



How to translate clinical trial results into gain in healthy life expectancy for individual patients

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Treatment effects from randomised trials are typically expressed as numbers needed to treat to prevent one adverse disease event during a fixed time interval (eg, five or 10 years). In the actual patient, however, many diseases are chronically progressive, despite treatment. Examples are diabetic nephropathy, some types of malignancies, osteoporosis, and atherosclerosis. In these examples, the aim of treatment is not to prevent but to delay the occurrence of symptomatic disease. Thus the actual effect of treatment is gain in disease-free life expectancy

Healthy life expectancy is a customary outcome type in cost effectiveness studies at group level, but predictions can also be made at individual patient level.¹² In this article we explain how clinical trial results can be translated into gains in healthy life expectancy for individual patients. We use aspirin in the primary prevention of cardiovascular disease as an illustrative example, based on real data from the Women's Health Study.³⁴

Lifetime prediction models

Traditionally, prediction models for disease risk in individual patients are limited to the follow-up time (eg, five or 10 years) of the original study. In a few studies, most of the study participants may have reached an endpoint

before the end of follow-up.⁵⁶ Conventional statistical models can then suffice for making lifetime predictions. Usually, however, the remaining life expectancy of study participants is much longer than the follow-up duration of studies. Many participants are still healthy and alive at the end of the study. Simple extrapolation of risk predictions beyond the follow-up time of the original study is often precarious. Therefore, lifetime models compared with traditional survival models use age instead of follow-up time as the underlying timescale. A participant does not enter the study at time 0 but rather at his or her age at study entry. Similarly, the time to event or censoring is defined by the age of study exit. This is called left truncation and right censoring, respectively. Each study participant contributes data to the survival model from the age of entry until the age of censoring or disease event.^{7,8} As a result, predictions of lifetime models are not limited by the follow-up time of the study but rather by the age distribution of study participants. Therefore, observations in elderly patients are essential for stable long term predictions.

Competing risks

Competing risks are events that prevent a disease from occurring, such as mortality from other causes than the disease outcome of interest. In traditional survival analyses, competing events are handled by censoring of patients in studies. Often, however, this type of censoring is non-random because competing events and disease do not occur independently. This is the case when events share mutual risk factors. Smoking, for example, is a risk factor for both cardiovascular disease events and non-cardiovascular disease mortality. In such cases, failure to account for competing risks can lead to erroneous conclusions about the relative effect of risk factors and treatment.^{9,10}

In addition, failure to account for competing risks leads to overestimation of the cumulative incidence of disease.⁹⁻¹² This is because patients who die from other causes than the disease outcome of interest, in reality are no longer at risk for the disease. Traditional survival analyses do not account for this gradual decline of the population at risk. However, the assumption that people will not die from other causes becomes increasingly inappropriate in the long term.¹¹ Thus, adjustment for competing risk is essential for predicting the lifetime risk of disease. A more extensive discussion on competing risks has been published.⁹

Competing risk adjusted lifetime prediction models

For making lifetime predictions, the techniques of adjustment for competing risk and an age based time

SUMMARY POINTS

- Gain in disease-free life expectancy is a more intuitive measure of treatment effect than number needed to treat for lifelong treatment for chronically progressive conditions
- Treatment effect as gain in healthy life expectancy can be predicted based on a combination of the relative effect of treatment from a randomised trial and a lifetime prediction model
- Lifetime prediction models are characterised by left truncation and adjustment for competing risks and can be developed using data from either observational cohort or clinical trials
- The highest treatment effect in terms of disease-free life years gained is generally achieved in younger patients with otherwise high risk factors for disease, but not necessarily a high risk for disease, although at the cost of longer duration of drug use and exposure to possible adverse events

Table 1 | Life table for individual patient scenario A* with and without aspirin treatment

Life years	Without aspirin			With aspirin		
	Cumulative survival (e _t)	% CVD risk (a _t)	% non-CVD mortality risk (b _t)	Cumulative survival (e _t)	% CVD risk (a _t)	% non-CVD mortality risk (b _t)
48-49	1.00	0.8	0.0	1.00	0.8	0.0
49-50	0.99	0.8	0.1	0.99	0.8	0.2
50-51	0.98	2.3	0.3	0.98	2.2	0.3
51-52	0.96	0.9	0.2	0.96	0.9	0.2
52-53	0.94	1.0	0.1	0.95	0.9	0.1
53-54	0.93	1.5	0.4	0.94	1.4	0.4
54-55	0.92	1.2	0.3	0.92	1.1	0.3
55-56	0.90	1.2	0.3	0.91	1.1	0.3
56-57	0.89	1.6	0.4	0.90	1.5	0.4
57-58	0.87	1.7	0.3	0.88	1.6	0.4
58-59	0.85	2.0	0.3	0.86	1.9	0.3
59-60	0.83	1.8	0.3	0.84	1.6	0.3
60-61	0.82	2.4	0.6	0.83	2.2	0.6
61-62	0.79	1.8	0.5	0.80	1.7	0.5
62-63	0.77	3.3	0.6	0.79	3.0	0.6
63-64	0.74	1.8	0.6	0.76	1.7	0.6
64-65	0.73	3.9	0.6	0.74	3.5	0.6
65-66	0.69	2.7	0.8	0.71	2.5	0.8
66-67	0.67	2.9	1.0	0.69	2.7	1.0
67-68	0.64	4.2	0.6	0.66	3.8	0.6
68-69	0.61	4.3	0.8	0.63	3.9	0.8
69-70	0.58	3.5	0.8	0.60	3.2	0.8
70-71	0.56	4.5	0.8	0.58	4.2	0.8
71-72	0.53	5.2	1.3	0.55	4.8	1.3
72-73	0.49	4.5	1.0	0.51	4.2	1.1
73-74	0.46	5.4	1.5	0.49	4.9	1.5
74-75	0.43	8.4	0.6	0.46	7.7	0.6
75-76	0.39	6.0	1.1	0.42	5.5	1.2
76-77	0.37	9.8	1.7	0.39	9.0	1.8
77-78	0.32	8.0	1.8	0.35	7.4	1.9
78-79	0.29	10.4	2.6	0.32	9.6	2.7
79-80	0.25	6.0	3.4	0.28	5.5	3.5
80-81	0.23	7.8	3.4	0.25	7.1	3.5
81-82	0.20	11.2	3.0	0.23	10.3	3.1
82-83	0.18	12.6	4.8	0.20	11.6	5.0
83-84	0.14	2.7	7.5	0.16	2.5	7.7
84-85	0.13	11.7	4.3	0.15	10.8	4.4
85	0.11	-	-	0.12	-	-
$\sum_{e_t+t} \times \text{interval width}$	22.2 years			22.8 years		

*48 year old female smoker with diabetes, non-high density lipoprotein cholesterol level of 155 mg/dL, and systolic blood pressure of 140 mm Hg. Treatment effect is the cumulative survival difference with and without aspirin treatment. This is 0.6 years, which equals seven months

axis need to be combined. A well known example of such a model is the JBS3 calculator (www.jbs3risk.com/).^{13,14} For this purpose, methods adapted from the Fine and Gray model are available for standard statistical software.^{8,15} Such risk scores consist of separate cause specific models for the event of interest and the competing event. As with any prediction model, it is recommended to limit the number of predictor variables and choose readily available patient characteristics to optimise ease of use in clinical practice. The same set of variables is used for prediction of the event of interest and the competing event. This is because dropping a variable for the prediction of only one of both outcomes leads to loss of information without the benefit of a simpler model. A covariate for the effect of

treatment should be included in the models that are based on trial datasets.

Estimation of (gain in) disease-free life expectancy

Lifetime prediction models adjusted for competing risk can be used to compute a life table for estimation of disease-free survival of individual patients.¹³ This life table starts at the current age of the individual and is subdivided by arbitrary age intervals (eg, years). For each interval, the life table contains the following probabilities:

e_t = probability of being healthy and alive at start of interval t (starting from 1, at current age of individual)

a_t = probability of experiencing a disease event during interval t given disease-free survival up to start of interval t
 b_t = probability of experiencing a competing event during interval t given disease-free survival up to start of interval t

Probabilities a_t and b_t can be predicted for each age interval t using a competing risk adjusted lifetime model. For each subsequent age interval t , the probability of being healthy and alive at the start of that interval (e_{t+1}) can be calculated as $e_t \times (1 - a_t - b_t)$. The disease-free life expectancy of an individual patient follows from this life table as the sum of e_{t+1} multiplied by the width of each interval t ($\sum e_{t+1} \times \text{interval width}$). This is illustrated in the real data example and table 1.

The survival curve for an individual patient results from plotting of the life table. Notably, the area under this survival curve is equal to $\sum e_{t+1} \times \text{interval width}$. Thus, the area under the survival curve is a graphical representation of the individual disease-free life expectancy. The effect of treatment on disease-free survival can be obtained by computing the survival difference with and without treatment. The treatment effect, in terms of gain in healthy life expectancy, is equal to the difference between the area under the survival curves of both scenarios.

Real data example: aspirin

Aspirin is effective for preventing cardiovascular disease in the primary prevention setting.¹⁶ Similar to other types of treatment for the prevention of cardiovascular disease, aspirin is thought to be most effective in people with a high risk of cardiovascular disease in the next 10 years. This is because the NNT is generally lower (that is, more favourable) in patients at high risk.^{17,18} Because age is by far the most important determinant of 10 year cardiovascular disease risk, aspirin is thought to be most effective in older patients (>65 years).¹⁷ Yet age is also the most important determinant of death from non-cardiovascular causes. In this case, such death may precede the occurrence of a cardiovascular disease event, and thus it must be considered a competing risk. This is because patients who die from non-cardiovascular causes may not benefit from aspirin at all, even when their 10 year risk of cardiovascular disease is high. Therefore, aspirin treatment is a classic example where doctors need to consider competing risks when estimating the treatment effect for individual patients.

To illustrate these concepts we developed a competing risk adjusted lifetime model based on data from the Women's Health Study. This study was a randomised trial evaluating the effect of aspirin 100 mg on alternate days compared with placebo for the primary prevention of cardiovascular disease among initially healthy women aged 45 or older.³⁴ For the present example, we use data on 27 939 participants who provided baseline plasma samples. After a mean follow-up of 10.1 years, the hazard ratio for occurrence of the primary endpoint was 0.91 (95% confidence interval 0.80 to 1.03), favouring aspirin treatment. The competing outcomes were

defined as cardiovascular disease (myocardial infarction, stroke, or cardiovascular death) and non-cardiovascular disease mortality. In addition to aspirin treatment, several well established cardiovascular risk factors were prespecified as predictors: smoking, diabetes mellitus, systolic blood pressure, and non-high density lipoprotein cholesterol level. Because observations in very elderly people were limited in the Women's Health Study, we truncated lifetime predictions at age 85. Supplementary appendix 1 provides additional details on the development and validation of the model.

Table 1 shows how the lifetime model was used to construct a life table for a hypothetical patient scenario. Starting from the current age of this patient (in this case 48 years), the cumulative survival without cardiovascular disease (e_t) gradually decreases towards zero conditional on the yearly rates of cardiovascular disease (a_t) and non-cardiovascular disease mortality (b_t). The cardiovascular disease-free life expectancy follows from this table as the sum of the cumulative survivals for each life year; in this case 22.2 years without aspirin and 22.8 years with lifelong aspirin treatment. The aspirin treatment effect for this patient is 0.6 years, which equals seven months gain in cardiovascular disease-free life expectancy. In figure 1, we have plotted the cumulative survival for this individual patient scenario as a survival curve with and without aspirin treatment. The effect of aspirin is represented by the size of the white area between the curves, which is also equal to seven months.

Figure 1 also illustrates the estimated cumulative cardiovascular disease-free survival for the hypothetical patient with no adjustment for competing risks (ie, adding up unadjusted estimates of cardiovascular disease and non-cardiovascular disease mortality). The yearly rates of non-cardiovascular disease mortality presented in table 1 may seem relatively unimportant.

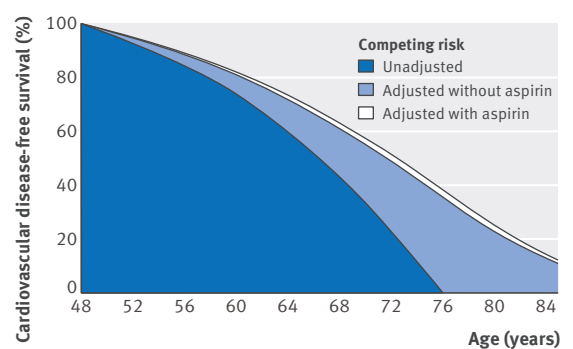


Fig 1 | Predicted treatment effect for hypothetical patient scenario. Cumulative survival free of cardiovascular disease and mortality for 48 year old female smoker with diabetes, non-high density lipoprotein cholesterol level of 155 mg/dL, and systolic blood pressure of 140 mm Hg. Competing risk unadjusted survival was computed using the added cumulative incidences of separate survival models for cardiovascular disease and non-cardiovascular disease mortality. The effect of aspirin is represented by the size of the white area between the curves, equal to seven months

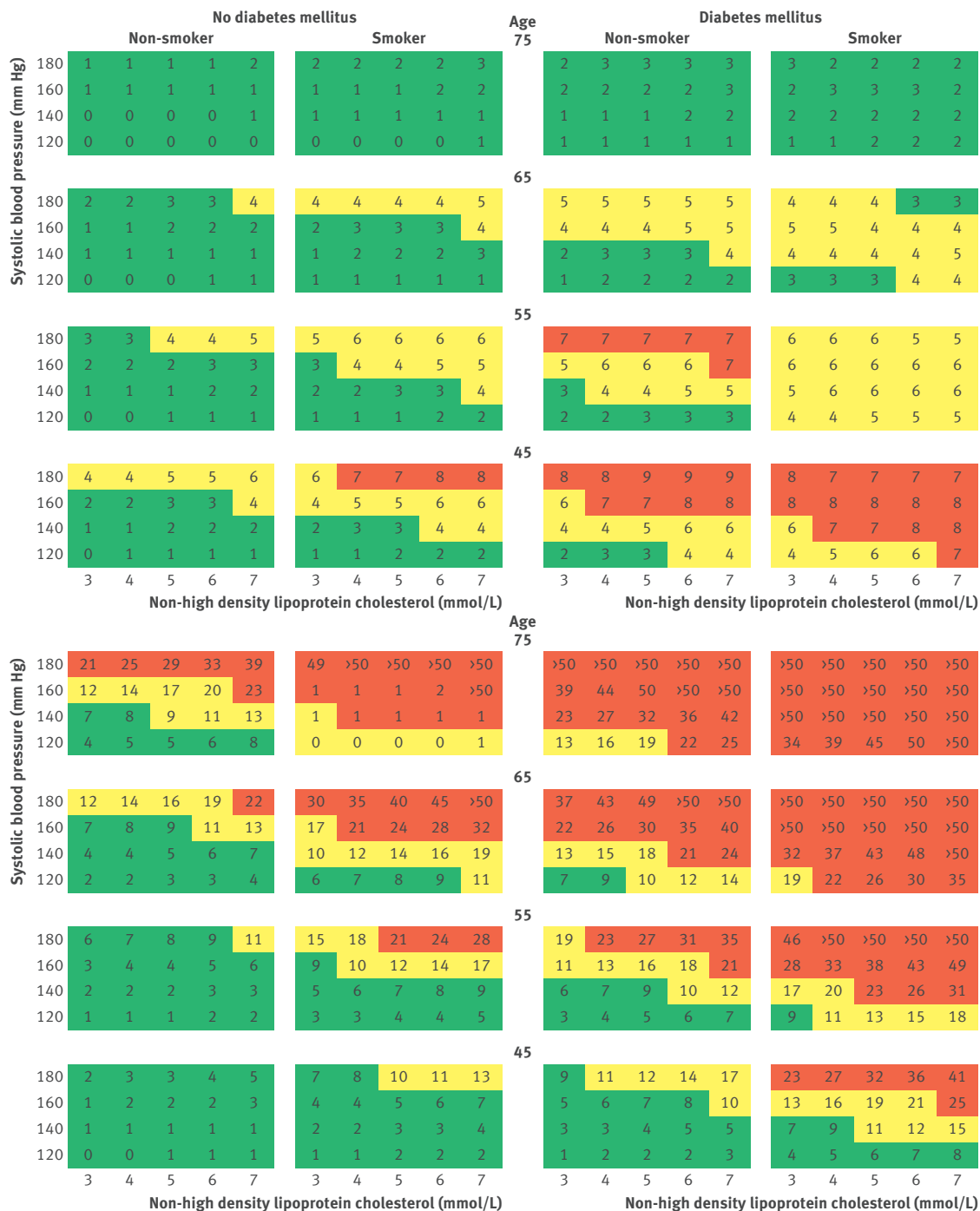


Fig 2 | (Top charts) Predicted aspirin treatment effect: numbers of months gain in cardiovascular disease-free life expectancy to age 85 for individual patients resulting from lifelong aspirin treatment. A zero means no treatment effect. A 6 means that lifelong aspirin treatment is expected to prolong the patient’s cardiovascular disease-free life expectancy by six months. A high treatment effect is generally achieved in young patients with otherwise high risk factors for disease. (Bottom charts) Predicted 10 year cardiovascular disease risk for individual patients (%). High risk is correlated with high age. Notably, there is only limited correspondence between the distributions of predicted lifetime treatment effect (top charts) and 10 year cardiovascular disease risk (bottom charts). Colour coding top charts: green=low treatment effect (≤3 months); yellow=intermediate treatment effect (>3 and ≤6 months); red=high treatment effect (>6 months). Colour coding bottom charts: green=low risk (<10%); yellow=intermediate risk (≥10% and <20%); red=high risk (≥20%)

Yet, failure to account for these competing risks leads to overly pessimistic estimations of cardiovascular disease-free survival. As a result, the survival curve unadjusted for competing risk may even go below 0, as it does in figure 1.

Similar calculations can be performed for all other combinations of risk factor levels (figure 2, top charts). The figure shows the predicted effect of lifelong aspirin treatment for each combination of risk factor levels as the number of months gain in cardiovascular

disease-free life expectancy to age 85. These charts can be used to predict the effect of lifelong aspirin treatment for individual patients. Alternatively, an interactive calculator can be used for individual treatment effect predictions (see appendix 2). Notably, an inverse association can be observed between treatment effect and age. The highest treatment effect for aspirin is obtained in younger patients with otherwise high risk factor levels. This is explained by the fact that these patients are at lower risk for competing non-cardiovascular disease mortality. Longer remaining lifetime means longer time at risk for cardiovascular disease events and therefore more benefit from preventive treatment. These findings agree with those from microsimulation studies on both aspirin and statin treatment.²¹⁹ Importantly, starting lifelong treatment at a younger age also means that patients will be exposed to possible adverse events during a longer period. This should be taken into account when making decisions based on predictions of lifetime treatment effect.

For comparison, the bottom charts in figure 2 show the absolute 10 year risk of cardiovascular disease for individual patients. We computed this risk using the same competing risk adjusted model, but based on age specific baseline survival rates for prediction of 10 year risk without the use of a life table (see appendix 1 for details). Similar to other risk scores, these colour charts show that the 10 year risk of cardiovascular disease was still higher with increasing age.^{20,21} Yet apparently a high 10 year cardiovascular disease risk is not always associated with a high treatment effect. This is because older people have a shorter remaining lifetime during which they are at risk for cardiovascular disease events.

Validation of lifetime modelling

Because lifetime models predict survival well beyond the duration of the study data, it is often impossible to validate the accuracy of these long term predictions. The example from the Women's Health Study is, however, an exception. After the randomised treatment period of the study had ended, participants were invited for further observational follow-up, resulting in a total follow-up of 17.5 years.⁴ Because we used only the first 10.1 years of follow-up data for model development, this allowed us to perform temporal validation. A calibration plot (fig 3) shows that the model's long term survival probabilities closely match those of the actual (observed) Kaplan-Meier survival in our example. This finding supports, at least for this example, the robustness of the described lifetime prediction methods.

Additional considerations

Although the highest treatment effect is achieved in younger patients, this comes at the cost of a longer duration of treatment (that is, during the remaining lifetime). For a better comparison of the efficiency of treatment, standardisation of treatment duration may still be considered. For example, the model could be truncated to predict average gain in disease-free life expectancy in the next 10 years. Although lifetime predictions can be insightful for some, others may feel more

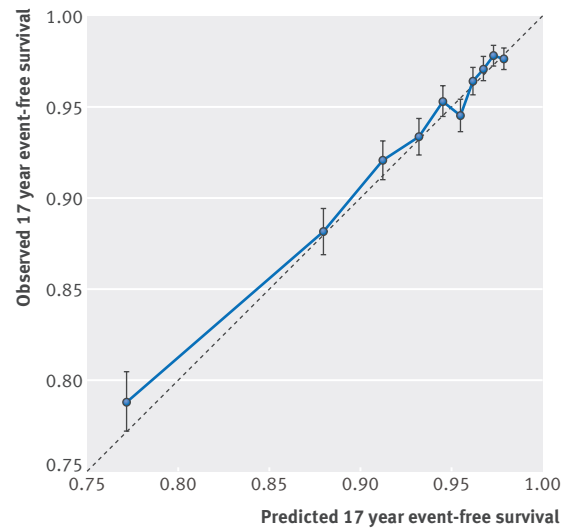


Fig 3 | Validity of model at 17 years' follow-up. Predicted and observed 17 year cardiovascular disease-free survival. Predicted survival is based on competing risk adjusted models for cardiovascular disease and non-cardiovascular disease mortality as calculated for all participants aged ≤ 68 years in the Women's Health Study. Observed survival was based on Kaplan-Meier estimates for the composite endpoint of cardiovascular disease and non-cardiovascular disease mortality within 10ths of predicted survival in the extended follow-up dataset

motivated by short term effects (that is, retaining good health in the near future).

Furthermore, in the example we did not account for changes in risk factor levels over time, such as age related changes in blood pressure and cholesterol concentrations. Large fluctuations in these biomarkers are usually not seen until a first cardiovascular disease event. This may be different for other treatment scenarios, which may necessitate the updating of risk factors.

In the example, the effect of aspirin was modelled based on randomised trial data. Predictions were truncated at 85 years owing to a limited number of observations in women aged more than 85 years. This is a frequently encountered limitation of randomised trial data, because stringent enrolment criteria result in the exclusion of elderly patients. Moreover, model predictions only apply to patients who would have been eligible to enrol in the trial. Yet observational cohort studies, which usually enrol more heterogeneous patient populations, may also be used for developing competing risk adjusted lifetime models.^{213 14} Assumptions on the relative effect of treatment can then be made on the basis of meta-analyses of trials, if available, and added to the model coefficients.

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- Briggs A, Claxton K, Sculpher M, eds. *Decision modelling for health economic evaluation*. Oxford University Press, 2006.
- Ferret BS, van Kempen BJ, Heeringa J, et al. Personalized prediction of lifetime benefits with statin therapy for asymptomatic individuals: a modeling study. *PLoS Med* 2012;9:e1001361. doi:10.1371/journal.pmed.1001361 pmid:23300388.
- Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. *N Engl J Med* 2005;352:1293-304. doi:10.1056/NEJMoa050613 pmid:15753114.
- Cook NR, Lee IM, Zhang SM, Moorthy MV, Buring JE. Alternate-day, low-dose aspirin and cancer risk: long-term observational follow-up of a randomized trial. *Ann Intern Med* 2013;159:77-85. doi:10.7326/0003-4819-159-2-201307160-00002 pmid:23856681.
- Wang SJ, Fuller CD, Kim JS, Sittig DF, Thomas CR Jr, Ravdin PM. Prediction model for estimating the survival benefit of adjuvant radiotherapy for gallbladder cancer. *J Clin Oncol* 2008;26:2112-7. doi:10.1200/JCO.2007.14.7934 pmid:18378567.
- Lee ES, Son DS, Kim SH, et al. Prediction of recurrence-free survival in postoperative non-small cell lung cancer patients by using an integrated model of clinical information and gene expression. *Clin Cancer Res* 2008;14:7397-404. doi:10.1158/1078-0432.CCR-07-4937 pmid:19010856.
- Lloyd-Jones DM, Leip EP, Larson MG, et al. Prediction of lifetime risk for cardiovascular disease by risk factor burden at 50 years of age. *Circulation* 2006;113:791-8. doi:10.1161/CIRCULATIONAHA.105.548206 pmid:16461820.
- Beiser A, D'Agostino RBS Sr, Seshadri S, Sullivan LM, Wolf PA. Computing estimates of incidence, including lifetime risk: Alzheimer's disease in the Framingham Study. The Practical Incidence Estimators (PIE) macro[pil]. *Stat Med* 2000;19:1495-522. doi:10.1002/(SICI)1097-0258(20000615/30)19:11<1495::AID-SIM441>3.0.CO;2-E pmid:10844714.
- Wolkewitz M, Cooper BS, Bonten MJ, Barnett AG, Schumacher M. Interpreting and comparing risks in the presence of competing events. *BMJ* 2014;349:g5060. doi:10.1136/bmj.g5060 pmid:25146097.
- Koller MT, Raatz H, Steyerberg EW, Wolbers M. Competing risks and the clinical community: irrelevance or ignorance?. *Stat Med* 2012;31:1089-97. doi:10.1002/sim.4384 pmid:21953401.
- Koller MT, Leening MJ, Wolbers M, et al. Development and validation of a coronary risk prediction model for older U.S. and European persons in the Cardiovascular Health Study and the Rotterdam Study. *Ann Intern Med* 2012;157:389-97. doi:10.7326/0003-4819-157-6-201209180-00002 pmid:22986376.
- Kent DM, Alsheikh-Ali A, Hayward RA. Competing risk and heterogeneity of treatment effect in clinical trials. *Trials* 2008;9:30. doi:10.1186/1745-6215-9-30.
- JBS3 Board. Joint British Societies' consensus recommendations for the prevention of cardiovascular disease (JBS3). *Heart* 2014;100(Suppl 2):ii1-67. doi:10.1136/heartjnl-2014-305693 pmid:24667225.
- Hippisley-Cox J, Coupland C, Robson J, Brindle P. Derivation, validation, and evaluation of a new QRISK model to estimate lifetime risk of cardiovascular disease: cohort study using QResearch database. *BMJ* 2010;341:c6624. doi:10.1136/bmj.c6624 pmid:21148212.
- Geskus RB. Cause-specific cumulative incidence estimation and the fine and gray model under both left truncation and right censoring. *Biometrics* 2011;67:39-49. doi:10.1111/j.1541-0420.2010.01420.x pmid:20377575.
- Antithrombotic Trialists' (ATT) Collaboration Baigent C, Blackwell L, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. *Lancet* 2009;373:1849-60. doi:10.1016/S0140-6736(09)60503-1 pmid:19482214.
- Dorresteijn JA, Visseren FL, Ridker PM, et al. Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects. *Eur Heart J* 2011;32:2962-9. doi:10.1093/eurheartj/ehr423 pmid:22090661.
- Dorresteijn JA, Visseren FL, Ridker PM, et al. Estimating treatment effects for individual patients based on the results of randomised clinical trials. *BMJ* 2011;343:d5888. doi:10.1136/bmj.d5888 pmid:21968126.
- Dehmer SP, Maciosek MV, Flottesmesch TJ, et al. Aspirin use to prevent cardiovascular disease and colorectal cancer: a decision analysis: Technical report [internet]. *Ann Intern Med* PMID: 26491755
- D'Agostino RBS Sr, Vasan RS, Pencina MJ, et al. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. *Circulation* 2008;117:743-53. doi:10.1161/CIRCULATIONAHA.107.699579 pmid:18212285.
- Perk J, De Backer G, Gohlke H, et al. European Association for Cardiovascular Prevention & Rehabilitation (EACPR) ESC Committee for Practice Guidelines (CPG). European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). *Eur Heart J* 2012;33:1635-701. doi:10.1093/eurheartj/ehs092 pmid:22555213.

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Web extra: appendix 1

Web extra: calculation sheet for treatment effect with aspirin