Effective Health Care Program

Heart and Blood Vessel Conditions
Venous Thromboembolism Prophylaxis in Orthopedic Surgery

# Venous Thromboembolism Prophylaxis in Orthopedic Surgery

## Research Focus for Clinicians

A systematic review of 179 articles published between January 1980 and May 2011 sought to determine the comparative effectiveness, benefits, and adverse effects of venous thromboembolism (VTE) prophylaxis for patients undergoing orthopedic surgery. The review did not cover the effectiveness of the oral direct factor Xa inhibitor, rivaroxaban. However, after the report was prepared, rivaroxaban was approved by the U.S. Food and Drug Administration (FDA). The comparative effectiveness of rivaroxaban versus enoxaparin from four large phase III trials are briefly reviewed in a separate section of this summary. This summary is provided to inform discussions of options with patients and to assist in decisionmaking that considers a patient's values and preferences. However, reviews of evidence should not be construed to represent clinical recommendations or guidelines. The full report is available at www.effectivehealthcare.ahrq.gov/thrombo.cfm.

## Background

Major orthopedic surgical procedures—total hip replacement (THR), total knee replacement (TKR), and hip fracture surgery—carry a high risk of VTE.

Strategies to prevent VTE include pharmacological and mechanical modalities, used alone or in combination. Pharmacological prophylaxis carries risks and limitations including bleeding.

The magnitude of benefit and adverse effects in contemporary practice in the United States among the orthopedic population are not well known. This summary highlights findings from the review including baseline risk for VTE with major orthopedic surgery, the comparative effectiveness of different pharmacological or mechanical modalities, how duration of prophylaxis affects outcomes, and evidence regarding combination pharmacological and mechanical prophylaxis.

## Conclusions

The estimated native (i.e., without pharmacological prophylaxis) incidence of deep vein thrombosis (DVT) after THR and TKR was 39 percent and 46 percent, respectively. Pharmacological prophylaxis decreases the risk of DVT with some increased risk of minor bleeding when compared with no pharmacological prophylaxis. There is some evidence that low-molecular-weight heparin (LMWH) decreases risk for DVT when compared with warfarin at the expense of increases in major and minor bleeding. LMWH provides greater protection against DVT and pulmonary embolism (PE) when compared with unfractionated heparin (UFH) while reducing the risk of bleeding and heparin-induced thrombocytopenia.

In contrast, LMWH was not as effective in protecting against the risk of DVT when compared with an injectable factor Xa inhibitor, although the odds of bleeding were reduced. Prolonged prophylaxis decreased the risk of thromboembolism at the risk of increased minor bleeding when compared with standard-duration prophylaxis. No differences in mortality outcomes were observed for any of the interventions compared; however, this may be related to the infrequency of this outcome and length of followup.

After the review was completed, rivaroxaban, an oral factor Xa inhibitor, was approved by the FDA for this population of patients primarily based on the four Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) trials. Rivaroxaban decreased the risk of the composite primary outcome of DVT, nonfatal PE, or all-cause mortality in patients undergoing major orthopedic surgery. RECORD 1 and 2 showed superiority of prolonged prophylaxis with rivaroxaban versus enoxaparin (prolonged or standard-duration prophylaxis) with a decreased risk of the primary outcome in patients undergoing THR. RECORD 3 and 4 suggested that rivaroxaban decreases the risk of the primary outcome versus enoxaparin when used for prophylaxis for patients undergoing TKR. There were no significant differences in mortality or the risk for bleeding outcomes in all four trials.

## Clinical Bottom Line

### Baseline Incidence of VTE

Most of the literature evaluated THR and TKR surgery with very little evaluation of hip fracture surgery. The baseline risk of VTE and bleeding outcomes in the absence of pharmacological prophylaxis are as follows (THR percentage, TKR percentage):

- Pulmonary embolism (6%, 1%) ●○○
- DVT (39%, 46%) ●○○
- Major bleeding (1% ●●○, 3% ●○○)
- Minor bleeding (5% ●○○, 5% ●●○)

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**Strength of Evidence Scale**

| | | |
|---|---|---|
| High: | ●●● | There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect. |
| Moderate: | ●●○ | Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate. |
| Low: | ●○○ | Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate. |
| Insufficient: | ○○○ | Evidence either is unavailable or does not permit estimation of an effect. |

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## Clinical Bottom Line *(Continued)*

### Pharmacological Versus No Pharmacological Prophylaxis

Pharmacological prophylaxis:

- Decreased risk of proximal DVT ●●● or distal DVT ●●●; DVT ●●○; VTE ●○○; and asymptomatic DVT ●●○.
- Increased risk for minor bleeding. ●●●

### Comparative Effectiveness of Pharmacological Prophylaxis

LMWH, when compared with warfarin:

- Decreased risk of DVT ●○○ and distal DVT ●●○.
- Increased risk for minor bleeding ●●○ and increased the odds of surgical site bleeding ●○○ and major bleeding ●●●.

LMWH, when compared with UFH:

- Decreased risk of proximal DVT ●●● and DVT ●●○, and decreased the odds of PE ●●○.
- Decreased the odds of major bleeding ●●● and heparin-induced thrombocytopenia ●●○.

UFH versus the direct thrombin inhibitor desirudin increased the risks for DVT and proximal DVT by 2-fold and more than 5-fold, respectively. ●●○

The LMWH enoxaparin, when compared with the factor Xa inhibitor fondaparinux, demonstrated:

- Increased risk of DVT ●●○ and distal DVT ●●●, and increased odds of proximal DVT ●○○.
- Decreased odds of major ●●○ and minor ●○○ bleeding.

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### Standard Versus Prolonged Prophylaxis

When compared with patients who received standard-duration prophylaxis (7–10 days), patients who received prolonged prophylaxis (≥28 days) had:

- Decreased odds of PE ●●●, symptomatic DVT ●●●, and nonfatal PE ●●○, as well as decreased risk of asymptomatic DVT ●●●, proximal DVT ●●●, symptomatic, objectively confirmed VTE ●●○, and DVT ●●○.
- No increased odds of major bleeding ●○○, although the odds of minor bleeding did increase ●●●.

### Pharmacological and Mechanical Prophylaxis

Warfarin, when compared with mechanical prophylaxis, decreased the risk of proximal DVT by 66 percent. ●●○

Aspirin, when compared with mechanical prophylaxis, had a higher rate of DVT. ●●○

Pharmacological plus mechanical prophylaxis reduced the risk of DVT when compared with pharmacological prophylaxis alone. ●●○

### Characteristics That May Affect Risk of VTE

Patients who receive general anesthesia may have a higher risk of DVT than those who receive regional anesthesia. ●○○

No difference in risk of DVT or proximal DVT was found among patients receiving cemented versus noncemented arthroplasty. ●○○

Observational data suggest that patients with congestive heart failure were at an increased risk for symptomatic, objectively confirmed VTE when compared with those without it. ●●○

## Table 1. Major Outcomes of Interest

| Comparators | Magnitude of Effect; Risk/Odds (95% CI), NNT/NNH, SOE | | | | | |
|---|---|---|---|---|---|---|
| | DVT | Proximal DVT | Symptomatic VTE | PE | Major Bleeding | Minor Bleeding |
| Pharmacological prophylaxis vs. no prophylaxis | Decreased risk by 44%; RR 0.56 (0.47 to 0.68), NNT 3 to 33 ●●○ | Decreased risk by 47%; RR 0.53 (0.39 to 0.74), NNT 4 to 213 ●●● | NR | No difference; OR 0.38 (0.13 to 1.07) ●○○ | No difference; RR 0.74 (0.36 to 1.51) ●●○ | Relative risk is higher for prophylaxis by 67%; RR 1.67 (1.18 to 2.38), NNH 30 to 75 ●●● |
| LMWH vs. UFH | Decreased risk by 20%; RR 0.80 (0.65 to 0.99), NNT 12 to 100 ●●○ | Decreased risk by 40%; RR 0.60 (0.38 to 0.93), NNT 14 to 50 ●●● | NR | Decreased odds by 52%; OR 0.48 (0.24 to 0.95), NNT 8 ●●○ | Decreased odds by 35%; OR 0.57 (0.37 to 0.88), NNT 41 ●●● | No difference; RR 0.90 (0.63 to 1.28) ●●○ |
| Enoxaparin vs. fondaparinux | Relative risk is higher for enoxaparin by 99%; RR 1.99 (1.57 to 2.51), NNH 13 to 26 ●●○ | Odds are higher for enoxaparin by 219%; OR 2.19 (1.52 to 3.16), NNH 44 to 122 ●○○ | No difference; OR 0.70 (0.48 to 1.02) ●○○ | No difference; OR 3.34 (0.58 to 19.32) (SOE not rated) | Decreased odds by 35%; OR 0.65 (0.48 to 0.89), NNT 74 to 145 ●●○ | Decreased odds by 43%; OR 0.57 (0.35 to 0.94), NNT 31 to 60 ●○○ |

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## Table 1. Major Outcomes of Interest *(Continued)*

| Comparators | Magnitude of Effect; Risk/Odds (95% CI), NNT/NNH, SOE | | | | | |
|---|---|---|---|---|---|---|
| | DVT | Proximal DVT | Symptomatic VTE | PE | Major Bleeding | Minor Bleeding |
| LMWH vs. warfarin | Decreased risk by 34%; RR 0.66 (0.55 to 0.79), NNT 6 to 13 ●○○ | No difference; RR 0.63 (0.39 to 1.00) ●○○ | No difference; OR 1.00 (0.69 to 1.46) ●○○ | No difference; OR 1.11 (0.57 to 2.19) ●●○ | Odds are higher for LMWH by 92%; OR 1.92 (1.27 to 2.91), NNH 57 to 220 ●●● | Relative risk is higher for LMWH by 23%; RR 1.23 (1.06 to 1.43), NNH 18 to 218 ●●○ |
| UFH vs. desirudin | Relative risk is higher for UFH by 231%; RR 2.31 (1.34 to 4.00), NNH 5 to 11 ●●○ | Odds are higher for UFH by 477%; OR 4.74 (2.99 to 7.49), NNH 11 ●●○ | NR | No difference; OR 3.23 (0.56 to 18.98) ●○○ | NR | NR |
| Prolonged vs. standard-duration prophylaxis | Decreased risk by 63%; RR 0.37 (0.21 to 0.64), NNT 5 to 32 ●●○ | Decreased risk by 71%; RR 0.29 (0.16 to 0.52), NNT 9 to 71 ●●● | Decreased risk by 62%; RR 0.38 (0.19 to 0.77), NNT 8 to 54 ●●○ | Decreased odds by 87%; OR 0.13 (0.04 to 0.47), NNT 24 to 232 ●●● | No difference; OR 2.18 (0.73 to 6.51) ●○○ | Odds are higher for prolonged prophylaxis by 244%; OR 2.44 (1.41 to 4.20), NNH 11 to 118 ●●● |
| Pharmacological + mechanical vs. pharmacological only | Decreased risk by 52%; RR 0.48 (0.32 to 0.72), NNT 3 to 67 ●●○ | No difference; RR 0.33 (0.09 to 1.22) ●○○ | NR | No difference; OR 1.03 (0.14 to 7.34) ●○○ | NR | NR |

95% CI = 95-percent confidence interval; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; major bleeding (e.g., bleeding leading to greater transfusion requirements and/or reoperation); minor bleeding (e.g., surgical site bleeding, bleeding leading to infection, or bleeding leading to transfusion but not reoperation); NNH = number needed to harm (the calculated range); NNT = number needed to treat (the calculated range); NR = not reported or insufficient evidence to permit conclusions; OR = odds ratio; PE = pulmonary embolism; SOE = strength of evidence rating; THR = total hip replacement surgery; TKR = total knee replacement surgery; UFH = unfractionated heparin; VTE = venous thromboembolism

**Strength of Evidence Scale**

- High: ●●● There is high confidence that the evidence reflects the true effect. Further research is very unlikely to change our confidence in the estimate of effect.
- Moderate: ●●○ Moderate confidence that the evidence reflects the true effect. Further research may change our confidence in the estimate of effect and may change the estimate.
- Low: ●○○ Low confidence that the evidence reflects the true effect. Further research is likely to change our confidence in the estimate of effect and is likely to change the estimate.
- Insufficient: ○○○ Evidence either is unavailable or does not permit estimation of an effect.

## Summary of RECORD Trials Outcomes

- After the comparative effectiveness review was prepared, an oral direct factor Xa inhibitor, rivaroxaban, was approved by the FDA for preventing DVT, which may be associated with PE, in patients undergoing knee- or hip-replacement surgery. This decision was based, in part, on the findings of four phase III trials known as the Regulation of Coagulation in Orthopedic Surgery to Prevent Deep Venous Thrombosis and Pulmonary Embolism (RECORD) trials. The RECORD program investigated various regimens of rivaroxaban for preventing VTE after THR (RECORD 1 and 2) or TKR (RECORD 3 and 4) when compared with enoxaparin.
- The RECORD 1 and 2 trials demonstrated a consistent reduction in the risk of the composite primary outcome of DVT, nonfatal PE, or all-cause mortality with prolonged rivaroxaban (started 6–8 hours postoperatively, for 35 ± 4 days) when compared with enoxaparin given as either prolonged (started the evening before surgery, for 36 ± 4 days) or standard-duration (started the evening before surgery, for 13 ± 2 days) prophylaxis.
- The RECORD 3 and 4 trials suggested that rivaroxaban decreased the risk of the composite primary outcome of DVT, nonfatal PE, or all-cause mortality when compared with enoxaparin in patients who had TKR.
- In all four trials, there were no significant differences in the risk for the primary safety outcome of major bleeding as well as minor bleeding or mortality.

## Gaps in Knowledge

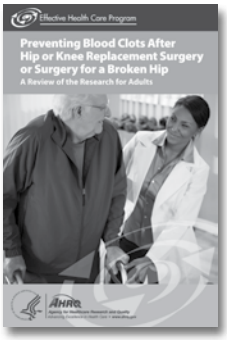
- Inadequate data did not permit conclusions about the comparative benefits and adverse effects associated with VTE prophylaxis in non–joint-replacement surgery.
- More information is needed on the following aspects of VTE prophylaxis in the setting of major orthopedic surgery:
  - Clinically important outcomes including symptomatic VTE, post-thrombotic syndrome, clinically relevant bleeding, prosthetic infection, reoperation, and mortality and whether intermediate outcomes predict health outcomes
  - Surgical, postsurgical, or patient factors that predict outcomes
  - The optimal followup period needed to determine longer term outcomes
  - Optimal duration of thromboprophylaxis
  - The role of combined pharmacological and mechanical prophylaxis

## What To Discuss With Your Patients

- General background information on the risk of thromboembolic disease
- That thromboembolic disease is a major risk after joint-replacement surgery and why some form of prophylactic treatment is indicated
- Options for prophylaxis
- Bleeding as the major risk of pharmacological prophylaxis

## Resource for Patients

*Preventing Blood Clots After Hip or Knee Replacement Surgery or Surgery for a Broken Hip, A Review of the Research for Adults* is a free companion to this clinician research summary. It can help patients talk with their health care professionals about the many options for treatment. It provides information about:




- Pharmacological options for preventing VTE
- Nonpharmacological options for preventing VTE
- Current evidence of the effectiveness and harms associated with VTE-prevention methods
- Questions for patients to ask their doctor

## Ordering Information

For electronic copies of *Preventing Blood Clots After Hip or Knee Replacement Surgery or Surgery for a Broken Hip, A Review of the Research for Adults*, this clinician research summary, and the full systematic review, visit www.effectivehealthcare.ahrq.gov/thrombo.cfm. To order free print copies, call the AHRQ Publications Clearinghouse at 800-358-9295.

## Source

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