Rapid Resource

Anticoagulation FORUM | ANTICOAGULATION Centers of Excellence

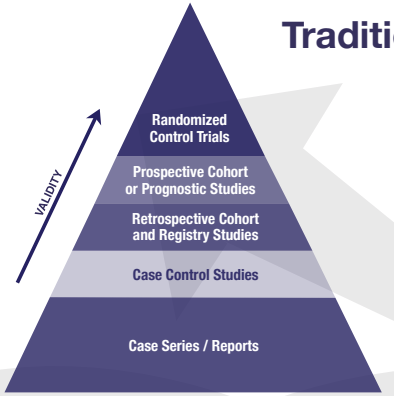
Evaluation of Comparative Therapy Literature

excellence.acforum.org

Background: In the era of evidenced based medicine (EBM), clinicians need to understand how to critically evaluate medical literature. While hierarchies of medical evidence based on study design have been well established and provide an appropriate foundation to begin assessing medical literature, it is important for clinicians to be aware of and able to evaluate other factors that may affect the quality and strength of evidence which are independent of study design such as methodological limitations, imprecision, inconsistency and indirectness. This resource provides an overview of the different types of study designs and is intended as a tool to assist clinicians in critically evaluating and assessing the quality of various forms of medical literature.

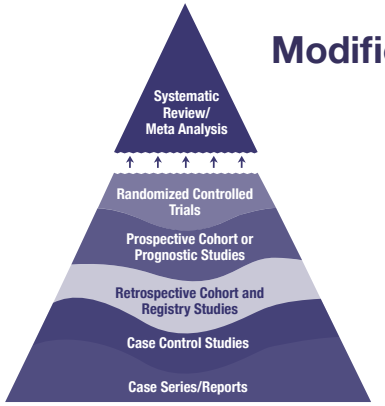
Hierarchy of Medical Evidence Based on Study Design

Traditional Evidence-Based Pyramid



The traditional evidence-based pyramid visualized the hierarchy of evidence by placing weaker study designs at the bottom and graduating to stronger study designs as one approached the top. While the traditional pyramid represented a hierarchy of internal validity, it was deemed to be too simplistic as it did not account for study limitations and methodological designs.[1]

Modified Evidence-Based Pyramid



The modified evidence-based pyramid accounts for the various domains of the quality of evidence, as study design appears to be insufficient on its own as a surrogate for risk of bias. Additionally, the quality of evidence of any study can also be affected by factors that are independent of study design such as methodological limitations, imprecision, inconsistency, and indirectness.[1]

Overview of Study Design

Type	Description	Utilization	Advantages	Limitations	Examples
Observational Studies					
Case Report Case Series	Description of a single or several patients	Rare events where data is limited	Can help identify new diseases or treatments	Very limited data, no comparison	Vaccine induced immune thrombotic thrombocytopenia (VITT)
Case Control	Cases are identified and 'matched' to control	Attempting to establish a link between an 'exposure' and disease	Quick and relatively inexpensive	Can never match on all risk factors Research in reverse—starts with disease and then looks for a risk	Patients that had recurrent intracranial bleeding after restarting warfarin are matched to those that restarted a direct oral anticoagulant (DOAC)
Retrospective Cohort	In comparative effectiveness studies, two or more groups of patients are compared	Effectiveness of two treatments when no head-to-head randomized trials are available	Faster and less expensive than prospective cohort studies because the data is already available	Missing data due to reliance on what is documented, which can affect completeness of outcome ascertainment, & limitations of important prognostic factors	Comparing efficacy and safety of one DOAC to another
Prospective Cohort Studies	May not have a comparison group but still 'experimental' if a new treatment is used or an established treatment is used in a new manner	To get an estimate on safety and efficacy of new treatment (i.e., new drug or new way to use an established treatment/drug) when there is no established standard treatment for comparison	More complete outcome ascertainment due to patient consent, allowing collection of important comorbidities that might not be documented otherwise Well-done cohort studies MAY yield stronger evidence than a poorly conducted randomized trial Useful for a new treatment when there is not a standard for comparison	Selection bias of patients can result in different treatment options chosen based on patient characteristics which will make the groups dissimilar Unable to control for all variables/confounders	Specific DOAC reversal agents Use of a specific DOAC periprocedural interruption protocol
Interventional Studies					
Randomized Trials	The gold standard for comparing treatments	New drug development or comparing approved treatment	Randomization is the best opportunity to have patients in each group be similar for risk factors that are known and unknown	Often the most expensive and time-consuming type of study/trial Trial population may not be truly reflective of the general population based on inclusion and exclusion criteria	DOAC development and approval

Overview of Study Design

Type	Description	Utilization	Advantages	Limitations	Examples
Reviews					
Systematic Review	Compilation of studies related to the clinical question	Overview of a treatment	Can give a broader picture of a treatment effect	Not all systematic reviews are rigorous, include a 'protocol' for the review, or follow guidelines on how to do a good review	Narrative reviews might not be rigorous but can provide an overview of a topic Rigorous reviews can serve as a foundation for guidelines & at times, pool data for comparative effectiveness
Meta-analysis	Based on a systematic review that pools data	Comparing the relative effect of two treatments from multiple studies Can be done from both observational and interventional studies or a combination of both	Gives a broader sense of the magnitude of treatments by pooling results from multiple studies	Identified studies used to pool data should be based on a rigorous systematic review and treatments in each study should be similar to warrant combining the studies	DOAC vs. warfarin in atrial fibrillation
Guidance Statements	Expert opinion guidance based on the available evidence	When treatments are evolving or data is sparse	Quick and nimble	Expert opinion can be biased and data supporting suggestions/recommendations might be weak	Guidance early in the COVID pandemic on use of prophylactic anticoagulation
Guidelines	Should be based on rigorous systematic reviews Rigorous rules on the selection of panel members to mitigate bias	Helps set treatment standards	Summary of recommendations and suggestions with discussion on strength of evidence	Can take a long time to develop and new data can emerge between updates	Guidelines may help inform treatment decisions, however, even in well-done guidelines, most options are suggestions and not recommendations due to limited/lacking evidence to support firm recommendations

Overview of Factors that Impact the Quality of Evidence[3]

Factors that may REDUCE the quality of evidence						Factors that may INCREASE the quality of evidence	
Risk of Bias	Inconsistency	Indirectness	Imprecision	Publication Bias	Confounding	Dose Response	Magnitude of Effect
Factors that can systematically affect the observations and conclusions of a study to cause them to be incorrect. Several types of biases exist. Click here for detailed overview.	**Unexplained heterogeneity or variability of results across studies. The quality of evidence is reduced when inconsistency is large or unexplained.**	Directness refers to research that directly compares interventions of interest, that are applied to populations of interest, and which measure outcomes important to patients. The quality of evidence may increase the more direct the comparisons are and decrease if indirectness is present.	Results of a study are considered imprecise when there is a wide 95% confidence interval around the estimate of the effect, which leads to uncertainty about the results.	Occurs when there is failure to publish the results of a study based on the direction or strength of the study findings.	Observational studies are generally associated with providing only low-quality evidence due to residual confounding or bias (i.e., unmeasured or unknown determinants of outcome unaccounted for in the adjusted analysis that are likely to be distributed unequally between intervention and control groups)	Dose gradient response is an important criterion for believing a presumed cause-effect relationship. For example, the observation that, in patients receiving anticoagulation with warfarin, there is a dose response gradient between higher levels of the international normalized ratio (INR), an indicator of the degree of anticoagulation, and an increased risk of bleeding, improves confidence that supratherapeutic anticoagulation levels increase bleeding risk.	Confidence in results is increased when a body of evidence from observational studies yields large or very large estimates in cases where 1) the effect is rapid and/or consistent across subjects, 2) previous trajectory of disease is reversed, and/or 3) the effect is supported by indirect evidence.

References: 1. Murad MH, et. al. New evidence pyramid. Evid Based Med. 2016 Aug;21(4):125-7. PMID: 27339128 2. Wang X, Kattan MW. Cohort Studies: Design, Analysis, and Reporting. Chest. 2020 Jul;158(1S):S72-S78. PMID 32658655 3. Schünemann, H., Brożek, J., Guyatt, G., & Oxman, A. (2013, October). GRADE Handbook. Accessed. June 5, 2023. https://gradepro.org/handbook/

Faculty: Bishoy Ragheb, PharmD, BCACP, CACP | Gabe Fontaine, PharmD, MBA, BCCCP, BCPS | Scott Kaatz, DO, MSc

This content was developed independently by the Anticoagulation Forum. Support for this project provided by AstraZeneca.

Last updated 6/2023