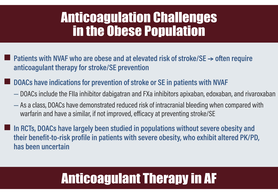
Perspectives for Pharmacy Practice:

Examining All the Evidence to Facilitate the Effective and Safe Use of Direct Oral Anticoagulants in Patients With NVAF Who Are Obese

Introduction

Increasing prevalence of obesity (BMI >30 kg/m²) and severe obesity (BMI >40 kg/m²) in the United States

Risk of AF increases linearly with increasing BMI



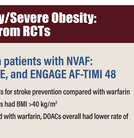
Anticoagulation Challenges in the Obese Population

- Patients with NVAF who are obese and at elevated risk of stroke/SE → often require anticoagulant therapy for stroke/SE prevention
- DOACs have indications for prevention of stroke or SE in patients with NVAF
  - DOACs include the Factor IIa inhibitor dabigatran and FXa inhibitors apixaban, edoxaban, and rivaroxaban
  - As a class, DOACs have demonstrated reduced risk of intracranial bleeding when compared with warfarin and have a similar, if not improved, efficacy at preventing stroke/SE
- In RCTs, DOACs have largely been studied in populations without severe obesity and their benefit-to-risk profile in patients with severe obesity, who exhibit altered PK/PD, has been uncertain

Anticoagulant Therapy in AF

Balance of Anticoagulant Therapy in AF

PK/PD Alterations in Obesity

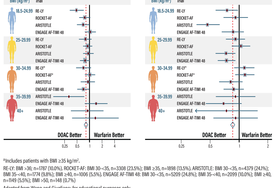


DOAC Use in Obesity/Severe Obesity: Evidence From RCTs

4 pivotal DOAC trials in patients with NVAF: RE-LY, ROCKET-AF, ARISTOTLE, and ENGAGE AF-TIMI 48

- All trials highlighted safety and efficacy of DOACs for stroke prevention compared with warfarin
- Few subjects (approximately 6%) in these trials had BMI >40 kg/m²
- In patients with BMI <40 kg/m², when compared with warfarin, DOACs overall had lower rate of
  - Stroke or SE
  - Intracranial bleeding

DOACs by BMI



*Includes patients with BMI ≥35 kg/m².

RE-LY: BMI <30, n=1787 (10.0%); ROCKET-AF: BMI 30–35, n=3269 (23.5%); BMI ≥35, n=1898 (13.5%); ARISTOTLE: BMI 30–35, n=4379 (24.7%); BMI ≥35, n=2149 (12.1%); ENGAGE AF-TIMI 48: BMI 30–35, n=5091 (24.8%); BMI ≥35, n=2699 (13.2%); BMI <40, n=9411 (46.0%); BMI ≥40, n=1148 (5.7%)

Adapted from Wang and Giugliano; for educational purposes only.

Though RCTs demonstrate acceptable benefit-to-risk profile of DOACs in obesity/extreme obesity, the number of patients with extreme obesity was relatively small, challenging the application of data to practice.

Based on these RCTs, ISTH 2016 Guidelines for NVAF:

- Recommend DOACs should be avoided in those with BMI >40 kg/m² or those weighing >120 kg
- Recommend if DOACs are used, drug concentrations should be monitored
- Provide no consensus on how to best monitor DOAC concentration or indication of what therapeutic range should be

Post-ISTH analyses shed some light on DOAC use in the context of obesity. Pharmacists can consider these data as part of all available evidence to inform DOAC use and decision-making in obesity.

Selected Examples of Post-ISTH Analyses

Single center retrospective studies:

Study 1

BMI >40 kg/m²

- **OAC:** apixaban (n=150), rivaroxaban (n=325), warfarin (n=395)
- **DOAC vs warfarin:**
  - Stroke: $p = .71$
  - Major bleeding: $p = .063$

Kushner et al.

Study 2

BMI >40 kg/m² or weight >120 kg

- **OAC:** apixaban (n=19), dabigatran (n=20), rivaroxaban (n=25), warfarin (n=64)
- **DOAC vs warfarin:**
  - Stroke/TIA: $p = .80$
  - Major bleeding: no difference
- **Rate of stroke/TIA**
  - Dabigatran (4.03%/yr)
  - Rivaroxaban (1.7%/yr)
  - Apixaban (0%)

Kido and Ngorsuraches.

Meta-analyses:

Study 3

BMI >40 kg/m² or weight >120 kg

- **Included 5 studies**
- **DOAC vs warfarin**
  - Stroke/SE: OR=0.85 ($p = .35$)
  - Major bleeding: OR=0.63; ($p = .02$)

Kido et al. 2020.

Study 4

BMI >40 kg/m²

- **Included 9 studies**
- **DOAC vs warfarin**
  - Stroke/SE: OR=0.87 ($p = .32$)
  - Major bleeding: OR=0.90 ($p = .08$)

Zhou et al.

Considering the totality of evidence, including RCTs and post-ISTH data from more than 25 studies of different DOACs (dabigatran [n=1], rivaroxaban [n=9], apixaban [n=4], edoxaban [n=1]) and multiple DOACs (n=10) in patients with AF or VTE and obesity, more detailed recommendations have been made.

	DOAC	Recommendation
✓	Apixaban	Use ***with caution*** is supported[a]
✓	Rivaroxaban	Use ***with caution*** is supported[a]
✗	Dabigatran	***Avoid*** because of potentially poor outcomes
?	Edoxaban	Insufficient evidence; no recommendation possible

[a] Recommendations are made with caution because evidence is limited.

Pearls for Practice

DOAC vs warfarin:
evaluate patient to inform benefit-to-risk

- Preferences: medication and monitoring
- Lifestyle: diet and travel
- Adherence
- Weight/BMI
- DOACs used in past: efficacy and safety

DOAC selection:
available literature supports cautious use of apixaban or rivaroxaban

DOAC dosing:
standard dosing with appropriate monitoring

Abbreviations:

AF: atrial fibrillation; BMI: body mass index; DOAC: direct oral anticoagulant; HR: hazard ratio; ISTH: International Society on Thrombosis and Haemostasis; NVAF: nonvalvular atrial fibrillation; OAC: oral anticoagulant; OR: odds ratio; PK/PD: pharmacokinetics/ pharmacodynamics; RCT: randomized controlled trial; SE: systemic embolism; TIA: transient ischemic attack; VTE: venous thromboembolism.

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