Enabling person-centred guidance by accounting for direct treatment disutility and competing risks

Enabling person-centred guidance by accounting for direct treatment disutility and competing risks: A case-study in primary prevention of cardiovascular disease

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Background

UK guidelines recommend statins for people with a 10-year risk of cardiovascular events (QRisk) exceeding 10% (NICE CG181[1]), on the grounds that they improve quality-adjusted life years (QALYs) by delaying cardiovascular events and therefore increasing both life expectancy and quality of life.

However, many cardiovascular risk factors are also risk factors for other life-threatening illnesses. These competing causes of mortality and morbidity might decrease people's capacity to benefit from statins.

In addition, emerging evidence suggests that, for many, the act of taking daily pills such as statins is not benign. A time-trade-off exercise[2] found that most patients and members of the public would be willing to live for a slightly shorter time if they could avoid taking statins, i.e. they are associated with 'direct treatment disutility' (DTD).

Previous analyses – including the health economic model underpinning CG181 – have not accounted for how competing risks and DTD might influence the balance of benefits, harms and costs associated with statins. We explored how doing so might enable person-centred guidance, by reflecting the circumstances and preferences of people to whom we would currently offer statins.

Methods

We replicated and modified the state-transition model from CG181 (NHS perspective, lifetime horizon, 3.5% discount rate). This model simulates the occurrence of cardiovascular events and death in people with no history of cardiovascular disease, comparing 'high-intensity statins' (atorvastatin 20mg once daily) with none.

To ensure that competing risk of non-cardiovascular death varies appropriately with cardiovascular risk, we fitted a relative survival model[3] to a large, national dataset (UKCPRD), using 10-year QRisk3 as a covariate of non-cardiovascular survival. We applied the resulting hazard ratios to national lifetables from 2017–19. We also explored the impact of greater or lesser competing hazards of death.

We explored DTD of statins for primary prevention in 3 scenarios: one assumed no DTD; one used the mean disutility estimated by Thompson et al.[2] (0.033); one assumed DTD would linearly decline from 0.033 to 0 over 10 years.

We updated statin costs to 2019–20 and used a new analysis of UKCPRD data to assign the types of first cardiovascular event experienced by people at different ages and levels of risk. We undertook a new analysis of Health Survey for England data to estimate the underlying quality of life of people with no cardiovascular history.

Results

When assessing the benefits of statins, the impact of adjusting for competing risk depends on a person's cardiovascular risk compared with an average person of their sex and age. For example, a 60-year-old woman with a 10-year QRisk of 10% has above-average risk, so her expected QALYs decrease by around 0.65. This means she is likely to die before she accrues all of the benefits of statins previously predicted for her (see table). Conversely, a 60-year-old man with a 10-year QRisk of 10% has below-average risk, so he accrues around 0.6 QALYs more when adjusting for competing risk, potentially increasing his capacity to benefit from statins (see table). However, these adjustments affect treatment and non-treatment arms to a fairly similar extent, so statins remain cost effective for all people with a 10-year QRisk of 10% (incremental cost-effectiveness ratios [ICERs] remain under £5,000 per QALY gained; see table).

Because statins are associated with very little disutility in the CG181 model, they generate some degree of QALY benefit for people at any age and any level of cardiovascular risk (see left-hand column of figure). However, when we introduce DTD, the optimal threshold for treatment begins to depend on age. For someone who is persistently averse to pill-taking (implying lifelong DTD; right-hand column of figure), many combinations of age and risk result in statins doing more harm than good (black area in figure). For example, people with such preferences in their mid-70s and older would need a 10-year QRisk of over 30% before statins would be net-beneficial. If they had additional long-term conditions leading to a doubled risk of non-cardiovascular death, that threshold would rise to 40%. Even if we assume taking pills is something people get used to (time-limited DTD), it is easy to find combinations of age and risk where statins' DTD outweighs their cardiovascular benefits.

Figure: Expected QALY gains associated with statins according to age, CV risk, DTD and competing mortality (50:50 men:women)

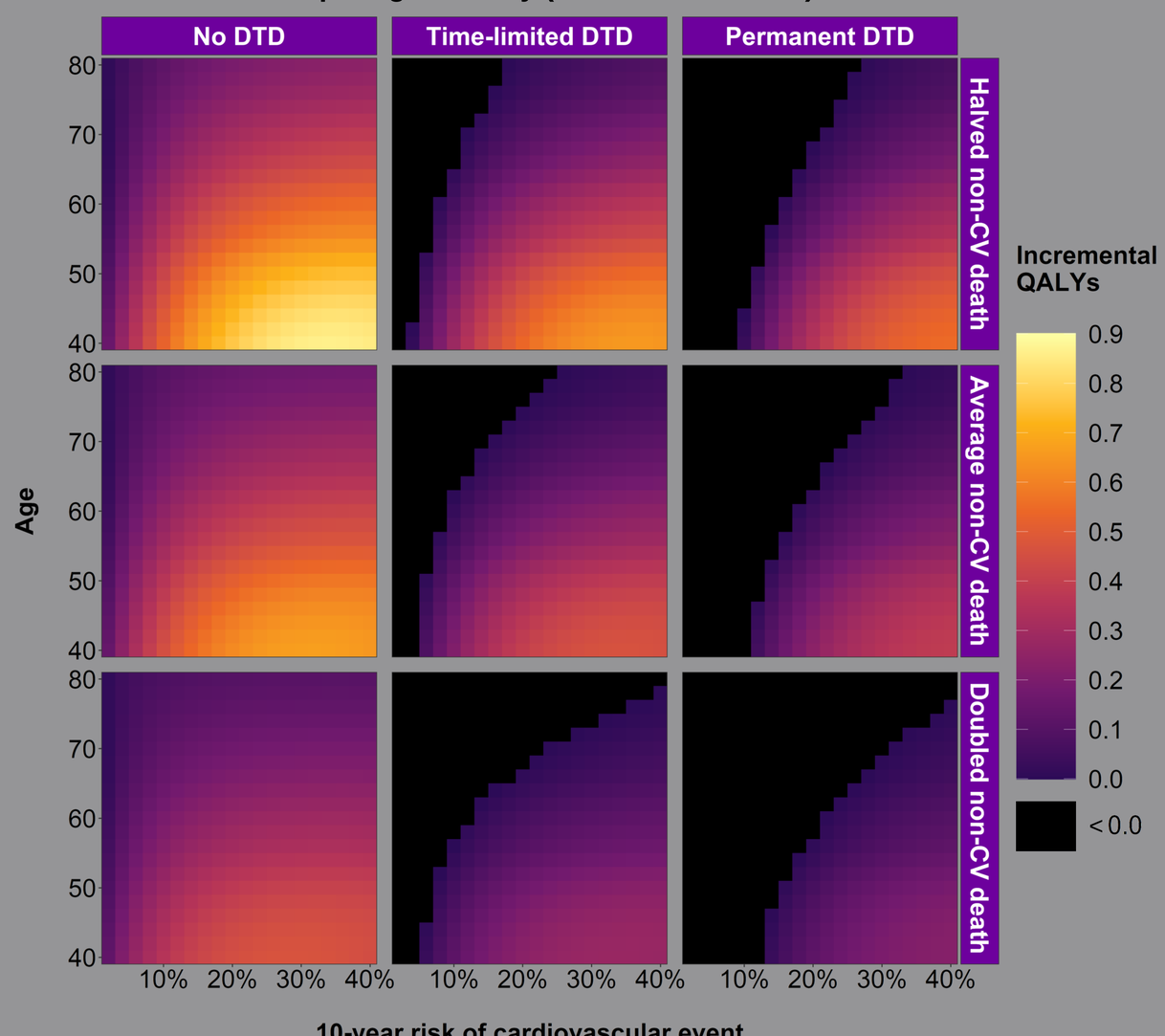

Table: Cost–utility results for 60-year-olds with a 10-year CV risk of 10% (no DTD)

	Absolute		Incremental		
	Costs	QALYs	Costs	QALYs	ICER
Unadjusted non-CV mortality (per CG181)					
Women					
No statins	£3,010	13.002			
High-intensity statins	£4,207	13.263	£1,196	0.261	£4,583
Men					
No statins	£3,113	12.668			
High-intensity statins	£4,288	12.905	£1,175	0.237	£4,957
Non-CV mortality adjusted for CV risk					
Women					
No statins	£2,694	12.346			
High-intensity statins	£3,826	12.582	£1,131	0.235	£4,805
Men					
No statins	£3,470	13.260			
High-intensity statins	£4,720	13.519	£1,250	0.258	£4,843

Implications

Accounting for competing risks decreases the QALY-gain associated with statins for people at higher-than-average risk for their age and increases it for people with lower-than-average risk. However, statins remain good value for money for almost everyone.

Recent evidence suggests that adverse events commonly ascribed to statins are predominantly nocebo effects[4]. We think DTD provides a useful paradigm in which to conceptualise these effects as an authentic harm of treatment. Our results could be used to alter population-level guidance (e.g. by applying average DTD for the whole population). However, we argue that it is more appropriate to consider these factors on an individual level, to facilitate person-centred care. Prescribers should consider that, when benefits of statins are re-evaluated according to competing risk, they may no longer be worth the perceived burden of treatment.

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FUNDED BY NIHR | National Institute for Health Research

This research is funded by the National Institute for Health Research (NIHR) Health Services and Delivery Research (15/12/22). The views expressed are those of the authors and not necessarily those of the NIHR or the Department of Health and Social Care.

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