Dear Drs Heseltine and Murray

Re: letter regarding BHIVA rapid guidance on statins for primary prevention of CVD

Thank you for your letter and apologies for the time taken to respond.

Holistic prevention

We agree with your statement 'As clinicians we can do better than simply administering statins to those >40'. Indeed, our first recommendation in the BHIVA statin guidance emphasises the importance of a holistic approach to managing CVD risk, with explicit mention of the lifestyle modifications that you mention in the final paragraph of your letter, and recommendations of signposting to appropriate support for those who need or want it.

Prioritisation

We also agree that it is a priority to manage people with the highest estimated CVD risk in line with existing national guidelines (NICE and SIGN) first. That said, recognising the shortfalls of short-term risk assessment and the benefits of a lifetime risk-based approach, NICE now recommends that statins can be discussed and initiated as part of shared decision-making in those with an estimated risk below 10% over 10 years. In keeping with this, we have therefore suggested clinics prioritise those with an estimated risk greater than 5%; this is in line with NICE guidance which recognises that QRISK3 may underestimate risk in people with HIV (consistent with data you have flagged). This recommendation would certainly cover the 20% of people in your own cohort who are at high risk and not currently on a statin.

The case for shared decision-making and preserving health rather than treating disease is highlighted by recent studies. The Global Cardiovascular Risk Consortium showed that amongst more than 1.5 million people, approximately 57% of all CVD and 20% of deaths from any cause, could be attributed to five modifiable risk factors [1]. Even in childhood the presence of CVD risk factors strongly identifies those most likely to develop CVD in early adult life [2]. Moreover, the relative risk reduction per mmol/L lowering of LDL-cholesterol with statins, and other lipid lowering therapies, is nearly double among those with annualised event rates of <1% versus >2% (39% *vs* 21% over 5 years, respectively), likely reflecting a lower atherosclerosis burden [3]. The same study concluded that the absolute risk reduction in CVD events in people with a 10-year estimated risk less than 10% 'greatly exceeds any known hazards of statin therapy'. Taken together we believe our recommendations are consistent with the totality of understanding about the life-course of atherosclerosis and benefits of early intervention.

CT coronary angiography (CTCA)

There are no national recommendations for CTCA as a screening tool for asymptomatic CVD. Indeed, when NICE recommended CTCA as a first-line investigation for suspected cardiac chest pain in 2016, significant concerns were raised regarding capacity to provide equitable access to the test [4]. A

recent publication highlighted a shortage of appropriate scanners and personnel as a challenge for implementing CTCA in line with national guidance [5], let alone extending its application to asymptomatic people. We would question the ethics of BHIVA routinely recommending a test for which there is insufficient capacity to meet existing national recommendations, and that would likely increase health inequalities in a population that is already disproportionately affected by these for many reasons.

We disagree with your suggestion that CTCA is the optimal measure of 'true cardiovascular risk'. Atherosclerosis is driven by a complex interaction between inherited genetic vulnerability and inherited or lifestyle-related risk factors over time [6]. Positive remodelling, whereby an increase of up to 40% in intima–media size can occur before luminal narrowing is apparent on angiography, means the substrate for atherosclerotic CVD is already abundant by the time arterial stenosis is evident [7]. Furthermore, one study you quote in support of the purported lack of benefit of statins was a retrospective cohort of people without HIV undergoing coronary artery calcium scoring (CACS) which examined the impact of non-randomised statin use [8]. Since these people did not undergo CTCA the trial does not support your assertion that 'individuals with no evidence of coronary plaque on CTCA….derive no benefit from statin therapy'. Moreover, another study you reference [9] demonstrated that people with HIV have less calcified plaque than their counterparts without HIV, thus raising the question of how valid CACS is as a predictive tool. Our concern is consistent with other analyses which have concluded that further research is necessary [10].

We disagree with your interpretation of the CTCA sub-study of REPRIEVE as showing 'most individuals, across all risk profiles, had no coronary plaque on CT'. Almost half (49%) of the 755 participants undergoing baseline CTCA had evidence of coronary plaque, including 30% of the individuals with ASCVD risk scores of 0–<2.5% [11]. While critical stenosis was rare, around 20% had higher-risk plaque features. We interpret this as showing that people with HIV have a significant prevalence of coronary plaque, despite a low to moderate estimated CVD risk; a similar interpretation was made by the authors of the paper.

With respect to imaging, global guidelines recommend assessing the vessel wall, through CACS, which is known to reclassify approximately 20% of patients. None of these major guidelines recommend CTCA, as you suggest, which focuses on luminal disease [12]. Where an individual has a CACS of zero calcium, the short-term event rate is low and the benefit of any intervention modest in the short term. In that situation we agree that this can be considered when reviewing the relative benefit of starting a statin as part of individualised joint decision-making and we have added a point of clarification to this effect. However, any decision must consider both short-term and lifetime approaches where lifetime risk may be high. An exemplar from another disease area would be CACS in familial hypercholesterolaemia where a calcium score of zero in a relatively young person would not provide reassurance about lifetime risk.

Diabetes risk

Thank you for highlighting the association between statin use and incident diabetes, as also summarised in the BHIVA guidance. While we acknowledge your concern that 'type II diabetes was induced in four participants for each type 1 myocardial infarction prevented', this does not account for the fact that it is generally agreed that CVD benefit outweighs diabetes risk when the totality of evidence is considered from all statin trials [13]. Here for every 1000 years of exposure approximately seven total CVD events (not just myocardial infarction) would be prevented for every

extra case of diabetes. Further evidence, if necessary, is provided by an analysis of the JUPITER trial [14]. Individuals with one or more major diabetes risk factors were at higher risk of developing diabetes than those with none. Among those with diabetes risk factors, statins prevented 134 vascular events or deaths for every 54 new cases of diabetes. For those with no major diabetes risk factors, statins prevented 86 vascular events or deaths with no new cases of diabetes diagnosed. In the 486 participants who developed diabetes during follow-up (270 on rosuvastatin *vs* 216 on placebo) statins yielded a similar CVD risk reduction to that for the whole trial population. By comparison with placebo, statins accelerated the average time to diagnosis of diabetes by 5.4 weeks (84.3 *vs* 89.7 weeks on placebo). Please note that within the REPRIEVE trial new-onset diabetes was defined using the MedDRA system organ classification adverse event reporting (Table S7), not through the systematic measurement of fasting glucose/HbA1c and initiation of glucose-lowering medications through a formal blinded adjudication process (which is now the routine assessment for novel therapies). In this regard there was no worsening of glucose in REPRIEVE (Figure S6) consistent with meta-analyses of pitavastatin, which failed to show an association between dose or duration of treatment and diabetes risk [15]. Furthermore, the use of a dichotomous definition of diabetes in REPRIEVE means that even small changes in HbA1C, which themselves may be clinically unimportant, may label an individual as having diabetes, a condition in which CVD risk is heterogeneous [16].

Finally, recent US guidance on statins for primary prevention of CVD in people with HIV is consistent with BHIVA guidance, recommending an at least moderate-intensity statin to people over 40 years of age with an estimated 10-year CVD risk of 5–20% and favouring a statin for those with a risk of less than 5% [17].

In summary, we thank you again for your comments and have made the aforementioned amendment to a revised version of the guidance. CVD is an increasingly important issue for people with HIV and BHIVA guidance will evolve. There is insufficient evidence for CTCA as a screening tool or for significant harm resulting from any small impact of statins on glycaemic control; should evidence to the contrary emerge our guidance will be updated accordingly.

Yours sincerely,

Laura Waters, Yvonne Gilleece, Jasmini Alagaratnam, Ben Cromarty, Ming Lee, Nadia Naous, Nicoletta Policek, Caroline Sabin, John Walsh, Alan Winston, Kausik K Ray

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