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ILLUSTRATED REVIEW

Direct oral anticoagulants for treatment of venous thrombosis: illustrated review of appropriate use

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Abstract

Direct oral anticoagulants (DOACs) have become the preferred option for treatment of venous thromboembolism due to their favorable profile compared with other agents such as vitamin K antagonists or low-molecular-weight heparin. However, findings from randomized controlled trials suggest efficacy and/or safety concerns with DOAC use in some clinical contexts. This illustrated review will summarize indications where DOACs have proven efficacy and safety, situations where they fall short, and situations where uncertainty remains compared with other treatments for venous thromboembolism.

KEYWORDS
anticoagulants, direct oral anticoagulants, low-molecular-weight heparin, venous thromboembolism, Vitamin K Antagonists

Essentials

- Randomized trials suggest that direct oral anticoagulants (DOACs) may not be as safe or effective for mangement of venous thromboembolism (VTE) in certain situations.
- We review scenarios where DOACs are safe and effective, where they have reduced safety or efficacy, and when their safety and/or efficacy are uncertain.
- DOACs are not advised for VTE in antiphospholipid syndrome or luminal cancers.
- The safety and efficacy of DOACs for VTE remain uncertain in some conditions.

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CAPSULE 1

Direct Oral Anticoagulants

for Treatment of Venous Thrombosis

Illustrated Review of Appropriate Use

Direct Oral Anticoagulants (DOACs) are the preferred agents for treating venous thromboembolism (VTE) due to their favorable safety profile compared to other agents such as Vitamin K Antagonists (VKAs) or low molecular weight heparins.

Ease of use	Fewer drug-drug and food-drug interactions	No routine INR monitoring needed
		

Professional guidelines including ACCP, AHA, ASH, ESC, and ISTH have endorsed their use.[1-5]

However:

- **Some randomized controlled trials (RCTs) suggests that in certain scenarios, direct oral anticoagulants (DOACs) might be less effective or safe than other treatments.**
- **The efficacy and safety of DOACs remain uncertain in some situations.**

This illustrated review will explain the following three scenarios:

DOACs

Safe and effective

- Acute management of VTE
- Extended duration management of VTE
- Cancer associated VTE (Other than gastrointestinal and genitourinary cancer)

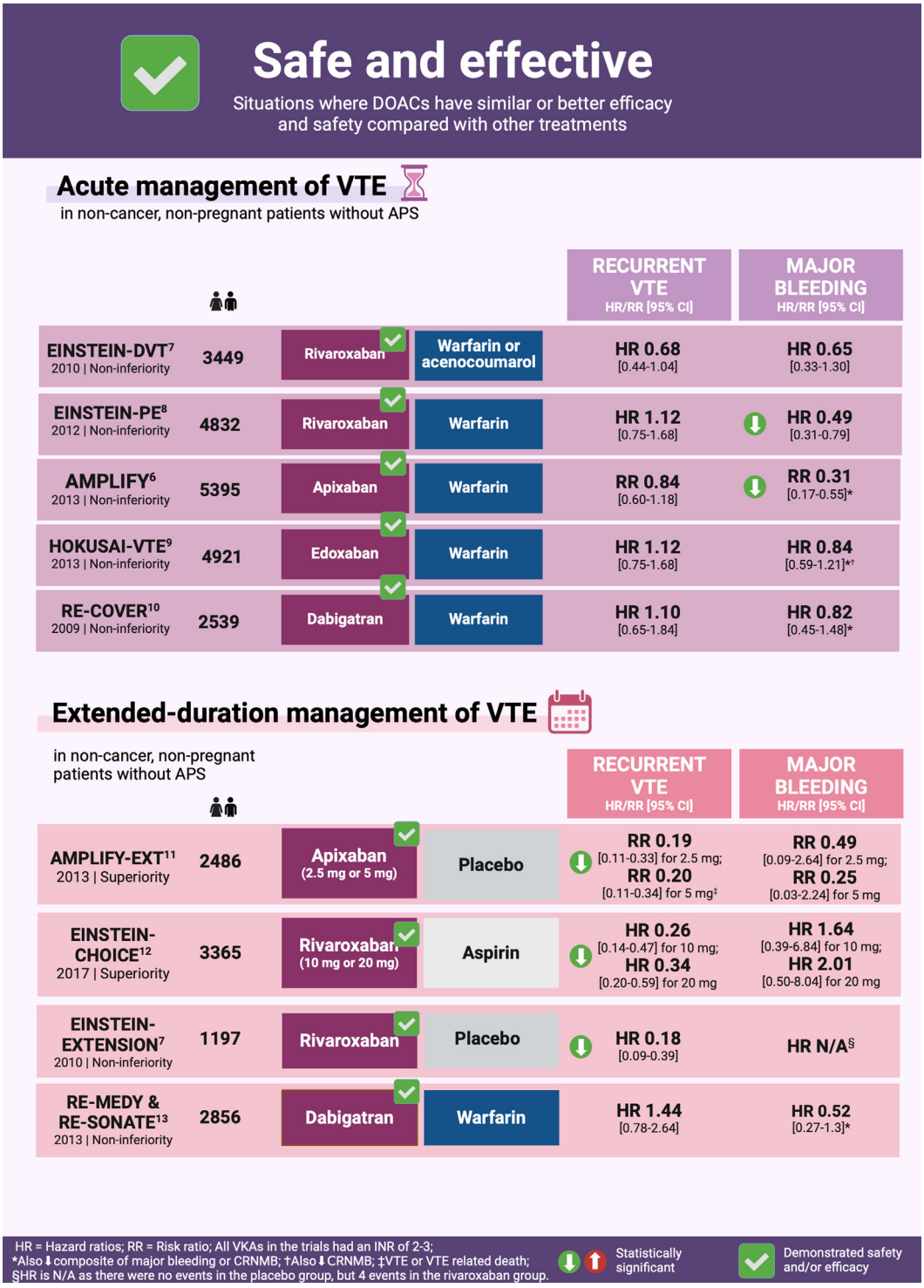
Reduced safety, efficacy, or both

- Thrombotic antiphoshpholipid syndrome
- Luminal gastrointestinal and genitourinary cancer

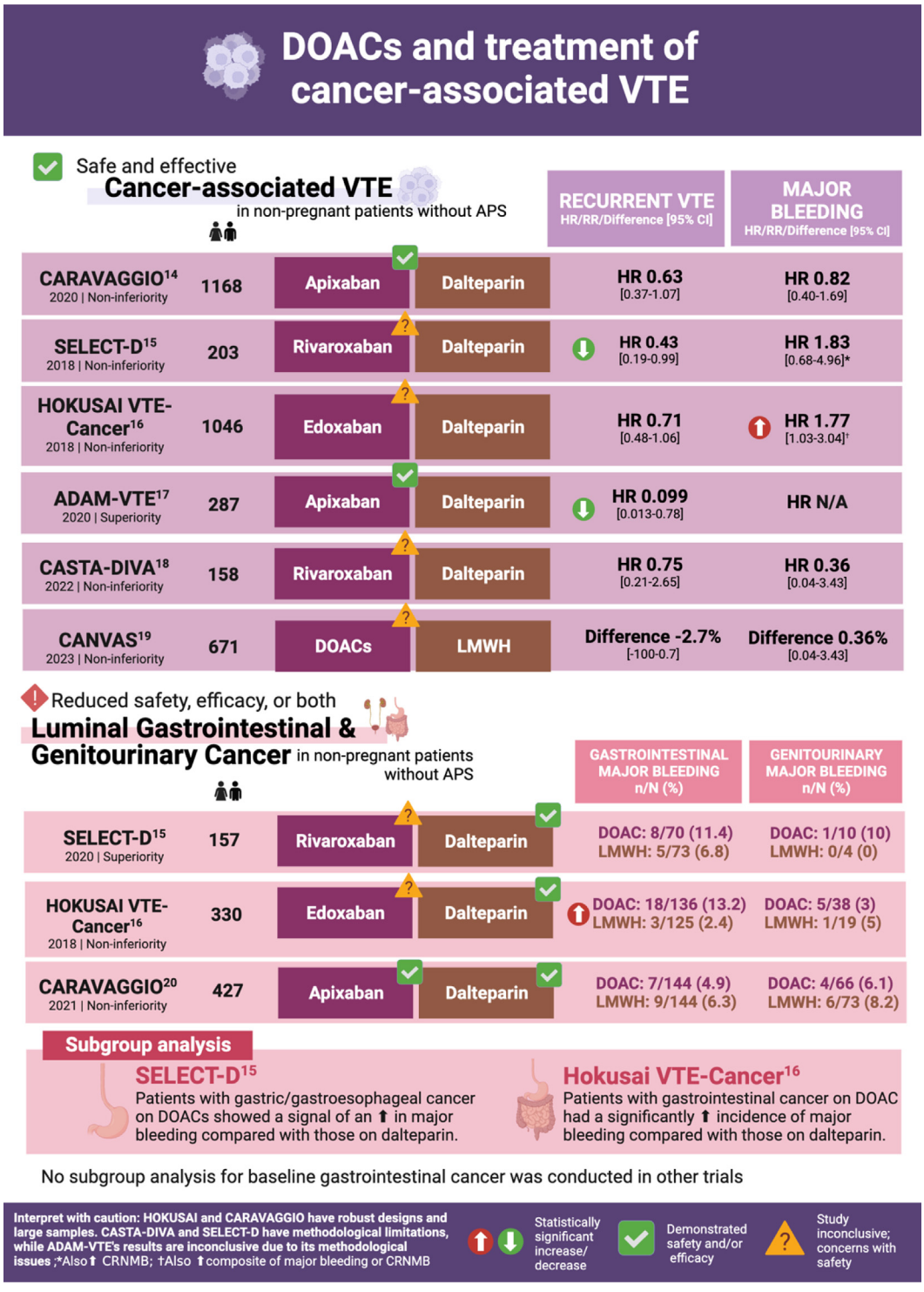
Uncertainty about safety and/or efficacy

- Catheter associated DVT
- Cerebral venous sinus thrombosis
- Splanchnic vein thrombosis
- Advanced chronic renal dysfunction
- Bariatric surgery
- Asian ethnicity
- Extremes of high and low body weight
- Pregnancy
- Breastfeeding

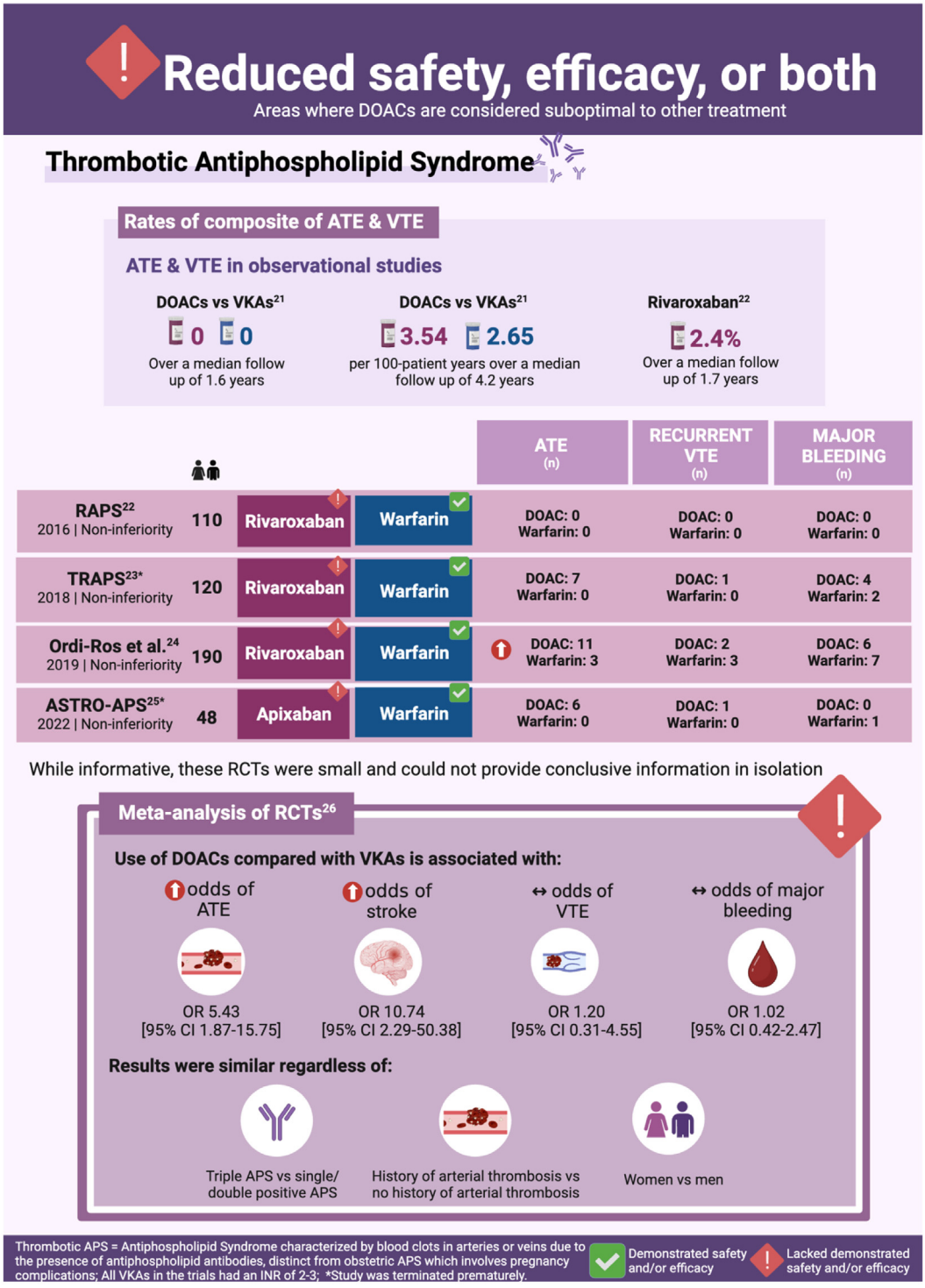
CAPSULE 2


Safe and effective
Situations where DOACs have similar or better efficacy and safety compared with other treatments
Acute management of VTE
in non-cancer, non-pregnant patients without APS
RECURRENT VTE HR/RR [95% CI]
MAJOR BLEEDING HR/RR [95% CI]
EINSTEIN-DVT[7] 2010 | Non-inferiority 3449 Rivaroxaban Warfarin or acenocoumarol HR 0.68 [0.44-1.04] HR 0.65 [0.33-1.30]
EINSTEIN-PE[8] 2012 | Non-inferiority 4832 Rivaroxaban Warfarin HR 1.12 [0.75-1.68] HR 0.49 [0.31-0.79]
AMPLIFY[6] 2013 | Non-inferiority 5395 Apixaban Warfarin RR 0.84 [0.60-1.18] RR 0.31 [0.17-0.55]*
HOKUSAI-VTE[9] 2013 | Non-inferiority 4921 Edoxaban Warfarin HR 1.12 [0.75-1.68] HR 0.84 [0.59-1.21]*†
RE-COVER[10] 2009 | Non-inferiority 2539 Dabigatran Warfarin HR 1.10 [0.65-1.84] HR 0.82 [0.45-1.48]*
Extended-duration management of VTE
in non-cancer, non-pregnant patients without APS
RECURRENT VTE HR/RR [95% CI]
MAJOR BLEEDING HR/RR [95% CI]
AMPLIFY-EXT[11] 2013 | Superiority 2486 Apixaban (2.5 mg or 5 mg) Placebo RR 0.19 [0.11-0.33] for 2.5 mg; RR 0.20 [0.11-0.34] for 5 mg‡ RR 0.49 [0.09-2.64] for 2.5 mg; RR 0.25 [0.03-2.24] for 5 mg
EINSTEIN-CHOICE[12] 2017 | Superiority 3365 Rivaroxaban (10 mg or 20 mg) Aspirin HR 0.26 [0.14-0.47] for 10 mg; HR 0.34 [0.20-0.59] for 20 mg HR 1.64 [0.39-6.84] for 10 mg; HR 2.01 [0.50-8.04] for 20 mg
EINSTEIN-EXTENSION[7] 2010 | Non-inferiority 1197 Rivaroxaban Placebo HR 0.18 [0.09-0.39] HR N/A§
RE-MEDY & RE-SONATE[13] 2013 | Non-inferiority 2856 Dabigatran Warfarin HR 1.44 [0.78-2.64] HR 0.52 [0.27-1.3]*
HR = Hazard ratios; RR = Risk ratio; All VKAs in the trials had an INR of 2-3;
*Also ⬇ composite of major bleeding or CRNMB; †Also ⬇ CRNMB; ‡VTE or VTE related death;
§HR is N/A as there were no events in the placebo group, but 4 events in the rivaroxaban group.
Statistically significant
Demonstrated safety and/or efficacy

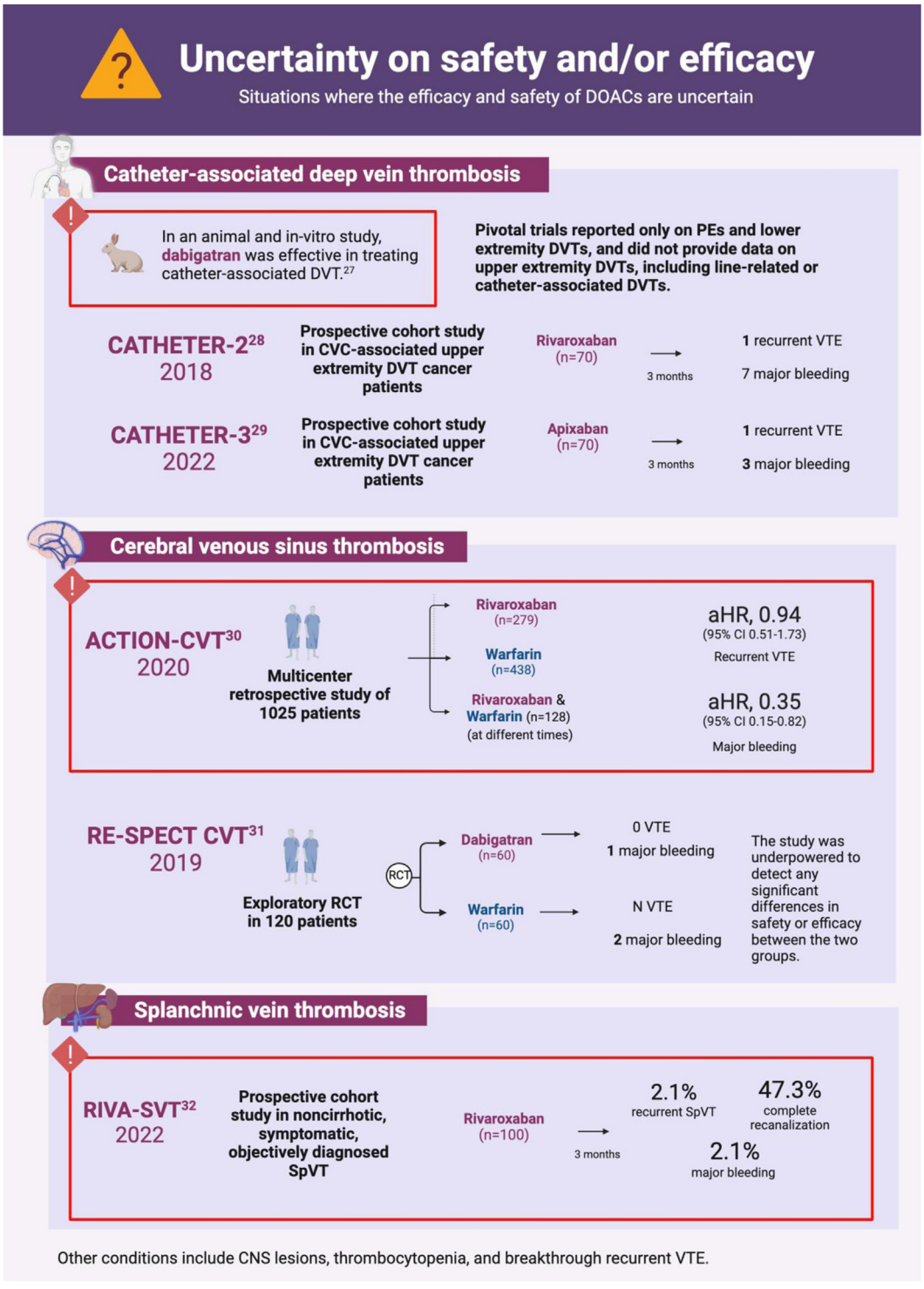
CAPSULE 3


DOACs and treatment of cancer-associated VTE
Safe and effective
Cancer-associated VTE
in non-pregnant patients without APS
RECURRENT VTE
HR/RR/Difference [95% CI]
MAJOR BLEEDING
HR/RR/Difference [95% CI]
CARAVAGGIO14 2020 | Non-inferiority 1168 Apixaban Dalteparin HR 0.63 [0.37-1.07] HR 0.82 [0.40-1.69]
SELECT-D15 2018 | Non-inferiority 203 Rivaroxaban Dalteparin HR 0.43 [0.19-0.99] HR 1.83 [0.68-4.96]*
HOKUSAI VTE-Cancer16 2018 | Non-inferiority 1046 Edoxaban Dalteparin HR 0.71 [0.48-1.06] HR 1.77 [1.03-3.04]†
ADAM-VTE17 2020 | Superiority 287 Apixaban Dalteparin HR 0.099 [0.013-0.78] HR N/A
CASTA-DIVA18 2022 | Non-inferiority 158 Rivaroxaban Dalteparin HR 0.75 [0.21-2.65] HR 0.36 [0.04-3.43]
CANVAS19 2023 | Non-inferiority 671 DOACs LMWH Difference -2.7% [-100-0.7] Difference 0.36% [0.04-3.43]
Reduced safety, efficacy, or both
Luminal Gastrointestinal & Genitourinary Cancer in non-pregnant patients without APS
GASTROINTESTINAL MAJOR BLEEDING n/N (%)
GENITOURINARY MAJOR BLEEDING n/N (%)
SELECT-D15 2020 | Superiority 157 Rivaroxaban Dalteparin DOAC: 8/70 (11.4) LMWH: 5/73 (6.8) DOAC: 1/10 (10) LMWH: 0/4 (0)
HOKUSAI VTE-Cancer16 2018 | Non-inferiority 330 Edoxaban Dalteparin DOAC: 18/136 (13.2) LMWH: 3/125 (2.4) DOAC: 5/38 (3) LMWH: 1/19 (5)
CARAVAGGIO20 2021 | Non-inferiority 427 Apixaban Dalteparin DOAC: 7/144 (4.9) LMWH: 9/144 (6.3) DOAC: 4/66 (6.1) LMWH: 6/73 (8.2)
Subgroup analysis
SELECT-D15
Patients with gastric/gastroesophageal cancer on DOACs showed a signal of an ⬆ in major bleeding compared with those on dalteparin.
Hokusai VTE-Cancer16
Patients with gastrointestinal cancer on DOAC had a significantly ⬆ incidence of major bleeding compared with those on dalteparin.
No subgroup analysis for baseline gastrointestinal cancer was conducted in other trials
Interpret with caution: HOKUSAI and CARAVAGGIO have robust designs and large samples. CASTA-DIVA and SELECT-D have methodological limitations, while ADAM-VTE's results are inconclusive due to its methodological issues ;*Also⬆ CRNMB; †Also ⬆composite of major bleeding or CRNMB
Statistically significant increase/ decrease
Demonstrated safety and/or efficacy
Study inconclusive; concerns with safety

CAPSULE 4

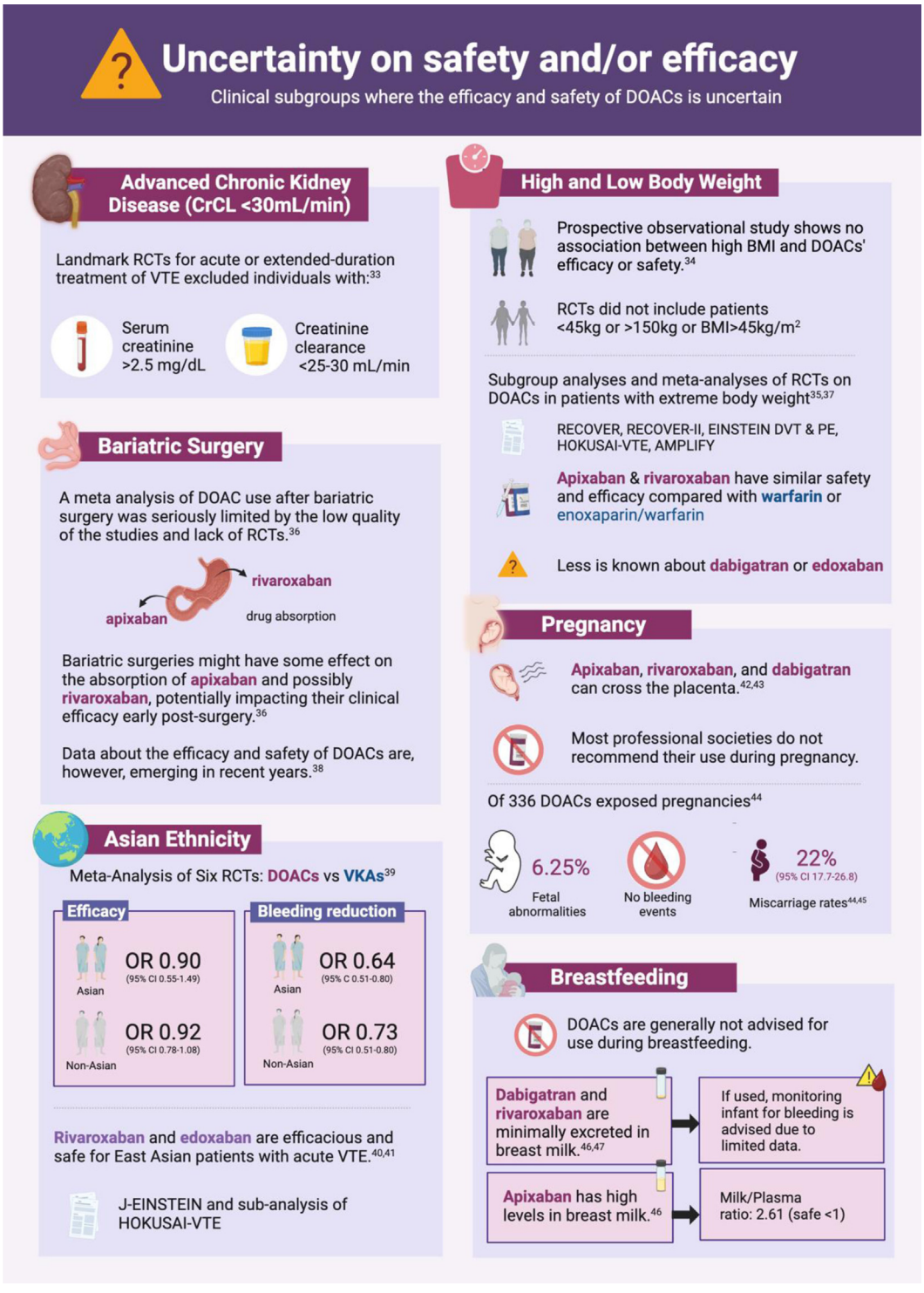

Reduced safety, efficacy, or both
Areas where DOACs are considered suboptimal to other treatment
Thrombotic Antiphospholipid Syndrome
Rates of composite of ATE & VTE
ATE & VTE in observational studies
DOACs vs VKAs[21]
0 0
Over a median follow up of 1.6 years
DOACs vs VKAs[21]
3.54 2.65
per 100-patient years over a median follow up of 4.2 years
Rivaroxaban[22]
2.4%
Over a median follow up of 1.7 years
ATE (n)
RECURRENT VTE (n)
MAJOR BLEEDING (n)
RAPS[22] 2016 | Non-inferiority 110 Rivaroxaban Warfarin DOAC: 0 Warfarin: 0 DOAC: 0 Warfarin: 0 DOAC: 0 Warfarin: 0
TRAPS[23*] 2018 | Non-inferiority 120 Rivaroxaban Warfarin DOAC: 7 Warfarin: 0 DOAC: 1 Warfarin: 0 DOAC: 4 Warfarin: 2
Ordi-Ros et al.[24] 2019 | Non-inferiority 190 Rivaroxaban Warfarin DOAC: 11 Warfarin: 3 DOAC: 2 Warfarin: 3 DOAC: 6 Warfarin: 7
ASTRO-APS[25*] 2022 | Non-inferiority 48 Apixaban Warfarin DOAC: 6 Warfarin: 0 DOAC: 1 Warfarin: 0 DOAC: 0 Warfarin: 1
While informative, these RCTs were small and could not provide conclusive information in isolation
Meta-analysis of RCTs[26]
Use of DOACs compared with VKAs is associated with:
odds of ATE
OR 5.43 [95% CI 1.87-15.75]
odds of stroke
OR 10.74 [95% CI 2.29-50.38]
↔ odds of VTE
OR 1.20 [95% CI 0.31-4.55]
↔ odds of major bleeding
OR 1.02 [95% CI 0.42-2.47]
Results were similar regardless of:
Triple APS vs single/ double positive APS
History of arterial thrombosis vs no history of arterial thrombosis
Women vs men
Thrombotic APS = Antiphospholipid Syndrome characterized by blood clots in arteries or veins due to the presence of antiphospholipid antibodies, distinct from obstetric APS which involves pregnancy complications; All VKAs in the trials had an INR of 2-3; *Study was terminated prematurely.
Demonstrated safety and/or efficacy
Lacked demonstrated safety and/or efficacy

CAPSULE 5

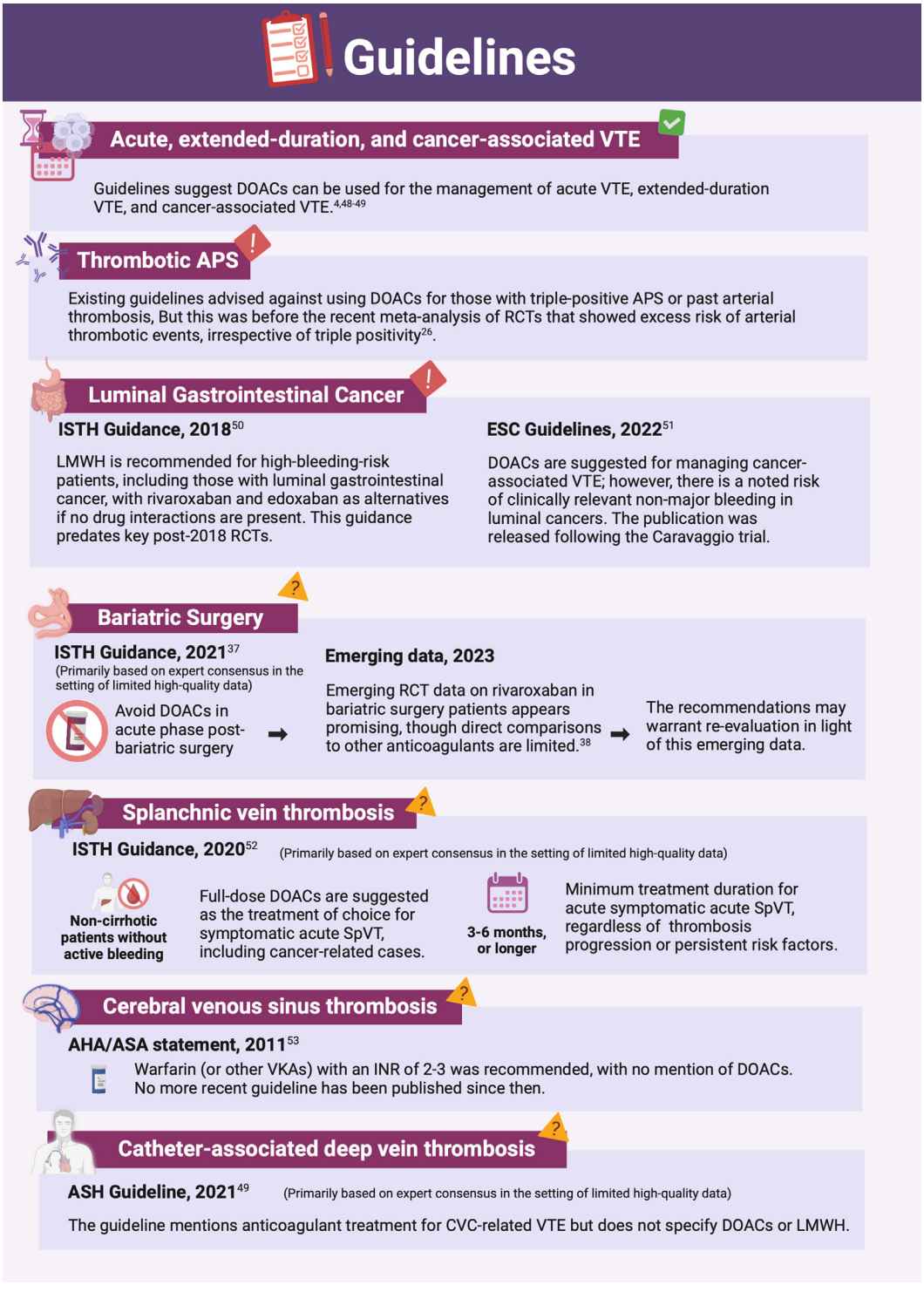


Other conditions include CNS lesions, thrombocytopenia, and breakthrough recurrent VTE.

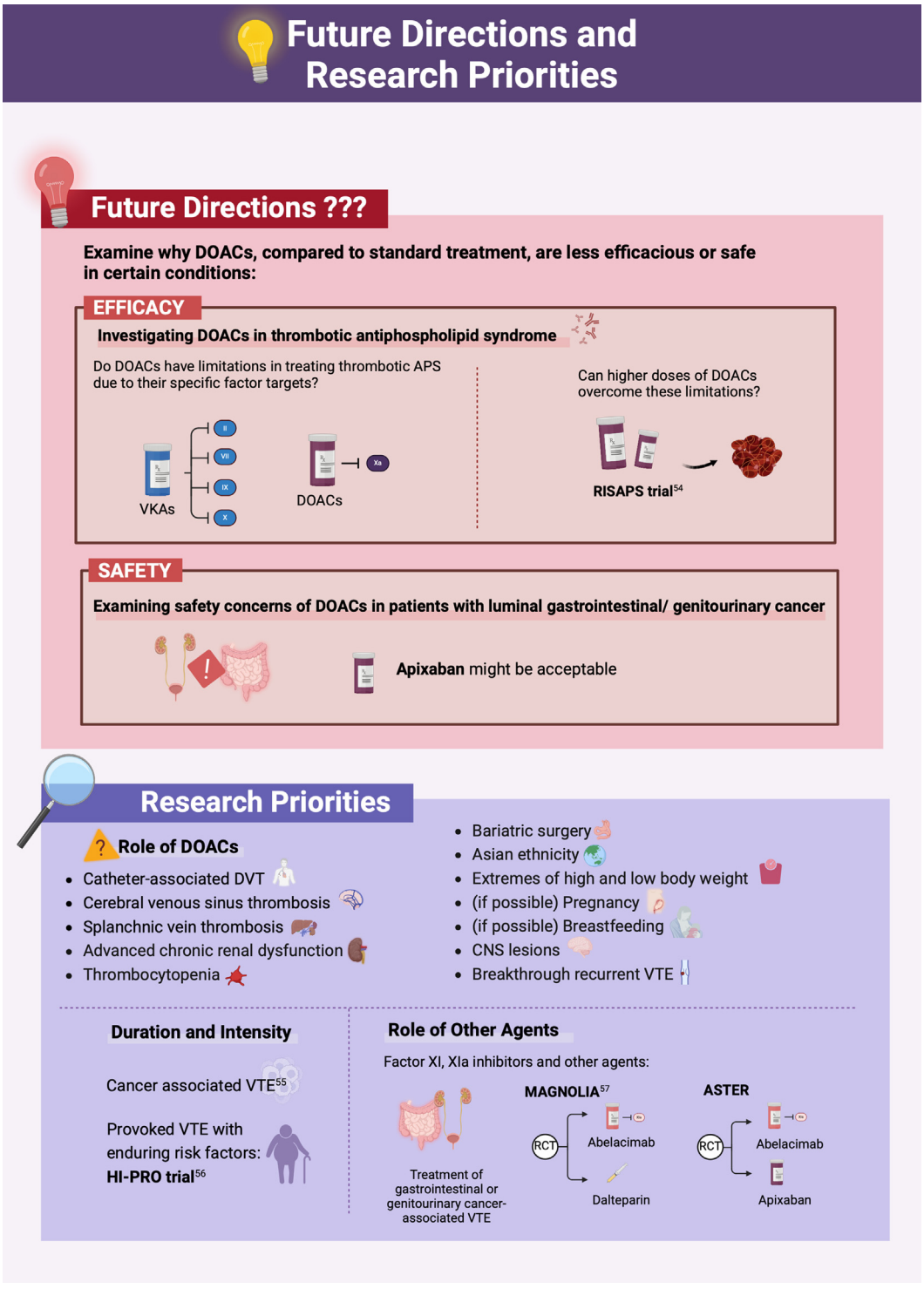
CAPSULE 6


Uncertainty on safety and/or efficacy
Clinical subgroups where the efficacy and safety of DOACs is uncertain
Advanced Chronic Kidney Disease (CrCL <30mL/min)
Landmark RCTs for acute or extended-duration treatment of VTE excluded individuals with:[33]
Serum creatinine >2.5 mg/dL
Creatinine clearance <25-30 mL/min
Bariatric Surgery
A meta analysis of DOAC use after bariatric surgery was seriously limited by the low quality of the studies and lack of RCTs.[36]
rivaroxaban
apixaban
drug absorption
Bariatric surgeries might have some effect on the absorption of apixaban and possibly rivaroxaban, potentially impacting their clinical efficacy early post-surgery.[36]
Data about the efficacy and safety of DOACs are, however, emerging in recent years.[38]
Asian Ethnicity
Meta-Analysis of Six RCTs: DOACs vs VKAs[39]
Efficacy
Asian
OR 0.90
(95% CI 0.55-1.49)
Non-Asian
OR 0.92
(95% CI 0.78-1.08)
Bleeding reduction
Asian
OR 0.64
(95% C 0.51-0.80)
Non-Asian
OR 0.73
(95% CI 0.51-0.80)
Rivaroxaban and edoxaban are efficacious and safe for East Asian patients with acute VTE.[40,41]
J-EINSTEIN and sub-analysis of HOKUSAI-VTE
High and Low Body Weight
Prospective observational study shows no association between high BMI and DOACs' efficacy or safety.[34]
RCTs did not include patients <45kg or >150kg or BMI>45kg/m2
Subgroup analyses and meta-analyses of RCTs on DOACs in patients with extreme body weight[35,37]
RECOVER, RECOVER-II, EINSTEIN DVT & PE, HOKUSAI-VTE, AMPLIFY
Apixaban & rivaroxaban have similar safety and efficacy compared with warfarin or enoxaparin/warfarin
Less is known about dabigatran or edoxaban
Pregnancy
Apixaban, rivaroxaban, and dabigatran can cross the placenta.[42,43]
Most professional societies do not recommend their use during pregnancy.
Of 336 DOACs exposed pregnancies[44]
6.25%
Fetal abnormalities
No bleeding events
22%
(95% CI 17.7-26.8)
Miscarriage rates[44,45]
Breastfeeding
DOACs are generally not advised for use during breastfeeding.
Dabigatran and rivaroxaban are minimally excreted in breast milk.[46,47]
If used, monitoring infant for bleeding is advised due to limited data.
Apixaban has high levels in breast milk.[46]
Milk/Plasma ratio: 2.61 (safe <1)

CAPSULE 7


Guidelines
Acute, extended-duration, and cancer-associated VTE
Guidelines suggest DOACs can be used for the management of acute VTE, extended-duration VTE, and cancer-associated VTE.[4,48-49]
Thrombotic APS
Existing guidelines advised against using DOACs for those with triple-positive APS or past arterial thrombosis, But this was before the recent meta-analysis of RCTs that showed excess risk of arterial thrombotic events, irrespective of triple positivity[26].
Luminal Gastrointestinal Cancer
ISTH Guidance, 2018[50]
LMWH is recommended for high-bleeding-risk patients, including those with luminal gastrointestinal cancer, with rivaroxaban and edoxaban as alternatives if no drug interactions are present. This guidance predates key post-2018 RCTs.
ESC Guidelines, 2022[51]
DOACs are suggested for managing cancer-associated VTE; however, there is a noted risk of clinically relevant non-major bleeding in luminal cancers. The publication was released following the Caravaggio trial.
Bariatric Surgery
ISTH Guidance, 2021[37]
(Primarily based on expert consensus in the setting of limited high-quality data)
Avoid DOACs in acute phase post-bariatric surgery
Emerging data, 2023
Emerging RCT data on rivaroxaban in bariatric surgery patients appears promising, though direct comparisons to other anticoagulants are limited.[38]
The recommendations may warrant re-evaluation in light of this emerging data.
Splanchnic vein thrombosis
ISTH Guidance, 2020[52]
(Primarily based on expert consensus in the setting of limited high-quality data)
Non-cirrhotic patients without active bleeding
Full-dose DOACs are suggested as the treatment of choice for symptomatic acute SpVT, including cancer-related cases.
3-6 months, or longer
Minimum treatment duration for acute symptomatic acute SpVT, regardless of thrombosis progression or persistent risk factors.
Cerebral venous sinus thrombosis
AHA/ASA statement, 2011[53]
Warfarin (or other VKAs) with an INR of 2-3 was recommended, with no mention of DOACs. No more recent guideline has been published since then.
Catheter-associated deep vein thrombosis
ASH Guideline, 2021[49]
(Primarily based on expert consensus in the setting of limited high-quality data)
The guideline mentions anticoagulant treatment for CVC-related VTE but does not specify DOACs or LMWH.

CAPSULE 8


Future Directions and Research Priorities
Future Directions ???
Examine why DOACs, compared to standard treatment, are less efficacious or safe in certain conditions:
EFFICACY
Investigating DOACs in thrombotic antiphospholipid syndrome
Do DOACs have limitations in treating thrombotic APS due to their specific factor targets?
VKAs
DOACs
Can higher doses of DOACs overcome these limitations?
RISAPS trial54
SAFETY
Examining safety concerns of DOACs in patients with luminal gastrointestinal/ genitourinary cancer
Apixaban might be acceptable
Research Priorities
Role of DOACs
Catheter-associated DVT
Cerebral venous sinus thrombosis
Splanchnic vein thrombosis
Advanced chronic renal dysfunction
Thrombocytopenia
Bariatric surgery
Asian ethnicity
Extremes of high and low body weight
(if possible) Pregnancy
(if possible) Breastfeeding
CNS lesions
Breakthrough recurrent VTE
Duration and Intensity
Cancer associated VTE55
Provoked VTE with enduring risk factors: HI-PRO trial56
Role of Other Agents
Factor XI, XIa inhibitors and other agents:
Treatment of gastrointestinal or genitourinary cancer-associated VTE
MAGNOLIA57
RCT
Abelacimab
Dalteparin
ASTER
RCT
Abelacimab
Apixaban

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