### Background – Situation 2004

<table>
<thead>
<tr>
<th>Year</th>
<th>Event</th>
</tr>
</thead>
<tbody>
<tr>
<td>2000-2004</td>
<td>~350 clinical trials conducted on immediate and early loading</td>
</tr>
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<td></td>
<td>Distinct minority were RCTs.</td>
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<tr>
<td></td>
<td>No studies with a primary focus on full jaw maxillary FDPs</td>
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</tbody>
</table>
### Background – Situation 2004

#### 2000

<table>
<thead>
<tr>
<th>Authors</th>
<th>Patient Situation</th>
<th>Years</th>
<th>Implants</th>
<th>Prosthesis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cannizzaro &amp; Leone IJOMI 2003</td>
<td>Partial dentate mandible &amp; maxilla anterior &amp; posterior</td>
<td>2</td>
<td>Spline Twist MTX</td>
<td>Crown + 2-7i-FDP</td>
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<tr>
<td>Mau et al. IJOMI 2003</td>
<td>Edentulous mandible</td>
<td>5-1</td>
<td>IMZ / TPS</td>
<td>2i-bar- &amp; 4i-bar-overdenture</td>
</tr>
<tr>
<td>Roccuzzo et al. COIR 2001</td>
<td>Partial dentate mandible &amp; maxilla posterior</td>
<td>1</td>
<td>ITI-sla</td>
<td>&quot;Crowns + FDPs&quot;</td>
</tr>
<tr>
<td>Testori et al. PPAD 2003</td>
<td>Partial dentate mandible &amp; maxilla anterior &amp; posterior</td>
<td>2-0.5</td>
<td>Osseotide &amp; Osseotide NT</td>
<td>&gt;2i-FDP</td>
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</tbody>
</table>

#### 2000-2004


~350 clinical trials conducted on immediate and early loading

Distinct minority RCTs.

No studies with a primary focus on full jaw maxillary FDPs

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### Background – Situation 2004

**Assumptions:**

1. A poor fit between a suprastructure and implants is associated with increased risk of technical and biological complications (Brunski, Adv Dent Res 1999)
2. An improved fit will subject the supporting implants to less micromotion and thereby allow implant loading earlier than usual (Ericsson & Nilner, Int J Perio Restor Dent 2002)

Conventional casting without distortions is technique-sensitive

New fabrication techniques and position transfer devices have been developed to optimize FDP fit, e.g., single-block milling and laser-welding

Study designed in 2004/2005

Objective to appraise feasibility of interchanging conventional FDP with Cresco components in two different early loading protocols

Hypothesis 1: We expect no difference in bone loss between implants in the two Cresco-component FDPs versus implants supporting the conventionally made FDPs

Hypothesis 2: We expect no difference in bone loss between implants in the two Cresco groups when using a 10 days versus a 6-8 weeks post-healing loading protocol

Materials & methods
Materials & methods – Protocol development & administration

• European Community Directive 2001/20 for Medical Devices introduced May 2004
• Regional ethics institutional board in Norway (#S-04162, P.I. Dr. Asbjorn Jokstad, Oslo) & Sweden (#M102-04, P.I, Dr. Stefan Ellner, Kalmar)
• Patient confidentiality procedures followed national regulatory standards. Norwegian Patient privacy ombudsman approval (#11123)
• ClinicalTrials.gov identification number: NCT00922935
• Randomization allocation was done by external third part (Analytica International, Lörrach, Germany)
• Study progress & Case Report Form (CRF) documentation monitored by study sponsor according to ISO 14155 guidelines for clinical investigations of medical devices

Materials & methods: - Sample size calculation

• Calculated for a two-sided test to compare two independent groups
• Standard deviation of bone levels in previously published clinical trials varies from 0.1 to 0.3mm (Esposito et al., Cochrane 2004)
• Anticipating a standard deviation of 0.2mm and considering a mean difference of 0.1mm bone loss between groups 1 and 2 and the control group at 1 year as clinically significant, a study with 80% power with an overall significance level of $P=0.05$ indicated a minimum of 22 patients per group.
Materials & methods: - Study population

University clinic (Norway) + 4 public dental health centers (Sweden)
Patients with an edentulous maxilla desiring a 10/12-unit FDP
Recruited to partake in a blinded 3-arm RCT
Fully healed maxilla with grafting ≥ 6 months previously

Materials & methods: Surgical protocol

- Sterile conditions, local anesthetic and antibiotic coverage
- Standard implant placement protocol according to the manufacturer
- Six solid screw two-part implants ø3.3 or 4.1 mm (SLA Standard Plus, Straumann, Basel, Switzerland)
- Standard implant placement protocol according to the manufacturer
- Primary initial stability hand-tested by tightening of healing screw
- Symmetrical spread between tooth #4 and #13 (15-25)
Materials & methods: Study Arms Allocation

- A sealed, numbered, opaque envelope containing the randomized allocation was sent to the clinician prior to each individual scheduled implant surgery.
- Envelope opened first after completion of the implant surgery.

- Randomization list generated by the external clinical research organization (CRO).
- Randomization list kept with the CRO for future reference and comparison with clinicians’ lists.
- Opened envelopes were kept as source documents for audit by the external CRO according to EC directives.

Materials & methods: Surgery session – impression/restoration protocol if immediate loading allocation

- Impression copings & suturing
- Ready for impression
- Surgical stent used as impression tray
- Maxillo-mandibular index, Hor. & Vertical
- Impression pins removal, intaglio surf.
- Healing caps placed
- Old prosthesis relined with GC-Reline
- Hardened polyether impression elastomer

### Materials & methods: Study Arms & Interventions

#### Test group 1
- **FDP**, Cresco components (Cresco Ti Systems, Sarl, Lausanne, Switzerland)
- Implants loaded within 10 d. post-implant placement

#### Test group 2
- **FDP**, Cresco components
- Implants loaded 6-8 weeks post-implant placement

#### Control group
- FDP, conventional components
- Implants loaded 6-8 weeks post-implant placement

*10-12 units, screw retained. Each centre used local Cresco-accredited laboratories & consistent dental technician & process*

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**Materials & methods: Study Arms & Interventions**

10-12 units, screw retained. Each centre used local Cresco-accredited laboratories & consistent dental technician & process

Photos: Dr Stefan Ellner
Cresco Ti system - Procedure used in 2004 for FDP fabrication

- Cresco impression elements/pins in open/closed tray
- Cresco Replicas in stone master model (soft-tissue mask)
- Mounted antagonist stone model in CR
- Burn-out tubes mounted to replicas impression w/ process screw
- Tubes bent (→17°) for optimal FDP design
- Final adjustments & rotational placement
- Final adjustments & vertical height cut
- Wax-up of burn-out tubes
- Cast framework
- Potential casting distortion detection

Relational transfer from stone cast to a "Cresco Fixator"
Cresco Ti system - Procedure used in 2004 for FDP fabrication

Master cast lowering into plaster

Plaster is setting

Casting retained by set plaster

FDP supports screwed onto replicas in master cast

FDP supports in master cast are milled

Cast Framework legs in plaster are milled

Shades indicate vertical removal

FDP supports + framework legs laser-welded

Grind / polish / try-in

Ceramic veneering
**Materials & methods: Clinical outcomes**

- Patient complaints or any complications resulting from a change in health status
- Any implant-related complications, e.g., pain, paraesthesia or peri-implant infection
- Clinical-radiological examinations 3 & 6mths, 1, 2 & 3yrs
  - Periapical radiographs using customized film holders (Rinn XCP Film holder (Dentsply Rinn, Elgin, IL, USA) & a PVS putty impression)

- Oral hygiene was assessed using sulcus bleeding, plaque index and oral hygiene criteria (Mombelli et al., Oral Microbiol Immunol 1987)
- Patient satisfaction: perceived appearance, ability to chew, comfort, general satisfaction and ability to taste; rated: excellent / good / fair / poor

**Materials & methods: Radiographic measurements**

- Same type of film used throughout the study for consistency.
- Radiographs digitized (Nikon Coolpix 995, Melville, NY, USA)
- Measurements using public domain software (ImageJ, NIH, Bethesda, USA)
- Bone level measurement performed independently by an investigator unrelated to the study
  - Vertical distances in millimeters from the implant shoulder to the most apical initial point of first visible bone contact (depth of implant bone contact; DIB) measured for both proximal sites
  - Eventual misalignments of the film planes relative to the implant long axis were accounted for by calibrating the software for each measurement to the known thread pitch of the implants (1.25 mm).
Materials & methods: Statistical analyses

- Two approaches: 1. All implants were taken into account, the patients build the clusters in the dataset. 2. Only one implant chosen as representative of all - both a mixed model and a cumulated logit model was applied.
- The distribution of the continuous responses was appraised by the Kolmogorov-Smirnov test together with graphical presentation of the data.
- K-S test indicated that the premises were adequate for using a “mixed model with random cluster-specific effect and fixed effects TIME, GROUP and TIME x GROUP”

- The dependent response in both types of analysis was the change of bone level over time; specifically the difference in bone level between the 3 groups, i.e. the response of a matched pair design, evaluated by paired t-tests.
- An ANOVA type model was used, especially a mixed model with random effect “patient” and fixed effects GROUP (3 levels), TIME, TIME x GROUP.
- All statistical analyses were done using SPSS statistical software (SPSS Inc., Chicago, IL, USA)

Results
Results: Patient flow

Assessed for eligibility (n = 43)
Excluded (n = 3)
Insufficient bone (n = 3)

Implant placement (n = 40)
Randomized (n = 36)
Not randomized (n = 4)
Insufficient bone at surgery (n = 4)

Cresco, loading 10 days post-implant placement (n = 10)
Received intervention (n = 9)
Received intervention with protocol deviation (n = 1)
FDP supported by 5 implants (n = 1)

Cresco, loading 6-8 weeks post-implant placement (n = 14)
Received intervention (n = 14)
Received intervention with protocol deviation (n = 2)
FDP supported by 5 implants (n = 1)
Primary stability not achieved on all implants (n = 1)

Control: Cast, loading 6-8 weeks post-implant placement (n = 10)
Received intervention (n = 9)
Received intervention with protocol deviation (n = 1)
Primary stability not achieved on all implants (n = 1)

Baseline data - Distribution of implant types

- Other
- 4.1x14mm
- 4x13mm
- 4.1x10mm
- 3.3x12mm
- 3.3x10mm

Cresco 10M4 post-implant
Cresco 6-8 w. post-implant
Cast 6-8 w. post-implant
### Results: Baseline (per protocol groups)

<table>
<thead>
<tr>
<th></th>
<th>Cresco 10d (n=8 patients, 48 implants)</th>
<th>Cresco 6-8w (n=9 patients, 54 implants)</th>
<th>Control 6-8w (n=9 patients, 54 implants)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gender males (%)</td>
<td>5 (63)</td>
<td>6 (55)</td>
<td>1 (11)</td>
</tr>
<tr>
<td>Mean patient age (SD)</td>
<td>64 (12)</td>
<td>64 (11)</td>
<td>67 (7)</td>
</tr>
<tr>
<td>Clinical team (1-5): patients (n)</td>
<td>1:3 2:1 4:3 5:1</td>
<td>1:3 2:1 3:2 4:3</td>
<td>1:3 2:3 4:2 5:1</td>
</tr>
<tr>
<td>Bone quality (I - IV) (%)</td>
<td>II:37 III:50 IV:13</td>
<td>II:20 III:62 IV:18</td>
<td>II:0 III:56 IV:44</td>
</tr>
<tr>
<td>Crest width: &lt;5-6-7-8-9mm (%)</td>
<td>0 4 17 69 10 0</td>
<td>3 5 8 56 5 6</td>
<td>11 13 11 50 13 2</td>
</tr>
<tr>
<td>Bone height: &lt;10-10/11-12/13-13 mm (%)</td>
<td>15 15 54 17</td>
<td>2 12 73 23</td>
<td>13 17 69 2</td>
</tr>
<tr>
<td>Implant depth (mm) (SD) (min - max)</td>
<td>2.9 (0.7) (1.3 - 4.2)</td>
<td>2.1 (0.6) (0.3 - 3.3)</td>
<td>1.7 (0.3) (0.6 - 1.9)</td>
</tr>
</tbody>
</table>

*Significant differences between the groups
Results – Clinical outcomes over 3 years

- No implant-related complications
- A single occurrence of a localized peri-implantitis was treated uneventfully by penicillin.
- Prosthodontic complications and failures were rare (p > .05 amongst groups)
- Patient satisfaction scores were high in all 3 study groups regarding general satisfaction, comfort, satisfaction with appearance and ability to chew and taste (p > .05).
- Periodontal indices did not differ significantly amongst the three study groups (p > .05).

Results: Average sulcus bleeding index over 3 years

When a periodontal probe is passed along the gingival margin adjacent to the implant:
Score 0: no bleeding  Score 1: isolated bleeding spot visible  Score 2: blood forms a confluent red line on margin  Score 3: heavy or profuse bleeding.
Results – Bone changes at the 3 years follow up

- The adjusted means and ranges of changes in crestal bone levels were:
  - Group 1: -0.7 mm (-1.1 to -0.2)
  - Group 2: -0.5 mm (-0.7 to -0.3)
  - Group 3: -0.4 mm (-0.6 to -0.2) (p>0.05)

- The change from baseline was statistically significant in all treatment groups

Results – Bone changes at the 3 years follow up

- The average bone loss was 0.5 mm for the medial pair, 0.9 mm for the two implants in the cuspid regions and 0.5 mm for the two most distal implants. Thus, the cantilever did not seem to accelerate bone loss on the most distally placed implants.
Conclusions

By assuming a non-inferiority margin of 0.3 mm bone loss:
1. Clinically relevant superiority of the Cresco groups vs the control group can be excluded
2. Inferiority of the Cresco groups compared to the control group cannot be excluded

An additional change in bone level of -0.3 mm is expected by each 1 mm an implant is placed deeper

The vertical placement of the dental implant has more effect on bone loss than the fabrication technique used for the suprastructure and whether the implants were loaded after 10 days versus 6 to 8 weeks.
Per 2011: 34 RCT/CCT trials comparing immediate vs delay loading - 3 w/ focus on full arch maxilla

Per 2011: 52 papers reporting on immediate loading full arch FDP in maxilla
Confounding variables influencing the treatment outcome

- Patient inclusion and exclusion criteria (e.g. host factors, smoking, parafunction, bone type, etc.)
- State of remaining dentition and intra-oral implant placement site
- Number of implants to support the superstructure
- Nature of implant-supported superstructure
- Clinical procedures (e.g. stage of healing following extraction, site preparation, torque, etc.)
- Implant morphology (smooth, microrough, rough)
- Treatment outcome criteria
- Observation period

Per 2011; 6 papers reporting Cresco-fabricated FDPs

<table>
<thead>
<tr>
<th>Authors</th>
<th>Study type /Yrs</th>
<th>N pat.</th>
<th>Patient condition</th>
<th>Product (implants)</th>
<th>Cresco-Prosthesis</th>
<th>Survival (Imp.)(%)</th>
<th>Complications</th>
<th>Biological/ technical</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hjalmarsson et al. Int J Pros 2011</td>
<td>Retrospective</td>
<td>40</td>
<td>Edentulous Mx</td>
<td>Astra (213)+ (Brånemark / Straumann /3i (33))</td>
<td>Co-Cr+ceramic (15) Ti+acrylic-teeth (25)</td>
<td>99</td>
<td>Mucositis (5) Phonetics (2) Veneer fractures (4)</td>
<td></td>
</tr>
<tr>
<td>Jokstad et al. Clin Oral Imp Res 2011</td>
<td>Prospective</td>
<td>17</td>
<td>Edentulous Mx</td>
<td>Straumann-SLA (102)</td>
<td>High noble + ceramic (17)</td>
<td>100</td>
<td>Unable to fabricate (1) Remake (1)</td>
<td></td>
</tr>
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</table>
Acknowledgments

Co-investigators: Dr Stefan Ellner & Dr Anne M. Gussgard
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Thanks for Your attention!