Controversies in Anticoagulation in Pregnancy

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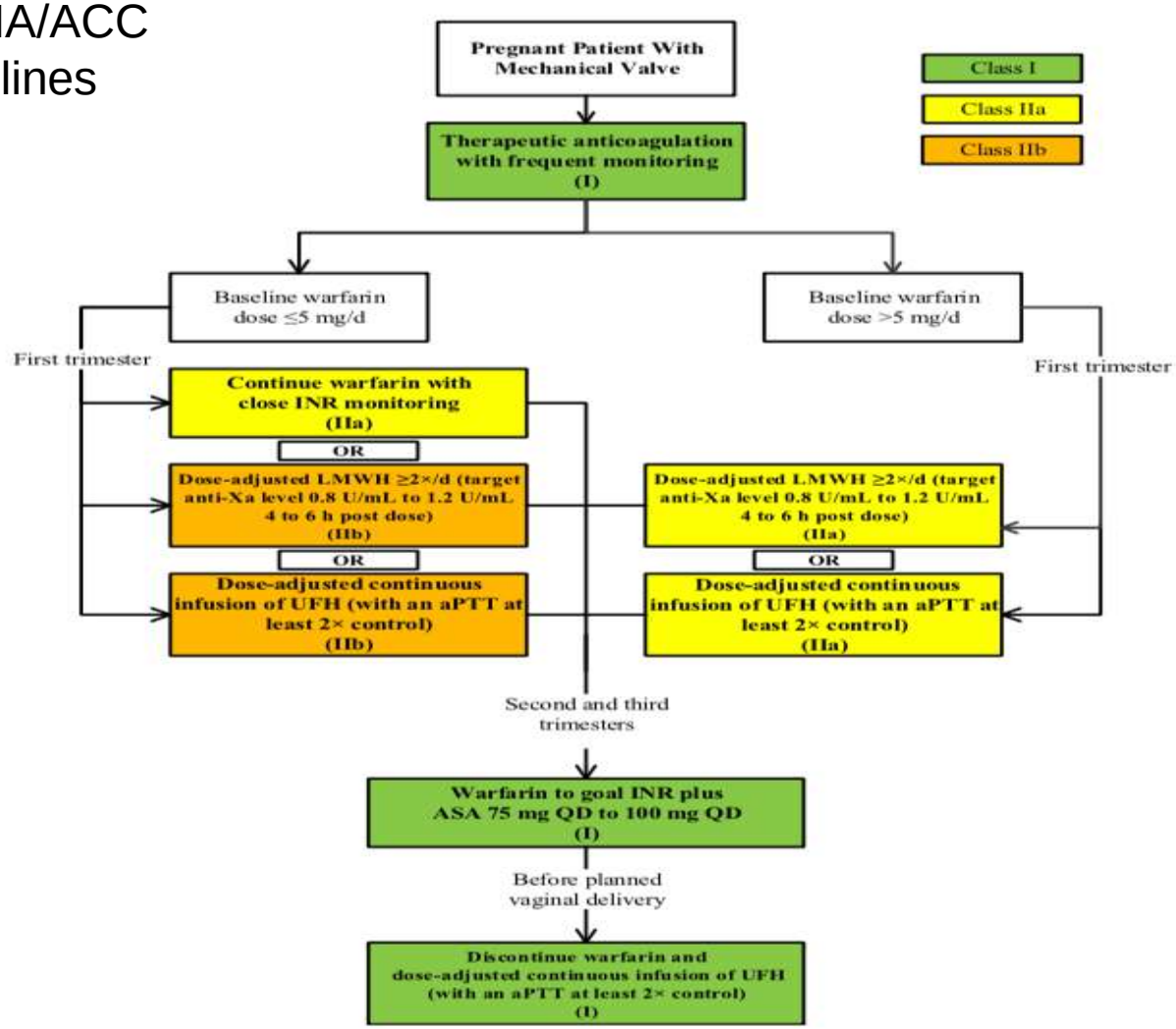
Anticoagulation of Pregnant Patients With Mechanical Valves

2014 AHA/ACC Guidelines



Low Molecular-Weight Heparin

- Similar to UFH, it does not cross the placental barrier.
- Superior SC absorption and bioavailability (90% vs 10%).
- Two to four fold longer half life.
- Does not bind to plasma proteins and therefore has a more predictable and stable dose response.
- Fewer bleeding complications.
- Lower risk of osteopenia and HIT.

AC for Pregnant Women With Mechanical PHV
A systemic review and meta-analysis

Anticoagulation	Maternal mortality	TE complications	Fetal Wastage	Fetal/neonatal Adverse effects
VKA	1.2%	3.7%	30.5%	2.9%
Sequential	2.0%	8.3%	19.8%	1.2%
LMWH alone	0.7%	10.2%*	8%	0%
UFH alone	3.0%	13.4%	35%	10%

* Except for 1 fatal case where peak anti Xa level was 1.0 U/ml (no trough level), all other cases were associated with non compliance and/or subtherapeutic anti Xa levels

D'Souza R et al Univ of Toronto, Eur Heart J 2017;38:1509-16

J Am Coll Cardiol 2017;69:2692-5

Anticoagulation Therapy for Pregnant Women With Mechanical Prosthetic Heart Valves

How to Improve Safety?*

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TABLE 1 Our Recommended Approach to AC Therapy With LMWH Throughout Pregnancy for Women With MPHVs

1.	Counseling risks and benefits of various AC regimens and determining likelihood of the patient and family to follow very strict follow-up and treatment regimens
2.	Baseline transthoracic echocardiogram and BNP or NT-proBNP levels
3.	Switch from VKA to LMWH in the hospital when INR <3.0, starting enoxaparin at 1 mg/kg every 12 h with daily monitoring of anti-factor Xa levels with dose adjustment to achieve a trough level of ≥0.6 IU/ml for low-risk patients and ≥0.7 IU/ml for high-risk patients* with peak level (4–5 h after administration) not exceeding 1.5 IU/ml.†
4.	Aspirin 75–100 mg/day
5.	Weekly clinical assessments and monitoring of trough and peak anti-factor Xa levels
6.	Return to clinic for monitoring of anti-factor Xa levels in 2–3 days after dose adjustment
7.	Repeat echocardiogram and BNP or NT-proBNP levels in case of worsening symptoms
8.	Hospitalization at 36–37 weeks for switching from LMWH to IV UFH at a dose adjusted to anti-factor Xa level of 0.8–1.0 IU/ml or APTT of >2.5
9.	Induction of labor at 38 weeks
10.	Stop IV UFH on onset of labor or >6 h prior to regional anesthesia
11.	Vaginal delivery unless fetal indications for a cesarean section delivery or maternal instability
12.	Resume UFH in 2–12 h, depending on risk of bleeding, and continue for 24–48 h before start of VKA
13.	Start VKA in the hospital after a wait of 24–48 h
14.	Continue IV UFH in the hospital until INR is therapeutic

USC Protocol for LMWH

1. Counseling risks and benefits of various AC regimens and determining likelihood of the patient and family to follow very strict follow-up and treatment regimens
2. Baseline transthoracic echocardiogram and BNP or NT-proBNP levels
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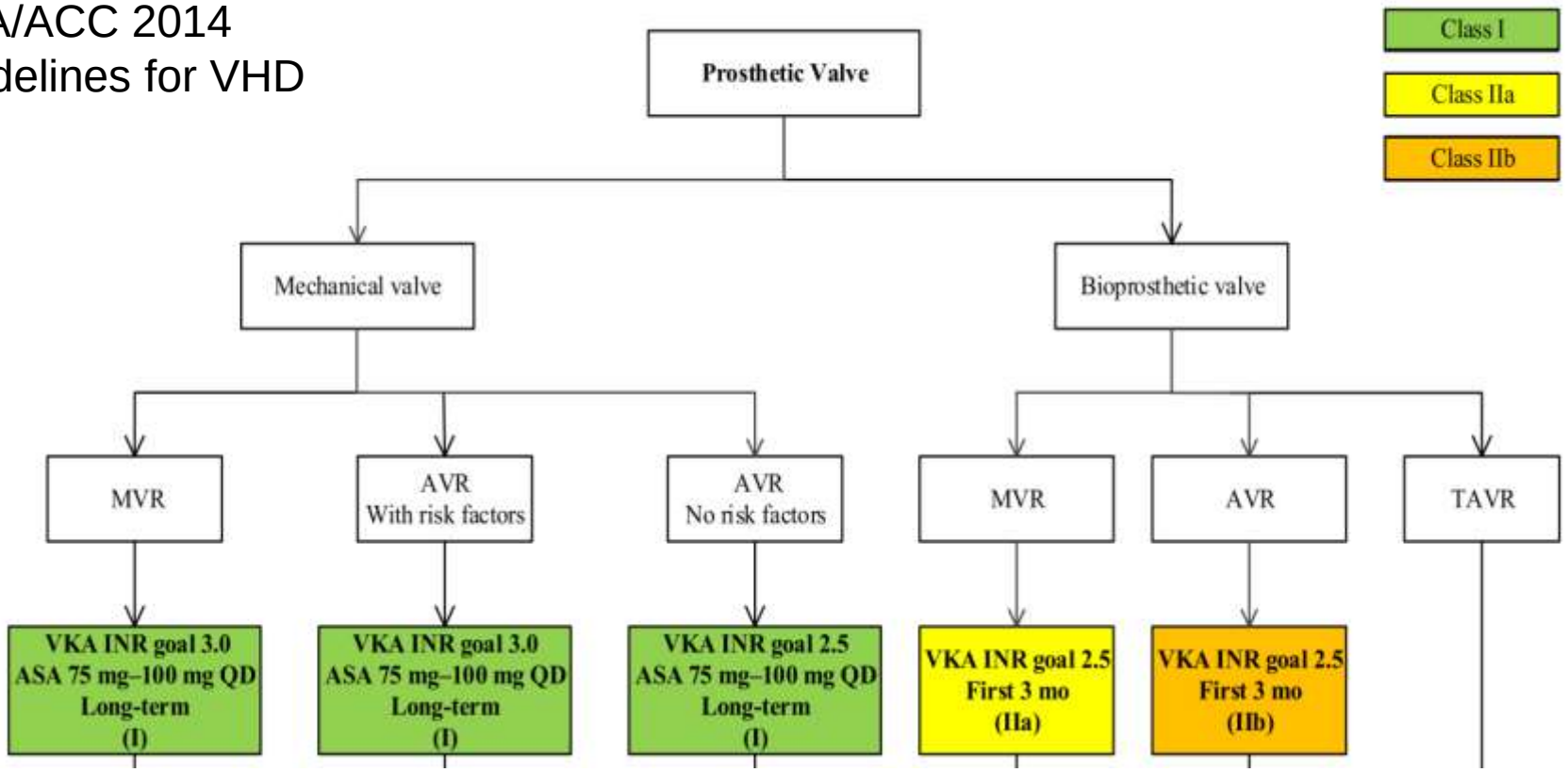
4. Aspirin 75–100 mg/day

Why Higher Dose for High Risk Patients?

AHA/ACC 2014
Guidelines for VHD



Higher risk: Mitral valve, Tricuspid valve, Atrial fibrillation, Hx of TE on anticoagulation, Hypercoagulable condition.

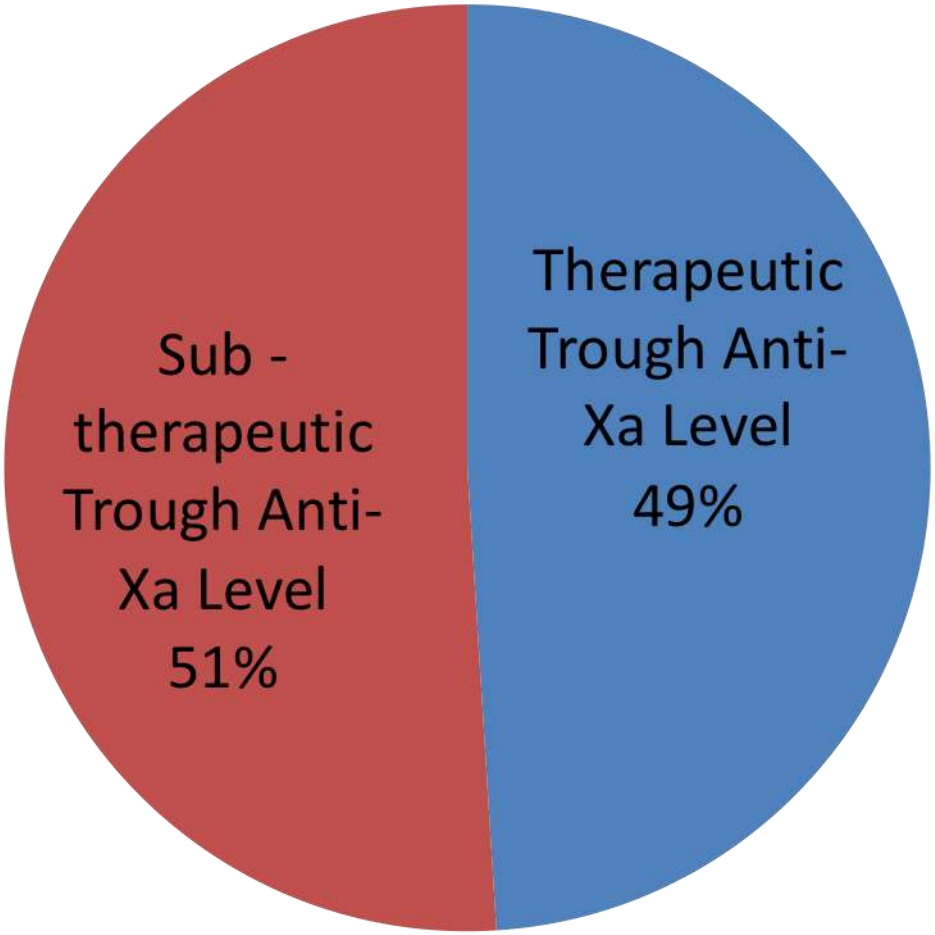
Table 1. Demographic and Clinical Characteristics of the Pregnant Patients With Prosthetic Valve Thrombosis

No.	Age, y	Prosthetic Valve	Thrombus Type	Elapsed Time Since Valve Surgery, mo	NYHA Class I–II	NYHA Class III–IV	Clinical Presentation	Anticoagulation at Prosthetic Valve Thrombosis Diagnosis—Dose	Tissue-Type Plasminogen Activator Dose	Gestational Week	Fetal Status	Maternal Final Results	Maternal Complication
1	22	Mitral	NOT	67	+		Palpitation	Warfarin—2.5 mg	50	11	A	S	None
2	31	Mitral	OT	124		+	Dyspnea	Warfarin—5 mg	50	20	H	S	None
3	38	Mitral	OT	11		+	Dyspnea	Warfarin—5 mg	25	34	H	S	None
4	38	Mitral	OT	74		+	Dyspnea	Warfarin—7.5 mg	25	18	H	S	None
5	35	Mitral	NOT	56	+		Palpitation	N/A	100	6	A	S	None
6	26	Mitral	NOT	36	+		Dyspnea	Warfarin—10 mg	50	25	H	S	None
7†	19	Mitral	NOT	27	+		Palpitation	LMWH—4000 IU	100	6	A	S	None
8† (Re)	21	Mitral	NOT	58	+		Asymptomatic	Warfarin—7.5 mg	25	11	H	S	None
9	22	Mitral aortic: N/F	NOT	13	+		Transient ischemic attack	Warfarin—2.5 ASA–100 mg	50	11	H	S	None
10‡	25	Mitral	OT	18		+	Dyspnea	LMWH–6000 IU	75	14	H	S	None
11‡ (Re)	25	Mitral	NOT	21	+		Dyspnea	Warfarin–5 mg	50	35	H	S	None
12§	25	Mitral	OT	26	+		Dyspnea	LMWH–6000 IU	100	6	H	S	None
13§ (Re)	25	Mitral	NOT	32	+		Palpitation	N/A	25	12	H	S	None
14	42	Mitral	OT	47		+	Dyspnea	Warfarin–7.5 mg	75	30	H¶	S#	PH
15	38	Mitral	OT	56		+	Dyspnea	Warfarin–5 mg	100	9	H	S	None
16	21	Mitral	NOT	77		+	Palpitation	LMWH– 6000 IU*	25	35	H	S	None
17	23	Mitral	OT	37		+	Dyspnea	Warfarin–5 mg	100	33	H	S	None
18	25	Mitral	OT	27		+	Dyspnea	Warfarin–5 mg ASA–100 mg	25	32	H	S	None
19	34	Mitral	OT	76		+	Dyspnea	Warfarin–7.5 mg	75	10	H	S	None
20	35	Mitral	NOT	15	+		Palpitation	LMWH–4000 IU	25	9	H	S	None
21	33	Mitral	NOT	45	+		Asymptomatic	LMWH–6000 IU	25	11	A	S	None
22	36	Mitral	NOT	17	+		Dyspnea	Warfarin–2.5 mg	25	36	H	S	None
23	27	Mitral	OT	16		+	Dyspnea	Warfarin–10 mg	50	9	A	S	None
24	28	Mitral	OT	23		+	Dyspnea	LMWH–6000 IU	25	36	H	S	None
25	35	Mitral	OT	60	+		Dyspnea	N/A	25	8	H	S	None
26‖	30	Mitral	OT	28		+	Dyspnea	LMWH–6000 IU	25	22	H	S	None
27‖ (Re)	30	Mitral	OT	38		+	Dyspnea	LMWH–4000 IU	25	32	H	S	None
28	28	Mitral	NOT	28	+		Asymptomatic	LMWH–6000 IU	25	9	H	S	Epistaxis

Ozkan M et al. valve thrombosis in pregnancy. Circulation 2013;128:532-40

Why Trough level?

Therapeutic and Sub therapeutic Trough Anti-Xa Levels at Goal Peak Anti-Xa Level (0.7-1.2 units/ml)

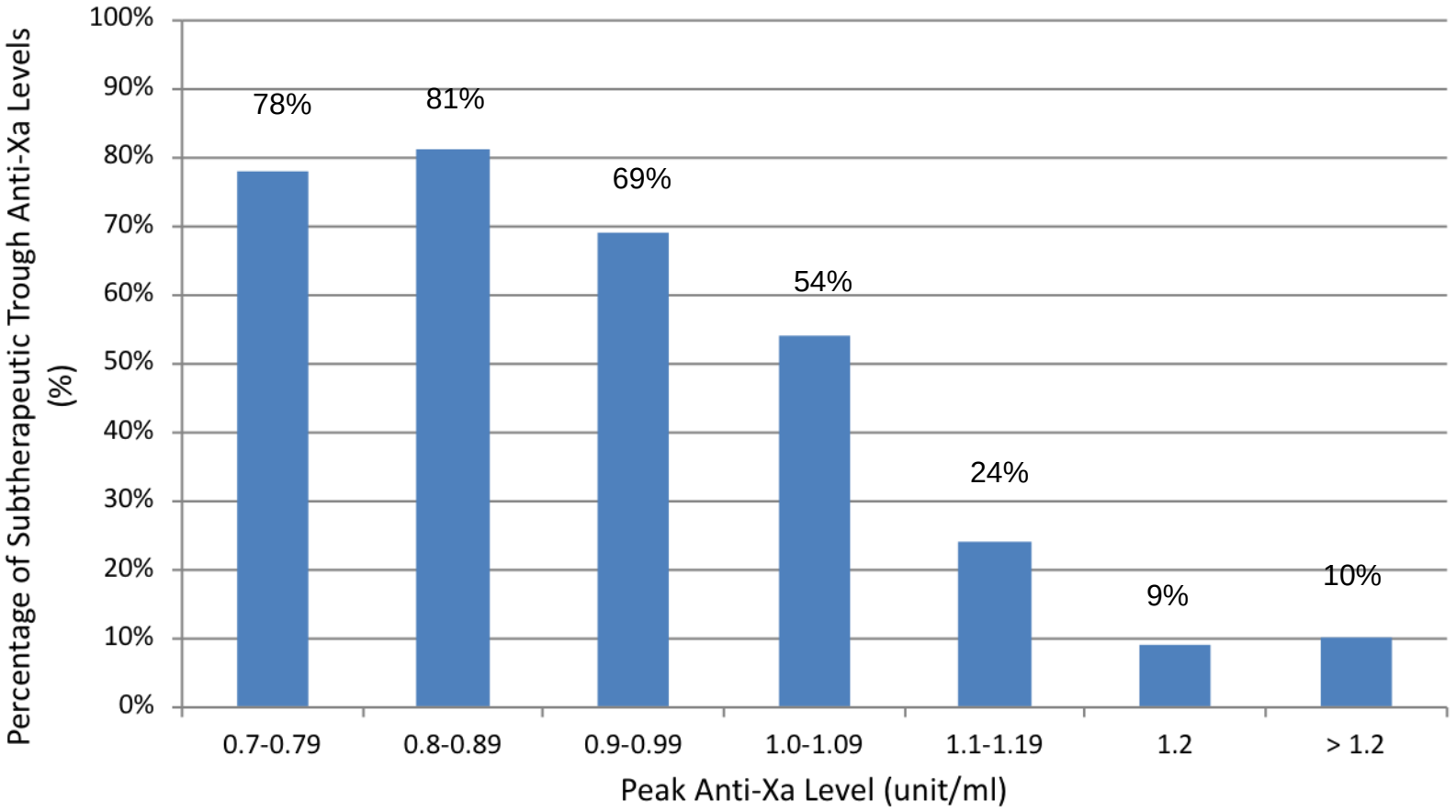


30 pregnant women receiving LMWH
187 paired determinations of Anti Xa levels.

Goland S, Elkayam U et al. J CV Pharmacol Ther 2014;19:451-6

Percent of Sub therapeutic Trough Anti-Xa levels According to Peak Anti Xa Levels

Goland, Elkayam et al J CV Pharmacol Ther 2014;19:451-6



USC Protocol for LMWH

5. Weekly clinical assessments and monitoring of trough and peak anti-factor Xa levels
6. Return to clinic for monitoring of anti-factor Xa levels in 2-3 days after dose adjustment
7. Repeat echocardiogram and BNP or NT-proBNP levels in case of worsening symptoms
8. Hospitalization at 36-37 weeks for switching from LMWH to IV UFH at a dose adjusted to anti-factor Xa level of 0.8-1.0 IU/ml or APTT of >2.5

Why 36-37 weeks?

Table 5. Outcome of Pregnancy in Women With a Mechanical Valve in Developed and Emerging Cou

	Developed Countries (n=56, 26%), n (%)	Emerging Countries (n=156, 74%), n (%)
Anticoagulation regimens*		
VKA-VKA-VKA	2 (4.0)	4 (2.9)
VKA-VKA-LMWH/UFH	5 (10.0)	32 (23.5)
LMWH-LMWH-LMWH	14 (28.0)	4 (2.9)
UFH-UFH-UFH	2 (4.0)	19 (14.0)
LMWH-VKA-LMWH/UFH	19 (38.0)	13 (9.6)
UFH-VKA-LMWH/UFH	1 (2.0)	47 (34.6)
Other	7 (14.0)	17 (12.5)
Outcome		
Maternal mortality	1 (1.8)	2 (1.3)
Hospital admission	30 (54.5)	47 (30.3)
Hospital admission for cardiac reason	18 (32.1)	30 (19.2)
Heart failure	5 (8.9)	11 (7.1)
Thrombotic events	6 (10.7)	7 (4.5)
Valve thrombosis	5 (8.9)	5 (3.2)
Hemorrhagic events	23 (41.1)	26 (16.7)
Cesarean section	33 (64.7)	63 (40.6)
Miscarriage <24 wk	6 (10.7)	27 (17.3)
Fetal mortality ≥24 wk	0 (0.0)	6 (3.8)
Apgar <7	7 (16.3)	5 (4.7)
Preterm birth <37 wk	19 (41.3)	10 (8.4)
Median birth weight (Q1–Q3)	2690 (2265 - 3035)	2945 (2715 - 3100)
Median pregnancy duration (Q1–Q3)	37.8 (35.1 - 38.9)	39.0 (38.0 - 39.6)

Why anti Xa?

Monitoring UFH in pregnant women with MPHV

Advantages of Anti Xa

Guervil DJ et al Ann Pharmacotherapy 2011 ;45:861

- Anti Xa is not influenced by extraneous factors, demonstrates less variability
- Monitoring UFH with anti-Xa results in a more expeditious achievement of therapeutic AC, more consistent therapeutic levels, and fewer lab tests and doses changes.

USC Protocol for LMWH

10. Stop IV UFH on onset of labor or >6 h prior to regional anesthesia
11. Vaginal delivery unless fetal indications for a cesarean section delivery or maternal instability
12. Resume UFH in 2-12 h, depending on risk of bleeding, and continue for 24-48 h before start of VKA
13. Start VKA in the hospital after a wait of 24-48 h
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Table 5. Outcome of Pregnancy in Women With a Mechanical Valve in Developed and Emerging Countries

	Developed Countries (n=56, 26%), n (%)	Emerging Countries (n=156, 74%), n (%)	*P* Value
Anticoagulation regimens*			<0.001
VKA-VKA-VKA	2 (4.0)	4 (2.9)	
VKA-VKA-LMWH/UFH	5 (10.0)	32 (23.5)	
LMWH-LMWH-LMWH	14 (28.0)	4 (2.9)	
UFH-UFH-UFH	2 (4.0)	19 (14.0)	
LMWH-VKA-LMWH/UFH	19 (38.0)	13 (9.6)	
UFH-VKA-LMWH/UFH	1 (2.0)	47 (34.6)	
Other	7 (14.0)	17 (12.5)	
Outcome			
Maternal mortality	1 (1.8)	2 (1.3)	1.00
Hospital admission	30 (54.5)	47 (30.3)	0.001
Hospital admission for cardiac reason	18 (32.1)	30 (19.2)	0.048
Heart failure	5 (8.9)	11 (7.1)	0.768
Thrombotic events	6 (10.7)	7 (4.5)	0.110
Valve thrombosis	5 (8.9)	5 (3.2)	0.134
Hemorrhagic events	23 (41.1)	26 (16.7)	<0.001
Cesarean section	33 (64.7)	63 (40.6)	0.003
Miscarriage <24 wk	6 (10.7)	27 (17.3)	0.243
Fetal mortality ≥24 wk	0 (0.0)	6 (3.8)	0.344
Apgar <7	7 (16.3)	5 (4.7)	0.039
Preterm birth <37 wk	19 (41.3)	10 (8.4)	<0.001
Median birth weight (Q1–Q3)	2690 (2265 - 3035)	2945 (2715 - 3100)	0.001
Median pregnancy duration (Q1–Q3)	37.8 (35.1 - 38.9)	39.0 (38.0 - 39.6)	<0.001

AC for Pregnant Women with MPHV

- Whichever regimen is chosen, it is clear that this is a dangerous situation that demands that anticoagulant control be as close to perfect as possible.

ROPAC Investigators

Circulation 2015

CPP

The 5th International Congress on Cardiac Problems in Pregnancy (CPP 2018)

22-25 February, 2018
Bologna, Italy

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