

How to Referee A Manuscript

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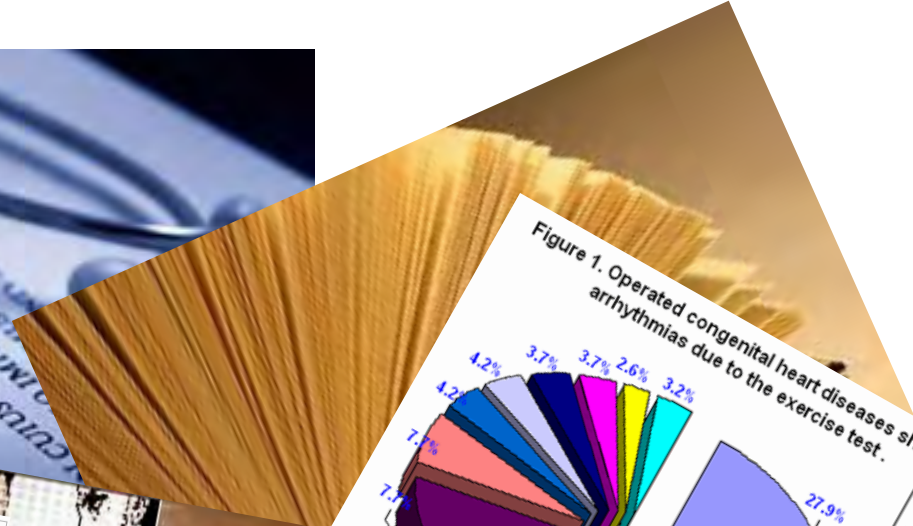
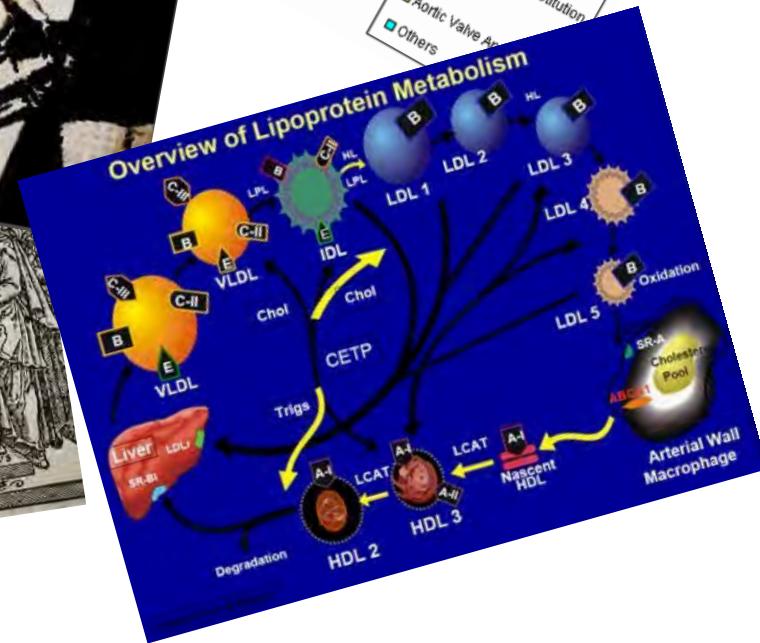
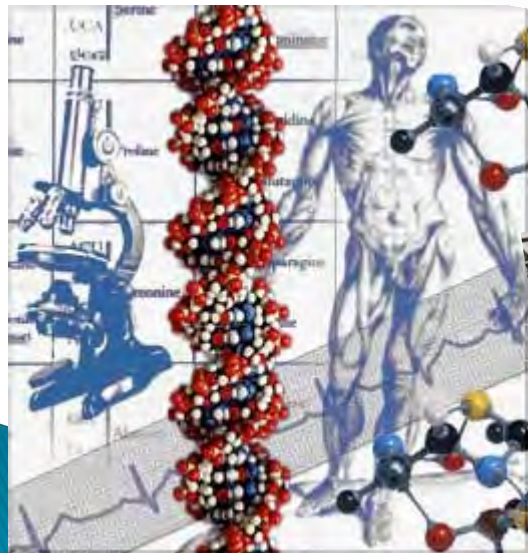
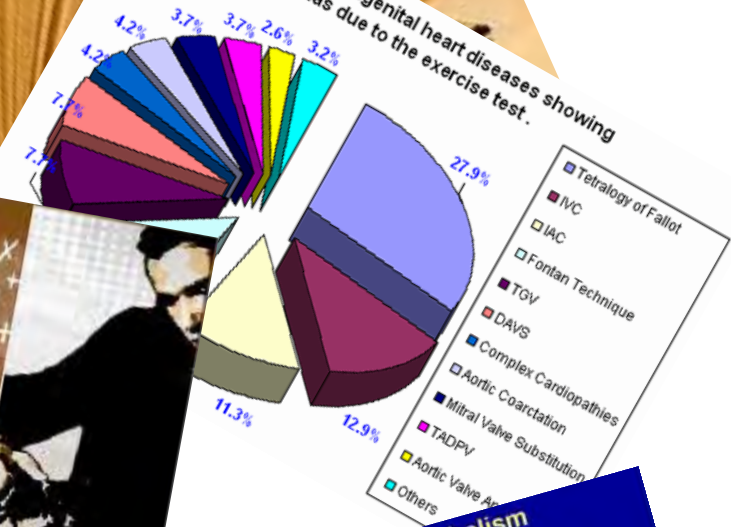


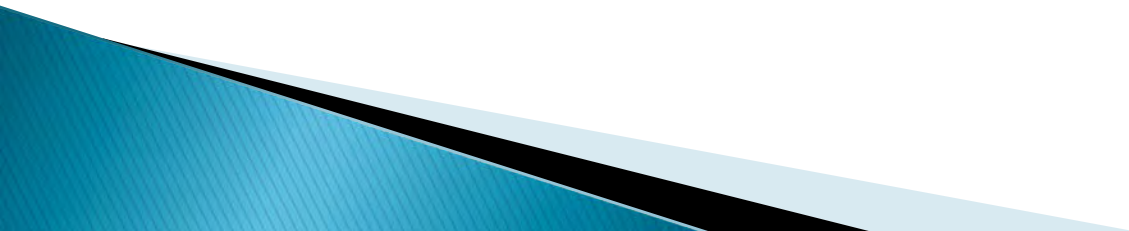
Figure 1. Operated congenital heart diseases showing arrhythmias due to the exercise test.



Responsibility

Q: What process maintains the veracity of the medical and scientific literature?

A:



Responsibility

Q: What process maintains the veracity of the medical and scientific literature?

A: *Peer review*



I WANT YOU

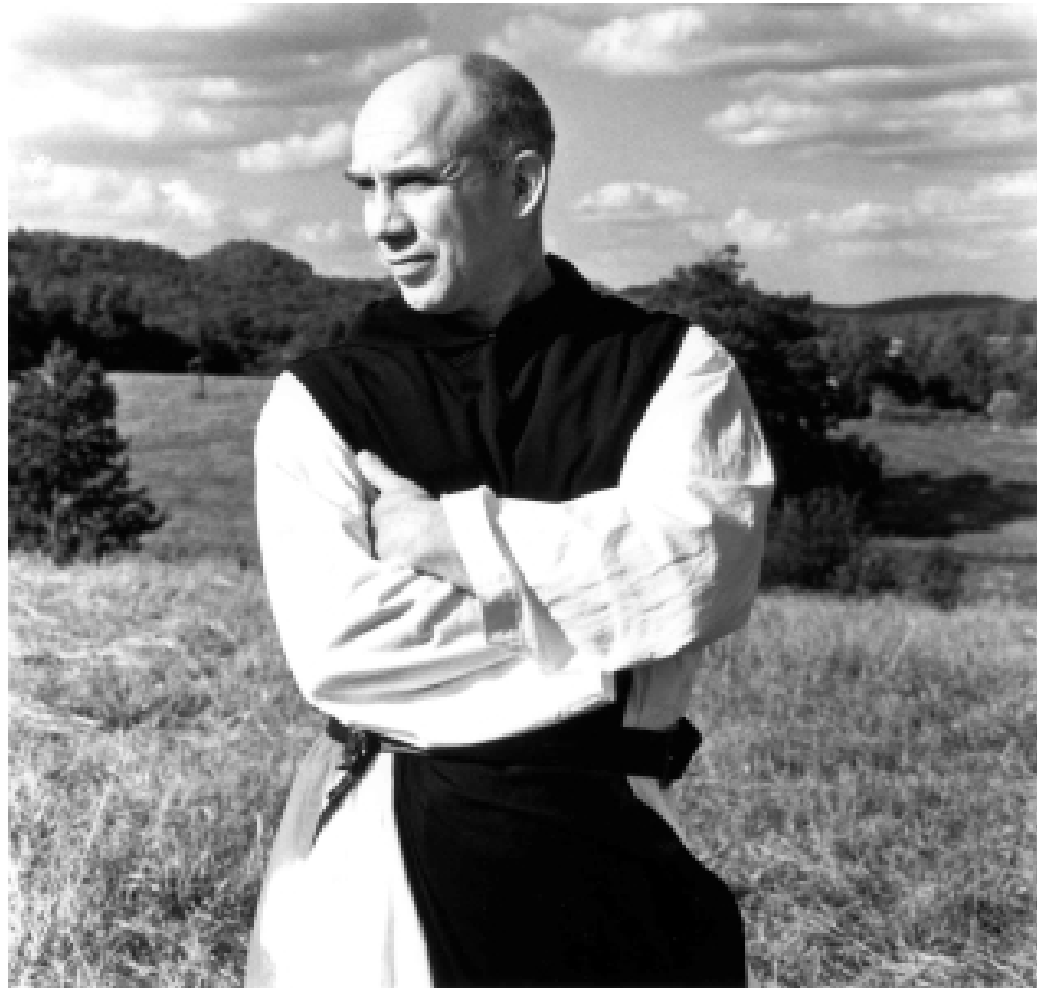
Roles of Reviewer

1. Keep bad stuff out
2. Help good stuff get in

Apply the same principles as for patient care:

Would you want people to base your mother's care on these data?










This is very important for you:

- ▶ Reputation, reputation, reputation!
 - ▶ Relationships with editors
 - ▶ Appointments to boards and panels
 - ▶ Profile and visibility
 - ▶ Knowledge about authors
 - ▶ Learn good writing styles
 - ▶ Learning about new developments
 - ▶ Academic activity
- 

How I Approach a Manuscript

- ▶ Print on paper
 - ▶ First read, with very few notes
 - ▶ Read again, intensely, many notes
 - ▶ Review backwards:
 - Conclusions supported by results?
 - Results follow from methods?
 - Methods logically address hypothesis?
 - Hypothesis well stated?
 - Address reasonable problem?
- 

Abstract: OBJECTIVE: Perioperative red cell transfusion is associated with increased morbidity and mortality following Coronary Artery Bypass Grafting (CABG). Whether transfusion is a cause of these outcomes or serves as a surrogate for a higher risk patient population remains uncertain. This retrospective study tests the hypothesis that an increased preoperative risk profile of patients receiving transfusion would explain the relationship between red cell transfusion and operative mortality in isolated CABG.

METHODS: 31,818 patients undergoing isolated CABG were entered into a statewide collaborative database between January 2006 and June 2010. Utilizing the STS risk calculator, patient cohorts were stratified into 4 groups based on a predicted risk of mortality (PROM) of <2%, 2-5%, >5-10% and >10%. The association between blood transfusion and mortality was tested at each stratum using a chi-square test. A Breslow-Day test for homogeneity of odds ratios was used to test whether or not the four odds ratios among the strata were similar, and a Cochran-Mantel-Haenszel was used to test the association between blood transfusion and mortality while controlling for predicted risk mortality strata.

RESULTS: 17,720 (55.7%) of all patients were transfused during the hospitalization. The incidence of transfusion increased step wise with risk level; 93.3% of patients with PROM >10% received blood. Operative mortality was 2.1% overall, 0.6% in the 44.3% of patients who were not transfused and 3.3% in the transfused group (OR 6.19, $p < 0.0001$). The association between blood transfusion and mortality was significant within each predicted risk stratum. The increased mortality associated with transfusion was statistically equivalent across all predicted risk strata ($p = 0.1778$). The association between blood transfusion and mortality for all patients lessened somewhat when controlling for the PROM (OR 2.99 vs. 6.19), yet remained highly significant ($p < 0.0001$).

CONCLUSION: The association between red cell transfusion and mortality following CABG is highly significant and independent of increased preoperative risk status. The correlation persists after controlling for increased PROM. This finding creates future opportunity to investigate the effect of the timing and the amount of transfusion.

Writing the Review

- ▶ Editing style has a rubric (pattern):
 - FOLLOW IT!
 - Explain all answers
- ▶ No rubric, just free text. My approach:
 - Summary: no comments, just facts
 - Major Concerns (critical to decision)
 - Minor edits (decision does not hinge on these)

Example: A “Rubric”

Reviewer 4

Reviewer Recommendation Term:	Revise/Accept Pending Review by Editor
Custom Review Question(s)	Response
Does this manuscript present information that is important, timely relevant, critical, and/or a prevalent problem?	1
Is the problem well stated and well formulated?	1
Is this a well-designed study (appropriate, rigorous, comprehensive design)?	1
Does this manuscript present a sophisticated approach to data analysis?	1
Is the sample size sufficiently large?	1
This manuscript contains thoughtful, focused, up-to-date review of the literature.	0
The manuscript has practical, useful implications.	1
The authors' interpretations took into account the limitations of the study.	1
Well written manuscript (clear, straightforward, easy to follow, logical).	1

Writing the Review


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Summary

- ▶ Include manuscript number and title
- ▶ Summarize the study purpose and major data presented
- ▶ Include statement summarizing authors' conclusions.

Review: JCVA-D-11-00103 Plasma levels of Potassium and Magnesium after Modified Ultrafiltration in Pediatric Cardiac surgery with Cardiopulmonary Bypass.


Summary: The authors report the impact of MUF on plasma levels of potassium (pK) and magnesium (pMg) in a cohort of 16 children undergoing cardiac surgery with cardiopulmonary bypass (CPB). The application of MUF resulted in a statistically significant decrease in pK, but not of pMg.




Major Concerns

- ▶ This is the heart of your review
- ▶ Start with general statement about the place of the study in the literature
- ▶ Start each topic with heading sentence, and then list reasons for concern

Remember your 6th grade criteria for writing a good paragraph!

- Be specific with criticism
 - Explain and teach, if appropriate
 - Enumerate, please
 - Third person
- 

Major Concern Topics


- ▶ Interesting problem?
 - ▶ References appropriate?
 - ▶ Hypothesis well stated?
 - ▶ Approach is sound?
 - ▶ Statistical approach: know thy self!
 - ▶ Results: address hypothesis?
 - ▶ Figures clear and tables accurate?
 - ▶ Discussion appropriate and focused?
 - ▶ Limitations discussed?
 - ▶ Conclusions supported by data?
- 

Example 1: Original text

Among cardiac surgical patients, it has been shown that the benefits of transfusion are offset by risks, such as the transmission of viral and other infectious diseases, allergic reactions, fever, lung injury, immunosuppression, and hemolytic reactions. Patients transfused during the perioperative period have higher early and long-term morbidity and mortality.²⁻⁴ Blood transfusion also increases the cost of the procedure, both directly and by prolonging length of stay.^{5,6}

As a result, there have been multiple initiatives to reduce transfusion for patients having cardiac surgery.⁷ Currently, the indications for transfusion are not standardized, as witnessed by the wide disparity in transfusion rates.⁸ The objective of our study was to assess the impact of a comprehensive, multidisciplinary blood conservation initiative on blood product utilization and clinical outcomes in our community cardiac surgery program.

Reviewer #3

- 2 1 What was the specific hypothesis? Why did you think that you would not be able to show that the blood conservation program would work in a community hospital setting?
 - 5 1, This Introduction does NOT explain why your study was needed. Others have shown that you can reduce blood use using such a program. Why would it be necessary to "assess the impact" of this approach in your system? What exactly is different about your system vs others that have been studied and reported on?
- 



Reviewer #2

2. **Problem well stated, formulated:** In the introduction, the authors mention some of the serious hazards of transfusion (viral transmission, etc), but they fail to mention that these are rare, and are not likely to be significant contributors to morbidity. What is really driving the push for decreased blood transfusion is what the authors mention in the next sentence: the association with morbidity and mortality, for reasons not well understood. Therefore, this reviewer feels the introduction could be strengthened by adding something like the following statement after the first sentence:

"These serious hazards of transfusion are rare in clinical practice. What is more real, and far more elusive, has been the observation that patients transfused during the perioperative period have higher early and long-term morbidity and mortality, for reasons that are unexplained by serious transfusion hazards, or by concurrent medical problems (2-4). Blood transfusion also significantly increases the cost of surgery, both directly and by prolonging length of stay (5,6)."

Reviewer #2

3. **Well-designed study:** The study compares the outcomes of a new management scheme to historical controls. This is an appropriate design to address the hypothesis. However, the design could be improved by considering the following:

a. Preoperative patient characteristics do not include anemia or hematocrit. The same is true for platelet count. These are important driving factors for transfusion, certainly more important than hyperlipidemia.

b. Preoperative hematocrit should also be included in the linear regression for red cell transfusion, and preoperative platelet count should be included in the regression for platelet transfusion. This reviewer speculates that with the addition of this risk factor, the impact of the program on platelet transfusion may become statistically significant.

Authors' response

These additions and revisions have been made to the 2nd paragraph on page 5.



Example 2: Original text

Objective: Our aim to evaluate the efficacy and safety of rFVIIa in cardiac surgical patients with refractory bleeding.

Design: The study was an observational design.

Setting: cardiac center

Participants: Data were collected in patients who had undergone cardiac surgery and complicated by refractory bleeding. The study included 35 patients, adults, and 8 children.


Interventions: rFVIIa administration


Measurements and main results: The rFVIIa effect was assessed by the decrease in the chest loss ($<3\text{ml/kg/hr}$ without accumulation of blood inside the chest) and number of blood products (Packed red blood cells, platelets, fresh frozen plasma, and cryoprecipitate) given before and after rFVIIa administration was recorded. The dose of rFVIIa was $93.72 \pm 17.39 \mu\text{g/kg}$. All patients received single dose of rFVIIa, but nine patients received a second dose through half to one hour following the initial dose. The blood losses before rFVIIa administration was $7.47 \pm 1.53 \text{ ml/kg/hr}$ and decreased significantly to 2.37 ± 0.67 and $1.08 \pm 0.42 \text{ ml/kg/hr}$ in the next six and eighteen hours respectively ($P=0.001$)[paired test]. Before rFVIIa administration, the number of transfused packed RBC, fresh frozen plasma, platelets and cryoprecipitates were 11.25 ± 3.57 , 11.35 ± 4.15 , 11.77 ± 4.40 and 10.16 ± 3.76 units and decreased significantly to

5.930±1.704, 3.86±1.52, 3.65±1.42 and 2.91±2.11 units respectively after rFVIIa (P=0.00).

Conclusion: In patients undergoing cardiac surgery exhibiting refractory bleeding, rFVIIa at a mean dose of 93.7±17µg/kg improved significantly hemostasis and decreased additional administration of blood products, without any complication related to rFVIIa.

Comments: The use of rFVIIa in cardiac surgery is a clinical dilemma, since the data necessary to balance the risks and benefits of therapy are inconsistent and often of poor quality. Hence, a study of the agent in this clinical setting is important. Having said that, this manuscript suffers from multiple methodological problems related to study design, which significantly diminish its contribution to the current literature.

1. There is no control group. The main reason why a control group is needed is that many of these patients may have had a decrease in their transfusion requirements without rFVIIa treatment, and comparison with a control is the only way to know efficacy. Had this study been performed ten years ago, it would have provided a useful addition to knowledge. But the literature is now rife with anecdotal evidence, case reports, case series, and retrospective cohort studies; the appropriate study to perform at this time is a controlled, blinded, randomized, prospective trial. This has been done in cardiac surgery (Gill et al, *Circulation* 2010, 121:e234). In fact, this trial was terminated early because the higher dose no longer reflected current practice (see [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/study/NCT00154427), NCT00154427). The authors do not reference this study. On page 2 of the introduction, they merely state that 17 other randomized studies exist, but do not list them.
- 

2. There is a severe lack of standardization and objectivity in the study. Methods, page 3, states that the patients were transfused according to a standardized transfusion protocol. Yet, later in the methods section, it states that the transfusion was “at the discretion” of a treating physician. This is not a protocol. Other definitions in the methods section are far from objective: “significant compromise in systemic hemodynamics,” “assessment of the surgical and anesthetic teams,” “severe enough to prevent or postpone chest closure,” and “common decision of the surgical and intensivist teams.” In addition, the patient population is highly heterogenous, including both adults and children undergoing a wide spectrum of surgical procedures.
 3. Five of 43 patients died, and one of 43 patients had a stroke. These are serious numbers associated with this therapy, but the authors dismiss them, claiming that they didn’t think the agent was responsible. This reviewer finds such numbers not only alarming and worthy of further investigation, but consistent with other reports that rFVIIa is associated with end-organ damage and is therefore not a benign therapy. Such dismissals by the authors are yet another reason why a controlled, randomized study is needed.
 4. The discussion is rambling and unfocused.
- 



Example 3: Original text

Although bradykinin is known to play a major role in the pathophysiology of ACEi-induced angioedema, so far none pharmacotherapy is approved to treat acute ACEi induced angioedema.

To evaluate a possible causal treatment option, we have treated eight patients with acute ACEi-induced angioedema with pasteurized C1-INH (Berinert® P) and eighteen patients with the bradykinin B2 receptor blocker icatibant. Both drugs are well known treatment options in the bradykinin induced hereditary angioedema. The angioedema attacks are all localised in the upper aerodigestive tract.


In addition, we assessed retrospectively the clinical course of 48 patients who were treated in our clinic due to an ACEi-induced angioedema within the last seven years.

These patients were administered with prednisolone and clemastine.

Following treatment with icatibant complete symptom remission was reported on average after 4.8 hours (SD: 1.6 hours) on the other hand 10.4 hours (SD: 3.4 hours) after application of C1-INH and 32.8 hours (SD: 19.3 hours) after treatment with prednisolone and clemastine.

Our results indicate that icatibant is for the treatment of ACEi induced angioedema the therapy of choice. C1-INH concentrate could be a satisfied alternative in absence of icatibant. The potential effectiveness of icatibant and C1-INH concentrate must be verified in a randomized study.


Possible Concerns:

- ▶ Standardization of symptom evaluation
 - ▶ Conclusions based on data?
 - ▶ Use of English language
 - ▶ Use of logic
- 


Review

Summary: The authors report their findings from a case series of 26 patients presenting with ACEi-induced angioedema. Of these, 8 were treated with C1-INH concentrate, and 18 were treated with icatibant, a bradykinin B2 receptor antagonist. The primary outcome appears to be time until resolution of symptoms: authors report time to symptom improvement and complete resolution and compare these with historical controls managed conventionally with steroids and H2 blockers.

Major concerns: Angioedema is a potentially life-threatening complication of ACEi therapy. The authors report their findings using two novel approaches: C1-INH concentrate and icatibant, which have been used in the management of the related disorder, hereditary angioedema. The approach is therefore logical, and data such as this deserve to be in the literature. However, there are numerous deficiencies in the manuscript, most of which involve conclusions which are not supported by the data, logical contradictions, and very nonstandard use of the English language.



1. Abstract: The abstract makes statements which are simply wrong. For example, the authors state “***so far none pharmacotherapy is approved to treat acute ACEi induced angioedema.***” Aside from the grammatical error, there is conventional treatment for ACEi-induced angioedema and the authors reference it (steroids and antihistamines) in the group of historical controls. The authors also claim icatibant is the “treatment of choice” based on this case series. Treatments of choice do not arise from a single series of patients; treatments of choice reflect the consensus of the medical community at large, based on convincingly appropriate data.
2. Methods: It is unclear whether the same criteria for symptom resolution were followed for the treated cases and the historical controls. The physicians performing the patient assessment were not blinded to the therapy, and may have been authors, inducing a possible conflict of interest in patient assessment. These flaws severely undermine the validity of the data.
3. Discussion: The authors make speculative claims. For example, in paragraph 3 of page 10, “***This probably occurs faster ... because C1-INH avoids an accumulation of bradykinin...***” is totally speculative. Next, the authors discredit their dose selection, “***it must be noted that the used 1000 IU dose of C1-INH could be too minor.***” It is unclear why the authors chose a dose that they knew may be insufficient, yet then proceeded to make claims about its efficacy.


6. References: There are numerous nonstandard journal abbreviations.
 7. The entire text is riddled with countless awkward sentences, grammatical errors, unreferenced claims, and logical contradictions. For example, on page 5, the authors describe in detail the mechanism of ACEi-induced angioedema via bradykinin receptors, and then claim “the mechanisms of the pathophysiology of ACEi-induced angioedema is not known.” Also, on page 10, first paragraph, the authors claim “at such a long time interval one can assume that spontaneous remission has occurred.” This conclusion can only be drawn by comparison to a placebo control.
- 



Example 4: Original Text

Ultramini-Abstract:

The E-selectin gene (S128R) polymorphism resulting in weaker E-selectin ligand binding has been associated with higher platelet activity and increased thromboembolic events after cardiac surgery. This relation has not been influenced by perioperative procedures.




Example 4: Review

Review: JCTVS-09-1282 Effect of the E-selectin gene polymorphism S128R on platelet activation and acute thrombotic events after coronary artery surgery.

Summary: The authors present data from a cohort of 148 subjects presenting for elective coronary bypass surgery. Associations are made between the S128R polymorphism of e-selectin, circulating markers of platelet activation (beta-thromboglobulin), and the incidence of postoperative thrombotic complications.


Major Concerns: While the authors have selected an appropriate candidate gene and an appropriate population for study, the methodology has numerous gaps, and falls significantly short of what should be expected for a genetic association study.



1. Study population: Importantly, the ethnicity of the cohort is not described. This is essential for any genetic association study because ethnic structure within the study population can easily skew the results. Also, it is not known whether these subjects were enrolled sequentially, or with some preference to particular surgeons or other practitioners. The authors need to clarify that the enrollment was not biased by disease severity or other factors.
2. Genotyping methods: The polymorphism under study was not in Hardy-Weinberg equilibrium. This suggests indirectly that there was an error in the genotyping methodology or that there was some inherent selection bias in the study population.
3. Blood sampling: The samples for beta-thromboglobulin and other assays were drawn 18-24 hours after the operation. This is a rather wide time window since many plasma levels are changing significantly in the postoperative period and consequently this induces unquantifiable variability in the results.
4. Definition of clinical endpoints: The endpoints of MI, stroke, pulmonary embolism, and death due to MI are not defined. These need to be clarified in terms of troponin levels, ECG changes, pulmonary angiogram, perfusion scan, neurologic exam, autopsy, and so forth. They need to be defined so specifically that another investigator in another institution could reasonably duplicate the findings. In the present study, there is absolutely no specification regarding how these endpoints were measured.
5. Postoperative management: It is also unclear whether or not many preoperative medications were continued in the immediate postoperative period. Medications such as beta blockers, statins, and ACE inhibitors may strongly impact thrombotic risk, yet no mention is made regarding whether these were continued postoperatively.
6. Statistical model: The authors perform a logistic regression analysis, but do not present the statistical model. It is important to clarify how the model was constructed (which covariates were selected, stepwise forward or backward methods, forcing covariates into the model, etc), and present the final mathematical model, along with an estimate of how much variability is explained by the independent variables. Again, this must be done with enough clarity that any other investigator could reasonably reproduce the statistical analysis.



Minor Edits

- ▶ Decision to reject / revision / accept does not depend on these
 - ▶ English language!
 - ▶ Figures and legends clear
 - ▶ Consistency in terminology
 - ▶ Use of jargon
 - ▶ Reference style
- 

Notes to Editor

- ▶ Regarding acceptance:

“They need to fix XXX or you should reject. This is crucial.”

- ▶ Regarding the revision:

“I’m willing (or not willing) to review the revision.”

- ▶ Ethical concerns:

“I’m concerned about the human subjects approval.”

- ▶ Editorial suggestions:

“I recommend an editorial or review article to accompany this paper. I suggest XXX as the author for the editorial.”



Additional Advice

- ▶ Be professional
 - ▶ Be prompt
 - ▶ Avoid auto-aggrandizement
 - ▶ Be honest
 - ▶ Be constructive where you can
 - ▶ Be specific with criticism
- 