Chapter

1

Introduction to Anticoagulation Management

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INTRODUCTION

In the setting where anticoagulation therapy is necessary, clinicians are faced with the challenge of utilizing agents that inherently have a small therapeutic window and the ability for medication mishaps when not used appropriately. However, this risk is balanced against the need to prevent against or treat thrombosis, which can also have life altering consequences. Therefore, clinicians utilizing anticoagulants must not only have a firm grasp of the pharmacology and pharmacokinetics of the agents they are utilizing, but they must also be current with the evidence regarding their use and understand how an individual patient's situation can influence management decisions.

This reference book was developed with these challenges in mind in order to seed thoughts and provide information that assists the clinician in assuring the safe and optimal use of anticoagulants. The information in the chapters is intended to provide key concepts based on the literature and experiences of the authors when evidence is more limited. Evidence-based recommendations by expert panels are included when available. This handbook is intended to provide insights that can assist in decision process and not to replace the clinician's judgment.

JOINT COMMISSION NATIONAL PATIENT SAFETY GOALS (NPSGS) FOR ANTICOAGULATION, 2010 VERSION (NPSG 03.05.01, FORMALLY NPSG 3E)[1]

- Because of the high incidence of reported adverse event rates associated with anticoagulation therapy or suboptimal approaches to prevention of VTE,

several regulatory agencies have initiated processes to address their concerns. One example is the NPSGs issued by the Joint Commission. The primary goal of the anticoagulation NPSGs is to reduce the likelihood of patient harm associated with the use of anticoagulant therapy.

- The full text and requirements of the NPSGs can be found at http://www.jointcommission.org/standards_information/npsgs.aspx.
- Of note is that the NPSGs are driven by the frequency of reported adverse events associated with anticoagulation therapy. Thus, newer agents, or infrequently used agents may not receive as much attention or regulatory oversight. This does not necessarily make their use any less challenging.

TABLE OF USEFUL RESOURCES

Table 1-1: Resources Involving Anticoagulation Therapy

Reference	Website	Comment
ACCP guidelines	http://chestjournal.chestpubs.org/content/133/6_suppl	The oldest and most established evidence-based guideline involving antithrombotic therapy
AHA guidelines	http://my.americanheart.org/professional/guidelines.jsp	The American Heart Association regularly published guidelines that cover different arterial disease states, often in conjunction with other societies
FDA	http://www.fda.gov/	The FDA regularly posts any alerts concerning marketed medications and materials that are reviewed by advisory committees
Clinical Trials.gov	http://www.clinicaltrials.gov/	Describes current clinical trials being conducted
PubMed	http://www.ncbi.nlm.nih.gov/pubmed/	Excellent free site available for searching Medline from the United States National Library of Medicine

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Table 1-1: (Continued)

Reference	Website	Comment
Anticoagulation Forum	http://www.acforum.org/	Multidisciplinary professional organization for those who manage anticoagulation therapy; helpful clinical resources are posted on the site
ClotCare	http://www.clotcare.com/clotcare/index.aspx	Regularly updated site mainly focused on keeping professionals abreast of cutting edge information involving antithrombotic therapy; site also does contain helpful information for patients

TOOLS FOR SUCCESS

Considerations in applying professional organizations' expert evidence-based guidelines to patient care:

- Expert panels representing the American College of Chest Physicians (ACCP) and American Heart Association (AHA) (published in conjunction with the American College of Cardiology (ACC)) have provided evidence-based recommendations to aid clinicians in selecting appropriate patient care. Often, these guidelines are considered the final word. Adherence to these guidelines by nature ignores how an individual patient situation may cause variance from the guidelines. It should be kept in mind that such guidelines are established based on the strength of the evidence available. In many cases, evidence or trials may have not included selected situations or populations, or negative experiences were not published. Clinicians need to view and use these guidelines as they are intended; evidence-based tools designed (or developed) to aid in patient care.
- The following tables explain the evidence ranking system of the both ACCP and AHA guidelines. These evidence grades are extensively mentioned in subsequent chapters.

Table 1-2: Interpreting the ACCP Antithrombotic and Thrombolytic Therapy Evidence-Based Clinical Practice Guidelines Evidence Grades[2,a]

Grade of Recommendation (recommendation strength/evidence grade)	Quality of Evidence	Implications
1A	Consistent findings from randomized clinical trials (RCTs) or extremely strong evidence from observational studies	Recommendation applies to most patients in most situations
1B	RCTs that have important limitations or strong evidence from observational studies	Recommendation applies to most patients in most situations
1C	At least one important outcome has been assessed in case series, observational studies, or from a seriously flawed RCTs; indirect evidence also can be used	Recommendation applies to most patients in many situations
2A	Consistent findings from randomized clinical trials (RCTs) or extremely strong evidence from observational studies	The appropriate treatment may vary based on patient/ society values
2B	RCTs have important limitations or strong evidence from observational studies	The appropriate treatment may vary based on patient/ society values
2C	At least one important outcome has been assessed in case series, observational studies, or from a seriously flawed RCTs; indirect evidence also can be used	Other treatment options may be equally desirable

[a]Grade 1 recommendations are considered "strong" recommendations and grade 2 are considered "weak" recommendations. Grade A evidence comes from RCTs or observational studies with very large effects. Grade B evidence comes from RCTs with limitations or strong evidence from observational trials. Grade C evidence comes from observational trials or RCTs with major limitations.

Table 1-3: Interpreting the ACC/AHA Evidence Grades Used in Scientific Statements[3]

Grade of Recommendation (class/evidence grade)	Quality of Evidence
1 (A)	Strong recommendation that a treatment or procedure is helpful; robust supporting data
1 (B)	Strong recommendation that a treatment or procedure is helpful; more limited supporting data
1 (C)	Strong recommendation that a treatment or procedure is helpful; largely based on expert opinion, standard of care, or case studies
IIa (A)	Recommendation that a treatment or procedure is helpful; data available contains some conflicting evidence
IIa (B)	Recommendation that a treatment or procedure is helpful; data available contains some conflicting evidence
IIa (C)	Recommendation that a treatment or procedure is helpful; largely based on expert opinion, standard of care, or case studies
IIb (A)	Recommendation that a treatment or procedure may be considered; supporting data contains significant conflicting evidence
IIb (B)	Recommendation that a treatment or procedure may be considered; available data contains significant conflicting evidence
IIb (C)	Recommendation that a treatment or procedure may be considered; largely based on expert opinion, standard of care, or case studies
III (A)	Recommendation that a treatment or procedure should *not* be considered; robust supporting data
III (B)	Recommendation that a treatment or procedure should *not* be considered; more limited supporting data
III (C)	Recommendation that a treatment or procedure should *not* be considered; largely based on expert opinion, standard of care, or case studies

Considerations when evaluating clinical trials involving anticoagulants

- Clinical trials frequently have preselected inclusion and exclusion criteria that create a focus for the concept being studied. In many cases with anticoagulation therapy, patient groups (advanced age, bleeding history, organ dysfunction, critically ill, hypercoagulable condition) initially excluded from the clinical trials may receive the therapy. Clinicians should consider that trials serve as a foundation to managing thrombosis, but that excluded populations may respond differently to a given therapy.
- Anticoagulants or reversal therapies may frequently be used in conditions where the agent has not been adequately explored. The limited evidence with such "off-label" use should be used with caution, with consideration that the optimal dose, duration or approach to their use in such settings has not been determined.
- In many situations, current approaches to anticoagulation regimens have evolved based on postmarketing experiences. Populations originally excluded in the clinical trials may provide signals on how therapies may need to be adapted. In some settings, limited single center case reports where no additional information exists may drive practice. In others, concepts based in theory but not yet validated (e.g., overlapping parenteral anticoagulants for two additional days after the INR on warfarin is over 2) are utilized.
- When reviewing data derived from observations collected from registries, the reviewer should consider the voluntary structure and potential cleaning of data prior to submission to eliminate any perception of poor management. The coding of the information prior to being extrapolated may also create certain bias, or limitations on the quality of the research.

Table 1-4: Additional Considerations When Evaluating Clinical Trials

Concept	Comment
Population studied	• The inclusion and exclusion criteria describe who was or was not studied in the analysis. Be sure the patients you are considering for therapy based on the trial would have been included. • The number of eligible subjects vs. those actually studied can also describe potential challenges in repeating the observations in the general population.

(*continued*)

Table 1-4: (Continued)

Concept	Comment
Methods	• The methods should be cross compared to the setting of the study. For example, ethnic differences in a region or the assay used may create results that may have some limitations when being implemented in a different setting.
Results	• Many of the new trials involving anticoagulants are "noninferiority" in design. If the medication is found to be "noninferior" to the comparator, be sure to carefully review the noninferiority criteria to assure it is appropriate. Also, when compared to warfarin, how well controlled was the warfarin? • Carefully consider the clinical significance of the primary endpoint of the trials. For example, many orthopedic trials commonly include venographically derived asymptomatic DVT, which many would argue is not as clinically significant as symptomatic DVT/PE. These results may be "statistically significant," but that is very different than "clinically significant." • Data should be carefully assessed for "robustness." Were any signals present suggesting different outcomes within the study population? Who was excluded? Where additional analysis done to confirm the primary endpoint findings or conclusions made? • Was any subgroup analysis included in the initial study design, or was it derived posthoc to create a positive spin on the study. Caution should be exercised if considering applying post hoc analysis to patient care. • When assessing a clinical observation or reported result, consider the potential error in the data. Single, unexpected, or atypical observations should be confirmed with additional analysis. • Trends in data that support a result create a higher level of confidence than the single outlier.
Limitations	Be sure the study clearly identifies the limitations of the analysis. The study should attempt to describe how the limitations affect interpretation/application of the results. It is also helpful if they have done additional data analysis to assess the impact of the limitations.
Summary/conclusion	Be sure the conclusion is appropriate considering the data and its limitations. Often, conclusions overreach the observed result, ignoring important limitations, which could potentially harm patients if applied without this consideration.

Meta-analysis interpretation cautions

- Guidelines strive to incorporate the best evidence available when developing recommendations. This frequently can be influenced by meta-analysis that explores similar trials. It should be kept in mind that trials may not be published, particularly small negative trials. This can create a literature base that is influenced by positive outcomes. In some cases, single large trials may dominate the observations. Such data basis should utilize concepts such a funnel plots to describe any potential bias in the data base. (See reference 4 for an example of how this can help detect publication bias.)[4]
- Differences in the approach to the study and the patients actually studied may have influenced the variable results reported in the meta-analysis. These trials, while having enough power to detect small treatment effects, often include a diverse population of patients by their nature.
- Medical advances in both technology and management approaches over time can independently influence outcomes. Since trials included in a meta-analysis are usually conducted during different time periods, this can create challenges in interpreting the results.

Treat the patient and consider all of the patient's potential needs

- Each patient is unique, and clinicians will combine their knowledge and experience along with resources, such as this handbook, to derive and adapt anticoagulation therapy. In many cases, deficiencies in the information used limit its application. Lab results or other surrogate markers may not be validated to hard outcomes of bleeding, thrombosis, morbidity, or death. Quality of life or limitations such as the ability to be adherent to the management plan, affordability of the therapy, or monitoring can influence management plans.
  - Observations away from the bedside may not always agree with the patient presentation. For example, increasing the level of anticoagulation based on laboratory results may not be optimal if the patient is bleeding. The lab test is intended to lend assistance in determining appropriate patient management and must not be interpreted apart from the individual patient situation. Caution should be considered with the management of anticoagulation therapy by assessing information solely from a computer screen, even in facilities with the most advanced electronic medical record systems. Critical information (bleeding, consideration

for an LP, potential invasive procedures) may be missed, due to delay in availability or ommission of information. This can limit the level of care provided.

  - Just because something is ordered does not mean the intended therapy is carried out. Handing out a prescription or order where hurdles to fulfill the prescription exist may delay or prevent therapy. (Classic example is the patient never filling the prescription when he or she leaves the hospital.)
  - Even when a patient is handed a dose, this does not always equate to the patient taking it. In time, this may be discovered by a lack of INR response to warfarin. One consideration is to assure the therapy is administered is by requesting nurse/family to witness swallowing of the medication.
  - When arranging ambulatory anticoagulation patient care followup, has the treatment team determined if the patient can get the prescribed followup laboratory monitoring? Are they capable of utilizing the medication prescribed, including injectables? Is the patient able to afford the prescribed medication regimen?

- The level of patient acuity should be considered. Clinical trials may not have explored critically ill patients, yet the therapy may be regularly used in such a population. Management plans may at times be short-term and should be adapted as changes occur. In many cases, therapy involves multiple agents or changing settings. A management plan should consider both short- and long-term goals, and what options are available. Sometimes, the agent chosen in a management plan may not be the one that is "best" based on evidence, but instead the agent that is most likely to succeed considering the patient's individual situation.
  - Often, newer agents may be preferable, but if financially unreasonable for the patient, could lead to suboptimal results.
  - Patients are often moving in or out of different care settings during therapy. This can influence the choice of agents utilized in the management plan.
  - Management should consider how the patient is clinically changing in interfering factors such as interacting drugs or disease states and adapt as necessary.
- Practitioners who also have practice management responsibilities should strive to break down transitional care barriers that lead to unsafe care. When patients are admitted, it is important to obtain an accurate medication history. This is particularly critical regarding their antithrombotic drug therapy, which is

often taken from electronic records and may not be current with the patients' actual regimen. Patients being discharged should be promptly handed off to the responsible managing clinician, with critical information relayed. The clinician needs to understand how the inpatient care experience may have influenced the patients' antithrombotic therapy needs. This is a particularly high-risk time period in the patients' therapy, and too often, patients do not understand their individual management plan, which leads to adverse drug events. Further, it also common for the medication reconciliation process to not be completed correctly at discharge. For example, patients can be put back on their home warfarin dosing (assuming it was correctly identified at admission!), which is no longer clinically appropriate considering their condition at discharge. Others may revise the regimen based on an altered response during an acute illness (elevated INR during acute decompensated heart failure or an infection), and not re-adjust the dose back once the patients baseline has been reestablished (heart failure or infection resolved). In this situation, a period of catch up may occur after discharge.

- Each patient is unique and hence a special population. However, generalizations of certain clinical situations create a "special management population." Examples include the elderly patients, pediatric patients, critically ill patients, patients with certain concurrent disease states, patients with a hypercoagulable condition, patients with multiple indications for anticoagulation, impaired organ function, etc. These patient populations are frequently discussed in this text.

REFERENCES

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