

## CHAPTER 5

# Cardiac Surgery Screening, Referral, Anticoagulation, and Postoperative Management

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As mentioned in **CHAPTER 4**, about a third of patients identified through district NCD clinics in Rwanda have valvular or congenital lesions amenable to surgical intervention. A much smaller number may benefit from surgical repair of pericardial lesions. The goal is to find these patients before they develop irreversible cardiomyopathies, severe pulmonary hypertension, or renal failure as a result of their disease, all of which would make them poorer surgical candidates later in life.

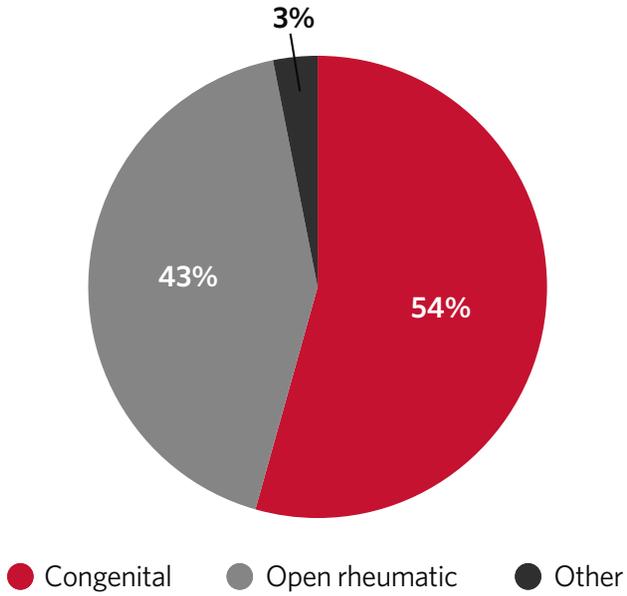
Cardiac surgery for children and young adults with congenital, valvular, or pericardial disease can be an excellent public health investment (see **APPENDIX B**). NCD clinics at district hospitals, working in conjunction with specialists from tertiary centers, can be the key to timely referral for possible surgical candidates. At the same time, good long-term outcomes for patients after cardiac surgery require strong chronic care infrastructure. In this way, cardiac surgery and chronic care integration are synergistic strategies for health-system strengthening.

This chapter discusses some of the issues specific to referral and follow-up of cardiac surgical patients, as well as issues around anticoagulation more broadly.

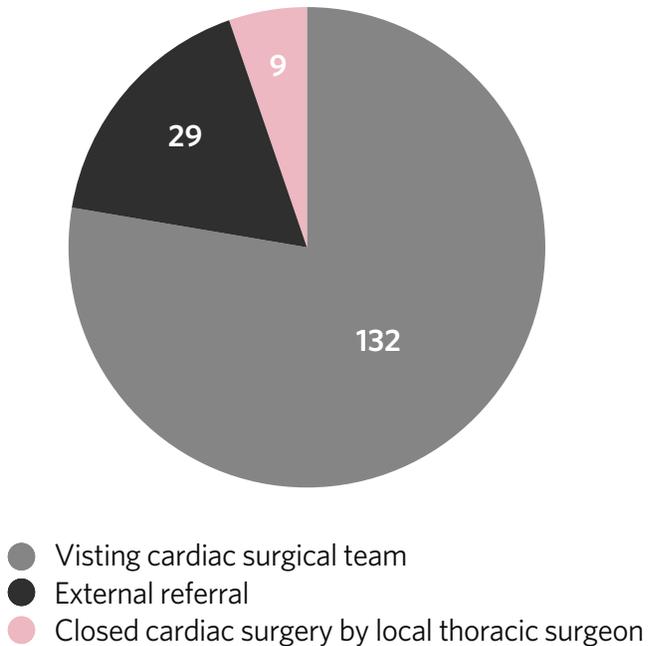
### 5.1 History of Cardiac Surgery in Rwanda

The history of cardiac surgery in Rwanda prior to 1994 is not well known. Between 1994 and about 2006, cardiac surgery was largely unavailable, even to relatively wealthy citizens. Since that time, a Rwandan pediatric cardiologist has returned from training in Belgium and has collaborated with the Rwandan Medical Referral Board and the King Faisal Hospital in Kigali to arrange for more patients to be sent out of country for cardiac surgery and to attract visiting cardiac surgical teams. The goal has been to ultimately establish a Rwandan cardiac surgical program. Between 2006 and 2011, there have been more than 200 cardiac surgical operations in Rwanda, with only 6 deaths. **FIGURE 5.1** and **FIGURE 5.2** show the distribution of indications and sources of surgery for Rwandan patients who received cardiac surgery between November 2007 and February 2010.

**FIGURE 5.1** Indication for Cardiac Surgery between Nov. 2007 and Feb. 2010 (%)



**FIGURE 5.2** Source of Cardiac Surgery in Rwanda between Nov. 2007 and Feb. 2010 (n)



### 5.1.1 Out-of-Country Referral to External Cardiac Surgical Centers

Referral to external cardiac surgical centers is the main source of cardiac surgery for many countries in sub-Saharan Africa. External referral plays an important role, even as African countries work to establish their own cardiac surgical programs. Visiting cardiac surgical teams are not available for emergency cases. Furthermore, external centers are often best equipped to manage complex cases requiring intense and prolonged post-operative care. However, in our experience, raising funds for external referral is challenging (see **FIGURE 5.2**).

There are two kinds of external centers: those that raise money themselves to provide surgery free of charge (philanthropic centers), and those that ask the referring organization to raise the required funds (fee-for-service centers). Both kinds of centers play an important role for increasing access to cardiac surgery.

#### 5.1.1.1 Philanthropic Centers

Many centers in the United States and Europe will occasionally perform cardiac surgery on a philanthropic basis. These centers must raise funds to cover the real costs of these procedures and often look to regional donors for support. However, the cost of care at these centers is high, regardless of who is paying for it. On the other hand, patients flown from Africa often raise awareness and lead to increased engagement from institutions in wealthy countries. These effects have value above and beyond the value of life-saving surgery itself. In the longer run, however, we feel that money raised for philanthropic cardiac surgery could be better directed toward supporting lower-cost care through regional centers in middle-income countries and in Africa itself.

A very important regional center for Central and Eastern Africa is the Salam Heart Center in Khartoum, Sudan.<sup>1</sup> This center is operated by the Italian non-governmental organization Emergency. Emergency raises the funds for the surgeries and hospitalization costs, but needs referring organizations to pay the cost of plane tickets. Emergency has estimated that their real cost per surgery is around \$14,000. Since 2007, this center has performed more than 3000 surgical operations.

The Walter Sisulu Heart Center in Johannesburg, South Africa, is another important site that performs a limited number of surgeries for pediatric patients.<sup>2</sup> Although these surgeries are provided free of charge to the referring organization, the real costs of these procedures are probably relatively high in South Africa.

Save A Child's Heart is an Israeli organization that both provides cardiac surgery for children from Africa, and trains African professionals.<sup>3,4</sup> The

funding for this organization is limited, and increasingly their center in Holon, Israel, is asking for a financial contribution from referring organizations.

#### 5.1.1.2 Fee-for-Service Centers

International fee-for-service centers are an important resource for African countries. There are many centers in India that provide excellent care through impressively high-volume, low-cost models. By one estimate, more than 60,000 open-heart surgeries are performed in India each year—around 600 for every 10 million people.<sup>5</sup> The experience in Rwanda has been primarily with the Miot center in Chennai.<sup>1</sup> Results from this center have been good, even with complex cases. The total charges per patient, including air transportation and housing, have been between \$10,000 and \$15,000.

#### 5.1.2 Visiting Cardiac Surgical Teams

Visiting cardiac surgical teams have played a critical role in development of cardiac surgical capacity in Rwanda. The real costs of surgeries performed by these teams may well be higher than the cost of transfer to external centers. We believe this cost is worth it as long as skills continue to be transferred to local professionals with each trip. In the end, the goal of the visiting cardiac surgical teams is to support self-sufficient local teams of surgeons, anesthesiologists, and nurses.

Visiting teams are, of necessity, large, and require substantial funds for travel, food, and lodging (see below). These costs are particularly high in Rwanda compared with other low-income countries. Moreover, up until the present, visiting teams have needed to ship large quantities of medication and equipment from abroad.

Cardiac surgical teams visiting Rwanda have raised money for equipment, supplies, and travel. Health providers have also donated their vacation time. These teams meticulously procure, label, pack, and ship nearly every single item needed for the performance of complex cardiac surgical procedures. These items include, but are not limited to, heart-lung machines, ultrasound equipment, and surgical instruments, as well as consumables such as perfusion supplies, medications, intravenous fluids, surgical masks, gowns, and prosthetic heart valves and rings. Some teams have also supported the cost of patient follow-up and social support (e.g., school fees, housing).

The Rwandan Ministry of Health (MOH) has made an equally important contribution. The MOH has paid for lodging costs for essential members of visiting teams. The MOH has also absorbed the hospitalization costs at the hosting institution, the King Faisal Hospital.

The first cardiac surgical team to operate in Rwanda was Operation Open Heart (OOH) in April 2006.<sup>6,7</sup> This Australian group already had several decades of experience supporting a cardiac program in Papua New Guinea and other Asian and Pacific island countries.<sup>8,9</sup> Since that time, OOH has operated in Rwanda every November. This surgical group performs adult and pediatric surgeries, and has paved the way for other visiting teams.

In April 2008, Team Heart became the second cardiac surgical group to operate in Rwanda.<sup>10</sup> Team Heart is a Boston-based cardiac surgical group affiliated with the Brigham and Women's Hospital. Team Heart has focused on surgery for teenagers and young adults with rheumatic valvular disease. This surgical group has completed an annual surgical mission for four consecutive years, most recently in February of 2011. Team Heart has also been an important advocate for strategies to prevent rheumatic heart disease and rheumatic fever, including school-based screening.

In February 2010, Healing Hearts Northwest (HHNW) joined the group of cardiac surgical teams supporting Rwanda through annual missions.<sup>11</sup> HHNW performs both adult and pediatric surgeries.

Chain of Hope Belgium has also brought pediatric interventional teams to Rwanda. Although there is no cardiac catheterization laboratory in Rwanda at present, Chain of Hope has been able to operate using echocardiographic and fluoroscopic guidance.<sup>12</sup> The Chain of Hope team has also been instrumental in training another Rwandan pediatric cardiologist, who recently returned from Belgium and joined the public sector.

## 5.2 Building a National Cardiac Surgery Program

There are very few national cardiac surgical programs in Africa.<sup>13-18</sup> The challenges of establishing such centers and achieving good surgical outcomes are significant. At the same time, countries with populations of 10 million or more people can easily justify the need for at least one local center to perform 300 or more surgeries per year. We have estimated that such centers could provide valvular replacements for under \$5000 per case (see **APPENDIX B**). Programs that operate on 300 or more cases per year must be able to rely on a strong system of chronic care capable of anticoagulation monitoring at district-hospital level. The following sections describe strategies for case finding and follow-up.

### 5.2.1 Cardiac Surgical Referral

Cardiac surgical programs need to have access to a large and nationally inclusive set of potential cardiac surgical candidates. One challenge for

cardiac surgical programs is ensuring that the poor living in rural communities, located far from the capital, have equal access to referral for cardiac surgery. Traditionally in Rwanda, as in many countries, cardiac surgery programs have relied upon a combination of existing referral systems and intermittent cardiac surgical screening camps. National scale-up of NCD clinics at district hospitals will play a crucial role in expanding and enriching the pool of possible cardiac surgical candidates available for evaluation by specialists at the University Teaching Hospitals (CHUK and CHUB) and King Faisal Hospital. Here we briefly describe how NCD clinics feed into the cardiac surgical selection system.

Once a district NCD clinic system is in place, heart failure cases are evaluated first at district-hospital level by the NCD nurse (see **CHAPTER 4**). Once the NCD nurse has confirmed probable heart failure and excluded a cardiomyopathy or hypertensive heart disease, the patient is referred to a cardiologist for complete evaluation and advanced echocardiography. Heart failure clinics are held on the same day each week and patients are divided into groups. This kind of organization allows both cardiologists from visiting teams and those working in the referral centers to do efficient outreach to district hospitals around the country.

Once the cardiologist determines that a patient is a suitable surgical candidate, he or she adds them to a national cardiac surgical waiting list. Prior to each cardiac surgical mission, visiting teams can review this list as part of their initial patient case selection.

**TABLE 5.1** shows the typical evaluations requested by cardiac surgical teams prior to surgery.

**TABLE 5.1 Typical Preoperative Evaluation for Cardiac Surgery**

<b>History</b>
<ul style="list-style-type: none"> <li>• Heart failure symptom class</li> <li>• Careful examination for possible tuberculosis</li> <li>• Social evaluation (including housing, education, and employment needs)</li> <li>• Reproductive history</li> </ul>
<b>Physical examination</b>
<ul style="list-style-type: none"> <li>• Evaluation for obvious comorbidities</li> <li>• Careful evaluation of the liver</li> <li>• Evaluation for malnutrition</li> <li>• Dental evaluation</li> </ul>
<b>Laboratory studies</b>
<ul style="list-style-type: none"> <li>• Complete blood cell count with differential</li> <li>• HIV</li> <li>• Hepatitis C</li> <li>• Liver function tests</li> <li>• Creatinine, glucose, electrolytes</li> <li>• Urinalysis</li> <li>• Blood smear for malaria</li> </ul>
<b>Imaging</b>
<ul style="list-style-type: none"> <li>• Chest x-ray</li> <li>• Echocardiogram (within 1 month)</li> </ul>

### 5.2.2 Principles of Case Selection

It has been the observation of visiting adult cardiac surgical teams in Rwanda that patients with rheumatic valvular disease, and particularly the poorest and those from rural areas, present late in their clinical course. By this time, these patients are already experiencing NYHA Class III and IV heart failure symptoms, with involvement of two, and sometimes three, cardiac valves.

Thus, while it is desirable that local cardiac surgery programs in Africa initially focus on lower-risk surgical candidates, systematically excluding salvageable patients with advanced disease is not a good option. This, among numerous additional factors, will impact the pace with which local, independent cardiac surgery programs can develop, and will continue to mandate involvement of visiting programs to perform surgeries, while training local personnel to assume direction of the programs.

In Rwanda, cardiac surgical case selection is coordinated nationally by the cardiac surgery program director with input from all cardiologists. Here we describe some principles of case selection in a setting where

available options for cardiac surgery include (1) limited numbers of visiting teams and, to a lesser degree, (2) external referral. The total number of available surgical slots has been around 60 per year, although this continues to grow.

First, given very limited access to cardiac surgery in Rwanda, patients under age 40 are prioritized.

Second, many patients unfortunately have disease that is so advanced that they are unlikely to have a good outcome even with surgery.

Third, some patients would require multiple staged surgeries to achieve a full repair (e.g., congenitally single ventricles). These patients are currently considered too complex to fix. For these patients, a palliative shunt is the best available option.

Fourth, most visiting cardiac surgical teams do not feel that it is safe to operate on more than one highly complex case per day. Visiting teams must balance the sometimes competing demands of patient acuity and complexity with the realities of postoperative care availability. Despite these resource limitations, more adult patients have received multiple, rather than single, valve procedures for the past 3 years. Over the past 4 years, multiple valve operations have become the norm for patients with rheumatic valvular disease, including several triple valve surgeries.

Fifth, out-of-country referral is used to make surgery available for emergent cases and reasonable candidates who are unlikely to survive for evaluation by the next visiting team.

As of December 2010, there were more than 100 patients awaiting cardiac surgery in Rwanda.

### 5.3 Common Procedures for Cardiac Valves

NCD nurses and generalist physicians working at district hospitals need to understand some of the basics of cardiac valvular surgery.<sup>19</sup> The follow-up issues for patients following cardiac surgery depend, in part, on the nature of the surgery they have undergone.

There are two basic types of valvular surgeries: valve repair and valve replacement. Mitral valves and tricuspid valves can sometimes be repaired. Valve repair has the advantage of preserving more of the normal function of the valve. On the other hand, patients with a valve repair often require a second operation later in life.

Access to heart surgery in Rwanda and surrounding countries is limited. Given the fact that reoperative heart surgery is not likely to be a priority in the near future, experienced visiting teams are opting more often for valve replacement therapy for patients with rheumatic heart disease.

The decision of mechanical versus tissue prostheses is often challenging, and must incorporate both medical as well as cultural factors. One of the common situations encountered is operating on a female of child-bearing age who may wish to have children. Mechanical valves require patients to take teratogenic anticoagulants. Even though tissue valves do not last as long in young individuals, in this circumstance, we choose to honor the patient's wishes, and give her tissue prostheses. Another not-uncommon situation is a patient who may be from such a remote part of the country that warfarin follow-up is not feasible. In this case, tissue valves would also be the safer option, though perhaps not the most durable. In most cases, mechanical valves are preferred, provided warfarin follow-up is available.

The sections below discuss the considerations involved with each type of surgery.

### 5.3.1 Mitral or Tricuspid Valve Repair

Some valvular damage is mild enough to be repaired. The main advantage of a valve repair is that it leaves the part of the valve below the leaflets intact. This contributes to better function of the associated ventricle. The risk of reoperation due to failure of the repair probably falls somewhere between the risks of failure in bioprosthetic and mechanical valves.<sup>20</sup>

For patients with mitral stenosis due to fusion of the anterior and posterior leaflets, successful surgery involves separating the two leaflets. This is called a *commissurotomy* (see **TABLE 5.2**). In patients with regurgitant mitral valve disease, a metal ring can be used to slightly narrow the valve. The ring is placed around the outer edge of the valve (also called the annulus). This procedure is called a *ring annuloplasty*. In addition, some patients may also need to have part of their valve cut away, or augmented with pericardium, to fix the regurgitation.

**TABLE 5.2** Types of Valve Repairs

	Ring annuloplasty	Commissurotomy
<i>Indication</i>	Mitral or tricuspid regurgitation	Mitral or tricuspid stenosis
<i>Anticoagulation</i>	Yes, with aspirin	Yes, with aspirin

### 5.3.2 Percutaneous Procedures

A minimally invasive procedure can open up stenotic valves and can close certain congenital heart lesions. A small catheter is placed through the groin (into the femoral artery or vein) and is passed upward toward the heart. Small corrective devices can be passed through these catheters to repair the defect. If this type of procedure can be done, it is preferred, since it carries the smallest risk.

Rwanda currently does not have a cardiac catheterization laboratory, but it is possible to perform some congenital procedures with echocardiographic and fluoroscopic guidance alone.

There are two issues with balloon valvuloplasty for mitral and tricuspid stenosis at this point. First, we have very few patients in our surgical series with pure mitral or tricuspid stenosis amenable to valvuloplasty. In order to maintain skills in this procedure, a certain volume is required, and it may be that this will only be possible at a later stage of health service development, when patients are diagnosed at an earlier stage of disease progression. Secondly, due to the risks of balloon valvuloplasty, there must be a cardiac surgical team available on site at the time of the procedure as back-up.

We feel that the main justifications for a cardiac catheterization laboratory early in the development of a cardiac surgical program are (1) the need for diagnostic catheterization, and (2) delivery of low-risk procedures for congenital heart disease.

### 5.3.3 Mechanical Valves

Mechanical valves are made out of an artificial material and are very durable. Once these valves are in place, the patient may never need another heart surgery. This is the great advantage of these valves, especially in settings where access to repeat cardiac surgery is very limited. The disadvantage of these kinds of valves is that they are all susceptible to forming clots on their surface. (See **TABLE 5.3**.) For this reason, patients with mechanical valves need to be continuously anticoagulated with warfarin to prevent stroke, valve thrombosis, and other complications. Warfarin is a drug with unpredictable effects and needs to be monitored closely (see **SECTION 5.8**).

Outcomes in general for patients with mechanical valves have been poor in Africa because of weak chronic care infrastructure.<sup>21</sup> We believe that use of community health workers to support adherence with therapy can improve these outcomes as they have in the case of HIV and tuberculosis.

In general, we prefer mechanical valves because of their durability. The following section describes types of patients for whom mechanical valves are not a good option.

### 5.3.4 Bioprosthetic Valves

Bioprosthetic valves are made from living tissue (from a cow, pig, or human) and are shaped to resemble a normal heart valve. Since they are made of living tissue, the risk of thrombosis is greatly reduced, and only aspirin (100 mg, 1x/day) is needed. However, normal heart function can damage these valves. They rarely last more than 10 years, and sometimes much less.<sup>22</sup> (See **TABLE 5.3.**)

Bioprosthetic valves are good for the following types of patients:

- 1. Young children.** Young children are likely to need a second operation at some point because they will outgrow their valve; a mechanical valve would expose them to extra risks without much benefit over a repair or replacement.
- 2. Women of child-bearing age who want to have children.** Warfarin causes birth defects in pregnancy and increases the risk of miscarriage. There is no ideal strategy for managing women who are pregnant and have a mechanical valve.<sup>23,24</sup> For all women of child-bearing age with a mechanical valve, contraception will be very important.
- 3. Patients that live in districts without chronic care infrastructure.** Mechanical valves can be dangerous if there is not a good system of follow-up close to the patient's home. In this scenario, a bioprosthetic valve may be a less risky option.

**TABLE 5.3** Types of Replacement Heart Valves

	Bioprosthetic	Mechanical
<i>Anticoagulation</i>	Aspirin	Warfarin
<i>Longevity</i>	~10 years, probably less	~20 years, potentially life-long
<i>Endocarditis risk</i>	Increased	Increased
<i>Used in</i>	<ul style="list-style-type: none"> <li>▪ children</li> <li>▪ women of child-bearing age who desire future pregnancies</li> </ul>	<ul style="list-style-type: none"> <li>▪ men</li> <li>▪ women of child-bearing age who do not desire more children</li> <li>▪ women not of child-bearing age</li> </ul>

## 5.4 Early Post-Operative Evaluation (First 3 Months)

In addition to their regular visits to a chronic care clinic, post-cardiac surgery patients should be seen by a cardiologist at least 4 times in the first year (1 month, 3 months, 6 months, and 12 months following their

operations).<sup>25</sup> Careful records should be kept for these patients on a post-cardiac surgery follow-up chart. In our system, patients who go to referral hospitals to follow up are asked to bring this chart. Information from each visit should also be recorded in a central electronic medical record. Ideally, a national cardiac surgery coordinator will oversee this process. Any concern about these patients should be communicated immediately to the larger cardiac surgery network.

At each post-operative visit, the patient should be physically examined (including auscultation) with special attention to crisp valve clicks (in the case of mechanical valves), and to the absence of new heart murmurs. Patients should have their vital signs measured (including weight, height, blood pressure, pulse, and respiratory rate if in any respiratory distress). They should then have their volume status assessed in the same manner as with preoperative heart failure patients (see **SECTION 4.7**). Patients should be asked about medication adherence. Women less than 49 years of age should be asked about birth control measures and referred accordingly (see **SECTION 3.5**). All patients should have a creatinine drawn if they are on any heart failure medications. Patients on anticoagulation should also have an INR drawn.

Certain complications, described below, are most common in the first 3 months after surgery.

#### 5.4.1 Heart Failure

Great shifts of fluid occur during heart surgery. The heart muscle can also be damaged. After 3 to 6 months, patients will often stabilize. During the early post-operative period in particular, careful attention must be paid to the patient's weight, and furosemide must be adjusted to prevent decompensation from fluid overload. Patients with persistently depressed left ventricular function after cardiac surgery should be treated for heart failure according to the cardiomyopathy protocol (see **PROTOCOL 4.4**). Patients with normal right and left heart function should ultimately not require any furosemide.

Continued heart failure—especially a change in the patient's status—can signify a new problem with a valve (such as endocarditis, thrombosis, or valve dehiscence/detachment). It can also signify pericardial tamponade (see below), or an arrhythmia (such as atrial fibrillation). For this reason, scheduled echocardiograms performed by a specialist are important shortly after surgery.

#### 5.4.2 Sternal Wound Infection and Dehiscence

To access the heart for surgery, the sternum must be cut. At the end of the procedure, the sternum is repaired using wires. On occasion, some

of these wires may separate, causing dehiscence and instability of the sternum. If this occurs, patients are at risk for infections of the wound and of the deeper structures of the heart. This is an emergency; patients need immediate treatment with antibiotics. At each of the early visits following surgery, the sternum should be checked for stability. A practitioner can check for instability by placing the palm of the hand on the sternum and rocking it back and forth. If there is instability, a click will be felt. Some post-operative sternal pain is normal, and usually resolves with time. But a sternum that moves significantly with gentle pushing is a concern and should quickly be brought to the attention of the cardiac surgery team.

### 5.4.3 Pericardial Tamponade

During cardiac surgery, the pericardium is opened. Most patients will have a small pericardial effusion that resolves after 3 to 6 months. In some patients, however, the fluid collection grows and eventually interferes with the heart's function (tamponade). This condition can kill the patient if the fluid is left undrained. A large effusion can be seen easily on a preliminary echocardiogram (see **FIGURE 4.9**), which should be attempted at each of the early follow-up visits. If there is a concern, the cardiac surgery team should be contacted immediately, and echocardiographic images should be transmitted by email if possible. In the event of cardiovascular collapse, bedside drainage of the effusion should be attempted if a clinician experienced in the procedure is available. Sometimes, there are fluid collections localized around just one part of the heart. These can cause problems and may only be noticed by a specialist. Clinicians should suspect pericardial tamponade if a post-operative patient presents with hypotension.

### 5.4.4 Endocarditis

Infection of a prosthetic heart valve can be aggressive. Although such infections can occur any time after surgery, they are particularly common in the first 6 months. On physical examination, new signs of heart failure or new murmurs can be suggestive of endocarditis. Most important, the patient's temperature should be checked at every visit.

Antibiotic prophylaxis is recommended prior to any dental procedure.<sup>26</sup> Amoxicillin should be given 60 minutes prior to the procedure in a single dose of 2 gm (adult) and 50 mg/kg (children  $\leq$  40 kg). Clindamycin is an alternative in those with a penicillin allergy: 600 mg in adults, 20 mg/kg in children (maximum 600 mg).

### 5.4.5 Atrial Arrhythmias

After cardiac surgery, patients are at high risk for developing atrial fibrillation. The use of beta-blockers in the post-operative setting helps

to reduce the risk of atrial fibrillation. Post-operative patients should be treated with a beta-blocker (generally atenolol) for the first 6 weeks after surgery. After that, the atenolol should be gradually reduced and eventually stopped.

## 5.5 Ongoing Monitoring of the Post-Operative Patient

After the early post-operative period, most patients should be able to be followed primarily at district level, in NCD clinics. Referral to a cardiologist or to referral centers should be on an as-needed basis. However, information about the patients should still be communicated to a central coordinator to aid with monitoring and evaluation of the national referral system.

Patients continue to be at risk for certain complications. NCD clinicians should evaluate for these at each follow-up visit. Any complication should be recorded in the patient chart and communicated to the national cardiac surgery coordinator.

### 5.5.1 Fever in Patients with Prosthetic Heart Valves

Patients with any type of prosthetic heart valve remain at risk for valve infections (endocarditis). The patient's temperature should be checked at each follow-up visit and the patient should be asked about subjective fevers. If a fever  $\geq 38^{\circ}\text{C}$  ( $\geq 100.4^{\circ}\text{F}$ ) is found, the practitioner should be concerned about endocarditis and involve the district hospital physician on call immediately. In Rwanda, the clinician sends an email message to the cardiac surgery network.

Methicillin-resistant *Staphylococcus aureus* has been identified as a cause of prosthetic valve endocarditis in Rwanda. An emergency stock of vancomycin should be made available to all district hospitals that are following patients after valvular heart surgery.

If a patient with a fever has a blood pressure  $\leq 80/40$  mmHg, signs of sepsis (tachycardia, labored breathing), or a new murmur, the patient should be immediately transferred to the inpatient district hospital ward. Two sets of blood should be drawn for cultures (each from a separate intravenous puncture). Blood cultures are generally positive in cases of endocarditis and are essential for the choice of long-term antibiotics. Blood is sent to the referral center lab in the capital, since district hospitals are currently unable to process blood cultures.

The patient should be stabilized at the district hospital (with fluids and peripheral vasopressors such as dopamine if needed) and then transferred to the capital for referral center-level care. Such transfers should

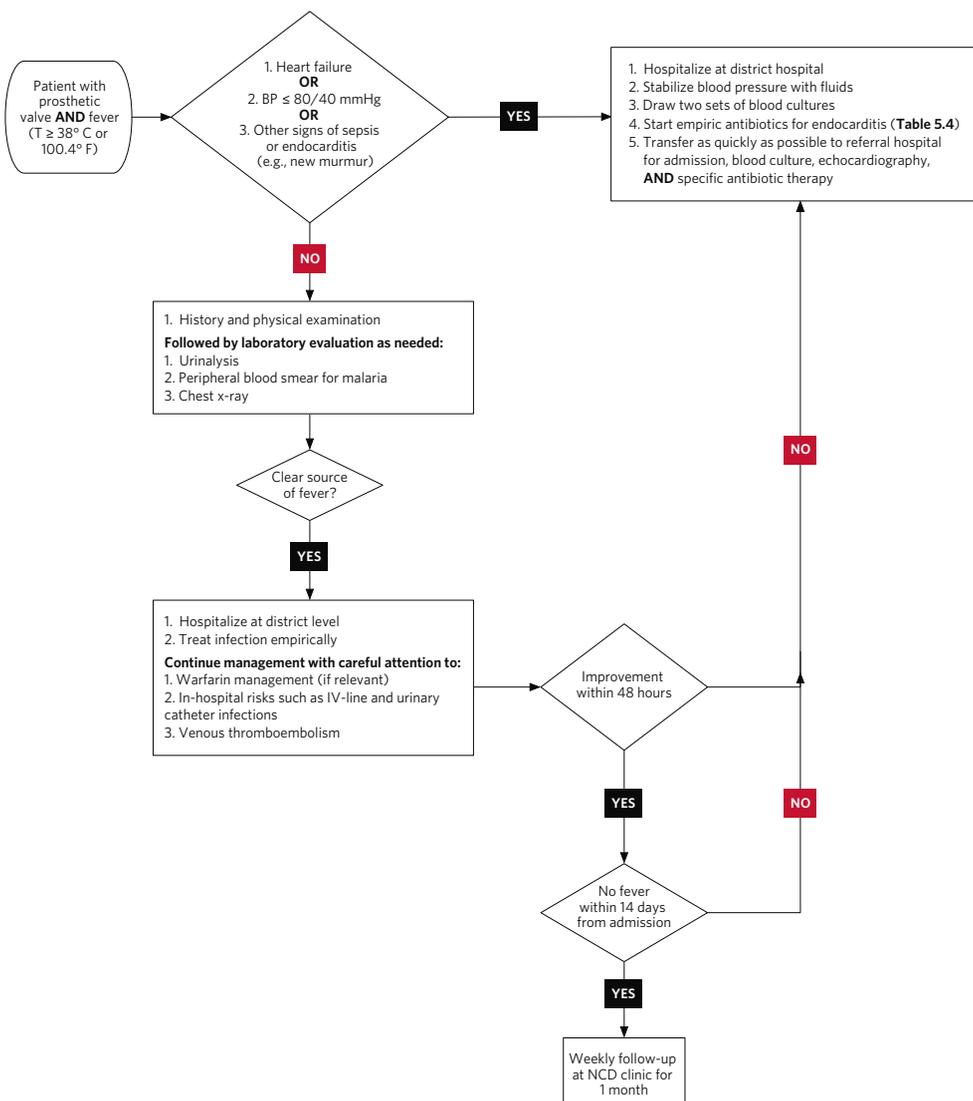
be communicated promptly to the national cardiac surgery coordinator and to the cardiologist following the patient.

After blood cultures are drawn, empiric antibiotics should be started. Intravenous vancomycin is the preferred empiric treatment, but if this drug is not available, then the combination of cloxacillin and ceftriaxone is an alternative (see **TABLE 5.4**).

**TABLE 5.4 Empiric Antibiotic Treatments for Endocarditis**

Antibiotic	Indication	Adult dose	Pediatrics dose	Effect on warfarin
Vancomycin	Empiric endocarditis therapy, methicillin-resistant <i>Staphylococcus aureus</i> , <i>Staphylococcus epidermidis</i> , enterococcus	1 gm/dose 2x/d	10 mg/kg/dose 4x/d (maximum 1 gram per dose)	No effect
<b>OR (Combination therapy with cloxacillin + ceftriaxone or penicillin G)</b>				
Cloxacillin	Empiric endocarditis therapy, methicillin-sensitive <i>Staphylococcus aureus</i> , empiric treatment of cellulitis in patients with prosthetic heart valves	2 gm/dose every 4 hours IV	50 mg/kg/dose every 4 hours IV	No effect
Ceftriaxone	Empiric endocarditis therapy, <i>Streptococcus viridans</i> , empiric treatment of urinary tract infection, pneumonia in patients with prosthetic heart valve	2 gm daily IV <b>OR</b> IM	100 mg/kg/daily IV <b>OR</b> IM (maximum 2 gm)	Decreases warfarin effect
Penicillin G	Empiric endocarditis therapy, <i>Streptococcus viridans</i>	4.5 million units/dose IV 4x/d	50,000 units/ kg/dose IV 4x/d (maximum 24 million units/day)	No effect

Patients who have a fever but none of the other warning signs can be evaluated for other common infections, such as malaria, urinary tract infections, pneumonia, or cellulitis. Blood cultures should be drawn and sent to the referral hospital before starting empiric antibiotics. Patients should be hospitalized while awaiting blood culture results. If there is no improvement in a patient's status within 24 hours, transfer to the referral center should be arranged. (See **PROTOCOL 5.1**.)

**PROTOCOL 5.1 Management of Fever in Patients with Prosthetic Heart Valves**

We do not address the long-term treatment of endocarditis in this guide. One major issue in the treatment of prosthetic-valve endocarditis is that it usually involves intravenous antibiotics for at least 6 weeks (see **TABLE 5.5**). Oral antibiotics alone are not an acceptable alternative to intravenous treatment, and the need to frequently change peripheral intravenous catheters can be a problem. Efforts should be made to introduce skills in midline intravenous catheter placement and care at the district hospital level.

An additional consideration is that many antibiotics modify the effect of warfarin (see **TABLE 5.6**). In patients taking warfarin, the international

normalized ratio (INR) should also be followed closely during antibiotic treatment.

Finally, *Staphylococcus aureus* endocarditis is particularly aggressive in prosthetic heart valves and may even require reoperation. All endocarditis cases should be managed very closely with the director of the national cardiac surgical program in discussion with the national cardiac surgical community.

**TABLE 5.5 Some Organism-Specific Treatments for Prosthetic Valve Endocarditis**

Antibiotic	Duration of therapy	Adult dose	Pediatrics dose	Effect on warfarin
<b>Staphylococcus aureus (methicillin-resistant): combination therapy</b>				
Vancomycin	6 weeks	1 gm/dose 2x/d	15 mg/kg/dose 4x/day (maximum 1 gram per dose)	No effect
Gentamicin	2 weeks	1 mg/kg/dose IV <b>OR</b> IM 3x/d	1 mg/kg/dose IV <b>OR</b> IM 3x/day	No effect
Rifampin	6 weeks	300 mg orally 3x/day	7 mg/kg/dose orally 3x/d	Markedly decreases warfarin effect
<b>Staphylococcus aureus (methicillin-sensitive): combination therapy</b>				
Cloxacillin	6 weeks	2 gm daily IV	50 mg/kg/dose every 6 hours IV	No effect
Gentamicin	2 weeks	1 mg/kg IV <b>OR</b> IM 3x/d	1 mg/kg/dose IV <b>OR</b> IM 3x/day	No effect
Rifampin	6 weeks	300 mg orally 3x/day	7 mg/kg/dose orally 3x/d	Markedly decreases warfarin effect
<b>Streptococcus viridans (ceftriaxone or penicillin G)</b>				
Ceftriaxone	6 weeks	2 grams daily IV <b>OR</b> IM	100 mg/kg/daily IV <b>OR</b> IM (maximum 2 gm)	Decreases warfarin effect
Penicillin G	6 weeks	4.5 million units/dose IV 4x/d	50,000 U/kg IV 4x/d (maximum 2.4 units/d)	No effect

### 5.5.2 Valve Thrombosis

All patients with mechanical heart valves should be on lifelong anticoagulation therapy with warfarin to prevent blood clots in the heart and strokes. If the level of anticoagulation drops below the goal range, patients will be at increased risk for the formation of blood clots on the valves (thrombosis). The risk of thrombosis varies with type and position of the valve. Mechanical tricuspid valves are at the highest risk, followed by mitral and aortic valves.

If thrombosis occurs in a patient with a mechanical valve, the heart valve will lose its usual crisp closing sound. Cardiac auscultation should be performed in all post-cardiac surgery patients with mechanical

valves. Appreciating the difference between a normal mechanical heart valve and one without a crisp sound can be difficult. This skill is usually acquired after listening to many normal mechanical valves. If there is a concern for valve thrombosis, the patient should be referred to the patient's cardiologist immediately. While preparing for transfer, these patients should have an INR checked and, if it is below goal range, should be given heparin subcutaneously to reduce the chance of further clot propagation.

### 5.5.3 Valve Dehiscence

When a valve is repaired or replaced, new components are generally attached to the heart's structure with sutures. In rare cases, these sutures may loosen, opening defects near the margin of the heart valve. Blood may then regurgitate through these defects, generating a new murmur. If a new murmur is noted during auscultation of a post-cardiac surgery patient's heart, the practitioner should suspect dehiscence or endocarditis and should refer the patient to the patient's cardiologist.

## 5.6 Penicillin Prophylaxis for Patients with Surgically Corrected Rheumatic Valvular Disease

Patients with rheumatic valvular disease should be treated with penicillin to prevent further streptococcal throat infections and recurrent rheumatic fever. In patients who have surgically repaired or replaced valves for rheumatic heart disease, penicillin prophylaxis should be continued. Repeat infections can result in damage to other heart valves, which may also require surgery. These outcomes can be avoided with the appropriate use of penicillin. See **TABLE 9.5** for details on the use of penicillin for prophylaxis.

## 5.7 Methods of Anticoagulation and Indications

Anticoagulation can be lifesaving for many patients. It is essential for post-cardiac surgery patients with mechanical valves. However, using anticoagulants safely in resource-poor settings has often been seen as unachievable. Here we detail our approach to this problem.

Anticoagulation can be achieved by several means. In Rwanda, the main options are aspirin, subcutaneous enoxaparin (Clexane), subcutaneous unfractionated heparin, and oral warfarin.

Aspirin is a safe, effective, and inexpensive option for patients who have an increased, but still relatively low, risk of thrombosis. These include patients with mitral stenosis in sinus rhythm and stable peripartum cardiomyopathies, as well as those who have bioprosthetic valves.

However, patients at higher risk of stroke, such as those with a known thrombus or a mechanical heart valve, require a greater degree of anticoagulation. This is achieved with warfarin, which inhibits synthesis of several blood coagulation proteins. Warfarin is a tricky drug. Metabolism varies greatly from person to person and within the same patient from day to day, and even hour to hour, depending on interactions with food and medications. **TABLE 5.6** lists some of the common medications that interact with warfarin.

**TABLE 5.6 Common Drug Interactions with Warfarin**

Drug	Effect on INR
Co-trimoxazole	Increase
Metronidazole	Increase
Ciprofloxacin	Increase
Cimetidine	Increase
Rifampin	Decrease
Antiretroviral drugs	Increase or decrease
Alcohol	Increase or decrease

Moreover, warfarin takes several days to achieve a therapeutic level of anticoagulation. Subcutaneous enoxaparin (Clexane) or subcutaneous unfractionated heparin is used in patients at a very high risk of stroke who require additional anticoagulation (a “bridge”) until the warfarin takes effect. District hospitals in Rwanda currently don’t use IV heparin because IV pumps for drips and PTT monitoring are not available.

The international normalized ratio, or INR, is the main blood test used to measure the degree of anticoagulation in patients on warfarin. The INR is calculated from a prothrombin time, which is compared to that of a normal individual. As the blood becomes more anticoagulated (or “thinner”), the INR value will rise. A normal INR is 1.0.

Different conditions can be more or less prone to the development of thrombosis. In general, conditions in which blood is stagnant are particularly thrombogenic. For instance, patients with mechanical mitral or tricuspid valves (where blood does not move at high velocities) are more likely to develop thrombosis compared to those with mechanical aortic valves. Different INR targets are used for the different types of indications.

Common indications for anticoagulation in our clinics and district hospitals include post-cardiac surgery status, atrial fibrillation, mitral stenosis, left

ventricular thrombus, atrial thrombus, deep venous thrombosis, and pulmonary embolism. Treatment aims to prevent stroke and other embolic disease while minimizing the risks of bleeding. **TABLE 5.7** lists our indications for anticoagulation and the agents we use.

**TABLE 5.7 Anticoagulation Agents and Indications**

Indications	Warfarin or aspirin?	Heparin bridge?	Goal INR	Duration of therapy
<b>Heart failure and atrial fibrillation</b>				
Peripartum cardiomyopathy	Aspirin	N/A	N/A	Lifelong
Mitral stenosis in sinus rhythm	Aspirin	N/A	N/A	Lifelong
Mitral stenosis with signs of prior stroke	Warfarin	No	2.0-2.5	Lifelong
Atrial fibrillation (without heart failure)	Aspirin	N/A	N/A	Lifelong
Atrial fibrillation (with heart failure)	Warfarin	No	2.0-2.5	Lifelong
<b>Prosthetic valves</b>				
Bioprosthetic tricuspid valve	Warfarin for the first 3 months, then aspirin	Yes	2.5-3.0	Lifelong
Other bioprosthetic valves (not tricuspid)	Aspirin	N/A	N/A	Lifelong
Mechanical aortic valve	Warfarin	Yes	2.5-3.0	Lifelong
Mechanical mitral valve	Warfarin	Yes	3.0-3.5	Lifelong
Mechanical tricuspid valve	Warfarin	Yes	3.0-3.5	Lifelong
<b>Thrombus</b>				
Ventricular thrombosis	Warfarin	Yes	2.0-2.5	6 months
Deep-vein thrombosis	Warfarin	Yes	2.0-2.5	3 months
Pulmonary embolism	Warfarin	Yes	2.0-2.5	6 months

## 5.8 Initiating Warfarin Therapy

Protocols in previous chapters have indicated when anticoagulation should be started in patients with heart failure and atrial fibrillation.

### 5.8.1 Contraindications to Warfarin Therapy

Before starting warfarin therapy, patients should be assessed for relative contraindications to warfarin therapy.

Warfarin in pregnancy can cause serious birth defects as well as fetal loss. The risks and benefits of initiating warfarin should be discussed with the woman. In some cases, such as the presence of a mechanical valve, the risk to the mother of not taking warfarin will likely outweigh

the risks to the fetus. In other cases, such as atrial fibrillation, the risk of an embolic event may be deemed low enough that the woman will choose not to take warfarin during the pregnancy.

Recent, serious bleeding is another relative contraindication. Again, this should be weighed against the risk of embolic events in deciding whether or not to start warfarin.

Patients should also be assessed for signs of liver disease. A patient with a large, palpable liver on exam, ascites, or a history of heavy alcohol use should have an INR checked prior to initiating warfarin therapy. Warfarin should still be given if the INR is below the goal range, but therapy should be started at half the normal dose.

### 5.8.2 Monitoring Warfarin

In many low-income settings, the costs of warfarin and of monitoring devices are seen as an insurmountable barrier to anticoagulation. In our experience, investment in this intervention is cost-effective and less dangerous than generally perceived. Patients are usually very vigilant about checking their own INR. Properly trained community health workers are a great aid in helping to monitor and titrate warfarin doses.

Patients who have an indication for warfarin should first be assessed for their risk of stroke or other embolic events. Patients at low risk of embolic events include those with atrial fibrillation. These patients may have warfarin initiated in the outpatient setting with close follow-up.

**TABLE 5.8** lists recommended dosing for outpatient initiation of warfarin. Note that this dosing is lower than typically used in settings with more intensive monitoring.

**TABLE 5.8 Initial Outpatient Warfarin Dosing**

Patient age	Initial dose
Adults	2.5 mg/day
Children (5–40 kg)	0.1–0.2 mg/kg/day (maximum 10 mg/dose)

Patients at high risk of embolic events include those with mechanical valves and those with an active clot in the heart or the deep veins of the legs. Any patient who is at very high risk of thrombosis and who therefore requires a heparin bridge must be started on warfarin in the hospital. Unfortunately, all low-molecular-weight heparins are relatively expensive and in our experience not affordable to procure on a large scale. Therefore, in Rwanda we often use subcutaneous heparin at treat-

ment doses as a bridging therapy. Partial thromboplastin time (PTT) is not available to monitor the level of anticoagulation. Because infusion pumps are not available at district hospitals, we use subcutaneous heparin. **TABLE 5.9** lists doses for bridging medications. Because warfarin takes 3 days to reach its full effect, the warfarin dose should not be increased more frequently than every 3 days.

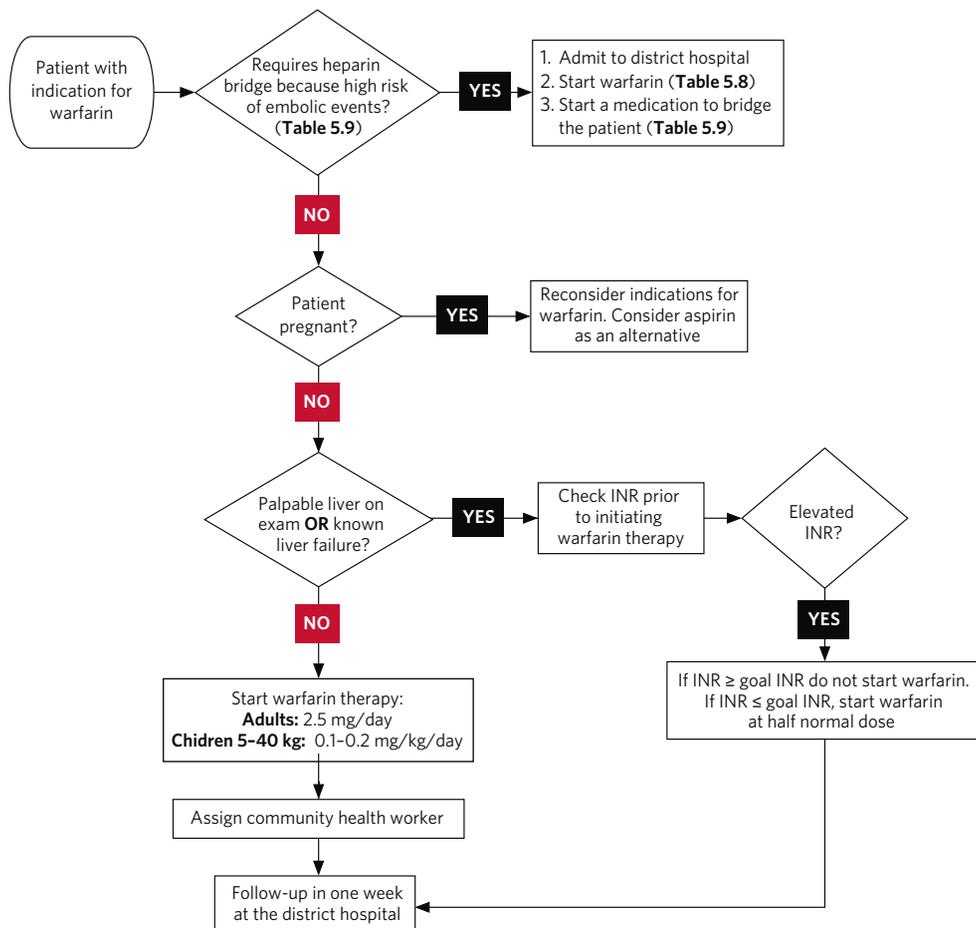
If the warfarin is discontinued and therapy has to be re-initiated due to an INR below 1.5, it is best to hospitalize the patient and administer another agent until the INR rises higher than 2.0.

**TABLE 5.9 Therapies For Bridging Anticoagulation**

Medication	Dosing
Enoxaparin (Clexane)	1 mg/kg/dose twice per day
Heparin (subcutaneous) <sup>27,28</sup>	<b>Adult:</b> 15,000 units/dose 2x/d <b>Child:</b> 250 units/kg/dose 2x/d

Some patients, such as those with atrial fibrillation, can be started on warfarin on an outpatient basis without a heparin bridge. **PROTOCOL 5.2** outlines the steps involved in initiating warfarin therapy.

## PROTOCOL 5.2 Initiating Warfarin Therapy



### 5.9 Titrating Warfarin Therapy

The main principle in adjusting warfarin is to make small, incremental changes in dosage. Warfarin is supplied in tablets of 1 mg and 5 mg. In general, dose adjustments of 0.5–1 mg (10%–20%) are appropriate. When a patient's INR is not in the therapeutic range, the clinician reviews the patient's diet, compliance with the medication, possible pharmacy or prescription errors, warfarin expiration date, and any medication changes (including herbal/traditional remedies) in detail. The clinician also reviews the recent trend in the INR relative to the recent doses of warfarin. If a patient's INR has remained in the goal range on a stable dose of warfarin for a few months, a current INR that is slightly out of range may return to the goal range in a few days without a change in dosage. Such patients may only need to follow up in a few weeks to verify that the INR has returned to the goal range. If a patient's

last INR was low and then increased to above the goal on an increased dose of warfarin, the appropriate dose may lie between the first and second doses.

In general, if a patient's INR is below the therapeutic range, the dose should be increased by 10%–20% (roughly 0.5–1 mg for adults). If the INR is above the therapeutic range, the dose should be decreased by 10%–20% (roughly 0.5–1 mg for adults). However, if a patient's INR is found to be increasing rapidly (for instance, from 2.0 to 5.0), the warfarin should be stopped for 2 days before being resumed at a lower dose (decreased by 20% or roughly 1 mg for adults).

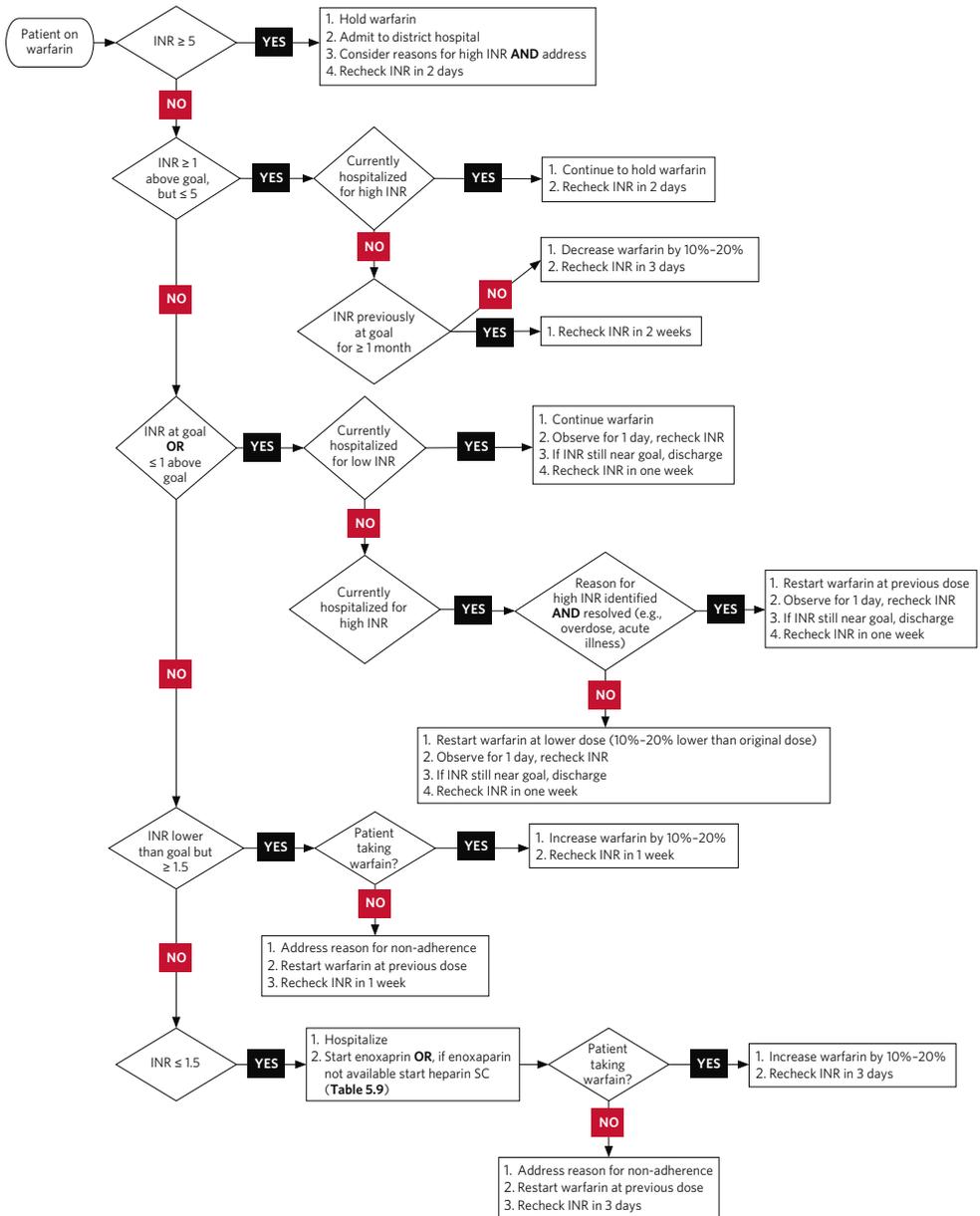
Most adult patients will require between 3 mg and 6 mg of warfarin each day, but responses can vary widely. One patient may require 20 mg each day; another may need only 2 mg. There is increasing evidence of genetic variation in warfarin metabolism.<sup>29,30</sup>

Despite a practitioner's best attempts to regulate a patient's warfarin, some patients may need frequent adjustments in the dose. This is especially true at the beginning of treatment. As time goes on, the patient's response to warfarin tends to stabilize. If there is ever a question about the appropriate warfarin dose for a patient, the provider should discuss the case with an experienced provider.

Because warfarin can cause birth defects, all women of childbearing age (15–49 years old) should be tested for pregnancy prior to initiating warfarin and referred to family planning.

**PROTOCOL 5.3** outlines the steps involved in adjusting warfarin dosing in all patients on anticoagulation. As noted, however, individual patients will respond differently to warfarin. When in doubt, the treating clinician should consult a more senior provider. NCD nurses in Rwanda are encouraged to call or email one of the cardiologists in the capitol for guidance.

### PROTOCOL 5.3 Titrating Warfarin Therapy



### 5.10 Drug Supply and Patient Monitoring

In Rwanda, aspirin is the only anticoagulant widely available at the district hospital level. PIH-supported district hospitals procure a limited supply of warfarin and heparin, and our district NCD clinics all have point-of-care INR machines to monitor patients. All patients on warfarin receive directly observed therapy administered by a community health

worker. Patients who require a heparin bridge until their INR is therapeutic are hospitalized.

Rwanda's National Cardiac Surgery program has created a need for anticoagulation services beyond the catchment area of current NCD clinics. As a stopgap measure, the cardiac surgery program has started to build a closely monitored system of central distribution to districts where the affected patients reside. A clinician at a nearby health facility is identified and contracted to follow the patient. These clinicians are given an INR machine, a protocol for warfarin adjustment, and a standardized form to record the patient's dose, lab values, and quantity of drugs reserved for them. The patient is then given a supply of anticoagulation materials. The clinician keeps track of this inventory at each visit and is responsible for requesting refills from the capitol when the patient has less than a 3-month supply left. All information is transmitted on a bimonthly basis to a central database.

### **5.11 Dangers of Anticoagulation**

Inappropriate anticoagulation can have very serious consequences. If the patient's INR is too low, thrombosis can occur, resulting in valve dysfunction or in stroke. If the patient's INR is too high, life-threatening bleeding can occur. Bleeding can be difficult to detect. Because of this, medication adherence is essential. If possible, all patients on warfarin anticoagulation should be assigned a community health worker to provide directly observed therapy.

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