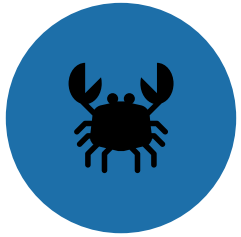
Statins and breast cancer survival: evidence and opportunities

"The Origin of the Statins"

One drug, many effects?



Breast cancer *incidence*

The University of Vermont
LARNER COLLEGE OF MEDICINE

recurrence MASTER trial

Thomas Ahern, PhD, MPH

The Origin of the Statins

The origin of the statins

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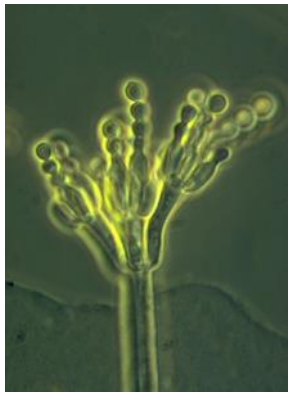
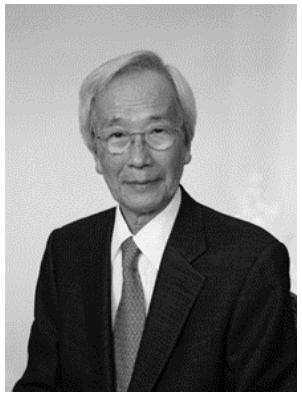
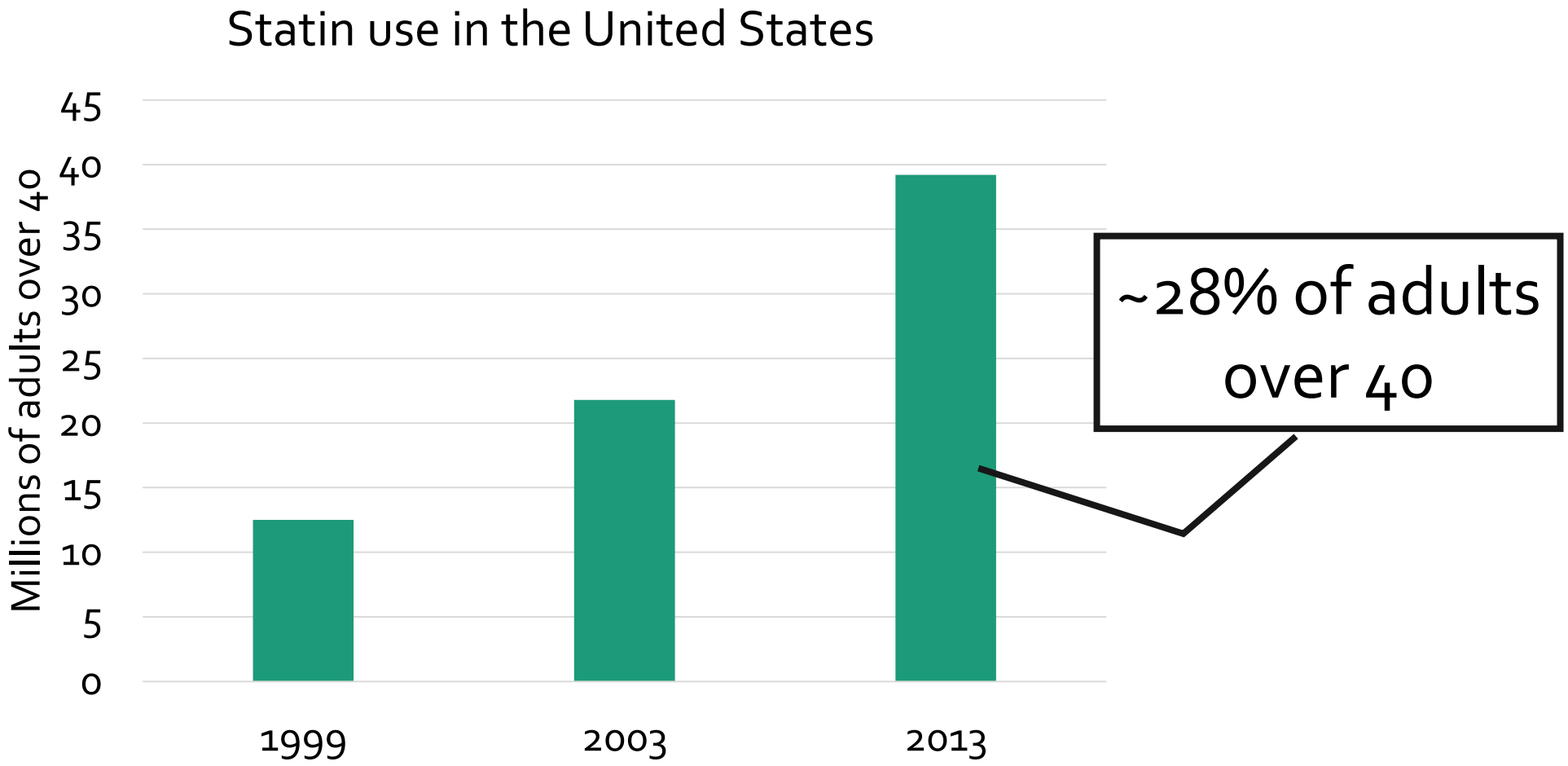
Abstract. In the early 1970s we isolated the first statin, mevastatin (formerly called compactin or ML-236B), from *Penicillium citrinum*, as a potent inhibitor of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase, the rate-controlling enzyme in cholesterol synthetic pathway. By the end of the 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

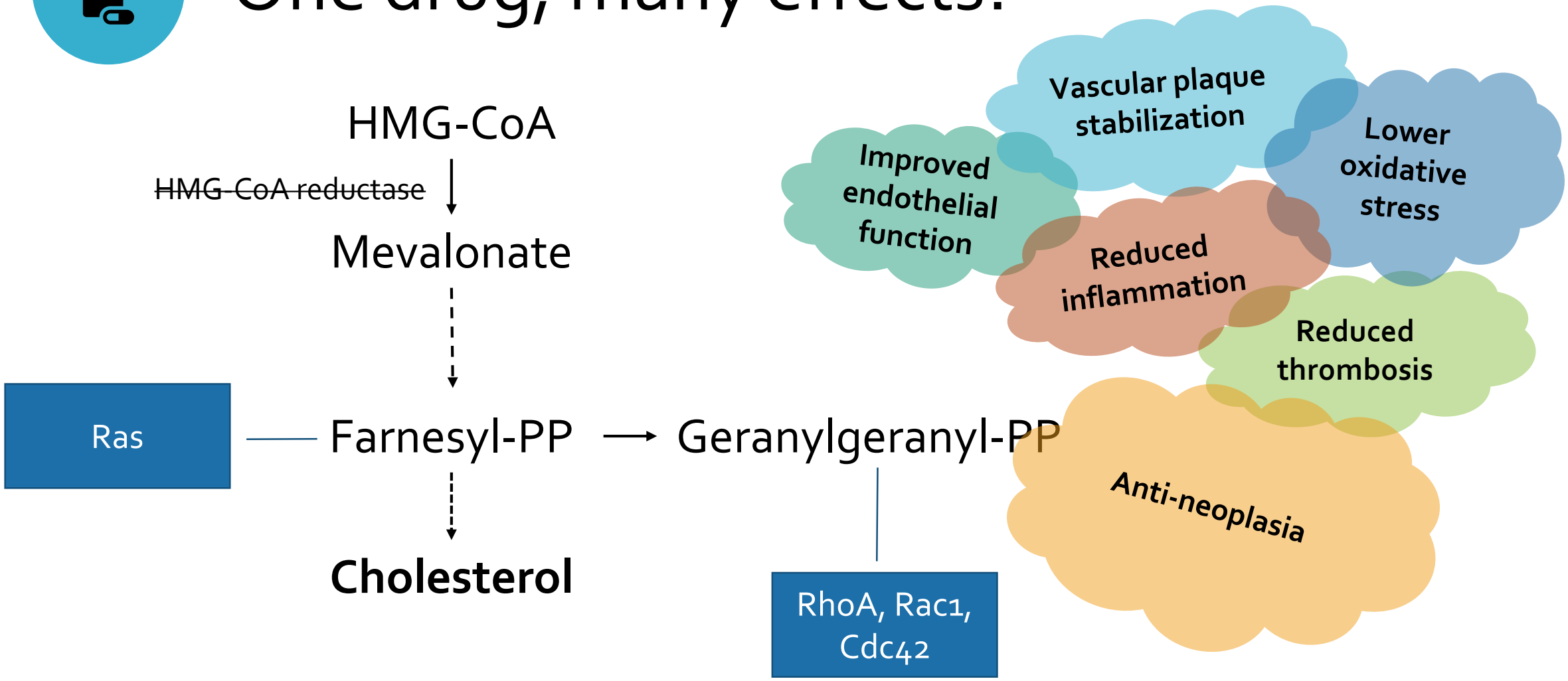




- Hypercholesterolemia → heart disease
- Cholesterol: diet & biosynthesis
- HMG-CoA reductase
- Screened fungi for natural inhibitors
- ML-236B from *P. citrinum* → mevastatin


Statin use in the United States
Millions of adults over 40
45
40
35
30
25
20
15
10
5
0
1999
2003
2013
~28% of adults over 40

One drug, many effects?



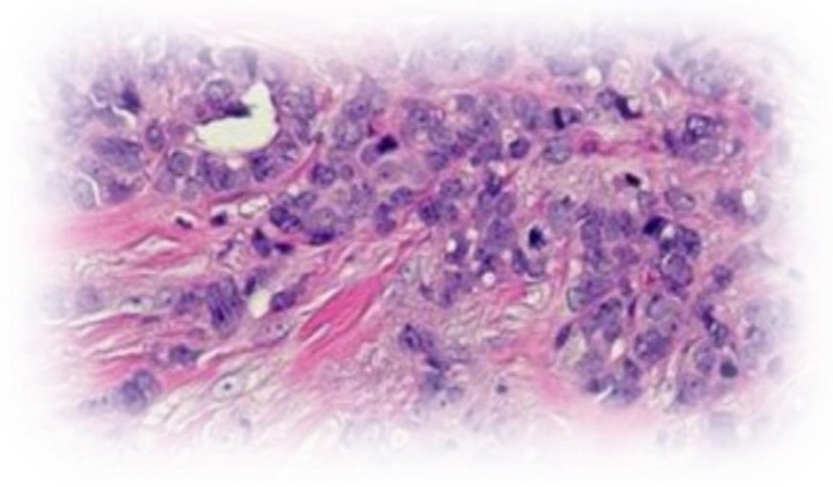
One drug, many effects?

	Drug	logP	Pleiotropic potential
Natural	Lovastatin	4.3	12.5 ★
	Pravastatin	-0.2	7.2
	Simvastatin	4.7	12.7 ★
Synthetic	Atorvastatin	4.1	12.2 ★
	~~Cerivastatin~~	1.5	9.5
	Fluvastatin	3.2	10.8
	Pitavastatin	1.5	9.7
	Rosuvastatin	-0.3	8.0

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

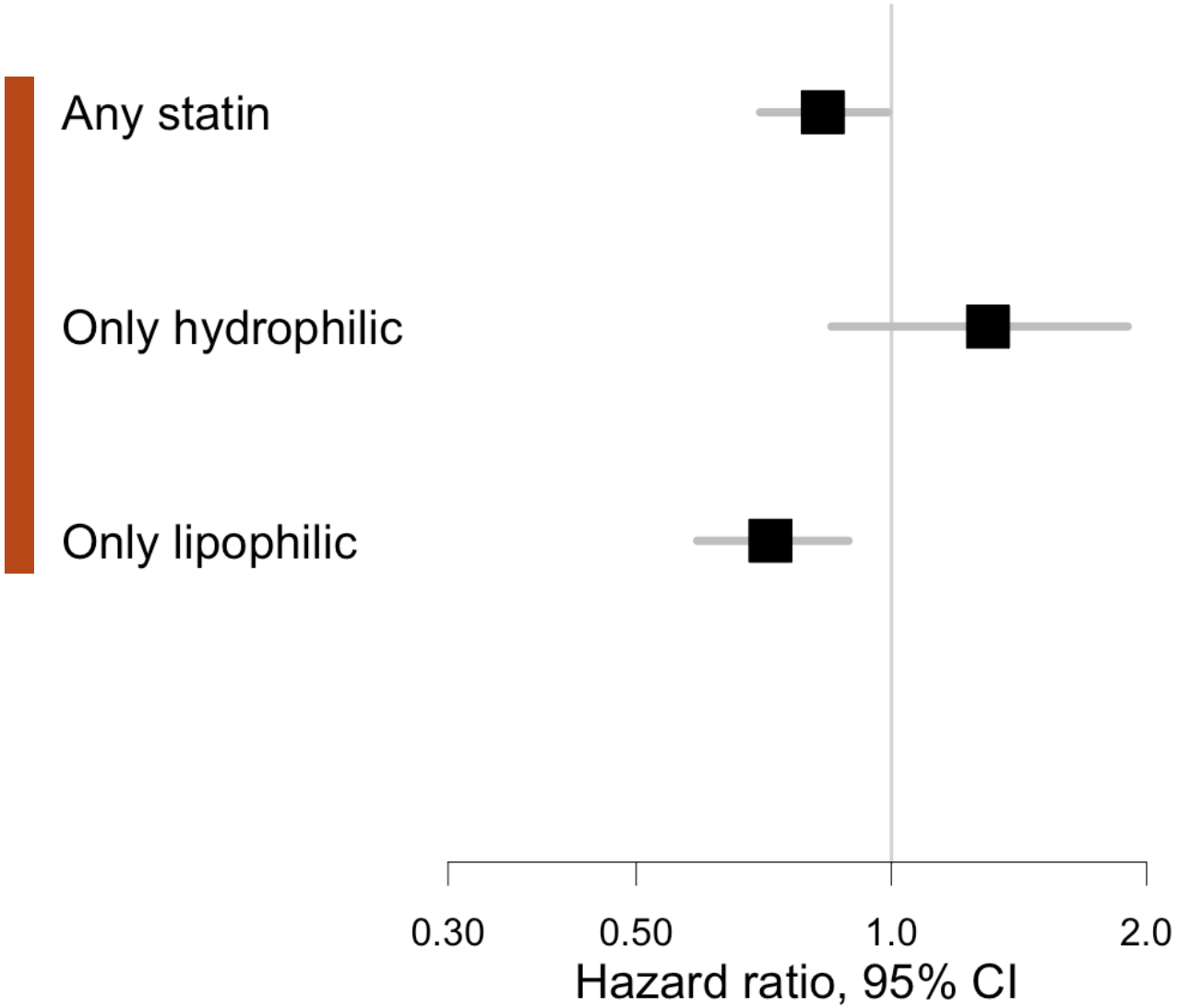
- All stage I-III invasive breast carcinomas, 1996-2003
- 10 years of recurrence follow-up
- National prescription data
- Cox regression of time-to-recurrence
  - time-varying drug exposures (yearly update)
  - 1-year lag period
  - adjusted for prognostic factors
  - isolated lipophilic/hydrophilic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

Aarhus, Denmark

Breast cancer recurrence

2,993 recurrences
among 18,769 women

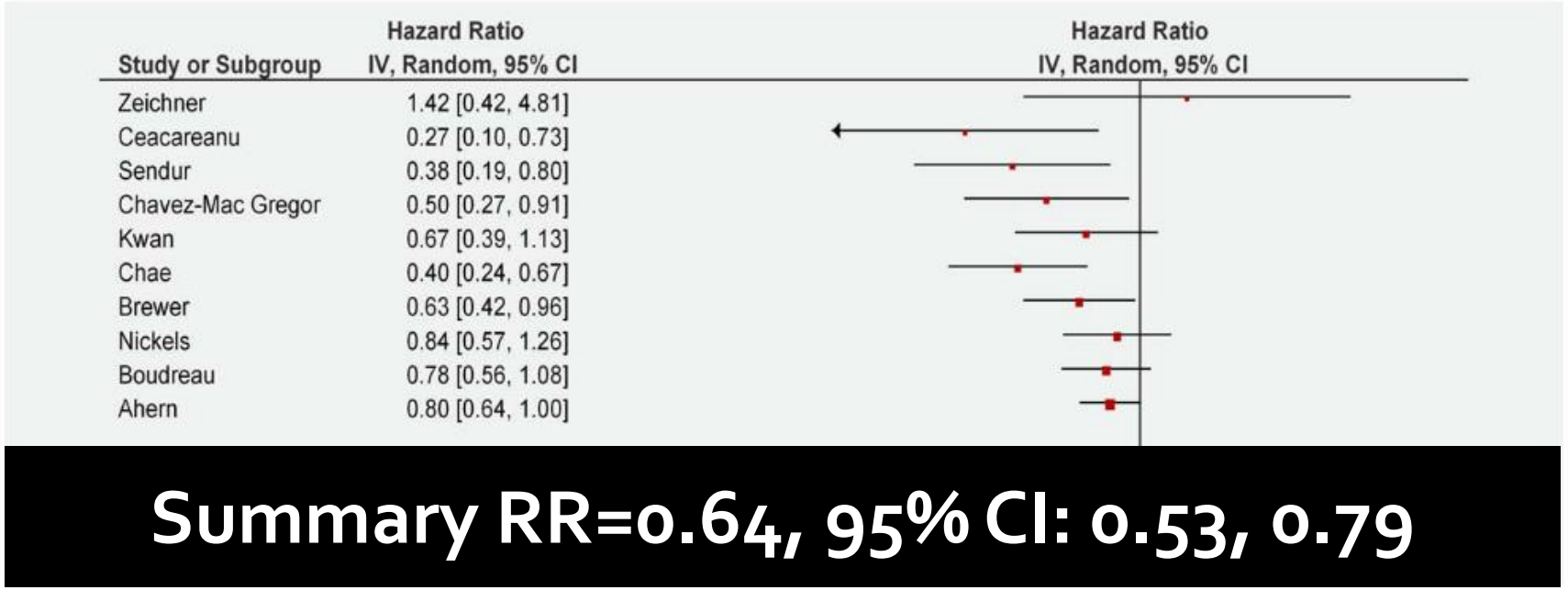
11 fewer recurrences
per 100 patients
over 10 years



Breast cancer recurrence

Impact of statin use on cancer recurrence and mortality in breast cancer: A systematic review and meta-analysis

Sashidhar Manthravadi[1], Anuj Shrestha[2] and Sheshadri Madhusudhana[2]



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

Signe Borgquist, Anita Giobbie-Hurder, Thomas P. Ahern, Judy E. Garber, Marco Colleoni, István Láng, Marc Debled, Bent Ejlertsen, Roger von Moos, Ian Smith, Alan S. Coates, Aron Goldhirsch, Manuela Rabaglio, Karen N. Price, Richard D. Gelber, Meredith M. Regan, and Beat Thürlimann

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

Breast cancer recurrence

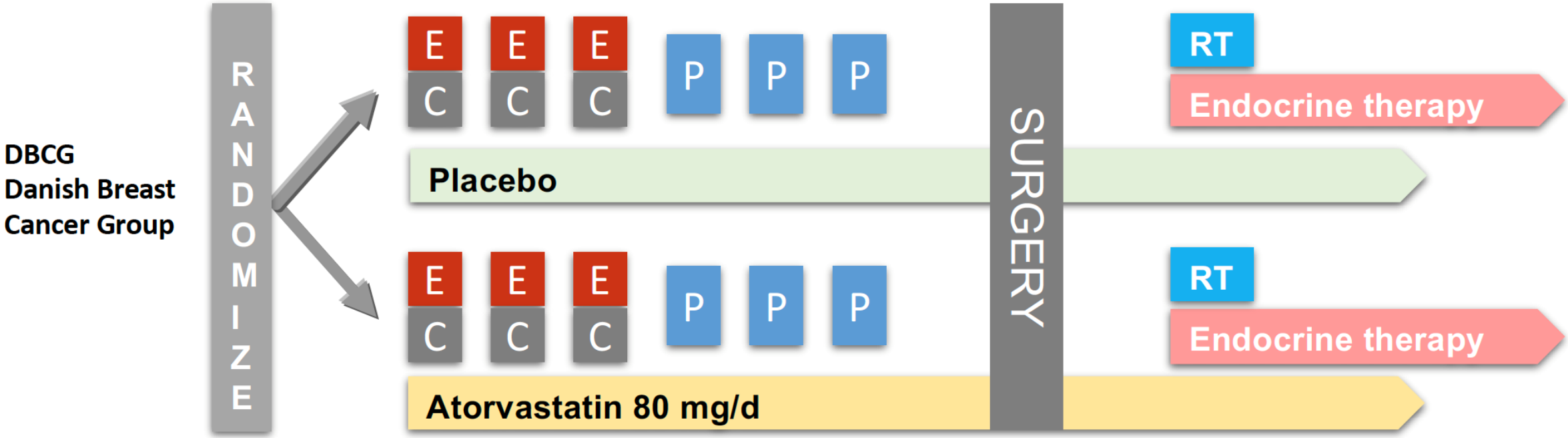
- CLM-naïve patients → Tam/Let
- Marginal structural Cox models

Endpoint	HR (95% CI)
Disease-free survival	0.79 (0.66, 0.95)
Breast cancer-free interval	0.76 (0.60, 0.97)
Distant recurrence-free interval	0.74 (0.56, 0.97)

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



Neo-adjuvant chemotherapy

E pirubicin 90 mg/m^2
C TX 600 mg/m^2
P aclitaxel 100 mg/m^2

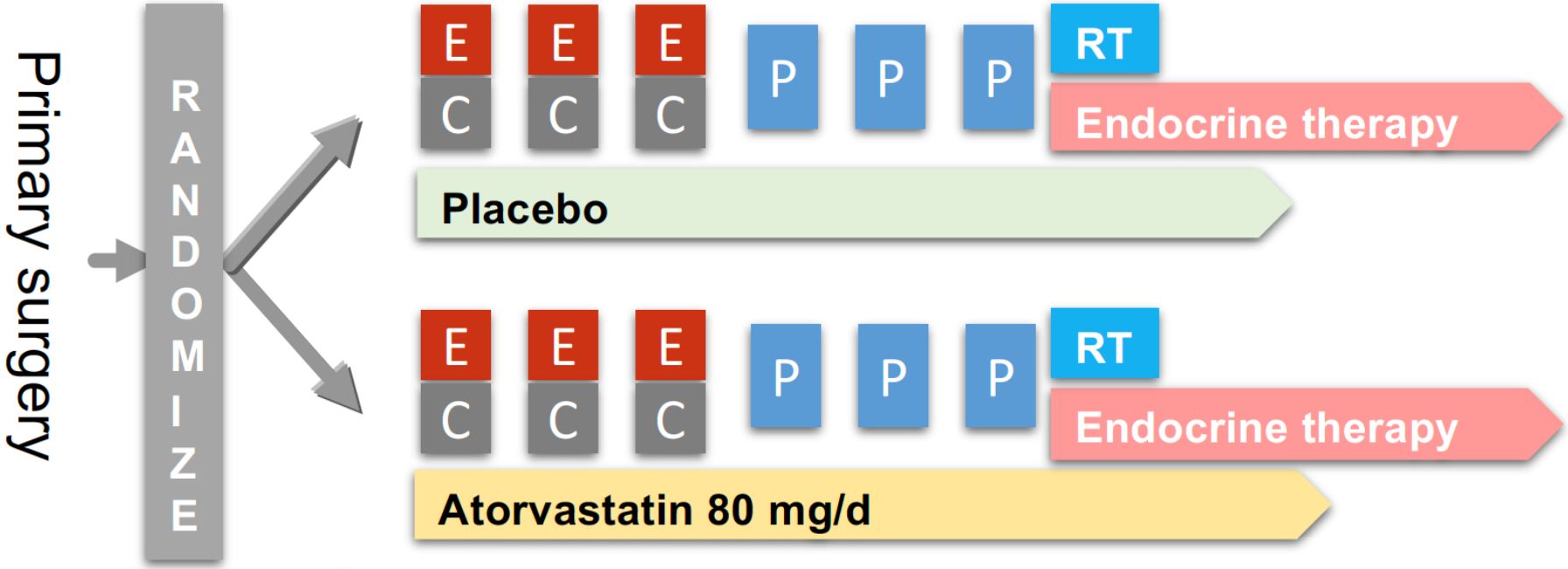
Endocrine therapy

L Postmenopausal: Letrozole 2,5 mg/d
T Premenopausal: Tamoxifen 20 mg/d

RT
Radiotherapy according to DBCG guidelines

Adjuvant setting

DBCG
Danish Breast
Cancer Group



Adjuvant chemotherapy

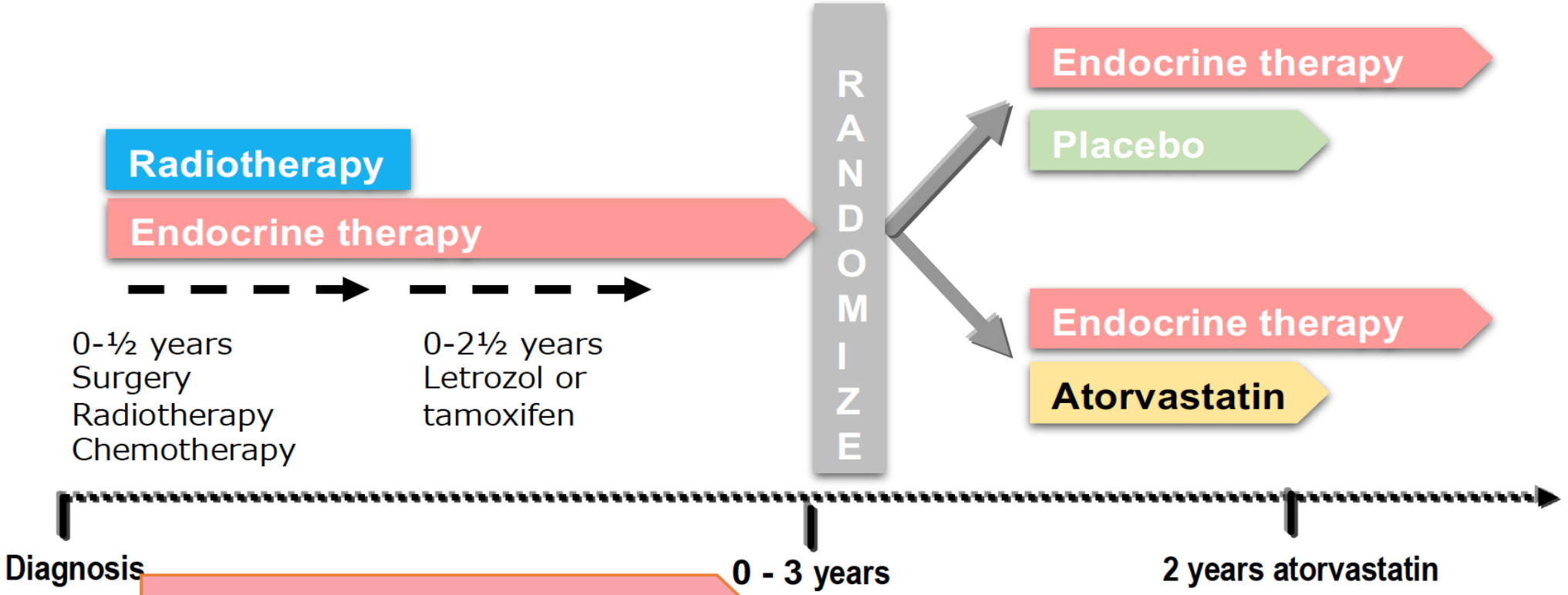
E pirubicin 90 mg/m^2
C TX 600 mg/m^2
P aclitaxel 100 mg/m^2

Endocrine therapy

L Postmenopausal: Letrozole 2,5 mg/d
T Premenopausal: Tamoxifen 20 mg/d

RT
Radiotherapy according to DBCG guidelines

Adjuvant (delayed) setting



DBCG
Danish Breast Cancer Group

Extensions

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

Acknowledgments

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