OPTUMRx

Therapeutic Class Overview
Injectable Anticoagulants

INTRODUCTION

- Venous thromboembolism (VTE) can lead to significant health problems, which may become potentially fatal. It may occur in young, otherwise healthy adults, although it often occurs in patients who sustain multiple trauma(s), undergo major surgery, are immobile for a lengthy period of time, or have a hypercoagulable disorder (such as cancer). Due to clot formation within the venous circulation, VTE manifests as a stroke, deep vein thrombosis (DVT) and/or a pulmonary embolism (PE). The disease is often clinically silent, and death from PE can occur within minutes after the onset of symptoms, before treatment can be given (Blann et al, 2006).
- The estimated incidence of VTE is 300,000 to 600,000 annually. This estimate is considered to be an underestimate, however, due to missed or wrong diagnoses. The VTE incidence is similar or higher among African Americans and lower among Asian Americans and Native Americans. Most PE deaths are sudden and both DVTs and PEs are usually attributed to underlying disease (e.g., cancer, other chronic heart, lung, or renal disease). The 30-day VTE survival is 72% (DVT alone, 94.5%; PE with or without DVT, 55.6%) (Benjamin et al, 2017).
- Stroke also causes significant morbidity and mortality. Stroke is the fifth leading cause of death after heart disease, cancer, and chronic lower respiratory disease and injuries/accidents, in which more women die (approximately 60% of all US stroke deaths) from stroke every year than men. Each year, approximately 795,000 people experience a new or recurrent stroke. Of all strokes, 87% are ischemic, 10% are intracerebral hemorrhage (ICH) strokes, and 3% are subarachnoid hemorrhage (SAH) strokes (Benjamin et al, 2017).
- The injectable anticoagulants include ARIXTRA®, FRAGMIN®, LOVENOX® and unfractionated heparin (UFH) and, in general, are Food and Drug Administration (FDA)-approved for prophylaxis and/or treatment of VTE.
  - Certain agents in the class are also FDA-approved for the treatment of acute ST-segment elevation myocardial infarction (STEMI) or for prophylaxis of ischemic complications in unstable angina (UA) and non-Q-wave MI.
  - Additional labeled indications for use of UFH include disseminated intravascular coagulation, prophylaxis and treatment of arterial embolism, and use in blood transfusions, extracorporeal circulation, and dialysis procedures. Heparin is also used as an anticoagulant for several other off-label indications.
- UFH is a mucopolysaccharide molecule that ranges in molecular weight from 3,000 to 30,000 daltons. Its primary effect as an anticoagulant is a result of its binding to antithrombin which inhibits clot formation. Additional anticoagulant effects of UFH include inhibition of factors (F) IIa (thrombin), Xa, IXa, XIa, and XIIa (Garcia et al, 2012).
- FRAGMIN and LOVENOX are classified as low molecular weight heparins (LMWH) and exert their anticoagulant effect by binding to antithrombin, an endogenous inhibitor of various activated clotting factors, including FXa and thrombin.
  - LMWH is a smaller fragment of UFH that is formed by enzymatic or chemical depolymerization processes. The difference in the average size of LMWH (5,000 daltons) compared to UFH contributes to the pharmacologic differences between the agents. The LMWH agents primarily inhibit FXa, and do so with much less effect on thrombin compared to UFH. The inhibition of thrombin requires a heparin molecule to bind simultaneously to antithrombin and thrombin to form a ternary complex. The UFH molecules are large enough for this while the LMWH molecules typically are not (Hirsh et al, 2008; Weitz JI, 1997).
- Because the LMWH agents are prepared using different methods of depolymerization, they differ somewhat in their pharmacokinetic properties and anticoagulant profiles. Therefore, these agents are not clinically interchangeable (Hirsh et al, 2008).
- ARIXTRA is a synthetic, selective FXa inhibitor that was developed to have an increased affinity to antithrombin. Its specific anti-FXa activity is higher than that of the LMWH agents (Hirsh et al, 2008).
- Medispan class: Anticoagulants; Heparins and Heparinoid-like agents (intravenous [IV], inpatient-only formulations excluded.

Table 1. Medications Included Within Class Review

Drug	Manufacturer	FDA Approval Date	Generic Availability
ARIXTRA (fondaparinux)	Mylan	12/17/2001	✔
FRAGMIN (dalteparin)	Pfizer Inc	12/22/1994	-
HEPARIN SODIUM (unfractionated heparin)	Pfizer	Approved prior to Jan 1, 1982	✔
LOVENOX (enoxaparin)	Sanofi-Aventis US	03/29/1993	✔

(Drugs@FDA, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017)

INDICATIONS

- In general, the injectable anticoagulants are FDA-approved for prophylaxis and/or treatment of VTE. The labeled indications for ARIXTRA, FRAGMIN, and LOVENOX are more specific than the labeled indications for UFH. However, UFH is considered an option for a number of off-label uses, including UA, NSTEMI, STEMI, and bridging in patients with atrial fibrillation (AF) and mechanical heart valves, by various guidelines.
- For most indications, UFH is administered IV; however, the subcutaneous (SC) route can be used for prophylaxis and/or treatment of VTE.
- Both LOVENOX and FRAGMIN are approved for prophylaxis of ischemic complications in UA and non-Q-wave MI.
- FRAGMIN is the only LMWH agent that is not approved for the treatment of acute VTE, yet it is the only agent in the class that is approved for the extended treatment of symptomatic VTE in patients with cancer.

Table 2. Food and Drug Administration Approved Indications

Indication	ARIXTRA (fondaparinux)	FRAGMIN (dalteparin)	HEPARIN SODIUM (unfractionated heparin)	LOVENOX (enoxaparin)
Extended treatment of symptomatic VTE (proximal DVT and/or PE) in patients with cancer		✔ ‖		
Prophylaxis of ischemic complications in UA and non-Q-wave MI		✔ ¶		✔ ¶
Treatment of acute DVT	✔ ‡			✔ **
Treatment of acute PE	✔ ‡			
Treatment of acute STEMI				✔ §
Prophylaxis and treatment of venous thrombosis and PE			✔	
Prophylaxis and treatment of thromboembolic complications associated with AF			✔	
Treatment of acute and chronic consumption coagulopathies (disseminated intravascular coagulation)			✔	
Prevention of clotting in arterial and cardiac surgery			✔	
Prophylaxis and treatment of peripheral arterial embolism			✔	
Anticoagulant use in blood transfusions, extracorporeal circulation, and dialysis procedures			✔	
Prophylaxis of DVT*				
Medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness		✔		✔
Patients undergoing abdominal surgery who are at risk for thromboembolic complications	✔	✔		✔
Patients undergoing hip fracture surgery	✔ †			
Patients undergoing hip replacement surgery	✔	✔		✔ #
Patients undergoing knee replacement surgery	✔			✔

‖In these patients therapy begins with the initial VTE treatment and continues for six months.
¶When concurrently administered with aspirin therapy.
*Which may lead to PE.
†Including extended prophylaxis.
#During and following hospitalization.
‡When administered in conjunction with warfarin.
**Indicated for inpatient treatment of acute DVT with or without PE, when administered in conjunction with warfarin, and for outpatient treatment of acute DVT without PE when administered in conjunction with warfarin.
§When administered in conjunction with warfarin when initial therapy is administered in the hospital.
††When administered concurrently with aspirin, enoxaparin has been shown to reduce the rate of the combined endpoint of recurrent MI or death in patients with acute STEMI receiving thrombolysis and being managed medically or with percutaneous coronary intervention.

(Prescribing information: ARIXTRA, 2015; FRAGMIN, 2016; LOVENOX, 2013, HEPARIN SODIUM, 2016)

Information on indications, mechanism of action, pharmacokinetics, dosing, and safety has been obtained from the prescribing information for the individual products, except where noted otherwise.

CLINICAL EFFICACY SUMMARY

- The evidence demonstrating the safety and efficacy of the injectable anticoagulants in FDA-approved indications is well established, and as mentioned previously, clinical guidelines support the use of these agents for these indications. Patients experiencing an acute coronary syndrome will generally receive treatment with an injectable anticoagulant in an acute hospital setting as recommended per current clinical guidelines (Levine et al 2011, O'Gara et al, 2013, Guyatt et al, 2012). When compared to UFH and placebo, LMWH was found to be superior or comparable to UFH treatment in patients with acute coronary syndrome.
- Currently, FRAGMIN is the only injectable anticoagulant approved for the extended treatment of VTE in patients with cancer. In a trial comparing FRAGMIN to oral anticoagulation (warfarin or acenocoumarol [not available in the United States]) in patients with symptomatic VTE, the incidence of symptomatic, recurrent VTE was significantly lower with FRAGMIN at six months. At six months there was no difference in mortality rates between the two treatments; however, a 12 month follow-up revealed a significant benefit in mortality with FRAGMIN in patients without known metastases of their cancer (Lee et al, 2003; Lee et al, 2005). The DALTECAN study found that the frequency of major bleeding events was lower during months 6 through 12 as compared to the first six months of FRAGMIN therapy in patients with cancer (Francis et al, 2015).
- An AHRQ Comparative Effectiveness Review found for the minority of patients at low or intermediate risk of recurrent ischemia, MI, or death, an initial conservative approach is recommended as LOVENOX reduced composite ischemic events and MI with mixed effects on bleeding when compared to UFH or ARIXTRA (Melloni et al, 2013).
- The evidence establishing the safety and efficacy of the injectable anticoagulants for VTE treatment and/or thromboprophylaxis is well established. Several placebo-controlled trials, meta-analyses, and systematic reviews with the various injectable anticoagulants in medical patients, immobilized patients, and those undergoing orthopedic surgery have been conducted and consistently demonstrate their efficacy (Alikhan et al, 2003; Bergqvist et al, 1996; Bergqvist et al, 2002; Eriksson et al, 2003; Fuji et al, 2008; Hull et al, 2010; Lassen et al, 1998; Leizorovicz et al, 2004; Michot et al, 2002; Planes et al, 1996; Samama et al, 1999; Testroote et al, 2014; Torholm et al, 1991; Uchino et al, 2012; Anderson et al, 2013). When the injectable anticoagulants are compared to other methods of treatment and thromboprophylaxis which include heparin, UFH, aspirin, and warfarin, "superiority" in terms of recurrent VTE and safety is not always consistent, which supports recommendations from current clinical guidelines (Andras et al, 2012; Bhutia et al, 2013; Colwell et al, 1994; Colwell et al, 1999; Cook et al, 2011; De et al, 2010; DeCarolis et al, 2012; Eriksson et al, 1991; Erkens et al, 2010; Ferres et al, 2011; Fitzgerald et al, 2001; Francis et al, 1997; Handoll et al, 2002; Kanaan et al, 2007; Kleber et al, 2003; Leclerc et al, 1996; McLeod et al, 2001; No authors listed, 1991; Othieno et al, 2007; Rasmussen et al, 2009; Salazar et al, 2010; Senaran et al, 2006; Anderson et al, 2013; Akl et al, 2014). For treatment and thromboprophylaxis in these patients, any of these options may be appropriate; however, LMWH or low-dose UFH are generally suggested in preference to the other agents recommended as alternatives (Guyatt et al, 2012). In a recent update to a Cochrane review comparing fixed dose LMWH with adjusted dose IV or SC UFH for initial VTE treatment, LMWH reduced the incidence of both recurrent VTE and major hemorrhage compared to UFH. Additionally, low-quality evidence suggested that LMWH also reduced the thrombus size compared to UFH. No difference in overall mortality was observed (Robertson et al, 2017).
- Although data comparing the LMWH agents to ARIXTRA has not demonstrated significant "superiority" for one therapy in all outcomes, treatment with ARIXTRA appears to be associated with a lower incidence of VTE, and a comparable incidence of major bleeding compared to LOVENOX (Bauer et al, 2001; Eriksson et al, 2001; Lassen et al, 2002; Turpie et al, 2002b). In a meta-analysis of randomized-controlled trials comparing ARIXTRA to LMWH therapy (LOVENOX), the incidence of VTE was significantly less and the incidence of major bleeding was significantly greater with ARIXTRA (Turpie et al, 2002a). Another trial noted no difference between ARIXTRA and FRAGMIN for the incidence of VTE and major bleeding (Agnelli et al, 2005).
- In general, recommendations from other clinical guidelines for other populations are in line with the American College of Chest Physicians (ACCP) guidelines (AAOS, 2011; Amsterdam et al, 2014; Levine et al, 2011; Kernan et al, 2014; Guyatt et al, 2012; Jaff et al, 2011; Bushnell et al, 2014; Lyman et al, 2015; O'Gara et al, 2013; January et al, 2014; Kernan et al, 2014). Treatment recommendations vary according to the indication.
    - For orthopedic (e.g., total hip or knee replacement) surgery, the American Academy of Orthopedic Surgeons (AAOS) does not recommend a specific medication (AAOS, 2011). The ACCP does favor LMWH over ARIXTRA, ELIQUIS, XARELTO, or UFH (Guyatt et al, 2012).
    - For non-orthopedic (e.g., general and abdominal-pelvic surgery) surgical patients requiring thromboprophylaxis who are at moderate to high risk for VTE and who are not at high risk for bleeding complications, LMWH and low dose UFH are both recommended as options (Guyatt et al, 2012).

- In patients with UA, NSTEMI, or STEMI, the American College of Cardiology (ACC) recommends anticoagulant therapy for a minimum of 48 hours and up to 8 days or until revascularization is performed in patients undergoing reperfusion. The recommended treatment options include UFH, LOVENOX and ARIXTRA (O'Gara et al, 2013; Kernan et al, 2014). For those patients undergoing PCI, LOVENOX, ARIXTRA, or UFH are recommended by most reputable guidelines. However, ARIXTRA should not be used as the sole anticoagulant administered due to risk of catheter thrombosis (Amsterdam et al, 2014; Levine et al, 2011). Bridging therapy with UFH or LMWH is recommended for patients with AF and a mechanical heart valve undergoing procedures or for various procedures (January et al, 2014).
- In acutely ill hospitalized (i.e., non-surgical) patients at increased risk of thrombosis, LMWH, low dose UFH, and ARIXTRA are recommended (Guyatt et al, 2012).
- For acute VTE (e.g., DVT or PE), LMWH or ARIXTRA is preferred over UFH (Guyatt et al, 2012; Lyman et al, 2015). For chronic management of VTE in patients with cancer, the American Society of Clinical Oncology (ASCO) guideline recommends LMWH for the initial six months due to its improved efficacy over warfarin. The guideline states that warfarin is an acceptable alternative for long-term therapy if LMWH is not readily available (Lyman et al, 2015). The most recent ACCP guidelines recommend PRADAXA (dabigatran), XARELTO (rivaroxaban), ELIQUIS (apixaban), or SAVAYSA (edoxaban) over warfarin for long-term VTE therapy (Kearon et al, 2016). They also recommend warfarin over LMWH; however, LMWH is preferred in patients with cancer. In patients with a VTE recurrence while on warfarin, PRADAXA, XARELTO, ELIQUIS, or SAVAYSA, treatment with a LMWH is recommended. Duration of anticoagulation after treatment of an acute thromboembolic event will depend on whether the patient was currently receiving anticoagulation therapy, if the event was provoked or unprovoked and/or caused by surgery or a nonsurgical transient risk factor, and if it was the first or second thromboembolic event (Guyatt et al, 2012).
- In general, pregnant women and women who are breast-feeding with a high-risk condition that would require anticoagulation outside of pregnancy, it is reasonable to use UFH, or LMWH (Bushnell et al, 2014; Kernan et al, 2014).
- Patients with mechanical heart valves, AF, or VTE at high risk of developing thromboembolism, whose oral anticoagulation therapy is to be interrupted prior to an invasive procedure, would require bridging therapy with LMWH or UFH. Providers need to carefully consider risks and benefits of bridging in patients with the above mentioned conditions and moderate risk for thromboembolism. No bridging is indicated for patients at low risk for thromboembolism (Douketis et al, 2012; Douketis et al, 2015; Clark et al 2015).

SAFETY SUMMARY

- A boxed warning exists for the injectable anticoagulants (e.g., ARIXTRA, FRAGMIN, and LOVENOX) warning of spinal or epidural hematomas when anticoagulated with LMWH or heparinoids and in patients who are receiving neuraxial anesthesia or undergoing spinal puncture. Optimal timing between the administration of ARIXTRA, FRAGMIN or LOVENOX and neuraxial procedures is not known.
- The injectable anticoagulants (e.g., ARIXTRA, FRAGMIN, and LOVENOX) are contraindicated with major active bleeding. These agents are associated with an increased risk of bleeding and hemorrhage; therefore, use with caution in conditions with increased risk of hemorrhage. In addition, thrombocytopenia can occur with these agents.
- UFH is contraindicated in patients with a history of heparin-induced thrombocytopenia and thrombosis or a history of hypersensitivity to heparin or pork products. Although major active bleeding is not contraindicated, it is a warning to avoid heparin in the presence of major bleeding unless the benefit outweighs the risk.
- All injectable anticoagulants warn of drug interactions with medications that may enhance the risk of hemorrhage, which should be discontinued prior to initiation of therapy with any of the injectable anticoagulants, unless these medications are essential. However, in clinical trials, ARIXTRA in combination with oral anticoagulants, platelet inhibitors, nonsteroidal anti-inflammatory drugs, and digoxin did not significantly affect the pharmacokinetics and pharmacodynamics of any of the medications.
- Adverse reactions associated with agents in class include:
  - Injection site reaction, rash, and fever as adverse events commonly observed; and serious adverse events include bleeding-related adverse events with ARIXTRA use.
  - Injection site reaction, pain, and hematomas as adverse events commonly observed; and serious adverse events include anaphylaxis, abnormal liver function tests, and those bleeding-related adverse events with FRAGMIN use.
  - Gastrointestinal reactions, abnormal liver function tests, fever, thrombocytopenia, and bleeding-related as adverse events commonly observed; and serious adverse events include AF, heart failure, dermatologic reactions, pneumonia, and those adverse events related to bleeding with LOVENOX use.

  - Hemorrhage, thrombocytopenia, hypersensitivity, and local injection reactions with UFH use.
- In November 2013, the FDA recommended that health care professionals consider the timing of spinal catheter placement and removal in patients taking anticoagulant drugs, such as LOVENOX, and delay dosing of anticoagulant medications for some time interval after catheter removal to decrease the risk of spinal column bleeding and subsequent paralysis after spinal injections, including epidural procedures and lumbar punctures. New timing recommendations, which can decrease the risk of epidural or spinal hematoma, were added to the labels of LMWHs.

DOSING AND ADMINISTRATION

- FRAGMIN is administered via SC injection, and should not be administered via intramuscular injection. Routine coagulation tests such as Prothrombin Time and Activated Partial Thromboplastin Time are relatively insensitive measures of FRAGMIN activity; therefore, these measurements are unsuitable for monitoring the anticoagulant effect of FRAGMIN. In addition, in patients receiving FRAGMIN who experience platelet counts between 50,000 and 100,000/mm^3, the daily dose should be reduced by 2,500 international units until the platelet count recovers to ≥ 100,000/mm^3. In patients receiving FRAGMIN who experience platelet counts < 50,000/mm^3, discontinue treatment until the platelet count returns to > 50,000/mm^3.
- ARIXTRA is to be administered via SC injection only. Routine coagulation tests such as Prothrombin Time and Activated Partial Thromboplastin Time are relatively insensitive measures of ARIXTRA activity; therefore, these measurements are unsuitable for monitoring the anticoagulant effect of ARIXTRA. The anti-FXA activity can be measured. ARIXTRA should be discontinued if the platelet count is < 100,000/mm^3.
- LOVENOX can be administered via SC injection or intravenously, and should not be administered via intramuscular injection. All patients should be evaluated for a bleeding disorder before receiving LOVENOX, unless the medication is needed urgently. Coagulation parameters are also unsuitable for monitoring LOVENOX activity; therefore, routine monitoring of coagulation parameters is not required. LOVENOX should be discontinued if the platelet count is < 100,000/mm^3.
- UFH can be administered via SC injection or IV, and should not be administered via intramuscular injection. When using full-dose heparin, activated partial thromboplastin time (aPTT) should be monitored to aid in dose adjustments. Additionally, platelet counts may need to be monitored regularly depending on the patient's risk of heparin-induced thrombocytopenia. UFH should be discontinued if the platelet count is < 100,000/mm^3 or if thrombosis occurs.

Table 3. Dosing and Administration

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing/ Administration Considerations
ARIXTRA (fondaparinux)	Injection: 2.5 mg/0.5 mL 5 mg/0.4 mL 7.5 mg/0.6 mL 10 mg/0.8 mL	Prophylaxis of DVT in patients undergoing abdominal surgery who are at risk for thromboembolic complications: Injection: 2.5 mg SC once-daily after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)* Prophylaxis of DVT in patients undergoing hip fracture surgery: Injection: 2.5 mg SC once-daily after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)†; an extended prophylaxis course of up to 24 additional days is recommended‡ Prophylaxis of DVT in patients undergoing hip replacement surgery: Injection: 2.5 mg SC once-daily after hemostasis has been established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)† Prophylaxis of DVT in patients undergoing knee replacement surgery: Injection: 2.5 mg SC once-daily after hemostasis has been	Do not mix other medications or solutions with ARIXTRA.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing/ Administration Considerations
		established, initiated no earlier than six to eight hours after surgery (usual duration, five to nine days)† Treatment of acute DVT: Injection: 5 (< 50 kg), 7.5 (50 to 100 kg) or 10 (> 100 kg) mg SC once-daily for ≥ 5 days and until a therapeutic oral anticoagulant effect is established (usual duration, five to nine days)§ Treatment of acute PE: Injection: 5 (< 50 kg), 7.5 (50 to 100 kg) or 10 (> 100 kg) mg SC once-daily for ≥ 5 days and until a therapeutic oral anticoagulant effect is established (usual duration, five to nine days)§	
FRAGMIN (dalteparin)	Injection: 2,500 IU/0.2 mL 5,000 IU/0.2 mL 7,500 IU/0.3 mL 10,000 IU/1 mL 12,500 IU/ 0.5 mL 15,000 IU/ 0.6 mL 18,000 IU/ 0.72 mL 95,000 IU/ 3.8 mL	Extended treatment of symptomatic VTE (proximal DVT and/or PE) in patients with cancer: Injection: initial, 200 IU/kg SC once-daily for 30 days; maintenance, approximately 150 IU/kg SC once-daily during months two through six; maximum, daily doses should not exceed 18,000 IU Prophylaxis of ischemic complications in UA and non-Q-wave MI: Injection: 120 IU/kg, but not more than 10,000 IU, SC every 12 hours; maintenance, continue treatment until the patient is clinically stabilized (usual duration, five to eight days) Prophylaxis of DVT in medical patients who are at risk for thromboembolic complications due to severely restricted mobility during acute illness: Injection: 5,000 IU SC once-daily‖ Prophylaxis of DVT in patients undergoing abdominal surgery who are at risk for thromboembolic complications: Injection: preoperatively, 2,500 IU SC once-daily one to two hours prior to surgery; postoperatively, 2,500 IU SC once-daily (usual duration, five to 10 days) In patients undergoing abdominal surgery with a high risk of thromboembolic complications, the recommended dose of dalteparin is 5,000 IU SC the evening before the surgery, then 5,000 IU SC once-daily postoperatively (usual duration, five to 10 days); alternatively, patients with malignancy can administer 2,500 IU SC one to two hours prior to surgery, followed by 2,500 IU SC 12 hours later, then 5,000 IU SC once-daily (usual duration, five to 10 days) Prophylaxis of DVT in patients undergoing hip replacement surgery: Injection: preoperatively, 5,000 IU SC 10 to 14 hours before surgery or 2,500 IU SC within two hours before surgery; postoperatively, 2,500 to 5,000 IU SC four to eight hours after surgery plus 5,000 IU SC once daily (usual duration, five to 10	Dosage reductions may be required in patients with cancer and acute symptomatic VTE who develop thrombocytopenia. FRAGMIN should not be mixed with other injections or infusions unless specific compatibility data are available that support such mixing.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing/ Administration Considerations
		days after surgery)¶	
HEPARIN SODIUM (unfractionated heparin)	Preservative-free injection (1,000 USP units/mL): 2,000 USP units/2 mL Injection (contains benzyl alcohol) (1,000 USP units/mL): 10,000 USP units/10 mL 30,000 USP units/30 mL (5,000 USP units/mL): 50,000 USP units/10 mL 5,000 USP units/mL (10,000 USP units/mL): 10,000 USP units/mL	Therapeutic anticoagulant effect with full-dose heparin *SC injection:* 333 units/kg initially followed by 250 units/kg every 12 hours *Intermittent IV injection*: 10,000 units initially followed by 5000 to 10,000 units every 4 to 6 hours *Continuous IV infusion*: 5000 units initially followed by 20,000 to 40,000 units per 24 hours Pediatric use Initial dose: 75 to 100 units/kg (IV bolus over 10 minutes) Maintenance dose: Infants: 25 to 30 units/kg/hour >1 year old: 18 to 20 units/kg/hour Cardiovascular surgery Minimum dose: 150 units/kg; higher doses of 300 units/kg is used for procedures that last 1 hour and 400 units/kg for procedures that last longer than 1 hour Low-dose prophylaxis of postoperative thromboembolism *SC injection:* 5000 units 2 hours before surgery and 5000 units every 8 to 12 hours for 7 days or until patient is ambulatory, whichever is longer Blood transfusion 400 to 600 USP units/100 mL of whole blood Extracorporeal dialysis 25 to 30 units/kg followed by 1500 to 2000 units/hour if specific manufacturers' recommendations are not available	Dosing recommendations are based on a 68 kg patient.
LOVENOX (enoxaparin)	Injection (100 mg/mL): 30 mg/0.3 mL 40 mg/0.4 mL 60 mg/0.6 mL 80 mg/0.8 mL 100 mg/1 mL 300 mg/3 mL Injection (150 mg/mL): 120 mg/0.8 mL 150 mg/1 mL	Prophylaxis of ischemic complications in UA and non-Q-wave MI: Injection: 1 mg/kg SC every 12 hours for a minimum of two days and continued until clinical stabilization (usual duration, two to eight days)# Injection (patients with creatinine clearance (CrCL) < 30 mL/minute): 1 mg/kg SC once-daily Prophylaxis of DVT in medical patients who are at risk of thromboembolic complications due to severely restricted mobility during acute illness: Injection: 40 mg SC once-daily (usual duration, six to 11 days)** Injection (patients with CrCL < 30 mL/minute): 30 mg SC once-daily Prophylaxis of DVT in patients undergoing abdominal surgery who are at risk for thromboembolic complications:	For IV administration, LOVENOX can be mixed with normal saline solution or 5% dextrose in water. For SC administration, LOVENOX should not be mixed with other injections or infusions.

Drug	Dosage Form: Strength	Usual Recommended Dose	Other Dosing/ Administration Considerations
		Injection: preoperatively, 40 mg SC two hours prior to surgery; postoperatively, 40 mg SC once-daily (usual duration, seven to 10 days)†† Injection (patients with CrCL < 30 mL/minute): 30 mg SC once-daily <u>Prophylaxis of DVT in patients undergoing hip replacement surgery:</u> Injection: initial, 30 mg SC 12 to 24 hours after surgery or 40 mg SC once-daily administered 12(±3) hours prior to surgery; maintenance, 40 mg SC once-daily for three weeks (usual duration, seven to 10 days)** Injection (patients with CrCL < 30 mL/minute): 30 mg SC once-daily <u>Prophylaxis of DVT in patients undergoing knee replacement surgery:</u> Injection: initial, 30 mg SC 12 to 24 after surgery (usual duration, seven to 10 days)** Injection (patients with CrCL < 30 mL/minute): 30 mg SC once-daily <u>Treatment of acute DVT:</u> Injection (outpatient): 1 mg/kg SC every 12 hours for a minimum of five days and until a therapeutic oral anticoagulant effect has been achieved (average duration, seven days)‡‡ Injection (outpatients with CrCL < 30 mL/minute): 1 mg/kg SC once-daily Injection (inpatient): 1 mg/kg SC twice-daily or 1.5 mg/kg SC once daily both for a minimum of five days and until a therapeutic oral anticoagulant effect has been achieved (average duration, seven days)‡‡ Injection (in patients with CrCL < 30 mL/minute): 1 mg/kg SC once-daily <u>Treatment of acute ST-segment elevation MI:</u> Injection: initial, 30 mg IV as a single bolus dose plus 1 mg/kg SC; maintenance, 1 mg/kg SC twice-daily; maximum, 100 mg for the first two doses, followed by 1 mg/kg dosing for the remaining doses Injection (patients < 75 years of age with CrCL < 30 mL/minute): initial, 30 mg IV as a single bolus dose plus 1 mg/kg SC; maintenance, 1 mg/kg SC once-daily Injection (patients ≥ 75 years of age with CrCL < 30 mL/minute): 1 mg/kg SC once-daily	

DVT=deep vein thrombosis, IU=international units, IV=intravenous, MI=myocardial infarction, PE=pulmonary embolism, SC=subcutaneous, UA=unstable angina, VTE=venous thromboembolism
*Up to 10 days of treatment have been administered in clinical trials.
†Up to 11 days of treatment have been administered in clinical trials.
‡A total of 32 days (perioperative and extended prophylaxis) was administered in clinical trials.
§Up to 26 days of treatment have been administered in clinical trials.
‖In clinical trials, the usual duration of administration was 12 to 14 days.
¶Up to 14 days of treatment have been well tolerated in clinical trials.
#Up to 12.5 days of treatment has been administered in clinical trials.
** Up to 14 days of treatment have been administered in clinical trials.
††Up to 12 days of treatment have been administered in clinical trials.
‡‡Up to 17 days of treatment have been administered in clinical trials.

SPECIAL POPULATIONS

Table 4. Special Populations

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
ARIXTRA (fondaparinux)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Serious adverse events increase with age. Due to the risk of increased adverse events in renal impairment, use caution as renal function generally declines with age.	Safety and efficacy in children have not been established	Use caution in patients with a CrCL 30 to 50 mL/minute. Contraindicated in patients with a CrCL < 30 mL/minute.	No dosage adjustment required, however a higher incidence of hemorrhage was observed in patients with moderate impairment.	Pregnancy Category B Unknown whether excreted in breast milk; use with caution.
FRAGMIN (dalteparin)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients. Due to the potential for an increased bleeding risk with increased age, use caution in older patients with low body weight, decreased renal function, and	Safety and efficacy in children have not been established Use caution with multiple-dose vials due to benzyl alcohol content	Renal dose adjustment is required; for CrCL < 30 mL/minute, monitor anti-Xa levels to determine the appropriate dose.	No dosage adjustment required.	Pregnancy Category B Minimally excreted in breast milk; use with caution.

Drug	Population and Precaution				
	Elderly	Pediatrics	Renal Dysfunction	Hepatic Dysfunction	Pregnancy* and Nursing
	concomitant medications.				
HEPARIN SODIUM (unfractionated heparin)	A higher incidence of bleeding has been reported in patients over 60 years of age, especially women. Lower doses may be required in these patients.	Although no adequate, well controlled studies have been conducted, pediatric dosing recommend-ations are based on clinical experience. The preservative-free formulation should be used in neonates and infants to avoid benzyl alcohol toxicity. Special attention should be given to ensure the correct strength of heparin is used to avoid fatal dosing errors.	Should be used with caution in severe renal disease due to an increased risk of hemorrhage.	Should be used with caution in liver disease with impaired hemostasis due to an increased risk of hemorrhage.	Pregnancy Category C Due to its high molecular weight, heparin is not likely to be excreted in human milk and would not be orally absorbed by the infant. Use caution when administering to a nursing mother and use the preservative-free formulation as benzyl alcohol is excreted in human milk and can be orally absorbed by the infant.
LOVENOX (enoxaparin)	No evidence of overall differences in safety or efficacy observed between elderly and younger adult patients.	Safety and efficacy in children have not been established	No dosage adjustment for moderate renal dysfunction is required. Renal dose adjustment is required for severe renal dysfunction (CrCL < 30 mL/minute).	Not studied in hepatic dysfunction; use with caution.	Pregnancy Category B; does not increase risk of major developmental abnormalities; monitor for bleeding. Due to benzyl alcohol content and its ability to cross the placenta, use of the multiple-dose vial should be used with caution. Unknown whether excreted in breast milk; use with caution.

Pregnancy Category B = No evidence of risk in humans, but there remains a remote possibility. Animal reproduction studies have failed to demonstrate a risk to the fetus, and there are no adequate and well-controlled studies in pregnant women.
Pregnancy Category C = Pregnancy Category C = Risk cannot be ruled out. Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.

CONCLUSION

- The injectable anticoagulants include UFH, LMWH agents (i.e., FRAGMIN, LOVENOX) and FXa inhibitors (i.e., ARIXTRA). The primary effect of UFH as an anticoagulant is a result of its binding to antithrombin which inhibits clot formation. Additional anticoagulant effects of UFH include inhibition of FIIa (thrombin), Xa, IXa, XIa, and XIIa (Garcia et al, 2012). The FXa inhibitors and LMWH agents work by binding to antithrombin, causing inhibition of the clotting factors thrombin and FXa. These agents have a greater inhibitory effect on FXa compared to thrombin (Hirsh et al, 2008; Weitz et al, 1997).
- Because the LMWH agents are prepared using different methods of depolymerization, the various agents in this class differ and are not clinically interchangeable (Hirsh et al, 2008).
- Currently, ARIXTRA, UFH, and LOVENOX are available generically (Micromedex, 2017; Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations, 2017).
- In general, the injectable anticoagulants are FDA-approved for prophylaxis and/or treatment of VTE. Certain agents in the class are also FDA-approved for the treatment of acute STEMI or for prophylaxis of ischemic complications UA and non-Q-wave MI; however, treatment for these indications will most likely be initiated in an acute hospital setting.
- UFH is considered an option for a number of off-label uses, including UA, NSTEMI, STEMI and use during PCI, by various guidelines. For most indications, UFH is administered IV; however, the SC route can be used for prophylaxis and/or treatment of VTE. For prophylaxis, the SC dose is administered two or three times daily and for treatment, the SC dose is administered twice daily.
- Outpatient or inpatient administration of the injectable anticoagulants for prophylaxis and treatment of VTE may be appropriate depending on the specific clinical situation. The most recent ACCP guidelines recommend PRADAXA, XARELTO, ELIQUIS, or SAVAYSA over warfarin for long-term VTE therapy (Kearon et al, 2016). They also recommend warfarin over LMWH; however, LMWH is preferred in patients with cancer.
- Evidence from clinical trials and recommendations from clinical guidelines support the use of the injectable anticoagulants in FDA-approved indications.
- Several placebo-controlled trials have consistently demonstrated the efficacy of the injectable anticoagulants, but when compared to other methods of anticoagulation (e.g., heparin, rivaroxaban, UFH, warfarin), their superiority in terms of recurrent VTE and safety has not always been demonstrated (Alikhan et al, 2003; Andras et al, 2012; Bergqvist et al, 1996; Bergqvist et al, 2002; Brookenthal et al, 2001; Colwell et al, 1994; Colwell et al, 1999; Cook et al, 2013; De et al, 2010; Eriksson et al, 1991; Eriksson et al, 2008; Erkens et al, 2010; Fitzgerald et al, 2001; Francis et al, 1997; Fuji et al, 2008; Handoll et al, 2002; Hull et al, 2010; Kakkar et al, 2008; Kanaan et al, 2007; Bauersachs, 2010; Buller, 2012; Kleber et al, 2003; Anderson et al, 2013; Lassen et al, 1998; Lassen et al, 2008; Leclerc et al, 1996; Leizorovicz et al, 2004; McLeod et al, 2001; Michot et al, 2002; No authors listed, 1991; Othieno et al, 2007; Planes et al, 1996; Rasmussen et al, 2009; Salazar et al, 2010; Samama et al, 1999; Senaran et al, 2006; Torholm et al, 1991; Turpie et al, 2009; Uchino et al, 2012; Melloni et al, 2013; van der Heijden, 2001; Akl et al, 2014). In a recent update to a Cochrane review comparing fixed dose LMWH with adjusted dose IV or SC UFH for initial VTE treatment, LMWH reduced the incidence of both recurrent VTE and major hemorrhage compared to UFH. Additionally, low-quality evidence suggested that LMWH also reduced the thrombus size compared to UFH. No difference in overall mortality was observed (Robertson et al, 2017).
- When comparing ARIXTRA to the LMWH agents, treatment with ARIXTRA has demonstrated superiority in terms of the incidence of VTE in the majority of clinical trials, while demonstrating a comparable rate of major bleeding (Agnelli et al, 2005; Bauer et al, 2001; Bauer et al, 2002; Eriksson et al, 2001; Eriksson et al, 2003; Lassen et al, 2002; Turpie et al, 2002; Turpie AG et al, 2002). However, data from two clinical trials revealed no difference between treatment with ARIXTRA compared to FRAGMIN and LOVENOX in the development of VTE (Eriksson et al, 2003; Turpie et al, 2002).
- One trial revealed no difference between FRAGMIN compared to UFH treatment in critically ill patients in decreasing the incidence of proximal DVT; however, the trial found a statistically lower incidence of PE (definite or probable) with FRAGMIN. This result did require a large number needed to treat of 111 patients in order to achieve this outcome (Cook et al, 2011).
- In terms of safety measures, one trial comparing patients who were given LOVENOX with moderate renal impairment to those with normal renal function resulted in significantly more major bleeds in patients with moderate renal impairment (DeCarolis et al, 2012). In women who met criteria for thromboprophylaxis (patients at high-risk for VTE) after cesarean, one study resulted in a greater proportion of women who had wound separation when given LOVENOX compared to those women who were not given LOVENOX (Ferres et al, 2011).

Table 5. Advantages and Disadvantages of Injectable Anticoagulants

Drug	Advantages	Disadvantages
ARIXTRA (fondaparinux)	May be used acutely for certain patients. May be used as alternative treatment in cases of heparin-induced thrombocytopenia (HIT).	Long half-life of 17 to 21 hours, which should be taken in account if managing a pre-operative patient. Not indicated in patients with symptomatic VTE and cancer or as prophylaxis of ischemic complications in UA and MI. No antidote effect Contraindicated in patients with severe renal impairment.
FRAGMIN (dalteparin)	Shorter half-life of 7 hours. Only agent approved for the extended treatment of symptomatic VTE in patients with cancer.	Not indicated in acute VTE or acute MI. Requires renal dose adjustment Partial antidote effect
HEPARIN SODIUM (unfractionated heparin)	Shortest half-life of 1 hour and therefore, can be reversed quickly No renal excretion Complete antidote effect	SC dosing is two to three times daily and not typically administered at home Most indications are for IV administration Most common cause of heparin-induced thrombocytopenia
LOVENOX (enoxaparin)	Shorter half-life of 7 hours. May be used acutely for certain patients.	Not FDA-approved specifically in cancer patients, although often prescribed. Requires renal dose adjustment Partial antidote effect

(Hilal-Dandan et al, 2014; Baroletti et al, 2006)

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Publication date: March 30, 2017