Demography, years of life lost and statins

Bendix Carstensen Steno Diabetes Center
Gentofte, Denmark
http://BendixCarstensen.com

SDC

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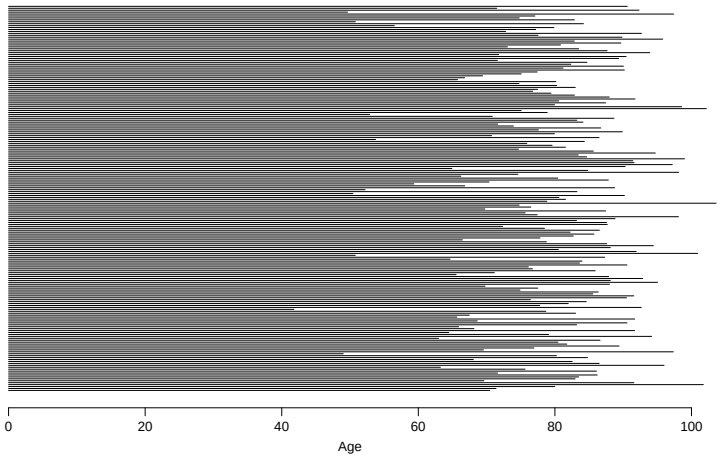
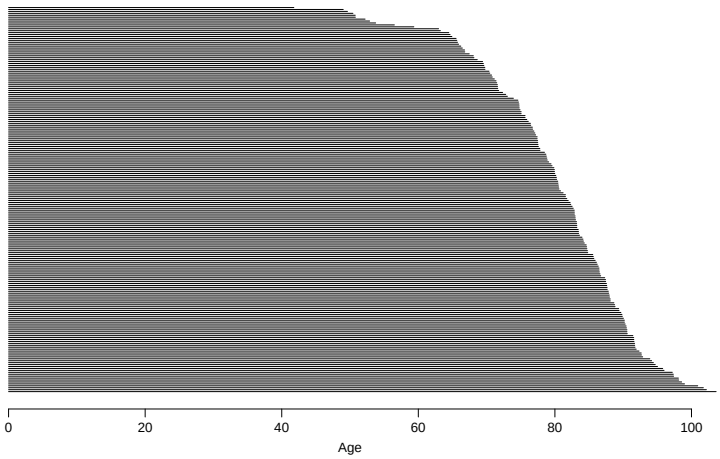
http://BendixCarstensen.com/DMreg/demoYLL.pdf

Expected life time

- Take, say 200, persons
- follow till all are dead
- compute the mean age at death (life time)
- — that is the **life expectancy** (at birth)
- . . . so let's do it and see how it works





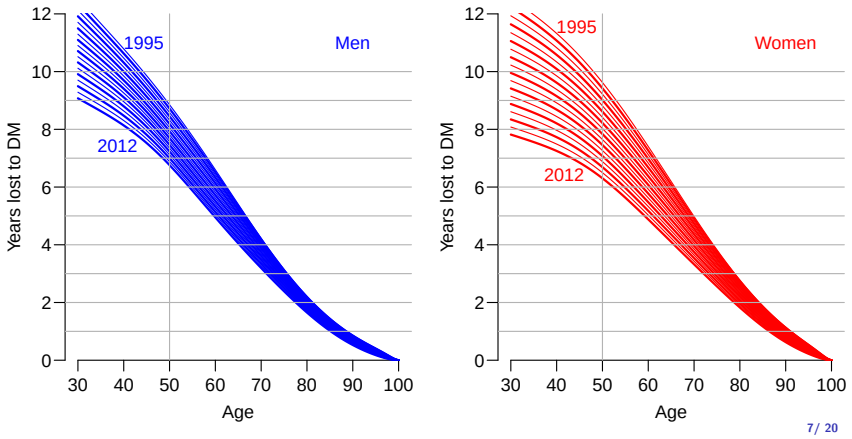
Expected life time and years lost

- **ERL** (**E**xpected **R**esidual **L**ifetime):
  Area under the survival curve
- **YLL** (**Y**ears of **L**ife **L**ost) (to diabetes):
  $ERL_{pop} - ERL_{DM}$
- **difference** between areas under the survival curves
- $\Rightarrow$ area **between** the curves
- . . . all the way till all are dead

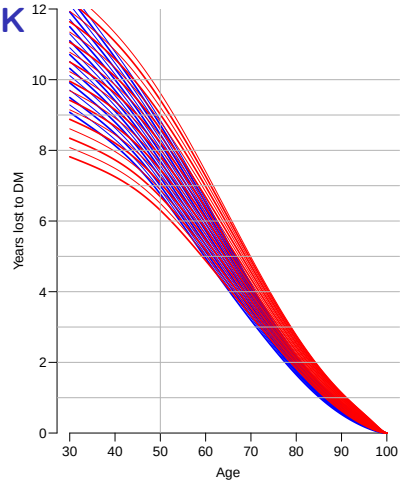
Expected life time and years lost to DM

- Survival curves for persons with/without DM at age 50 in 2012
- Compute difference in area under curve
- Repeat for all ages, both sexes, all years 1995 – 2012

Years lost to diabetes in DK



Years lost to diabetes in DK



BMJ Open

The effect of statins on average survival in randomised trials, an analysis of end point postponement

Malene Lopez Kristensen,[1] Palle Mark Christensen,[1] Jesper Hallas[1,2]

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ABSTRACT

Objective: To estimate the average postponement of death in statin trials.

Setting: A systematic literature review of all statin trials that presented all-cause survival curves for treated and untreated.

Intervention: Statin treatment compared to placebo.

Primary outcome measures: The average postponement of death as represented by the area between the survival curves.

Results: 6 studies for primary prevention and 5 for secondary prevention with a follow-up between 2.0 and 6.1 years were identified. Death was postponed between −5 and 19 days in primary prevention trials and between −10 and 27 days in secondary prevention trials. The median postponement of death for primary and secondary prevention trials were 3.2 and 4.1 days, respectively.

Conclusions: Statin treatment results in a surprisingly small average gain in overall survival within the trials' running time. For patients whose life expectancy is limited or who have adverse effects of treatment, withholding statin therapy should be considered.

Strengths and limitations of this study

- This is the first study ever to systematically evaluate statin trials using average postponement of death as the primary outcome.
- We have only estimated the survival gain achieved within the trials' running time, whereas in real life, treatment is often continued much longer.
- We have only focused on all-cause mortality. Other outcomes may also be relevant, for example, non-fatal cardiovascular end points.

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INTRODUCTION

HMG-CoA reductase inhibitors—or 'statins'—are important drugs for the prevention of atherosclerotic conditions such as stroke, myocardial infarction or limb ischaemia.[1] Current guidelines indicate that statins should be prescribed to all patients manifest-

to take or to prescribe the drug are largely unaffected by the NNT values given. Also, NNT may be criticised for not conveying a plausible model for how the benefit of statins is distributed.[10] The thinking behind NNT suggests a lottery-like model, where, for example, 1 patient in 40 receives full benefit from the drug, while in the remaining 39 patients, it has no effect. It is more plausible that statins will delay atherosclerotic progression in all those treated, to an extent where 1 in 40 patients will have his or her end point postponed until after the outcome is measured. The remaining 39 patients will also have their end points postponed, but none to an extent where they cross this timeline. As an alternative to the NNT, it has been suggested that the drug benefit may be conveyed by an estimate of the average post-

by Baigent *et al*.[12] The Baigent paper had retrieved all relevant papers published until the end of 2009. We supplemented the Baigent search and included the period 2010–2011. Our supplementary literature search yielded one further paper.[13]

The included trials in our analysis were defined by being randomised, having at least 1000 patients included, comparing a statin with no treatment or placebo, having at least 2 years of follow-up, having all-cause mortality as a pre-specified primary or secondary end point and by providing a Kaplan-Meier plot of all-cause mortality in treated versus untreated in the publication. The 11 included papers are listed in table 1. We have listed the excluded papers in online supplementary appendix A, also giving the reason for exclusion.

ANALYSIS

An example of the technical aspects of area calculations is shown in online supplementary appendix B. In brief, we magnified the Kaplan-Meier graphs from the publications by 300% and imported them into Paint (Microsoft Windows V.7). Ten of 11 publications were available in electronically processed format, the last[14] was available in a scanned copy. A vertical line was drawn at the cut point according to the original publication. A reference

RESULTS

Of the 26 publications provided in the original meta-analysis and the one retrieved by literature search, 11 could be included in our analysis. The most common reason for exclusion was lack of a KM survival plot for treated and untreated (9 studies). Among the included studies, six were on primary prevention and five were on secondary prevention.

The calculated end point postponement values are given in table 1, together with the effect measures provided in the original publications. Death was postponed between −5 and 19 days in primary prevention trials and between −10 and 27 days in secondary prevention trials. The median postponement of death for primary and secondary prevention trials were 3.2 and 4.1 days, respectively.

The quick method provided estimates that deviated from the pixel count method by <1 day in 7 of 11 trials (64%). The maximum difference between the two methods was 4.8 days, for the 4S trial (table 1).

The summary OR for all-cause mortality from the included trials was 0.89 (CI 0.84 to 0.93), compared to 0.91 (CI 0.86 to 0.96) for the excluded trials.

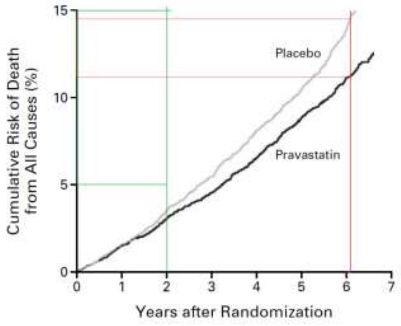
DISCUSSION

Table 1 Estimated postponement of death in 11 trials comparing statin therapy with no treatment or placebo

Study ID, reference, publication year	Number included	Intervention/ comparator	Prevention	Cut point, years	Dead: statin/ control, %	RR (95% CI)	NNT	Postponement, days (SD)	Postpone quick met days
ALLHAT-LLT[22] 2002	10 355	Pravastatin (40 mg) vs usual care	Primary	6	14.9/15.3	0.99 (0.89 to 1.11)	250	−4.96 (0.06)	−5.48
ASCOT-LLA[23] 2003	19 342	Atorvastatin (10 mg) vs placebo	Primary	3.5	3.6/4.1	0.87 (0.71 to 1.06)	200	1.99 (0.04)	1.94
CARDS[24] 2004	2838	Atorvastatin (10 mg) vs placebo	Primary	4.8	4.3/5.8	0.73 (0.52 to 1.01)	66.7	18.66 (0.04)	17.21
JUPITER[25] 2008	17 802	Rosuvastatin (20 mg) vs placebo	Primary	4	2.22/2.77	0.80 (0.67 to 0.97)	31	7.26 (0.01)	7.25
MEGA[26] 2006	7832	Pravastatin (5–20 mg) vs no treatment	Primary	5	1.11/1.66	0.68 (0.46 to 1.00)	182	4.42 (0.01)	4.47
WOSCOPS[27] 1995	6595	Pravastatin (40 mg) vs placebo	Primary	5	3.2/4.1	0.78 (0.60 to 1.00)	111	9.33 (0.10)	8.29
4S[28] 1994	4444	Simvastatin (10–40 mg) vs placebo	Secondary	5.8	8.7/12.3	0.7 (0.58 to 0.85)	27.8	27.18 (0.26)	31.96
GISSI-HF[29] 2008	4631	Rosuvastatin (10 mg) vs placebo	Secondary	4.4	28.8/28.1	1.00 (0.90 to 1.12)	−143	−9.51 (0.01)	−10.44
GISSI-P[14] 2000	4271	Pravastatin (20 mg) vs no treatment	Secondary	2.0	3.37/4.13	0.84 (0.61 to 1.14)	132	1.76 (0.07)	2.53
LIPID[30] 1998	9014	Pravastatin (40 mg) vs placebo	Secondary	6.1	11.0/14.1	0.78 (0.69 to 0.87)	32.3	22.05 (0.21)	26.59
CORONA[13] 2007	5011	Rosuvastatin (10 mg) vs placebo	Secondary	2.7	29.0/30.4	0.95 (0.86 to 1.05)	71	4.09 (0.04)	4.16

NNT, number needed to treat; RR, relative risk.

Appendix B
Example of calculation of endpoint postponement, LIPID study.



1. The graph is copied from the published article in PDF format to the program Paint (300% zoom) where it is saved in bitmap format. A reference area is drawn by straight lines, using the tick marks of the graph, here 0-2 years follow-up on the x-axis and 5-15% cumulative risk on the y-axis (green box). A vertical line to represent the right border of the area between curves is drawn at 6.1 years (red line).
2. The graph is imported into Adobe Photoshop Elements 10, and the area in the reference area and between survival curves is redrawn by using the polygonal lasso tool. The size of the areas can be read directly. In this example:

Size of reference area: 106220 pixels
Size of area between survival curves: 32118 pixels

3. The average postponement of delay is calculated as:

Pixel count (area between curves) * Δy (reference area) * Δx (reference area) / Pixel count (reference area)

In this example:

32118 * 0.10 * 2 years / 106220 = 22.07 days

What Kristensen et al. did

- Take a graph with overall survival curve in Statin/Placebo groups
- Compute the area between the graphs
- **only** during the study period
- . . . which varies between studies (most 4–6 years)
- assuming **age** has no influence on the years gained
- reported the average area between curves
- — averaging over differential ages and follow-up times
- Metanalysis gives an overall $\mathrm{RR} = 0.89 \ \ (0.84; 0.93)$

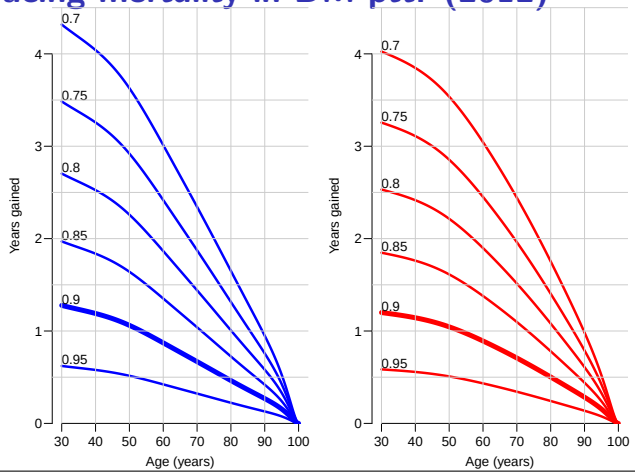
What they should have done

- Mortality curve (by age) for the entire population (placebo)
- Mortality curve (by age) for the entire population assuming a 16% smaller mortality (statin) — multiply by 0.84
- Calculate the **conditional** survival **given** that you are, say 60, for the two groups.
- (this is what demographers do from the mortality curve)
- Calculate the area between the two curves from age 60 to 120
- Repeat for age 65, 70, . . .
- Result: years of life gained by life-long statin treatment starting age 60, 65, . . .

What we did

- Mortality among diabetes patients, based on National Diabetes Register
- for all combinations of:
  - sex: M, F
  - age: 30, 31,. . . , 100
  - year: 1995,1996,. . . ,2012
  - mortality reduction: 1.0, 0.95,. . . , 0.70
- Compute conditional survival, and **ERL** for all ages
- Area between survival curves for $\mathrm{RR} = 0.95, \ldots 0.70$

Effect of reducing mortality in DM ptt. (2012)



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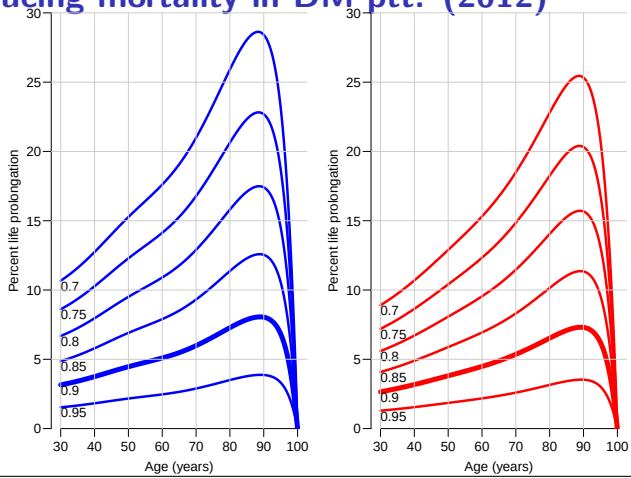

Conclusion

- Know what you are doing
- if it's about diabetes
  — talk to an endocrinologist
- if it's about medication
  — talk a a pharmacoepidemiologist
- if it's about demography
  — talk to a demographer
- **Thanks for your attention**