Daily Intake of Magnesium and Calcium From Drinking Water in Relation to Myocardial Infarction

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Background: A decreased risk for cardiovascular disease has been related to the hardness of drinking water, particularly high levels of magnesium. However, the evidence is still uncertain, especially in relation to individual intake from water.

Methods: We used data from the Stockholm Heart Epidemiology Program, a population-based case–control study conducted during 1992–1994, to study the association between myocardial infarction and the daily intake of drinking water magnesium and calcium. Our analyses are based on 497 cases age 45–70 years, and 677 controls matched on age, sex, and hospital catchment area. Individual data on magnesium, calcium, and hardness of the domestic drinking water were assessed from waterwork registers or analyses of well water.

Results: After adjustment for the matching variables and smoking, hypertension, socioeconomic status, job strain, body mass index, diabetes, and physical inactivity, the odds ratio for myocardial infarction was 1.09 (95% confidence interval = 0.81–1.46) associated with a tap water hardness above the median (>4.4 German hardness degrees) and 0.88 (0.67–1.15) associated with a water magnesium intake above the median (>1.86 mg/d). There was no apparent sign of any exposure–response pattern related to water intake of magnesium or calcium.

Conclusions: This study does not support previous reports of a protective effect on myocardial infarction associated with consumption of drinking water with higher levels of hardness, magnesium, or calcium.

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During the past 4 decades, numerous studies in different countries have reported a relation between "hard" drinking water containing dissolved minerals and low mortality from cardiovascular disease. Most investigations have been ecologic studies,[1–9] but some individual-level studies have described an inverse association between cardiovascular disease and the hardness of drinking water.[10–13] The evidence is still conflicting, however, and a recently large and detailed geographic study could not confirm these findings.[14]

The hardness of drinking water is largely determined by its content of calcium and magnesium. Although both calcium and magnesium have been investigated, the biologic mechanism for a potential protection in hard drinking water has mainly been suggested to involve magnesium.[15,16] It has been argued that magnesium in drinking water would provide protection against sudden death due to myocardial infarction (MI).[12,17–19] Magnesium deficiency has been suggested to predispose to cardiac arrhythmias,[20,21] and in 2 studies, magnesium levels in the heart tissue of people dying of ischemic heart disease were lower than levels in comparison groups.[22,23] Another early theory was that the corrosiveness of soft water might promote dissolution of cadmium, lead, and other toxic substances from the pipes of the water distribution system, which may affect the blood pressure and thus increase the risk for cardiovascular disease.[24,25]

One criticism of the magnesium theory is that only a small proportion (less than 5–10%) of the daily intake of magnesium comes from drinking water,[15] whereas the rest comes from diet, although it has been suggested that the water magnesium is more bioavailable.[26] A recent Swedish study including an oral loading test with magnesium suggests that the body magnesium level can be affected by magnesium in the drinking water.[27] However, only one study of MI and water hardness considers the dietary intake of magnesium and calcium according to the daily consumption of drinking water.[13] Therefore, we investigated the relation between MI and the daily drinking water intake of magnesium and calcium in a subset of individuals from a large case–control study in Stockholm (Stockholm Heart Epidemiology Program).

METHODS

This study has been described in detail elsewhere.[28] In brief, the study comprised all nonfatal and fatal first events of MI among Swedish citizens age 45–70 years who resided in

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Stockholm county during 1992–1993 for men and 1992–1994 for women, and population controls from the corresponding study base. The control subjects were matched on age, sex, and hospital catchment area. In total, the study included 2246 cases and 3206 controls.

All subjects received a postal questionnaire covering a large set of potential risk factors for MI, including physical and psychosocial work environment, social factors, lifestyle factors, and dietary intake. The questionnaire response rate among cases was 72% for women and 81% for men; corresponding figures among controls were 70% and 75%. A supplementary telephone interview was conducted to fill in missing data. For each case, 5 candidate control subjects were sampled from the study base, with the goal of equal number of cases and controls. However, the study includes more controls than cases due to nonparticipating cases or due to duplicate control participation when both the original control and the replacement finally agreed to participate. A special health examination was also carried out on hospitalized cases and their controls to collect data on various biologic parameters related to cardiovascular disease. A total of 4067 subjects responded to a special questionnaire on work and residence history.

The magnesium level ranges between 4 and 6 mg/L in the 3 largest waterworks in the region. To make the present study more efficient, we selected only the municipalities where large differences in magnesium levels could be expected, ie, where the small waterworks were situated and some of the subjects used private well water. Thus, all subjects living in the 3 catchment areas in the eastern part of the county in the 2 years before inclusion were selected, corresponding to 6 of the 26 municipalities within the county. This resulted in a study population of 1327 subjects (32% of the subjects with residential history). We contacted the local environment and health protection administration or the technical office of each municipality to link the address for each subject to a specific waterwork. Subsequently, information on drinking water quality during 1990–1994 was collected from registers of historical analyses at the waterworks. The frequency of chemical testing of the water varies between waterworks, but in general 3 to 4 samples are taken each year. Some regions receive their water from 2 waterworks, in which case we calculated the mean mineral content for the 2.

In the questionnaire, 137 subjects reported that their water supply came from a private well. To these addresses, a self-administered water-sampling bottle was mailed and these samples were analyzed with respect to the same parameters as in the waterwork protocols. Hence, individual residential levels of magnesium, calcium, and water hardness were calculated up to 2 years before inclusion in the study or thereafter for those using a private well.

Water hardness was measured in German hardness degrees, °dH (1 °dH = 7.1 mg calcium [Ca^{2+}] or 4.3 mg magnesium [Mg^{2+}] per 100 mL water). Subsequently, the individual level of hardness, magnesium, and calcium was multiplied by the amount of water consumed at home according to the questionnaire for each subject to obtain the daily dose in milligrams per day. Figure 1 shows the cumulative population distribution according to the concentration in the tap water and the daily dose from the water.

For reasons described subsequently, 12% of the cases and 10% of the controls had missing values on the drinking water constituents. For 9 subjects, the source of drinking water was not available in the questionnaire. One hundred addresses could not be linked to any waterwork because of incomplete address history in the questionnaire or lack of data in the municipal registers. Of the 137 subjects using private wells, 28 did not respond (despite one reminder) or could not be reached because of incomplete address information. Sixteen subjects responded as having both municipal water and a private well and had to be excluded from the analysis because it was unclear which water source they used for drinking water. The protocols may differ between the waterworks on some occasions, resulting in a different number of parameters analyzed. Thus, 1174 subjects had data on water hardness and 1173 on magnesium and calcium level.

Information on potential confounders was obtained from the postal questionnaire and study health examination. Smoking was classified in the categories never smokers, former smokers (quit smoking more than 2 years before

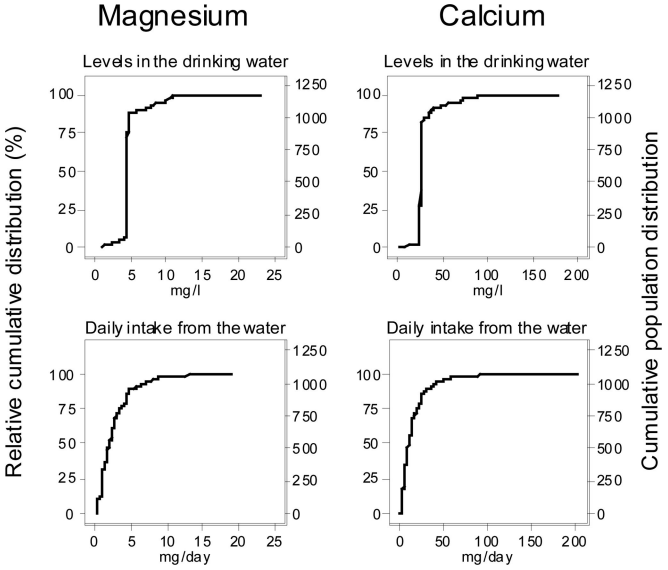

FIGURE 1. Cumulative population distribution according to the level of magnesium and calcium in the drinking water (n = 1173) and the daily intake of magnesium and calcium from the water (n = 1075) in Stockholm County 1990–1994 (1 subject omitted from the top right graph due to an extreme mean level of calcium of 610 mg/L).

inclusion), and current smokers. Subjects were defined as hypertensive if they received antihypertensive drug therapy when enrolled in the study, had a history of regular antihypertensive drug therapy during the last 5 years, or had a systolic blood pressure of at least 170 mm Hg or a diastolic blood pressure of at least 95 mm Hg at the health examination. Socioeconomic status was classified according to the most recent working period in 3 categories (blue collar workers, low-level white collar workers, and intermediate- to upper-level white collar workers). Job strain was measured in accordance with the Swedish version of the demand-control concept based on the Karasek-Theorell questionnaire,[29] using the 75th percentile among all controls as cut point. Diabetes mellitus was defined as using insulin, drug treatment, or diet control, or having a fasting blood glucose level above 6.7 mmol L^{-1}. Overweight was defined as body mass index (BMI) above 28 kg/m^2, which corresponds roughly to the 75th percentile for all controls (27.5 kg/m^2 for men and 28.1 kg/m^2 for women) calculated from height and weight measurements from the health examination (>90%) or from values reported in the questionnaire. Physical inactivity was based on leisure time activity (ie, those who reported inactive leisure time or only occasional walks during the last 5–10 years).

Statistical Analysis

We calculated adjusted odds ratios (ORs) and 95% confidence intervals (CIs) using unconditional logistic regression. The continuous drinking water variables were categorized in 2 or more categories at percentile values for all subjects with data available. All multivariate models included the matching variables age, sex, and catchment area. The covariates (dichotomous unless noted otherwise) included in the main regression model were the traditional coronary heart disease risk factors: smoking (3 levels), hypertension, socioeconomic status (3 levels), job strain, diabetes mellitus, BMI, and physical inactivity. Other models were also evaluated including environmental tobacco smoke, dietary factors (fat and fiber intake), and family history of cardiovascular disease. Dietary intake of magnesium and calcium, as well as beverages other than water, were also considered, especially coffee (total amount according to Hammar et al[30] in 3 levels) and alcohol (defined as grams of 100% ethanol/d from beer, wine, and spirits according to Romelsjö et al[31] in 3 levels). Effect estimates are given for men and women together, because there was no effect modification by sex in any analysis. Evaluation of possible impact of overmatching due to geography (hospital catchment area) was done by giving weights to the control subjects according to the demographic distribution in each strata from regional statistics using a SAS program previously used in a study on socioeconomic context and MI.[32]

RESULTS

After adjusting for the matching variables and for smoking, hypertension, socioeconomic status, job strain, diabetes mellitus, BMI, and physical inactivity, the odds ratio for MI was 1.09 (CI = 0.81–1.46) associated with a level of hardness in the tap water above the median (>4.4 hardness degrees [°dH]). The adjusted odds ratio associated with a tap water magnesium level above the median (>4.4 mg/L) was 1.16 (0.87–1.54) and for calcium (>25.1 mg/L) 1.03 (0.79–1.53). Changing the dichotomous cut point to higher percentiles resulted in similar estimates. Using data on the consumption of tap water to calculate the daily dose of magnesium and calcium from the water resulted in adjusted odds ratios for those above the median (1.9 mg/d for magnesium and 11.2 mg/d for calcium) of 0.88 (0.67–1.15) and 0.88 (0.67–1.16), respectively. The correlation between the daily dose of drinking water magnesium and calcium was 0.86 (Spearman's correlation coefficient).

Table 1 contains the results of analyses using quartiles of exposures and other cut points. We did not see any consistent trend of exposure–response for either of the water constituents, except for an indication of increasing odds ratios with increasing exposure to magnesium in the tap water (Table 1). In analyses of fatal cases and their controls, there was no association between magnesium or calcium intake from tap water using the 75th percentile or other cut points (Table 2). Different multivariate models produced only small differences in the effect estimates, indicating limited influence from confounding (Table 3). In particular, adjustments for dietary magnesium or calcium intake did not affect the results. Other factors potentially related to the amount of water consumption (eg, dietary fat or fiber intake, alcohol consumption, and coffee drinking) did not appear to influence the estimates. Including data on other modes of water consumption (eg, tea, soup, juice) in the dose calculation resulted in estimates close to one, indicating no association when considering total dose of magnesium or calcium from drinking water.

Considering drinking water quality only during the year of infarction or the preceding year did not change the results (data not shown). Exclusion of subjects using private wells had limited or no effects on the estimates (OR = 0.87 for a magnesium intake from the drinking water above the median, compared with OR = 0.88 for all subjects). Weighting the controls according to the regional distribution of individuals in each age, sex, and catchment stratum had very small effects on the results. The reweighting shifted the adjusted odds ratio from 1.16 to 1.13 among those with a tap-water magnesium level above the median and from 0.88 to 0.91 for a daily drinking water dose of magnesium above the median.

TABLE 1. Odds Ratios for Myocardial Infarction Associated With Magnesium, Calcium, and Water Hardness of Tap Water and Intake From Tap Water During 2 Yr Before Diagnosis in Stockholm, Sweden, 1992–1994

	No. of Cases	No. of Controls	OR*	(95% CI)
Magnesium level (mg/L)				
Quartiles				
1.0 to <4.3†	138	216	1.00	
≥4.3 to <4.4	141	209	1.06	(0.76–1.48)
≥4.4 to <4.7	94	148	1.15	(0.78–1.68)
≥4.7 to 23.0	79	93	1.36	(0.91–2.02)
Dichotomous‡				
≤8.0†	415	626	1.00	
>8.0	37	40	1.37	(0.82–2.30)
Calcium level (mg/L)				
Quartiles				
1.0 to <24.0†	123	184	1.00	
≥24.0 to <25.1	182	272	1.05	(0.76–1.46)
≥25.1 to <28.5	69	110	1.04	(0.69–1.58)
≥28.5 to 610.0	78	100	1.21	(0.78–1.87)
Dichotomous‡				
≤50.0†	422	621	1.00	
>50.0	30	45	0.98	(0.56–1.73)
Hardness (dH°)§				
Quartiles				
0.4 to <4.4†	124	187	1.00	
≥4.4 to <4.5	142	208	1.04	(0.74–1.45)
≥4.5 to <4.8	60	94	1.17	(0.75–1.82)
≥4.8 to 88.2	126	178	1.12	(0.78–1.60)
Dichotomous‡				
≤8.5†	420	621	1.00	
>8.5	32	46	1.04	(0.60–1.80)
Magnesium intake (mg/d)				
Quartiles				
0.20 to <0.9†	112	161	1.00	
≥0.9 to <1.9	103	141	1.07	(0.73–1.55)
≥1.9 to <3.5	89	155	0.86	(0.59–1.26)
≥3.5 to 19.2	158	158	0.97	(0.66–1.41)
Dichotomous‡				
≤6.9†	388	577	1.00	
>6.9	30	38	1.07	(0.63–1.82)
Calcium intake (mg/d)				
Quartiles				
0.2 to <5.0†	110	167	1.00	
≥5.0 to <11.2	106	136	1.20	(0.83–1.75)
≥11.2 to <20.2	92	165	0.90	(0.62–1.31)
≥20.2 to 202.0	110	147	1.04	(0.71–1.53)
Dichotomous‡				
≤42.4†	389	578	1.00	
>42.4	29	37	1.07	(0.62–1.85)

*Adjusted for age, sex, catchment area, smoking, hypertension, socioeconomy, job strain, diabetes mellitus, body mass index, and physical inactivity.

†Reference category.

‡Cut point at the 93rd percentile of exposed subjects, decided according to an assumption of biological effects from 8 mg/L of magnesium level in the water.

§German hardness degrees, °dH. One °dH = 7.1 mg calcium (Ca^{2+}) or 4.3 mg magnesium (Mg^{2+}) per 100 mL water.

TABLE 2. Odds Ratios for Myocardial Infarction Mortality During the First 28 Days From Diagnosis Associated With Magnesium and Calcium Intake From Tap Water During 2 Years Prior to Diagnosis

	No. of Cases	No. of Controls	OR*	(95% CI)
Magnesium intake (mg/d)				
≤3.5†	39	122	1.00	
>3.5	19	49	1.08	(0.50–2.33)
Calcium intake (mg/d)				
≤20.2†	40	128	1.00	
>20.2	18	43	1.19	(0.53–2.67)

*Adjusted for age, sex, catchment area, smoking, hypertension, socioeconomy, job strain, diabetes mellitus, body mass index, and physical inactivity.

†Reference category. Cut points are based on the 75th percentile among all subjects with data available (n = 1075).

DISCUSSION

In contrast to many earlier studies, we did not find any persistent pattern of protection against MI by magnesium, calcium, or drinking water hardness. Some point estimates for simple dichotomous calculated dose variables resulted in odds ratios below one and the corresponding tap water level variables showed odds ratios above one. Even so, analyses of multiple exposure categories and subgroup analyses did not indicate any clear pattern of any effect of these drinking water constituents. We considered both traditional coronary heart disease risk factors as well as other individual lifestyle factors, including magnesium and calcium intake from food.

This study is based on a large population-based case–control study with a high participation rate, high reliability of case identification, and low probability of selection bias.[28] The main advantage compared with other studies is the extensive information on other risk factors for cardiovascular disease, and data on individual intake of drinking water magnesium and calcium. We also had information on other beverages and other modes of water consumption as well as dietary intake of magnesium and calcium.

The levels of magnesium and calcium are lower than in most previous studies that have showed an inverse relation with the risk for cardiovascular disease. In addition, the ranges in exposure are limited in our study, as indicated by Figure 1. Approximately two thirds of both cases and controls received their water from one of the waterworks with a mean magnesium level of 4.4 mg/L, mean calcium level of 24.5 mg/L, and a hardness of 4.4 °dH. Other studies have reported mean magnesium levels above 10 mg/L, calcium levels above 30 mg/L, and hardness above 50 degrees,[14,33–35] which has

TABLE 3. Odds Ratios for Myocardial Infarction Associated With Magnesium and Calcium Intake From Tap Water According to Different Multivariate Models

	Model 1* OR (95% CI)[§]	Model 2[†] OR (95% CI)[§]	Model 3[‡] OR (95% CI)[§]
Magnesium intake (mg/d)[§]			
0.2 to <0.9[‖]	1.00	1.00	1.00
≥0.9 to <1.9	1.24 (0.86–1.80)	1.24 (0.84–1.84)	1.20 (0.81–1.79)
≥1.9 to <3.5	0.89 (0.61–1.30)	0.94 (0.63–1.40)	0.89 (0.59–1.34)
≥3.5 to 19.2	1.19 (0.82–1.73)	1.10 (0.73–1.64)	1.04 (0.69–1.57)
Calcium intake (mg/d)[§]			
0.2 to <5.0[‖]	1.00	1.00	1.00
≥5.0 to <11.2	1.36 (0.94–1.96)	1.34 (0.90–1.99)	1.29 (0.87–1.92)
≥11.2 to <20.2	0.90 (0.62–1.31)	0.95 (0.64–1.41)	0.91 (0.61–1.36)
≥20.2 to 202.0	1.30 (0.89–1.91)	1.18 (0.79–1.78)	1.13 (0.75–1.72)

*Model 1: Adjusted for the matching variables age, sex, and hospital catchment area.

[†]Model 2: Adjusted for the matching variables, plus traditional coronary heart disease risk factors (ie, smoking, hypertension, socioeconomic status, job strain, diabetes mellitus, body mass index, and physical inactivity).

[‡]Model 3: Adjusted for the matching variables and traditional coronary heart disease risk factors, plus intake of magnesium or calcium in food and fluids other than water (ie, coffee, alcohol, tea, soup).

[§]Only subjects with data on all variables in all 3 models are included (n = 917).

[‖]Reference category.

also been reported for some Swedish regions.[1,11] Some studies have indicated that a drinking water magnesium level of at least 8 to 10 mg/L is needed to prevent coronary heart disease.[3,11] Our data did not did not suggest a protective effect above that level, however. The dose estimates appear to be protective in some exposure categories, whereas the estimates associated with the concentration in the water was above one in all categories. This may imply that high water consumption has a protective effect in itself, which was recently demonstrated by others.[36] However, analysis using all subjects in the complete case–control study with data on water consumption (n = 3691) resulted in an odds ratio adjusted for age, sex, and catchment area in the highest tertile compared with the lowest of 1.04 (0.88–1.23), indicating no association between drinking water consumption and the MI risk in our population.

Another potential weakness is misclassification of exposure. The levels of drinking water constituents measured at the waterworks and in the samples taken from the private wells are probably good measures of the tap water levels at home. In Sweden, the levels of magnesium and calcium measured at the waterworks correlated well with those measured in water from the tap (r_{xy} = 0.96 and r_{xy} = 0.97, respectively), indicating small differences between the levels at the waterworks and in domestic tap water.[11] In addition, almost everyone in Sweden drinks tap water daily, and according to data from a national environmental health survey in 1999, less than 4% of the Swedish population do not drink tap water at home.[37] However, the quality of the address information and the linkage of home addresses to the correct waterwork may introduce some misclassification of exposure. The address data were attained in a special home-and-work questionnaire concerning the subject's lifetime residential history, which was completed by the study subjects themselves or their closest next of kin for fatal cases. Thus, recall bias could be present especially for the fatal cases. Because we only used address data regarding the 2 years directly preceding the infarction, the effect of such recall bias was reduced. According to time trends from the major waterwork, the hardness levels in the study area have been largely unchanged during 1980–1990, ranging between 4.0 and 4.6 hardness degrees.

The linkage of addresses to the waterworks was done by officials at the environmental health administration or the technical office of each municipality, who are responsible for the local water distribution in Sweden. In case an address obtains its water from more than one waterwork, the officials also made a calculation of the proportion of water from each waterwork. This could potentially have introduced a bias in the study. However, analysis using only those connected to one single waterwork did not change the results. Any such misclassification of exposure would presumably be independent of disease status and thus mainly affect the results toward the null. Therefore, nondifferential misclassification of exposure may have contributed to our results. However, attempts to decrease potential false questionnaire data from

relatives by restricting to nonfatal subjects did not affect the results. Because exposure of those using private wells was assessed according to the levels of magnesium and calcium measured subsequent to disease onset, analyses were also performed ignoring these subjects, resulting in estimates similar to those attained for all subjects. In addition, assessment of exposure using address data ignores exposure at other locations such as the workplace. Thus, water consumption outside the home could be a source of bias. However, adjusting for whether the subjects had a regular job in the last 2 years before inclusion in the study did not influence the results.

In addition to the variables included in the final model, we also checked for possible influence of many other potential confounders such as exposure to environmental tobacco smoke, dietary factors (fat and fiber intake), and family history of cardiovascular disease. These had a negligible impact on the results. In particular, we explored the potential influence of dietary magnesium and calcium intake using the calculated total intake of magnesium or calcium according to a large food-frequency questionnaire. Adjusting for magnesium or calcium intake from the diet had very small effects on the estimates, and there was no correlation between intake from food and water for magnesium or for calcium (r_{xy} = 0.004 and $r_{xy} = -0.173$, respectively). The mean amount of calculated magnesium intake from food was 276 mg/d and from drinking water 2.6 mg/d among those with data on both sources (n = 917). Neither dietary magnesium nor calcium seemed to be associated with a decreased MI risk in this study; adjusting for the matching variables, the ORs associated with a dietary intake above the median was 1.06 (CI = 0.93–1.20) for magnesium and 1.02 (0.90–1.16) for calcium. However, residual confounding might still be present. We also analyzed multichemical models, which indicated some influence of calcium on the estimates for magnesium and vice versa. The reason for this finding is uncertain, and the interrelation between these drinking water constituents on the effect estimates should be interpreted with caution. It is also unknown whether other metals in the distributed drinking water such as arsenic, cadmium, or lead could have contributed to the results. Because we did not have access to such data, we were unable to investigate the hypothesis of higher levels of toxic substances in soft water due to corrosion.

Because the chemical content of the drinking water depends on the waterwork linked to the address, the hardness of the tap water can be considered as a geographically dependent variable. Thus, the geographic matching of controls may have reduced the study power and potentially introduced a bias. In an attempt to avoid this sampling effect, we also analyzed the data using weights for the controls in each age, sex, and catchment area stratum according to the proportion of person-years in the study base contributing to that specific stratum. Thus, any effects of overmatching would be reduced. This resulted in very small differences compared with nonweighted estimates, implying limited problems with geographic overmatching.

In conclusion, our data do not support a substantial protective effect on MI associated with consumption of drinking water at moderate concentrations of hardness, magnesium, or calcium. However, potential misclassification of exposure, low mean levels, and limited ranges in exposure may have influenced the results.

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