Differential effects of the direct thrombin inhibitor dabigatran etexilate vs warfarin on platelet function

Giulia Renda\textsuperscript{1}, Gelsomina Malatesta\textsuperscript{1}, Valentina Bucciarelli\textsuperscript{1}, Alessia Napoleone\textsuperscript{1}, Loredana Candelori\textsuperscript{2}, Joanne Van Ryn\textsuperscript{3}, Luciano Moretti\textsuperscript{2}, Raffaele De Caterina\textsuperscript{1}

\textsuperscript{1} - G. d'Annunzio University, Institute of Cardiology and Center of Excellence on Aging, Chieti, Italy
\textsuperscript{2} - Mazzoni Hospital, Ascoli Piceno, Italy
\textsuperscript{3} - Boehringer Ingelheim Pharma, Biberach, Germany
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All anticoagulants are expected to have some indirect effects on platelet function, because they interfere with the generation of thrombin, which has potent platelet-activating properties.

**THROMBIN:**

- plays a pivotal role in hemostasis because it is the final enzyme of the coagulation cascade, which converts fibrinogen to fibrin resulting in fibrin clot
- is a potent platelet agonist interacting with receptors on platelets (and other cell types) and activating multiple downstream signaling systems
Background (2)

• Vitamin K antagonists (VKAs), the classical oral anticoagulants, interfere with the synthesis of several coagulation factors, and thereby interfere with the generation of thrombin

• New oral anticoagulants are emerging as alternatives to VKAs: particularly, dabigatran is a potent, direct, competitive inhibitor of thrombin
Aims

Inhibition of thrombin activity may have consequences on platelet activation

Our study therefore aimed at better characterizing the effects of dabigatran etexilate vs warfarin on platelet function
## Population

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>WARFARIN</th>
<th>CONTROL</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF pts</td>
<td>21</td>
<td>18</td>
<td>19</td>
</tr>
<tr>
<td>Treated</td>
<td>treated</td>
<td>treated</td>
<td>not treated</td>
</tr>
<tr>
<td>With dabigatran</td>
<td>with warfarin</td>
<td>not treated with antithrombotic drug</td>
<td></td>
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</tbody>
</table>

**Dabigatran:** pts were from the RE-LYABLE study, AF and CHADS ≥1

**Warfarin:** pts were chosen according to the same characteristics as the dabigatran group

**Control:** pts were not affected by AF and not treated with any anticoagulant

Patients chronically treated with ASA or taking NSAIDs in the week before the study visit were excluded
Methods

First evaluation → 3 months → Second evaluation

• Light transmittance plt aggregation, according to Born’s method:
  - ADP 2 - 5 μM
  - human γ-thrombin 1.5 - 3 - 6 ng/mL
  - TRAP 5 - 10 - 20 μM

• Routine hematochemical parameters
• Dabigatran plasma concentration
• INR in pts treated with warfarin
Results (1):
Platelet aggregation induced by ADP

ADP 2 μM

ADP 5 μM
Results (2): Platelet aggregation induced by γ-thrombin 1.5 ng/mL

P<0.001

% platelet aggregation

control  warfarin  dabigatran
Results (3): Platelet aggregation induced by γ-thrombin 6 ng/mL

P<0.001

% platelet aggregation

control  warfarin  dabigatran
Results (4): Platelet aggregation induced by TRAP 5 μM

P<0.001

% platelet aggregation

control  warfarin  dabigatran
Results (5): Platelet aggregation induced by TRAP 10 μM
**Discussion (1)**

**ADP-induced plt aggregation** was not inhibited in the 3 groups → as expected, probably ADP is not affected either by direct thrombin inhibition of dabigatran or by indirect inhibition of warfarin

**γ-thrombin-induced plt aggregation** was significantly lower in the dabigatran vs warfarin and control groups, and to a lesser extent in the warfarin vs control group → this result was expected for dabigatran, due to its mechanism of action, **but not for warfarin**, because warfarin inhibits the hepatic biosynthesis of prothrombin and reduces its availability in plasma, but it does not inhibit thrombin activity.
TRAP-induced plt aggregation was lower in both anticoagulated groups vs control (more pronounced for warfarin) → again this result was not anticipated, because TRAP-induced plt aggregation should bypass any direct effect of dabigatran or indirect effect of warfarin on thrombin.

This may indicate a lower degree of expression or activity of the platelet thrombin receptor(s) during long-term anticoagulant therapy with these agents.
Thrombin receptors (protease activated receptors, PARs) are rapidly phosphorylated, uncoupled from signaling and internalized after activation.
Such mechanism could explain the occurrence of a downregulation or desensitization, due to chronic anticoagulant therapy.
Clinical hypothesis

Such effects (especially the lower inhibition of TRAP-induced platelet aggregation by dabigatran vs warfarin) possibly contribute to the differential in vivo antithrombotic profile of dabigatran vs warfarin, e.g.:

• less bleeding?
• less protection by dabigatran from MI?