ALBUMINURIA as a TARGET for TREATMENT

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Michel Marre : conflicts of interest

<table>
<thead>
<tr>
<th>Pharmas</th>
<th>boards</th>
<th>lectures</th>
<th>scient. supports</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abbott</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>Lilly</td>
<td>no</td>
<td>yes</td>
<td>no</td>
</tr>
<tr>
<td>MSD</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Novartis</td>
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<td>no</td>
<td>yes</td>
</tr>
<tr>
<td>Novo-N</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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<tr>
<td>Sanofi</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
</tr>
<tr>
<td>Servier</td>
<td>yes</td>
<td>yes</td>
<td>yes</td>
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</tbody>
</table>
ALBUMINURIA? A target for what?

- To allocate a patient to a treatment strategy
- To predict treatment efficacy
Bijective relationship between High Blood Pressure and High Urinary Albumin

- **KIDNEY CULPRIT:**
  - A glomerular disease, signaled by high urinary albumin, provokes high blood pressure
  - **Type 1 Diabetes**

- **KIDNEY VICTIM:**
  - Essential hypertension affects target organs:
    - ->Heart: LVH
    - ->Kidney: UAE
  - Often associated with **Type 2 diabetes**
Systolic Blood Pressure (mm Hg)

Urinary Albumin Excretion (mg/24 h)

IDDM hypertension

Systolic Blood Pressure (mm Hg)
Albuminuria as a marker of a generalized exsudation phenomenon


Prognostic Value of Micro/Macroalbuminurinuria

- Kidney Failure
- Heart Failure
- CHD
- Stroke

Premature Death (CV and Cancer)
ALBUMINURIA to allocate a patient to a Treatment Strategy:

- *Primary vs secondary preventions*
- **Tools:** intensified blood glucose/pressure treatments
- **Diabetes:** type 1/ type 2

- $=>2 \times 2 \times 2 = 8 \text{ options}$
Primary Prevention: to prevent Micro/Macro and their predicted outcomes

- Intensified *blood glucose* strategy:
- *Type 1 diabetes*:
  - Preventing μ/Malbuminuria: YES (DCCT)
  - Preventing Kidney Failure: YES (DCCT/EDIC)
  - CV outcomes: YES (DCCT/EDIC)
- Preventing Death (wait for DCCT/EDIC study end)
DCCT primary prevention
Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes

Primary Prevention: to prevent Micro/Macro and their predicted outcomes

- Intensified *blood glucose* strategy:
- Type 2 diabetes:
- Preventing μ/M: YES (UKPDS)
- Preventing Kidney Failure: YES (ADVANCE)
- CV outcomes: YES (UKPDS follow-up)
- DEATH: YES (UKPDS follow-up)
UKPDS: Microalbuminuria onset

Urine albumin >50 mg/L

<table>
<thead>
<tr>
<th>Time (years)</th>
<th>Relative Risk (RR)</th>
<th>p</th>
<th>99% CI</th>
</tr>
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<tbody>
<tr>
<td>Baseline</td>
<td>0.89</td>
<td>0.24</td>
<td></td>
</tr>
<tr>
<td>Three years</td>
<td>0.83</td>
<td>0.043</td>
<td></td>
</tr>
<tr>
<td>Six years</td>
<td>0.88</td>
<td>0.13</td>
<td></td>
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<tr>
<td>Nine years</td>
<td>0.76</td>
<td>0.00062</td>
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<tr>
<td>Twelve years</td>
<td>0.67</td>
<td>0.000054</td>
<td></td>
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<tr>
<td>Fifteen years</td>
<td>0.70</td>
<td>0.033</td>
<td></td>
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</table>

Favours intensive vs. conventional
## Summary of major outcomes

<table>
<thead>
<tr>
<th>Event</th>
<th>Number of events</th>
<th>Hazard ratio</th>
<th>95% CI</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>ESKD</td>
<td>27</td>
<td>0.35</td>
<td>(0.15 - 0.83)</td>
<td>0.0167</td>
</tr>
<tr>
<td>Renal death</td>
<td>37</td>
<td>0.85</td>
<td>(0.45 - 1.63)</td>
<td>0.6250</td>
</tr>
<tr>
<td>ESKD or renal death</td>
<td>59</td>
<td>0.64</td>
<td>(0.38 - 1.08)</td>
<td>0.0930</td>
</tr>
<tr>
<td>Doubling to &gt; 200</td>
<td>129</td>
<td>1.15</td>
<td>(0.82 - 1.63)</td>
<td>0.4207</td>
</tr>
<tr>
<td>Sustained doubling &gt; 200</td>
<td>84</td>
<td>0.83</td>
<td>(0.54 - 1.27)</td>
<td>0.3859</td>
</tr>
<tr>
<td>All sustained doubling</td>
<td>220</td>
<td>0.80</td>
<td>(0.61 - 1.04)</td>
<td>0.0965</td>
</tr>
</tbody>
</table>

Doubling of creatinine: 45 reversed
84 sustained
Primary Prevention: to prevent Micro/Macro and their predicted outcomes

- Intensified \textit{blood pressure} strategy:
- \textit{-type 1 diabetes:}
- Preventing µ/M: NO (RAS Study)
- Preventing \textbf{Kidney Failure}: not shown
- \textbf{CV outcomes}: not shown
- \textbf{DEATH}: not shown
Primary Prevention: to prevent Micro/Macro and their predicted outcomes

- Intensified **blood pressure** strategy:
- **-type 2 diabetes:**
- Preventing μ/M: YES (UKPDS)
- Preventing **Kidney Failure:** ?
- CV outcomes: YES (HOPE)
- **DEATH:** YES
Secondary Prevention: to prevent the outcomes predicted by Micro/Macro

- Intensified *blood glucose* strategy:
- *type 1 diabetes:*
- Preventing *Kidney Failure: not clear* (DCCT/EDIC)
- *CV outcomes: YES* (DCCT/EDIC)
- *DEATH: wait...*
Figure 4. Cumulative incidence of long-term renal outcomes after the development of persistent microalbuminuria (time 0) among 325 participants in the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications study by Diabetes Control and Complications Trial treatment assignment. A, Regression to normoalbuminuria. B, Progression to macroalbuminuria. C, Impaired glomerular filtration rate (GFR). D, End-stage renal disease (ESRD).
Secondary Prevention: to prevent the outcomes predicted by Micro/Macro

- Intensified *blood glucose* strategy:
  - *type 2 diabetes*:
    - Preventing **Kidney Failure**: YES (ADVANCE)
    - **CV outcomes**: NO (ADVANCE)
    - **DEATH**: YES (UKPDS follow-up)
Secondary Prevention: to prevent the outcomes predicted by Micro/Macro

- Intensified *blood pressure* strategy:
- *-type 1 diabetes:*
- Preventing *Kidney Failure*: YES (Lewis et al, NEJM, 1993)
- **CV outcomes**: not shown (DCCT/EDIC)
- **DEATH**: no
Secondary Prevention: to prevent the outcomes predicted by Micro/Macro

- Intensified *blood pressure* strategy:
- *type 2 diabetes*:
- Preventing **Kidney Failure**: YES (Lewis et al, Brenner et al, 2001, ADVANCE)
- **CV outcomes**: YES (UKPDS, ADVANCE)
- **DEATH**: YES (UKPDS, ADVANCE)
Toshiharu Ninomiya et al.

Albuminuria and Kidney Function Independently Predict Cardiovascular and Renal Outcomes in Diabetes

JASN 20: 1813-1821, 2009
ALBUMINURIA as a target for treatment efficacy

• *Does alteration in a surrogate marker alter the final outcome?*
  - the matter of the dose

• *the matter of the outcome*
ALBUMINURIA as a target for treatment efficacy
-the matter of the dose

• In type 1 diabetes patients with persistent microalbuminuria, very small doses (1.25 mg/d) of ramipril reduced µalb as did usual (5 mg/d) doses (Marre et al, J Cardiovas Pharmacol, 1990, ATLANTIS study, Diabetes Care, 1992)
ALBUMINURIA as a target for treatment efficacy -the matter of the dose

• In type 2 diabetes patients with persistent microalbuminuria and hypertension, high doses (300 mg/d) of irbesartan reduced Malb better than lower (150 mg/d) doses (Parving et al, NEJM, 2001)
EFFECT OF IRBESARTAN ON THE DEVELOPMENT OF DIABETIC NEPHROPATHY IN PATIENTS WITH TYPE 2 DIABETES

No. at Risk
Placebo: 201, 201, 164, 154, 139, 129, 36
150 mg of irbesartan: 195, 195, 167, 161, 148, 142, 45
300 mg of irbesartan: 194, 194, 180, 172, 159, 150, 49
In patients with proteinuria, does reducing albuminuria with high doses make risk?

• The matter of renal autoregulation:
  • Kept safe in type 1 diabetic patients with µalb (Mathiesen E et al, Diabetologia, 1990)

• In those with proteinuria, short term vs long term (Björk et al, BMJ, 1992)…
Renal protective effect of enalapril in diabetic nephropathy
Björk S et al, BMJ, 1992
Advice to clinicians:

- In patients with proteinuria and reduced GFR, look at serum potassium, rather than creatinine, on the short term, when doses of renin blockers are increased.
Rapid response to treatment predicts final renal outcome
Initial angiotensin receptor blockade-induced decrease in albuminuria is associated with long-term renal outcome in type 2 diabetic patients with microalbuminuria.

Hellemons ME et al. Diabetes Care 2011, 34, 2078-83
Risk of CV death by albuminuria at baseline and achieved during follow-up in ADVANCE

At baseline

- Hazard ratio (95% CI)
- Baseline UACR (µg/mg)
- p for trend <0.0001*

During follow-up

- Hazard ratio (95% CI)
- Achieved UACR (µg/mg)
- p for trend <0.0001*

*Adjusted for age, sex, HbA1c, serum lipids, BMI, smoking, alcohol use, and study drug
ALBUMINURIA as a target for treatment efficacy: the matter of the outcome

- **Renal outcomes vs CV outcomes:**
  - In the DIABHYCAR study, $\mu$/M was reduced by small (1.25 mg/d) doses ramipril, but CV outcomes were not (Marre M et al, BMJ, 2004)
  - In the micro-HOPE study, $\mu$/M was reduced similarly by high (10 mg/d) doses ramipril, and CV outcomes were too (Gerstein H et al, Lancet, 2001)
Left ventricular mass regression (SECURE)
732 randomised patients. Follow-up: 1.5-2.2 years

- Placebo: 8.21%
- Ramipril 2.5mg: 7.86%
- Ramipril 10mg: -3.53%

Ramipril 2.5mg: no effect on left ventricular mass; no effect on atherosclerosis progression
Albuminuria as a target for treatment in patients with diabetes:

- Primary prevention of μ/M albuminuria is a valuable target for strict blood glucose and pressure controls and their final (renal and CV) outcomes
- Secondary interventions (strict blood glucose and pressure controls) on μ/M albuminuria are valuable for their final (renal and CV) outcomes
- Changes in μ/M albuminuria as responses to treatment are useful tools
- The lower the blood glucose and pressure (and the highest the renin blockers doses), the best it is for the final renal (and CV) outcomes