VOORKOMEN VAN BOTMETASTASEN

Dr. H.P. Sleeboom
Amersfoort 16 december 2013
### Clinical Importance and Prognosis of Bone Metastases

<table>
<thead>
<tr>
<th>Disease</th>
<th>Disease prevalence, U.S. (in thousands)</th>
<th>Bone mets. incidence (%)</th>
<th>Median survival (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myeloma</td>
<td>75 - 100</td>
<td>70 - 95</td>
<td>24</td>
</tr>
<tr>
<td>Renal</td>
<td>198</td>
<td>20 - 25</td>
<td>12</td>
</tr>
<tr>
<td>Melanoma</td>
<td>467</td>
<td>14 - 45</td>
<td>6</td>
</tr>
<tr>
<td>Bladder</td>
<td>582</td>
<td>40</td>
<td>6 - 9</td>
</tr>
<tr>
<td>Thyroid</td>
<td>207</td>
<td>60</td>
<td>48</td>
</tr>
<tr>
<td>Lung</td>
<td>386</td>
<td>30 - 40</td>
<td>7</td>
</tr>
<tr>
<td>Breast</td>
<td>1,993</td>
<td>65 - 75</td>
<td>24</td>
</tr>
<tr>
<td>Prostate</td>
<td>984</td>
<td>65 - 75</td>
<td>36</td>
</tr>
</tbody>
</table>

Osteolysis in Multiple Myeloma
Osteoblastic Vertebral Metastases
Dormant (isolated) tumor cells
The Bone Marrow Micro-environment

Osteolytic bone disease

1. Tumour cell
2. PTHrP
3. Osteoclast
4. TGF-β, IL-6

Osteoblastic bone disease

1. Tumour cell
2. PTHrP, IGFs, FGF, ET-1
3. Osteoblast
4. Osteoclast
5. Unknown GFs

GFs: Growth Factors
TGF-β: Transforming Growth Factor-beta
PTHrP: Parathyroid Hormone-related Protein
OPG: Osteoprotegerin
ET-1: Endothelin-1
TGF-β: Transforming Growth Factor-beta
Trabecular Bone Destroyed by Osteoclasts Due to Tumor Osteolysis

Figure from L Mosekilde
KLACHTEN / COMPLICATIES VAN BOTMETASTASSEN
- Pijn
- (Dreigende) fractuur
- Myelumcompressie
- Hypercalciaemie
AANWEZIGHEID VAN OSTEOPOROSE KAN DE BOTCOMPLICATIES VAN METASTASEN VERGROten
DEFINITIE OSTEOPOROSE
VERMINDERDE BOTDICHTHEID
GESTOORDE MICROARCHITEKTUUR

Verhoogde kans op fracturen
Prostaatcarcinoom op zichzelf verhoogt kans op fracturen

(OR 2,2; CI 1,9-2,5)

Abrahamsen 2007
KLACHTEN VAN UITZAAAIINGEN IN BOTTEN EN OSTEOPOROSE ZIJN NIET ALTIJD UIT ELKAAR TE HOUDEN
De systemische anti-tumorbehandeling is de hoeksteen van de behandeling.

Ook om botcomplicaties te voorkomen.
ALTIJD LOKALE BEHANDELING OVERWEGEN

- Radiotherapie
- Chirurgie
Botcomplicaties treden meestal laat in het ziektebeeld op.
Naast systemische anti-tumorthérapie kunnen behandelingen worden overwogen die specifiek gericht zijn op het tegengaan van botafbraak door osteoclasten.
- Bisfosfonaten
- Denosumab
- Radio-isotopen
Bone metastases may result in clinically significant and serious consequences of skeletal-related events (SREs)

- SREs are defined as¹,²:
  - Radiation to bone
  - Pathological fracture
  - Spinal cord compression
  - Surgery to bone

SREs are both common and frequent in patients with advanced cancer untreated for bone metastases.

Percentage of patients developing SREs

<table>
<thead>
<tr>
<th>Tumour Type</th>
<th>Percentage of Patients</th>
<th>Mean Number of SREs per Patient per Year</th>
</tr>
</thead>
<tbody>
<tr>
<td>Breast (24 months)</td>
<td>64%</td>
<td>3.70</td>
</tr>
<tr>
<td>Prostate (24 months)</td>
<td>49%</td>
<td>1.47</td>
</tr>
<tr>
<td>Lung and other solid tumours (21 months)</td>
<td>46%</td>
<td>2.71</td>
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</tbody>
</table>


Data are from the placebo arms of 3 major trials of placebo vs. IV bisphosphonate in different tumour types.
Prior SRE increases the risk for subsequent SRE

- Breast cancer\(^1\)
- Prostate cancer\(^2\)
- Lung cancer and other solid tumours\(^3\)

% of patients with on-study SREs

SREs increase the duration of hospital stays

Hospital length of stay for patients with breast or prostate cancer by presence of bone metastases or SREs in the UK

![Bar chart showing mean length of stay per patient (days) for breast and prostate cancer patients.]

- Breast (N=38,975):
  - Cancer only: 8 days
  - MBD: 24 days
  - MBD+SRE: 40 days

- Prostate (N=28,130):
  - Cancer only: 12 days
  - MBD: 28 days
  - MBD+SRE: 43 days

Oglesby A et al. Poster presented at ISPOR, Athens, Greece; 8–11 November, 2008. MBD, metastatic bone disease
- Bisfosfonaten
- Denosumab
Molecular Mechanism of Action of Zoledronic Acid

HMG-CoA \rightarrow Mevalonate \rightarrow Geranyl diphosphate (FPP) \rightarrow Farnesyl diphosphate (FPP) \rightarrow Geranylgeranyl diphosphate (GGPP)

N-BPs inhibit FPP synthase, thus blocking the prenylation of small signaling proteins essential for cell function and survival.

Ras, Rho, Rab

FTI, GGTI

Alakangas et al, Calcif Tissue Int. 2002;70:40-47.
Denosumab voorkomt binding van RANK Ligand en voorkomt Osteoclast vorming, functie en overleving.

In the presence of M-CSF.
CFU-M = colony forming unit macrophage.
M-CSF = macrophage colony stimulating factor.

Zijn bisfosfonaten en denosumab lood om oud ijzer?
Bisphosphonates and Denosumab are Distributed Differently

Bisphosphonates are adsorbed to bone surfaces at sites of bone turnover\textsuperscript{1-3}

\textbf{ALN on bone surfaces at 24 hrs}

Denosumab circulates in blood and extracellular fluid including bone tissue\textsuperscript{1,4}

\textbf{Control Denosumab}

- Mammacarcinoom
- Prostaatcarcinoom
- Andere maligniteiten
Prostaatcarcinoom
Pamidronate in Prostate Cancer
No Effect on Proportion of Patients With SRE and Mean SMR

(−HCM) at 6 months—Protocols 032 and INT05

Total N = 378

Denosumab Versus Zoledronic Acid for Treatment of Bone Metastases in Men With Castration-Resistant Prostate Cancer: A Randomised, Double-Blind Study
Study Design: International, Randomised, Double-Blind, Active-Controlled Study

Key Inclusion Criteria
- Castration-resistant prostate cancer and ≥1 bone metastases

Key Exclusion Criteria
- Current or prior IV bisphosphonate treatment

N = 950 denosumab 120 mg SC and placebo IV Q4W

Supplemental calcium and vitamin D strongly recommended

N = 951 zoledronic acid 4 mg IV* and placebo SC Q4W

Primary Endpoint
- Time to first on-study skeletal-related event (SRE) (noninferiority)

Secondary Endpoints
- Time to first on-study SRE (superiority)
- Time to first and subsequent on-study SRE(s) (superiority)

*Per protocol and Zometa® label, IV product dose adjusted for baseline creatinine clearance and subsequent dose intervals determined by serum creatinine. No SC dose adjustments made due to increased serum creatinine.

Primary Endpoint: Time to First On-Study SRE

HR = 0.82 (95% CI, 0.71–0.95)

$P < 0.001$ (noninferiority)

$P = 0.008$ (superiority)

Kaplan-Meier Estimate of Median Months

- Denosumab: 20.7 months
- Zoledronic acid: 17.1 months

Patients at Risk:
- Zoledronic acid: 951 733 544 407 299 207 140 93 64 47
- Denosumab: 950 758 582 472 361 259 168 115 70 39

Secondary Endpoint: Time to First and Subsequent On-Study SRE(s)* (Multiple-Event Analysis)

Rate ratio = 0.82 (95% CI, 0.71–0.94)

*Events occurring at least 21 days apart.

Zoledronic acid 951 708 507 356 246 168 108 74 50 33

Denosumab 950 715 518 370 273 180 111 71 51 32

Proportion of Patients Without Disease Progression

Patients at Risk:
- Denosumab: 950, 715, 518, 370, 273, 180, 111, 71, 51, 32

Study Month

Exploratory Endpoint: Overall Disease Progression

HR = 1.06 (95% CI, 0.95–1.18)

$P = 0.30$

Exploratory Endpoint: Overall Survival


HR = 1.03 (95% CI, 0.91–1.17)  
\( P = 0.65 \)

Proportion of Patients Survived

<table>
<thead>
<tr>
<th>Study Month</th>
<th>Denosumab</th>
<th>Zoledronic acid</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.00</td>
<td>1.00</td>
</tr>
<tr>
<td>3</td>
<td>0.98</td>
<td>0.99</td>
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<tr>
<td>6</td>
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<td>0.96</td>
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<td>9</td>
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<td>0.93</td>
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<td>12</td>
<td>0.86</td>
<td>0.88</td>
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<tr>
<td>15</td>
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<td>0.84</td>
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<td>18</td>
<td>0.76</td>
<td>0.79</td>
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<td>21</td>
<td>0.71</td>
<td>0.75</td>
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<tr>
<td>24</td>
<td>0.66</td>
<td>0.70</td>
</tr>
<tr>
<td>27</td>
<td>0.61</td>
<td>0.65</td>
</tr>
<tr>
<td>30</td>
<td>0.56</td>
<td>0.60</td>
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</table>

Patients at Risk:

<table>
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<tr>
<th></th>
<th>Zoledronic acid</th>
<th>Denosumab</th>
</tr>
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<tbody>
<tr>
<td>0</td>
<td>951</td>
<td>950</td>
</tr>
<tr>
<td>3</td>
<td>864</td>
<td>872</td>
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<td>6</td>
<td>745</td>
<td>746</td>
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<tr>
<td>24</td>
<td>143</td>
<td>156</td>
</tr>
<tr>
<td>27</td>
<td>98</td>
<td>99</td>
</tr>
<tr>
<td>30</td>
<td>55</td>
<td>54</td>
</tr>
</tbody>
</table>

NNT om eerste of volgende SRE te voorkomen:

5 – 10 patiënten
BIJWERKINGEN

- Nierfunctiestoornissen bij Zoledroninezuur.

- ONJ (necrose van de kaak) bij beide.
  - Tandarts vooraf.
  - Flucloxacilline en Metronidazol bij tandheelkundige ingrepen.

- Hypocalcicaemia meer bij Denosumab.
CASUS 1
56 jarige man: castratieresistent prostaatcarcinoom

R/ Zoladex en Androcur
CalciChew/D3 1 dd 1 gr/800E

<table>
<thead>
<tr>
<th>Test</th>
<th>Result</th>
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</thead>
<tbody>
<tr>
<td>Creatinine</td>
<td>63 µmol/l</td>
</tr>
<tr>
<td>Calcium</td>
<td>2,15 mmol/l</td>
</tr>
<tr>
<td>AF</td>
<td>1090 U/l</td>
</tr>
<tr>
<td>PSA</td>
<td>814 µg/l</td>
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</tbody>
</table>
Op 3 april 2012 Denosumab 60 mg als osteoporosebehandeling.

11 april 2012 opname: spierkrampen, tintelingen.

<table>
<thead>
<tr>
<th>Test</th>
<th>Resultaat</th>
<th>Normaalmarge</th>
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<tbody>
<tr>
<td>Calcium</td>
<td>1.39</td>
<td>mmol/l</td>
</tr>
<tr>
<td>AF</td>
<td>1815</td>
<td>U/l</td>
</tr>
<tr>
<td>25-OH Vit D</td>
<td>40</td>
<td>nmol/l</td>
</tr>
<tr>
<td>β-Crosslaps</td>
<td>0.490</td>
<td>ng/ml (&lt; 0.700)</td>
</tr>
<tr>
<td>P1NP</td>
<td>920</td>
<td>ng/ml (&lt; 59)</td>
</tr>
</tbody>
</table>
BEHANDELING

- Calciuminfuus 22 gr/dd, 6 gr Calcium oraal en Vitamine D
- Na 37 dagen Calcium genormaliseerd

<table>
<thead>
<tr>
<th></th>
<th>Value 1</th>
<th>Value 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF</td>
<td>1100 U/l</td>
<td>(1090)</td>
</tr>
<tr>
<td>PSA</td>
<td>250 µg/l</td>
<td>(814)</td>
</tr>
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BORSTKANKER
SC Denosumab Compared With IV Zoledronic Acid for the Treatment of Bone Metastases in Patients With Advanced Breast Cancer


Denosumab (120 mg Q4W) is not approved by the EMA for use in patients with advanced cancer to delay SREs. Denosumab is investigational in that setting.
Time to First and Subsequent SREs

IV zoledronic acid 4 mg every 4 weeks (n = 1020)
SC denosumab 120 mg every 4 weeks (n = 1026)

Rate Ratio 0.77 (95% CI: 0.66, 0.89)
P = .001 (superiority)

aAdjusted for multiplicity
Exploratory End Points: Overall Survival and Disease Progression

Overall Survival (proportion)

HR = 0.95 (95% CI, 0.81-1.11)
P = .49

No. at risk
IV zoledronic acid 1020 962 897 834 757 699 515 184 54
SC denosumab 1026 984 916 849 771 690 511 177 57

Proportion Without Disease Progression

HR = 1.00 (95% CI, 0.89-1.11)
P = .93

No. at risk
IV zoledronic acid 1020 962 897 834 757 699 515 184 54
SC denosumab 1026 984 916 849 771 690 511 177 57
CASUS 2

- Vrouw 81 jaar
- Gemetastaseerd mammacarcinoom
- Hormonaal uitbehandeld
- Ernstige osteoporose

- R/ CalciChew/D3 1 gr/800E per dag
- Risedroninezuur 35 mg per week
<table>
<thead>
<tr>
<th>Test</th>
<th>Value</th>
<th>Unit</th>
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<tr>
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<td>mmol/l</td>
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<tr>
<td>AF</td>
<td>695</td>
<td>U/l</td>
</tr>
<tr>
<td>β-Crosslaps</td>
<td>2280</td>
<td>ng/ml</td>
</tr>
<tr>
<td>P1NP</td>
<td>952</td>
<td>ng/ml</td>
</tr>
</tbody>
</table>
Risedroninezuur stop

Zoledroninezuur 5 mg iv
OPNAME HYPOCALCIAEMIE

- Calcium 1,41 mmol/l
- Alkalische fosfatase 342 U/l
Randomized, Double-Blind, Study of Denosumab vs Zoledronic Acid in the Treatment of Bone Metastases in Patients With Advanced Cancer (Excluding Breast and Prostate Cancer) or Multiple Myeloma


Denosumab 120 mg, Q4W is currently only authorised for marketing in the United States.
Het voorkomen / uitstellen van (bot) metastasen.
RADIO-ISOTOPEN
RADIUM-223
What is Radium-223?

- An alkaline earth metal
- A natural bone seeker\(^1\) because it is a ‘calcium mimetic’\(^2\)
- An emitter of radioactive \(\alpha\)-particles
  - Optimal for a radiopharmaceutical\(^3\)
  - Has a half-life of 11.4 days\(^3\)
- Has a strong tumor-cell killing effect\(^1\)
- \(\alpha\)-particles have a short track length (2–10 cell diameters)\(^4\)
  - Hence, damage to surrounding healthy tissue is minimized\(^3\)
- Comes as a solution of radium-223 dichloride (\(^{223}\)RaCl\(_2\))

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Radium-223 Has Preferential Uptake in Areas of New Bone Formation

Microautoradiography from a dog injected with radium-223: Distribution of α-particle tracks in normal spongious bone and an osteoblastic zone

Bone Metastases in Patients with Prostate Cancer

Underlying mechanisms
Factors are released by tumor cells that stimulate both osteoclast and osteoblast activity.

Excessive new bone formation occurs around tumor cell deposits, resulting in low bone strength and potential vertebral collapse.

Osteoclastic and osteoblastic activity releases growth factors that stimulate tumor cell growth, perpetuating the cycle of bone resorption and abnormal bone growth.

Bone biomarkers outlined are elevated.

ALP, alkaline phosphatase; BMP, bone morphogenetic protein; CTXI, cross-linked C-terminal telopeptides of type I collagen; ET-1, endothelin-1; FGF, fibroblast growth factor; GF, growth factor; ICTP, C-terminal telopeptides of type I collagen; IGF, insulin-like growth factor; IL-6, interleukin-6; PINP, amino-terminal procollagen propeptides of type I collagen; PTHrP, parathyroid hormone-related protein; TGF-β, transforming growth factor β; uPA, urokinase plasminogen activator.

Radium-223 Has a Targeted Mechanism of Action

Targets new bone, e.g. bone metastases

Irradiates adjacent tumor cells leading to highly localized tumor cell killing

**ALSYMPCA Trial Design**

**TREATMENT PHASE**
6 injections at 4-week intervals

- **R**: Radium-223 dichloride* 50 kBq/kg
- **R 2:1**: Saline* (placebo)

**FOLLOW-UP PHASE**

- **Stratification factors**
  - Total ALP < 220 U/L versus ≥ 220 U/L
  - Bisphosphonate use (Yes versus No)
  - Prior docetaxel (Yes versus No)

*Plus best standard of care.

Assessments

- **Month**
  - M0
  - M6
  - M8
  - M10
  - M12
  - M16
  - M20
  - M24
  - M28
  - M32
  - M36


ALSYMPCA Updated Analysis Time To First SRE*

<table>
<thead>
<tr>
<th>Month</th>
<th>Radium-223 dichloride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>614</td>
<td>307</td>
</tr>
<tr>
<td>3</td>
<td>487</td>
<td>207</td>
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<tr>
<td>6</td>
<td>332</td>
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<td>1</td>
</tr>
<tr>
<td>30</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median OS (months) Radium-223 dichloride: 12.2, Placebo: 6.7
Hazard ratio: 0.64
95% CI: 0.52–0.78
P < 0.0001

ALSYMPCA: Radium-223 Dichloride Significantly Improved Overall Survival

<table>
<thead>
<tr>
<th>Month</th>
<th>Radium-223 dichloride</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>614</td>
<td>307</td>
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<td>0</td>
<td>1</td>
</tr>
<tr>
<td>39</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Median OS (months) | Radium-223 dichloride 14.9 | Placebo 11.3
Hazard ratio | 0.695
95% CI | 0.581–0.832
P | < 0.0001

## ALSYMPCA: Grade 3/4 AEs Were Lower with Radium-223 Dichloride Than Placebo

### Patients with adverse events (AEs), n (%)

<table>
<thead>
<tr>
<th></th>
<th>Radium-223 dichloride (n = 600)</th>
<th>Placebo (n = 301)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All AEs</td>
<td>558 (93)</td>
<td>290 (96)</td>
</tr>
<tr>
<td>Grade 3 or 4 AEs</td>
<td>349 (58)</td>
<td>197 (66)</td>
</tr>
<tr>
<td>Serious AEs (SAEs)</td>
<td>281 (47)</td>
<td>181 (60)</td>
</tr>
<tr>
<td>Discontinuation due to AEs</td>
<td>99 (17)</td>
<td>62 (21)</td>
</tr>
<tr>
<td>Deaths due to AEs</td>
<td>96 (16)</td>
<td>67 (23)</td>
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## ALSYMPCA: Adverse Events of Interest

### Patients with adverse events (AEs), n (%)

<table>
<thead>
<tr>
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<th>All Grades</th>
<th>Grades 3 or 4</th>
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<td>Radium-223 dichloride (n = 600)</td>
<td>Placebo (n = 301)</td>
</tr>
<tr>
<td><strong>Hematologic</strong></td>
<td></td>
<td></td>
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<tr>
<td>Anemia</td>
<td>187 (31.2)</td>
<td>92 (31)</td>
</tr>
<tr>
<td>Neutropenia</td>
<td>30 (5)</td>
<td>3 (1)</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>69 (11.5)</td>
<td>17 (5.6)</td>
</tr>
<tr>
<td><strong>Non-hematologic</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bone pain</td>
<td>300 (50)</td>
<td>187 (62)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>151 (25)</td>
<td>45 (15)</td>
</tr>
<tr>
<td>Nausea</td>
<td>213 (35.5)</td>
<td>104 (35)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>111 (18.5)</td>
<td>41 (14)</td>
</tr>
<tr>
<td>Constipation</td>
<td>108 (18)</td>
<td>64 (21)</td>
</tr>
</tbody>
</table>

TOEKOMST
1. Mechanotransduction
2. Sclerostin production: bone formation ↓
3. FGF-23 production: renal P reabsorption ↓