Treatment of venous thromboembolism(VTE): Extended treatment with LMWH rather than warfarin, which one is better and how?

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- Coagulation is a normal physiological process
- causes prevention of significant blood loss following vascular injury.

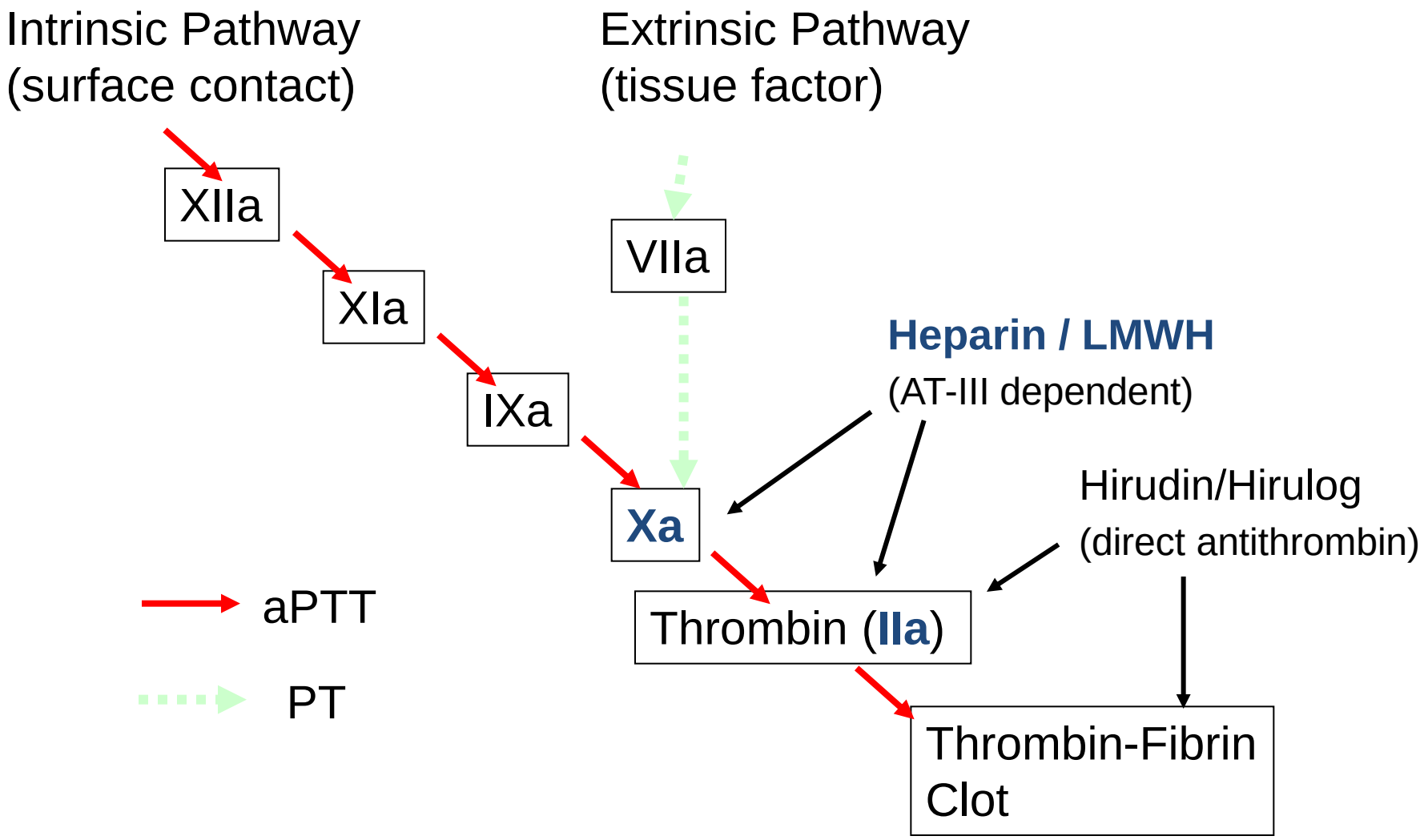
- there are times when a blood clot (thrombus) form
- when it is not needed.

- some high risk conditions such as
- prolonged immobilization, surgery, or cancer
- lead to the risk of development of a blood clot within the veins called venous thromboembolism(VTE)
- potentially lead to significant consequences.

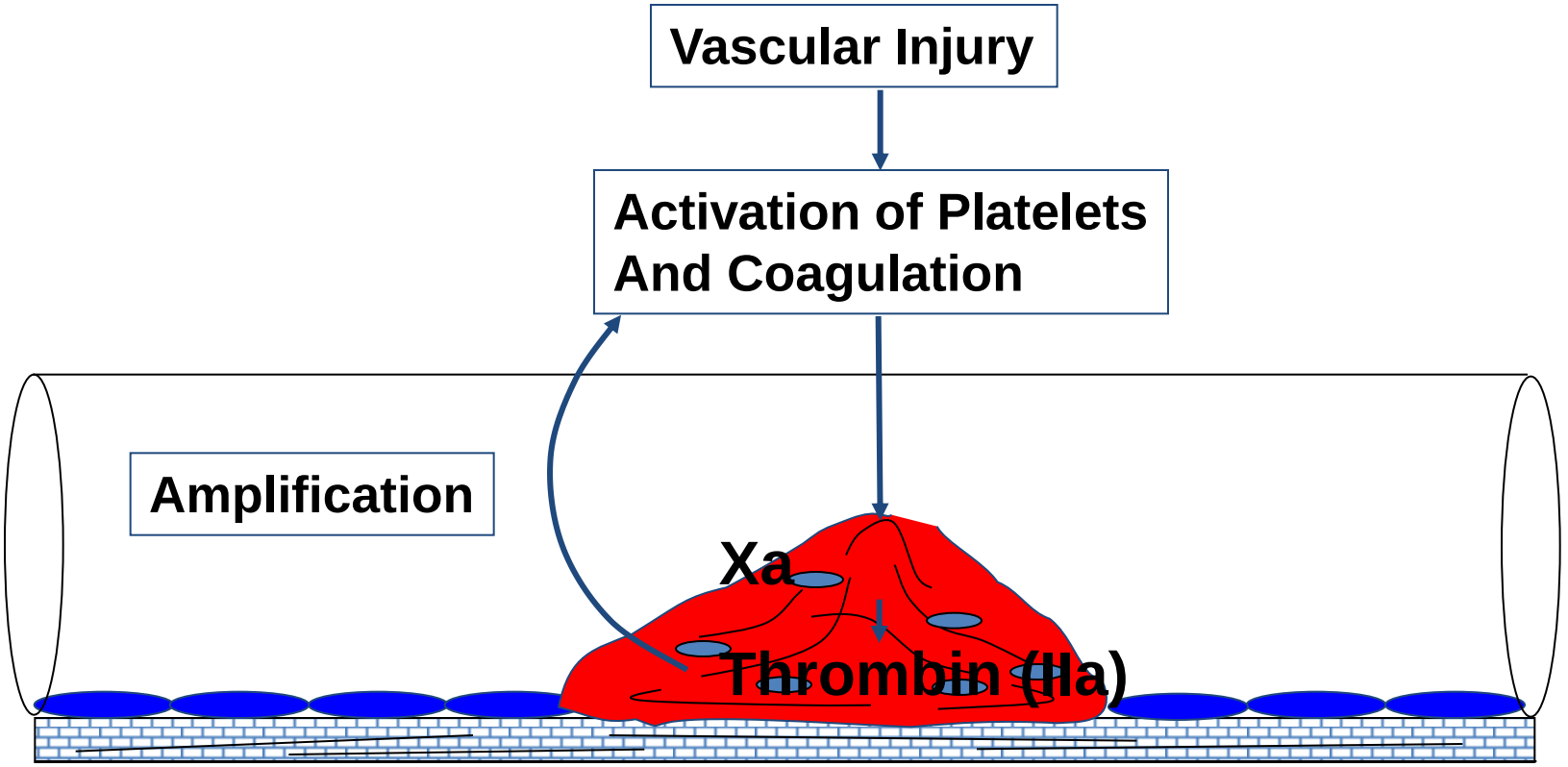
The Coagulation Cascade

- Central to the coagulation cascade is the generation **of thrombin (factor IIa)**
- thrombin is generated from prothrombin by the action of activated factor X (Xa)
- thrombin then acts on fibrinogen to generate fibrin clot

Coagulation Cascade



The Procoagulant State in Thrombolysis



- Antiplatelet medications in the prevention of arterial thrombosis and of less value in the prevention of venous thromboembolism. ,

- warfarin and LMWH are used in venous thromboembolism.

ANTICOAGULANTS

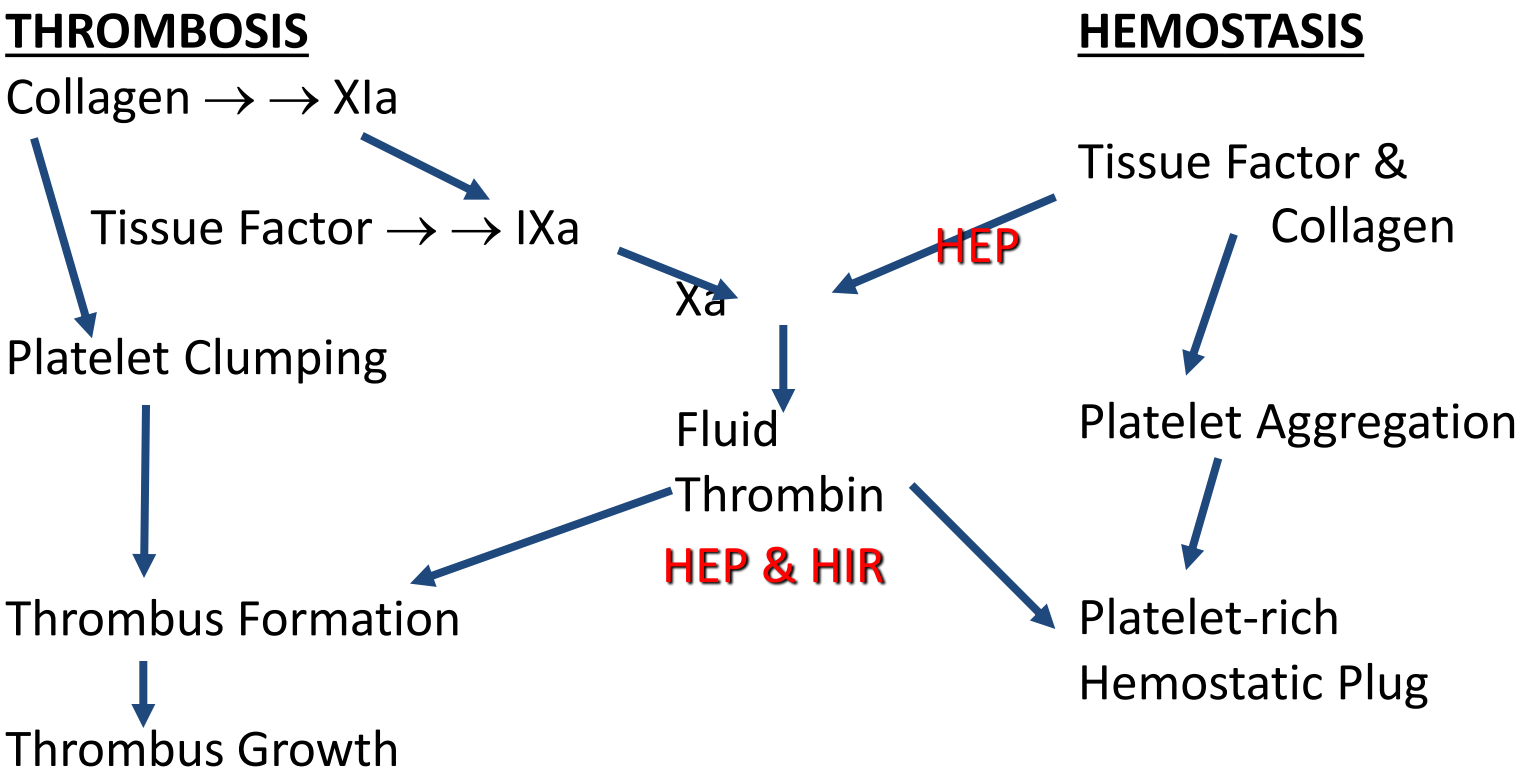
Three classes

- **Heparin and Low Molecular Weight Heparins (e.g. enoxaparin, dalteparin)**
- **Coumarin Derivatves e.g. Warfarin, Acenocoumarol**
- **Indandione Derivatves e.g. Phenindione, Anisindione**

Mechanism of Action of LMWH

- LMWH exerts their anticoagulation activity by **catalyzing antithrombin** (AT or AT III)
- Activated AT causes inactivation of the coagulation enzymes thrombin (factor IIa) and factor Xa.
- prolongs aPTT

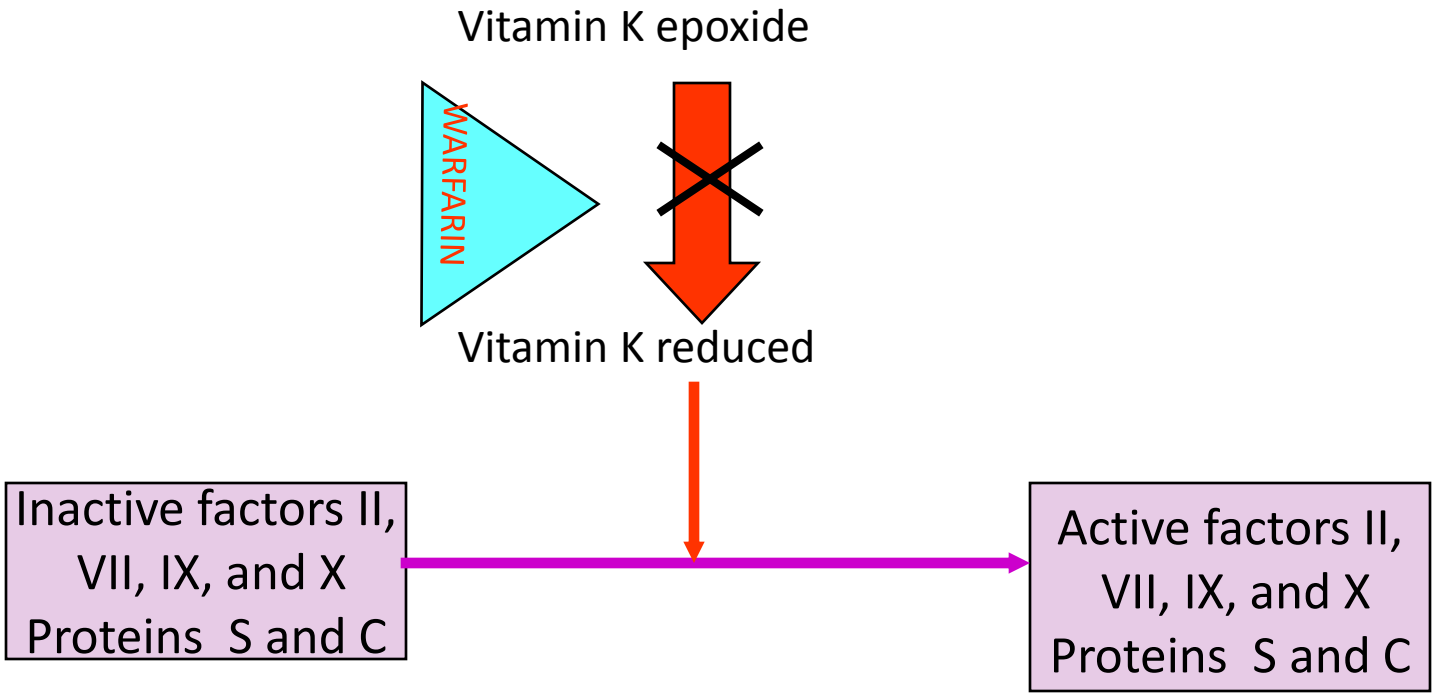
Heparin Inhibits Hemostasis



Mechanism of Action of Warfarin

- inhibits the enzyme **vitamin K epoxide reductase**
- interferes with vitamin K metabolism
- there by inhibiting vit K dependent clotting factor like II, VII, IX and X.

WARFARIN: MECHANISM OF ACTION



- Prevents the reduction of vitamin K, which is essential for activation of certain factors
- Has no effect on previously formed thrombus

Indications for Heparin

- **Prevention and treatment of VTE**
- Percutaneous coronary intervention
- Post thrombolysis for myocardial infarction
- Unstable angina pectoris
- Non-Q wave myocardial infarction
- Acute peripheral arterial occlusion
- Cardiopulmonary bypass
- Haemodialysis and haemofiltration

Indications for warfarin

- **Prevention and treatment of VTE**
- Arterial embolism
- Atrial fibrillation with specific stroke risk factors
- Mobile mural thrombus post-myocardial infarction
- Extensive anterior myocardial infarction
- Dilated cardiomyopathy
- Cardioversion
- Ischaemic stroke in antiphospholipid syndrome
- Mitral stenosis and mitral regurgitation with atrial fibrillation

Advantage of Warfarin

- can be used for many years
- less chance of antibody and allergic reactions.

Disadvantage of Warfarin

- interraction with many foods and drugs,
- chance of bleeding tendencies like CNS bleeding, purpura,
- long half life and tendency to bind to plasma protein
- crosses placental barrier producing teratogenic effects and
- needs close continuous monitoring of the patients

Drug Interactions

Increase Warfarin Response

- NSAIDS, ASA
- Acetaminophen > 2g/d
- Amiodarone
- Quinolones (e.g., Cipro), sulfonamides, metronidazole
- Fibrates
- Ginkgo, Garlic, Ginseng
- Grapefruit

Decrease Warfarin Response

- Phenobarbital
- Carbamazepine
- Phenytoin
- **Vitamin K rich foods**
  - **Green leafy vegetables**

Side effects of warfarin

- Hemorrhage
- Skin necrosis
- Purple toe syndrome
- Microembolization
- Teratogenecity

Agranulocytosis, leukopenia, diarrhoea, nausea, anorexia.

WHY TO MONITOR WARFARIN THERAPY?

- Narrow therapeutic range
- Can increase risk of bleeding

LMWH

- can be used for immediate action,
- short half life,
- less chance of bleeding,
- less chance of osteopenia
- less chance of drug interactions,
- does not cross the placental barrier
- needs no close monitoring of the patients..

Monitoring of LMWH

- Unnecessary in majority of patients
- May be useful in specific instances
  - **renal insufficiency (creatinine >2.0 mg/dl)**
  - **obese patients with altered drug pK**
  - **major bleeding risk factors**
- anti-factor Xa assay is more appropriate, but not widely available

LMWH

- available only in injection form,
- tendency to develop antibody, allergic reactions and thrombocytopenia,
- lifelong use of LMWH is thought to be restricted

Prolonged use of LMWH

- in several studies it has been shown that
- LMWH can be used for prolonged period of 3-6 months to years or lifelong.

LMWH in cancer patients with VTE

- Treatment with LMWH can be prolonged for 6 months in cancer patients;
- can be continued lifelong in cancer patients with distant metastasis or having spinal injury.

***Journal of Oncology Pharmacy Practice, 2007;* 13 (2): 85–97**

***Arch Intern Med.* 2002;162(15):1729-1735**

Trial with LMWH

- **Comparison of Low-Molecular-Weight Heparin and Warfarin for the Secondary Prevention of Venous Thromboembolism in Patients With Cancer: A Randomized Controlled Study**

Arch Intern Med. 2002;162(15):1729-1735.
doi:10.1001/archinte.162.15.1729.

Trial with LMWH

- the LMWH, (dalteparin)
- shown to have superior efficacy to warfarin
- in a patients with cancer and VTE
- without increasing the risk of bleeding.

N Engl J Med 2003; 349:146-153

CME.TheOncologist.com

LMWH in non Q MI

- In one trial (Essence Trial),
- LMWH was given for prolonged period (>30 days)
- in patients of rest angina or non Q MI.

LMWH in non Q MI

- It was demonstrated that
- treatment with LMWH for 30 days
- reduces the relative risk (RRR) of 15-17%
- considering the rate of death, MI or relative myocardial ischemia.

Warfarin in cancer patients

- Warfarin carries the
- disadvantage of having substantial inter- and intraindividual variability in dose requirement
- and the need for frequent dose monitoring,
- a problem, exaggerated in cancer patients.

Venous thromboembolism and cancer

- The CLOT study, published in 2003,
- showed that, in patients with malignancy and acute VTE,
- Dalteparin(LMWH) was more effective than warfarin in reducing the risk of recurrent embolic events.

***N Engl J Med* 2003; 349 (2): 146–53**

Venous thromboembolism and cancer

- Use of LMWH in cancer patients
- for at least the first 3 to 6 months of long-term treatment is recommended in numerous guidelines
- and is now regarded as a standard of care

Journal of Oncology Pharmacy Practice, 2007; **13 (2): 85–97.**

LMWH as prophylaxis of VTE

- LMWH can be used on an
- outpatient basis as a safer and more effective alternative to classical oral anticoagulant therapy
- for the secondary prophylaxis of selected patients with VTE.

N Engl J Med 1993; 329:1370-1376

- **In a study "Low molecular weight heparin versus warfarin in the prevention of recurrences after deep vein thrombosis".**
- Pini M, Aiello S, Manotti C, Pattacini C, Quintavalla R, Poli T, Tagliaferri A, Dettori AG

Reported that

- Low-molecular-weight heparin can be used safely and effectively to treat patients with proximal deep-vein thrombosis at home.

A Double-blind, Randomized Comparison

- Concluded that:
- Extended dalteparin(LMWH) prophylaxis
- resulted in significantly lower frequencies of deep vein thrombosis
- compared with in-hospital warfarin therapy

N Engl J Med. 1986;315925- 929

Recent studies

- 1. **Double-blind RE-MEDY trial, 2866** patients designated by investigators to be at increased risk for recurrence of VTE to receive dabigatran(LMWH), or warfarin

- 2. **RE-SONATE trial, 1353 patients** were randomly assigned to receive dabigatran or placebo for 6 months.
- 3. **AMPLIFY-EXT** (Apixaban after the Initial Management of Pulmonary Embolism and Deep Vein Thrombosis with First-Line Therapy–Extended Treatment) study

- **Extended Use of Dabigatran, Warfarin, or Placebo in Venous Thromboembolism**

- **N Engl J Med 2013; 368:709-718February 21, 2013DOI: 10.1056/NEJMoa1113697**

two double-blind, randomized trials,

- compared
- dabigatran(LMWH) at a dose of 150 mg twice daily with
- warfarin (active-control study) or with placebo (placebo-control study)
- in patients with VTE who had completed at least 6 initial months of therapy

In the active-control study,

- recurrent VTE occurred
- in 26 of 1430 patients in the dabigatran group (1.8%) and
- 18 of 1426 patients in the warfarin group (1.3%) (hazard ratio with dabigatran, 1.44; 95% confidence interval [CI], 0.78 to 2.64; P=0.01 for noninferiority).

In the active-control study,

- Major bleeding occurred
- in 13 patients in the dabigatran group (0.9%) and
- 25 patients in the warfarin group (1.8%) (hazard ratio, 0.52; 95% CI, 0.27 to 1.02).

In the active-control study,

- Major or clinically relevant bleeding
- less frequent with dabigatran

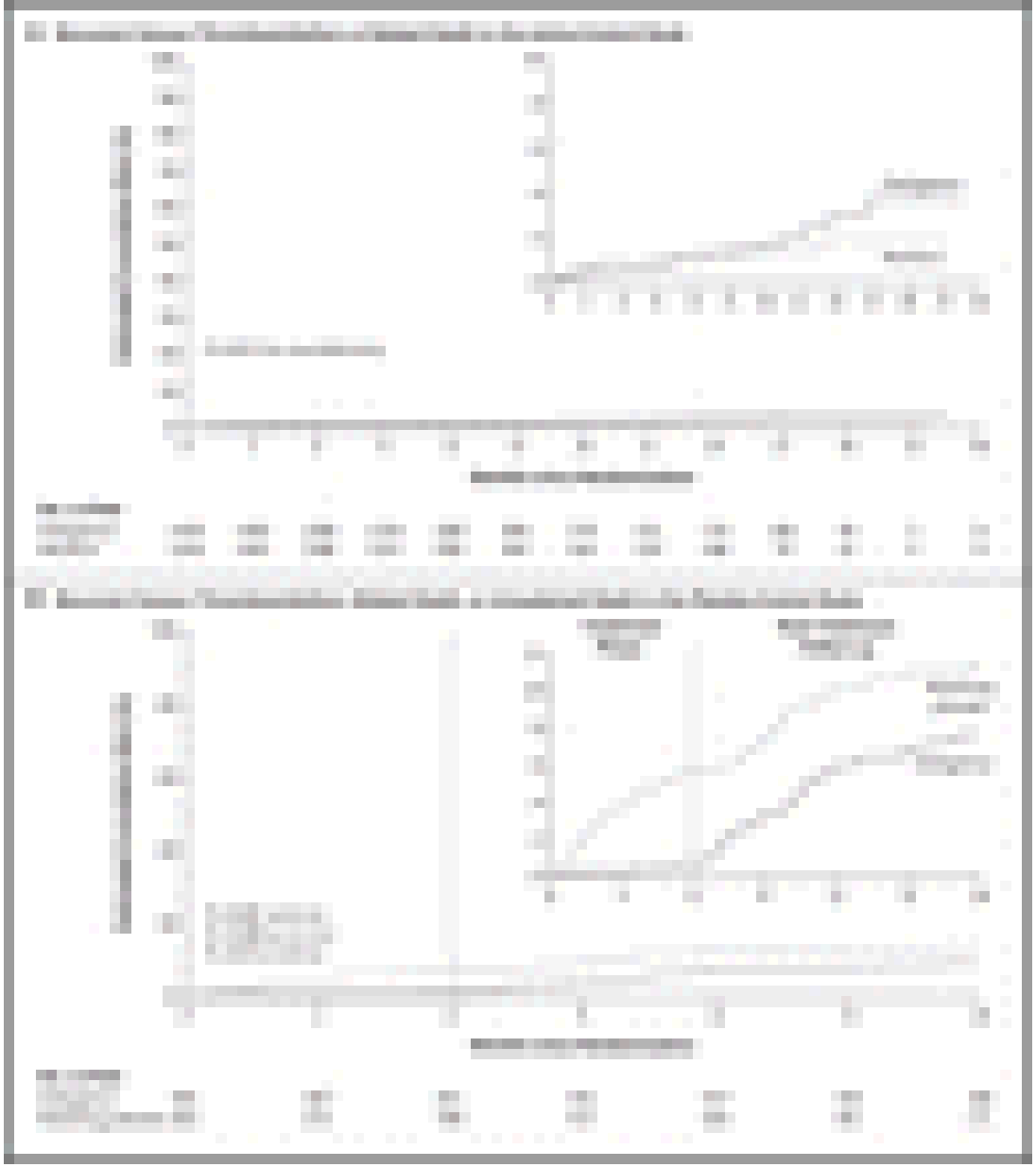
(hazard ratio, 0.54; 95% CI, 0.41 to 0.71).

In the placebo-control study,

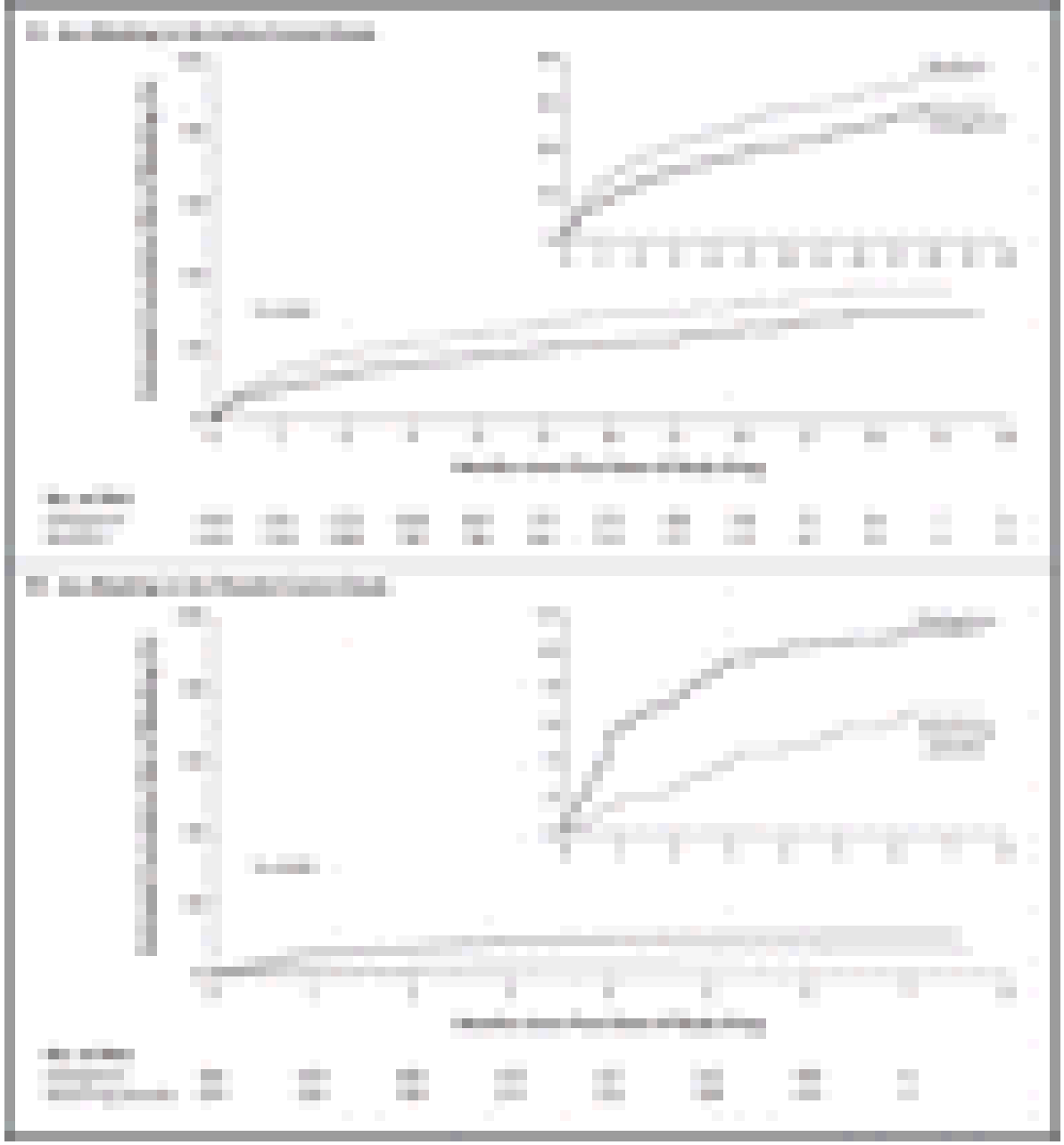
- recurrent VTE occurred
- in 3 of 681 patients in the dabigatran group (0.4%) and
- 37 of 662 patients in the placebo group (5.6%) (hazard ratio, 0.08; 95% CI, 0.02 to 0.25; P<0.001).

In the placebo-control study,

- Major or clinically relevant bleeding occurred
- in 36 patients in the dabigatran group (5.3%) and
- 12 patients in the placebo group (1.8%) (hazard ratio, 2.92; 95% CI, 1.52 to 5.60).



Cumulative Risk of Recurrent VTE or Related Death (or Unexplained Death in the Placebo-Control Study).



Cumulative Risk of Any Bleeding.

Conclusions of this study

- Dabigatran (LMWH)
- effective in the **extended** treatment of VTE and
- carried a lower risk of major or clinically relevant bleeding than warfarin but a higher risk than placebo

- The increase in the rate of acute coronary events with dabigatran as compared with warfarin, requires further evaluation.

LMWH in Pregnancy

- As warfarin is teratogenic,
- LMWH has been used in pregnancy
- with primary or secondary anti phospholipid syndrome
- to prevent recurrent abortion and thrombosis.

LMWH Vs Warfarin

- LMWH can be a good alternative to warfarin
- in high risk patients like pregnancy,
- in patients with major bleeding disorders
- can be used as Out Patient basis in secondary prophylaxis of VTE

Thrombosis and Haemostasis [1997, 77(1):39-43]

N Engl J Med 1992;326: 975–82

Cost effectiveness of LMWH

Warfarin is less expensive and more compliant

But the fact that,

overall cost of its use is increased by the need to monitor the intensity of anticoagulation.

Arch Intern Med. 1997;157:298-303

Oral heparin

- Oral heparin not absorbed from gastrointestinal tract.
- Hypothesis of oral preparation considered,
- a delivery agent called N acetyl amino acid forms covalent bonds with heparin and accelerates absorption

Take home message

- After reviewing all the studies, it can be concluded that,
- In the treatment of VTE, prolong treatment with LMWH
- may be preferred rather than warfarin.

Take home message

- **LMWH prophylaxis, as effective as oral anticoagulants,**
- **with a marked improvement in safety.**


Thanks
‘May Peace be upon you’