

## Best Practice Policy Statement for the

# Prevention of Deep Vein Thrombosis in Patients Undergoing Urologic Surgery



**American  
Urological  
Association**

Education and Research, Inc.

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## Abbreviations and Acronyms

AUA	American Urological Association
BOD	Board of Directors
DVT	deep vein thrombosis
GCS	graduated compression stockings
IPC	intermittent pneumatic compression
LDUH	low-dose unfractionated heparin
LMWH	low molecular weight heparin
PGC	Practice Guidelines Committee
PTE	pulmonary thromboembolism
RCTs	randomized control trials
TURP	transurethral resection of the prostate
VTE	venous thromboembolism

## **Introduction**

Deep vein thrombosis (DVT) with its potential fatal sequela of pulmonary thromboembolism (PTE) is a common complication of surgical procedures and thus an issue of importance for practicing urologists. In fact, PTE is one of the most common causes of nonsurgical death in patients undergoing urologic surgery.<sup>1</sup> In addition to the mortality associated with PTE, long-term complications such as post-thrombotic syndromes can occur with significant morbidity<sup>2,3</sup> and economic impact.<sup>4</sup> Because of the enormity of the problem and its potential for preventable mortality and morbidity, DVT prophylaxis has been identified by a number of organizations as a marker of good quality of patient care. At the request of the Board of Directors (BOD) of the American Urological Association (AUA) and under the guidance of the Practice Guidelines Committee (PGC) of the AUA, a Panel was convened to develop a Best Practice Statement for the prevention of DVT in patients undergoing urologic surgery.

## **Methodology**

Assessment of the literature by the AUA PGC found insufficient outcomes data to support a formal meta-analysis and an evidence-based guideline on the prevention of DVT during urological surgery. The evidence was generally of a low level, being derived overwhelmingly from nonrandomized studies. Thus, the Panel was charged with developing a Best Practice Statement, which employs published data in concert with expert opinion. The initial Medline search was supplemented by review of bibliographies and additional focused searches. In all, 105 articles were deemed by the Panel members to be suitable for scrutiny. From these papers, the Panel identified four categories of urologic surgeries which appeared to be candidates for DVT prophylaxis: transurethral surgery, anti-incontinence and pelvic reconstructive surgery,

laparoscopic urologic and/or robotically assisted laparoscopic procedures, and open urologic surgery. Pediatric urologic surgery and renal transplantation were excluded because of the relative paucity of literature concerning these areas. Each Panel member was assigned to assess the evidence relevant to their area of expertise and to draft a section of the document based on their review of the literature and expertise. Due to the lack of robust data, an evidence table could not be developed.

This document was submitted for peer review, and comments from 23 physicians and researchers were considered by the Panel in making revisions. The final document was approved by the AUA PGC and the BOD. Funding of the Panel was provided by the AUA; members received no remuneration for their work. Each Panel member provided a conflict of interest disclosure to the AUA.

## **Therapeutic options for thromboprophylaxis**

Depending on the level of patient risk for thromboembolism, the following therapies can be used alone or in combination as options for the prevention of DVT in the surgical setting (see Appendix 3):

- mechanical (nonpharmacologic) therapies – early ambulation, graduated compression stockings (GCS), and intermittent pneumatic compression (IPC), and
- pharmacologic agents – low-dose unfractionated heparin (LDUH) and low molecular weight heparin (LMWH)

In an analysis of randomized controlled studies involving nonorthopedic surgeries, GCS and IPC were found to reduce the incidence of DVT, but the low numbers of placebo-treated

patients overall precluded drawing conclusions regarding the impact of these interventions on PTE.<sup>5</sup> Both LDUH<sup>5</sup> and LMWH<sup>6</sup> have been found to significantly reduce the incidence of DVT and fatal PTE in general surgical patients as well as reduce the incidence of DVT in urologic surgical patients.<sup>7</sup> Additionally, the combination of both mechanical and pharmacologic prevention strategies have been demonstrated in nonurologic procedures to be superior to either modality alone.<sup>5</sup> Aspirin and other antiplatelet drugs, while highly effective at reducing vascular events associated with atherosclerotic disease, are not recommended for VTE prophylaxis in surgical patients.<sup>8</sup>

When considering the pharmacologic options, the risk of bleeding complications should be considered. An analysis of 33 randomized controlled trials (RCTs) found that the rates of injection site bleeding and wound hematomas in general surgery patients were significantly higher in those receiving pharmacologic prevention (LDUH and LMWH) than in those receiving placebo. The incidence of major bleeding complications such as gastrointestinal tract or retroperitoneal bleeding was very low (0.2% and 0.08%, respectively) with pharmacologic prophylaxis.<sup>9</sup> Postmarketing reports of epidural or spinal hematomas with the use of LMWH and concurrent spinal/epidural anesthesia or puncture prompted the United States Food and Drug Administration to issue a black box warning about this complication<sup>10</sup>; this complication also has been reported, although less frequently, with LDUH.<sup>8</sup>

Other studies have compared the efficacy and risk of bleeding complications of LDUH with that of LMWH. An analysis of the outcomes of 16 studies involving patients undergoing abdominal surgery found comparable efficacy while data were inconsistent as to the relative risks of bleeding complications.<sup>11</sup> Some large, randomized trials have reported significantly

lower risks of bleeding complications, severe bleeding, or wound hematoma with LMWH<sup>12,13</sup> while others have reported no significant differences.<sup>14</sup> For a listing of considerations in the use of pharmacologic prophylaxis, see Appendix 3.

## Defining risk levels

Patient-specific predisposing factors increase the risk of DVT in patients undergoing urologic surgery. These factors are wide ranging and include immobility, trauma, malignancy, previous cancer therapy, past history of DVT, increasing age, pregnancy, estrogen therapy, obesity, smoking, and venous varicosities; these as well as additional factors increasing the risk of DVT are listed in Table 1.

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**Table 1: Risk Factors for Increased Development  
of Deep Vein Thrombosis<sup>8</sup>**

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Surgery

Trauma (major or lower extremity)

Immobility, paresis

Malignancy

Cancer therapy (hormonal, chemotherapy, or radiotherapy)

Previous Venous Thromboembolism

Increasing age

Pregnancy and the postpartum period

Estrogen-containing oral contraception or hormone  
replacement therapy

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**Selective estrogen receptor modulators**

**Acute medical illness**

**Heart or respiratory failure**

**Inflammatory bowel disease**

**Nephrotic syndrome**

**Myeloproliferative disorders**

**Paroxysmal nocturnal hemoglobinuria**

**Obesity**

**Smoking**

**Varicose veins**

**Central venous catheterization**

**Inherited or acquired thrombophilia**

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Adapted with permission from Geerts et al. Chest 2004.<sup>8</sup>

When assessing the risk of DVT for an individual patient, both the procedure, with its inherent risk, and the patient's specific, predisposing factors must be considered. The appropriate DVT prophylaxis for a low-risk procedure may be more complex in a patient with a high-risk profile. A risk stratification table has been constructed to provide guidance in choosing the appropriate preventative measures (Table 2).<sup>8</sup>



**Table 2: Patient Risk Stratification<sup>8</sup>**

Low risk	Minor* surgery in patients <40 years with no additional risk factors
Moderate risk	Minor* surgery in patients with additional risk factors Surgery in patients aged 40-60 years with no additional risk factors
High risk	Surgery in patients >60 years Surgery in patients aged 40-60 years with additional risk factors (prior venous thromboembolism, cancer, hypercoagulable state, see table I)
Highest risk	Surgery in patients with multiple risk factors (age >40 years, cancer, prior venous thromboembolism)

\* For the purposes of this paper, minor surgery is defined as a procedure with a relatively short operating time in which the patient is rapidly ambulatory. Adapted with permission from Geerts et al. Chest 2004.<sup>8</sup>

Once a patient's risk profile has been identified, one must determine the specific risk category to which a particular urologic procedure belongs. Procedures within a category, such as a suburethral sling procedure compared with an open sacrocolpopexy, may require markedly different approaches for DVT prophylaxis.

## **Transurethral surgery**

**For the vast majority of transurethral procedures, early ambulation is recommended for DVT prophylaxis. For patients at increased risk of DVT undergoing transurethral resection of the prostate (TURP), the use of GCS, IPC, postoperative LDUH or LMWH may be indicated.**

No RCTs assessing the role of various DVT prophylaxes for urologic transurethral procedures were identified by the Panel, nor was a true estimate of the risks of DVT for these procedures readily obtainable. Based on an analysis of the literature, most of which was published several decades ago, the incidence of DVT in patients undergoing TURP in the absence of prophylaxis ranged from 2% to 10%.<sup>5</sup> However, an analysis of a large database (The California Patient Discharge Data Set) determined that the incidence of symptomatic venous thromboembolism (VTE) within 91 days of TURP was 0.3% and 0.5% for those with and without malignancy<sup>15</sup>, suggesting that the overall incidence may be low. In a retrospective analysis of 883 patients undergoing TURP, the reported incidence of postoperative PTE was 0.45% with the routine use of GCS; these data were compared to an incidence of 0.55% in studies without data on prophylaxis (presumably with leg elevation alone) and 0.35% with the use of LDUH based on a review of the literature, although these data were felt to be an underestimation of the true incidence because of the retrospective nature of the study.<sup>16</sup> Limited data exist concerning the risk of blood loss following TURP with the use of pharmacologic DVT prophylaxis, with some studies suggesting that greater blood loss and higher transfusion rates are associated with the use of LDUH compared with those not receiving heparin<sup>17,18</sup>, and other studies observing no increase in bleeding risk.<sup>19</sup> It is unclear whether these risks also apply to LMWH.

## **Anti-incontinence and pelvic reconstructive surgery**

**The prevention of DVT in patients undergoing anti-incontinence and pelvic reconstructive surgeries should be dictated by preoperative individual patient risk factors and procedure-specific risk factors for DVT formation.**

- **For low-risk patients undergoing minor procedures the use of early postoperative ambulation appears to be sufficient.**
- **For moderate-risk patients undergoing higher risk procedures, the use of IPC, LDUH, or LMWH should be utilized.**
- **For high-risk and highest-risk patients undergoing higher-risk procedures, combination therapy with IPC plus LDUH or LMWH should be utilized unless the bleeding risk is considered unacceptably high.**

Anti-incontinence and pelvic reconstructive surgeries include a large spectrum of procedures. Some procedures, such as periurethral bulking, suburethral slings, and other cystoscopic procedures, are at low risk of DVT and subsequent PTE. However, a number of high-risk surgeries are also included, such as anterior and posterior vaginal wall repairs, uterosacral vault suspension, sacrospinous ligament fixation, paravaginal repair, and abdominal sacrocolpopexy.

The rates of DVT in patients undergoing major gynecologic surgery in the absence of DVT prophylaxis are reported in various reviews as 6% to 29%<sup>20</sup>, 15% to 40% for the combination of benign and malignant disease<sup>8</sup>, and 14% for gynecologic surgery for benign disease.<sup>5</sup> These findings suggest that the risk of DVT with subsequent PTE in patients undergoing pelvic reconstructive surgery is unacceptably high if DVT prophylaxis is not employed. Patients wearing GCS while undergoing major gynecologic surgery had a reduced risk of DVT compared to patients not wearing stockings in one study<sup>21</sup> while in other studies IPC, LDUH, and LMWH appeared to be equally effective in preventing DVT in these surgeries.<sup>22,23</sup> In these studies of patients undergoing surgery for gynecologic malignancy, one

reported an increased risk of postoperative bleeding in patients receiving LDUH compared to IPC<sup>22</sup> while the other reported no increased risk between patients receiving LMWH compared to IPC.<sup>23</sup> Two randomized trials involving women undergoing major gynecologic surgery, most with malignant disease, compared LMWH with standard heparin in thrombosis prophylaxis; there was no significant difference in the risk of thromboembolic events or hemorrhagic complications between groups.<sup>24,25</sup>

## **Urologic laparoscopic and/or robotically assisted urologic laparoscopic procedures**

**In view of the lack of large RCTs addressing this issue as well as the concerns for increased retroperitoneal bleeding at the time of urologic laparoscopic procedures, the Panel recommends the use of IPC devices at the time of the laparoscopic procedure. High-risk groups which may require the use of LDUH and LMWH may be identified.**

In recent years, the performance of urologic laparoscopic operations such as laparoscopic nephrectomy and retroperitoneal prostatectomy has increased in frequency. The paucity of prospective data addressing DVT prophylaxis in the case of urologic laparoscopic procedures is, however, especially marked. The risk of PTE in this group appears to be low. In one study, there was one PTE among 482 patients undergoing laparoscopic nephrectomy (0.2%)<sup>26</sup>, although it is not clear from this report what, if any, VTE prophylaxis measures were taken. One study involving prospective and retrospective data of patients undergoing laparoscopic surgery of the upper retroperitoneum found that the rate of VTE (1.2%) was identical in patients receiving either IPC or LMWH, but that the incidence of hemorrhagic complications was increased with the use of heparin.<sup>27</sup> A recent retrospective multi-institutional study evaluated symptomatic DVT

and PTE in patients undergoing laparoscopic or robotically-assisted laparoscopic radical prostatectomy.<sup>28</sup> Of 5951 patients, 31 (0.5%) developed symptomatic VTE (22 DVT only, 4 PTE without identified DVT, and 5 with both); there were 2 deaths due to PTE.<sup>28</sup> Preoperative risk factors for DVT in their pooled retrospective series are smoking and past history of DVT while intraoperative correlates to the development of DVT are operative time, including reoperation for bleeding, and prostate gland size which correlated to operative time.<sup>28</sup> In univariate analysis, heparin administration (received by 67% of patients in the study) was not found to be a significant predictor of VTE.<sup>28</sup>

## **Open urologic surgery**

**The Panel recommends the use of IPC in patients undergoing open urologic procedures.**

**Given the increased risk factors within this patient population, in many patients undergoing open urologic procedures, more aggressive regimens combining the use of IPC with pharmacologic prophylaxis may be considered.**

All adult patients undergoing open urologic surgery are at risk for development of DVT and subsequent PTE. Every patient has the presence or absence of definable risk factors (Table 1) coupled with the inherent DVT risk factors associated uniquely with each procedure. Most of the urologic literature related to DVT prophylaxis in patients undergoing open urologic surgery relates to patients undergoing open radical prostatectomy. The risk of DVT was estimated to be 32% for patients undergoing retropubic prostatectomy in the absence of prophylaxis.<sup>5</sup>

Contemporary radical prostatectomy series have reported rates of thromboembolic complications (based on clinical signs and including both DVT and PTE) ranging from 0.8% to 6.2% with the

use of various prophylactic measures.<sup>15,29-33</sup> Not unexpectedly, DVT rates are higher if screening imaging techniques are utilized rather than clinical findings.<sup>34</sup>

There is evidence to support the use of IPC devices and GCS with the finding of a reduction in the risk of DVT in patients undergoing both general and gynecologic surgery.<sup>8</sup> In a large single institution series of patients undergoing radical prostatectomy in which all had mechanical prophylaxis (GCS and IPC) followed by next-day ambulation, there were only three VTEs, with no PTEs or deaths due to VTE.<sup>35</sup> Another large study of thromboembolic complications following radical prostatectomy found that the use of IPC did not decrease the incidence of VTE, but did significantly delay the time to onset of these events ( $20\pm 2$  days) when compared to patients not having such treatment ( $11\pm 5$  days).<sup>31</sup> For clinicians, these findings underscore the importance of recognizing that the majority of patients who present with PTE following radical prostatectomy will do so after discharge from the hospital.<sup>31</sup> Therefore, it is important that patients be counseled on the signs and symptoms of DVT and PTE after hospital discharge.

Two studies evaluated the risks of hemorrhage and lymphocele formation associated with heparin prophylaxis in patients undergoing radical prostatectomy.<sup>36,37</sup> One study of patients treated with radical prostatectomy compares 73 consecutive patients receiving LMWH to a control group of 89 patients using only “elastic stockings”. The patients receiving heparin experienced a total of 7.8% hemorrhagic complications while the patients with elastic stockings reported 0% (those occurring during and after hospitalization). However, the patients receiving heparin showed a decrease in the risk of VTE when compared to the patients using only elastic stockings (0% vs. 3.3%, respectively).<sup>36</sup> In a prospective study of men undergoing pelvic lymphadectomy usually in association with radical prostatectomy, there was no significant

difference in blood loss or lymphocele formation between the 478 men receiving heparin prophylaxis and the 102 that did not receive heparin; the risk of VTE was 2.2% in the heparin group and 4% in the controls, a nonsignificant difference.<sup>37</sup> Pelvic lymphocele, a potential sequela of heparin prophylaxis, has been found to be an additional risk factor for the development of DVT, presumably secondary to pelvic venous compression.<sup>29</sup>

Radical cystectomy with urinary diversion, continent or incontinent, remains one of the most technically challenging while commonly performed procedures.<sup>38,39</sup> Inherently, this surgical procedure is performed in an older age group<sup>1,38,40</sup> with increased associated risk factors. The most common causes of perioperative mortality found in a study of radical cystectomy were cardiovascular-related events, septic complications, and PTE.<sup>1</sup> In the absence of prophylaxis, the DVT risk in urologic patients undergoing pelvic surgery has been estimated at 22%.<sup>41</sup> With DVT prophylaxis, the reported PTE rate varied from 0.0% to 2.0%.<sup>1,35,42</sup> Varying regimens for DVT prophylaxis have been reported, including IPC with early ambulation<sup>35,43</sup>, immediate postoperative warfarin<sup>1</sup>, and LDUH or LMWH.<sup>7,11</sup> In this high-risk group, consideration should be given to the use of combination DVT prophylaxis measures. The risks of bleeding must be weighed against the benefits of prophylaxis in determining the timing of initiation of DVT pharmacologic prophylaxis in combination with mechanical prophylaxis.

## **Conclusion**

DVT prophylaxis should be considered in all patients undergoing urologic surgical procedures. In many patients undergoing low-risk procedures, early ambulation may be the only DVT prophylactic measure that is indicated. However, in patients with a high-risk profile undergoing a high-risk procedure, an assessment of all risk factors inherent to the patient and planned

procedure should dictate the appropriate DVT prophylaxis. Future randomized trials comparing the different pharmacologic interventions would be useful and should be developed; the economics of thromboprophylaxis also should be evaluated.



## Conflict of Interest Disclosures

All panel members completed Conflict of Interest disclosures. Those marked with (C) indicate that compensation was received; relationships designated by (U) indicate no compensation was received.

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## **Acknowledgements and Disclaimers**

### **AUA Best Practice Statement for the Prevention of Deep Vein Thrombosis in Patients Undergoing Urologic Surgery**

The supporting systematic literature review and the drafting of this document were conducted by the Prevention of Deep Vein Thrombosis in Patients Undergoing Urologic Surgery Panel (the Panel) created in 2006 by the AUA. The PGC of the AUA selected the Panel chair who in turn appointed the additional Panel members with specific expertise in this disease.

The mission of the Panel was to develop either analysis- or consensus-based recommendations, depending on the type of evidence available and Panel processes, to support optimal clinical practices in the prevention of deep vein thrombosis in patients undergoing urologic surgery.

This document was submitted to 23 urologists and other health care professionals for peer review. After revision of the document based upon the peer review comments, the guideline was submitted to and approved by the PGC and the BOD of the AUA. Funding of the Panel and of the PGC was provided by the AUA. Panel members received no remuneration for their work. Each member of the PGC and of the Panel furnished a current conflict of interest disclosure to the AUA.

The final report is intended to provide medical practitioners with a current understanding of the principles and strategies for the prevention of deep vein thrombosis in patients undergoing urologic surgery. The report is based on review of available professional literature as well as clinical experience and expert opinion.

This document provides guidance only and does not establish a fixed set of rules or define the legal standard of care. As medical knowledge expands and technology advances, this guideline will change. Today they represent not absolute mandates but provisional proposals or recommendations for treatment under the specific conditions described. For all these reasons, this best practice statement does not preempt physician judgment in individual cases. Also, treating physicians must take into account variations in resources, and in patient tolerances, needs and preferences. Conformance with the best practice statement reflected in this document cannot guarantee a successful outcome.

# **Appendix 1. Prevention of Deep Vein Thrombosis in Patients Undergoing Urologic Surgery Best Practice Panel**

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## Appendix 2. VTE Prophylaxis Recommendations

LEVEL OF RISK	PROPHYLACTIC TREATMENT
Low Risk	<ul style="list-style-type: none"> <li>No prophylaxis other than early ambulation</li> </ul>
Moderate Risk	<ul style="list-style-type: none"> <li>Heparin 5000 units every 12 hours subcutaneous starting after surgery</li> <li><b>OR</b> *Enoxaparin 40 mg. (Cr Cl &lt; 30 ml/min. = 30 mg.) subcutaneous daily</li> <li><b>OR</b> Pneumatic compression device if risk of bleeding is high</li> </ul>
High Risk	<ul style="list-style-type: none"> <li>Heparin 5000 units every 8 hours subcutaneous starting after surgery</li> <li><b>OR</b> *Enoxaparin 40 mg. (Cr Cl &lt; 30 ml/min. = 30 mg.) subcutaneous daily</li> <li><b>OR</b> Pneumatic compression device if risk of bleeding is high</li> </ul>
Very High Risk	<ul style="list-style-type: none"> <li>*Enoxaparin 40 mg. (Cr Cl &lt; 30 ml/min. = 30 mg.) subcutaneous daily <b>and</b> adjuvant pneumatic compression device, or</li> <li>Heparin 5000 units every 8 hours subcutaneous starting after surgery <b>and</b> adjuvant pneumatic compression device</li> </ul>

### **\*Guidelines and Cautions for Enoxaparin Use**

- In patients with a body weight > 150 Kg. consider increasing prophylaxis dose of Enoxaparin to 40 mg. subcutaneous every 12 hours.
- Withhold Enoxaparin generally for at least 2 to 3 days after major trauma, and then only consider use after review of current patient condition and risk benefit ratio.
- For planned manipulation of an epidural or spinal catheter (insertion, removal), Enoxaparin should be avoided/held for 24 hours BEFORE planned manipulation and should be resumed no earlier than 2 hours FOLLOWING manipulation.
- Special testing may be indicated for Enoxaparin in a patient with a history of heparin-induced thrombocytopenia.
- The risks of bleeding must be weighed against the benefits of prophylaxis in determining the timing of initiation of DVT pharmacologic prophylaxis in combination with mechanical prophylaxis.**

***In selected very high-risk patients, clinicians should consider post-discharge Enoxaparin or Warfarin.***

Key: mg, milligram; Cr Cl, creatinine clearance; ml, milliliter; min, minute; Kg, kilogram

### Appendix 3. Considerations for use of pharmacologic prophylaxis.

(1) This list is not all-encompassing. (2) Physicians are advised to review the complete prescribing information before using any listed agents.

	CONTRAINDICATIONS	PRECAUTIONS	ADVERSE REACTIONS
Low molecular weight heparin (enoxaparin sodium; <sup>1</sup> tinzaparin sodium; <sup>2</sup> dalteparin sodium <sup>3</sup> )	<p>Should not be used in patients with:</p> <ul style="list-style-type: none"> <li>• Active major bleeding</li> <li>• Thrombocytopenia with a positive <i>in vitro</i> test for antiplatelet antibody in the presence of the drug [enoxaparin; dalteparin] or history of heparin-induced thrombocytopenia [tinzaparin]</li> <li>• Known sensitivity to the agent, heparin, sulfites, benzyl alcohol or pork products</li> <li>• Patients aged 90 years or older with creatinine clearance &lt;60 ml/min [tinzaparin]</li> </ul>	<p>Should be used with extreme caution in patients with:</p> <ul style="list-style-type: none"> <li>• Thrombocytopenia (patients with any degree of thrombocytopenia should be actively monitored)</li> <li>• Liver failure with elevated INR (&gt;1.5)</li> <li>• Uncontrolled arterial hypertension (Systolic &gt;200, diastolic &gt;110)</li> <li>• Conditions associated with increased risk of hemorrhage*</li> <li>• Severe renal impairment<sup>†</sup></li> <li>• Concurrent spinal/epidural anesthesia or spinal puncture</li> </ul>	<ul style="list-style-type: none"> <li>• Nonfatal or fatal hemorrhage at any site, tissue or organ</li> <li>• Thrombocytopenia</li> <li>• Elevations of serum aminotransferases</li> <li>• Local reactions, including irritation, pain, hematoma, ecchymosis and erythema</li> <li>• Hypersensitivity reactions</li> <li>• Spinal/epidural hematoma with spinal/epidural anesthesia or spinal puncture</li> </ul>
Heparin sodium <sup>4</sup>	<p>Should not be used in patients with:</p> <ul style="list-style-type: none"> <li>• Severe thrombocytopenia</li> <li>• Uncontrollable active bleeding state, except when due to</li> </ul>	<ul style="list-style-type: none"> <li>• Should be used in extreme caution in patients with conditions associated with increased risk of hemorrhage<sup>‡</sup> and with concurrent oral anticoagulants and antiplatelet</li> </ul>	<ul style="list-style-type: none"> <li>• Hemorrhage at any site</li> <li>• Thrombocytopenia</li> <li>• Elevations of aminotransferases</li> </ul>

	<p>disseminated intravascular coagulation</p> <ul style="list-style-type: none"> <li>An inability to receive appropriate blood coagulation tests (applies only to full-dose heparin, not low-dose heparin)</li> </ul>	<p>drugs</p> <ul style="list-style-type: none"> <li>In cases of documented hypersensitivity to heparin, should not be used except in clearly life-threatening situations</li> <li>White clot syndrome<sup>¶</sup></li> <li>Increased resistance to heparin with various conditions<sup>#</sup></li> <li>A higher incidence of bleeding reported in patients (particularly women) over 60 years of age</li> </ul>	<ul style="list-style-type: none"> <li>Local reactions, including irritation, erythema, mild pain, hematoma or ulceration</li> <li>Hypersensitivity reactions</li> </ul>
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INR, international normalized ratio; ml, milliliter; min, minute

<sup>1</sup>Lovenox<sup>®</sup> (enoxaparin sodium injection ) prescribing information, Sanofi-Aventis, U.S., LLC, October 2007.

<sup>2</sup>Innohep<sup>®</sup> (tinzaparin sodium injection) prescribing information, Celgene Corp, Boulder, CO; April 2008.

<sup>3</sup>Fragmin<sup>®</sup> (dalteparin sodium injection) prescribing information, Eisai, Inc. and Pfizer Health AB, New York, NY; April 2007.

<sup>4</sup>Heparin Sodium Injection, USP (from beef lung), Pharmacia & Upjohn Co., revised April 2006.

\*e.g. bacterial endocarditis, congenital or acquired bleeding disorders, active ulcerative and angiodysplastic gastrointestinal disease, a history of recent gastrointestinal ulceration, diabetic retinopathy, hemorrhagic stroke, or shortly after brain, spinal, or ophthalmological surgery, or in patients treated concomitantly with platelet inhibitors.

<sup>†</sup>Dose adjustment recommended for patients with creatinine clearance <30 mL/min

<sup>‡</sup> e.g. subacute bacterial endocarditis, severe hypertension, during and immediately following spinal puncture or spinal anesthesia or major surgery (especially involving the brain, spinal cord, or eye), conditions associated with bleeding tendencies such as hemophilia, thrombocytopenia, some vascular purpuras, gastrointestinal ulcerative lesions and continuous tube drainage of the stomach or small intestine, menstruation, and liver disease with impaired hemostasis; reduced dosage of heparin is recommended during treatment with antithrombin III (human).

<sup>¶</sup>A syndrome in which new thrombus formation in association with thrombocytopenia resulting from irreversible aggregation of platelets may lead to skin necrosis, gangrene of the extremities, myocardial infarction, pulmonary embolism, stroke, or death; promptly discontinue heparin administration if a patient develops new thrombosis in association with a reduction in platelet count.

<sup>#</sup>e.g. Fever, thrombosis, thrombophlebitis, infections with thrombosing tendencies, myocardial infarction, cancer, in postsurgical patients, and patients with antithrombin III deficiency.



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