My 7 WARNINGS about Direct Oral Anticoagulants (DOACs) in aged patients

Controversy – Pros and Cons of using DOACs in the very olds

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CONFLICT OF INTEREST DISCLOSURE

I have no potential conflict of interest to report

Prof. Dr. Med. Lang Pierre Olivier
WARNING #1

- DOACs are not all similar -

APIXABAN has probably the best efficacy/safety ratio
WARNING #1

– DOACs are not all similar –

However, Apixaban must not be considered as the OAC that is suitable for all older patients.

Saldon et al, Swiss Med Wkly 2016;146:w14356
Ferahta et al, J Cardiovascular Med Cardiol 2017;4(3):038-48
WARNING #2

Chronic kidney disease

With moderate (GFR 30-50 mL/min) and severe (10-30 mL/min) kidney disease, the area under the concentration-time curve (AUC) increases 2.7 and 6-fold respectively.

The plasma elimination half-life increases at least two-fold.

DABIGATRAN – 80% eliminated through kidneys
RIVAROXABAN – 33% eliminated through Kidneys
APIXABAN – 25% eliminated through the kidneys

The application of DOACs in chronic kidney disease should be performed with caution.
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BUT is it realistic to think that the plasma half-life of APIXABAN is similar when GFR is 31 and 61 mL/min?
WARNING #3

And what about the liver function?

The application of DOACs in chronic liver disease should be performed with caution.

Child-Pugh Classification of Cirrhosis

<table>
<thead>
<tr>
<th>Factor</th>
<th>Units</th>
<th>1</th>
<th>2</th>
<th>3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum bilirubin</td>
<td>mol/L mg/dL</td>
<td>&lt;34 &lt;2.0</td>
<td>34-51 2.0-3.0</td>
<td>&gt;51 &gt;3.0</td>
</tr>
<tr>
<td>Serum albumin</td>
<td>g/L g/dL</td>
<td>&gt;35 &gt;3.5</td>
<td>30-35 3.0-3.5</td>
<td>&lt;30 &lt;3.0</td>
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<tr>
<td>Prothrombin time</td>
<td>seconds</td>
<td>&gt;12.5</td>
<td>12-12.5</td>
<td>&gt;12.5</td>
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<tr>
<td>Ascites</td>
<td></td>
<td>None</td>
<td>Easily controlled</td>
<td>Poorly controlled</td>
</tr>
<tr>
<td>Hepatic encephalopathy</td>
<td></td>
<td>None</td>
<td>Minimal</td>
<td>Advanced</td>
</tr>
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For DOACs, dose adjustments are required according to the stage.
In general, therapy monitoring is not necessary

**BUT, ARE OLDER ADULTS A “GENERAL SITUATION”?**

There are pharmacological changes due to physiological ageing of the liver

**Child-Pugh Classification of Cirrhosis**

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<td>2.0-3.0</td>
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<td>Prothrombin time</td>
<td>seconds, prolonged INR</td>
<td>&lt;1.5</td>
<td>1.7-2.3</td>
<td>&gt;2.3</td>
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<tr>
<td>Ascites</td>
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<td>None</td>
<td>Easily controlled</td>
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**WARNING #3**

**And what about the liver function?**

How to estimate the hepatic clearance rate in practice?

For DOACs, dose adjustments are required according to the stage
There are drug-drug and food-drug interactions

This concern is particularly focused on drugs and foods that can interact with efflux membrane transporters and particularly the P-gp

- Good activity of the P-gp is one of the main factors contributing to the reduced risk of intra-cranial hemorrhage associated with DOACs
- Reduced activity of the P-gp alters the benefits of DOACs over VKAs
- Drug and food implicated are commons

Mekaj et al, Ther Clin Risk Manag 2015;11:967-77

Mohammad et al, Therapeutics 2017; in press
WARNING #4

There are drug-drug and food-drug interactions

**Pharmacological inhibitors**: amiodarone, clarithromycin, colchicine, erythromycin, proton pomp inhibitors, calcium channel blockers (verapamil, nifedipine, felodipine, diltiazem), SSRI (paroxetine, sertraline), and many others. Saint John’s Wort.

**Food compound inhibitors**: grapefruit juice, cheese and foods rich in biogenic amine tyramine, and flavonoids.

**Health conditions**: Alzheimer’s disease has been found to decrease P-gp expression in the brain, for example.
WARNING #4

There are drug-drug and food-drug interactions

- When this is a big concern for P-gp
  - It is also a concern for CYPs450 (3A4)
  
  Mekaj et al, Ther Clin Risk Manag 2015;11:967-77
  Mohammad et al, Therapeutics 2017; in press

At least a careful review of chronic treatment regimen is necessary (including OTC drugs)
- DOACs are drugs with short half-life –

The result is a **rapid onset** and **offset** of action, which is a **disadvantage** if your patient,

- forgets to take the drug or misses only one dose (**↑** risk of thromboembolic events)
- forgets he/she has already taken the daily dose (**↑** risk of bleeding events)

Mekaj et al, Ther Clin Risk Manag 2015;11:967-77
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WARNING #5

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- forgets to take the drug or misses only one dose (risk of thromboembolic events)
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Compliance, treatment adherence, and cognitive functioning must be properly assessed

Mekaj et al, Ther Clin Risk Manag 2015;11:967-77
Mohammad et al, Therapeutics 2017; in press
WARNING #6

– They are associated with higher risk of GI bleeding –

This risk of GI bleedings associated with DOACs compared to VKA is further increased

- With advancing age
- With greater quality of VKA monitoring (Time in therapeutic range - TTR)

Ferahta et al, J Cardiovascular Med Cardiol 2017;4(3):038-48
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Compared to VKA, the risk of MAJOR BLEEDING associated with DOACs raises
- With increasing age
- With greater quality of VKA monitoring (time in therapeutic range - TTR)
- With higher CHADS₂ score

Ferahta et al, J Cardiovascular Med Cardiol 2017;4(3):038-48
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Benefit/Risk of DOACs is reduced in vulnerable patients

Ferahta et al, J Cardiovascular Med Cardiol 2017;4(3):038-48
WARNING #7

– Frail and older patients are different populations –
### Table 1: Baseline characteristics of included trials

<table>
<thead>
<tr>
<th>Study (year)</th>
<th>Indication</th>
<th>Study drug</th>
<th>Control drug</th>
<th>Duration (month)</th>
<th>Mean age (year)</th>
<th>ISTH Bleeding definition</th>
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<tr>
<td></td>
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<td>Drug</td>
<td>Dosage</td>
<td>N</td>
<td>VKA INR N</td>
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<tr>
<td>Botticelli (2008)</td>
<td>VTE</td>
<td>Apixaban</td>
<td>5 mg BD</td>
<td>134</td>
<td>Warfarin Acenocoumarol Phennprocoumon 2-3 128</td>
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<td>Aristotle (2011)</td>
<td>AF</td>
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<td>Amplify (2013)</td>
<td>VTE</td>
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<td>10 mg BD for 7 days then 5 mg BD 2091</td>
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<td>57.2±10.0 56.7±10.0</td>
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<td>Amplify-J (2015)</td>
<td>VTE</td>
<td>Apixaban</td>
<td>10 mg BD for 7 days then 5 mg BD 40</td>
<td>Warfarin 1.5-2.5 40</td>
<td>6</td>
<td>64.3±13.4 66.1±17.7</td>
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<td>EDOX US-EU (2010)</td>
<td>AF</td>
<td>Edoxaban</td>
<td>60 mg QD</td>
<td>235</td>
<td>Warfarin 2-3 251</td>
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<tr>
<td>EDOX Asia (2010)</td>
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<td>Edoxaban</td>
<td>60 mg QD</td>
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<td>EDOX Japan (2011)</td>
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<td>Edoxaban</td>
<td>60 mg QD</td>
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<td>60 mg QD</td>
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<td>Warfarin 2-3 4149</td>
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<td>Explore-Xa (2013)</td>
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<td>Betrixaban</td>
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<td>OPAL-1 (2010)</td>
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<td>Warfarin NA 94</td>
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<td>OPAL-2 (2014)</td>
<td>AF</td>
<td>Darenxban</td>
<td>120 mg OD</td>
<td>163</td>
<td>Warfarin 2-3 163</td>
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<tr>
<td>Einstein DVT (2006)</td>
<td>VTE</td>
<td>Rivaroxaban</td>
<td>15 mg BD for 21 days then 20 mg QD 134</td>
<td>137</td>
<td>3</td>
<td>55.0±16.4 56.4±16.3</td>
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<tr>
<td>Einstein DVT (2010)</td>
<td>VTE</td>
<td>Rivaroxaban</td>
<td>15 mg BD for 21 days then 20 mg QD 1731</td>
<td>1718</td>
<td>12</td>
<td>57.9±7.3 57.5±7.2</td>
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<tr>
<td>Rocket-AF (2011)</td>
<td>AF</td>
<td>Rivaroxaban</td>
<td>20 mg QD</td>
<td>7111</td>
<td>Warfarin 2-3 7125</td>
<td>23.2*</td>
</tr>
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<td>Einstein PE (2012)</td>
<td>VTE</td>
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<td>15 mg BD for 21 days then 20 mg QD 2420</td>
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<td>6</td>
<td>68.0±12.2 63.4±18.3</td>
</tr>
</tbody>
</table>

* Median value; ISTH International Society on Thrombosis and Haemostasis; BD Twice daily; QD Once daily; VKA Vitamin K antagonist; INR International normalized ratio; VTE Venous thromboembolism; AF Atrial fibrillation; NA Not available.
WARNING #7

– Frail and older patients are different populations –

Are those people like your patients?
WARNING #7

-Frail and older patients are different populations-

Are those people like your patients?

My own are more similar to those patients

C. Aznavour, 92 y.o.
HRH The Queen Elisabeth, 91 y.o.
Sir J. Stewart, 78 y.o.
E. Sheperd, 74 y.o.

With cognitive impairment or dementia
With walking disorders, and fallers
Exposed to polypharmacy
Malnourished or undernourished
Your Doggy Bag

My **KEY** messages

There is no doubt that **DOACs** represent a **considerable innovation** in anticoagulant pharmacotherapy.

They are **part of the therapeutic arsenal**...

...**but the arsenal must not be restricted to DOACs**
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... **but the arsenal must not be restricted to DOACs**

**DOACs can be much more harmful than VKA in frail, old and very old patients**
As a light reminder

My 7 warnings about DOACs

1. APIXABAN has the best profile in terms of safety/efficacy, but ...
2. DOACs need caution application with kidney disease
3. DOACs need caution application with “aged” liver
4. There are drug-drug and food-drug interaction with DOACs
5. Like with all OACs, poor adherence and compliance are dangerous
6. The risk of GI bleeding increases with vulnerability
7. Our patients are not those enrolled in RCTs (real word study?)
How could we approach the use of (D)OACs in very old patients?

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Who IS the ideal candidate for DOACs?

From a PATIENT point of view

1. Should have a high likelihood for adherence to DOAC therapy and follow-up,
2. no contraindications to the DOAC,
3. adequate kidney and liver function,
4. and not exposed to significant drug-drug interactions.

1. The ability to obtain and afford the DOAC for the duration of therapy could be also aspects to consider.
Who **IS** the ideal candidate for DOACs?

From a MEDICATION point of view

1. In the lake of safety and efficacy data in very old patients,
2. APIXABAN is the only agent whose dosing is affected by age (NVFA).
3. Dosing becomes more difficult in old patients because of the increased prevalence of comorbid conditions, and polypharmacy.
4. Proper **oversight** and **monitoring** must be in place to ensure that the safety is not compromised.
Patients on VKA with INR stable in therapeutic range should stay on it

Clinical Frailty Scale

1. Very Fit — People who are robust, active, energetic and motivated. These people commonly exercise regularly. They are among the fittest for their age.

2. Well — People who have no active disease symptoms but are less fit than category 1. Often, they exercise or are very active occasionally, e.g., seasonally.

3. Managing Well — People whose medical problems are well controlled, but are not regularly active beyond routine walking.

4. Vulnerable — While not dependent on others for daily help, they require some support, often symptoms limit activities. A common complaint is being “slow down”, and/or being tired during the day.

5. Mildly Frail — These people often have more evident slowing, and need help in high order ADLs (finances, transportation, heavy housework, medications). Typically, mildly frail progressively impair shopping and walking outside alone, meal preparation and housework.

6. Moderately Frail — People need help with all outside activities and with keeping house. Inside, they often have problems with stairs and need help with bathing and might need minimal assistance (cuing, standing) with dressing.

7. Severely Frail — Completely dependent for personal care from whatever cause (physical or cognitive). Even so, they seem stable and not at high risk of dying (within ~ 6 months).

8. Very Severely Frail — Completely dependent, approaching the end of life. Typically, they could not recover even from a minor illness.

9. Terminally Ill — Approaching the end of life. This category applies to people with a life expectancy <6 months who are not otherwise evidently frail.

Scoring frailty in people with dementia

The degree of frailty corresponds to the degree of dementia. Common symptoms in mild dementia include forgetting the details of a recent event, though still remembering the event itself, repeating the same questions, and social withdrawal.

In moderate dementia, recent memory is very impaired, even though they seemingly can remember their past life events well. They can do personal care with prompting. In severe dementia, they cannot do personal care without help.
And may be, we can go further ...

Patients on VKA with INR stable in therapeutic range should stay on it
The call for ABSTRACT for:
- Oral communications
- Posters
- Symposia

IS NOW OPENED

WITH DEAD LINE
on 6 December 2017