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β-Fibrinogen −455G>A (rs1800790) in a sample of Libyan Patients with Cardiovascular Disease: A Pilot Study with Hardy–Weinberg Assessment

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A B S T R A C T

Background: Cardiovascular and thromboembolic diseases are major contributors to morbidity in Libya, yet the distribution and potential relevance of coagulation-related genetic variants—including the β-fibrinogen −455G>A promoter polymorphism (rs1800790)—remain poorly characterized in North African populations.

Aims: To provide a preliminary descriptive characterization of rs1800790 in Libyan patients with cardiovascular disease, and to document the methodological considerations—principally Hardy–Weinberg equilibrium (HWE) deviation and treatment confounding—that should inform future adequately powered studies.

Methods: This descriptive case series was conducted at Al Fouad Cardiac Center, Tripoli, Libya, between April and August 2025. Forty-four Libyan patients with established cardiovascular disease were included. rs1800790 was genotyped using the CVD StripAssay (ViennaLab Diagnostics GmbH). Genotyping succeeded at first pass in 38 of 44 patients; the remaining six were repeated once from the same DNA and all gave interpretable results. HWE was assessed by an exact test. Four imputed D-dimer entries were identified and excluded. Three post hoc exploratory comparisons by genotype (coronary artery disease, coronary stenting, and D-dimer >1.0 µg/mL) used Fisher's exact test with a single Haldane–Anscombe-corrected odds ratio estimator and Bonferroni correction ($\alpha = 0.0167$).

Results: Only G/G (16; 36.4%) and G/A (28; 63.6%) genotypes were observed. The genotype distribution deviated from HWE (conditional exact $P = 0.0017$; Pearson $\chi^2 = 9.58$, 1 df, $P = 0.0020$), with a heterozygote excess and absent A/A homozygotes. This is reported as a quality-control finding requiring investigation, not as proof of assay failure. Among the 40 patients with a measured D-dimer, a value >1.0 µg/mL was more frequent in G/A than G/G patients (14/24, 58.3% vs 1/16, 6.3%; corrected OR 14.3, 95% CI 2.2–91.2; Fisher's exact $P = 0.0009$), and this survived Bonferroni correction. Coronary artery disease (85.7% vs 56.3%; corrected OR 4.30; $P = 0.067$) and coronary stenting (64.3% vs 37.5%; corrected OR 2.85; $P = 0.12$) did not differ significantly. Lipid values were treatment-confounded, with 88.6% of patients receiving statins.

Conclusions: This report offers preliminary genotype data for rs1800790 in Libyan patients with cardiovascular disease. The HWE deviation, absence of A/A homozygotes, lack of an age-comparable control group and absence of orthogonal validation mean that the results are hypothesis-generating only. The post hoc association with raised D-dimer warrants confirmation in a larger, validated, case–control study.

Keywords: *β-fibrinogen; FGB; rs1800790; cardiovascular disease; short report; Hardy–Weinberg equilibrium; Libya.*

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1. Introduction

Cardiovascular disease remains a leading cause of morbidity and mortality worldwide, and thromboembolic events—including arterial thrombosis and venous thromboembolism—are important clinical manifestations of vascular disease. Virchow's triad attributes thrombus formation to endothelial injury, altered blood flow and hypercoagulability, with fibrinogen playing a central structural role as the precursor of fibrin (1,2). Fibrinogen (Factor I) is a hepatic glycoprotein that thrombin converts into fibrin, the structural matrix of both physiological homeostatic clots and pathological thrombi (3). The β chain is encoded by FGB on chromosome 4q31.3 (4). The −455G>A promoter polymorphism (rs1800790) has been associated in some populations with altered fibrinogen expression and circulating fibrinogen concentration, and because fibrinogen concentration and fibrin structure may influence thrombus formation and persistence, the variant has been investigated as a potential cardiovascular risk modifier (5–9).

Despite evidence of population genetic structure and a substantial burden of cardiometabolic disease, data on thrombophilia-related variants in North African and specifically Libyan populations remain limited (10,11). Multiplex reverse-hybridization platforms such as the CE-IVD-marked CVD StripAssay provide an accessible route to detecting multiple cardiovascular risk alleles in resource-constrained settings. However, the analytical performance of such platforms in understudied populations requires explicit quality-control assessment.

Aims:

This short report therefore aims to (i) describe the genotype and allele distribution of the β-fibrinogen −455G>A variant in Libyan patients with cardiovascular disease, using HWE as a quality-control check; and (ii) record exploratory observations and methodological limits that can inform future adequately powered studies. The three genotype comparisons reported are post hoc and exploratory.

2. Methods

2.1 Study design and setting

This descriptive case series was conducted between April and August 2025 at Al Fouad Cardiac Center, Tripoli, Libya. Molecular assays were performed at the Carthage International Laboratory for Research and Medical Analysis. The study was designed as a feasibility and descriptive investigation using existing clinical samples, not as a case–control study. The work was self-funded by the authors; no institutional, national or international grant supported the laboratory analyses, sample collection or personnel time.

2.2 Participants selection

Eighty-two Libyan adults were screened (Figure 1). Twenty-six were excluded because of suboptimal genomic DNA yield or purity (A260/A280 outside 1.7–1.9), severe systemic comorbidity considered confounding, or missing clinical or pharmacological data. The remaining 56 comprised 44 patients with cardiovascular disease (aged 34–80 years) and 12 healthy volunteers (aged 25–50 years; mean 36.8 ± 7.1 years). Because the volunteers were substantially younger than the patients (64.0 ± 11.7 years) and lacked their comorbidity profile, they were not used as a comparison group; their genotypes are reported for completeness only. Cases had established cardiovascular disease, verified by standard diagnostic imaging or clinical criteria. The original classification counted three records with cerebrovascular or vascular diagnoses as coronary artery disease. These three records were re-adjudicated against the clinical notes: each was retained as

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coronary artery disease only where coronary disease was independently documented, and otherwise reclassified as other vascular disease. The revised counts are given in Table 1. Disease categories overlapped in some patients; the categories are therefore not mutually exclusive, and the sum of category counts exceeds the number of patients. All genotype-stratified comparisons are within case.

2.3 Sample size and statistical power

No a priori sample size calculation was performed, because this was a pilot descriptive study. For future work, a G*Power calculation (version 3.1.9.7) for a two-group comparison under a dominant model (control minor allele frequency 0.20; carrier frequency 0.36; odds ratio 1.8; $\alpha = 0.05$; power 80%) indicated a requirement of approximately 187 participants per group (approximately 375 in total). The present sample of 44 patients is well below this, and no multivariable modelling was attempted, because 44 cases support at most one or two covariates.

2.4 Ethics

This study was conducted in accordance with the Declaration of Helsinki. Ethical approval was obtained from the National Committee for Biosafety and Bioethics in Libyan Academy of Postgraduate Studies ((Reference: NBC: 026.H.25.7), 26 Jan 2025). Written informed consent was obtained from all participants.

2.5 Genotyping protocol

Genomic DNA was isolated from EDTA-anticoagulated whole blood using a standard salting-out extraction method. DNA concentration and purity were assessed by NanoDrop spectrophotometry, and A260/A280 ratios between 1.7 and 1.9 were required for inclusion; DNA quality metrics were recorded for all samples.

The −455G>A variant was assessed by multiplex PCR followed by reverse hybridization to allele-specific oligonucleotide probes immobilized on nitrocellulose strips (CVD StripAssay, ViennaLab Diagnostics GmbH) according to the manufacturer's instructions. Genotype calls were taken from the strip-reading sheet; observers were not formally blinded. Manufacturer-supplied positive and negative controls were run with each batch, and the built-in control band on each strip confirmed the detection step. Genotyping succeeded at first pass in 38 of 44 patients; the six samples with failed amplification or uninterpretable strips were repeated once from the same DNA, and all six then gave an interpretable result. Because of resource constraints, no orthogonal validation (for example, Sanger sequencing) was performed, and genotypes are therefore reported as strip-assay calls.

2.6 D-dimer measurement

D-dimer was measured on [platform] and is reported in [fibrinogen-equivalent units (FEU) / D-dimer units (DDU)]; the cutoff of 1.0 µg/mL used here is a conventional threshold for an elevated result and was not derived from this dataset. Samples were collected during the index

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admission, and anticoagulant status at the time of sampling was recorded in the clinical notes. Because event timing and anticoagulation may influence D-dimer independently of genotype, the continuous comparison is presented as the primary analysis and the dichotomised comparison as secondary.

2.7 Statistical framework

Descriptive statistics are presented as means ± standard deviations, medians (interquartile range), or n/N (%), as appropriate. Genotype frequencies are given with Wilson 95% confidence intervals. Allele frequencies are reported as naive descriptive estimates without confidence intervals, because the genotype distribution departs from HWE and the usual interval assumes independent allele copies; a valid interval would require a model for the departure, which this dataset cannot support. HWE was tested with a conditional exact test, with the Pearson chi-square goodness-of-fit result given for comparison. Only measured laboratory values were analysed. Prothrombin time, activated partial thromboplastin time, troponin and electrolytes were unavailable for most patients and are not reported. Four D-dimer entries that had been imputed during data entry rather than measured were identified and excluded; no imputation was performed for the reported analysis, leaving 40 patients with a measured D-dimer.

Three post hoc exploratory comparisons by genotype (coronary artery disease, coronary stenting, and D-dimer >1.0 µg/mL) used Fisher's exact test. These three comparisons constitute the multiple-testing family; Bonferroni correction was applied within this family ($\alpha = 0.0167$), and no other comparisons were corrected. Odds ratios are reported with a single estimator throughout—the Haldane–Anscombe correction with Woolf 95% confidence intervals—applied to all three comparisons; raw odds ratios are given in a footnote for transparency where a zero cell is present. D-dimer as a continuous variable was compared by the Mann–Whitney U test. These comparisons were not pre-specified, are unadjusted, and are hypothesis-generating only. Smoking status was not recorded. All tests were two-sided. Analyses were performed in SPSS version 27, with HWE exact tests computed in Python (SciPy).

3. Results

3.1 Baseline characteristics of cases

The final analytical cohort comprised 44 patients with a mean age of 64.0 ± 11.7 years; 26 (59.1%) were female. Coronary artery disease was present in [revised n] patients ([revised %]), hypertension in 29 (65.9%), and type 2 diabetes mellitus in 16 (36.4%). Coronary stenting was recorded in 24 patients (54.5%), and 39 patients (88.6%) were receiving statin therapy at the time of assessment (Table 1).

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Table 1. Baseline characteristics of cases (n = 44).

Characteristic	Value
Age, years (mean ± SD)	64.0 ± 11.7
Female sex, n (%)	26 (59.1)
Coronary artery disease, n (%)	33 (75.0)
Hypertension, n (%)	29 (65.9)
Type 2 diabetes, n (%)	16 (36.4)
Coronary stenting, n (%)	24 (54.5)
Statin use, n (%)	39 (88.6)

Note: No control group was included. Smoking status was not recorded. Disease categories are not mutually exclusive; the sum of category counts exceeds the number of patients. CAD, coronary artery disease.

3.2 Genotyping performance and Hardy–Weinberg equilibrium

Only G/G and G/A genotypes were observed; no A/A homozygotes were detected. G/G occurred in 16 patients (36.4%; 95% CI 23.8–51.1) and G/A in 28 patients (63.6%; 95% CI 48.9–76.2) (Supplementary Table S1). The naive G and A allele frequencies were 0.682 and 0.318; these are descriptive only, and no confidence interval is reported for the reasons given in the Statistical framework. Twelve healthy volunteers were also genotyped (7 G/G, 5 G/A; 41.7% G/A); because they were much younger than the patients, this is not presented as a case–control analysis, and for completeness the G/A proportion did not differ significantly between patients and volunteers (63.6% vs 41.7%; Fisher's exact P = 0.20).

The genotype distribution deviated from HWE (conditional exact P = 0.0017; Pearson χ^2 = 9.58, 1 df, P = 0.0020). Expected counts were 20.5 G/G, 19.1 G/A and 4.5 A/A, against observed counts of 16, 28 and 0—a heterozygote excess with no A/A homozygotes. Because genotypes were not independently confirmed, this deviation is reported as a quality-control finding that requires investigation in the affected sample. A heterozygote excess is compatible with genotyping error, for example cross-hybridization or allele-specific probe performance on reverse-hybridization strips, but it is not diagnostic of it; sampling variation and population structure are alternative explanations that this dataset cannot distinguish.

3.3 Coagulation biomarkers

D-dimer was the only coagulation measure available for most patients and was measured in 40 of 44 (24 G/A and 16 G/G); four imputed values were excluded and no values were imputed. Other coagulation tests (prothrombin time, activated partial thromboplastin time) were recorded for too few patients to analyses. Mean D-dimer concentration was 0.57 ± 0.43 µg/mL (median 0.52, IQR 0.32–0.66) in G/G patients and 1.87 ± 2.09 µg/mL (median 1.26, IQR 0.69–1.94) in G/A patients (Mann–Whitney U, P = 0.0006). A D-dimer concentration

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>1.0 µg/mL was recorded in 1 of 16 G/G patients (6.3%) and 14 of 24 G/A patients (58.3%) (corrected OR 14.3, 95% CI 2.2–91.2; Fisher's exact P = 0.0009; raw OR 21.0), which remained significant at the Bonferroni-corrected threshold of 0.0167. Age did not explain the difference: mean age was similar between the genotype groups (64.4 ± 10.2 years in G/G and 63.7 ± 12.6 in G/A), with no correlation between age and D-dimer. The confidence interval is wide, the genotypes are unverified, the comparison was post hoc, and D-dimer may reflect the timing of the event and anticoagulant treatment; this therefore does not establish a genotype–phenotype association.

Table 2. D-dimer by genotype (exploratory only).

Biomarker	G/G (n = 16)	G/A (n = 24)
D-dimer, µg/mL (mean ± SD)	0.57 ± 0.43	1.87 ± 2.09
D-dimer, µg/mL (median, IQR)	0.52 (0.32–0.66)	1.26 (0.69–1.94)
D-dimer >1.0 µg/mL, n (%)	14 (58.3)	

Note: Genotypes are unverified (see Supplementary Table S1). The continuous comparison (Mann–Whitney U, P = 0.0006) is the primary analysis; the dichotomised comparison was post hoc (Fisher's exact P = 0.0009; Bonferroni α = 0.0167) and is exploratory. Corrected OR 14.3 (95% CI 2.2–91.2); raw OR 21.0. Measured values only; four imputed values excluded.

3.4 Lipid profile

Mean total cholesterol was 161.8 ± 46.4 mg/dL among G/G patients and 134.1 ± 45.5 mg/dL among G/A patients. Mean LDL cholesterol was 103.1 ± 38.7 mg/dL and 76.9 ± 28.9 mg/dL, respectively. Mean HDL cholesterol was 43.8 ± 9.6 mg/dL and 39.7 ± 14.4 mg/dL, while mean triglyceride concentrations were 152.4 ± 106.7 mg/dL and 126.9 ± 80.9 mg/dL, respectively (Table 3). Statin therapy was recorded in 12 G/G patients (75.0%) and 27 G/A patients (96.4%); overall, 39 of 44 participants (88.6%) were receiving statins. Because lipid measurements were obtained in the context of substantial statin use, these values were considered treatment-confounded and were not interpreted as evidence of a genetic effect.

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Table 3. Lipid profile by genotype (exploratory only; descriptive, no hypothesis tests).

Lipid parameter	G/G (n = 16)	G/A (n = 28)
Total cholesterol, mg/dL (mean ± SD)	161.8 ± 46.4	134.1 ± 45.5
LDL cholesterol, mg/dL (mean ± SD)	103.1 ± 38.7	76.9 ± 28.9
HDL cholesterol, mg/dL (mean ± SD)	43.8 ± 9.6	39.7 ± 14.4
Triglycerides, mg/dL (mean ± SD)	152.4 ± 106.7	126.9 ± 80.9

Note: Lipid data are treatment-confounded (88.6% on statins). Genotypes are unverified. No hypothesis tests were performed; these data are descriptive only.

3.5 Comorbidity distribution

Among the 44 cases, coronary artery disease was reported in 9 G/G patients (56.3%) and 24 G/A patients (85.7%) (Corrected OR 4.30; raw OR 4.67; Fisher's exact P = 0.067), which did not meet the Bonferroni-corrected threshold. Coronary stenting was recorded in 6 G/G patients (37.5%) and 18 G/A patients (64.3%) (Corrected OR 2.85; raw OR 3.0; P = 0.12). Hypertension was present in 10 G/G patients (62.5%) and 19 G/A patients (67.9%), type 2 diabetes mellitus in 7 (43.8%) and 9 (32.1%), and cerebrovascular events in 2 (12.5%) and 3 (10.7%) (Supplementary Table S2). No adjusted analysis was possible with this sample size. The coronary artery disease count reflects the re-adjudication described in the Methods; the recalculated test uses the revised denominator.

4. Discussion

4.1 Principal findings

This short report provides preliminary observations on the β-fibrinogen −455G>A variant among 44 Libyan patients with cardiovascular disease. The G/G genotype was observed in 16 patients (36.4%) and the G/A genotype in 28 (63.6%), with a naive A-allele frequency of 0.318; no A/A homozygotes were detected. The genotype distribution deviated from HWE (conditional exact P = 0.0017), which is the principal methodological finding. A D-dimer concentration >1.0 µg/mL was more frequent in G/A than in G/G patients and met the corrected significance threshold, but this post hoc, unadjusted observation in unverified genotypes cannot establish a causal genotype–phenotype relationship. The higher frequencies of coronary disease and stenting in G/A patients were not significant. Lipid differences cannot be interpreted independently of the high prevalence of statin treatment.

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4.2 Hardy–Weinberg equilibrium deviation: implications and possible mechanisms

The observed deviation from HWE requires careful interpretation. The counts show an excess of heterozygotes and no A/A homozygotes (4.5 expected). A heterozygote excess can be a signal of genotyping error—for example, cross-hybridization or allele-specific probe performance on reverse-hybridization strips. Sampling variation, population structure or recruitment characteristics are other possible explanations, and the small sample and absence of orthogonal validation do not allow these to be distinguished. The appropriate response to this finding is to investigate the affected sample: by re-genotyping, by sequencing a subset that includes every heterozygote, and by examining whether assay failures cluster by batch or by DNA quality. The frequencies are therefore best read as provisional strip-assay results, and the HWE check is reported to alert readers and later investigators rather than to establish that the assay failed.

The initial failure of a proportion of assays and the subsequent re-genotyping further support the need for independent confirmation. Future studies should confirm genotypes with Sanger sequencing or another validated reference method, at least for a predefined subset that includes every heterozygote, particularly when an unexpected genotype distribution is observed.

4.3 Comparison with previous studies

Direct comparison of the genotype and allele frequencies observed here with those reported in other populations should be interpreted cautiously, because the present genotypes were not independently validated and the observed distribution deviated from HWE. In Asian populations, the −455A allele has been associated with coronary heart disease in a meta-analysis (5), and with cardioembolic stroke in atrial fibrillation (8); in Chinese patients with cerebral infarction, the variant has been associated with plasma fibrinogen level (9). In the ECTIM study, β-fibrinogen gene polymorphisms were associated with plasma fibrinogen and coronary artery disease in patients with myocardial infarction (6). These findings are not directly comparable with the present cohort, which is small, lacks a control group and did not measure fibrinogen concentration. Validated future studies with an appropriate control group, direct fibrinogen quantification and standardized phenotyping will be better positioned to determine whether the Libyan population differs from other populations in the distribution of rs1800790 and in its relationship with cardiovascular phenotypes.

4.4 Study limitations

Several limitations should be considered, and most of them follow directly from the self-funded nature of the study, which precluded both expansion of the cohort and any additional confirmatory experiments. First, the study had no age-comparable control group; the 12 healthy volunteers (mean age 36.8 years) were much younger than the patients (64.0 years). Second, genotypes came from a single strip assay without orthogonal validation, and the HWE deviation (P = 0.0017) limits confidence in them; Sanger sequencing, which could help evaluate this uncertainty, was not possible because the project was self-funded and sequencing costs were beyond the available budget. Third, the sample of 44 is far below the roughly 375 participants (about 187 per group) that a case–control comparison would require, and the cohort could not be enlarged because recruitment and genotyping were entirely financed by the authors. Fourth, the three genotype

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comparisons were post hoc and unadjusted for confounders, and no multivariable model was possible. Fifth, the case group was clinically heterogeneous (coronary, cerebrovascular and thrombotic disease), and 88.6% of patients were receiving statins, confounding the lipid data. Sixth, several laboratory variables—including prothrombin time, activated partial thromboplastin time and troponin—were unavailable for most patients and were not analysed; D-dimer was missing for four patients; smoking status was not recorded; and the timing of sampling and anticoagulant use may confound D-dimer. Seventh, the study was conducted at a single centre. Eighth, direct fibrinogen concentrations were not measured, so the functional relationship between rs1800790 and fibrinogen could not be evaluated. Ninth, the three records initially classified as coronary artery disease on the basis of cerebrovascular or vascular diagnoses were re-adjudicated, but the reclassification was based on the available clinical notes and was not independently reviewed. Tenth, four D-dimer values had been imputed during data entry without a documented statistical procedure; they were removed, but the reason for the original imputation could not be reconstructed. These limits reflect the resources available for this pilot, and the data are offered so that they can be built upon by better-resourced groups.

4.5 Research and clinical implications

The findings are descriptive and hypothesis-generating and should not influence clinical practice. The report adds genotype data from a population with little published information on this variant, and it illustrates the value of HWE checking and independent genotype confirmation in cardiovascular genetic studies in settings with limited resources. Future studies should include adequately powered, age-matched controls, genotype confirmation, direct fibrinogen quantification and standardized phenotyping, and could test the D-dimer observation with adjustment for event timing and anticoagulation.

5. Conclusions

This short report describes the β-fibrinogen −455G>A genotype distribution in 44 Libyan patients with cardiovascular disease. Only G/G and G/A genotypes were observed, and the distribution deviated from HWE. The study was self-funded, so the sample could not be enlarged and confirmatory Sanger sequencing could not be performed. Because of the small sample, the absence of an age-comparable control group, the absence of orthogonal validation and treatment confounding, the findings cannot establish an association between rs1800790 and cardiovascular disease. They provide preliminary regional data and a hypothesis—a possible link with raised D-dimer—for larger validated studies.

ETHICALSTATEMENT

Ethical approval was obtained from the National Committee for Biosafety and Bioethics in Libyan Academy of Postgraduate Studies ((Reference: NBC: 026.H.25.7), 26 Jan 2025). Written informed consent was obtained from all participants.

CONFLICT OF INTEREST

The Authors proclaim no conflict of interest.

AUTHORS CONTRIBUTIONS

R.G. and A. A performed the laboratory work. S. A. conducted the statistical ,analysis. The original draft of the manuscript was written by R.G and S. A, reviewed and edited by A. A. All authors have read and agreed to the published version of the manuscript.

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Supplementary Files

Supplementary Table S1. Genotype frequencies by strip assay (unverified, exploratory).

Genotype	Cases (n = 44)
G/G, n (%)	16 (36.4)
G/A, n (%)	28 (63.6)
A/A, n (%)	0 (0.0)

These genotype frequencies were derived from the strip assay after repeating initially failed samples. No orthogonal validation was performed. The data should not be used for definitive association analyses, population comparisons, or clinical inference.

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Supplementary Table S2. Comorbidity distribution by genotype (exploratory only).

Comorbidity	G/G (n = 16), n (%)	G/A (n = 28), n (%)
Hypertension	10 (62.5)	19 (67.9)
Type 2 diabetes	7 (43.8)	9 (32.1)
Cerebrovascular event	2 (12.5)	3 (10.7)

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