ROLE OF LOW MOLECULAR WEIGHT HEPARIN IN THE AGE OF DIRECT ORAL ANTICOAGULANTS

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Nomenclature

direct oral anticoagulant (DOAC)

RECOMMENDATIONS AND GUIDELINES

Recommendation on the nomenclature for oral anticoagulants: communication from the SSC of the ISTH

G. D. BARNES,* W. AGENO,† J. ANSELL‡ and S. KAATZ,§ FOR THE SUBCOMMITTEE ON THE CONTROL OF ANTICOAGULATION

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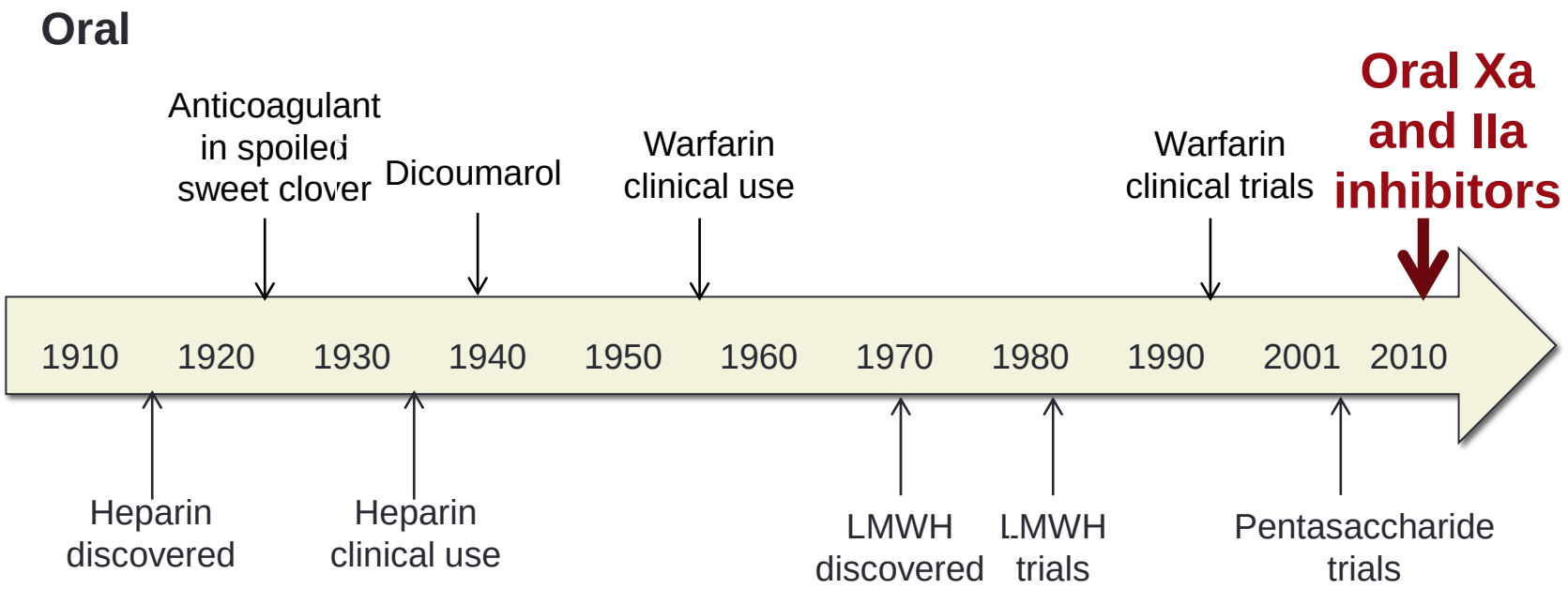
preferred over NOACs

J Thromb and Haemost 2015, 13;1154-1156

DOAC revolution

http://www.acepnow.com/article/

Last 100 years in anticoagulant history



DOACs are default choice for VTE

Chest 2016; 149(2):315-352
J Thromb and Thrombolysis 2016; 41(1): 32-67

Is warfarin obsolete?

Is warfarin obsolete? No

COST

mechanical heart valve

severe renal impairment

heparin-induced thrombocytopenia

antiphospholipid syndrome

Is warfarin obsolete? No

COST

mechanical heart valve

severe renal impairment

heparin-induced thrombocytopenia

antiphospholipid syndrome

rat poison

IS LMWH obsolete?

NO

Cancer associated thrombosis

Pregnancy associated thrombosis

CANCER-ASSOCIATED THROMBOSIS

LMWH is standard of care for treatment of cancer associated thrombosis: CLOT

CLOT trial: design

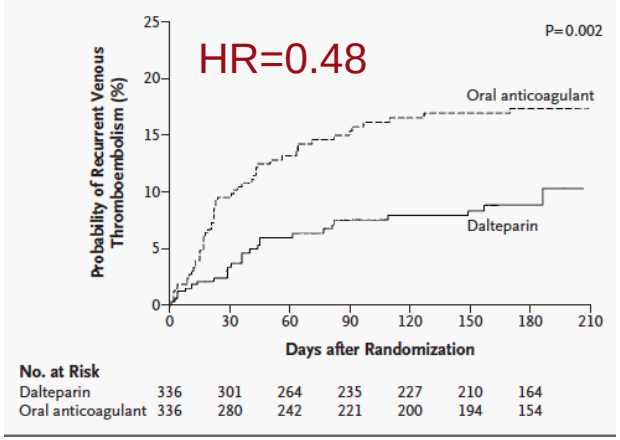
Patients with active cancer and acute DVT +/- PE N=676

- **Dalteparin** — **6 months**
- **Dalteparin plus VKA** — **6 months**

Primary efficacy: recurrent VTE (symptomatic)

Safety: MB, death

CLOT trial: results



Primary efficacy: 8% vs 15.8% p=0.002

Major bleeding: 6% vs 4% p=0.27

Death: 39% vs 41% p=0.53

Lee et al NEJM 2003

LMWH is standard of care for treatment of cancer associated thrombosis: CATCH

CATCH trial: design

Patients with active cancer and acute DVT +/- PE N=900

Tinzaparin

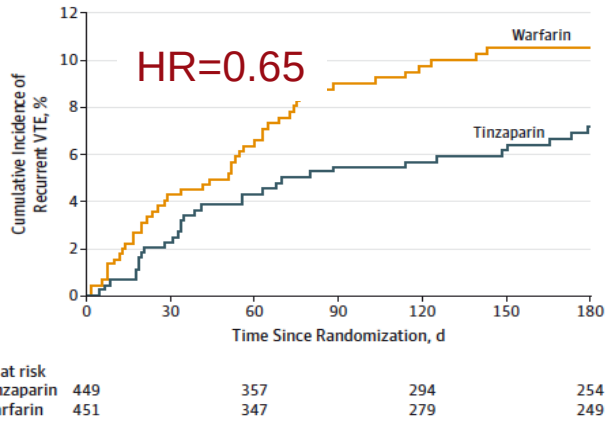
6 months

Tinzaparin plus VKA

Primary efficacy: recurrent VTE (symptomatic + incidental)

Safety: MB, death

CATCH trial: results



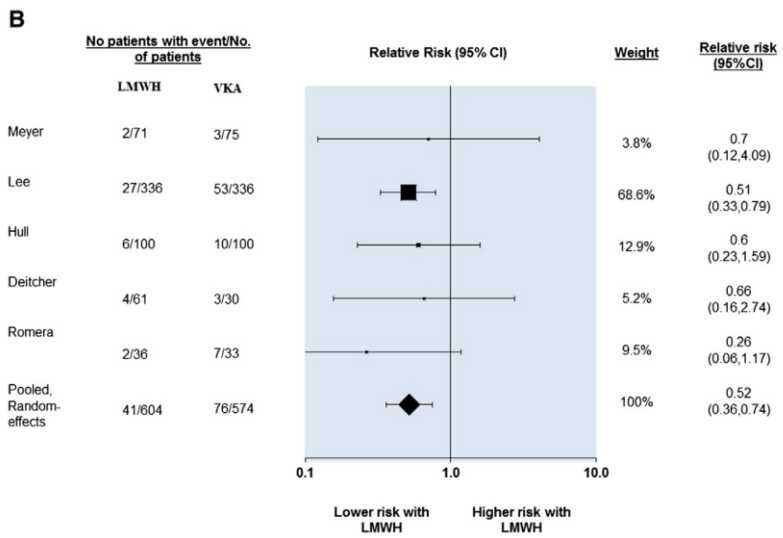
Primary efficacy: 7.2% vs 10.5% p=0.07

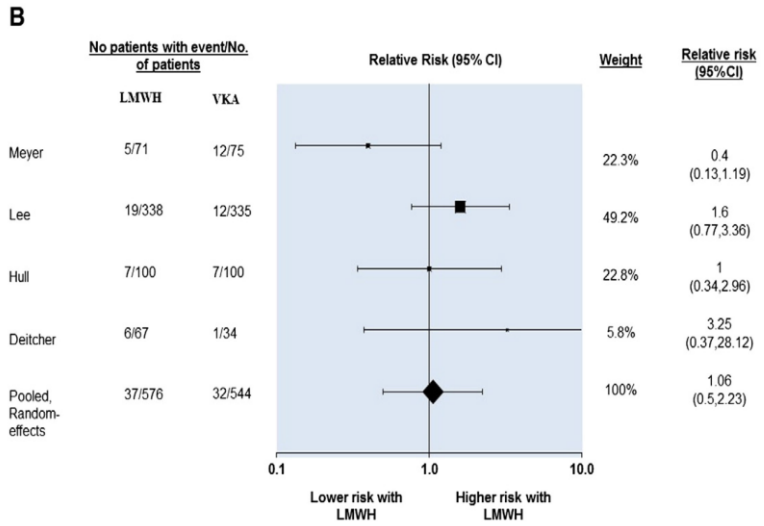
Major bleeding: 2.7% vs 2.4% p=0.77

Death: 34.7% vs 32.2% p=0.54

Lee et al JAMA 2015

LMWH for cancer associated thrombosis: meta-analysis, 5 studies, n=1178





Efficacy

Recurrent VTE

RR 0.52 95% CI 0.36-0.74

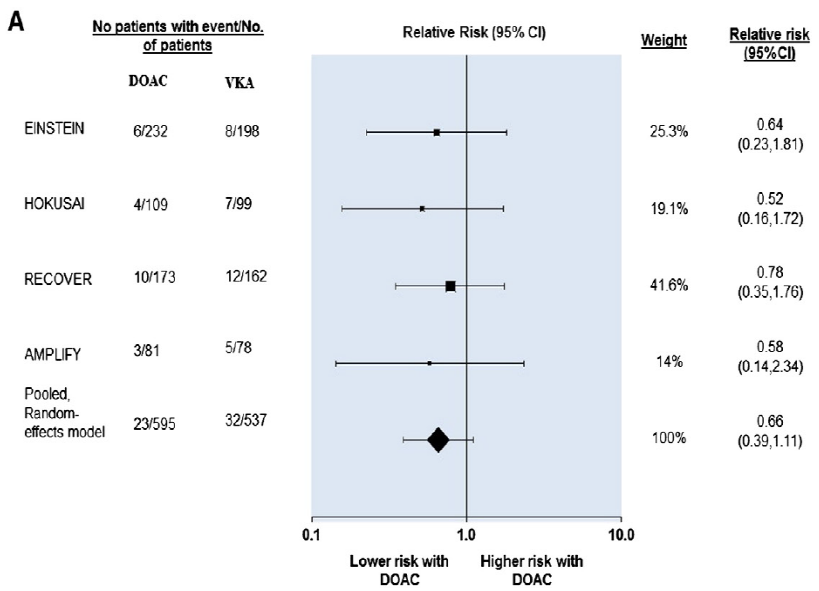
Safety

Major bleeding

RR 1.06, 95% CI 0.50-2.23

Carrier et al Thromb Res 2014

DOACs for cancer associated thrombosis: meta-analysis, 4 studies, n=1132



Efficacy

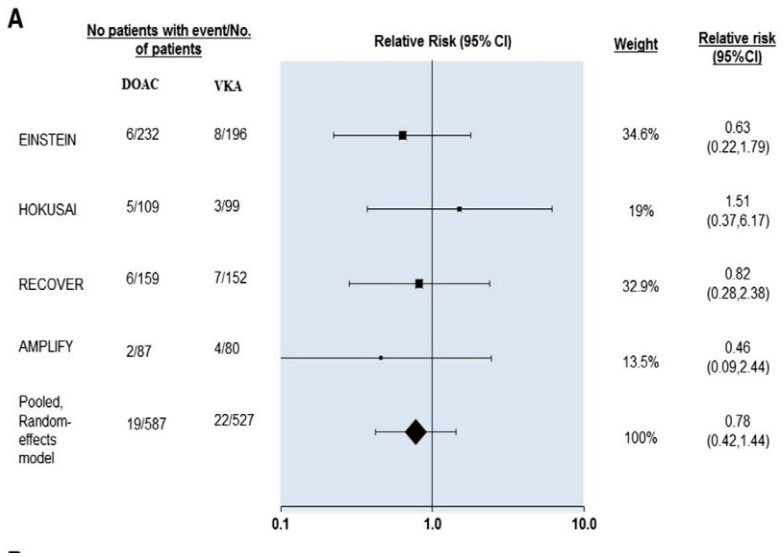
Recurrent VTE

RR 0.66, 95% CI 0.39-1.11

Median annualised recurrence risk

VKA arm 10.5 (5.0-12.4) DOAC studies

VKA arm 16.5 (10-29.1) LMWH studies



Safety

Major bleeding

RR 0.78, 95% CI 0.42-1.44

Median annualised bleeding risk

VKA arm 5.5 (4.2-23.5) DOAC studies

VKA arm 7.1 (5.0-50.2) LMWH studies

Carrier et al Thromb Res 2014

Guidelines

No direct comparison RCTs for DOAC vs LMWH

Cancer patient population in DOAC studies different

	NCCN 2014	ASCO 2015	ACCP 2016
Initial therapy	LMWH preferred	LMWH recommended	LMWH recommended
Chronic therapy	LMWH preferred over warfarin for first 6 months	LMWH preferred for ≥ 6 months	LMWH preferred In patients for ≥ 3 months, in patients receiving LMWH, VKA preferred over DOAC

Additional concerns for DOACs in cancer

- Drug-drug interaction with antineoplastic agents, especially P-gp inhibitors or inducers
- Gastrointestinal absorption in vomiting cancer patients or chemotherapy-induced mucosal defects
- However, DOACs are cheaper and more convenient

DOACS vs LMWH for cancer associated thrombosis: on-going trials

DOAC	Comparator	Primary outcome	Design	Target
apixaban	dalteparin	MB	Randomised Open label	315
edoxaban	dalteparin	Recurrent VTE + MB	Randomised Open label	1000
rivaroxaban	LMWH	Patient satisfaction	Randomised Open label	450
rivaroxaban	dalteparin	Recurrent VTE	Randomised Open label	530

LMWH IS STANDARD OF CARE FOR TREATMENT OF CANCER ASSOCIATED THROMBOSIS

PREGNANCY-ASSOCIATED THROMBOSIS

Problems

- Potential for both maternal and fetal complications
- Recommendations extrapolated from data in non-pregnant patients
- Lack of high quality evidence

Warfarin is not safe for fetus

Fetal effects	Dose
Embryopathy: 1st trimester 6-9 weeks (nasal hypoplasia, stippled epiphyses)	?Dose related Likely no safe (≤ 5mg) dose
Fetopathy: 2nd and 3rd trimester (CNS and ocular abnormalities, late fetal loss, stillbirth)	Dose related

(In MHV, warfarin has lowest maternal death)

Table I Primary maternal and foetal outcomes

Anticoagulation regimen	Maternal mortality				Thromboembolism				Livebirth rate				Anticoagulant-related foetal/neonatal adverse events			
	Studies	Events	Estimate (%)	I^2 (%)	Studies	Events	Estimate (%)	I^2 (%)	Studies	Events	Estimate (%)	I^2 (%)	Studies	Events	Estimate (%)	I^2 (%)
Vitamin K antagonists (INR target 2.5-3.5)	11	7/581	0.9 (0.1, 1.6)	0	11	22/581	2.7 (1.4, 4.0)	0	10	369/531	64.5 (48.8, 80.2)	95	11	12/407	2.0 (0.3, 3.7)[a]	24
Sequential treatment	20	11/530	2.0 (0.8, 3.1)	0	20	44/530	5.8 (3.8, 7.7)	29	18	381/475	79.9 (74.3, 85.6)	61	19	5/431	1.4 (0.3, 2.5)[b]	0
LMWH alone	10	1/132	2.9 (0.2, 5.7)	0	9	13/127	8.7 (3.9, 13.4)	0	7	68/74	92.0 (86.1, 98.0)	0	8	0/103	NA	0

Systematic review/meta-analysis

- VKA: lowest maternal mortality and TEC, lowest livebirth
- LMWH: highest livebirths
- Safety of UFH and warfarin ≤5 mg/day is unconfirmed

D'Souza 2017 European Heart Journal

LMWH is preferred over UFH

- LMWH has a better pharmacokinetic than UFH with predictable dose to anticoagulant response, less inter-patient variability and longer duration of action

- LMWH has a better safety profile than UFH with lower bleeding, heparin-induced thrombocytopenia and heparin-associated osteoporosis

LMWH is safe for fetus

- LMWH does not cross the placenta
- LMWH is detected at very low levels in breast milk, very low oral bioavailability and unlikely to be harmful to nursing infant

LMWH is safe for the mother

Table 3. Complications reported with LMWH use in pregnancy for different indications and different LMWHs

Indication and LMWH used	Total, no.	DVT, no. (%)	PE, no. (%)	Other or unspecified VTE, no. (%)	Arterial thrombosis, no. (%)	Severe antenatal bleeding, no. (%)	PPH exceeding 500 mL, no. (%)	Wound hematoma, no. (%)	Allergy, no. (%)	Low platelet count, no. (%)	Osteoporosis, no. (%)
Treatment											
Enoxaparin	105	1 (0.95)	0 (0)	0 (0)	0 (0)	1 (0.95)	1 (0.95)	0 (0)	2 (1.90)	1 (0.95)	0 (0)
Dalteparin	49	1 (2.04)	0 (0)	0 (0)	0 (0)	0 (0)	1 (2.04)	0 (0)	0 (0)	0 (0)	0 (0)
Nadroparin	20	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Subtotal	174	2 (1.15)	0 (0)	0 (0)	0 (0)	1 (0.57)	2 (1.15)	0 (0)	2 (1.15)	1 (0.57)	0 (0)

Systematic review of LMWH for treatment and prophylaxis.

15 studies with 174 VTE patients

Complications: bleeding (0.57% antenatal, 1.15% PPH, 0% wound hematoma), 0% HIT and 1.15% recurrent DVT

Greet et al Blood 2005

DOACS in pregnancy: not recommended

DOAC	Animal reproductive toxicity	Animal milk	Human milk
rivaroxaban	yes	yes	yes
dabigatran	yes	unknown	unknown
apixaban	no direct or indirect harmful effects	Yes	unknown
edoxaban	yes	yes	unknown

Product inserts

Pregnancy outcomes in DOAC exposure

Drug	Total exposures reported n=233	No out-come data available n=93	Pregnancy ongoing n=3	Outcome available n=137		
				Live birth n=67	Miscar-riage n=31	Elective termi-nation of pregnancy n=39
Apixaban; n (%)	21	9/21 (42.9)	0/21 (0)	5/21 (23.8)	4/21 (19)	3/21 (14.3)
Dabigatran; n (%)	26	14/26 (53.8)	0/26 (0)	3/26 (11.5)	2/26 (7.7)	7/26 (26.9)
Edoxaban; n (%)	10	0/10 (0)	0/10 (0)	6/10 (60)	1/10 (10)	3/10 (30)
Rivaroxaban; n (%)	176	70/176 (39.8)	3/176 (1.7)	53/176 (30.1)	24/176 (13.6)	26/176 (14.8)

- N=233 cases, n=137 with outcome, n=3/7 of abnormalities with embryopathy
- Results do not suggest DOAC exposure carries high risk of embryopathy or should be used to direct patient counselling towards termination

Beyer-Westendorf et al 2016 Coagulation and Fibrinolysis

ISTH DOAC pregnancy exposure

PARTICIPATE! REGISTRY OF PREGNANCY IN PATIENTS EXPOSED TO DOACS

Thursday, September 22, 2016 (0 Comments)

Posted by: Luke Blount

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A registry of women who have been pregnant while receiving anticoagulant treatment with a DOAC is an ongoing project of the SSC Subcommittee on Women's Issues in Thrombosis and Hemostasis. If you have eligible patients, we would appreciate your participation in the study. The goal is to assess the effects of exposure to DOACs in utero on the fetus and the child in the long-term. It is a multicenter, international, observational cohort study, and the registry is designed to collect both retrospective and prospective data. Eligibility criteria for enrollment are women with 1) confirmed use of a DOAC, and 2) a confirmed pregnancy during DOAC use.

SSC Scientific and Standardization Committee

This registry is led by Jan Beyer (University Hospital Carl Gustav Carus Dresden, Germany), Saskia Middeldorp (AMC, the Netherlands) and Peter Verhamme (KU Leuven, Belgium), under the auspices and with the support of the SSC of the ISTH.

If you want to add a patient to the registry, please email Marjolein Brekelmans and Suzanne Bleker for detailed instructions.

https://www.isth.org/news/news.asp?id=308993

Guidelines

	ACOG 2012	SOGC 2014	RCOG 2015	ACCP 2016
Pregnancy	Heparin compounds preferred	LMWH preferred over UFH	LMWH preferred	LMWH recommended
Breast feeding	Warfarin LMWH and UFH are compatible		UFH, LMWH, warfarin not contraindicated	Continue warfarin, UFH or LWMH

LMWH IS STANDARD OF CARE FOR TREATMENT OF PREGNANCY ASSOCIATED THROMBOSIS

Conclusion

Low molecular weight heparin remains standard of care

for treatment of

cancer-associated thrombosis and

pregnancy-associated thrombosis