SECOND EDITION

Anticoagulation Therapy

A CLINICAL PRACTICE GUIDE

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DEDICATION

Without the continuous support and encouragement from family, colleagues, students, and residents, this book—now in its second edition—could never have come to fruition.

To all the patients who have needed our services and desire to learn and improve their care.

Edith

To my parents who instilled a work ethic and passion to serve others. For my wife Karen and children William R, Jessica, and Laura for their constant encouragement and understanding throughout the years: I am forever grateful.

Bill

To my parents, Daniel and Constance Gulseth: Thank you for showing me the path to take on life—living faithfully, cherishing family, and pursuing worthy opportunities.

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PREFACE

Ensuring the safe and appropriate use of anticoagulants continues to be major challenge. Despite the release of the direct-acting oral anticoagulants (DOACs), which many hoped would improve patient safety, in 2016 the U.S. Food and Drug Administration (FDA) Adverse Event Reporting System received 18,878 reports of anticoagulant-related serious injury and 3018 deaths.[1] In a recent study by the Centers for Disease Control and Prevention, anticoagulants accounted for 17.6% of all U.S. emergency department visits, and nearly half of these patients needed to be hospitalized.[2] The increasing complexity of patients and advances in technologies, such as cardiac circulatory devices, has made anticoagulant management approaches even more challenging. We (the editors) are clinicians and face the challenge of using anticoagulants in a safe and effective way on a daily basis. From this experience, we decided now was the right time to update our practical guide on anticoagulation drug therapy. Our goal is to give the clinician quick access to evidence-based and/or expert opinion information for the challenging clinical situations they may face.

New features of this second edition include:

- Extensive new information on the DOACs—most agents were not approved when the first edition was written
- Expanded information on anticoagulation reversal due to the release of DOACs and expanded options in management
- Five new chapters on the following topics:
    - Use of anticoagulants, including DOACs, in special patient populations
    - Use of anticoagulants in patients with mechanical devices
    - Anticoagulation care delivery standards, regulatory issues, and practice resources beyond this text
- Three new appendixes covering:
    - Nutritional influences with anticoagulation, types of central nervous system hemorrhage, and transitioning heparin measurements using the anti-factor Xa instead of the aPTT

As with the first edition, the book is:

- *Light on text.* The amount of "book style text" was intentionally minimized so a clinician did not have to read a whole chapter to find the "one nugget" they were seeking.
- *Heavy on tables/figures.* Our hope is that this allows the clinician to rapidly find the answers they are seeking.
- *Easy to find key points.* Clinical pearls and highlighted key references make it easy to find critical information.
- *Easy to digest.* The use of bullets and clinical pearl examples both present the information in a succinct fashion, and highlight how the information applies to real-life care.
- *Comprehensive.* Although no text can cover every foreseeable topic, this book covers a lot of the potential challenges that clinicians face.

- *Expertly written.* All the authors are experts in the areas in which they are writing, and all chapters were carefully reviewed by the editors including the chapters written by other editors.
- *Applicable to patients across the continuum of care.* This book covers topics as diverse as how to care for the ambulatory patient in need of anticoagulation bridging for an invasive procedure to the pediatric patient on extracorporeal membrane oxygenation.
- *Useful to a broad scope of disciplines.* This handbook was intentionally designed to be a useful guide for clinicians in any discipline caring for patients on anticoagulation therapy.

The editors are deeply indebted to the authors who were *again* willing to take on one more project and provide their expertise to improve the care of patients receiving anticoagulation therapy. We can never repay them for the time they took away from family and other professional commitments.

Finally, as with the first edition, we must say thank you to all clinicians who tackle the challenges these medications pose on a daily basis. There is no such thing as a "safe" anticoagulant, yet your efforts are what ensure that these agents are used "safely" and in an evidence-based fashion. For that, we wish to thank you on behalf of your patients.

William E. Dager
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Edith A. Nutescu

References

1. Part II: oral anticoagulants—the nation's top risk of acute injury from drugs. *Acute Care ISMP Medication Safety Alert!* July 27, 2017;22(15):1-4.
2. Shehab N, Lovegrove MC, Geller AI, et al. U.S. Emergency Department Visits for Outpatient Adverse Drug Events, 2013–2014. *JAMA.* Nov 22 2016;316(20):2115-2125.

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ABBREVIATIONS

A	apixaban
AAOS	American Association of Orthopedic Surgery
AAP	American Academy of Pediatrics
ACA	anticardiolipin antibody (also often abbreviated as aCL)
ACC	American College of Cardiology
ACC/AHA	American College of Cardiology/American Heart Association
ACCP	American College of Chest Physicians
ACS	acute coronary syndrome
ACT	activated clotting time
AF	atrial fibrillation
AFFIRM	Atrial Fibrillation Follow-up Investigation of Rhythm Management
AHA	American Heart Association
AHA/ASA	American Heart Association/American Stroke Association
AIS	arterial ischemic stroke
ALL	acute lymphoblastic leukemia
ALT	alanine aminotransferase
AMI	acute myocardial infarction
AP	antiplatelet
APC	activated protein C
APLA syndrome	antiphospholipid antibody syndrome (also often abbreviated APS and APLS)
APLAs	antiphospholipid antibodies
aPTT	activated partial thromboplastin time
ASA	aspirin
ASSENT	Assessment of the Safety and Efficacy of a New Thrombolytic
AST	aspartate aminotransferase
AT	antithrombin
AUC	area under the serum concentration versus time curve
AVR	aortic valve replacement
BID	twice daily dosing
BMI	body mass index
BP	blood pressure

CABG	coronary artery bypass graft
CAD	coronary artery disease
CAP	College of American Pathologists
CBC	complete blood count (including platelets)
CBS	cystathionine-β-synthase
CHD	coronary heart disease
CI	confidence interval
CLIA	Clinical Laboratory Improvement Amendments
CLSI	Clinical Laboratory Standards Institute (formerly NCCLS or National Committee on Clinical Laboratory Standards)
C_{max}	maximum serum concentration
CPK	creatinine phosphokinase
CPR	cardiopulmonary resuscitation
CrCl	creatinine clearance
CRRT	continuous renal replacement technique
CRUSADE	Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA guidelines
CSCT	colloidal-silica clotting time
CT	computed tomographic
CVA	cerebrovascular accident
CVAD	central venous access device
CVL	central venous line
D	dabigatran
D5W	5% dextrose in water
DBP	diastolic blood pressure
Dec	decrease
DIC	disseminated intravascular coagulation
dL	deciliter
DOAC	direct-acting oral anticoagulant
dPT	dilute prothrombin time
dRVVT	dilute Russell's viper-venom time
DTI	direct thrombin inhibitor

ABBREVIATIONS (continued)

DVT	deep vein thrombosis
ECG	electrocardiogram
ECLS	extracorporeal life support
ECMO	extracorporeal membrane oxygenation
ELISA	enzyme-linked-immunosorbent assay
Enox	enoxaparin
EU	European Union
FDA	Food and Drug Administration
FFP	fresh frozen plasma
FVL	factor V Leiden mutation
GAGs	glycosaminoglycans
GCS	Glasgow Coma Scale
GCS	graduated compression stockings
GI	gastrointestinal
Gp IIb/IIIa	glycoprotein IIb/IIIa receptor
GUSTO	global use of strategies to open occluded coronary arteries
HAT	heparin-associated thrombocytopenia (nonimmune mediated)
Hct	hematocrit
Hgb	hemoglobin
HIT	heparin-induced thrombocytopenia (immune mediated)
HITTS	heparin-induced thrombocytopenia thrombosis syndrome (immune mediated)
hr	hour
HR-ACT	high response activated clotting time
HR	heart rate
HTN	hypertension
IBD	inflammatory bowel disease
ICD	implantable cardioverter defibrillator
ICH	intracranial hemorrhage
IgG (IgA, etc.)	immune globulin G, etc.
IM	intramuscular
Inc	increase

ABBREVIATIONS (continued)

INR	international normalized ratio
IPC	intermittent pneumatic compression
ISI	International Sensitivity Index
ISTH	International Society of Thrombosis and Haemostasis
IUGR	intrauterine growth restriction
IV	intravenous
IVC	inferior vena cava
KCT	kaolin clotting time
kD	kilodalton
kg	kilogram
kg/m²	kilogram/meter squared
LA	lupus anticoagulant
LIA	latex immunoassay
LMWH	low molecular weight heparin
LR ACT	low range activated clotting time
LV	left ventricular
mg	milligrams
Mg	magnesium
MI	myocardial infarction
min	minutes
mL/min	milliliter/minute
MODS	multiple organ dysfunction syndrome
MRI	magnetic resonance imaging
MTHFR	methylene-tetrahydrofolate reductase
MVP	mechanical valve prosthesis
MVR	mitral valve replacement
NA	not applicable
NHP	normal human plasma
NIBSC	National Institute of Biological Standards and Controls
NINDS	National Institute of Neurological Disorders and Stroke
NPSG	National Patient Safety Goal

NS	normal saline
NSAIDs	nonsteroidal anti-inflammatory drugs
NSR	normal sinus rhythm
NSTE	non-ST-segment elevation
NSTEMI	non-ST-segment elevation myocardial infarction
OR	operation room
PAD	peripheral arterial disease
PCC	prothrombin complex concentrate
PCI	percutaneous coronary intervention
PE	pulmonary embolism
PF-4	platelet factor 4
PICC	peripherally inserted central catheter
Plt	platelet
POC	point of care
PPH	primary pulmonary hypertension
PRBCs	packed red blood cells
PT	prothrombin time
Pt yr	patient-year
R	rivaroxaban
RACE	RAte Control vs. Electrical cardioversion for persistent atrial fibrillation study
RCT	randomized clinical trial
rFVIIa	recombinant factor VII activated
RRR	relative risk reduction
rt-PA	recombinant tissue plasminogen activator
RVT	renal vein thrombosis
SBP	systolic blood pressure
SC	subcutaneous
SCAI	Society for Cardiac Angiography and Interventions
SCD	sickle cell disease
SCr	serum creatinine
sec	seconds

ABBREVIATIONS (continued)

SOB	shortness of breath
sub-Q	subcutaneous
SRA	serotonin release assay
SSC	Scientific Subcommittee (part of ISTH)
SSRI	selective serotonin reuptake inhibitors
STEMI	ST-segment elevation myocardial infarction
$T_{1/2}$	elimination half life
TAVR	transcatheter aortic valve replacement
TBW	total body weight
TE	thromboembolism
TEE	transesophageal echocardiography
THR	total hip replacement
TIA	transient ischemic attack
TIMI	thrombolysis in myocardial infarction
TKR	total knee replacement
TMA	thrombotic microangiopathy
T_{max}	time to maximum serum concentration
TNK	tenecteplase
tPA	tissue plasminogen activator
TPN	total parenteral nutrition
TT	thrombin time
TTE	transthoracic echocardiography
UFH	unfractionated heparin
units	International Units
Vit K	vitamin K or phytonadione
VKA	vitamin K antagonist
VKOR	vitamin K epoxide reductase
VTE	venous thromboembolism
vWF	von Willebrand's factor
WARSS/APASS	Warfarin vs. Aspirin Recurrent Stroke Study/Antiphospholipid Antibodies in Stroke Study
WHO	World Health Organization

PART I.

ANTICOAGULATION MEDICATION MANAGEMENT