Clinical Case Studies: Employing Patient-specific Approaches to Care

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FACULTY

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Part Two

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Learning Objectives

- Taking into account individual patient circumstances, determine the appropriate dose and interval of a long-acting factor.
- Review the benefits of long-acting replacement products with respect to reduced frequency of administration, potential to achieve high trough levels, and the potential for improved adherence.
- Illustrate situations (e.g., development of inhibitors, acute bleeds, development of a chronic illness, such as cardiovascular disease) that would require a change in therapy.

On average how many unique patients with hemophilia A (not patient encounters) do you personally provide care to each month?

a. Less than 5 patients/month
b. 6-10 patients/month
c. 11-15 patients/month
d. More than 15 patients/month
e. None – I am not directly involved in patient care

Hemophilia

- The word Hemophilia derived from two Greek words
  - Hemo: blood
  - Philia: affection, like
- Inherited or acquired bleeding disorder
  - Deficiency of clotting factor
- Hemophilia Types
  - Inherited Hemophilia A: Factor VIII (FVIII) deficiency (classic hemophilia)
  - Inherited Hemophilia B: Factor IX (FIX) deficiency (Christmas disease)
  - Acquired: most common factor VIII

Centers for Disease Control and Prevention. "What is Hemophilia?" www.cdc.gov/ncbddd/hemophilia/facts.html.
Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Clinical Classification of Congenital Hemophilia

Mild
- ❑Baseline factor level 5-40%
- ❑Rare spontaneous bleeding
- ❑Severe bleeding with major surgery or trauma
- ❑Median age at diagnosis: 36 months

Moderate
- ❑Baseline factor level 1-5%
- ❑Occasional spontaneous bleeding
- ❑Prolonged bleeding with minor trauma or surgery
- ❑Median age at diagnosis: 18 months

Severe
- ❑Baseline factor level <1%
- ❑Spontaneous bleeding
  - ❑Joint, muscles
- ❑Median age at diagnosis: 1 month

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Bleeding in Hemophilia A

Bleeding severity	Bleeding Sites	Approximate Frequency
Serious	Joints (hemarthrosis)	70-80%
	Muscles (deep compartments: iliopsoas, calf, forearm)	10-20%
	Mucous membrane (mouth, gum, nose, genitourinary tract)	
Life-threatening	Intracranial	<5%
	Neck/throat	5-10%
	Gastrointestinal tract	

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Treatment of Bleeding Episodes

- Initiate treatment as soon as possible
  - Within 2 hours of onset of symptoms
  - Before imaging
- Replacement of the deficient clotting factor
  - Increase FVIII with desmopressin
  - Factor VIII concentrates
    - Intermittent bolus or continuous infusion
- Utilization of bypassing agent (BPA) if inhibitors (i.e., antibodies to clotting factors) present
  - Recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC)

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Factor Dosing in Hemophilia

- Dosed in **units**
  - 1 unit is the amount of factor present in 1 mL of normal plasma
- Current and desired clotting factor level
  - Refer to the World Federation Hemophilia Guidelines for desired level
- Half-life of the factor
  - FVIII - 12 hours
- Recovery of factor level
  - 1 unit/kg of FVIII raises plasma level by 2%

$$Dose = (desired\ level - baseline\ level)\ X\ 0.5\ X\ weight$$

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Adverse Effects of Factor Replacement

- Inhibitor development
- Transfusion-transmitted infections
  - HIV
  - Hepatitis C virus

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Inhibitors in Hemophilia A

	Severe hemophilia	Mild, moderate hemophilia
Incidence	20-30%	5-10%
Median age of diagnosis	3 years old	30 years old
Pathophysiology	Inactivation of exogenously administered clotting factor	Inactivation of exogenously administered clotting factor, and endogenously synthesized factor VIII
Timing of inhibitor development	Within 150 exposure days to CFC	After intensive CFC exposure during surgery
Bleeding sites	Joint bleed	Mucocutaneous, urogenital, gastrointestinal bleed

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Inhibitors in Hemophilia A: Treatment Strategies

Treatment of bleed, if present

- Bypassing agents (BPA)
- Recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC)

Treatment to eradicate the inhibitor

- Immune tolerance induction (ITI)
  - Severe hemophilia
  - High dose factor VIII 100 units/kg/day
- Immunosuppressants
  - Mild, moderate hemophilia
  - Rituximab, cyclophosphamide, corticosteroids

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Treatment of Hemarthrosis

- On-demand treatment of acute joint bleeds
- Prophylactic treatment
  - Prevent joint bleed, and destruction
  - Preserve normal musculoskeletal function
  - Factor replacement
    - Short-acting factor concentrates
    - Long-acting (extended half-life [EHL]) factor concentrates
  - Non-factor replacement
    - Emicizumab-kxwh

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Case 1: FM

FM is a 25-year-old male with severe hemophilia A. He has been on prophylactic recombinant factor VIII since he was a kid. He self administers his factor product three times weekly. He presents to the hemophilia treatment center clinic today for his annual visit.

FM: Case Discussion

- What are the comprehensive care services that should be offered to FM?
- What are the issues that contribute to FM's suboptimal prophylactic factor replacement therapy?
- What options does FM have?

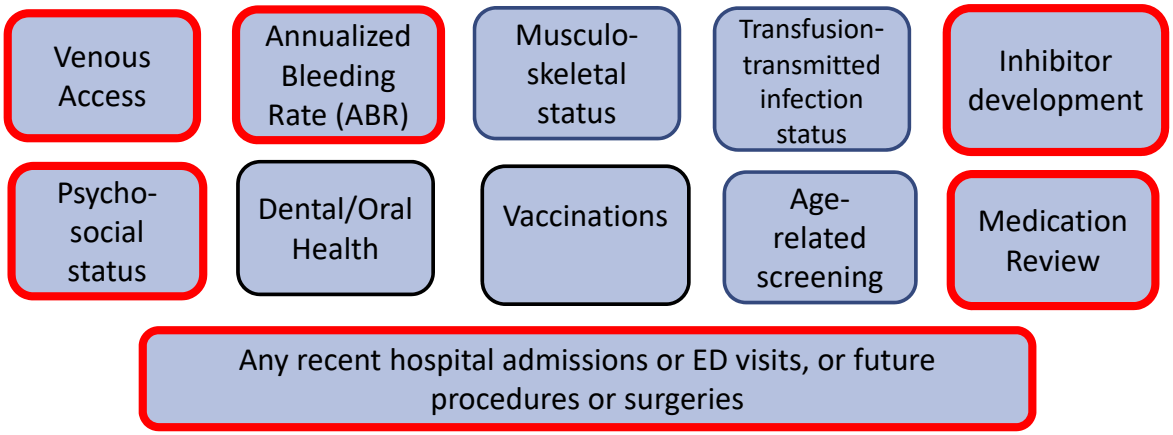
Comprehensive Care Services

- Comprehensive evaluation
  - ➢ **Medical history, physical examination**
  - ➢ **Nursing evaluation**
  - ➢ **Physical therapy evaluation**
  - ➢ **Psychosocial evaluation**
  - ➢ **Laboratory evaluation**
  - – Dental evaluation
  - – Laboratory testing
- Genetic counseling
- ➢ **Treatment products**
  - ➢ **Medication access**
- ➢ **Home and self infusion**
- Psychosocial services
- Hemophilia carriers
  - – Symptomatic
  - – Pregnancy

National Hemophilia Foundation Medical and Scientific Advisory Council (MASAC). #132: www.hemophilia.org/sites/default/files/document/files/masac132.pdf

Hemophilia Treatment Centers

Regular evaluations at least every 12 months (adults), 6 months (children)



Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Comprehensive Care Services

- Comprehensive evaluation
  - Medical history, physical examination
    - ***FM reports feeling pretty tired of the three times weekly administration***
    - ***Slight swelling in right knee***
    - ***ABR 6***
  - Nursing evaluation
    - ***Venous access challenging***
  - *Laboratory evaluation*
    - ***Factor VIII trough level 1%***
    - ***Factor VIII inhibitor level not detected***
  - Physical therapy evaluation
    - ***Slight decrease in range of motion of right knee***
  - Psychosocial evaluation
    - ***New job***
  - Treatment products
    - Medication access
      - ***Missed a couple of doses***
  - Home and self infusion
    - ***Venous access getting harder***

MASAC #132: https://www.hemophilia.org/sites/default/files/document/files/masac132.pdf

What are the issues that contribute to FM's suboptimal prophylactic factor replacement therapy?

a. ABR 6
b. Nonadherence
c. Swelling and decreased range of motion in right knee
d. Challenging venous access
e. All of the above

FM: Case Discussion

- FM is not satisfied with his current factor replacement therapy. He just started a new job. He works as a cashier at the grocery store. His knees hurt after work. He has been missing his factor doses as he gets very tired after work, and just can't get the energy to mix all the bottles, find a vein, and administer the factor.

What options does FM have?

a. No change in his current factor replacement therapy
b. Change to recombinant pegylated factor VIII 40 units/kg once weekly
c. Change to recombinant factor VIII, FC fusion protein product 40 units/kg two times weekly
d. Change to recombinant glycopegylated factor VIII 40 units/kg once every 2 weeks

Prophylactic EHL Factor VIII Concentrates

	FDA approval	Half-life (hours)	Prophylactic dosing
AHF, pegylated (Adynovate)	Nov 2015	14.69	40-50 units/kg IV two times weekly
AHF, Fc fusion protein (Eloctate)	June 2014	16.4	50 units/kg IV every 4 days
AHF, pegylated-aucl (Jivi)	Aug 2018	21.4	30-40 units/kg IV two times weekly
AHF, glycopegylated-exei (Esperoct)	Feb 2019	21.7	50 units/kg IV every 4 days
AHF: Antihemophilic Factor (also known as Factor VIII)			

Recommend patient self administer factor product before work

Adynovate [prescribing information]. Lexington, MA: Baxalta US, Inc.; November 2018.
Eloctate [prescribing information]. Cambridge, MA: Biogen; January 2017.
Jivi [prescribing information]. Whippany, NJ: Bayer Healthcare LLC; August 2018.
Esperoct [prescribing information]. Plainsboro, NJ: Novo Nordisk, Inc.; 2019.

FM Returns in Three Months

- Comprehensive evaluation
  - Medical history, physical examination
    - ***He reports feeling much better about the new therapy***
    - ***No more swelling in right knee***
    - ***No bleeding episode in 3 months***
  - Nursing evaluation
  - ***Venous access still challenging but administration less frequent***
  - *Laboratory evaluation*
    - ***Factor VIII trough level 5%***
  - Physical therapy evaluation
    - ***Normal range of motion of right knee***
  - Psychosocial evaluation
    - ***New job: doing better***
  - Treatment products
    - Medication access
      - ***Did not miss doses***
      - ***Patient self administered before work***
  - Home and self infusion

FM: Case Summary

- FM was non adherent to his prophylaxis, with a negative outcome (right knee bleeding)
- Comprehensive evaluation during the visit allowed for identification of issues that contributed to the non adherence and negative outcome
- The use of extended half-life factor products allow for less frequent administration, therefore improving adherence and providing better outcomes with higher trough levels

Case 2: JD

JD is a 45-year-old male who presented to the ED with left eye swelling after a work-related injury.

- Past medical history (PMH)
  - Mild hemophilia A (baseline level 15%), with no history of inhibitor or factor concentrate use
- Medications
  - Lisinopril 20 mg orally daily
- Vital signs
  - Blood pressure (BP) 116/78 mm Hg
  - Heart rate (HR) 76 bpm
  - Weight 90 kg
- Labs
  - Serum creatinine 0.8 mg/dL
  - Hemoglobin 13.5 g/dL
  - Platelets 357 x 10^9/L
  - APTT 45 seconds (prolonged)
  - PT 10.5 seconds (within normal limits)
- Insurance: Workers Comp

JD: Case Discussion

- What would be the recommended treatment for JD?
  - What factor replacement therapy would be recommended for JD?
  - Duration of factor replacement therapy for JD?
- What would be the monitoring parameters for JD?

What dose should JD receive?

a. Recombinant factor VIII 4500 units IV every 12 hours
b. Recombinant factor VIII 3825 units IV every 12 hours
c. Recombinant factor VIII 2700 units IV every 12 hours
d. Activated prothrombin complex concentrate 9000 units IV every 12 hours

Factor Dosing in Hemophilia

- Dosed in **units**
  - 1 unit is the amount of factor present in 1 mL of normal plasma
- **Current and desired clotting factor level**
  - Refer to the World Federation Hemophilia Guidelines for desired level
- **Half-life of the factor**
  - **FVIII - 12 hours**
- Recovery of factor level
  - **1 unit/kg of FVIII raises plasma level by 2%**

$$Dose = (desired\ level - baseline\ level)\ X\ 0.5\ X\ weight$$

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

JD's Factor Dose Calculation

- Patient has mild hemophilia A
  - baseline level 15%, Weight 90 kg
- Eye bleed: desired level 100%
- Dose = (100%-15%) X 0.5 X 90 kg
  = 3825 units
- Half-life of FVIII 12 hours
- Dose 3825 units every 12 hours

Dose = (desired level – baseline level) X 0.5 X weight

Type of hemorrhage	Desired level (%)	Duration (days)
Joint	40-60	1-2
Iliopsoas and deep muscle Initial Maintenance	 80-100 30-60	 1-2 3-5
CNS/head Initial	 80-100	 1-7
Maintenance	50	8-21
Throat and neck Initial Maintenance	 80-100 50	 1-7 8-14

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Duration of JD's Factor Replacement Therapy

- Duration
  - Depends on patient's clinical condition
  - Likely 5-7 days
  - Maintenance therapy for second week depends on the patient's recovery

Type of hemorrhage	Desired level (%)	Duration (days)
Joint	40-60	1-2
Iliopsoas and deep muscle Initial Maintenance	 80-100 30-60	 1-2 3-5
CNS/head Initial Maintenance	 80-100 50	 1-7 8-21
Throat and neck Initial Maintenance	 80-100 50	 1-7 8-14

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

What would be the monitoring parameters for JD?

- Factor activity levels
  - Peak FVIII level 30 minutes after the first dose
    - Target level 100%
  - Trough FVIII level before morning dose daily
    - Target level 80-100%
- Factor inhibitor level
- Complete blood count

JD: Case Discussion

- JD was in the hospital for 1 week. He received a total of 7 days of factor replacement therapy. The swelling of his left eye had improved. He was discharged with pain medications and a follow-up appointment at the hemophilia treatment center in a month.

- However, 1 week before his appointment, JD presented to the ED with abdominal pain that started 2 days earlier.

JD: Case Discussion

- What is the cause of JD's abdominal pain?
- What would be the recommended treatment for JD?
  - What factor product should JD receive?
  - Duration of factor replacement therapy for JD?
- What would be the monitoring parameters for JD?

What is the cause of JD's abdominal pain?

JD is a 45-year-old male who presented to the ED with abdominal pain. He reports that the pain started 2 days ago and is getting worse. He denies any new or prior trauma to his abdomen.

- PMH
  - Mild Hemophilia A (baseline level 15%), with no history of inhibitor or factor concentrate use
- Medications
  - Lisinopril 20 mg orally daily
- Vital signs
  - BP 138/85 mm Hg
  - HR 96 bpm
  - Weight 90 kg
- Labs
  - Serum creatinine 0.8 mg/dL
  - Hemoglobin 11.5 g/dL
  - Platelets 289 x 10^9/L
  - **APTT 75 seconds (prolonged)**
  - PT 11 seconds (within normal limits)
- Insurance: Workers Comp
- **CT: retroperitoneal bleeding**

What happened to JD?

a. JD had delayed bleeding from his work-related injury.
b. JD had delayed bleeding unrelated to the work-related injury.
c. JD had inadequate factor replacement therapy for his work-related injury four weeks ago, and developed a new bleed.
d. JD had developed a new spontaneous, non-trauma related bleed due to development of an inhibitor.

Inhibitors in Hemophilia A

	Severe hemophilia	Mild, moderate hemophilia
Incidence	20-30%	5-10%
Median age of diagnosis	3 years old	30 years old
Pathophysiology	Inactivation of exogenously administered clotting factor	Inactivation of exogenously administered clotting factor, and endogenously synthesized factor VIII
Timing of inhibitor development	Within 150 exposure days to CFC	After intensive CFC exposure during surgery
Bleeding sites	Joint bleed	Mucocutaneous, urogenital, gastrointestinal bleed

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

JD: Case Discussion

- JD's laboratory results
  - Factor VIII level was <1%
  - Factor VIII inhibitor level 18 BU (Bethesda units)

What would be the recommended treatment for JD?

a. Recombinant factor VIII 3825 units IV every 12 hours
b. Recombinant factor VIII 4500 units IV every 12 hours
c. Recombinant factor VIII continuous IV infusion 320 units/hour
d. Recombinant activated factor VII (rFVIIa) 8 mg IV every 2 hours until hemostasis achieved

Inhibitors in Hemophilia A: Treatment Strategies

Treatment of bleed, if present

- Bypassing agents (BPA)
- Recombinant activated factor VII (rFVIIa) or activated prothrombin complex concentrate (aPCC)

Treatment to eradicate the inhibitor

- Immune tolerance induction (ITI)
  - Severe hemophilia
  - High dose factor VIII 100 units/kg/day
- Immunosuppressants
  - Mild, moderate hemophilia
  - Rituximab, cyclophosphamide, corticosteroids

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

Treating Bleeding in Patients with Inhibitors

- Activated prothrombin complex concentrate
  - 50-100 units/kg every 8-12 hours, maximum 200 units/kg/day
  - Dose >200 units/kg/day = increased risk of disseminated intravascular coagulation (DIC)
  - Risk of thrombosis
  - Breakthrough bleeding
  - No in vitro assay available to measure hemostatic efficacy
- rFVIIa
  - Severe bleeding
    - 90 mcg/kg every 2 hours until hemostasis achieved, then every 3-6 hours
  - Minor, moderate bleeding
    - 90 mcg/kg every 2 hours until hemostasis achieved

FEIBA [prescribing information]. Lexington, MA: Baxalta US, Inc.; Jan 2019.
Novoseven [prescribing information]. Princeton, NJ: Novo Nordisk, Inc.; Jan 2019.

Duration of JD's Factor Replacement Therapy

- Duration
  - Depends on patient's clinical condition
  - Likely 3-5 days
- Dosing
  - Frequency of dosing may be extended every 3-6 hours depending on patient's clinical condition

Type of hemorrhage	Desired level (%)	Duration (days)
Joint	40-60	1-2
Iliopsoas and deep muscle Initial Maintenance	 80-100 30-60	 1-2 3-5
CNS/head Initial Maintenance	 80-100 50	 1-7 8-21
Throat and neck Initial Maintenance	 80-100 50	 1-7 8-14

Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.

What would be the monitoring parameters for JD?

- Factor activity levels
  - FVIII level <1% → severe hemophilia, risk of spontaneous bleeds
  - APTT prolonged to a greater extent
    - APTT 45 seconds before inhibitor development, 75 seconds after
- Factor inhibitor levels
  - Measured in Bethesda units
- Complete blood count
- Signs and symptoms of thrombosis

JD: Case Summary

- High suspicion for inhibitor development if a patient with mild or moderate hemophilia presents with spontaneous bleeding episodes 2-4 weeks after intensive factor replacement therapy
- Treatment strategies for these patients
  - Treatment of bleeding with bypassing agents
  - Treatment to eradicate inhibitor
    - Immunosuppressants

Case 3: ST

ST is a 63-year-old male with mild hemophilia A. He presents to the Hemophilia Treatment Center today as a new patient for evaluation of bleeding risk on anticoagulation, which was recommended by his cardiologist for his new onset atrial fibrillation.

Comprehensive Care Services

- **Medical history, physical examination**
- **Nursing evaluation**
- Physical therapy evaluation
- **Psychosocial evaluation**
- Dental evaluation
- **Laboratory testing**
- **Genetic counseling**
- **Treatment products**
  - **Medication access**
- Home and self infusion
- Psychosocial services
- Hemophilia carriers
  - Symptomatic
  - Pregnancy

MASAC #132: https://www.hemophilia.org/sites/default/files/document/files/masac132.pdf

Comprehensive Evaluation

- Medical history, physical examination
  - **No major bleeding with colonoscopy, dental extraction**
  - **Nose bleed during winter**
  - **Weight 75 kg**
  - **$CHADS_2$ score 2 (moderate risk)**
- Nursing evaluation
  - **Venous access in case home infusion required**
- Psychosocial evaluation
  - **Family support**
  - **Insurance**
- Laboratory testing
  - **FVIII level 20%**
  - **Inhibitor not present**
- Genetic counseling
  - **Family tree**
    - **Genetic testing**
- Treatment products
  - **Medication access**

MASAC #132: https://www.hemophilia.org/sites/default/files/document/files/masac132.pdf

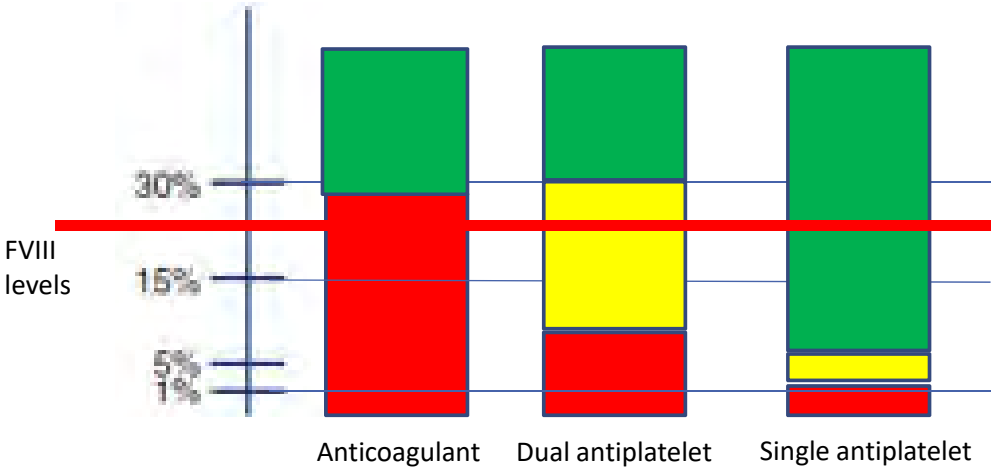
ST: Case Discussion

- Baseline factor VIII level 20%
- $CHADS_2$ =2

Antithrombotic therapy based on baseline FVIII level and stroke risk						
Baseline FVIII level ≥30%		Baseline FVIII level 5-30%	Baseline FVIII level 1-5%		Baseline FVIII level <1% If patient on prophylaxis	
$CHADS_2$ <2	$CHADS_2$ ≥2	Any $CHADS_2$	$CHADS_2$ <2	$CHADS_2$ ≥2	$CHADS_2$ <2	$CHADS_2$ ≥2
Low dose aspirin	VKA	Low dose aspirin	No therapy	Low dose aspirin	No therapy	Low dose aspirin
If patients with baseline FVIII level <1%, and not on prophylaxis, no therapy						
VKA: vitamin K antagonists						

Martin K, Key NS. *Blood.* 2016; 128:178-84.

FVIII Goals for the Use of Anticoagulant and Antiplatelet Agents



Considerations:
1. Bleeding phenotype
2. Intensity of anticoagulant therapy
3. Characteristics of anticoagulant
4. Planned duration of therapy

Martin K, Key NS. *Blood.* 2016; 128:178-84.

Other Considerations

- Acute Coronary Syndrome (ACS)
  - Percutaneous cardiac intervention (PCI) preferred over coronary artery bypass graft (CABG) surgery
    - CABG considered with three-vessel disease, left main stenosis, stenosis of proximal left anterior descending artery
  - Radial artery access site preferred over femoral to minimize risk of retroperitoneal or groin bleeding
  - Drug-eluting balloon to avoid stenting may be considered
  - Second-generation drug-eluting stents or bare metal stents preferred over first-generation drug-eluting stents
    - Short duration of dual antiplatelet therapy (1 month)
- Valve replacement
  - Bioprosthetic valve preferred over mechanical valve

Staritz P et al. *Haemophilia.* 2013; 19:833-40. Mannucci PM et al. *Blood.* 2009; 114:5256-63. Ferraris VA et al. *Cardiol Rev*. 2015; 23:53-68.

ST: Case Summary

- Patients with hemophilia and cardiovascular diseases
  - Special considerations for cardiac procedures, antithrombotic therapy
  - Evaluation of patient's bleeding risk
    - Collaboration between the hematologist and cardiologist

Practice Changes

- Investigate which care models my institution uses for the care of persons with congenital bleeding disorders.
- Read my institution's protocols for the monitoring of patients with hemophilia A.
- Review which factor replacement products are available at my institution.
- Discuss with colleagues how to assess the need for a change in therapy (e.g., development of inhibitors, acute bleeding, or onset of chronic illness).
- Educate colleagues on the appropriate dosing of long-acting factors.

Selected Resources

- Srivastava A et al. *Haemophilia*. 2013; 19:e1-e47.
- National Hemophilia Foundation Medical and Scientific Advisory Committee (MASAC) recommendations. https://www.hemophilia.org/Researchers-Healthcare-Providers/Medical-and-Scientific-Advisory-Council-MASAC/MASAC-Recommendations