Managing DOACs at the Extremes of Weight

Presenter:

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Introduction

- In 2017-2018, the prevalence of obesity was **42.4%**\(^1\), moving further from the Healthy People 2020 goal of 30.5%.\(^2\)
- The costs for medical care of obesity in the US are high. In 2008, these costs were estimated to be **$147 billion**.\(^3\)
# Obesity and the Impact on Thrombotic Conditions

**OBESITY***

<table>
<thead>
<tr>
<th>High Prevalence in the US(^1)</th>
<th>A Contributing Factor to AF and VTE(^2,3)</th>
<th>Increases the Risk of Developing AF and VTE</th>
</tr>
</thead>
<tbody>
<tr>
<td>~40% of patients have obesity</td>
<td>Inducing a pro-thrombotic and pro-inflammatory state(^2,3)</td>
<td>+49% increased risk of AF compared to nonobese patients(^5,6)</td>
</tr>
<tr>
<td>~8% of patients have morbid obesity</td>
<td>Reducing drug effect and levels(^2,3):</td>
<td>Increasing patient risk for thrombotic events(^5,6):</td>
</tr>
<tr>
<td></td>
<td>• Obese patients taking warfarin are less likely to achieve therapeutic INR, take longer to achieve therapeutic INR, take a higher average daily dose, and have a higher mean dose at discharge(^4)</td>
<td>• ~2x risk of first occurrence of VTE(^2,3)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Increasing the likelihood of recurrent VTE</td>
</tr>
</tbody>
</table>

*The CDC defines obesity as BMI ≥30 kg/m\(^2\) and severe (morbid) obesity ≥40 kg/m\(^2\).\(^7\)
*Based on a 2007 meta-analysis, including 16 studies and 123,249 patients.\(^1\)
*Based on a meta-analysis of 1 cohort and 8 case-control studies (8125 patients with VTE; 23,272 control patients).\(^6\)
AF=atrial fibrillation; VTE=venous thromboembolism; INR=International Normalized Ratio.

## Definitions

<table>
<thead>
<tr>
<th>Classification</th>
<th>Body mass index (kg/m²) a</th>
<th>Total body weight (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Underweight</td>
<td>&lt;18.5</td>
<td>&lt;60kg b or ≤60.2kg c</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sub-categories of thinness:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild:</td>
<td>17-18.49</td>
<td></td>
</tr>
<tr>
<td>Moderate:</td>
<td>16-16.99</td>
<td></td>
</tr>
<tr>
<td>Severe:</td>
<td>&lt;16</td>
<td></td>
</tr>
<tr>
<td>Normal weight</td>
<td>18.5-24.99</td>
<td>≥60 up to 70kg b or &gt;56.3 up to 76.6kg c</td>
</tr>
<tr>
<td>Overweight (pre-obesity)</td>
<td>25-29.99</td>
<td>≥70 up to 100kg b or &gt;76.7 up to 92.0kg c</td>
</tr>
<tr>
<td>Obesity</td>
<td>≥30</td>
<td>&gt;100kg b or ≥ 92.1kg c; or &gt;20% greater than the ideal body weight d</td>
</tr>
<tr>
<td>Class 1</td>
<td>30-34.99</td>
<td>&gt;100% greater than the ideal body weight d</td>
</tr>
<tr>
<td>Class 2 (moderate obesity)</td>
<td>35-39.99</td>
<td>≥150kg b or ≥122.9kg c</td>
</tr>
<tr>
<td>Class 3 (severe or morbid obesity)</td>
<td>≥40</td>
<td>&gt;225% greater than the ideal body weight</td>
</tr>
<tr>
<td>Class 4 (super-obesity)</td>
<td>≥50</td>
<td></td>
</tr>
<tr>
<td>Class 5 (super-super or extreme obesity)</td>
<td>≥60</td>
<td></td>
</tr>
</tbody>
</table>

a. According to the WHO classification for adults [≥20 years, female, and male subjects; [http://www.who.int/topics/obesity/en/](http://www.who.int/topics/obesity/en/) (January 2018)] unless otherwise indicated.
b. Thresholds often used to define underweight in RCT or clinical studies for both female and male subjects.
d. Ideal body weight according to modified Devine’s formula: men: 51.65 kg + 1.85 kg/inch of height greater than 5 feet; Women: 48.67 kg + 1.65 kg/inch of height greater than 5 feet.

Scenario:

A man with Acute VTE who has obesity and receiving multiple different medications
How could we manage this patient?

• 65-year-old man
• Obese at 130 kg
• Hypercholesterolaemia
• Mild renal impairment (CrCl 45 mL/min)
• Gastric ulcer 2 years ago

• Poorly controlled hypertension
• Type II diabetes
• Receiving several different medications for his chronic conditions (polypharmacy)
QUESTION: Would this patient’s obesity impact your decision to prescribe a DOAC?

1. Yes
2. No
3. More information needed
4. Unsure
**QUESTION:** Which DOAC would you prescribe?

1. Apixaban
2. Dabigatran
3. Edoxaban
4. Rivaroxaban
Recommend appropriate standard dosing of direct oral anticoagulants (DOACs) in patients with BMI ≤ 40 kg/m² and weight ≤ 120 kg.

Suggest not using DOACs in patients with BMI >40 kg/m² or weight >120 kg.

If DOACs are used in BMI >40 kg/m² or weight >120 kg, suggest checking drug-specific peak and trough level.

- DOACs= apixaban, dabigatran, edoxaban, rivaroxaban
- Based on limited clinical data and available PK data at the time
2021 ISTH Updated Summary Guidance Statements

- The use of any DOAC is appropriate for patients with BMI up to 40 kg/m² or weight 120 kg. For patients with BMI >40 kg/m² or weight >120 kg, ISTH recommends that the individual DOACs should be used as follows:
- For treatment of VTE, ISTH suggests that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Fewer supportive data exist for apixaban than rivaroxaban. VKA, weight based LMWH (per manufacturers' recommendations), and fondaparinux are also options.
- For primary prevention of VTE, ISTH suggests that standard doses of rivaroxaban or apixaban are among appropriate anticoagulant options regardless of high BMI and weight. Drug approval is restricted to elective hip and knee arthroplasty and (in some countries) extended VTE prevention following acute medical illness.
- Suggests not to use dabigatran, edoxaban, or betrixaban for VTE treatment and prevention in patients with BMI >40 kg/m² or weight >120 kg, given unconvincing data for dabigatran, and lack of clinical or PK/PD data for edoxaban and betrixaban.
- Suggests not to regularly follow peak or trough drug-specific DOAC levels because there are insufficient data to influence management decisions.
ISTH Guidance Statements (cont’d)

- Suggests not to use DOAC for treatment or prevention of VTE in the acute setting after bariatric surgery (because of concerns of decreased absorption), and instead, to initiate such patients on parenteral anticoagulation in the early postsurgical phase. Suggests that switching to VKA or DOAC may be considered after at least 4 weeks of parenteral treatment, and if so, suggest obtaining a DOAC trough level to check for drug absorption and bioavailability.

DOAC = direct oral anticoagulant; ISTH = International Society on Thrombosis and Haemostasis; VTE = venous thromboembolism; VKA = vitamin K antagonist.
# Antithrombotic therapy and body mass: an expert position paper of the ESC Working Group on Thrombosis

## Antithrombotic, Fixed-Dose Drugs in Underweight and Obesity

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban</th>
<th>Edoxaban</th>
<th>Dabigatran</th>
<th>Apixaban</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Clinical Use</strong></td>
<td>Afib, VTE treatment; post-ACS*</td>
<td>Afib and VTE</td>
<td>Afib, and VTE</td>
<td>Afib and VTE</td>
</tr>
<tr>
<td><strong>Underweight</strong></td>
<td>No change for Afib and VTE</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(&lt;18.5 kg/m²)</td>
<td>ACS* (5mg BID): caution if co-administered with clopidogrel and aspirin for BW &lt;60 kg</td>
<td>30 mg for BW ≤ 60 kg</td>
<td></td>
<td>Very limited data. Patients &lt;50kg have a higher plasma levels and close surveillance is needed, especially if women</td>
</tr>
<tr>
<td><strong>Normal weight</strong></td>
<td>Afib: 20 mg O.D. VTE: 10 mg O.D. ACS*: 2.5 mg BID</td>
<td>60 mg O.D.</td>
<td>Afib: 150 mg BID VTE: 220 mg O.D.</td>
<td>Afib: 5 mg BID VTE: 10 mg BID 7 days and then 5 mg BID</td>
</tr>
<tr>
<td><strong>Obesity</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class 1 (&lt;30-34.9 kg/m²)</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
<td>No change</td>
</tr>
<tr>
<td>Class 2 (35-39.9 kg/m²)</td>
<td>No change</td>
<td>No data</td>
<td>Insufficient data Check ECT or dTT if used</td>
<td>Insufficient data</td>
</tr>
<tr>
<td>Class ≥3 (≥40 kg/m²)</td>
<td>Insufficient data, prefer VKA; check peak and trough anti-Xa activity if used</td>
<td>No data</td>
<td>No data, prefer VKA; check peak and trough ECT or dTT if used</td>
<td>Insufficient data</td>
</tr>
</tbody>
</table>

*ACS is NOT an approved indication in the US.

ESC = European Society of Cardiology


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**Note:** The table provides a summary of clinical use, dosing, and monitoring recommendations for antithrombotic drugs in patients with various body mass indices. The information is based on the expert position paper by the ESC Working Group on Thrombosis, focusing on rivaroxaban, edoxaban, dabigatran, and apixaban. The dosing and monitoring strategies vary depending on the body mass index category, with considerations for underweight, normal weight, and obesity classes. Special notes include caution for co-administration of clopidogrel and aspirin with rivaroxaban in underweight patients, and recommendations for monitoring peak and trough levels of anti-Xa activity for specific patient groups. The table also highlights that ACS is not approved as an indication in the US for these drugs. Further details and references are provided in the original paper.
Issues for clinicians around Obesity

- The AHA/ACC/HRS guidelines do not include special recommendation for obese patients
- DOAC label language does not recommend dose adjustments for obese patients
## Summary of Clinical Data

<table>
<thead>
<tr>
<th></th>
<th>Phase 3 Studies Comparing DOACs with VKA in VTE</th>
<th>Phase 4 Studies Comparing DOAC with VKA in VTE (Including Retrospective and Prospective Studies and Meta-analyses)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>BMI &gt;35 or BW &gt;120 kg</td>
<td>BMI &gt;40</td>
</tr>
<tr>
<td>Apixaban</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Similar outcomes(^7)</td>
<td>X</td>
</tr>
<tr>
<td>Pooled DOAC</td>
<td>Similar outcomes(^11)</td>
<td>X</td>
</tr>
</tbody>
</table>

Note: Similar outcome = DOAC compared with LMWH/VKA; X = no available data.

Abbreviations: BMI, body mass index, expressed in kg/m\(^2\); BW, body weight; DOAC, direct oral anticoagulant; LMWH, low molecular weight heparin; VKA, vitamin K antagonist; VTE, venous thromboembolism.
Background for Observational Studies

• Post Hoc analyses and adequately powered (ie, large) real-world studies of existing medications offer insight into comparative effectiveness

• The outcomes of interest must be present within the dataset studied

• The study design must be prespecified and transparent
Summary of Clinical Studies
Rivaroxaban Relative Efficacy by Body Weight and/or BMI

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban n/N (%)</th>
<th>Comparator n/N (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EINSTEIN DVT</strong>1,2</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>≤70 kg</td>
<td>12/494 (2.4)</td>
<td>21/524 (4.0)</td>
</tr>
<tr>
<td></td>
<td>&gt;70-90 kg</td>
<td>13/740 (1.8)</td>
<td>19/707 (2.7)</td>
</tr>
<tr>
<td></td>
<td>&gt;90 kg</td>
<td>11/491 (2.2)</td>
<td>11/486 (2.3)</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;30 kg/m²</td>
<td>24/1206 (2.0)</td>
<td>39/1222 (3.2)</td>
</tr>
<tr>
<td></td>
<td>≥30 kg/m²</td>
<td>12/511 (2.3)</td>
<td>21/484 (2.5)</td>
</tr>
<tr>
<td><strong>EINSTEIN PE</strong>2,3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>≤70 kg</td>
<td>17/653 (2.6)</td>
<td>10/621 (1.6)</td>
</tr>
<tr>
<td></td>
<td>&gt;70-90 kg</td>
<td>20/1081 (1.9)</td>
<td>24/1119 (2.1)</td>
</tr>
<tr>
<td></td>
<td>&gt;90 kg</td>
<td>13/683 (1.9)</td>
<td>10/672 (1.5)</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;30 kg/m²</td>
<td>39/1668 (2.3)</td>
<td>32/1643 (1.9)</td>
</tr>
<tr>
<td></td>
<td>≥30 kg/m²</td>
<td>11/741 (1.5)</td>
<td>11/755 (1.5)</td>
</tr>
<tr>
<td><strong>EINSTEIN CHOICE</strong>2,4</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td>&lt;90 kg</td>
<td>8/737 (1.1)</td>
<td>32/764 (4.2)</td>
</tr>
<tr>
<td></td>
<td>≥90 kg</td>
<td>5/390 (1.3)</td>
<td>18/367 (4.9)</td>
</tr>
<tr>
<td>BMI</td>
<td>&lt;30 kg/m²</td>
<td>7/751 (0.9)</td>
<td>36/756 (4.8)</td>
</tr>
<tr>
<td></td>
<td>≥30 kg/m²</td>
<td>6/376 (1.6)</td>
<td>14/375 (3.7)</td>
</tr>
</tbody>
</table>

An overall lack of effect on the efficacy of rivaroxaban was observed when different weights were analyzed across the clinical trials.

### Summary of Clinical Studies

#### Rivaroxaban Relative Safety by Body Weight and/or BMI

<table>
<thead>
<tr>
<th>Rivaroxaban n/N (%)</th>
<th>Comparator n/N (%)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>EINSTEIN DVT</strong>¹,²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤70 kg</td>
<td>48/492 (9.8)</td>
<td>42/522 (8.0)</td>
</tr>
<tr>
<td>&gt;70-90 kg</td>
<td>59/733 (8.0)</td>
<td>57/708 (8.1)</td>
</tr>
<tr>
<td>&gt;90 kg</td>
<td>31/488 (6.4)</td>
<td>39/481 (8.1)</td>
</tr>
<tr>
<td></td>
<td>1.17 (0.77-1.77)</td>
<td>0.96 (0.66-1.38)</td>
</tr>
<tr>
<td></td>
<td>0.77 (0.48-1.23)</td>
<td></td>
</tr>
<tr>
<td><strong>EINSTEIN PE</strong>²,³</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤70 kg</td>
<td>71/649 (10.9)</td>
<td>79/618 (12.8)</td>
</tr>
<tr>
<td>&gt;70-90 kg</td>
<td>110/1078 (10.2)</td>
<td>134/1116 (12.0)</td>
</tr>
<tr>
<td>&gt;90 kg</td>
<td>68/683 (10.0)</td>
<td>61/670 (9.1)</td>
</tr>
<tr>
<td></td>
<td>0.85 (0.62-1.18)</td>
<td>0.83 (0.65-1.07)</td>
</tr>
<tr>
<td></td>
<td>1.10 (0.78-1.55)</td>
<td></td>
</tr>
<tr>
<td><strong>EINSTEIN CHOICE</strong>²,⁴</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body weight</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤70 kg</td>
<td>7/283 (2.5)</td>
<td>5/277 (1.8)</td>
</tr>
<tr>
<td>&gt;70-90 kg</td>
<td>11/480 (2.3)</td>
<td>12/508 (2.4)</td>
</tr>
<tr>
<td>&gt;90 kg</td>
<td>9/364 (2.5)</td>
<td>6/346 (1.7)</td>
</tr>
<tr>
<td></td>
<td>1.38 (0.44-4.36)</td>
<td>0.93 (0.41-2.10)</td>
</tr>
<tr>
<td></td>
<td>1.41 (0.50-3.96)</td>
<td></td>
</tr>
</tbody>
</table>

An overall lack of effect on the safety of rivaroxaban was observed when different weights were analyzed across the clinical trials.

Apixaban- post-hoc analysis of AMPLIFY*

Similar rates of recurrent VTE/ VTE-related death and lower rates of bleeding for apixaban compared with VKA across body weight and BMI categories

*Not included in ISTH guidance

<table>
<thead>
<tr>
<th>VTE or VTE-related death</th>
<th>Major bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td>BMI category</td>
<td>Apixaban, n/N</td>
</tr>
<tr>
<td>≤ 25 kg/m²</td>
<td>16/693</td>
</tr>
<tr>
<td>&gt; 25 to 30 kg/m²</td>
<td>27/985</td>
</tr>
<tr>
<td>&gt; 30 to 35 kg/m²</td>
<td>9/568</td>
</tr>
<tr>
<td>&gt; 35 to 40 kg/m²</td>
<td>4/227</td>
</tr>
<tr>
<td>&gt; 40 kg/m²</td>
<td>3/122</td>
</tr>
</tbody>
</table>
**Meta-analysis of VTE RCT shows similar outcomes**

<table>
<thead>
<tr>
<th>Citation</th>
<th>Sample</th>
<th>Context</th>
<th>Conclusions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Di Minno</td>
<td>&gt;5,400 patients in high-body weight (HBW)</td>
<td>Meta-analysis of RCT DOAC vs VKA</td>
<td>In HBW (&gt;90-100 kg) subgroup:</td>
</tr>
<tr>
<td>Ann Med</td>
<td></td>
<td></td>
<td>• VTE and VTE-related death: RR 0.98 (0.72-1.35)</td>
</tr>
<tr>
<td>2015</td>
<td></td>
<td></td>
<td>• MB + clinically relevant, non-major bleeding: RR 0.9 (0.65-1.32)</td>
</tr>
</tbody>
</table>

VTE: venous thromboembolism; MB: major bleeding

*VTE and VTE-related death
Major Bleeding*

<table>
<thead>
<tr>
<th>Study or S</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Study or Subgroup</td>
<td>DOACs</td>
<td>Events</td>
<td>Total</td>
</tr>
<tr>
<td>AMPLIFY</td>
<td>1</td>
<td>521</td>
<td>0.10 [0.01, 0.77]</td>
</tr>
<tr>
<td>EINSTEIN-DVT</td>
<td>31</td>
<td>488</td>
<td>0.78 [0.50, 1.23]</td>
</tr>
<tr>
<td>EINSTEIN-PE</td>
<td>68</td>
<td>683</td>
<td>1.09 [0.79, 1.52]</td>
</tr>
<tr>
<td>HOKUSAI</td>
<td>54</td>
<td>611</td>
<td>1.07 [0.75, 1.54]</td>
</tr>
<tr>
<td>Total (95%)</td>
<td>2303</td>
<td>2323</td>
<td>0.93 [0.65, 1.32]</td>
</tr>
<tr>
<td>Total event</td>
<td>154</td>
<td>164</td>
<td>100.0%</td>
</tr>
<tr>
<td>Heterogen Test for overall effect</td>
<td>Z = 0.43 (P = 0.67)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Conclusions from clinical data

- When compared individually to VKA, rivaroxaban and apixaban have at least similar efficacy and safety in patients with obesity.

- Studies pooling DOACs show similar rates of efficacy and safety outcomes either compared with VKA or across weight categories.

- No studies limiting analysis to betrixaban, dabigatran or edoxaban individually for treatment of VTE.
Rivaroxaban and Obesity Clinical Pharmacology

Analysis of the clinical pharmacology studies and population PK/PD analyses of Phase 2 & 3 clinical trials indicate that high weight/BMI does not have a clinically meaningful impact on the pharmacology of rivaroxaban. Minor PK changes observed were within the observed range of interpatient variability.

Figure 1  Mean rivaroxaban plasma concentration-time curve after administration of a single 10-mg oral dose. Each weight group included 12 healthy subjects. Reprinted from Kubitza et al (2007)
Scenario:

A man with NVAF, who has obesity and receiving multiple different medications
How could we manage this patient?

- Poorly controlled hypertension
- Type II diabetes
- Risk assessments
  - CHA₂DS₂-VASc: 3
  - HAS-BLED: 2
- Receiving several different medications for his chronic conditions (polypharmacy)

- 65-year-old man
- Obese at 130 kg
- Hypercholesterolaemia
- Moderate renal impairment (CrCl 45 mL/min)
- Gastric ulcer 2 years ago
QUESTION: Would this patient’s obesity impact your decision to prescribe a NOAC?

1. Yes
2. No
3. More information needed
4. Unsure
NVAF

- There are no specific dosing recommendations based on body weight in the apixaban or rivaroxaban prescribing information.
- Pharmacokinetic and pharmacodynamic data indicate that high weight/BMI does not influence apixaban and rivaroxaban exposure or have a clinically meaningful impact on the pharmacology of apixaban or rivaroxaban.
- In ARISTOTLE and ROCKET AF, body weight did not have a clinically relevant effect on treatment efficacy or major bleeding and nonmajor clinically relevant bleeding when apixaban and rivaroxaban was used for reducing the risk of stroke and/or systemic embolism in patients with nonvalvular atrial fibrillation.³
**ARISTOPHANES**: patients who were obese and treated with apixaban or rivaroxaban experienced similar effectiveness and safety to the RCT trials when treated with NOACs versus warfarin.

Subgroup analysis: obese patients (BMI ≥30 kg/m²)

- Study population (N=88,461) with 1:1 PSM*
- Pooled analysis

Patients with NVAF and a BMI ≥30 kg/m², who had ≥1 pharmacy claim for a NOAC or warfarin between 1 Jan 2013 and 30 Sept 2015.

<table>
<thead>
<tr>
<th>NOAC</th>
<th>VKA</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (n=18,181)</td>
<td>Warfarin (n=18,181)</td>
</tr>
<tr>
<td>Rivaroxaban (n=22,053)</td>
<td>Warfarin (n=22,053)</td>
</tr>
<tr>
<td>Dabigatran (n=6646)</td>
<td>Warfarin (n=6646)</td>
</tr>
</tbody>
</table>

**Effectiveness:** stroke/SE

- **Apixaban vs warfarin**
- **Rivaroxaban vs warfarin**
- **Dabigatran vs warfarin**

**Safety:** major bleeding

- **HR** (95% CI)

---

*Based on PSM cohorts generated by logistic regression based on demographics, Charlson Comorbidity Index score, common comorbidities and baseline comediations. BMI, body mass index.
**ARISTOPHANES**: patients who were obese experienced some differences in effectiveness and safety between NOACs

Subgroup analysis: obese patients (BMI ≥30 kg/m²)

Patients with NVAF and a BMI ≥30 kg/m², who had ≥1 pharmacy claim for a NOAC or warfarin between 1 Jan 2013 and 30 Sept 2015

<table>
<thead>
<tr>
<th>NOAC</th>
<th>NOAC (ref)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban (n=20,431)</td>
<td>Rivaroxaban (n=20,431)</td>
</tr>
<tr>
<td>86.3%</td>
<td>75.9%</td>
</tr>
<tr>
<td>Apixaban (n=6884)</td>
<td>Dabigatran (n=6884)</td>
</tr>
<tr>
<td>87.8%</td>
<td>86.9%</td>
</tr>
<tr>
<td>Dabigatran (n=7103)</td>
<td>Rivaroxaban (n=7103)</td>
</tr>
<tr>
<td>87.2%</td>
<td>80.2%</td>
</tr>
</tbody>
</table>

**Effectiveness:** stroke/SE

<table>
<thead>
<tr>
<th></th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban vs rivaroxaban (ref)</td>
<td></td>
</tr>
<tr>
<td>Apixaban vs dabigatran (ref)</td>
<td></td>
</tr>
<tr>
<td>Dabigatran vs rivaroxaban (ref)</td>
<td></td>
</tr>
</tbody>
</table>

**Safety:** major bleeding

<table>
<thead>
<tr>
<th></th>
<th>HR* (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban (n=7103)</td>
<td></td>
</tr>
<tr>
<td>80.2%</td>
<td></td>
</tr>
</tbody>
</table>

There are no head-to-head studies comparing the NOACs; direct comparisons cannot be made between individual NOACs based on these data. Real-world data have some limitations, such as the potential for selection bias, differing outcomes definitions and the potential presence of unmeasured confounders. They are able to show associations but cannot determine causality.

Discuss Validity of ICD Codes for Obesity

- ICD-9 codes used for obesity:
  - 278.00 (obesity, unspecified)
  - 278.01 (morbid obesity)
  - 278.03 (obesity hypoventilation syndrome)
  - V85.3 (BMI of 30–39 kg/m²)
  - V85.4 (BMI of ≥40 kg/m²)

<table>
<thead>
<tr>
<th></th>
<th>Obesity</th>
<th>Morbid obesity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sensitivity</td>
<td>49% (47–50%)</td>
<td>63% (59–66%)</td>
</tr>
<tr>
<td>Specificity</td>
<td>95% (95–96%)</td>
<td>96% (96–97%)</td>
</tr>
<tr>
<td>Positive predictive value</td>
<td>90% (88–91%)</td>
<td>68% (64–71%)</td>
</tr>
</tbody>
</table>

BMI, body mass index; ICD, international classification of diseases

• Sample of Categories of RWD Obesity Studies Available to Date and Expanding

• Study based on claims data and ICD codes in 5 pooled databases, NVAF, multiple DOACs (Lip et al.)

• Study based on EHRs, NVAF, OPTUM database, rivaroxaban vs. warfarin (Costa et al.)

• VA studies (Briasoulis et al.)
Conclusions from clinical data

- When compared individually to VKA, rivaroxaban and apixaban have at least similar efficacy and safety in patients with obesity.

- Studies pooling DOACs show similar rates of efficacy and safety outcomes either compared with VKA or across weight categories.

- No studies limiting analysis to betrixaban, dabigatran or edoxaban individually for treatment of NVAF.
Conclusions / Key Takeaways / Obesity

• Real world evidence aims to reaffirm clinical observations from Phase III RCTs\textsuperscript{1}

• We need a combination of RCTs and real world evidence:\textsuperscript{1-3}
  • Offers a greater depth and range of clinical insight than either one alone
  • The FDAs framework is most useful in informing decisions around the use of medicines in response to patients’ needs

Questions?
DOAC Use in the Setting of Bariatric Surgery and Feeding Tubes

AC Forum Rapid Resource

https://acforum-excellence.org/Resource-Center/
## Bariatric surgery and DOACs

<table>
<thead>
<tr>
<th>DOAC</th>
<th>Site of absorption in gastrointestinal tract</th>
<th>Surgical intervention and anticipated effect on absorption</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>Primarily upper GI tract, with possible limited absorption in the colon; absorption decreased by when delivered to the distal small bowel compared with oral administration(^{39})</td>
<td>unlikely affected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>unlikely affected</td>
</tr>
<tr>
<td></td>
<td></td>
<td>possibly reduced</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>Lower stomach and proximal small intestine(^{41,42,49})</td>
<td>possibly reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>possibly reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>possibly reduced</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>Proximal small intestine, dependent on acidic environment (^{43,44})</td>
<td>possibly reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>possibly reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>possibly reduced</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>Largely stomach, some small intestine, but absorption reduced when released distal to stomach(^{43-45})</td>
<td>possibly reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>possibly reduced</td>
</tr>
<tr>
<td></td>
<td></td>
<td>possibly reduced</td>
</tr>
</tbody>
</table>

*Martin et al J Thromb Haemost 2021*