

**Cover title:** Bleeding costs on long-term antiplatelet therapy

**Title:** Costs of bleeding on long-term antiplatelet treatment without routine co-prescription of proton-pump inhibitors

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**Tables:** 1. Baseline characteristics

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**Background** Long-term antiplatelet treatment is associated with major bleeding.

**Aims** To determine the costs associated with major bleeding in patients treated with aspirin-based antiplatelet treatment for secondary prevention of vascular events without routine prescription of proton-pump inhibitors (PPI) and to estimate the likely long-term savings from routine co-prescription.

**Methods** In a prospective population-based cohort study of TIA, ischaemic stroke, and MI treated with antiplatelet drugs, we evaluated hospital care costs associated with bleed management during 10-year follow-up. Bleeding-associated costs were averaged across all patients. For upper GI-bleeds, mean costs were compared with the cost of routine co-prescription of PPI.

**Results** Among 3166 patients on antiplatelet therapy with 405 first bleeding events, the average cost of major bleeding was \$13,093 (S.D. 20,501), with similar costs for upper GI bleeds and intracranial bleeds ( $p=0.235$ ), but a greater total population cost for upper GI bleeds (\$1,158,385 vs. \$740,123). Averaged across all patients, the 10-year cost of major bleeding was \$838 (95%CI: 680-1,007), \$411 due to upper GI bleeding, the cost of which increased from \$175 in those aged <75 years to \$644 at age  $\geq 75$  years ( $p<0.0001$ ). The corresponding costs of routine life-long co-prescription of PPI to those patients not on prior treatment were \$85 (84-88) and \$39 (38-42).

**Conclusions** In secondary prevention with aspirin-based antiplatelet treatment without routine PPI use, the long-term costs of upper-GI bleeding at age  $\geq 75$  years are much higher than at younger age groups, and are at least 10-fold greater than the drug cost of routine co-prescription of PPI.

## Introduction

Antiplatelet drugs are effective for preventing recurrent ischaemic vascular events and a large proportion of adults aged  $\geq 75$  years routinely take aspirin or other antiplatelet drugs for secondary prevention, consistent with guideline recommendations for life-long treatment.<sup>1,2</sup> However, randomised trials have shown that antiplatelet drugs increase the risk of major bleeding, especially upper-gastrointestinal (GI) bleeds,<sup>3</sup> particularly at older ages.<sup>4</sup> Moreover, the severity and outcome of bleeds during secondary prevention of vascular events with antiplatelet therapy appear to be worse than previous trial evidence might suggest, particularly in the elderly.<sup>5</sup>

One approach to reduce the long-term risks of bleeding in older individuals taking aspirin for secondary prevention is co-prescription with proton pump inhibitors (PPI).<sup>8</sup> However, although risk of upper GI bleeding can be reduced by at least 50% by PPI with low cost (treatment with lansoprazole 15mg costs less than \$0.03 a day in the UK),<sup>6,7</sup> current guidelines make no recommendations on co-prescription of PPI,<sup>1,2</sup> and their use is not routine.

Low rates of PPI co-prescription could be due to the belief that upper-GI bleeding is relatively benign with low case fatality rates observed in trials, but there is now good evidence that this is not the case in older individuals in routine clinical practice.<sup>5</sup> Low rates may also reflect concerns about adverse events particularly of long-term use,<sup>8</sup> some of which, including cancer and dementia, could undermine cost-effectiveness even at relatively low rates. However, very recent trial evidence has shown that PPI are well tolerated during long-term follow-up, with no evidence in those receiving PPI of increased rates of dementia, cancer, or other major adverse events, when compared to placebo.<sup>9,10</sup>

Given this recent evidence of higher than expected risks of major upper GI bleeding on antiplatelet treatment at older ages, and of the long-term safety of PPI, guidelines on routine co-prescription of PPI in clinical practice will require estimates of cost-effectiveness. The impact of treating upper-GI bleeds on the healthcare system is non-negligible, with previous studies highlighting high levels of costs after bleeding (Online supplementary material Appendix 1). However, none of the previous cost studies evaluated the costs of bleeding specifically in secondary prevention of vascular events with antiplatelet therapy and the majority included only younger patients.

Using data from a prospective population-based study of all patients with transient ischaemic attack (TIA), ischaemic stroke or myocardial infarction (MI) treated with antiplatelet agents without routine use of PPI, we aimed to determine the hospital care costs associated with major bleeding in patients treated with aspirin-based antiplatelet treatment for secondary prevention of vascular events without routine prescription of PPI and to estimate the likely long-term bleed-related cost saving from routine co-prescription.

## Methods

The Oxford Vascular Study (OXVASC) is a population-based study of the incidence and outcome of all acute vascular events in a population of 92,728 individuals, irrespective of age, registered with 100 general practitioners in nine general practices in Oxfordshire, UK. The definitions of vascular events, and the multiple overlapping methods used to achieve near complete ascertainment of all individuals with TIA, stroke or MI have been reported previously (online supplementary material Appendix 2).<sup>5,11</sup> Bleeding events were identified by face-to-face follow-up, daily searches of all hospital admissions, review of administrative diagnostic codes from hospital and primary care records, and by regular searches of centralised blood transfusion records as reported previously.<sup>5</sup> All deaths (with causes) during follow-up were also recorded from death certificates and coroners' reports.

We studied consecutive patients with first-in-the-study-period acute TIA, ischaemic stroke or MI who were treated with antiplatelet drugs after the event from 2002-2012 with follow-up to 2013. Patients who started or continued oral anticoagulants after an event were excluded, but those on pre-morbid oral anticoagulants who were switched to antiplatelet therapy post-event were included. Patients who took anticoagulants during subsequent follow-up were censored at the time of starting but patients coming off antiplatelet treatment were included (<15% at 5-years). Patients were followed up face-to-face at 30 days, 6 months, 1, 5 and 10 years by a study nurse or physician.

For this analysis only the first major (both non-life- and life-threatening, which required hospital attention) and fatal bleeds were included. Site of bleeding was classified as intracranial (intracerebral, subdural or subarachnoid) and extracranial (upper-GI, lower-GI, epistaxis, genitourinary, and other). Only the cost and outcome of the first bleed are assessed in this study, as after the first bleed, antiplatelet therapy would often be stopped and/or gastric protection such as a PPI started. We did not include the costs of treating serious adverse events relating to long-term use of PPI as randomised evidence shows no significant increase in such events when compared to placebo.<sup>9,10</sup>

### Resource use

All patients' centralised Hospital Episodes Statistics (HES) records, as well as those from the Oxford University Hospitals NHS Foundation Trust, are reviewed. Information on any accident and emergency visit, emergency transport, day case, or hospitalisation were obtained. For each admission into hospital, paper and electronic medical records were reviewed and details of bleeds

recorded.<sup>5</sup> Information was recorded on the date of admission and discharges, including the dates of transfers between different specialty wards. Hospitalisations during which patients were admitted and discharged on the same day were classified as day cases.

For all patients with major bleeds, hospital resource use was obtained from the date of TIA, ischaemic stroke or MI until death or 31 March 2014. This allowed us to obtain hospital resource use for at least one year after the date of the bleed. For this analysis we only included hospital resource use and costs directly attributable to major bleeds, which we defined as the first hospital admission occurring within 7 days of the bleed, which was further confirmed by subsequent paper record review.

Additionally, if the patient was discharged from hospital and then subsequently admitted to hospital or A&E within 7 days of discharge that hospitalisation or A&E visit was also linked to the bleed.

All healthcare unit costs were derived from the schedule of National Health Service reference costs,<sup>12</sup> and costs are reported in 2016/17 prices.<sup>13</sup> All costs were converted from UK pounds sterling (£) to US dollars (\$), based on the rate of purchasing power parities in 2017 (\$1 is equal to £0.691-  
<https://data.oecd.org/conversion/purchasing-power-parities-ppp.htm#indicator-chart>).

#### Statistical analysis

Hospital costs associated with bleeding were estimated for all those patients with major/fatal bleeding, and reported as means together with standard deviation (S.D.). We assessed whether the costs varied univariately in terms of age, initial ischaemic event, bleeding site, and severity of major bleed. A generalised linear gamma model with log identity was used to assess the independent baseline predictors of total costs after the bleed including these variables, gender and time elapsed between bleed and initial vascular event.

Mean bleed-related costs were averaged across all patients on antiplatelet therapy after a TIA, ischaemic stroke or MI to assess the overall 10-year cost. Not all patients were followed-up for ascertainment of a bleeding event for the full 10 years. To avoid underestimating costs by assuming that patients who did not reach full follow-up ceased having major bleeding events after the point where they were last observed, 10-year cost results are presented for the whole patient sample after adjusting for censoring.<sup>14</sup> Mean-censor adjusted costs are reported as means together with their 95%

confidence intervals (CIs), which were derived using 1,000 bootstrap estimates. Costs incurred by patients after the first year were also discounted using an annual rate of 3.5%.

We estimated the proportion of this cost attributable to antiplatelet-therapy. We applied the relative risk estimates for major intracranial and extracranial bleeding on aspirin vs. placebo in secondary prevention.<sup>3</sup> For patients aged  $\geq 75$  years, we also performed sensitivity analyses using the equivalent estimates from the ASPREE trial.<sup>4</sup> Relative risks of the impact of antiplatelet therapy on bleeding were converted to population attributable fractions (PAF), which were combined with the censor-adjusted mean costs to obtain a mean censor-adjusted bleeding cost attributable to antiplatelet therapy alongside 95% CI.

The average 10-year costs of routine co-prescription of PPI to all patients after TIA, stroke or MI onset with lansoprazole 15 mg were also estimated. The daily cost of lansoprazole (£0.02, \$0.03)<sup>7</sup> was applied until major upper GI bleed or death, with 10-year mean costs of PPI co-prescription also adjusted for censoring. Using information on the 10-year mean costs of PPI co-prescription, mean costs of upper GI bleeds, and the effect of routine PPI co-prescription at preventing upper GI bleeds,<sup>6</sup> we evaluated the 10-year mean cost savings associated with routine PPI co-prescription. Given that meta-analyses of small studies can overestimate the effectiveness of the intervention,<sup>15</sup> and in light of new evidence from the COMPASS trial,<sup>16</sup> we performed a sensitivity analysis by reducing the efficacy of routine PPI co-prescription (i.e. from a relative risk of 0.26 to 0.50). In addition, as 24% (n=773) and 33% (n=947) of patients were on gastric protection pre-morbidly and 1 month after the initial ischaemic event, respectively, we undertook additional sensitivity analyses by excluding these patients.

All analyses were undertaken in STATA SE13, with statistical significance being set at  $p < 0.050$ .

## Results

Of 3,166 patients (**Table 1**), 2,072 (65.4%) with cerebrovascular events (895 TIA and 1,177 ischaemic stroke) and 1,094 (34.6%) presented with MI. 1,582 (50.0%) were aged  $\geq 75$  years. Less than a quarter of these patients (n=773, 24%) were on premorbid gastric protection (PPI or H2-antagonist). Of 405 bleeding events presenting to medical attention during 13,509 patient-years of follow-up, 187 bleeds were major (63 non-life threatening, 80 life-threatening and 44 fatal).

For patients with a major bleed, the mean related-bleed cost was \$13,093 (25,501 – **Table 2**).

Patients with major life-threatening bleeds incurred the highest costs, \$19,217 (25,619), followed by non-life-threatening bleeds (\$12,046), and fatal bleeds (\$3,453;  $p < 0.0001$ ). There were no differences in hospital care costs in terms of bleed site ( $p = 0.342$ ), type of initial ischaemic event ( $p = 0.520$ ) and age groups ( $p = 0.800$ ), with consistent results in regression analysis (online supplementary material Appendix 3).

Averaged over the 3,166 patients on long-term antiplatelet therapy, the 10-year cost of major bleeding was \$838 (680-1,007 - **Table 3**). The 10-year costs of bleeding were, Costs were significantly higher (\$1,149, 810-1,470) in those aged  $\geq 75$  years than in those aged  $< 75$  years (\$525, 329-770,  $p < 0.0001$ ). The online supplementary material Appendices 4 and 5 provide further cost breakdowns by narrower age groups, and also report discounted cost results.

50% (\$411) of the bleed-cost was due to upper GI bleeds (**Table 3**), of which \$259 (77-384) were likely to be due to antiplatelet therapy. These costs increased with age: \$110 (26-227) in those aged  $< 75$  compared with \$407 (120-618) in those aged  $\geq 75$  years ( $p < 0.001$ ). The online supplementary Appendix 6 reports costs results using more conservative PAF estimates based on ASPREE.

Assuming a relative risk of 0.26, routine PPI co-prescription in patients treated with aspirin-based antiplatelet treatment for secondary prevention of vascular events would reduce mean 10-year costs of upper GI bleeding from \$411 to \$107 (95%CI: 51-195, **Table 4**). By contrast, the mean costs of routine PPI co-prescription over 10 years would be \$67 (95%CI: 65-68), with routine PPI co-prescription generating mean net cost savings of \$237 (95%CI: 126-359) per patient. Cost savings of routine PPI co-prescription increased by age, from \$45 (95%CI: -38-156) in those aged  $< 75$  years to \$437 (95%CI: 155-692) in those aged  $\geq 75$  years.



Results of the sensitivity analyses are reported in the. In all the scenarios investigated in the sensitivity analyses (online supplementary material Appendix 7), routine co-prescription of PPI generated cost savings in those aged  $\geq 75$  years.

## Discussion

We previously found that the risks at age  $\geq 75$  years were higher and more sustained than at younger ages, and outcome was much worse, with a substantial risk of disabling/fatal upper-GI bleeding.<sup>5</sup> In this study, we find that although the costs of treating an individual major bleed did not vary significantly by age, the 10-year economic burden of major bleeding was also considerably higher in older age groups.

As far as we are aware, this is the first study to evaluate the costs of major bleeding in a population on long-term antiplatelet therapy for secondary prevention of vascular events, allowing us to compare, in the same population, the costs of major bleeding indifferent sites. Our study found that the individual costs of treating major bleeding are considerable. On average, the cost per patient of treating a major bleed was \$13,093, with similar costs identified for intracranial and upper GI bleeds (\$16,446 vs. \$11,941, respectively,  $p=0.235$ ).

We found that the expected 10-year costs of PPI provision in patients on long-term antiplatelet therapy after an initial ischaemic event would be \$67 per patient. These costs were considerably lower than the average 10-year costs associated with upper GI bleeding (\$411 per patient), especially in older age groups. We estimated the mean 10-year cost savings of routine PPI co-prescription in patients treated with aspirin-based antiplatelet treatment for secondary prevention of vascular events to be \$237 per patient. These savings increased considerably with age from \$45 for those aged  $<75$  years to \$437 for those aged  $\geq 75$  years. Our results, therefore, further strengthen the case for PPI co-prescription, and suggest its use might be most cost-saving in older ages.

Strengths of our study are its prospective population-based design with inclusion of all treated patients irrespective of age and frailty, long-term face-to-face follow-up, reliable ascertainment of bleeding events through multiple sources, and assessment of outcome, but there are limitations. First, PPI costs are higher in countries like the USA,<sup>17</sup> which might limit generalisability of our findings. However, these countries also have higher overall healthcare costs,<sup>18</sup> making it likely that the costs upper GI bleed treatment is also higher. As a result, we believe that the implications of this research are generalisable to other developed countries.

Secondly, many patients had not yet reached full ten-year follow-up and were treated as censored. Thirdly, our estimates of the population attributable factor may have been conservative. We applied the reported increased risk of major bleeding on aspirin in secondary prevention trials to all age groups in our non-trial population.<sup>3</sup> Although we also performed a sensitivity analysis using recent estimates from the ASPREE trial,<sup>4</sup> which was done in older healthy individuals, the relative risk of major bleeding in primary prevention may underestimate that expected in a more frail secondary prevention population. Finally, as recent long-term randomised evidence from the AspECT and COMPASS trials have shown that PPI was well tolerated and safe, we did not attempt to estimate the hospital costs in relation to potential adverse effects of long-term PPI use.<sup>6</sup> In AspECT, during a median follow-up of 8.9 years, the proportion of patients with serious adverse reactions relating to PPI was less than 1% in both patients treated with low- and high-dose esomeprazole.<sup>9</sup> In the COMPASS trial,<sup>10</sup> where mean patient age was 68 years and mean follow-up was 3 years, PPI therapy was only found to be associated with an increased risk of enteric infections and the absolute risk was very low.

In conclusion, in secondary prevention with aspirin-based antiplatelet treatment without routine PPI use, the long-term costs associated with bleeding at age  $\geq 75$  years are much higher than in the younger age groups included in previous trials, with a particularly higher economic burden of upper-GI bleeding. Our results further strengthen the case for PPI co-prescription, particularly in those  $\geq 75$  years.

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**Table 1. Baseline characteristics**

<b>All patients (n=3,166)</b>	
<b>Age at time of event</b> , years mean (S.D.)	73(13)
<b>Females</b>	1,449(46)
<b>Initial ischaemic event</b>	
Ischaemic stroke	1,177(37)
Transient ischaemic attack	895(28)
Myocardial infarction	1,094(35)
<b>Bleed severity</b>	
No bleeding	2,761(87)
Minor	218(7)
Major – non-life threatening	63(2)
Major – life-threatening	80(3)
Fatal	44(1)
<b>Bleed site</b>	
No bleeding	2,761(87)
Intracranial	45(1)
Upper gastrointestinal	162(5)
Lower gastrointestinal	56(2)
Other	142(4)
<b>Time elapsed from event to bleed</b> , years mean (S.D.)	1.66(2.06)
<b>Major bleed patients (n=187)</b>	
<b>Age at time of event</b> , years mean (S.D.)	78(10)
<b>Age at time of bleed</b> , years mean (S.D.)	80(10)
<b>Females</b>	89(48)
<b>Initial ischaemic event</b>	
Ischaemic stroke	69(37)
Transient ischaemic attack	48(26)
Myocardial infarction	70(37)
<b>Bleed severity</b>	
Major – non-life threatening	63(34)
Major – life-threatening	80(43)
Fatal	44(24)
<b>Bleed site</b>	
Intracranial	45(24)
Upper gastrointestinal	97(52)
Lower gastrointestinal	16(9)
Other	29(16)
<b>Time elapsed from event to bleed</b> , years mean (S.D.)	1.46(1.89)

All variables reported as n (%) unless otherwise specified

**Table 2. Hospital care costs after major bleeding, mean \$ (S.D.)**

	<b>no.</b>	<b>A&amp;E costs</b>	<b>Ambulance costs</b>	<b>Inpatient stay costs</b>	<b>Day cases costs</b>	<b>Total costs</b>
All bleeds	187	93(124)	132(187)	12,751(20,327)	117(470)	13,093(20,501)
<b>Bleed severity</b>						
Major – non-life threat	63	69(124)	97(177)	11,781(17,067)	98(315)	12,046(17,185)
Major – life threat	80	94(123)	139(190)	18,836(25,360)	148(544)	19,217(25,619)
Fatal	44	113(124)	171(191)	3,078(4,444)	91(512)	3,453(4,440)
<b>Bleed site</b>						
Intracranial	45	137(126)	210(203)	15,970(25,705)	129(533)	16,446(25,740)
Upper GI	97	78(130)	116(191)	11,598(17,955)	149(525)	11,941(18,301)
Lower GI	16	49(90)	51(110)	6,654(6,116)	0	6,754(6,096)
Other	29	82(100)	113(149)	14,975(23,097)	59(236)	15,230(23,067)
<b>Initial ischaemic event</b>						
MI	70	82(133)	116(185)	11,088(19,272)	48(399)	11,334(17,829)
TIA	48	113(116)	169(184)	15,369(24,692)	91(276)	15,742(24,764)
Stroke	69	84(120)	124(191)	12,618(19,460)	207(612)	13,033(19,873)
<b>Age at time of bleed</b>						
< 75 years	52	72(104)	114(168)	13,003(20,984)	62(284)	13,252(21,019)
≥ 75 to < 85 years	72	103(146)	149(220)	13,747(21,488)	135(382)	14,133(21,693)
≥ 85 years	63	91(113)	127(161)	11,407(18,589)	143(653)	11,768(18,852)



**Table 3. 10-year mean bleeding costs after acute vascular events on antiplatelet therapy**

	<b>Mean bleeding costs, \$ (95% CI)</b>	<b>Bleeding due to antiplatelet therapy, PAF (95% CI)</b>	<b>Mean bleeding costs due to antiplatelet therapy, \$ (95% CI)</b>
<b>All ages (n=3,166)</b>			
<b>All bleeds</b>	838(680-1,007)		473(182-654)
<b>Intracranial</b>	243(151-329)	0.40(-0.03-0.66)	96(-9-182)
<b>Upper GI</b>	411(307-524)	0.63(0.20-0.83)	259(77-384)
<b>Lower GI</b>	42(23-62)	0.63(0.20-0.83)	26(7-46)
<b>Other bleeds</b>	146(80-229)	0.63(0.20-0.83)	93(23-169)
<b>&lt; 75 years (n=1,583)</b>			
<b>All bleeds</b>	525(329-770)		281(103-456)
<b>Intracranial</b>	217(107-356)	0.40(-0.03-0.66)	87(-9-178)
<b>Upper GI</b>	175(69-329)	0.63(0.20-0.83)	110(26-227)
<b>Lower GI</b>	19(3-39)	0.63(0.20-0.83)	12(1-26)
<b>Other bleeds</b>	114(23-259)	0.63(0.20-0.83)	72(9-177)
<b>≥ 75 years (n=1,583)</b>			
<b>All bleeds</b>	1,149(810-1,470)		664(265-939)
<b>Intracranial</b>	262(109-449)	0.40(-0.03-0.66)	104(-10-223)
<b>Upper GI</b>	644(420-889)	0.63(0.20-0.83)	407(120-618)
<b>Lower GI</b>	64(16-87)	0.63(0.20-0.83)	41(7-58)
<b>Other bleeds</b>	178(71-327)	0.63(0.20-0.83)	113(25-219)

**Table 4. 10-year cost savings in upper GI related-bleed costs after routine PPI co-prescription**

	(A) Mean upper GI bleeding costs without routine PPI co- prescription, \$ (95% CI)	(B) Relative risk of bleeding with routine PPI (95% CI)	(C=AxB) Mean upper GI bleeding costs with routine PPI, \$ (95% CI)	(D) Mean routine PPI costs, \$ (95% CI)	(E=C-A+D) Mean cost <u>savings</u> with routine PPI, \$ (95% CI)
<b>All patients</b>	411(307-524)	0.26(0.14-0.49)	107(51-195)	67(65-68)	237(126-359)
<b>&lt;75 years</b>	175(69-329)		45(14-113)	85(84-88)	45(-38-156)
<b>≥75 years</b>	644(420-889)		168(52-310)	39(38-42)	437(155-692)