Statins and breast cancer survival: evidence and opportunities

“The Origin of the Statins”

One drug, many effects?

Breast cancer incidence

recurrence

MASTER trial

Thomas Ahern, PhD, MPH
The Origin of the Statins

The origin of the statins

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Abstract. In the early 1970s, we isolated the first statin, mevastatin (formerly called compactin or ML-236B), from Penicillium citrinum, as a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-controlling enzyme in cholesterol synthetic pathway. By the end of the 1970s, we had demonstrated that mevastatin was highly effective in lowering serum total and low-density lipoprotein (LDL) cholesterol in both experimental animals and patients with primary hypercholesterolemia. The discovery of mevastatin paved the way for the worldwide development of its analogues (statins), and since then several statins—lovastatin, simvastatin, pravastatin, fluvastatin and atorvastatin—have been approved in many countries and are currently used by millions of patients. © 2004 Elsevier B.V. All rights reserved.

Keywords: Cholesterol; HMG-CoA reductase inhibitors; Statins; Mevastatin; Lovastatin

- Hypercholesterolemia → heart disease
- Cholesterol: diet & biosynthesis
- HMG-CoA reductase
- Screened fungi for natural inhibitors
- ML-236B from *P. citrinum* → mevastatin
Millions of adults over 40

Statin use in the United States

1999: 10
2003: 20
2013: 40

~28% of adults over 40
One drug, many effects?

HMG-CoA → Mevalonate → Farnesyl-PP → Geranylgeranyl-PP

- HMG-CoA reductase
- Farnesyl-PP
- Geranylgeranyl-PP
- RhoA, Rac1, Cdc42

Effects:
- Improved endothelial function
- Vascular plaque stabilization
- Lower oxidative stress
- Reduced inflammation
- Reduced thrombosis
- Anti-neoplasia

Cholesterol
One drug, many effects?

<table>
<thead>
<tr>
<th>Drug</th>
<th>logP</th>
<th>Pleiotropic potential</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lovastatin</td>
<td>4.3</td>
<td>12.5 ⭐</td>
</tr>
<tr>
<td>Pravastatin</td>
<td>-0.2</td>
<td>7.2</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>4.7</td>
<td>12.7 ⭐</td>
</tr>
<tr>
<td>Atorvastatin</td>
<td>4.1</td>
<td>12.2 ⭐</td>
</tr>
<tr>
<td>Cerivastatin</td>
<td>1.5</td>
<td>9.5</td>
</tr>
<tr>
<td>Fluvastatin</td>
<td>3.2</td>
<td>10.8</td>
</tr>
<tr>
<td>Pitavastatin</td>
<td>1.5</td>
<td>9.7</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>-0.3</td>
<td>8.0</td>
</tr>
</tbody>
</table>

Lipophilic drugs

- Not confined to the liver
- Interact with extrahepatic systems
Anticancer mechanisms

- Systemic cholesterol reduction (27-OH-cholesterol)
- Enhanced immune surveillance
- Blocked tumor HMG-CoA-reductase
- Interrupted oncogenic signaling
Breast cancer incidence

- Highly heterogeneous results
- Meta-analyses are null

Efficacy and safety of more intensive lowering of LDL cholesterol: a meta-analysis of data from 170,000 participants in 26 randomised trials

*Cholesterol Treatment Trialists’ (CTT) Collaboration*

Statin vs. control
Breast cancer IRR=1.04, 95% CI: 0.80, 1.34
Breast cancer recurrence

Danish nationwide cohort study

• All stage I-III invasive breast carcinomas, 1996-2003
• 10 years of recurrence follow-up
• National prescription data
• Cox regression of time-to-recurrence
  • time-varying drug exposures (yearly update)
  • 1-year lag period
  • adjusted for prognostic factors
  • isolated lipophilic/hydrophilic statin exposure

Aarhus, Denmark
Breast cancer recurrence

2,993 recurrences among 18,769 women

11 fewer recurrences per 100 patients over 10 years
Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis

Sashidhar Manthravadi¹, Anuj Shrestha² and Sheshadri Madhusudhana²

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
<th>Hazard Ratio IV, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeichner</td>
<td>1.42 [0.42, 4.81]</td>
<td></td>
</tr>
<tr>
<td>Cescareanu</td>
<td>0.27 [0.10, 0.73]</td>
<td></td>
</tr>
<tr>
<td>Sendur</td>
<td>0.38 [0.19, 0.80]</td>
<td></td>
</tr>
<tr>
<td>Chavez-Mac Gregor</td>
<td>0.50 [0.27, 0.91]</td>
<td></td>
</tr>
<tr>
<td>Kwan</td>
<td>0.67 [0.39, 1.13]</td>
<td></td>
</tr>
<tr>
<td>Chae</td>
<td>0.40 [0.24, 0.67]</td>
<td></td>
</tr>
<tr>
<td>Brewer</td>
<td>0.63 [0.42, 0.98]</td>
<td></td>
</tr>
<tr>
<td>Nickels</td>
<td>0.84 [0.57, 1.26]</td>
<td></td>
</tr>
<tr>
<td>Boudreau</td>
<td>0.78 [0.58, 1.08]</td>
<td></td>
</tr>
<tr>
<td>Ahern</td>
<td>0.80 [0.64, 1.00]</td>
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</tbody>
</table>

Summary RR=0.64, 95% CI: 0.53, 0.79
Statins and breast cancer prognosis: evidence and opportunities

Thomas P Ahern, Timothy L Lash, Per Damkier, Peer M Christiansen, Deirdre P Cronin-Fenton

• Preclinical evidence
• Epidemiologic evidence
• Why further study won’t move the needle
• Solutions to trial design challenges

Dr. Signe Borgquist
Lund University
Breast cancer recurrence

Cholesterol, Cholesterol-Lowering Medication Use, and Breast Cancer Outcome in the BIG 1-98 Study


Aromatase inhibitors induce hypercholesterolemia → Increased 27-hydroxy-cholesterol → Attenuation of therapeutic effect?
Breast cancer recurrence

- CLM-naïve patients → Tam/Let

- Marginal structural Cox models

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Disease-free survival</td>
<td>0.79 ( (0.66, 0.95) )</td>
</tr>
<tr>
<td>Breast cancer-free interval</td>
<td>0.76 ( (0.60, 0.97) )</td>
</tr>
<tr>
<td>Distant recurrence-free interval</td>
<td>0.74 ( (0.56, 0.97) )</td>
</tr>
</tbody>
</table>
The MASTER Trial

- **MAmmary cancer STatin ER-positive**
- Danish Breast Cancer Group
- Randomized, double-blind, placebo-controlled
- Atorvastatin, 80 mg/day for 2 years
- Neoadjuvant/Adjuvant settings
Neo-adjuvant setting

DBCG Danish Breast Cancer Group

Randomize

Atorvastatin 80 mg/d

Placebo

Neo-adjuvant chemotherapy

- Epirubicin 90 mg/m²
- TX 600 mg/m²
- Paclitaxel 100 mg/m²

Endocrine therapy

- Postmenopausal: Letrozole 2.5 mg/d
- Premenopausal: Tamoxifen 20 mg/d

RT Radiotherapy according to DBCG guidelines
Adjuvant setting

DBCG
Danish Breast Cancer Group

Primary surgery

Randomize

Adjuvant chemotherapy
- Epirubicin 90 mg/m²
- TX 600 mg/m²

Endocrine therapy
- Postmenopausal: Letrozole 2.5 mg/d
- Premenopausal: Tamoxifen 20 mg/d

Atorvastatin 80 mg/d

Placebo

Endocrine therapy

RT
Radiotherapy according to DBCG guidelines
Adjuvant (delayed) setting

- **Diagnosis**
  - Endocrine therapy
  - Radiotherapy
  - Surgery
  - Chemotherapy

- **0 - 3 years**
  - Endocrine therapy
    - Postmenopausal: Letrozole 2.5 mg/d
    - Premenopausal: Tamoxifen 20 mg/d

- **0 - 2.5 years**
  - Letrozole or tamoxifen

- **2 years atorvastatin**
  - Endocrine therapy
  - Placebo

- **Randomize**

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**RT**
Radiotherapy according to DBCG guidelines
Extensions

• ER-negative breast cancer
• Black women
• Developing countries
• Extended treatment duration
• Predictive biomarkers
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