Innovations for Active Healing

Wearable Tech Meets Bone Healing: The Future of Ultrasound in Orthopedics and Podiatry

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Faculty Disclosures

- **Thomas J. Chang, DPM**: Advisory Board—Ossio, Paragon 28 (Biomet/Zimmer), Bioventus

Program Information

- This program is provided by HMP Education, an HMP Global company
- Supported by an educational grant from Bioventus

Learning Objectives

- Review current evidence on LIPUS for healing fractures in high-risk patients, including those with delayed or nonunion and chronic conditions
- Demonstrate how to use ultrasound bone healing in podiatry and orthopedics, especially for stress fractures and post-surgical care
- Explore new advances and challenges in ultrasound bone stimulation, including wearables, patient use, and cost concerns

LIPUS = low-intensity pulsed ultrasound.

Ultrasound Bone Healing System Indications

- Accelerated healing of indicated fresh fractures*
  - Distal radius: closed, posteriorly displaced
  - Midshaft tibia: closed or Grade I open
- Established nonunions†
  - Excluding skull and vertebrae

***Fractures managed by closed reduction and cast immobilization; †A nonunion is considered to be established when the fracture site shows no visibly progressive signs of healing.**

Higgins A, et al. *Appl Health Econ Health Policy*. 2014;12(5):477-484.

Many Articles to Support LIPUS

- 38% faster healing of approved fresh fractures
- 86% heal rate for nonunions
- Robust mechanism of action supports clinical findings
  - Upregulation of COX-2, VEGF, BMPs
  - Increased angiogenesis5, mineralization

COX-2 = cyclooxygenase 2; VEGF = vascular endothelial growth factor; BMP = bone morphogenetic protein.

Heckman JD, et al. *J Bone Joint Surg Am*. 1994;76(1):26-34. Kristiansen TK, et al. *J Bone Joint Surg Am*. 1997;79(7):961-973. Nolte PA, et al. *J Trauma*. 2001;51(4):693-702. Naruse K, et al. *Ultrasound Med Biol*. 2010;36(7):1098-1108. Leung KS, et al. *Clin Orthop Rel Res*. 2004;418:253-259. Tang CH, et al. *Mol Pharmacol*. 2006;69(6):2047-2057. Sant'Anna EF, et al. *J Orthop Res*. 2005;23:646-652.

LIPUS Safety

- Safety and effectiveness have not been established for
  - Skeletally immature patients
  - Pregnant or nursing women
  - Patients with pacemakers, poor circulation, or blood clotting problems
  - Fractures linked to bone cancer
- Some patients may be sensitive to the ultrasound gel

Nonunions – Comes with Surgery

Nonunions

18-Year-Old Female: Painful Tailor's Bunion Nonunion

9 Months Post-Op (Jones FX Nonunion)

Injury

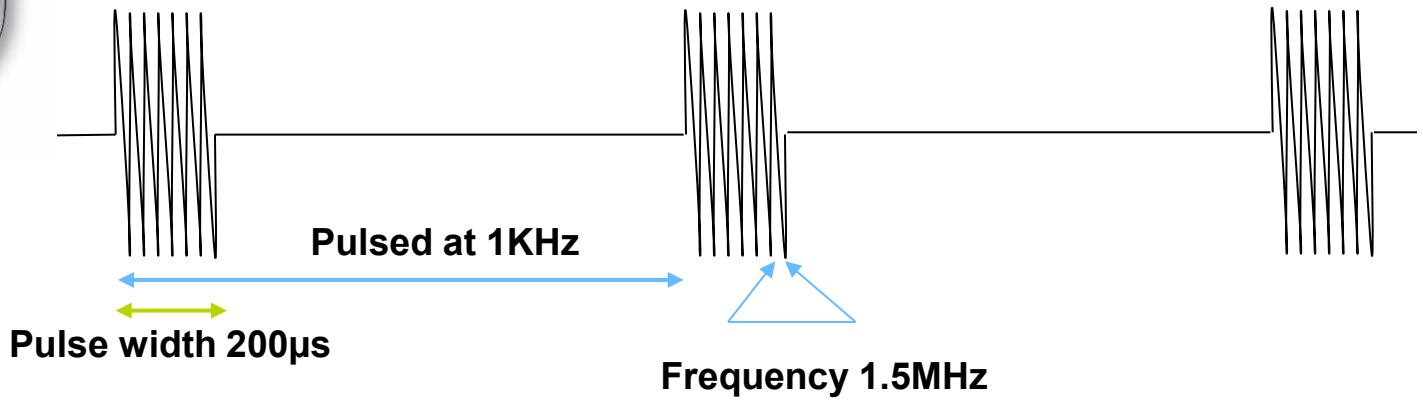
US stimulation 3 months

5 months

FX = fracture; US = ultrasound.

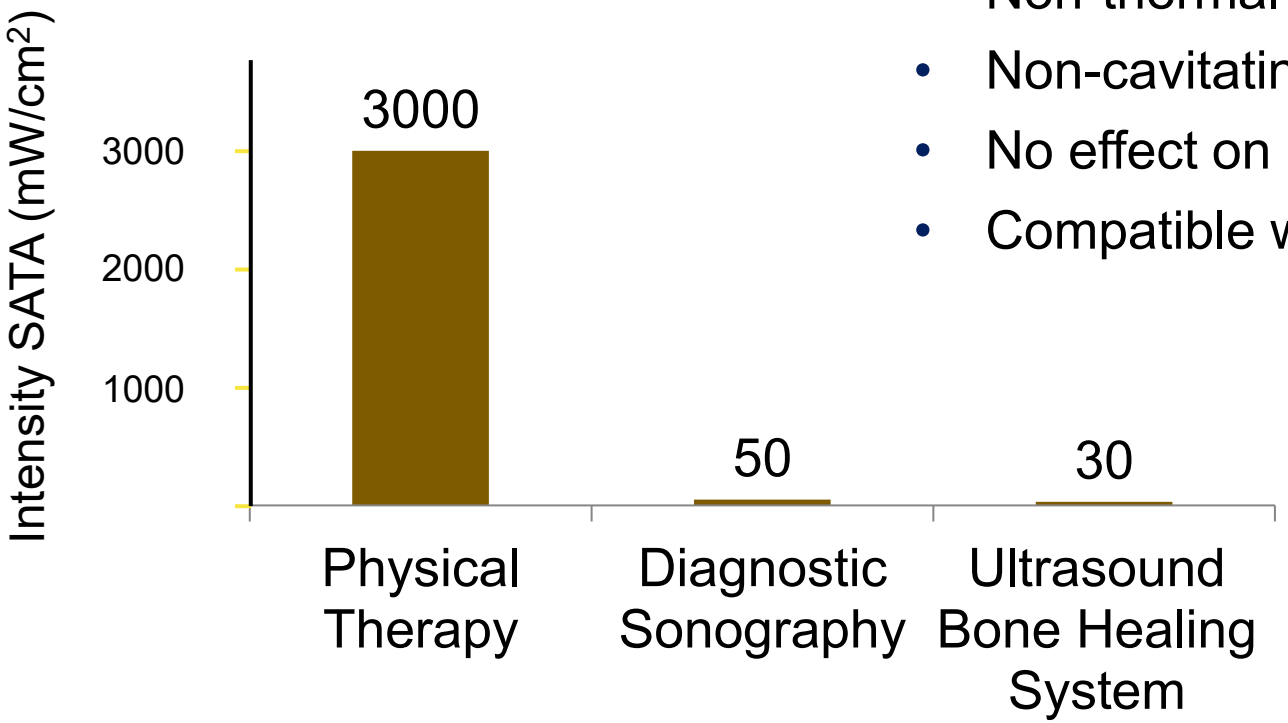
Ultrasound Bone Healing System Uses LIPUS

- Physical pressure wave
- Patients self-administer at home
- 20-minute treatment session once daily
- Transducer must touch skin



US Stimulation and Non-Weight Bearing Cast x 3 Months

Intensity



- Non-thermal
- Non-cavitating
- No effect on screw torque
- Compatible with all fixation

SATA = spatial average temporal average.

Daeschler SC, et al. *Front Neurol*. 2018;9:1057.

LIPUS and Metal Fixation (Nonunion)

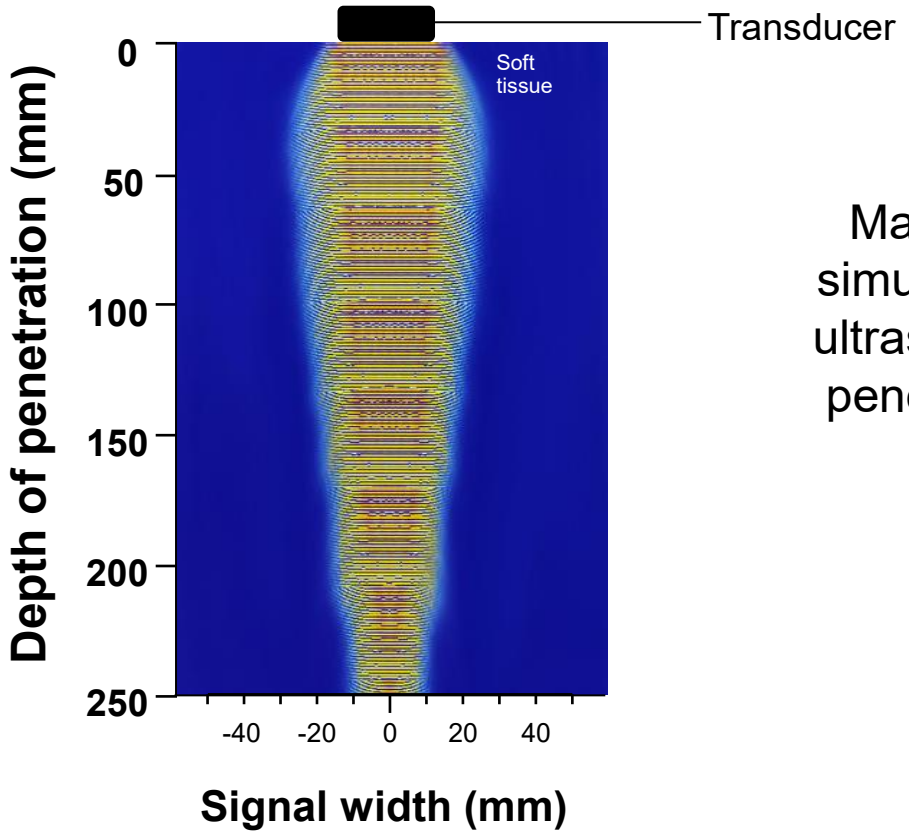
- No negative effects in the presence of metal implants
- Non-cavitating, non-thermal
- No metal degradation
- No effect on screw stability or screw torque removal

LIPUS may be used with internal fixation in nonunions and has no known contraindications.

X-ray courtesy of Bob Zura, MD.

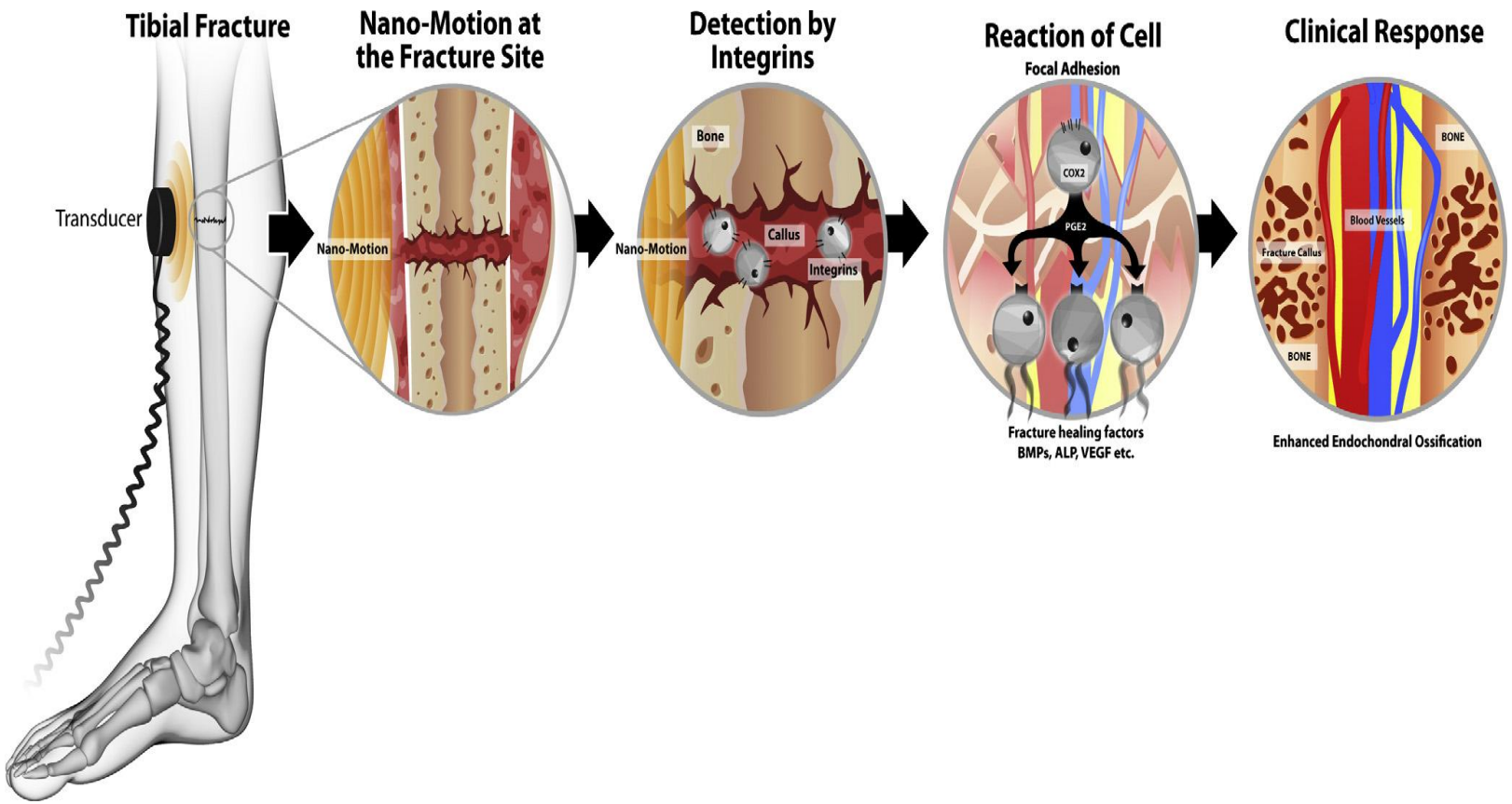
Lehmann JF, et al. *Arch Phys Med Rehabil*. 1959;40:483-438. Lotsova E. *Mech Compos Mater*. 1979;15(3):330. Gersten, JW. *Am Phys Med*. 1958;37(2):75-82.

LIPUS Signal Depth of Penetration



Mathematical simulation of the ultrasound beam penetrating soft tissue.

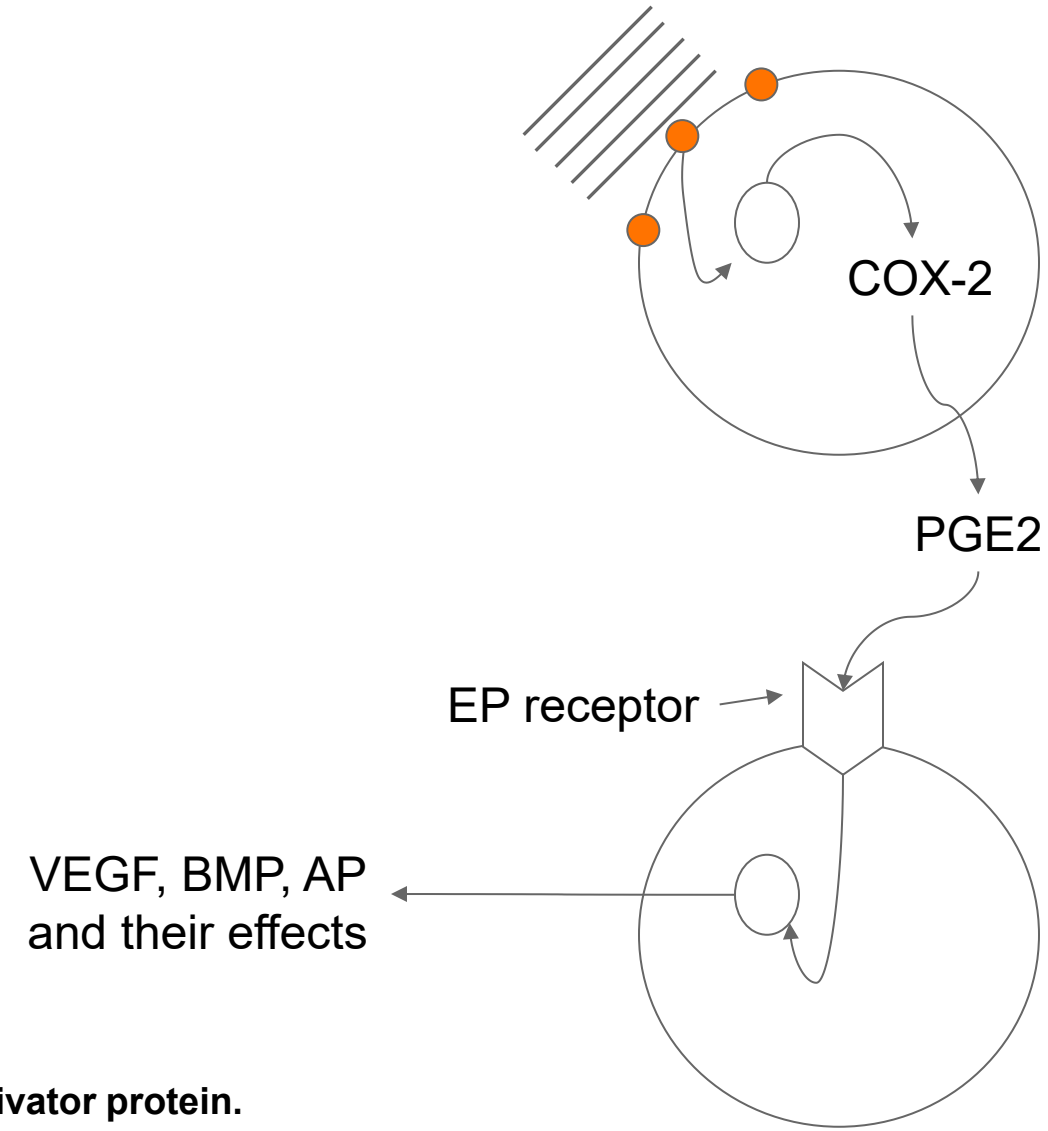
Summary: LIPUS Mode and MOA



MOA = mechanism of action.

Harrison A, et al. *Ultrasonics*. 2016;70;45-52.

Role of COX-2

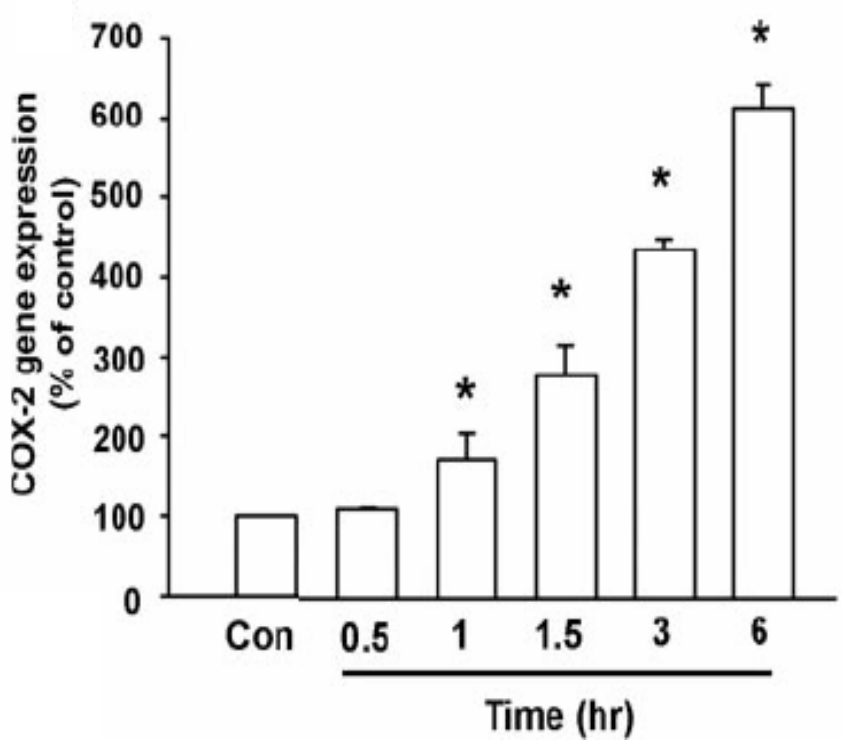


PGE2 = prostaglandin E2; AP = activator protein.

Naruse K, et al. *Ultrasound Med Biol*. 2010;36(7):1098-1108.

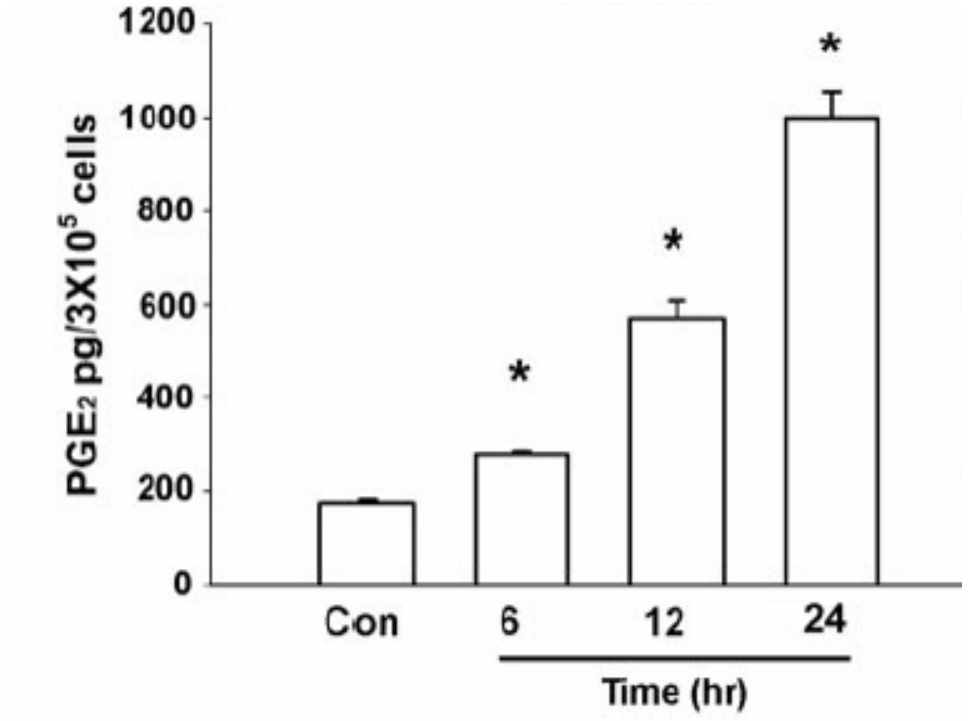
COX-2 Upregulated after LIPUS

COX-2 is the main enzyme that produces prostaglandin E2



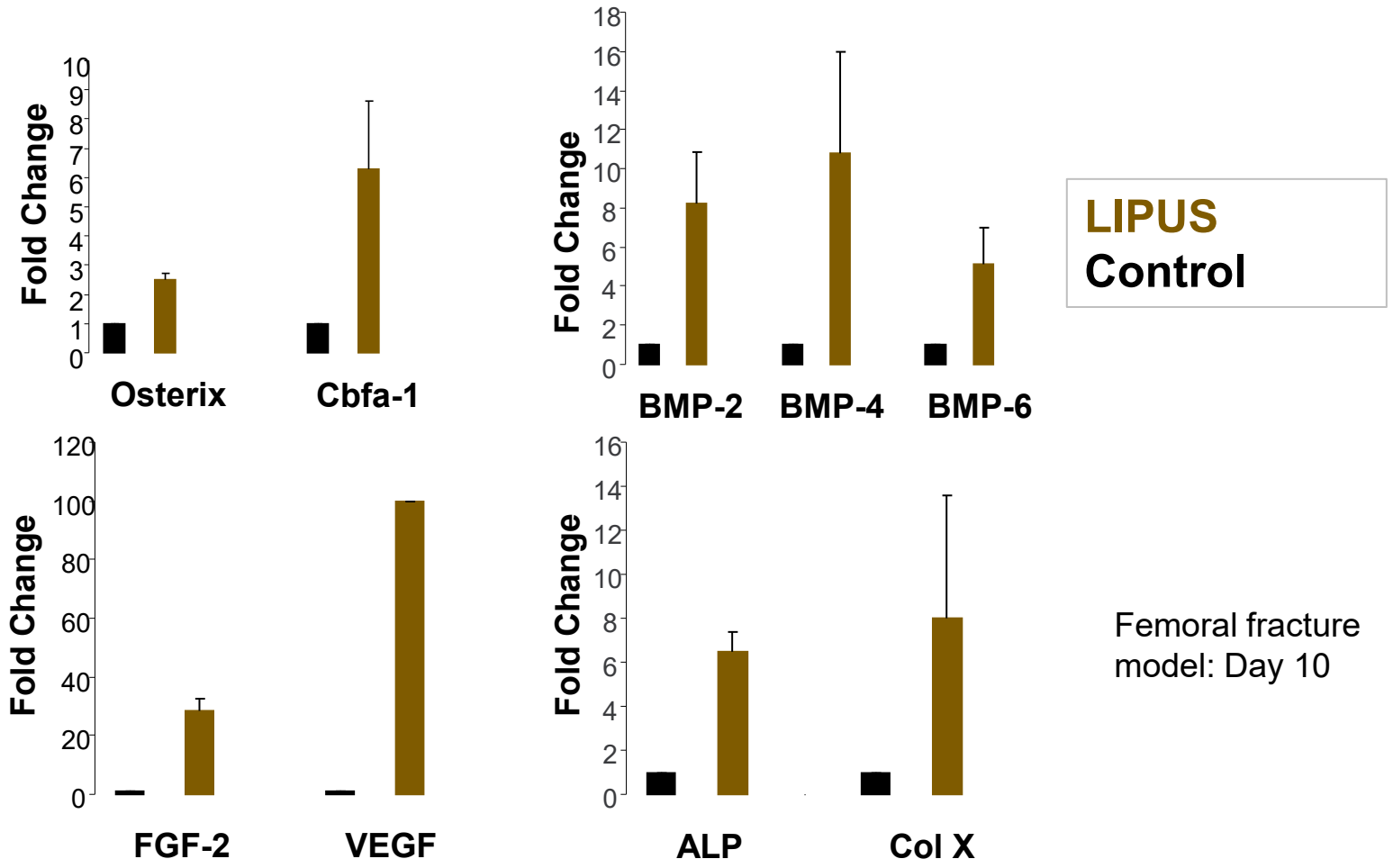
Tang CH, et al. *Mol Pharmacol*. 2006;69(6):2047-2057.

PGE2 Upregulated after LIPUS



Tang CH, et al. *Mol Pharmacol*. 2006;69(6):2047-2057.

Gene Expression in the Callus



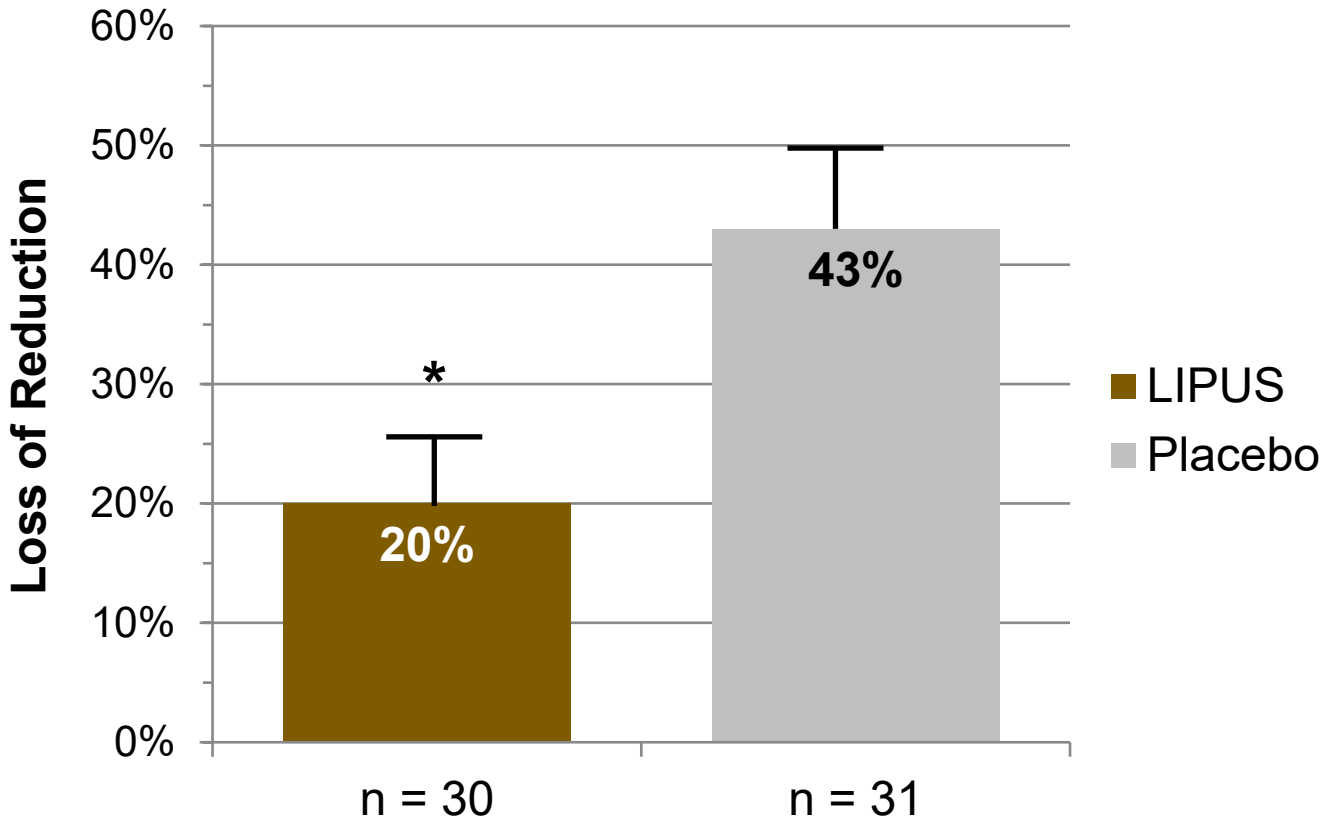
ALP = alkaline phosphatase; cbfa = core-binding factor; FGF = fibroblast growth factor.

Naruse K, et al. *Ultrasound Med Biol*. 2010;36(7):1098-108.

LIPUS Clinical Data
Indicated in Fresh Factures

Clinical Evidence: Fresh Fractures

Using LIPUS reduces the loss of reduction in cancellous radial fractures (as determined by change in volar angulation).



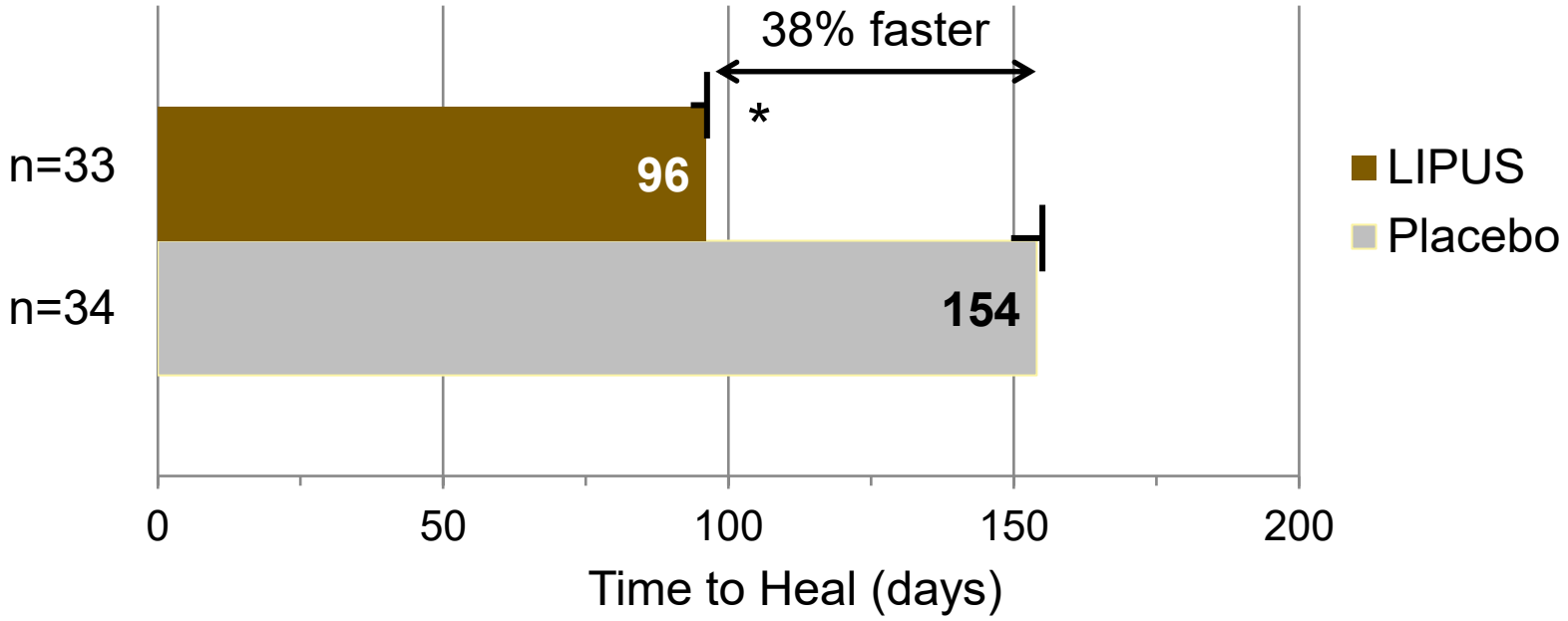
***P*<.01.**

Data are shown as means ± standard error.

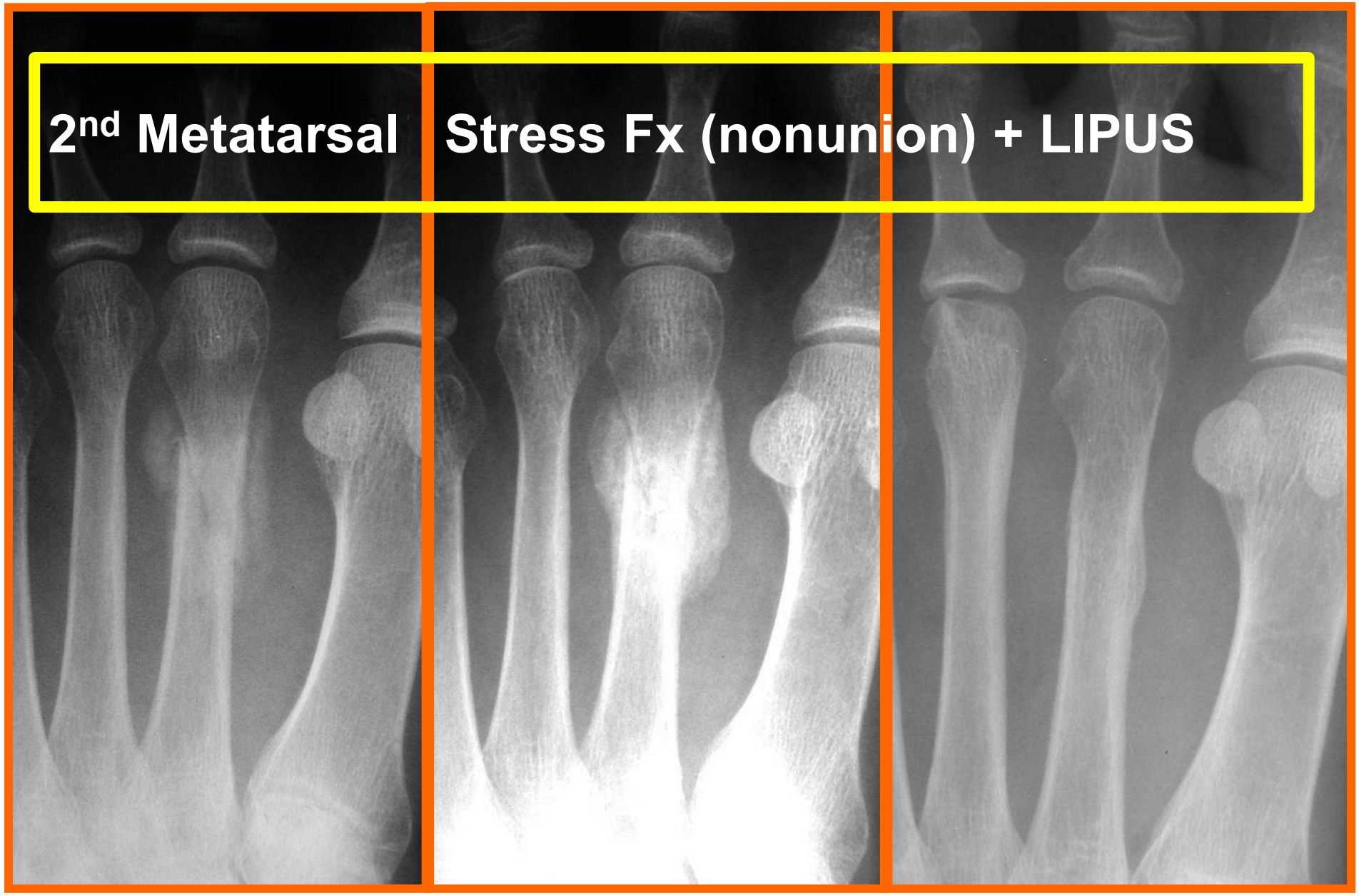
Kristiansen TK, et al. *J Bone Joint Surg Am*. 1997;79(7):961-973.

Clinical Evidence: Fresh Tibia Fractures

- Prospective, randomized, placebo-controlled, double-blind, multicenter study
- Acute closed or Grade I open tibia fractures—short oblique
  or transverse fractures with <50% displacement
- Treatment 20 min/day until healed
  - 3 cortices bridged, no pain on weight bearing or palpitation

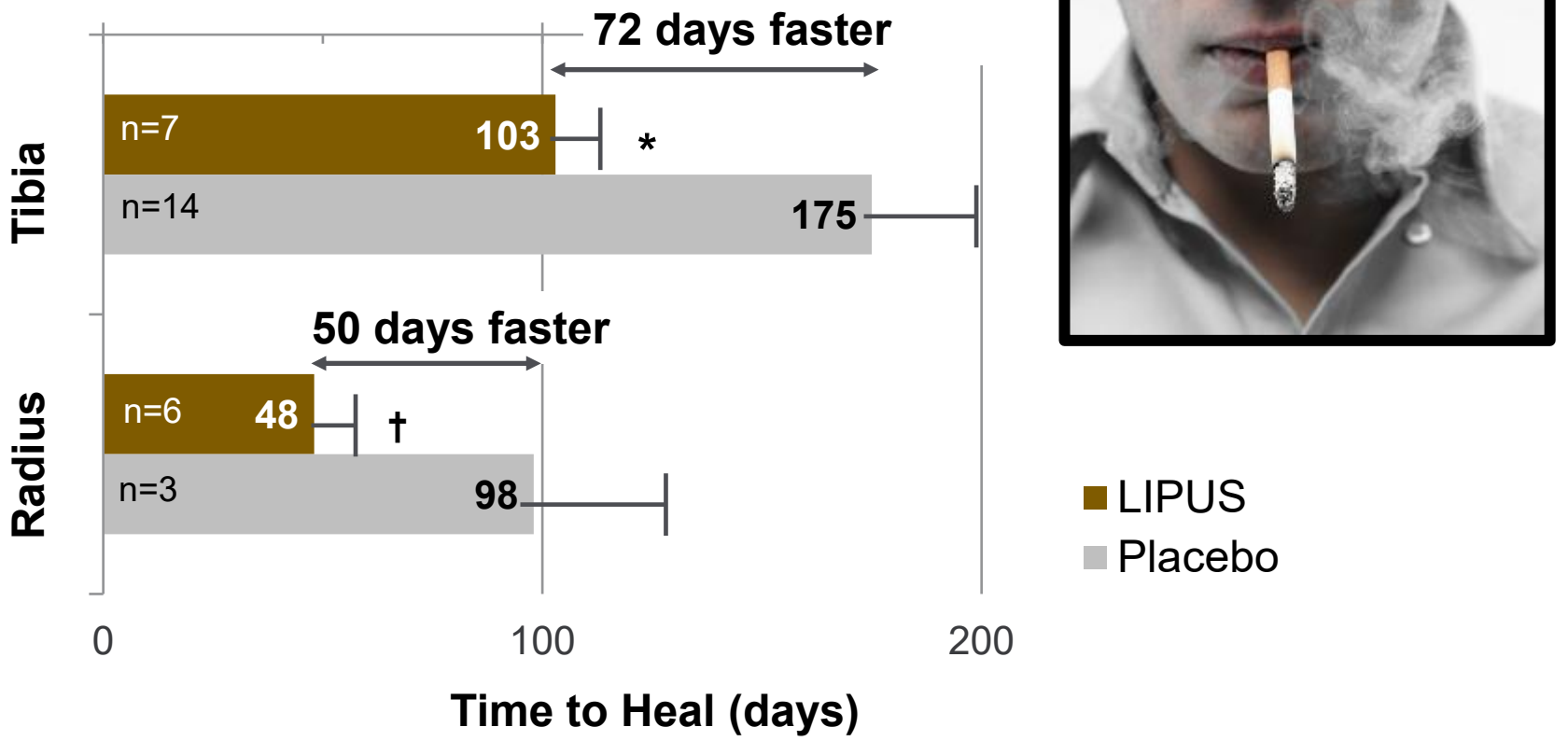


****P*=0.0001**
Data are shown as means ± standard error.
Heckman JD, et al. *J Bone Joint Surg Am*. 1994;76(1):26-34.


2nd Metatarsal
Stress Fx (nonunion) + LIPUS

LIPUS and Smoking

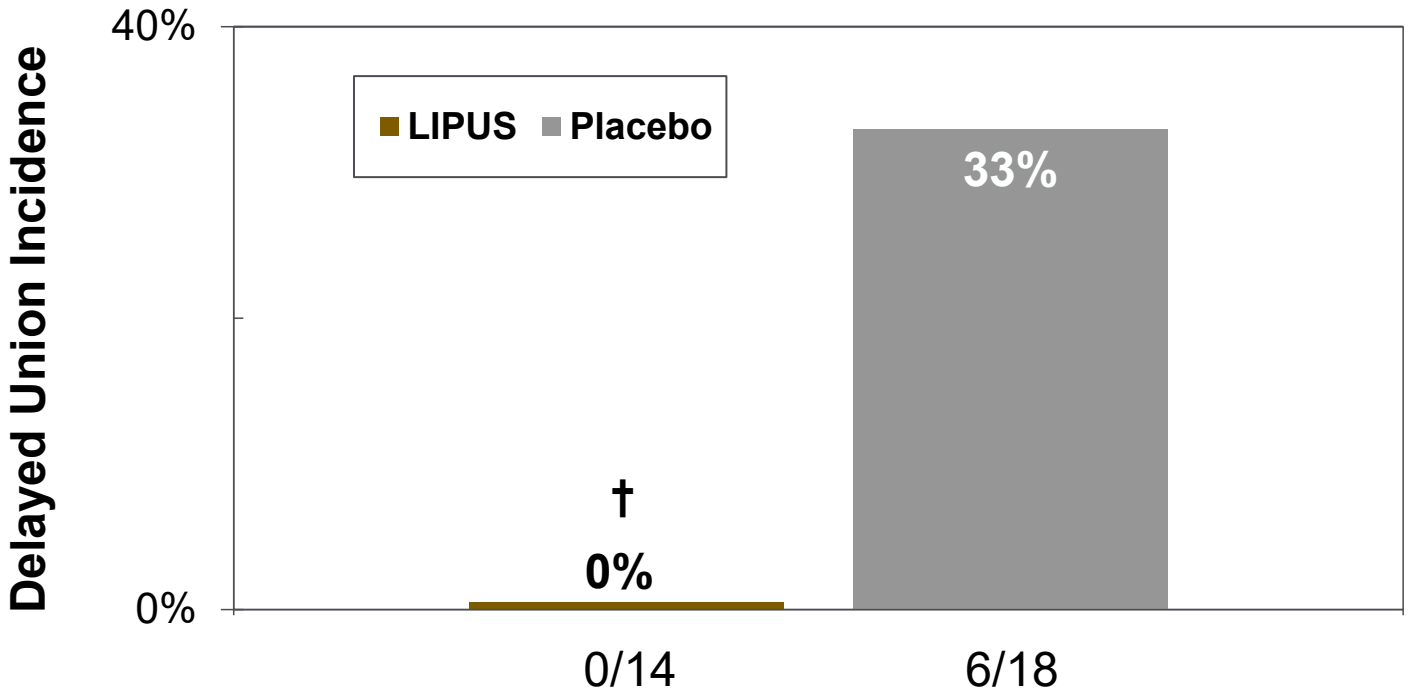
LIPUS accelerates healing of fresh fractures in patients who smoke.



*P<.006; †P<.003
Data are shown as means ± standard error.
Cook SD. *Clin Orthop Relat Res*. 1997;1(337):197-207.

LIPUS and Smoking: Tibia

No LIPUS-treated smokers* developed a delayed union

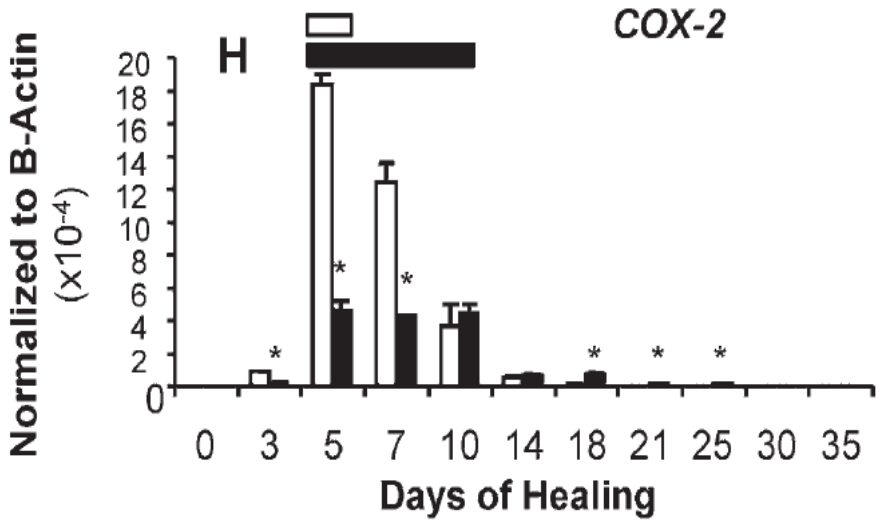


***Current smokers and those who quit smoking more than 10 years ago; †*P*<.02**
Data are shown as means ± standard error.
Cook SD. *Clin Orthop Relat Res*. 1997;1(337):197-207.

Age and Fractures: The Problem

- Increasing age is a risk factor for fracture nonunion
- Older mice produce less COX-2
- Reduced COX-2 expression in aged mice is associated with impaired fracture healing, as seen with reductions in mineral and vascular volume at the fracture site

Preclinical Study

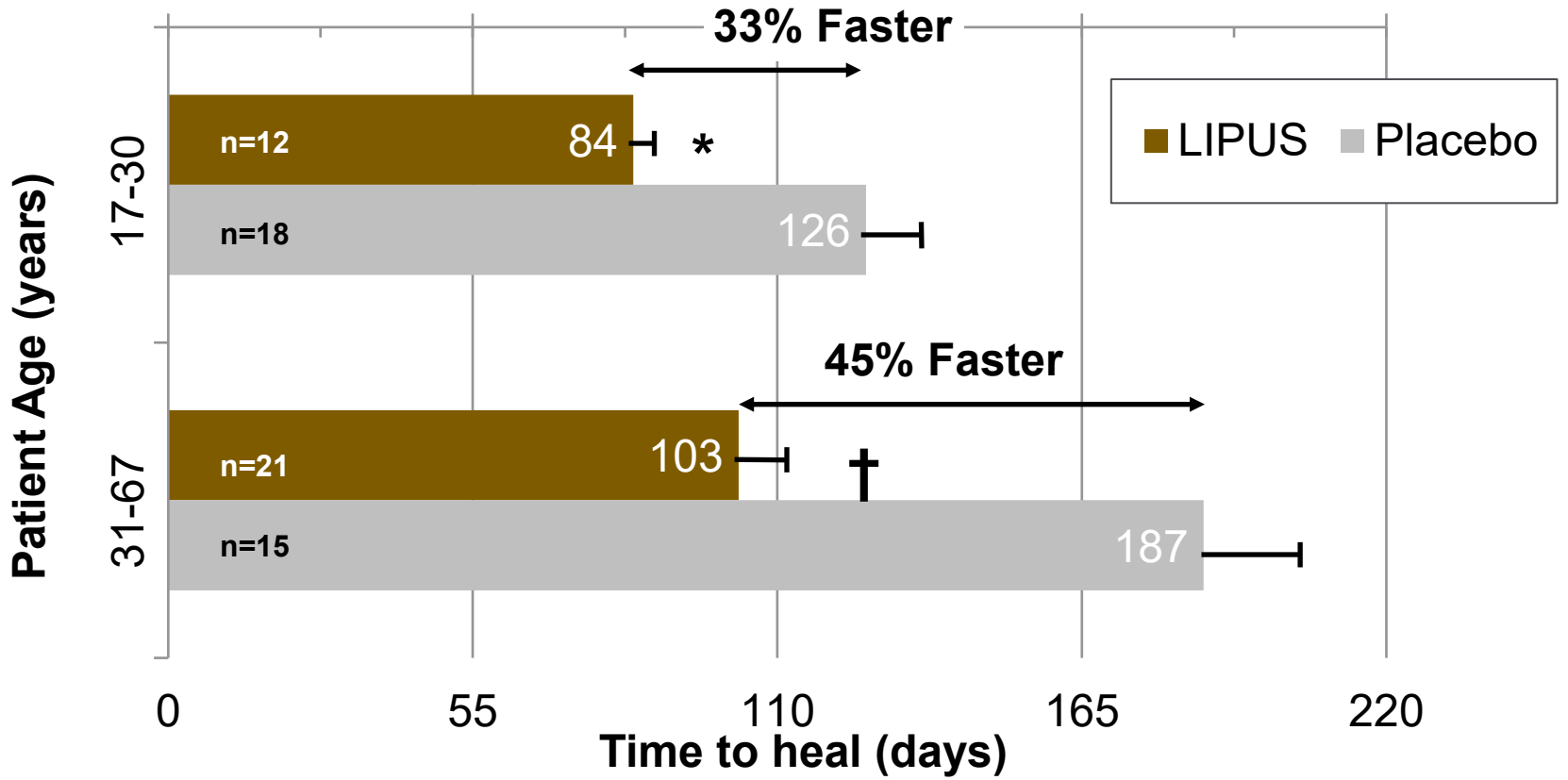


mRNA levels of COX-2 in young (open bars) and old (filled bars) in mice.

*$P<.05$.

Heckman JD, et al. *Bull Hosp Jt Dis*. 1997;56(1):63-72. Claes L, et al. *Langenbecks Arch Surg*. 2002;387(3-4):146-152. Naik AA, et al. *J Bone Miner Res*. 2009;24(2):251-264. Zura R, et al. *BMC Musculoskelet Disord*. 2015;16:45.

Effectiveness of LIPUS by Patient Age



*P<.02; †P<.0001.

Heckman JD, et al. *Bull Hosp Jt Dis*. 1997;56(1):63-72.

LIPUS Nonunion Data Analysis

Clinical Evidence: Fracture Gaps

- The study included 59 fractures initially treated with surgery, a minimum fracture age of 6 months and a fracture gap smaller than 10 mm
- 7 (4 unstable) of 59 fractures failed to heal
- Heal rate 88%
- Fracture gaps <10 mm do not affect heal rate

Roussignol X, et al. *Orthop Traumatol Surg Res*. 2012;98(2):206-213.

Clinical Evidence: Nonunions

- Prospective case series of 36 nonunions and 64 delayed unions
- Inclusion criteria: stable, vital fragments, no infections, atrophic or hypertrophic fracture, >90 days from last surgery or treatment changes, >120 days since fracture
- LIPUS 20 min/day was the only change in treatment

	Fracture Age (days)	LIPUS Heal Rate
Nonunion	680 ± 187	**86.1%** (31/36)
Atrophic	306 ± 81	**83.3%** (70/84)
Hypertrophic	475 ± 140	**100%** (16/16)

Mayr E, et al. *Unfallchirurg*. 2002 Feb;105(2):108-115.

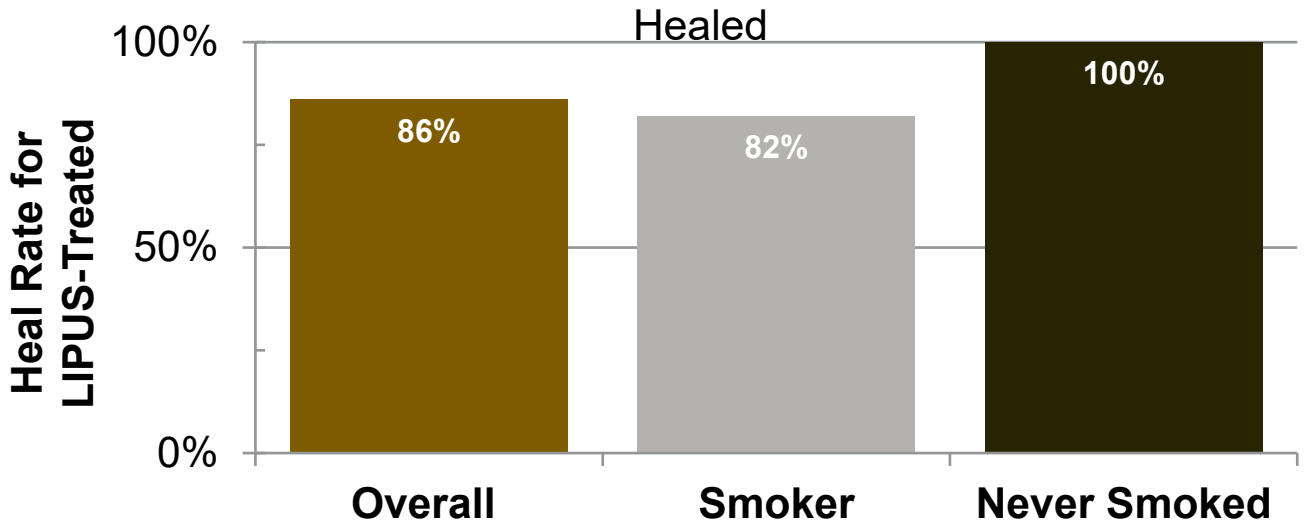
Hypertrophic

Atrophic

Mayr E, et al. *Unfallchirurg*. 2002 Feb;105(2):108-115.

Clinical Evidence: Nonunions

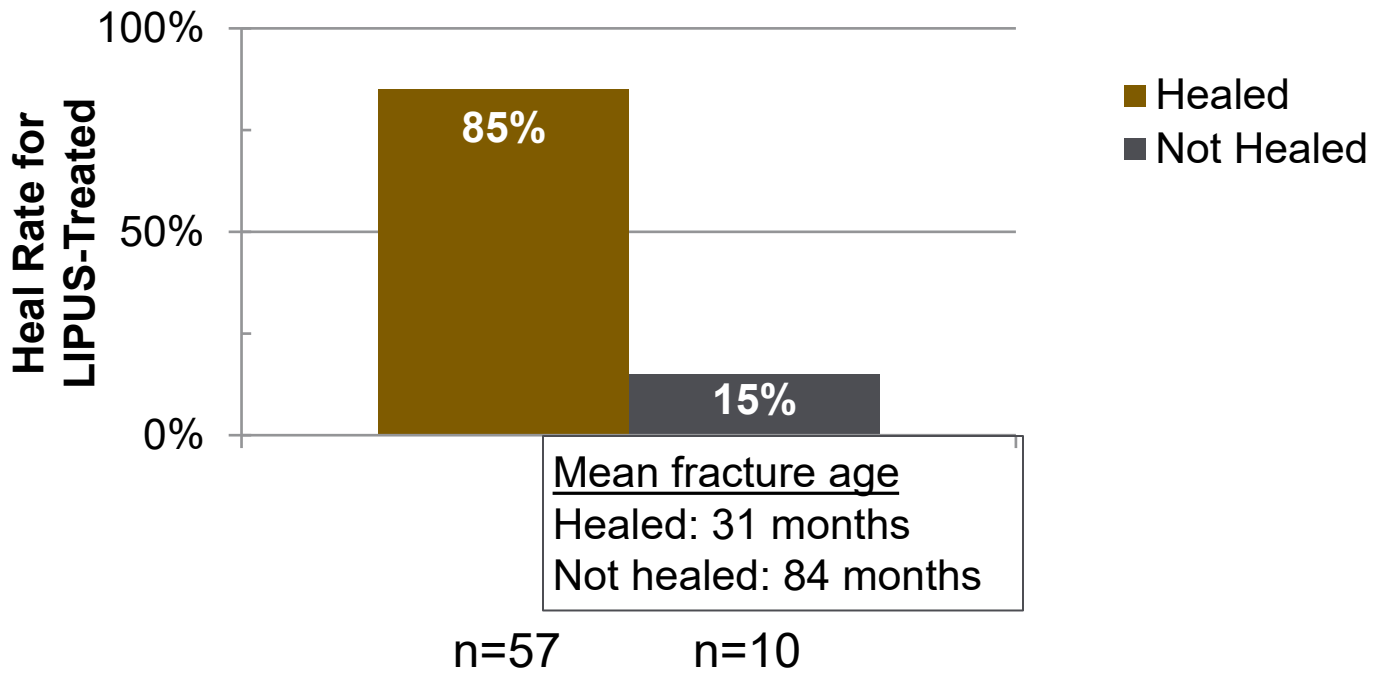
- Prospective case series of 29 nonunions
- 5 atrophic, 12 hypertrophic, 12 oligotrophic
- Mean fracture age = 1.2 years, mean time after last surgery = 1 year
- Average 1.4 failed surgery
- LIPUS 20 min/day was the only change in treatment



Nolte PA, et al. *J Trauma*. 2001;51(4):693-702.

Clinical Evidence: Nonunions

- Prospective case series of 67 nonunions
- Inclusion criteria: stable, no infection, ≥8 months minimum fracture age, >4 months since last intervention, ≥3 months no radiographic healing
- Mean fracture age 39 months; mean of 2 failed surgeries
- LIPUS 20 min/day was the only change in treatment
- 89% treatment compliance rate



Gebauer D, et al. *Ultrasound Med Biol*. 2005;31(10):1391-1402.

Clinical Trial: Treatment of Chronic Fracture Nonunion

Treatment of chronic (>1 year) fracture nonunion: Heal rate in a cohort of 767 patients treated with low-intensity pulsed ultrasound (LIPUS)

Robert Zura [a], Gregory J. Della Rocca [b], Samir Mehta [c], Andrew Harrison [d], Chris Brodie [e], John Jones [e], R. Grant Steen [e,*]

[a] Department of Orthopaedic Surgery, Duke University Medical Center, Durham, NC, USA
[b] Department of Orthopaedic Surgery, University of Missouri, Columbia, MO, USA
[c] Department of Orthopaedic Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA, USA
[d] Bioventus LLC, Amsterdam, Netherlands
[e] Bioventus LLC, Durham, NC 27703, USA

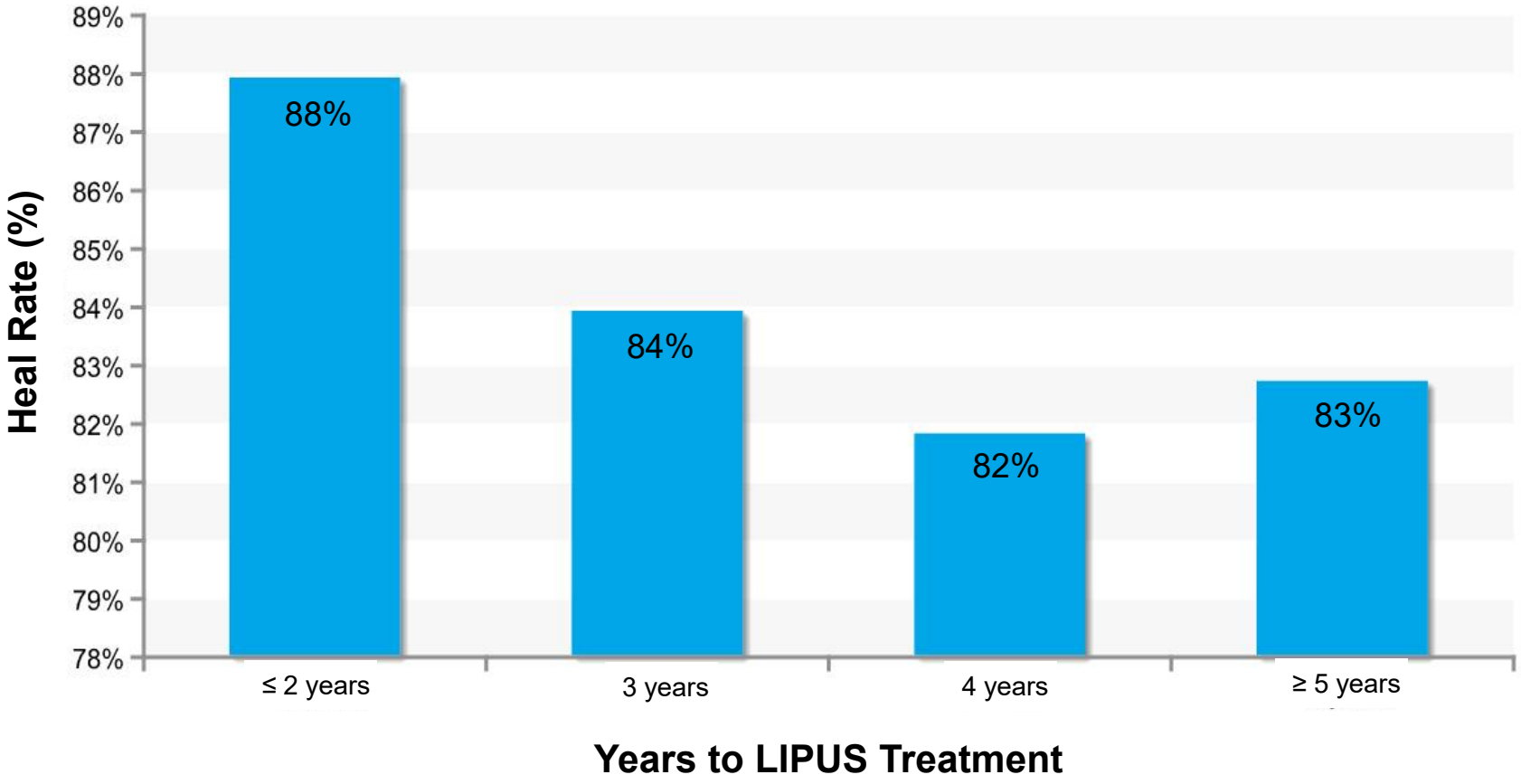
Zura R, et al. *Injury*. 2015;46(10):2036-2041.

Study Design

- Based on FDA-required prospective registry of all patients treated with LIPUS, 1994-1998 (N=11,433)
- Selected cohort: 767 chronic nonunions
- Fracture age ≥1 year
- All bones, fixation methods, ages, treatment histories, and medical histories

Zura R, et al. *Injury*. 2015;46(10):2036-2041.

Chronic Nonunion



Zura R, et al. *Injury*. 2015;46(10):2036-2041.

Chronic Nonunion

Treatment of chronic (>1 year) fracture nonunion: heal rate (HR) in a cohort of 767 patients treated with LIPUS

- 86.2% HR in 767 nonunions ≥1 year
- 82.7% HR in 98 nonunions ≥5 years
- Age associated with slightly higher risk of treatment failure
- Not linked to risk of treatment failure: smoking, BMI, open/closed, # prior surgeries, # comorbidities, # prescription meds
- No significant differences in HR by location or fixation type
- 85.7% HR in 91 nonunions where LIPUS treatment began >90 days after most recent surgery (mean 449.6 days)

BMI = body-mass index.

Zura R, et al. *Injury*. 2015;46(10):2036-2041.

HR by Open/Closed and Fracture Location

Bone	Healed	Failed	HR (%)	Lower CI (%)	Upper CI (%)
All fractures	661	106	86.2	83.7	88.6
All closed fractures	503	85	85.5	82.7	88.4
All open fractures	100	11	90.1	84.5	95.6
Tibia	168	21	88.9	84.4	93.4
Femur	129	24	84.3	78.6	90.1
Radius/Ulna	60	10	85.7	77.5	93.9
Humerus	52	13	80.0	70.3	89.7
Tibia/Fibula	50	6	89.3	81.2	97.4
Scaphoid	48	7	87.5	78.5	96.1
Ankle	35	6	85.4	74.5	96.2
Metatarsal	31	5	86.1	74.8	97.4
Foot	20	3	87.0	73.2	100.0

No significant differences in HR for open vs closed or by fracture location.

Zura R, et al. *Injury*. 2015;46(10):2036-2041.

Study Summary

- 86.2% HR in 767 nonunions ≥1 year
  - 82.7% HR in 98 nonunions ≥5 years
- Age associated with higher risk of treatment failure
  - Regression equation: HR = 96.2% (0.2%/year)
  - Example: 80.2% HR at age 80 years
- Not linked to risk of treatment failure: smoking, BMI, open/closed, # prior surgeries, # comorbidities, # prescription meds
- No significant differences in HR by location or fixation type
- 85.7% HR in 91 nonunions when LIPUS treatment began >90 days after most recent surgery (mean 449.6 days)

Zura R, et al. *Injury*. 2015;46(10):2036-2041.

72-Year-Old Female Nonunion Second Metatarsal

US stim

3 months

Summary

- 38% faster healing of approved fresh fractures
- 86% heal rate for nonunions
- Robust mechanism of action supports clinical findings
  - Upregulation of COX-2, VEGF, BMPs
  - Increased angiogenesis5, mineralization

Heckman JD, et al. *J Bone Joint Surg Am*. 1994;76(1):26-34. Kristiansen TK, et al. *J Bone Joint Surg Am*. 1997;79(7):961-973. Nolte PA, et al. *J Trauma*. 2001;51(4):693-702. Naruse K, et al. *Ultrasound Med Biol*. 2010;36(7):1098-1108. Leung KS, et al. *Clin Orthop Rel Res*. 2004;418:253-259. Tang CH, et al. *Mol Pharmacol*. 2006;69(6):2047-2057. Sant'Anna EF, et al. *J Orthop Res*. 2005;23:646-652.

Summary: Ultrasound Bone Stimulation

- Need exists in your practice
- Unique indications
  - Fresh fractures
  - Nonunions
- Effective
- Non-invasive
- Good adherence
  - 20 minutes (vs 10 hours)
- Safe

8 Months

4 Months

Multiple Metatarsals

OT-SP-141, 02-2016

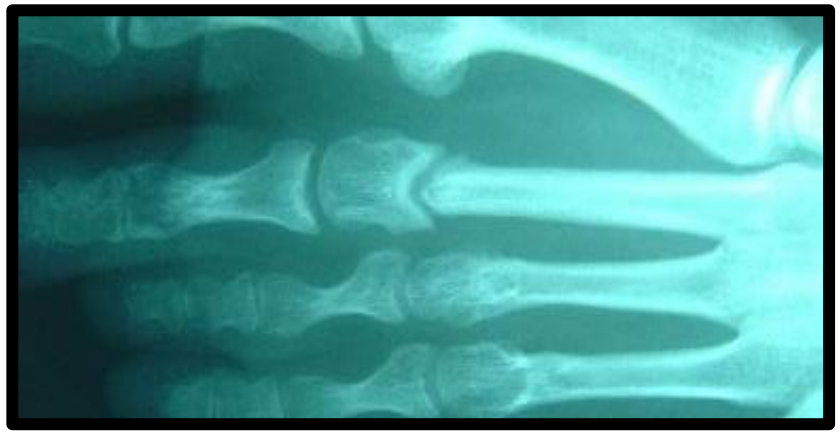
Summary: Risk Factors

- LIPUS accelerates healing time in smokers
- LIPUS affects angiogenesis and neovascularization in animal models
- Risk factors such as smoking, diabetes, patient age, NSAID use are commonly seen to affect bone healing

NSAID = non-steroidal anti-inflammatory drug.

Conclusions

- Established mode and MOA
  - Pressure wave—nanomotion—transduced by integrins
  - Gene/cytokine upregulation at callus
- COX-2 → PGE2 → BMPs, VEGF, ColX, MSCs, etc.
- Nonunion heal rates: 86%
- Accelerated healing in fresh fractures: 38%
- Efficacious in patients with risk factors
  - Smoking, diabetes



MSC = mesenchymal stem cell.