Frequency of Cardiovascular Events in Patients Treated with Antihypertensive Agents: A Cohort Study Based on Claims Data Generated by Primary Care Practice

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ABSTRACT

Background: Large-scale clinical trials have shown that antihypertensive drugs reduce the risk for cardiovascular events. However, little is known about the effectiveness of these drugs in the primary care setting.

Objective: The aim of this study was to investigate the frequency of cardiovascular events during treatment with either of 2 of the most frequently prescribed antihypertensive drugs.

Methods: This observational, longitudinal, cohort study considered the entire population listed in the administrative databases of the Local Health Authority of Ravenna, Italy (356,000 residents). The demographic registry and the pharmaceutical and nosocomial databases were cross-linked to determine drug treatment, as well as the frequency of cardiovascular events on a patient-by-patient basis. Each patient aged >18 years receiving a first prescription for amlodipine or enalapril in the period between January 1, 1996, and December 31, 2000, with ≥ 6 months of continuous treatment with the drug was included. The follow-up period varied from 6 months to 4.5 years.

Results: Of the 7500 patients analyzed (4092 women and 3408 men; mean [SD] age, 68.0 [12.4] years), 2231 (29.7%) were given amlodipine and 5269 (70.3%) were given enalapril. The observed rate of cardiovascular events was higher among patients treated with amlodipine (54 per 1000 patient-years vs 46 per 1000 patient-years; $P = 0.007$), with a hazard ratio 17% higher compared with enalapril (95% CI, 5.0–24.0; $P = 0.007$). The result was also confirmed using Cox multivariate regression analysis. The combination of enalapril plus diuretic showed the lowest risk for cardiovascular events (0.73; 95% CI, –36.0 to –16.0; $P < 0.001$).

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Conclusion: This analysis showed that treatment with enalapril was associated with a significantly lower frequency of cardiovascular events compared with amlodipine. (*Curr Ther Res Clin Exp.* 2004;65:398–412) Copyright © 2004 Excerpta Medica, Inc.

Key words: epidemiology, hypertension, pharmacology, statistics.

INTRODUCTION

Coronary heart disease (CHD) remains one of the main causes of death in industrialized countries, despite a considerable increase in recent years in the implementation of procedures to control cardiovascular risk factors.^{1–5} Among the various risk factors involved in the pathogenesis of CHD (eg, hypercholesterolemia, diabetes mellitus, age, cigarette smoking, obesity, family history), arterial hypertension plays a leading role.^{6–9}

A series of large-scale, randomized, controlled trials^{10–15} (RCTs) have clearly established that pharmacologic treatment of hypertension reduces the frequency of fatal and major nonfatal cardiovascular events. To make an overall assessment of the therapeutic effectiveness of the drugs, these studies were conducted under strict treatment conditions, requiring absolute adherence to criteria such as persistence with treatment, a dosage-titration model, follow-up, and tolerability (including the patient's quality of life). In general practice, the implementation of a therapeutic strategy designed to achieve certain therapeutic objectives, such as a reduction in the risk for cardiovascular events, is not an easy task, especially with regard to persistence with treatment.^{16–19} General practitioners work under conditions that are different from conditions in RCTs.^{20,21} In the general practice setting, moreover, the amount of information on the reduction of cardiovascular events associated with antihypertensive treatment is limited.

Considering the high prevalence of hypertension (especially in light of the progressive aging of the population) and the resulting economic impact, it is clear that, for the Italian National Health Service (NHS), hypertension represents both a cause for concern and an important challenge in the rational management of resources.

The primary objective of this study was to analyze the combined frequency of fatal and nonfatal cardiovascular events in patients undergoing treatment with either of 2 of the most frequently prescribed antihypertensive drugs by examining real primary care data stored in a large population database. We also assessed the patterns of patient exposure to antihypertensive drugs, considering the levels of persistence, discontinuation, switching, and combination therapy.

PATIENTS AND METHODS

Study Design

This observational, longitudinal, cohort study was designed to measure the frequency of cardiovascular events in a cohort of patients registered with the Local Health Authority (LHA) of Ravenna (a mid-northern region of Italy with a population of ~356,000 people) who were undergoing treatment with enalapril or amlodipine between January 1, 1996, and December 31, 2000. Assessment of the use of the antihypertensive drugs was based on the results obtained from cross-linking administrative data derived from the clinical practices of all 320 general practitioners in the LHA of Ravenna. LHA is a government organization that provides health care services to the entire population of a given region (generally a province) and works toward achieving the public health objectives of the NHS.

The procedure we used to cross-link claims data has been extensively applied by us in the past, and it provided methodologically and statistically reliable results.^{19,22-25} The follow-up period lasted from a minimum of 6 months to a maximum of 4.5 years.

Data

The data examined were taken from a database developed by the LHA for administrative purposes. In particular, the demographic registry and the pharmaceutical and nosocomial databases were used (**Figure 1**). A database with this structure makes it possible to analyze the health events of each patient individually; it is useful in performing epidemiologic and economic studies.²⁶ The information contained in the 3 databases was cross-linked using the personal health code, which uniquely identifies each patient, making it possible to scan individual longitudinal records to search for all the health events registered in the period considered.

On January 1, 1996, the LHA of Ravenna set up an information technology system to record the costs of drugs dispensed and the reimbursements to be paid to the local pharmacies for the drugs dispensed. The pharmaceutical service database includes every prescription filled since January 1, 1996, and comprises the following information: personal health code of the patient, code of the prescribing physician, the anatomic therapeutic chemical (ATC) code of the drug purchased, the number of packages prescribed, the number of units per package, doses per unit, and the prescription date.

The demographic registry, which includes the date and cause of death, and the nosocomial database have been in use since January 1, 1996, and January 1, 1991, respectively. The information concerning health services analyzed (specifically, prescriptions for antihypertensive drugs) was completed for each patient by adding data including age, gender, hospital admissions, and death (the last 2 items are encoded by disease according to the *Ninth Revision of the International Classification of Diseases [ICD-9]*).

Figure 1. Source of study data.

Patient Population and Study Procedures

Patients were considered eligible for enrollment in the study if the following inclusion criteria were satisfied: age >18 years; a first prescription for enalapril (ATC, C09AA02) or amlodipine (ATC, C08CA01), combination therapy with enalapril (ATC, C09BA02 [tablets containing enalapril 20 mg + hydrochlorothiazide 12.5 mg]), or the addition of any class of diuretic to a treatment regimen with enalapril or amlodipine between January 1, 1996, and June 30, 2000 (the enrollment period); and continuous use of the antihypertensive treatment for ≥ 6 months. The exclusion criteria comprised the following: a history of a cardiovascular event (registered as any hospital admission for cardiovascular reasons between 1991 and 1996), or only 1 prescription recorded during the enrollment period.

The combined assessment of fatal and nonfatal cardiovascular events was carried out on the basis of hospital admissions (the main diagnosis being cardiovascular) and death data classified according to the following *ICD-9* codes: acute myocardial infarction (410), CHD (411–414), stroke/transient ischemic attack (430–437), heart failure (428), arterial hypertension (401–404), atherosclerotic and aneurysmatic lesions (440–442), and chronic renal insufficiency (585).

Comorbidities were identified from a detailed analysis of the pharmaceutical database. In a patient using enalapril or amlodipine, the presence of refilled

prescriptions for antidiabetic drugs (ATC, A10 [insulins and oral antidiabetic drugs]) and/or for other cardiovascular drugs (ATC, C01 [eg, cardiac glycosides, nitrates, other vasodilators]) indicated, respectively, the comorbidity of diabetes or a cardiac abnormality at baseline.

According to procedures previously adopted in other studies on antihypertensive drug use, *persistence with treatment* was arbitrarily defined as treatment lasting >273 days after the enrollment period.^{19,22,23}

Patients given antihypertensive treatment were classified as follows: (1) *continuers* = patients who persisted with the antihypertensive drug initially prescribed, including those receiving combination therapy with diuretics; (2) *switchers* = patients who changed their initially prescribed antihypertensive drug; and (3) *discontinuers* = patients who did not receive a prescription for an antihypertensive drug for ≥ 3 months after the initial period of continuous antihypertensive drug therapy. In patients who discontinued treatment, the percentage of those who subsequently resumed treatment with enalapril or amlodipine (*re-treaters*) was also calculated.

Statistical Analysis

The continuous variables are expressed as mean (SD). The statistical significance between mean values was calculated using the independent-samples *t* test, and significance between proportions was calculated using the Pearson chi-square test or the *z* test. All *P* values were 2-sided, and values <0.05 were considered significant. To determine the combined frequency of cardiovascular events among treatment groups, after testing the proportional hazards assumption, the Cox regression model was adopted to assess the effects of the confounding variables (age, sex, and comorbidity). Amlodipine versus enalapril and monotherapy versus combination therapy (including diuretics) were considered stratification factors in the regression model. In the multivariate analysis, a 3-level factor was considered: continuers, switchers, and discontinuers.

In analyzing the cardiovascular events, patients who moved away during the observation period and those who died from causes other than cardiovascular events were considered censored cases in the statistical analysis. The statistical significance between rates was calculated using the Wald test.²⁷ All the statistical analyses were performed using SPSS software version 10.1 (SPSS Inc., Chicago, Illinois).

RESULTS

A total of 7500 patients (11.4% of the cumulative incident patients who were prescribed an antihypertensive drug between 1996 and 2000 in the LHA of Ravenna) met the inclusion criteria. Of these, 2231 (29.7%) were given amlodipine and 5269 (70.3%) patients were given enalapril. The demographic and clinical characteristics of the 2 groups are shown in **Table I**. The mean age was similar between the 2 groups. In contrast, statistically significant differences

Table I. Baseline demographic and clinical characteristics of the study patients (N = 7500).

Characteristic	Amlodipine (n = 2231)	Enalapril (n = 5269)	P
Age, y			
Mean (SD)	68 (12.2)	68 (12.5)	NS*
Range	19–100	19–105	
Sex, no. (%)			<0.001 [†]
Female	1117 (50.1)	2975 (56.5)	
Male	1114 (49.9)	2294 (43.5)	
Comorbidity, no. (%)			0.001 [†]
CVD	219 (9.8)	690 (13.1)	<0.001 [†]
DM	107 (4.8)	244 (4.6)	0.752 [†]
CVD + DM	29 (1.3)	54 (1.0)	0.307 [†]
None of the above	1876 (84.1)	4281 (81.2)	0.004 [†]

CVD = cardiovascular disease; DM = diabetes mellitus.

*† Test for independent variables.

†Chi-square test.

were found between the 2 groups with regard to sex and the presence of comorbidities at baseline. The proportion of women was higher in the enalapril group than in the amlodipine group (56.6% vs 50.1%, respectively; $P < 0.001$). At baseline, the frequency of cardiovascular disease was significantly higher in the enalapril-treated patients than in the amlodipine-treated patients (13.1% vs 9.8%, respectively; $P < 0.001$), indicating a more impaired clinical condition in some enalapril-treated patients at the start of treatment. During the observation period in the amlodipine and enalapril groups, the percentages of patients who moved away (1.5% vs 1.2%, respectively) or died from causes other than cardiovascular events (7.4% vs 7.7%, respectively) were similar.

The pharmacoutilization profile by treatment group is shown in **Table II**. In the enalapril group compared with the amlodipine group, respectively, the percentage of continuers was significantly higher (37.0% vs 33.6%; $P = 0.005$) and the percentage of switchers was significantly lower (13.2% vs 16.6%; $P < 0.001$). Among continuers, the mean (SD) duration of exposure to treatment was not different between groups (both, 4.0 [1.3] years). Regardless of the antihypertensive drug prescribed, 49.8% of patients in each group discontinued treatment. During the subsequent follow-up, the majority of these patients (3279 corresponding to 87.8%) were again given antihypertensive treatment, with 90.9% (corresponding to 2981) receiving the same antihypertensive drug they had previously received. A lower percentage of patients in the amlodipine group than in the enalapril group received initial combination therapy that included a diuretic (18.5% vs 42.3% [enalapril/hydrochlorothiazide], respectively; $P < 0.001$). As the treatment proceeded, combination therapy with a

Table II. Pharmacoutilization profile. (Values are expressed as no. [%] of patients.)

Patient Classification*	Amlodipine (n = 2231)	Enalapril (n = 5269 [†])	P
Continuers	750 (33.6)	1950 (37.0)	0.005 [‡]
Received combination	653 (29.3)	2708 (51.4)	<0.001 [‡]
Initial treatment [§]	412 (18.5)	2228 (42.3)	<0.001 [‡]
During follow-up	241 (10.8)	480 (9.1)	0.026 [‡]
Switchers	371 (16.6)	695 (13.2)	<0.001 [‡]
Discontinuers	1110 (49.8)	2624 (49.8)	0.980 [‡]
Re-treaters	869 (78.3)	2112 (80.5)	0.137 [‡]

*Continuers = patients who persisted with the antihypertensive drug initially prescribed, including those receiving combination therapy with diuretics; switchers = patients who changed their initially prescribed antihypertensive drug; discontinuers = patients who did not receive a prescription for an antihypertensive drug for ≥ 3 months after the initial period of continuous antihypertensive drug therapy; re-treaters = patients who discontinued treatment and subsequently resumed treatment with enalapril or amlodipine.

[†] $P < 0.001$ versus amlodipine (chi-square test).

[‡]Z Test.

[§]Combination therapy with a diuretic (predefined combination for enalapril [ATC: C09BA02]).

diuretic was slightly but significantly higher in the amlodipine group compared with the enalapril group (10.8% vs 9.1%; $P = 0.026$).

Table III shows the bivariate analysis of the frequency of cardiovascular events in both groups. The combined rate of cardiovascular events was greater in the amlodipine group than in the enalapril group (54 vs 46 per 1000 patient-years, respectively; $P = 0.007$). The risk for a cardiovascular event in patients treated with amlodipine was 17% higher compared with enalapril (95% CI, 5.0%–24.0%; $P = 0.007$). Furthermore, in patients without comorbidities and in those with concomitant cardiovascular disease and diabetes, a significantly greater decrease in the frequency of cardiovascular events was observed in the enalapril group compared with the amlodipine group, corresponding to relative reductions of 16.7% and 57.9%, respectively ($P = 0.014$ and $P = 0.007$, respectively). Although statistical significance was not reached, in hypertensive patients with either cardiovascular disease or diabetes, a slightly higher reduction in the frequency of cardiovascular events was observed in the enalapril group compared with the amlodipine group (the rate per 1000 patient-years declined by 11.7% among patients with cardiovascular disease and by 26.5% among diabetic patients). The mean (SD) number of hospitalizations (ie, nonfatal cardiovascular events) per patient was also significantly higher in the amlodipine group than in the enalapril group (1.73 [0.35] vs 1.62 [0.82]; $P = 0.008$).

Table IV shows the multivariate analyses and cumulative incidences of fatal and nonfatal cardiovascular events by treatment group. In amlodipine-treated patients, the risk for a cardiovascular event was 14.0% higher than in the enalapril group (95% CI, 2.1%–28.1%; $P = 0.024$) (**Figure 2**). When use of combination

Table III. Bivariate analysis of the frequency of cardiovascular events.

Variable	Amlodipine (n = 2231)	Enalapril (n = 5269)	Absolute Risk Variation, %	95% CI	P
No. (%) of patients with CV event*	465 (54) 1.17	995 (46) 1.00	-8.0 17.0 [‡]	-2.1 to -13.0 5.0 to 24.2	0.007 [†] 0.007 [†]
Hazard ratio					
No. (%) of patients with CV event*: baseline comorbidities					
CVD + DM	20 (278)	22 (117)	-161.0	-292.0 to -29.0	0.007 [†]
CVD	99 (137)	293 (121)	-16.0	-47.0 to 15.3	0.297 [†]
DM	33 (83)	58 (61)	-22.0	-56.0 to 10.0	0.157 [†]
None of the above	313 (42)	622 (35)	-7.0	-12.2 to -1.0	0.014 [†]
Patients hospitalized, no. (%)	428 (19.2)	912 (17.3)	-	-	-
Hospitalizations, no.	743	1483	-	-	-
Hospitalizations per patient, mean (SD)	1.73 (0.35)	1.62 (0.82)	-0.11	-0.19 to -0.03	0.008 [§]

CV = cardiovascular; CVD = cardiovascular disease; DM = diabetes mellitus.

*Combined fatal and nonfatal CV events. Values are presented as no. of patients (rate per 1000 patient-years). Fatal events occurred in 118 (5.3%) and 244 (4.6%) cases in amlodipine and enalapril groups, respectively.

[†]Wald test.[‡]Relative percentage variation.[§]t Test for independent samples.

Table IV. Multivariate analysis of the prevalence of cardiovascular events (N = 7500).

Drug(s)	Hazard Ratio	Relative Risk Variation, %	95% CI	p*
Enalapril [†]	1.00	—	—	—
Amlodipine [†]	1.14	14.0	2.0 to 28.1	0.024
Enalapril [‡]	1.00	—	—	—
Amlodipine [‡]	0.96	−4.0	−16.0 to 10.0	0.571
Amlodipine + diuretic [‡]	1.15 [‡]	15.0	−6.0 to 41.3	0.167
Enalapril + diuretic [‡]	0.73 [‡]	−27.0	−36.1 to −16.0	<0.001

*Wald test.

[†]Hazard ratio data adjusted for age, sex, and comorbidity.[‡]Hazard ratio data adjusted for age, sex, comorbidity, and combination with a diuretic (as a stratification factor).

Figure 2. Cumulative incidence of fatal and nonfatal cardiovascular events. Multivariate analysis with data adjusted for age, sex, and comorbidity. Each treatment group includes monotherapy and combination therapy.

therapy with a diuretic was analyzed, enalapril + hydrochlorothiazide was associated with the significant highest reduction of risk for cardiovascular events (27.0%; 95% CI, -36.1% to -16.0%; $P < 0.001$) (**Figure 3**). Furthermore, in patients given monotherapy with amlodipine or enalapril, the cumulative incidence of cardiovascular events was similar (**Figure 3**).

Finally, when the 2 components (fatal and nonfatal outcomes) were analyzed separately, a significant difference in hospital admissions (42 vs 50 per 1000 patient-years for enalapril and amlodipine, respectively; $P = 0.007$) but not in deaths (4.1 vs 4.5 per 1000 patient-years for enalapril and amlodipine, respectively) was seen.

DISCUSSION

Analysis of administrative data for the entire population of an Italian LHA showed that patients receiving antihypertensive treatment with enalapril for the first time experienced a greater reduction in the occurrence of cardiovascular events compared with amlodipine-treated patients.

Compared with previous randomized, controlled, parallel-group studies (eg, Losartan Intervention For Endpoint reduction in hypertension study [LIFE],²⁸

Figure 3. Cumulative incidence of fatal and nonfatal cardiovascular events. Multivariate analysis with data adjusted for age, sex, and comorbidity. Each treatment group is broken down by single therapy.

Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial [ALLHAT]¹⁵) of the effects of antihypertensive treatments on the frequency of cardiovascular morbidity and mortality in patients with essential hypertension and left ventricular hypertrophy or in high-risk hypertensive patients, the results of the present study are remarkably different. In this study in patients with baseline clinical characteristics comparable to those of the above-mentioned trials (ie, the concomitant presence of both cardiovascular disease and diabetes mellitus), the rate of events per 1000 patient-years was at least double or triple the rates in those studies.^{15,28} These findings might be explained by the restrictive procedures followed in experimental settings. Unlike in observational studies, data in RCTs are typically collected on a narrowly targeted population that meets specific clinically relevant criteria and follows carefully defined treatment protocols, such as strict adherence to therapy or a treatment combination orderly scheduled. Thus, the lower incidence of cardiovascular events in the RCTs may not reflect actual use of health care resources in primary care, which are issues of particular importance to the NHS and LHAs.

In this study, the lowest frequency of cardiovascular outcomes was associated with a treatment combination (enalapril + diuretic) ($P < 0.001$). Despite the structural differences between RCTs and observational studies, this finding is consistent with findings in some recent landmark studies.^{5,12,29} The use of a diuretic was also particularly effective in an experimental setting, such as the ALLHAT study.¹⁵ Moreover, in the Hypertension Optimal Treatment (HOT) study,¹² blood pressure control and the significant reduction of the risk for cardiovascular events were achieved by gradually switching the majority of the patients (70%) to combination therapy consisting of ≥ 2 antihypertensive drugs. This effect was not observed in the present study in the group of patients given amlodipine + diuretic. Nevertheless, these results might be correlated with persistence with treatment (continuers), which was significantly lower in the amlodipine + diuretic group compared with patients treated with amlodipine monotherapy (30.9% vs 35.5%; $P = 0.042$). When amlodipine and enalapril monotherapy were compared, no significant differences were found in the cumulative incidence of cardiovascular events.

Performing the separate analysis of the cardiovascular events, no significant difference in mortality was observed between the 2 treatment groups, although the proportion of patients with concomitant disease (cardiovascular disease) at baseline was significantly higher in the enalapril group ($P < 0.001$).

The levels of discontinuation and persistence with treatment in general practice suggest the importance of paying attention to the overall use of health care resources. Approximately 50% of all patients discontinued their treatment compared with 36% (weighted mean value) who continued it. These values were higher and lower, respectively, compared with desirable rates, although the data are unfortunately consistent with findings reported by other investigators.^{16,19,30,31} Persistence and dosage affect the efficacy of the pharmacologic treatment of hypertension. The full clinical benefit of treatment, as reported in

the RCTs, can be achieved only if the drug is taken regularly (daily) and *quoad vitam*.^{10,32} Although it cannot be assumed to be a causal relationship, the higher persistence rate of treatment with enalapril recorded in the present study might help explain the lower incidence of cardiovascular events observed in patients given enalapril compared with amlodipine.

Some other issues of this assessment must be considered. The study was based on an analysis of prescriptions for antihypertensive drugs rather than on the diagnosis of hypertension. This could have resulted in a selection bias of the cohort considered to be eligible for the study because not all patients prescribed an antihypertensive drug are necessarily hypertensive. The selection bias, however, might be caused by patients who had received single or occasional prescriptions and not by those who had used the drugs continuously for ≥ 6 months.

Moreover, the exclusion of patients with previous hospital admissions for cardiovascular reasons and the similar percentage of patients with other diseases that the study drugs could also have been used to treat (based on the analysis of renewed prescriptions) should have almost completely eliminated the possibility of including nonhypertensive patients.

Overall, the frequency of outcomes may have been due to different background covariates in the treatment groups. In patients given enalapril, the lower percentage of men or the greater proportion of combination therapy prescribed as initial treatment could have influenced potential benefits from lowering blood pressure. However, these differences tended to be balanced by the lower frequency of cardiovascular disease at baseline in patients treated with amlodipine.

The lack of data on the intermediate outcome of the magnitude of blood pressure reduction compared with baseline values is a clear limitation of this study. Effectively, reduction of the risk for a cardiovascular event can depend on achieving the recommended blood pressure target or, if this target is not achieved, on the magnitude of the reduction achieved. However, in routine clinical practice, physicians are unlikely to continue prescribing an antihypertensive drug, and patients are unlikely to continue using the drug if there is no evidence of efficacy or tolerability; discontinuing or switching therapy is much more likely.

At present, assessing data collected in clinical practice to determine the effectiveness of a given antihypertensive drug is not a simple process. Indeed, until this study, the studies using data gathered in general practice examined individual issues of antihypertensive therapy, such as pharmacoepidemiology, compliance, treatment patterns, or the tendency to adhere to guidelines.^{30,33–36} Other investigators have examined data on persistence with treatment in detail, reaching, albeit with different methodologic approaches, similar conclusions to those reported in this analysis.^{23,37,38} According to a MEDLINE search (key terms: *antihypertensive drugs*, *administrative database*, and *outcomes*; years: 1970–2004), this study is one of the first to assess the outcome of the use

of antihypertensive drug therapy based on data stored in administrative databases. Findings basically associated with a lower number of hospital admissions in the enalapril group are both clinically and economically relevant because the costs involved in hospital care are much higher than those necessary to establish an appropriate, continuing pharmacologic treatment for hypertension.^{39,40}

CONCLUSIONS

In this study, the use of enalapril in patients undergoing antihypertensive treatment for the first time was associated with a significantly lower frequency of cardiovascular events than in patients prescribed amlodipine. This was due to the reduced number of patients hospitalized as a result of a cardiovascular event. Even though the data on the risk reduction of cardiovascular events are encouraging, the low percentage of patients who are persistent with treatment emphasizes the need to implement programs in general practice, including medical education programs, that make it easier to plan and achieve the objectives of antihypertensive therapy.

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