In summary therefore, long-term, low-dose prophylactic aspirin would seem to be remarkably safe, probably far safer than implied by Cuzick et al. with their estimate of 2 deaths caused by aspirin for every 17 vascular and cancer deaths prevented. Furthermore, if subjects are adequately screened for gastric pathology and for hypertension and appropriately treated if present, fatal internal bleeding attributable to aspirin is likely to be exceedingly rare.

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disclosure
PE is an occasional advisor to Bayer HealthCare. All remaining authors have declared no conflicts of interest.

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Reply to the letter to the editor
‘The harms of low-dose aspirin prophylaxis are overstated’ by P. Elwood and G. Morgan

We thank Elwood and Morgan [1] for drawing attention to estimation of harms in our paper [2]. As stated in our paper, we opted for conservative analyses, and this implied that we chose to err on the side of over-estimating harms. Therefore, as Elwood and Morgan [1] suggest, it is possible that the true harms of prophylactic aspirin are lower than we estimated. We also undertook an extensive assessment of harms and this is now published as a separate paper [3]. Here, we draw attention to some important findings in support of our approach for estimation of harms associated with aspirin use.

The two extra deaths per 1000 persons reported in the media [4] comprise of deaths due stroke, GI bleeding or peptic ulcer. Stroke deaths account for approximately two thirds of these extra deaths. The ATT Collaborators’ meta-analysis [5] reported a 21% increase in stroke deaths with aspirin use in primary prevention trials. This excess was primarily driven by an increase in the number of fatal haemorrhagic strokes (73% increase, \(P = 0.02\)); the number of other fatal strokes were similar in users and non-users. We used this effect size to estimate excess stroke deaths as the ATT data are most relevant for prophylactic use in the general population [2, 3], even though the overall increase in fatal strokes was not statistically significant.

Elwood and Morgan [1] suggest that 5% of GI bleeds are fatal. Our systematic search [3] identified studies reporting rates between 5% and 10.7%. We also noted that co-morbidities were associated with a higher death rate [6–8] and the risk of death also increased with increasing age [9, 10]. Therefore, we assumed fatality rates of 5% below age 70 years and 10% above that age in our analyses. However, we acknowledge that these fatality rates were derived from hospital-based studies, i.e. the denominator was major bleeding and, therefore, the fatality rates for all bleeding (major and minor) in general population are likely to be lower [3]. Indeed, we found that the rates of deaths attributable to GI bleeding or peptic ulcer reported by the Office of National Statistics (ONS) for the year 2008 were 50%–60% lower than our estimates [3], although the ONS rates could also be an under-estimate.

Several systematic reviews [5, 11–13] have reported that the relative increase in aspirin-associated risk of fatal bleeding is lower (20%–30%) than the increase in the risk of bleeding overall [3]. We agree with Elwood and Morgan [1] that this suggests that bleeding associated with aspirin is less likely to be fatal. However, further evidence (and perhaps an improved mechanistic understanding) is necessary before such effect can be incorporated into benefit-harm models. We also agree with Elwood and Morgan that optimal control of hypertension should be an important consideration in mitigation of aspirin related harms as we have already discussed [2, 3].

Three primary prevention trials—the Women’s Health Study (WHS), the Physician’s Health Study (PHS) and the British Doctors’ Trial (BDT) have reported on peptic ulcers. All three show an aspirin-associated 20%–60% increase in the risk of peptic
ulcer [14–16]. The fatality rates in complicated peptic ulcers are high—for example above 15%–20% for perforated gastric or duodenal ulcers in individuals aged 65 or older [10]. Therefore, we disagree with Elwood and Morgan’s [1] assertion that aspirin is unlikely to be responsible for peptic ulceration or fatal ulceration.

Excess bleeding events are more frequent during initial period after starting aspirin [13, 17] and the excess risk disappears after 5 years of aspirin use [13]. Observational studies such as the Health Professionals Follow-up Study (HPFS) [18] and the Nurses’ Health Study (NHS) [19] also show that the excess bleeding risk is lower in long-term users (>5 years). Apart from gastric adaptation, use of gastro-protective drugs or stopping of aspirin use could also contribute to this effect [3]. Since we took an average increase in the risk over a prolonged period of time, this already accounts for the initial sharp rise in the risk (often twofold or more) and minimal or no increase in the risk later on.

In summary, it is quite possible that the harms due to aspirin use are lower than what we have estimated, but the conservative approach we have used [2, 3] ensures that they are very unlikely to be higher.

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**Albumin to globulin ratio, a predictor or a misleading tool?**

On the grounds of progressive improvements in medicine, both doctors and patients are seeking more data about diseases, especially the most frightening one, cancer. As studied by Suh et al. [1], chronic inflammatory markers have been studied for this purpose in the last 10 years. The retrospective analysis of Suh et al. provided important clues about simple laboratory test, albumin/ globulin ratio. Similar to other studies about inflammatory parameters, it is a difficult area to study. For a better conclusion, some points should have been pointed out in the analysis.

The exclusion of causatives of chronic inflammation and decreased albumin production is an important part of the design. In addition to chronic diseases, rheumatologic diseases which are important causatives of chronic inflammation should have been excluded in the analysis. Another important issue that can mislead the results is the elderly population which constitutes the 24.2% of the study group. The geriatric population, due to increased incidence of geriatric syndromes, is prone to malnutrition and also hypoalbuminemia. This result can be observed in the Table 1 in which patients in the group of >60 years of age have more tendencies to have albumin/ globulin ratio <1.1. When risk and cancer types are analyzed, increased risk was found in the low albumin/globulin ratio group. The risk was found to be more in the gastrointestinal cancers when compared with breast and lung cancer. This may also be a result of