ESPRIT Trial

by Khanh Nguyen 2010 Pharm.D. Candidate, Caterina Equinozio 2009 Pharm.D. Candidate, and Craig Stern, Pharm.D., MBA

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The ESPRIT* study was conducted in order to resolve inconsistent results from previous trials that evaluated the effectiveness of commonly used therapies in patients who had an ischemic stroke of presumed arterial origin within the past six months. The trial compared aspirin plus dipyridamole therapy versus aspirin alone in order to determine which therapy is more effective in the secondary prevention of vascular events. The primary outcome measure was the composite of deaths from all vascular causes, non fatal stroke, non-fatal myocardial infarction, or major bleeding complication. Authors of the study concluded that the combination regimen of dipyridamole and aspirin was a superior antithrombotic therapy in comparison to aspirin alone. The purpose of this evidence-based evaluation of ESPRIT is to determine if it is a valid and useful addition to a health care

Element	Criteria	Comments
Study Design Assessment	Is the design appropriate to the research question?	ESPRIT had an open label randomized controlled study design to assess treatment strategies for the prevention of stroke. ***THREAT***: Open label trials can lead to a significant bias and misrepresentation of outcome measures.
Selection Bias	Are groups truly randomized (concealment of allocation strategies, similar group characteristics, etc.)?	Treatment was allocated by means of computer generated randomization codes. ***THREAT***: Unclear if concealment of allocation was carried out in order to preserve true randomization and minimize direction of participants into a particular group.
Performance Bias	Has double-blinding been successfully employed? Are there any other performance biases such as differences between groups, except for what is under study?	***THREAT***: This study was not double blinded. ***THREAT***: Both the lack of blinding as well as the presence of other potentially confounding factors (e.g., possible differences in use of concomitant medications, possible differences in how the groups experienced their care or were treated by non-blinded clinicians) may have resulted in distortion of the study results.
Attrition Bias	Are there any missing data points?	***THREAT***: 34% of patients taking the combination therapy discontinued medication, mostly due to adverse effects and 13% of patients on aspirin alone discontinued treatment, mostly due to a medical reason. The large numbers of loss itself threatens the internal validity of the study. ***THREAT***: Dropouts in the combination group were more than double those in the aspirin only group. There is a significant differential of loss between the groups.
Assessment Bias	Are assessors blinded? What is the likelihood of findings due to chance? Is there statistical significance and do confidence intervals support conclusions? Intention-to-treat analysis? Modeling?	The investigators had no knowledge of the treatment allocation and the result was statistically significant using the reported intention-to-treat (ITT) analysis. ***THREAT***: Not a true ITT analysis. The number of drop outs was very significant. There was not enough information regarding missing data points except for Cox proportional hazard ratios. These factors have a significant potential to distort outcomes.
Usefulness Assessment	Is there a clinically significant area and sufficient benefit size?	***THREAT***: Although the study focused on a clinically significant area, the marginal risk reduction of treatment, along with the significant threats to validity, indicate that the benefit size is not sufficient to ascertain the clinical utility of one treatment over the other.
External Validity	How likely are research results to be realized in the real world?	***THREAT***: Due to the considerable flaws in the study that pose extensive threats to internal validity, an evaluation of external validity is not appropriate.

**ESPRIT = European/Australasian Stroke Prevention in Reversible Ischaemia Trial*

*** Performance bias definition - Bias present in the intervention or care procedures or other study performance. Frequently this is a bias that can result when there are difference in care other than the intervention under study. For more information, visit: www.delfini.org/page_Glossary.htm*

provider's resources when treating for the secondary prevention of stroke.

Author's Results and Conclusions: Mean follow-up time per patient was 3.5 years. Median aspirin dose was 75mg in both treatment groups with a range of 30 – 325mg; extended-release dipyridamole was used by 83% of patients on the combination regimen. Primary outcome events arose in 173 (13%) patients on aspirin and dipyridamole and in 216 (16%) on aspirin alone. Patients on aspirin and dipyridamole discontinued trial medication more often than those on aspirin alone (470 vs. 184), mainly because of headache, an adverse reaction. The authors of the study concluded that the combination regimen of aspirin and dipyridamole is preferred over aspirin alone as an antithrombotic therapy after cerebral ischaemia of arterial origin.

Reviewer's Conclusion: Although the ESPRIT trial focused on a clinically significant area of study, the threats to validity limit its application in clinical practice. The open design of the study is an inherent flaw of the study that introduces participant and investigator bias from the very beginning of the trial and raises concerns about the ability to accurately interpret the results. The flawed methodology includes lack of standardized aspirin doses and dipyridamole dosage forms. The wide range in aspirin dosing (30-325mg) created variation within the groups, from low doses that may be sub-therapeutic to high doses that may result in greater adverse effects. The use of different formulations of dipyridamole (regular vs. extended-release) created additional disparity. It is unclear whether or not allocation of treatment was concealed and this has the potential to create a selection bias in the trial. Additional selection bias is due to the modification of the randomization scheme part way through the study in which the 3-arm scheme (anticoagulation vs. aspirin with dipyridamole vs. aspirin alone) was switched to the 2-arm scheme used (aspirin with dipyridamole vs. aspirin alone) for this analysis. Performance bias is a significant threat to the internal validity of the study. Both the lack of blinding as well as confounding factors (eg: protective concomitant and non-blinded clinicians who may treat patients in the groups differently) create potential differences in the groups, limiting confidence in the study findings because biases can result in distortion of study results. The significant number of drop outs, both within each group and as a comparison of the differential between the two groups, demonstrates a significant attrition bias. Intention-to-treat analysis attempts to limit the bias created by drop outs and increase internal validity, however, the large number of drop outs and significant amount of missing data in the combination therapy group limits the intention-to-treat analysis and may weaken the validity of the results. The significant flaws in the study contribute to major threats to internal validity. These threats, along with marginally statistically significant results, do not provide enough evidence

Delfini Evidence Grading Scale
Grade A Evidence: Useful The evidence is strong and appears sufficient to use in making health care decisions - it is both valid and useful (e.g., meets standards for clinical significance, sufficient magnitude of effect size, physician and patient acceptability, etc.).
Grade B Evidence: Probably Useful The evidence appears potentially strong and is probably sufficient to use in making health care decisions - some threats to validity were identified.
Grade B-U Evidence: Possible to Uncertain Usefulness The evidence might be sufficient to use in making health care decisions; however, there remains sufficient uncertainty that the evidence cannot fully reach a Grade B and the uncertainty is not great enough to fully warrant a Grade U-sufficient threats to validity place the study into a "borderline" category.
Grade U Evidence: Uncertain Usefulness
There is sufficient uncertainty that caution is urged regarding its use in making health care decisions. Modified from Delfini Evidence Grading Tool.© Delfini Group, LLC, 2005-2008. All Rights Reserved World Wide.

to assert one form of treatment over the other. Overall, the ESPRIT trial does not provide sufficient evidence to conclude that there is an advantage of one treatment over the other when comparing aspirin with dipyridamole versus aspirin alone for the secondary prevention of vascular events.

Overall Grade: U = Uncertain in validity and usefulness.

About the Authors & Guest Editors

Khanh Nguyen and Caterina Equinozio are both 2009 Pharm. D. Candidates at the USC School of Pharmacy. Craig Stern, Pharm. D., MBA is President of ProPharma Pharmaceutical Consultants, Inc. and the current CPhA ERC Chair.

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The content expertise of Dr. Michael E. Stuart and Sheri A. Strite of Delfini Group is well-documented. To learn more, visit www.delifini.org.

References

ESPRIT Study Group. Halkes PH. van Gijn J. Kappelle LJ. Koudstaal PJ. Algra A. Aspirin plus dipyridamole versus aspirin alone after cerebral ischaemia of arterial origin (ESPRIT). Lancet. 367(9523):1665-73, 2006 May 20.

Chart adapted from Delfini Group,LLC. Short Critical Appraisal Checklist