Valvular Heart Disease

Dose-dependency of fetal effects of vitamin K antagonists: Fact or fiction?

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No conflicts of interest

Valvular Heart Disease

Dose-dependency of fetal effects of vitamin K antagonists:

Fact or fiction?

- Review information on adverse fetal effects of vitamin K antagonists
- Focus on dose-dependency of these effects

Vitamin K antagonists

(warfarin, acenocoumarol, phenprocoumon):

the safest anticoagulation therapy to prevent thrombo-embolic complications in women with mechanical heart valve prosthesis

associated with embryopathy and fetopathy and increased fetal loss:
dose dependent?

D Souza EHJ 2017; Steinberg JACC 2017; Regitz ESC guidelines EHJ 2011; ACC/AHA guidelines Circ 2014; Hassouna Int Card thor surg 2014; Xu Can J Card 2016

ESC guidelines (2011) and AHA/ACC guidelines (2014)

IC recommendation to use VKA in 2nd/3rd trimester independent of dosage (VKA is recommended)

IIaC recommendation to use VKA in 1st trimester when warfarin dose requirement < 5mg/day (VKA should be considered)

level of evidence C: expert consensus

Regitz ESC guidelines EHJ 2011; ACC/AHA guidelines Circ 2014; Baumgartner ESC giudelines EHJ 2017

Questions to be answered:

1. Is first trimester embryopathy dose-dependent?

2. Are other adverse fetal effects (fetopathy, fetal loss) dose-dependent?

3. Will dose requirement increase during pregnancy?

4. Is a lower target INR range safe for pregnant women?

Questions to be answered:

1. Is first trimester embryopathy dose-dependent?

2. Are other adverse fetal effects (fetopathy, fetal loss) dose-dependent?

Vitamin K antagonists and the fetus:

- embryopathy (6-9 weeks)
  - nasal hypoplasia,
  - stippled epiphysis

- fetopathy
  - CNS and ocular abnormalities
  - (throughout pregnancy)

- fetal loss, stillbirth

“We recommend that they prevent further pregnancies”

Lancet 1994

“Women with cardiac valve prostheses should be counseled against becoming pregnant”

Circulation 1984

Dose-dependent adverse effects:

20 pregnancies

- warfarin < 5 mg daily pre-pregnancy
- no thromboembolic complications
- 20 live births, no fetal loss
- no embryopathy

71 pregnancies **(38 low dose, 33 high dose warfarin)**

- fetal loss 5% with warfarin < 5mg
- fetal loss 78% with warfarin >5mg

- 2 embryopathy with warfarin >5mg
- 1 embryopathy with warfarin < 5 mg

Cotrufo 1991, Vitale 1999, Cotrufo 2002

Dose-dependent adverse effects:

Most series retrospective
relatively small

No randomized trials

Systematic reviews and meta-analyses:

D' Souza et al, Eur Heart J 2017

Steinberg et al; JACC 2017

Xu et al; Can J Card 2016

Aim: reporting adverse maternal and fetal outcomes in women with different anticoagulation regimen

Hassouna – Allam, Int Card Thor Surg 2014

Aim: evaluation of fetal and maternal outcomes in women using low dose warfarin throughout pregnancy

D' Souza et al, Eur Heart J 2017

outcomes mother: mortality, thrombo-embolic events
outcomes baby: livebirths, fetopathy, embryopathy

	Mat mort	TE	livebirths	embryopathy/ fetopathy
VKA (N=407-581)	0.9%	2.7%	64.5%	2.0%
Sequential (N=431-530)	2.9%	5.8%	79.9%	1.4%
LMWH (N=74-132)	8.7%	8.7%	92.0%	0%

D' Souza et al, Eur Heart J 2017

Livebirths 83.6%

LOW DOSE

Warfarin ≤ 5 mg	Studies	Events	Estimate (%)	I^2 (%)
Livebirths	10	264/312	83.6 (75.8, 91.4)	81
Foetal adverse events	9	11/305	2.3 (0.7, 4.0)	0

HIGH DOSE

Warfarin > 5 mg	Studies	Events	Estimate (%)	I^2 (%)
Livebirths	5	54/121	43.9 (32.8, 55.0)	36
Foetal adverse events	4	9/63	12.4 (3.3, 21.6)	16

43.9%

D' Souza et al, Eur Heart J 2017

Fetal adverse events 2.3%

LOW DOSE

Warfarin ≤ 5 mg	Studies	Events	Estimate (%)	I^2 (%)
Livebirths	10	264/312	83.6 (75.8, 91.4)	81
Foetal adverse events	9	11/305	2.3 (0.7, 4.0)	0

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Livebirths	5	54/121	43.9 (32.8, 55.0)	36
Foetal adverse events	4	9/63	12.4 (3.3, 21.6)	16

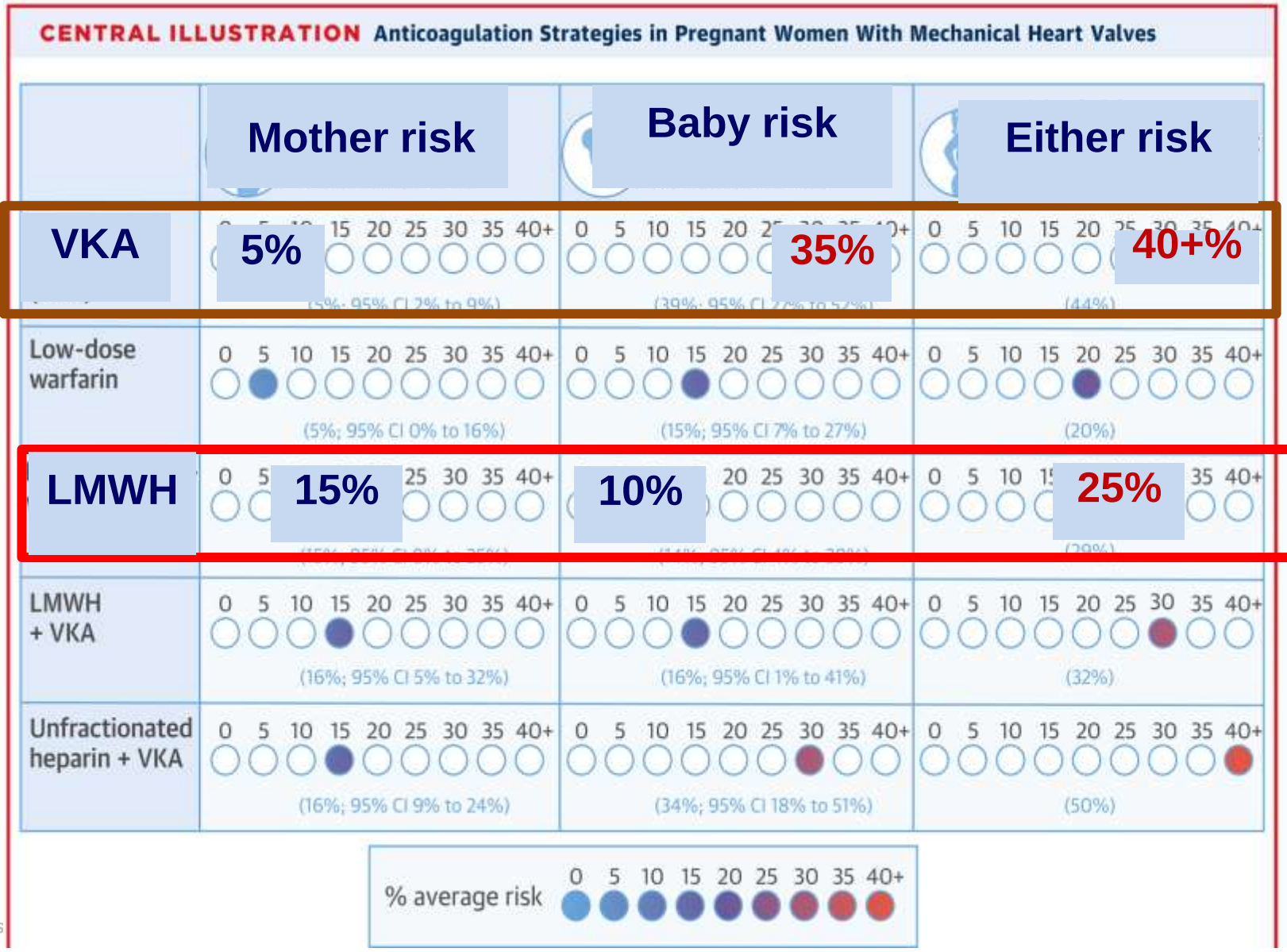
12.4%

Steinberg et al, JACC 2017; 800 pregnancies

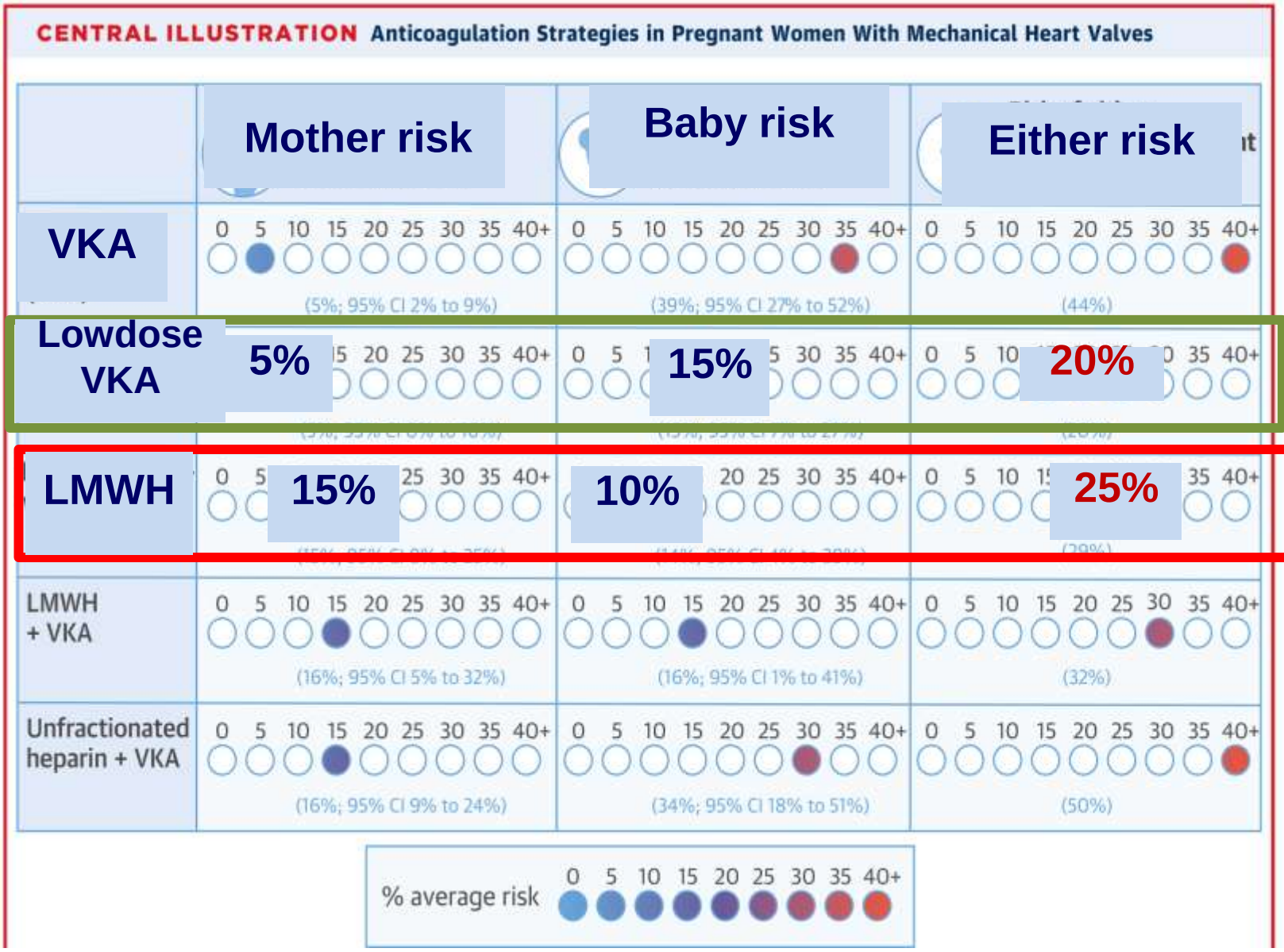
Outcomes mother: composite of
death, prosthetic valve failure, thrombo-embolism

Outcomes baby: composite of
spontaneous abortion, fetal death,
any congenital defect

Steinberg et al, JACC 2017; 800 pregnancies



Steinberg et al, JACC 2017; 800 pregnancies



Xu et al Can J Card 2016

2113 pregnancies, 51 studies

	Fetal wastage	Embryopathy
Low dose VKA	**19%**	**0.45%**
High dose VKA	**64%**	**8.25%**
P value	**<0.001**	**< 0.001**

Hassouna et al, Int Cardiovasc Thor Surg 2014

494 pregnancies on low dose warfarin:

Prosthetic valve thrombosis	0.6%
Thromboembolic events	1.8%
Maternal bleeding	3.4%
Maternal mortality	0%
Embryopathy/cong malformations	0.9%
Spontaneous abortion	12.8%
Stillbirth	0.6%
Total foetal loss (**abortion/stillbirth/ neonatal death**)	13.4%

Question 3:

Will dose requirement increase during pregnancy?

Increase of dosage needed to achieve target INR can be expected:

1. hypercoagulative state, increase in vitamin K dependent coagulation factors (II, VII, IX, X), shortening of PT /INR

2. upregulation of CYP2C9

Women who use a ‘safe’ dosage before pregnancy may need a more fetotoxic dose during pregnancy

Question 3:

Will dose requirement increase during pregnancy?

- several cohort studies reported increase of dose requirement during pregnancy

- several studies did not report the actual dose received during pregnancy

Question 3:

Will dose requirement increase during pregnancy?

Clinical trial: women with mitral mechanical valve on < 5 mg warfarin, INR 2.5-3.5

75 pregnant women and 75 non-pregnant women

Pregnant group more often failed to achieve target INR than non-pregnant patients **(p<0.002)**

Pregnant patients received larger dosages of oral anticoagulant **(p<0.0001)**

Question 3:

Will dose requirement increase during pregnancy?

Counselling of women with mechanical valves and low dose warfarin:

address possibility of dose increase

Question 4:

Is a lower target INR range safe for pregnant women?

Hassouna review:

3 prospective studies, 1991-2012
INR 1.5-2.5

Ce Bian 2012, Cotrufo 1991, De Santo 2012

Question 4:

Is a lower target INR range safe for pregnant women?

96 patients,
lower mean dose than other patients in review

Prosthetic valve thrombosis	1 %
Thromboembolic events	1 %
Maternal bleeding	1 %
Maternal mortality	0 %
Embryopathy/cong malformations	2 %
Spontaneous abortion	2 %
Stillbirth	0 %
Total foetal loss **(SA, stillbirth, neonatal death)**	2 %

In conclusion,

- data from 4 systematic reviews and meta-analyses all indicate a low fetal complication rate with low-dose warfarin during pregnancy

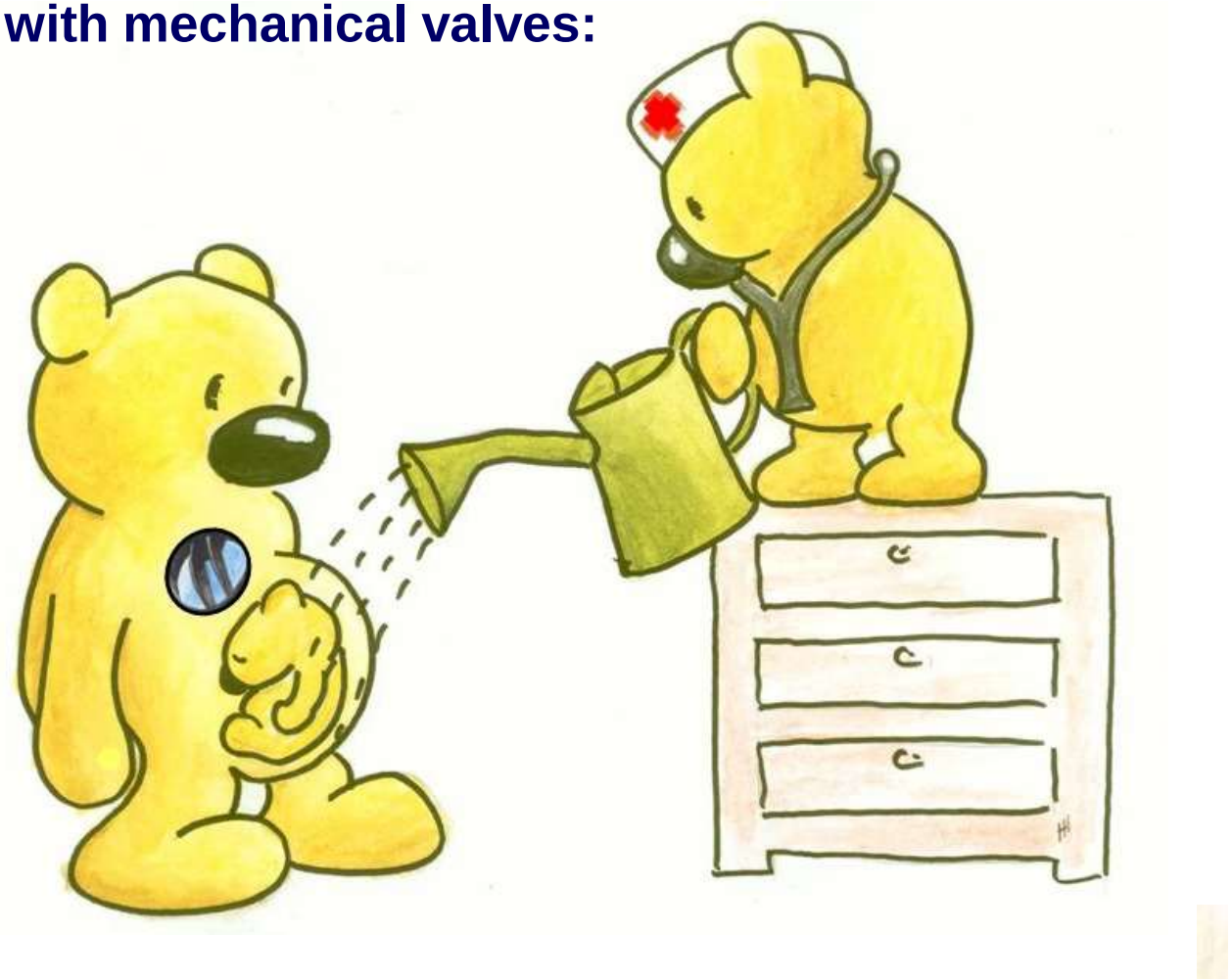
- however, embryopathy is not completely eliminated

- dose requirement of warfarin may increase during pregnancy

- a target INR of 1.5-2.5 seems safe for the mother

- however, the amount of data is limited and conclusions must be drawn with caution

Low dose warfarin in pregnant women with mechanical valves:



Yes, with caution, only after thorough discussion of risks and possible benefits with the mother