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Brief Original Report

Implications of lower risk thresholds for statin treatment in primary prevention: Analysis of CPRD and simulation modelling of annual cholesterol monitoring

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ABSTRACT

Objective: To estimate numbers affected by a recent change in UK guidelines for statin use in primary prevention of cardiovascular disease.

Method: We modelled cholesterol ratio over time using a sample of 45,151 men (≥40 years) and 36,168 women (≥55 years) in 2006, without statin treatment or previous cardiovascular disease, from the Clinical Practice Research Datalink. Using simulation methods, we estimated numbers indicated for new statin treatment, if cholesterol was measured annually and used in the QRISK2 CVD risk calculator, using the previous 20% and newly recommended 10% thresholds.

Results: We estimate that 58% of men and 55% of women would be indicated for treatment by five years and 71% of men and 73% of women by ten years using the 20% threshold. Using the proposed threshold of 10%, 84% of men and 90% of women would be indicated for treatment by 5 years and 92% of men and 98% of women by ten years.

Conclusion: The proposed change of risk threshold from 20% to 10% would result in the substantial majority of those recommended for cholesterol testing being indicated for statin treatment. Implications depend on the value of statins in those at low to medium risk, and whether there are harms.

Introduction

Lipid modification guidelines for cardiovascular disease (CVD) prevention recommend that patients who are deemed to be at high risk of CVD should be prescribed statins to lower their LDL-cholesterol (Cooper et al., 2010). In the UK, high risk is currently assessed using 10-year CVD risk equations that contain a combination of demographic and clinical risk factors, including the ratio of total to HDL-cholesterol (Anderson et al., 1991; Hippisley-Cox et al., 2008; Woodward et al., 2007). Until recently, treatment was indicated if the calculated risk score exceeds 20% (Cooper et al., 2010). In 2014 the National Institute for Health and Care Excellence (NICE) recommended reducing the threshold for treatment to 10% (National Institute for Health and Care Excellence, 2014). If implemented, this decision would lead to an increase in the number of individuals indicated for treatment; while it has been suggested that millions of patients may be affected (Price, 2014; Thompson et al., 2014), estimated numbers have not been published. We therefore evaluate cholesterol testing and associated CVD risk prediction, in primary prevention patients representative of those attending monitoring in UK general practice, to estimate the number indicated for treatment under monitoring schemes using the previous 20% and the newly recommended 10% risk thresholds. Cholesterol, like most biochemical markers, is measured with biological variability as well as assay variability, in the sense that two cholesterol measurements on the same person will rarely give exactly the same result. This uncertainty in cholesterol measurements will translate into uncertainty in calculated CVD risk estimates. We therefore include in our model a distinction between true CVD risk, based on underlying, usual cholesterol ratio, and observed or estimated CVD risk, based on the cholesterol ratio in a blood sample taken at a particular clinic visit.

Methods

Data were a sample of 45,151 men aged over 40 years and 36,168 women aged over 55 years, without previous CVD and statin treatment, from the Clinical Practice Research Datalink (CPRD) (CPRD, 2013). Age was restricted to the earliest monitoring age in the NHS Health Check programme (NHS Choices, 2014) to minimise potential cholesterol changes throughout menopause (Bittner, 2009; Matthews et al., 2009). We use a random-effects model to estimate the between-subject variation, the average rate of change over time and its variation between individuals, and the short-term variability in

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any single measurement (Stevens et al., 2010). We used previously published simulation methods (Stevens et al., 2010) to estimate the number of men and women who would be indicated for new statin treatment if their cholesterol was measured annually and used in the QRISK2 CVD risk calculator (Hippisley-Cox et al., 2008), using the previous threshold of 20% and the new threshold of 10%. We assumed annual measurement because the median (interquartile range) time between cholesterol measurements for individuals in our CPRD sample with more than one test was 1.02 (0.56–1.65) years. We used estimates of within-measurement variability to model the relationship between the observed and the underlying, usual cholesterol ratio, and hence distinguish true CVD risk from estimated CVD risk. We estimate the distribution of true CVD risk amongst those with estimated CVD risk above threshold. Stata 12.1 (StataCorp, 2011) was used for all analyses.

Results

The mean (SD) age, total to HDL-cholesterol ratio and systolic blood pressure were 60.3 (12.0) years, 4.3 (1.3) and 139 (18) mm Hg in men and 68.5 (9.0) years, 3.8 (1.1) and 142 (19) mm Hg in women. The prevalence of diabetes was 13.4% in men and 9.9% in women. Approximately one third of men (35.4%) and half of women (49.8%) were non-smokers; 45.2% of men and 36.8% of women were ex-smokers; and 19.4% of men and 13.5% of women currently smoked (5.3%, 7.3% and 6.8% of men and 4.7%, 5.1% and 3.7% of women were light, moderate and heavy smokers respectively, as defined in QRISK2) (Hippisley-Cox et al., 2008).

The estimated SD of the within-measurement variability in total to HDL-cholesterol ratio was 0.37 in men and 0.23 in women: that is, (for example) within an individual man, the measured cholesterol ratio on any given clinic visit can vary by ±0.37 (SD) or ±0.73 (normal range) around his usual value.

On average there was little change in cholesterol ratio over time: mean change across all men in the cohort was −0.001 (95%CI −0.004 to 0.002) per year and mean change across all women in the cohort was 0.002 (95%CI −0.001 to 0.004) per year. However, individuals varied greatly around these averages: the SD of rate of change was 0.097 per year in men and 0.090 per year in women. (Thus, for 95% of men, rate of change lies between a 0.19 per year decrease and a 0.19 per year increase. Similarly for 95% of women, rate of change lies between a 0.17 per year decrease and a 0.18 per year increase.)

Table 1 shows the estimated numbers indicated for treatment per 10,000 under the assumption that cholesterol ratio is measured annually and that treatment is indicated if QRISK2 score exceeds 20%, as in previous guidelines. We estimate that 58% of men and 55% of women would be indicated for treatment by five years and 71% of men and 73% of women by ten years. Table 1 also shows, in these men and women with estimated risk above 20%, the modelled distribution of true CVD risks; only a small number of those indicated for treatment had true risk below 20% and none had true risk below 15%.

Table 2 shows the corresponding results, under the assumption that treatment is indicated if QRISK2 score exceeds 10%, as recommended in the new guidelines. We estimate that 84% of men and 90% of women would be indicated for treatment by 5 years and 92% of men and 98% of women by ten years. Of those indicated for treatment, few had true risk below 10% and (data not shown) none had true risk below 5%.

Discussion

The recent change of risk threshold from 20% to 10% would result in the substantial majority of men and women above the recommended age for cholesterol testing being indicated for statin treatment. However, using mathematical modelling we estimate that only a small proportion of those indicated for treatment would be due to false positive tests, and that these are primarily amongst those close to the threshold whether this is at 20% or 10%.

In the absence of large randomised trials powered to compare cardiovascular risk assessment at different thresholds, we have used established modelling methods and data representative of routine general practice in the UK. One limitation of these analyses is the (unlikely) assumption that CVD risk factors other than age and cholesterol level remain constant over time. We have also not attempted to model the complexity of individual

Table 1
Men and women from the Clinical Practice Research Datalink in 2006 indicated for new statin treatment when 10-year CVD risk is estimated annually with QRISK2 and compared to threshold of 20% (previous guidelines for primary prevention). Bold font denotes those whose true CVD risk is concordant with their estimated risk.

Years since first test	Cumulative number indicated for treatment per 10,000	True CVD risk amongst those indicated for treatment, cumulative number per 10,000			
		<10%	10 to <15%	15 to <20%	**≥20%**
Men					
0	4151	0	0	149	**4002**
1	4581	0	0	210	**4371**
2	4913	0	0	227	**4686**
3	5221	0	0	227	**4993**
4	5520	0	0	225	**5295**
5	5810	0	0	220	**5590**
6	6090	0	0	211	**5878**
7	6357	0	0	205	**6152**
8	6612	0	0	199	**6414**
9	6861	0	0	193	**6667**
10	7103	0	0	188	**6915**
Women					
0	3778	0	0	103	**3675**
1	4152	0	0	132	**4020**
2	4477	0	0	139	**4338**
3	4801	0	0	143	**4658**
4	5127	0	0	143	**4984**
5	5463	0	0	144	**5319**
6	5815	0	0	151	**5664**
7	6178	0	0	154	**6024**
8	6555	0	0	158	**6397**
9	6938	0	0	157	**6781**
10	7320	0	0	151	**7169**

Table 2
Men and women from the Clinical Practice Research Datalink in 2006 indicated for new statin treatment when 10-year CVD risk is estimated annually with QRISK2 and compared to threshold of 10% (new guidelines for primary prevention). Bold font denotes those whose true CVD risk is concordant with their estimated risk.

Years since first test	Cumulative number indicated for treatment per 10,000	True CVD risk amongst those indicated for treatment, cumulative number per 10,000			
		<10%	**10 to <15%**	**15 to <20%**	**≥20%**
Men					
0	7167	95	**1409**	**1484**	**4179**
1	7468	115	**1401**	**1487**	**4466**
2	7709	116	**1366**	**1464**	**4763**
3	7935	110	**1339**	**1421**	**5065**
4	8150	104	**1312**	**1370**	**5365**
5	8352	96	**1279**	**1319**	**5657**
6	8540	92	**1232**	**1273**	**5943**
7	8721	88	**1181**	**1239**	**6213**
8	8891	82	**1124**	**1212**	**6473**
9	9050	77	**1063**	**1185**	**6725**
10	9199	72	**1005**	**1150**	**6972**
Women					
0	7336	117	**1957**	**1466**	**3795**
1	7737	119	**2034**	**1485**	**4099**
2	8073	111	**2043**	**1509**	**4410**
3	8388	108	**2004**	**1546**	**4729**
4	8690	100	**1936**	**1595**	**5059**
5	8969	88	**1843**	**1643**	**5394**
6	9220	75	**1727**	**1676**	**5741**
7	9431	59	**1591**	**1676**	**6105**
8	9603	47	**1428**	**1646**	**6481**
9	9736	35	**1244**	**1590**	**6867**
10	9834	24	**1044**	**1511**	**7255**

treatment decision making, however the analyses presented here aim to form the basis for evaluation of national monitoring strategies.

Implications depend on the value of statins in those at low to medium risk, and whether there are harms. The extensive literature on non-cardiovascular effects of statins has recently been reviewed (Desai et al., 2014): the best documented harms include an increased risk of diabetes, for example (Rajpathak et al., 2009; Sattar et al., 2010). Recent systematic reviews (Finegold et al., 2014; Ganga et al., 2014) found no increase in muscle problems in statin groups compared to placebo groups across randomised trials; however two trials not included in those reviews did find such effects (Golomb et al., 2012; Parker et al., 2013). Beyond actual and putative harms of treatment, it is not known whether there are other harms associated with monitoring: a harm associated with 'labelling' has been found for hypertension (Hamer et al., 2010). If we accept the conclusions published by the Cholesterol Treatment Trialists' Collaboration (Mihaylova et al., 2012) that statins have net benefit in those at low risk, then the shift to a lower threshold corresponds to the extension of a treatment, from which almost all middle-aged men and women stand to benefit, to an increasingly high percentage of the population.

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Conflict of interest statement

The authors declare that there are no conflicts of interests.

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