OBJECTIVE:

To provide guidance about the management of direct oral anticoagulants (DOACs) in obese patients.

BACKGROUND:

Four DOACs are approved for clinical use in Canada: apixaban, dabigatran, edoxaban and rivaroxaban. The clinical guides for each of the DOACs contains information about mechanism of action, licensed indications, side-effect profiles, and approved dosing regimens [see Clinical Guides Apixaban (Eliquis®), Dabigatran (Pradaxa®), Edoxaban (Lixiana®), and Rivaroxaban (Xarelto®)]. According to the Health Canada, obesity is defined by a body mass index (BMI) >30 kg/m².

CLINICAL EFFICACY AND SAFETY OF DOACS IN OBSESE PATIENTS:

No randomized controlled trials have examined the safety and efficacy of DOACs only in obese or very obese patients. In most instances, <20% of patients enrolled in DOAC trials weighed >90-100 kg or BMI >30 kg/m². A high weight alone does not necessarily indicate obesity, thereby limiting the interpretation of data from trials that reported weight only. Although information remains somewhat limited for some indications, based on the data below, there is increasing comfort using DOACs in patients with class I (BMI 30.0-34.9) and class II (BMI 35.0-39.9) obesity.

- **Studies in venous thromboembolism**: In a systematic review and meta-analysis of patients with VTE treated with apixaban, dabigatran, and rivaroxaban, anticoagulant efficacy was similar in patients <100 kg and ≥100 kg. Another study found no association between BMI and risk of VTE recurrence or bleeding events in rivaroxaban-treated patients. A third retrospective study of apixaban vs warfarin used pooled data from various U.S. databases to analyze outcomes in over 43,000 patients with VTE who were classified as either obese or morbidly obese. No significant difference in recurrent VTE or major bleeding were identified (slightly lower risk for both outcomes in the apixaban arm). Subgroup analysis of patients in the Hokusai VTE study with edoxaban showed no significant difference in efficacy or safety in the >100kg or <100kg groups.

- **Studies in atrial fibrillation**: A systematic review and subsequently published post-hoc subgroup analyses of large randomized trials suggest that, among atrial fibrillation patients, apixaban, dabigatran, rivaroxaban and edoxaban are equivalent to vitamin K antagonists in terms of efficacy and safety in obese patients. A retrospective study was done at an integrated multisite health-care system of DOAC use across all BMI categories. No differences were found in stroke rates or risk of intracranial hemorrhage between normal BMI and those with category 1 or higher obesity (43.9% apixaban, 36.4% rivaroxaban, 9.5% dabigatran and 0.1% edoxaban).

- **Studies in orthopedic surgery**: In a study that compared clinical outcomes in patients undergoing total hip and knee arthroplasty, no significant differences between the efficacy and safety of...
dabigatran and enoxaparin in patients with a BMI>30 were noted. A study evaluating patients undergoing total hip or knee arthroplasty found no differences in the reduction in venous thromboembolism (VTE) risk with rivaroxaban versus enoxaparin in patients >90kg compared with those with lower weights. Finally, in a subgroup analysis of pooled data from studies comparing apixaban and enoxaparin, there were no differences in VTE or bleeding events when patients with BMI<30 were compared with those with a BMI >30.

USE OF DOACs IN PATIENTS WITH CLASS III OBESITY (BMI > 40 kg/m²):

- Data and clinical experience supporting the use of DOACs in patients with a BMI >40 or weight >120 kg remain limited to retrospective and observational studies, but clinical efficacy and safety results are encouraging. Randomized controlled trial testing of DOACs vs. warfarin in this population are needed to validate these findings. A systematic review of 5 observational studies comprising real-world data has been carried out on patients with bodyweight >120kg or BMI >40kg/m² and acute VTE (n=6585). The major DOACs used were rivaroxaban and apixaban, which limits generalizability of results. The meta-analysis concluded that the DOAC’s are non-inferior to warfarin in reducing the primary efficacy outcome of VTE recurrence (OR 1.07, 95% CI 0.93-1.23) and primary safety outcome of major bleeding (OR 0.80, 95% CI 0.54-1.17).

- A post hoc analysis of the ARISTOTLE randomized controlled trial (apixaban vs warfarin in atrial fibrillation) compared outcomes stratified by weight [1985 (10.5%) patients were < 60kg, 15 172 (83.6%) were >60-120kg and 982 (5.4%) were >120kg]. Efficacy for prevention of stroke and systemic embolization was maintained in the apixaban arms across all weight categories. Major bleeding continued to remain lower in apixaban than warfarin across all weight categories.

- In a post hoc analysis of the ENGAGE AF-TIMI 48 randomized controlled trial (edoxaban vs warfarin in atrial fibrillation), the efficacy and safety profile of edoxaban were similar across all BMI categories from 18.5 to >40 [177 (0.8%) patients had a BMI <18.5, 4491 (21.4%) had a BMI 18.5 to <25, 7903 (37.6%) had a BMI 25 to <30, 5209 (24.8%) had a BMI 30 to <35, 2099 (10.0%) had a BMI 35 to <40, and 1149 (5.5%) had BMI >/=40].

- In a retrospective matched cohort study of 1840 adults with a primary admission diagnosis of acute VTE who received a DOAC (apixaban, dabigatran, or rivaroxaban [632 patients]) or warfarin (1208 patients) and who had a body weight more than 100 kg and less than 300 kg, no significant difference was seen in the rate of recurrent venous thromboembolism or bleeding in the two treatment groups. In this study, the median BMI was 38.8 kg/m² in the DOAC group and 39.2 kg/m² in the warfarin group; in the DOAC group, 43.6% had a BMI >40, while in the warfarin group this was 45.3%.

- A retrospective 1:1 propensity score matched cohort study of 2890 VTE patients from US claims data (using ICD-9 and ICD-10 codes for morbid obesity) showed similar bleeding and recurrent VTE risk between warfarin and rivaroxaban. A similar study from the same group looking at 3563 atrial fibrillation patients showed similar bleeding and stroke/systemic embolism risk between warfarin and rivaroxaban.
• If DOACs are to be used in patients with a BMI >40 or >120 kg, patients should be informed of the limitations of the available information and potential risk of under-dosing.

**SPECIAL CONSIDERATIONS:**
Data regarding safety and efficacy of DOACs in the pediatric population are very limited. DOACs are contraindicated in pregnancy and while breast feeding.

**OTHER RELEVANT THROMBOSIS CANADA CLINICAL GUIDES:**
- Apixaban (Eliquis®)
- Dabigatran (Pradaxa®)
- Deep Vein Thrombosis (DVT): Treatment
- Edoxaban (Lixiana®)
- Pregnancy: Thromboprophylaxis
- Pregnancy: Venous Thromboembolism Treatment
- Pulmonary Embolism (PE): Treatment
- Rivaroxaban (Xarelto®)
- Thromboprophylaxis: Orthopedic Surgery

**REFERENCES:**


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