APSC BUSAN 2025

APSC 2025 & KSC

Asian Pacific Society of Cardiology Congress 2025

April 17 (Thur.) - 19 (Sat.), 2025
BEXCO, Busan, South Korea

Clinical challenges & unmet needs in stroke prevention in the DOAC era

Prof Nwe Nwe, Myanmar

Declaration

- I have no disclosure.

Outline

- Common Clinical challenges
- Comorbidities affecting DOAC Pharmacokinetics
- DOACs in Recurrent Stroke
- DOACs after Major Hemorrhage
- Initiation & Management of DOACs in special populations
- Conclusion

DOACs & Management of thromboembolic disorders

- DOACs: widespread acceptance in clinical practice for thrombosis prevention in several CV conditions
- A substantial transformation in the field of VTE management
- Selection as a first-line therapy for the prevention of ischemic stroke in patients with AF
- Despite the existence of comprehensive guidelines, often encounter challenges in selecting the appropriate anticoagulants, particularly in complex clinical cases with multiple comorbidities

Common Clinical challenges	Comorbidities affecting DOAC Pharmacokinetics
▪ Non-valvular AF & PCI ▪ Stable Cardiovascular Disease ▪ AF & Artificial Heart Valves ▪ Left Ventricular Thrombi ▪ Cancer-Associated Thromboembolism ▪ Pregnancy & Anticoagulation	▪ Kidney Disease ▪ Liver Disease ▪ Extreme Body Weights

Non-valvular AF & PCI

- The concurrence of AF in patients with CCS or ACS, undergoing PCI requires the additional anticoagulant, on top of DAPT

- Need to balance between ischemic & bleeding risk

Non-valvular AF & PCI (Evidence)

- **Pioneer AF-PCI (Prevention of Bleeding in Patients with AF Undergoing PCI) trial**

  - Dual with low-dose Rivaroxaban (15 mg or 10 mg od) & P2Y12 inhibitor (Clopidogrel) or triple therapy with very low-dose Rivaroxaban (2.5 mg bd) plus DAPT was associated with lower bleeding risk in comparison to triple therapy, including VKA and DAPT, but similar ischemic events

- **Re-Dual PCI (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran vs Triple Therapy with Warfarin in Patients with NVAF Undergoing PCI) trial**

- Dual with Dabigatran (150 mg or 110 mg bd) and P2Y12 inhibitor (Clopidogrel) had lower risk of bleeding compared with triple therapy, including VKA and DAPT

Non-valvular AF & PCI (Evidence)

- **AUGUSTUS (Antithrombotic Therapy After Acute Coronary Syndrome or PCI in Atrial Fibrillation) trial**

  - comparing triple to triple & dual to dual therapy

  - Apixaban in combination with a P2Y12 inhibitor (without aspirin) resulted in less bleeding & fewer hospitalizations without significantly effecting the number of ischemic events than regimens that included VKA, aspirin, or both

Non-valvular AF & PCI

- Clopidogrel is the most adopted P2Y12 inhibitor in concurrent NVAF & PCI, despite the residual thrombotic risk associated to high platelet reactivity (HPR) on Clopidogrel
- Platelet function tests can be utilized to evaluate the effectiveness of Clopidogrel
- Triple antithrombotic therapy or alternative antiplatelet agent in combination with DOACs if resistance to Clopidogrel detected
- Should be confident to use DOACs (dabigatran, rivaroxaban, and apixaban) in combination with a P2Y12 inhibitor, without aspirin, the bleeding risk will be significantly lower, with the same ischemic risk in NVAF & PCI

Stable Cardiovascular Disease

- **ESC Guidelines (2019)on CCS suggest that patients with a previous MI, with high risk of ischemic events (including CAD and PAD) and low risk of fatal bleeding, should be considered for long-term DAPT with aspirin and either a P2Y12- inhibitor or very low-dose rivaroxaban, unless they have an indication for an OAC such as AF**

CCS with AF

2019 Guidelines	Class	Level	2024 Guidelines	Class	Level
Long-term antithrombotic therapy in patients with chronic coronary syndrome and an indication for oral anticoagulation					
When oral anticoagulation is initiated in a patient with atrial fibrillation who is eligible for a NOAC, a NOAC is recommended in preference to a VKA.	I	A	In CCS patients with a long-term indication for OAC, an AF-therapeutic-dose of VKA alone or, preferably, of DOAC alone (unless contraindicated) is recommended lifelong.	I	B
Long-term OAC therapy (NOAC or VKA with time in therapeutic range >70%) is recommended in patients with atrial fibrillation and a CHA_2DS_2-VASc score ≥2 in males and ≥3 in females.	I	A			

2024 ESC Guidelines for the management of chronic coronary syndromes
(European Heart Journal; 2024 – doi: 10.1093/eurheartj/ehae177)

AF & Artificial Heart Valves (Evidence)

- The coexistence of valvular heart disease and AF is common, and independently contributes to thromboembolic events and mortality
- RE-ALIGN(Dabigatran Versus Warfarin in Patients with Mechanical Heart Valves) trial

  - It was terminated prematurely, because of an excess of thromboembolic & bleeding events among patients in the Dabigatran group
- INVICTUS-VKA (INVestIgation of rheumatiC AF Treatment Using VKAs, rivaroxaban or aspirin Studies) trial

  - Among patients with rheumatic heart disease-associated AF, VKAs led to a lower rate of a composite of cardiovascular events or death than rivaroxaban, without a higher rate of bleeding, confirming the current recommendations

AF & Artificial Heart Valves (Evidence)

- Limited studies demonstrated the effectiveness & safety of DOACs in patients with trans-catheter or surgical bio-prosthetic valve implantation or valve repairs and concurrent AF

- ATLANTIS trial:
  - to evaluate the impact of Apixaban in patients undergoing TAVI
  - Apixaban was not superior to standard of care (antiplatelet/OAC)
  - thrombosis rates were similar between Apixaban and VKA

- For patients requiring anticoagulation undergoing TAVI, Apixaban would be an alternative to warfarin

AF & Artificial Heart Valves

- The available evidence suggests that the use of DOACs should not be precluded, in the presence of biological heart valves and a baseline indication for anticoagulation

- VKAs remain the current standard of care, for patients with mechanical heart valves and rheumatic heart disease

Left Ventricular Thrombi

- LVT can occur as a complication of post-acute myocardial infarction or in non-ischaemic cardiomyopathies
- The current clinical practice suggests VKAs as the choice of anticoagulation therapy
- The off-label adoption of DOACs for these patients is becoming an attractive alternative
- The dissimilarities between LVT (stasis and endocardial changes) and AF-related LAAT (stasis) could be attributed to intrinsic differences, resulting in variant anticoagulation responsiveness

Left Ventricular Thrombi

- The recommended dosage of DOACs, for LVT, has not yet been clarified
- The formation of LVT, subsequent to AMI, further complicates the selection of appropriate dosage of DOACs, on top of DAPT
- DOACs are considered to be a reasonable alternative to VKAs in patients with LVT, although larger randomized studies are needed to confirm the benefits and appropriate dosage

Cancer-Associated Thromboembolism

- Patients with active cancer can be at high risk of both venous thromboembolism and bleeding events
- European Society of Medical Oncology (ESMO) : the treatment of CAT is divided into 3 phases: acute phase (first 5–10 days after diagnosis), long-term phase (first 3–6 months), and extended phase (beyond 6 months)
- LMWH is preferred treatment for acute phase
- The long-term and extended phase regimen includes LMWH & DOACs (apixaban, edoxaban, and rivaroxaban)
- DOACs were associated with higher incidence of clinically relevant non-major bleedings, particularly in patients with gastrointestinal cancer

Pregnancy & Anticoagulation

- Anticoagulant therapy is indicated in pregnancy:
  - ✓ NVAF,
  - ✓ presence of mechanical heart valves,
  - ✓ treatment of VTE
  - ✓ pregnancy with anti-thrombin deficiency, anti-phospholipid antibody (APLA) syndrome, or other thrombophilias with a prior VTE
- Preferred anticoagulants during pregnancy are UFH or LMWH
- VKAs can cross the placenta & has a risk of embryopathy
- VKA should be interrupted between 6 and 12 weeks & after 36th week

  and be replaced by UFH or LMWH
- Despite DOAC embryopathy is lower than that of VKA, it still justifies the avoidance of DOAC in pregnancy

Comorbidities affecting DOAC pharmacokinetics

Kidney Disease

- Increased prevalence of AF in patients with ESRD
- Association between the high thromboembolic risk and major hemorrhagic risk with declining renal function
- Warfarin has been the preferred anticoagulant for patients with CKD especially ESRD (CrCl<15 mL/min) despite the lack of substantial data for efficacy & safety
- Considering Warfarin-induced acceleration of vascular calcification (calciphylaxis) as well as the tubular necrosis, leading to faster progression of CKD, more appropriate alternatives would be?

Kidney Disease

- DOACs are a therapeutic option with evident advantages
- Dabigatran is the most renal eliminated, accountable for 80%, followed by Edoxaban, Rivaroxaban, and Apixaban : 50%, 36%, and 27% respectively
- Dose adjustment is mandatory, due to their distinct pharmacokinetic & variable degree of renal clearance
- Assessment of renal function is critical, for initiation & during the treatment of DOACs
- Need to be aware of patients with CrCl<30mL/min (<25 mL/min for apixaban) were excluded from major trials

Kidney Disease (Evidence)

- **COMBINE AF database : data from the four major clinical trials concerned AF on DOACs**

- To evaluate the efficacy and safety of DOACs vs warfarin across the whole spectrum of kidney function

- The results showed that standard-dose DOACs were more effective and safer than warfarin down to a CrCl of 25 mL/min, while the lower-dose were associated with a higher incidence of SSE and death and did not significantly reduce the incidence of bleeding compared to standard dose

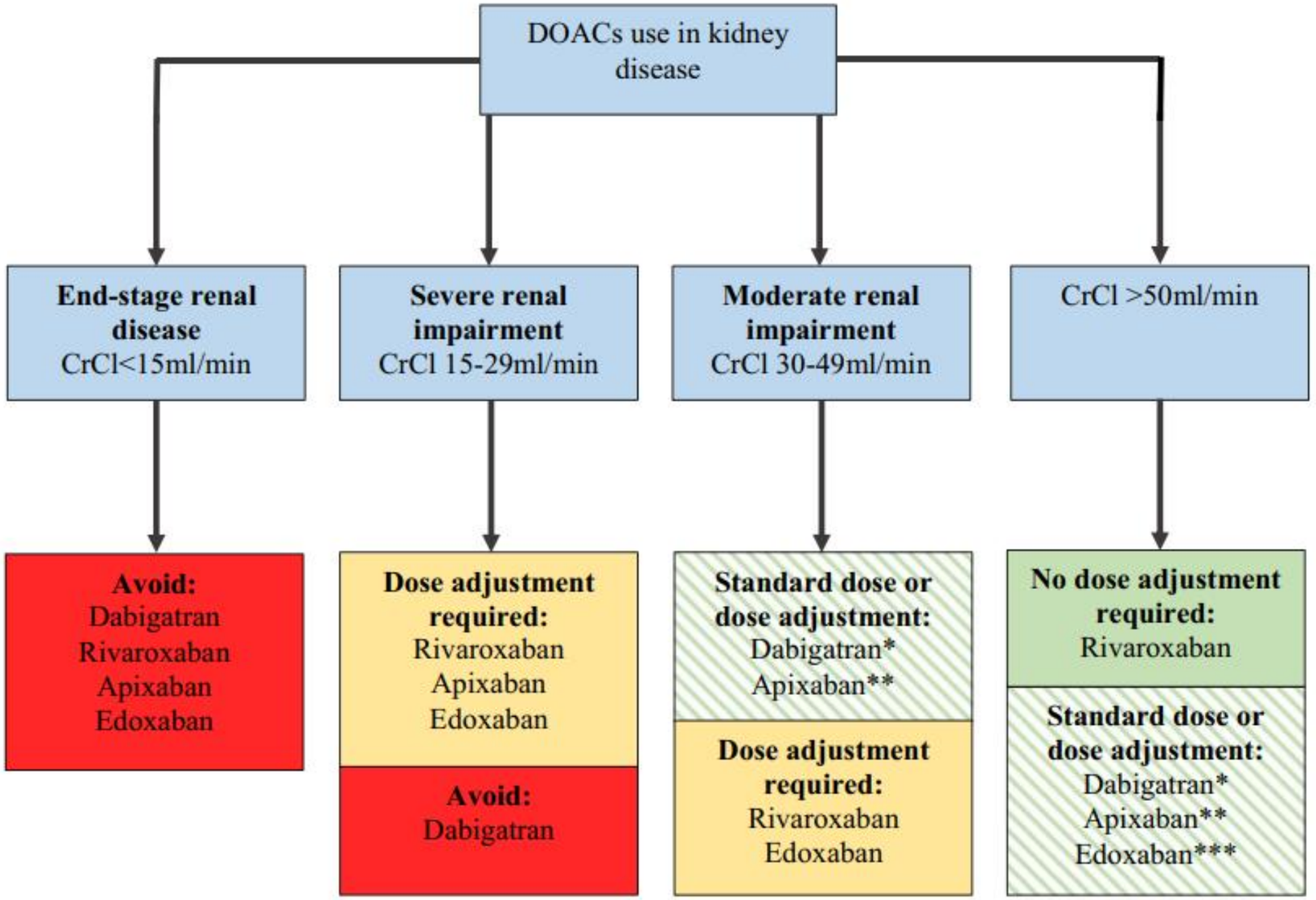


Fig. 1 DOAC use in kidney disease. *Dose adjustment depends on the following: age ≥ 80 years, concomitant use of verapamil, but mainly depends on individual assessment of thromboembolic and bleeding risk. **Dose adjustment in patients with two of the following characteristics: age ≥ 80 years, body weight ≤ 60 kg, creatinine ≥ 1.5 mg/dL. ***Other dose adjustment criteria may apply: weight ≤ 60 kg, concomitant use of P-gp inhibitors. Also, according to EMA, edoxaban should be used with caution in CrCl > 95 mL/min, only after a careful evaluation of the individual thromboembolic and bleeding risk

Liver Disease

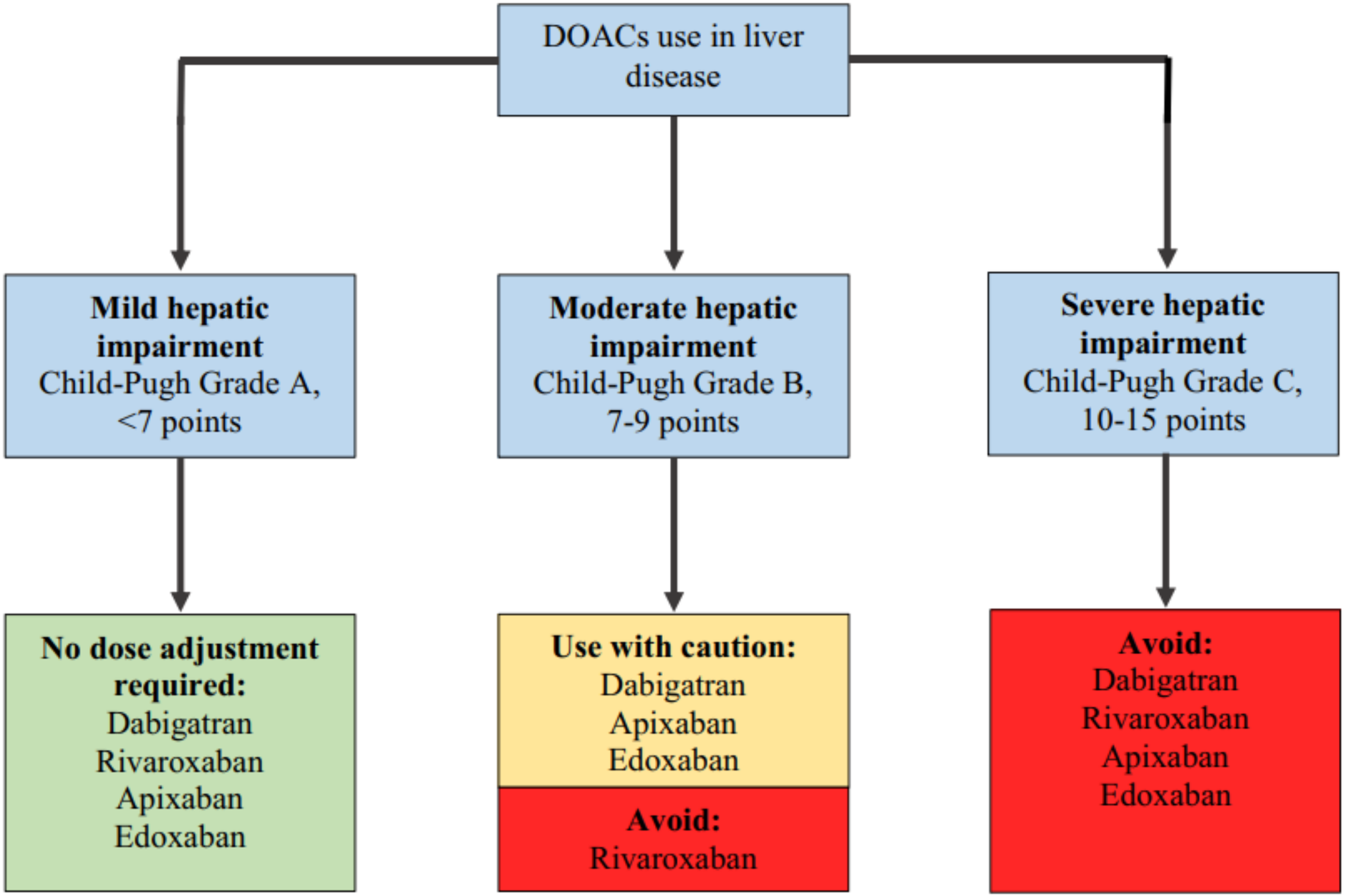
- Risk of thrombotic or bleeding events due to unstable equilibrium between pro- and anticoagulant factors
- Anticoagulant therapy is needed for concurrent AF, treatment/prevention of VTE, portal vein thrombosis, or Budd-Chiari syndrome
- Although current guidelines recommend as main anticoagulant, LMWH or VKA, both agents have significant limitations: frequent SC injections or INR monitoring
- DOACs could be an interesting alternative option

Liver Disease

- Apixaban is the most dependent agent on hepatic metabolism, with approximately 75% elimination, followed by Rivaroxaban, Edoxaban, & Dabigatran: 65%, 50%, and 20% respectively

- Apixaban and Rivaroxaban require cytochrome P450 (CYP3A4-type) enzymes for metabolism, while Dabigatran and Edoxaban require minimal to nothing CYP metabolism

DOAC use in liver disease



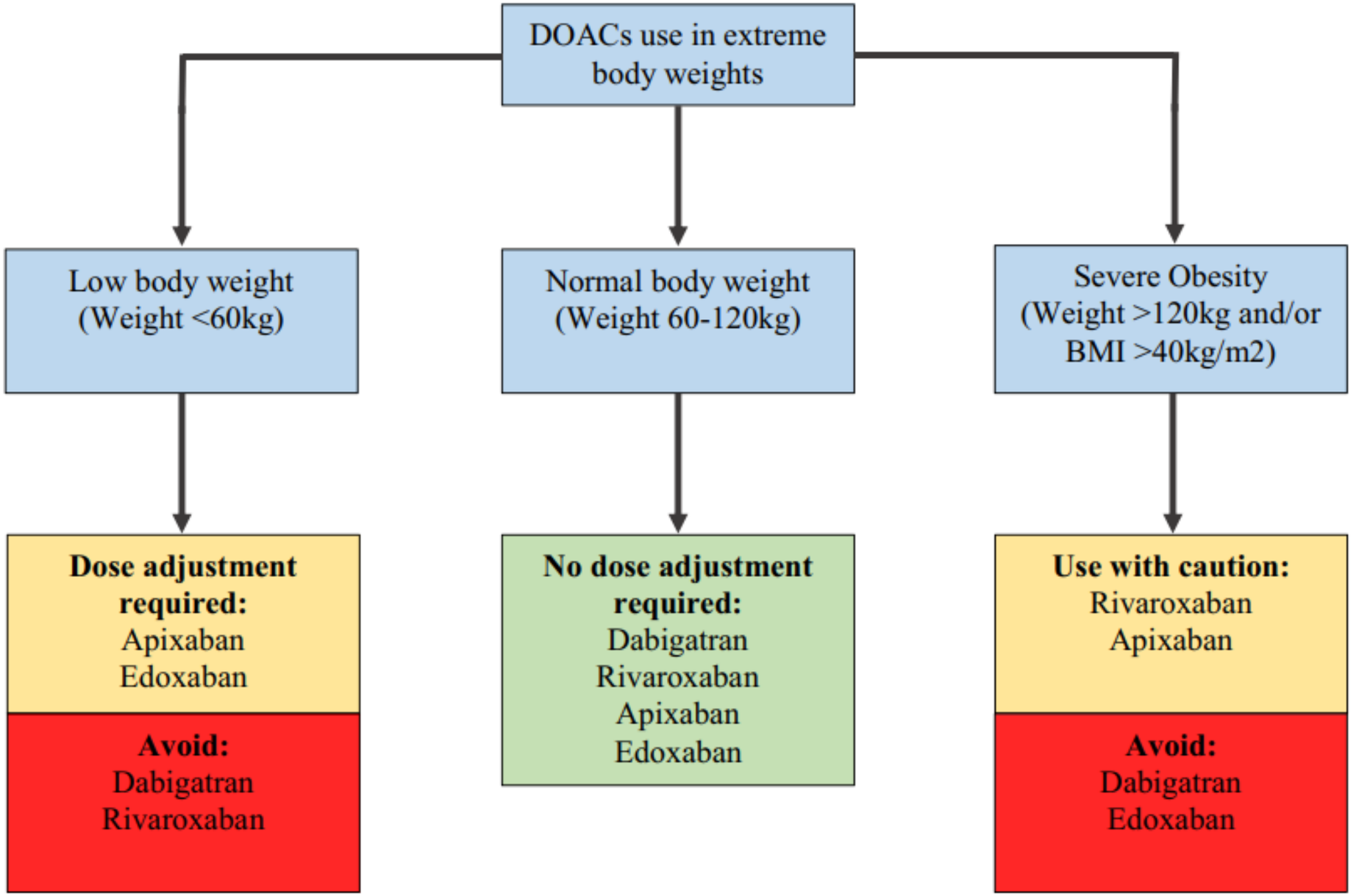
Extreme Body Weights

- Weight &BMI can significantly impact various aspects of pharmacokinetics, especially of lipophilic drugs
- Analysis of trials conducted by the International Society on Thrombosis & Haemostasis (ISTH) refers that DOACs are safe in patient's weight ≤ 120 kg at standard doses
- DOACs are not recommended in severely obese patients (weight>120 kg and/ or BMI>40 kg/m2) due to existing concern about under-dosing
- If DOACs are used, drug-specific peak and trough level must be checked
- If the level is below the expected range, change to VKA

Extreme Body Weights

- Special care is needed also for under-weight population (BMI < 18.5 kg/m2)
- Increased exposure to DOAC with excessive bleeding risk compared to normal body weight
- These patients frequently present comorbidities such as elderly age, frailty, and renal impairment that predispose to adverse outcomes
- Renal function is commonly overestimated due to reduced muscle mass

DOAC use in extreme body weight



DOACs in Recurrent Stroke

- **Strategies for secondary prevention** in patients with anticoagulation are not well defined
- **Low dose administration, LA enlargement, hyperlipidemia, high CHADs score** are high risk for recurrent cardio-embolic stroke
- No evidence to switch to VKA, different NOACs, addition of antiplatelet
- **Re-initiation** of anticoagulation is reasonable **between 4-14 days** of stroke , with **longer delays** after larger infarct

(Based on infarct size, NIHSS score > 15 & > 1 infarcted territories)

DOACs after Major Hemorrhage

- ICH occurs ~ 0.5% per year (DOACs<VKA)
- ESC guidelines recommend DOACs over VKA based on safety profile, no RCT in patients with AF, based on high ischemic risk & history of ICH,
- Conflicting evidence of GI bleeding (VKA < DOACs), Rivaroxaban was associated with higher rates of major GIB among DOACs
- Should be balanced severity of bleeding event & underlying thromboembolic risk
- Resumption at least 4 weeks after acute phase of ICH, 2 weeks after major GIB
- LAA occlusion should be considered in patient with high risk of ICH recurrence

Initiation & Management of DOACs in special populations

Initial evaluation	History: CKD, cancer, major bleeding Weight, current medications to identify interaction
DOACs selection	Age, renal function, frailty, falling risk, Extreme weight, polypharmacy, interaction
Dosing & monitoring	Age, GFR, weight, drug interaction
Complications management	Reversal agents, resumption consideration, assess compliance & efficacy of current tx, LAA device consideration
Follow up	Adherence & side effects, life style modification, creatinine, drug levels
Treatment modifications	Continuous assessment, treatment adjustment based on changes in conditions

Conclusion

- DOACs have significantly transformed the landscape of anticoagulation Mx
- Become the cornerstone Rx for stroke prevention in AF & Mx of VTE
- Despite the large available evidence & current comprehensive guidelines for DOACs usage, there are still clinical challenges & unmet needs in prevention of thromboembolism
- A carefully considered approach, tailored to the individual patient & their comorbidities will navigate the effective DOACs prescribing where clinical uncertainty exists

THANK YOU