Multimodality imaging: Bird's eye view from the 2019 American College of Cardiology Scientific Sessions

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The 2019 American College of Cardiology Scientific Sessions displayed innovation in many areas for the evaluation and management of cardiovascular disease from preventive evaluation and care to advanced interventions. Imaging played a central role in these developments with a highlight of the conference being the imaging research presented. This review will summarize key imaging studies which were presented at this scientific meeting which will lead to innovation in the evaluation and management of cardiovascular disease. Experts in nuclear imaging (DW/MA), echocardiography (MS), cardiac magnetic resonance (SL), and cardiac computed tomography (RB) selected abstracts which they found to be of particular interest to the multimodality imaging audience and were integrated into this review (LP).

Key Words: Echo • CT • MRI • PET • SPECT

PLANAR AND SPECT

Multiple studies presented at ACC19 focused on SPECT imaging with focuses seen on quality metrics and specific populations. Early descriptive data on 18 practices participating in the ImageGuide Registry were presented at ACC 2019.[1] Half were clinic-based (n = 9) imaging facilities and the majority were accredited by the Intersocietal Accreditation Commission (n = 14, 77.8% vs American College of Radiology, n = 4). Only 0.59% out of n = 9540 individual imaging studies were reported to be ''rarely appropriate.'' The majority of studies were performed with a pharmacological vasodilator (52.7% vs 31.6% with exercise). Stress first imaging was uncommon (6.6%). Further valuable data will become available as more sites participate in the ImageGuide Registry.

Khan et al reported results from a cohort of patients with mildly elevated high-sensitivity cardiac troponin (hscTn) after presenting to the emergency department with suspected acute coronary syndrome (ACS).[2] The patients were categorized based on hscTn using ''rule-in,'' ''observation,'' and ''rule-out'' ranges, referring to the likelihood of ACS. One-third (32.3%, n = 1714) of suspected ACS patients had hscTn in the observation range, of whom 213 underwent perfusion imaging. Roughly, 14% of these patients had ischemia (n = 29), none of whom experienced ventricular arrhythmia or

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MI. These data suggest this may be a safe testing algorithm for patients with mildly elevated hscTn.

Colon et al retrospectively evaluated the risk of cardiovascular events based on heart rate response (HRR) in a cohort of patients who underwent regadenoson SPECT MPI within 90 days of a type 2 MI.[3] The cohort was identified using the universal definition of MI and adjudicated by 2 physicians. In their population of 234 patients, both HRR < 30% and abnormal perfusion (≥ 5% ischemic myocardium) were associated with higher risk of the composite death/MI/late revascularization. Further details in a subsequent manuscript would include a detailed logistic regression that accounts for baseline characteristics and the interaction between HRR and perfusion.

Physicians in the emergency medical setting struggle with selecting the ''best'' test for patients with acute chest pain syndromes. In a retrospective cohort of 454 patients, Tamrat et al reported on time to discharge and outcomes among patients subjected to anatomic vs functional testing.[4] Time to discharge was reduced for anatomic (computed tomography coronary angiography, CCTA) testing (10.8 hours) vs functional testing (28.7 hours, $P < 0.001$). Substantial variation in the two strategies was observed with the proportion of tests ordered using an anatomic strategy ranging from ~ 5 to ~ 90%, when stratified by individual clinician. Unlike prior studies addressing this clinical quandary, invasive coronary angiography ($P = 0.98$) and revascularization ($P = 0.80$) rates were not different between the two strategies.

Nieves et al reported on their initial experience conducting quantitative coronary blood flow analysis using the cadmium-zinc-telluride DSPECT platform (Spectrum Dynamics, Sarasota FL).[5] A rest/stress Tc-99m sestamibi imaging protocol was used (Figure 1) with the 4DM platform (INVIA, Ann Arbor MI); manual adjustments were made for tissue and blood pool regions of interest. Data quality was sufficient to calculate coronary flow for 120 of 122 patients. The authors note that this strategy required ''significant operator input'' that could compromise reliability of the findings; adoption could be impacted as well.

PET

Multiple studies presented at ACC19 focused on positron emission tomography (PET) and its role in clinical cardiology. In particular, PET derived myocardial blood flow (MBF) utilization in everyday clinical practice and how it can guide clinical decision making was studied. One of the clinical areas where PET could have an impact is in patients with advanced liver failure who have significant splanchnic and peripheral vasodilation. Whether coronary vasodilatory response occurs in patients with end-stage liver disease undergoing PET vasodilator stress testing is not confirmed. A total of 174 patients with liver failure referred to vasodilator stress PET and were included, of which 75% received regadenoson and 25% received dipyridamole. The mean resting and peak MBF were 1.3 ± 0.4 and 2.5 ± 0.9 mL/g/min, respectively. The peak MBF was significantly higher than the rest flow in both regadenoson and dipyridamole groups (mean difference of 1.1 ± 0.04, $P < 0.001$, and 1.4 ± 0.1, $P < 0.001$, respectively).[6] Similar response was seen in patients with or without detectable CAC or CAC ≥ than 100. Thus, this study suggests an intact vasodilatory response in patients with end-stage liver disease.

Lopez et al investigated whether exercise treadmill test (ETT) can detect patients with coronary microvascular disease. They included 430 consecutive patients who underwent both ETT and PET within 36 months.[7] The sensitivity and specificity of a positive ETT to detect coronary microvascular disease were 11.7% (95% confidence interval (CI) 7.5 to 17.2%) and 89.7% (95% CI 85.1 to 93.2%), respectively, with an area under the curve of 0.54 (95% CI 0.49 to 0.59). The correlation

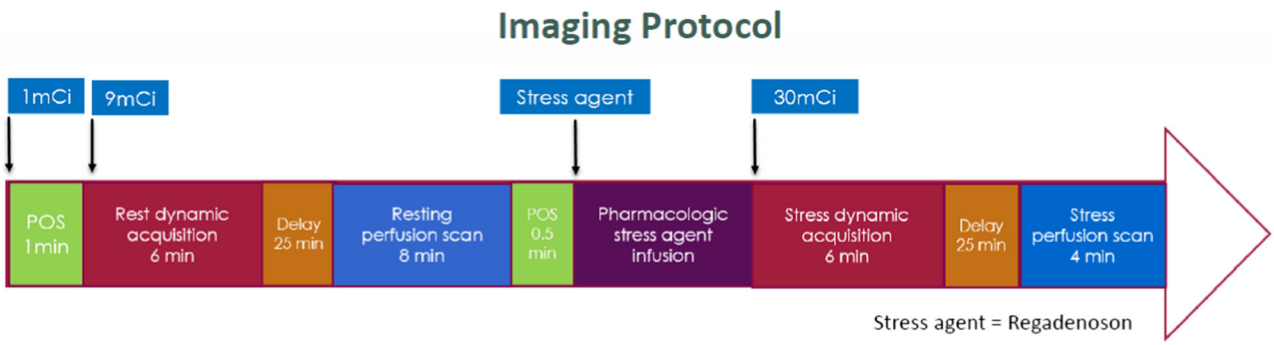

Figure 1. Outline of imaging protocol used in this study.

between coronary microvascular disease and renal function was studied in 2985 patients (mean age of 59.3 ± 11.4, 61.5% females) who underwent PET with coronary flow reserve and renal function assessment within five days. The authors noted a weak, but statistically significant correlation between peak myocardial blood flow ($r = 0.161$, $P < 0.0001$), coronary flow reserve ($r = 0.220$, $P < 0.0001$), and renal function which remained significant after adjusting for confounders.[8]

Kumar et al used PET to identify patients with documented left main (LM) disease on angiography. Of 349 patients who underwent PET MPI and angiography, 34 (9.7%) had LM disease. All patients had evidence of inducible ischemia with relative perfusion assessment (mean % ischemia 21.1 ± 12.5). 79% of patients had coronary flow reserve (CFR < 1.9) while 65% had drop in left ventricular ejection fraction was seen in 65% of the study cohort.[9] In another analysis from the same group, the main predictors of three-vessel coronary disease or left main disease were ischemic burden, higher coronary calcium score, lower CFR, and lower left ventricular ejection fraction reserve. The absence of the above four findings had a negative predictive value of 98% for severe coronary disease. A prediction model/score was developed with a C-statistic of 0.802; sensitivity of 90%; specificity of 60%.[10]

On the other hand, not every patient with severely abnormal PET imaging is referred to coronary angiography, despite the higher accuracy. Thomas et al studied a random sample of 100 such patients from 2015 to 2016 and determined potential patient and physician reasons for non-referral for angiography. The top reasons for non-referral were patients' preference for medical management (23%), uncertainty regarding accuracy of test results to account for the patient's presenting symptoms (13%), elderly patient with concomitant cognitive or physical decline (11%), renal failure (11%), and cancer (7%).[11]

Vascular applications of PET are also growing. The PET imaging group from Memorial Sloan Kettering utilized Fluorine-18 sodium fluoride (NaF), a bone-seeking radiopharmaceutical used to detect osseous metastases, to determine if atherosclerosis of penile arteries is associated with erectile dysfunction. This study, which was simultaneously published in the Journal of the American College of Cardiology, included 437 prostate cancer patients of which 336 (76.9%) had prevalent erectile dysfunction and 60 incident erectile dysfunction (13.7). Standardized uptake value maximum (SUVmax) in patients with prevalent (median 1.88; interquartile range [IQR]: 1.67 to 2.16) or incident (median 1.86; IQR: 1.72 to 2.08) erectile dysfunction was significantly higher than no erectile dysfunction.[12] This study suggests that atherosclerosis is associated with erectile dysfunction in prostate cancer patients and should be confirmed in the general population.

PET is also frequently used in patients with suspect cardiac sarcoidosis. However, there are no data for its repeatability. A study from Yale University which was simultaneously published in the Journal of the American College of Cardiology looked at 15 patients who had two cardiac FDG PET/CT studies. Qualitative (visual) and quantitative (including left ventricular blood pool [LVBP] standard uptake values [SUV], cardiac maximum SUV [SUV_{max}], cardiac metabolic volume [CMV], and cardiac metabolic activity = [CMA]) analyses were performed. There was good correlation between free fatty acids (0.65 ± 0.13 mM vs. 0.70 ± 0.22 mM, respectively; ICC = 0.80; $r = 0.79$) between the two studies which showed excellent repeatability in all cardiac measurements for FDG uptake. In addition, the inter- and intraobserver measurement variations demonstrated excellent repeatability (ICC = 0.94 to 0.98; r = 0.90 to 0.98).[13]

ECHOCARDIOGRAPHY

The abstracts presented at the 2019 ACC Scientific Sessions demonstrated the essential role of echocardiography in addressing important diagnostic and clinical questions. Thematically, they fell into three categories: (1) use of standard echocardiography techniques and measurements to assess clinical outcomes; (2) use of echocardiography prior to, during, and after transcatheter cardiac procedures; and (3) use of novel echocardiographic techniques and equipment at all levels of care.

Standard Echocardiography to Assess Disease Outcomes

In an observational study of 748 patients with at least moderate to severe native aortic regurgitation and no prior history of either overt coronary artery disease or heart surgery, Yang et al showed the power of left ventricular end-systolic diameter indexed for body surface area (LVESDi), a basic echocardiographic parameter, in predicting outcomes.[14] Compared to patients having LVESDi < 20 mm/m^2, those with ≥ 20 mm/m^2 had increased risks of death. LVESDi was the only LV parameter independently associated with all-cause mortality. This study suggests that the ideal cut-off for aortic valve surgery may be lower than recommended in current guidelines (> 25 mm/m^2).

Severe low-gradient native aortic stenosis is a heterogeneous disorder that classically included 2 forms of low-flow, low-gradient aortic stenosis with normal

and diminished left ventricular ejection fraction, respectively. More recently, the 3rd form—normal-flow and low-gradient, has been recognized. Hammadah et al presented a single-center study which included patients with echocardiographically measured stroke volume index, low-gradient (mean < 40 mm Hg) and severe aortic stenosis (AVA < 1 cm^2), and undergoing TAVR.[15] After a median follow-up of 386 days, normal-flow low-gradient aortic stenosis was associated with similar adverse outcomes in comparison with patients with low-flow forms of severe aortic stenosis.

Echocardiography in Percutaneous Interventions

Candidates for TAVR often present with other valvular disease. There is a paucity of data on possible improvement in mitral and tricuspid regurgitation (TR) post-TAVR. In a study of 187 patients receiving both a baseline and a one-year follow-up echocardiogram, Tang et al presented that persistent or worsening TR post-TAVR was associated with higher one-year mortality.[16] Mild or greater intraoperative paravalvular aortic regurgitation increased the odds of TR worsening or persisting after TAVR.

Conventional and strain echocardiographic evaluation of all 4 cardiac chambers (volumes and area, ejection fraction, longitudinal strain, and fractional area change) was performed in patients with high-risk (HR) vs. low-surgical risk (LR) patients undergoing TAVR.[17] Cardiac function in all 4 chambers was better in LR patients ($P < 0.01$) except for ejection fraction of the right atrium. Left and right atrial sizes were smaller for LR while ventricular size was similar in LR and HR (except for left ventricular end-systolic volume. In addition to standard clinical features defining surgical risk, four cardiac chamber's size and function by echocardiography may differentiate LR and HR TAVR populations.

New Echocardiographic Techniques and Equipment

Using newer generation software, mitral valve deformation by 3D transesophageal echocardiography was performed in 32 normals and 48 mitral valve prolapse (MVP) subjects with or without significant mitral regurgitation (MR).[18] Mitral annular and leaflet areas were largest in MVP subjects with MR, intermediate in subjects with MVP and no MR, and smallest in normals. Mitral strain was highest in MVP subject with MR and lowest in normals (Figure 2). Strain determination has the potential to improve characterization of MV properties and evaluate its prognostic impact.

Echocardiography is being used by an ever-expanding group of medical professionals by handheld devices. In a pilot study, Ramm et al evaluated left ventricular function and aortic and mitral valve disease assessment independently at the point of care by a cardiologist and a primary care physician (PCP) using basic echocardiogram views with and without color Doppler.[19] PCPs can generate high-quality images using handhelds and interpret them with a high degree of accuracy for LV function and mitral and aortic valve disease.

COMPUTED TOMOGRAPHY

The abstracts presented at the 2019 ACC Scientific Sessions demonstrated the essential role of cardiac computed tomography in both diagnostic utility and responsiveness to treatment regimens. Patel et al presented the 1-year results from the ADVANCE.[20] This was a multicenter registry designed to assess downstream procedures and outcomes among patients undergoing FFR-CT. A total of 5083 patients from 38 sites were enrolled. Among 4288 patients who had 1-year data, 1428 (33.3%) were negative by FFR-CT. Overall, all patients had low rates of major adverse cardiovascular events at 1 year, and patients who had an FFR-CT > 0.8 were more likely to undergo conservative management, and had a significantly lower rate of cardiovascular death or MI. Thus, this study provided further support regarding the adoption of FFR-CT and the safety of avoiding invasive evaluation in cases of negative FFR-CT.

Rosendael et al presented results of an analysis from the PRADIGM registry to evaluate the association of clinical, laboratory, and coronary atherosclerotic predictors with statin non-response.[21] This study included 2,252 patients who underwent serial CCTA >2 years apart, and statin non-response was defined as (1) annualized percent atheroma volume progression >1.0%, corrected for calcium progression, (2) increase in high-risk plaques, and (3) MACE (death, myocardial infarction, or revascularization) after follow-up CCTA. Among 485 patients on statin therapy followed for 6.8 ± 2.6 years, 158 (32.6%) were non-responders. Variables associated with statin non-response included diabetes, HbA1c, baseline plaque volume, and high-risk plaques. Although the definition of statin non-response was broad, this study highlighted that there is marked variability in response to statin therapy and certain patient sub-groups in whom disease progression may occur despite medical therapy.

Another study evaluating the impact of stating therapy on plaque changes was presented by Yang et al.[22] This study performed quantitative plaque analysis on 287 Chinese patients who underwent serial

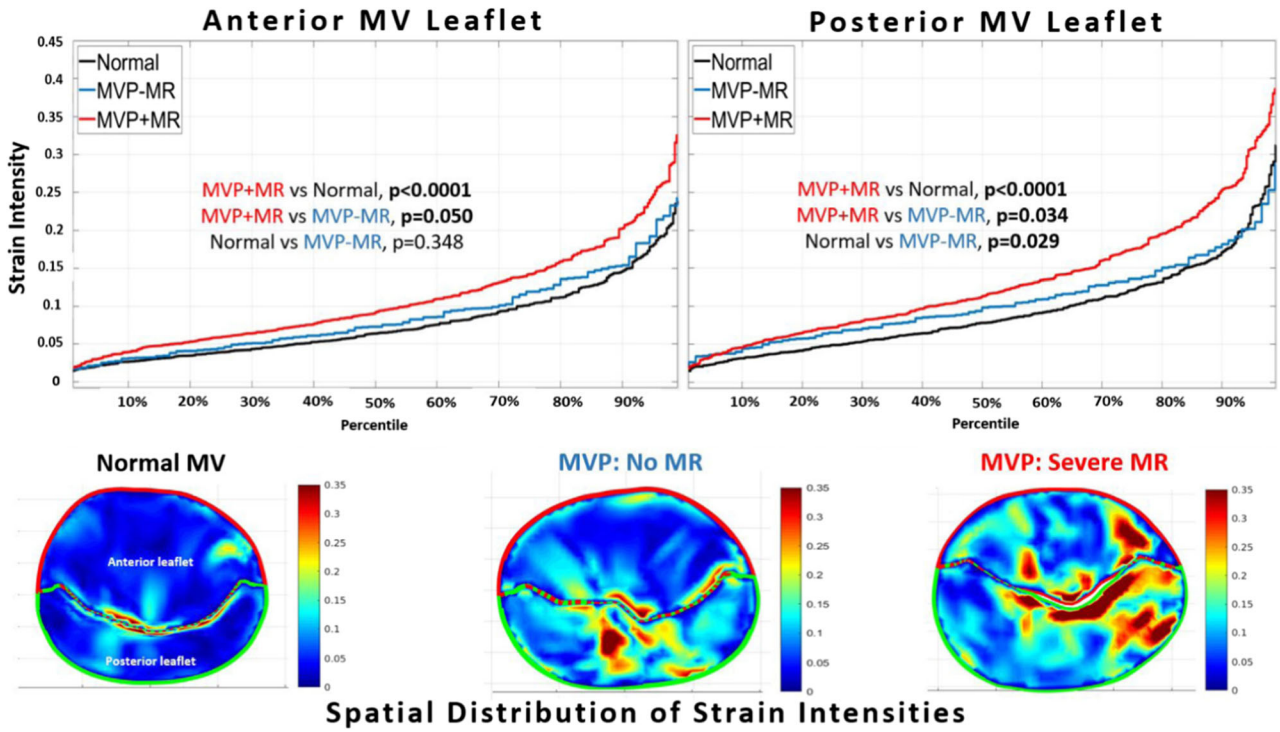

Figure 2. Mitral valve strain patterns compared in patients with MVP without MR, MVP with MR, and normals.

coronary computed tomography angiography scans. Despite the fact that statin intensity was mild to moderate, as per clinical practice in China, plaque regression occurred in 69 (24%) patients, and occurred more frequently in those with higher baseline LDL cholesterol level or those who achieved a greater relative reduction in LDL cholesterol. This study provides evidence that regression of coronary plaque with low to moderate intensity statin therapy is feasible and may be related to the LDL cholesterol reduction achieved.

CARDIAC MAGNETIC RESONANCE IMAGING

Cardiac MR (CMR) is a key modality for evaluation of patients with suspected myocarditis. Abdelhaleem et al studied 100 patients with acute myocarditis, with clinical and CMR evaluations including baseline diagnosis and at 12 months.[23] Seventy-two patients showed Late Gadolinium Enhancement (LGE) and 57 had abnormal T2 signal. The extent of LGE decreased from baseline to 12 months (8.5 ± 9.2 to 3.0 ± 5.2%), and T2 global signal ratio decreased (1.85 ± 0.3 to 1.56 ± 0.2), $P < 0.05$ for both. LV volumes and EF improved at 12 months, but the T2 signal and the LGE were not predictors of improvement of LVEF or volumes conclude that while all these markers of tissue injury and the volumes and EF improved, improvement in these markers is not related to the improvement in function.

Late Gadolinium Enhancement is often used to evaluate patients with cardiomyopathy and the presence or absence (and extent) of LGE is known to provide information on prognosis in these patients. The prognostic value of various patterns of LGE is not as well known. Ota et al studied 101 patients with idiopathic dilated cardiomyopathy with CMR, 48 of whom had no LGE, 29 had mid-wall fibrosis (MWF), and 24 had heterogeneous distributed fibrosis (HDF). Patients were followed for a median of 950 days. Five patients died: 4 had HDF and 1 had MWF (HR 1.76, 95% CI 1.07 to 3.04, $P < 0.05$).[24] Ten patients had arrhythmia events: 1 was in a patient with MWF and the other 9 in those with HDF (HR 1.85, 95% CI 1.06 to 3.50, $P < 0.05$). The authors concluded that the HDF phenotype has higher risk than those with no LGE or with mid-wall fibrosis. This abstract adds further value to information routinely obtained from CMR examinations.

Cardiac Resynchronization Therapy (CRT) has become a commonly used and well accepted means of treating heart failure. Assessment of the Response to therapy is most commonly done by echocardiography; CMR may offer advantages by its ability to provide high-resolution visualization of the entire left and right ventricles (LV and RV), but there are challenges to

imaging patients with Cardiac Implanted Electronic Devices (CIED). Gao et al studied 20 patients and compared standard gradient recalled echo (GRE) imaging to steady-state free precession (SSFP) technique.[25] They found that GRE was preferable in 11 (mainly due to less artifacts), and SSFP preferred in 9, with better image quality and acceptable artifacts. They found that using all information, in 17 patients with intact AV node conduction, 59% had improvement in LVEF, 35% did not change, and 6% worsened with CRT vs atrial only pacing. This study further adds to the array of uses of CMR in patients with CIED and provides high-quality data on response to CRT.

CMR is attractive as a means of assessing cardiac transplant graft rejection. Two main types of acute rejection such as acute cellular rejection (ACR) and antibody-mediated rejection (AMR) have different histopathologic changes. Miller et al hypothesized that AMR, ACR, and biopsy-negative rejection (BNR) have different global T1, T2, and LGE imaging.[26] They studied 44 cardiac transplant patients who underwent 79 CMR scans, at a median of 5.4 years from transplant and included those with ACR, AMR, BNR, and No Rejection. Native T1 was increased in patients with ACR (1099 ± 78 ms) or AMR (1101 ± 80 ms), compared to those without rejection (1018 ± 81 ms; $P < 0.05$ for both groups). T2 was marginally higher in ACR (52.7 ± 7.4 ms) vs No Rejection (48.2 ± 3.8, $P = 0.048$), but not higher in AMR vs No Rejection. Scar by LGE was higher in ACR and AMR compared to No Rejection. BNR differed from No Rejection only in LVEF (35.9 vs 48.5%, $P < 0.05$). They propose that CMR with native T1, T2, LGE, and LVEF assessments is useful in differentiating ACR, AMR, BMR, and No Rejection using this multiparametric approach. However, they did not propose a grading scale or cut-offs for these values and hence the sensitivity, specificity, and usefulness of these parameters on an individual patient basis is not known. Further work is needed.

Hypertension is a well-known factor associated with cognitive impairment, but the link between all of the cardiovascular parameters and their effect on brain function and anatomy is not fully known. Amier et al examined the effects of hypertension on the heart and on the brain in patients with cardiovascular risk factors, among those with and without vascular brain injury and the association with cognitive impairment.[27] They studied 431 patients, age 69 ± 9 years, with diagnoses of heart failure, carotid artery occlusive disease, or vascular cognitive impairment. They determined LV mass, aortic stiffness by pulse wave velocity (PWV), and cerebral small vessel disease by white matter lesions, microbleeds, lacunar infarcts, and perivascular space, using brain and heart magnetic resonance. Patients underwent extensive neuropsychological testing. 66.4 % of patients had cerebral small vessel abnormalities, with 32.4% having cognitive impairment. Aortic PWV (OR 1.1, $P < 0.05$) and LV mass (OR 1.18, $P < 0.05$) were associated with cerebral small vessel disease independent of other examined factors of age, sex, education, and LVEF, while Aortic PWV was associated with cognitive impairment (OR 1.08, $P < 0.05$) independent of those same factors. They conclude that these measures of vascular effects of hypertensive disease may be indicators of risk of brain structural disease and cognition. These relatively easy-to-determine parameters from CMR may become important in clinical assessments of risk of progression to cognitive impairment.

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