LMWH Use in Hemodialysis…. Its Time Has Come!

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Financial Disclosure and Potential Conflict of Interest

Honorarium

- Speaker
- Advisory board
- Consultant

Amgen, Genzyme, Leo Pharma, Novartis, Ortho-Biotech, Pfizer, Shire

Learning Objectives (1)

- Review treatment recommendations of the European Best Practice Guidelines
- Describe the avantages and disavantages of LMWH versus UFH for the prevention of clotting of the extracorporeal circuit during hemodialysis
- Describe the therapeutic experiences of two Canadian dialysis centers using LMWH in hemodialysis

Learning Objectives (2)

- Describe the Net Impact Analysis Model for LMWH use in hemodialysis
- Describe the use of LMWH as a catheter lock solution
- Describe the use of LMWH for nocturnal dialysis

European Best Practice Guidelines on Anticoagulation in Chronic Hemodialysis

- Guideline V.1.1
  - To prevent clotting in the extracorporeal circuit during hemodialysis anticoagulation/ antithrombotic treatment is mandatory
- Guideline V.1.2
  - Differences in thrombogenicity should be considered in the choice of the dialyser
    (evidence level: B)

European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. *Nephrol Dial Transpant* 2002; 17(Suppl 7):63-71.

European Best Practice Guidelines on Anticoagulation in Chronic Hemodialysis

- Guideline V.2.1
  - In patients without elevated bleeding risk, low-dose UFH or LMWH can be used to prevent clotting of the extracorporeal system during hemodialysis (evidence level: A)

European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. *Nephrol Dial Transpant* 2002; 17(Suppl 7):63-71.

European Best Practice Guidelines on Anticoagulation in Chronic Hemodialysis

- Guideline V.2.2
  - Because of proven safety (evidence level: A), equal efficacy (evidence level: A) and easy handling (evidence level: C), the use of LMWHs is to be preferred over UFH
  - Other benefits of LMWH are:
    - Improved lipid profile (evidence level: B)
    - Less hyperkalemia (evidence level: B)
    - Less blood loss (evidence level: C)

European Best Practice Guidelines Expert Group on Hemodialysis, European Renal Association. *Nephrol Dial Transpant* 2002; 17(Suppl 7):63-71.

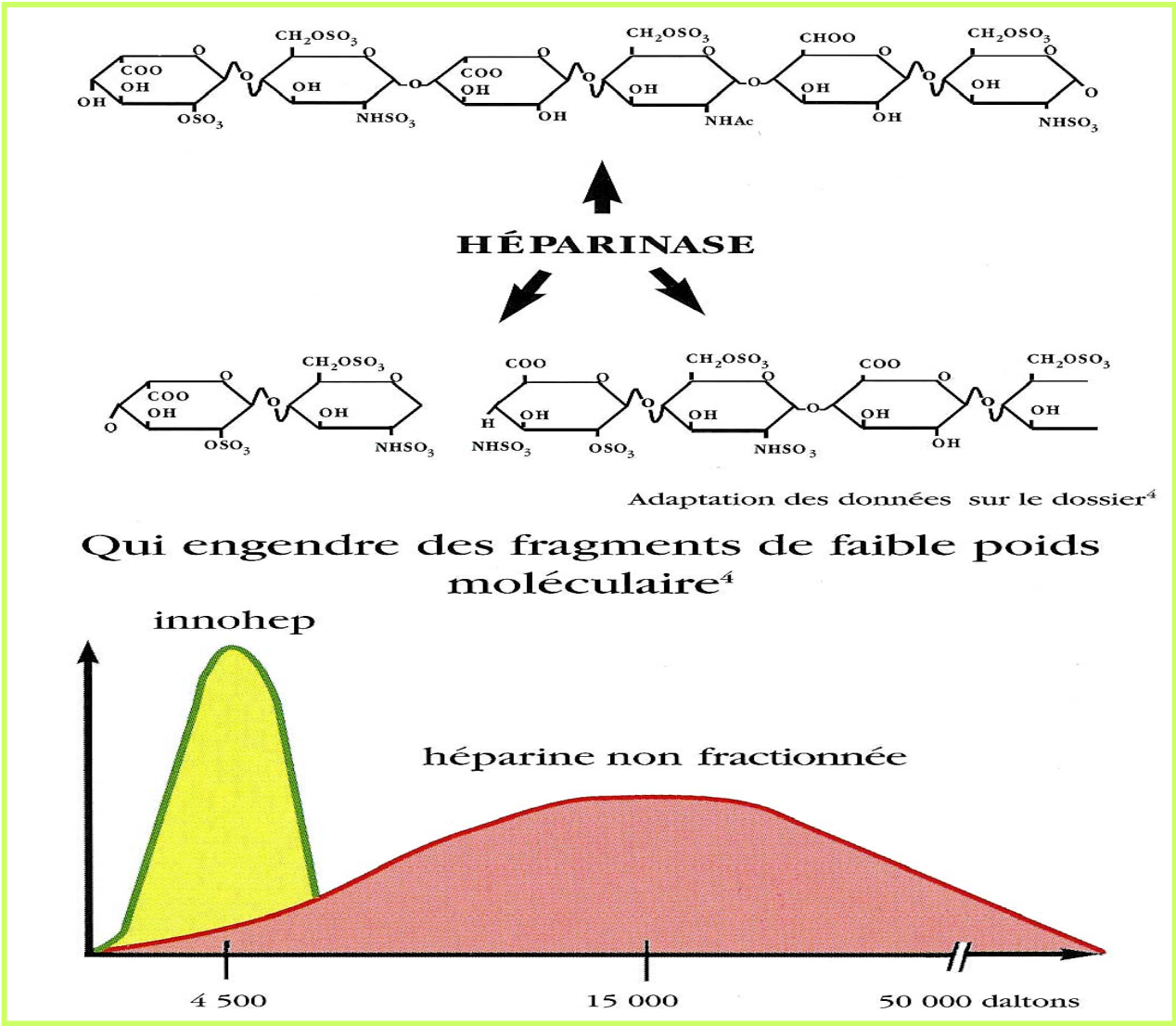
Anticoagulation with Heparin

- Introduction of unfractionated heparin (UFH) was a major breakthrough in the development of hemodialysis
- Individual patients differ in their metabolism of UFH
- UFH is metabolized both in the liver and the endothelium
- Highly negatively charged with sulfate groups thus non-specifically binds to the endothelium, plasma proteins and macrophages

Low-molecular-weight heparins (LMWHs)

- LMWH are produced by treating UFH chemically or enzymatically decreasing the polysacccharide chain
- LMWH contain the active pentasaccharide motif maintaining the antithrombin binding caracteristics but loosing their effet against thrombin
- Reduced protein binding
- Less interaction with platelets

Heparin depolymerization



Characteristics of LMWHs

Characteristics	Standard heparin	Dalteparin (Fragmin)	Enoxaparin (Lovenox)	Nadroparin (Fraxiparin)	Tinzaparin (Innohep)
Method of depolymerization		Nitrous acid	Benzylation followed by alkaline polymerization	Nitrous acid	Heparinase
Mean molecular weight (range) (Da)	12,000-15,000 (3,000-30,000)	5,000-6,000 (2,000-9,000)	3,500-5,600 (3,000-8,000)	4,500 (2,000-8,000)	4,500-5,500 (3,000-6,000)
Number of saccharides	40-50	7-30	10-28	7-27	10-20
anti-Xa/anti-IIa ratio	1:1	2.0-4.0 :1	2.7- 3.9 : 1	1.6 – 3.6 :1	1.5- 2.0 :1
Elimination half-life (h)	0.5 –3.0	2.0 – 5.0	2.2 – 6.0	2.2 – 6.0	1.4 – 1.9

Low-molecular-weight heparins (LMWHs)

- Advantages
  - Better bioavailability
  - Longer half-life
  - Easy to administer
  - Anti-Xa monitoring not required
  - Less risk of bleeding
  - Less osteoporosis
  - Reduced risk of HIT

Heparin-induced thrombocytopenia

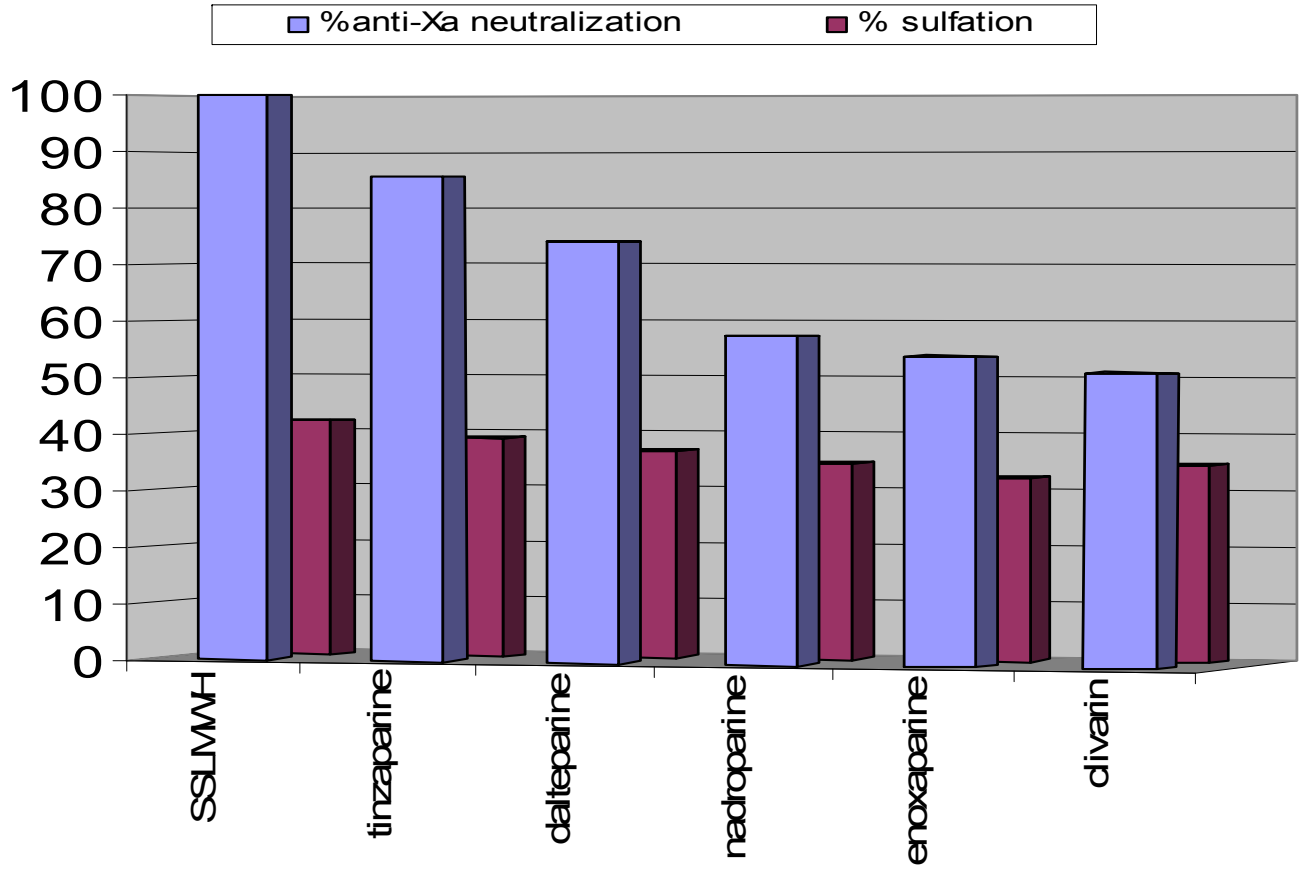
- Incidence:
  - Standard heparin: 1-3%
  - LMWH: 0.2-0.4%
- *In vitro* cross-reactivity: > 60%
- Alternatives:
  - lepirudin
  - argatroban
  - danaparoid
  - fondaparinux

Chest 2009

Low-molecular-weight heparins (LMWHs)

- Disadvantages
  - Renal elimination
  - Partial neutralization of effect of LMWHs with protamine sulfate
    - Protamine 1 mg per 100 IU anti-Xa

Anti-Xa Neutralization of LMWHs by Protamine



Crowther M et al; Br J Haematol 2002: 116; 178-186

Experience using dalteparin (FRAGMIN) in hemodialysis

2003-2007

Hôpital Charles LeMoyne

Greenfield Park, Qc

Introduction

- Low-molecular-weight heparins are used mainly in Europe
- Dalteparin (Fragmin) has been approved in Canada
- Recommended fixed dose = 5,000 units IV
- Objectives:
  - *Efficacy at adapted dose of 60-70 units/kg*
  - *Document the incidence of clotting/bleeding events*

Methodology

- Observational study on the use of dalteparin in hemodialysis between April 2003 and March 2004

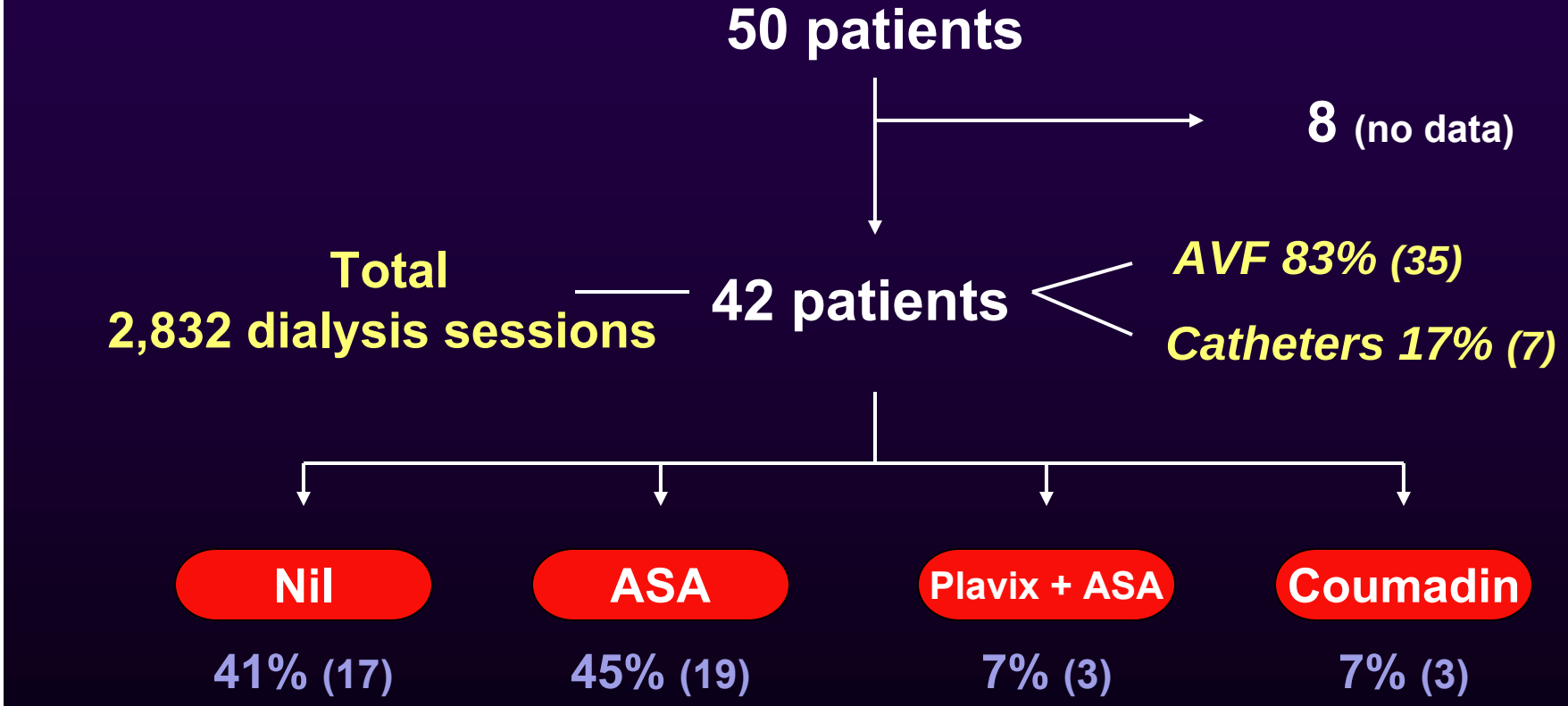
- All patients at the satellite dialysis unit and other stable in-center dialysis patients

- Repeated measurements of anti-Xa activity at regular intervals
  - *dialysis no. 1*
  - *dialysis no. 4*
  - *dialysis no. 13*
  - *dialysis no. 25*

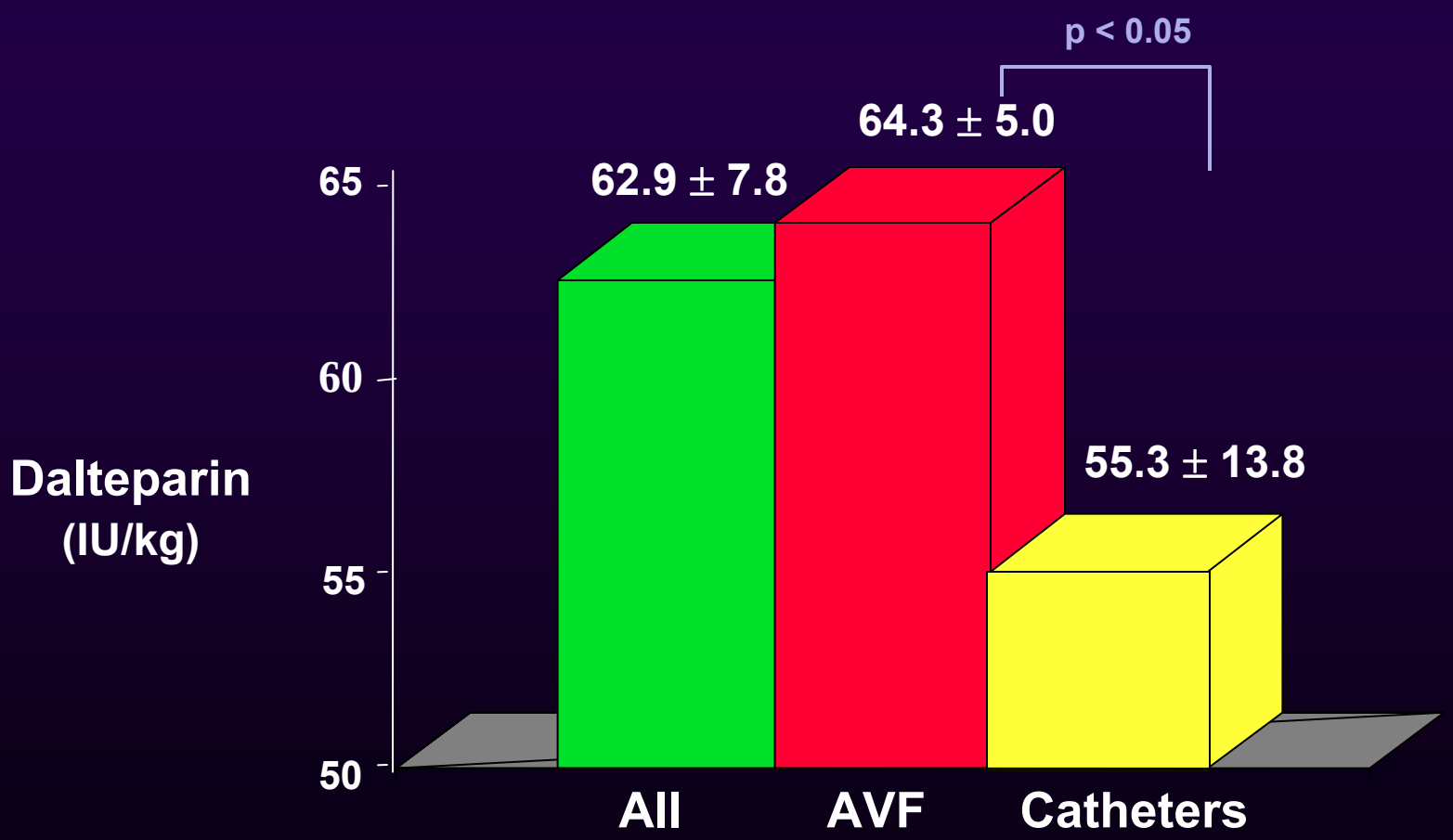
Methodology

- Visual evaluation of the extracorporeal circuit
  - *stage 1*: clear circuit
  - *stage 2*: fibrin ring
  - *stage 3*: clot
  - *stage 4*: circuit coagulation
- Report on bleeding episodes
  - *minor bleeding*
  - *major bleeding*

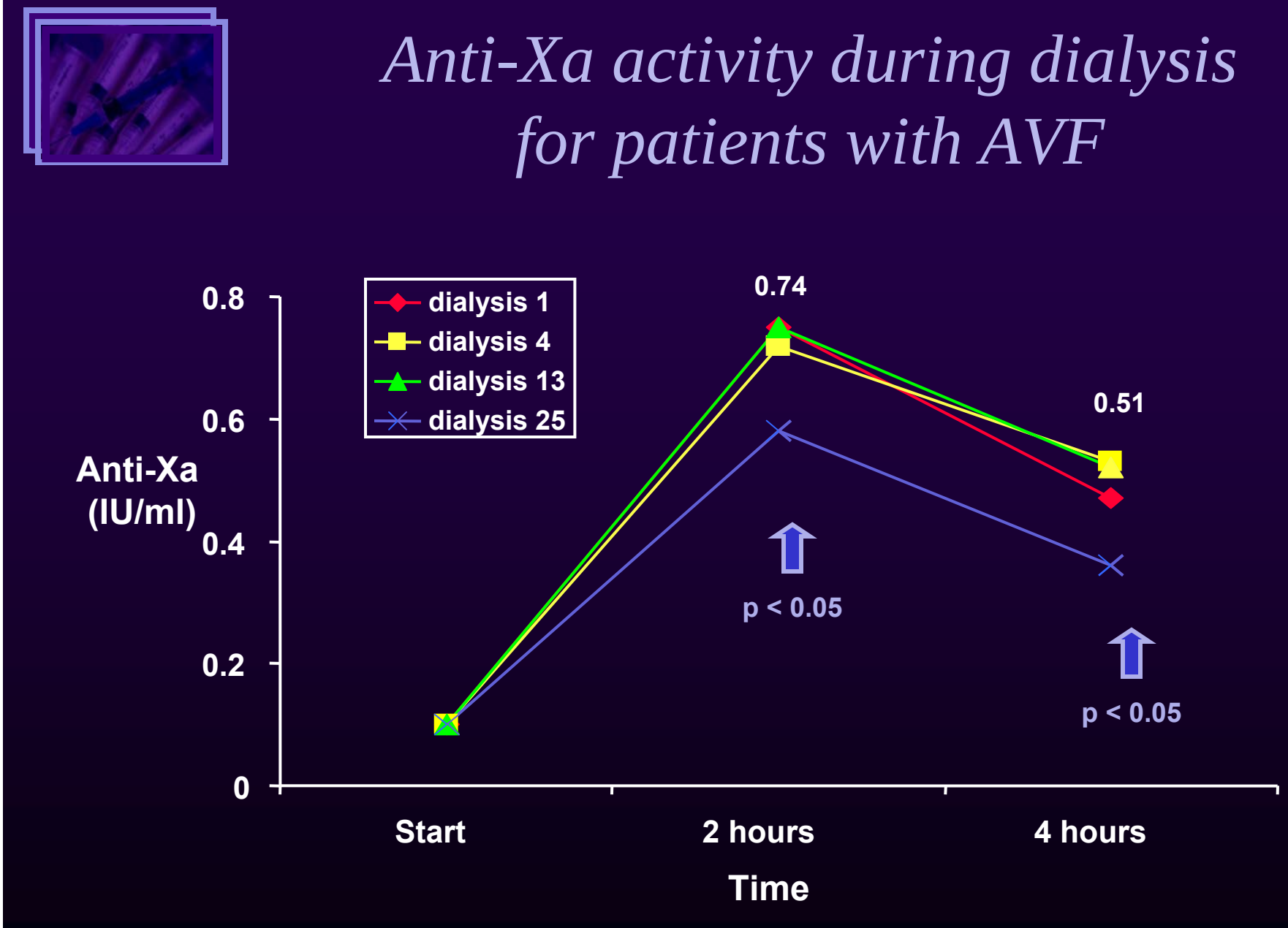
Results


50 patients
8 (no data)
Total
2,832 dialysis sessions
42 patients
AVF 83% (35)
Catheters 17% (7)
Nil
ASA
Plavix + ASA
Coumadin
41% (17)
45% (19)
7% (3)
7% (3)

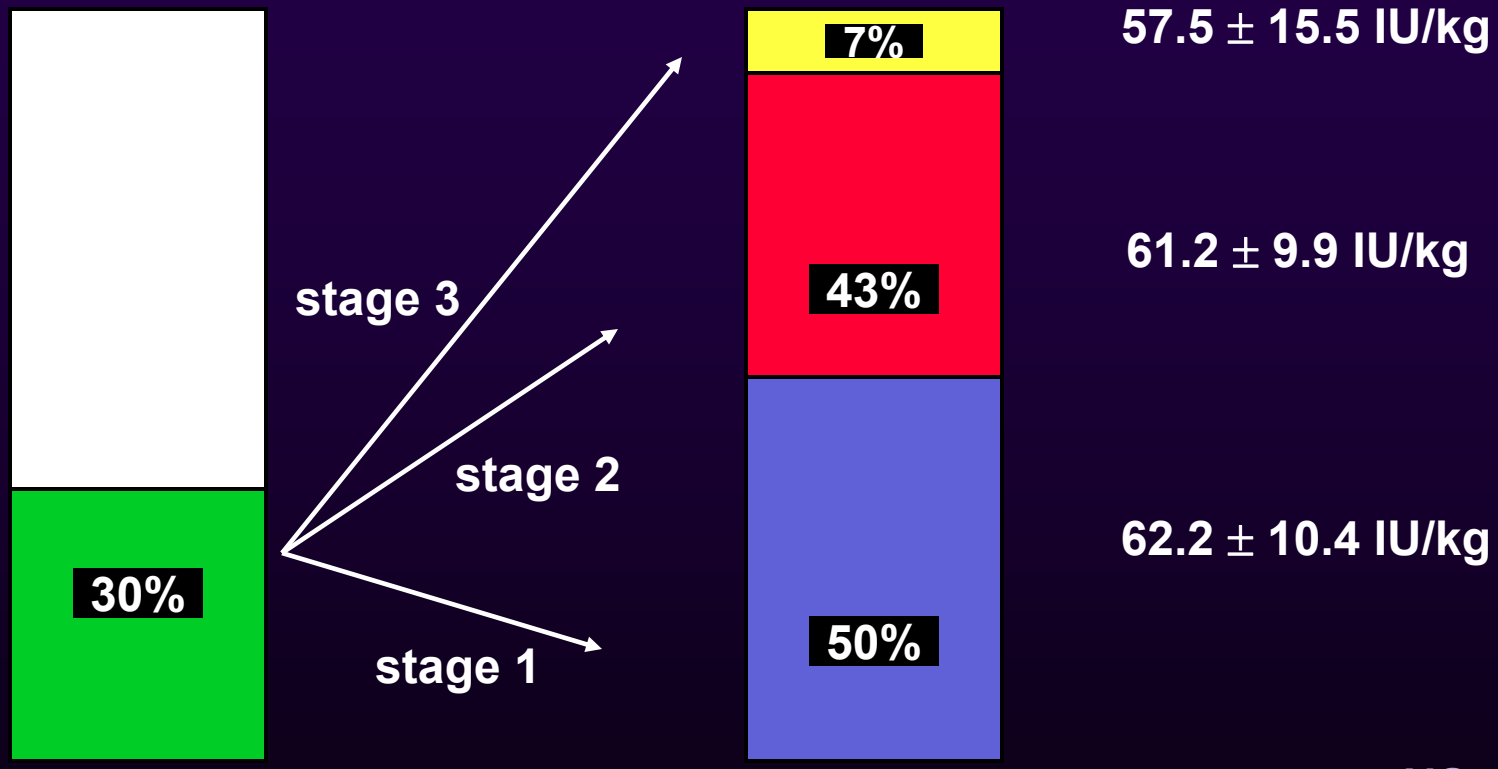
Dalteparin dose by type of access



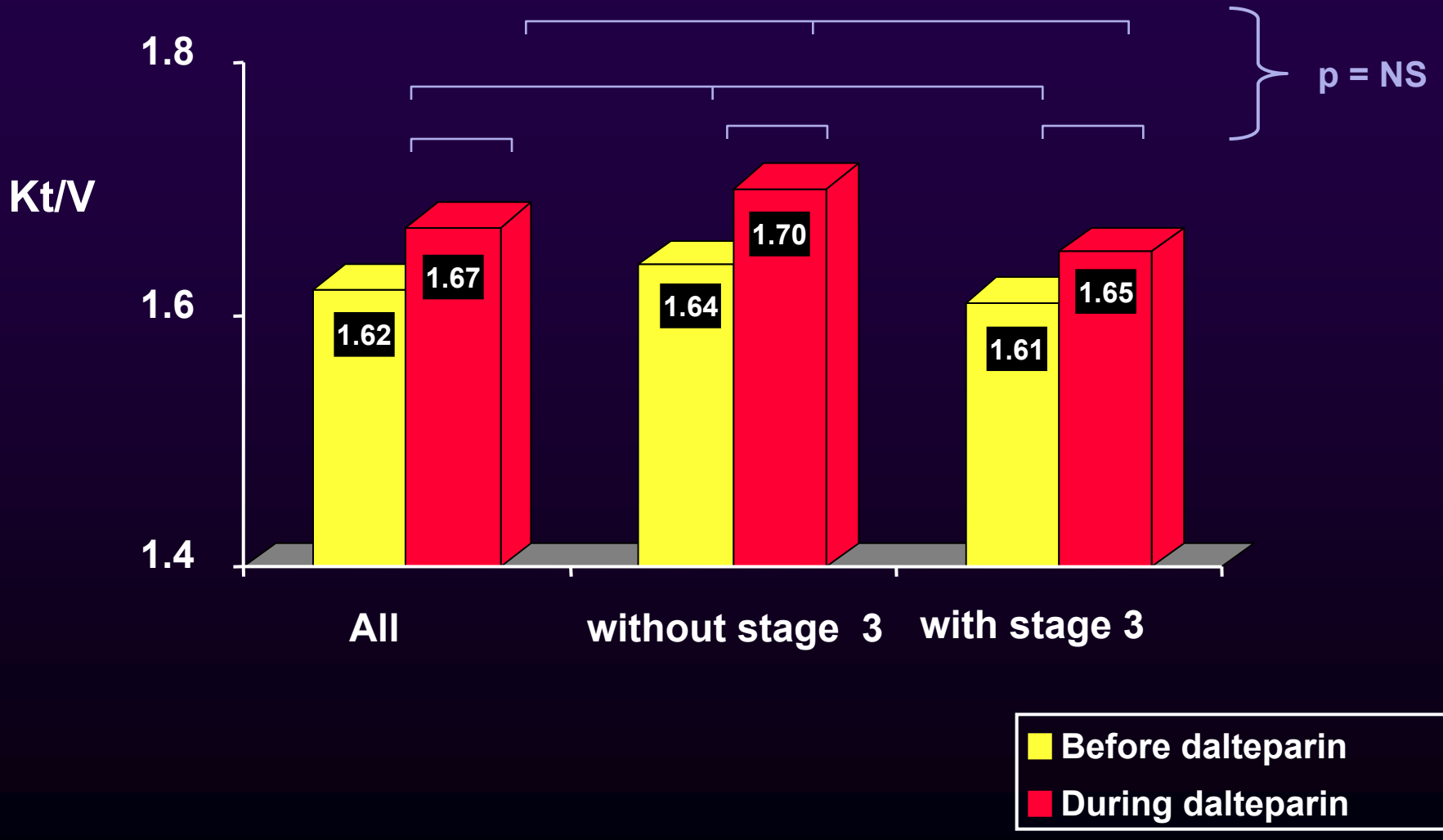
Anti-Xa activity during dialysis for patients with AVF



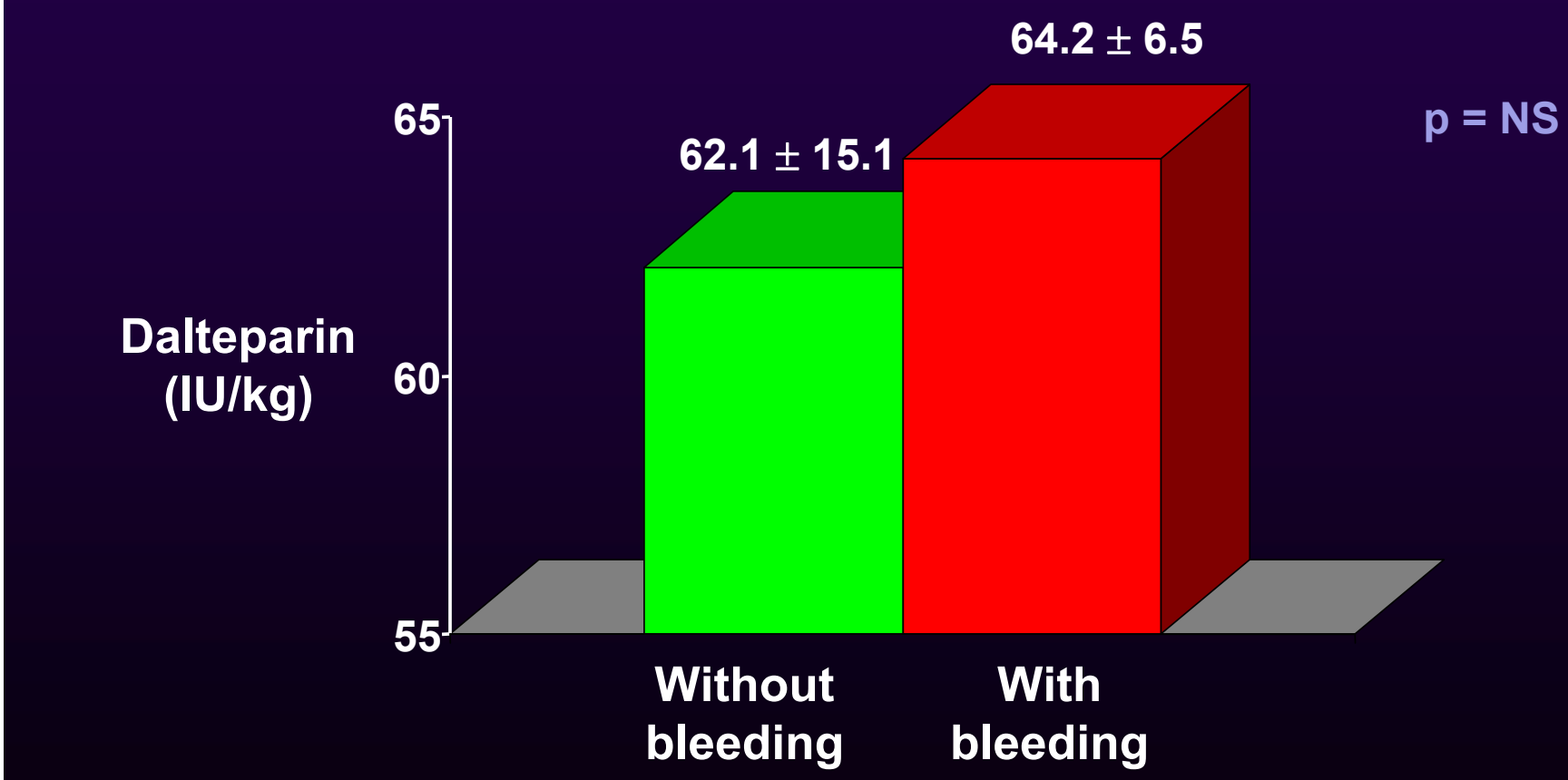
Pre-coagulation (stages) of the circuit for patients with AVF



Evolution of Kt/V on Dalteparin



Dalteparin dose in patients with and without bleeding episodes



Episodes of bleeding

1.5%

42 episodes / 2,832 dialysis sessions

Nil	ASA	Plavix + ASA	Coumadin
15	15	12	0
64.1 ± 8.2 IU/kg	62.7 ± 6.5 IU/kg	65.6 ± 2.9 IU/kg	58.2 ± 7.2 IU/kg

Summary

- Effective anticoagulation of the extracorporeal circuit with approximately 60 IU/kg (or probably less) dalteparin
- No significant clotting problem reported
- No major bleeding event reported
- Acceptable risk of bleeding, probably less than with standard heparin
- Quality of dialysis unchanged

Conclusion

Dalteparin in hemodialysis is an effective and safe method of extracorporeal circuit anticoagulation and adapts very well to satellite dialysis units

Transition to tinzaparin

- After 4 years of dalteparin use
- 187 patients were converted to tinzaparin
- Dalteparin dose was reduced by 10% *
  - dalteparin 5,000 IU→ tinzaparin 4,500 IU
  - dalteparin 4,000 IU → tinzaparin 3,500 UI
- Prefilled syringes: 80% of doses
- Multidose vials: 20% of doses

* Beijering R et al: Clin Drug Invest 2003;23(2):85-97

Experience with tinzaparin (INNOHEP) in hemodialysis

2001-2009

Hôpital Maisonneuve-Rosemont

Montréal

Comparison between Tinzaparin and Standard Heparin for Chronic Hemodialysis in a Canadian Center

Hélène Lord[a] Nicole Jean[a] Marc Dumont[c] Jeannine Kassis[b]
Martine Leblanc[a]

Hemodialysis Unit, [a]Nephrology Division, and [b]Hematology Division, Maisonneuve-Rosemont Hospital, and [c]Biostatistics Department, University of Montreal, Canada

- Small comparative study of 32 chronic hemodialysis patients with peripheral accesses
- Randomly divided into two groups in a cross-over design: tinzaparin for 4 weeks followed by standard heparin for 4 weeks, or vice-versa
- Hemodialysis was performed thrice weekly over 3,5-4h using large surface reused filters
- Initial tinzaparin dose was 3,500 IU if receiving less than 7,500 U of standard heparin

Lord H et al: Am J Nephrol 2002;22:58-66

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- Initial tinzaparin dose was 4,500 IU if receiving more than 7,500 U of standard heparin
- Injected in the arterial line at the beginning of hemodialysis
- Dosage adjustments were made by increments or decrements of 500 IU
- Visual aspects of the tubing and the dialyzers at the end of the sessions were charted
- Time of compression of the vascular access was also charted

Lord H et al: Am J Nephrol 2002;22:58-66

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- Experience with tinzaparin was positive
- Represents a simple and easy way to offer anticoagulation during maintenance hemodialysis
- Seems associated with less postdialysis bleeding
- Saves precious nursing time
- Widely appreciated by patients and staff

Lord H et al: Am J Nephrol 2002;22:58-66

Tinzaparin implementation at HMR

- Clinical study in 2001: 32 patients
- January 2008: 180 /352 patients
  - Multidose vials only
- September 2008: 330 / 370 patients
  - Prefilled 3500 /4500 syringes
  - Multidose vials
- March 2010 – all patients except those using Nephral or saline flush
  - Prefilled 2500 / 3500 / 4500 syringes (80%)
  - Multidose vials (20%)

How to convert from heparin to tinzaparin or dalteparin

- Evidence from a number of clinical trials and practical experience has shown that patients who converted from heparin to tinzaparin need only about **40 to 50% of their former heparin dose.**
- Roundoff to dose of prefilled tinzaparin or dalteparin syringe available
  - Total heparin dose (bolus+ infusion)= 10,000 U

Heparin 10,000 U x 40% - 50% = 4,000 – 5,000 U tinzaparin→ administer 4,500 IU or dalteparin 5,000 IU

Initiating LMWH in a new hemodialysis patient

- Total heparinization
  - Calculate 60 U/ kg x 80 kg → 4,800 U → administer 4,500 U (prefilled tinzaparin syringe) or 5,000 U (préfilled dalteparin syringe)
- Tight heparinization
  - Calculate 30 U/kg x 80kg → 2,400 U → administer 2,500 U (prefilled tinzaparin or dalteparin syringe)

Monitoring

- In routine clinical practice of outpatient hemodialysis there is no regular monitoring of anti Xa activity
- Rely on clinical inspection of the dialyser and the venous bubble trap
- Increase the bolus dose by 500-1000 U if stage 2 (fibrin) or stage 3 (small clot) present
- Decrease the dose if prolonged bleeding after fistula needles are removed

Davenport A et al :Handbook of Dialysis, 4th ed 2007; 204-18

Time and motion

Net Impact Model Description

Net Impact Model:

- Provides a detailed analysis of the financial consequences of using a drug on healthcare resources utilization in real clinical context.
- It is a trend now to use Net Impact Analysis in drug submission for provincial reimbursement.
- It is mandatory for Quebec reimbursement submission to the Conseil du Médicament.

Net Impact Model Description

Net Impact Model :

- Describes the net cost difference between a drug and its comparator(s) that are used for the same indication
- Exposes all costs related to the use of the drug and not only its acquisition cost
- Takes into account potential cost and time (professionals, chair) savings for a given drug versus its comparator(s)

Net Impact Analysis Methodology

Net Impact Analysis:

- Experts in the field (pharmacists, physicians, nurses) are consulted to define treatment parameters including all resource utilization required for a specific treatment.
- References such as published clinical data and data on file.
- The calculation is done using Pharmaco-Management Software© that has a provincial resource costs database.
  - RAMQ (drug costs)
  - Quebec Ministry of Health & Hospital (professionals hourly rate, overhead costs, lab tests, chair time, etc)
  - Buyer groups (medical supplies)

Analyses details

Based on: Thrice weekly dialysis for a total of 156 dialysis/patient/year.

First year: patient starting hemodialysis will start anticoagulant therapy which includes dose adjustment protocol.

Subsequent year: patient is already on anticoagulant, no dose adjustment protocol, take in consideration only administration cost related.

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Costs Evaluated in the Model

First year:

- **Treatment costs:** Include drug acquisition cost for Innohep and UFH.

- **Preparation costs:** Include costs associated with dose adjustment protocol
  - TCA tests for UFH
  - Anti-Xa tests for Innohep

- **Administration costs:** Include costs related to drug administration for Innohep and UFH.

Note: based on thrice weekly dialysis for a total of 156 dialysis/pt/year

Costs Evaluated in the Model

Subsequent year:

- **Treatment costs:** Include drug acquisition cost for Innohep and UFH.
- **Preparation costs:** No cost
- **Administration costs:** Include costs related to drug administration for Innohep and UFH.

Note: based on thrice weekly dialysis for a total of 156 dialysis/pt/year

Quebec Net Budget Impact – Cost Analysis

Innohep versus UFH
Cost per patient per year

Net Impact Analysis	Innohep	UFH	Innohep	UFH
Cost per patient per year	First Year	First Year	Subsequent Year	Subsequent Year
Treatment cost	$898.56	$546.75	$898.56	$546.75
Preparation & Administration	$163.43	$567.10	$19.99	$439.63
Total	**$1 061.99**	**$1 113.85**	**$918.55**	**$986.38**
Difference	**($51.86)**		**($67.83)**	

Note:
- Calculation based on 156 dialyses/year (thrice weekly)
- First year includes dosage adjustment time for Innohep and UFH

symbiose
PARTENARIAT & MARKETING STRATÉGIQUE

Net Budget Impact
to treat 200 patients/year

Innohep versus UFH
Cost difference for 200 patients/year

First year

	Coût / patient	Nbre de patients	Coût total
Produit A : Innohep (tinzaparine sodique)	1 062$	200	212 398$
Produit B : héparine non-fractionnée	1 114$		222 770$
Différence:	-52$		-10 372$

Subsequent year

	Coût / patient	Nbre de patients	Coût total
Produit A : Innohep (tinzaparine sodique)	919$	200	183 710$
Produit B : héparine non-fractionnée	986$		197 276$
Différence:	-68$		-13 566$

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Nursing time potentially saved

Time for preparation and administration per patient per year: Innohep versus UFH

First year

Nursing time (min) to treat one patient/year	Innohep	UFH
	Nursing time/pt/year	Nursing time/pt/year
Time for preparation (dose adjustment protocol)	9.28 min	85.41 min
Time for administration	39.00 min	787.80 min
Total	48.28 min	873.21 min
Difference	**(824.93 min) or (13.7 hrs)**	

Subsequent year

Nursing time (min) to treat one patient/year	Innohep	UFH
	Nursing time/pt/year	Nursing time/pt/year
Time for administration	39.00 min	787.80 min
Difference	**(748.8 min) or (12.5 hrs)**	

Note: Calculation is made for 156 haemodialysis per patient per year

symbiose
PARTENARIAT & MARKETING STRATÉGIQUE

Nursing time potentially saved

Innohep versus UFH (200 patients total)

First year

Nursing time (hour) to treat 200 patients/year	Innohep	UFH
	Hour/year	Hour/year
Time for preparation (dose adjustment protocol)	30.9 hrs	284.7 hrs
Time for administration	130.0 hrs	2 626.0 hrs
Total	160.9 hrs	2 910.7 hrs
Difference	**(2 749.8 hrs) or (379 days)**	

Subsequent year

Nursing time (hour) to treat 200 patients/year	Innohep	UFH
	Hour/year	Hour/year
Time for administration	130.0 hrs	2 626.0 hrs
Difference	**(2 496 hrs) or (344 days)**	

Note: Calculation is based on 7.25 hours per working day.

Analysis summary

- The analysis shows that despite an acquisition cost superior to UFH, **Innohep** (tinzaparin sodium) has a lower net impact on healthcare system and overall nephrology department.

- Using **Innohep** instead of UFH could reduce nursing time spent on dose adjustment and administration.

Analysis summary

- In a context of staff shortage, hospital administrators are looking to do more with less. Nursing time saved could be re-attributed to do other tasks such as:
  - Review and update drug lists
  - Anemia management
  - Vascular access follow-up
  - Mineral metabolism management
  - Diabetic foot care and prevention
  - Laboratory review
  - Diet review
  - Promotion of self-care and development of patient's autonomy
  - Patient training / rehab program
  - Patient exercise program

LMWH as a catheter lock

CHAT Study

Comparison Between Standard Heparin and Tinzaparin For Haemodialysis Catheter Lock

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Carine Jolicoeur, M.Sc.
Fannie Thériault, M.Sc.

Lynne Senécal, MD, nephrologist
Pierre Chouinard, DPH[1,2]
Jean Lachaîne, PhD[2]
Michel Savoie, M.Sc.[1,2]

1. Hôpital Maisonneuve-Rosemont
2. Pharmacy Faculty, University of Montréal

Methodology

- Doses
  - UFH: 5,000 IU/lumen injected after each hemodialysis session
  - Tinzaparin: 2,000 IU /lumen injected after each hemodialysis session
  - Alteplase: 2 mg /lumen injected as required in the event of catheter dysfunction

Malo,J. ASAIO Journal 2010; 56: 42-47

Principal objective

- Compare the efficacy of tinzaparin and UFH as locks for hemodialysis tunnelled central venous catheter to prevent catheter dysfunction requiring the use of alteplase

Malo,J. ASAIO Journal 2010; 56: 42-47

Secondary objectives

- Compare the efficacy of tinzaparin and UFH as locks for hemodialysis tunnelled central venous catheter based on the following parameters:
  - Reasons for alteplase use
  - Mean pressure of venous and arterial branches of the catheter
  - Mean blood flow during dialysis
  - Inverted catheter function
  - Removal of catheter
  - Reasons for removal of catheter
  - Online Kt/V

Malo,J. ASAIO Journal 2010; 56: 42-47

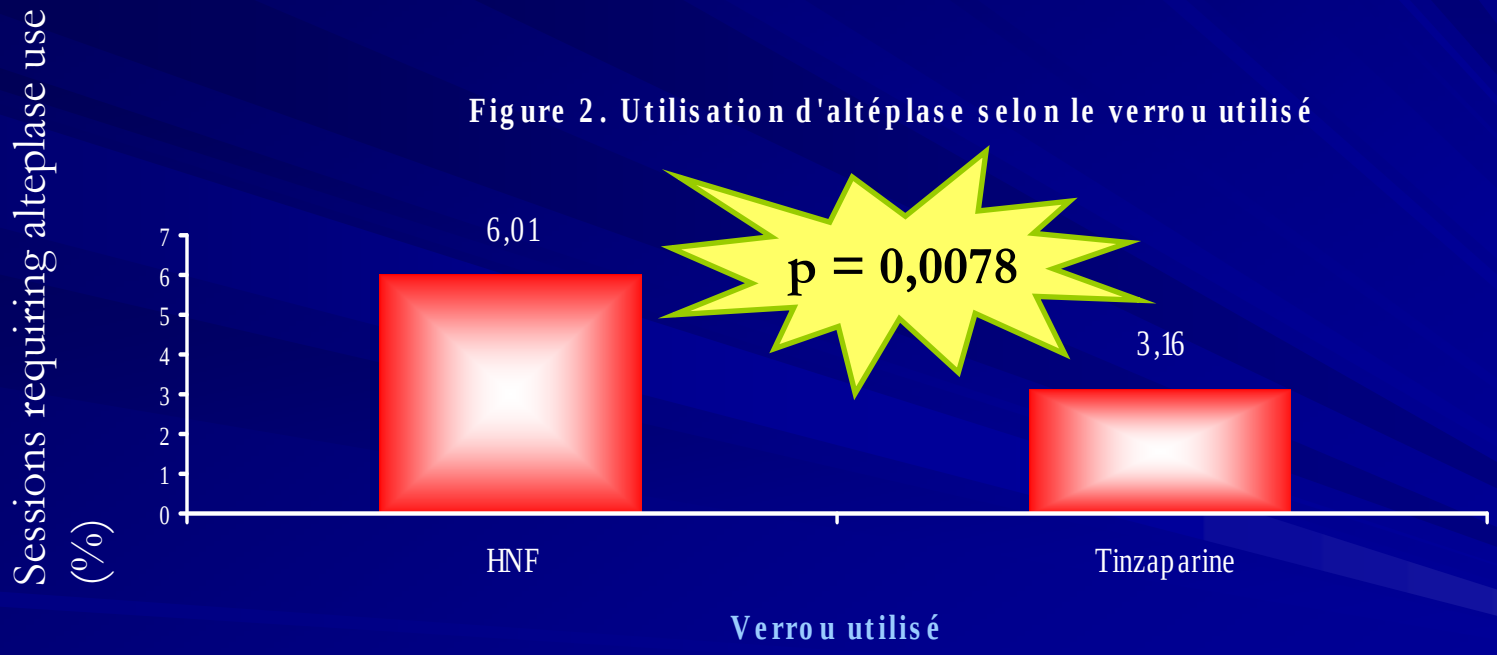
Results:
Principal outcome

- Percentage of sessions requiring alteplase use:
  - Tinzaparin: 3.16 % of sessions
    - 23 sessions / 729 total sessions
  - UFH: 6.01 % of sessions
    - 49 sessions / 815 total sessions

↓ 47.4 % reduction in alteplase use

Malo,J. ASAIO Journal 2010; 56: 42-47

Results:
Principal outcome



Malo,J. ASAIO Journal 2010; 56: 42-47

Results:
Secondary outcomes

- No statistically significant secondary outcome
- No major adverse affect attributable to the locking solution

Malo,J. ASAIO Journal 2010; 56: 42-47

LMWH in nocturnal dialysis…

The final frontier

LMWH for nocturnal dialysis…

- Home HD (8-10h every 2 days)
- n=15
- Nov 2009
  - Incident patients start training with tinzaparin (n=5)
  - Single I.V.bolus
    - 4h = 60 IU/kg
    - 8h= 120 IU/kg
- Ongoing evaluation

Summary (1)

- LMWH have become the extracorporeal anticoagulant of choice in Europe
- LMWH may cause less thrombosis in the extracorporeal circuit than UFH
- Economical parity with UFH although they may initially appear a more expensive option than UFH for routine hemodialysis

European Best Practice Guidelines; Nephrol Dial. Transpant 2002;17 (Suppl 7) 63-71

Summary (2)

- Simple to administer, single bolus using a prefilled syringe
- Bleeding risk of LMWH seems at least equivalent to UFH
- Intravenous doses of LMWH resulting in short-term therapeutic anticoagulation for the prevention of dialysis circuit thrombosis are lower than subcutaneous doses administered for therapeutic anticoagulation

Summary (3)

- Predictable clinical effet
- Anti-Xa monitoring is not required
- Saves precious nursing time
- Greatly appreciated by patients and staff


Si vous n’êtes pas trop épuisé…
Des questions ?