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 traumas, 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 due to missed or wrong diagnoses, also data is ≥ 10 years old. The VTE incidence is similar or higher among African Americans and lower among Asian Americans and Native Americans than among whites. Most PE deaths are sudden and both DVTs and PEs are usually attributed to underlying diseases (eg, cancer, other chronic heart, lung, or renal disease) (*Benjamin et al 2018)*.
- Stroke also causes significant morbidity and mortality. Stroke is the fifth leading cause of death after heart disease, cancer, chronic lower respiratory disease, and injuries/accidents. 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 2018*).
- 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, use in blood transfusions, extracorporeal circulation, and dialysis procedures. Heparin is also used as an anticoagulant for several other off-label indications (*Micromedex 2018*).
- 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, Weitz1997*).
- 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

Table 1. Medications Included Within Class Review

Drug	Generic Availability
Arixtra (fondaparinux)	✔
Fragmin (dalteparin)	-
Heparin Sodium (unfractionated heparin)	✔
Lovenox (enoxaparin)	✔

(*Drugs@FDA 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*)

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)
Treatment of acute DVT with or without PE	✔ ‡			✔ *
Treatment of acute STEMI managed medically or with subsequent percutaneous coronary intervention (PCI)				✔ §
Prophylaxis of ischemic complications in UA and non-Q-wave MI		✔ ¶		✔ ¶
Extended treatment of symptomatic VTE (proximal DVT and/or PE) in patients with cancer		✔ ‖		
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		✔		✔

Indication	Arixtra (fondaparinux)	Fragmin (dalteparin)	Heparin sodium (unfractionated heparin)	Lovenox (enoxaparin)
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	✔			✔
Limitations of use				
Not indicated for the acute treatment of VTE		✔		

*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.
†Including extended prophylaxis.
‡When administered in conjunction with warfarin.
§When administered in conjunction with aspirin when initial therapy is administered in the hospital.
‖In these patients therapy begins with the initial VTE treatment and continues for 6 months.
¶When concurrently administered with aspirin therapy.
#During and following hospitalization.
††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 2017, Fragmin 2017, Lovenox 2017, Lovenox (preservative-free) 2017, Heparin sodium 2017)

- 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 6 months. At 6 months, there was no difference in mortality rates between the 2 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 6 months of Fragmin therapy in patients with cancer (*Francis et al 2015*). A Cochcrane review comparing LMWH, UFH, and Arixtra for VTE treatment in cancer patients found that LMWH may possibly be superior to UFH in reducing mortality at 3 months but it doesn't ensure a clinically significant decrease in VTE recurrence (*Hakoum et al 2018*). 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 (MAs), and systematic reviews (SRs) 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 al2013, Colwell et al1994, Colwell et al1999, 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 the incidence of major bleeding compared to Lovenox has had mixed reports (*Bauer et al 2001, Eriksson et al 2001, Lassen et al 2002, Turpie et al 2002b*). In a MA of randomized-controlled trials (RCTs) 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*). One MA/SR assessed the peri-operative use of Arixtra vs Lovenox in patients with acute coronary syndrome and found that mortality was similar between groups after a 10 day (Odds ratio [OR], 1.05; P = 0.84) and 30 day follow-up (OR, 0.90; P = 0.66); however, major bleeding was significantly lower with Arixtra after a 10 day (OR, 0.46; P = 0.0001) and 30 day follow-up (OR, 0.49; P = 0.03) (*Bundhun et al 2017*). Another trial noted no difference between Arixtra and Fragmin for the incidence of VTE and major bleeding (*Agnelli et al 2005*).

CLINICAL GUIDELINES

- 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, Mazzolai et al 2017, Powers et al 2018*). Treatment recommendations vary according to the indication.
  - For orthopedic (eg, 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 (eg, 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 (ie, non-surgical) patients at increased risk of thrombosis, LMWH, low dose UFH, and Arixtra are recommended (*Guyatt et al 2012*).
  - For acute VTE (eg, 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 6 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*).
  - In patients with acute ischemic stroke, urgent anticoagulation with the goal of preventing early recurrent stroke, stopping neurological worsening, or improving outcomes after an acute ischemic stroke is not recommended. The benefit of urgent anticoagulation in some patients may be warranted; however, use is not well established. In patients undergoing DVT prophylaxis after an acute ischemic stroke when prophylactic anticoagulation is used, the use benefit of prophylactic LMWH over prophylactic UFH is uncertain (*Powers et al 2018)*.

SAFETY SUMMARY

- A boxed warning exists for the injectable anticoagulants (eg, 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 (ie, Arixtra, Fragmin, and Lovenox) are contraindicated with active major 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. Lovenox, UFH, and Fragmin are contraindicated in patients with hypersensitivity to heparin or pork products.
- Arixtra is also contraindicated in patients with bacterial endocarditis, thrombocytopenia in the presence of Arixtra, patients with body weight of less than 50 kg if using it for VTE prophylaxis, and in patients with CrCL less than 30 mL/min when using it for treatment or prophylaxis of VTE.
- Contraindications to the use of UFH include severe thrombocytopenia, and uncontrolled active bleeding unless it is due to disseminated intravascular coagulation.
- Lovenox is contraindicated in patients with a history of hepain-induced thrombocytopenia (HIT) within the past 100 days. Lovenox is contraindicated in patients with hypersensitivity to benzyl alcohol.
- Fragmin is contraindicated in patients with a history of HIT or HIT with thrombosis. It is also not to be used for treatment of unstable angina and non-Q-wave MI or for prolonged VTE prophylaxis in patients undergoing Epidural/Neuraxial anesthesia.
- 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.
- Warnings and Precautions and 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. An increased bleeding risk is associated in patients with renal impairment and in patients with a low body weight (< 50 kg). Do not use Arixtra for VTE prophylaxis and treatment in patients with creatinine clearance (CrCL) < 30 mL/min or as prophylactic therapy in patients < 50 kg undergoing hip, abdominal, or knee surgery.
  - 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 events 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.
  - “Gasping syndrome,” characterized by CNS depression, metabolic acidosis, and gasping respirations, which is reported in infants and neonates due to the benzyl alcohol content in multiple-dose formulations of Fragmin and UFH.

DOSING AND ADMINISTRATION

Table 3. Dosing and Administration

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
Arixtra(fondaparinux)	Injection	SC	Once daily	Usual duration is 5 to 9 days; extended durations up to 24 additional days may be warranted for DVT prophylaxis after a hip fracture surgery. A total of 32 days (perioperative and extended prophylaxis) was administered in clinical trials. Administer 6 to 8 hours after surgery. A higher incidence of hemorrhage was observed in patients with moderate hepatic impairment. Caution in patients with CrCL 30 to 50 mL/min and use is contraindicated in CrCL < 30 mL/min.
Fragmin (dalteparin)	Injection	SC	Once or twice daily	Usual duration is 5 to 10 days; extended durations up to 6 additional months may be warranted. Administer 4 to 8 hours after surgery. Dosage reductions may be required in patients with cancer and acute symptomatic VTE who develop thrombocytopenia. Use caution with multiple-dose vials in pregnancy, nursing mothers and pediatric patients due to benzyl alcohol content. Monitor anti-Xa levels in patients with CrCL < 30 mL/min.
Heparin sodium (unfractionated heparin)	Injection (including benzyl alcohol and preservative-free formulations)	IV, SC	Once to 6 times daily; continuous infusion or as needed use may also be warranted.	Dosing recommendations are based on a 68 kg patient. The preservative-free formulation should be used in pregnancy, nursing mothers, neonates, and infants to avoid benzyl alcohol toxicity. Caution should be exercised in patients with severe renal impairment

Drug	Available Formulations	Route	Usual Recommended Frequency	Comments
				or liver disease due to an increased risk of hemorrhage.
Lovenox (enoxaparin)	Injection	IV, SC	Once or twice daily	Usual duration is 2 to 11 days; extended durations of up to 17 days have been studied in trials. Multiple-dose vials are not approved for use in neonates and infants due to the benzyl alcohol content. Pregnant women and nursing mothers should use preservative-free formulations, when available. For IV administration, Lovenox can be mixed with normal saline solution or 5% dextrose in water.

See the current prescribing information for full details

CONCLUSION

- The injectable anticoagulants include UFH, LMWH agents (ie, Fragmin, Lovenox) and FXa inhibitors (ie, 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 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 2018, Orange Book: Approved Drug Products with Therapeutic Equivalence Evaluations 2018*).
- 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 in 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 2 or 3 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 (eg, 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, Büller 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; however, the risk of major bleeding is not clear (*Agnelli et al 2005, Bauer et al 2001, Bauer et al 2002, Bundhun et al 2017, Eriksson et al 2001, Eriksson et al 2003, Lassen et al 2002, Turpie et al 2002, Turpie AG et al 2002*). Data from 2 clinical trials revealed no difference between treatment with Arixtra compared to Fragminand 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, 1 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, 1 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*).

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