-blockers.

Variable	Total (N = 649)	β-blocker (n = 260)	Digoxin (n = 101)	β-blocker + digoxine (n = 115)	Control (n = 173)	p
Age (mean ± SD, year)	53.57 ± 16.37	54.99 ± 15.58	52.34 ± 16.20	51.35 ± 16.96	53.64 ± 17.13	0.199
Sex (Female)	247 (38.06)	100 (38.46)	40 (39.60)	43 (37.39)	64 (36.99)	0.9734
Sex-ratio	0.6	0.6	0.6	0.6	0.6	-
Area of residence (Abidjan)	489 (75.35)	198 (76.15)	76 (75.25)	82 (71.30)	133 (76.88)	0.7239
CRF	412 (63.48)	173 (66.54)	53 (52.48)	79 (68.70)	107 (61.85)	0.0487
HBP	405 (62.40)	159 (61.15)	63 (62.38)	70 (60.87)	113 (65.32)	0.8219
Diabetes mellitus	188 (28.97)	83 (31.92)	13 (12.87)	17 (14.78)	75 (43.35)	< 0.0000
Sedentarity lifestyle	422 (65.02)	173 (66.54)	51 (50.50)	82 (71.30)	116 (67.05)	0.0076
Previous LVEF	386 (59.48)	170 (65.38)	42 (41.58)	57 (49.57)	117 (67.63)	< 0.0000
History of hospitalisation / CHF	424 (65.33)	195 (75.00)	43 (42.57)	45 (39.13)	141 (81.50)	< 0.0000
Cardiomegaly	615 (94.76)	244 (93.85)	96 (95.05)	112 (97.39)	163 (94.22)	0.5399
CTI (mean ± SD)	0.65 ± 0.07	0.65 ± 0.07	0.65 ± 0.07	0.65 ± 0.06	0.66 ± 0.08	0.463
HR (mean ± SD)	98.61 ± 23.37	96.48 ± 21.51	101.30 ± 20.11	107.68 ± 24.55	94.27 ± 25.31	< 0.0000
SBP (mean ± SD)	127.18 ± 32.10	134.99 ± 30.90	107.56 ± 27.55	121.00 ± 31.10	131.01 ± 31.67	< 0.0000
DBP (mean ± SD)	85.92 ± 22.09	90.06 ± 21.43	76.23 ± 21.57	85.70 ± 22.84	85.50 ± 21.19	< 0.0000
HF type (global)	290 (44.68)	86 (33.08)	84 (83.17)	98 (85.22)	22 (12.72)	< 0.0000
HRT	198 (30.51)	47 (18.08)	54 (53.47)	79 (68.70)	18 (10.40)	< 0.0000
CCD	208 (32.05)	96 (36.92)	39 (38.61)	30 (26.09)	43 (24.86)	0.0127
Natremia (elevated)	20 (3.08)	8 (3.08)	2 (1.98)	0 (0.00)	10 (5.78)	0.0399
Kalemia (elevated)	70 (10.79)	22 (8.46)	9 (8.91)	8 (6.96)	31 (17.92)	0.0249
Uremia (elevated)	307 (47.30)	111 (42.69)	62 (61.39)	52 (45.22)	82 (47.40)	0.0506
Creatininaemia (elevated)	223 (34.36)	82 (31.54)	39 (38.61)	46 (40.00)	56 (32.37)	0.1185
Oxygen therapy on admission	599 (92.30)	240 (92.31)	100 (99.01)	115 (100.00)	144 (83.24)	< 0.0000
Diuretics	626 (96.47)	253 (97.31)	101 (100.00)	115 (100.00)	157 (90.75)	< 0.0000
Nitrate derivatives	233 (35.90)	117 (45.00)	9 (8.91)	38 (33.04)	69 (39.88)	< 0.0000
Anticoagulants	460 (70.88)	212 (81.54)	36 (35.64)	74 (64.35)	138 (79.77)	< 0.0000
Antiaggregants	278 (42.84)	113 (43.46)	52 (51.49)	54 (46.96)	59 (34.10)	0.0254
Statins	237 (36.52)	100 (38.46)	51 (50.50)	47 (40.87)	39 (22.54)	< 0.0000
Vasodilators	501 (77.20)	242 (93.08)	54 (53.47)	74 (64.35)	131 (75.72)	< 0.0000
Overall mortality	37 (5.70)	8 (3.08)	16 (15.84)	6 (5.22)	7 (4.05)	< 0.0000

Table 2. Univariate analysis of predictors of all-cause mortality in patients with heart failure (Simple logistic regression).

Predictive factor	Relative risk (95% CI)	P
Treatment with beta blocker (vs non-beta blocker)	0.423 (0.209-0.829)	0.0137
Treatment with digoxin (vs non-digoxin)	3.160 (1.616-6.342)	0.0009
Treatment with beta blocker alone (vs control*)	0.753 (0.265-2.185)	0.59
Treatment with digoxin alone (vs control)	4.464 (1.831-11.998)	0.0015
Treatment with beta blocker and digoxin (vs control)	1.305 (0.410-4.031)	0.64
Age	1.011 (0.991-1.033)	0.2976
Male	2.765 (1.264-6.940)	0.0174
Abidjan	1.737 (0.762-4.689)	0.2254
CRF	0.742 (0.381-1.472)	0.3831
HBP	0.877 (0.450-1.757)	0.7036
Diabetes mellitus	1.040 (0.484-2.097)	0.9162
Sedentarity lifestyle	1.128 (0.567-2.368)	0.7383
Previous LVEF	0.560 (0.284-1.090)	0.0879
History of hospitalization / CHF	0.540 (0.276-1.057)	0.0694
Cardiomegaly	0.605 (0.202-2.606)	0.4245
CTI	0.928 (0.008-96.038)	0.9752

Table 2. Cont'd

HR	0.991 (0.977-1.005)	0.2158
SBP	0.985 (0.972-0.996)	0.014
DBP	0.975 (0.958-0.991)	0.0033
HF type (right)	0.634 (0.315-1.248)	0.1909
HRT	2.274 (1.158-4.448)	0.0159
CCD	1.312 (0.646-2.575)	0.4384
Natremia (elevated)	5.594 (1.176-20.368)	0.0144
Kalemia (elevated)	2.516 (1.021-5.630)	0.0319
Uremia (elevated)	1.816 (0.928-3.682)	0.0870
Creatininaemia (elevated)	1.492 (0.747-2.935)	0.2481
Oxygen therapy on admission	0.671 (0.253-2.320)	0.4683
Diuretics	-	-
Nitrate derivatives	0.340 (0.159-0.872)	0.0316
Anticoagulants	0.288 (0.145-0.564)	0.0003
Antiaggregants	1.439 (0.738-2.815)	0.2832
Statins	1.348 (0.679-2.627)	0.3831
Vasodilators	0.682 (0.337-1.471)	0.3037

*Control = Patients not treated with beta-blocker or digoxin. SD: standard deviation, CRF: cardiovascular risk factors, LVEF: Left ventricular ejection fraction, HBP: High Blood Pressure, CHF: congestive heart failure, CTI: cardiothoracic index, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, HRT: rhythm disorder, CCD: cardiac conduction disorder.

betablockers and digoxin was associated with a non-significant increased risk of death (RR 1.31, p=0.64). Digoxin taken alone without a betablocker, compared with the control group, was associated with a significantly elevated risk of death (RR 4.46, p=0.0015). Also, digoxin taken with or without a betablocker resulted in a statistically elevated risk of death (RR 3.16, p=0.0009).

Certain factors were associated with better survival: mean systolic blood pressure (RR 0.99, p=0.014) and mean diastolic blood pressure around normal (RR 0.98, p=0.003), use of nitrates (RR 0.34, p=0.032) and anticoagulants (RR 0.29, p=0.0003). Other factors were associated with a higher risk of death: being male (RR 2.77, p=0.017), having a rhythm disorder (RR 2.27, p=0.02), hypernatremia (RR 5.59, p=0.014) and hyperkalaemia (RR 2.52, p=0.032). The other factors were not associated with death (Table 2).

The search for interaction with the two variables of interest (betablocker and digoxin) led to the retention of natraemia (p=0.01), which proved to be non-significant in the final model.

After adjustment, treatment with betablocker alone (aRR [adjust Relative Risk] 0.77, p=0.62) or combined with digoxin compared with control (aRR 1.13, p=0.84) was not significantly associated with death, nor was treatment with betablocker vs non-betablocker (aRR 0.58, p=0.14) (Table 3). As for digoxin, treatment with digoxin alone compared with control (aRR 3.13, p=0.0388) was significantly associated with death, as was treatment with digoxin vs non-digoxin (aRR 2.41, p=0.0209).

Three factors were associated with mortality in multivariate analysis: being male (aRR 2.59, p=0.0320), having hypernatremia (aRR 8.18, p=0.0073) and taking anticoagulants (aRR 0.39, p=0.01) (Table 3).

DISCUSSION

In this study, the most commonly used betablocker was bisoprolol (92%); this use of bisoprolol was identical to that found in Mali by Maiga et al. (2019) (87%). This could be due to the hemodynamic state of our patients. In Malaysia, Lu et al. (2016) showed a predominance of Metoprolol use in their study (46%). In Switzerland, Lopes and Sartori (2018) reported greater use of Carvedilol. This preference for Carvedilol could be explained by its favourable vasodilatory, anti-endothelin-1, antioxidant and metabolic effects (Bakris et al., 2004). The present study showed that betablockers did not provide any additional benefit to the standard treatment of heart failure, whereas digoxin appeared to be deleterious.

The results contrasted with the conclusions of the DIG randomized trial, which showed that digoxin had no effect on the risk of death but did reduce the number of hospital admissions for heart failure (Digitalis Investigation Group, 1997).

This may be due to a number of differences between the two studies. The digoxin users in this cohort were black African subjects with congestive heart failure with cardiomegaly, tachycardia, rhythm and conduction disorders. They appeared to be more clinically severe

Table 3. Multivariate analysis of predictors of all-cause mortality in patients with heart failure (Multiple Logistic Regression).

Variable	Initial model, n= 649			Final model, n= 649		
	Coefficient	p	RR	Coefficient	p	RR
Treatment with beta blocker (vs non-beta blocker)	0.05781	0.93383	1.060	-0.5468	0.13784	0.5788
Treatment with digoxin (vs non-digoxin)	-0.9215	0.33435	0.3979	0.8812	0.0209	2.413
Treatment with beta blocker alone (vs control*)	0.1887	0.7625	1.208	-0.2611	0.624	0.7702
Treatment with digoxin alone (vs control)	2.048	0.04224	7.75	1.1421	0.03882	3.1332
Treatment with beta blocker and digoxin (vs control)	-0.5717	0.6952	0.5646	0.1233	0.84134	1.1313
Sex (Male)	1.005	0.03674	2.732	0.9505	0.03196	2.5871
Area of residence (Abidjan)	1.093	0.06064	2.9822			
Previous LVEF	-0.5542	0.36942	0.5746			
History of hospitalization / CHF	-0.04124	0.95331	0.9596			
HR	-0.01518	0.09219	0.9849			
SBP	0.001528	0.86721	1.0015			
DBP	-0.0119	0.34586	0.9688			
HF type (right)	1.134	0.06183	3.108			
HRT	1.094	0.03379	2.9871			
Natremia (elevated)	1.139	0.37077	3.1241	2.1020	0.00729	8.1827
Kalemia (elevated)	0.9664	0.05815	2.629			
Uremia (elevated)	0.1696	0.72223	1.185			
Creatininaemia (elevated)	-0.03173	0.94709	0.9688			
Nitrate derivatives	-0.2929	0.56894	0.7461			
Anticoagulants	-1.151	0.00765	0.3162	-0.9519	0.01295	0.3860
Natremia elevated: betablocker	-16.22	0.99413	0.00			
Natremia low: betablocker	-0.6624	0.44672	0.5156			
Natremia elevated: digoxin	21.88	0.99604	$3.168 10^{9}$			
Natremia low: digoxin	2.449	0.01541	11.5764			

*Control = patients not treated with beta-blocker or digoxin. LVEF: Left ventricular ejection fraction, CHF: congestive heart failure, CTI: cardiothoracic index, HR: heart rate, SBP: systolic blood pressure, DBP: diastolic blood pressure, HRT: rhythm disorder.

patients. However, the patients taking betablockers were hypertensive and diabetics taking anticoagulants and nitrates. These results suggest significant differences in the epidemiology of heart failure treated with these two drugs. Digoxin and betablockers block the atrioventricular nodes. It was hypothesized that their combination could lead to heart block or bradycardia, resulting in significant morbidity and mortality. However, it was found that the results of this study with digoxin were similar in the presence or absence of betablocker use. Another possible explanation for the difference between our results and those of the DIG trial could be the structure of the study. The DIG trial was an intention-to-treat interventional study.

Apart from the DIG trial, several studies have also reported the benefit of digoxin with or without betablockers (Adams et al., 1997; Ahmed et al., 2009; Andrey et al., 2011; Gheorghiade et al., 2013; Ziff et al., 2015). However, Andrey et al. (2011) carried out one of the few recent studies showing a positive influence of digoxin on mortality and morbidity, which was not based on data from the DIG study. In fact, the vast majority of studies were conducted a few years ago, which makes their conclusions questionable in an era of widespread use of betablockers.

Two other studies looked specifically at the use of digoxin and betablockers. Fauchier et al. (2009) showed that digoxin alone had a neutral impact on survival, but the addition of a betablocker significantly improved outcomes. In their study, treatment with betablocker alone and digoxin plus betablocker had a similar positive effect, but their patients had both heart failure and atrial fibrillation. Katz et al. (2016) reported similar results in a cohort of heart failure patients, some of whom had atrial fibrillation.

Other studies (Khand et al., 2003) have also shown that in patients with heart failure and atrial fibrillation, the combination of digoxin and carvedilol reduced symptoms, improved ventricular function and symptom scores, and led to better control of ventricular rate than either agent alone. However, follow-up was short and mortality was not addressed.

These results extend reports from recent observational studies suggesting a higher risk of death with digoxin in

the current era of treatment, probably related to the severity of the clinical pictures, as seen in the present study (Al-Khateeb et al., 2017; Freeman et al., 2013; Katz et al., 2016; Madelaire et al., 2016; Migaj et al., 2018). In the same vein, Hashim et al. concluded at the end of the DIG ancillary trial that digoxin did not influence the outcome of patients with heart failure, without, however, mentioning the increased risk of mortality (Hashim et al., 2014).

This excess risk of digoxin-related mortality in our study could be due to digoxinemia outside the therapeutic range of this drug. Several authors have shown that low serum digoxin concentrations are associated with better outcomes (0.5 to 0.7 ng/ml, HR 0.77 (Adams et al., 2016) or 0.5 to 0.9 ng/ml, HR 0.77 (Ahmed et al., 2006)) and that digoxin reduces one-year mortality (HR 0.89) and the risk of hospitalisation (HR 0.82) in heart failure patients treated with Angiotensin Converting Enzyme (ACE) (Ahmed et al., 2009). These authors attributed the increased mortality of patients on digoxin to its toxicity, that is, high doses and high serum concentrations. Unfortunately, serum digoxin concentrations were not available for this analysis, but daily doses were those recommended (Yves, 2007). A post hoc analysis of the DIG trial by Rathore et al (Rathore et al., 2003) also suggested that the efficacy and safety of digoxin may vary according to serum digoxin concentration.

In this cohort, there was no significant difference in digoxin dose between those who died and those who survived, but digoxin concentrations were not systematically checked, reflecting community practice of measuring concentrations only if digoxin toxicity was suspected. Normal digoxinemia has been reported in patients with clinical signs of digitalis intoxication at Abidjan Heart Institute (Bamba-Kamagate et al., 2013). The results also call into question the post hoc analysis of the DIG trial by Rathore et al. (2002), which showed that digoxin was associated with a significantly higher risk of death in women (HR, 1.23; 95% CI, 1.02-1.47) but not in men (HR, 0.93; 95% CI, 0.85 to 1.02; p = 0.014 for interaction). The authors suggested that these results may be due to sex-related differences in digoxin pharmacokinetics, indicating that a lower dose may be required for women to maintain an optimal serum digoxin concentration. However, subsequent studies did not demonstrate differential pharmacokinetics of digoxin based on patient sex, and results showed that outcomes associated with digoxin use did not vary between men and women, despite men being more likely to die from heart failure. Hypernatremia and male gender appeared to be detrimental factors in mortality, multiplying the risk by 8 and 2.5, respectively. Optimal treatment of heart failure and the use of anticoagulants thus seem to be appropriate strategies in this black African population, consistent with findings from the study by Migaj et al. (2018). In this context, digoxin is indicated for heart failure in patients with NYHA stages III and IV and is used in cases of atrial fibrillation to control the rate during the congestive stage, as betablockers cannot be used.

Beta-blockers are reserved for use during recovery from congestion. Non-interventional studies like this one can be useful as they illuminate the use of competing or concomitant treatment options in current practice and include high-risk patients who are often not represented in clinical trials.

STUDY LIMITATION

As a non-interventional study of outcomes associated with therapy, the possibility of residual confounding in terms of clinical outcomes, treatments associated with the treatment of interest, and the quality of patient management cannot be completely excluded. Attrition bias was corrected by intention to treat. The lack of systematic measurement of digoxin levels also posed a limitation. However, the average daily dose was 0.25 mg per day (1/2 to 1 tablet per day). Despite these limitations, this preliminary exploratory study in black Africans has the merit of being conducted in a real-life situation. Finally, this work contributes to the understanding of the value of beta-blockers and digoxin in heart failure.

Conclusion

The management of heart failure in black Africans in Côte d'Ivoire with or without betablockers and/or digoxin would have a different mortality. The contribution of digoxin to in-hospital mortality in black Africans does not appear to be beneficial compared with betablockers. Digoxin appears to be administered in severe congestive heart failure in emergency situations. These results could be confirmed by a long-term cohort study of larger black subjects.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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