CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ANESTHETIC and LIFE SUPPORT DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 02/05/98

CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ANESTHETIC and LIFE SUPPORT DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 02/05/98

SLIDES

Is Regional Anesthesia Contraindicated in Anticoagulated Patients?

Terese T. Horlocker, M.D.
Associate Professor of Anesthesiology
Mayo Clinic

Spinal Hematoma in the Anticoagulated Patient
Incidence and Etiology

Incidence*

1 in 150,000 epidural anesthetics

1 in 200,000 spinal anesthetics

Etiology

Trauma, neoplasm, vascular malformation, spontaneous

Site of bleeding

Epidural, subdural, subarachnoid

*Tryba, 1993

Anticoagulation and Regional Anesthesia
Spinal Hematoma

- 61 cases of spinal hematoma after central neural blockade
- 42 of 61 (68%) evidence of hemostatic abnormality
  - 25 standard or LMWH
  - 1 oral anticoagulant
  - 3 antiplatelet agents
  - 2 thrombolytics
  - 11 thrombocytopenia or coagulopathy
- Needle placement difficult in 15 (25%) or bloody in 15 (25%) of 61 cases

Vandermeulen, Anesth Analg, 1994

Anticoagulation and Regional Anesthesia
Spinal Hematoma-Regional Technique

- 15 spinal anesthetics
- 46 epidural anesthetics
  - 6 single dose
  - 32 continuous catheter
  - 8 unspecified
- 12 of 32 epidural catheters removed in the presence of systemic heparinization
- Spinal bleeding occurred at the time of catheter removal in nearly half of cases

Vandermeulen, Anesth Analg, 1994

Anticoagulation and Regional Anesthesia
Spinal Hematoma-Neurologic Outcome

- 3 of 61 (4%) neurologically intact, spinal hematoma discovered at autopsy
- 23 of 61 (38%) partial or good neurologic recovery
  - 15 laminectomies (10 performed within 8 hours)
    - 1 complete spontaneous recovery
    - 1 partial spontaneous recovery
    - 6 unspecified intervention

Vandermeulen, Anesth Analg, 1994

Anticoagulation and Regional Anesthesia
Spinal Hematoma-Neurologic Outcome (cont)

29 of 61 (48%) poor neurologic recovery

- 17 laminectomies (10 performed more than 24 hours after development of paraplegia)
- 8 no surgical procedure
- 4 unspecified intervention

- 6 of 61 (10%) outcome unknown

Vandermeulen, Anesth Analg, 1994

Heparin and Spinal or Epidural Anaesthesia: Clinical Decision Making

Review by Schwander and Bachman in 1991

- Spinal or epidural anesthesia in combination with subcutaneous standard heparin (SH) or the LMWH
- 5,000 patients received SH (various doses/schedules)
- 14,000 patients received LMWH (different formulations/doses/schedules)
- No major neurologic sequelae

Low Molecular Weight Heparin and Regional Anesthesia

- Spinal or epidural anesthesia administered in conjunction with LMWH in 9,013 patients
- No case of spinal hematoma with neurologic dysfunction
- Pharmaceutical companies estimated over 1 million patients had received central neural blockade in combination with LMWH

Bergqvist, 1992

Low Molecular Weight Heparin: Biochemistry and Guidelines for Regional Anesthetic Management

- 15,151 spinal/epidural anesthetics in LMWH patients
  - 7420 spinal anesthetics (20 continuous)
  - 2957 epidural anesthetics (457 continuous)
  - 4774 "spinal or epidural" anesthetics

- Preoperative dosing initiated in nearly 90% of cases
- LMWH administered once daily in over 95% of cases
- Eight published and 16 "reported" spinal hematomas

Horlocker, 1997

Low Molecular Weight Heparin: Biochemistry and Guidelines for Regional Anesthetic Management

- 24 "reported" spinal hematomas associated with regional anesthesia and LMWH
- Regional anesthetic technique
  - 18 continuous epidural
  - 1 single dose epidural
  - 3 spinal, including 1 spinal after failed epidural
  - 2 unspecified
- 7 of 18 with indwelling catheters became paraplegic upon catheter removal

Horlocker, 1997

Low Molecular Weight Heparin: Biochemistry and Guidelines for Regional Anesthetic Management

Additional risk factors

- 2 intraoperative Dextran and intravenous heparin
- 5 concomitant antiplatelet therapy
- 6 preoperative LMWH therapy
- 12 LMWH initiated within 24 hours postoperatively

Horlocker, 1997

Spinal Hematoma and Low Molecular Weight Heparin The European Experience

Regional anesthesia often used with LMWH therapy

Recommendations by Michael Tryba in 1993:

- Delay needle/catheter placement and removal at least 10-12 hours after LMWH dose
- Subsequent LMWH dose administered 8 hours after catheter removal

European dosing once daily, smaller daily dose

Preference for less traumatic techniques

Spinal Hematoma and Regional Anesthesia

Hemorrhage may occur after any regional anesthetic technique. Bleeding into spinal canal may be catastrophic.

Spinal hematoma is rare; practice guidelines based upon

- Pharmacology
- Clinical studies
- Case reports

Anesthetic management guided by individual risk/benefit assessment

Prevention of Perioperative Thromboembolic Complications with Low Molecular Weight Heparin in Patients Receiving Epidural/Spinal Anesthesia:

Risk/Benefit Considerations

Graham Pineo, M.D.
Professor of Medicine
Director Thrombosis Research Unit
Department of Medicine
University of Calgary

Pulmonary Embolism (PE)

- Cause of death in 100,000 patients/yr in U.S. and contributes to the death of another 100,000
- May be the most common preventable cause of hospital death
- Overall incidence (fatal and nonfatal) of clinically recognized PE is 1.6% (general surgery)
- Incidence of fatal PE is 0.8% (general surgery)
- Patients undergoing major orthopedic surgery are at even higher risk

Clagett 1995 Chest 108:312s-334s

Venous Thromboembolism Prevalence Following Major Orthopedic Surgery of the Leg

	DVT %*		PE %	
Procedure	**Total**	**Proximal**	**Total**	**Fatal**
Total hip replacement	45-57	23-36	6.7-30	3.4-6
Total knee replacement	40-84	9-20	1.8-7	0.7
Hip fracture surgery	36-60	17-36	4.3-24	3.6-12.9

* Data based on mandatory postoperative venography from recent placebo-controlled, randomized trials

Clagett 1995 Chest 108:312s-334s

DVT Rates in Patients Receiving General or Spinal/Epidural Anesthesia

Total: 1207 Patients

663 Spinal/Epidural

554 General

- All pts received prophylaxis (LMWH or warfarin)
- No difference in DVT rate

Hull 1993

LMWH Prophylaxis

- Studies directly comparing LMWHs and UFH demonstrate equivalent or superior efficacy with LMWHs

- Postoperative prophylaxis with LMWH is equivalent to warfarin in preventing DVT after THR and superior to warfarin after TKR

  Hull 1993, Levine 1991, LeClerc 1996, Heit 1994 &1997

- Preoperative prophylaxis with LMWH is significantly more effective than warfarin in preventing DVT after THR

  Francis 1997

LMWHs and Epidural/Spinal Anesthesia: Incidence of Spinal Hematoma Clinical Trial Experience

- Bergqvist (1993) - no cases reported in 19 clinical trials (9,013 patients)

- Horlocker (1997) - no cases reported in 39 clinical trials (15,151 patients)

Epidural/Spinal Hematoma Risk Factors

- Anticoagulation therapy (including NSAIDs)
- Clotting disorder
- Indwelling catheter
- Difficult or complicated puncture

North American Fragmin Trial
(NAFT)

- Multicenter, double-blind, randomized study
- 1500 patients in U.S. and Canada
- 3-arm study of Fragmin vs. warfarin in total hip replacement surgery
- Designed to determine the efficacy of thromboprophylaxis with different treatment regimens
  (pre-op Fragmin vs. post-op Fragmin vs. warfarin)

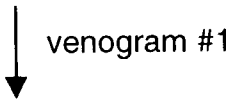
North American Fragmin Trial

(NAFT)

Total Hip Replacement

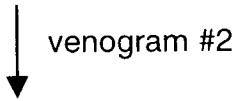
PHASE I [day 0 - day 6(±2)]

Arm #1		**Arm #2**		**Arm #3**
Pre-op Fragmin	vs.	Post-op Fragmin	vs.	Warfarin



PHASE II [day 6(±2) - day 35(±2)]

Arm #1		**Arm #2**		**Arm #3**
Fragmin	vs.	Fragmin	vs.	Placebo



FOLLOW-UP [week 12(± 1)]

Risk Reduction Strategy for LMWH
Based on the NAFT Trial

- Epidural/spinal puncture is not allowed for patients receiving anticoagulant therapy, NSAIDs, or steroids
- LMWH administered ***after*** epidural/spinal puncture
- No LMWH if bleeding, complicated puncture, or clotting disorder
- Dosing: pre-op 2,500 IU x 1
  post-op 2,500 IU x 1 (evening after surgery)
  then 5,000 IU daily
- Epidural catheter is removed 8-12 hours after the last dose

Experience with Fragmin

(dalteparin sodium injection)

Mårten Rosenqvist, M.D., Ph.D.

Medical Director

Cardiovascular Disease and Thrombosis

Pharmacia & Upjohn

Fragmin

(dalteparin sodium injection)

- Introduced in Germany in 1985; marketed in 48 countries
- Worldwide 27 million pts have received Fragmin for thromboprophylaxis

Prophylactic Dosing for Fragmin

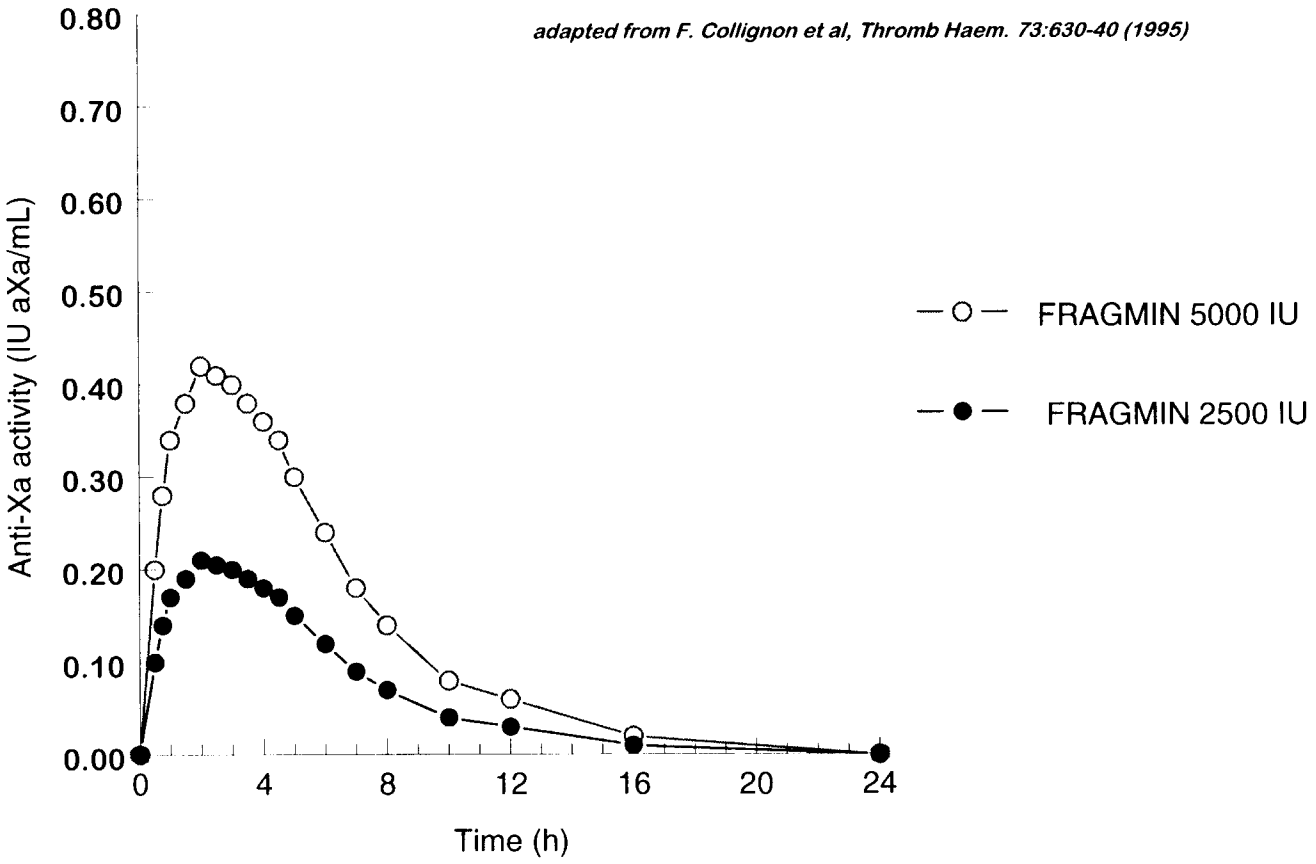
- Moderate Risk: 2500 IU, 1-2 hr pre-op
  2500 IU, daily starting on the first post-op day

- High Risk: 2500 IU, 1-2 hr pre-op
  2500 IU, evening of surgery
  5000 IU, daily starting on the first post-op day

Alternate dosing regimen:

5000 IU, 10-12 hr pre-op and repeated once daily

Mean Time Course of Anti-Xa Activity After S.C. Injection



Epidural/Spinal Hematoma

Experience with Fragmin

- No cases reported in clinical trials

  (1,653 patients received Fragmin + epidural or spinal anesthesia)

- Estimates from sales figures suggest that at least 2,700,000 patients have received Fragmin in the setting of epidural/spinal anesthesia

- Spontaneous reports = 2

Epidural/Spinal Hematoma
Case #1

65 year old male admitted with right costal pain and jaundice

Procedure: cholecystectomy + partial pancreatectomy

Fragmin: 2,500 IU pre-op, then 2,500 IU daily

Hospital Course:

- epidural catheter placed - six days post-op (pain control)
- last dose of Fragmin at 8:00 am; epidural placed at 11:30 am
- complicated puncture
- 10 min. later - rapid drop in BP/sensory and motor blockade (T8)
- hematoma suspected; decompressive laminectomy performed 18 hr later

Follow-up:

- paraplegia/neurological deficits corresponding to the T8 level

Epidural/Spinal Hematoma
Case #2

51 year old female with left femoral neck fracture

PMH : MS with partial lower extremity paralysis

Concomitant medication: Toradol 60 mg (day of surgery)

Fragmin: 2,500 IU - 1 hour pre-op

Spinal: Slightly blood-tinged CSF emerged/cleared

Post-op: 5000 IU Fragmin, 10 hr post-op

Hosp. Course: increasing back pain 10-30 hours post-spinal

- decompressive laminectomy 40 hr after spinal

Follow-up: near total lower extremity paralysis

Risk Reduction Strategy for Fragmin
Based on the NAFT Trial

- Epidural/spinal puncture is not allowed for patients receiving anticoagulant therapy, NSAIDs, or steroids
- LMWH administered ***after*** epidural/spinal puncture
- No LMWH if bleeding, complicated puncture, or clotting disorder
- Dosing: pre-op 2,500 IU x 1
  post-op 2,500 IU x 1 (evening after surgery)
  then 5,000 IU daily
- Epidural catheter is removed 8-12 hours after the last dose

Summary

- DVT and PE remain a significant clinical problem in post-operative patients
- LMWH significantly reduces the risk of thromboembolic events
- Usage of regional anesthesia is increasing
- Risk factors for epidural/spinal hematomas can be identified prior to surgery and must be weighed against potential benefits
- Clinical practice guidelines for the concurrent use of regional anesthesia and anticoagulant prophylactic therapy should be developed

ORGARAN™

(danaparoid sodium) Injection

ORGARAN™
(danaparoid sodium) Injection

Orgaran™ is indicated for the prophylaxis of postoperative deep venous thrombosis (DVT), which may lead to pulmonary embolism (PE), in patients undergoing elective hip replacement surgery.

Dosage: 750 anti-Xa units s.c.,b.i.d.

ORGARAN™
(danaparoid sodium) Injection
Product Characteristics of Orgaran™

Constituents	**Percentage in Orgaran™**
Heparan sulfate	~84
HA heparan sulfate	~4
LA heparan sulfate	~80
Dermatan sulfate	12
Chondroitin sulfate	4
Average Molecular Weight	5,500 D

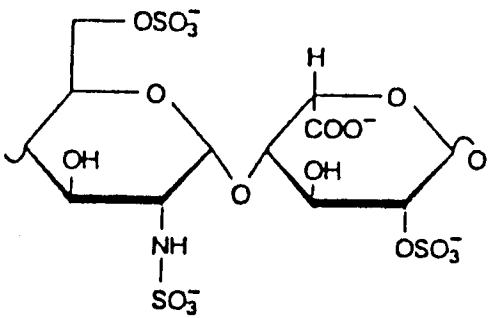
HA = Fraction with high affinity for AT III; LA = fraction with low affinity for AT III

Adapted From Meuleman, Haemostasis

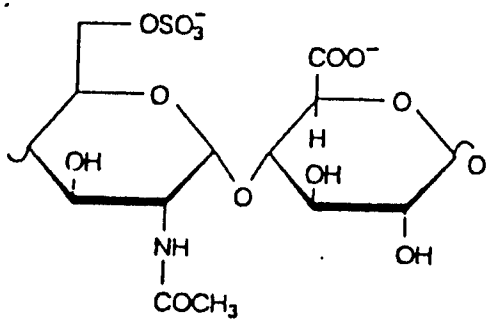
Organon

ORGARAN™

(danaparoid sodium) Injection



Heparin



Orgaran

ORGARAN™
(danaparoid sodium) Injection

Orgaran™ is an antithrombotic agent which prevents fibrin formation in the coagulation pathway via thrombin generation inhibition by anti-Xa and anti-IIa (thrombin) effects.

The anti-Xa:anti-IIa activity ratio is greater than 22. Inactivation of factor Xa is mediated by antithrombin III while factor IIa inactivation is mediated by both AT-III and heparin cofactor II.

Orgaran™ has only a minor effect on platelet function and platelet aggregability.

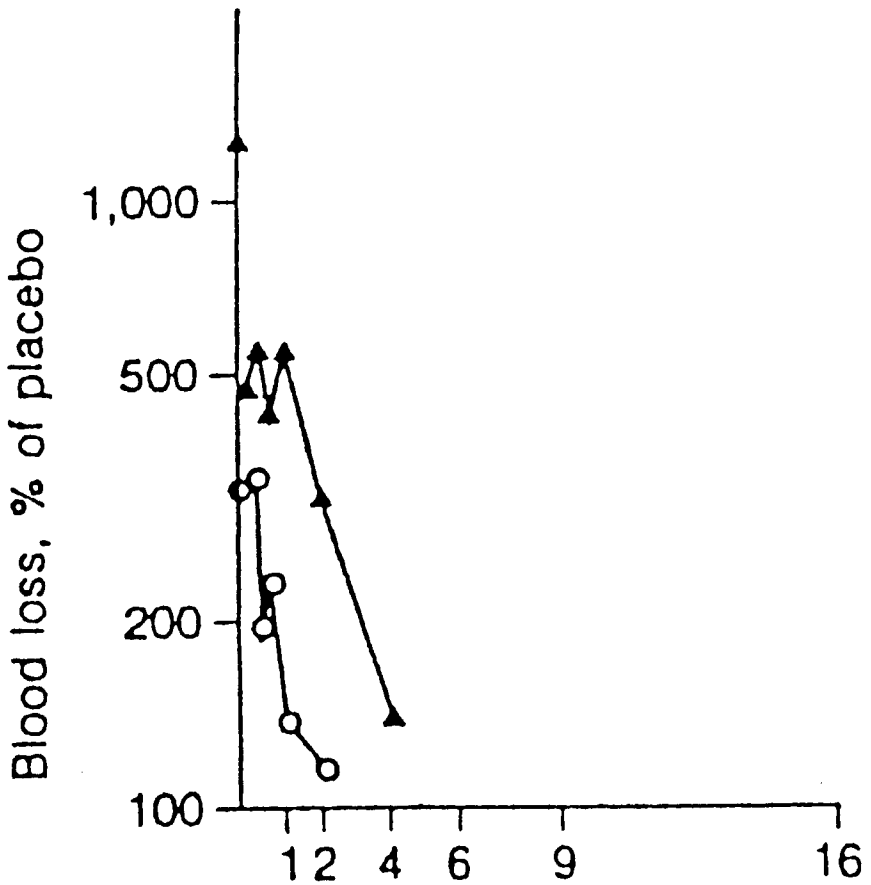
Organon

ORGARAN™
(danaparoid sodium) Injection
Effects of Orgaran™ on Blood Platelets

System		Orgaran	Heparin
In vitro platelet aggregation by:			
ADP	(human platelets)	0	↑↑
Collagen	(human platelets)	0	↑↑
	(rabbit platelets)	0/↓	↓
Thrombin	(human platelets)	↓	↓↓↓
	(rabbit platelets)	↓	↓↓↓
In vivo platelet aggregation by:			
Collagen (in rats)		0	↓↓
Serotonin release (rabbit platelets)		0	↓
Platelet deposition in hemostatic plugs		↓	↓↓
Platelet deposition in thrombi		0/↓	↓↓

0 = No effect; ↑ = potentiation; ↓ = inhibition; ↑↑, ↓↓ = moderate; ↑↑↑, ↓↓↓ = strong; 0/↑, 0/↓ = very weak.

ORGARAN™
(danaparoid sodium) Injection
Blood Loss Orgaran™ vs Heparin



Orgaran™ (o) and heparin (▲)

ORGARAN™
(danaparoid sodium) Injection
Xa:IIa Ratio

Orgaran™	>22 : 1
Lovenox®	2.46 - 4.27[1] : 1
Normiflo®	1.7 - 2.4[2] : 1
Fragmin®	~2.0 : 1
Unfractionated Heparin	1 : 1

---

[1]Lovenox package insert, 3/97

[2]Normiflo package insert 5/97

ORGARAN™
(danaparoid sodium) Injection

Type of Surgery	Type of Anesthesia							Protocol Number
	General	Spinal	Epidural	Mixed (General & Spinal/Epidural)	Other	Unknown	Total	
Elective Hip Surgery	103 170	68 9 (not separated)	48	20	37[a]	12	268 199	83066, 85140, 86002 004-023
Fractured Hip Surgery	154	110	28	0	5[b]	16	313	004-004 A & B, 85143, 62004
General Surgery	267	40	11	7	0	1	326	83001, 84017, 85145

[a] psoas block plus inhalation
[b] total anesthesia

Organon

ORGARAN™
(danaparoid sodium) Injection

Approximately 4500 subjects exposed to Orgaran™ during clinical trials

378 received spinal/epidural anesthesia alone or in combination

0 spinal hematomas reported

Organon

ORGARAN™
(danaparoid sodium) Injection
Countries in which Orgaran™ is approved:

Australia
Belgium
Canada
Denmark
France
Great Britain
Greece
Ireland
Italy
Korea
Luxemburg
Netherlands
New Zealand
Norway
Portugal
Sweden
Switzerland
United States

Organon

ORGARAN™
(danaparoid sodium) Injection

No reported cases of spinal hematoma

- clinical trials
- worldwide postmarketing surveillance

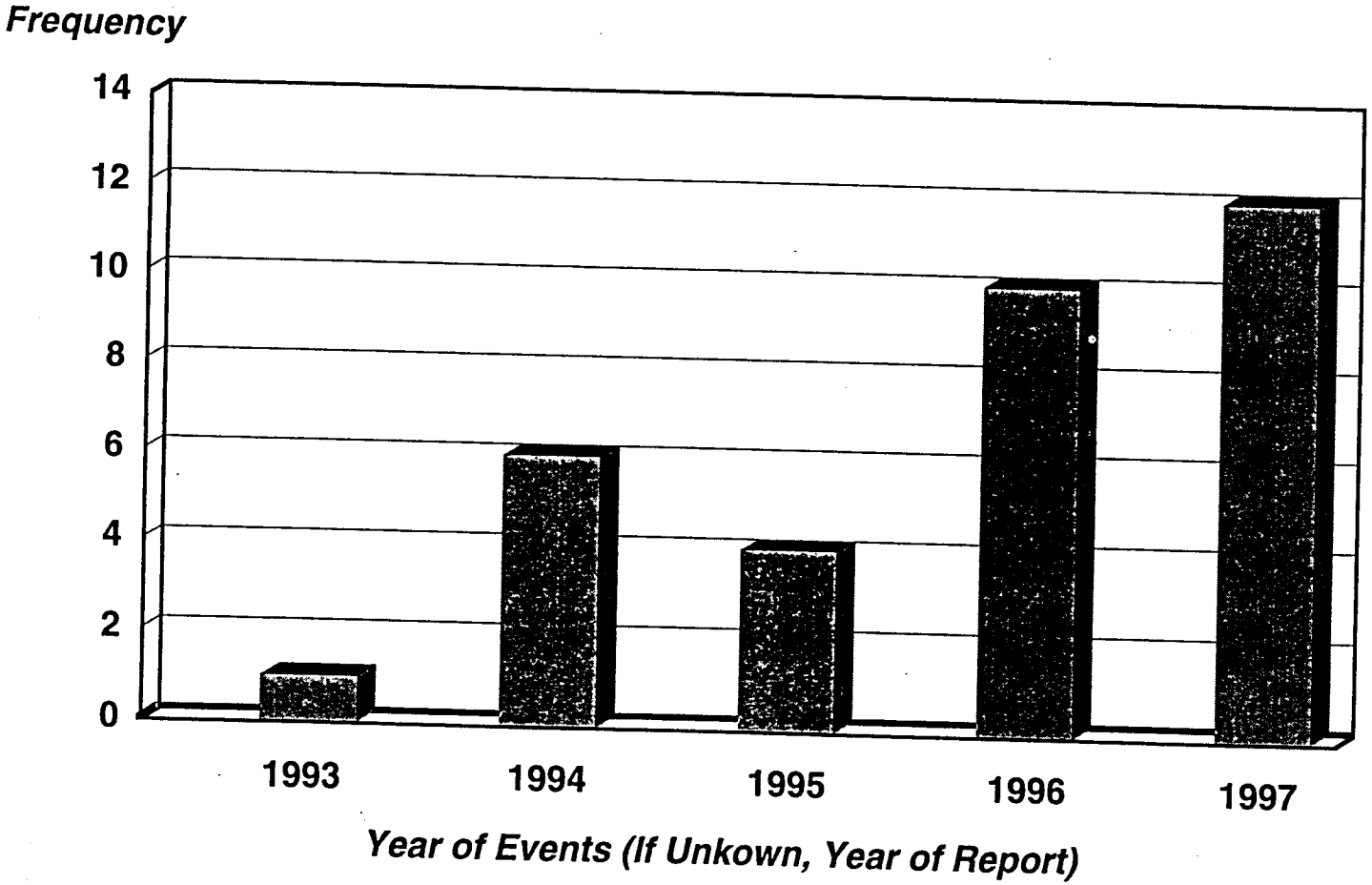
ORGARAN™
(danaparoid sodium) Injection

Organon Inc. concurs with the inclusion of the black box in the labeling for Orgaran™.

We feel this warning should emphasize the risk of the procedure. We believe health care providers need guidance with regards to safe use of antithrombotics during spinal and epidural procedures.

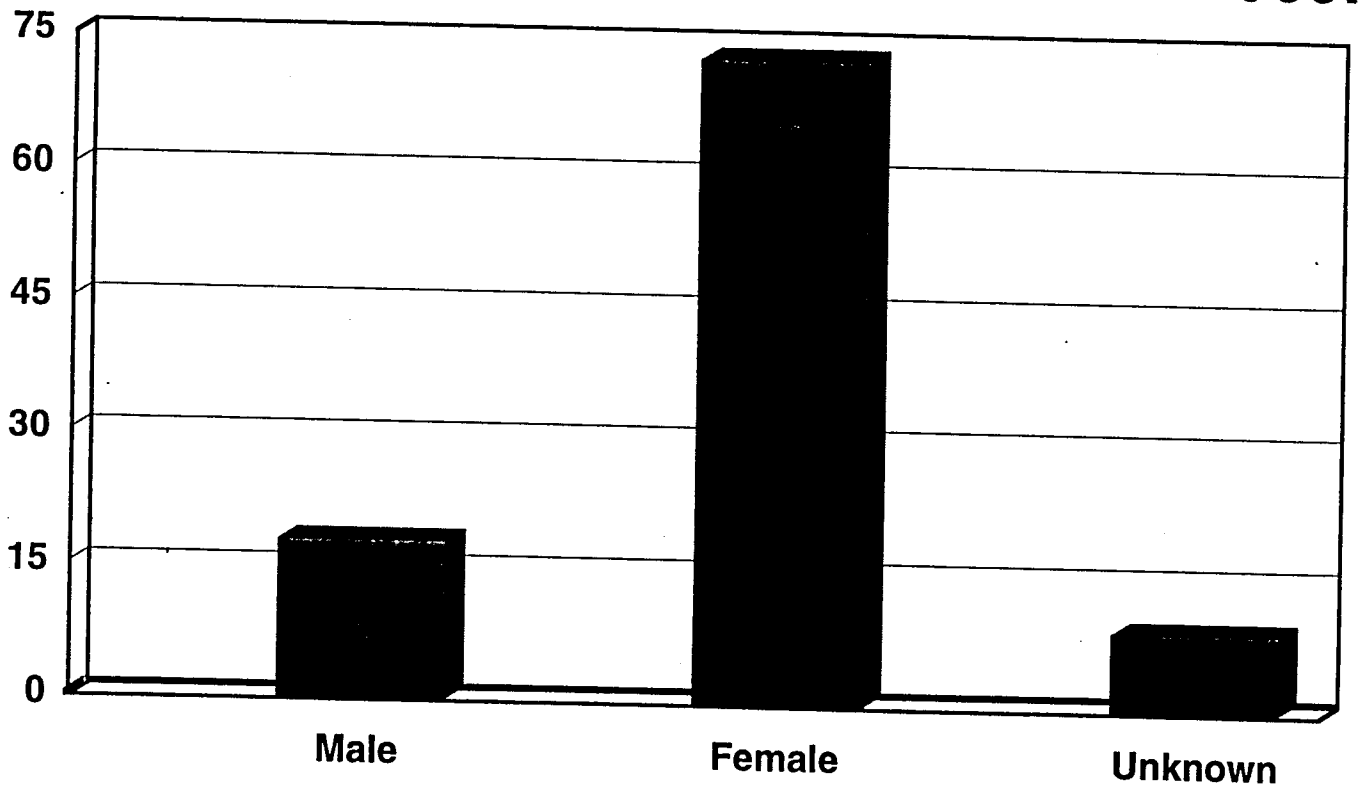
As a manufacturer of heparin, we believe that this boxed warning should be extended to include all parenteral and oral antithrombotic agents.

Number of Spinal and Epidural Hematomas/Bleeds in U.S. Lovenox Users, Reported to the FDA, By Year of Event or Report, From Marketing in 1993 through January 7, 1998



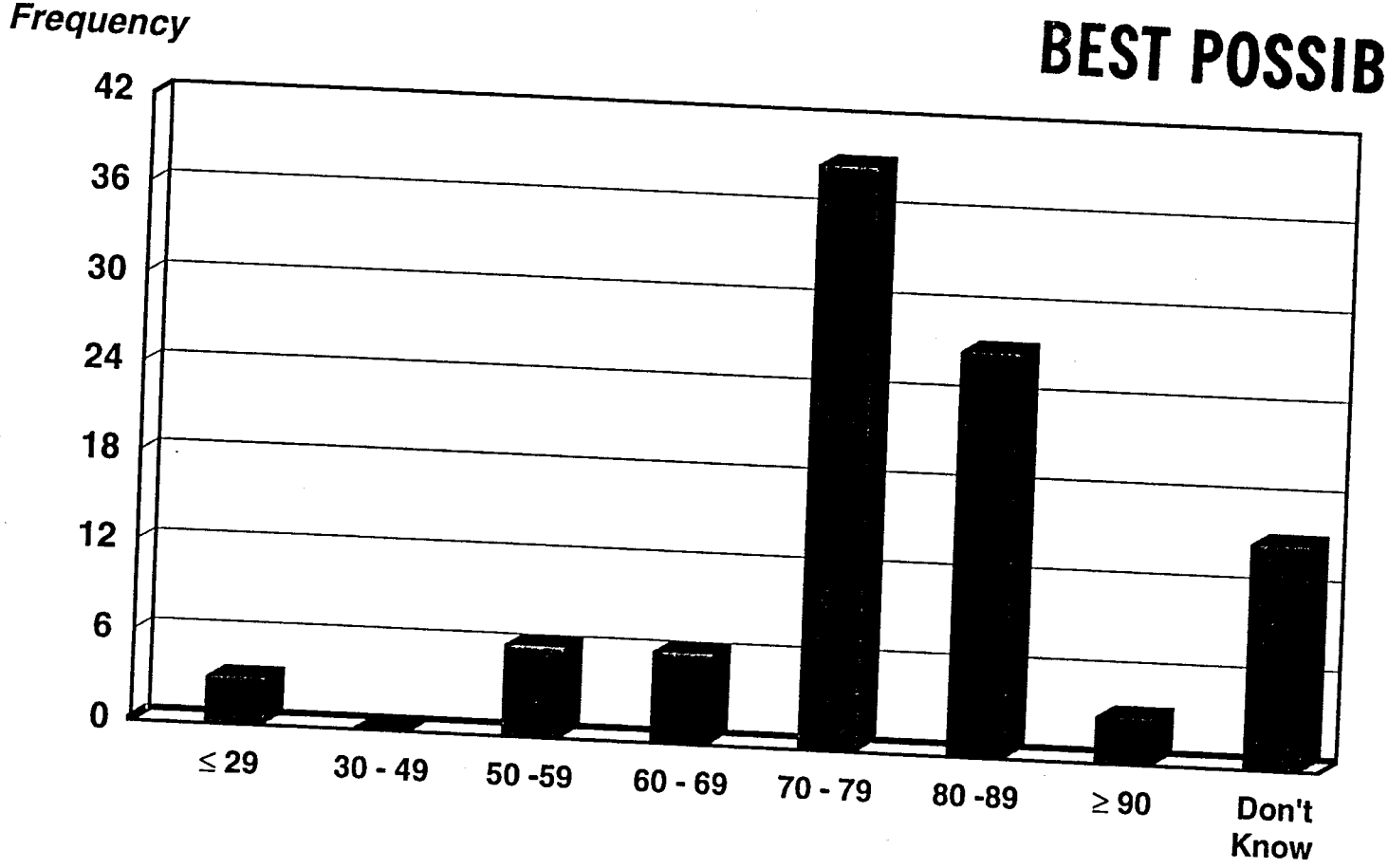
Wysowski, D#274, 01/98, AS

Frequency, By Gender, of U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing through January 7, 1998



Wysowski, D#274, 01/98, AS

Frequency, By Age Group, of U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing through January 7, 1998



Wysowski, D#274, 01/98, AS

U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

Age Distribution

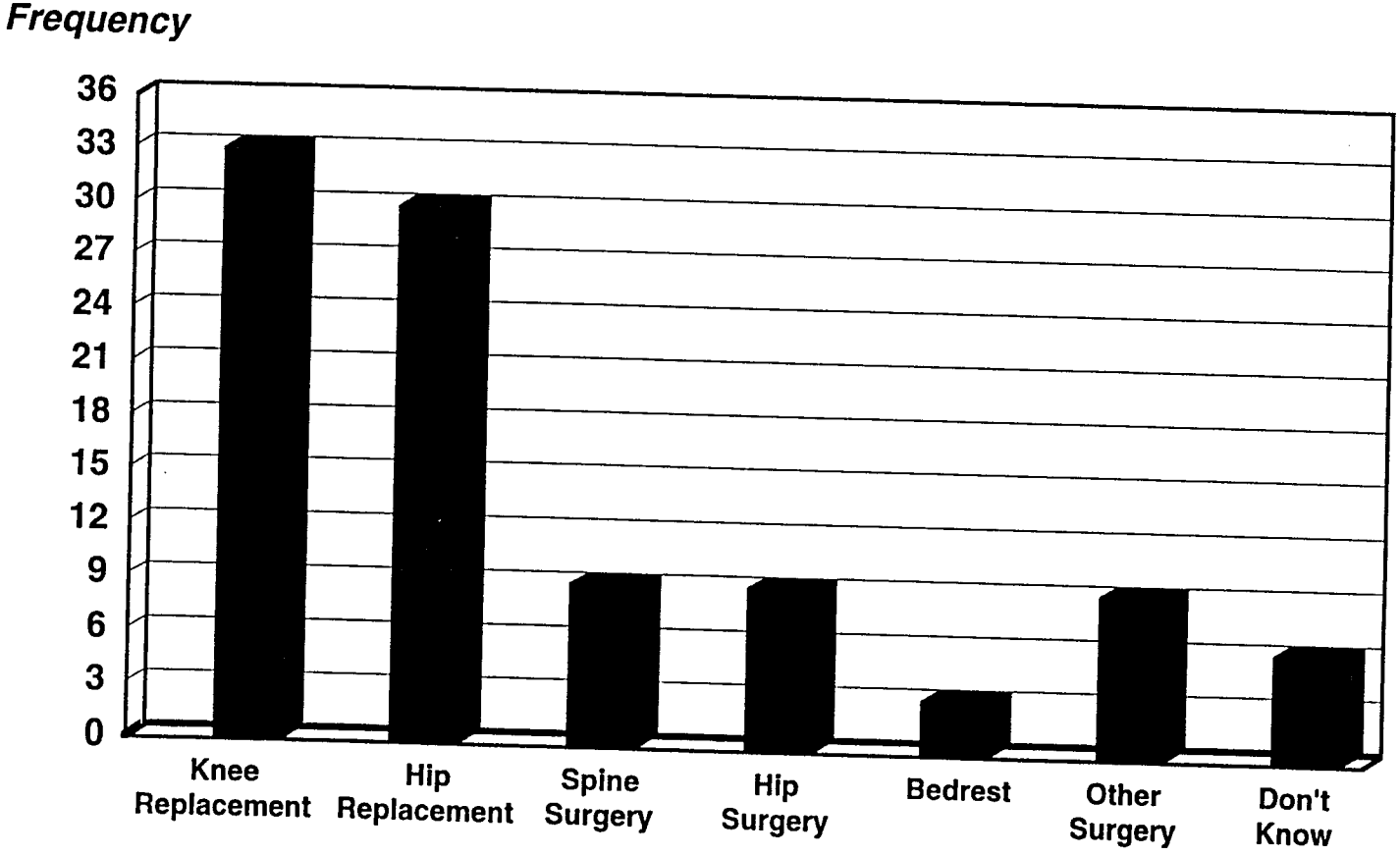
No. with age reported = 28

Range = 28-90 years

Mean = 74 years

Median = 76.5 years

Frequency, by Indication, of U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, in Reports to the FDA, from Marketing through January 7, 1998



Wysowski, D#274, 01/98, AS

Indications for Lovenox Use in U.S. Cases with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

Thromboprophylaxis in Association with:

	N	%
Knee replacement surgery	11	34%
Hip replacement surgery	10	30%
Spinal/back surgery (spinal fusion, "back surgery," lumbar laminectomy spinal stenosis)	3	9%
Hip surgery (fixation femoral neck fracture, "hip surgery")	3	9%
Prolonged bedrest	1	3%
Other (1 patient with knee replacement and 2 GI surgeries; 1 lateral meniscectomy; 1 vascular rejection after cardiac transplant)	3	9%
Don't Know - unspecified	2	6%
TOTAL	33	100%

Wysowski 1/28/98 kcm(B)/as (A)

Doses of Lovenox in U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

Lovenox Dose	N	%
30 mg	2	6
60 mg	22	67
80 mg	1	3
120 mg	1	3
Don't Know - unspecified	7	21
TOTAL	33	100

Wysowski 1/28/98 kcm(B)/as (A)

Days of Lovenox Therapy to Onset of Symptoms in U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

No. of patients with information on duration of Lovenox use to onset of symptoms = 27

Range = same day (after first dose) to 12 days

Mean = 3.4 days

Median = 3 days

Surgery to Evacuate Spinal and Epidural Hematomas in U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

	N	%
Number of Patients with Surgeries to Evacuate Clot		
Yes	21	64
No - pt. refusal	1	3
Don't know - no mention	10	30
Not required - leg symptoms resolved with removal of catheter	1	3
TOTAL	33	100

Wysowski 1/28/98 kcm(B)/as (A)

Outcomes in U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

	N	%
Patients with paralysis not resolved	13	40
Patients with paralysis partially resolved	7	21
Patients with paralysis resolved	6	18
Don't know - no mention	7	21
TOTAL	33	100

Concomitant Medications that May Have Increased the Risk of Bleeding in U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

Number of Patients with Concomitant Medications that May Have Increased the Risk of Bleeding:

	N	%
Single Medications		
Warfarin (Coumadin)	1	
Ketorolac(Toradol)	3	
ASA	0	
Other NSAIDs	1	
Timentin	1	
Combinations		
ASA and other NSAID	3	
Ketorolac and NSAID	1	
ASA (before surgery), ketorolac (after surgery)	1	
Warfarin and ketorolac	1	
Subtotal	12	36
Number of Patients with Concomitant Medications not Known to be Associated with Bleeding	9	27
Number of Patients with No Mention of Concomitant Medications	12	36

Wysowski 1/28/98 kcm(B)/as (A)

Epidural Catheter Attempts/Placement in U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

	N	%
Patients with epidural catheter attempts/placement	23	70
(specific mention of multiple attempts/traumatic placements in 4 patients)		
Specific mention of catheter left indwelling	12	36

Potential Risk Factors in U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

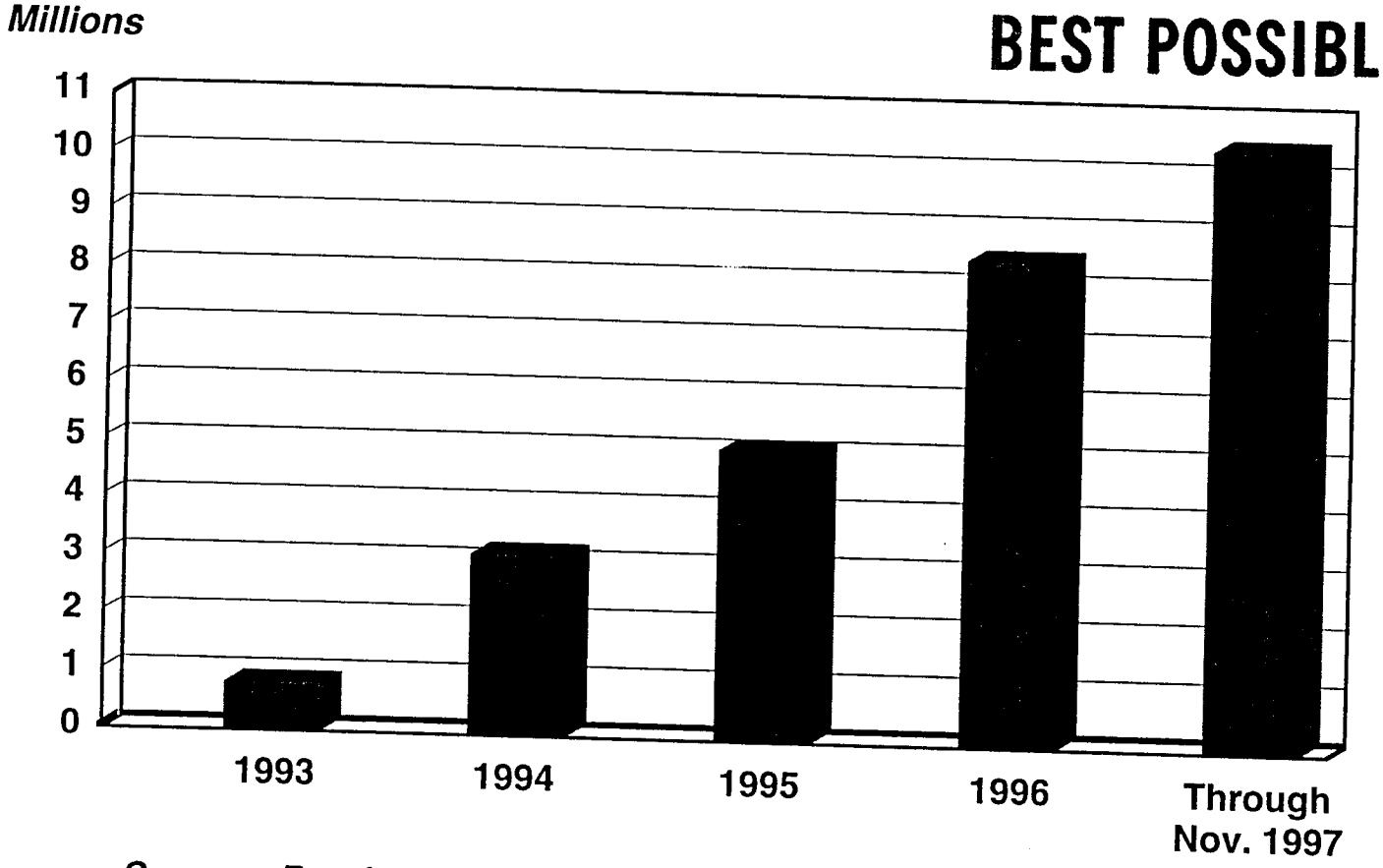
	N	%
Patients with:		
1) Invasion of epidural space, spine (spinal anesthesia, analgesia, tap, surgery, or injection)		
Yes	31	94
No (pt. with cardiac allograft, thoracentesis)	1	
Don't Know - sparse info.	1	
2) Recommended dose Lovenox exceeded (includes pt. with cardiac allograft)	2	6
3) Epidural catheter attempts/placement	23	70
Left indwelling	12	36
4) Concomitant medications that possibly increased bleeding risk	12	36
5) Age $\geq$70 years	23	70
6) Female gender	24	73

Wysowski 1/28/98 kcm(B)/as (A)

Other Potential Risk Factors in U.S. Lovenox Users with Spinal and Epidural Hematomas/Bleeds, Reported to the FDA, from Marketing (5/93) through January 7, 1998

Patients with:	N
1) Ankylosing spondylitis	2
2) History previous laminectomy	1
3) More than one surgery within 3 weeks	1
4) Renal, hepatic dysfunction	1
5) Clotting time prolonged, low factor X	2
6) Platelets < 200,000	2
7) Hematocrit decline	2

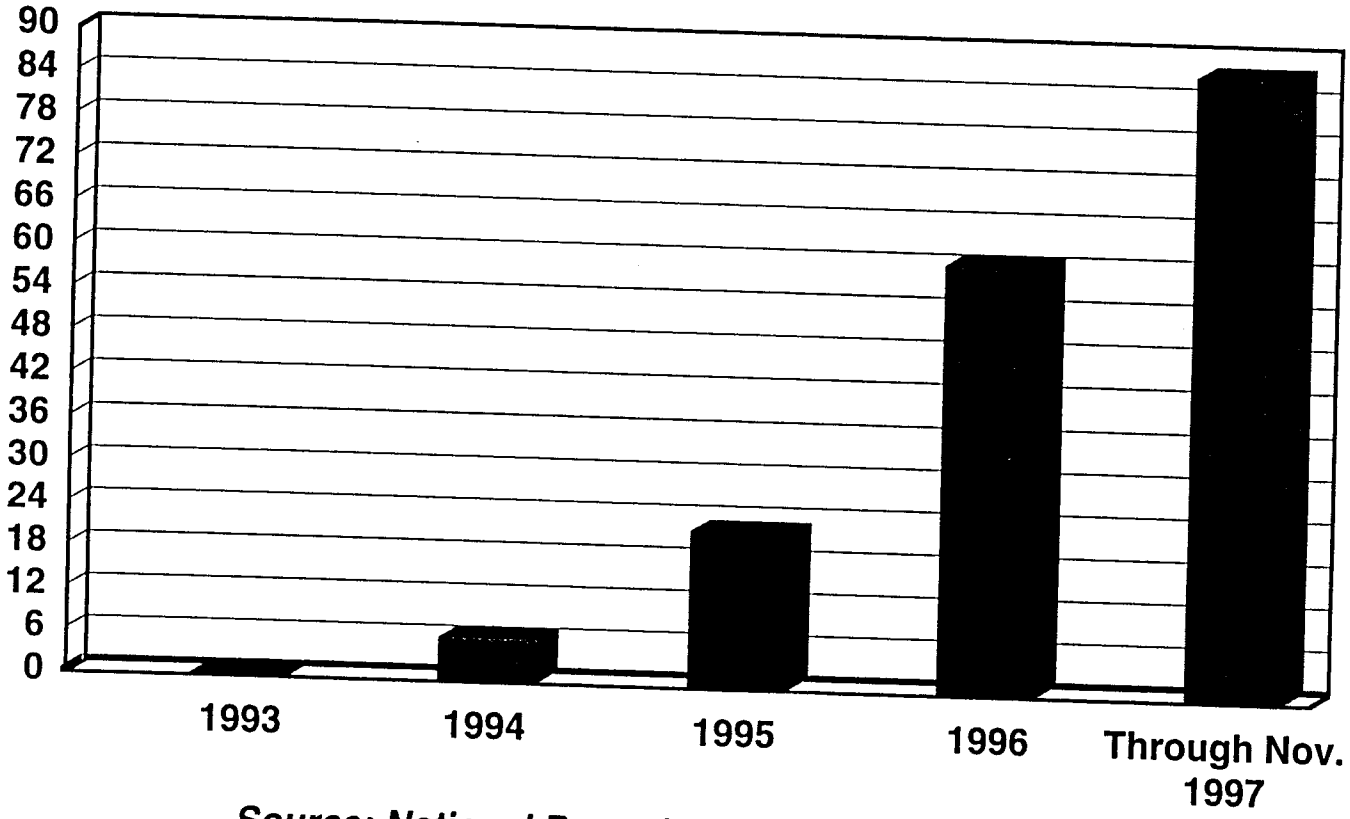
Number of Syringes of Lovenox Sold to U.S. Hospitals, by Year, from Marketing (5/93) through November 1997



Source: Provider Perspective, IMS America, Hospital data include those from hospitals, long-term care, clinics, and closed wall HMO's.

Estimated Number of Dispensed Outpatient Prescriptions for Lovenox, U.S., by Year, from Marketing (5/93) through November 1997

In Thousands

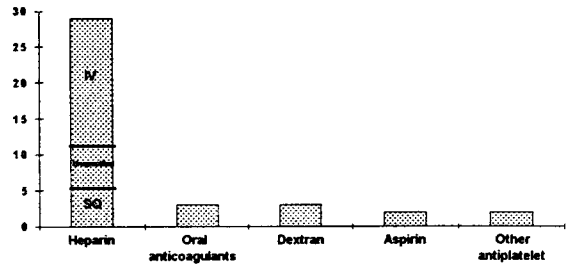


Source: National Prescription Audit, IMS America

Introduction

- Low Molecular Weight Heparins are effective medications for the prevention of deep venous thrombosis and pulmonary embolism
- Even after previous labeling changes and efforts to inform the medical community, cases of neuraxial hematomas continue to occur when low molecular weight heparins and heparinoids are used in the setting of spinal and epidural anesthesia
- From reported cases, identification of risk factors and formulation of guidelines

Published Case Reports of Neuraxial Hematomas in Patients Undergoing Regional Anesthesia and Receiving Anticoagulation or Antiplatelet Therapy (Excluding LMWH and Heparinoids)



Neuraxial Hematoma Reports Outside US

DRUG	Syringes or Doses (Year introduced through 1997)*	Reports Neuraxial Hematoma (NAH)	Reports NAH / 100,000,000 Doses	
			Rate	95% CI
Lovenox (enoxaparin)	352,059,000	6	1.70	[0.6-3.7]
Fragmin (dalteparin)	201,280,000	2	0.99	[0.3-4.4]
Fraxiparin (nadroparin)	407,840,000	3	0.74	[0.2-2.1]
Sandoparin (certoparin)	189,591,000	1	0.53	[0.01-2.9]

*Projected Sales 1997; IMS/IMDAS

Potential differences, US vs. Rest of World

- **Anesthetic & Surgical practices**
  - Percentage of patients receiving spinal, epidural anesthesia
  - Postoperative indwelling catheter for pain control
  - Length and "stiffness" of indwelling catheter
  - Anesthetic agent choice for postop analgesia
  - Demographics of surgical population (age, gender, risk factors)
- **Reporting differences**
  - Event assumed to be related to procedure rather than drug
  - Date of introduction (reports more likely on newer products)
  - Public awareness
- **Dose regimen in orthopedic surgery**
  - US & Canada: Lovenox 30 mg q 12 hr., started postoperatively
  - Rest of world: Lovenox 40 mg once-daily, started preoperatively

An Example of Reporting Differences, US vs. Rest of World

Suprofen (Suprol)

- Clinical trials involved 2500-3000 patients in Europe, 2100 patients in US. Flank pain syndrome not identified
- Marketed in Europe 1982; flank pain syndrome not identified
- Marketed in US 1986
- Flank pain syndrome: 163 cases in US (23.3 / 100,000); 17 cases in rest of world (0.7 / 100,000)

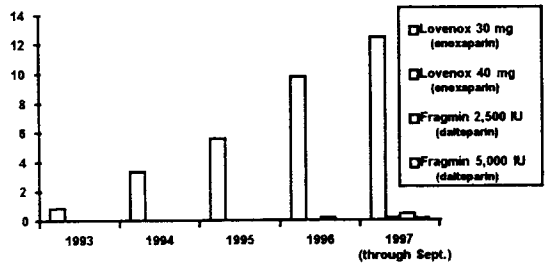
Strom, Clin Pharmacol Ther, 1989
Rossi, JAMA, 1988

Results of Lovenox Hip Replacement Clinical Trials including 30 mg q 12h and 40 mg qd Dose Regimens

	LOVENOX			HEPARIN
	10 mg qd	*40 mg qd*	*30 mg q12h*	*5000 u q8h*
Study 525		n = 203	n = 194	n = 194
Total DVT		15%	5 % *	12%
Proximal DVT		4%	2%	5%
Study 526	n = 161	n = 199	n = 208	
Total DVT	25 %	14% **	11% **	
Proximal DVT	11%	5%	4%	

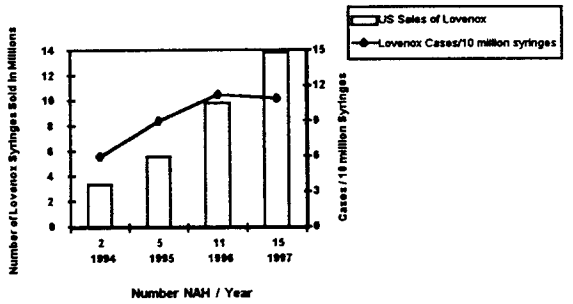
* $p \leq 0.05$ versus Lovenox 10 mg ** $p \leq 0.05$ versus Lovenox qd or heparin
Note: All studies performed with a postoperative (12-24 h) dosing regimen.

US Market 1993-1997
Low Molecular Weight Heparins
(Syringes in millions)



Source: IMS/MIDAS

Neuraxial Hematoma
in US Patients Receiving Lovenox



LOVENOX LABELING CHRONOLOGY

- March 1993 NDA APPROVAL
- March 1995 FIRST LABELING CHANGE
  - Response to two cases epidural hematoma
  - Warning regarding indwelling catheters and risk of epidural or intraspinal hematoma
- January 1996 SECOND LABELING CHANGE
  - Warning that varying degrees of neurologic injury may occur, including paralysis
- January 1998 BLACK BOX WARNING

Dissemination of Information on Neuraxial Hematoma

- Dear Healthcare Professional and Dear Doctor Mailings
  - January 1996
  - June 1997
  - January 1998
- RPR provided details, case reports
  - Hynson, *Anesth Analg*, 1996
  - Horlocker, *Anesth Analg*, 1997
  - Tryba and Wedel, *Acta Anaesth Scan*, 1997
- Interactions of professional representatives with physicians

Neuraxial Hematoma
(Characteristics of 38 Patients with Neuraxial Anesthesia or Spinal/Epidural Puncture and Exposure to Lovenox)

- Female gender 30
- Epidural anesthesia 27
- Epidural Catheter > 24 hrs 13
- Medications / Anti-platelet 12
- Nonconformance with dosing interval 6
- Traumatic / Multiple Attempts 8
- Catheter withdrawal at peak activity 2

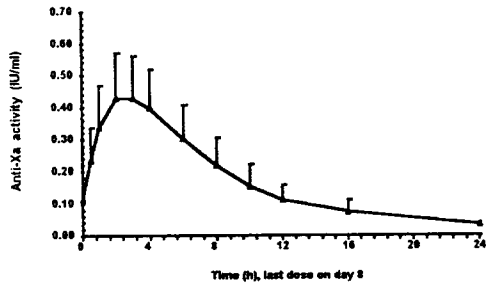
Orthopedic Surgery in US Patients Exposed to Lovenox-
Neuraxial Hematoma with Various Types of Neuraxial Anesthesia and Analgesia in US
US "Reporting Rate" 1995-1997

Neuraxial Anesthesia	Total Joint Arthroplasty + Lovenox (est)	Cases Neuraxial Hematoma	"Reporting Rate" / 10,000 Exposed	"Reporting Rate" 1 / Population Exposed
Spinal	105,000	4	0.4	26,250
Epidural <24 hours	59,000	2	0.3	29,500
SUBTOTAL	164,000	6	0.4	27,333
Epidural >24 hours	37,000	10	2.7	3,700
TOTAL	201,000	19*	0.9	10,579

* Note: For 3 cases, the type of neuraxial anesthesia was not specified

Steady-State Plasma Anti-Xa Activity in Patients Undergoing Total Hip Replacement Surgery

30 mg q 12 h, last dose on Day 8 (Mean + or - SD)



Proposed Recommendations for Dosage and Administration of Anticoagulants for DVT Prophylaxis

- Omit preoperative dose if neuraxial anesthesia is planned
- Remove epidural catheter at least 2-8? hours prior to initiation of anticoagulant, if possible
- In case of indwelling catheter for postoperative analgesia, 24 hours should elapse between the previous dose of anticoagulant and the removal of the cathether. Next dose given no sooner than 2-8? hours after catheter removal

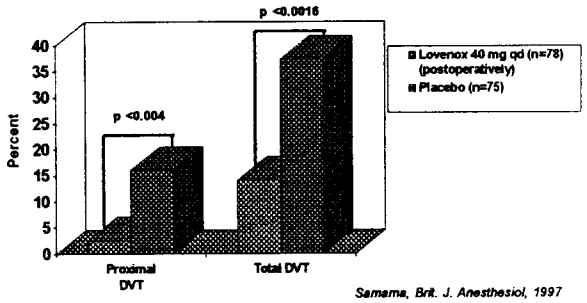
Fourth Consensus Conference on Antithrombotic Therapy

American College of Chest Physicians

	Most effective	Less effective
Total hip arthroplasty	LMWH, fixed dose . twice daily Oral anticoagulation (INR 2.0-3.0) Adjusted-dose heparin	Low-dose heparin Aspirin Dextran Intermittent pneumatic compression
Total knee arthroplasty	LMWH, fixed dose twice daily Intermittent pneumatic compression	

Clagett, Chest, 1995

Efficacy of Lovenox in Total Hip Arthroplasty Performed under Spinal Anesthesia



Samama, Brit. J. Anesthesiol, 1997

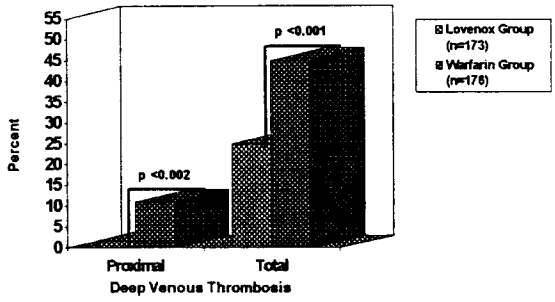
Efficacy of Normiflo vs. Warfarin in Total Hip & Total Knee Arthroplasty

Treatment Regimen	No. of Patients	Deep-Vein Thrombosis (%) Total	Deep-Vein Thrombosis (%) Proximal	Deep-Vein Thrombosis or Pulmonary Embolism (%)	P Value†
Total hip arthroplasty	523				
Normiflo bid	178	7	3	8	0.07
Normiflo qd	171	13	7	14	0.82
Warfarin	174	11	6	14	–
Total knee arthroplasty	446				
Normiflo bid	150	25	6	26	0.004
Normiflo qd	149	28	5	30	0.04
Warfarin	147	41	10	43	–

†Compared with warfarin, with use of the Cochran-Mantel-Haenszel test. All p values are two-tailed.

RD Heparin Arthoplasty Group, J. Bone Joint Surg 1994

Efficacy Of Warfarin vs. Lovenox In Total Knee Arthroplasty



Spiro and Fitzgerald, Thromb. Haemost., 1995

Conclusion

- LMWH are the most efficacious pharmacologic modality to prevent thromboembolic complications of hip and knee replacement surgery
- Neuraxial hematomas have been reported with all anticoagulants
- Even with previous labeling changes and efforts to inform the medical community, cases continue to occur
  - Educational efforts must be increased, including development of guidelines from professional societies
  - Recommendations for use of DVT prophylaxis in setting of neuraxial anesthesia should be included in respective package circulars

FDA Advisory Committee, February 5, 1998

APPEARS THIS WAY
ON ORIGINAL

COUMADIN® (Warfarin Sodium, USP)

David Grandison, M.D., Ph.D.
Vice President, Medical Affairs
The DuPont Merck Pharmaceutical Co.
Wilmington, Delaware

DuPont Merck
2/5/98

COUMADIN®

Presentation

Epidural or Spinal Hematoma Associated with Epidural/Spinal Procedures in Patients Receiving Warfarin

- Pertinent current COUMADIN labeling
- Company's adverse event database
  (Dec. 1967 → Mid-Jan. 1998)
- Clinical literature
  (Jan. 1966 → Mid-Jan. 1998)
- Conclusions

DuPont Merck
2/5/98

Current Labeling

- COUMADIN is CONTRAINDICATED in:

  "Spinal puncture and other diagnostic or therapeutic procedures with potential for uncontrollable bleeding."

  "...major regional, lumbar block anesthesia..."

Current Labeling

Under WARNINGS, it is stated:

"The most serious risk[s] associated with anticoagulant therapy with sodium warfarin" is "hemorrhage in any tissue or organ..."

"The risk of hemorrhage is related to the level of intensity and the duration of anticoagulant therapy."

(continued)

Current Labeling

Under WARNINGS, it is stated: (continued)

"Caution should be observed when COUMADIN is administered in any situation or in the presence of any predisposing condition where added risk of hemorrhage ... is present."

"The decision to administer anticoagulants in the following condition[s] must be based upon clinical judgment in which the risks of anticoagulant therapy are weighed against the benefits: ... Indwelling catheters."

Current Labeling

Under ADVERSE REACTIONS, it is stated:

"Potential adverse reactions to COUMADIN may include:

Fatal or nonfatal hemorrhage from any tissue or organ. This is a consequence of the anticoagulant effect. The signs, symptoms, and severity will vary according to the location and degree or extent of the bleeding. Hemorrhagic complications may present as paralysis; paresthesia; headache, chest, abdomen, joint, muscle or other pain; dizziness; shortness of breath, difficult breathing or swallowing; unexplained swelling; weakness; hypotension; or unexplained shock."

COUMADIN®

*Warfarin-Treated Patients Who Developed Epidural/Spinal Hematoma Post Epidural or Lumbar Puncture (n=4)**

Case No.	Age (yrs)	Sex	Anticoagulation Rx Type	Anticoagulation Rx Dosage	PT (sec)	Procedure	Outcome
1	19	F	Warfarin D/C 1 day prior to LP	NA	21.8 & 21.7	Lumbar puncture	Paralysis
2	51	F	Heparin Started 1 day prior to LP	5000 u IV q4h for ~ 3 days, then 7500 u IV q4h	NA	Lumbar puncture	Transient paraplegia
			COUMADIN Started ~ 3 days post LP	10 mg qd			
3	NA	F	COUMADIN Started night prior to surgery	3 mg qd	17.3	Epidural anesthesia & analgesia	Right-sided foot drop
4	47	M	COUMADIN D/C ~ 2 days prior to surgery	NA	NA	Epidural anesthesia	Paraplegia

*Adverse Event Database and Literature (~ 1967 -1998)

DuPont Merck
2/5/98

Literature Review

(January 1996 → Mid-January 1998)

- Four published studies.*
- Total of 746 warfarin-treated patients who received epidural or spinal anesthesia/analgesia.
- No reported cases of epidural or spinal hematoma.

* Dalldorf et al, 1994
Horlocker et al, 1994
Wu and Perkins, 1996
Benzon and Esposito, 1997

COUMADIN®

Literature and Adverse Event Database Review
(30-Year Period)

- Four patients developed an epidural or spinal hematoma associated with the use of warfarin, following epidural anesthesia/analgesia or spinal puncture.

DuPont Merck
2/5/98

Conclusions

- Based on the extensive review of our Company's adverse event database and pertinent literature during the past 30 years, epidural or spinal hematoma appeared to be extremely rare in association with warfarin therapy in patients requiring epidural/spinal procedures.

- The current labeling has been adequate to protect this patient population.

(continued)

Conclusions (continued)

- Proposed class labeling and boxed warning for low molecular weight heparins should not be extended to include warfarin products.