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.
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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 10⁹/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 thrombocytopenia).

PROBABLE CASE:
1. Onset of symptoms between 4-28 days after vaccination.
2. Platelets <150x 10⁹/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), splanchenic 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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**Symptoms of VITT**
Persistent and severe headache, focal neurological symptoms, seizures, blurred vision, shortness of breath, chest or abdominal pain, swelling and redness in a limb, pallor and coldness in a limb

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**Onset between 4-28 days after vaccination**

- Do not proceed to HIT testing
- **POSSIBLE CASE**
  - Unlikely
  - **Probable Case**
    - Platelets $<150 \times 10^9/L$ or $<50\%$ from base line
    - D-Dimer (2-4mcg/mL) or $>4$mcg/mL
    - Low/normal fibrinogen
  - **Confirmed Case**
    - Negative
      - Seek alternative cause for thrombocytopenia and /or thrombosis (TTP, DIC, atypical HUS, PNH, medications or malignancy) and manage as appropriate
    - Positive
      - AVOID platelet transfusion
      - AVOID all forms of heparin including heparin-based flushes
      - Give IVIG (a dose of 1 g/kg of body weight daily on 2 consecutive days)
      - ANTICOAGULATE with non-heparin-based therapies (refer to HIT management protocol)
      - Keep fibrinogen above 1.5 g/L with fibrinogen concentrate or cryoprecipitate
      - Consult Hematology

- Likely
  - **Probable Case**
    - Platelets $<150 \times 10^9/L$ or $<50\%$ from base line
    - D-Dimer 2-4 mcg/mL
  - **Confirmed Case**
    - Negative
      - Monitor Plt daily for worsening parameter
      - Seek alternative cause for thrombosis and manage as appropriate
      - Follow up is needed
    - Positive
      - Seek alternative cause for thrombocytopenia and manage as appropriate
      - Follow up is needed

**CBC to confirm thrombocytopenia**
- PT, aPTT, D-Dimer, fibrinogen
- Imaging to check for thrombosis
- Platelets $>150 \times 10^9/L$ or $<50\%$ from base line
- D-Dimer $\leq 2$ mcg/mL
- Normal fibrinogen
- No thrombosis

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**Unlikely**

**Possible Case**

- Monitor Plt daily for worsening parameter
- Seek alternative cause for thrombosis and manage as appropriate
- Follow up is needed

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**Confirmed Case**

- Send serum sample PF4 antibody (ELISA) HIT assay prior to treatment

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**Confirmed Case**

- AVOID platelet transfusion
- AVOID all forms of heparin including heparin-based flushes
- Give IVIG (a dose of 1 g/kg of body weight daily on 2 consecutive days)
- ANTICOAGULATE with non-heparin-based therapies (refer to HIT management protocol)
- Keep fibrinogen above 1.5 g/L with fibrinogen concentrate or cryoprecipitate
- Consult Hematology

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**Confirmed Case**

- Monitor Plt daily for worsening parameter
- Seek alternative cause for thrombosis and manage as appropriate
- Follow up is needed
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<td>Intravenous Immunoglobulin (IVIG)</td>
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- IgA-deficient patients with antibodies against IgA and history of hypersensitivity to human immune globulin treatment

- 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.

- Pregnancy

- Required dose adjustment

- Medication

- Contraindication

- Major Drug Interactions

- Required dose adjustment

- Pregnancy

- 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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| Fondaparinux (first line) | - Active major bleeding | - Avoid combination  
  - Apixaban: May enhance the anticoagulant effect of Anticoagulants.  
  - Darbepoetin: 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. | - 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 for 10 days for total hip or knee replacement or 28 to 35 days for hip fracture surgery (study dosing)  
- Geriatric: Use with caution  
- Hemodialfiltration 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 |
| 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. | - 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) | - 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. | 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 (Guyatt2012). |
| Thrombocytopenia associated with positive in vitro test for antiplatelet antibody in the presence of fondaparinux sodium |  |  |  |  |
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| Argatroban (second line) when fondaparinux is contraindicated | - Hypersensitivity to argatroban or to any component of the product | o Apixaban: May enhance the anticoagulant effect of Anticoagulants.  
o Dabigatran Exelilate: May enhance the anticoagulant effect of Anticoagulants  
o Edoxaban: May enhance the anticoagulant effect of Anticoagulants  
o Hemin: Hemin may enhance the anticoagulant 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. | - 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) | - 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. |

- 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.  
- 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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| Bivalirudin      | - 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.  
 o Apixaban: May enhance the anticoagulant effect of Anticoagulants.  
 o Dabigatran Eletilate: May enhance the anticoagulant effect of Anticoagulants.  
 o Edoxaban: May enhance the anticoagulant effect of Anticoagulants.  
 o Hemin: May enhance the anticoagulant effect of Anticoagulants.  
 o Mifepristone: May enhance the adverse/toxic effect of Anticoagulants.  
 o Omacetaxine: Anticoagulants may enhance the adverse/toxic effect of Omacetaxine.  
 o Rivaroxaban: Anticoagulants may enhance the anticoagulant effect of Rivaroxaban.  
 o Urokinase: May enhance the anticoagulant effect of Anticoagulants  
 o Vorapaxar: May enhance the adverse/toxic effect of Anticoagulants. | - Obesity (BMI up to 51 kg/m(2)): No dosing adjustment required when actual body weight-based dosing to target coagulation response is utilized  
 - 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  
  - MIFERPlStone: May enhance the adverse/toxic effect of Anticoagulants.  
  - Omacetaxine: May enhance the anticoagulant effect of Anticoagulants.  
  - Rivaroxaban: Anticoagulants may enhance the anticoagulant effect of Rivaroxaban.  
  - St John's Wort: May decrease the serum concentration of Apixaban.  
  - 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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<td><strong>Contraindication</strong></td>
<td><strong>Nonsteroidal Anti-Inflammatory Agents (Nonselective):</strong> A comprehensive risk 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.</td>
<td>- Hematocrit 0.5 (severe, Child-Pugh class C): Not recommended</td>
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<td><strong>Medication</strong></td>
<td><strong>Progestins:</strong> 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.</td>
<td>- 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</td>
<td>- 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</td>
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<tr>
<td><strong>Medication</strong></td>
<td><strong>Required dose adjustment</strong></td>
<td>- Body weight 60 kg or less in nonvalvular atrial fibrillation: 2.5 mg orally twice daily in patients</td>
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- Hepatic impairment (severe, Child-Pugh class C): Not recommended
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<td><strong>Warfarin</strong></td>
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<td>ulcerations or overt bleeding</td>
<td>o 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.</td>
<td>- 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</td>
<td>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.</td>
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<td>- Hemorrhagic tendencies</td>
<td>o 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.</td>
<td>- Bariatric surgery (Roux-en-Y gastric bypass or sleeve gastrectomy): May require approximately 25% reduction in daily dosage in the postoperative period</td>
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<td>- Hypersensitivity to warfarin or any component of the product</td>
<td>o 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.</td>
<td>- Discontinuing therapy: Abru</td>
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<td>- Major regional or lumbar block anesthesia</td>
<td>o 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.</td>
<td>pt discontinuation is suggested rather than gradual tapering of the dose (ACCP guidelines)</td>
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<td>- Malignant hypertension</td>
<td>o 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.</td>
<td>- 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</td>
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<td>- Pericarditis and pericardial effusion</td>
<td>o 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.</td>
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<td>- Pregnancy, except in pregnant women with mechanical heart valves, who are at high risk of thromboembolism</td>
<td>o 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.</td>
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<td>- Recent or potential surgery of central nervous system or eye</td>
<td>o 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.</td>
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<td>- Recent or potential traumatic surgery</td>
<td>o 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.</td>
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<td>o 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.</td>
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### Medication Related Information

<table>
<thead>
<tr>
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<td>Estrogen Derivatives (Contraceptive):</td>
<td>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.</td>
<td>- 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.</td>
<td>women with mechanical heart valves, warfarin can be resumed 24 hours after delivery, with overlapping IV UFH (or LMWH) until therapeutic on warfarin</td>
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<td>- Spinal puncture and other procedures with potential for uncontrollable bleeding</td>
<td>- Unsupervised and potentially noncompliant patients</td>
<td>- 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</td>
<td></td>
<td>- 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)</td>
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<tr>
<td>- Unsupervised and potentially noncompliant patients</td>
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<td>- 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).</td>
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<td>- Fibrin Acid Derivatives: Consider reducing the oral anticoagulant dose by 25% to 33% when initiating a fibrin acid derivative. Monitor for toxic or reduced anticoagulant effects if a fibrin acid derivative is initiated/dose increased, or discontinued/dose decreased, respectively</td>
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<td>- 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.</td>
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<tr>
<td>- 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 when combined with fluconazole.</td>
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<td>- 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.</td>
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<td>- 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.</td>
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<td>- 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.</td>
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<td>- 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.</td>
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# Saudi MoH Protocol for Vaccine-Induced Thrombosis and Thrombocytopenia (VITT)

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Saudi MoH Protocol for
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<td>Salicylates</td>
<td>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 bleeding.</td>
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<td>Sodium Zirconium Cyclosilicate</td>
<td>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).</td>
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<td>SORAFenib</td>
<td>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.</td>
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<td>St John's Wort</td>
<td>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.</td>
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<td>Sulfonamide Antibiotics</td>
<td>Consider reducing the vitamin K antagonist dose by 10% to 20% prior to starting the sulfonamide antibiotic. Monitor INR closely to further guide dosing.</td>
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References:
- UpToDate last access March 2021
- Micromedex last access March 2021
- Greinacher, A. Thrombotic Thrombocytopenia after ChAdOx1 nCov-19 Vaccination, NEJM, April 9, 2021
- Schultz, N. Thrombosis and Thrombocytopenia after ChAdOx1 nCoV-19 Vaccination, NEJM, April 9, 2021