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Abstract: Background: Oesophageal adenocarcinoma (OA) is the sixth commonest cause of cancer death worldwide and Barrett's oesophagus (BO) is the most significant risk factor. We evaluated the efficacy of high-dose esomeprazole proton pump inhibitor acid suppression (PPI) and aspirin in improving outcome for BE patients in the largest such randomized controlled trial.

Methods: Patients with ≥1cm BO in UK and Canadian hospitals were randomized 1:1:1:1 in a 2X2 factorial design to high-dose (40mg twice-daily) or low-dose (20mg once-daily) PPI, alone or with aspirin (UK: 300mg/day, Canada: 325mg/day), unblinded (reporting pathologists blinded). The primary composite endpoint was time to all-cause mortality, OA, or high-grade dysplasia, analysed using accelerated failure time modelling adjusted for minimization factors (age, BO length, intestinal metaplasia).

Findings: Recruited patients (N=2557) were followed for 8·9 years (median; interquartile range 8·2-9·8), collecting 20,095 follow-up years and 99·9% of planned data. There were 313 primary events. High-dose PPI was superior to low-dose PPI (p=0·037, N=2535, time ratio (TR)=1·27, 95%CI=1·01-1·58). Aspirin was not significantly better than no aspirin (p=0·068, N=2280, TR=1·24, 95%CI=0·98-1·57). If patients using NSAIDs were censored at time of first use, aspirin was significantly better (p=0·043, N=2,236, TR=1·29 95%CI=1·01-1·66). Combining high-dose PPI with aspirin had the strongest effect compared with low-dose PPI without aspirin (p=0·007, TR=1·59, 95%CI=1·14-2·23). NNT for PPI and aspirin benefit is 34 and 43, respectively. Only 1·0% of participants reported study-treatment-related serious adverse events.

Interpretation: High-dose PPI and aspirin chemoprevention therapy, especially in combination, significantly and safely improve outcome in BO patients.

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Title: Randomized factorial trial of esomeprazole and aspirin in Barrett's oesophagus: the Aspirin and Esomeprazole Chemoprevention in Barrett's metaplasia Trial (AspECT)

Short title: AspECT Chemoprevention Trial

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96 Dr. Harrison reports and RFH and JJ are related.

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Abstract

Background: Oesophageal adenocarcinoma (OA) is the sixth commonest cause of cancer death worldwide and Barrett's oesophagus (BO) is the most significant risk factor. We evaluated the efficacy of high-dose esomeprazole proton pump inhibitor acid suppression (PPI) and aspirin in improving outcome for BO patients in the largest such randomized controlled trial.

Methods: Patients with ≥1cm BO in UK and Canadian hospitals were randomized 1:1:1:1 using a computer-generated schedule held in a central trials unit in a 2X2 factorial design to high-dose (40mg twice-daily) or low-dose (20mg once-daily) PPI, alone or with aspirin (UK: 300mg/day, Canada: 325mg/day), unblinded (reporting pathologists blinded). The primary composite endpoint was time to all-cause mortality, OA, or high-grade dysplasia, analysed using accelerated failure time modelling adjusted for minimization factors (age, BO length, intestinal metaplasia).

Findings: Recruited patients (N=2557) were followed for 8·9 years (median; interquartile range 8·2–9·8), collecting 20,095 follow-up years and 99·9% of planned data. There were 313 primary events. High-dose PPI was superior to low-dose PPI (p=0·037, N=1265 (low dose), N=1270 (high dose), time ratio (TR)=1·27, 95%CI=1·01–1·58). Aspirin was not significantly better than no aspirin (p=0·068, N=1142 (no aspirin), N = 1138 (aspirin), TR=1·24, 95%CI=0·98–1·57). If patients using NSAIDs were censored at time of first use, aspirin was significantly better than no Aspirin (p=0·043, N=2,236, TR=1·29 95%CI=1·01–1·66). Combining high-dose PPI with aspirin had the strongest effect compared with low-dose PPI without aspirin (p=0·0068, TR=1·59, 95%CI=1·14–2·23). NNT for PPI and aspirin benefit is 34 and 43, respectively. Only 1·0% (28) of participants reported study-treatment-related serious adverse events.

Interpretation: High-dose PPI and aspirin chemoprevention therapy, especially in combination, significantly and safely improve outcome in BO patients.

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New Findings:

High dose proton pump inhibitor therapy (80 mg Esomeprazole/day) reduced the combination of all-cause mortality, oesophageal adenocarcinoma and high-grade dysplasia in Barrett's oesophagus patients compared to low dose [20 mg/day] (number needed to treat (NNT) = 34 over 9 years, and Hazard ratio 0.80)

Aspirin also had an effect on these endpoints in BO (NNT = 43 over 9 yrs, Hazard ratio 0.78)

Both treatments appear to have an additive effect

Significant side effects were rare<1%.

Background

Oesophageal adenocarcinoma (OA) incidence has increased dramatically in North America and Europe over the last 40 years.[1] The incidence may be plateauing, although areas such as Hawaii are still seeing 8% annual increases.[1] There are over 52,000 cases of OA worldwide annually and 5-year survival is <10% when detected through symptoms. Increasing incidence of OA is probably related to the rise in gastro-oesophageal reflux disease in Western populations.[2-5]

Gastro-oesophageal reflux is one of the main risk factors for Barrett's oesophagus (BO), where a portion of the oesophagus usually lined with squamous epithelium undergoes metaplastic change to columnar mucosa. BO is a complex, genetically predisposed, pre-malignant condition,[6] affecting 2% of the adult population and can progress to adenocarcinoma, following the sequence oesophagitis-metaplasia-dysplasia-adenocarcinoma.[7, 8] Current strategies for improving OA survival include BO surveillance to detect early stage cancer. This has modestly improved outlook of OA, prolonging median survival from 6 to 10 months.[9] Strategies to prevent progression to OA could give more dramatic gains. For example, colorectal cancer screening has proved successful with approximately 33% of colorectal cancer deaths now prevented by early detection versus 66% by polyp removal (i.e. prevention).[10]

Early detection of BO is confined to research settings, however there are promising chemoprevention strategies. Proton pump inhibitors (PPIs) effectively reduce acid reflux, thought to be one of the main drivers for BO. After BO development, PPIs down-regulate cylogogenase-2 expression, which may protect against neoplastic progression.[11] Observational data have suggested that BO patients taking PPIs have reduced neoplastic progression,[12] but this is low quality, controversial evidence.[13] A recent systematic review

supports the view that more powerful acid suppression may reduce risk of neoplasia.[14] Esomeprazole is the commonest PPI used in the USA, allowing healing of oesophagitis without promoting clonal expansion of Barrett's.[15] Observational data suggest that aspirin use is associated with reduced risk of OA,[16-19] but this is not a universal finding.[20] Finally, although BO is a major risk factor for OA, only a minority of BO patients die from OA; most die from cardiovascular disease or chest infections.[21] Preventative strategies should ideally impact overall mortality.

No randomised trial has evaluated PPI or aspirin for improving outcome including preventing neoplastic progression in BO patients. We evaluated the efficacy of these agents in the Aspirin and Esomeprazole Chemoprevention in Barrett's metaplasia Trial (AspECT). AspECT is a phase III, randomised prospective factorial study of chemoprevention by aspirin and esomeprazole in patients with BO, assessing the efficacy and safety of these interventions in reducing all-cause mortality, OA, and high-grade dysplasia (HGD).

Methods

Participants. Participants were recruited by gastroenterologists and upper gastrointestinal surgeons through hospital clinics and endoscopy lists, including new and existing BO diagnoses. There were 84 centres across England, Scotland, Wales, and Northern Ireland, and 1 in McMaster Health Sciences Centre, Canada. Participants ≥18 years old with globally accepted criteria for BO, at least 1 cm of histologically proven columnar-lined oesophagus,[22] were eligible. Exclusion criteria included pre-existing OA, HGD, or taking NSAIDs at baseline. Detailed inclusion and exclusion criteria are given in Supplementary Table 1. As women with BO have a lower risk of OA than men[22], we limited recruitment of women to approximately 500.

Randomisation and masking

Participants were randomized using a computer-generated schedule administered by a central trials unit to maintain allocation concealment. Some had contra-indications to or were already taking Aspirin for cardiovascular secondary prevention. We allowed these participants to enter PPI randomisation only. We therefore expected more participants in the PPI than the aspirin randomisation.

Randomisation was by minimisation with a random element of 0·8. The minimisation factors chosen were possible risk factors for the development of HGD, adenocarcinoma, and death:

Length of BO: tongue, <2cm, ≥2cm and ≤3cm, >3cm and ≤8cm, >8cm

Age in years: 18-49, 50-59, 60-69, ≥70

Intestinal metaplasia: yes, no

Using minimisation with the same variables, women and men were randomised separately, as were those only taking part in the PPI randomization. Treatment was not blinded.

Participants were randomised 1:1:1:1 in a 2X2 factorial design to esomeprazole at either high (40mg twice-daily) or low (20mg once-daily) dose, alone or in combination with aspirin (one standard-dose tablet, UK: 300mg/day, Canada: 325mg/day).

Trial procedures and interventions.

At annual follow-up, all patients were asked about hospital admissions and medical records checked for Serious Adverse Events. Follow-up in years 1,3,5,7,9 was by face to face or telephone interview, and in years 2,4,6,8,10 patients underwent endoscopy. All centres were trained and centrally monitored for endoscopy and pathology quality: strict adherence was essential for both site set up and for individual participant recruitment, with trial office validation of criteria on faxed/scanned endoscopy and pathology forms before enrolment. Intestinal metaplasia (IM) was present in 2266 (89%) at initial endoscopy, the remainder a mosaic of gastric metaplasia, increasing to 100% with IM on subsequent endoscopies.[23, 24]

Trial endoscopists received training in use of C and M endoscopy criteria with central monitoring of images and videos.[25] Standardised pathology criteria for reporting BO biopsies were developed, with training overseen by a central pathology panel as published.[24] At each endoscopy, four-quadrant BO biopsies every 2cm, with separate targeted biopsy of any macroscopic abnormalities, were fixed in buffered formalin, transported to the pathology lab, processed within 24 hours, embedded in wax, cut, stained with H&E and assessed by local gastrointestinal pathologists. All cases of dysplasia or cancer were double reviewed by regional pathology teams, with arbitration by central pathology panel if uncertainty. Local and central pathologists were blinded to treatment allocation. Many cases of dysplasia/cancer and a random 10% of all non-dysplastic cases were reviewed by a central expert pathology panel. Reports were seen by the local clinical team, decisions actioned and then faxed to the central trial office for validation/checking. All centres in all countries adhered to the same

protocol except for the dose of aspirin which was 300mg per day in the UK and 325 mg per day in Canada.

Outcomes. The co-primary aims were efficacy of high- versus low-dose PPI, and efficacy of aspirin versus no aspirin. The primary composite endpoint was time to the first of all-cause mortality, OA, or HGD. Secondary aims (which were not fully powered) included each treatment's effect on time to each of all-cause mortality, OA, HGD, cause-specific mortality and effect of gender.

Statistics and sample size power calculations. We used intention-to-treat analysis, including all randomised participants who did not rescind consent, analysing them in the treatment groups they were randomised to. We checked the significance of the treatment interaction term by first adding an interaction term to a primary model before using 'at the margins' and 'within table' results to produce an interaction ratio. Whilst recognising that the power was low for this interaction comparison, the appropriateness of an analysis using the factorial design was concluded.

All analyses used accelerated failure time (AFT) modelling, adjusting for minimisation factors. An accelerated failure time model was interpreted in terms of the speed of time to an event using time ratio (TR). TR>1 for the composite endpoint implied that the treatment prolonged time to an event. AFT was used due to the intuitive nature of the time ratio which models survival time, it's benefit of reporting results as a delay in event over the entire trial period compared to the hazard ratio result which is interpreted as risk of an event at any one given time. Cox proportional hazards survival analyses, and where appropriate, Cox competing risks survival analyses were also performed on all comparisons to allow for

comparison with other research. Before the use of both AFT and Cox survival models, the assumption of proportional hazards was tested using Schoenfeld tests and plots of residuals.

Median follow-up was calculated using a reverse Kaplan-Meier method.[26]

The trial aimed to recruit 5000 participants (1250 in each intervention group), assuming no interaction between the effects of aspirin and PPI interventions, an exponential time-to-composite-event with a constant event rate of 0·76% per year, a composite event hazard ratio of 1·4, recruiting over 2 years, follow-up for 8 years, 10% loss to follow-up, 20% non-compliance with medication, 80% power, and a 2-sided test at 5% significance. In October 2008, at the TSC, DSMC and funder's request, sample size was amended to allow emerging external data to be incorporated into the statistical calculations, namely published evidence showing an expected higher effect of aspirin (the raw data was available pre-publication with permission as JJ was a co-author),[27] higher conversion rate to cancer and the realisation that the initial composite event rate was too cautious.[21] It was agreed to be more efficient and cost effective to decrease the recruitment target but to extend follow-up to 10 years to allow more events to accrue in the ageing trial population. The new sample size of 2224 participants (196 events) was based on the above calculations but changed the constant event rate for the composite event (death, cancer or HGD) to a conservative 1% per year, the composite event hazard ratio to 1·5, recruitment to 3 years, follow-up for a maximum of 10 years, and removed the adjustment for medication compliance. With TSC and DSMC agreement, the funder permitted the trial to recruit until the end of February 2009 or 2224 participants, whichever was later. We recruited 2557 patients, 15% over the minimum power needed.

The primary aim was analysed and presented confidentially to the trial's data safety monitoring committee as specified in the protocol after 2 and 4 years of follow-up as interim analyses considering $p \leq 0{\cdot}001$ as significant. The committee recommended trial continuation and neither interim analysis was disseminated further.

The 2x2 factorial design provides two co-primary comparisons, high dose PPI compared to low dose PPI and aspirin compared to no aspirin. Secondary analyses of each element of the composite endpoint (HGD, OA, all-cause mortality) were evaluated in the same way as the primary comparisons using both AFT and Cox survival analyses. A per protocol population was defined based on treatment and trial compliance detailed in supplementary tables 17 and 18, with all analyses repeated as per primary methods. There were no missing data present in variables used in the primary and secondary analyses. There was no adjustment made to any analysis for multiple testing. Number needed to treat and number needed to harm were calculated using 1/absolute risk difference of primary event or adverse event respectively. Safety data are presented in descriptive form with no statistical analysis performed. All analyses were performed using StataCorp Version 15.0.

The funder had no role in data collection, analysis, interpretation, writing and decision to submit. The authors who had access to all the data were the Trial Management Group: John de Caestecker, Janusz Jankowski (JJ), Yeng Ang, Stephen Attwood, Sharon Love, Rebecca Harrison, Danielle Morris, Hugh Barr, Scott Sanders, Peter Watson, Adelyn Wise, Claire Brooks, Gavin Reilly, Pradeep Bhandari and Paul Moayyedi. Those who took a decision to submit were Janusz Jankowski, Paul Moayyedi, Sharon Love, Gavin Reilly, John de Caestecker, Hugh Barr, Scott Sanders, Rebecca Harrison, Claire Brooks.

Ethics. AspECT was approved by the Main Research Ethics Committee in the UK (REC reference: P1/04/Q0603/1) and by the Hamilton Integrated Research Ethics Board in Canada (reference:06-2731). All participants provided fully informed consent.

Results

Recruitment

We recruited 2557 BO patients from March 2005 to March 2009 and followed them for 8·9 years (median; interquartile range 8·2–9·8), collecting 20,095 patient-years of data. There were 313 primary endpoint events. Follow-up was completed by March 2017 (see CONSORT diagram in Figure 1 and supplementary table 2). Participants' baseline characteristics are in Table 1 and supplementary table 2 and compliance with medication in Supplementary Figure 1. The trial achieved a data return rate of 99·9%, with only one case report form outstanding out of 66,200.

Treatment interaction

The PPI/aspirin interaction term was not significant, leading to separate analysis of the PPI and aspirin comparisons (p=0·2807, N=2280, TR=1·30, 95% CI=0·81–2·09). Supplementary Table 4 gives the event rates in each arm.

Primary analysis for PPI

The primary analysis for PPI (Figure 2(a)) found that high-dose was significantly more effective than low-dose (p=0·0375, N=2535, TR=1·27, 95% CI=1·01–1·58). High-dose PPI significantly lengthened the time to reach endpoints, indicating that high-dose PPI delays death, cancer, and dysplasia. If the expected time to the composite event whilst taking low-dose PPI was 8 years, taking high-dose would increase this to 10·2 years (95% CI=8·1–12·6).

Primary analysis for aspirin

The primary analysis for aspirin (Figure 2(b)) was not significant (p=0·0683, N=2280, TR=1·24, 95% CI=0·98–1·57). UK sites also collected information on non-steroidal anti-inflammatory drug (NSAID) use. As specified in the statistical analysis plan, we included only UK participants and censored follow-up when a participant began taking NSAIDs. We

could then compare aspirin use with no aspirin, in the absence of NSAIDs. Aspirin had a significant effect on the composite endpoint when not combined with NSAIDs (p=0·0431, N=2,236, TR=1·29 95% CI=1·01–1·66).

Primary analysis for combined therapy

The beneficial effects of PPI and aspirin appeared additive when taken in combination (Figure 2(c)). Combining aspirin with high-dose PPI had the strongest effect, compared with low-dose PPI and no aspirin (p=0·0068, TR=1·59, 95% CI=1·14–2·23). We also compared the effect of aspirin combined with high-dose PPI to high-dose PPI alone, with a TR to endpoint of 1·38 (95% CI 0·98-1·94; p=0·0680), suggesting primary event delay of an additional 38% in high-dose PPI and aspirin compared to high-dose PPI alone. The confidence interval suggests support for this effect, though not statistically significant as the trial was not powered for this analysis (high-dose PPI & aspirin combination: 52 events vs. high-dose PPI: 87).

Secondary analyses

Table 2 gives the results of the secondary analyses. Aspirin appears protective against HGD (the precursor lesion to OA) showing marginal significance (p=0·0526, TR=1·51, 95% CI=1·00–2·29).

We designed the trial to use accelerated failure time modelling and give TRs, as these are easier to interpret than other estimates. Supplementary Table 5 gives the results from a Cox model in hazard ratios to allow comparison with other studies. We also supply Kaplan Meier plots for effects on all-cause mortality and HGD/OA separately (Supplementary figure 2) respectively for Aspirin vs no Aspirin (Figures 2a and 2b) and high dose vs low dose PPI (Figures 2c and 2d).

We calculated the number needed to treat (NNT) to prevent HGD, adenocarcinoma or death with both primary therapies (aspirin v no aspirin, low-dose v high-dose PPI). In the aspirin comparison, we estimated that on average 43 patients would need to be treated with aspirin to prevent one event (95% CI:20-250). In the PPI comparison, we calculated an NNT of 34 for high-dose PPI, i.e. 34 patients needed to be treated with high-dose instead of low-dose PPI to prevent one event (95% CI:18-333).

Long-term safety of aspirin and PPI therapy

There were 1132 serious adverse events (SAEs) in 718 participants, of which 65 SAEs in 61 participants were considered related to one or both treatments. Those with Common Terminology Criteria for Adverse Events (CTCAE) grade 3–5 are shown in Table 3. Only 1% of participants had an SAE of CTCAE grade 3–5 related to a study treatment (Table 3; Supplementary Tables 6 and 7). Sixty-four episodes of haemorrhage were recorded in 59 trial patients, with more events in the aspirin arms, but <1% of all patients experienced a CTCAE grade 3–5 bleed. There were 7 grade 3–5 gastrointestinal bleeds (Supplementary Tables 8 and 9). Total SAEs for high-dose PPI was 303 (in 704 patients) versus 274 (in 571 patients) for high-dose PPI & aspirin combination with little difference between them.

Discussion

This is the first randomised trial evaluating PPI and aspirin chemoprevention in BO and is the largest randomised trial ever conducted in BO, with 20,095 participant-years of follow-up in 2557 patients. We have shown that high-dose PPI use protects against a composite of all-cause mortality, OA, and HGD. Aspirin use also protects against the composite endpoint, when patient follow-up is censored at start of concomitant NSAID use. The data suggest the two therapies are additive, as the group who took both high-dose PPI and aspirin had the strongest benefit. High-dose PPI appeared to confer the single biggest effect, and combination with aspirin added another 38% benefit. Both agents were well-tolerated with few serious events. It seems likely that the use of aspirin and PPI would improve survival in BO if given for at least 9 years.

This study has several limitations. As we assessed only a small fraction of BO patients in predominantly white populations in five countries, our results may not be fully generalisable to all ethnic populations. However, BO is currently predominantly seen in Caucasians worldwide. We also limited the study to only approximately 500 women. Although our drug treatment was not blinded, the outcomes of OA and all-cause mortality are objective and unlikely to be biased by lack of blinding. A masked pathology panel with double reporting was used to minimise bias in evaluating HGD and OA. Two hundred and fifty-five patients took part only in the PPI randomisation due to being aspirin intolerant or not able to stop taking aspirin so this is a more generalisable group reflecting the situation in the population at large; since these were randomised between low-dose and high-dose PPI we would not expect an effect on the PPI comparison. The 95% confidence intervals are wide and the lower limit close to unity when each drug is evaluated individually, suggesting that the results are not robust. As aspirin and NSAIDs are available over the counter, participants could have

taken these drugs without reporting to the investigator. This would have biased the results towards the null hypothesis and therefore would only underestimate aspirin's efficacy.

Our data are supported by a meta-analysis of selected randomized controlled cardiovascular prevention trials evaluating aspirin versus placebo, which found that OA was reduced.[17] There are concerns about these data,[18] and the studies in the meta-analysis did not evaluate patients with BO. Nevertheless, our data add support to the possibility that aspirin prevents OA. Although a systematic review of observational studies suggested that PPI therapy reduces the risk of OA and HGD,[14] these results are liable to bias or confounding inherent in observational study design.

Our results with PPI are supported at the physiological level by studies showing that twice-daily PPI produces more effective suppression of acid reflux than once-daily dosing and more provocatively that high-dose PPI also allows preferential healing of BO segments into squamous epithelium.[15, 28] There is little data in the literature on combining PPI and aspirin to prevent neoplastic progression of BO, and this is the first randomised trial data to suggest the drugs may have additive effects.

Our results have implications for clinical practice. Current Barrett's and reflux oesophagitis guidelines in the UK and North America propose that the 'lowest effective dose to minimise reflux symptoms should be used'.[22, 29] Our data indicate that high-dose PPI (40 mg twice-daily) is better than low-dose (20 mg once-daily) for BO patients in delaying death, cancer, and dysplasia. Our data also suggest that 300/325 mg daily aspirin is effective in reducing the composite endpoint, although we do not know if this is the optimal dose. The NNT for high-dose PPI and aspirin is 34 and 43 respectively to prevent one event. Combining high-dose PPI and aspirin appears more effective in reducing the composite endpoint than either treatment alone. The combination appears safe, with only 1% of participants reporting an

SAE of CTCAE grade 3–5 with little increase when adding aspirin to high-dose PPI. Current guidelines do not address the possibility of giving aspirin to reduce neoplastic progression in BO; our results suggest review of existing guidelines is warranted.

Several questions remain unanswered. How long must patients take PPI and aspirin combined to benefit from chemopreventative effects on oesophageal stem cells? We know that before 5 years neither therapy had a significant benefit,[19] but that after 8·9 years of follow-up, the effect was significant. We also do not yet know the pharmacogenomics of who responds best to either or both therapies.[8] This work is now ongoing.[30] These data also raise the possibility that all patients needing long-term PPI to control reflux symptoms might benefit from aspirin co-prescribed with acid suppression. The PPI could reduce the upper gastrointestinal bleeding associated with aspirin whilst the benefits of aspirin remain. This hypothesis should be evaluated in large population-based trials.

This is the largest randomised controlled chemoprevention trial of BO. We have shown that high-dose PPI and aspirin chemoprevention therapy, especially in combination, significantly and safely reduce combined rates of HGD, OA and all-cause mortality.

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Figure 1: CONSORT diagram for AspECT – see supplementary table 1 for list of excluded other reasons

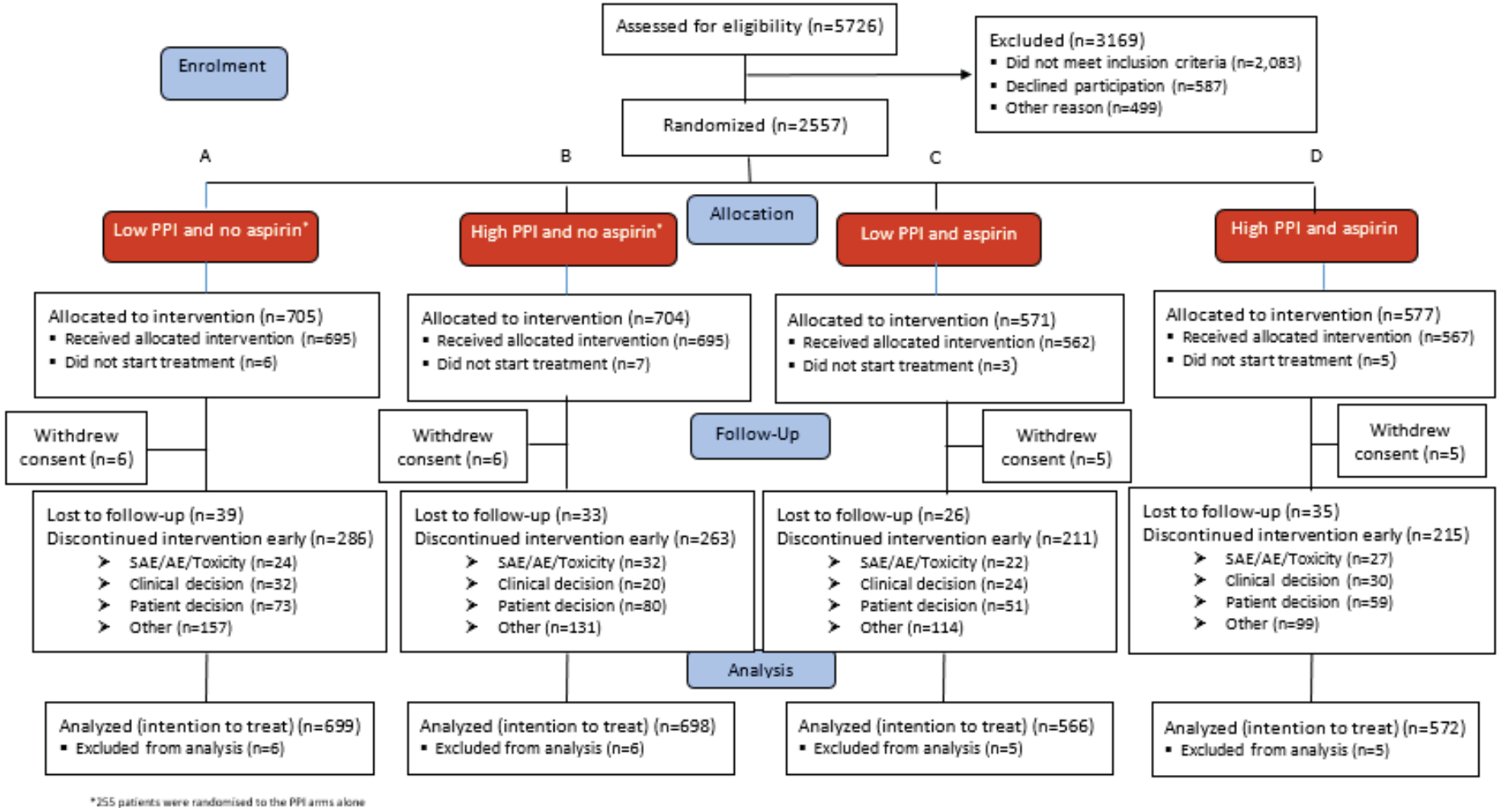


Table 1: Baseline characteristics of AspECT trial participants, stratified by treatment group

Variable at baseline	Low PPI N=1265	High PPI N=1270	No aspirin N=1142	Aspirin N=1138
Length of Barrett's metaplasia at randomization	N=2413*		N=2159	
(strata for minimization and median (IQR), cm)	4 (3 , 6)	4 (2 , 6)	4 (2 , 6)	4 (3 ,6)
Length of Barrett's (stratification group)	N=2535		N=2280	
<2 cm	123 (10%)	124 (10%)	108 (9%)	109 (10%)
2-3 cm	434 (34%)	435 (34%)	398 (35%)	395 (35%)
3-8 cm	538 (43%)	539 (42%)	491 (43%)	493 (43%)
>8 cm	130 (10%)	129 (10%)	117 (10%)	118 (10%)
Tongues	40 (3%)	43 (3%)	28 (3%)	23 (2%)
Age	N=2535		N=2280	
(strata for minimization, median (IQR),years)	59 (51 , 65)	59 (51 , 65)	58 (50 , 64)	58 (50 , 65)
Age (stratification grouping)	N=2535		N=2280	
<50 years	283 (22%)	280 (22%)	269 (24%)	272 (24%)
50-60 years	388 (31%)	390 (31%)	365 (32%)	358 (31%)
60-70 years	447 (35%)	445 (35%)	386 (34%)	388 (34%)
>70 years	147 (12%)	155 (12%)	122 (10%)	122 (11%)
	N=2535		N=2280	
Intestinal metaplasia				
Yes	1,130 (89%)	1,136 (90%)	1,042 (91%)	1,035 (91%)
No	134 (11%)	134 (10%)	100 (9%)	103 (9%)
	N=2535		N=2280	
Sex				
Male	1012 (80%)	1010 (80%)	900 (79%)	896 (79%)
Female	253 (20%)	260 (20%)	242 (21%)	242 (21%)

* we required the length of Barrett's stratification group for randomization. The actual length of Barrett's was collected on the baseline data form and was missing for 122 patients.

Figure 2(a)

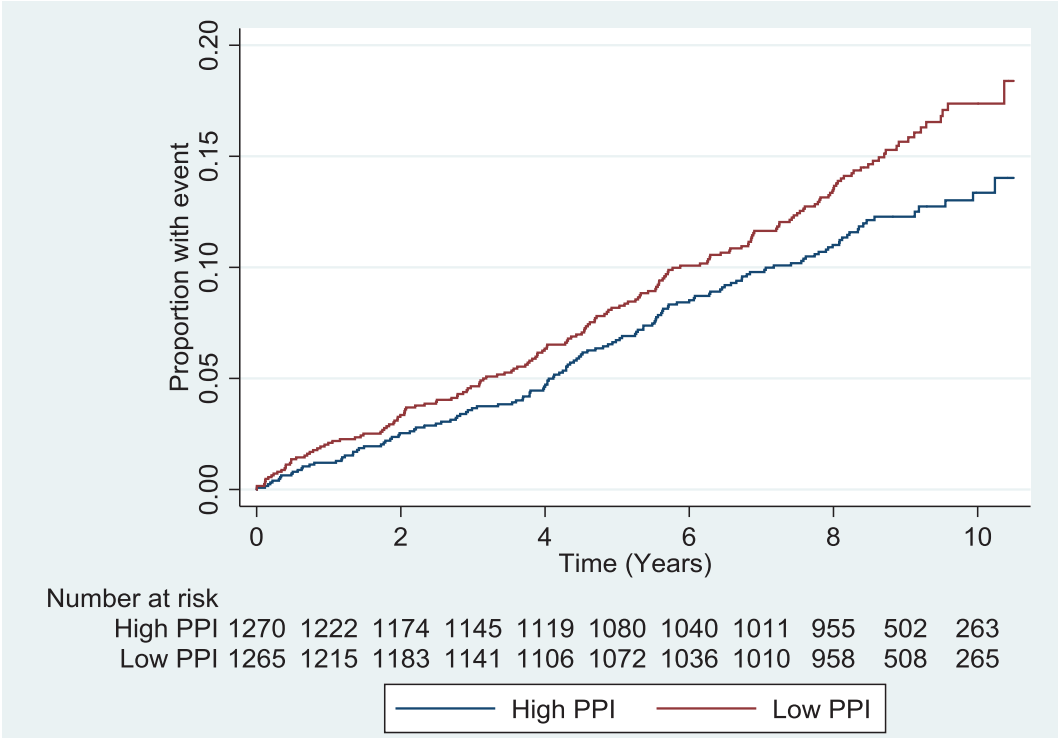


Figure 2(b)

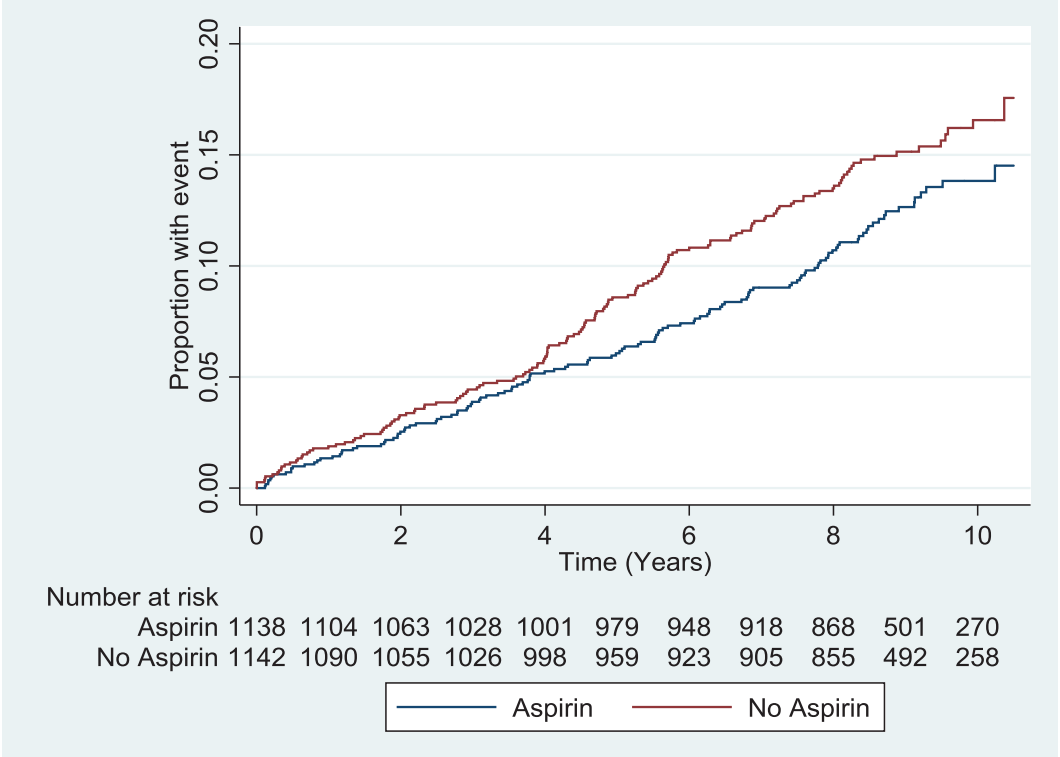


Figure 2(c)

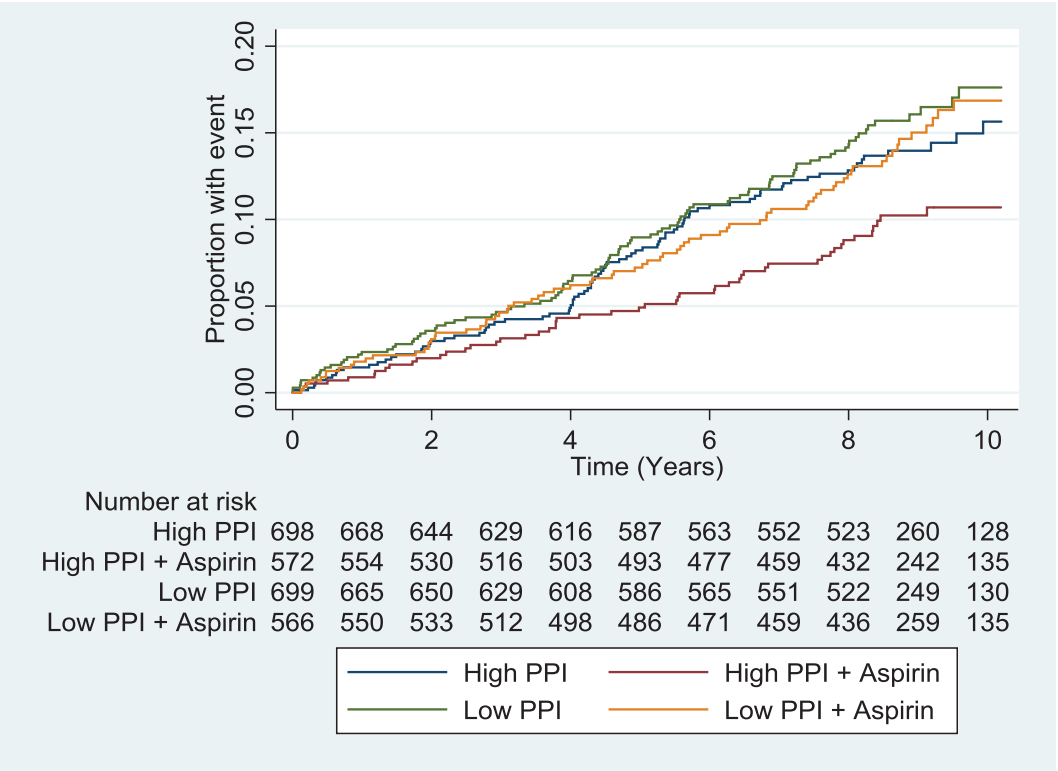


Figure 2: Survival curves comparing patients on (a) high-dose PPI and low-dose PPI, (b) aspirin and no aspirin, and (c) all four treatment groups

Secondary aim	High PPI vs low PPI				Aspirin vs no aspirin			
	Number of patients	Time ratio	95% CI	P value	Number of patients	Time ratio	95% CI	P value
All-cause mortality	2,535	1·36	1·01-1·82	0·039	2,280	1·25	0·92-1·70	0·16
Oesophageal adenocarcinoma	2,535	1·04	0·67-1·61	0·86	2,280	1·02	0·64-1·64	0·92
High-grade dysplasia	2,535	1·36	0·92-2·02	0·12	2,280	1·51	1·00-2·29	0·053
Cause-specific mortality	2,535	1·55	0·63-3·80	0·34	2,280	1·01	0·38-2·69	0·98
Males only, composite endpoint	2,022	1·26	0·99-1·61	0·06	1,796	1·26	0·98-1·64	0·07
Females only, composite endpoint	513	1·27	0·72-2·27	0·41	484	1·13	0·63-2·02	0·69

Table 2: Accelerated failure time modelling for secondary endpoints

Table 3: Serious adverse events and serious adverse reactions of Common Terminology Criteria for Adverse Events grade 3-5, by treatment group*

	Low or high PPI		No aspirin or aspirin	
System affected by serious adverse event	Low PPI N=1265	High PPI N=1270	No aspirin N=1142	Aspirin N=1138
Serious adverse events				
Blood and lymphatic system disorders	4	3	1	4
Cardiac disorders	57	56	42	53
Ear and labyrinth disorders	1	2	1	2
Endocrine disorders	1	1	1	1
Eye disorders	1	3	1	3
Gastrointestinal disorders	30	28	22	32
General disorders and administration site conditions	7	11	9	8
Hepatobiliary disorders	16	10	12	12
Immune system disorders	1	2	3	0
Infections and infestations	57	66	48	64
Injury, poisoning and procedural complications	28	23	22	24
Investigations	2	1	1	2
Metabolism and nutrition disorders	2	7	5	2
Musculoskeletal and connective tissue disorders	7	4	4	7
Neoplasms benign, malignant and unspecified (including cysts and polyps)	56	52	52	41
Nervous system disorders	31	26	25	28
Psychiatric disorders	4	8	4	5
Renal and urinary disorders	7	10	3	8
Respiratory, thoracic and mediastinal disorders	8	7	4	8
Skin and subcutaneous tissue disorders	0	1	0	0
Vascular disorders	15	14	12	14
Total	**335**	**335**	**272**	**318**
Serious adverse reactions				
Related to aspirin	9	6	0	15
Related to esomeprazole	4	9	8	4
Related to both aspirin & esomeprazole	0	0	0	0
Total	**13**	**15**	**8**	**19**

*There are 19 serious adverse events that are missing a Common Terminology Criteria for Adverse Events grade.

Supplementary Data

Supplementary Table 1: AspECT inclusion and exclusion criteria

Original eligibility criteria	Change in criteria, date of change, and further information	Final eligibility criteria
Inclusion criteria		
Male aged 40–75 years	Age limit modified in Protocol V6·0 dated 20 Jan 2006, now 18 years and over Up to 500 women entered for generalizability	Aged ≥18 years
Circumferential Barrett's metaplasia at least 2 cm from the gastro-esophageal junction (histologically proven by intestinal metaplasia in at least one sample)	Changed to circumferential Barrett's metaplasia at least 1 cm long in Protocol_V6·0_dated 20Jan2006 Added a past history of, but not current, intestinal metaplasia in Protocol_V6·0_dated 20Jan2006 Changed in Protocol V9·0 dated 25 Sep 2007 to no need for intestinal metaplasia and allowing non-circumferential tongues of Barrett's esophagus >2 cm as enough for inclusion	Circumferential Barrett's esophagus of at least 1 cm in length (≥C1M1) or a tongue of Barrett's esophagus of at least 2 cm in length (≥C0M2), irrespective of the presence now or historically of histologically proven intestinal metaplasia
Able to give written informed consent	Unchanged	Able to give written informed consent
WHO activity profile of 0 or 1, i.e., fully active and self-caring	Unchanged	WHO activity profile of 0 or 1, i.e., fully active and self-caring
Exclusion criteria		
High-grade dysplasia or carcinoma at enrolment	Unchanged	High-grade dysplasia or carcinoma at enrolment
Medical conditions that would make endoscopy or completing the trial	Exact definitions of what constituted 'severe' or 'frequent' for these medical	Medical conditions that would make

difficult, including: • Frequent transient ischemic attacks (3 or more) or severe cerebral vascular accident in the previous 6 months* • Severe respiratory disease with arterial oxygen saturation of less than 90% at rest • Severe ischemic heart disease (exercise tolerance less than 100 yards or life expectancy <4 years) or myocardial infarction in the previous 3 months • Severe inflammatory bowel disease requiring at least one hospital admission of 5 days in the last year or bowels open >6 times/day * Patients answering yes to this criterion were eligible for the PPI-only (non-aspirin) randomization.	conditions were added to the protocol from Protocol V10·0 dated 30 Jul 2010	endoscopy or completing the trial difficult, including: • Frequent transient ischemic attacks (3 or more) or severe cerebral vascular accident in the previous 6 months* • Severe respiratory disease with arterial oxygen saturation of less than 90% at rest • Severe ischemic heart disease (exercise tolerance less than 100 yards or life expectancy <4 years) or myocardial infarction in the previous 3 months • Severe inflammatory bowel disease requiring at least one hospital admission of 5 days in the last year or bowels open >6 times/day * Patients answering yes to this criterion were eligible for the PPI-only (non-aspirin) randomization.
Continuous/frequent non-steroidal anti-inflammatory drug use or COX-2 inhibitors (more than 60 days/year in total)	Unchanged	Continuous/frequent non-steroidal anti-inflammatory drug use or COX-2 inhibitors (more than 60 days/year in total)
Patients with absolute contraindications to PPIs, aspirin or their excipients	Unchanged	Patients with absolute contraindications to

i.e. allergies, ulcers, renal impairment or use of oral anticoagulants.		PPIs, aspirin or their excipients i.e. allergies, ulcers, renal impairment or use of oral anticoagulants.
	Added Protocol V5·0 dated 27 Jul 2005: Pregnant or lactating women	Pregnant or lactating women
	Added Protocol V6·0 dated 20 Jan 2006: Previous aspirin users will be entered providing they agree to stop aspirin use if not randomized to it	Previous aspirin users will be entered providing they agree to stop aspirin use if not randomized to it
	Added Protocol V9·0 dated 25 Sep 2007: Patients not wishing to stop aspirin or who have an absolute contraindication to it can be randomized to low/high PPI and will be analyzed for that comparison only	Patients not wishing to stop aspirin or who have an absolute contraindication to it can be randomized to low/high PPI and will be analyzed for that comparison only

Supplementary table 2: Reasons for non-enrolment in AspECT of patients meeting inclusion criteria

Exclusion Reason	Number of Patients
ALCOHOLIC	9
DECEASED	18
MISUNDERSTANDING OF TRIAL	6
NO RESPONSE	132
NO SURVEILLANCE	28
NOT MOBILE	6
ON HOLIDAY	1
ON TRIAL	22
OPTED FOR SURGERY	13
PRISONER	1
QUOTA REACHED	3
RELOCATING	26
SELF DISCHARGED	1
UNABLE TO COMPLETE FOLLOW UP	17
UNABLE TO GIVE CONSENT	8
UNSPECIFIED INELIGIBILITY	114
UNWILLING TO ADOPT TRIAL TREATMENT	13
OTHER	81
TOTAL	**499**

Supplementary Table 3: Baseline characteristics by treatment comparison for variables only asked of patients recruited in the first 2 years of recruitment

Variable at baseline	Low PPI N=1247	High PPI N=1244	No Aspirin N=1120	Aspirin N=1116
BMI (kg/m^2)	N=1254		N=1039	
median(IQR)	27 (25 , 30)	27 (25 , 30)	27 (25 , 30)	27 (25 , 30)
Duration of Barrett's pre randomisation (years)	N=2373		N=2123	
Median (IQR)	2·5 (0·4 , 5·7)	2·4 (0·4 , 6·1)	2·5 (0·4 , 5·9)	2·3 (0·4 , 5·8)
Alcohol use	N=1033		N=1032	
None	131 (25%)	125 (24%)	131 (25%)	125 (24%)
Some	385 (75%)	392 (76%)	386 (75%)	390 (76%)
(For some group, median (IQR), units per week)	10 (4 , 20)	10 (4 , 20)	10 (5 , 20)	10 (4 , 20)
Smoker	N=1031		N=1031	
Never	223 (43%)	223 (43%)	223 (43%)	222 (43%)
Ex	209 (41%)	201 (39%)	202 (39%)	208 (41%)
Current	84 (16%)	91 (18%)	94 (18%)	81 (16%)
Myocardial infarction	N=1393		N=1143	
Yes	13 (2%)	13 (2 %)	1 (0·2%)	1 (0·2%)
No	688 (98%)	679 (98%)	573 (99·8%)	568 (99·8%)
Angina	N=1394		N=1143	
Yes	24 (3%)	26 (4%)	3 (0·5%)	6 (1%)
No	677 (97%)	667 (96%)	572 (99·5%)	562 (99%)
Coronary Intervention	N=1394		N=1143	
Yes	13 (2%)	12 (2%)	0	2 (0·4%)
No	688 (98%)	681 (98%)	575 (100%)	566 (99·6%)
Stenosis	N=1393		N=1141	
Yes	2 (0·3%)	5 (0·7%)	0	1 (0·2%)
No	700 (99·7%)	686 (99·3%)	575 (100%)	565 (99·8%)
Cardiac catheterisation	N=1392		N=1140	
Yes	13 (2%)	15 (2%)	2 (0·4%)	2 (0·4%)
No	688 (98%)	676 (98%)	572 (99·6%)	564 (99·6)
Cerebrovascular	N=1392		N=1140	
Yes	2 (0·3%)	8 (1%)	1 (0·2%)	3 (0·5%)
No	699 (99·7%)	683 (99%)	573 (99·8%)	564 (99·5%)
TIA	N=1390		N=1139	
Yes	2 (0·3%)	5 (0·7%)	0	2 (0·4%)
No	696 (99·7%)	687 (99·3%)	572 (100%)	565 (99·6%)
Peripheral Vascular Disease	N=1378		N=1131	
Yes	6 (1%)	9 (1%)	3 (0·5%)	5 (1%)
No	686 (99%)	677 (99%)	565 (99·5%)	558 (99%)
Diabetes	N=1032		N=1031	
Yes	18 (3%)	13 (3%)	13 (3%)	18 (4%)
No	499 (97%)	502 (97%)	503 (97%)	497 (96%)
Hypertension	N=1032		N=1031	
Yes	116 (23%)	129 (25%)	122 (24%)	123 (24%)
No	399 (77%)	288 (75%)	393 (76%)	393 (76%)
Hyperlipidaemia	N=1034		N=1033	
Yes	47 (9%)	43 (8%)	46 (9%)	44 (9%)
No	287 (56%)	262 (51%)	275 (53%)	273 (53%)
Unknown	182 (35%)	213 (41%)	198 (38%)	197 (38%)

Supplementary Figure 1: Participant compliance with (a) PPI and (b) aspirin medication, by treatment group

Figure 1(a): PPI compliance

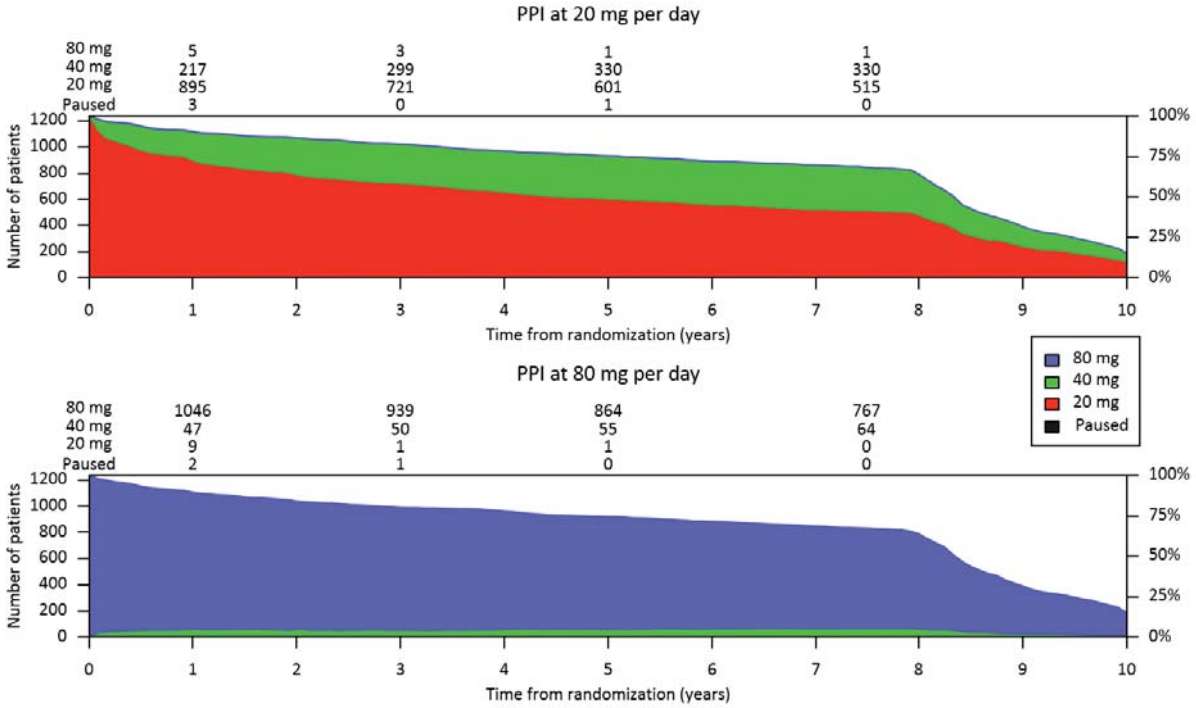
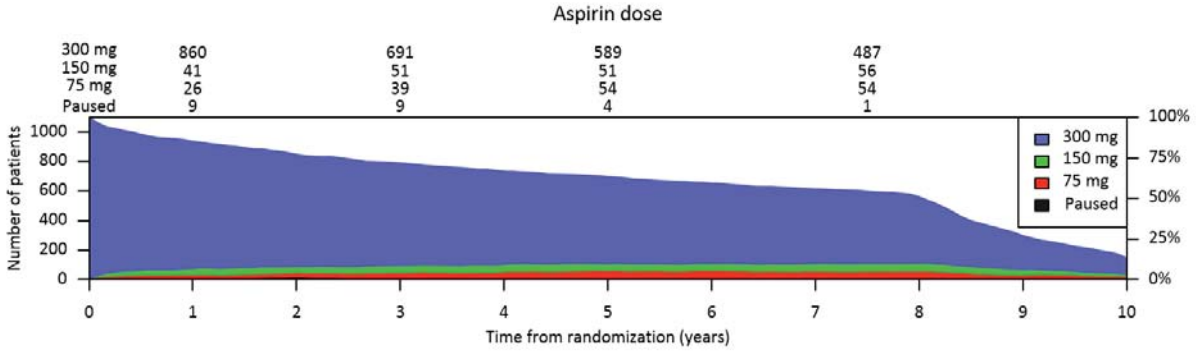


Figure 1(b): Aspirin compliance



PPI and aspirin dose changes shown above were pre-specified in the protocol and permitted.

		PPI			
		High-dose		Low-dose	
Aspirin	Yes	52 / 572 = 0·091		75 / 566 = 0·133	
		All-cause mortality	25 (48%)	All-cause mortality	37 (50%)
		Oesophageal adenocarcinoma	12 (23%)	Oesophageal adenocarcinoma	19 (25%)
		High-grade dysphasia	15 (29%)	High-grade dysphasia	19 (25%)
	No	87 / 698 = 0·125		99 / 699 = 0·142	
		All-cause mortality	43 (49%)	All-cause mortality	50 (51%)
		Oesophageal adenocarcinoma	19 (22%)	Oesophageal adenocarcinoma	11 (11%)
		High-grade dysphasia	25 (29%)	High-grade dysphasia	38 (38%)

Supplementary table 4: Details of primary outcome breakdown by treatment arm

Supplementary Table 5: Primary and secondary analyses repeated using a Cox proportional hazards model

	High PPI vs low PPI				Aspirin vs no aspirin			
	Number of patients	Hazard ratio	95% CI	P value	Number of patients	Hazard ratio	95% CI	P value
Primary aim								
All-cause mortality or esophageal adenocarcinoma or high-grade dysplasia	2535	0·79	0·63-0·99	0·0379	2280	0·8*	0·64-1·02	0·07
Secondary aim								
All-cause mortality	2,535	0·74	0·55-0·99	0·0431	2,280	0·80	0·59-1·09	0·16
Esophageal adenocarcinoma	2,535	0·97	0·63-1·50	0·89	2,280	1·00	0·62-1·58	0·97
High-grade dysplasia**	2,535	0·63	0·42-0·96	0·0329	2,280	0·62	0·40-0·95	0·0283
Cause-specific mortality**	2,535	0·65	0·27-1·57	0·34	Too few events			
Males only, composite endpoint	2,022	0·79	0·62-1·01	0·06	1,796	0·79	0·61-1·02	0·08
Females only, composite endpoint	513	0·77	0·43-1·37	0·37	484	0·90	0·50-1·60	0·71

* A patient taking aspirin is estimated to be 0·8 times more likely to have an event than a patient not taking aspirin

** Competing risks Cox modelling was used for high-grade dysplasia and cause-specific mortality as the competing risk of death might have a large effect

Supplementary Table 6: Serious adverse events and serious adverse reactions by Common Terminology Criteria for Adverse Events grade

	CTCAE Grade					
All serious adverse events by system	**1**	**2**	**3**	**4**	**5**	**Total**
Blood and lymphatic system disorders	5	3	5	2	0	15
Cardiac disorders	9	36	77	24	12	158
Ear and labyrinth disorders	1	1	3	0	0	5
Endocrine disorders	0	0	2	0	0	2
Eye disorders	0	3	4	0	0	7
Gastrointestinal disorders	24	69	50	6	2	151
General disorders and administration site conditions	11	15	18	0	0	44
Hepatobiliary disorders	2	15	19	2	5	43
Immune system disorders	1	1	2	1	0	5
Infections and infestations	7	57	109	9	5	187
Injury, poisoning and procedural complications	7	23	41	4	6	81
Investigations	1	0	0	3	0	4
Metabolism and nutrition disorders	3	6	5	4	0	18
Musculoskeletal and connective tissue disorders	3	12	10	1	0	26
Neoplasms benign, malignant and unspecified (including cysts and polyps)	3	16	41	22	45	127
Nervous system disorders	16	41	37	13	7	114
Psychiatric disorders	1	3	6	4	2	16
Renal and urinary disorders	5	14	16	1	0	36
Respiratory, thoracic and mediastinal disorders	5	18	12	3	0	38
Skin and subcutaneous tissue disorders	0	0	1	0	0	1
Vascular disorders	1	5	19	6	4	35
Total	105	338	477	105	88	1113*
***Nineteen serious adverse events are missing a CTCAE grade.**						
Serious adverse reactions						
Related to aspirin	9	19	12	2	1	43*
Related to esomeprazole	2	4	10	2	1	19
Related to both aspirin and esomeprazole	0	2	0	0	0	2
Total	11	25	22	4	2	64*
***One serious adverse reaction is missing a CTCAE grade**						

CTCAE: Common Terminology Criteria for Adverse Events.

Supplementary Table 7: Total SAEs by treatment arm

	Treatment Arm				
SAE System / Category	**Low PPI**	**High PPI**	**Low PPI Asp**	**High PPI Asp**	**Total**
Blood and lymphatic system disorders	2	5	9	1	17
Cardiac disorders	37	50	38	35	160
Ear and labyrinth disorders	0	1	1	3	5
Endocrine disorders	1	0	0	1	2
Eye disorders	0	2	1	4	7
Gastrointestinal disorders	39	34	41	38	152
General disorders and administration site conditions	8	16	8	15	47
Hepatobiliary disorders	10	8	14	11	43
Immune system disorders	1	3	0	1	5
Infections and infestations	49	46	35	58	188
Injury, poisoning and procedural complications	18	26	24	14	82
Investigations	1	1	1	1	4
Metabolism and nutrition disorders	5	8	1	4	18
Musculoskeletal and connective tissue disorders	9	2	6	9	26
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	38	41	28	27	134
Nervous system disorders	30	27	31	26	114
Pregnancy, puerperium and perinatal conditions	1	0	0	0	1
Psychiatric disorders	4	6	1	5	16
Renal and urinary disorders	14	9	5	8	36
Respiratory, thoracic and mediastinal disorders	9	6	18	6	39
Skin and subcutaneous tissue disorders	0	1	0	0	1
Vascular disorders	7	11	10	7	35
OVERALL TOTAL	**283**	**303**	**272**	**274**	**1132**

Supplementary Table 8: Gastrointestinal and non-gastrointestinal bleeds classified as serious adverse events in each treatment group.

	Low or high PPI		Aspirin or no aspirin	
Serious adverse events by system / category	Low PPI	High PPI	Aspirin	No aspirin
Gastrointestinal bleeds (CTCAE grade 3–5 bleeds)				
Colonic hemorrhage	1 (0)	0 (0)	0 (0)	1 (0)
Duodenal hemorrhage	0 (0)	2 (1)	2 (1)	0 (0)
Esophageal hemorrhage	3 (1)	1 (0)	3 (1)	1 (0)
Esophageal varices hemorrhage	0 (0)	1 (1)	0 (0)	1 (1)
Gastric hemorrhage	3 (1)	3 (1)	4 (1)	1 (1)
Hemorrhoidal hemorrhage	2 (1)	1 (0)	3 (1)	0 (0)
Rectal hemorrhage	1 (0)	2 (0)	2 (0)	1 (0)
Upper gastrointestinal hemorrhage	3 (0)	5 (1)	4 (1)	1 (0)
Total	13 (3)	15 (4)	18 (5)	6 (2)
Non-gastrointestinal bleeds (CTCAE grade 3–5)				
Postoperative hemorrhage	3 (3)	2 (0)	3 (3)	2 (0)
Intracranial hemorrhage	5 (4)	5 (2)	5 (4)	5 (4)
Hematuria	3 (0)	3 (2)	2 (2)	1 (0)
Epistaxis	11 (1)	4 (0)	13 (2)	2 (0)
Total	22 (8)	14 (4)	23 (11)	10 (4)
Overall total	35 (11)	29 (9)	41 (14)	16 (6)

Presented as total bleeds in each category (grade 3–5 bleeds in that category).

CTCAE: Common Terminology Criteria for Adverse Events

Supplementary Table 9: Details of Gastrointestinal and non-gastrointestinal bleeds by treatment arm

	Treatment Arm				
SAE System / Category	**Low PPI**	**High PPI**	**Low PPI Asp**	**High PPI Asp**	**Total**
Gastrointestinal disorders					
Colonic hemorrhage	1	0	0	0	1
Duodenal hemorrhage	0	0	0	2	2
Esophageal hemorrhage	1	0	2	1	4
Esophageal varices hemorrhage	0	1	0	0	1
Gastric hemorrhage	1	1	2	2	6
Hemorrhoidal hemorrhage	0	0	2	1	3
Rectal hemorrhage	1	0	0	2	3
Upper gastrointestinal hemorrhage	1	3	2	2	8
Total	**5**	**5**	**8**	**10**	**28**
Injury, poisoning and procedural complications					
Postoperative hemorrhage	0	2	3	0	5
Total	**0**	**2**	**3**	**0**	**5**
Nervous system disorders					
Intracranial hemorrhage	3	2	2	3	10
Total	**3**	**2**	**2**	**3**	**10**
Renal and urinary disorders					
Hematuria	3	1	0	2	6
Total	**3**	**1**	**0**	**2**	**6**
Respiratory, thoracic and mediastinal disorders					
Epistaxis	2	0	9	4	15
Total	**2**	**0**	**9**	**4**	**15**
OVERALL TOTAL	**13**	**10**	**22**	**19**	**64**

Supplementary Table 10: Primary analyses by age group

	Number of patients	Time ratio (TR)	95% CI	P value
<60				
Aspirin vs no aspirin	1264	1.22	0.82 , 1.81	0.326
High PPI vs low PPI	1341	1.22	0.84 , 1.79	0.296
60+				
Aspirin vs no aspirin	1016	1.26	0.94 , 1.69	0.118
High PPI vs low PPI	1194	1.30	0.98 , 1.71	0.064

Supplementary Table 11: Details of numbers with LGD at baseline and newly diagnosed at follow up

	Arm A	Arm B	Arm C	Arm D	Total
LGD at baseline	31	15	11	14	71
LGD diagnosed at follow up	72	60	61	56	249

Supplementary table 12: Primary analyses by treatment withdrawal or completion

	Number of patients	Time ratio (TR)	95% CI	P value
Withdrawn Treatment Early				
Aspirin vs no aspirin	866	1.22	0.95 , 1.56	0.114
High PPI vs low PPI	975	1.20	0.95 , 1.52	0.125
Completed Treatment				
Aspirin vs no aspirin	1414	1.73	0.76 , 3.96	0.192
High PPI vs low PPI	1560	1.11	0.51 , 2.44	0.787

Supplementary table 13: Cardiac Disorder Details

Details of cardiac disorders by aspirin allocation

Cardiac Disorder	Aspirin	No Aspirin
Acute coronary syndrome	5	4
Aortic stenosis	1	
Aortic valve disease	1	1
Atrial fibrillation	2	4
Atrioventricular block complete	2	
Cardiac arrest	1	2
Cardiomyopathy	2	3
Chest pain - cardiac	5	4
Heart failure	5	2
Myocardial infarction	21	21
Pericardial effusion	1	1
Sinus bradycardia	6	
Ventricular tachycardia	1	
	53	42

Supplementary table 14. Primary analysis by gender

	Number of patients	Time ratio (TR)	95% CI	P value
Men				
Aspirin vs no aspirin	1,796	1.26	0.98 , 1.64	0.074
High PPI vs low PPI	2,022	1.26	0.99 , 1.61	0.059
Women				
Aspirin vs no aspirin	484	1.13	0.63 , 2.02	0.687
High PPI vs low PPI	513	1.27	0.72 , 2.27	0.411

Supplementary table 15: Baseline of AspECT trial participants, stratified by randomised group

Variable at baseline	Low PPI no aspirin N=699	High PPI no aspirin N=698	Low PPI and aspirin N=566	High PPI and aspirin N=572	TOTAL
Maximum Length of Barrett's metaplasia at randomisation (cm) median (IQR)	4 (3 , 6)	4 (2 , 6)	4 (3 , 6)	4 (3 , 6)	**2,413**
Length of Barrett's (stratification group)					
<2cm	69 (10%)	69 (10%)	54 (9%)	55 (9%)	
2-3cm	237 (34%)	237 (34%)	197 (35%)	198 (35%)	**2,535**
3-8cm	293 (42%)	291 (42%)	245 (43%)	248 (43%)	
>8cm	71 (10%)	70 (10%)	59 (10%)	59 (10%)	
Tongues	29 (4%)	31 (5%)	11 (2%)	12 (2%)	
Age (years) (median (IQR))	59 (51 , 65)	59 (51 , 66)	58 (50 , 64)	58 (50 , 65)	**2,535**
Age (stratification grouping)					
<50 years	148 (21%)	143 (21%)	135 (24%)	137 (24%)	
50-60 years	210 (30%)	210 (30%)	178 (31%)	180 (31%)	**2,535**
60-70 years	252 (36%)	252 (36%)	195 (35%)	193 (34%)	
>70 years	89 (13%)	93 (13%)	58 (10%)	62 (11%)	
Sex					
Male	564 (81%)	562 (81%)	448 (79%)	448 (78%)	**2,535**
Female	135 (19%)	136 (19%)	118 (21%)	124 (22%)	
Intestinal metaplasia (stratification group)					**2,535**
Yes	616 (88%)	615 (88%)	514 (91%)	521 (91%)	
No	83 (12%)	83 (12%)	52 (9%)	51 (9%)	

Supplementary table 16: Serious adverse events CTCAE grade 3-5 by treatment arm

System affected by serious adverse event	Arm A N=1265	Arm B N=1270	Arm C N=1142	Arm D N=1138
Serious adverse events				
Blood and lymphatic system disorders		3	4	
Cardiac disorders	29	31	28	25
Ear and labyrinth disorders		1	1	1
Endocrine disorders	1			1
Eye disorders		1	1	2
Gastrointestinal disorders	15	11	15	17
General disorders and administration site conditions	5	5	2	6
Hepatobiliary disorders	8	6	8	4
Immune system disorders	1	2		
Infections and infestations	32	27	25	39
Injury, poisoning and procedural complications	13	14	15	9
Investigations	1		1	1
Metabolism and nutrition disorders	2	5		2
Musculoskeletal and connective tissue disorders	4		3	4
Neoplasms benign, malignant and unspecified (including cysts and polyps)	33	34	23	18
Nervous system disorders	16	13	15	13
Psychiatric disorders	3	4	1	4
Renal and urinary disorders	4	5	3	5
Respiratory, thoracic and mediastinal disorders	3	4	5	3
Skin and subcutaneous tissue disorders		1		
Vascular disorders	6	9	9	5
Total	**176**	**176**	**159**	**159**
Serious adverse reactions				
Related to aspirin	0	0	6	1
Related to esomeprazole	4	4	0	2
Related to both aspirin & esomeprazole	0	0	0	0
Total	**4**	**4**	**6**	**3**

Supplementary table 17: Inclusion criteria for per protocol population

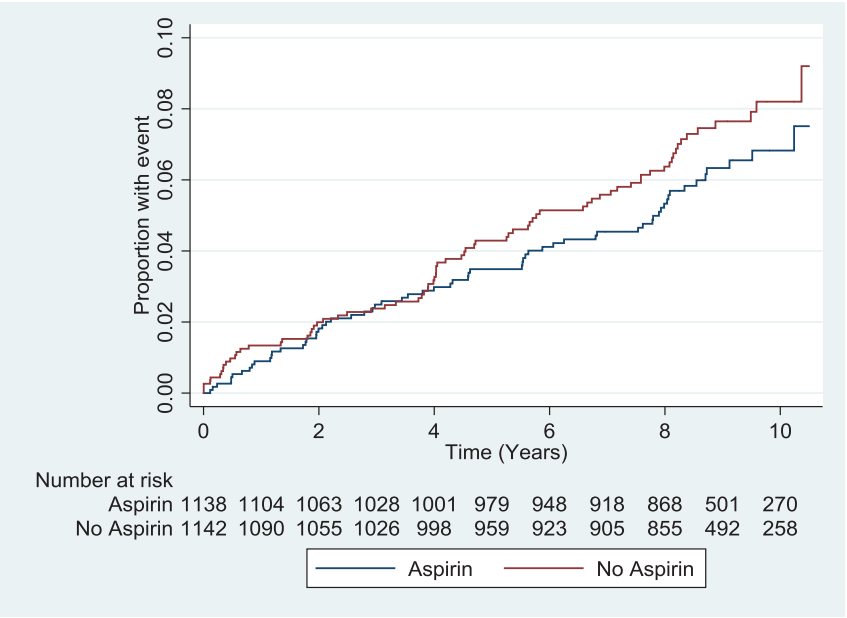
Treatment	**Therapeutic dose**
Low PPI no aspirin High PPI no aspirin	1 year of esomeprazole at randomised dose OR event before 1 year and esomeprazole at randomised dose until the event
Low PPI + aspirin High PPI + aspirin	1 year of esomeprazole at randomised dose and at least 6 months of aspirin at randomised dose OR event before 6 months and esomeprazole and aspirin at randomised dose until the event OR event between 6 and 12 months and esomeprazole at randomised dose until the event and aspirin at randomised dose for at least 6 months

Supplementary table 18: Accelerated failure time per protocol analysis for both primary comparisons

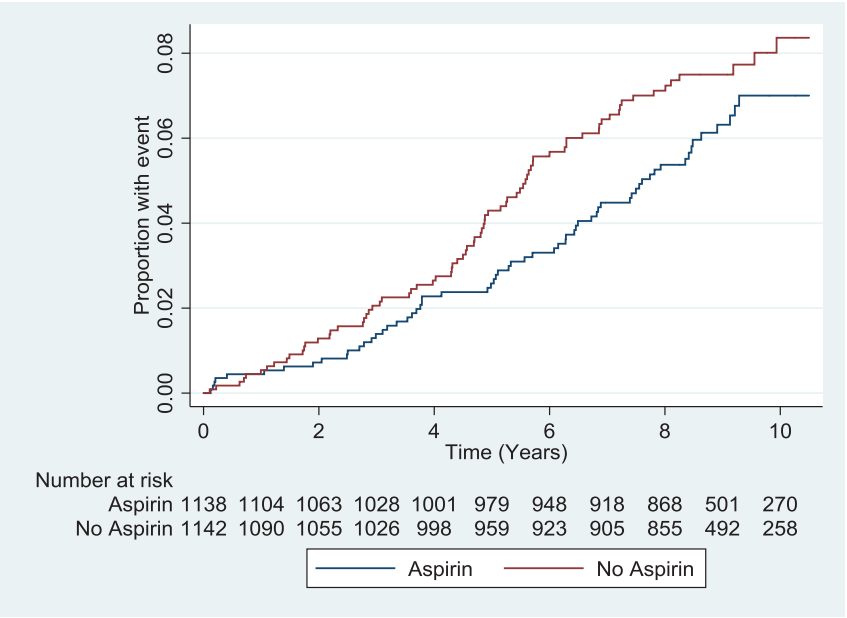
	Number of patients	Time ratio (TR)	95% CI	P value
Aspirin vs no aspirin	1,812	1.25	0.96 , 1.63	0.101
High PPI vs low PPI	2,008	1.16	0.90 , 1.48	0.252

Supplementary figure 2: Kaplan Meier curves for comparison of Aspirin vs no Aspirin and high dose PPI vs low dose PPI

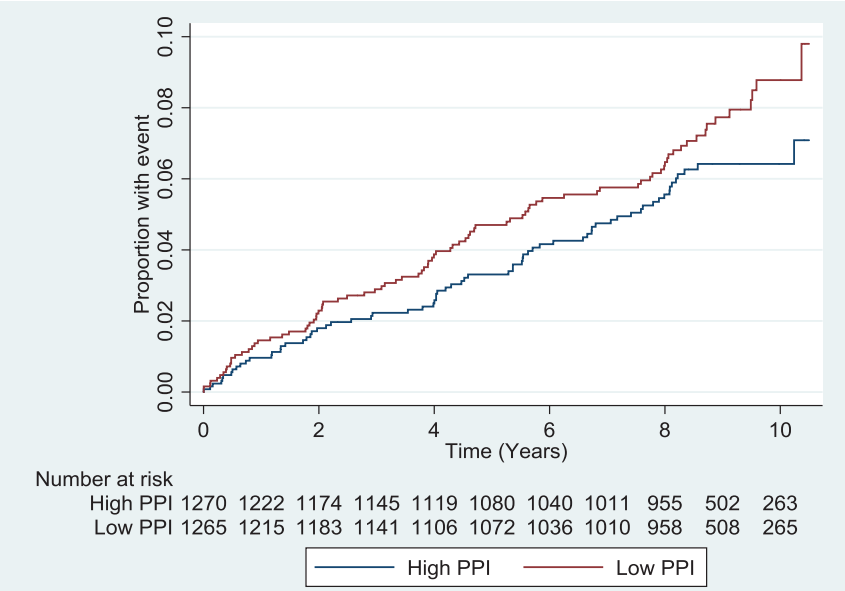
2 (a). Aspirin and HGD/Adenocarcinoma:



2(b): Aspirin and all-cause mortality:



2(c) PPI and HGD/Adenocarcinoma:



2 (d) PPI and all-cause mortality: