Osteoarthritis
perspectives of need

Stefan Lohmander, MD, PhD

presentation roadmap

• what do we know about OA?
• what do we need to treat?
• when do we need to treat?
• who do we need to treat?
• what do we need to get there?

what do we know about OA?
• by far the most common joint disease
• accounts for more functional limitation & disability than any other chronic disease among the elderly
• most common indication for total joint replacement
• costs ~ 2% of GNP in developed countries
• patients often have co-morbid medical conditions
• associated w. significant excess mortality
• modest efficacy of symptom-modifying therapy
• no disease-modifying therapy

should we treat …
or should we treat…?

• symptoms:
persistent knee pain,
limited morning stiffness, function impairment
• findings:
crepitus, restricted movement, bony enlargement
• ROA probability 99%

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Stefan Lohmander
OARSI Imaging Workshop 2012
Objectives

- Randomized trial of cholesterol lowering in 4,444 patients with CAD: The Scandinavian Simvastatin Survival Study.
- To investigate whether long-term simvastatin therapy reduces total mortality and coronary events in post-MI and/or angina patients with total cholesterol between 212-309 mg/dL.
Design

- Double-blind, randomized, placebo-controlled
  - 94 centers in 5 countries
  - 4,444 men and women 35 to 70 years of age
  - Inclusion Criteria: Prior MI and/or angina pectoris
  - Total Cholesterol: 212-309 mg/dL
  - Follow-up: until 440 deaths occurred.

Endpoints

- Primary: Total Mortality
- Secondary: Major adverse coronary events
  - Coronary deaths
  - Nonfatal MIs
- Tertiary: Effect on:
  - PTCA/CABG procedures
  - Survival without atherosclerotic event (event-free survival)
  - Any coronary event
  - Non-MI acute CHD events

Primary Endpoint: Overall Survival

- 30% risk reduction
- p = 0.0003

PTCA/CABG procedures

- 37% Risk Reduction
- p<0.00001

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could this work also in OA?
OA progression

More OA

Insult → Acute → Chronic → OA → Time → Age

prospective population-based study

N=1,500
Colon radiography 1980-97
Mean age 60 years
Follow-up 11-28 years
Incidence of THR for OA by linkage with the national Icelandic TJR register

OA progression

More OA

Insult → Acute → Chronic → OA → Time → Age

does radiographic OA predict THR?

Hazard Ratios for getting THR
Cox multivariate regression adj for age & sex

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<th>K&amp;L grade</th>
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<td>33 (16-68)</td>
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<tr>
<td>0-1.0</td>
<td>51 (28-93)</td>
<td>4</td>
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*ref JS>3.5mm or K&L 0

Franklin J et al. 2011 AC&R

only 17% of those with radiographic hip OA at baseline had undergone THR for OA at the end of the 11-28 year study

positive & negative predictive values of radiographic hip OA

- PPV 0.40
- NPV 0.96

Franklin J et al. 2011 AC&R
radiographic OA: diagnostic criterion or risk factor?

when to dmodal?

- **primary prevention?**
  - person w. high genetic risk?
  - person w. obesity?
  - person w. joint injury?
  - person w. structural joint change, no symptoms?

- **secondary prevention?**
  - person w. OA symptoms, no joint change?
  - person w. symptoms+ROA, to slow progress?

- **tertiary prevention?**
  - patient w. one replaced joint, to slow or prevent progress in other joint(s)?

needs & expectations will (obviously) vary with person

- retired overweight physically inactive 64y female w end-stage hip OA
- working physically active 47y male w prev. meniscectomy & symptomatic knee ROA
- 31y female athlete w prev. ACL tear and w symptomatic knee ROA
- 23y male athlete w ACL tear & planned ACLR

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in particular, consider

- patients with symptomatic OA who are unresponsive to conventional “care-as-usual” but are not suitable for joint replacement
  - 47y male...
  - 31y female...
- "treatment gap"
presentation roadmap

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what ”there”?

outcomes of research?

issue identification
project specification, selection, granting, inputs from previous research

research process

primary outputs

research process

dissemination

secondary outputs

patient benefit

research process

patient benefit

Event-Free Survival

Survival without atherosclerotic event

26% Risk Reduction
p<0.0001

TC LDL HDL TGs

Changes in Lipoprotein Levels

Simvastatin vs placebo, at study end

% Change

-25 -35 -10 0 10 20 30 40 50 60 70 80 90 100

Simvastatin Placebo

SCORE - European Low Risk Chart

guidelines and recommendations for primary prevention in individuals

The Lancet, Vol 344, November 19, 1994

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OARSI Imaging Workshop 2012
what does biomarker add to other easily obtained risk factors or diagnostic criteria?

(age, symptoms, clinical exam, BMI, history of injury, family history, plain x-ray…)

is this test useful?

• "risk" biomarker
  – does test & resulting prevention or treatment lead to fewer persons getting the disease, really?

• "prognostic" biomarker
  – does information provided lead to other decision or management leading to better survival, symptom or qol outcome, really?

"cost of biomarker failure is high, patients have died…"

evidence matters

state of OA biomarkers?

"our lab results suggest that you are a rather short person"

"AV PROVRRESULTATEN FRAMGÅR ATT NI ÄR KORTVUXEN!"
'it is always too early (for rigorous evaluation) until, unfortunately, it's suddenly too late'

(Buxton’s law)

the numbers game
what should we be aiming for?

Scandinavian Simvastatin Survival Study (4S)

The Lancet, Vol. 344, November 19, 1994

Primary Endpoint: Overall Survival

Number Needed to Treat?

- for the 4S study, NNT for simvastatin was about 12 over 5 years
- for a lower risk population (no prior CAD event), 5y statin NNT is about 50
- for treatment of modest hypertension, the NNT may be 600-800 to prevent one major event

Number Needed to Treat?

- for a patient with "major" (30%) 10 year risk of "major OP fracture" the NNT for bisphosphonate treatment is about 10
- with a 10 year risk of 10%, the NNT is about 33
  - this means that 97/100 patients have no benefit from a 10 year treatment
- it is argued (by some) in the US that 3% 10y risk should be treated...
we really, really need...

1. better long-term natural history data
2. a web-based, public, quick & easy tool to identify those at risk of future joint failure
3. "prognostic" biomarkers to improve precision of (2)
4. "efficacy" biomarkers & endpoints for use in drug trials, esp. in early-stage development