

Review

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# Editorial review: guidance for future atrial fibrillation research

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## Abstract

The following is a brief review and commentary covering the content of the Special Issue of *Vessel Plus* entitled Current state of knowledge: Atrial Fibrillation and Cardiac Surgery. All articles in this issue are highlighted with a brief comment for the busy reader, the idea being to facilitate and encourage reading of the original work.

**Keywords:** Editorial review, atrial fibrillation, cardiac surgery, postoperative

## COMMENTARY/REVIEW

### This is an old story

A quarter century ago, three senior authors from this Special Issue (Drs. Almassi, Shroyer, and Grover) initiated an ambitious Department of Veterans Affairs (VA)-sponsored research project entitled “Processes, Structures, and Outcomes of Care in Cardiac Surgery” (PSOCS study, CSP #5; Drs. Karl Hammermeister, A. Laurie Shroyer, and Fred Grover - co-Principal Investigators)<sup>[1]</sup>. The PSOCS study’s overarching goal was to identify the patient-based: (1) risk factors; (2) preoperative, intraoperative, and postoperative processes of



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care; and (3) structures of care associated with hospital-related adverse clinical outcomes and resource use<sup>[2]</sup>. With longitudinal follow-up, the PSOCS patients' six-month clinical outcomes and resource utilization were also assessed. From September 1993 to December 1996, 3,998 patients at 14 VA medical centers were enrolled in the PSOCS prospective cohort study. For these patients, nearly 1,100 patient-specific data elements were captured along with over 300 other provider-specific and facility-specific structures of care attributed to each Veteran record<sup>[3-5]</sup>.

As a pre-approved PSOCS sub-analysis, Veterans with preoperative atrial fibrillation (AF) and new onset of postoperative atrial fibrillation (POAF) were closely monitored for their subsequent outcomes and resource utilization patterns<sup>[5]</sup>. Patients undergoing a wide diversity of cardiac surgical procedures were evaluated, including coronary artery bypass grafting (CABG = 81%), aortic valve replacement or repair procedures (AVR = 6%), mitral valve replacement or repair procedures (MVR = 1%), CABG combination procedures (CABG + AVR = 6%, CABG + MVR = 1%, CABG + other procedures = 2%), and other cardiac procedures (3%). For this VA PSOCS cardiac surgery patient population, the POAF incidence was 29.6%. Across all other PSOCS complications, this atrial fibrillation rate (~30%) was higher than any other postoperative PSOCS complication reported<sup>[4,5]</sup>.

As a game-changing manuscript, the PSOCS patients' baseline patient risk factors associated with POAF were reported, including advanced age, chronic obstructive pulmonary disease (COPD), digoxin use, low resting pulse rate, and high resting systolic blood pressure. POAF patients had increased rates of all measured adverse outcomes and resource metrics compared to non-POAF patients<sup>[5]</sup>. Pointing to work from a decade earlier<sup>[6]</sup> showing very similar POAF rates and the fact that, for example, it was already known that beta-blockers had a prophylactic and overall benign effect, additional research was recommended to identify strategies to reduce the high incidence of POAF. Interestingly, this 1997 VA PSOCS atrial fibrillation publication was highly cited, ranking in the 100 most highly cited papers for CABG (i.e., #16 in 2019) and for AVR (i.e., #93 in 2020)<sup>[7,8]</sup>. As of August 2023, this paper had been cited 541 times per Web of Science citation index.

### **This is a contemporary story**

Despite this historical wide-spread interest, POAF remains the most prevalent cardiac surgical complication faced by cardiothoracic surgeons worldwide today. To guide future AF and POAF-related research, this Special Issue of *Vessel Plus* was created as an anthology. To date, despite conflicting bias in the literature, it remains unclear if POAF just shares risk factors with other adverse outcomes or is actually a driver of adverse outcomes. The result, unfortunately, is that the clinical recommendations for daily atrial fibrillation patient care are not universally agreed upon. Even today, cardiac surgeons encounter difficulties in caring for individual patients with pre-existing atrial fibrillation as well as new onset postoperative atrial fibrillation; timing and utilization of different therapies (i.e., anticoagulation and other pharmacotherapy) after the occurrence of post-op atrial fibrillation remain at the discretion of the individual physicians. Additionally, the utilization of ablative therapies in cases beyond mitral valve surgery is left to the surgeon. While professional society guidelines have increased in numbers, they remain general or only applicable to limited diagnostic groups. Despite a half-century struggle with POAF, amassing a large body of literature, there are very limited data-driven evidence-based recommendations pertaining to individual common clinical timing issues and therapeutic choices. Optimizing patient-focused cardiac surgery decision making based on existing data has been hampered, in large part, by the absence of universal definitions for preoperative and postoperative atrial fibrillation. The lack of consistently applied definitions routinely causes inherent difficulties in coordinating state-based, regional, or national database analyses<sup>[9]</sup>. Similar to the PSOCS study<sup>[1-5]</sup>, in this special edition of *Vessel Plus*, the POAF-relevant risk factors, processes and structures of care, and outcomes have been identified across the spectrum of cardiac interventions; the

POAF associations with clinical morbid/mortal events are reported.

Amazingly, despite publications including meta-analyses, there is still little consensus about pharmacoprophylaxis for POAF. To date, calcium channel blockers, beta-blockers, Sotalol, Amiodarone, Quinidine, and Digoxin have all been explored as prophylactic agents. To identify state-of-the-art POAF prophylaxis strategies, Waterford *et al.* systematically reviewed the literature, evaluating the impact of prophylaxis regimens (e.g., Amiodarone) that may be applied before, during, and following cardiac interventions<sup>[10]</sup>. As one of the most common antiarrhythmic agents used prophylactically for POAF, amiodarone was approved by the Food and Drug Administration (FDA) in 1995. Waterford *et al.* discuss the advantages and disadvantages of amiodarone for atrial fibrillation management<sup>[10]</sup>. Although viewed as effective and safe, clinicians using this medication need to be fully aware of contraindications, the potential for Amiodarone interactions with other drugs, and common side effects. Moreover, prior to using Amiodarone, different POAF treatment strategies (e.g., a trial of rate control agents) or other antiarrhythmic drugs (e.g., sotalol or propafenone) should be considered<sup>[10]</sup>. Although some POAF patient sub-groups have responded positively to Amiodarone treatment, one size does not fit all; thus, innovative POAF preventive medications with broader-based patient applicability remain desperately needed.

Quin *et al.* utilized the VA Randomized On-/Off-Bypass (ROOBY) trial's database to evaluate the impact of post-CABG POAF on longer-term outcomes<sup>[11]</sup>. Based on historical VA findings<sup>[5]</sup>, it was not surprising to find that the ROOBY coronary artery bypass graft (CABG) survivors that initially had new-onset POAF complications also had higher AF rates at 10-year follow-up as compared to non-POAF patients. After risk adjustment, however, it was very interesting to learn that POAF was not associated with increased 10-year mortality. Furthermore, contrary to popular belief, using an off-pump (OPCAB) approach did not avert POAF or differentially impact the ROOBY POAF patients' risk-adjusted 10-year survival<sup>[11]</sup>. In addition, it confirmed previous knowledge that non-Maze surgical incisions into the atria neither encourage nor discourage POAF.

Although CABG patients' POAF rates have been reportedly high<sup>[5,11]</sup>, Dokko's systematic review reported that the highest cardiac surgical post-procedural POAF rates have been found for mitral valve replacement or repair (MVR) procedures; moreover, the authors reported that very innovative technological advances have taken place<sup>[12]</sup>. For all MVR patients with preoperative AF and POAF, medical therapy should be evaluated as a treatment to avoid POAF. However, as efficacious treatment options, surgical ablation for medically resistant preoperative AF and transcatheter ablation for medically resistant new onset of POAF were reported. In the United States, patients with pre-op AF having MVR may commonly receive a concomitant atrial fibrillation surgical procedure (e.g. Maze procedure) or another atrial ablation procedure unless the patient is at very high risk. During a patient's index hospitalization, Dokko's team reported that these surgical and transcatheter procedures reduced the post-MVR patient's rates of inpatient thromboembolic events (e.g., stroke); however, the ideal timing for either catheter-based and/or surgical-based ablation procedures warrant further study. Fundamentally, it is unclear if catheter-based ablation should be recommended during the same hospitalization (i.e., before, during, or after the MVR procedure) or within 30 days of discharge. As a matter of discussion, the role of a prophylactic occlusion of the LA appendage (LAAO), which has been evaluated (LAAOS III trial) during surgical MVR procedures to avoid post-MVR thromboembolic events (e.g., stroke), should find its way into treatment algorithms<sup>[12]</sup>.

Recording an industry-wide transformation, the field of aortic valve interventions has undergone a major upheaval. As documented in Tummala *et al.*'s systematic review, the number of mechanical valves implanted has dramatically decreased - from over 50% (20 years ago) to currently around 25%<sup>[13]</sup>. For

surgical aortic valve replacement procedures (SAVR), the POAF rates have remained stable as compared to 25 years ago. As the new “kid on the block”, transcatheter aortic valve replacement (TAVR) procedural rates now exceed SAVR rates within the United States of America and Europe. Although TAVR was historically considered to be the ultimate “no touch” procedure, POAF persists as the most common post-TAVR complication. Additionally, as novel information is presented, POAF is still a monumental challenge following SAVR and TAVR. For AV-specific interventions, POAF has been reported to be associated with increased short-term and long-term mortality as well as with an increased risk of post-procedural stroke<sup>[13]</sup>. As these AV interventional findings may not have been adequately risk-adjusted to address other confounders, additional AV POAF research now appears to be warranted.

Focused on the risk factors associated with preoperative AF, Novotny *et al.* are to be commended for their innovative retrospective cohort analysis of the New York State Statewide Planning and Research Cooperative System (SPARCS) database<sup>[14]</sup>. As a first-in-kind report, preoperative AF was observed in 334 repeat AVR (r-AVR) patients (0.5% of the initial 73,945 adults who had initially undergone an AVR procedure) who did not have a history of or concomitant cardiac interventions. The risk-adjusted outcomes following repeat surgical AVR (r-SAVR;  $n = 87$  or 42.4% of the r-AVR population) or repeat transcatheter AVR (viv-TAVR;  $n = 65$  or 50.4% of the r-AVR population) were identified. For risk-adjusted outcomes, there was no association of r-AVR patients’ preoperative AF with short-term mortality or 30-day readmissions; however, viv-TAVR procedures had lower rates of short-term mortality. Given this New York State-wide study’s very small r-AVR patient sample size, future research will be required to rigorously identify the association between AF and postoperative major complications, short-term mortality, and 30-day readmission rates<sup>[14]</sup>.

The potential for a causal relationship between POAF and stroke was assessed by Rademacher *et al.*<sup>[15]</sup>. This systematic review ascertained the published evidence related to using anticoagulation for POAF patients to prevent adverse outcomes (e.g., stroke). Given that AF and stroke patients inherently have many overlapping risk factors (e.g., age, smoking, and hypertension), it is inherently difficult to ascertain if POAF may influence stroke complication rates. Across eight meta-analyses, the unadjusted pooled odds ratio estimates for stroke risk in the POAF cardiac surgery patients ranged from 1.36 to 4.09. Evaluating the impact of anticoagulation medication in reducing POAF patients’ stroke risk, 66% of these studies’ findings supported anticoagulant use; the other two studies had inconclusive findings. In summary, this review was unable to conclude that POAF was causally associated with subsequent stroke; however, substantial evidence supporting a potential POAF-stroke relationship was provided. As key confounders, the interventions currently used to reduce patients’ cardiovascular risk overall also appeared to lower their long-term stroke risk. Challenges were discussed as to the optimal management of a POAF patient’s anticoagulation medication regimen as part of their overall cardiovascular risk management plan. Therefore, to optimize future patient outcomes, future POAF research appears warranted to directly address this hypothesis by taking a more patient-focused (rather than a treatment-focused or medication-focused) approach to identifying a potential stroke impact<sup>[15]</sup>.

Although many publications on first-time aortic valve replacement and repair procedures (AVR) and the association with POAF exist, a paucity of knowledge persists regarding the POAF impact upon repeat aortic valve replacement (r-AVR) procedural patients’ outcomes and resource utilization; additionally, the risk factors associated with r-AVR patients’ new-onset POAF complications have not been well studied. To address this knowledge gap, Dokko’s research team utilized the New York State’s SPARCS database for r-AVR patients’ records from 2005-2018; using these r-AVR records, new multivariable models identified the factors associated with new-onset POAF complications, as well as POAF’s impact upon risk-adjusted

outcomes including a mortality/morbidity composite (comprised of 30-day operative mortality and/or major morbidity) and 30-day readmission<sup>[16]</sup>.

Based on 242 r-AVR NY adult residents' records, 147 patients underwent repeat surgical aortic valve replacements (r-SAVR) and 95 patients underwent valve-in-valve transcatheter aortic valve replacements (ViV-TAVR); of these, 39.46% of r-SAVR and 43.16% of ViV-TAVR patients experienced new-onset POAF complications. Enhanced POAF risk was found for the elderly (i.e., age = 80+) and cerebral vascular disease r-AVR patients. As POAF was associated with increased rates of 30-day readmission but no increased composite endpoint rates, additional r-AVR research now appears warranted to improve POAF patients' post-discharge continuity of care to prevent future readmissions<sup>[16]</sup>.

Interestingly, both preoperative AF and POAF have not been well studied for heart failure patients requiring mechanical ventricular assist devices<sup>[17]</sup>. As one rationale put forward for this knowledge gap, the patients placed on mechanical ventricular support devices - until very recently - did not live long enough to experience the sequelae of POAF. Given their overwhelming problems due to their heart failure, both preoperative AF and POAF were not considered major health burdens for this very high-risk patient population. Up to recently, the primary goal has been to discharge these extremely sick patients post ventilator support alive. Furthermore, many of these heart failure patients were already being treated using what is considered "AF standard therapy"; hence, the effect of preoperative AF or POAF was historically extremely difficult to tease out. Within this highly specialized cardiac surgical field, however, Obeid *et al.* reviewed the pertinent literature and found recent data suggesting that POAF may have negative consequences; the mechanical support patients with preoperative AF and POAF had higher rates of complications and earlier death<sup>[17]</sup>.

In general, mentally ill patients have been underserved; thus, it is not entirely surprising that these vulnerable patients have also been poorly studied within the cardiac interventional field. In the United States (US), ~6% of the population will experience post-traumatic stress disorder (PTSD) at some point in their lives; the PTSD rate for women is estimated at ~8%, which is higher than for men (~4%)<sup>[18]</sup>. According to the National Institute of Mental Health, ~8% of US-based adults have had at least one major depressive episode (i.e., at least a two-week period where their lack of pleasure or loss of interest in life impacted their daily functionality); depressive episodes were nearly twice as common among women (~11%) as compared to men (~6%)<sup>[19]</sup>. Additionally, it was estimated that 9% of Americans had an anxiety disorder in the past year; this rate was again much higher for women (~23%) as compared to men (~14%)<sup>[19]</sup>.

In spite of the high prevalence of these mental illnesses, the impact of mental illness as a preoperative comorbidity for cardiac surgical procedures has not been well studied. Addressing this "knowledge chasm", Kolba and her team examined preoperative mental illness diagnoses and the association of mental illness with post-procedural new-onset atrial fibrillation for both aortic valve replacement [AVR] procedures including surgical aortic valve replacements [SAVR] procedures and transcatheter aortic valve replacements [TAVR] procedures<sup>[20]</sup>. Given the inherently higher post-procedural risk for adverse events, they also evaluated the impact of preoperative mental illness on repeat AVR procedures including repeat SAVR [r-SAVR] and valve-in-valve TAVR [viv-TAVR] procedures. Using New York SPARCS records from 2005 to 2018, no mental illness relationship with POAF was found when comparing non-mentally ill to mentally ill patients for either AVR or r-AVR procedures. Moreover, mental illness risk factors had no impact on the risk-adjusted AVR or r-AVR procedural endpoints, such as 30-day readmission or mortality/morbidity composite rates. Interestingly, however, a differential AVR and r-AVR procedural selection process emerged, with clinicians more frequently opting for percutaneous transcatheter rather than open surgical

AVR and r-AVR procedures for mentally ill patients. Regarding the vulnerable mentally ill patient subpopulation, this study raised several important research questions as to the rationale for clinician selection bias.

Kuruvillea *et al.* identified a second “knowledge chasm” related to patients undergoing open thoracic aortic aneurysm (TAA) and endovascular interventions<sup>[21]</sup>. In this extensive literature search, only two papers reported the prevalence of pre-TAA repair AF rates; these publications’ AF rates ranged from 5% to 26.5%. Additionally, there were only six publications that identified TAA patients with POAF; these rates varied dramatically based on the TAA’s location (i.e., ascending versus descending thoracic aorta) and intervention studied (e.g., open arch replacement). Of these publications, only two identified the risk factors associated with POAF using multivariable modeling. In these multivariable models, the TAA patients’ characteristics predictive of POAF included advanced age, cardiac dysfunction, and diabetes; however, TAA procedure type was also an important predictor. Disappointingly, this paper reported that the recent TAA guidelines promulgated in 2021 were completely silent on the topics of preoperative and postoperative atrial fibrillation. As a new voice calling attention to issues that must now be heard, this TAA manuscript shares insightful clinical perspectives and raises important clinical questions to guide future research endeavors.

In order to improve POAF patient outcomes and reduce wasteful resource utilization following cardiac procedures, the publications by Pardo<sup>[22]</sup> and Rove<sup>[23]</sup> have independently identified that the first and most important step forward will be to *establish new universally accepted definitions for both preoperative AF and new-onset POAF*. As a second step recommended, AF and POAF should be closely monitored and evaluated while comparing risk-adjusted outcomes of potential treatments. Following treatment, more precise data need to be captured to assess the comparative effectiveness of these interventions. Specifically, details for the type and timing of atrial fibrillation treatments need to be uniformly collected in national cardiac procedure-related databases - such as the VA Surgical Quality Improvement Database ([VA SQIP], previously known as the VA Continuous Improvement in Cardiac Surgery Program [CICSP])<sup>[24,25]</sup>, the Society of Thoracic Surgeons’ National Adult Cardiac Surgery Database [STS ACSD]<sup>[26]</sup>, and the American College of Cardiology’s National Cardiology Data Registry [ACC NCDR]<sup>[27]</sup>. Additional treatment-specific details (e.g., the details for all medications’ dose, duration, frequency, and mode of administration) must also be gathered and analyzed. For POAF surgical or catheterization-related treatments, moreover, the operative details (e.g., concomitant catheter-based ablation procedure during an MVR procedure) and perioperative patient management approaches used (e.g., placement in an intensive care unit [ICU] or telemetry bed) should also be recorded. Bridging both the cardiology and cardiac surgery disciplines, these data should be consolidated into a *single new cardiac procedure-based atrial fibrillation database* that includes records from the federal government [VA SQIP] and the private sector [STS ACSD and ACC NCDR]<sup>[24-28]</sup>. Within the US, the existing multiple national and local databases used are not efficient, diluting the ability to address these AF and POAF research questions and inherently limiting the evidence-based improvements that may be facilitated to improve future POAF patients’ quality of care.

### **This is a global story**

Magnifying the current challenge of consolidating data from multiple divergent databases, Pardo *et al.* have identified tremendous global variation in the marginal impact of POAF upon resource consumption patterns, as evidenced by global variations in postoperative length of stay for cardiac surgery versus non-cardiac surgery patients<sup>[28]</sup>. Their systematic review evaluated 28 articles’ variations in the reported POAF. Based on this review, they recommended that clinical protocols should be developed to reduce what appears to be unnecessary variations in clinical practice patterns. In the meantime, however, it is urgent that Professional Society guidelines providing industry-wide standards be promulgated to support daily decision making for individual AF and POAF patients. Even if these guidelines may be currently based on the 2000

Oxford level of evidence class V (i.e., clinical expert consensus), these professional guidelines will pave the way to support future research to improve the quality of AF and POAF care.

Using the 2012 to 2020 Virginia Cardiac Services Quality Initiative (VCSQI) database, Hawkins *et al.* directly evaluated the association between post-CABG POAF and increased resource consumption (e.g., increased length of stay, hospital cost, and discharges) using propensity score adjustment<sup>[29]</sup>. Of the 27,307 CABG patients, 23% had POAF; across all resource consumption metrics, POAF patients had higher utilization rates. Compared to non-POAF patients, the POAF patients incurred 9 additional ICU hours, 2 postoperative days, and 33% greater readmissions. For every CABG hospital stay, an additional \$6,705 was spent for a POAF patient. Therefore, by reducing POAF rates, significant cost containment and quality improvement can be attained simultaneously.

Both Pardo's article<sup>[28]</sup> and Hawkins's article<sup>[29]</sup> document the tremendous impact of cardiac patients' POAF on their post-procedural resources consumed. As no evidence-based AF and POAF treatment guidelines have yet been promulgated, these articles raise questions as to the efficacy and effectiveness of current AF-related prophylaxis and POAF treatment regimens. Moreover, current POAF hospital-based practices may drive larger post-procedural costs (e.g., 30-day readmissions and 30-day emergency room visits). Building upon the challenges for lack of POAF definitional uniformity, the lack of uniformity for recommendations in AF and POAF patient care practices across the diversity of procedure-specific professional society guidelines represents a major barrier to optimizing current postoperative cardiac and non-cardiac surgical POAF care; although selected local hospitals and ambulatory care centers may have their own clinical pathways well established, national and international standards will be required to identify the appropriate health care to provide to AF and POAF patients under specific clinical circumstances.

Lastly, very little has been written to date on the impact of AF or POAF on cardiac post-surgical patients' health-related quality of life or patients' self-reported procedural satisfaction<sup>[30,31]</sup>. Assuming that POAF patients survive to home discharge, comparing POAF to non-POAF patient's self-reported perceptions of their functionality, pain levels, and satisfaction with care should become a future research priority. Upon discharge, patients want to be able to not only independently perform daily tasks of living - but also live a fulfilling, pain-free, worry-free life. With a patient-centered focus, the impact of preprocedural AF and post-procedural POAF on a patient's self-reported satisfaction or self-assessment of their health-related quality of life represents another "knowledge gap" - with currently unmeasured, but critically important patient-centered clinical outcome metrics. Medication compliance in the setting of polypharmacy in this patient population has never been studied.

## CONCLUSION

In conclusion, this Special Issue of *Vessel Plus* provides a first-in-kind *call to research action*. This issue's publications provide state-of-the-art guidance to support academic research scientists, as well as practicing cardiologists and cardiac surgeons. Throughout the writing of this Special Issue, the question has been raised during the peer-review process as to "what is new" within this field. Specifically, a variety of reviewers have asked "What are recent POAF advancements in prevention and treatment?", "Have there been any novel AF biomarkers developed?", and "Has POAF impacted other clinical or resource utilization outcomes?". Stuningly, the answer to these questions is that not much is known; substantially, not much has changed since the original cardiac surgical POAF publications<sup>[5,6]</sup>. For patients undergoing cardiac interventions, this fact is astonishing in light of nearly 50 years of awareness of AF, particularly the adoption of POAF-focused treatments. Although dramatic reductions in cardiothoracic mortality (i.e., 30-day operative death) and perioperative major complication rates have been achieved, the proportion of cardiac

surgical patients with preoperative AF and experiencing POAF post-procedure has virtually not changed. Although it is well established that AF accompanies heart failure, it is not known if AF causes heart failure to occur or if AF is just a marker predictive of myocardial damage. Across the array of cardiac interventions herein reported, the potential of POAF treatments to reduce rates of other post-procedural adverse clinical events (e.g., postoperative stroke) has not been rigorously evaluated. As noted by Donabedian in 1982, “An ideal physician is defined as one who selects and implements the strategy of care that maximizes health status improvement without wasted resources”<sup>[32,33]</sup>. For the practicing physician, this remains a vexing and often elusive goal hampered by multiple, often contradictory guidelines<sup>[9]</sup>. Hence, this worthy goal, as established by Dr. Donabedian, must guide forthcoming cardiothoracic AF-related and POAF investigations.

## DECLARATIONS

### Authors' contributions

Contributed equally to all aspects of this commentary/review, writing, concept, reviewing, revising: Bilfinger TV, Almassi GH, Shroyer ALW

### Availability of data and materials

Not applicable.

### Financial support and materials

None.

### Conflict of interest

Shroyer ALW is an Editorial Board member of the journal *Vessel Plus*, while the other authors have declared that they have no conflicts of interest.

### Ethical approval and consent to participate

Not applicable.

### Consent for publication

Not applicable.

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