Saudi MoH Protocol for

Vaccine-Induced Thrombosis and Thrombocytopenia (VITT)

(Version 1), 17/04/2021

Disclaimer: **This is a living guidance that is subject to change as more evidence accumulates. It will be updated regularly and whenever needed.**

INTRODUCTION:

- Vaccines are important for managing the COVID-19 pandemic caused by SARS-CoV-2.
- Reports have emerged of some vaccine recipients developing unusual thrombotic events and thrombocytopenia.
- Between Dec 2020 and Mar 2021, European Medical Agency approved 4 vaccines:
  - BNT162b2, mRNA encoding spike protein antigen encapsulated in lipid nanoparticle
  - mRNA-1273, encoding spike protein antigen encapsulated in lipid nanoparticle.
  - ChAdOx1 nCov-19, a recombinant chimpanzee adenoviral vector encoding spike glycoprotein.
  - Ad26.COV2.S, a recombinant adenovirus type 26 vector encoding spike glycoprotein.
- First cases of thrombosis with thrombocytopenia reported in Feb/Mar 2021 with ~15-20M doses.
- **Because of the rarity of these events and the potential severity of COVID-19, the European Medicines Agency (EMA) concluded that the overall benefits of the vaccine continue to outweigh the risk.**
- The WHO stated that a causal relationship, while plausible*, has not been confirmed*, and that the very rare incidence should be weighed against the risk of morbidity from COVID-19.
- Covid-19 vaccine induced thrombosis and thrombocytopenia (VITT) is a very rare complication following vaccine exposure.
- Some experts have suggested that these events could be related to vaccine-induced autoantibodies directed against a PF4 platelet antigen, similar to those associated with heparin-induced thrombocytopenia (HIT).
- Typical presentation is 4-28 days following administration of vaccine.
- Recipients of any vaccine should be aware of the possible association and seek immediate care for signs and symptoms suggestive of thrombocytopenia (petechiae around the vaccination site after several days) or thrombotic complications (including shortness of breath, chest pain, lower extremity edema, persistent abdominal pain, unabating severe headache, focal neurologic symptoms, and seizures).
- Among approximately 34 million vaccine recipients in the United Kingdom and European Economic Area, there were 169 cases of cerebral venous sinus thrombosis (CVST) and 53 cases of splanchnic vein thrombosis reported through safety surveillance systems however, VTE occurring in other sites cannot be excluded.

EVALUATION:

- Any patient with unusual symptoms within 28 days of receiving vaccine with symptoms of VITT (persistent and severe headache; focal neurological symptoms (including blurred vision); shortness of breath; abdominal or chest pain; swelling and redness in a limb; or pallor and coldness in a limb should be assessed by health care provider and should report to SFDA.
- Patients with severe symptoms should urgently seek medical attention at their nearest emergency department.

DIAGNOSIS:

- 'Diagnosis of exclusion' as there is currently no validated confirmatory assay.
- Timing of vaccine (4 – 28 days prior to presentation).
- Unexplained platelet count less than 150x 10^9/L or <50% from baseline (BL)
- No LMWH/UFH exposure or history of HIT.
- Other causes of DIC or thrombocytopenia excluded.
- Demonstration of PF4-dependent antibodies essential.
- HIT ELISA is sensitive but nonspecific.
- Non-ELISA HIT assays are neither sensitive nor specific, and false positive rates are not yet known.
- Functional assay required to confirm presence of platelet-activating antibodies.

DEFINITIONS:

UNLIKELY CASE:

1. If symptoms of VTE or arterial ischemia+/-Thrombocytopenia fall outside of the 4 to 28 day time frame and alternative cause for thrombocytopenia and/or thrombosis (TTP, DIC, atypical HUS, PNH, medications or malignancy) present.

POSSIBLE CASE:

1. Onset of symptoms between 4-28 days after vaccination.
2. Symptoms of VITT (Acute thrombosis and new onset thrmbocytopenia).

PROBABLE CASE:

1. Onset of symptoms between 4-28 days after vaccination.
2. Platelets <150x 10^9/L or <50% from baseline .
3. Low or normal fibrinogen.

4. Evidence of thrombosis and D-Dimer 2-4mcg/mL or D-Dimer >4mcg/mL .

CONFIRMED CASE:

1. Onset of symptoms between 4-28 days after vaccination.
2. Platelet count <150 x10^9/L or <50% from baseline.
3. D-Dimers >4 mcg/mL or between (2-4 mcg/mL) +/- inappropriately low fibrinogen.
4. Confirmed cerebral venous thrombosis (CVT), splanchnic venous thrombosis or other sites of VTE as well as arterial ischemia may also occur.
5. Positive ELISA HIT assay.

*Note: If there is high index of clinical suspicion but PF4 antibodies (HIT ELISA assay) are negative, send serum and EDTA for HIPA testing for confirmation

Management of a **PROBABLE CASE / CONFIRMED CASE** –

- **Probable case should be managed as confirmed case while awaiting confirmatory diagnosis**

1. Rule out heparin exposure and other causes of DIC/thrombocytopenia.
2. Collect sample for HIT ELISA assay and notify lab of suspected VIPIT.
3. GIVE intravenous immunoglobulin (IVIG) urgently: 1g/kg IV for 2 days irrespective of the degree of thrombocytopenia and review clinical course.
4. AVOID platelet transfusions.
5. Consult Hematology.
6. ANTICOAGULATE with non-heparin-based therapies such as fondaparinux, argatroban, **(refer to HIT protocol)** or DOACs**.**
7. Plasma exchange may also be considered.
8. Antiplatelet agents are not recommended based on current experience.
9. If no overt thrombosis, but thrombocytopenia with raised D Dimer, thromboprophylaxis with nonheparin-based anticoagulants should be considered (DOAC or fondaparinux) can be used.

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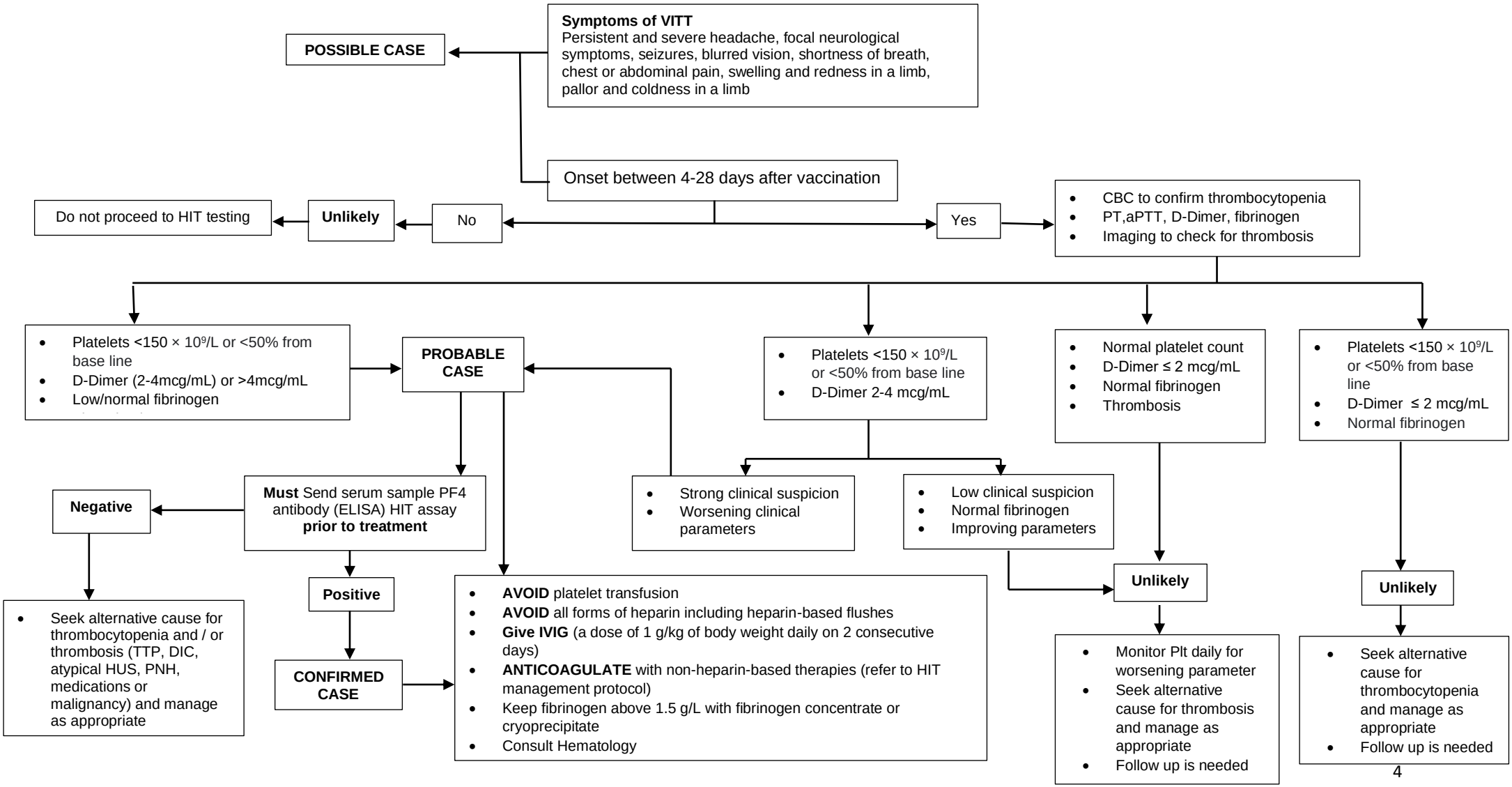

Medication Related Information				
Medication	**Contraindication**	**Major Drug Interactions**	**Required dose adjustment**	**Pregnancy**
Intravenous Immunoglobulin (IVIG) **Dose: 1g/kg/day for 2 days**	- Anaphylactic or severe systemic reaction to human immune globulin - IgA-deficient patients with antibodies against IgA and history of hypersensitivity to human immune globulin treatment	- To Consider therapy modification. o Vaccines (Live): Immune Globulins may diminish the therapeutic effect of Vaccines (Live). Management: Consult full interaction monograph for dose interval recommendations. This interaction does not apply to oral Ty21a typhoid vaccine or others listed as exceptions.	- Dosing: Renal Impairment: Adult IV: Use with caution due to risk of immune globulin-induced renal dysfunction; the rate of infusion and concentration of solution should be minimized. Discontinue if renal function deteriorates during treatment. IM: There are no dosage adjustments provided in the manufacturer's labeling. SubQ infusion: There are no dosage adjustments provided in the manufacturer's labeling; consider lower, more frequent dosing. - Dosing: Hepatic Impairment: Adult IM, IV, SubQ infusion: There are no dosage adjustments provided in the manufacturer's labeling. - Dosing: Obesity: Adult Some clinicians dose IGIV on ideal body weight or an adjusted ideal body weight in	- Placental transfer of human IgG is dependent upon the IgG subclass and gestational age, - Exogenous immune globulin was shown to cross the placenta similar to endogenous immune globulin.

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			morbidly obese patients (Siegel 2010).	
Fondaparinux (first line) **Dose:** **(2.5 mg/0.5 mL,** **5 mg/0.4 mL** **7.5 mg/0.6 mL** **and** **10 mg/0.8 mL)** **injection.**	- Active major bleeding - Body weight less than 50 kg in patients requiring prophylaxis for venous thromboembolism - History of serious hypersensitivity reaction (eg, angioedema, anaphylactoid or anaphylactic reactions) - Severe renal impairment (ie, CrCl less than 30 mL/minute) Thrombocytopenia associated with positive in vitro test for antiplatelet antibody in the presence of fondaparinux sodium	• Avoid combination ○ Apixaban: May enhance the anticoagulant effect of Anticoagulants. ○ Dabigatran Etexilate: May enhance the anticoagulant effect of Anticoagulants. ○ Edoxaban: May enhance the anticoagulant effect of Anticoagulants ○ Hemin: May enhance the anticoagulant effect of Anticoagulants. ○ Mifepristone: May enhance the adverse/toxic effect of Anticoagulants. ○ Omacetaxine: Anticoagulants may enhance the adverse/toxic effect of Omacetaxine. ○ Rivaroxaban: Anticoagulants may enhance the anticoagulant effect of Rivaroxaban. ○ Urokinase: May enhance the anticoagulant effect of Anticoagulants. ○ Vorapaxar: May enhance the adverse/toxic effect of Anticoagulants. • To Consider therapy modification. ○ Desirudin: Discontinue treatment with other anticoagulants prior to desirudin initiation. If concomitant use cannot be avoided, monitor patients receiving these combinations closely for clinical and laboratory evidence of excessive anticoagulation. ○ Estrogen Derivatives: Carefully weigh the prospective benefits of estrogens against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations. ○ Herbs (Anticoagulant/Antiplatelet Properties): Avoid such combinations when possible. If used concomitantly, increase diligence in monitoring for adverse effects (eg, bleeding, bruising, altered mental status due to CNS bleeds). Progestins: Carefully weigh the prospective benefits of progestins against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations.	- Renal impairment, CrCl 30 to 50 mL/min: Use with caution (manufacturer dosing) - Renal impairment, CrCl 20 to 50 mL/min (VTE prophylaxis): 1.5 mg subQ once daily starting 6 hours or more (ideally 8 hours) postoperatively for10 days for total hip or knee replacement or 28 to 35 days for hip fracture surgery (study dosing) - Geriatric: Use with caution - Hemodiafiltration in patients with heparin-induced thrombocytopenia: Initiate at 0.03 mg/kg postdialysis body weight, administered via the efferent line of the dialyzer; titrate in increments of 0.01 mg/kg postdialysis body weight based on postdialysis anti-Xa activity (study dosing)	Pregnancy Considerations Based on case reports, small amounts of fondaparinux have been detected in the umbilical cord following multiple doses during pregnancy (Dempfle2004). Use of fondaparinux in pregnancy should be limited to those women who have severe allergic reactions to heparin, including heparin-induced thrombocytopenia, and who cannot receive danaparoid (Guyatt 2012).

Medication Related Information

Medication	Contraindication	Major Drug Interactions	Required dose adjustment	Pregnancy
			- Body weight less than 50 kg (VTE prophylaxis): Contraindicated - Body weight less than 50 kg (VTE treatment): Use with caution - Body weight greater than 100 kg (DVT treatment): 10 mg subQ daily (guideline dosing)	
Argatroban (second line)(when fondaparinux is contraindicated) (Refer to nomogram for doses)	- Hypersensitivity to argatroban or to any component of the product - Major bleeding	○ Apixaban: May enhance the anticoagulant effect of Anticoagulants. ○ Dabigatran Etexilate: May enhance the anticoagulant effect of Anticoagulants ○ Edoxaban: May enhance the anticoagulant effect of Anticoagulants ○ Hemin: Hemin may enhance the anticoagulant effect of Anticoagulants ○ Mifepristone: MiFEPRIStone may enhance the adverse/toxic effect of Anticoagulants. Specifically, the risk of bleeding may be increased. ○ Omacetaxine: Anticoagulants may enhance the adverse/toxic effect of Omacetaxine. ○ Rivaroxaban: Anticoagulants may enhance the anticoagulant effect of Rivaroxaban. ○ Urokinase: May enhance the anticoagulant effect of Anticoagulants. ○ Vorapaxar: May enhance the adverse/toxic effect of Anticoagulants. • To Consider therapy modification. ○ Desirudin: Anticoagulants may enhance the anticoagulant effect of Desirudin. Management: Discontinue treatment with other anticoagulants prior to desirudin initiation. If concomitant use cannot be avoided, monitor patients receiving these combinations closely for clinical and laboratory evidence of excessive anticoagulation. ○ Estrogen Derivatives: Carefully weigh the prospective benefits of estrogens against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations. ○ Herbs (Anticoagulant/Antiplatelet Properties): Avoid such combinations when possible. If used concomitantly, increase diligence in monitoring for adverse effects (eg, bleeding, bruising, altered mental status due to CNS bleeds). ○ Progestins: Carefully weigh the prospective benefits of progestins against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations.	- Hepatic impairment (moderate to severe, Child-Pugh class B and C) in heparin-induced thrombocytopenia (HIT): Avoid use or use a reduced dose. - In patients with bilirubin of greater than 1.5 mg/dL, use a dose of 0.5 to 1.2 mcg/kg/min. Adjust aPTT to 1.5 to 3 times baseline - Hepatic impairment (moderate to severe) in (HIT): Initial dose 0.5 mcg/kg/min; monitor aPTT closely and adjust dosage as clinically indicated. Achievement of steady state aPTT levels may take longer and require more dose adjustments in patients with hepatic impairment	Pregnancy Considerations Information related to Argatroban in pregnancy is limited. Use of parenteral direct thrombin inhibitors in pregnancy should be limited to those women who have severe allergic reactions to heparin, including heparin-induced thrombocytopenia, and who cannot receive danaparoid (Guyatt 2012).

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			compared to patients with normal hepatic function - Hepatic impairment in percutaneous coronary intervention (PCI): Avoid use with clinically significant hepatic disease or AST/ALT levels 3 or more times the ULN. In other patients, titrate carefully until the desired level of anticoagulation is achieved - Critically ill patients without organ failure in HIT: Initial, 1 mcg/kg/min - Critically ill patients with multiple organ failure or heart failure in HIT: Initial, 0.5 to 0.6 mcg/kg/min - Critically ill patients with multiple organ failure in HIT: Initial, 0.2 mcg/kg/min - Heart failure, multiple organ system failure, or severe anasarca, or post-cardiac surgery in HIT: Initial, 0.5 to 1.2 mcg/kg/min	

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			- Obesity (BMI up to 51 kg/m(2)): No dosing adjustment required when actual body weight-based dosing to target coagulation response is utilized	
Bivalirudin (Restricted for PCI patient with HIT)	- Active major bleeding - Hypersensitivity to bivalirudin or its components - Acute gastric or duodenal ulcer - Cerebral hemorrhage - Bacterial endocarditis - Diabetic or hemorrhagic retinopathy - Proximal use of spinal/epidural anesthesia	• Avoid combination. ○ Apixaban: May enhance the anticoagulant effect of Anticoagulants. ○ Dabigatran Etexilate: May enhance the anticoagulant effect of Anticoagulants. ○ Edoxaban: May enhance the anticoagulant effect of Anticoagulants. ○ Hemin: May enhance the anticoagulant effect of Anticoagulants. ○ Mifepristone: May enhance the adverse/toxic effect of Anticoagulants. ○ Omacetaxine: Anticoagulants may enhance the adverse/toxic effect of Omacetaxine. ○ Rivaroxaban: Anticoagulants may enhance the anticoagulant effect of Rivaroxaban. ○ Urokinase: May enhance the anticoagulant effect of Anticoagulants ○ Vorapaxar: May enhance the adverse/toxic effect of Anticoagulants. • To Consider therapy modification. ○ Desirudin: Discontinue treatment with other anticoagulants prior to desirudin initiation. If concomitant use cannot be avoided, monitor patients receiving these combinations closely for clinical and laboratory evidence of excessive anticoagulation. ○ Estrogen Derivatives: Carefully weigh the prospective benefits of estrogens against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations. ○ Herbs (Anticoagulant/Antiplatelet Properties): Avoid such combinations when possible. If used concomitantly, increase diligence in monitoring for adverse effects (eg, bleeding, bruising, altered mental status due to CNS bleeds). ○ Progestins: Carefully weigh the prospective benefits of progestins against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations.	- Renal impairment (CrCl less than 30 mL/min): Reduce infusion rate to 1 mg/kg/hr; monitor the anticoagulant status more frequently - Hemodialysis: Reduce infusion rate to 0.25 mg/kg/hr; no bolus dose reduction is necessary - Obesity: The actual measured body weight (total body weight) should be used for dose calculations, according to a retrospective review in patients with heparin-induced thrombocytopenia (HIT) (n=135); in the obese group, the mean total body weight was 105 +/- 21.2 kg (range, 78 to 176 kg) and mean BMI 37.7 +/- 6.7 kg/m(2) (range, 30.1 to 56.2 kg/m(2))	Pregnancy Considerations Bivalirudin is used in conjunction with aspirin, which may lead to maternal or fetal adverse effects, especially during the third trimester. Use of parenteral direct thrombin inhibitors in pregnancy should be limited to those women who have severe allergic reactions to heparin, including heparin-induced thrombocytopenia, and who cannot receive danaparoid (Guyatt 2012).

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Apixaban	- Active pathological bleeding - Severe hypersensitivity (eg, anaphylactic reactions) to apixaban	• Avoid combination. ○ Anticoagulants: Apixaban may enhance the anticoagulant effect of Anticoagulants. ○ Dabigatran Etexilate: May enhance the anticoagulant effect of Anticoagulants. ○ Edoxaban: May enhance the anticoagulant effect of Anticoagulants. ○ Hemin: May enhance the anticoagulant effect of Anticoagulants. ○ Inducers of CYP3A4 (Strong) and P-glycoprotein: May decrease the serum concentration of Apixaban ○ MiFEPRIStone: May enhance the adverse/toxic effect of Anticoagulants. ○ Omacetaxine: Anticoagulants may enhance the adverse/toxic effect of Omacetaxine. ○ Rivaroxaban: Anticoagulants may enhance the anticoagulant effect of Rivaroxaban. ○ St John's Wort: May decrease the serum concentration of Apixaban. ○ Urokinase: May enhance the anticoagulant effect of Anticoagulants. ○ Vorapaxar: May enhance the adverse/toxic effect of Anticoagulants. • To Consider therapy modification. ○ Antiplatelet Agents (P2Y12 Inhibitors): Carefully consider risks and benefits of this combination and monitor closely; Canadian labeling recommends avoiding prasugrel or ticagrelor. ○ Aspirin: Carefully consider risks and benefits of this combination and monitor closely. ○ CYP3A4 Inducers (Strong): Avoid concurrent use of apixaban with strong CYP3A4 inducers whenever possible. Use of a strong CYP3A4 inducer with apixaban should be strictly avoided in any patient who is using an agent (either the CYP3A4 inducer or a third drug) that induces P-gp. ○ Estrogen Derivatives : Carefully weigh the prospective benefits of estrogens against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations. ○ Fusidic Acid (Systemic): Consider alternatives to this combination when possible. Apixaban dose adjustments may be required when used with systemic fusidic acid. Patients using this combination should be monitored extra closely. ○ Herbs (Anticoagulant/Antiplatelet Properties): Avoid such combinations when possible. If used concomitantly, increase diligence in monitoring for adverse effects (eg, bleeding, bruising, altered mental status due to CNS bleeds). ○ Inhibitors of CYP3A4 (Strong) and P-glycoprotein : US labeling recommends a 50% apixaban dose reduction in patients who would otherwise receive 5 or 10 mg twice daily, and avoiding in patients who would otherwise receive 2.5 mg twice daily. Canadian labeling lists any combined use as contraindicated.	- Renal impairment in nonvalvular atrial fibrillation: 2.5 mg orally twice daily in patients with at least 2 of the following characteristics, age 80 years or older, body weight 60 kg or less, or serum creatinine 1.5 mg/dL (133 mcmol/L) or higher - Renal impairment in DVT prophylaxis following hip or knee replacement, or DVT or pulmonary embolism (PE) treatment or secondary prophylaxis: No dosage adjustment is necessary - Hepatic impairment (mild, Child-Pugh class A): No dosage adjustment necessary - Hepatic impairment (moderate, Child-Pugh class B): Dosing recommendations are not provided, as the impact on the coagulation cascade and its relationship to efficacy and bleeding is not clearly understood in patients with moderate impairment	Based on placenta perfusion studies, apixaban is expected to cross the placenta. Information specific to the use of apixaban in pregnancy is limited there is potential for fetal bleeding or subclinical placental bleeding which may increase the risk of miscarriage, preterm delivery, fetal compromise, or stillbirth Data are insufficient to evaluate the safety of direct acting oral anticoagulants during pregnancy and use in pregnant patients is not recommended (ACOG 2018; Regitz-Zagrosek [ESC 2018]).

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		○ Naproxen: A comprehensive risk to benefit assessment should be done for all patients before any concurrent use of apixaban and naproxen. If combined, monitor patients extra closely for signs and symptoms of bleeding. ○ Nonsteroidal Anti-Inflammatory Agents (Nonselective): A comprehensive risk to benefit assessment should be done for all patients before any concurrent use of apixaban and nonsteroidal anti-inflammatory drugs (NSAIDs). If combined, monitor patients extra closely for signs and symptoms of bleeding ○ Progestins: Carefully weigh the prospective benefits of progestins against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations.	- Hepatic impairment (severe, Child-Pugh class C): Not recommended - Dialysis in DVT prophylaxis following hip or knee replacement, or treatment or secondary prophylaxis of DVT or pulmonary embolism (PE): No dosage adjustment is necessary - Hemodialysis in stroke prevention: In a pharmacokinetics study, 2.5 mg twice daily resulted in drug exposure comparable to 5 mg twice daily in patients with preserved renal function - Geriatric in nonvalvular atrial fibrillation: 2.5 mg orally twice daily in patients with at least 2 of the following characteristics, age 80 years or older, body weight 60 kg or less, or serum creatinine 1.5 mg/dL (133 mcmol/L) or higher - Body weight 60 kg or less in nonvalvular atrial fibrillation: 2.5 mg orally twice daily in patients	

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			with at least 2 of the following characteristics, age 80 years or older, body weight 60 kg or less, or serum creatinine 1.5 mg/dL (133 mcmol/L) or higher - Combined P-glycoprotein and strong CYP3A4 inhibitor (eg, ketoconazole, itraconazole, ritonavir): Decrease dosage by 50% for patients receiving apixaban doses greater than 2.5 mg orally twice daily; avoid coadministration in patients already receiving apixaban 2.5 mg twice daily	
Warfarin	- Blood dyscrasias - Cerebral aneurysms - CNS hemorrhage - Dissecting aorta - Eclampsia, preeclampsia, threatened abortion - Gastrointestinal, genitourinary, or respiratory tract	• Avoid combination. ○ Hemin: May enhance the anticoagulant effect of Anticoagulants. ○ MiFEPRIStone : May enhance the adverse/toxic effect of Vitamin K Antagonists. ○ Omacetaxine : Anticoagulants may enhance the adverse/toxic effect of Omacetaxine. ○ Oxatomide: May enhance the anticoagulant effect of Vitamin K Antagonists. ○ Streptokinase: May enhance the anticoagulant effect of Vitamin K Antagonists. ○ Tamoxifen : May increase the serum concentration of Vitamin K Antagonists. ○ Urokinase: May enhance the anticoagulant effect of Anticoagulants. ○ Vorapaxar: May enhance the adverse/toxic effect of Anticoagulants. • To Consider therapy modification.	- Renal impairment: No adjustment necessary; monitor INR more frequently in patients with compromised renal function to maintain INR within the therapeutic range - Geriatric: Consider using lower initial and maintenance dosage - Asian patients: Consider using lower initial and maintenance dosage	Use is contraindicated during pregnancy except in patients with mechanical heart valves who are at high risk for thromboembolism; use is also contraindicated in patients with threatened abortion, eclampsia, or preeclampsia.

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Medication	**Contraindication**	**Major Drug Interactions**	**Required dose adjustment**	**Pregnancy**
	ulcerations or overt bleeding -Hemorrhagic tendencies - Hypersensitivity to warfarin or any component of the product - Major regional or lumbar block anesthesia - Malignant hypertension - Pericarditis and pericardial effusion - Pregnancy, except in pregnant women with mechanical heart valves, who are at high risk of thromboembolism - Recent or potential surgery of central nervous system or eye - Recent or potential traumatic surgery	○ Allopurinol: Monitor for increased prothrombin times (PT)/therapeutic effects of oral anticoagulants if allopurinol is initiated/dose increased, or decreased effects if allopurinol is discontinued/dose decreased. Reductions in coumarin dosage will likely be needed. ○ Amiodarone: Monitor patients extra closely for evidence of increased anticoagulant effects if amiodarone is started. Consider empiric reduction of 30% to 50% in warfarin dose, though no specific guidelines on dose adjustment have been published. ○ Androgens: Monitor for increased effects of vitamin K antagonists if an androgen is initiated/dose increased, or decreased effects if androgen is discontinued/dose decreased. Significant reductions in vitamin K antagonist dose are likely required. ○ Barbiturates: Monitor INR more closely. Anticoagulant dose increases of 30% to 60% may be needed after a barbiturate is initiated or given at an increased dose. Anticoagulant dose decreases may be needed following barbiturate discontinuation or dose reduction. ○ CarBAMazepine: Monitor for decreased INR and effects of vitamin K antagonists if carbamazepine is initiated/dose increased, or increased INR and effects if carbamazepine is discontinued/dose decreased. Vitamin K antagonist dose adjustments will likely be required. ○ Cholestyramine Resin: Separate the administration of vitamin K antagonists and cholestyramine by at least 3 to 4 hours. Monitor patients closely for reduced vitamin K antagonist effects (eg, decreased INR, thrombosis) when these agents are combined. ○ Cimetidine: Avoid coadministration of cimetidine and vitamin K antagonists. If unavoidable, monitor for increased effects of vitamin K antagonists when cimetidine is initiated/dose increased, or decreased effects if cimetidine is discontinued/dose decreased. ○ Desirudin: Discontinue treatment with other anticoagulants prior to desirudin initiation. If concomitant use cannot be avoided, monitor patients receiving these combinations closely for clinical and laboratory evidence of excessive anticoagulation. ○ Enzalutamide: Avoid concurrent use of vitamin K antagonists and enzalutamide when possible. If combined, monitor for reduced vitamin K antagonist effects (ie, decreased INR, thrombosis) and increase vitamin K antagonist doses as needed. ○ Estrogen Derivatives : Carefully weigh the prospective benefits of estrogens against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations.	- INR; single out of range value, below or above the therapeutic INR by 0.5 or less, continue current warfarin dose and test INR within 1 to 2 weeks - Bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy): May require approximately 25% reduction in daily dosage in the postoperative period - Discontinuing therapy: Abrupt discontinuation is suggested rather than gradual tapering of the dose (ACCP guidelines) - Postpartum: Women who require more than 6 weeks of postpartum anticoagulation may be initiated on warfarin (initial dose, 5 mg daily for 2 days, then adjusted per INR) and bridged with adjusted-dose low-molecular-weight heparin (LMWH) or unfractionated heparin (UFH) until INR is in the therapeutic range of 2 to 3 for 2 days, or a direct oral anticoagulant if not breastfeeding. For	Use of warfarin during the first trimester may be considered if the therapeutic INR can be achieved with a dose ≤5 mg/day. Alternately, adjusted-dose low molecular weight heparin or adjusted-dose heparin may be used until after the first trimester, when therapy can be changed to warfarin, if required. Warfarin should be discontinued and changed to heparin at least 1 week prior to delivery (ACC/AHA [Otto 2021]). Consult current recommendations for appropriate use in pregnancy.

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	resulting in large open surface - Spinal puncture and other procedures with potential for uncontrollable bleeding - Unsupervised and potentially noncompliant patients	○ Estrogen Derivatives (Contraceptive): Avoid coadministration of estrogen-containing contraceptives and vitamin K antagonists. Consider nonhormonal methods of contraception in patients requiring vitamin K antagonists. If combined, monitor for changes in coagulation status. ○ Ethotoin: Anticoagulant dose adjustment will likely be necessary when ethotoin is initiated or discontinued. Monitor patients extra closely (INR and signs/symptoms of bleeding) when using this combination. ○ Fenofibrate and Derivatives: Monitor for signs and symptoms of bleeding, and increase INR monitoring in patients taking warfarin who are initiated on fenofibrate derivatives. Warfarin dose reductions will likely be required ○ Fenugreek: Seek alternatives to fenugreek in patients receiving vitamin K antagonists. Monitor patients receiving these combinations closely for increases in INR and systemic effects of the vitamin K antagonist (particularly easy bruising and bleeding). ○ Fibric Acid Derivatives: Consider reducing the oral anticoagulant dose by 25% to 33% when initiating a fibric acid derivative. Monitor for toxic or reduced anticoagulant effects if a fibric acid derivative is initiated/dose increased, or discontinued/dose decreased, respectively ○ Fluconazole: Consider reducing the vitamin K antagonist dose by 10% to 20% if combined with fluconazole. Monitor for increased anticoagulant effects (ie, increased INR, bleeding) to guide further dose adjustments. ○ Fluorouracil Products: Monitor INR and for signs/symptoms of bleeding closely when a fluorouracil product is combined with a vitamin K antagonist (eg, warfarin). Anticoagulant dose adjustment will likely be necessary ○ Fosphenytoin: Anticoagulant dose adjustment will likely be necessary when phenytoin is initiated or discontinued. Monitor patients extra closely (INR and signs/symptoms of bleeding) when using this combination. ○ Fusidic Acid (Systemic): Vitamin K antagonist dose adjustments may be required when used with systemic fusidic acid. Patients using this combination should be monitored extra closely for evidence of bleeding and to determine appropriate dose. ○ Ginkgo Biloba: Consider avoiding the use of this combination of agents. Monitor for signs and symptoms of bleeding if vitamin K antagonists and Ginkgo biloba are used concomitantly. ○ Glutethimide: Consider avoiding glutethimide in patients receiving vitamin K antagonists. Monitor for reduced anticoagulant effects if glutethimide is initiated/dose increased or increased effects if glutethimide is discontinued/dose decreased.	women with mechanical heart valves, warfarin can be resumed 24 hours after delivery, with overlapping IV UFH (or LMWH) until therapeutic on warfarin - Pregnancy, mechanical valve: Warfarin to goal INR plus aspirin 75 mg to 100 mg/day during second and third trimesters; during first trimester, warfarin may be continued in patients who can achieve therapeutic INR with doses of 5 mg/day or less. Frequent monitoring required. Discontinue warfarin and initiate continuous infusion unfractionated heparin prior to planned vaginal delivery (guideline dosing)	

Medication Related Information				
Medication	**Contraindication**	**Major Drug Interactions**	**Required dose adjustment**	**Pregnancy**
		○ Herbs (Anticoagulant/Antiplatelet Properties): Avoid such combinations when possible. If used concomitantly, increase diligence in monitoring for adverse effects (eg, bleeding, bruising, altered mental status due to CNS bleeds). ○ Imatinib: Consider using low-molecular-weight heparin or heparin instead of warfarin. If warfarin and imatinib must be coadministrered, increase monitoring of INR and for signs/symptoms of bleeding. ○ Menatetrenone: Coadministration is not recommended. If concomitant use of menatetrenone and vitamin K antagonists cannot be avoided, monitor coagulation parameters, such as PT/INR. ○ MetroNIDAZOLE (Systemic): Consider alternatives to concomitant therapy with these agents. If concomitant therapy cannot be avoided, consider reducing the dose of the vitamin K antagonist and monitor for increased INR/bleeding ○ Miconazole (Topical): Avoid using any miconazole-containing preparation in patients who are taking warfarin. If coadministration is unavoidable, consider reducing warfarin dose 10% to 20% and monitor for increased warfarin effects (eg, INR, bleeding). ○ Nafcillin: Consider choosing an alternative antibiotic. Monitor for decreased therapeutic effects and need for dose adjustments of oral anticoagulants if nafcillin is initiated/dose increased, or increased effects if nafcillin is discontinued/dose decreased. ○ Nonsteroidal Anti-Inflammatory Agents (Nonselective): Consider alternatives to this combination when possible. If the combination must be used, monitor coagulation status closely and advise patients to promptly report any evidence of bleeding or bruising ○ Phenytoin: Anticoagulant dose adjustment will likely be necessary when phenytoin is initiated or discontinued. Monitor patients extra closely (INR and signs/symptoms of bleeding) when using this combination. ○ Progestins : Carefully weigh the prospective benefits of progestins against the potential increased risk of procoagulant effects and thromboembolism. Use is considered contraindicated under some circumstances. Refer to related guidelines for specific recommendations. ○ Progestins (Contraceptive): When possible, concomitant hormonal contraceptives and coumarin derivatives should be avoided in order to eliminate the risk of thromboembolic disorders. Consider using an alternative, nonhormonal contraceptive. ○ Rifamycin Derivatives: Monitor for reduced anticoagulant effects (ie, decreased INR, thromboembolic events) if a rifamycin derivative is initiated in a vitamin K antagonist treated patient. Vitamin K antagonist dose adjustments will likely be required.		

Medication Related Information				
Medication	**Contraindication**	**Major Drug Interactions**	**Required dose adjustment**	**Pregnancy**
		○ Salicylates : Avoid as needed use of salicylates in patients taking vitamin K antagonists. Aspirin (80 to 325 mg/day) may be used with warfarin for prevention of cardiovascular events. If coadministering salicylates and vitamin K antagonists, monitor for bledding. ○ Sodium Zirconium Cyclosilicate: Separate the administration of sodium zirconium cyclosilicate and warfarin by at least 2 hours. If simultaneous administration is required, monitor for signs and symptoms of warfarin toxicity (eg, elevated INR, bleeding). ○ SORAfenib: Warfarin dose adjustment will likely be necessary. Increase frequency of INR monitoring during sorafenib therapy (particularly when starting or stopping therapy), and increase monitoring for signs and symptoms of bleeding. ○ St John's Wort: Consider avoiding coadministration of St John's Wort and vitamin K antagonists. If combined, monitor for decreased anticoagulant therapeutic effects (eg, decreased INR, thromboembolic events) if St John's Wort is initiated/dose increased. ○ Sulfonamide Antibiotics: Consider reducing the vitamin K antagonist dose by 10% to 20% prior to starting the sulfonamide antibiotic. Monitor INR closely to further guide dosing.		

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