The Use of Direct Oral Anticoagulants in Obese Individuals with Atrial Fibrillation - A Systematic Review

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Background

- Anticoagulants are the cornerstone of therapy for prevention of stroke and systemic embolism in patients with atrial fibrillation (AF)
- Obesity is associated with an increased risk of new onset AF as well as recurrence of AF after successful ablation
- World Health Organization defines obesity as a Body Mass Index (BMI) ≥ 30 kg/m^2 and morbid obesity as a BMI of ≥ 40 kg/m^2
- Direct Oral Anticoagulants (DOACs) are recommended as first line therapy for anticoagulation in patients with AF
- Given variations of drug effects in obese patients based on variable pharmacokinetics, namely volume of distribution and clearance, clinicians have been reluctant to use DOACs in obese patients with AF
- International Society on Thrombosis and Haemostasis (2016) recommends avoiding DOACs in individuals with BMI ≥ 40 kg/m^2 or weight > 120kg

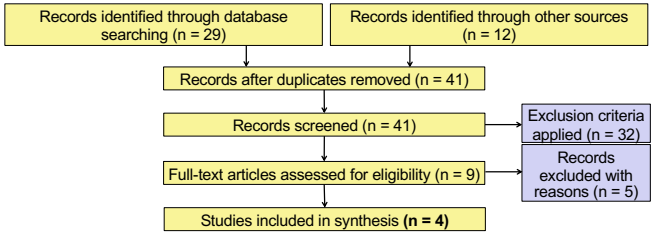
Objectives

- Primary
  - To provide an overview of the available literature concerning the use of DOACs in obese individuals with atrial fibrillation for prevention of stroke and systemic embolism
- Secondary
  - To provide an overview of the available literature regarding safety of DOACs in obese individuals with atrial fibrillation

Methods

- Search Strategy:
  - Databases:
    - MEDLINE, EMBASE, clinicaltrials.gov
  - MeSH headings and keywords:
    - (Novel Oral Anticoagulant OR NOAC OR direct oral anticoagulant OR DOAC OR dabigatran OR rivaroxaban OR apixaban OR edoxaban) AND atrial fibrillation AND (obese OR obesity)
  - Hand searched references of relevant papers.
  - Timeline: through September 1, 2020
- Inclusion Criteria:
  - Randomized controlled trials, systematic reviews
- Exclusion Criteria:
  - Retrospective reviews, case reports, case series
  - Studies also assessing DOACs in venous thromboembolism

Figure 1. PRISMA flow diagram of included studies



Results

Table 1: Included and summarized trials

Study	Design	Population	Intervention	Comparator	Results
Balla SR et al. Am J Cardiol 2017; 119:1989-96	Post-hoc analysis of ROCKET-AF	n= 14,031	Rivaroxaban[a] OR Warfarin[b] and BMI 18.5 to 24.99 kg/m^2	Patients receiving rivaroxaban[a] or warfarin[b] with a BMI 25.0 to 29.99 and BMI ≥ 30 kg/m^2	**Outcome Event Rate per 100 patient-years**: **BMI 18.5 to 24.99** (n = 3289); **BMI 25.0 to 29.99** (n = 5535); **BMI ≥ 30** (n = 5206) Composite of stroke and systemic embolism: 2.93; 2.28; 1.88 HR 0.78 (0.64-0.96); **HR 0.65 (0.52-0.8)** Stroke: 2.81; 2.11; 1.69 HR 0.75 (0.61-0.93); **HR 0.61 (0.49-0.76)** Major Bleeding: 3.69; 3.62; 3.33 HR 0.99 (0.82-1.18); HR 0.91 (0.75-1.10)

Sandhu RK et al. Eur Heart J 2016;37:2869-78	Post-hoc analysis of ARISTOTLE	n=19,913	Apixaban[c]	Warfarin[b]	**Outcome Events (%/Year)**	**BMI 18.5 to 24.9** (n = 4052)			**BMI 25 to 29.9** (n = 6702)			**BMI 30 and above** (n = 7159)		
						Apix	**Warf**	**HR (95% CI)**	**Apix**	**Warf**	**HR (95% CI)**	**Apix**	**Warf**	**HR (95% CI)**
					Stroke/SE	1.65	2.36	0.70 (0.50-0.97)	1.37	1.47	0.93 (0.69-1.26)	0.97	1.28	0.76 (0.55-1.05)
					Mortality	5.11	5.78	0.89 (0.73-1.08)	3.38	3.48	0.97 (0.80-1.17)	2.61	3.21	**0.81 (0.67-0.99)**
					Major Bleeding	2.22	4.70	0.47 (0.36-0.63)	2.04	2.82	0.73 (0.57-0.92)	2.12	2.51	0.84 (0.67-1.07)

Hohnloser SH et al. Circulation 2019;139:2292-2300	Post-hoc analysis of ARISTOTLE	n=18,139	Apixaban[c]	Warfarin[b]	**Outcome Event Rate per 100 patient-years**	**≤ 60 kg** (n = 1985)			**61 to 120 kg** (n = 15,172)			**> 120 kg** (n = 982)		
						Apix	**Warf**	**HR (95% CI)**	**Apix**	**Warf**	**HR (95% CI)**	**Apix**	**Warf**	**HR (95% CI)**
					Stroke/SE	2.01	3.20	0.63 (0.41-0.96)	1.23	1.44	0.85 (0.70-1.05)	0.44	1.13	0.39 (0.12-1.22)
					Stroke	1.95	2.95	0.66 (0.42-1.03)	1.14	1.37	0.84 (0.68-1.03)	0.44	1.03	0.43 (0.13-1.36)
					Major Bleeding	2.33	4.28	0.55 (0.36-0.82)	2.15	3.02	0.71 (0.61-0.83)	1.55	2.08	0.74 (0.37-1.50)

Boriani G et al. Eur Heart J 2019;40:1541-49	Post-hoc analysis of ENGAGE-AF TIMI 48	n=21,028	Edoxaban[d]	Warfarin[b]	**Outcome Events (%)**	**BMI 30 to 34.9** (n = 3467)			**BMI 35 to 39.9** (n = 1383)			**BMI ≥ 40** (n = 779)		
						Edox	**Warf**	**HR (95% CI)**	**Edox**	**Warf**	**HR (95% CI)**	**Edox**	**Warf**	**HR (95% CI)**
					Stroke/SE	1.8	1.3	0.70 (0.50-0.97)	1.0	1.2	1.43 (0.76-2.7)	0.5	0.8	1.37 (0.37-5.05)
					Mortality	3.7	3.6	0.96 (0.78-1.19)	3.2	3.4	1.03 (0.72-1.47)	2.8	3.4	1.38 (0.82-2.32)
					Major Bleeding	3.3	3.0	0.88 (0.69-1.13)	3.4	2.3	0.69 (0.45-1.07)	3.5	2.9	0.92 (0.54-1.57)

[a] 20 mg po daily (15 mg po daily in patients with creatinine clearance of 30 to 49 mL/min)
[b] Titrated to an INR target of 2 to 3
[c] 5 mg po BID (2.5 mg twice daily if they met two of the following criteria: age ≥80 years, body weight ≤60 kg, or serum creatinine level ≥1.5 mg/dL)
[d] 60 mg po daily (High dose edoxaban) OR edoxaban 30 mg po daily (Low dose edoxaban. Dose decreased by 50% if any of the following criteria: CrCl < 50mL/min, body weight < 60kg or concomitant use of verapamil, quinidine, dronedarone (P-GP inhibitors)

Conclusions

- Although data is limited in obese patients, there is some evidence from post-hoc analysis of landmark AF trials to support the use of DOACs in obese patients with atrial fibrillation
- There are also many (n = 19) retrospective reports to support the efficacy and safety of DOACs in obese patients with AF
- Existing evidence suggests that the efficacy and safety of apixaban or edoxaban in patients with BMI ≥ 40 kg/m^2 or weight > 120kg is similar to that of warfarin for prevention of stroke and systemic embolism in patients with AF, whereas data to support the use of rivaroxaban and dabigatran is limited in this population
- There is an "obesity paradox" observed in the literature which suggests that the presence of obesity is associated with lower stroke rates in patients with existing AF