USING A CAUSE-OF-DEATH-BASED MORTALITY MODEL TO IDENTIFY THE INDIVIDUALS WHO WOULD BENEFIT MOST FROM PRIMARY PREVENTION WITH STATINS.

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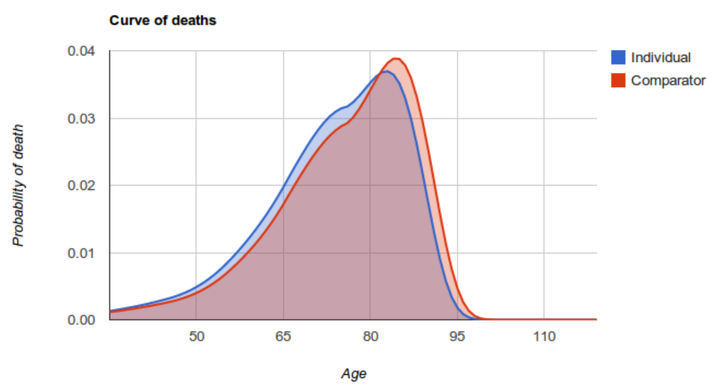
Objectives

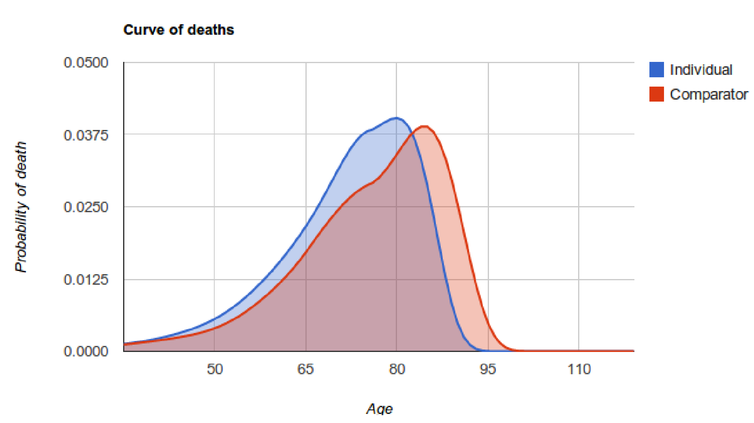
The use of statins has been demonstrated to reduce cardiovascular mortality significantly in a number of studies. The effect size is reasonably stable across different studies with an approximate 35% relative risk reduction (RRR) in cardiovascular death for a low density lipoprotein (LDL) reduction of 1. Randomised controlled trials (RCTs) have investigated their use in in a range of risk profiles including those without existing cardiovascular disease (CVD). It is reasonable to assume that the RRR is independent of prior risk, and that the cost-benefit analysis used will focus on the absolute reduction in risk. This absolute reduction will be greatly influenced by other major cardiovascular risk factors like smoking and blood pressure. It is not feasible to conduct RCTs to explore the absolute effect of statins on risk in all combinations of risk factors, and so modelling studies can give insights into the benefit that could be expected in the absence of more reliable data across a range of combinations of risk factors.

Table 1 showing the specific causes of death modelled and their associated risk factors.

Cause of death	ICD definition	Risk factors
Lung cancer	C33:C34	Cigarettes consumed per day (CPD)
Other cancers	C00:C32;C35:D48	CPD
Cardiovascular disease	I00:I99	CPD, body mass index (BMI), Systolic blood pressure (SBP), total cholesterol (TC) to high density lipoprotein (HDL) ratio (TC/HDL)
Chronic Lung disease	J40:J47	CPD
Other respiratory disease	J00:J39;J48:J99	CPD
All other causes	A00:B99;D49:H99;K00:R99; U509;V01:Y89	CPD



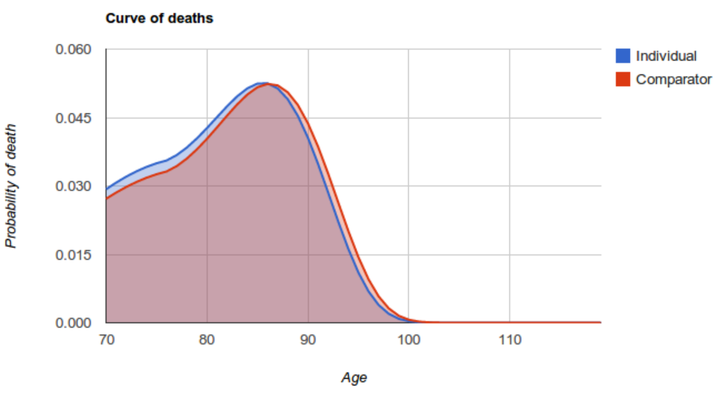
Male
Age: 35
BMI: 20
SBP: 150 mmHg
Pre-treatment TC: 6.6 mmol/l
Pre-treatment HDL: 1.3 mmo;/l
TC/HDL ratio: 5.1
Post-treatment TC: 5.0 mmol/l
Post-treatment HDL: 1.4 mmol/
TC/HDL ratio: 3.5
Smoker: 15 cigarettes per day



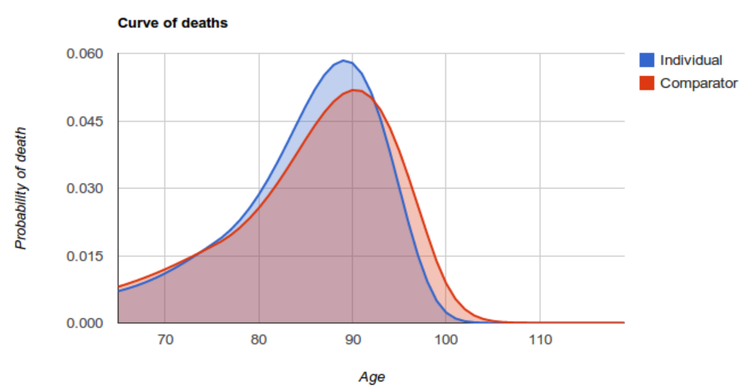
Female
Age: 35
BMI: 20
SBP: 150 mmHg
Pre-treatment TC: 6.7 mmol/l
Pre-treatment HDL: 1.1 mmo;/l
TC/HDL: 6.1
Post-treatment TC: 5.0 mmol/l
Post-treatment HDL: 1.2 mmol/l
TC/HDL ratio: 4.2
Smoker: 15 cigarettes per day

Scan this QR code to go to the model.

Or access the model here: www.crystallise.uk.com/Mortality+model



Male
Age: 70
BMI: 20
SBP: 140 mmHg
Pre-treatment TC: 6.0 mmol/l
Pre-treatment HDL: 1.5 mmo;/l
TC/HDL ratio: 5
Post-treatment TC: 4.5 mmol/l
Post-treatment HDL: 1.6 mmol/l
TC/HDL ratio: 2.8
Smoker: 10 cigarettes per day



Female
Age: 65
BMI: 30
SBP: 140 mmHg
Pre-treatment TC: 7.3 mmol/l
Pre-treatment HDL: 1.2 mmo;/l
TC/HDL: 6.1
Post-treatment TC: 5.5 mmol/l
Post-treatment HDL: 1.3 mmol/l
TC/HDL ratio: 4.2
Non-smoker

Method

A linear hazard model of all-cause mortality was constructed from a series of component linear models of specific causes of death as shown in table 1 and the specific risk factors used to adjust the cause-specific mortality rates are shown in table 1. All factors were assumed to have a linear relationship to the final risk and the coefficients were derived from published estimates of relative risk. Using estimated hazard ratios (R) from defined lower and upper reference points (U, L), an origin of the projected linear hazard ratio was identified (pivot point P). For TC/HDL, the upper and lower reference values used were 4.0 and 5.0 to reflect the higher than average values found in in RCTs. The hazard ratio applied to the baseline cause-specific central mortality rates were calculated using equation 1.

$$R = \frac{(V - P)}{(M - P)}$$

Equation 1. *The calculation of the hazard ratio R to be applied to baseline cause-specific central mortality rates, based on risk factor values (V), the mean value for the risk factor (M) and the pivot point of the linear risk (P).*

A total of 11,520 individual scenarios were generated by systematically finding all combinations of the risk factor segmentations as shown in table 2. The scenarios were modelled, generating estimates of the mean expected age of death for each individual with the given combination of risk factor values.

The impact of the use of statins was estimated applying a reduction in TC of 25% and an increase in HDL of 8%, which are typical of those found in randomized controlled trials of statin use. Using a minimum significant benefit threshold (MSB) of 6 months for a clinically significant increase in mean life expectancy (MLE) for every 10 years of statin use, risk factor combinations that fell upon this threshold were identified.

Table 2 showing the segmentation of risk factors.

Risk factor	Units	Values
Age	years	35, 40, 45, 50, 55, 60, 65, 70
Gender	-	Male or Female
Systolic blood pressure	mmHg	120, 125, 130, 135, 140, 145, 150, 155, 160
TC / HDL	ratio	2.1, 2.8, 3.5, 4.2
BMI	kg/m^2	20, 25, 30, 35, 40
Cigarettes per day	#	0, 5, 10, 15

Results

Example subjects with risk factor combinations that resulted in life expectancy gains that fell close to the MSB threshold include: men aged 35 with SBP of 150 mmHg, BMI of 20 kg/m^2, smoking 15 cigarettes per day, and a TC:HDL ratio of 3.5; men aged 70 with SBP of 140 mmHg, BMI of 20 kg/m^2, smoking 10 cigarettes per day, and a TC:HDL ratio of 2.8; women aged 35 with SBP of 135 mmHg, BMI of 20 kg/m^2, smoking 15 cigarettes per day, and a TC:HDL ratio of 4.2 or higher; and women aged 65 with SBP of 140 mmHg, BMI of 30 kg/m^2, who are non-smokers, and a TC:HDL ratio of 4.2.

Conclusions

Paper based tables such as those used in the Joint British Societies Guidelines are useful tools in clinical practice. However, as the number of risk factors taken into account rises, it becomes harder to represent this multidimensional data easily on paper, and harder to identify straightforward risk factor based rules on when to intervene with statins. Interactive mortality modelling may facilitate decision-making about when to start preventive treatment.

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