

Viability of a single infusion of zoledronic acid (ZOL) to reduce implant failure rate in THA

Results from a randomized, double-blind, controlled trial

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Rationale

Revision in primary THR

The Swedish National Hip Arthroplasty Register (<http://www.jru.orthop.gu.se>)
1979 – 2005: ~ 30.000 THR

1.	Aseptic loosening	75%
2.	Deep infection	7%
3.	Dislocation	7%
4.	Periprosthetic fracture	6%
5.	Others	5%

Rationale

Periprosthetic Bone Mass

Substantial bone loss after THR

Maloney WJ, 1996, CORR:

Cementless stems at mean fu 6 years (1.5 – 13.5 yrs)

- Periprosthetic cortical bone area: up to -40%

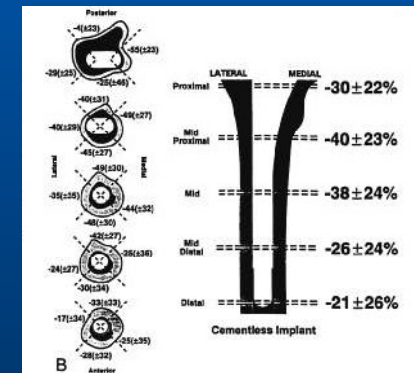
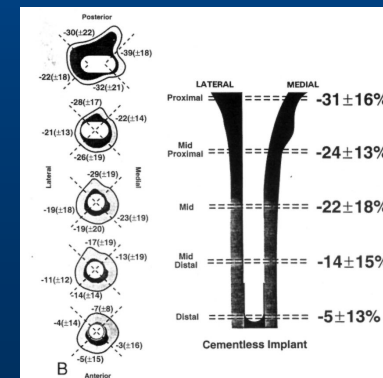
- Periprosthetic BMD: up to -30%

The Otto Aufranc Award

Skeletal Response to Well Fixed Femoral Components Inserted With and Without Cement

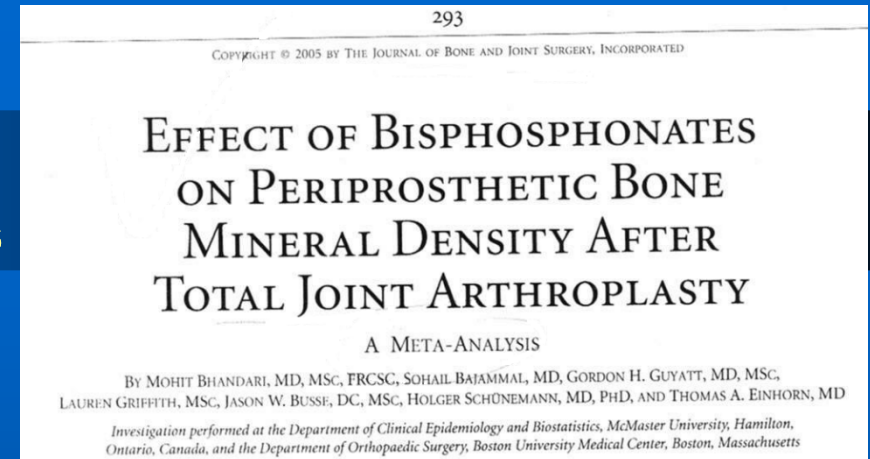
William J. Maloney, MD*; Christi Sychterz, MSE**; Charles Bragdon, BS†; Thomas McGovern, MD**; Murali Jasty, MD†; Charles A. Engh, MD**; and William H. Harris, MD†

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Rationale

Periprosthetic BMD and Bisphosphonates



Bhandari M, 2005, JBJS Am:
A Meta-Analysis of 6 randomized controlled trials in TJR

- 24-52 wks treatment with Bisphosphonates →
- Beneficial effects in maintaining periprosthetic BMD

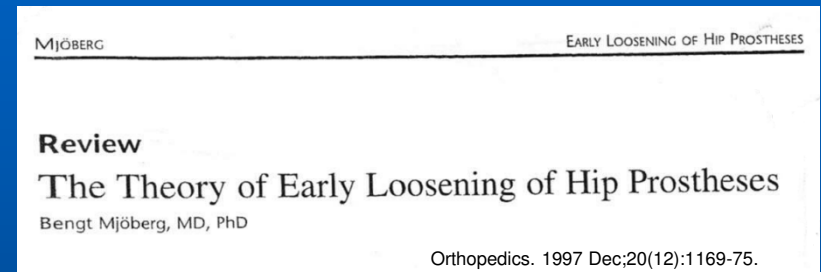
?? Predictive value of BMD for aseptic loosening??

Rationale

Prosthetic Migration

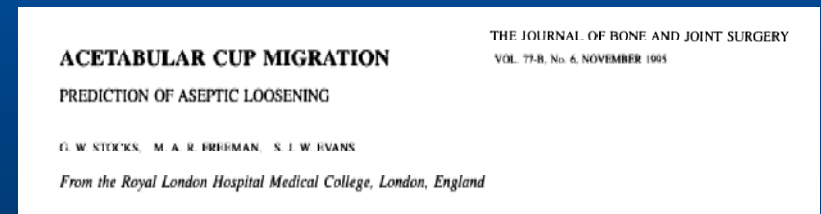
Mjöberg B, 1997, Orthopedics:
Theory based on findings in RSA

- Loosening begins at early stage due to insufficiency of initial fixation.



Stocks GW, 1995, JBJS Br: 265 THRs with 4 acetabular systems

- Migration rate of cups at 2 years was significantly predictive for loosening within a period of 6.5 yrs



Krismer, 1999, JBJS Br: 240 THR with 3 stem systems

- Migration of stems at 2 yrs was related with loosening, fu 10 years



Aim of the Study

Radl R, 2005, Acta Orthopaedica

Higher failure rate in ON-FH compared with OA was associated with higher migration.

→ Efficacy of a single infusion of ZOL on reducing the early migration rate of acetabular and femoral components in ON-FH

Secondary endpoints

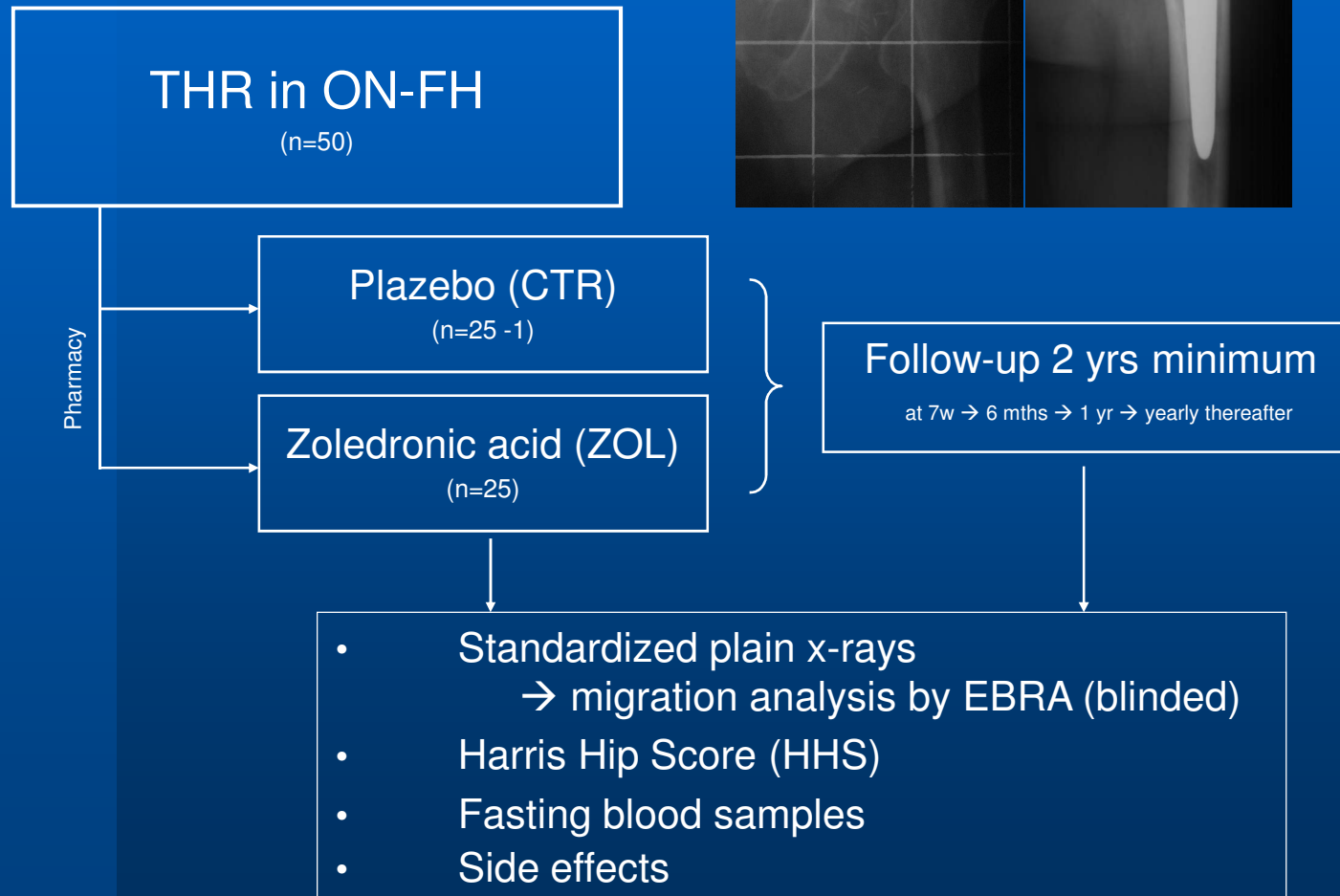
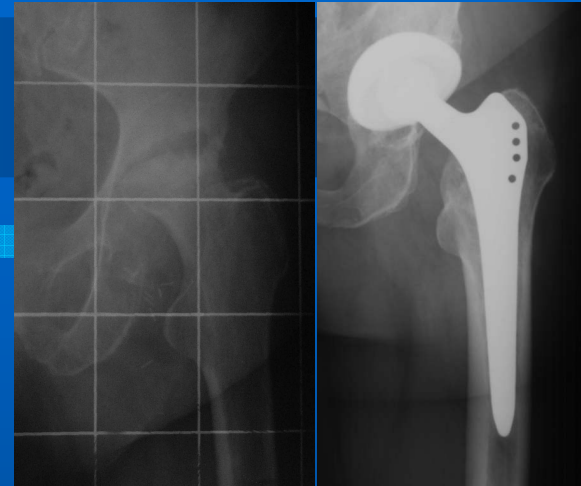
- Biochemical bone resorption and formation markers
- Clinical outcome
- Safety

Higher failure rate and stem migration of an uncemented femoral component in patients with femoral head osteonecrosis than in patients with osteoarthritis

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Study Design



Methods

Approved by local ethics committee (No 12-152ex01/02)

Surgery

- Cementless rectangular straight titanium stem without collar (n=49)
- Cementless titanium-backed press-fit acetabular cup (n=46)
- Weight bearing limited to half of BW for 6 weeks

Study medication

- Staff and patients were fully blinded, randomization by pharmacist
- Infusion of 20 ml intravenously over a 15 minute-period
- Patients were instructed to supplement 1000 mg Ca / 400 IU vitamin D

Endpoint measurements

- EBRA: ≥ 2 independent investigators blinded to randomization
- Fasting-blood analysis by core-facility of the University Hospital (GLP)
- Blinding was opened after all patients had a minimum fu of 2 years and measurements had been finished

Results

1. Baseline Characteristics

Characteristic of Patients	Total (n=49)	ZOL (n=25)	CTR (n=24)	P
Age, [years]	61.0 ± 12.8	63.9 ± 9.7	57.8 ± 15.0	NS ^a
Body weight, [kg]	79.0 ± 16.1	76.8 ± 16.6	81.1 ± 15.4	NS ^a
Body mass index, [kg/m ²]	28.4 ± 4.4	28.5 ± 4.8	28.4 ± 4.0	NS ^a
Gender, female / male	27 / 22	17 / 8	10 / 14	NS ^b
Tobacco abuse, n	11 (22%)	5 (20%)	6 (25%)	NS ^b
Pathogenesis				
Idiopathic, n	19 (39%)	10 (40%)	9 (38%)	NS ^b
Secondary, n	30 (61%)	15 (60%)	15 (62%)	NS ^b
Side				
right / left side treated, n	33 / 16	18 / 7	15 / 9	NS ^b
Characteristics of THA	Total	ZOL	CTR	P
Stem size 2 / 3 / 4 / 5 / 6 / 7 / 8, n ^d	2 / 4 / 9 / 14 / 12 / 6 / 2	2 / 2 / 6 / 5 / 6 / 3 / 1	- / 2 / 3 / 9 / 6 / 3 / 1	NS ^c
Cup size, [mm] ^e	53.5 ± 4.5	53.0 ± 4.4	54.0 ± 4.6	NS ^a
Cups secured with screws, n ^e	17 (37%)	7 (30%)	10 (42%)	NS ^b
Inclination of the cups, [°] ^e	41.2 ± 6.2	40.8 ± 3.0	41.7 ± 2.5	NS ^a
Head size S / M / L / XL, n ^d	7 / 11 / 29 / 2	2 / 5 / 16 / 2	5 / 6 / 13 / -	NS ^c

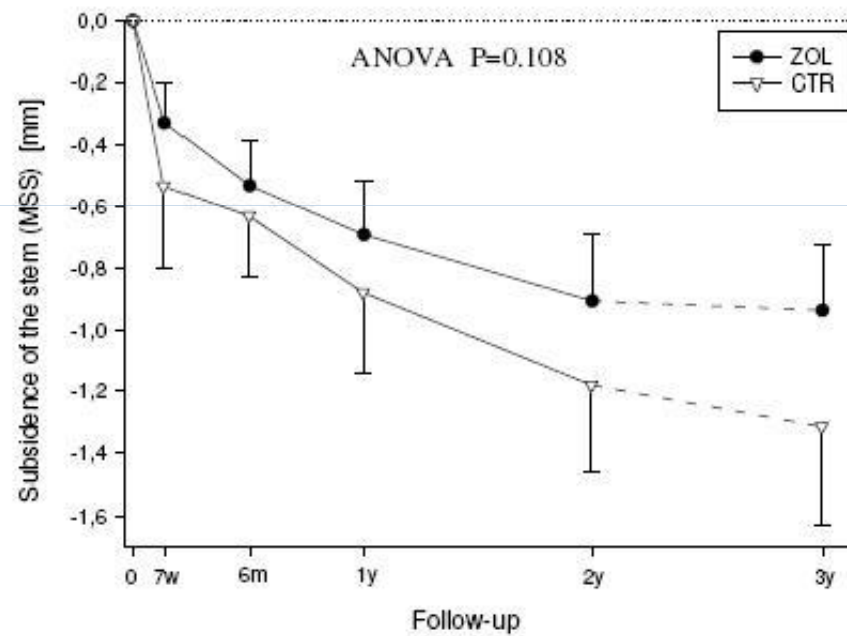
Plus-minus values are mean ± SD.

^a Mann-Whitney U test. ^b Fisher Exact test. ^c Chi-square test. NS P>0.05 for comparisons between randomization groups.

^d n=25 in ZOL and n=24 in CTR. ^e An alternative cup system had to be implanted in 3 patients (2 in ZOL, 1 in CTR; n=23 in each randomization group).

Results

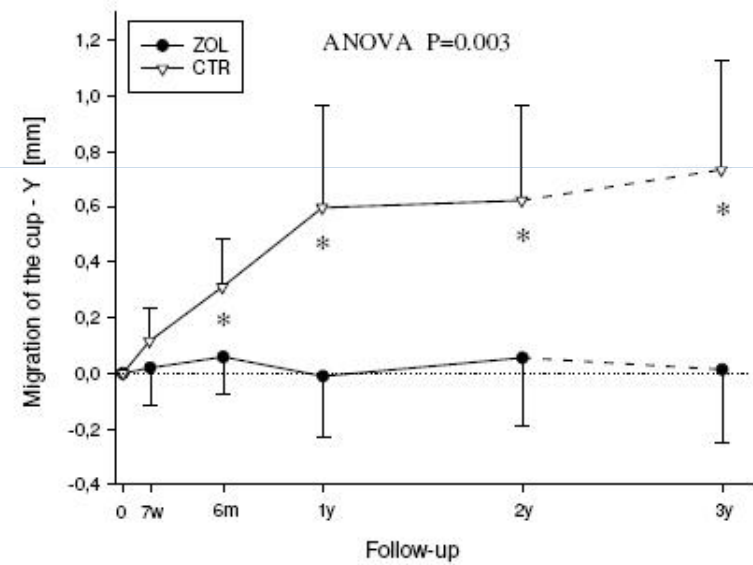
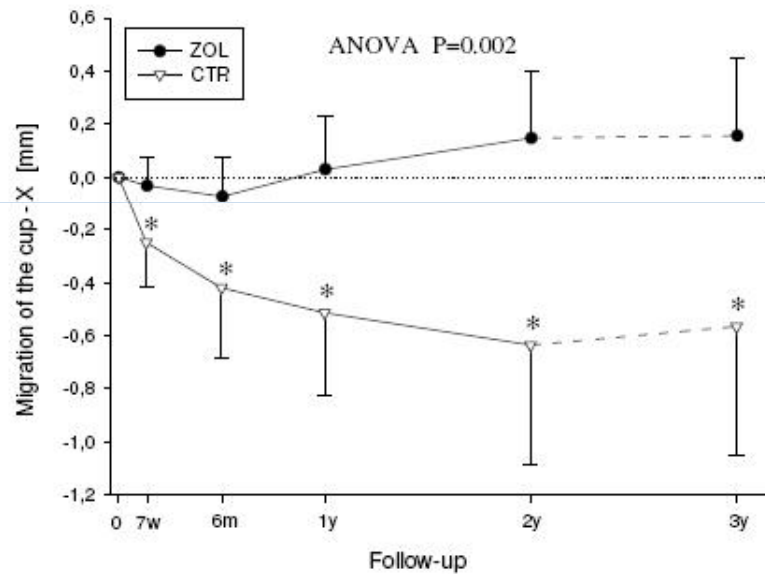
2.1 Migration Analysis - Stems



Median follow-up 2.8 yrs

Results

2.2 Migration Analysis - Cups



Median follow-up 2.8 yrs

Results

3.1 Harris Hip Rating Scale

Follow-up	CTR			ZOL			P-Value ^a
	HHS	Range	IQ-Range	HHS	Range	IQ-Range	
Baseline	31	9 – 55	26 – 42	23	9 – 62	18 – 30	P=0.017
7 weeks	86	75 – 100	80 – 89	94	76 – 100	89 – 98	P=0.001
6 months	88	78 – 100	85 – 94	100	87 – 100	94 – 100	P<0.001
1 year	92	76 – 100	88 – 100	100	89 – 100	99 – 100	P<0.001
2 years	96	87 – 100	90 – 100	100	90 – 100	100 – 100	P<0.001
3 years ^b	96	87 – 100	91 – 100	100	94 – 100	100 – 100	P<0.001
ANOVA on ranks: CTR versus ZOL: P=0.008							
Values of Harris hip score (HHS) are median values. IQ 25%-75% interquartile range. ^a Mann-Whitney <i>U</i> test; ^b Median follow-up was 2.8 years, last value was carried forward							

Results

3.2 Side Effects / Complications

Surgery/Implants

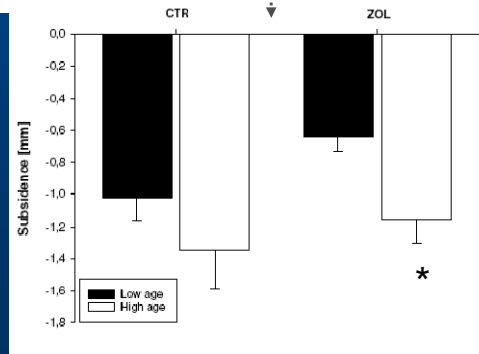
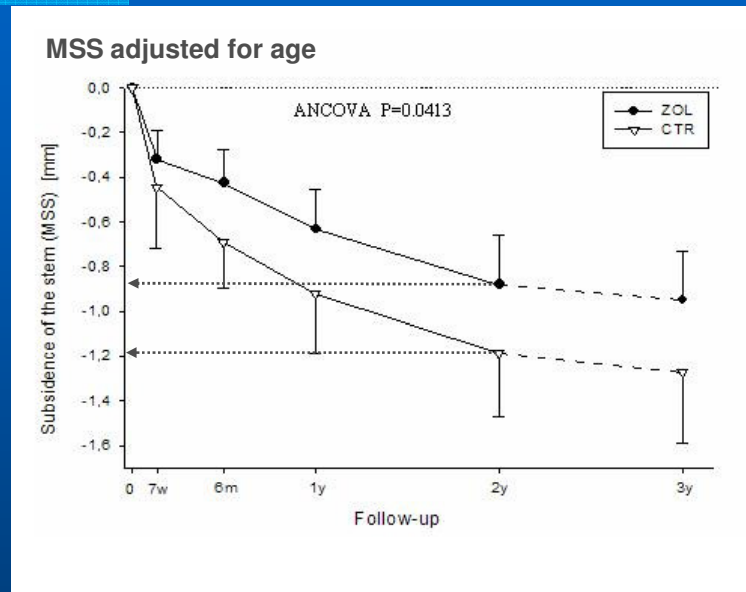
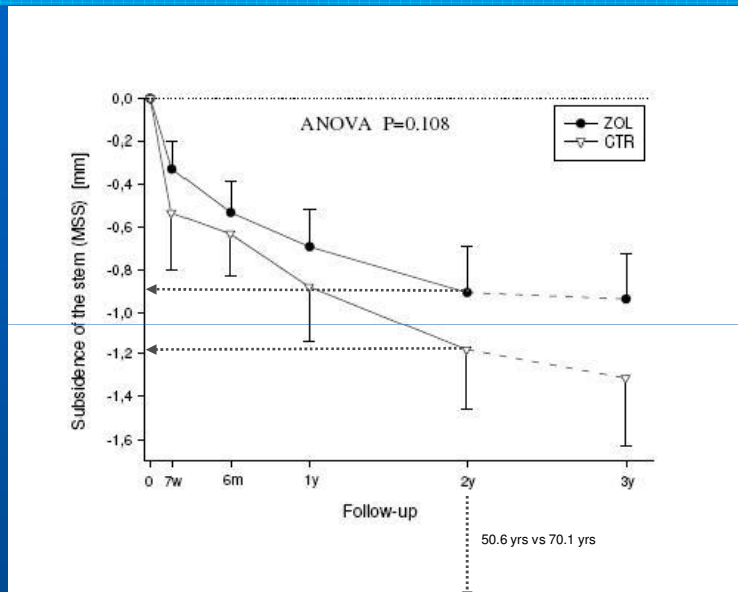
- One revision surgery because of recurrent dislocations
→ excluded (CTR)
- No complications related surgery
- No case of impending loosening during follow-up

Study Medication

- Fairly well tolerated
- No serious adverse event
- “flue-like” symptoms with increase of $+1.7^{\circ}\text{C} \pm 0.6 \text{ SD}$ for < 2 days:
in ZOL: 14 of 25 (56%)
in CTR: 3 of 25 (12%)

Results

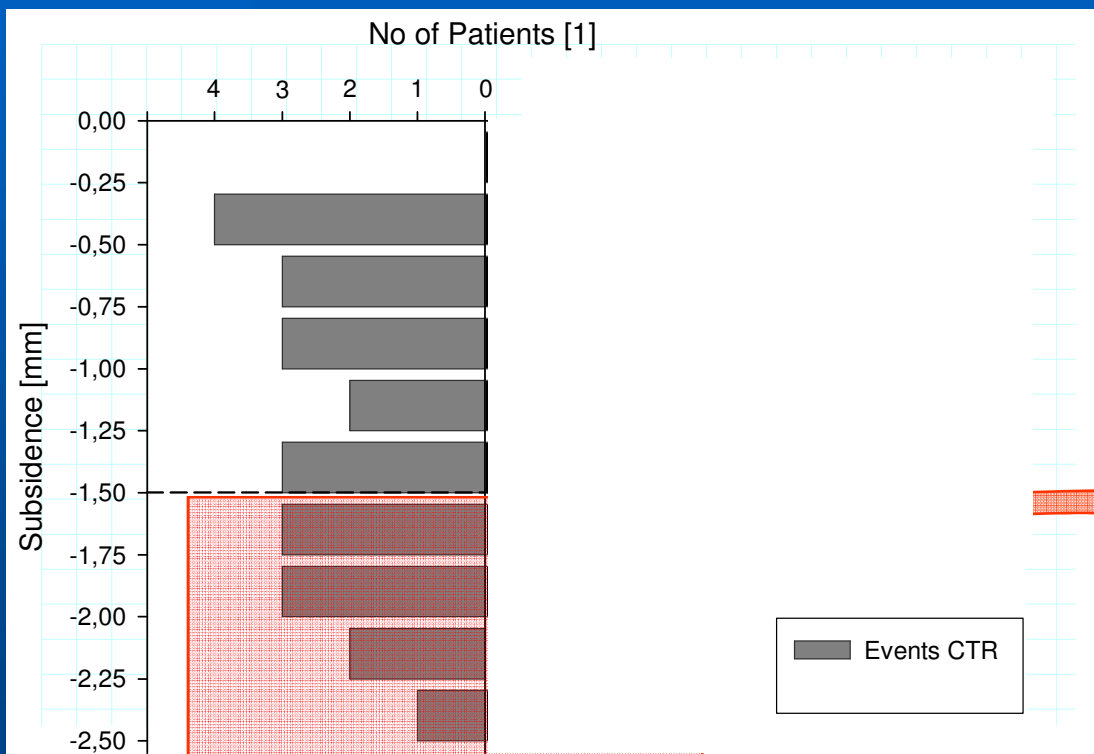
3.3 Analysis of Covariance



- No influence of age on cup migration
- Outcome was not affected by other covariates (i.e, risk factors of ON-FH, Gender, BW, BMI)

Discussion

1.1 Histogram – Subsidence at 2 yrs

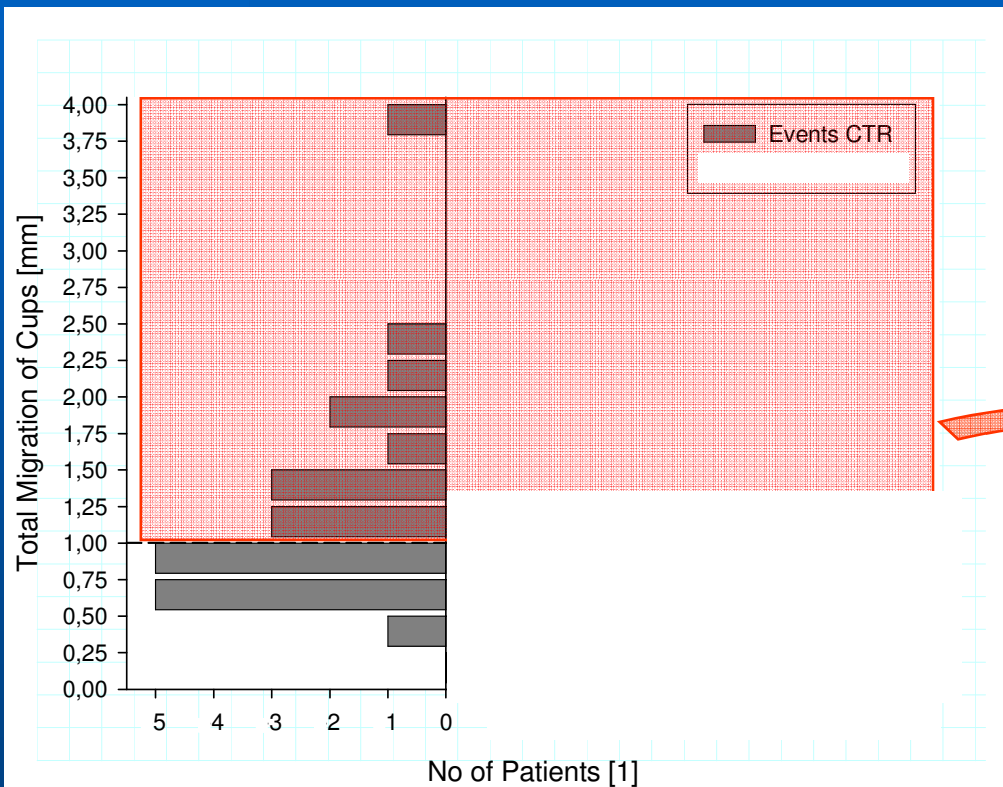


Krismer et al., 1999, JBJs Br.
EBRA of 158 stems at 2 yrs
→ Subsidence of ≥ 1.5 mm
Sens 69% / Spec 80% for aseptic
loosening at mean fu of 10 years

9/24 (CTR) vs 3/25 (ZOL)
 $P < 0.05$, Fisher Exact Test

Discussion

1.2 Histogram – Total Migration of Cups at 2 yrs



Krismer et al., 1996, JBJS Br.
EBRA of 102 cups at 2 yrs
→ Migration of ≥ 1.0 mm
Sens & Spec > 80% for aseptic
loosening at mean fu of 8.7 years

12/23 (CTR) vs 4/23 (ZOL)
P < 0.05, Fisher Exact Test

Summary

- ZOL was safe, but frequently caused “flue-like” symptoms
- Single-dose ZOL → significant effects on implant migration

	Cups	Stems
Implant Migration (CTR)	Reached plateau phase	Slowed down, but continued
Efficacy of ZOL	Prevented migration	Diminished migration
Age	Not influenced	Related to age

- Some positive effect on clinical outcome (HHS)
- JBJS Am.; Feb 2009; 91:274-81

Conclusion

A single infusion of ZOL was found to improve initial fixation in cementless THA and shows therefore promise as treatment adjunct in an effort to reduce implant failure in the long term.

Prospective long-term studies needed.

Acknowledgement

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