Anticoagulants in the Cath Lab: The Ongoing Battle

Khiet Nguyen, Pharm.D.

PGY1 Pharmacy Resident

Valley Baptist Medical Center - Brownsville

January 25, 2017

I. Objectives

a. Describe the rationale for using anticoagulants during percutaneous coronary interventions (PCI)
b. Summarize the early studies that support the use of bivalirudin
c. Discuss the major studies that generate the controversy between bivalirudin and UFH
d. Evaluate the current state and future direction for anticoagulation therapy during PCI

II. Percutaneous Coronary Intervention

a. PCI is recommended for patients with ACS
b. PCI can cause intracoronary thrombosis
c. Antithrombotic therapy needed to decrease risk of early thrombosis
d. UFH was used in percutaneous transluminal coronary angioplasty (before stent era)

III. Bivalirudin vs. UFH

	UFH	Bivalirudin
Clotting factor target	IIa and Xa	IIa
Clotting factor inhibition	Indirect (Antithrombin)	Direct
Anticoagulant activity	33%	100%
Onset of action	Immediate	Immediate
Half-life	30-60 minutes	25 minutes
Monitoring in cath lab	ACT	None (or ACT)
Elimination	Reticulo-endothelial system	Enzymatic/Renal
Inhibits clot-bound thrombin	No	Yes
Platelet binding	Yes	No
Antidote	Yes	No

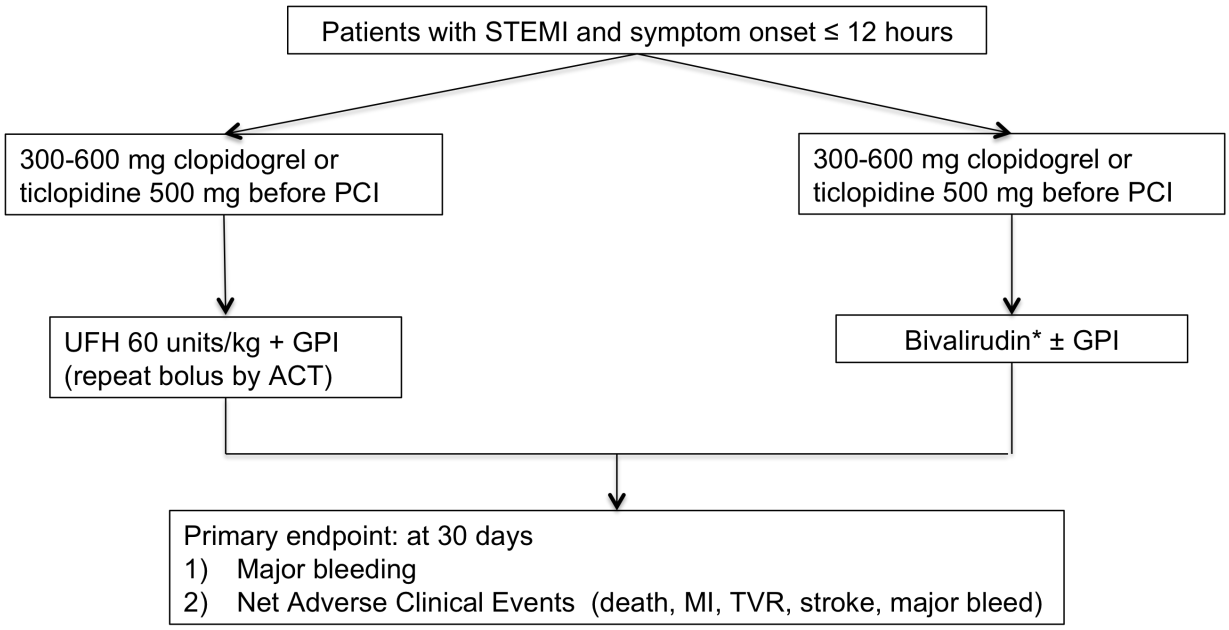
IV. Early Studies

Study	Population	Intervention	Outcome
CACHET 2002	Patients with elective PTCA N = 268	Bivalirudin (3 dosing arms) ± GPI (2 arms) vs UFH (70 u/kg) + GPI	- No difference in 30 days death, MI, or uTVR - No difference in major bleeding
REPLACE-1 2004	Patients with elective or urgent PCI	Bivalirudin ± GPI vs UFH (60-70 u/kg) ± GPI	- No difference in death, MI, or uTVR by hospital discharge or within 48 hours or randomization - No difference in major bleeding
REPLACE-2 2003	Patients with elective or urgent PCI	Bivalirudin ± GPI vs UFH (65 u/kg) + GPI	- No difference in 30 day death, MI, or uTVR **- Major bleeding lower with bivalirudin (2.4% vs 4.1%; p < 0.001; NNH = 77)**

ACUITY-PCI 2006	Patients with moderate- or high-risk ACS N = 13,819	Bivalirudin vs Bivalirudin + GPI vs UFH (60 u/kg) or LMWH + GPI	Bivalirudin vs UFH + GPI - No difference in 30 day death, MI, uTVR, or stent thrombosis **- Major bleeding lower with bivalirudin (3.0% vs 5.7%; p < 0.001, NNH = 37)**

V. HORIZONS-AMI

- Design: multinational, multicenter, open-label randomized controlled trial
- N = 3,602 patients with STEMI undergoing primary PCI
- Enrollment: March 2005 - May 2007
- Follow-up: 30-days, 6 months, 1 year, and yearly for 5 years
- Analysis: intention to treat



HORIZONS-AMI: Baseline Characteristics:

Demographics	Age 60.2 years; male 76.6%
Past Medical History	Diabetes (15.6%), hypertention (51.8%), hyperlipidemia (43.4%),
Cardiac History	Prior MI (10.4%), prior PCI (10.5%), prior CABG (3.3%)
Weight	80 kg
Interval from symptom onset to	2.2 hours
LVEF	50%

HORIZONS-AMI: Methodology:

- 92.7% patients received PCI
- P2Y12 use:
  - 61% loaded with 600 mg clopidogrel
  - 34% loaded with 300 mg clopidogrel
  - No ticagrelor or prasugrel

- GPI use
  - UFH: 98% (planned)
  - Bivalirudin: 7.2% (provisional)
- Radial access: 7%
- 66% of patients in the bivalirudin group received heparin before cardiac catherization

HORIZONS-AMI: Results

Endpoint	UFH + GPI N = 1802 (%)	Bivalirudin N = 1800 (%)	NNT/NNH	p-value
Net adverse clinical events	**12.1**	**9.2**	**35**	**0.005**
Major bleeding, non-CABG related	**8.3**	**4.9**	**29**	**<0.001**
Major adverse cardiovascular events	**5.5**	**5.4**	**-**	**0.95**
All-cause mortality	**3.1**	**2.1**	**100**	**0.047**
Stent thrombosis, acute (≤ 24 hour)	**0.3**	**1.3**	**100**	**<0.001**
Stent thrombosis, subacute (> 24 hour – 30 days)	**1.7**	**1.2**	**-**	**0.28**

HORIZONS-AMI: Impact

2013 ACCF/AHA STEMI Guidelines

- For patients with STEMI undergoing primary PCI, the following supportive anticoagulant regimens are recommended
  a. UFH, with additional boluses administered as needed to maintain therapeutic activated clotting time levels, taking into account whether a GP IIb/IIIa receptor antagonist has been administered (Class I, level C); or
  b. Bivalirudin with or without prior treatment with UFH (Class I, level B)
- For patients with STEMI undergoing PCI who are at high risk of bleeding, it is reasonable to use bivalirudin monotherapy in preference to the combination of UFH and GP IIb/IIIa receptor antagonist (Class IIa, level B)

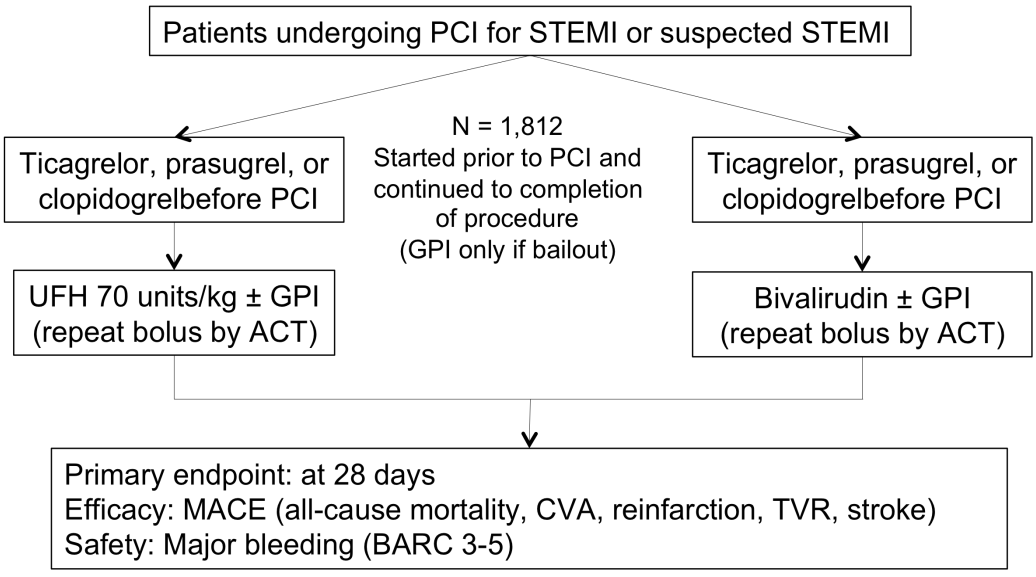
Other studies along with HORIZONS-AMI

Study	Population	Interventions	Outcome
ISAR-REACT 2008	Stable/unstable angina with PCI N = 4,570	Bivalirudin* vs UFH (140 units/kg)	- No difference at 30 days death, MI, or uTVR (5.9% Bival vs 5.0% UFH) - Major bleeding lower with bivalirudin (NNH = 67)
ISAR-REACT 3a 2010	Stable/unstable angina with PCI N = 1,056	UFH (100 units/kg) vs ISAR REACT UFH arm (140 units/kg)	- UFH 100 units/kg non-inferior to bivalirudin NACE at 30 days - Major bleeding lower with 100 units/kg (NNH = 100; p = 0.03)

EuroMAX 2013	STEMI N = 2,218	Bivalirudin* ± GPI vs UFH (60-100 units/kg) ± GPI; drugs started on transport to hospital	- No difference in 30 days MACE (6% bivalirudin vs 5.5% UFH ± GPI) - No difference in mortality at 30 days - Major bleeding lower with bivalirudin (NNH = 29, p = <0.001)

VI. HEAT PPCI

- Single-center, open-label, blocked, randomized controlled trial
- Inclusion: undergoing PCI for STEMI or suspected STEMI
- N = 1,812
- Enrollment: February 2012 to November 2013
- Mean follow-up: 28 days
- Analysis: intention to treat



*Bivalirudin was given bolus 0.75 mg/kg followed by 1.75 mg/kg/h infusion

All patients received dual antiplatelet before PPCI (ASA + clopidogrel, prasugrel, or ticagrelor)

HEAT PPCI: Baseline Characteristics

Demographics	**Age 63.3 years; male 72%**
Past Medical History	**Diabetes (14%), hypertention (41%), hyperlipidemia (41%), current**
Cardiac History	**Prior MI (12%), prior PCI (7%), prior CABG (2%)**
Weight	**80 kg**
Interval from symptom onset to	**2.8 hours**

HEAT PPCI: Methodology

- 82% patients received PCI
- P2Y12 use:
  - Ticagrelor ~ 62%
  - Prasugrel ~ 27%

  - Clopidogrel ~ 11%
- GPI use (bailout):
  - Bivalirudin: 13%
  - UFH: 15%
- Radial access: 81%

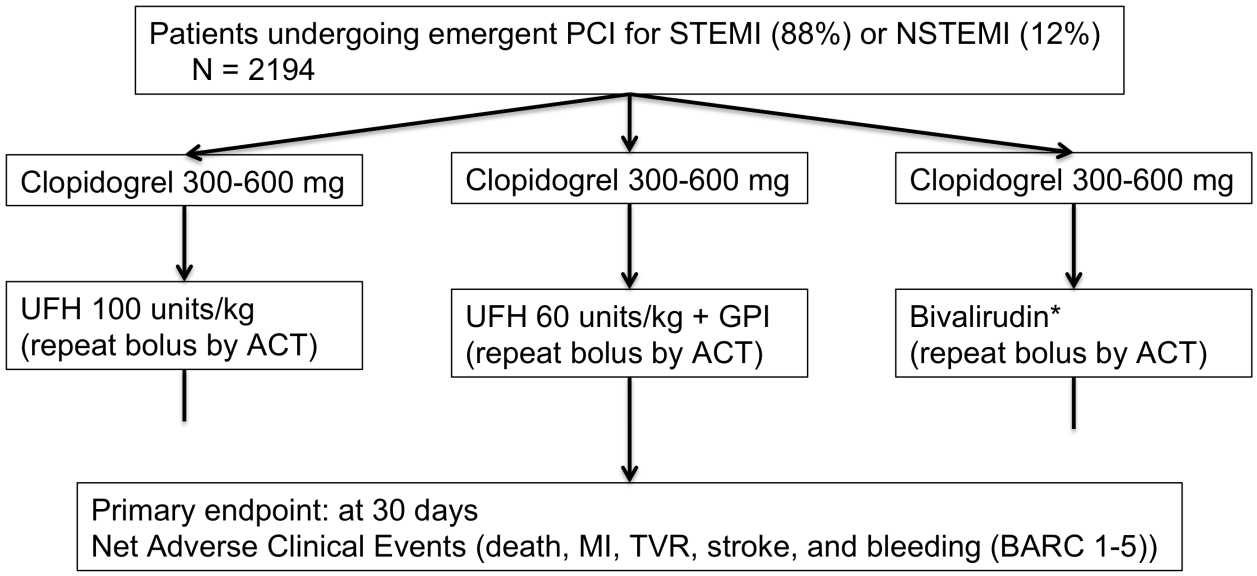
HEAT PPCI: Results

Endpoint	UFH N = 907 (%)	Bivalirudin N = 905 (%)	NNT/ NNH	p-value
Major adverse cardiovascular events	5.7	8.7	33	0.01
Death	4.3	5.1	-	0.43
Cerebrovascular accident	1.2	1.6	-	0.43
New MI or reinfarction	0.9	2.7	56	0.04
Unplanned TVR	0.7	2.7	50	0.001
Major bleeding (BARC 3-5)	3.1	3.5	-	0.59
Stent thrombosis	0.9	3.4	40	0.001

HEAT PPCI: Impact

- Provided strong evidence against the bleeding reduction benefit of bivalirudin
- Use of bivalirudin is decreased for primary PCI and only in patients intolerant to heparin
- 2013 ACCF/AHA guidelines have not been updated

VII. BRIGHT



*Bivalirudin was given bolus 0.75 mg/kg followed by 1.75 mg/kg/h infusion

BRIGHT: Results

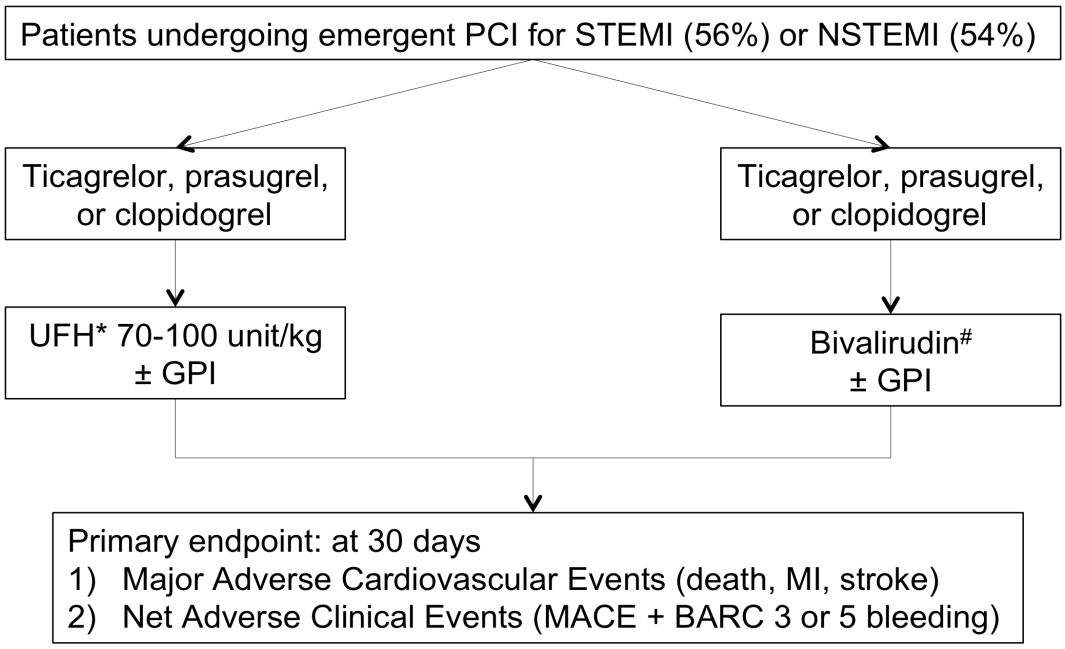
Endpoint (at 30 days)	UFH N = 729 (%)	Bivalirudin N = 735 (%)	NNT/NNH	p-value
Net adverse clinical events	13.2	8.8	22.7	0.008
Major adverse cardiovascular events	5.8	5.0	125	0.74
Major bleeding (BARC 1- 5)	7.5	4.1	29.4	<0.001
Stent thrombosis	1.0	0.6	333.3	0.81

- Lower bleeding rate of bivalirudin was driven by BARC 1-2
  - No difference in major bleeding (BARC 3-5)
- UFH dose (100 units/kg) is not commonly used
- Open-label study done in China

VIII. MATRIX Antithrombin

- Design: multicenter, open-label, nested randomized controlled trial
- N = 7,213 patients with STEMI (56%) or NSTEMI (46%) requiring emergent PCI
- Enrollment: October 2011 to November 2014
- Follow-up: 30 days
- Analysis: intention to treat

MATRIX Antithrombin: Interventions



#Bivalirudin was given bolus 0.75 mg/kg followed by 1.75 mg/kg/h infusion
*For patient not receiving GPI, heparin was given at dose 70-100 units/kg
*For patient receiving GPI, heparin was given at dose 50-70 units/kg

MATRIX Antithrombin: Methodology

- Included both NSTEMI and STEMI patients
- 94.4% of patients underwent PCI
- P2Y12 use:

  - Clopidogrel (45.9%), ticagrelor (23.7%), prasugrel (12.8%)
- GPI use:
  - Heparin (25.9%), bivalirudin (4.6%)
- 50% had radial access
  - Author claimed radial or femoral access did not affect any of the major outcomes

MATRIX Antithrombin: Results

Endpoint (at 30 days)	UFH N = 3603 (%)	Bivalirudin N = 3610 (%)	NNT/ NNH	p-value
Net adverse clinical events	12.4	11.2	-	0.12
Major adverse cardiovascular events	10.9	10.3	-	0.44
Major bleeding (BARC 3 or 5)	2.5	1.4	91	<0.001
Death from any cause	2.3	1.7	167	0.04
Stent thrombosis	0.6	1.0	250	0.048

MATRIX Antithrombin: Controversies

- P2Y12 loading different from previous trials
- Asymmetry use of GPI
  - UFH: 25.9% (21.8% planned + 4.1% bailout)
  - Bivalirudin: 4.6%
- Much lower number of cases used radial access approach (50%) than HEAT PPCI
- Wide range of heparin dose (70-100 units/kg) when no GPI, otherwise 50-70 units/kg

IX. What does all this leave us?

	HORIZONS-AMI 2008	HEAT PPCI 2014	MATRIX 2015
Patients received PCI	**92.7%**	**82%**	**94.4%**
Ticagrelor or Prasugrel Use	**0%**	**90%**	**36.5%**
GPI Use	**Bivalirudin: 7% UFH: 98%**	**Bivalirudin: 13% UFH: 15%**	**Bivalirudin: 4.6% UFH: 25.9%**
Radial access	**7%**	**81%**	**50%**
MACE	**No difference**	**Lower with UFH**	**No difference**
Major Bleeding (different definition)	**Lower with bivalirudin**	**No difference**	**Lower with bivalirudin**
Stent thrombosis	**Greater with bivalirudin (1.3%)**	**Greater with bivalirudin (3.4%)**	**Greater with bivalirudin (1.0%)**

X. Current State of Battle

a. HEAT PPCI have different results from HORIZONS-AMI, BRIGHT, and MATRIX-Antithrombin
b. These studies had different methodologies
c. Many hope the VALIDATE-SWEDEHEART trial will offer more insight
d. Hybrid registry-based randomized controlled trial
e. Will enroll 6,000 STEMI/NSTEMI patients getting PCI
f. Will use death, MI, and BARC 2, 3, or 5 as composite endpoints
g. Prasugrel, ticagrelor, or cangrelor as part of DAPT

XI. Key Takeaways

a. Practice changes, such as radial access, limited GPI use, use of newer P2Y12 inhibitors, new generation of DES have changed the risk of ischemia, bleeding, and stent thrombosis in cath lab
b. Recent bivalirudin vs UFH studies have shown conflicting results due to inconsistent methodology
c. For patients undergoing PCI with radial access, UFH is preferred over bivalirudin.
d. For patients undergoing PCI with high risk of bleeding, bivalirudin is preferred over UFH.

APPENDIX A - Abbreviations

PCI: percutaneous coronary intervention	PTCA: percutaneous transluminal coronary angioplasty
uTVR: urgent target-vessel revascularization	GPI: glycoprotein IIb/IIIa inhibitor
ACS: acute coronary syndrome	MI: myocardial infarction
STEMI: ST-segment elevation myocardial infarction	UFH: unfractionated heparin
CVA: cerebrovascular accident	MACE: major adverse cardiovascular events
NACE: net adverse clinical events	DES: Drug-eluting stent
CAD: coronary artery disease	

APPENDIX B - Bleeding Academic Research Consortium

Type	Definition
Type 0	No bleeding
Type 1	Bleeding that is not actionable and does not cause the patient to seek unscheduled performance of studies, hospitalization, or treatment by a healthcare professional; may include episodes leading to self-discontinuation of medical therapy by the patient without consulting a healthcare professional
Type 2	Any overt, actionable sign of hemorrhage (eg, more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for type 3, 4, or 5 but does meet at least one of the following criteria: (1) requiring nonsurgical, medical intervention by a healthcare professional, (2) leading to hospitalization or increased level of care, or (3) prompting evaluation
Type 3a	▪ Overt bleeding plus hemoglobin drop of 3 to <5 g/dL* (provided hemoglobin drop is related to bleed) ▪ Any transfusion with overt bleeding
Type 3b	▪ Overt bleeding plus hemoglobin drop ≥5 g/dL* (provided hemoglobin drop is related to bleed) ▪ Cardiac tamponade ▪ Bleeding requiring surgical intervention for control (excluding dental/nasal/skin/hemorrhoid) ▪ Bleeding requiring intravenous vasoactive agents
Type 3c	▪ Intracranial hemorrhage (does not include microbleeds or hemorrhagic transformation, does include intraspinal) ▪ Subcategories confirmed by autopsy or imaging or lumbar puncture ▪ Intraocular bleed compromising vision
Type 4	▪ Perioperative intracranial bleeding within 48 h ▪ Reoperation after closure of sternotomy for the purpose of controlling bleeding ▪ Transfusion of ≥5 U whole blood or packed red blood cells within a 48-h period¶ ▪ Chest tube output ≥2 L within a 24-h period
Type 5a	Probable fatal bleeding; no autopsy or imaging confirmation but clinically suspicious
Type 5b	Definite fatal bleeding; overt bleeding or autopsy or imaging confirmation

APPENDIX C - Definition of major bleeding

	Definition
TIMI (1998)	Intracranial bleed Hgb ↓ >5 g/dL or Hct ↓ >15 percent
GUSTO (1997)	Intracranial bleed Hemodynamic compromise requiring intervention
ISAR trials (2000-2005)	Intracranial bleed Hgb ↓ >5 g/dL or Hct ↓ >15 percent

ACUITY (2006)	Intracranial or intraocular Hgb ↓ ≥3 g/dL with overt bleeding Any Hgb ↓ ≥4 g/dL Any transfusion Access site bleeding requiring intervention Hematoma ≥5 cm Reoperation for bleeding
REPLACE-2 (2007	Intracranial, intraocular, or retroperitoneal Hgb ↓ ≥3 g/dL with overt bleeding Any Hgb ↓ ≥4 g/dL Transfusion ≥2 units of PRBCs
HORIZONS-AMI (2009)	Intracranial or intraocular Hgb ↓ ≥3 g/dL with overt bleeding Any Hgb ↓ ≥4 g/dL Any transfusion Access site bleeding requiring intervention Hematoma ≥5 cm Reoperation for bleeding