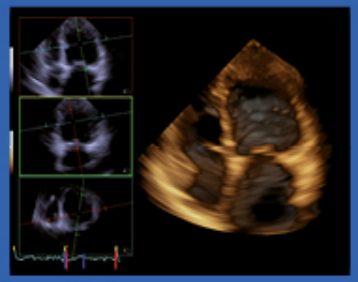

EuroValve

March 27 - 28, 2015

How to Manage Anticoagulant Therapy in Valve Disease Before and During Pregnancy

Bernard Iung
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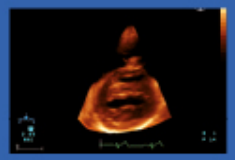
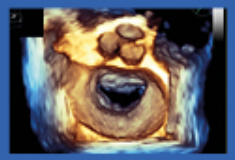
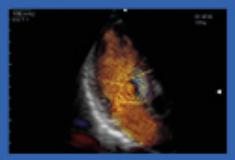
DHU FIRE

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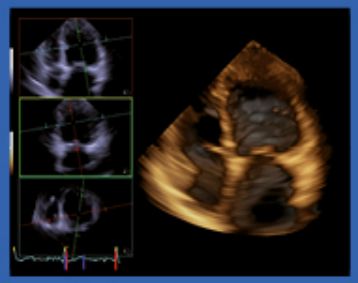


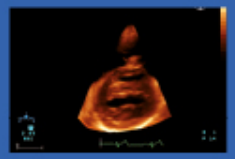
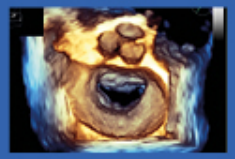
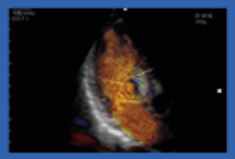
EuroValve
March 27 - 28, 2015

Faculty disclosure

Bernard Iung

I disclose the following financial relationships:

Consultant for Abbott Boehringer Ingelheim, Valtexch
Paid speaker for Edwards Lifesceinces

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Pregnancy and Heart Valve Prosthesis

- Good haemodynamics
- The problem is related to anticoagulant therapy for mechanical prosthesis
  - Hypercoagulable state
  - Each antithrombotic regimen has drawbacks
    - unfractionated heparin
    - low-molecular weight heparins
    - vitamin K blockers
  - Limited information from clinical studies

➢ No consensus in clinical practice

Background

- Changes toward hypercoagulability
  - ↑ coagulation factors
  - ↑ thrombin-ATIII complex
  - ↓ protein S
  - impaired fibrinolysis

(Hellgren Semin Thromb Hemost 2003;29:125-30)

- Risk of venous thromboembolism x 2-4

(Ginsberg et al. J Thromb Haemost 2003;1:1435-42)

- Anticoagulant therapy is an independent adverse predictor of fetal outcome

(Siu et al. Circulation 2001;104:515-21)

Unfractionated Heparin

- No placenta crossing : no embryopathy
- Modified activity because of changes in haemostasis : need for increased doses
- Concerns on the reliability of aPTT
  - target aPTT ≥ 2
  - anti-Xa activity 0.3 to 0.5 U/ml

(Ginsberg et al. Arch Intern Med 2003;163:394-8)

- Short half-life : problems of stability, feasibility
- Risks of osteoporosis and thrombocytopenia

Low Molecular Weight Heparin

- No placenta crossing : no embryopathy
- Better stability and predictability of the antithrombotic effect
- Need for increased and adapted doses during pregnancy

  (Lebaudy et al. Clin Parmacol Ther 2008;84:370-7)
- Lower risks of osteoporosis and thrombocytopenia
- Concerns regarding clinical efficacy in pregnant patients with mechanical prosthesis

Vitamin K Blockers

- Placenta crossing : risk of embryopathy
  - ≈ 5%, mainly during the 1st trimester (6-12 wks)

    (Chan et al. Arch Interm Med 2000;160:191-6)
  - Nasal hypoplasia, epiphyseal stippling
  - Few or no consequences on further growth and cognitive development

    (Van Driel et al. Am J Med Genet 2000;95:438-43)

    (Wesseling et al. Thromb Hemostasis 2001;85:609-13)
- Long half-life (fetus > mother)
  - Fetal bleeding risk on delivery

Anticoagulation

- Heparin throughout pregnancy 23%
- Vitamin K blockers throughout pregnancy 35%
- Heparin at 1st trimester then warfarin 42%

	Mechanical Prosthesis 151 / 133	***Bioprosthesis 63 / 49***
Spontaneous abortion	17 (11%)	6 (10%)
Stillbirth	9 (6%)	2 (3%)
Embryopathy	0	0
Thrombo-embolism		
Prosthetic thrombosis	13 (9%)	0
Peripheral embolism	8 (5%)	0
Major bleeding	7 (5%)	0
Emergency surgery for valve deterioration	0	2 (3%)
Maternal death	6 (4.5%) (4 by valve thr.)	0

(Sbarouni and Oakley Br Heart J 1994;71:196-200)

Anticoagulation

- Heparin throughout pregnancy 41%
- Vitamin K blockers throughout pregnancy 32%
- Heparin at 1st trimester then warfarin 27%

	Mechanical Prosthesis 95 / 61	*Bioprosthesis 60 / 42*
Spontaneous abortion	16 (17%)	4 (7%)
Stillbirth	5 (5%)	4 (7%)
Embryopathy	0	0
Thrombo-embolism		
Prosthetic thrombosis	10 (10%)	0
Peripheral embolism	9 (9%)	0
Major bleeding	4 (4%)	0
Emergency surgery for valve deterioration	0	0
Maternal death	4 (4.2%) (3 by valve thr.)	0

(Hanania et al. Eur Heart J 1994;15:1651-8)

Mechanical Prosthesis and Pregnancy

1234 pregnancies in 976 women (2/3 mitral prostheses)

Anticoagulation	*Embryopathy (%)*	*Spontaneous Abortion (%)*	*Thrombo-Embolism (%)*	*Maternal Death (%)*
Warfarin throughout pregnancy	**6.4**	**25**	**3.9**	**1.8**
Heparin throughout pregnancy	**0**	**24**	**33**	**15**
- low-dose	0	20	60	40
- adjusted-dose	0	25	25	6.7
Heparin during the first trimester, then warfarin	**3.4**	**25**	**9.2**	**4.2**

(Chan et al. Arch Interm Med 2000;160:191-6)

Mechanical Prosthesis and Pregnancy

Anticoagulation	*Embryopathy (%)*	*Spontaneous Abortion (%)*	*Thrombo-Embolism (%)*	*Maternal Death (%)*
Stillesen et al. (70 pregnancies)				
Warfarin throughout pregnancy	1 (4%)	3 (12%)	0	0
UFH throughout pregnancy	0	0	3 (38%)	1 (13%)
UFH during the first trimester, then warfain	0	1 (4%)	1 (4%)	1 (4%)
Basude et al. (32 pregnancies)				
Warfarin throughout pregnancy	0	17 (77%)	2 (9%)	1 (5%)
LMWH (anti-Xa monitoring)	0	1 (25%)	0	0
LMWH during the first trimester, then warfarin	0	3 (50%)	1 (25%)	0

(Stillesen et al. Eur J Cardiothorac Surg 2011;40:448-54)
(Basude et al. BJOG 2012;119:1008-13)

Mechanical Prosthesis and Pregnancy

	Oran	Quinn	Abilgaard	Yinon
n pregnancies	81	12	12	23
n women	75	11	11	17
Age (yrs)	-	30	29	30
Prosthesis				
- **Mitral**	44	4	4	14
- **Aortic**	8	2	5	8
- **Mitral + Aortic**	5	3	2	1
- **Tricuspid**	0	2	0	0
LMWH 2nd and 3rd trim. (%)	74	92	100	100
Anti-Xa Monitoring (%)	63	100	100	100
Aspirin (%)	NA	33	50	100
Thrombo-embolic events	10 (12%)	1 (8%)*	2 (17)*	1 (4%)
Prosthetic thrombosis	7 (9%)	1(8%)*	1 (8)*	1 (4%)
Maternal death	0	0	0	1 (4%)

* Subtherapeutic antiicoagulation

(Oran et al. Thromb Haemost 2004;92:747-51)
(Quinn et al. Haematologica 2009;94:1608-12)
(Abildgaard et al. Thromb Res 2009;124:262-7)
(Yinon et al. Am J Cardiol 2009;104:1259-63)

Warfarin Throughout Pregnancy

71 pregnancies in 52 patients with mechanical prosthesis

Warfarin throughout pregnancy
(Target INR 2.25-4.0)
Elective cesarean section at 37th week

- 23 spontaneous abortions (32%)
- 4 cases of embryopathy (5.6%) (2/4 alive)
- No thromboembolism
- No bleeding
- No maternal mortality

(Cotrufo et al. Obstet Gynecol 2002;99:35-40)

Outcome of Pregnancy

Influence of Warfarin Dose

58 pregnancies in 43 women with warfarin throughout pregnancy

	Warfarin ≤ 5 mg (n=33)	*Warfarin > 5 mg (n=25)*
Warfarin dose (mg)	4.0±0.8	7.5±0.9
INR	2.9±0.4	3.0±0.4
Healthy babies	28	3
Spontaneous abortion		
1st trimester	4	12
2nd- trimester	0	6
Stillbirth (3nd- trimester)	0	1
Fetal growth retardation	1	0
Embryopathy	0	2*
Prosthetic thrombosis	1	1

** : abortion at 6 months* *(Vitale et al. J Am Coll Cardiol 1999;33:1637-41)*

Target Anticoagulation

- LMWH
  - Target anti-Xa 0.8 - 1.2 U/ml
  - Need for continuous dose adjustment
  - Need for peak and through monitoring?

(Friedrich et al. J Perinatol 2010;30:253-7)

- Vit. K blockers
  - Same target INR as in non-pregnant patients.

(ACC/AHA and ESC Guidelines)

  - Possibility of low target INR [1.5-2.5] in women with mechanic aortic prostheses ?

(De Santo et al. J Am Coll Cardiol 2012;59:1110-5)

Delivery

- No delivery under vit K blockers
  - Fetal risk of cerebral bleeding

    (Sareli et al. Am J Cardiol 1989;63:1462-5)
  - Prolonged anticoagulation in the fetus
- Substitution by heparin at 36th week
  - Heparin discontinued at the onset of labour and resumed 4-6 h after delivery
- Cesarean section
  - ↓ risk of intracerebral fetal haemorrhage
  - ↑ maternal risk of bleeding and thromboembolism
- Vaginal delivery
  - Consider risk of peridural analgesia

ESC Guidelines on the management of cardiovascular diseases during pregnancy

The Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC)

Endorsed by the European Society of Gynecology (ESG), the Association for European Paediatric Cardiology (AEPC), and the German Society for Gender Medicine (DGesGM)

Authors/Task Force Members Vera Regitz-Zagrosek (Chairperson) (Germany)*, Carina Blomstrom Lundqvist (Sweden), Claudio Borghi (Italy), Renata Cifkova (Czech Republic), Rafael Ferreira (Portugal), Jean-Michel Foidart† (Belgium), J. Simon R. Gibbs (UK), Christa Gohlke-Baerwolf (Germany), Bulent Gorenek (Turkey), Bernard Iung (France), Mike Kirby (UK), Angela H. E. M. Maas (The Netherlands), Joao Morais (Portugal), Petros Nihoyannopoulos (UK), Petronella G. Pieper (The Netherlands), Patrizia Presbitero (Italy), Jolien W. Roos-Hesselink (The Netherlands), Maria Schaufelberger (Sweden), Ute Seeland (Germany), Lucia Torracca (Italy).

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Recommendations for the management of valvular heart disease

Recommendations	Class	Level
Continuation of OACs should be considered during the first trimester if the warfarin dose required for therapeutic anticoagulation is < 5 mg/day (or phenprocoumon < 3 mg/day or acenocoumarol < 2 mg/day), after patient information and consent.	IIa	C
Discontinuation of OAC between weeks 6 and 12 and replacement by adjusted-dose UFH (a PTT ≥ 2 × control; in high risk patients applied as intravenous infusion) or LMWH twice daily, (with dose adjustment according to weight and target anti-Xa level 4-6 hours post-dose 0.8-1.2 U/mL) should be considered in patients with a warfarin dose required of more than 5 mg/day (or phenprocoumon > 3 mg/day or acenocoumarol > 2 mg/day).	IIa	C
LMWH should be avoided, unless anti-Xa levels are monitored.	III	C

European Heart Journal 2011, doi: 10.1093/eurheartj/ehr218

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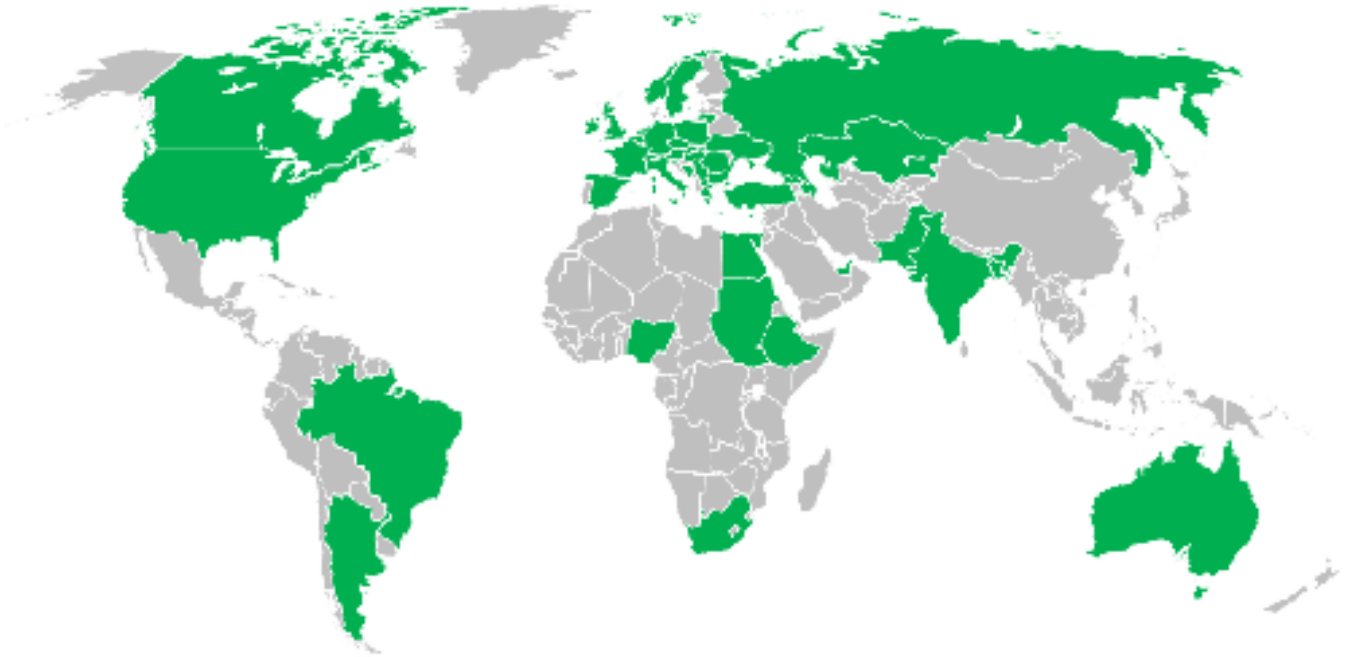
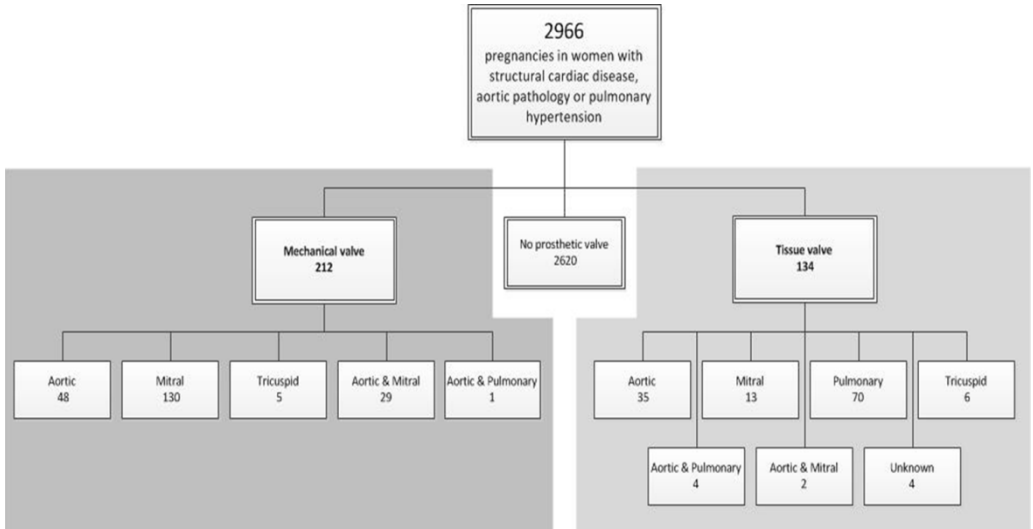
Recommendations for the management of valvular heart disease

Recommendations	Class	Level
OAC should be discontinued and dose-adjusted UFH (a PTT ≥ 2 × control) or adjusted-dose LMWH (target anti-Xa level 4-6 hours post-dose 0.8-1.2 U/mL) started at the 36th week of gestation.	I	C
In pregnant women managed with LMWH, the 4-6 hours post-dose anti-Xa level should be assessed weekly.	I	C
LMWH should be replaced by intravenous UFH at least 36 hours before planned delivery. UFH should be continued until 4-6 hours before planned delivery and restarted 4-6 hours after delivery if there are no bleeding complications.	I	C

European Heart Journal 2011, doi: 10.1093/eurheartj/ehr218

ROPAC Registry
48 countries, 132 centers, 2966 pregnancies





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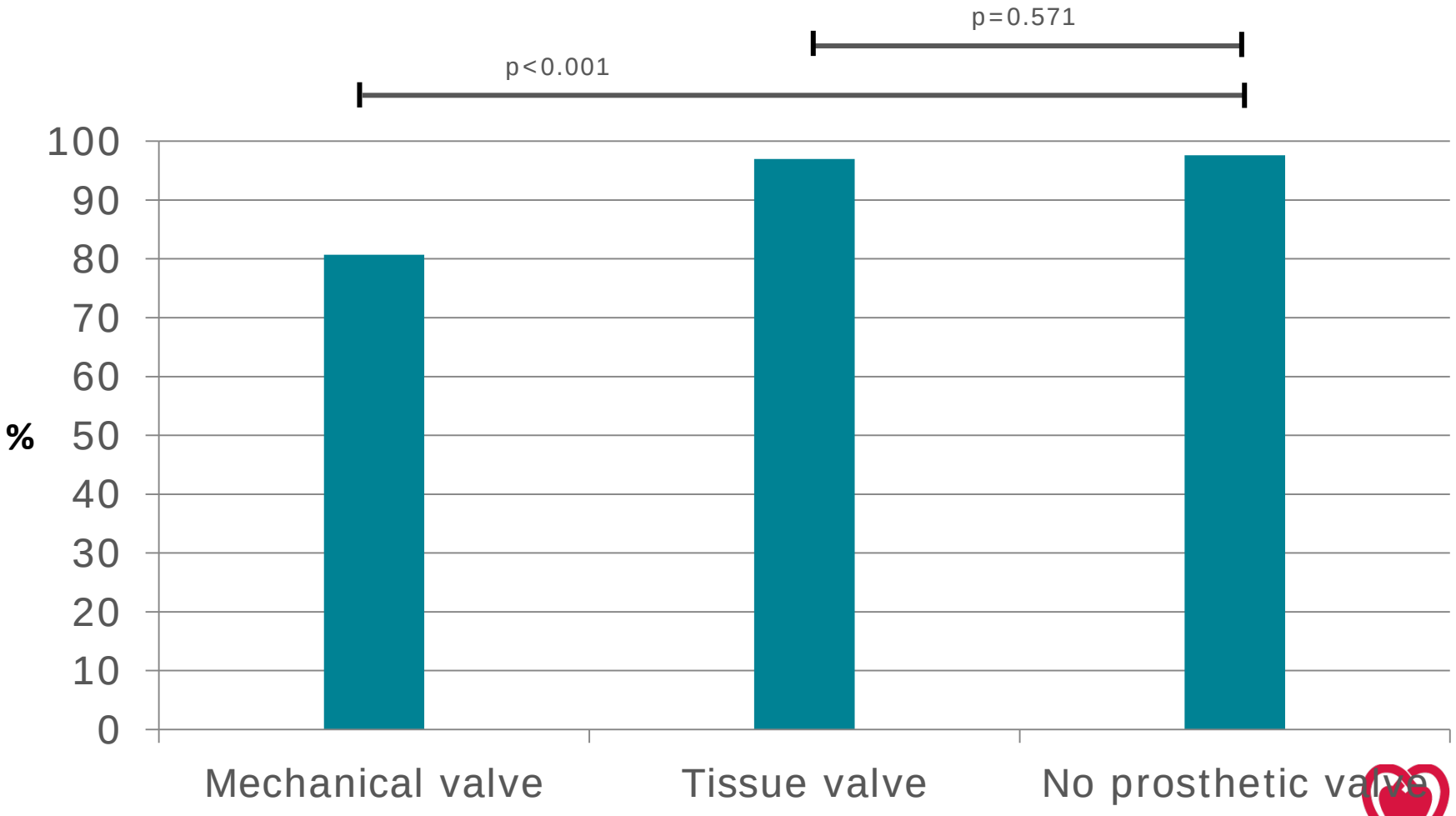
Results *Complications*

	Mechanical valve 212	Cardiac patients No prosthesis 2620
Maternal mortality	1.4%	0.2%*
Thrombotic event	6.1%	0.4%*
Haemorrhagic event	23%	5%*
Miscarriage <24 wks	15.6%	1.7%*
Fetal mortal >24 wks	2.8%	0.6%*

* $p<0.05$

Results *Live births*

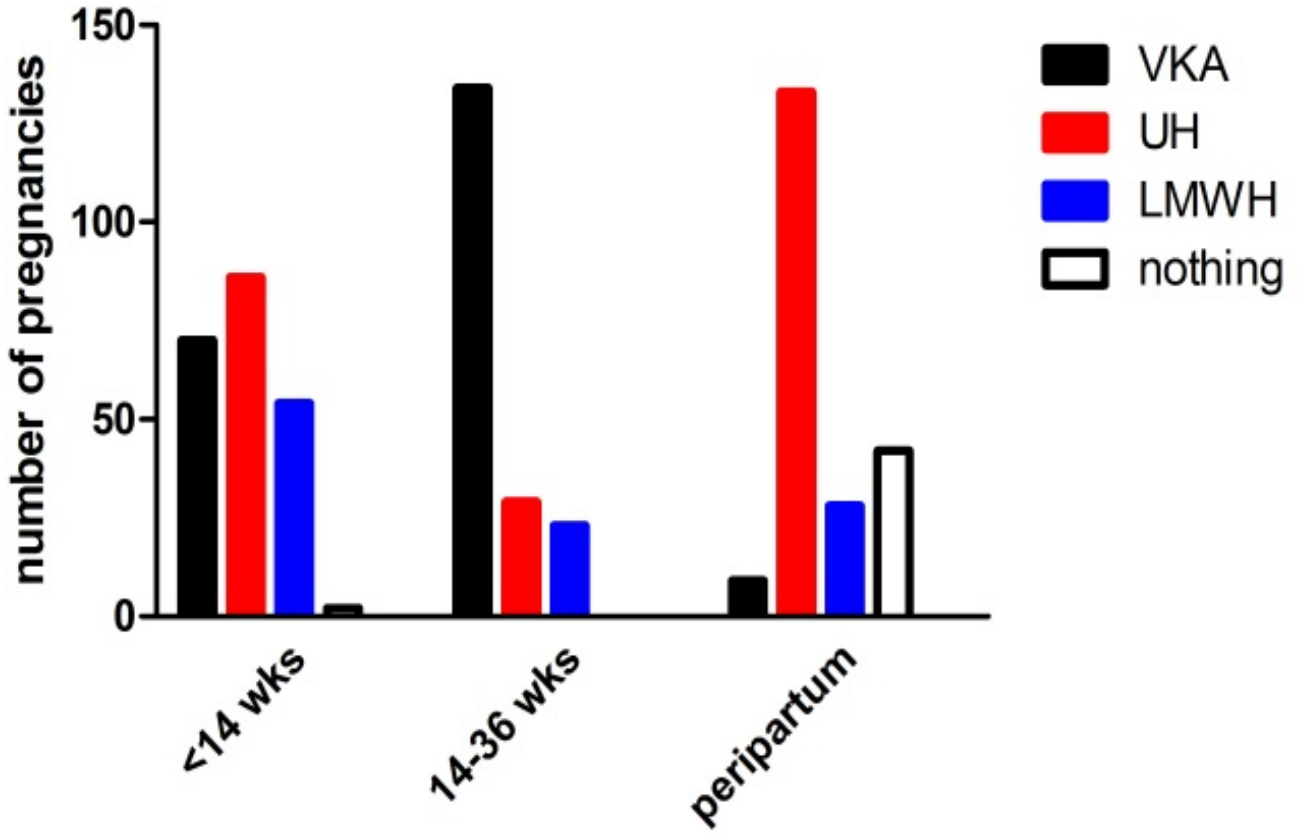


Results *Mechanical valve thrombosis*

Incidence: 10 patients (4.7%)

	Total	VKA	Heparin
1st trimester	**5**	0	5
2nd trimester	**2**	1	1
3rd trimester	**3**	3	0

Results *Anticoagulation*



Other Indications of Anticoagulant Therapy during Pregnancy

- Atrial fibrillation +
  - Native valve disease
  - Bioprostheses
- Lower thromboembolic risk
- LMWH favoured during the first trimester
- Vit. K blockers favoured afterwards
- Contra-indication of direct anticoagulants (anti IIa – anti Xa)

Conclusion (I)

- Pregnancy with mechanical prosthesis is always at high risk
- No consensus on the optimal anticoagulant therapy in pregnant women with a mechanical prosthesis
  - Vit. K blockers favored between the 12th and 36th week
  - The choice for the first trimester should be made after risk assessment and patient information taking into account:
  - Continuous warfarin therapy until 36th week is the safest treatment for the mother

Conclusion (II)

- UFH is associated with a high thromboembolic risk
- The use of LMWH needs close anti-Xa monitoring and refinements in dose adjustement
- Multidisciplinary collaboration is mandatory at every stage of pregnancy
- Patient information
  - Choice of the type of prosthesis in young women
  - Optimal contraception and early diagnosis of pregnancy
  - Anticoagulation regimen if needed
- Need for contemporary prospective registries

Thromboembolic Complications with Mechanical Prosthesis

- 20 events / 151 pregnancies (13%)
  - 13 cases of prosthetic thrombosis (4 deaths)
  - 8 peripheral embolic events (2 deaths)

  (71% occurred with heparin, 29% with warfarin)

  (Sbarouni and Oakley Br Heart J 1994;71:196-200)

- 16 events / 95 pregnancies (17%) *(37 per 100 pt-yr)*
  - 10 cases of prosthetic thrombosis (3 deaths)

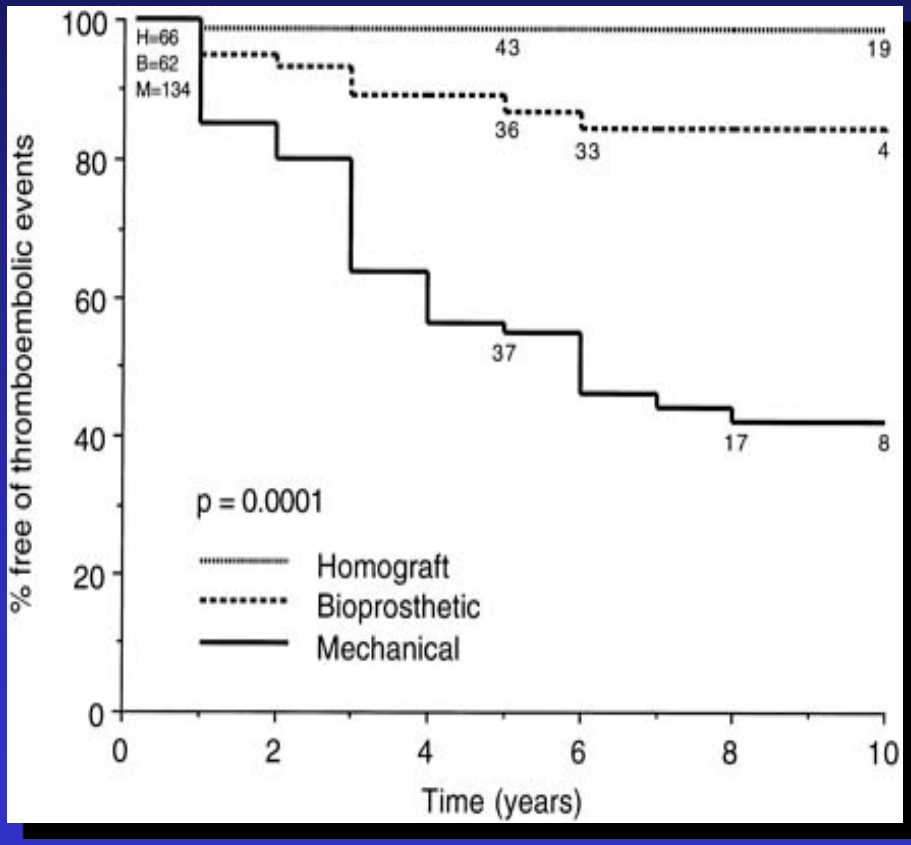
    (20 per 100 pt-yr)
  - 9 peripheral embolic events (no death)

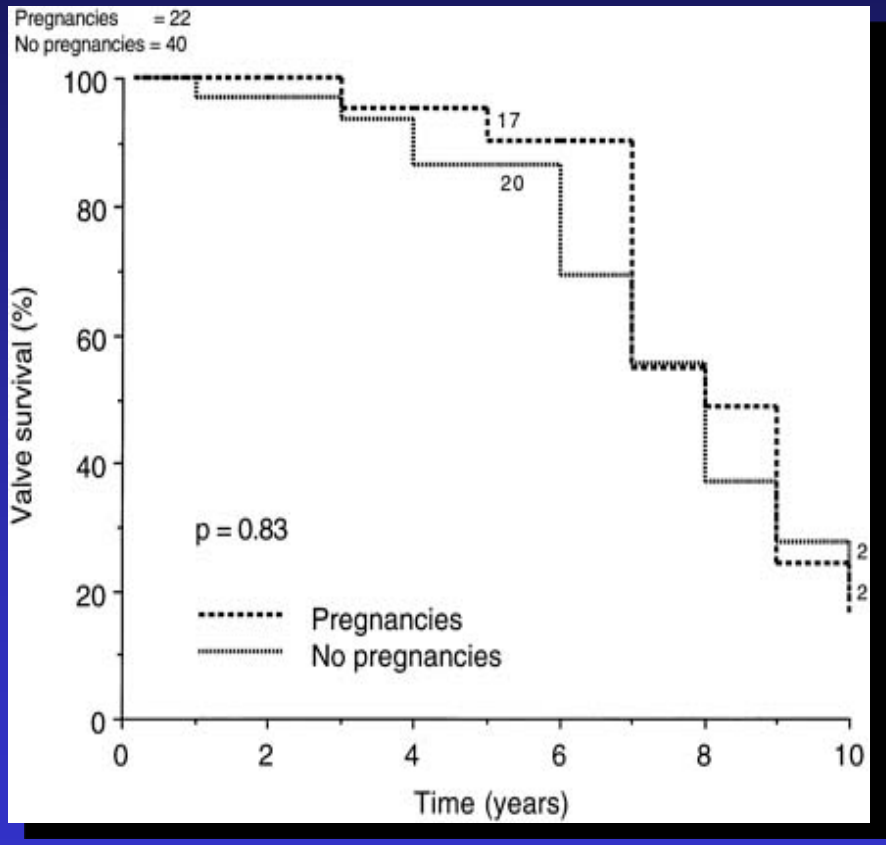
  (46 per 100 pt-yr on heparin , 10 per 100 pt-yr on vit.K blockers)

  (Hanania et al. Eur Heart J 1994;15:1651-8)

Which Valvular Substitute for Young Women ?

232 women (12 - 35 yrs) - 132 pregnancies in 78 women





Freedom from thrombo-embolism

Structural deterioration

(North et al. Circulation 1999;99:2669-76)

Contraception

- **Oral contraception**
  - Estro-progestatives : thrombo-embolic risk, interactions with anticoagulant tharapy
  - Low-dose progestatives : concern about efficacy and tolerance

- **Intra-uterine devices**
  - Bleeding
  - Endocarditis
    risk factors : previous infection, poor social conditions
    No endocarditis in 170 pts

(Abdalla et al. Contraception 1992;45:73-80)

Method adapted to the risk of the patient

Subcutaneous Heparin during the First Trimester

40 pregnancies in 37 patients with mechanical prosthesis

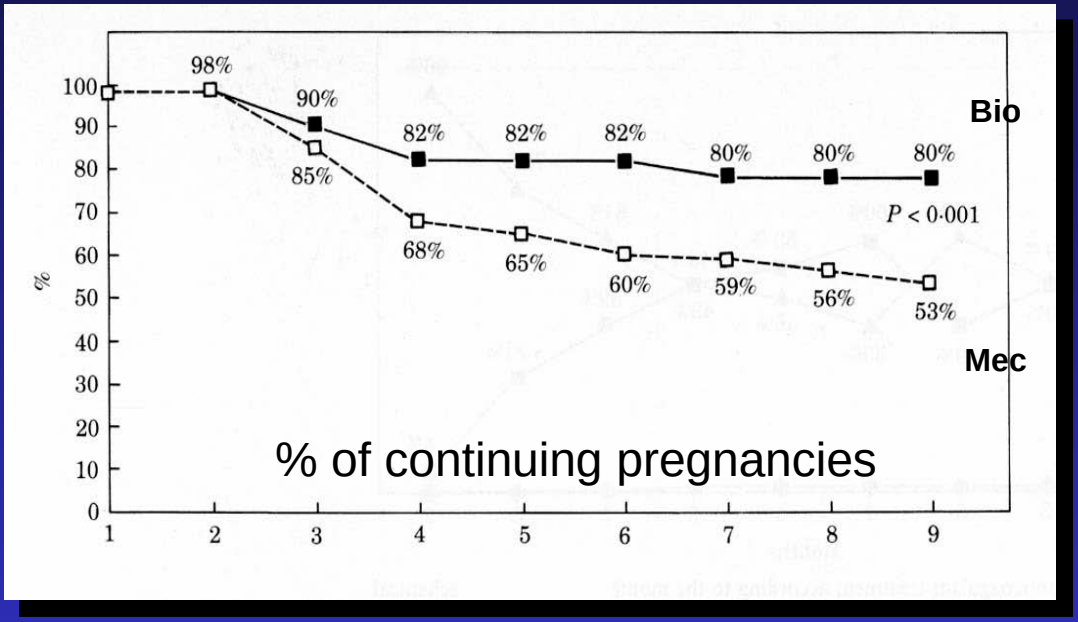
Subcutaneous heparin between 6th and 12th weeks and during the last 2 weeks
(3 or 4 injections / 24 h. → aPTT 1.5-2.5)

- 23 spontaneous abortions (37%)
- No embryopathy
- 2 cases of fatal prosthetic thrombosis (5%)
- 1 fatal bleeding (2.5%)
- Maternal mortality : 8.1%

(Salazar et al. J Am Coll Cardiol 1996;27:1698-703)

Outcome of Pregnancies

- According to the type of prosthesis



- According to anticoagulant therapy
  - Normal pregnancies:
    46% on anticoagulant therapy vs. 84% (p<0.001)
  - Spontaneous abortion: 17% vs. 4% (p<0.02)

(Hanania et al. Eur Heart J 1994;15:1651-8)

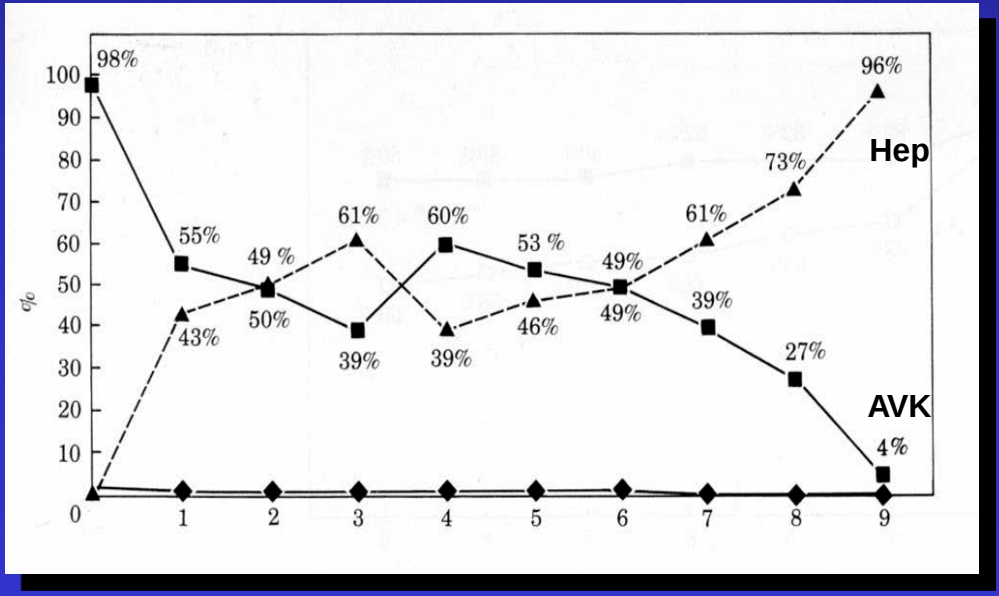
Pregnancy and Heart Valve Prosthesis

Anticoagulant Therapy

- 100% of mechanical prostheses
- 15% of bioprostheses

During the first trimester :

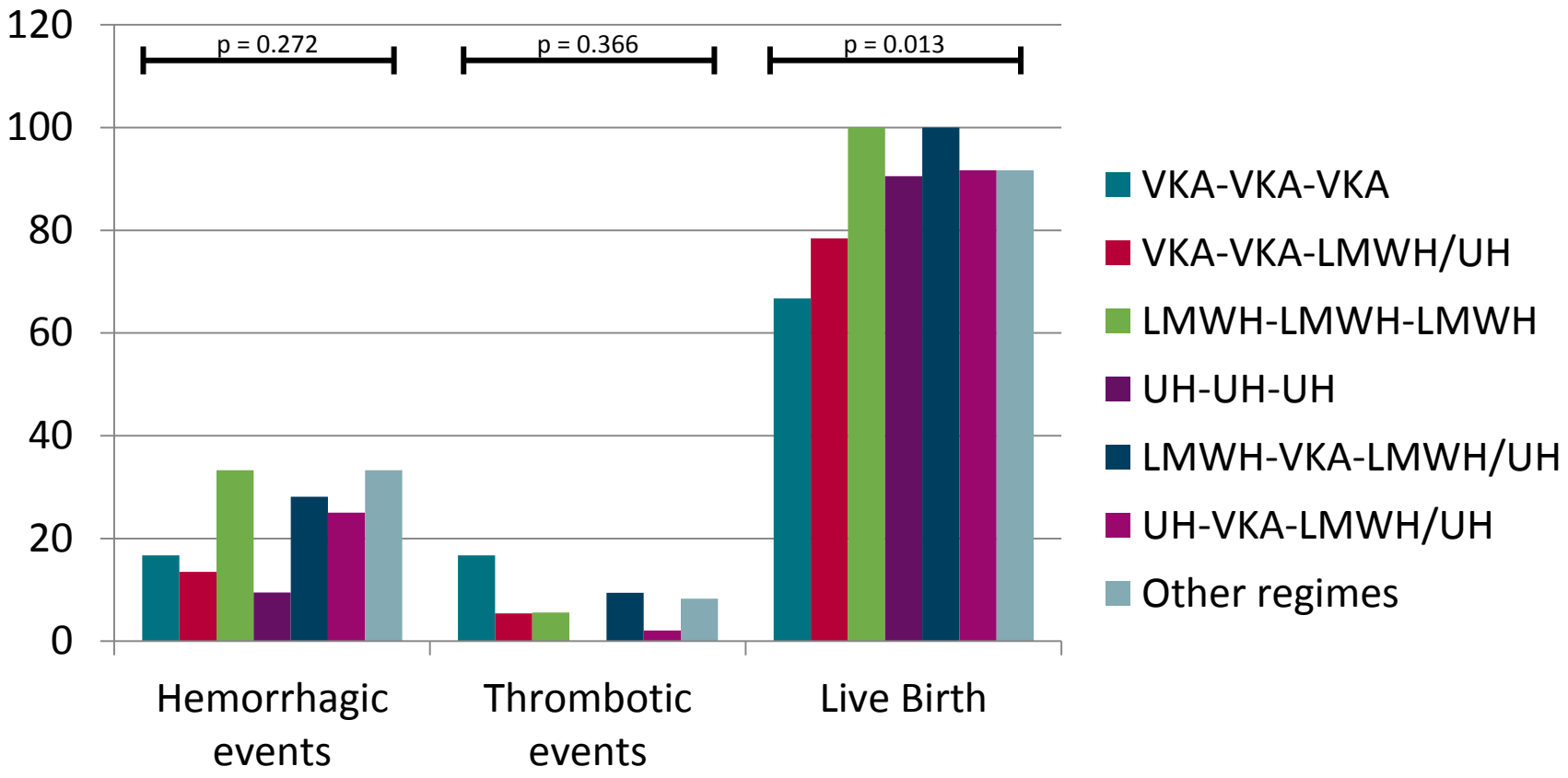
- 32% had vitamin K blockers
- 68% had heparin



ACC/AHA Guidelines

For pregnant patients with mechanical prosthetic valves, up to 36 weeks of gestation, the therapeutic choice of continuous intravenous or dose-adjusted subcutaneous UFH, dose-adjusted LMWH, or warfarin should be discussed fully. If continuous intravenous UFH is used, the fetal risk is lower, but the maternal risks of prosthetic valve thrombosis, systemic embolization, infection, osteoporosis, and heparin-induced thrombocytopenia are relatively higher.	**I C**
In pregnant patients with mechanical prosthetic valves who receive dose-adjusted LMWH, the LMWH should be administered twice daily subcutaneously to maintain the anti-Xa level between 0.7 and 1.2 U per ml 4 h after administration.	**I C**
In patients with mechanical prosthetic valves, it is reasonable to avoid warfarin between weeks 6 and 12 of gestation owing to the high risk of fetal defects.	**IIa C**
In patients with mechanical prosthetic valves, it is reasonable to give low-dose aspirin (75 to 100 mg per day) in the second and third trimesters of pregnancy in addition to anticoagulation with warfarin or heparin.	**IIa C**
LMWH should not be administered to pregnant patients with mechanical prosthetic valves unless anti-Xa levels are monitored 4 to 6 h after administration.	**III C**

Results *Regimes*



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