Challenges of VTE Prophylaxis in Orthopaedics

C. W. Colwell, Jr., M.D.
Scripps SCORE
At Scripps Clinic

Grand Rounds
Scripps Green Hospital
May 5, 2010

Challenges of VTE Prophylaxis in Orthopaedics

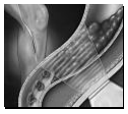
I have a potential conflict with this presentation due to receiving research funds from:

- **Bayer Healthcare**
- **Medical Compression Systems**
- **Boehringer Ingelheim**

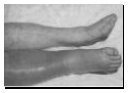
I will be discussing drugs not yet approved by the FDA:

- **Rivaroxaban**
- **Dabigatran**

Deep Venous Thrombosis (DVT)



- **Rate without prophylaxis:**
  - **40 – 80%**



- **~90% symptomatic pulmonary emboli originate from lower extremity DVT**

Risk for DVT/VTE

Surgery/condition	Risk of all DVT if untreated
General Surgery	25%
THR	54%
TKR	64%
Neurosurgery	28%
Trauma	30-60%
Acute spinal cord injury	80%
Ischemic stroke	55%
Medical condition	16%
Cancer	50%
Pediatrics	3-15%

Geerts et al; Chest 2001, 2004

Prevalence of DVT in Orthopaedic Surgery *Without Prophylaxis*

	DVT	Proximal DVT
Hip	42 – 57%	18 – 36%
Knee	41 – 85%	5 – 22%
Hip Fx Surgery	46 – 60%	23 – 30%

Geerts, et al., Chest 2008

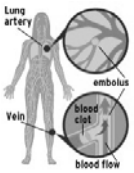
Prevalence of PE in Orthopaedic Surgery *Without Prophylaxis*

	Symptomatic	Fatal
Hip	0.9 – 28%	0.1 – 2.0%
Knee	1.5 – 10%	0.1 – 1.7%
Hip Fx Surgery	3 – 11%	0.3 – 7.5%

Geerts, et al., Chest 2008

What are We Attempting to Prevent ?

- Pulmonary Death
- Symptomatic and Asymptomatic PE
- DVT Proximal and Distal
- Chronic Pulmonary Hypertension
- Post-Thrombotic Syndrome



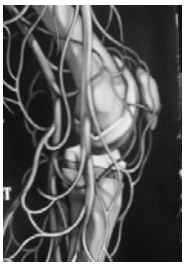
Ideal Prophylactic Methods

- Effective (clinically proven)
- Low risk of side effects
- Practical for use
  - Easy to administer and monitor
- Cost effective

No single modality meets ideal requirements or is appropriate for every patient condition

Orthopaedists have single and additive mechanical and pharmacological protocols, with different time frames of patient exposure

Traditional Prophylactic Therapy Modalities

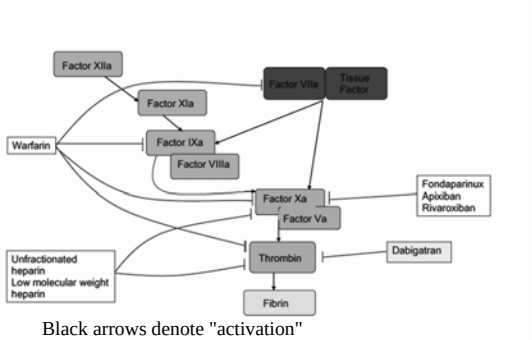


- Pharmacological
- Mechanical

Pharmacological Agents

- Aspirin
- Warfarin
- LMWH
- Pentasaccharide
- Direct Thrombin Inhibitor

Coagulation Cascade



Black arrows denote "activation"
Red lines ending in vertical lines imply "inhibition"

Aspirin

- Acetylsalicylic acid
- Cyclooxygenase inactivator
- Arachidonic acid + cyclooxygenase = thromboxane A2; vasoconstriction, platelet aggregation

Aspirin Alone

- Number of trials report no significant benefit from ASA VTE prophylaxis

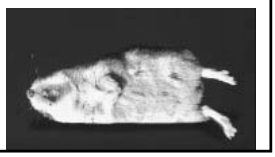
  PEP Trial 2000, McKenna 1980, Powers 1989, Westrich 1996
- Others found ASA inferior to other modalities
  - *Westrich 1996, Graor 1992, Gent 2003*

Aspirin Combinations

- Combined with
  - Early mobilization
  - Regional anesthesia
  - Foot pumps
  - Improved surgical techniques
- Reported in AAOS guidelines as acceptable for preventing fatal PE

Warfarin

- Dose
  - INR 2-3 (PT 1.3-1.5xControl)
- Action
  - Inhibits proper synthesis of Vitamin K-dependent coagulation factors (II, VII, IX, X)
- Onset of action
  - 4-5 days



Warfarin

- Advantages
  - Given orally
  - Inexpensive

- Disadvantages
  - Continuous lab monitoring
  - Dose adjustment
  - Time to reach peak function
  - Affected by other drugs and food

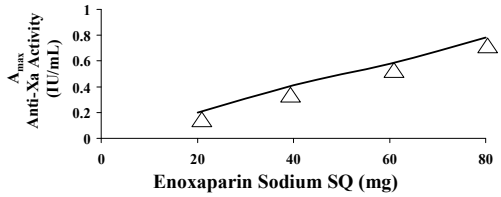
Low Molecular Weight Heparins (LMWH)

LMWH	Approval
• Enoxaparin (Lovenox®)	• FDA approved for TJA
• Dalteparin (Fragmin®)	• FDA approved for THA

What is LMWH?

- **Fragments of unfractionated heparin produced by either chemical or enzymatic depolymerization**
- **Mean molecular weights from 4,000 to 6,500 daltons**

Predictable Concentrations



No need to monitor coagulation times in patients with normal presurgical coagulation parameters

Frydman et al: JClinPharmacol, 1988

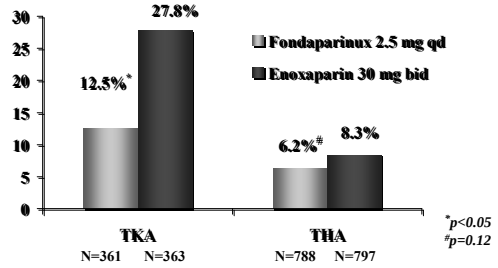
Fondaparinux

Synthetic Pentasaccharide

- **Highly potent and indirect selective inhibitor of factor Xa**
- **First product of a new generation of obtained by chemical synthesis**
- **Devoid of antithrombin activity**
- **Does not potentiate ADP or collagen induced platelet aggregation**

Fondaparinux vs. Enoxaparin Results

North American Studies



Bauer BA, Eriksson BI, et al. N Engl J Med, 345(18): 1305-10.

Symptomatic VTE after In-hospital prophylaxis for TJR

Author, year	Op	No.	Prophylaxis	Duration	Symptomatic VTE, no. (%)	Fatal PE no. (%)
Robinson,	THR	249	Warfarin	9.8 d	3 (1.2)	0
1997	TKR	257	Warfarin	9.8 d	2 (0.8)	0
Leclerc, 1998	THR	1142	LMWH	9.0 d	49 (4.3)	0
	TKR	842	LMWH	9.0 d	33 (3.9)	3 (0.4)
Colwell, 1999	THR	1516	LMWH	7.5 d	55 (3.6)	2 (0.1)
	THR	1494	Warfarin	7.0 d	56 (3.7)	2 (0.1)
Heit, 2000	THR	588	LMWH	7.3 d	12 (2.0)	0

LMWH Prophylaxis After THA following hospital prophylaxis

		Total DVT %		Proximal DVT %	
Author, year	Patients	Placebo	LMWH	Placebo	LMWH
Bergqvist, 1996	223	37	18	24	7
Planes, 1996	173	19	7	8	6
Dahl, 1997	218	32	19	13	9
Spiro, 1997	435	23	8	13	3
Lassen, 1998	215	12	4	5	1
Hull, 2000	533	37	20	9	3
Combined	*1807*	*27*	*14*	*12*	*4*

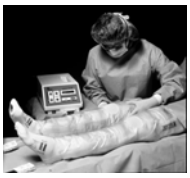
Mechanical Devices

- **Primary attraction is lack of bleeding potential**
- **Types of devices**
  - **Graduated compression stockings (GCS)**
  - **Intermittent pneumatic compression devices (IPC)**
  - **Venous foot pump (VFP)**

Intermittent Pneumatic Compression

Regimen

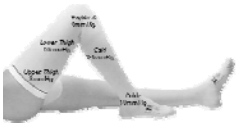
- **Applied preoperatively and during surgical procedure**
- **Continued postoperatively until patient is ambulatory**



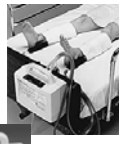
No clinically significant side effects. Bleeding no greater than placebo trials or 4%

Mechanical Thropboprophylaxis

- Methods do not even have to demonstrate they provide any protection against VTE to be approved and marketed
- Unsubstantiated assumption that all are effective and equivalent



Mechanical Compression Devices



- **Nearly complication free**
- **Time worn = effectiveness**
- **Ensure do not actually impede ambulation**

Mobile Compression Device (*MCD*)*

- **Miniature**
- **Portable**
- **Battery Powered**
- **Can be worn out of bed and out**

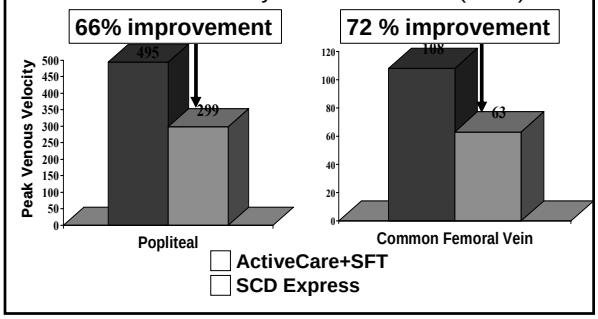
**ActiveCare ® +SFT*

Synchronized Flow Technology (*SFT*)

- **Triggers compression in synchronization with respiratory rate**
- **Provides natural phasic venous flow**
- **Patient compliance monitored by device**
- **Patient compliance clearly visible on device screen**

Hemodynamic Study

ActiveCare+SFT vs SCD Express
Peak venous velocity with Calf sleeves (n=11)



Multi-Center Randomized Prospective Study

- All primary total hip arthroplasties
- Exclusion
  - Self-reported or documented hx DVT or PE
  - Routine use of anticoagulant or antiplatelet drug
- Patients signed HSC approved consent

Large Prospective Randomized Multi-centered Clinical Trial

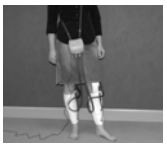
Hosp Special Surg, NY
Siani Hosp, Baltimore, MD
Cleveland Clinic, OH
Indiana Research Found., IN
Mayo Clinic, MN
Ortho & Neuro Center of Cascades, OR
Loma Linda Univ, CA
Kerlan Jobe Ortho Clinic, CA
SCORE at Scripps Clinic, CA

Methods

- Prospective randomized study
  - MCD group
    - Compression device ± aspirin 81 mg daily
  - LMWH group
    - Enoxaparin 30 mg twice daily in hospital
    - Enoxaparin 40 mg once daily after discharge

Methods

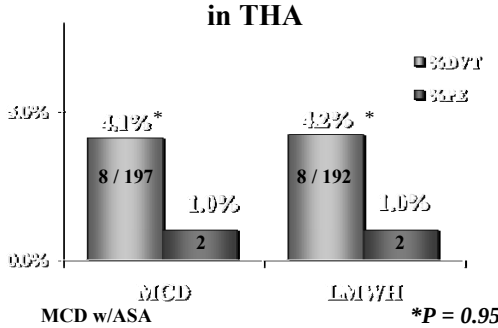
- Treatment for 10 days with MCD or LMWH
- Bilateral duplex ultrasound on day 10 – 12
- Compliance rate checked on MCD



Methods

- 3 months postop – clinical exam
- Signs and symptoms
  - DVT
  - PE

% VTE by Treatment in THA



MCD w/ASA
- 4 DVT
- 1 PE

*P = 0.953

Results

- No fatal PE or deaths
- Major bleeding
  - MCD 0%
  - LMWH 5.6%*

*p = .0007

MCD Compliance

Compliance = 86%

Mean days worn = 11 (2 – 14)

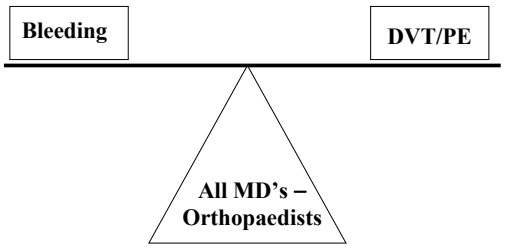
Mean hours worn = 219 (4 – 850)

Average daily ~ 20 hrs/day

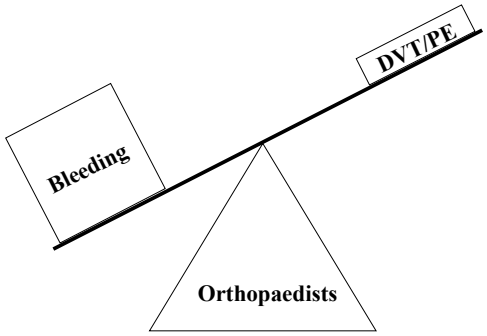
Strength of any recommendation depends on two factors

1. Trade-off between benefits and risks
2. Strength of methodology leading to estimates of treatment effect

Evaluation of Safety vs. Efficacy



Evaluation of Safety vs. Efficacy



Definition of Practice Guidelines

Practice guidelines are systematically developed statements to assist practitioner and patient decisions about appropriate health care for specific clinical circumstances.

Guidelines for Guidelines

- **Validity**
- **Reliability/ Reproducibility**
- **Clinical Applicability**
- **Clinical Flexibility**
- **Clarity**
- **Multidisciplinary Process**
- **Scheduled Review**
- **Documentation**

The Joint Commission

National Standards for Prevention and Care of VTE: Proposed VTE Performance Measures

VTE Risk Assessment/Prophylaxis

1. **Documentation of VTE risk assessment and prophylaxis within 24 hours of hospital admission if prophylaxis indicated.**
2. **Documentation of VTE risk assessment and prophylaxis within 24 hours of ICU admission if prophylaxis indicated.** *(Nov 2009)*

www.JointCommission.org/PerformanceMeasurement

NQF / JCAHO National Standards for the Prevention and Care of VTE

Policy Statement:

"Every healthcare organization shall have a *written policy* appropriate for its scope, that is *evidence-based* and *drives continuous quality improvement* related to venous thromboembolism (VTE) *risk assessment, prophylaxis, diagnosis* and *treatment*."

SCIP Surgical Care Improvement Project
A National Quality Partnership

Goal: To reduce preventable surgical morbidity and mortality 25% by 2010.

http://www.medqic.org/

SCIP Surgical Care Improvement Project
A National Quality Partnership

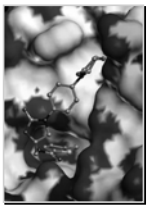
VTE Measures

For surgical patients:

1. **Has recommended VTE prophylaxis* been ordered;**
2. **Has recommended prophylaxis* actually been commenced within 24 hours after surgery.**

http://www.medqic.org/ *** Grade 1 ACCP recommendations**

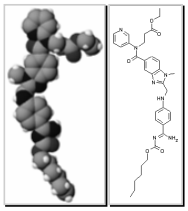
Rivaroxaban: An Oral Direct Factor Xa Inhibitor



- Direct, competitive Factor Xa inhibitor
- Rapid onset within 2-4 hours
- High bioavailability: >80%
- No dosage adjustment for gender, age, extreme body weight
- Half-life: 7-11 hours
- Approved in Canada, Europe

Gulseth MP, et al. *Am J Health Syst Pharm.* 2008;65(16):1520-9.

Dabigatran Etexilate: An Oral Direct Thrombin Inhibitor



- Specific, competitive, reversible thrombin inhibitor
- Rapid onset within 2 hours
- Low bioavailability: 3.5-5%
- Half life: 12-17 hours
- Approved in Canada, Europe

Eikelboom JE, Weitz JI. *Thromb Haemost.* 2009;101(1):2-4.

New Oral Anticoagulants:

Strengths

- Oral administration
- No laboratory monitoring
- Few drug interactions
- Rapid onset
- Won't cause HIT
- Potential major impact on clinical: more patients get prophylaxis practice

Limitations

- Limited indications
- No hip fracture data
- No specific reversibility agents
- New; short track record

Research → Practice

- Evaluation
  - Changes in outcomes
  - Economic
- Education
  - All caregivers
  - Ongoing
- Practice guidelines & standard orders
- Periodic check of outcomes - QA