Korean Guidelines for the Prevention of Venous Thromboembolism

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Received: 23 February 2010
Accepted: 5 July 2010

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INTRODUCTION

Venous thromboembolism (VTE) is a thrombotic disorder of the venous system, which includes deep vein thrombosis (DVT) and pulmonary embolism (PE). Approximately half of all untreated DVT cases are complicated by PE, and conversely, 50% to 80% of all untreated PE cases are associated with DVT (1, 2).

VTE is a well-recognized, public health issue in developed countries. In the United States of America, 200,000 new cases of PE occur each year, and 50,000 of these result in death. PE is the third most common fatal vascular disorder following coronary artery disease (CAD) and cerebrovascular accident (CVA) (3). Thromboprophylaxis has been recommended for the following reasons: the high incidence of VTE in hospitalized patients; the difficulty of early diagnosis due to vague symptomatology; the cost-effectiveness of medical prophylaxis; and, the high mortality of PE without early diagnosis and adequate treatment. Health authorities in developed countries have established guidelines

This guideline focuses on the primary prevention of venous thromboembolism (VTE) in Korea. The guidelines should be individualized and aim at patients scheduled for major surgery, as well as patients with a history of trauma, high-risk pregnancy, cancer, or other severe medical illnesses. Currently, no nation-wide data on the incidence of VTE exist, and randomized controlled trials aiming at the prevention of VTE in Korea have yielded few results. Therefore, these guidelines were based on the second edition of the Japanese Guidelines for the Prevention of VTE and the eighth edition of the American College of Chest Physicians (ACCP) Evidenced-Based Clinical Practice Guidelines. These guidelines establish low-, moderate-, and high-risk groups, and recommend appropriate thromboprophylaxis for each group.

Key Words: Guideline; Prevention; Venous Thromboembolism

Based on the available evidence and recommended thromboprophylaxis to medical societies in order to improve health standards and reduce health costs (4, 5).

The incidence of VTE in the Korean population has known to be lower than in the Caucasian population; however, it appears to be rapidly increasing in large part from the widespread adoption of the Western lifestyle. Additionally, the elderly comprise the largest proportion of the Korean population, and advanced age has been recognized as a risk factor for VTE. Despite the rise in the incidence of VTE, many physicians in Korea still are not aware of the significance of VTE and the risk of sudden death associated with inappropriate management of this condition. Recently, we published a guideline which was a revised version of the Japanese Guidelines for the Prevention of VTE; however, it was cumbersome for physicians to read (6). The following guidelines represent a simplified, practical version of the aforementioned guidelines, complete with risk stratification (low, moderate, and high) and thromboprophylaxis recommenda-
they are not cost-effective. Pharmacologic methods are reason-
high bleeding risk. However, supportive evidence is limited, and
mended for detection of VTE instead of pharmacoprophylaxis.
expensive and unreliable at times. These are not routinely recom-
VTE in some patients, like only in high-risk patients who can
computed tomography (CT) angiography can be used to detect
Screening compression ultrasonography (CUS) or pulmonary
Exercise increases venous blood flow and reduces venous sta-
tions for each group.
GENERAL GUIDELINES
Risk stratification
Accurate and prompt stratification of thrombotic risk should be
undertaken for every patient based on available evidence. The
method for risk evaluation should be simple, efficient, and cost-
effective. Most hospitalized patients have at least one risk factor
for VTE, and decisions regarding the risk of VTE should include
considerations of current and future risks (7). Accepted risk fac-
tors for the development of VTE include previous VTE; major
surgery; pelvis or femur fracture; major trauma; cancer; preg-
nancy and the postpartum period; long-term immobilization;
comorbidities such as congestive heart failure (CHF), chronic
obstructive pulmonary disease (COPD) requiring mechanical
ventilation, or CVA; spinal cord injury (SCI), old age, obesity,
estrogen replacement therapy, varicose veins, and other acquired
or hereditary thrombophilic conditions.
Selection of the appropriate thromboprophylaxis depends
upon the level of thrombotic risk taken on by each patient (8-
10). The general consensus establishes obesity, exogenous es-
trogen, and varicose veins as low-risk conditions; advanced age,
prolonged immobilization, CHF; COPD, central venous catheter
placement, chemotherapy, and sepsis as moderate-risk condi-
tions; and, previous VTE, hereditary thrombophilia, and lower
extremity paralysis as high-risk conditions.
The American College of Chest Physicians (ACCP) Evidenced-
Based Clinical Practice Guidelines (8th Edition) for the Preven-
tion of VTE uses three thrombotic risk groups (low, moderate,
and high) based on clinical evidence in the Caucasian popula-
tion. Thromboprophylaxis is recommended for all patients with
a moderate or high risk for VTE (11). However, the Japanese
Guideline recommends that active prophylaxis should be initi-
ated at one level higher than the ACCP guidelines because the
Japanese population is less susceptible to VTE than the Cauca-
sian population. The Korean Society on Thrombosis and He-
mostasis (KSTH) adopted the Japanese risk stratification guide-
lines due to the ethnic similarity between the Korean and Japa-
nese populations.
Thromboprophylaxis
Screening compression ultrasonography (CUS) or pulmonary
computed tomography (CT) angiography can be used to detect
VTE in some patients, like only in high-risk patients who can
not receive thromboprophylaxis; however, these modalities are ex-
pensive and unreliable at times. These are not routinely recom-
mended for detection of VTE instead of pharmacoprophylaxis.
Non-pharmacologic methods are applicable in patients with a
high bleeding risk. However, supportive evidence is limited, and
they are not cost-effective. Pharmacologic methods are reason-
able and cost-effective, and are therefore recommended as the
initial form of prophylaxis in most patients without a high bleed-
ing risk.
Non-pharmacologic methods
Exercise increases venous blood flow and reduces venous sta-
is, and thus, helps prevent VTE. However, no standardized ex-
ercise has been implemented for the prevention of VTE in hos-
pitalized patients. The application of graduated compression
stockings (GCS) at the time of admission can prevent VTE in at-
risk patients. Use of intermittent pneumatic compression (IPC)
can be helpful in at-risk surgical patients (Table 1) (12). Place-
ment of an inferior vena cava (IVC) filter is only recommended
for patients at high-risk of VTE when pharmacologic thrombo-
 prophylaxis is contraindicated (13-16).
Pharmacologic methods
Pharmacologic methods for thromboprophylaxis include low-
molecular weight heparin (LMWH), low-dose unfractionated
heparin (LDUH), fondaparinux, warfarin, dabigatran, and riva-
roxaban. The recommended daily doses are LMWH 20-100 U/
kg (0.2-1 mg/kg) subcutaneously (SC) daily; LDUH 5,000 U ev-
ery 8 to 12 hr SC, fondaparinux 2.5 mg SC daily; dabigatran etex-
ilate 150 mg every 12 hr orally; and, rivaroxaban 10 mg orally
each day. Warfarin should be dosed daily to maintain an inter-
national normalized ratio (INR) in the range 1.5 to 2.5 (Table 1).
The duration of thromboprophylaxis depends upon the per-
ceived benefits of anticoagulation versus the risks of bleeding
and overall cost.
Stratification of VTE risk in hospitalized patients
Based on clinical evidence, the risk of VTE in surgical patients
can be stratified from low to high (Table 2). High-risk situations
include major surgery in patients with previous VTE or a hyper-
coagulable state, major orthopedic surgery, CVA, major trauma,
or SCI.
The Korean guidelines are not based upon clinical evidence,
but rather upon a consensus in experts panel of Korean Society of Thrombosis and Hemostasis (KSTH). Therefore, these guidelines represent the most current opinions for good clinical practices for the prevention of VTE. The ultimate decision regarding thromboprophylaxis should be individualized by case and determined by the attending physician.

**GENERAL SURGERY**

The principles of risk assessment for general surgery are based on the type of surgery (minor or major), age (<40 yr, 40-60 yr, and ≥60 yr), and the presence of additional risk factors, such as cancer or previous VTE (11). According to these principles, cases were classified into three risk groups (Table 3). Early and frequent ambulation was recommended for low-risk patients. Mechanical methods (GCS and/or IPC) or pharmacologic methods (LMWH, LDUH, or fondaparinux) are recommended for moderate-risk patients. LMWH, fondaparinux, or warfarin are recommended for high-risk patients scheduled for major cancer surgery with additional risk factors for VTE and for high-risk patients with a previous VTE or thrombophilia. When anticoagulation is contraindicated in a high-risk patient, IPC is recommended. For patients undergoing entirely laparoscopic procedures who do not have additional thromboembolic risk factors, routine use of thromboprophylaxis (other than early and frequent ambulation) is discouraged (17).

**ORTHOPEDIC SURGERY**

Patients scheduled for major orthopedic surgery, including total hip replacement (THR), total knee replacement (TKR), and hip fracture surgery (HFS), represent a group at particularly high risk of VTE. In the West, the incidence of VTE among patients that undergo major orthopedic surgery ranges from 41% to 60%, but the epidemiological data on the incidence of VTE in the Asian population varies (11). A recent Korean study found the incidence of postoperative VTE in TKR, THR, and HFS, to be 40.4%, 8.7%, and 16.4%, respectively, using CT pulmonary angiography and indirect CT venography (18).

For patients scheduled to undergo TKR, THR, or HFS, LMWH, warfarin or fondaparinux is recommended for thromboprophylaxis (Table 4) (19, 20). GCS and/or IPC are recommended in patients with a risk of bleeding. The current recommended duration for anticoagulation is 7 to 10 days, but extended use through 35 days has been proposed in the 8th ACCP guideline for the prevention of VTE after discharge from the hospital (4).

Patients scheduled for vertebral surgery have a moderate risk for VTE and should wear GCS and/or utilize IPC. Patients scheduled for surgery of the upper extremity or lower leg (distal to the knee) has a low risk for VTE and do not require prophylaxis. Routine CUS screening is not helpful in these patients.

**NEUROSURGERY**

The incidence of DVT and subsequent PE in neurosurgery patients has been reported as high as 25%, and the PE mortality rate has been reported from 9% to 50% (21, 22). The risk factors that contribute to the high frequency of VTE in neurosurgical patients include a prior VTE; type of surgery (cranial, spinal, or vascular); duration of surgery; malignancy; infection; immobilization; venous stasis; chronic lower extremity swelling; lower extremity burn; severe trauma; obesity; lower extremity amputation; and the use of a compressive garment for at least 48 hours. In patients with a previous VTE, LMWH, warfarin, or fondaparinux is recommended for thromboprophylaxis (Table 4) (19, 20). GCS and/or IPC are recommended in patients with a risk of bleeding. The current recommended duration for anticoagulation is 7 to 10 days, but extended use through 35 days has been proposed in the 8th ACCP guideline for the prevention of VTE after discharge from the hospital (4).

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**Table 2.** VTE risk-stratification and recommended prophylactic methods for each risk group

| Risk Group | Patients or Surgery | Thromboprophylaxis |
|------------|---------------------|---------------------|
| Low        | Minor surgery in mobile patients, Medical patients who are fully mobile | Not necessary and Early ambulation |
| Moderate   | General open gynecological surgery, General open urologic surgery, Medical patients on bed rest or sick | GCS, IPC, LMWH, LDUH or Fondaparinux |
| High       | THR, TKR, HFS, Major trauma, Spinal cord injury, Major surgery in patients with previous VTE or thrombophilia | LMWH, Warfarin or Fondaparinux; IPC* |

*Recommended for patients with a risk of bleeding; consider switching to anticoagulants when the bleeding risk abates.

**Table 3.** Levels of VTE risk and recommendations for general surgery

| Risk Group | Procedures | Thromboprophylaxis |
|------------|------------|---------------------|
| Low        | Major surgery in age <40 yr, Minor surgery in age <60 yr | Early ambulation |
| Moderate   | Major surgery in age >40 yr or with risk factor, Non-major surgery in age >60 yr or with risk factor | GCS, IPC, LMWH, LDUH, or Fondaparinux |
| High       | Major cancer surgery with additional risk factor, Major surgery in patients with previous VTE or thrombophilia | LMWH, Warfarin, or Fondaparinux; IPC* |

*Recommended in patients with a risk of bleeding; consider switching to anticoagulants when the bleeding risk abates.

**Table 4.** Levels of VTE risk and recommendations for orthopedic surgery

| Risk Group | Procedures | Thromboprophylaxis |
|------------|------------|---------------------|
| Low        | Surgery of upper extremity, Surgery of fracture distal to the knee | Early ambulation |
| Moderate   | Vertebral surgery | GCS or IPC |
| High       | Total hip replacement, Total knee replacement, Hip fracture surgery | LMWH, Warfarin, or Fondaparinux; IPC* |

*Recommended in patients with a risk of bleeding; consider switching to anticoagulants when the bleeding risk abates.

VTE, venous thromboembolism; GCS, graduated compression stockings; IPC, intermittent pneumatic compression; LMWH, low-molecular-weight heparin; LDUH, low-dose unfractionated heparin; VTE, venous thromboembolism.
extremity trauma; advanced age; CHF; obesity; and, sleep apnea.

Early and frequent ambulation for low-risk neurosurgery patients who have undergone surgery (not craniotomy) is recommended. For moderate-risk patients scheduled for craniotomy (for reasons other than brain tumor), GCS and/or IPC is recommended. IPC, LDUH or LMWH are suggested for patients scheduled for craniotomy for a brain tumor. For high-risk patients scheduled for craniotomy with a concomitant history of VTE or thrombophilia, a combined thromboprophylactic approach with a mechanical method (GCS and/or IPC) and a pharmacologic method (LMWH or LDUH) is recommended.

**UROLOGIC SURGERY**

Risk factors for VTE in urologic surgery patients include an age ≥40 yr, obesity, malignancy, recent surgery, previous VTE, an open (vs transurethral) procedure, general anesthesia, and a long operation time. Major urologic surgery may present higher risks of PE and VTE than general surgery.

The risk of VTE has been associated with operation time (<45 min and ≥45 min). For patients scheduled for a low-risk procedure, early ambulation and exercise without any other form of thromboprophylaxis is recommended. On the other hand, for patients scheduled for major surgery, thromboprophylaxis with GCS or IPC; LMWH, LDUH, or fondaparinux; or a combination of mechanical and pharmacologic thromboprophylaxis is indicated. For abdominal (open) surgery on the kidney or retroperitoneum, the aforementioned principles outlined for general surgery should be followed. Nephrectomy presents the same level of risk as radical prostatectomy.

**OBSTETRIC AND GYNECOLOGIC SURGERY**

The incidence of VTE is high in pregnancy and may occur at any stage during pregnancy or in the weeks following delivery. The risk factors for VTE in pregnant women include previous VTE, a family history of VTE, presence of anti-phospholipid antibody, age ≥40 yr, prolonged bed rest, placenta previa, Caesarian section, and lower extremities varicosities. For women with a history of abortion, intrauterine death, toxemia, placenta previa, and intrauterine growth retardation, monitoring for thrombophilia and evaluating for thrombosis must be continued throughout the pregnancy.

Giant uterine myoma, previous surgery for an ovarian tumor, ovarian cancer, uterine or cervical cancer, severe intrapelvic adhesions, ovarian hyperstimulation syndrome, hormonal therapy, and particularly, protracted lymph node dissection requiring transfusion are considered important risk factors for VTE (23, 24). Estrogen or progesterone should be administered with caution in postmenopausal women with a high risk of VTE.

For patients with risk factors, general thromboprophylaxis, such as, lower extremity exercise on a bed, GCS, IPC, and adequate hydration postpartum are recommended. Early ambulation should be encouraged even after a normal delivery in low-risk patients. In addition, pharmacologic thromboprophylaxis with LMWH or warfarin should be considered in patients with risk factors other than Caesarian section. For high-risk pregnancies with documented thrombophilia, such as, positive anti-phospholipid antibody or previous VTE, pharmacologic thromboprophylaxis with LMWH is recommended (25). Warfarin is contraindicated during pregnancy (category X) (26). However, warfarin can replace LMWH after delivery and be used for 6 weeks to 3 months for continued postpartum thromboprophylaxis (25). For patients with gynecologic disease, management strategies should follow those outlined for general surgery patients.

**MEDICAL CONDITIONS**

Acutely ill medical patients represent a clinically heterogeneous group and demonstrate differing risks of VTE. Despite extensive studies in medical patients, the morbidity and mortality of VTE remains significant. Without prophylaxis, the incidence of DVT and PE in general medical patients has been reported to range from 10% to 30% (5, 27, 28).

The risk of VTE was determined by assessing the probability of VTE in acutely ill medical patients according to predisposing risk factors (age >70 yr, obesity, long-term immobility, tobacco use, varicosities, dehydration, estrogens, cancer, previous DVT, paraplegia, congenital or acquired thrombophilia, and inflammatory bowel disease [IBD]) and acute medical illnesses currently under treatment (COPD exacerbation, mechanical ventilator therapy, infection, CHF, and CVA) (Table 5). Acute ischemic

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**Table 5. Risk factors of VTE in general medical patients**

| Baseline risk factors                                                                 | Acute medical illness                                      |
|---------------------------------------------------------------------------------------|-----------------------------------------------------------|
| Low Obesity, Smoking, Varicose vein, Dehydration, HRT, OCs                              | Acute exacerbation of COPD without mechanical ventilation  |
| Intermediate Old age (>70 yr), Long term immobilization, Active cancer, Pregnancy,    | Infection associated with immobility, Acute exacerbation of |
| Central venous catheterization, Nephrotic syndrome,                                  | COPD with mechanical ventilation, Sepsis, MI, CHF (NYHA   |
| Inflammatory bowel disease                                                            | grade III or IV)                                           |
| High Past history of VTE, Thrombophilia*, Paraplegia                                 | Cerebral stroke complicated with paralysis                 |

*congenital thrombophilia such as antithrombin III deficiency or protein C or S deficiency, or acquired thrombophilia like antiphospholipid antibody syndrome.

VTE, venous thromboembolism; HRT, hormone replacement therapy; OCs, oral contraceptives; COPD, chronic obstructive pulmonary disease; MI, myocardial infarction; CHF, congestive heart failure; NYHA, New York Heart Association; VTE, venous thromboembolism.
stroke patients with restricted mobility should have LDUH or LMWH administrated 24 hr after thrombolytic therapy. If a patient has an acute intracranial hemorrhage or a contraindication to anticoagulation, GCS and/or IPC can be used. However, GCS and IPC can increase venous return and should be used carefully in cases of fluid overload, such as severe CHF. For ambulatory cancer patients with cyclic chemotherapy, routine thromboprophylaxis is not recommended; however, cancer patients with restricted mobility due to other acute medical illnesses are considered high-risk and should have thromboprophylaxis administered (4).

Patients with CHF, COPD, sepsis, or IBD also have a higher prevalence of VTE, and thromboprophylaxis using GCS, IPC, LMWH, LDUH, or fondaparinux is recommended (29, 30). The majority of patients admitted to the intensive care unit (ICU) have multiple risk factors for VTE. These patients should be routinely assessed and offered thromboprophylaxis with LDUH or LMWH. GCS and/or IPC can be used when there is a contraindication to anticoagulation.

MAJOR TRAUMA AND SPINAL CORD INJURY

Patients with major trauma are classified as high-risk. Major trauma includes multiple serious injuries, head trauma with mental status changes, severe pelvic fracture, and multiple fractures of a lower extremity. VTE can cause significant morbidity in patients experiencing major trauma and occurs in up to 50% of patients without thromboprophylaxis (31). Furthermore, PE represents the third-leading cause of death among those who survive beyond 24 hr.

Routine thromboprophylaxis is recommended for all major trauma patients. Those patients with a high bleeding risk should receive LMWH or LDUH after primary hemostasis. On the other hand, if pharmacologic thromboprophylaxis is contraindicated due to active bleeding or a sustained high risk of bleeding, mechanical (GCS and/or IPC) thromboprophylaxis should be implemented.

All patients with acute SCI should receive routine thromboprophylaxis. Initially, GCS and/or IPC and careful observation for bleeding is recommended, followed by LMWH thromboprophylaxis when primary hemostasis is complete. For patients with a high bleeding risk, such as those with intra-abdominal bleeding, traumatic subarachnoid hemorrhage, or spinal hematoma, pharmacologic thromboprophylaxis should be delayed until the risk of further bleeding has diminished.

NEURAXIAL ANESTHESIA

Neuraxial anesthesia is a comprehensive term used for spinal, epidural, and caudal blocks. The risk for the development of spinal or epidural hematoma may be elevated by the concomitant use of anticoagulants and antiplatelet agents (32, 33). The established risk factors for spinal or epidural hematoma after neuraxial blockade include an underlying hemostatic disorder, an anatomically-deformed vertebral column, traumatic insertion of a needle or catheter, repeated insertion attempts, concomitant anticoagulation, continuous use of epidural catheters, and old age (11, 34).

To improve the safety of neuraxial blockade in patients receiving or scheduled to receive anticoagulant prophylaxis, several guidelines have been established. Neuraxial anesthesia/analgesia should generally be avoided in patients with a bleeding disorder and in situations when preoperative hemostasis is impaired by antithrombotic drugs. An epidural catheter should be removed when the anticoagulant effect is minimal (usually just before the next scheduled SC injection). Anticoagulation prophylaxis should be delayed for at least 2 hr after the removal of a spinal needle or epidural catheter. If warfarin is required, continuous epidural analgesia should not be used for longer than 1 or 2 days. Finally, monitoring for cord compression syndrome is required when patients are receiving anticoagulation medication (32, 35).

SUMMARY

These guidelines emphasize the primary prevention of VTE with thromboprophylaxis for Korean patients experiencing surgery, obstetric delivery, trauma, cancer, and severe medical illness. Based on VTE risk factors (age, immobility, history of VTE, comorbid illness, and type of surgery or trauma), patients can be stratified into low-, moderate-, and high-risk groups. For high-risk patients (major orthopedic surgery, major trauma, SCI, and major surgery with a history of VTE or thrombophilia), thromboprophylaxis with LMWH, warfarin, or fondaparinux is recommended. Mechanical methods of thromboprophylaxis should be used primarily in patients with a high bleeding risk. For moderate-risk patients (general open gynecological surgery, general open urologic surgery, and medical patients on bed rest), thromboprophylaxis with either a mechanical method (GCS and/or IPC) or a pharmacologic method (LMWH, LDUH, or fondaparinux) can be utilized. For low-risk patients (minor surgery in mobile patients and medical patients who are fully mobile), early and frequent ambulation is the only recommended thromboprophylaxis. In conclusion, this article outlines the first Korean guidelines issued for primary VTE prevention and provides a useful reference for clinicians. These guidelines need to be updated based on results from well controlled studies conducted in Korea.

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