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ORIGINAL PAPER

Gate-keeper to coronary angiography: comparison of exercise testing, myocardial perfusion SPECT and individually tailored approach for risk stratification

Stefano Muzzarelli · Matthias Emil Pfisterer · Jan Müller-Brand · Michael Johannes Zellweger

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Abstract We aimed to evaluate the differences between exercise testing (ET), myocardial perfusion SPECT (MPS) and a combination of ET and MPS based risk assessment as outlined by the guidelines with respect to their "gate-keeper" role to coronary angiography (cath) and the associated diagnostic procedural costs if prognostic considerations, as those proposed by the current guidelines and the recent literature, were taken into account. The Duke-score and the summed difference score (SDS; extent of ischemia) were assessed in 955 consecutive patients referred for MPS combined with ET. According to the guidelines and the available literature, three different algorithms for risk stratification were retrospectively applied: (1) ET based risk stratification and cath if intermediate or high risk Duke-score; (2) MPS based risk stratification and cath if SDS $\geq$ 8; (3) combined approach with ET as first step and MPS in case of intermediate risk Duke-score. A cath would have been suggested in every patient with either high risk Duke-score or SDS $\geq$ 8 in patients with intermediate risk Duke-score. The referral rate to cath was 27% according to the ET alone, 13% using MPS, and finally 12% applying the combined risk stratification. The cost of the diagnostic work-up including cath were: 615€, 1'299€, and 598€ per patient, respectively. The coronary angiography referral rate widely depends on the diagnostic modality used for risk stratification and according to the referral criteria provided by the guidelines. In the present study, the use of a stress imaging modality (MPS) and published prognostic data was associated with a lower referral rate to cath as compared to exercise testing alone and thus underlines the advantage of a risk based approach applying stress imaging in patients with intermediate risk Duke-score.

Keywords Coronary artery disease · Myocardial perfusion SPECT · Exercise testing · Duke-score · Coronary angiography · Cost effectiveness

S. Muzzarelli · M. E. Pfisterer · M. J. Zellweger (✉)
Cardiology Department, University Hospital Basel, Petersgraben 4, 4031 Basel, Switzerland
e-mail: zellwegerm@uhbs.ch

S. Muzzarelli
Radiology Department, Cardiac and Pulmonary Imaging, University of California, San Francisco, USA

J. Müller-Brand
Nuclear Medicine Department, University Hospital Basel, Basel, Switzerland

Introduction

Exercise testing and myocardial perfusion SPECT (MPS) are well established for the diagnostic and

prognostic assessment of patients with suspected or known coronary artery disease (CAD). The results of both non-invasive diagnostic modalities help to guide the therapeutic approach and identify candidates for coronary angiography among patients with stable CAD. According to the American College of Cardiology/American Heart Association (ACC/AHA) guidelines, patients with stable CAD stratified to low risk after exercise testing can be managed medically without need of coronary angiography and patients at high risk should be referred for coronary angiography. For patients with intermediate risk according to exercise testing, the guidelines suggest either a coronary angiography or an exercise imaging test [1]. Even if MPS is considered superior to exercise testing for risk stratification of patients with CAD, to date there is no direct comparison between these diagnostic modalities with respect to the their "gate-keeper" role for coronary angiography if indications as outlined by the available guidelines and the prognostic literature are applied [2–6]. In this context, and considering that the guidelines advise either direct coronary angiography or supplementary imaging based risk stratification for patients with intermediate risk Duke-score, we aimed to compare the hypothetical referral rate to coronary angiography based on three different risk stratification algorithms: (a) risk stratification based on exercise testing alone, (b) risk stratification based on MPS alone, and (c) risk stratification based on combined diagnostic modalities with exercise testing as first line assessment and subsequent MPS for patients with intermediate risk according to exercise testing. Furthermore we aimed to compare the costs of the above described diagnostic approaches.

Materials and methods

Patient population

Consecutive patients referred for MPS for CAD evaluation ($n = 1{,}132$) who were able to undergo exercise stress (bicycle ergometry) were included in this analysis. Patients with ST-segment depression $\geq$1 mm or left bundle branch block on their baseline electrocardiogram were excluded ($n = 177$). Detailed medical history has been collected in all patients. Whenever possible, beta-blocking medications as well as negative chronotropic calcium antagonists were withheld for 48 h and long-acting nitrates for 24 h before exercise testing.

Exercise testing

Resting heart rate, blood pressure and 12-lead ECG were recorded before exercise. A standardized, stepwise and symptom limited bicycle exercise test was performed in all subjects to the end points as defined in the exercise testing guidelines [7]. A 12-lead ECG was continuously recorded during exercise and recovery. Blood pressure was recorded every minute during exercise and recovery. ST-segment deviation was assessed automatically (CARDIOVIT CS-200®, Schiller) and visually controlled and interpreted by an experienced cardiologist, who was blinded for the MPS results. Maximum ST-segment depression (STD in mm, 1 mm = 0.1 mV) was defined as the maximal exercise-induced ST-segment depression 80 ms after the J point, which was horizontal or downsloping; it was calculated by subtracting the maximum ST-segment deviation during exercise or post exercise from the resting ST-segment level in the corresponding lead. Maximum STD was considered ischemic if $\geq$1 mm. Exercise testing was considered positive in case of typical exercise induced angina or significant STD (horizontal or downsloping and $\geq$1 mm). The workload was expressed in metabolic equivalents (METs). Based on the exercise testing variables a modified Duke-score for bicycle ergometry was calculated using the following definition: (exercise capacity in METs−[5 × maximum ST-segment depression in mm]−[4 × angina index]) with angina index defined as a value of 0 if no angina occurred, 1 if typical non-test limiting angina, and 2 if test limiting angina occurred [8, 9]. According to previous published data and to the ACC/AHA guidelines for patients with chronic stable angina, patients were stratified in a low risk group if the Duke-score was $\geq$5, intermediate between -10 and 4, and a high risk $\leq$−11 [1, 9].

Myocardial perfusion imaging

All patients underwent routine rest/stress (ergometry) dual isotope (Tl-201 rest/Tc-99 m sestamibi) MPS protocol as previously described [10, 11]. Rest-SPECT was obtained after administration of 111 MBq Tl-201. Tl-201 SPECT was performed 10 min after tracer

injection. At near-maximal exercise, a 740 MBq dose of Tc-99 m sestamibi was injected and exercise was continued for at least an additional minute after injection. Post-stress gated SPECT was acquired in average 95–100 min post-stress. SPECT imaging was performed following standard protocols. No attenuation or scatter correction was used. SPECT images were acquired and processed as previously described, with a circular 180^0 acquisition. During imaging, two energy windows were used for Tl-201, including a 30% window centered on the 70-keV peak and a 20% window centered on the 167-keV peak. For Tc-99 m sestamibi SPECT, a 15% window centered on the 140-keV peak was used.

Semiquantitative visual interpretation was performed using a 20-segment model. Each segment was scored using a five-point scoring system: 0 = normal, 1 = equivocal, 2 = moderate, 3 = severe reduction of radioisotope uptake, and 4 = apparent absence of detectable tracer uptake in a segment. A summed stress score (SSS) was calculated by adding the scores of the 20 segments of the stress images, and a summed rest score (SRS) by adding the scores of the 20 segments of the rest images. To assess defect reversibility, a summed difference score (SDS) was calculated by subtracting SRS from SSS, reflecting the severity and extent of ischemia. MPS was considered abnormal in case of scar (SRS $\geq$ 4) or ischemia (SDS $\geq$ 2). Moderate to severe ischemia was defined as an SDS $\geq$ 8.

Risk stratification according to exercise test, myocardial perfusion SPECT and combined approach. Study algorithm for referral to coronary angiography

According to the available literature and to the guidelines three different algorithms were defined based on prognostic information derived from the exercise test and MPS to refer patients for coronary angiography (see Table 1) [1, 12–16]. Each of the described algorithms for risk stratification has been retrospectively applied to all 955 patients to assess the hypothetical referral rate to coronary angiography.

Cost analysis

The costs generated by the different diagnostic procedures were calculated based on the official Swiss medical system TARMED. The cost estimates were as follows: coronary angiography 1810 €, myocardial perfusion SPECT 1060 € and exercise test 130 €. The cost per patient generated by the exercise test based risk stratification was calculated adding the cost of the exercise tests for all patients and the cost of the coronary angiography for patients with intermediate to high risk exercise test results divided by the total number of patients included in the present analysis. In analogy, the cost per patient generated by MPS based risk stratification was calculated adding the cost of an MPS for all patients and the cost of coronary angiography for patients with a SDS $\geq$8 divided by the total number of patients. Finally, the cost per patient generated by the combined approach for risk stratification was calculated by summing up the cost of the exercise test for all patients, the cost of the MPS for patients with intermediate Duke-score and the cost of the coronary angiography for patients who qualified for a further invasive diagnostic procedure as described in the methods, divided by the total number of patients.

Statistics

Numerical data are presented as mean ± SD. Categorical data are presented as numbers and percentages. The different hypothetical referral rates to coronary angiography of the exercise testing, MPS and the combined approach were compared with a Chi-square test. Univariate predictors for discrepant findings between exercise testing and MPS results with respect to risk stratification were tested by Fisher's test for nominal variables, Students *t*-test for numerical variables with equal distribution and Mann–Whitney test for numerical variables with non-equally distribution. Independent predictors of discrepant findings of exercise testing and MPS results with respect to risk stratification were identified including the univariate significant variables ($P \leq 0.05$) in a multivariable logistic regression. The differences between the diagnostic procedural costs of the different strategies for risk assessment were compared by the Wilcoxon test. A *P*-value of $\leq$0.05 was considered statistically significant. Analyses were performed using the commercially available statistical package SPSS version 15.0.

Table 1 Prognostic criteria for referral to coronary angiography according to the 3 different diagnostic and risk stratification approaches

Exercise testing	MPS	Combination of exercise testing and MPS
Positive ET with intermediate to high risk Duke-score	SDS $\geq$ 8	Positive ET and high risk Duke-score
		Positive ET, intermediate risk Duke-score and SDS $\geq$ 8

ET exercise testing, *SDS* summed difference score

Results

Patient characteristics

Patient characteristics are summarized in Table 2. The mean age of the 955 patients was almost 61 years and the majority were male (70%). Approximately half of the patients had a history of prior CAD.

Results of stress ECG and myocardial perfusion SPECT

As shown in Table 3, the majority of patients achieved the submaximal predicted heart rate and the maximal double product (peak heart rate x maximal systolic blood pressure) was consistent with an adequate stress test. Stress ECG was positive in 266 patients (28%). Among those, 10 patients (4%) had a low risk, 230 (86%) had an intermediate risk and 26 (10%) had a high risk.

Myocardial perfusion SPECT was considered abnormal in almost half of the patients (scar, ischemia, or both). Among patients with evidence of ischemia ($n = 367$, 38%) 126 (13% of the entire collective) had a SDS $\geq$8, consistent with a prognostic high risk ischemia, likely to benefit from revascularization (Table 4).

Impact of the different algorithms for risk stratification on referral to coronary angiography and procedural costs

As depicted in Table 5, applying the exercise testing based algorithm for risk stratification, 256 patients (27%) would have been referred to coronary angiography because of a positive exercise test and a Duke-score <5. Using MPS as a first line and only diagnostic modality for risk stratification, 126 patients (13%) would have been referred to coronary angiography because of SDS $\geq$8. Finally, applying the algorithm with exercise testing as first tool for risk stratification with subsequent MPS in case of intermediate risk exercise testing 112 patients (12%) would have been referred to coronary angiography; 26 because of a high risk Duke-score and 86 because of an intermediate risk Duke-score with SDS $\geq$8. The cost per patient of the diagnostic procedure generated by the three different algorithms were: 615€, 1'299€,

Table 2 Baseline characteristics

	Overall ($n = 955$)
Male gender (%)	666 (70)
Age (years $\pm$ SD)	61 $\pm$ 11
BMI (kg/m^2 $\pm$ SD)	27.5 $\pm$ 4.6
Known CAD (%)	409 (43)
Prior MI (%)	249 (26)
Prior revascularization (%)	377 (40)
Symptoms	
Typical angina (%)	219 (23)
Atypical angina (%)	304 (32)
Dyspnoea (%)	321 (34)
Risk factors	
Diabetes (%)	222 (23)
Hypercholesterolemia (%)	559 (59)
Hypertension (%)	605 (63)
Family history (%)	303 (32)
Smoking (%)	424 (44)
Medication	
Aspirin (%)	653 (68)
β-blockers (%)	540 (57)
Nitrates (%)	66 (7)
Ca-antagonist (%)	154 (16)
ACE-inhibitors (%)	226 (24)
ATII-antagonist (%)	219 (23)
Statins (%)	522 (55)

BMI body mass index, *CAD* coronary artery disease, *MI* myocardial infarction, *ACE* angiotensin converting enzyme, *ATII* angiotensin II

Table 3 Exercise testing variables

	Overall ($n = 955$)
Heart rate	
Resting HR (bpm ± SD)	80 ± 15
Peak HR (bpm ± SD)	148 ± 16
Blood pressure	
Resting SBP (mmHg ± SD)	129 ± 24
Peak SBP (mmHg ± SD)	213 ± 35
Resting DBP (mmHg ± SD)	81 ± 13
Peak DBP (mmHg ± SD)	79 ± 21
Maximal workload (METs ± SD)	7.2 ± 1.8
Exercise test duration (minutes ± SD)	6 ± 1
Submaximal predicted HR achieved (%)	908 (95)
Double product reached (±SD)	31,590 ± 6,417
Typical angina during exercise (%)	126 (13)
STD ≥ 1 mm (%)	215 (22)
Positive stress ECG (%)	266 (28)

HR heart rate, *bpm* beats pro minute, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MET* metabolic equivalent, *STD* maximal ST-segment depression

Table 4 Results of the myocardial perfusion SPECT

	Overall ($n = 955$)
Scar: SRS ≥ 4 (%)	274 (29)
Ischemia: SDS ≥ 2 (%)	367 (38)
Severe ischemia: SDS ≥ 8 (%)	126 (13)
Abnormal MPS (%)	453 (47)
SRS (median, IQR)	0 (0–4)
SSS (median, IQR)	2 (0–9)
SDS (median, IQR)	0 (0–4)

SRS summed rest score, *SDS* summed difference score, *MPS* myocardial perfusion SPECT, *abnormal MPS* MPS consistent with scar or ischemia, *IQR* interquartile range

and 598€ for exercise testing only, MPS, and the combined approach, respectively (Table 5).

In a subgroup analysis, patients without history of CAD were evaluated ($n = 546$, 57%). Of these, 124 (23%) had a positive exercise test and 116 (21%) would have been referred to coronary angiography according to the exercise testing based risk stratification (Duke-score < 5). Myocardial perfusion SPECT was abnormal in 153 patients (28%), 132 (24%) had myocardial ischemia (SDS ≥ 2) and 58 patients (11%) would have been referred to coronary angiography based on the MPS risk stratification (SDS ≥ 8). Finally, applying the combined diagnostic approach for risk stratification, 56 (10%) patients would have been referred to coronary angiography; 15 because of a high risk exercise test and 41 because of an intermediate risk exercise test with SDS ≥8 (Table 5).

Correlation between exercise testing and myocardial perfusion results

The correlation between Duke-score and extent of ischemia is shown in Fig. 1. As illustrated, the proportion of patients with greater extent of ischemia increased as a function of the Duke-score (*P*-for trend < 0.01). Of note, among the 699 (73%) patients with negative exercise test or positive exercise test but low risk Duke-score only 18 patients (2.6%) and 1.8% of the entire collective had a SDS ≥8. Among patients with a positive exercise test and intermediate risk Duke-score 38% had a SDS ≥8. And finally, among patients with high risk Duke-score 81% had a SDS ≥8 (see Fig. 1).

In a univariate analysis, patients with intermediate or high risk based on exercise testing but SDS <8 on MPS (58%) more often were female (22 vs. 13%; $P = 0.04$), were younger (62.4 ± 9.2 vs. 65.0 ± 10.5 years; $P = 0.05$), more often had stopped beta-blockers before exercise testing (60 vs. 42%; $P < 0.01$), had achieved a higher peak heart rate during exercise (147 ± 15 vs. 140 ± 17 beat/minute; $P < 0.01$) and were less likely to have a history of typical angina (38 vs. 60%; $P < 0.01$). In the multivariate regression analysis, female sex (95% CI: 1.1–4.3; $P = 0.04$), discontinuation of beta-blockers before exercise testing (95% CI: 1.2–3.5; $P < 0.01$), as well as absence of typical angina (95% CI: 1.5–4.3; $P < 0.01$) were independent predictors of SDS <8 despite of a Duke-score <5.

Discussion

To our knowledge this study is the first one evaluating different diagnostic CAD algorithms based on the most recent risk stratification data and comparing the costs of these different approaches [12, 17]. The present study suggests that the risk stratification of patients evaluated for known or suspected CAD may substantially differ depending on the diagnostic

Table 5 Referral rates to coronary angiography and procedural costs associated with the different diagnostic and risk stratification approaches

All patients ($n = 955$)	ET	MPS	*P*-value*	ET and MPS	*P*-value**
Patients referred to coronary angiography (%)	256 (27)	126 (13)	<0.01	112 (12)	<0.01
Costs of the diagnostic procedure (per patient, €)	615	1299	<0.01	598	0.02
Patients without known CAD ($n = 546$)					
Patients referred to coronary angiography (%)	116 (21)	58 (11)	<0.01	56 (10)	<0.01
Costs of the diagnostic procedure (per patient, €)	515	1252	<0.01	512	0.08

ET exercise test, *MPS* myocardial perfusion SPECT, € Euro, *P-value** comparison between MPS and ET, *P-value*** comparison between combination of ET/MPS and ET alone

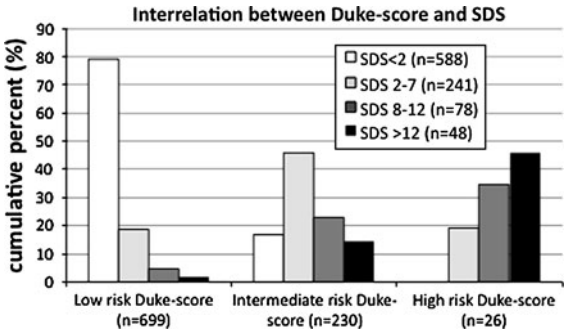

Fig. 1 Interrelation between Duke-score and SDS categories (*P*-for trend < 0.01). Note the relevant proportion of patients with moderate to severe ischemia among patients with high risk Duke-score and the low percentage of patients with moderate to severe ischemia among patients with low risk Duke-score

modality used for risk stratification. In this context, MPS based risk stratification, as well as the combined approach with exercise testing as first approach and MPS in case of intermediate risk, may have both a stronger "gate-keeper" role with respect to referral to coronary angiography as compared to exercise testing alone if prognostic considerations of current guidelines and the recent literature are taken into account. Based on the proposed prognostic decisional algorithm, the number of coronary angiographies would have been reduced by more than 50% using MPS or the combined approach for risk stratification. Notably, the lower coronary angiography referral rate was similar in patients with and without history of CAD. Of note, the total costs of the diagnostic procedure were substantially higher if MPS was used in all patients as a first line modality for risk stratification. On the other hand, the combined approach with stress imaging applied only in selected patients with intermediate risk during exercise testing demonstrated a very low risk of misclassification (meaning that only a minority of patients with low risk Duke-score had a relevant myocardial ischemia), and a good cost performance if only costs related to the diagnostic work-up are considered.

There is plenty of evidence, that imaging modalities, as MPS, provide incremental prognostic value with respect to prediction of major cardiovascular events as compared to exercise testing alone. These findings have been confirmed by several studies and in different subsets of patients evaluated for known or suspected CAD [2–6]. Even though, the different impact of imaging based risk stratification as compared to exercise testing with respect to clinical decision making and referral to subsequent coronary angiography has not been analyzed by all of the above mentioned studies.

The prognostic benefit of revascularization procedures in patients with stable CAD has been questioned by several recent randomized trials [18–23]. The recently published COURAGE and BARI 2D studies showed that percutaneous coronary intervention in addition to optimal medical treatment was not superior to medical therapy alone in terms of prognosis and quality of life [18, 19, 24]. Of note, a documented ischemia was an inclusion criterion of the COURAGE trial, but no minimal threshold of myocardium ischemic was taken into account for inclusion and patients with severe ischemia were excluded [18]. This aspect is of particular importance considering that the benefit of a revascularization procedure may be dependent on the extent of ischemic myocardium. A study reported by Hachamovitch et al. suggested that myocardial revascularization compared to medical therapy had greater survival benefit only in patients with moderate to large amount of inducible ischemia (>10% myocardium ischemic) [12]. This seems to hold true also

for asymptomatic patients [14]. Similarly, the nuclear substudy of the COURAGE trial indicates that patients with moderate to severe pre-treatment ischemia had a worse prognosis and were more likely to benefit from revascularization in terms of reduction of myocardium ischemic and increased event free survival as compared to patients with less severe ischemia [13]. In this context, the value of non-invasive risk stratification for patients with stable CAD seems to be of outstanding importance, in order to select and identify low risk patients, who can safely be treated medically without further testing and on the other hand high risk patients, who may benefit from angiography and potential revascularization [25].

The present study provides the evidence that patients' allocation to a specific risk category may widely differ according to the diagnostic modality used for risk assessment. As a consequence, performing risk stratification with MPS or combination of exercise testing and MPS on an individual basis result in less patients being referred to coronary angiography as compared to exercise testing alone. Additionally, the costs of the diagnostic procedure were almost the same if exercise testing alone or the more "sophisticated" combined risk stratification approach was used. This was due to the reduced number of coronary angiographies in the combined scenario. Therefore, the present study underlines possible advantages of a combined approach with stress imaging applied in patients with an intermediate risk exercise test even applying prognostic considerations. Of note, also considering the results of risk stratification the proportion of patients with high risk MPS results was very low (2.6%) among patients with a Duke-score indicating a low risk and on the other hand high (81%) among patients with a high risk Duke-score. Therefore, among patients stratified to low or high risk according to the exercise testing alone, there was a good concordance between exercise testing and MPS with respect to the hypothetical treatment allocation (medically vs. coronary angiography). In contrast, among patients with intermediate Duke-score a great proportion of patients (62%) did not meet high-risk criteria on MPS. Patients of female gender, as well as patients who discontinued beta-blocking medications before exercise testing or patients without typical angina were particularly prone to have discordant results with respect to risk stratification between exercise testing and MPS, meaning low risk MPS findings despite of intermediate to high risk exercise testing. Keeping in mind, that MPS is superior to exercise testing for risk stratification, the present results suggest that further risk stratification based on MPS in patients with an intermediate exercise testing Duke-score may be favorable, in order to reduce the referral rate to coronary angiography if strictly prognostic considerations, as those proposed by the current guidelines and the recent literature, are taken into account. Still, this study is not intended to provide any definitive advice regarding procedure for risk stratification of patients evaluated for CAD, but may point to the relevant differences in risk stratification depending of the diagnostic modality used.

Limitations

The study is an observational study, no randomized allocation to different diagnostic procedures for risk stratification was performed and no follow-up data were available. The accepted gold standard of coronary angiography can't be provided in this study. Coronary angiography is superior to MPS to establish the diagnosis of CAD, even though, the combination of clinical data and myocardial perfusion data has been shown to be superior than the combination of clinical data and coronary angiography data for prognostic purposes [26]. Indeed, even when angiographic CAD is present, MPS is a powerful method for risk stratification. In this context, as the proposed decisional algorithm is based strictly on prognostic consideration, the absence of the angiographic data should not compromise the conclusion of the present study. Of course, this data only applies to patients who are able to undergo an adequate ergometry test (i.e. this data can't be used for pharmacologically stressed patients).

Conclusion

The patients' allocation to specific risk categories and the referral rate to coronary angiography may be widely different depending on the diagnostic modality used for risk stratification as outlined by the guidelines. In the present study population, the use of a stress imaging modality as MPS was associated with a lower referral rate to coronary angiography as

compared to exercise testing alone if prognostic information, as those proposed by the current guidelines and the recent literature, were considered. The present study indicates possible advantages of a combined approach with individually tailored use of stress imaging in patients with intermediate risk exercise tests due to a very low risk of a prognostic misclassifications for patients with low Duke-score (meaning that only a minority of patients with low risk Duke-score had a relevant myocardial ischemia), and to its good cost performance.

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Conflict of interest None of the authors has conflicts of interest.

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