Literature Review *Open Access*

Journal of Innovative Clinical Trials and Case Reports

ISSN: 3068 - 1936

DOI: doi.org/10.63721/26JCTC0162

When Exposure Meets Electrophysiology: Palm-Derived Tocotrienols, Neutral Tocovid Trial Evidence, and the Future of Perioperative Atrial Fibrillation Prevention

Loso Judijanto

IPOSS Jakarta, Indonesia

Citation: *Loso Judijanto (2026) When Exposure Meets Electrophysiology: Palm-Derived Tocotrienols, Neutral Tocovid Trial Evidence, and the Future of Perioperative Atrial Fibrillation Prevention. J. of Inn Clin Trail Case Reports 2(5), 1-17. WMJ/JCTC-162*

Abstract

Background: *Postoperative atrial fibrillation (POAF) remains frequent after coronary artery bypass grafting (CABG), motivating interest in palm-derived tocotrienols as anti-inflammatory and antioxidant adjuncts. Objective: This review critically interprets the neutral Tocovid evidence and defines a decision-ready translational pathway.*

Methods: *A qualitative literature review integrates purposively selected clinical, mechanistic, pharmacokinetic and methods literature published during 2020–2026. Peer-reviewed blinded Tocovid analyses are distinguished from the subsequently available unblinded preprint.*

Results: *The preprint reports no statistically significant POAF reduction, alongside low postoperative tocotrienol measurements and exploratory secondary outcomes. The causal attribution of trial neutrality to exposure failure remains unproven because sparse concentrations cannot distinguish absorption, disposition, target engagement and timing. Contemporary evidence indicates that atrial substrate, inflammation, autonomic triggers, co-interventions and ECG surveillance affect both pathogenesis and outcome measurement.*

Discussion: *A formulation–exposure–mechanism–arrhythmia–patient benefit framework requires separate validation at each transition. A staged program should establish reproducible perioperative pharmacokinetics and human target-related signals before a definitive randomized prevention trial. Conclusion: Routine Tocovid use for POAF prevention is not supported by current clinical evidence; more informative experiments should prioritize assay validity, safety and clinically important outcomes.*

***Corresponding author**: Loso Judijanto, IPOSS Jakarta, Indonesia.

Submitted: 15.10.2026 **Accepted**: 22.10.2026 **Published**: 30.10.2026

Keywords: Palm Oil, Tocotrienols, Tocovid, Coronary Artery Bypass Grafting, Postoperative Atrial Fibrillation, Pharmacokinetics, Oxidative Stress, Inflammation, Randomized Trials, Qualitative Literature Review

JEL Classification: I10; I12; I18; O31; Q56.

Introduction

Clinical Significance and an Unresolved Preventive Need

Postoperative atrial fibrillation (POAF) is a consequential disturbance of cardiac rhythm after coronary artery bypass grafting (CABG), but the disorder should not be described as merely an inconvenient electrocardiographic observation. It may require additional monitoring, medical treatment, hemodynamic assessment and longer hospitalization, while associations with subsequent stroke, heart failure and mortality create concern long after surgical discharge. The observed associations are not all causal, because age, atrial disease and cardiovascular comorbidities can contribute both to POAF and to adverse outcomes. This distinction is critical when proposing a preventive intervention: lowering a rhythm-monitoring threshold or transient biochemical marker is not automatically equivalent to improving survival or quality of life [1-5].

Recent CABG-specific data strengthen the clinical case for studying outcomes beyond a first recorded arrhythmia episode. In a statewide linkage of 18,377 isolated-CABG patients, postoperative AF was associated with higher index procedural costs and greater subsequent readmissions for AF, heart failure and major bleeding; residual confounding nevertheless limits causal interpretation. The 2026 Society of Thoracic Surgeons (STS) guideline reinforces the need to benchmark investigational prophylaxis against contemporary evidence-based cardiac-surgery care rather than against the absence of preventive treatment [6,7].

Reported POAF incidence varies according to the operation, population, observation window and definition of an episode. Isolated CABG, valve surgery and combined procedures should not be pooled without recognizing differences in atrial tissue injury and exposure to postoperative inflammatory stress. A documented episode requiring treatment may satisfy one trial definition, whereas short, asymptomatic episodes captured by continuous electrocardiography may satisfy another. Consequently, trials that use different denominators and detection intensity can report dissimilar event rates despite similar underlying biological risk. Any evaluation of perioperative tocotrienols must therefore begin by defining what is counted as POAF, when observation starts and ends, and how missing rhythm data are handled [8-11].

Contemporary perioperative care employs established interventions, including continuation or initiation of indicated beta-blockade, selective amiodarone, correction of precipitating factors and surgical measures for selected patients. Nevertheless, POAF remains sufficiently frequent to justify investigation of safe additional strategies. The appeal of a nutritional antioxidant arises from the possibility of intervening upstream of electrophysiological instability without imposing the same burdens as invasive treatment. Such appeal cannot displace a realistic comparator or standard clinical management, especially in a perioperative population exposed to antiplatelet therapy, heparin, changing organ function and competing postoperative risks. An adjunct must show clinically relevant incremental benefit on top of sound care rather than benefit relative to an artificially untreated patient [3,12-14].

The STS 2026 clinical practice guideline makes the comparator question particularly concrete. Its graded recommendations address perioperative amiodarone, beta-blockers, posterior pericardiotomy and treatment of hemodynamically unstable POAF, while explicitly recognizing uncertainties for several proposed preventive approaches. Any tocotrienol trial should identify which co-interventions are permitted, indicated or contraindicated within the local surgical pathway, because a placebo-controlled add-on study is interpretable only against clinically defensible background care [7].

The Tocovid Contradiction and the Danger of Premature Explanations

Palm-derived tocotrienols are members of the vitamin E family and differ from tocopherols in their unsaturated side chains, isoform composition and potential pharmacological behavior. Experimental literature

suggests effects on oxidative and inflammatory pathways that are plausible contributors to atrial injury. However, a biologically plausible ingredient is not the same as a reproducibly absorbed preparation, and a detectable plasma concentration is not the same as an effective concentration in atrial tissue. For oral lipid-soluble molecules, the relationship among meals, formulation, absorption, surgical fasting and systemic redistribution requires explicit study rather than inference from preoperative dosing alone [15-18].

The Tocovid program offers a particularly instructive example. A 2021 peer-reviewed interim report and a 2022 peer-reviewed end-of-cycle analysis described cohort characteristics and pooled outcomes without providing an unblinded comparative treatment-effect estimate. Neither publication established comparative efficacy of Tocovid against placebo. A subsequently released unblinded 2022 report available as a Qeios preprint described no statistically significant reduction in POAF, alongside temporal differences in measured tocotrienol levels and exploratory observations concerning pleural effusion and sleep. The distinction between peer-reviewed blinded analyses and the unblinded preprint matters for evidential certainty, and a preprint conclusion concerning causation must not be treated as definitive trial adjudication [3,19-21].

The central ambiguity is whether a neutral intervention contrast reflects inadequate drug exposure, insufficient impact on a relevant biological target, a pathway that does not dominate postoperative arrhythmogenesis, or methodological limitations. These interpretations imply different experiments and can coexist. A postoperative fall in measured circulating tocotrienol concentrations, for example, is consistent with impaired absorption but also with changes in distribution, elimination, sample timing or perioperative care. It does not by itself establish a causal explanation of the treatment result. A productive review must therefore distinguish observed concentrations from proposed pharmacokinetic mechanisms and preserve the possibility that the biological target was poorly chosen [1,2,17,22,23].

Purpose, Scope and Original Contribution

This critical qualitative literature review asks how the trial signal should shape rather than terminate clinical translation. Its objectives are to interpret the direct human evidence, specify mechanistic and pharmacokinetic gaps, identify clinically meaningful POAF endpoints, compare realistic preventive pathways and formulate a falsifiable development program. The review focuses on CABG while selectively using evidence from other cardiac operations to understand mechanisms and research design. Those adjacent studies are explicitly indirect: a mixed cardiac-surgery cohort cannot establish a treatment effect in a particular CABG population, and an effect on another postoperative complication cannot stand in for prevention of POAF [1,2,11,19-21,24].

The proposed contribution is an exposure-mechanism-arrhythmia framework that requires evidence for each link rather than treating the full chain as a single assumed causal pathway. Product identity and dose lead to measured systemic exposure, relevant tissue engagement, electrophysiological effects and ultimately patient-valued outcomes. A negative result at one link directs a specific next decision, whereas a positive intermediate biomarker cannot substitute for clinical benefit. The framework also makes competing explanations visible: inflammation, sympathetic activation, atrial substrate, fluid accumulation and medication-related effects may influence POAF in different proportions among patients [25-28].

Literature Review

Atrial Substrate, Triggering events and Postoperative Rhythm Instability

POAF should be conceptualized as the interaction between a vulnerable atrial substrate and perioperative triggers rather than as a unitary inflammatory disease. Aging, atrial enlargement, fibrosis, hypertension, prior myocardial injury and renal dysfunction can alter conduction or refractoriness before surgery. CABG then imposes changing autonomic drive, catecholamine exposure, ischemia-reperfusion stress, electrolyte shifts and pericardial irritation. These mechanisms need not peak at the same postoperative hour and may differ by use of cardiopulmonary bypass. A tocotrienol intervention aimed principally at oxidative stress could be ineffective if untreated electrical or mechanical contributors dominate the individual patient's arrhythmia risk [1,2,9,24,29].

Inflammation can promote atrial remodeling through infiltrating immune cells, cytokine release and altered

ion handling. The NLRP3 inflammasome offers a plausible mechanism linking inflammatory stress to cardiomyocyte signaling, and calcium-handling abnormalities can increase triggers for abnormal atrial activity. Yet this biology is not equivalent to demonstrating that tocotrienols inhibit NLRP3 in patients undergoing CABG at a sufficient dose and in the proper time window. The mechanism should be treated as a hypothesis-generating bridge, supported by direct perioperative biomarkers or human target-engagement measures before claims of specific antifibrillatory action are made [25-27,30].

Reactive oxygen species are implicated in tissue injury, but the distinction between harmful excess and physiologic signaling is important. Redox processes participate in innate defense, mitochondrial adaptation and normal cellular responses to stress; unrestricted antioxidant suppression cannot be assumed beneficial. Moreover, common systemic measures such as malondialdehyde are imperfect proxies for atrial redox state. A favorable change in a circulating biomarker could reflect processes outside the heart or a response to reduced procedural stress rather than a direct effect on the electrophysiological substrate. Trials must therefore relate each assay to a predeclared causal target and a measured concentration of the tested isoform [15,16,24,25].

The temporal pattern of POAF further complicates mechanistic interpretation. Early postoperative periods may be dominated by sympathetic activation, hemodynamic changes and exposure to inotropes, whereas later episodes can reflect ongoing inflammation, fluid balance and atrial vulnerability. A once-daily oral preparation may generate a concentration profile that poorly overlaps with the hazard period. Conversely, a high preoperative value may not indicate sustained exposure when episodes actually occur. Trial design should align concentration sampling, medication administration and continuous rhythm surveillance rather than rely on a single postoperative specimen [3,19-21,31,32].

Tocotrienol Chemistry and Evidence from Human Intervention Studies

The expression tocotrienol-rich fraction conceals differences in alpha-, gamma- and delta-tocotrienols, residual tocopherols, excipients, extraction methods and manufacturing stability. Preparations from palm oil should be distinguished from annatto-derived products rather than discussed as interchangeable vitamin E interventions. Their isoform profiles can affect laboratory assays, absorption and metabolism. The batch used in a trial must be described in enough detail to allow independent replication, including content uniformity, storage requirements and analytical validation. Without such information, a neutral clinical trial cannot readily be compared with a new formulation advertised under the same broad ingredient label [15,17,18,22].

Evidence from diverse human trials has not shown an invariant anti-inflammatory effect of tocotrienol supplementation. A meta-analysis of randomized investigations reported that effects on circulating inflammatory and oxidative biomarkers were inconsistent; particular summary findings could be disproportionately influenced by a single study or formulation. That finding matters when translating to CABG, because reliance on generalized antioxidant labels implies a reproducibility that the human evidence does not guarantee. The rational hypothesis should specify the isoform, dose, bioavailable exposure and pathway expected to change, together with an uncertainty interval rather than a categorical promise of protection [16,22,33,34].

Clinical studies outside cardiac surgery are relevant mainly for feasibility and pharmacology. For example, tocotrienol-rich vitamin E has been tested in people with diabetic kidney disease, where disease stage and long-term exposure differ greatly from perioperative CABG. Such trials show that oral preparations can be studied systematically and monitored for safety, but their biomarker or organ-function outcomes are not evidence of antiarrhythmic effectiveness. Any generalized claim of cardiovascular protection needs to be decomposed into mechanisms and endpoints: reducing one chronic inflammation marker is not identical to preventing an acute postoperative episode of AF [16,22,33,34].

Absorption, Distribution and the Perioperative Exposure Window

Tocotrienols are lipophilic and generally administered in oil-based preparations, making gastrointestinal processes central to systemic availability. Dietary fat, bile secretion, digestive transit and formulation characteristics may influence uptake. A surgical

patient experiences fasting, anesthesia, nausea, postoperative ileus, changing enteral intake and medication interruptions, which may collectively reduce or destabilize delivered exposure. However, these clinical circumstances are plausible mechanisms, not proof that they caused concentrations observed in a particular trial. Formulation-specific pharmacokinetic measurements under realistic perioperative conditions are required to estimate the magnitude and timing of each contribution [17-21].

Self-emulsifying delivery systems, lipid-based carriers and other formulations have been proposed to improve tocotrienol solubility and availability. Their success must be evaluated using appropriate comparative measures, such as area under the plasma concentration-time curve, maximum concentration, concentration at the arrhythmia hazard period and variability among patients. A higher peak concentration alone may be unhelpful if it occurs after the causal window or if tissue exposure remains inadequate. Model-informed dosing may assist dose selection, but only after a sufficient empirical pharmacokinetic foundation exists for the specific product and population [17,18,23,36].

Interpretation of plasma data requires attention to baseline concentrations, sample processing, isoform-specific assay sensitivity and timing relative to meals and doses. Concentrations obtained before surgery, immediately after bypass, at discharge and several weeks later cannot be treated as a continuous pharmacokinetic curve. Their differences may reflect time-dependent physiological processes, adherence and measurement artifacts. Furthermore, plasma is an imperfect proxy for myocardial or atrial accumulation. Ethical constraints may preclude repeated tissue sampling, making integrated pharmacokinetic-pharmacodynamic modeling and carefully designed blood collection especially important for identifying the boundary between observed evidence and inference [17,19-21,23,35].

A useful future design would first characterize within-patient exposure around CABG rather than immediately testing another large clinical endpoint. Serial standardized sampling could include the final preoperative dosing interval, early recovery and the period in which POAF usually emerges. Clinical records would document fasting duration, enteral intake, emesis, vasoactive medication exposure and renal or hepatic changes. The resulting model could quantify whether the original regimen plausibly achieved sufficient exposure, while acknowledging that the effective antiarrhythmic concentration is itself unknown. Finding low concentrations would justify exposure studies; it would not automatically justify claims that a higher dose will prevent AF [17,18,19-21,23].

Prevention Comparators and the Clinical Standard of Care

Beta-blockers, selective amiodarone and perioperative optimization occupy established positions in POAF prevention, although applicability depends on contraindications, bradycardia, hypotension and other patient factors. A new nutraceutical should not be tested by withholding these strategies when clinically indicated. A well-designed add-on trial asks whether Tocovid provides incremental prevention beyond protocolized standard management. It should record use of antiarrhythmics, electrolyte replacement, inotropes and sedatives as potential effect modifiers or intercurrent treatments. Such documentation improves interpretability and prevents uneven care from masquerading as a supplement effect [3,12-14].

Posterior pericardiotomy provides a useful example of how a targeted mechanical pathway can affect postoperative rhythm outcomes. Randomized and synthesized evidence supports reduction of POAF through alteration of pericardial fluid accumulation, but trial populations and procedural practices vary. These findings demonstrate that not all POAF prevention operates primarily through systemic antioxidant mechanisms. The possibility of pleural effusion changes in a tocotrienol study should therefore be examined independently from the rhythm result rather than woven retrospectively into an unsupported chain of anti-inflammatory cardioprotection [1,2,3,37,38] .

Trials and meta-analyses of colchicine, magnesium and broader anti-inflammatory strategies reveal heterogeneous treatment signals. Evidence depends on drug, timing, surgical population, background treatment and adverse-event definitions. A favorable pooled effect for one drug class neither proves that systemic inflammation is the only cause of POAF nor establishes the efficacy of an unrelated antioxidant. Comparative

literature is most useful for specifying realistic event rates, feasibility constraints and safety measurement, while leaving the Tocovid causal question to direct randomized evidence [24,39-41].

Definitions and Detection of Clinically Meaningful POAF

An episode of atrial fibrillation may be asymptomatic and readily missed when monitoring ceases at discharge. Continuous inpatient telemetry, wearable patches, implantable monitors and clinic ECGs have different detection sensitivity and windows. Evidence from randomized enhanced monitoring shows that additional surveillance identifies otherwise unrecognized episodes, while longer-term recurrence studies challenge the assumption that all POAF is transient. Consequently, a preventive trial must prespecify whether its endpoint is any newly detected rhythm episode, sustained clinically treated POAF, total AF burden or an event requiring healthcare intervention. Definitions should be applied consistently across groups and interpreted in relation to ascertainment intensity [10,31,32,42].

Contemporary follow-up cohorts illustrate why recurrence cannot be inferred from an in-hospital label alone. In a dedicated cardiac-surgery follow-up clinic, 94 of 881 patients (10.7%) had AF recurrence detected through structured follow-up that incorporated 14-day ambulatory ECG monitoring, whereas a prospective multicentre isolated-CABG cohort reported no statistically significant one-year recurrence difference between those with and without in-hospital POAF. The contrasting estimates reflect meaningful differences in populations, sampling schedules and ascertainment methods; they should not be presented as directly comparable measures of a single recurrence risk [43,44].

Patient-important benefits extend beyond preventing a short ECG episode. Outcomes may include symptomatic AF, adverse drug reactions, thromboembolic events, ICU days, readmission, quality of life and the costs or burden of monitoring. Yet a modest trial may lack power for rare outcomes such as stroke; those should not be made definitive claims from imprecise exploratory comparisons. Clinical interpretation is particularly sensitive to anticoagulation decisions after CABG, where thromboembolic and bleeding considerations differ from established chronic AF. An intervention that changes monitoring-defined POAF but not subsequent clinical burden must be described accurately rather than portrayed as proven cardio protection [5,45,46,47].

Method: Critical Qualitative Literature Review

Review Logic and Source Selection

This study uses a critical qualitative literature review (QLR), not a systematic literature review, scoping review or meta-analysis. Its analytic unit is the explanatory link connecting an oral palm-derived tocotrienol formulation to perioperative exposure, relevant physiological responses and observed arrhythmia outcomes. Literature published between January 2020 and 15 October 2026 was considered for contemporary perspectives, emphasizing indexed clinical journals, randomized studies, mechanism-focused reviews and guidance on trial design. The 2022 unblinded Tocovid report is identified separately as a preprint, whereas the 2021 and 2022 blinded analyses are peer-reviewed journal publications [1,2,11,19-21].

Purposive, iterative searches combined concepts concerning CABG, POAF, tocotrienols, Tocovid, postoperative oxidative stress, inflammatory signaling, vitamin E pharmacokinetics, continuous ECG monitoring and randomized-trial methodology. PubMed, journal websites and linked citation records informed source selection, and citation chaining was used to connect clinical findings to pharmacological explanation. Unlike an SLR, the procedure does not claim exhaustive screening, PRISMA enumeration, pooled treatment effects or numerical certainty grading. The review instead asks whether distinct evidence streams answer the same causal question and identifies where assumptions would require direct testing [1,2,17,24,48].

Critical Appraisal and Interpretive Coding

The literature was appraised qualitatively for directness, study design, population, treatment formulation, dose, observation period, endpoint definition, comparator and potential sources of bias. A blinded pooled analysis cannot reveal treatment efficacy, whereas an unblinded preprint allows provisional comparison but warrants separate qualification concerning publication status and robustness. Reviews of other preventive drugs or operations contribute contextual evidence

rather than borrowed efficacy. Studies that report biomarker changes are considered mechanistic or pharmacodynamic unless they prospectively connect those changes to arrhythmia outcomes [preprint] [16,19-21,40,49,50].

The thematic coding framework distinguishes six interlocking questions: chemical identity, achieved exposure, biological target, arrhythmogenic context, outcome detection and safety or treatment burden. Alternative explanations for neutral results are compared abductively, with special attention to observations that could falsify each explanation. For example, a delivery explanation would become less credible if adequate atrial target exposure were documented but no physiological effect occurred. An endpoint explanation would become less credible if an adequately powered, rigorously monitored trial remained neutral across complementary clinical definitions. This disciplined logic seeks explanatory usefulness without treating narrative consistency as proof of causation [1,2,23,28,49,50].

Boundaries and Limitations

The strongest constraints arise from the heterogeneity of trial populations and the limited direct comparative Tocovid evidence. Reviews of vitamin E interventions differ in source material, isoform content, dose, biological setting and duration, limiting clinical extrapolation. QLR also permits selection bias and cannot establish that all eligible studies have been located. Accordingly, no pooled relative risk of Tocovid is manufactured, and the paper avoids claiming that measured concentrations identify a causal pharmacokinetic failure. The aim is a transparent model of uncertainty and a specific clinical development agenda that can be updated when additional peer-reviewed treatment-effect reports appear [16,17,19-22].

Results: Thematic Findings

Theme I: The Direct Clinical Evidence is Neutral and Publication Status Matters

The two peer-reviewed publications from the Tocovid study are informative about participants, operative context, pooled event rates and feasibility, but did not provide the finalized unblinded treatment comparison. Their blinded design means they should not be cited as confirming or rejecting the treatment effect. The later unblinded Qeios preprint describes recruitment of 250 patients, comparison of Tocovid with palm-superolein placebo, and no statistically significant between-group difference in POAF. Its reported overall event incidence and exploratory differences should be attributed explicitly to the preprint rather than re-labeled as peer-reviewed efficacy findings. The clinically responsible synthesis is that the publicly accessible unblinded report does not establish POAF prevention; its publication status also warrants explicit qualification [3,19-21].

The preprint suggests an important association between timing of low postoperative tocotrienol concentrations and occurrence of POAF. However, association within the observation schedule is insufficient to establish exposure as a causal mediator. Because the measured values represent sparse time points, their interpretation depends on dose administration, fasting and clinical events. A valid mediation claim would require an appropriate causal framework, reliable measurement of the intermediate variable and assurance that the intervention modifies the mediator in the required direction before the outcome occurs. The current evidence is best viewed as identifying an exposure hypothesis that merits targeted verification [17,19-21,23,28].

The preprint also raises the possibility of effects on pleural effusion, cardiac ICU stay and certain quality-of-life measures. These are interesting secondary signals but are vulnerable to multiplicity, baseline imbalances, treatment pathway differences and imprecise estimation. They should be framed as exploratory rather than as independent proof of cardioprotection. Particularly after neutral primary results, selectively emphasizing favorable secondary outcomes can create a misleading impression of overall success. A future trial would need prospective hypotheses, clear endpoint hierarchy, event adjudication and adequate power for each claimed benefit [19-21,28,48,51].

Theme II: A Low Plasma Level is not Automatically a Proven Absorption Failure

The pharmacokinetic concern is credible because tocotrienols are hydrophobic and surgery disrupts typical conditions for oral absorption. Nevertheless, plasma measurements alone cannot distinguish reduced uptake from accelerated clearance, altered volume of distribution or changed sampling intervals. It is also

possible that nominal concentrations in circulation differ from pharmacologically relevant tissue levels. These uncertainties imply that formulation comparisons in healthy volunteers are only an initial step. Their applicability to fasting patients immediately after CABG must be verified using perioperative pharmacokinetic observations and clinical covariate data [17,18,23,35].

The repeated-dose regimen described in the trial provides an opportunity to learn from timing. It is conceptually possible that a longer preoperative loading phase or delivery platform might improve perioperative exposure, but such changes introduce distinct experimental interventions. They cannot be assumed superior merely because an earlier approach was neutral. Any next-generation preparation must document its isoform composition, intended absorption enhancement, batch consistency, tolerance and reproducible pharmacokinetic response. Regulatory and patient-safety concerns become particularly important when modifying exposure in patients receiving multiple cardiovascular medicines [12,18,19-21,36].

Even a well-characterized plasma profile cannot establish that the antiarrhythmic target has been engaged. The relevant electrophysiological tissue compartment may not share the concentration-time trajectory of plasma, and the biological pathways involved are distributed across cardiomyocytes, immune cells, pericardial tissue and autonomic networks. A pharmacokinetic-pharmacodynamic program should select feasible indicators that genuinely correspond to the hypothesized target, such as prespecified inflammatory mediators coupled to atrial electrical measures. It should recognize that target engagement may not be measurable directly and that the absence of a validated surrogate limits interpretations of a positive biomarker signal [23,25,27,49,50].

Theme III: Inflammation is Relevant but Insufficient as a Single Explanation

Modern research confirms that inflammation and oxidative stress form part of the biological context of atrial fibrillation. Yet their role is interwoven with aging, fibrosis, autonomic influences and the specific insult associated with surgery. A generalized reduction in circulating inflammation does not establish that a compound prevents atrial ectopy or re-entry. Tocotrienol trials in other diseases further show that systemic inflammatory markers may respond inconsistently across formulations and populations. A convincing antiarrhythmic mechanism therefore needs dose- and time-aligned measurements linking the compound to a defined atrial process and to POAF burden [16,25,26,30].

NLRP3-related pathways, calcium cycling and reactive oxygen signaling are attractive candidates for mechanistic assessment, but each represents only part of the perioperative cascade. Biomarker panels should be chosen because their temporal change would distinguish competing explanations, not because they are fashionable or numerous. Some patients may have high inflammatory risk but relatively low electrical susceptibility, while others may display an established atrial substrate despite modest biomarker changes. Effect modification should be specified using clinical and mechanistic criteria developed before treatment allocation is revealed [9,25,27,29].

A central finding is therefore a negative boundary condition: anti-inflammatory plausibility cannot override a neutral clinical contrast. The most fruitful scientific question is whether adequate exposure modifies the particular pathway that drives POAF within a precisely described subpopulation. Without that link, multiplying antioxidant assays risks generating a positive narrative divorced from patient outcomes. This review treats molecular evidence as a means of designing falsifiable tests and recognizing biological complexity rather than as a surrogate replacement for an adequately designed randomized endpoint [16,22,24,49,50].

Theme IV: Monitoring Intensity can Change the Observed Endpoint

POAF incidence is partly an observed-data construct rather than a fixed underlying truth. Continuous telemetry identifies brief and asymptomatic episodes that symptom-driven ECG testing may miss, while monitoring discontinuation at discharge truncates the hazard window. Extended patch-based or implanted monitoring can uncover recurrence but introduces differences in participant adherence and analytic thresholds. Thus, a treatment trial that changes detection intensity between groups could generate misleading differences even if the latent arrhythmia burden were

unchanged. Standardized blinded ascertainment and a common episode-duration threshold are prerequisites for interpreting event reduction [10,31,32,41].

The choice of primary arrhythmia endpoint should reflect the decision being made. For an early mechanistic study, total AF burden and timing of episodes may help determine whether improved drug exposure changes physiology. For a definitive preventive study, sustained or clinically managed POAF may be more relevant, complemented by standardized rhythm monitoring and patient burden. Clinically meaningful endpoints must be selected independently of which choice yields the most favorable numerical effect. Prespecified definitions also allow researchers to interpret discordant results across episode incidence, total duration and need for treatment without post hoc reclassification [10,28,47,48].

Continuous-rhythm research provides additional evidence that the burden and timing of AF episodes deserve consideration alongside binary incidence. The RACE V prospective cohort used prolonged continuous monitoring to examine postoperative AF burden and later episodes over approximately 2.5 years, highlighting distinctions among early event detection, cumulative AF burden and longer-term recurrence. For a Tocovid efficacy trial, these findings support a prespecified short-term, clinically interpretable primary endpoint and separately defined longer-term exploratory endpoints, with identical ascertainment procedures in randomized groups [42,52].

Theme V: Co-Interventions and Background Risk can Obscure Small Effects

The CABG environment exposes patients to multiple changing therapies, including beta-blockers, antiarrhythmics, catecholamines, analgesics, fluids and electrolyte replacement. Some of these measures act on the same pathways invoked to explain tocotrienol action; others influence the timing or recognition of POAF. Even perfect randomization cannot make an intervention clinically interpretable if major co-interventions are poorly recorded or are allowed to differ systematically after allocation. A future protocol must identify essential standard care, allowable rescue treatment and the estimand for patients who discontinue supplements, require repeat surgery or develop complications before monitoring is complete [12,13,14,28].

The heterogeneity of risk also affects statistical efficiency. Age, renal impairment, atrial size, previous cardiovascular conditions and procedural characteristics are relevant predictors, although existing risk scores have limited discrimination in some settings. Enrolling indiscriminately may dilute a plausible treatment response among high-risk patients, but selecting subgroups after a negative trial risk producing an unreliable false-positive story. Enrichment should be justified using external knowledge, and interaction estimates should be interpreted with appropriate uncertainty. Baseline stratification and event-rate estimation are therefore methodological prerequisites for a future adequately powered trial rather than tools for retroactive rescue of an intervention [9,11,29,31].

Theme VI: Safety and Pharmacoeconomic Significance are Inseparable from Efficacy

The safety threshold for preventive supplementation should be demanding because many surgical patients would otherwise recover without POAF. Potential harms include gastrointestinal intolerance, formulation-related adverse effects, interactions with medication schedules and unexpected consequences of altering exposure during hemostatic recovery. The review does not claim that Tocovid causes a clinically important bleeding interaction; rather, it identifies concurrent antiplatelet and anticoagulant use as a reason for explicit surveillance. A protocol that reports only serious adverse events without prospectively soliciting relevant perioperative harms would not adequately characterize the net value of prevention [12,13,14,51].

Length of ICU stay, pleural effusion, readmission and quality of life are relevant to patients and health systems, but their relationship to POAF is not always causal. A drug that shortens ICU admission through an unrelated process could have value even if it does not prevent arrhythmia; conversely, a reduction in brief asymptomatic episodes might yield little patient benefit. Economic arguments therefore need a transparent endpoint hierarchy and costs measured in the setting of actual care. Distinct benefits should be evaluated as distinct hypotheses rather than conflated under a broad label of cardioprotection [5,8,19-21,53].

A recent statewide CABG analysis also links POAF

with higher measured care costs and downstream utilization, although such observational comparisons cannot determine what proportion of those costs is prevented by an effective antiarrhythmic intervention. Therefore, cost-effectiveness should be modeled only after credible treatment effects and real-world treatment expenditures are available. An incremental economic analysis would additionally need to capture supplement acquisition, assay or monitoring costs, bleeding or medication-related harms, and postdischarge utilization rather than extrapolate cost savings from a laboratory signal [6].

Discussion and Analysis

The Exposure-Mechanism-Arrhythmia Pathway

Figure 1 presents the review's main causal model. It separates product identity, administered dose, measured systemic exposure, tissue target engagement, electrophysiological response and clinically ascertained POAF. Each transition is a separate proposition requiring its own data, and failure at one step invalidates an inference that jumps directly from dosing to efficacy. Importantly, a favorable systemic exposure profile is not the same as demonstrating atrial delivery, and a change in inflammatory markers is not the same as reducing arrhythmia burden. This figure should therefore be read as a research logic map rather than as a demonstrated biological pathway [17,23,25,49,50].

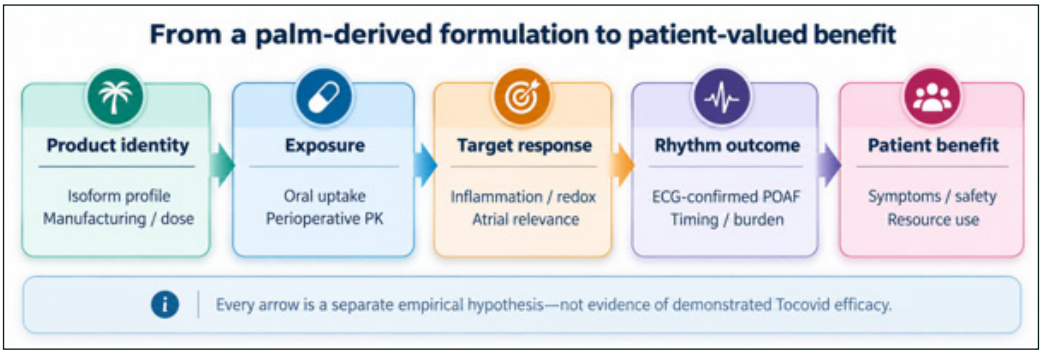


Figure 1: Causal transitions from product identity and perioperative exposure to measured POAF and patient benefit. Each arrow is a hypothesis requiring separate validation.

The model also depicts contextual variables that cannot be neatly assigned to one step: fasting, surgical technique, cardiopulmonary bypass, patient substrate, co-medication, rhythm surveillance and medication adherence. These factors can modify both actual treatment exposure and the observable endpoint. The point of making them visible is not to produce an impossibly complex trial, but to identify a limited set of prespecified measures capable of discriminating among competing explanations. Clinical development becomes more efficient when the next experiment is chosen to resolve a specific uncertainty, rather than to reiterate a primary efficacy comparison without understanding the product's exposure [9,10,12,18].

What the Neutral Tocovid Result can and cannot Mean

The published blinded analyses and the unblinded preprint should be interpreted within their respective evidential boundaries. The blinded papers describe a clinical cohort and trial feasibility but do not supply a comparative treatment estimate. The preprint reports a neutral POAF contrast but requires explicit labeling because it has not been verified here as a final peer-reviewed efficacy publication. Its authors' suggestion that low postoperative tocotrienol levels explain the result is plausible but not established by causal mediation analysis. An intellectually honest QLR can discuss that hypothesis while also evaluating inadequate target selection, insufficient treatment window and substantial mechanistic redundancy [1,2,17,19-21,28].

A neutral finding neither establishes equivalence nor proves that all tocotrienol preparations are ineffective. At the same time, it prevents routine clinical recommendation of the tested regimen for POAF prevention. The burden of proof belongs to a modified intervention, which must demonstrate what changed and why that

change is likely to alter the patient outcome. This distinction protects against an unfalsifiable development strategy where every negative trial is attributed to an unspecified dose or formulation problem. It also respects the opportunity cost of exposing surgical patients to interventions that have not demonstrated incremental benefit against good existing care [3,13,22,48].

Translating Measured Drug Exposure into a Testable Biological Hypothesis

The first research priority is measurement rather than dose escalation. A perioperative pharmacokinetic study should use a precisely identified product, standardized administration and validated assays that distinguish tocotrienol isoforms from tocopherols. It should document the relationship of concentrations to meals, operating-room timing, return of enteral nutrition and medications that influence gastrointestinal function. Sparse sampling designs may be adapted to clinical workflow, but a defensible model should report parameter uncertainty and between-patient variability. Investigators should not assume that pharmacokinetic estimates obtained from healthy fed volunteers can be transported unchanged into post-CABG care [17,18,23,35].

Only after adequate systemic exposure is reproducibly documented should a program seek human target-engagement evidence. Its biomarkers must reflect the hypothesized mechanism and be selected before inspecting treatment differences. A combination of inflammatory markers, oxidative indices and temporal ECG characteristics may help, but each measure has potential confounding and limited specificity for atrial pathways. Where measurement cannot identify causal target engagement directly, investigators should state that limitation and define the experiment's aim as pharmacodynamic plausibility rather than proof. The translation bridge is strengthened by concordant concentration-response and timing data, not by increasing the number of unvalidated laboratory endpoints [22,25,27,49,50].

A rational design should also distinguish drug presence from drug action. If plasma concentrations rise without a measurable biological response, investigators should revisit the target hypothesis and sensitivity of assays rather than assume that even greater exposure is beneficial. If a biological response occurs without a change in AF burden, the pathway may be insufficient to affect clinical rhythm or the chosen population may not depend strongly on that pathway. Such negative findings are informative because they discriminate among development decisions and can prevent ethically questionable escalation to larger trials without a persuasive foundation [15,16,28,54,55].

Clinical Trial Architecture and Estimands

Figure 2 translates this reasoning into a staged go/no-go clinical development pathway. A formulation-and-exposure stage establishes product quality and perioperative pharmacokinetics; a mechanistic pilot stage establishes tolerability and prespecified target-related effects; only then should a larger randomized trial test clinically defined POAF prevention. Each gate requires threshold criteria agreed before observing the next study's findings. A failed gate can warrant formulation redesign or discontinuation, not an announcement of efficacy. Trial protocols should distinguish exploratory stages from confirmatory stages and should make the benefit-risk premise explicit [23,48,54-58].

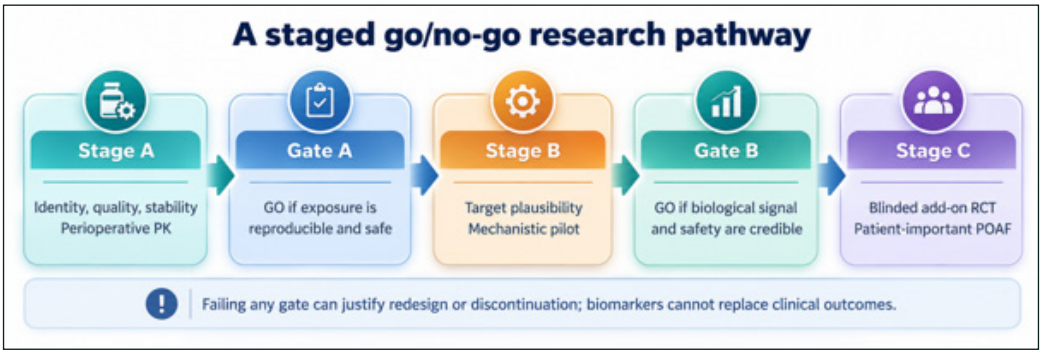


Figure 2: A staged pharmacokinetic, mechanistic and clinical development pathway with prospectively declared

continuation criteria.

For a definitive trial, randomization should be concealed and background preventive care standardized. Tocovid would usually be evaluated as an adjunct to appropriate conventional prophylaxis rather than as a replacement for clinically indicated treatment. Eligibility might focus on isolated CABG patients at an elevated but precisely defined POAF risk to limit heterogeneity. The timing of intervention initiation must be feasible and compatible with perioperative fasting. A matched control should account for capsule characteristics and placebo composition, and adherence should be documented rather than inferred solely from dispensing. Assessor blinding is important for adjudicating ECGs and secondary endpoints independently of treatment expectations [3,12,13,14].

Protocol development should also reflect the STS 2026 recommendations, especially their distinction between strongly recommended therapies and measures for which evidence remains uncertain. Eligibility criteria need to record contraindications to standard prophylaxis, and the trial should report protocol adherence as well as actual beta-blocker or amiodarone exposure. In this design, the intervention estimand becomes the incremental effect of a chemically specified tocotrienol product on clinically adjudicated POAF while the participants continue to receive appropriate perioperative care [7,48,56].

The primary estimand should define population, interventions, event and handling of intercurrent treatment. For example, the treatment-policy effect of adding a formulation to standard care on sustained POAF within a fixed observation window is distinct from an effect among patients who maintain complete oral dosing. Rescue antiarrhythmics, early discharge, death, withdrawal and missing ECG monitoring cannot simply be ignored when assessing efficacy. Trial reporting should communicate both absolute and relative estimates with confidence intervals, not only p values, and prespecify how multiplicity is handled for secondary outcomes such as ICU stay or sleep quality [28,48,51,56].

Figure 3 shows a proposed timeline integrating medication, serial blood sampling, risk period, telemetry and longer-term rhythm follow-up. This visualization highlights that exposure and events must be measured on an aligned clock. Discharge-only concentrations may be too late to characterize the initial hazard, whereas a preoperative value alone cannot establish exposure throughout recovery. Extended rhythm monitoring may reveal recurrence, but its incremental interpretive value depends on adherence and the clinical question. The figure is schematic rather than a one-size-fits-all schedule, and actual times should follow feasibility work and the surgical service's workflow [10,19-21,31,32].

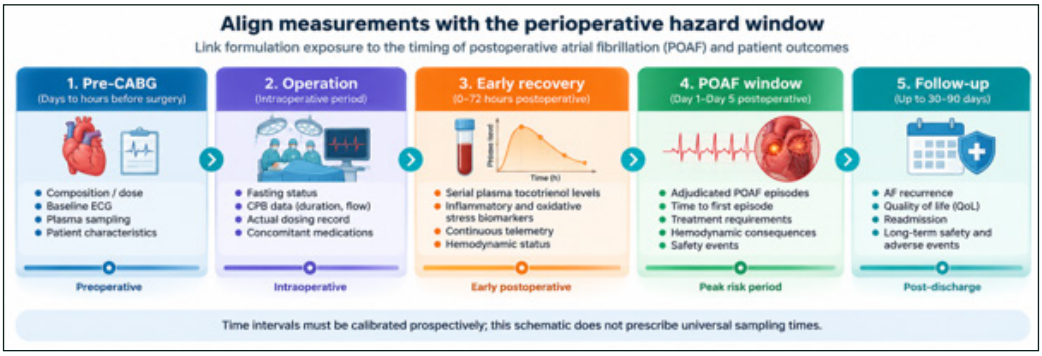


Figure 3: Schematic alignment of treatment dosing, pharmacokinetic assessment, perioperative ECG surveillance and follow-up. Exact intervals require feasibility assessment.

The operational meaning of Figure 3 is that drug administration, sample timing and arrhythmia ascertainment must be recorded using a common temporal reference. A delayed concentration measurement cannot substitute for observations during the onset of arrhythmic risk, and short clinical telemetry cannot measure later asymptomatic recurrence. Trial investigators should therefore predefine both the postoperative observation period and

longer-term monitoring objectives, with feasibility and participant burden considered explicitly [10,19-21,32].

Comparator Evidence and Limitations of Cross-Intervention Inference

The relative success of some mechanical preventive strategies should sharpen rather than distract from the tocotrienol hypothesis. Posterior pericardiotomy, for example, targets fluid-related physiology, and several trials suggest reduced POAF. Such evidence confirms that atrial triggers extend beyond systemic inflammation. It is incorrect to treat the favorable result of one approach as support for Tocovid simply because both are intended to prevent POAF. Instead, comparisons should identify mechanistic independence, possible interactions with background care and expected baseline event rates in similar CABG populations [1,2,37,38,40].

Colchicine, magnesium and anti-inflammatory interventions reveal a second lesson: timing, tolerability and procedural setting can modify both efficacy and harm. Synthesized effects differ by study selection, dose and co-intervention; published meta-analyses are useful guides to uncertainty rather than a mandate to copy a particular regimen. For Tocovid, a negative trial with inadequate exposure characterization justifies a precise pharmacokinetic pilot, whereas a future negative trial with confirmed exposure and target engagement would demand much stronger grounds for continued development. Every proposed design change must respond to a demonstrated knowledge gap, not an arbitrary effort to obtain statistical significance [24,39,40].

Patient Safety, Ethics and Responsible Commercialization

Patient safety should be assessed as a separate outcome domain rather than assumed from tocotrienols' nutritional origin. Cardiac surgery involves dynamically changing bleeding risk, antiplatelet treatment, intermittent anticoagulation and variable organ function. The mechanistic possibility of a drug interaction does not prove clinical harm; nevertheless, an investigational supplement must be evaluated through predefined monitoring of bleeding, transfusion, arrhythmias, liver or renal laboratory abnormalities and tolerability. Discontinuation criteria and rescue care should be stated explicitly. Sponsors should report ingredient sources, manufacturing quality and conflicts of interest, including commercial provision of the active product or placebo [12,19-21,51,56].

A post-CABG patient may understandably consider antioxidant supplementation attractive if it is framed as a natural means of recovery. Ethical recruitment requires clear communication that the currently available unblinded study did not show a significant POAF reduction, and that a proposed new delivery system has not yet demonstrated clinical benefit. The informed-consent discussion should avoid both therapeutic misconception and exaggerated dismissal of legitimate scientific uncertainty. Independent analysis, registered protocols and publication of negative results help ensure that commercial incentives do not transform interesting mechanistic findings into unsupported clinical advertising [22,48,51,56].

The environmental and economic origin of palm-derived compounds requires another conceptual separation. A traceable agricultural supply chain can be evaluated for quality and sustainability, but it cannot establish cardiac efficacy. Source authentication matters pharmacologically because isoform composition and manufacturing processes can affect drug exposure. Nevertheless, any claims of sustainability or affordability should be supported by life-cycle and supply data rather than inferred from the word palm. Conversely, demonstration of a biological effect would not excuse poor material traceability or deficient product safety [12,15,18,22].

Prioritized Research Agenda and Limitations of the QLR

The research agenda has three priorities. First, characterize perioperative pharmacokinetics under actual CABG conditions using analytically specified Tocovid or another formulation. Second, test whether adequate exposure produces measurable target-related physiological effects without unacceptable harms. Third, undertake a properly powered randomized clinical comparison only if the first two questions yield credible, prespecified evidence supporting benefit. A negative result at any gate should lead to explicit reassessment rather than automatic escalation. These priorities offer more information per enrolled patient than simply repeating the original intervention with a higher nominal dose [17,23,54-56].

The review also identifies constraints that cannot be eliminated by conceptual elegance. Direct evidence rests heavily on one trial program; the unblinded efficacy report remains a preprint in the sources evaluated. Other trials differ in isoform composition, indication and exposure duration, while mechanistic observations from nonoperative populations may be poor surrogates for the acute CABG environment. QLR uses purposive rather than exhaustive retrieval, and thematic synthesis cannot quantify a pooled intervention effect or exclude unknown studies. These limitations are stated because the proposed framework is a testable hypothesis generator, not a validated clinical prediction model [preprint] [11,19-22,49,50].

The practical implication is a shift from asking whether antioxidant activity is broadly beneficial to asking precisely which product reaches which compartment, at what time and for which event. This shift prevents the common translation error of mistaking attractive chemistry, a favorable plasma biomarker or an exploratory postoperative outcome for demonstrated reduction of clinically important POAF. It also allows negative trials to serve scientific progress by resolving the place of an intervention within a complex causal system. For patients, the correct present-day message remains that Tocovid is not established as a routine postoperative AF prophylactic [1,2,3,17,48].

Conclusion

Synthesis and Recommendations

Palm-derived tocotrienols remain pharmacologically interesting, but their potential antioxidant and anti-inflammatory actions do not establish prevention of postoperative atrial fibrillation after coronary bypass surgery. Peer-reviewed blinded analyses of the Tocovid trial illuminate the perioperative clinical context, whereas an openly available unblinded preprint reports a neutral POAF treatment comparison. The reported low postoperative concentrations invite a pharmacokinetic hypothesis without proving that inadequate absorption caused the clinical result. The most defensible interpretation therefore keeps treatment efficacy, exposure, mechanistic effects and secondary recovery outcomes analytically separate.

A responsible next step is not routine clinical adoption or unqualified dose escalation. Investigators should authenticate the palm-derived formulation, establish serial perioperative exposure, test a prespecified physiological target and demonstrate safety before advancing to a definitive trial. Any confirmatory study should maintain appropriate standard care, capture rhythm consistently and evaluate meaningful patient outcomes with transparent treatment-effect estimates. Independent replication and publication of unfavorable results will be essential to determine whether the translational pathway warrants continuation or discontinuation.

References

1. Mario Gaudino , Antonino Di Franco , Lisa Q Rong , Jonathan Piccini , Michael Mack (2023) Postoperative atrial fibrillation: from mechanisms to treatment. European Heart Journal 44: 1020-1039.
2. Mario Gaudino, Tommaso Sanna, Karla V Ballman, N Bryce Robinson, Irbaz Hameed, et al. (2021) Posterior left pericardiotomy for the prevention of atrial fibrillation after cardiac surgery: an adaptive, single-centre, single-blind, randomised, controlled trial. The Lancet 398: 2075-2083.
3. Orlando R Suero, Ahmed K Ali, Lauren R Barron, Matthew W Segar, Marc R Moon, et al. (2024) Postoperative atrial fibrillation (POAF) after cardiac surgery: clinical practice review. Journal of Thoracic Disease 16:1503-1520.
4. Rachel Eikelboom, Rohan Sanjanwala, Me-Linh Le, Michael H Yamashita, Rakesh C Arora, et al. (2021) Postoperative Atrial Fibrillation After Cardiac Surgery: A Systematic Review and Meta-Analysis. Annals of Thoracic Surgery 111: 544-554.
5. Ahmed K Awad, Mohammed A Elbahloul, Omar Al-Omoush, Omar Abdelnasser, Momen Hajali, et al. (2025) Impact of postoperative atrial fibrillation (POAF) on outcomes after coronary artery bypass grafting: A meta-analysis of unique 247,270 patients from 50 studies. American Heart Journal Plus 59: 100621.
6. Ad N, Fonner CE, Alejo D, Riojas R, Whitman GJR, et al. (2025) The clinical and financial impact of new-onset atrial fibrillation after coronary bypass grafting: From indexed procedure to long-term follow-up. JTCVS Open 28: 146-156.
7. Chatterjee S, Grant MC, Hui DS, Schwann TA, Alexander JH, et al. (2026) The Society of Thoracic Surgeons 2026 Clinical Practice Guidelines for the Prevention and Treatment of New-Onset Postoperative Atrial Fibrillation After Cardiac

Surgery. The Annals of Thoracic Surgery 122: 255-277.
8. Kei Woldendorp, James Farag, Sam Khadra, Deborah Black, Benjamin Robinsonet, al. (2021) Postoperative Atrial Fibrillation After Cardiac Surgery: A Meta-Analysis. Annals of Thoracic Surgery 112: 2084-2093.
9. Eun Ji Seo, Joonhwa Hong, Hyeon-Ju Lee, Youn-Jung Son (2021) Perioperative risk factors for new-onset postoperative atrial fibrillation after coronary artery bypass grafting: a systematic review. BMC Cardiovascular Disorders 21: 418.
10. Andrew C T Ha, Subodh Verma, C David Mazer, Adrian Quan, Bobby Yanagawa, et al. (2021) Effect of Continuous Electrocardiogram Monitoring on Detection of Undiagnosed Atrial Fibrillation After Hospitalization for Cardiac Surgery: A Randomized Clinical Trial. JAMA Network Open. 4: e2121867.
11. Ivy Quan, Emilie P Belley-Côté, Jessica Spence, Austine Wang, Karen Sidhom, et al. (2024) A Systematic Review of Ongoing Registered Research Studies on Post-Operative Atrial Fibrillation after Cardiac Surgery. Journal of Clinical Medicine 13: 4948.
12. Michael C Grant, Cheryl Crisafi, Adrian Alvarez, Rakesh C Arora, Mary E Brindle, et al. (2024) Perioperative Care in Cardiac Surgery: A Joint Consensus Statement by the Enhanced Recovery After Surgery (ERAS) Cardiac Society, ERAS International Society, and The Society of Thoracic Surgeons (STS). Annals of Thoracic Surgery 117: 669-689.
13. Isabelle C Van Gelder, Michiel Rienstra, Karina V Bunting, Ruben Casado-Arroyo, Valeria Caso, et al. (2024) 2024 ESC Guidelines for the management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). European Heart Journal 45: 3314-3414.
14. José A Joglar, Mina K Chung, Anastasia L Armbruster 1, Emelia J Benjamin, Janice Y Chyou, et al. (2024) 2023 ACC/AHA/ACCP/HRS Guideline for the Diagnosis and Management of Atrial Fibrillation. Circulation 149: e1-e156.
15. Zainal Z, Khaza'ai H, Radhakrishnan AK, Chang SK (2022) Therapeutic potential of palm oil vitamin E-derived tocotrienols in inflammation and chronic diseases: Evidence from preclinical and clinical studies. Food Research International 156: 111175.
16. Ban-Hock Khor, Hui-Ci Tiong, Shing Cheng Tan, Sok Kuan Wong, Kok-Yong Chin, et al. (2021) Effects of tocotrienols supplementation on markers of inflammation and oxidative stress: A systematic review and meta-analysis of randomized controlled trials. PLOS ONE 16: e0255205.
17. Mahjabeen Sharif, Dilshad Ahmed Khan, Kulsoom Farhat, Mudassar Noor, Mohammad Asghar Khanet, al. (2023) Pharmacokinetics and bioavailability of tocotrienols in healthy human volunteers: a systematic review. Journal of the Pakistan Medical Association 73: 603-610.
18. Mohamad NV (2023) 'Strategies to Enhance the Solubility and Bioavailability of Tocotrienols Using Self-Emulsifying Drug Delivery System Pharmaceuticals 16: 1403.
19. Musa AF, Dillon J, Md Taib ME, Yunus AM, Sanusi AR, et al. (2021) A double-blind randomised controlled trial on the effect of Tocovid, a tocotrienol-rich capsule on postoperative atrial fibrillation at the National Heart Institute, Kuala Lumpur: an interim blinded analysis. Journal of Cardiothoracic Surgery 16: 340.
20. Musa AF, Dillon J, Md Taib ME, Yunus AM, Sanusi AR, et al. (2022a) 'Incidence and Outcomes of Postoperative Atrial Fibrillation after Coronary Artery Bypass Grafting of a Randomized Controlled Trial: A Blinded End-of-cycle Analysis. Reviews in Cardiovascular Medicine 23: 122.
21. Musa AF, Dillon J, Md Taib ME, Yunus AM, Sanusi AR, et al. (2022b) Does Tocovid, a Tocotrienol-rich Vitamin E, Mitigate Postoperative Atrial Fibrillation after Coronary Artery Bypass Grafting (CABG) Surgery? A Single-Centre Double-blind Randomised Controlled Trial. preprint https://www.qeios.com/read/GL22XT.2.
22. Aaron Deming Looi, Uma Devi Palanisamy, Mohanambal Moorthy, Ammu K Radhakrishnan (2025) Health Benefits of Palm Tocotrienol-Rich Fraction: A Systematic Review of Randomized Controlled Trials. Nutrition Reviews 83: 307-328.
23. Karen Rowland Yeo, Eva Gil Berglund, Yuan Chen (2024) Dose Optimization Informed by PBPK Modeling: State-of-the Art and Future. Clinical Pharmacology & Therapeutics 116: 563-576.
24. Yousef Rezaei, Mohammad Mehdi Peighambari, Shayan Naghshbandi, Niloufar Samiei, Alireza

Alizadeh Ghavidel, et al. (2020) Postoperative Atrial Fibrillation Following Cardiac Surgery: From Pathogenesis to Potential Therapies. American Journal of Cardiovascular Drugs 20: 19-49.

25. Amir Ajoolabady, Stanley Nattel, Gregory YH Lip, Jun Ren (2022) Inflammasome Signaling in Atrial Fibrillation: JACC State-of-the-Art Review. Journal of the American College of Cardiology 79: 23.
26. Nso Nso, Kaveh R Bookani, Mark Metzl, Farshid Radparvar (2020) Role of inflammation in atrial fibrillation: A comprehensive review of current knowledge. Journal of Arrhythmia 37: 1-10.
27. Xiaolei Wang, Xiaohui Chen, Dobromir Dobrev, Na Li (2021) The crosstalk between cardiomyocyte calcium and inflammasome signaling pathways in atrial fibrillation. Pflügers Archiv 473: 389-405.
28. Suzie Cro, Brennan C Kahan, Sunita Rehal, Anca Chis Ster, James R Carpenter, et al. (2022) 'Evaluating how clear the questions being investigated in randomised trials are: systematic review of estimands. BMJ 378: e070146.
29. Hugh Fleet, David Pilcher, Rinaldo Bellomo, Tim G Coulson (2023) Predicting atrial fibrillation after cardiac surgery: a scoping review of associated factors and systematic review of existing prediction models. Perfusion 38.
30. Xiaoxu Zhou, Samuel C Dudley (2020) Evidence for Inflammation as a Driver of Atrial Fibrillation. Frontiers in Cardiovascular Medicine 7.
31. Mary Rezk, Amar Taha, Susanne J Nielsen, Tomas Gudbjartsson, Lennart Bergfeldt, et al. (2022) Clinical Course of Postoperative Atrial Fibrillation After Cardiac Surgery and Long-term Outcome. Annals of Thoracic Surgery 114: 2209-2215.
32. Makoto Hibino, Arjun K. Pandey, Subodh Verma, Pankaj Puar, Hwee Teoh, et al. (2023) Wearable Cardiac Rhythm Monitoring Device for Detection of Postoperative Atrial Fibrillation. Annals of Thoracic Surgery 116: 854-858.
33. Ali M, Sheikh Abdul Kadir SH, Ibrahim E, Albaraikan A (2026) Tocotrienol-rich fraction of vitamin E in diabetes and cardiovascular disease: From molecular mechanisms to clinical application. International Journal of Cardiology and Cardiovascular Risk and Prevention 30.
34. Yan Yi Koay, Gerald Chen Jie Tan, Sonia Chew Wen Phang, J-Ian Ho, Pei Fen Chuar, et al. (2021) 'A Phase IIb Randomized Controlled Trial Investigating the Effects of Tocotrienol-Rich Vitamin E on Diabetic Kidney Disease. Nutrients 13: 258.
35. Sandhya Mandlekar, Dhruvitkumar S Sutaria, Xiaoyun Yang, Ryan Johnson, Yixuan Zou, et al. (2024) Evaluation of Patient-Centric Sample Collection Technologies for Pharmacokinetic Assessment of Large and Small Molecules. Clinical Pharmacology & Therapeutics 116: 782-794.
36. Elena Maria Tosca, Alessandro De Carlo, Davide Ronchi, Paolo Magni, et al. (2024) Model-Informed Reinforcement Learning for Enabling Precision Dosing Via Adaptive Dosing. Clinical Pharmacology & Therapeutics 116: 619-636.
37. Giovanni Jr Soletti, Roberto Perezgrovas-Olaria, LLamia Harik, Mohamed Rahouma, Arnaldo Dimagli, et al. (2022) Effect of posterior pericardiotomy in cardiac surgery: A systematic review and meta-analysis of randomized controlled trials. Frontiers in Cardiovascular Medicine 9: 1090102.
38. Taw Moe Myat San, Khin Phue Phue Han, Muhammad Ismail, Lei Myint Thu, Myat Soe Thet (2024) Pericardiotomy and atrial fibrillation after isolated coronary artery bypass grafting: A systematic review and meta-analysis of 16 randomised controlled trials. Cardiovascular Revascularization Medicine 66: 27-32.
39. Peibing Ge, Yu Fu, Qi Su, Mengdi Jin, Li Guo, et al. (2022) Colchicine for prevention of post-operative atrial fibrillation: Meta-analysis of randomized controlled trials. Frontiers in Cardiovascular Medicine 9:1032116.
40. Sara Ghazizadeh, Alireza Malektojari, Zahra Javidfar, Shaghayegh Lahuti, Rahele Shokraei, et al. (2025) Magnesium for Prevention of New-onset Postoperative Atrial Fibrillation Following Cardiac Surgery: A Systematic Review and Meta-analysis of Randomized Controlled Trials. Heart International 19: 3-11.
41. Alireza Malektojari, Zahra Javidfar, Sara Ghazizadeh, Shaghayegh Lahuti, Rahele Shokraei, et al. (2025) 'Effectiveness of Anti-Inflammatory Agents to Prevent Atrial Fibrillation After Cardiac Surgery: A Systematic Review and Network Meta-Analysis. CJC Open 7: 35-45.
42. Hargun Kaur, Brendan Tao, Max Silverman, Jeffrey S Healey, Emilie P Belley-Cote, et al. (2024)

Recurrence of new-onset post-operative AF after cardiac surgery: detected by implantable loop recorders: A systematic review and Meta-analysis. International Journal of Cardiology 404:131930.
43. Suri RS, Belley-Cote EP, Baigent SM, Veloce NP, Ahmed M, et al. (2026) Recurrence of Postoperative Atrial Fibrillation After Cardiac Surgery: Insights from a Tertiary Follow-Up Clinic. CJC Open 8: 24-30.
44. Nikolaou M, Pattakos G, Hitas C, Koniari K, Pitsis A, et al. (2025) Atrial fibrillation post CABG and the risk of arrhythmia recurrence: the AFRODITE study. Hellenic Journal of Cardiology 84: 13-21.
45. Mileen R D van de Kar, Thomas J van Brakel, Marcel Van't Veer, Gijs J van Steenbergen, Edgar J Daeter, et al. (2024) Anticoagulation for post-operative atrial fibrillation after isolated coronary artery bypass grafting: a meta-analysis. European Heart Journal 45: 2620-2630.
46. Ren Jie R Yao, Nathaniel M Hawkins, Yasaman Lavaie, Marc W Deyell, Jason G Andrade, et al. (2021) Anticoagulation management of postoperative atrial fibrillation after cardiac surgery: A systematic review. Journal of Cardiac Surgery 36: 2081-2094.
47. Muneeb Ahmed, Emilie P Belley-Coté, Yuan Qiu, Peter Belesiotis, Brendan Tao, et al. (2023) Rhythm vs. Rate Control in Patients with Postoperative Atrial Fibrillation after Cardiac Surgery: A Systematic Review and Meta-Analysis. Journal of Clinical Medicine 12: 4534.
48. Sally Hopewell, An-Wen Chan, Gary S Collins, Asbjørn Hróbjartsson, David Moher, et al. (2025) CONSORT 2025 statement: updated guideline for reporting randomised trials. BMJ 31: 1776-1783.
49. Anthony Muchai Manyara, Philippa Davies, Derek Stewart, Christopher J Weir, Amber E Young, et al. (2024a) Reporting of surrogate endpoints in randomised controlled trial reports (CONSORT-Surrogate): extension checklist with explanation and elaboration. BMJ. 386:e078524.
50. Anthony Muchai Manyara, Philippa Davies, Derek Stewart, Christopher J Weir, Amber E Young, et al. (2024b) Reporting of surrogate endpoints in randomised controlled trial protocols (SPIRIT-Surrogate): extension checklist with explanation and elaboration. BMJ 386:e078525.
51. Daniela R Junqueira, Liliane Zorzela, Susan Golder, Yoon Loke, Joel J Gagnier, et al. (2023) CONSORT Harms 2022 statement, explanation, and elaboration: updated guideline for the reporting of harms in randomised trials. BMJ 381:e073725.
52. Gilbers Kawczynski, Bidar E, Maesen B, Isaacs A, Winters J, et al. (2025) Determinants and impact of postoperative atrial fibrillation burden during 2.5 years of continuous rhythm monitoring after cardiac surgery: Results from the RACE V prospective cohort study. Heart Rhythm 22: 647-660.
53. Fangzhou Qu, Wei Yang, Ni He, Shangcheng Qu, Xiao Zhou, et al. (2024) Effect of Postoperative Atrial Fibrillation After Cardiac Surgery: A Meta-Analysis. Clinical Cardiology 47: e70053.
54. Christina Yap, Jan Rekowski, Moreno Ursino, Olga Solovyeva, Dhrusti Patel, et al. (2023a) 'Enhancing quality and impact of early phase dose-finding clinical trial protocols: SPIRIT Dose-finding Extension (SPIRIT-DEFINE) guidance. BMJ 383:e076386.
55. Christina Yap, Olga Solovyeva, Johann de Bono, Jan Rekowski, Dhrusti Patel, et al. (2023b) Enhancing reporting quality and impact of early phase dose-finding clinical trials: CONSORT Dose-finding Extension (CONSORT-DEFINE) guidance. BMJ 383:e076387.
56. An-Wen Chan, Isabelle Boutron, Sally Hopewell, David Moher, Kenneth F Schulz, et al. (2025) 'SPIRIT 2025 statement: updated guideline for protocols of randomised trials. BMJ 22: e1004589.
57. Asbjørn Hróbjartsson, Isabelle Boutron, Sally Hopewell, David Moher, Kenneth F Schulz, et al. (2025) SPIRIT 2025 explanation and elaboration: updated guideline for protocols of randomised trials. BMJ 389: e081660.
58. Brennan C Kahan, Edmund Juszczak, Elaine Beller, Megan Birchenall, An-Wen Chan, et al. (2025) Guidance for protocol content and reporting of factorial randomised trials: explanation and elaboration of the CONSORT 2010 and SPIRIT 2013 extensions. BMJ 388: e080785.

Copyright: ©2026 Loso Judijanto. This is an open-access article distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.