



# THE INTERNET STROKE CENTER

PRESENTATIONS AND DISCUSSIONS ON STROKE MANAGEMENT

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## Anticoagulation in Acute Ischemic Stroke



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# **An Introduction to Heparin**

## **What is Heparin?**

- Heterogeneous collection of straight chain anionic sulfated mucopolysaccharides usually obtained from animal lung or intestine
- Potentiates activity of antithrombin III - an endogenous inhibitor of coagulation factors IIa, IXa and Xa
- Binds to platelets and plasma proteins

## **Heparinoids and Low Molecular Weight Heparinseparin**

### **Pharmacological**

- Reduced anti-IIa effect, primary effect on Xa
- Reduced platelet interaction
- Reduced plasma protein binding

### **Clinical**

- Assay activity as anti-Xa units
- Longer half-life
- Reduced bleeding

## **Intravenous Heparin for Partial Stable Stroke**

- 225 patients with acute ischemic stroke and partial motor deficits
- Onset within 48 hours
- Exclusions:
  - Progression within 1 hour
  - Diastolic BP > 110
  - Cardiac source

### **Progression at 7 days**

- Heparin - 19/112 (17%)
- Placebo - 22/113 (19.5%)
- $p=.62$  - 95% CI -8.7 to +13.7%
  - No difference in number improved, overall functional status or death

### **Late Results**

- Three months
  - No difference in functional activity level
- One year
  - Higher mortality in heparin group ( $p<.01$ )
  - No difference in functional activity level

Source: Ann Internal Med 1986; 105:825-828

# Clinical Trials of Anticoagulation in Stroke

## Recently Published Clinical Trials

- International Stroke Trial (IST)
- Lancet 1997; 349: 1569-1581
- Hong Kong Nadroparin Trial (HK)
- New England Journal of Medicine 1995; 333:1588-1593
- Trial of ORG 10172 in Acute Stroke Treatment (TOAST)
- Journal of the American Medical Association 1998; 279: 1588-1593

## Trial Format

	<b>IST</b>	<b>HK</b>	<b>TOAST</b>
<b>Entry</b>	<48 hrs	<48 hrs	<24 hrs
<b>Endpoint</b>	Dead/Dependent	Dead/Dependent	Good
<b>Duration</b>	6 months	6 months	3 months
<b>Drug</b>	Heparin	Nadroparin	ORG 10172
<b>Class</b>		LMWH	Heparinoid
<b>Dose</b>	5000 SC BID 12,500 SC BID	4100 SC QD 4100 SC BID	7200 IV/day
<b>Time</b>	14 days	10 days	7 days

## Recurrent Ischemic Stroke

	<b>IST</b>	<b>HK</b>	<b>TOAST</b>
<b>Time</b>	14 days	10 days	7 days
<b>HD</b>	3.2%	2%	1.1%
<b>LD</b>	2.6%	1%	
<b>Control</b>	3.8%	1%	1.1%

**Percent with Poor Outcome**

	<b>IST</b>	<b>HK</b>	<b>TOAST</b>
<b>HD</b>	62.6%	45%	24.8%*
<b>LD</b>	63.1%	52%	
<b>Control</b>	62.9%	65%	26.3*
<b>Results</b>	Negative	p=.007	Negative

**Intracranial Hemorrhage**

	<b>IST</b>	<b>HK</b>	<b>TOAST</b>
<b>Time</b>	14 days	10 days	10 days
<b>HD</b>	1.8%	0%	2.2%
<b>LD</b>	0.7%	2%	
<b>Control</b>	0.4%*	1.0%	0.6%
	*p<.05		

**Major Extracranial Hemorrhage**

	<b>IST</b>	<b>HK</b>	<b>TOAST</b>
<b>Time</b>	14 days	10 days	10 days
<b>HD</b>	2%	0%	5%
<b>LD</b>	0.6%	0%	
<b>Control</b>	0.4%*	1%	1.6%
	*p<.05 HK data for major GI hemorrhages only		

## Additional Studies

### Fraxiparine in Ischemic Stroke Study

Death / Dependency at Six Months

	<b>Placebo</b>	<b>LD</b>	<b>HD</b>
<b>Number</b>	250	272	245
<b>Death</b>	68	73	73
<b>Barthel &lt;85</b>	74	82	75
<b>Combined</b>	56.8%	57.2%	59.2%

Fraxiparine is the proprietary name for nadroparin

Source: [New England Journal of Medicine 1995 Dec 14;333\(24\):1588-1593](#)

### Heparin

Complications in Patients with Cerebrovascular Disease

- Symptomatic CNS hemorrhage in 1-4%
- Serious non-CNS hemorrhage in 2-3%

Sources:

Rothrock & Hart: Annals of Internal Medicine 1991; 115:885-895

Camerlingo et al: Archives of Neurology 1994; 51:462-467

### Anticoagulant Treatment in Progressing Stroke

Unblinded, randomized trial of heparin (125 mg IV x1, IM q6H x 2) then phenindione PT 2-3x control for 3 weeks. Number recovered or improved at 6 months:

- Control 19/38
- Anticoagulation 26/38 (p=.16)

Source: British Medical Journal 1961 2:70-73

### Anticoagulant Therapy in Thrombosis in Evolution

Unblinded, randomized trial of heparin (50 mg IV q4h if < 1 week until dicumarol therapeutic) then dicumarol for PT 15-25%. Progression of deficit:

- 1 month - control 10/67 vs Rx 8/61
- 6 months - control 13/67 vs Rx 8/61

- 12 months - control 18/67 vs Rx 9/61

Source: Fisher, Neurology 1961 11:119-131, Baker et al, Neurology 1962 12:823-835

### **Heparin Treatment of Progressing Stroke-I**

Prospective study of 36 patients who worsened after admission and were then treated with heparin for 7 hours to 21 days. Further progression:

- Carotid 13/19
- Vertebrobasilar 2/8
- Lacunar 2/9

Source: Haley et al: Stroke 1988; 19:10-14

### **Heparin Treatment of Progressing Stroke-II**

Retrospective chart review of 69 patients:

- 27 (39%) continued to deteriorate
- 2 due to CNS hemorrhage
- 12 (17%) stabilized
- 30 (44%) improved
- 10 (14%) developed hemorrhagic side effects

Source: Slivka & Levy, Stroke 1990; 21:1657-1662

## Additional Studies and Conclusions

### Cerebral Embolism Study Group

Un-blinded, prospective randomized study of clinically diagnosed cardio-embolic stroke within 48 hours treated with heparin for 48 hours then warfarin. Results at 14 days:

- Stroke - control 2/21 vs Rx 0/24
- Death - control 2/21 vs Rx 0/24

Source: Stroke 1983; 14:668-670-1662

### International Stroke Trial

Atrial Fibrillation

	<b>Heparin</b>	<b>Control</b>
Number randomized	1557	1612
Recurrent Ischemic Stroke	2.8%	4.9%
Hemorrhagic Stroke	2.1%	0.4%
Total New Stroke	4.9%	5.3%
Data for first 14 days		
Source: <a href="#">Lancet 1997; 349:1569-1581</a>		

## **Trial of ORG 10172 in Acute Stroke Treatment (TOAST)**

### Cardioembolism

	ORG 1072	Control
Number randomized	143	129
Recurrent Stroke	0%	1.6%
Data for first 7 days		
Source: <a href="#">Journal of the American Medical Association 1998; 279: 1588-1593</a>		

### Retrospective Stroke Subtype Analysis

- Five subtypes analyzed for two different endpoints in addition to 4 analyses for total group = 14 analyses
  - $p < .05/14 = p < .0036$
- Large artery atherosclerosis
  - Favorable outcome  $p = .04$
  - Very favorable outcome  $p = .02$
- No significant difference

### **Cardiac Embolism Conclusions**

- IST showed no benefit for the subgroup with atrial fibrillation
- TOAST showed no benefit for the subgroup with cardioembolism

### **Summary**

Patients with lower extremity paralysis should receive DVT prophylaxis with low dose anticoagulation. Anticoagulation with heparin or heparin like drugs has no beneficial effect on:

- Progression or early recurrence
- Long term functional status
- Any subgroup of patients

## References

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