Anticoagulation in Cardiovascular Diseases

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Shermeen B. Memon, Lara Bakhos, and Mushabbar A. Syed

Introduction

A 74-year-old Caucasian male presented to the emergency department after an episode of unwitnessed syncope. His wife found him on the floor with a laceration on the back of his head. The patient had no recollection of the event and only remembered waking up on the floor. There was blood on the floor, a broken coffee table, and a knocked down floor lamp. The patient denied headache, chest pain, palpitations, or focal weakness/numbness. Past medical history included atrial fibrillation, coronary artery disease, hypertension, hyperlipidemia, and prostate cancer. His outpatient medications were rivaroxaban, amlodipine, atenolol, atorvastatin, enalapril, tamsulosin, omeprazole, and multivitamins. On examination, he was alert and oriented responding appropriately to questions. There were no significant abnormalities on a neurological examination. He was in atrial fibrillation with heart rate of 120/min, BP was 125/70 mmHg, and the rest of the cardiovascular exam was within normal limits. Head CT in the emergency department showed a small left frontoparietal subdural hematoma without midline shift or herniation (Fig. 15.1a). A repeat head CT later that day showed progression in the size of the subdural hematoma (Fig. 15.1b) and Four-Factor Prothrombin Complex Concentrate (Kcentra) was administered. Subsequent CTs showed a stable hematoma size over the next 48 h. No neurosurgical intervention was performed. Atrial fibrillation was managed with a beta-blocker and digoxin. Patient was subsequently discharged to an inpatient rehabilitation facility 1 week after presentation. He was discharged home from the rehabilitation facility after another week and presented to the emergency department within 24 h with new onset dysphasia. A head CT showed a large acute on chronic subdural hematoma with associated mass effect (Fig. 15.2). An emergent craniotomy was performed and the subdural hematoma was evacuated. The postoperative period was complicated by rapid atrial fibrillation and hypotension, which were successfully managed with IV fluids and IV metoprolol later transitioning to oral regimen. The rest of the hospital course was unremarkable. Management of this patient poses significant challenges including managing the acute intracranial hemorrhage related to a new anticoagulation agent, assessing the risk and benefit for long-term anticoagulation, timing of restarting anticoagulation, and the risk of rebleeding in the future.

S.B. Memon, M.D. • L. Bakhos, M.D. • M.A. Syed, M.D., F.A.C.C. (✉)
Department of Medicine-Cardiology, Heart & Vascular Institute, Loyola University Medical Center, 2160 S. First Ave, Maywood, IL 60153, USA
e-mail: shermeen.memon@gmail.com; larabakhos@gmail.com; masyed@lumc.edu

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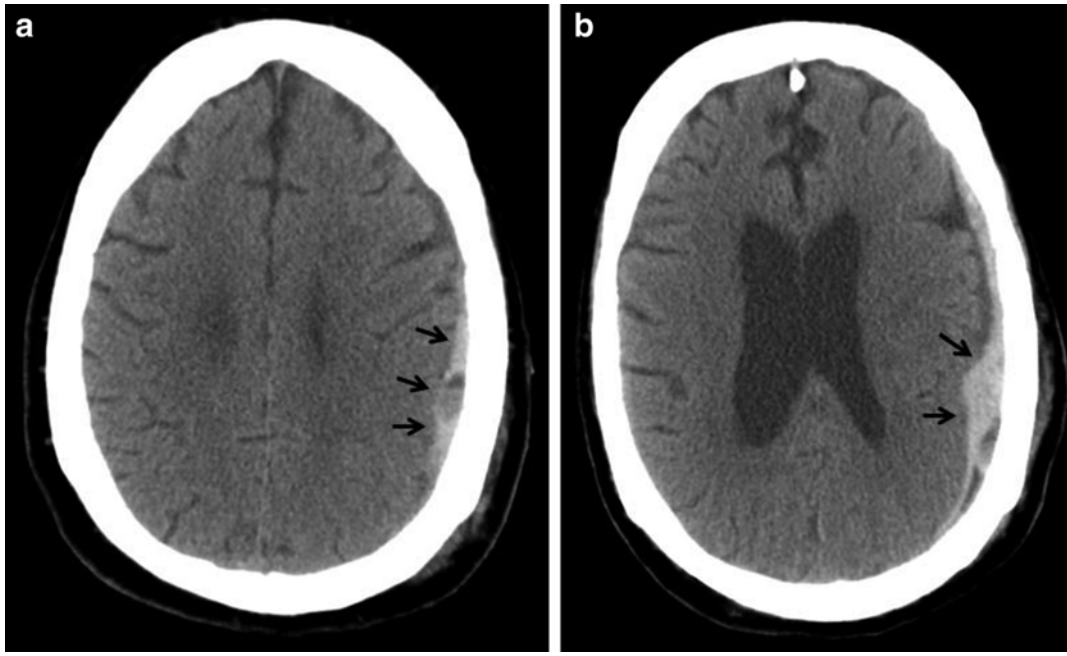

Fig. 15.1 Head CT showing acute subdural hematoma (*black arrows*)

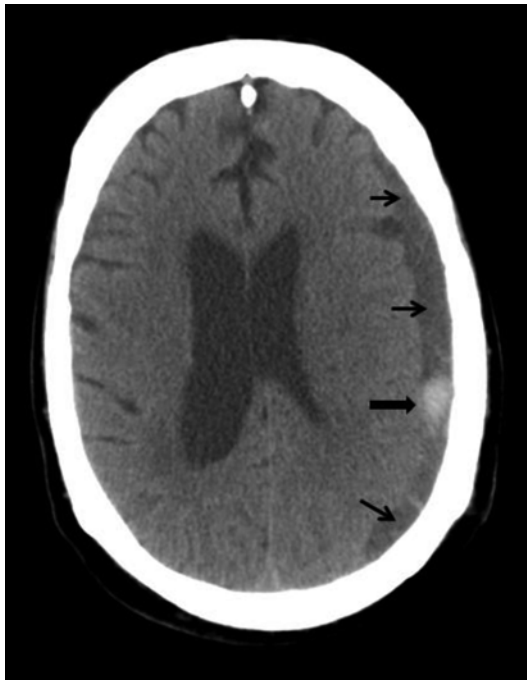

Fig. 15.2 Head CT with subacute (*small arrows*) and acute (*thick arrow*) subdural hematoma with mass effect

In cardiology practice, increasing number of patients are being diagnosed with atrial fibrillation or flutter due to aging of the general population leading to increased use of long term oral systemic anticoagulation. Given the increasing use of these medications, physicians are more likely to see these patients in the emergent, urgent, and elective surgical situations; thus, it is important to understand which cardiac conditions necessitate the use of these agents, the pharmacology of these agents, and the management of such agents in the preoperative, perioperative, and postoperative setting. This chapter aims to summarize these concepts.

Anticoagulation Agents

Short-term anticoagulation is usually achieved by intravenous or subcutaneous use of heparin while long-term use requires oral agents. For a long time warfarin was the only oral agent available in clinical practice; however, recently

several novel agents have become clinically available with their unique challenges and limitations (Table 15.1).

Heparin: Unfractionated and Low Molecular Weight Heparins

Unfractionated heparin (UH) is an intravenously available anticoagulant that is used in the management and treatment of stroke prevention in atrial fibrillation, systemic thromboembolic disease, and acute coronary syndromes. UH binds to the enzyme inhibitor antithrombin, resulting in the activation of this enzyme. The activated antithrombin then inactivates thrombin and other proteases involved in blood clotting, most notable factor Xa [1]. Simply put, UH is referred to as an indirect thrombin inhibitor. Although effective for both primary and secondary prevention of stroke in the setting of atrial fibrillation as well as for thromboembolic disease, UH has a number of limitations including the need for intravenous therapy, a narrow therapeutic window, and a highly variable dose–response relation requiring close laboratory monitoring. Monitoring is achieved by following the activated partial thromboplastin time (aPTT) or the activated clotting time (ACT) when high doses of UH are administered. Baseline measures of aPTT and blood counts are made prior to initiation and then monitored every 4–6 h thereafter or after any dose change. The therapeutic level of UH that should be attained within the first 24 h of initiation is 1.5–2 times the upper limit of the control [2]. Failure to promptly achieve a therapeutic aPTT level in patients with venous thromboembolism (VTE) treated with UH has been associated with an increase in the risk of subsequent recurrent thromboembolism [3]. Complications from UH include bleeding, heparin-induced thrombocytopenia, skin lesions/necrosis, and hypersensitivity. Furthermore, given the need for intravenous administration, UH is most commonly used as a bridge to oral anticoagulant therapy.

Low molecular weight heparin (LMWH) is another anticoagulant and is very similar to UH. Unlike antithrombin activated by UH, antithrombin activated by LMWH cannot directly inhibit thrombin but instead inhibits clotting factor Xa. Due to its mechanism of action, the activity of LMWH is monitored by measuring Factor Xa activity as opposed to aPTT or ACT measurements [4]. However, given its predictable anticoagulant properties, most dosing schemes do not require routine laboratory monitoring. Moreover, the duration of the anticoagulant effect is greater than that of UH, allowing for twice a day dosing. The anticoagulant response to LMWH is highly correlated with body-weight and is dosed based on 1 mg/kg dosing; however, the dose may have to be adjusted for patients who are extremely obese or have renal insufficiency. Furthermore, laboratory monitoring is not necessary in non-pregnant patients. LMWH is less likely to induce immune-mediated thrombocytopenia; however, extreme caution must be taken in those individuals with a history of heparin-induced thrombocytopenia as this could still occur. LMWH can also be safely administered in the outpatient setting at is it administered subcutaneously as opposed to intravenously. LMWH provides many advantages over UH and is an effective, viable management and treatment strategy for patients with atrial fibrillation, acute coronary syndrome (ACS), and VTE.

Warfarin

Vitamin K antagonists (VKAs) have been the only oral anticoagulants used in clinical practice for many decades. Warfarin, the most commonly known and used VKA, was initially used as a pesticide for rats and mice. In the 1950s, warfarin was found to be effective and relatively safe for preventing and treating thrombosis in humans, leading to its approval in 1954 [5]. Warfarin's anticoagulant effects are due to its ability to inhibit vitamin K dependent gamma-carboxylation of coagulation factors II, VII, IX,

Table 15.1 Summary of anticoagulation drugs

Medication	Pharmacology	Time to peak action	Route	Dosing	Monitoring	Uses	Reversal agents	Adverse effects
Unfractionated heparin	Indirect thrombin inhibitor	Immediate	IV	IV infusion (weight based dosing per institutional nomogram)	aPTT: 1.5–2× ULN	1. Atrial fibrillation 2. VTE 3. Unstable angina/ NSTEMI 4. Prosthetic valves 5. LV thrombus 6. LVAD	Protamine sulfate	Bleeding Heparin induced thrombocytopenia and thrombosis Skin necrosis
Low molecular weight heparin[a]	Inhibits clotting Factor Xa	3–5 h	SQ	1 mg/kg as twice a day dosing	Factor Xa levels (not routinely monitored)	1. Atrial fibrillation 2. VTE 3. Unstable angina/ NSTEM I 4. LV thrombus	Protamine sulfate	Bleeding Heparin induced thrombocytopenia (less frequent as compared to unfractionated heparin) Skin necrosis Elevation in LFTs
Warfarin	Vitamin K antagonist	24–72 h	Oral	Dosing individualized and guided by INR	PT/INR	1. Atrial Fibrillation (INR goal 2–3) 2. VTE (INR goal 2–3) 3. Prosthetic valves (INR goal 2.5–3.5) 4. LV thrombus 5. LVADs-goal based on specific device	Vitamin K	Bleeding Ecchymosis Skin necrosis Hypersensitivity
Rivaroxaban[a]	Direct factor Xa inhibitor	2–4 h	Oral	1. Nonvalvular atrial fibrillation: 20 mg once daily 2. VTE: 15 mg twice daily for 21 days followed by 20 mg once daily	Non0065	1. Nonvalvular atrial fibrillation 2. VTE	Please see text for details regarding reversal agents	Bleeding Thrombocytopenia Agranulocytosis Hepatitis Elevated LFTs

Apixaban[a]	Direct Factor Xa inhibitor	3–4 h	Oral	1. Nonvalvular atrial fibrillation: 5 mg twice daily[b] 2. VTE: 10 mg twice daily for 7 days followed by 5 mg twice daily	None	1. Nonvalvular atrial fibrillation 2. VTE	Please see test for details regarding reversal agents	Bleeding Hypersensitivity Syncope
Dabigatran[a]	Direct thrombin inhibitor	1 h	Oral	1. Nonvalvular atrial fibrillation: 150 mg twice daily 2. VTE: 150 mg twice daily (after 5–10 of IV anticoagulation)	None	1. Nonvalvular atrial fibrillation 2. VTE	Please see test for details regarding reversal agents	Bleeding Dyspepsia Gastritis Thrombocytopenia
Aspirin	Antiplatelet	~l–2 h	Oral	81–32 mg daily	None	Coronary artery disease Atrial fibrillation	Platelet infusion	Bleeding Gastrointestinal distress
P2Y12 inhibitors (i.e., clopidogrel)	Antiplatelet	Dose dependent	Oral		None	Coronary artery disease		Bleeding

ULN upper limits of normal, *NSTEMI* non-ST elevation myocardial infarction

[a]Medication should be dose reduced for patients with renal insufficiency

[b]Apixiban should be dose reduced in those with any two of the following criteria: Age ≥80 years, body weight ≤60 kg, or serum creatinine ≥1.5 mg/dL, then reduce dose to 2.5 mg twice daily

and X, thereby rendering these proteins inactive [6, 7]. With a high bioavailability, it is rapidly absorbed in the proximal small bowel and metabolically cleared via the hepatic cytochrome P450 [6]. The anticoagulant effects are monitored using the International Normalized Ratio (INR), with a goal of 2.0–3.0 reflecting appropriate anticoagulation in most clinical scenarios for both primary and secondary prevention of thrombosis. The most common clinical indications for warfarin use are atrial fibrillation, artificial heart valves, arterial and venous thromboembolic phenomenon, and hypercoagulable syndromes.

Despite being the most widely prescribed oral anticoagulant, warfarin has many shortcomings. Given that it works by antagonizing vitamin K recycling, patients must have stable dietary habits for vitamin K to allow for proper INR control. Also, numerous drugs interact with warfarin leading to over- or under-anticoagulation. Due to these factors, frequent INR serum assays must be obtained to ensure appropriate anticoagulation, with most algorithms suggesting these measurements be obtained at least every 4 weeks. Despite this, studies have shown only 60 % of patients are maintained within a therapeutic INR range of 2.0–3.0 [8].

Furthermore, patients on warfarin are also at increased risk of bleeding due to its potent anticoagulant effects. Thus, numerous risk scores have been developed to assess this bleeding risk. The HAS-BLED (**H**ypertension, **A**bnormal renal and liver function, **S**troke, **B**leeding tendency/predisposition, **L**abile INRs, **E**lderly with age greater than 65 years, **D**rugs or alcohol) score is a common method utilized to weigh the risk of bleeding versus the benefits of thromboembolic prevention in patients with cardiac disorders such as atrial fibrillation. In the event of a bleed, warfarin's anticoagulant effects can be reversed with the use of vitamin K as well as with replacement of Factors II, VII, IX, and X.

Novel Oral Anticoagulants

Due to the limitations of warfarin's use, options for anticoagulation have steadily been expanding with the introduction of novel oral anticoagulants (NOACs) that target the enzymatic activity of thrombin and factor Xa. Dabigatran extexilate, the only oral direct thrombin inhibitor, is a prodrug that is converted in the liver to dabigatran, which inhibits clot-bound and circulating thrombin [9]. Unlike warfarin, the maximum anticoagulant effects are achieved within 2–3 h of ingestion, absorption is not affected by dietary habits, and monitoring with lab testing is not required [10]. Furthermore, dose changes are generally not required with concomitant administration of cytochrome P450 inducers and inhibitors since dabigatran is renally metabolized; dosing is solely based on clinical indication and renal function. Published in 2009, the RE-LY trial randomized 18,000 patients with moderate to high risk of thromboembolic stroke and nonvalvular AF to dabigatran or warfarin. After a median follow-up of 2 years, dabigatran 150 mg twice daily was shown to be noninferior to warfarin in stroke reduction [11]. Dabigatran has since been approved for use in primary and secondary prevention of venous thromboembolism, treatment of venous thromboembolism, and stroke prevention in atrial fibrillation. Of note, the RE-ALIGN study demonstrated that patients with mechanical aortic or mitral valves receiving dabigatran as opposed to warfarin had increased bleeding and thromboembolic risk [12]. Therefore, dabigatran should not be used in patients with valvular atrial fibrillation or prosthetic heart valves. Moreover, this medication should not be used in pregnant patients as it is associated with an increase in reproductive risks [13]. However, for its approved indications, dabigatran offers a great alternative to warfarin therapy.

The other target used by NOACs is Factor Xa. Factor Xa is a protease that plays a key role in the blood coagulation cascade. Holding a central position that links both the intrinsic and extrinsic pathways to the final common coagulation pathway, factor Xa converts prothrombin to thrombin leading to the formation of thrombus. Rivaroxaban, apixaban, and edoxaban are currently available oral factor Xa inhibitors that block this final common pathway, effectively reducing the risk of thrombus formation.

Rivaroxaban is an orally available factor Xa inhibitor with a half-life of 7–17 h and once a

ay dosing. As with dabigatran, rivaroxaban is given at fixed doses without the need for routine monitoring. Dosing is based on a patient's clinical indication and renal function; it is not recommended in those patients with a creatinine clearance less than 30 mL/min or in those with severe hepatic impairment. Rivaroxaban does interact with medications that are inhibitors or inducers of cytochrome P3A4 and P-glycoprotein, such as antifungal agents. In the ROCKET-AF trial, 14,264 patients with nonvalvular atrial fibrillation with at least moderate risk of stroke were randomized to rivaroxaban or warfarin [14]. Rivaroxaban was shown to be noninferior to warfarin in reducing thromboembolic events without increasing bleeding consequences. Rivaroxaban has not been approved for use in pregnant patients, those with prosthetic heart valves, or valvular atrial fibrillation due to the lack of clinical studies. Rivaroxaban provides a practical therapeutic option for use in the primary and secondary prevention of venous thromboembolism, treatment of venous thromboembolism, and stroke prevention in atrial fibrillation.

Apixaban is also an oral factor Xa inhibitor that has a half-life of 5–9 h, requiring a twice a day dosing schedule. Dosing is based on the patient's clinical indication, age, weight, and renal function. As with rivaroxaban, apixaban is generally given at a fixed dose without the need for monitoring and also interacts with medications that are inhibitors or inducers of cytochrome P3A4 and P-glycoprotein. It too is used in the prevention and management of venous thromboembolic disease and stroke prevention in atrial fibrillation. Apixaban's use in nonvalvular atrial fibrillation was evaluated in 18,201 patients in the ARISTOTLE trial, which demonstrated that apixaban was superior to warfarin in reducing stroke and systemic embolism [15]. As with rivaroxaban, apixaban is not approved for use in pregnant patients, those with prosthetic heart valves, or valvular atrial fibrillation.

Edoxaban is another oral factor Xa inhibitor with a half-life of 6–11 h and is typically dosed once a day. As with the previously discussed factor Xa inhibitors, edoxaban is given at a fixed dose without monitoring; dosing is based on a patient's clinical indication and renal function. It is also used in the prevention and management of venous thromboembolic disease and stroke prevention in atrial fibrillation and is similarly contraindicated for use in prosthetic heart valves or during pregnancy.

NOACs offer patients a viable alternative to warfarin therapy in prevention and management of thromboembolic disease. Given their predictable anticoagulant effects, these medications provide reliable anticoagulation in patients at risk for these potentially catastrophic consequences. Although warfarin is more cumbersome for patients due its continued need for monitoring, its numerous drug interactions, and dietary constraints, it remains vital to medical therapy. Its use has been studied in a wider array of medical conditions; warfarin can be prescribed not only in the management of venous thromboembolisms and nonvalvular atrial fibrillation but also in patients with valvular atrial fibrillation, prosthetic heart valves, and various myocardial diseases.

Cardiovascular Indications for Anticoagulation

Atrial Fibrillation

Atrial fibrillation (AF) is the most common sustained cardiac rhythm disturbance and is defined as a supraventricular tachyarrhythmia that results from uncoordinated atrial activity, resulting in ineffective atrial contraction. Rapidly firing ectopic foci, most commonly found in the left atrium and more specifically around the pulmonary veins, bombard the atrioventricular (AV) node, resulting in rapid ventricular rates. These rates and unorganized atrial activity can lead to clinical symptoms or long term consequences such as deterioration in hemodynamic status, increased risk of embolic events, and progressive left ventricular dysfunction.

AF affects between 2.7 million and 6.1 million American adults and is expected to double over the next 25 years [16]. The prevalence of AF increases with age, with up to 12 % of patients

between the ages of 75 and 84 and more than one-third of patients over the age of 80 being affected by AF [17]. In addition to advanced age, AF is often associated with structural heart disease and chronic comorbidities, with the most common being hypertension, ischemic heart disease, and heart failure. These comorbidities along with atrial structural abnormalities such as inflammation, fibrosis, dilatation, ischemia, infiltration, and hypertrophy predispose individuals to the development of this arrhythmia [18].

The diagnosis of AF is commonly made by detecting an irregular pulse on physical examination and/or irregular R-R intervals and absence of distinct P-waves with irregularity of the atrial activity on ECG. Clinically, patients can be asymptomatic or present with palpitations, fatigue, dizziness, pre-syncope, and syncope; more severe clinical consequences can result in hospitalizations due to hemodynamic compromise, heart failure, and thromboembolic events. In addition to being a symptomatic burden, AF also is associated with a fivefold increased risk of stroke [19], a threefold increased risk of heart failure [20–22] and twofold increased risk of mortality [19].

Initial evaluation should include ECG documentation, investigation for underlying systemic disease, and evaluation for structural heart disease with a transthoracic echocardiogram (TTE) [18]. TTE evaluates for atrial structural changes such as dilatation and hypertrophy as well as for valvular abnormalities commonly associated with AF such as mitral valve disease. AF related to such valvular disease is referred to as valvular AF.

In addition to understanding the etiology of AF, two principal management decisions must be addressed:

1. The symptom management strategy
2. The need for oral anticoagulation for the reduction in thromboembolic consequences.

Two large clinical trials have compared rate versus rhythm control strategies in patients with AF. The 2002 Atrial Fibrillation Follow-up Investigation of Rhythm Management (AFFIRM) trial was the first and largest study to compare these two strategies. This study randomized 4060 patients with recurrent AF to either rate control or to rhythm control. Enrolled patients had to be ≥65 years of age and/or have other risk factors for stroke or death. Individuals were excluded if patients had contraindications to antiarrhythmic or anticoagulation therapies. After a mean follow-up of 3.5 years, there was no significant difference in the primary end-point of all-cause mortality or composite secondary end points of death, ischemic stroke, anoxic encephalopathy, major bleeding, or cardiac arrest. Moreover, there was no significant difference in functional status or quality of life between the two groups [23]. The RACE (Rate Control versus Electrical Cardioversion for Persistent Atrial Fibrillation) study randomized 522 patients with recurrent persistent AF or atrial flutter of less than 1 year duration who required one or two direct-current cardioversions (DCCV) within the prior 2 years to either rate or rhythm control therapies. After a mean follow-up of 2.3 years, there was no significant difference in primary end-point of composite cardiovascular death, admission for heart failure, thromboembolic event, severe bleeding, pacemaker implantation, or severe side effects from antiarrhythmic medications. As in the AFFIRM trial, there were no significant differences in quality of life between the rate and rhythm control groups [24].

Controlling ventricular rates with medical therapy is an important strategy since attaining rate control can often alleviate a patient's symptoms. Medical therapy for rate control includes beta-blockers, nondihydropyridine calcium channel blockers, digoxin, and certain antiarrhythmic medications, e.g., amiodarone and sotalol. Acutely, beta-blockers such as metoprolol or esmolol are effective when administered intravenously. For chronic management of AF, oral administration of beta-blockers is often used. The nondihydropyridine calcium channel blockers used for ventricular rate control are verapamil and diltiazem; these agents should not be used in patients with decompensated heart failure as they may precipitate further hemodynamic compromise due to their negative inotropic effect. Choice of medication is determined by a patient's symptoms, hemodynamic status, comorbidities, and potential precipitants of AF.

Although digoxin can also be used for rate control, it is usually not first line therapy as it has a slow onset of action and is effective only in controlling heart rates during rest. Furthermore, caution must be used in patients with renal dysfunction, the elderly, and in the presence of other drugs that affect its excretion. Digoxin has a narrow therapeutic window with toxicity manifesting as atrioventricular block, ventricular arrhythmias, and/or aggravation of sinus node dysfunction. Antiarrhythmic drugs, e.g., amiodarone should be avoided for rate control as it can chemically restore sinus rhythm, which could lead to detrimental effects if the patient is not properly anticoagulated.

With regards to heart rate goals, a resting heart rate of less than 80 beats per minute (bpm) is reasonable for symptomatic management of AF (Class IIa) and a lenient goal of less than 110 bpm may be reasonable if the patient remains asymptomatic and left ventricular systolic function is preserved (Class IIb). When medical therapies have proven ineffective in controlling heart rates, referral to an electrophysiologist and invasive procedures can be pursued (class IIa) [18].

Rhythm control is another treatment strategy often employed as a means to restore and/or maintain sinus rhythm. Factors that may favor a rhythm control strategy include inadequate rate control, patient's age (younger being more favorable), first episode of AF, AF precipitated by an acute illness, tachycardia-mediated cardiomyopathy, and patient preference [18]. Antiarrhythmic medications utilized in this strategy include amiodarone, dofetilide, dronedarone, flecainide, propfenone, and sotalol. Medication selection is often times guided by the drug's safety profile and the patient's comorbidities as opposed to the drug efficacy.

In addition to antiarrhythmic medications, DCCV, which involves delivering an electrical shock that is synchronized with the patient's QRS complex, can also be used to restore sinus rhythm and is often times used in conjunction with use of antiarrhythmic drugs.

Finally, a third method of rhythm control is catheter ablation, which provides an alternative to traditional medical therapy. Cardiac ablation is an invasive technique using multiple catheters to localize the foci in the atrium generating these chaotic, irregular impulses. These foci are typically located around the pulmonary veins in the left atrium; however, other foci can be identified with electrophysiologic mapping. Radiofrequency energy or cryotherapy can then be applied to these areas in an attempt to terminate the ectopic electrical activity.

Currently, cardiac catheter ablation is usually considered in patients with symptomatic paroxysmal or persistent AF refractory to or intolerant to at least one class I or class III antiarrhythmic drug (class IIa). In addition, after weighing the risks and benefits with the patient, ablative therapy can be offered to patients with symptomatic paroxysmal or persistent AF prior to a trial of antiarrhythmic therapies (class IIA) [18].

Regardless of the rate or rhythm control strategy, appropriate anticoagulation must be employed to reduce thromboembolic events in both the acute care setting as well as with chronic management of these patients. Due to the uncoordinated atrial activity resulting in ineffective atrial contraction, blood stasis occurs in the "quivering" atria, leading to increased risk of thrombi formation. Dislodgement of such thrombi that are usually found in the left atrium or left atrial appendage, results in ischemic strokes as well as other peripheral thromboembolic events. Due to such devastating consequences, antithrombotic medication is prescribed based on the patient's risk of thromboembolism and irrespective of whether the AF pattern is paroxysmal, persistent, or permanent.

The CHA_2DS_2-VASc scoring system, which has been validated in multiple studies, predicts a patient's risk of thromboembolic events. The components of this scoring system include: **C**ongestive heart failure, **H**ypertension, **A**ge, **D**iabetes mellitus, **S**troke/transient ischemic attack (TIA)/thromboembolic event, **V**ascular disease, **A**ge 65–74, and **S**ex (female gender) (Table 15.2). The higher the score, the higher the thromboembolic risk. This risk is then weighed against the risk of bleeding to determine an individual's need for an antithrombotic agent. For patients with nonvalvular AF and a CHA_2DS_2-VASc of 0, it is reasonable not

Table 15.2 Estimating the risk of thromboembolism in atrial fibrillation

CHA_2DS_2-VASc scoring system	
Acronym definition	Score
Congestive Heart Failure	1
Hypertension	1
Age ≥75 years	2
Diabetes Mellitus	1
Stroke/Transient Ischemic Attack/ Thromboembolic Event	2
Vascular Disease (prior myocardial infraction, peripheral arterial disease, or aortic plaque)	1
Age 65–74 years	1
Sex (Female gender)	1
Maximum score	9
Stroke risk stratification based on score	
Score	Estimated stroke risk per year (%)
0	0
1	1.3
2	2.2
3	3.2
4	4.0
5	6.7
6	9.8
7	9.6
8	6.7
9	15.2

to initiate anticoagulation (Class IIA). For patients with nonvalvular AF and a CHA_2DS_2-VASc score of 1, the use of antithrombotic agents or the use of full dose aspirin (325 mg) is left to the patient and physician's discretion (Class IIb). For patients with nonvalvular AF with prior stroke, TIA, or a CHA_2DS_2-VASc ≥ 2, oral antithrombotic agents are recommended for long-term management (class I) [18]. It is important to recognize that individuals who have had an AV node ablation for rate control still require anticoagulation as deemed appropriate by the CHA_2DS_2-VASc score since these individuals continue to have uncoordinated atrial activity. It is also important to recognize that CHA_2DS_2-VASc scoring system does not apply to patients with valvular AF; these individuals require anticoagulation regardless of score.

Another caveat is in those patients undergoing restoration of sinus rhythm with DCCV. Thromboembolism after cardioversion, electrically or chemically, can be due to migration of thrombi present at the time of cardioversion or the formation of subsequent thrombi in the post-cardioversion period while atrial function is still depressed. For patients with AF of less than 48-h duration who are at low thromboembolic risk, anticoagulation or no antithrombotic therapy may be considered for DCCV without the need for post-cardioversion anticoagulation (Class IIB). However, if the duration of the episode exceeds 48 h or if the duration is unknown, patients must be anticoagulated for the preceding 3 weeks and for at least 4 weeks post-DCCV (class I) [18]. Thromboembolic risk after cardioversion is highest in the first 72 h and the majority of events occur within 10 days of cardioversion. If it is not plausible to wait 3 weeks for cardioversion, a transesophageal echocardiogram (TEE) may be performed to look for thrombi in the left atrium and left atrial appendage; if no thrombus is identified and patient has achieved therapeutic anticoagulation, cardioversion can be performed. Following the 4 weeks of anticoagulation in the post-cardioversion setting, the need for chronic anticoagulation is assessed by the CHA_2DS_2-VASc scoring system.

Antithrombotic agents used for stroke prevention include unfractionated heparin, low-molecular weight heparin, warfarin, direct thrombin inhibitors, and factor Xa inhibitors. The specific antithrombotic agent utilized in stroke reduction in patients with AF is based on the medication's safety profile, the patient's risk factors, and patient preference as discussed earlier in the chapter.

Atrial Flutter

Atrial Flutter (AFL) is another supraventricular tachyarrhythmia that is often times associated with atrial fibrillation. AFL differs in its electrophysiologic properties and is due to a reentry circuit typically localized to the isthmus between the tricuspid valve annulus and inferior vena cava

in the right atrium. Despite these differences, atrial flutter is managed in a similar manner to AF. According to the AHA/ACC/HRS Atrial Fibrillation guidelines of 2014, antithrombotic therapy is recommended in AFL according to the same risk profile used for AF (class I) [18].

Valvular Heart Disease

Valvular heart disease (VHD) is defined as damage to or a defect in one or more of the four cardiac valves: aortic, mitral, tricuspid, or pulmonic valves. With the dramatic decline in rheumatic disease, VHD in developed countries is most commonly attributed to degenerative changes and is considered a disease of the elderly. Its prevalence is estimated at 2.5 % in industrialized countries [25]. Valvular defects can result in regurgitation or stenosis of the valve. Progression of these defects can result in irreversible ventricular dysfunction, pulmonary hypertension, stroke, and atrial fibrillation. Some of these valvular abnormalities require anticoagulation, as they are associated with increased risk of thromboembolic events.

Mitral stenosis (MS) results from thickening and immobility of the mitral leaflets and causes an obstruction of blood flow from the left atrium to the left ventricle. MS is most often secondary to rheumatic heart disease or senile calcific disease. Regardless of etiology, the mechanical obstruction causes an increase in pressure in the left atrium, pulmonary vasculature and the right side of the heart leading to symptoms of dyspnea, hemoptysis, and right-sided heart failure. Elevated left atrial pressures results in left atrial dilatation, increasing the risk of developing AF as well as left atrial thrombi. Due to such association, indefinite anticoagulation with warfarin is indicated in all patients with MS and AF, MS and a prior embolic event, or MS and a left atrial thrombus with a goal INR of 2.0–3.0 (Class I) [26]. Because the efficacy of NOACs in preventing embolic events has not been studied in patients with valvular heart disease, warfarin is the only oral anticoagulant recommended in this population.

Progression of valvular regurgitation or stenosis causes significant morbidity and mortality. The purpose of valvular intervention is to improve symptoms, prolong survival, and minimize the risk of irreversible ventricular dysfunction, pulmonary hypertension, stroke, and atrial fibrillation [26]. When a surgical heart valve replacement is warranted, a choice is made between a mechanical or bioprosthetic valve. The choice of valve prosthesis is based on several factors including the patient's age, expected life span, potential risk of lifelong anticoagulation, valve durability, clinical circumstances, and patient preference.

Mechanical valves are durable in patients of any age with a low risk for the need for reoperation; however, these valves require lifelong anticoagulation with warfarin. The goal INR for each patient is based on the mechanical valve position along with a patient's risk factors, which include AF, prior thromboembolism, LV dysfunction, or hypercoagulable states. Three basic types of mechanical valve design are: bileaflet, monoleaflet, and caged ball valves. *Given their risk of thrombosis, anticoagulation with warfarin is recommended for all patients with mechanical valves*. An INR goal of 2.0–3.0 is recommended in patients with a mechanical aortic valve replacement (AVR) with bileaflet mechanical or Medtronic Hall valve and no risk factors for thromboembolism (Class I). Patients with an AVR and any additional risk factor as listed above, those with an older mechanical AVR (Starr–Edwards or disk valves other than Medtronic Hall), or those with a mitral valve replacement (MVR) with any mechanical valve should have a higher goal INR of 2.5–3.5 (Class I). In addition to warfarin, aspirin 75–100 mg/day is recommended in all patients with a mechanical valve prosthesis (Class I) [26].

Bioprosthetic valves are also a viable option for patients with severe valvular disease to avoid the need for lifelong anticoagulation; however, due to their limited life span, patients may require reoperation due to valve degeneration. *Furthermore, despite the use of a bioprosthesis, anticoagulation with warfarin is still considered reasonable in the first 3 months after a*

bioprosthetic AVR, MVR, or MV repair with a goal INR of 2.0–3.0 [26, 27]. As with mechanical valves, those with bioprosthetic valves in the aortic or mitral valve positions should be considered for aspirin therapy (75–100 mg). Anticoagulation early after the valve implantation is intended to decrease the risk of thromboembolism until the prosthetic valve has completely endothelialized [26]. The risks versus benefits of anticoagulation should be discussed with patients and individualized based on the patient's comorbidities and risk factors.

More recently, patients with aortic stenosis (AS) who are too high risk for surgery have been undergoing transcatheter aortic valve replacement (TAVR). These valves are biological prostheses mounted on an expandable metallic frame. These individuals do not require anticoagulation; however, clopidogrel 75 mg daily is used for the 6 months following the procedure in addition to lifeline aspirin therapy (75–100 mg daily) (Class IIb) [26].

Of note, newer oral antithrombotic agents are not approved in patients with mechanical or bioprosthetic valves. Patients should receive warfarin regardless of whether the anticoagulation is for the valve alone or for the valve in addition to another indication. The RE-ALIGN trial was prematurely stopped as the incidence of stroke, valve thrombosis, and bleeding was all significantly higher in the dabigatran group compared to warfarin [12]. Other NOACs have not been studied in patients with prosthetic heart valves.

Myocardial Diseases

Myocardial Infarction

Myocardial infarction (MI) is defined as acute myocardial ischemia and/or necrosis secondary to coronary plaque rupture resulting in an imbalance of myocardial oxygen supply and demand. With over 700,000 Americans suffering from an MI yearly, these events are a major cause of morbidity and mortality [28]. Clinically, these events are diagnosed when a patients presents with symptoms of ischemia (e.g., chest pain), a rise and/or fall in cardiac biomarkers, new ischemic changes on an electrocardiogram (ECG) (ST-segment changes, left bundle branch block or development of pathologic Q waves), identification of intracoronary thrombus by angiography, or imaging evidence of new loss of viable myocardium or a new regional wall motion abnormality of the left ventricle [29]. The mainstay of therapy for these individuals includes pharmacotherapy in addition to coronary revascularization. Following percutaneous coronary interventions, patients are placed on dual-antiplatelet therapy with aspirin along with a P2Y12 receptor inhibitor such as clopidogrel, prasugrel, or ticagrelor.

Both bare-metal (BMS) and drug-eluting stents (DES) are options during a percutaneous coronary intervention. In patients receiving a drug eluting stent for a non-acute coronary syndrome (ACS) indication, clopidogrel 75 mg daily should be given for at least 12 months if the patient is not at high risk of bleeding. In patients receiving BMS for a non-ACS indication, clopidogrel should be given for a minimum of 1 month and ideally up to 12 months. As noted earlier, a P2Y12 inhibitor and aspirin should be administered for up to 12 months in all patients with ACS who are treated with either an early invasive or ischemia-guided strategy [30].

Balloon angioplasty is an additional option that refers to dilation of coronary stenosis by means of a balloon catheter without stent placement. Although no randomized trials have directly assessed duration of dual antiplatelet therapy in patients undergoing balloon angioplasty, current recommendations suggest 1 month of dual antiplatelet therapy with aspirin and a P2Y12 inhibitor since there is a potential risk of thrombosis caused by iatrogenic plaque rupture [31].

Left ventricular (LV) thrombus is one of the more common complications of myocardial infarctions and varies with infarct location and size. Acute anterior infarction, LV function less than or equal to 35 %, and apical dyskinesia or aneurysm formation are associated with an increased risk in the formation of an LV thrombus [32, 33]. *The risk of embolization in patients with a documented LV thrombus who are not treated with anticoagulant therapy has been*

estimated at 10–15 % [34]. *Thus, anticoagulant therapy with a vitamin K antagonist should be considered for patients with acute myocardial infarction and asymptomatic LV mural thrombus (Class IIa)*. Moreover, in patients with an acute myocardial infarction and anterior apical akinesis or dyskinesis without thrombus development, anticoagulant therapy may be considered. Given these patients are also likely to be on dual antiplatelet therapy with aspirin and a P2Y12 receptor inhibitors, a lower INR goal of 2.0–2.5 should be targeted to mitigate the increased risk of bleeding (Class IIB). Treatment can be limited to 3 months in patients with or at risk for LV thrombus formation at which time reevaluation with a TTE may be helpful to guide cessation or prolonged treatment [35]. Of note, NOACs have not been evaluated for use in this context.

Heart Failure

Heart failure (HF) is a common clinical syndrome that results from any structural or functional cardiovascular disorder causing a decrease in systemic perfusion that is inadequate to meet the body's metabolic demands. It is caused by a variety of disorders that affect the pericardium, myocardium, endocardium, cardiac valves, vasculature, or metabolism. Systolic and/or diastolic dysfunction can contribute to a reduced cardiac output and the hallmark symptoms of heart failure, which include dyspnea, fatigue, and fluid retention. Coronary artery disease accounts for approximately two-thirds of patients with LV systolic dysfunction with the remainder of these patients having nonischemic causes such as hypertension, valvular disease, myocarditis, or idiopathic dilated cardiomyopathy [36].

Patients with heart failure and LV systolic dysfunction are at an increased risk of thromboembolic events due to stasis of blood in dilated hypokinetic cardiac chambers and peripheral blood vessels in addition to increased activity in procoagulant factors. This increased risk, however, does not seem to translate to outcomes. Several retrospective analyses have shown that patients with heart failure taking warfarin had similar rates of thromboembolic events when compared to patients not taking anticoagulants. Furthermore, large studies have shown that the risk of thromboembolism in clinically stable patients with depressed ejection fraction (EF) and echocardiographic evidence of intracardiac thrombi is as low as 1–3 % per year [37–39]. Due to such low incidence of events, the risk of anticoagulation may outweigh the benefit; thus, *anticoagulation is not recommended in patients with chronic systolic heart failure without AF, a prior thromboembolic event or a cardioembolic source (Class III)* [36].

Left Ventricular Assist Devices

A subset of patients with advanced systolic heart failure will develop end-stage heart failure refractory to optimal medical therapy, resulting in a very poor prognosis. Cardiac transplantation is a viable option but is only available for a minority of patients due to the lack of suitable donor hearts. The lack of effective therapies for advanced heart failure has led to the development of mechanical circulatory support devices. Initially developed for temporary support in the setting of acute decompensated heart failure, the left ventricular assist device (LVAD) has become a mainstay of therapy for those with end-stage heart failure as a means to "bridge to transplant" as well as for "destination therapy" for those not eligible for transplant. One-fourth of all US heart transplant recipients are supported with these devices prior to transplantation and their use for permanent/destination therapy is increasing [40]. An LVAD allows for the dysfunctional left ventricle to act as a passive conduit through which the mechanical pump fills and provides continuous effective systemic blood flow throughout the cardiac cycle. Though LVADs have become a viable option for numerous patients, such devices introduce a new set of complications including thrombosis and bleeding.

Pump thrombosis causes device obstruction and is clinically suggested by the development of hemolysis and changes in LVAD parameters. To prevent this complication as well as the thromboembolic events associated with it, *patients with LVADs require antiplatelet therapy with aspirin and anticoagulation with warfarin* [41]. INR goals are determined by each device manufacturer.

Despite that, for continuous flow devices, the rate of pump thrombosis ranges from 0.01 to 0.11 per patient [42, 43]. This complication can often times effectively be treated with intensifying anticoagulation. However, if pharmacologic therapy is not effective, immediate pump exchange or heart transplantation is required [41].

Furthermore, these patients are also at increased risk for neurologic complications. Ischemic and hemorrhagic stroke following LVAD placement has been reported to be between 8 and 25 % [44, 45]. Strokes in these patients tend to occur with greater frequency in the right hemisphere, suggestive of a cardioembolic source [46, 47].

Bleeding is the most common complication associated with LVADs, with the incidence of major bleeding being >20 % [43]. This increased risk of bleeding events is not only due to the use of warfarin but also due to the development of acquired von Willebrand disease and gastrointestinal (GI) arteriovenous malformations. In randomized trials comparing different types of LVADs, the leading cause of death in all groups was cerebral hemorrhage [48]. If a hemorrhagic stroke is identified, anticoagulation is discontinued and reversed. In the setting of recurrent GI bleeding with no clear source or a source that is not amenable to therapy, the goal INR or even the use of warfarin all together should be reevaluated [41]. Discontinuation of anticoagulation due to bleeding requires careful monitoring of the LVAD parameters to avoid thrombotic complications and should only be performed under the close supervision of an advanced heart failure specialist.

Left Ventricular Noncompaction

Noncompaction of the ventricular myocardium is classified by the American Heart Association as a primary genetic cardiomyopathy [49]. The prevalence of left ventricular noncompaction (LVNC) has been estimated at 0.05 % of the general population [50]. This cardiomyopathy is thought to be secondary to defects in cardiac embryogenesis resulting in the intrauterine arrest of the compaction of the loose meshwork that makes up the fetal myocardium, resulting in a hypertrabeculated non-compacted layer of myocardium (spongy myocardium). LVNC can be an isolated finding or may be associated with other congenital anomalies such as Ebstein's anomaly, bicuspid aortic valve, and atrial or ventricular septal defects.

The clinical presentation is variable, ranging from asymptomatic to advanced heart failure, ventricular and atrial arrhythmias, and thromboembolic events including stroke. Oechslin et al. described the outcomes of 34 adults with LVNC. Seventy-nine percent of patients reported dyspnea, 35 % presented in New York Heart Association class III or IV heart failure, 41 % experienced ventricular tachycardia, and 24 % were noted to have thromboembolic events [51]. The role of oral anticoagulation for primary prevention is unclear in patients with LVNC particularly with normal LV function and absence of LV hypertrophy [52]. In clinical practice patients with LVNC and systolic dysfunction routinely receive long-term warfarin due to increased risk of thromboembolism.

Venous Thromboembolism/Antiphospholipid Syndrome

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), has an annual incidence of approximately 0.1–0.27 % [53]. Approximately 20 % of patients with PE die before the diagnosis is made or on the first day following the diagnosis [54]. Risk factors for VTE include but are not limited to immobility due to trauma or surgery, pregnancy, malignancy, use of prothrombotic medications such as hormone replacement therapy, and inherited or acquired hypercoagulable states. When VTE is first diagnosed, the principal objective of therapy is to prevent DVT extension and PE occurrence. Initial treatment requires the use of antithrombotics such as intravenous heparin, subcutaneous low molecular weight heparin, warfarin (INR goal of 2.0–3.0), dabigatran, rivaroxaban, or apixaban, all of which have been approved for this indication. The duration of treatment for VTE/PE should be individualized according to the presence or absence of provoking

events, risk factors for recurrence and bleeding, as well as to the individual patient's preferences. A 3-month duration of anticoagulation therapy is recommended for patients with VTE/PE in the postoperative setting, with transient risk factors, and in patients at high risk of bleeding. Consideration can be given to extend or indefinitely continue therapy in patients with unprovoked VTE/PE after weighing the risks and benefits [55].

Management of Anticoagulation and Antiplatelet Therapy in the Perioperative Setting

Millions of individuals receive long-term anticoagulation and/or antiplatelet therapy for the prevention and treatment of thromboembolism due to atrial fibrillation, prosthetic heart valves, myocardial diseases, left ventricular assist devices, and venous thromboembolism. Annually, approximately 10 % of patients taking antithrombotic agents undergo surgical or other invasive procedures that require temporary discontinuation of therapy [56]. The management of anticoagulation in patients undergoing surgery is challenging and requires a balance between reducing the risk of thromboembolism during the interruption of anticoagulation and preventing excessive bleeding associated with the particular invasive procedure. Both of these outcomes adversely affect mortality. Appropriate decision-making should be individualized and requires knowledge of a patient's thrombotic risk, procedure-related bleeding risk, concepts of bridging anticoagulation therapy, and timing of cessation and reinitiation of antithrombotic therapy.

Periprocedural thrombotic risk is generally extrapolated from risks outside the periprocedural period. The risk of thromboembolic events in patients with nonvalvular atrial fibrillation is assessed with the use of the CHA_2DS_2-Vasc score, a higher scoring indicating greater risk as detailed above and in Table 15.2. Risk factors for thromboembolic events in patients with prosthetic heart valves, specifically mechanical heart valves, is determined by the type of valve, the location of the prosthesis, the number of prosthetic valves, and the presence or absence of additional risk factors including atrial fibrillation, severe left ventricular systolic function, prior thromboembolism, and a hypercoagulable state. *Mitral valve prosthesis carries a higher risk of thrombosis than aortic valve prosthesis*. For patients with venous thromboembolism, the risk of recurrent events and embolization is elevated in the first 3 months following the diagnosis and initiation of anticoagulation therapy [55]. If the venous thromboembolism was provoked, the risk of recurrence decreases with resolution of the underlying risk factor. *Patients with coronary artery disease with recent coronary stenting require dual antiplatelet therapy*. Premature discontinuation of dual antiplatelet therapy for an invasive procedure increases the risk of stent thrombosis, potentially precipitating a myocardial infarction with a mortality rate of greater than 50 % [55]. Thromboembolic risk in the perioperative and postoperative period is estimated based on the underlying indication for anticoagulation.

The risk of procedure related bleeding depends on the type of procedure, the residual effects of antithrombotic agents, comorbidities, history of prior bleeding, and timing of reinitiation of anticoagulation. High bleeding risk procedures include coronary artery bypass surgery, neurosurgical procedures, and any procedure lasting greater than 45 min. Low bleeding risk procedures include laparoscopic cholecystectomy, carpal tunnel repair, and endoscopic procedures [57]. Major bleeding is generally defined as bleeding that is fatal, intracranial, requires surgery to correct, lowers hemoglobin by $\geq$2 g/dL, or requires transfusion of $\geq$2 units packed red blood cells [58]. The risk of bleeding is higher for urgent or emergent procedures when compared to elective procedures, as emergent operations do not allow for proper discontinuation of antithrombotic therapy prior to the procedure. Patient factors also contribute to bleeding risk; numerous bleeding risk scores have been developed including the HAS-BLED score. A HAS-BLED risk score of $\geq$3 was found to be the most predictive for bleeding [59]. Evaluation of these risks allows physicians, surgeons, and patients to make informed decisions prior to any invasive procedure.

Once the thromboembolic and bleeding risks have been weighed, the decision can be made to continue, interrupt or bridge anticoagulation therapy. When anticoagulation is discontinued in patients at risk for thromboembolic events, the interval without therapy should be as short as possible. The medication used for antithrombotic therapy as well as renal and hepatic function determines the timing in the cessation of these anticoagulants. For warfarin, an INR range between 2.0 and 3.5 indicates adequate anticoagulation for thromboembolic risk reduction [60]. A relatively normal zone of hemostasis exists when the INR is 1.0–2.0. Approximately 93 % of patients with an INR in the therapeutic range will have an INR of less than 1.5 approximately 5 days after warfarin therapy has been discontinued [61]. An INR of 1.5 or less is considered safe for high-risk procedures, although some surgeons recommend an INR as close to 1.0 for procedures with high bleeding risk. *In patients at high risk for thromboembolic events, anticoagulation bridging is considered standard of care. Bridging therapy with intravenous heparin or subcutaneous low molecular weight heparin is utilized in those patients on warfarin once the INR falls below therapeutic range (<2.0). Intravenous heparin is stopped 4–6 h before the procedure; the last dose of subcutaneous low molecular weight heparin is given 24 h prior to the procedure. Post-procedurally, bridging therapy is resumed once hemostasis has been achieved and warfarin restarted; bridging is continued until the INR has reached the therapeutic range*.

With the use of novel oral anticoagulants that achieve reliable therapeutic levels within a few hours with daily or twice a day dosing, the use of bridging therapy is not needed. The timing for discontinuation of these medications prior to an invasive procedure is based on a patient's creatinine clearance. Dabigatran is held 1–2 days prior to the procedure if the patient has normal renal function (creatinine clearance ≥50 mL/min) and 3–5 days with a creatinine clearance ≤50 mL/min. Rivaroxaban and apixaban, factor Xa inhibitors, are held between 1 and 5 days prior to a procedure and timing is based on a patient's renal function. More conservative approaches are often times recommended in patients undergoing very high-risk surgeries.

Aspirin and P2Y12 receptor inhibitors such as clopidogrel, prasugrel, and ticagrelor are commonly encountered medications in patients with cardiovascular diseases. Aspirin is often used alone as well as in combination with other antiplatelet agents. Low dose aspirin alone does not substantially increase the risk of clinically significant bleeding after an invasive procedure but is often times stopped prior to very high-risk procedures [62]. Aspirin along with P2Y12 receptor inhibitors are typically suspended 5–7 days prior to surgery. Appropriate timing in the cessation of antithrombotic and antiplatelet medications provides thromboembolic risk reduction without increasing the risk of periprocedural bleeding for an elective procedure.

Urgent and emergent procedures do not allow physicians the luxury of time when making decisions regarding holding anticoagulation therapy. The administration of reversal agents, if available, may be considered if the risk of bleeding outweighs the risk of thrombotic events. For warfarin, the INR can be reliably reversed within 24–48 h by administering vitamin K. Fresh frozen plasma is usually used to rapidly reverse the INR for a short duration. Prothrombin complex concentrates (PCC) are also used in cases of significant bleeding. PCC contains a combination of blood clotting factors II, VII, IX, X and proteins C and S. For patients receiving direct thrombin or factor Xa inhibitors, there is no specific antidote available for reversal as vitamin K for warfarin. For patients taking dabigatran who have life threatening bleeding, hemodialysis or charcoal hemoperfusion can be considered. Oral activated charcoal can be used to remove the unabsorbed prodrug from the gastrointestinal tract if the last dose was within the previous 2 h. PCC can also be used in life threatening bleeding; however, PCC is not considered standard of care for the management of dabigatran associated bleeding due to the prothrombotic risks as well as lack of evidence from clinical studies. Likewise, reversal with PCC can also be used for those patients with life-threatening bleeds taking rivaroxaban or apixaban. Again, given the risk of thrombosis as

well as the lack of clinical studies evaluating its effectiveness, PCC is only considered appropriate in an imminent life-threatening bleed. Administration of an antifibrinolytic agent such as tranexamic acid or ε-aminocaproic acid can also be utilized in these situations.

Postoperatively, anticoagulant and antiplatelet therapy should be resumed once appropriate hemostasis has been achieved and deemed safe from the surgical perspective. In most instances, patients with a high-risk of thromboembolic events are restarted on warfarin and are bridged with heparin or low molecular weight heparin until therapeutic INRs are achieved. The novel oral anticoagulants are initiated without the need of bridging therapy due to their effectiveness of achieving adequate anticoagulation within a short duration. Resumption of antithrombotic therapy is dictated by achieving proper postoperative hemostasis in order to reduce the risk of postoperative bleeding.

For patients receiving long-term antithrombotic therapy, the approach to periprocedural use of these agents is individualized. Physicians must consider the patient's thromboembolic risk, the procedure's bleeding risk, and the urgency of the procedure to determine the need for possible bridging therapy as well as the appropriate timing for possible cessation of therapy. Emergencies require knowledge regarding possible reversible agents and their risks associated with administration.

Anticoagulation Issues with Mechanical Prosthetic Valves

Given the need for anticoagulation to prevent thrombosis in patients with mechanical prosthetic heart valves, physicians and surgeons are often faced with the important question of anticoagulation management in the setting of various types of procedures. Warfarin with a therapeutic INR is recommended in patients with mechanical heart valves undergoing minor procedures such as dental extractions or cataract removal, where bleeding is easily controlled. *For more invasive surgical procedure, temporary interruption of warfarin without bridging agents is recommended in patients with a bileaflet mechanical aortic valve prosthesis and no other risk factors for thrombosis. But, in patients with a mechanical aortic valve and any thromboembolic risk factor or an older generation mechanical aortic valve, IV UH or subcutaneous LMWH is recommended when the INR is subtherapeutic prior to surgery* [26].

Emergent procedures in this subset of patients require a balance between decreasing a patient's risk of bleeding as well as preventing valve thrombosis. *Fresh frozen plasma or prothrombin complex concentrate (see above) is reasonable in these patients who have uncontrollable bleeding or require emergency surgery* [26]. Following these procedures, patients should immediately be started on parenteral anticoagulation followed by warfarin when appropriate hemostasis has been achieved as deemed by the surgical team.

Anticoagulation in the Setting of Dual Antiplatelet Therapy

With expanding population with myocardial infarction, atrial fibrillation, prosthetic valves etc., *the concomitant use of dual antiplatelet therapy and oral anticoagulation, referred to as triple therapy, is increasing*. However, triple therapy should be used cautiously in these patients, many of them elderly, to balance the benefits with the risk of bleeding. Therefore, triple therapy with warfarin, aspirin, and a P2Y12 should be restricted to specific situations in which the risk of venous thromboembolism or stent thrombosis is considered to exceed the risk of bleeding [35]. It is estimated that between 5 and 10 % of patients scheduled to undergo percutaneous coronary intervention are also on oral anticoagulation [63]. For such patients, the avoidance of drug eluting stents is strongly preferred to limit the duration of triple therapy. Moreover, consideration may be given to lower the target INR goal to 2.0–2.5 (Class IIb) [35]. According to the European Society of Cardiology guidelines, the type of stent utilized, bare metal versus drug eluting stent, as well as the context of

the coronary event, elective versus urgent, also dictates the duration of triple therapy. *Patients who have a low risk of bleeding and are undergoing elective procedures with the use of bare metal stents are recommended to receive triple therapy for 1 month followed by up to 12 months of antiplatelet therapy with clopidogrel or aspirin in addition to warfarin. In these same patients who receive drug-eluting stents, triple therapy should be extended to 3 months followed by 12 months of warfarin and either clopidogrel or aspirin*. For emergent procedures in patients with high risk of bleeding, 4 weeks of triple therapy should be prescribed [35]. Of note, the use of NOACs has not been evaluated in this context.

Conclusion

With an ever-growing population requiring the use of oral anticoagulation, physicians are likely to encounter patients taking these medications in both the inpatient and outpatient settings. To provide appropriate care to these patients, it is imperative to understand the clinical indications for prescribing anticoagulation, the pharmacology of these agents as well as the management of such medications in the elective, urgent, and emergent situations.

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