

Regulatory shortcomings and  
Potential Solutions;  
Provider Community Responsibility  
The example of BMP-2

Marc F. Swiontkowski MD  
Professor and Chairman  
Department of Orthopaedic Surgery  
University of Minnesota

# Outline

- Brief Review of History of the BMP2 story
- Status of Clinical Trials
- Current Availability/ Information
- Regulatory Shortcomings
- Suggested solutions
- Provider responsibility

# Disclosure

- I served as a consultant on the design of the open tibia fracture clinical trial
- I participated in the Phase I (Safety) study
- I enrolled patients in the US phase III trial
- Paid consultant Genetics Institute →  
Wyeth → Medtronic
- No Royalties, Stock

# History

- Urist' work in the 1970's, 1980's
- Key active protein within Demineralized Bone Matrix
- Mouse quadriceps "assay"
- Movement from Bovine to Human DBM source
- Clinical Effectiveness at UCLA
- Cloning of Protein in 80's

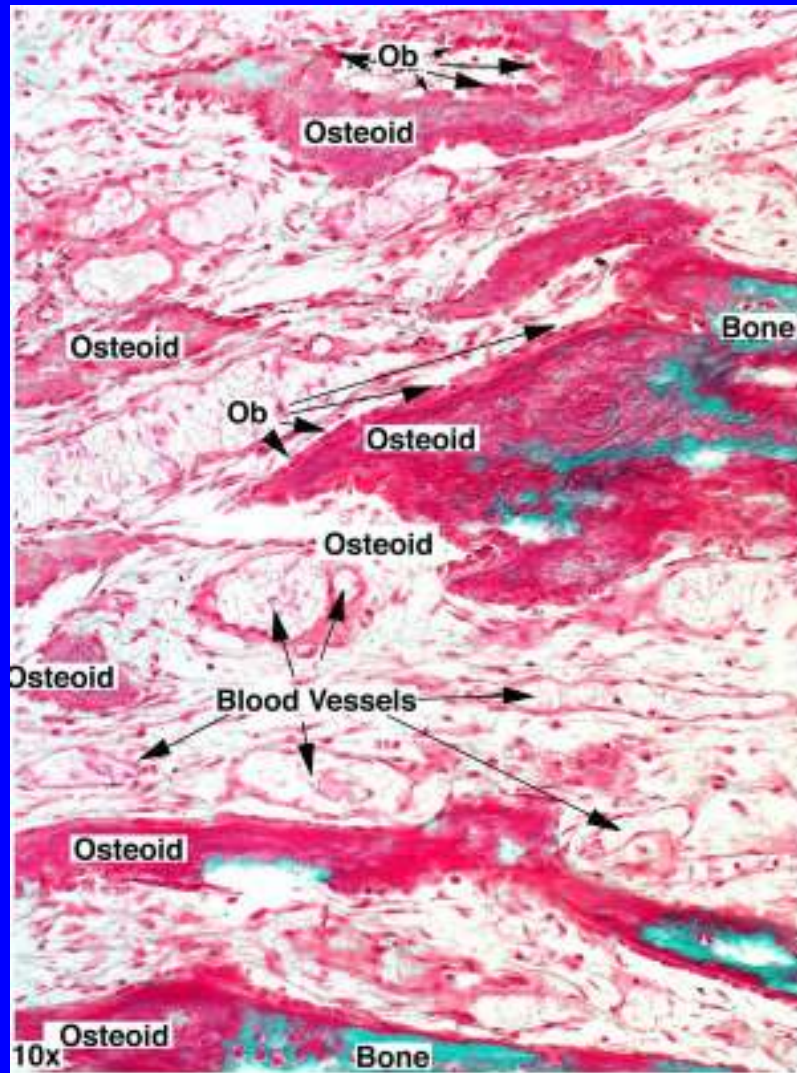
# Basic Science Review

- Sequencing identifies 15 BMP's
- Group of proteins within the TGF beta Superfamily
- Osteogenesis in Mature Osteoblasts
- BMP 2,6,9 Osteoblast differentiation-stem cells

# Basic Science Review

- Bone induction and increased vascularity
- Initial increase in resorption in some settings
- Carrier Science is just as important
  - Release rates
  - Binding of Protein

# rhBMP-2 induces bone

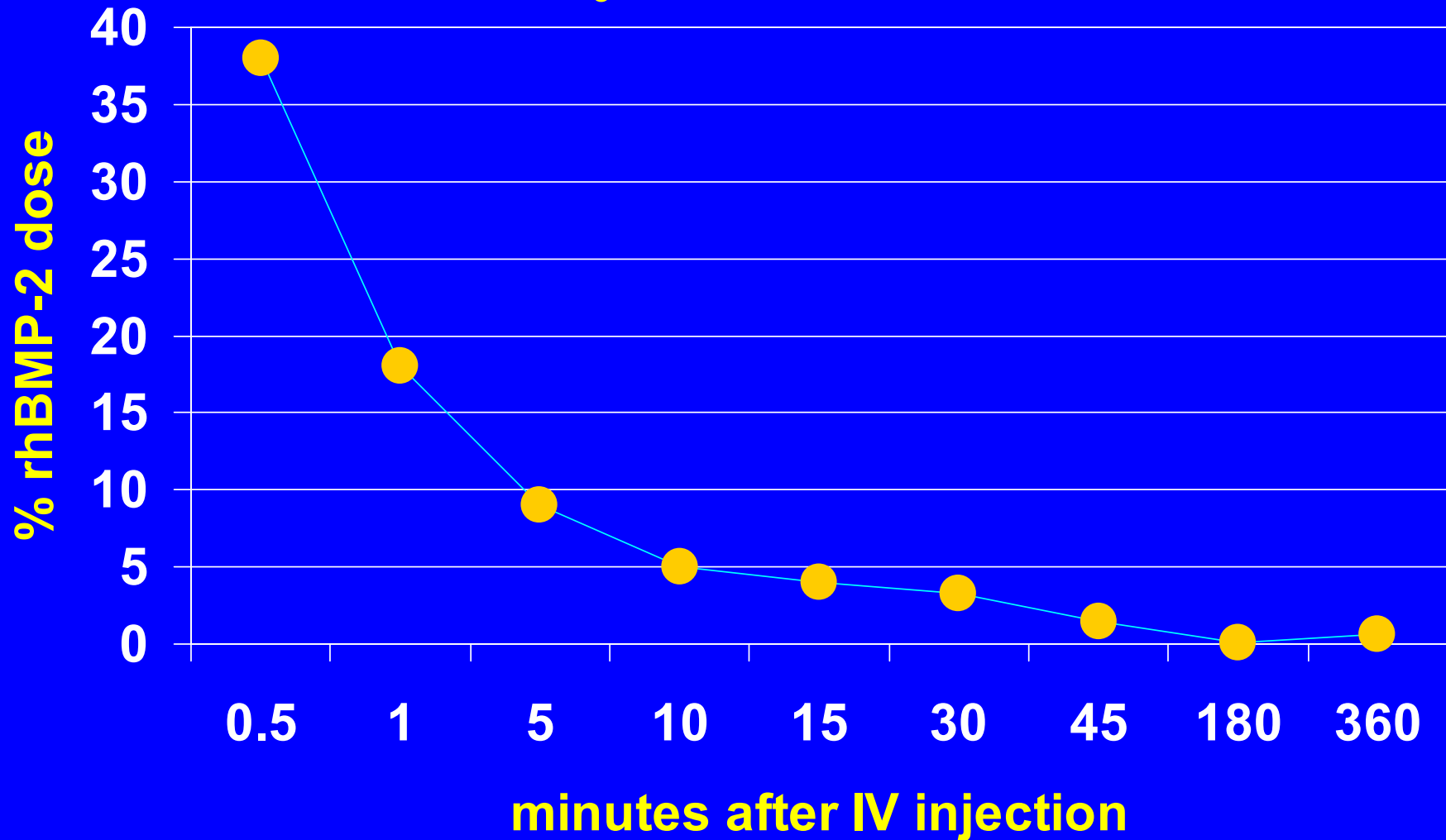


- Chemotaxis/ proliferation
- Differentiation of mesenchymal cells
- Bone induction
  - trabecular, woven bone
  - remodels appropriately
- Increased vascularity

# Materials evaluated as carriers

- Putties
- Sponges
- Blocks
- Granules
- Gels
- Pastes
- Films
- Aggregates

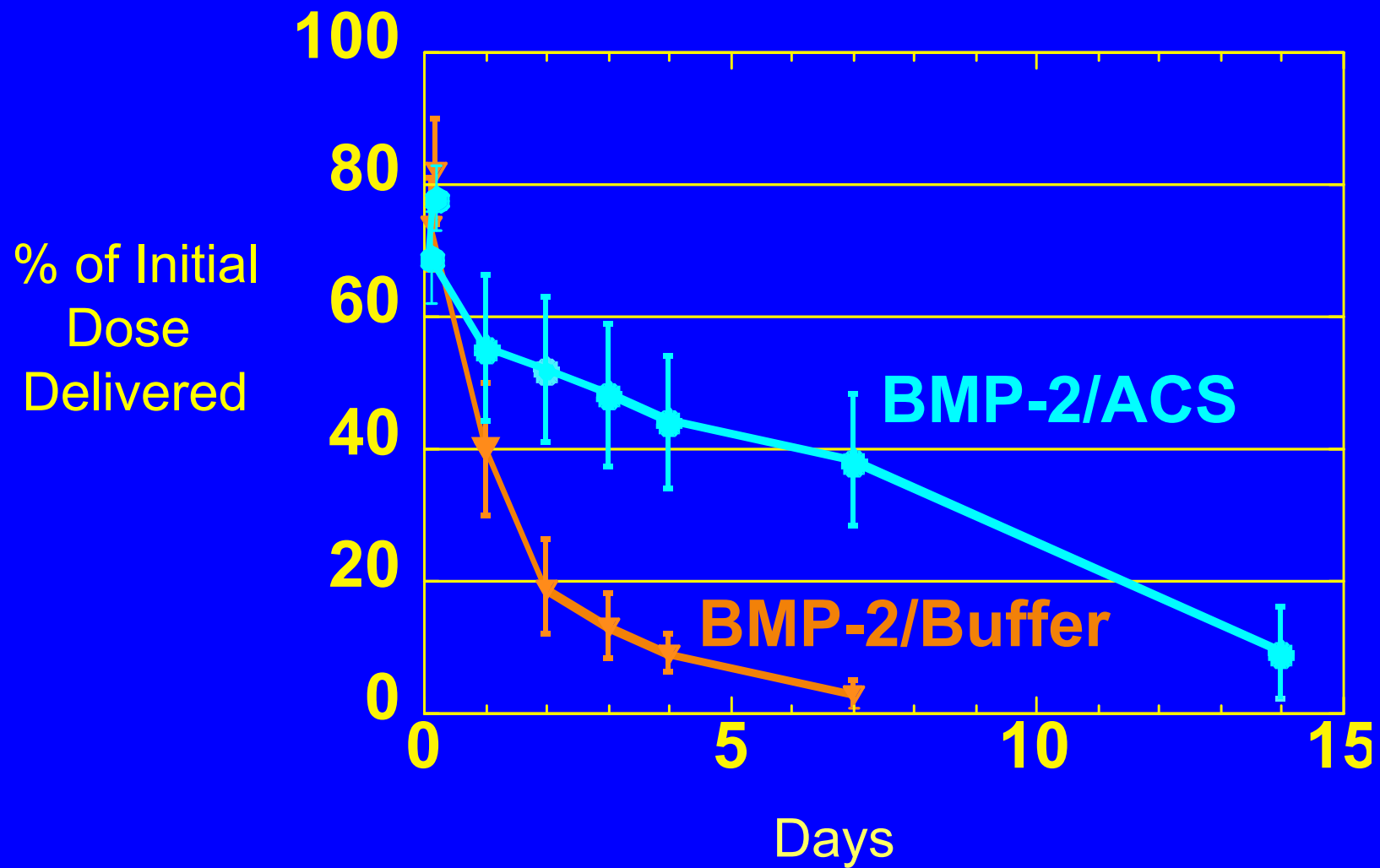
# rhBMP-2 is rapidly cleared from the systemic circulation



# ACS augments rhBMP-2 retention at implantation site

- Radiolabelled rhBMP-2 applied to ACS
- Rabbit ulnar osteotomy model
- Gamma camera data collection
- Methods validated by direct measurement

# In vivo Retention of rhBMP-2



# FDA Processes

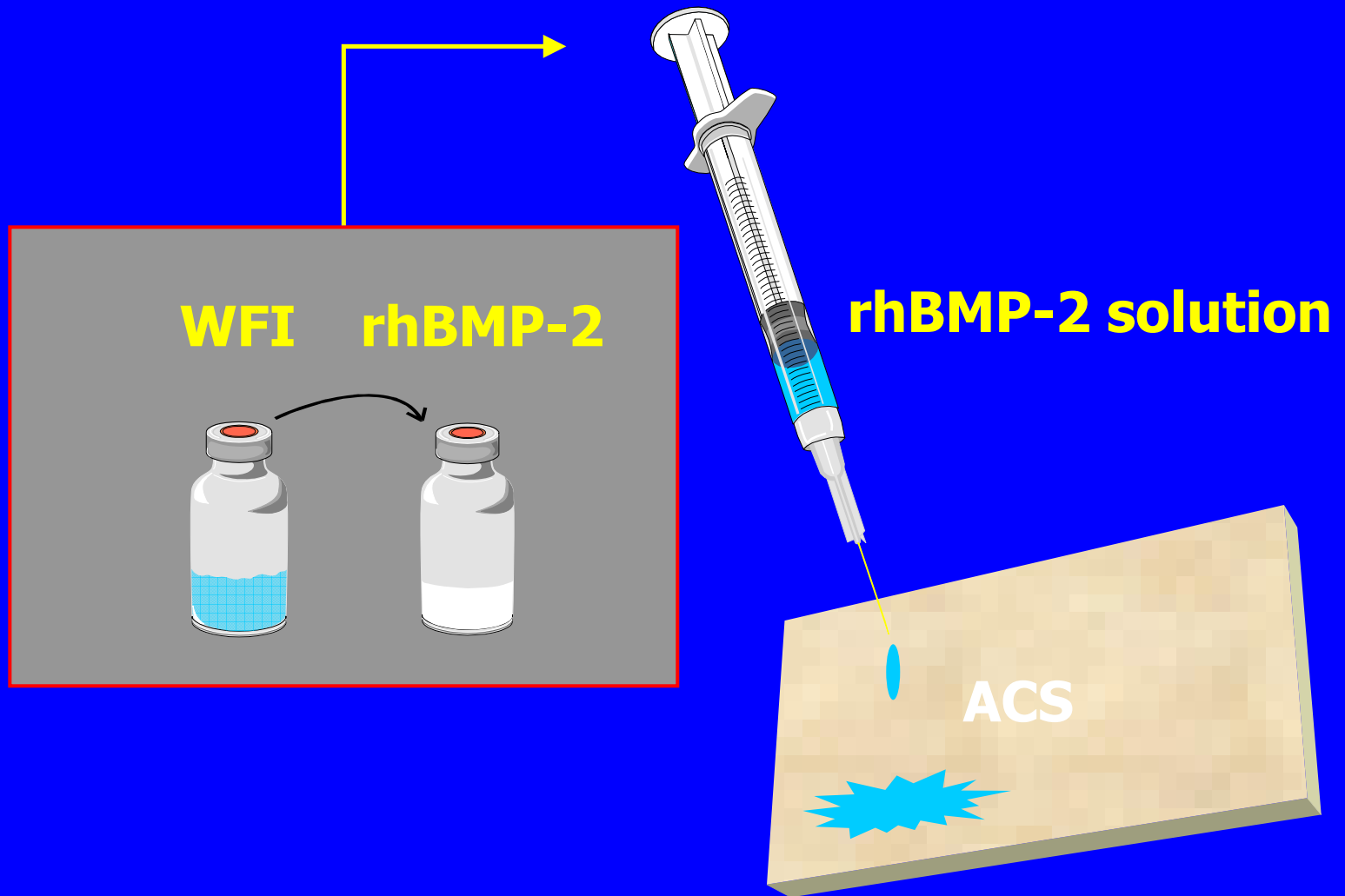
- Phase I (Safety) study- 15 patients
- Phase II feasibility study
- Phase III pivotal trial
  - Primary and secondary endpoints
  - Blinding where possible
  - Power calculations
- Results presented to Advisory Panel; Public Vote  
**High Stakes!**

# Clinical Trial Information



sinus floor augmentation

# rhBMP-2/ACS preparation

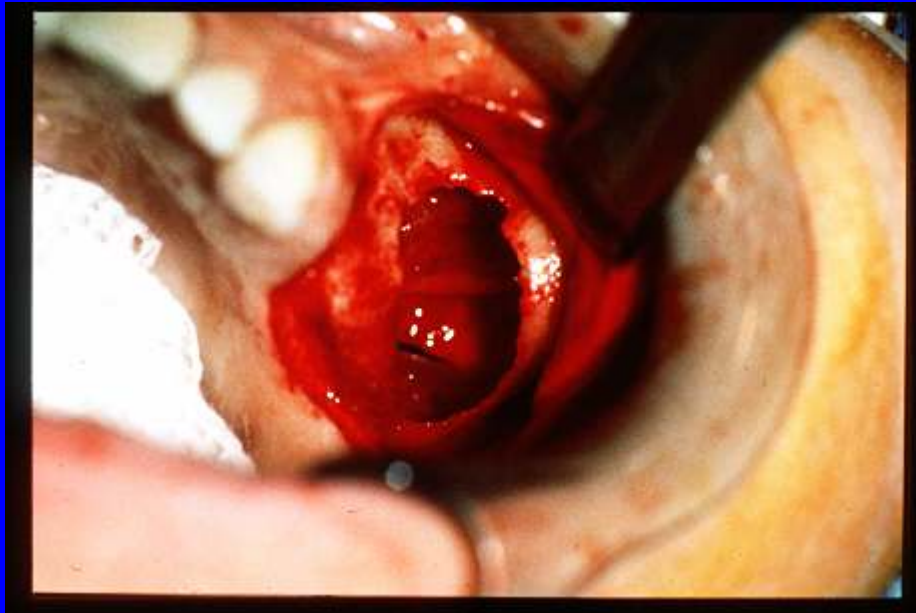


**P. J. Boyne, R. E. Marx, M. Nevins,  
G. Triplett, E. Lazaro, L.C. Lilly,  
M. Alder, P. Nummikowski**

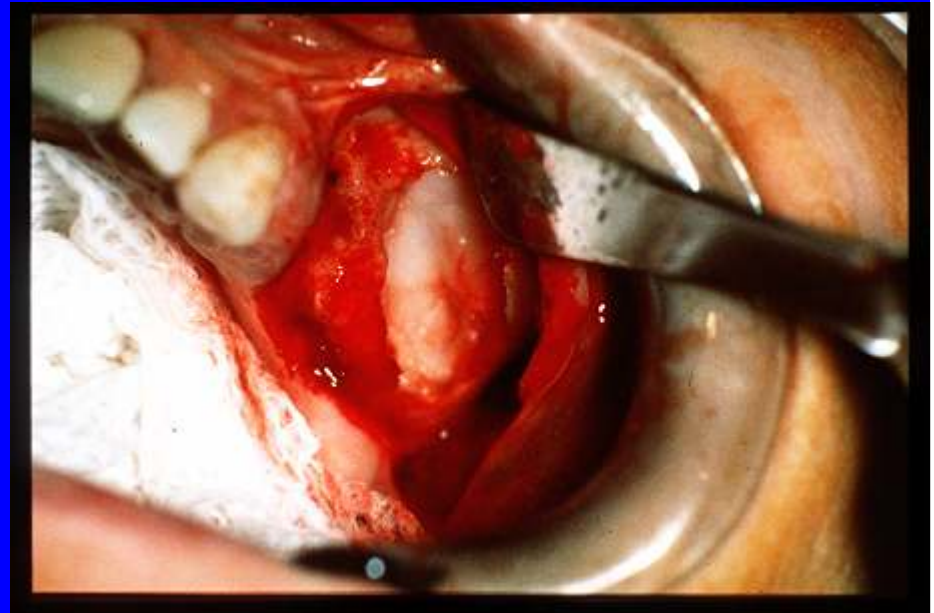
**International Journal of Periodontics  
and Restorative Dentistry 17: 11-25 (1997).**

*A feasibility study evaluating rhBMP-2/absorbable collagen  
sponge for maxillary sinus floor augmentation*

# Surgical procedure

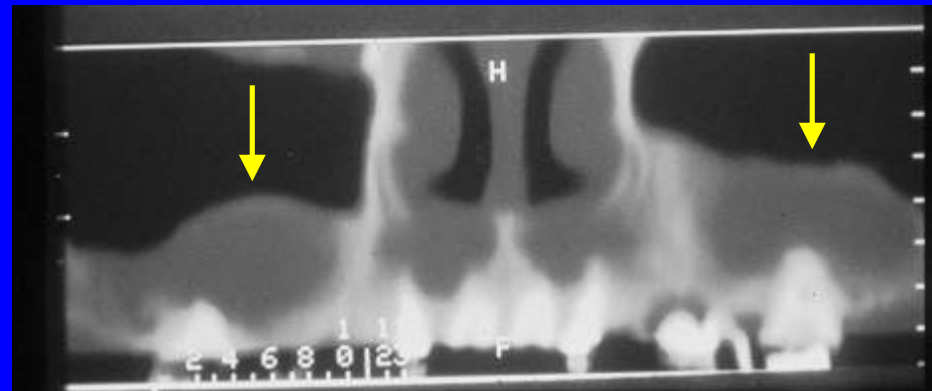
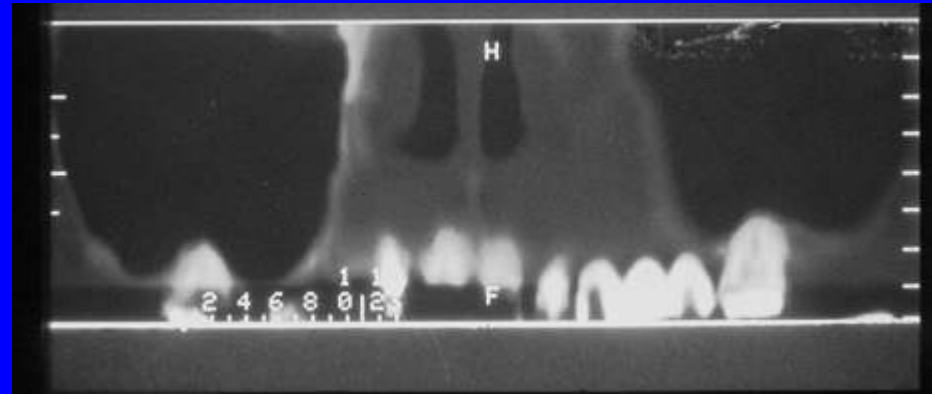


Pre-implantation

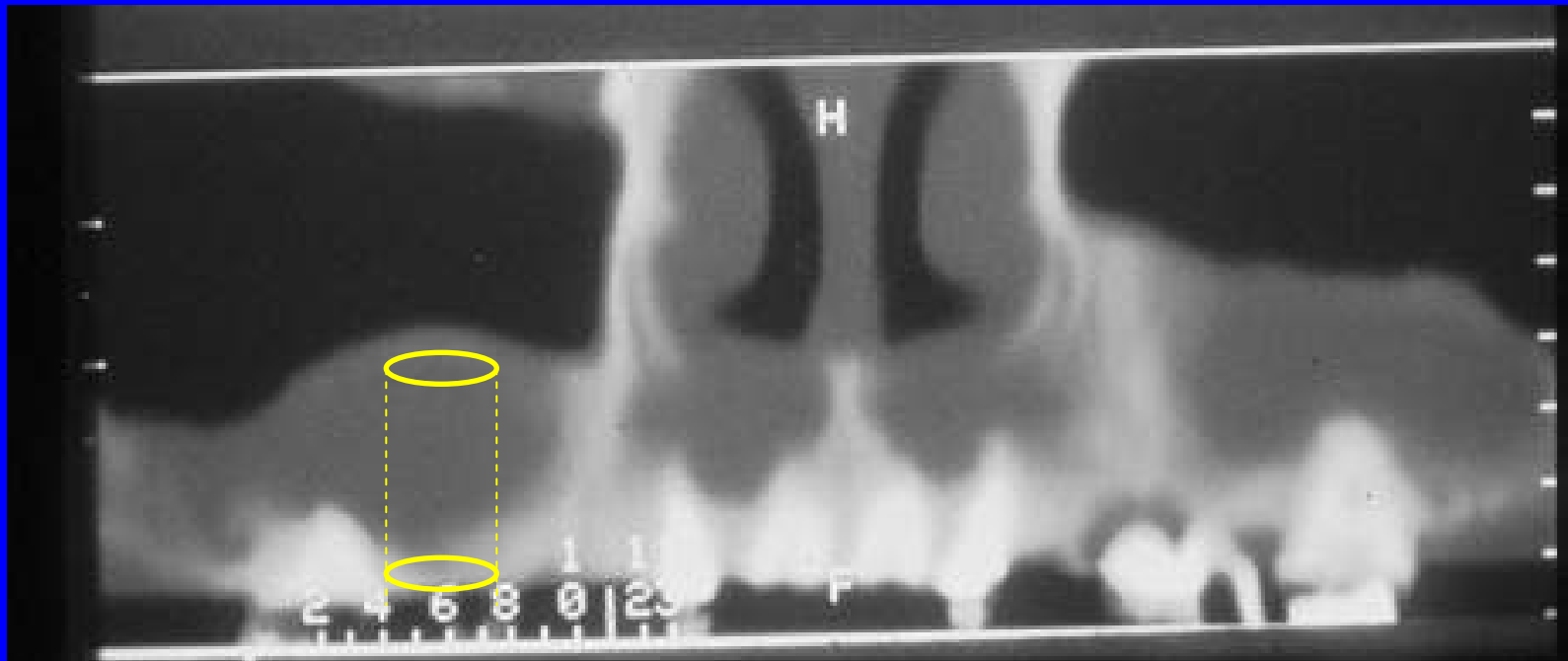


Post-implantation

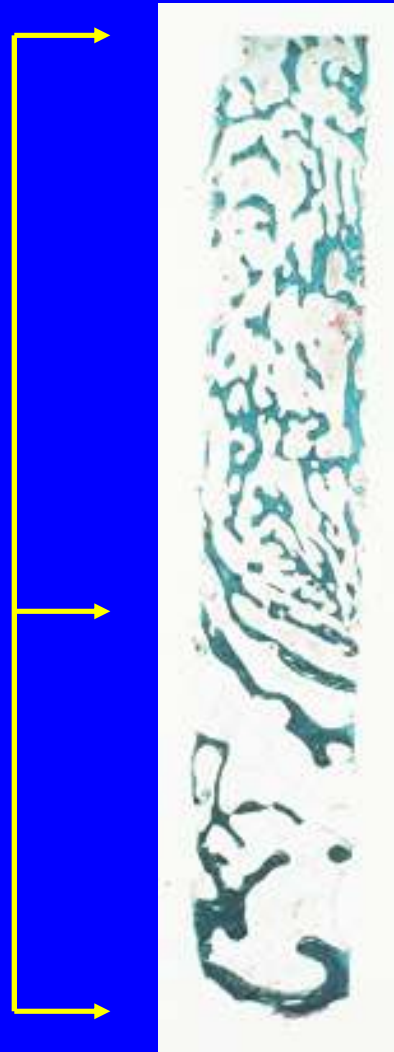
# CT scans of bone induced by rhBMP-2



# Biopsies of bone induced by rhBMP-2



# Histology of bone induced by rhBMP-2

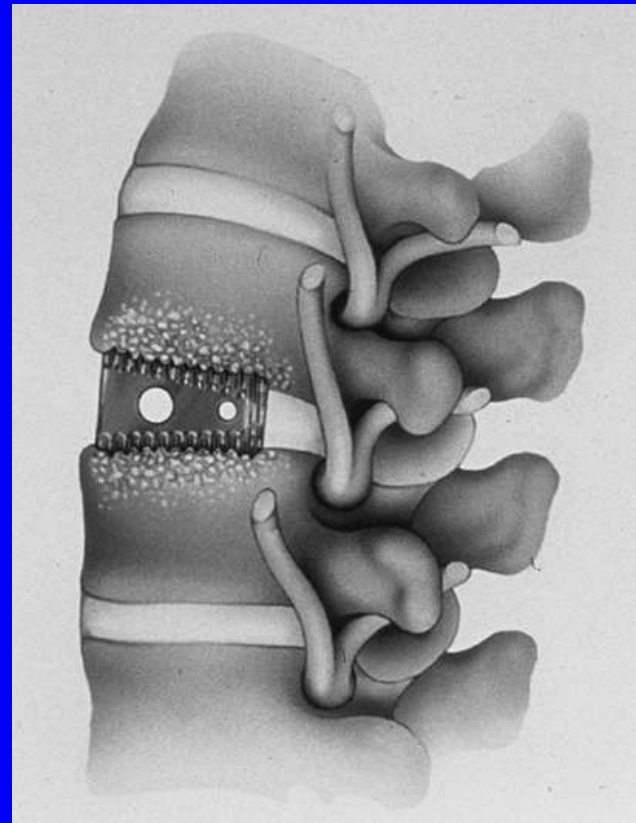


**S.D. Boden, T.A. Zdeblick, H.S. Sandhu,  
S.E. Heim**

**SPINE 25:376-381 (2000)**

The use of rhBMP-2 in interbody fusion cages -  
definitive evidence of osteoinduction in humans:  
a preliminary report

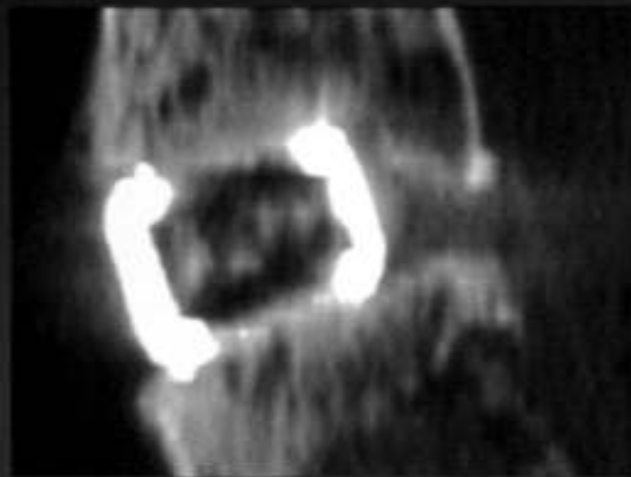
# Lumbar interbody fusion fusion cage, anterior approach



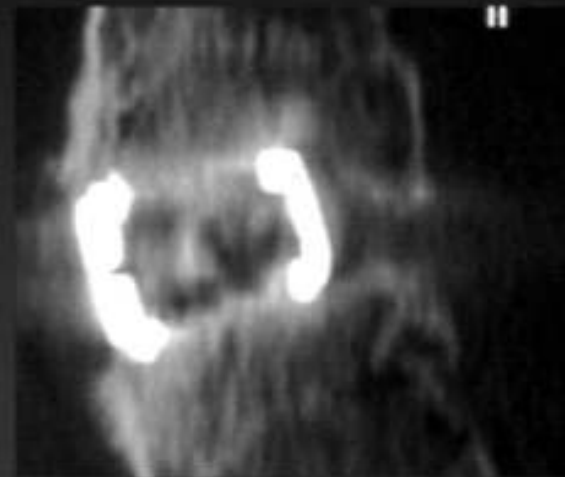
**rhBMP-2/ACS +  
Lordotec® tapered fusion device  
(for lumbar interbody fusion)**



# CT Evidence For Spine Fusion



6 months



12 months



24 months

# Difficulties with Surgical Trials

- Procedures are not pills
- Ethical issues with placebo procedures
- Need rapid recruitment as systems evolve rapidly
- Surgical experience an issue
- Multicenter is best- International issues
- Equipoise is rare

# Search for the Best Trauma Model

- Trauma situation difficult; little time for informed consent
- Accurate data regarding case volumes not available- sample recruitment data critical
- Little understanding among surgeons RE appropriate conduct of drug/implant trials



# FDA Decisions

- Phase III recommendation for underpowered study
- Prompts Company to go to International design
- Leads to 4 year debate RE applicability of treatment settings and surgical standards to US patient population

# Material and methods

- Prospective
- Randomized
- Multicenter
- Single blinded study
- ITT analysis

# Eligibility Criteria

- **Inclusion criteria**

- Age  $\geq 18$
- Acute, diaphyseal open tibia fracture
- Definitive fixation with IM nail
- Final soft tissue closure  $\leq 14$  days of injury
- Segmental fractures included if coverage of both fx lines possible with one sponge
- Glasgow coma scale  $>15$
- Patient informed consent

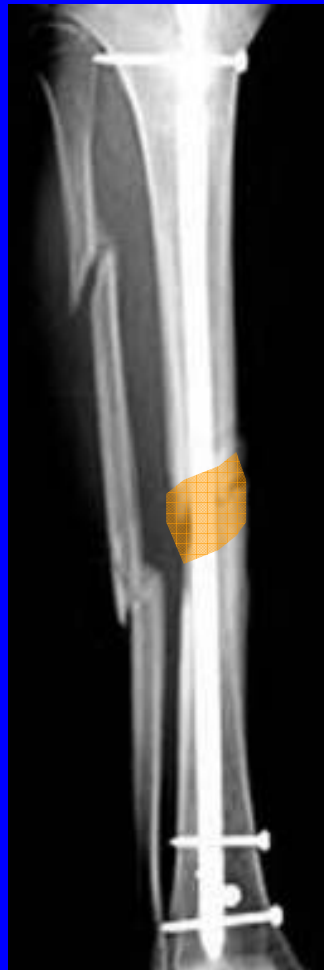
- **Exclusion criteria**

- Gustilo IIC fractures
- Patients with local infection or compartment syndrome
- Patients with history of malignancy, radiotherapy or chemotherapy within 5 years
- Patients with history of autoimmune disease
- Pregnant or nursing patients

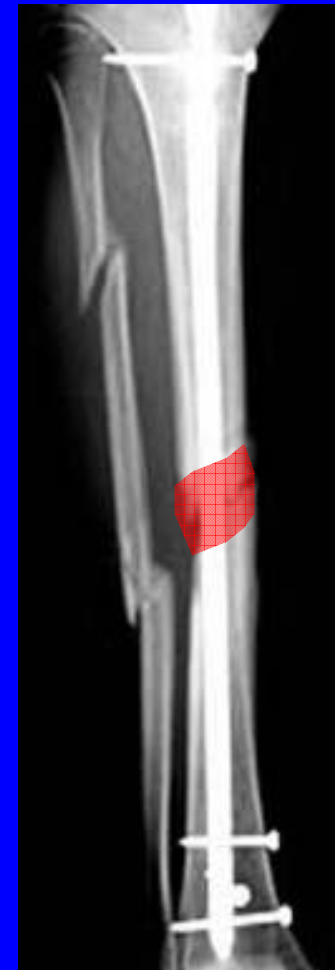
# Treatment groups



**Control**



**rhBMP-2/ACS 0.75 mg**



**rhBMP-2/ACS 1.5 mg**



# Patient enrollment

- April 1997 to December 1999
- 49 centres
- 11 countries
- 450 patients

# Patient Demographics

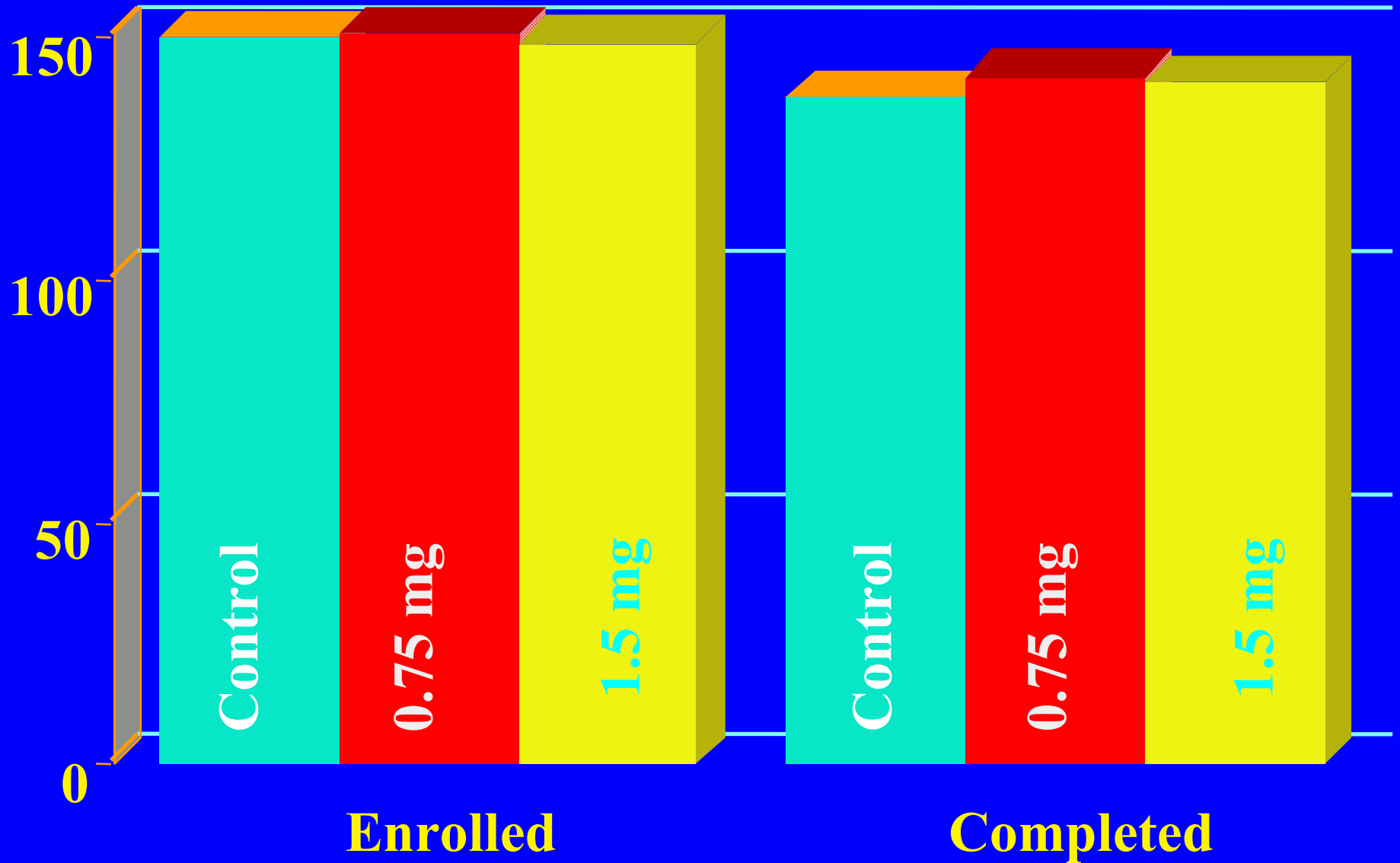
	<b>Control</b> <b>n= 150</b>	<b>rhBMP- 2/ACS 0.75 mg/mL</b> <b>n= 151</b>	<b>rhBMP- 2/ACS 1.5 mg/mL</b> <b>n= 149</b>
<b>Median Age (years)</b>	<b>33</b>	<b>33</b>	<b>31*</b>
<b>Range</b>	<b>17 - 87</b>	<b>17 - 78</b>	<b>18 - 77</b>
<b>Male (%)</b>	<b>78.7</b>	<b>79.5</b>	<b>84.6</b>
<b>Caucasian (%)</b>	<b>71.3</b>	<b>71.5</b>	<b>76.5</b>

# Endpoints

- Reoperation rate for failed union
  - Incidence of adverse events and immune response
  - Time to union (blinded radiologists)

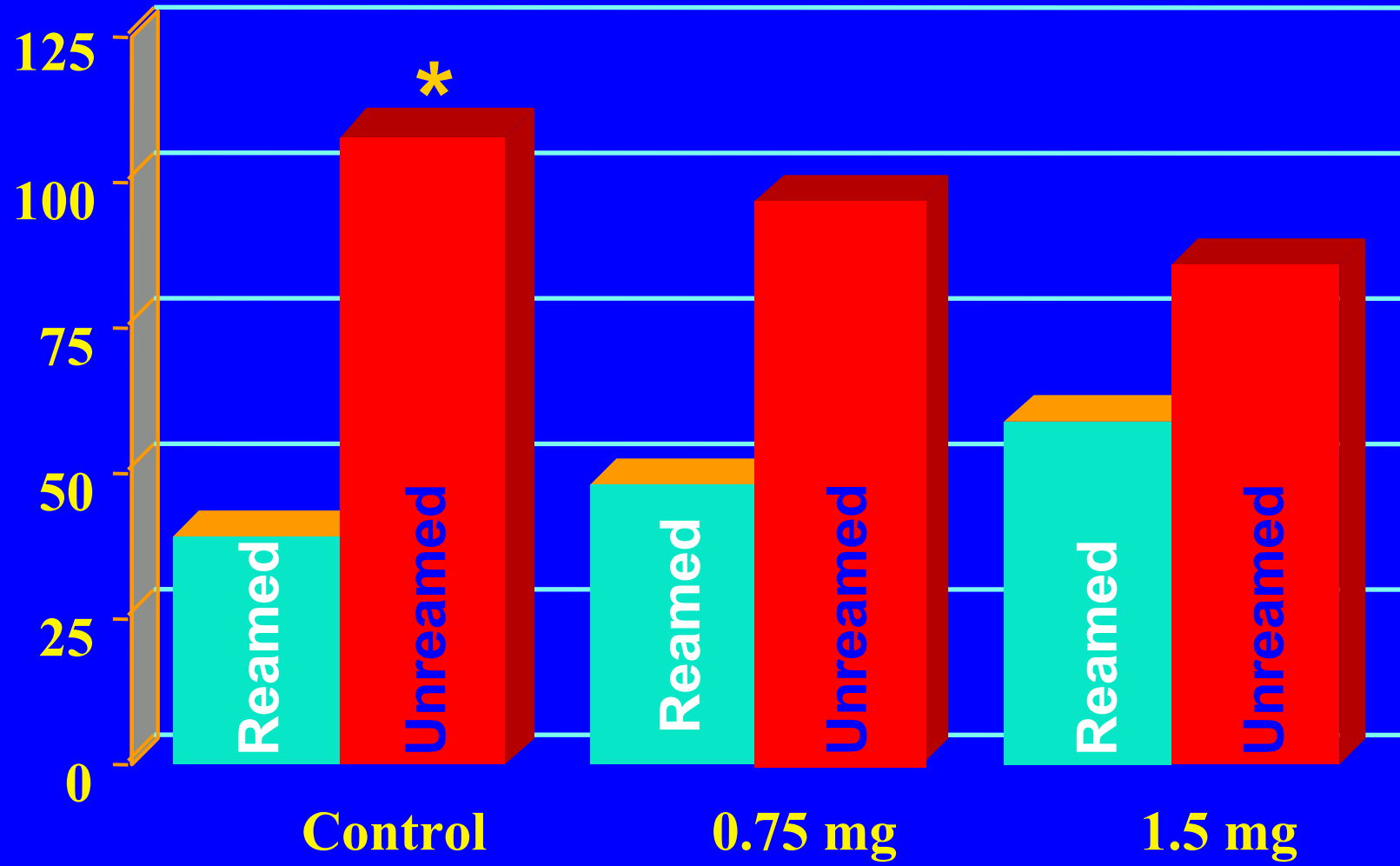
# Patient Completion

No of patients



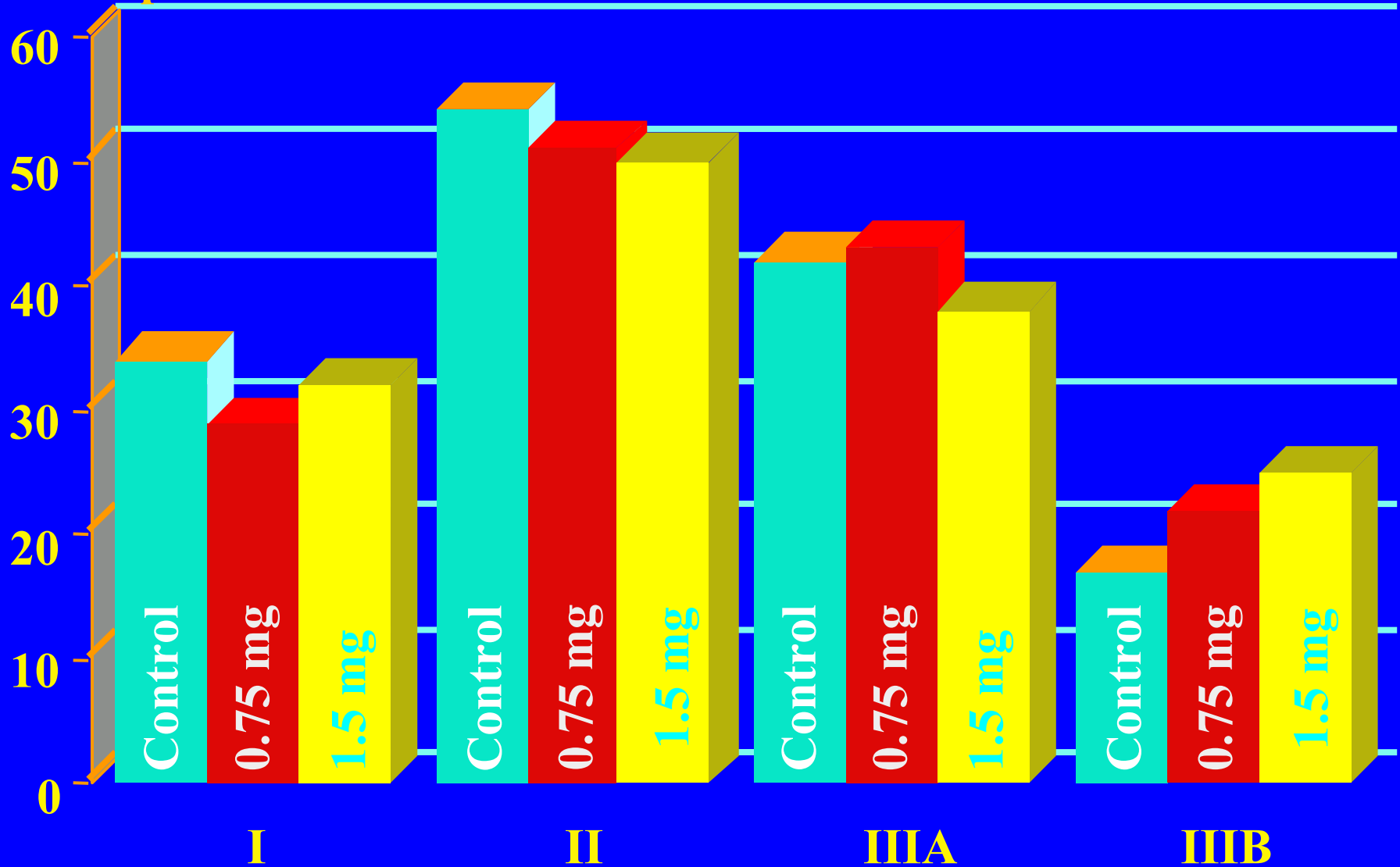
# Type of nail

No of patients



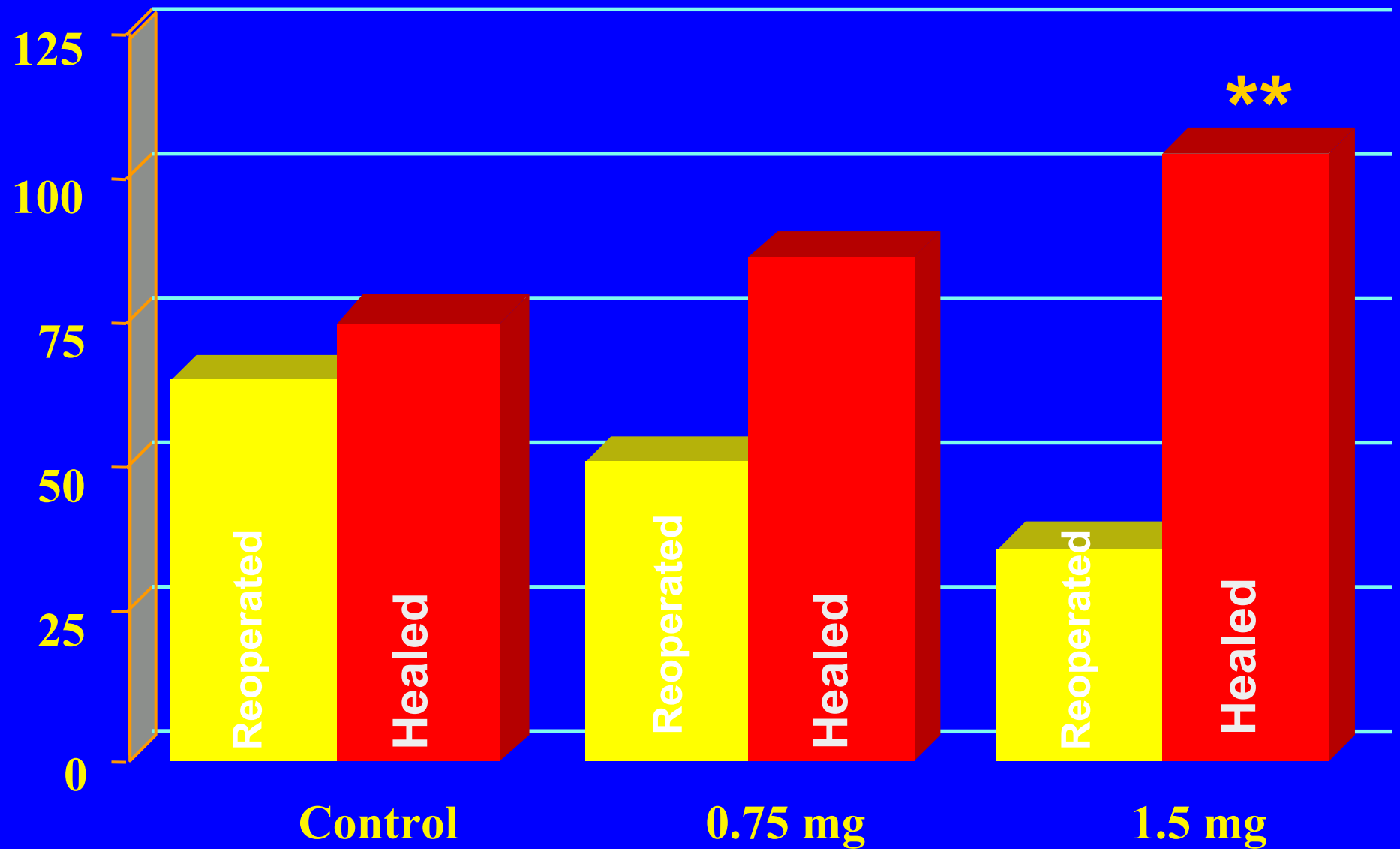
# Gustillo-Anderson classification

No of patients



# Rate of reoperation

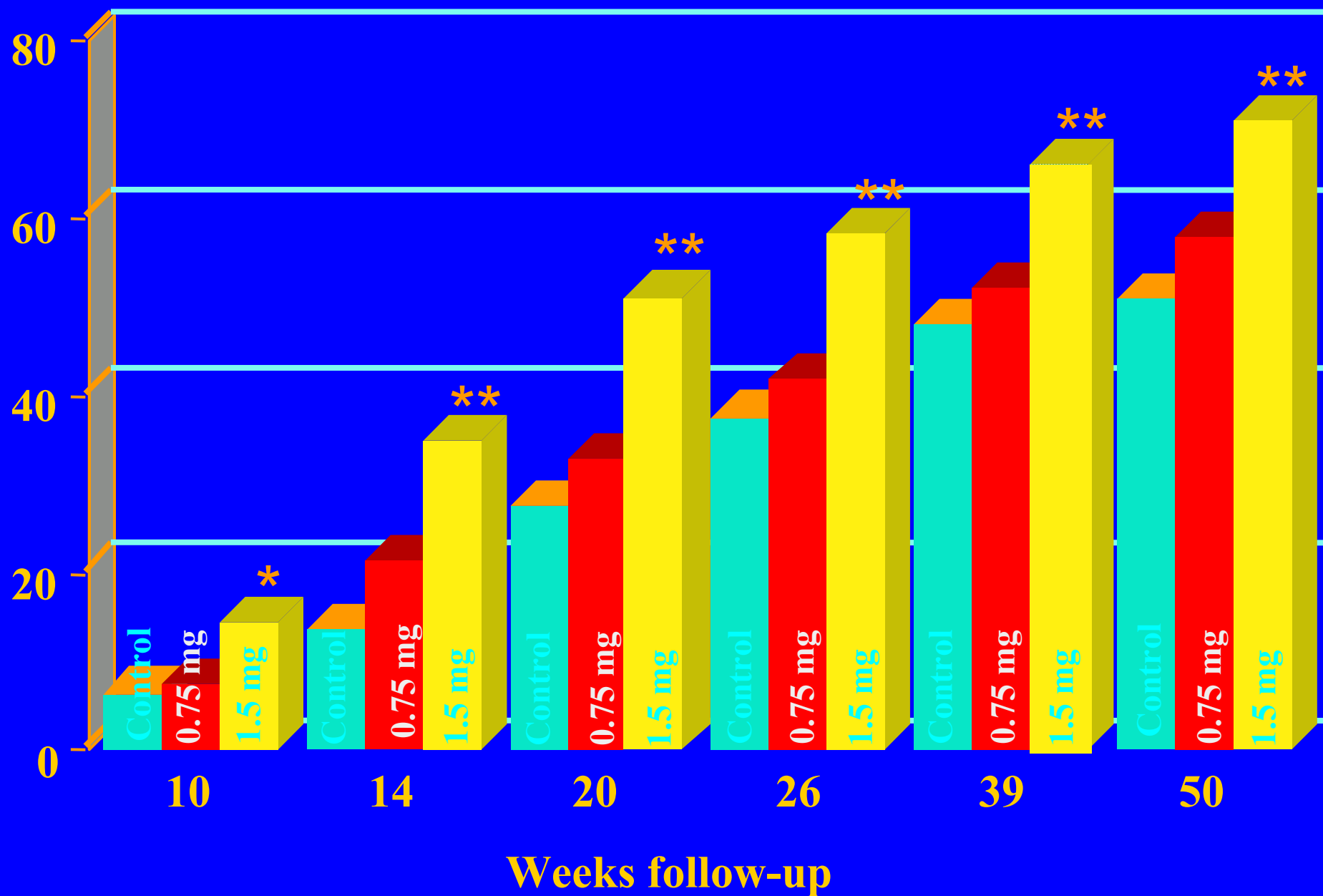
No of patients



# Interventions for delayed and nonunion

	Control	rhBMP-2/ACS (0.75 mg/ml)	rhBMP-2/ACS (1.50 mg/ml)
	N=139	N=130	N=135
Most invasive (#)	29	26	12*
Less invasive (#)	29	21	18
Non-invasive (#)	0	0	2
Total (#)	58	46	32*

# Rate of healing (%)



# Hardware failure (RUS)

	<b>Control</b>	<b>rhBMP-2/ACS (0.75 mg/ml)</b>	<b>rhBMP-2/ACS (1.50 mg/ml)</b>
	<b>N=147</b>	<b>N=145</b>	<b>N=145</b>
<b>Hardware failure</b>	<b>22%</b>	<b>17%</b>	<b>11%*</b>
<b>Patients with reamed nails</b>	<b>18%</b>	<b>17%</b>	<b>3%*</b>
<b>Patients with unreamed nails</b>	<b>23%</b>	<b>18%</b>	<b>16%</b>

# Current Clinical Availability

- OP-1 (BMP-7) approved Nov 2001 for Compassionate use- Stryker
- BMP-2 approved for Spinal fusion with Cage Nov 2002- InFuse
- BMP-2 for open tibial fracture approved Nov 2004
- BMP-2 injectible formulation in Clinical Trials

# Regulatory (FDA) issues

- Changing personnel
- Device vs. Drug (Now resolved)
- One indication at a time
- Internal advisors limited experience
- Blinding issues with surgical trials
- Overloaded System despite increased revenue from industry
- Delay in decisions produce unanticipated impact

# Suggestions for improving Regulatory processes

- Written records of dialogue between Industry and FDA should be kept and adhered to
- Experts should be impaneled by FDA not Industry
- In-house expertise should not trump external expertise
- Responsibility should focus equally on safety and effectiveness
- Assessments of “off-label” indications should be planned- not registries

# Unanticipated Results of Delay

- Companies set price based on rate of recovery of investment
- One market for the product is not all markets
- Higher reimbursement indication sets the bar
- CMS has been responsive to cost-effectiveness data

# Surgeon Community Response

- “Off-label” use rapidly increases
- No regard for costs
- “I wanted to be confident so I added BMP”
- Mixed incentives Physicians vs Hospital Administration
- Failure to recognize Professionalism component – Just distribution of resources

# Recommendation to Surgeons

- Off-label use should be done with IRB approved protocols
- Avoid the temptation to add these proteins as “extra-insurance”
- Follow the clinical trials and product approval-FDA announcements carefully
- Read the package insert