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

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Nomenclature

direct oral anticoagulant (DOAC)

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
DOAC revolution

http://www.acepnow.com/article/
Last 100 years in anticoagulant history

Oral

1910: Heparin discovered
1920: Anticoagulant in spoiled sweet clover
1930: Dicoumarol
1940: Warfarin clinical use
1950: Warfarin clinical trials
1960: Oral Xa and IIa inhibitors
1970: LMWH discovered
1980: LMWH trials
1990: Pentasaccharide trials
2001: Oral trials
2010: Parenteral

Parenteral

1910: Dicoumarol
1920: Warfarin clinical use
1930: Oral
1940: Parenteral
1950: Parenteral
1960: Parenteral
1970: Parenteral
1980: Parenteral
1990: Parenteral
2001: Parenteral
2010: Parenteral
DOACs are default choice for VTE
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

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

HR=0.48

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

HR=0.65

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

<table>
<thead>
<tr>
<th></th>
<th>NCCN 2014</th>
<th>ASCO 2015</th>
<th>ACCP 2016</th>
</tr>
</thead>
<tbody>
<tr>
<td>Initial therapy</td>
<td>LMWH preferred</td>
<td>LMWH recommended</td>
<td>LMWH recommended</td>
</tr>
<tr>
<td>Chronic therapy</td>
<td>LMWH preferred over warfarin for first 6 months</td>
<td>LMWH preferred for ≥ 6 months</td>
<td>LMWH preferred In patients for ≥ 3 months, in patients receiving LMWH, VKA preferred over DOAC</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Comparator</th>
<th>Primary outcome</th>
<th>Design</th>
<th>Target</th>
</tr>
</thead>
<tbody>
<tr>
<td>apixaban</td>
<td>dalteparin</td>
<td>MB</td>
<td>Randomised Open label</td>
<td>315</td>
</tr>
<tr>
<td>edoxaban</td>
<td>dalteparin</td>
<td>Recurrent VTE + MB</td>
<td>Randomised Open label</td>
<td>1000</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>LMWH</td>
<td>Patient satisfaction</td>
<td>Randomised Open label</td>
<td>450</td>
</tr>
<tr>
<td>rivaroxaban</td>
<td>dalteparin</td>
<td>Recurrent VTE</td>
<td>Randomised Open label</td>
<td>530</td>
</tr>
</tbody>
</table>
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

<table>
<thead>
<tr>
<th>Fetal effects</th>
<th>Dose</th>
</tr>
</thead>
<tbody>
<tr>
<td>Embryopathy: 1\textsuperscript{st} trimester 6-9 weeks (nasal hypoplasia, stippled epiphyses)</td>
<td>?Dose related. Likely no safe (≤ 5mg) dose</td>
</tr>
<tr>
<td>Fetopathy: 2\textsuperscript{nd} and 3\textsuperscript{rd} trimester (CNS and ocular abnormalities, late fetal loss, stillbirth)</td>
<td>Dose related</td>
</tr>
</tbody>
</table>
**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
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

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

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

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

Greet et al Blood 2005
# DOACS in pregnancy: not recommended

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Animal reproductive toxicity</th>
<th>Animal milk</th>
<th>Human milk</th>
</tr>
</thead>
<tbody>
<tr>
<td>rivaroxaban</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>dabigatran</td>
<td>yes</td>
<td>unknown</td>
<td>unknown</td>
</tr>
<tr>
<td>apixaban</td>
<td>no direct or indirect harmful effects</td>
<td>Yes</td>
<td>unknown</td>
</tr>
<tr>
<td>edoxaban</td>
<td>yes</td>
<td>yes</td>
<td>unknown</td>
</tr>
</tbody>
</table>
Pregnancy outcomes in DOAC exposure

<table>
<thead>
<tr>
<th>Drug</th>
<th>Total exposures reported n=233</th>
<th>No outcome data available n=93</th>
<th>Pregnancy ongoing n=3</th>
<th>Outcome available n=137</th>
<th>Live birth n=67</th>
<th>Miscarriage n=31</th>
<th>Elective termination of pregnancy n=39</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban; n (%)</td>
<td>21</td>
<td>9/21 (42.9)</td>
<td>0/21 (0)</td>
<td>5/21 (23.8)</td>
<td>4/21 (19)</td>
<td></td>
<td>3/21 (14.3)</td>
</tr>
<tr>
<td>Dabigatran; n (%)</td>
<td>26</td>
<td>14/26 (53.8)</td>
<td>0/26 (0)</td>
<td>3/26 (11.5)</td>
<td>2/26 (7.7)</td>
<td></td>
<td>7/26 (26.9)</td>
</tr>
<tr>
<td>Edoxaban; n (%)</td>
<td>10</td>
<td>0/10 (0)</td>
<td>0/10 (0)</td>
<td>6/10 (60)</td>
<td>1/10 (10)</td>
<td></td>
<td>3/10 (30)</td>
</tr>
<tr>
<td>Rivaroxaban; n (%)</td>
<td>176</td>
<td>70/176 (39.8)</td>
<td>3/176 (1.7)</td>
<td>53/176 (30.1)</td>
<td>24/176 (13.6)</td>
<td></td>
<td>26/176 (14.8)</td>
</tr>
</tbody>
</table>

- 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
PARTICIPATE! REGISTRY OF PREGNANCY IN PATIENTS EXPOSED TO DOACs

Thursday, September 22, 2016  (0 Comments)
Posted by: Luke Blount

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.

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.

## Guidelines

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy</td>
<td>Heparin compounds preferred</td>
<td>LMWH preferred over UFH</td>
<td>LMWH preferred</td>
<td>LMWH recommended</td>
</tr>
<tr>
<td>Breast feeding</td>
<td>Warfarin</td>
<td></td>
<td>UFH, LMWH, warfarin not contraindicated</td>
<td>Continue warfarin, UFH or LWMH</td>
</tr>
</tbody>
</table>
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