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Title: Angiotensin receptor blocker use and gastro-oesophageal cancer survival: a population-based cohort study

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Running title: ARBs and gastro-oesophageal cancer survival

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Summary

Background: Angiotensin receptor blockers (ARBs; including candesartan, losartan, olmesartan and valsartan) are widely used to treat hypertension, heart failure and diabetic neuropathy. There is considerable preclinical evidence that ARBs can reduce cancer progression, particularly for gastric cancer. Despite this, epidemiological studies have yet to assess the impact of ARB use on gastro-oesophageal cancer survival.

Aim: To investigate the association between post-diagnosis ARB use and gastro-oesophageal cancer survival.

Methods: We selected a cohort of patients with newly-diagnosed gastro-oesophageal cancer between 1998 and 2012 from English cancer registries. We linked to prescription and clinical records from the Clinical Practice Research Datalink, and to death records from the Office for National Statistics. We used time-dependant Cox-regression models to calculate hazard ratios (HRs) comparing gastro-oesophageal cancer-specific mortality between post-diagnosis ARB users and non-users, after adjusting for demographics, comorbidities and post-diagnosis aspirin or statin use.

Results: Our cohort included 5,124 gastro-oesophageal cancer patients, of which 360 used ARBs, and 3,345 died due to their gastro-oesophageal cancer during follow-up. After adjustment, ARB users had moderately lower risk of gastro-oesophageal cancer mortality than the non-users (HR=0.83, 95% CI: 0.71, 0.98). There was evidence of a dose-response relationship with the lowest HRs observed among patients receiving at least two years of prescriptions (HR=0.42, 95% CI: 0.25, 0.72).

Conclusions: In this large population-based gastro-oesophageal cancer cohort, we found moderately reduced cancer-specific mortality among ARB users. However, confirmation in further independent epidemiological studies with sufficient staging information is required.

1 Introduction

2 Oesophageal and gastric cancer are among the most common cancers in the world, with around
3 456,000 and 952,000 new cases diagnosed annually.¹ Prognosis is extremely poor, even in developed
4 countries such as the United Kingdom, where 55% of patients die within one year of diagnosis.²
5 Those who survive suffer a marked reduction in their quality of life during treatment and recovery.^{3,4}

6

7 Angiotensin receptor blockers (ARBs; including candesartan, losartan, olmesartan and valsartan) are
8 widely used and effective treatments for hypertension, heart failure and diabetic neuropathy.^{5, 6} In
9 England, ARBs are recommended as a first-line pharmacological treatment for hypertension patients
10 aged under fifty-five or with comorbid diabetes,^{7, 8} and nearly 20 million prescriptions are dispensed
11 annually.⁹ An estimated 200 million patients are treated with ARBs worldwide, representing 25% of
12 all antihypertensive agents.¹⁰ ARBs reduce blood pressure by blocking angiotensin II type I receptors
13 within the renin-angiotensin system, however evidence of local expression of renin-angiotensin
14 system components within cancer cells^{11, 12} has fuelled debate that they might also affect cancer
15 tumour development.^{11, 13} In-vitro and mouse models at various cancer sites have shown that ARBs
16 reduce tumour growth, stimulate cell apoptosis, reduce metastasis, and inhibit angiogenesis,
17 suggesting that several chemopreventive mechanisms are possible.¹⁴⁻¹⁸ More specifically, ARBs have
18 been shown to slow proliferation, inhibit fibrosis, and prevent stress-induced injury in gastric cancer
19 cell line and animal model studies.¹⁹⁻²³

20

21 Despite convincing preclinical evidence that ARBs could influence cancer risk and progression,
22 studies in humans are inconsistent. A meta-analysis of secondary outcomes from randomised
23 controlled trials found little evidence of an association between ARB use and cancer risk²⁴, while a
24 meta-analysis of observational studies reported reduced cancer risk among long-term ARB users.²⁵
25 Observational studies of cancer progression are fewer, but have found improved outcomes among
26 ARB or angiotensin converting enzyme inhibitor (an alternative antihypertensive medication which

27 also inhibits the renin-angiotensin system) users across several cancer sites, while also highlighting
28 methodological issues with the current literature such as poor generalisability, short follow-up,
29 inadequate case-mix adjustment and potential exposure misclassification.^{26, 27} To date, no studies
30 have investigated ARB use and gastro-oesophageal mortality, although olmesartan has been shown
31 to cause severe enteropathy in some patients, suggesting upper-gastrointestinal effects.²⁸
32 Consequently, we used a large population-based dataset from the UK to robustly assess this
33 association.

34 Methods

35 Data Sources

36 Our study used data from the English National Cancer Data Repository, linked to GP records from the
37 UK Clinical Practice Research Datalink, deprivation indices from census information, and death
38 registration data from the Office for National Statistics . The National Cancer Data Repository holds
39 UK-wide data from English cancer registries compiled from general practices, National Health Service
40 and private hospitals, and death certificates. It contains detailed information about the patient's
41 cancer, including year of diagnosis, stage, histologic grade, tumour type (adenocarcinoma or
42 squamous cell carcinoma) and treatment (surgery, chemotherapy, and radiotherapy). The Clinical
43 Practice Research Datalink contains computerised medical records from 674 general practices
44 (approximately 7% of the UK population) which are audited for data completeness and quality.
45 Practices meeting a predefined quality threshold are deemed 'up to standard' and included in future
46 extracts. Data recorded within the Clinical Practice Research Datalink include patient demographics,
47 clinical diagnoses (using Read codes) and prescription medication use. Previous research has found
48 prescription and clinical information to be of high quality.²⁹ Office for National Statistics death-
49 registration data provide details on the date and cause(s) of death.

50

51 Ethical approval for all purely observational research using anonymised Clinical Practice Research
52 Datalink data was obtained from a National Research Ethics Service Committee. The protocol for
53 this study was approved by the Clinical Practice Research Datalink Independent Scientific Advisory
54 Committee (Ref: 15_096R), and has been made available to reviewers.

55

56 Study Design and Population

57 We identified a cohort of patients with newly-diagnosed gastro-oesophageal cancer from English
58 cancer registry records (ICD-10 codes C15 or C16) between 1998 and 2012. Cohort members with a

59 previous diagnosis of cancer (excluding non-melanoma skin cancer) were identified and excluded
60 using a list of cancer Read codes modified for use in the Clinical Practice Research Datalink.³⁰
61 Patients were excluded if they were diagnosed: (a) before they were registered with a Clinical
62 Practice Research Datalink practice, (b) before their practice was deemed up to research standard,
63 (c) after they left a Clinical Practice Research Datalink practice, or (d) after data were last collected
64 from their practice by the Clinical Practice Research Datalink. A small number of patients had more
65 than one gastro-oesophageal cancer record in the National Cancer Data Repository; when this
66 occurred we used their first record.

67

68 Deaths were identified from Office for National Statistics records, and gastro-oesophageal cancer
69 specific deaths were defined as those with an underlying cause of gastro-oesophageal cancer (ICD-
70 10 codes C15, C16 or C26). Patients with less than six months follow-up were excluded as it is
71 unlikely that these could be influenced by post-diagnosis medication use. Therefore the follow-up
72 period started from six months after diagnosis. The end of follow-up was the earliest date of: death,
73 end of registration with the practice, last collection of data from the practice, or end of death record
74 follow-up.

75

76 [Definition of exposure](#)

77 We used the British National Formulary³¹ to compile a list of proprietary and generic medication
78 names to identify ARB use (Appendix 1). We added a lag of six months to ARB use as these
79 medications are unlikely to have an immediate effect on gastro-oesophageal cancer progression,
80 and to prevent reverse causation.^{32, 33} A diagram illustrating our design is shown in Appendix 2. We
81 defined patients as users after they received their first prescription during the exposure period. To
82 enable the testing of dose-response relationships we extracted data on the number of tablets and
83 medication strength, and calculated defined daily doses (DDDs). The DDD system is a validated
84 measure of drug consumption maintained by the World Health Organisation. A single DDD is the

85 average maintenance dose per day of a drug used for its main indication in adults (e.g. hypertension
86 for ARBs). There was insufficient information to calculate DDDs for 0.1% of prescriptions, and
87 implausible values were recorded in a further 0.1%. In these cases we assumed the most common
88 DDD based on other prescriptions with complete information. We calculated a running DDD total for
89 each patient and identified the day when patients received their 1st (first use), 183th (six months'
90 use), 365th (one year's use) and 730th (two years' use) DDDs.

91

92 Covariates

93 Patients' age, smoking (current, former, never), units of alcohol consumed per week (0,1-14, 15-28,
94 29-42, 43+), and body mass index (BMI; underweight [BMI<18.5], normal weight [18.5≤BMI<25],
95 overweight [25≤BMI<30] and obese [BMI≥30]) data were determined from the closest GP record
96 before gastro-oesophageal cancer diagnosis (values more than 10 years before diagnoses were
97 discarded). We used GP records to identify pre-diagnosis comorbidities (cerebrovascular disease,
98 chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction,
99 peptic ulcer disease, peripheral vascular disease, renal disease) using a list of Read codes modified
100 for use in the Clinical Practice Research Datalink.³⁰ Deprivation data were available from census
101 information, and based on the 2010 Index of Multiple Deprivation score of the patient's postcode.
102 We used Clinical Practice Research Datalink prescription records to identify patients using statins or
103 aspirin after diagnosis, as these have been shown to influence cancer progression previously.^{34, 35}

104

105 Statistical analysis

106 We calculated descriptive statistics and compared the demographic, lifestyle and clinical
107 characteristics of the ARB users and non-users. We produced survival graphs using the Simon–
108 Makuch method, which is an alternative to the Kaplan-Meier but appropriately accounts for time-
109 varying covariates.³⁶ We used time-dependant Cox regression models to calculate hazard ratios
110 (HRs) comparing gastro-oesophageal cancer-specific death between ARB users and non-users. We

111 conducted analyses for gastro-oesophageal cancer, and separately for oesophageal (ICD-10 code
112 C15) and gastric (ICD-10 code C16) cancer. In our primary analysis we included ARB use as a time-
113 varying covariate to avoid immortal time bias.³⁷ Therefore patients were initially included within the
114 analysis as non-users until six months after their first use (due to the exposure lag), after which they
115 were included as users until the end of follow-up. Our primary analysis adjusted for age at diagnosis,
116 year of diagnosis (separate term for each year), deprivation quintile, comorbidities (separate terms
117 for each), post-diagnosis use of aspirin or statins (using time-varying covariates and a six month lag
118 after their first prescription), cancer site (gastric or oesophageal), and treatment within six months
119 of diagnosis (separate terms for surgery, chemotherapy, radiotherapy). We repeated our analysis by
120 number of DDDs prescribed (e.g. patients were included in the 1-364 DDD group until six months
121 after they received their 365th DDD), and for candesartan and losartan, the most commonly
122 prescribed ARBs.⁹ Again, the use of time-varying covariates negates immortal time bias. We
123 conducted interaction tests to assess differences by tumour type.

124

125 Sensitivity and subgroup analyses

126 We conducted sensitivity analysis for all-cause mortality, and for cause-specific mortality where
127 deaths with a secondary cause (i.e. listed as an 'other cause of death' on death certificate) of gastro-
128 oesophageal cancer were included. We also conducted sensitivity analyses with a lag period of zero
129 (patients followed-up from diagnosis) and twelve months (patients followed-up from twelve months
130 after diagnosis). We performed two simplified analyses which controlled for immortal time bias
131 without time-varying covariates.³⁷ Firstly, we based ARB usage on the six months after diagnosis, and
132 followed-up patients from six months after diagnosis. Secondly, we investigated ARB usage in the
133 year prior to diagnosis, and followed-up patients from the date of diagnosis. Diagrams illustrating
134 the design of our sensitivity analyses which vary the exposure lag and/or period are given in
135 Appendix 2. We conducted subgroup analysis by tumour type (i.e. adenocarcinoma and squamous
136 cell carcinoma), as these differ in incidence, risk factors and pathogenesis. We also carried out sub-

137 group analysis restricted to patients receiving surgery, as they are likely to form a more homogenous
138 group of earlier-stage patients.

139

140 To assess if confounding by indication was driving our results, we conducted three further sensitivity
141 analyses restricted to patients with similar clinical diagnoses. First, we restricted our analysis to
142 patients with a hypertension diagnosis (Read code categories G20 and 662) in the year prior to
143 cancer diagnosis. Second, we restricted our analysis to patients who received an antihypertensive
144 medication (diuretics, vasodilator antihypertensive drugs, centrally acting antihypertensive drugs,
145 alpha-adrenoceptor blocking drugs, beta-blockers, angiotensin converting enzyme [ACE] inhibitors,
146 ARBs, renin inhibitors, and calcium channel blockers) in the year prior to cancer diagnosis. Third, we
147 compared patients who received ARBs to those who received a different antihypertensive
148 medication after diagnosis (using a time-varying covariate), as the use of an active comparison can
149 overcome several common pharmacoepidemiological biases.³⁸ Similarly, we conducted negative
150 control analyses³⁹ for ACE inhibitors as they have similar indications to ARBs, but a distinct biological
151 mechanism within the renin-angiotensin system. Therefore, if confounding was driving our ARB
152 analyses we would expect to see similar associations for ACE inhibitors. Conversely, findings of a
153 substantial association for ARBs, which are not replicated among the negative controls, would
154 support a causal interpretation.

155

156 We performed additional sensitivity analysis adjusting for tumour prognostic features (stage, grade)
157 and patient lifestyle factors (smoking, alcohol consumption, BMI) using multiple imputation with
158 chained equations. Briefly, this is a simulation-based approach for handling missing data which leads
159 to valid statistical inferences under certain assumptions.⁴⁰ The imputation used ordered logit models
160 with age, deprivation, death indicator and the baseline hazard function as covariates. Lastly, we
161 used the Fine and Gray sub-distribution hazard model to assess the impact of competing risks from
162 non-gastro-oesophageal cancer deaths.⁴¹

163 Results

164 Cohort Description

165 We identified 9,714 gastro-oesophageal cancer cases with no prior cancer diagnosis registered at
166 Clinical Practice Research Datalink practices. We excluded 4,590 patients as they had either less than
167 six months follow-up (n=4,582) or a duplicate record in the National Cancer Data Repository (n=8),
168 leaving 5,124 patients for analysis. Median follow-up was 1.4 years (maximum 17.2 years). ARB users
169 were more likely to be female, have comorbidities (particularly diabetes, renal disease and
170 congestive heart disease), be treated with statins or aspirin after diagnosis, undergo surgery, be non-
171 or ex- smokers, and be obese (Table 1).

172

173 Association between ARB use and survival

174 Overall, ARB users were at a moderately lower risk of gastro-oesophageal cancer death than non-
175 users both before (unadjusted HR=0.80, 95% CI: 0.69, 0.94; Figure 1) and after adjustment for
176 demographics, comorbidities, cancer treatments and post-diagnosis aspirin or statin use (adjusted
177 HR=0.83, 95% CI: 0.71, 0.98; Table 2). There was evidence of a dose-response relationship (p-value
178 for trend=0.003); the largest differences in mortality were found among those who had received at
179 least 730 DDDs (adjusted HR=0.42, 95% CI: 0.25, 0.72), although associations were relatively similar
180 for those receiving 1-182, 183-364, 365-729 DDDs. We observed broadly similar estimates for
181 losartan (adjusted HR=0.84, 95% CI: 0.59, 1.21) and candesartan (adjusted HR=0.73, 95% CI: 0.49,
182 1.09). We found slightly stronger association among patients with gastric (adjusted HR=0.79, 95% CI:
183 0.62, 1.00) than oesophageal (adjusted HR=0.89, 95% CI: 0.71, 1.10) cancer, although the dose-
184 response patterns were comparable to the combined analysis, with very large decreases in cancer-
185 specific mortality among both oesophageal (adjusted HR=0.44, 95% CI: 0.21, 0.94) and gastric
186 (adjusted HR=0.40, 95% CI: 0.19, 0.84) patients receiving at least 730 DDDs of ARBs. The full results
187 of the gastro-oesophageal model are given in Appendix 3.

188

189 Sensitivity and subgroup analyses

190 Our results were similar in the simpler analysis basing ARB use on the year prior, or six-months after
191 diagnosis (Table 3). Our conclusions were unchanged when expanding our cancer-specific death
192 definition to include secondary death causes, and for all-cause mortality. Our results were robust to
193 alterations in the exposure lag period from zero to twelve months, and did not change appreciably
194 when adjusting for tumour prognostic features (i.e. stage, grade), or patient lifestyle factors (i.e.
195 smoking, alcohol, BMI) using multiple imputation methods.

196

197 We observed broadly similar hazard ratios when restricting our analysis to patients who received
198 surgical treatment (adjusted HR=0.81; 95% CI: 0.63, 1.05), or with a prior diagnosis of hypertension
199 (adjusted HR=0.83; 95% CI: 0.62, 1.09). Likewise, our results were broadly similar when restricting to
200 those in receipt of antihypertensive medications before diagnosis (adjusted HR=0.80; 95% CI: 0.67,
201 0.94), or when comparing ARB users to patients receiving a different antihypertensive medication
202 after gastro-oesophageal cancer diagnosis (adjusted HR=0.83; 95% CI: 0.71, 0.98). We did not find
203 any evidence of an association between ACE inhibitor use and gastro-oesophageal survival (adjusted
204 HR: 0.98, 95% CI: 0.89, 1.08; Appendix 4). The association between ARB use and cancer-mortality
205 was slightly stronger for patients with adenocarcinoma (adjusted HR=0.78, 95% CI: 0.65, 0.94) than
206 squamous cell carcinoma (adjusted HR=0.95, 95% CI: 0.63, 1.43), although this difference was not
207 statistically significant (p -value for interaction=0.52).

208 Discussion

209 Summary of main findings

210 In this large, population-based cohort of newly-diagnosed gastro-oesophageal cancer patients, we
211 found a statistically significant reduction of 17% in cancer-specific mortality among ARB users after
212 adjustment for patient demographics, comorbidities, cancer treatments and post-diagnosis aspirin
213 or statin use. There was some evidence of a dose-response relationship with the largest decreases in
214 mortality observed among patients receiving at least 2 years' worth of prescriptions.

215

216 Strengths and weaknesses

217 This is the first study to investigate ARB use and survival from gastro-oesophageal cancer. Our study
218 is based on a high-quality population-based cohort of patients with registry-confirmed gastro-
219 oesophageal cancer which was followed-up for up to 17 years.²⁹ Linkage to Office for National
220 Statistics death registration data allowed robust verification of death, and facilitated a gastro-
221 oesophageal cancer-specific analysis, which should be more sensitive to small changes in disease-
222 specific mortality, and less susceptible to confounding by indication than all-cause deaths.^{33, 42}
223 Although some misclassification of death cause is possible, studies have shown this is likely to have a
224 limited impact on our estimates (as there is no obvious mechanism for differential
225 misclassification)⁴³, and our results were similar when including deaths where gastro-oesophageal
226 cancer was not the underlying cause. We used prescribing data collected as part of routine clinical
227 care which accurately reflects GP prescribing practices and negates the risk of recall bias. These data
228 also included detailed information on the type of ARB, and the strength, quantity and timing of
229 prescription, which allowed us to investigate dose-response relationships, and conduct separate
230 analyses for specific medications. ARBs are not available over-the-counter in the UK, which negates
231 exposure misclassification due to over-the-counter usage.

232

233 Our study had several potential weaknesses. We necessarily excluded patients who lived for less
234 than six months after diagnosis, therefore our results cannot be applied to those with a very poor
235 prognosis. Our study is observational and hence open to confounding by incomplete or unmeasured
236 covariates. Although we have adjusted for several key determinants of gastro-oesophageal cancer
237 survival (e.g. age, comorbidities and cancer treatments), some were incompletely recorded (e.g.
238 smoking history) and others were not available within our dataset (e.g. ethnicity and family history).
239 The lack of complete information on cancer stage is of particular concern, especially as ARB users
240 were more frequently diagnosed with lower-stage cancers than non-users (e.g. 16.9% vs. 9.4% stage
241 1). It is also possible that our study could be subject to a 'healthy user effect' whereby patients who
242 receive one preventative therapy (ARBs) are more likely to use other therapies (e.g. endoscopy), or
243 more closely follow medical advice (e.g. attend medical appointments).⁴⁴

244

245 Nevertheless, the findings from our sensitivity analyses suggest that confounding or missing data
246 issues were not solely driving our results. For example, the protective association for ARBs was
247 preserved when using other antihypertensive medications as an active comparator, when restricting
248 to those who received surgery (who should form a more homogeneous cohort of lower-stage
249 patients), and when limiting our analysis to patients with a prior hypertension diagnosis. Similarly,
250 we observed little evidence of an association between gastro-oesophageal cancer mortality and ACE
251 inhibitor use, which have similar indications to ARBs. Lastly, our conclusions were unchanged when
252 using multiple imputation to adjust for cancer stage and grade, albeit this analysis is particularly
253 sensitive to departures from the 'missing at random' assumption due to the large proportion of
254 missing data for these variables.⁴⁵ We do not know if patients adhered to their prescribed
255 medications, however our main conclusions were similar when restricting our analysis to patients
256 who received multiple ARB prescriptions (≥ 730 DDDs), where non-compliance is less of a concern.
257 Finally, ARBs were one of six medications investigated within a broader programme of work,
258 meaning that multiple testing could be a potential concern.

259

260 [Comparison with the previous literature](#)

261 We are unaware of any other studies comparing gastro-oesophageal cancer mortality between ARB
262 users and non-users. Several studies have previously investigated the role of renin-angiotensin
263 system blockade on cancer survival. However they have generally combined ACE inhibitors with
264 ARBs²⁷, potentially obfuscating the therapeutic effect of each medication as they have distinct
265 mechanisms of action within the renin-angiotensin system, and are known to differ in their side
266 effect profiles. Our finding of a much stronger association with gastro-oesophageal survival among
267 ARB than ACE inhibitor users could suggest that separate analyses are indeed preferable.

268

269 Nevertheless, our results are consistent with findings of longer survival among gastro-oesophageal
270 cancer patients using renin-angiotensin system blockade medications in two other studies based in
271 Taiwan and Korea.^{46, 47} However, each of these were substantially limited by poor generalisability
272 (e.g. restricted to advanced gastric cancer), an inability to identify cancer-specific deaths,
273 inappropriate statistical methods (e.g. chi-squared test) and small sample size (196 patients in total).
274 Our study improves on the current literature by using appropriate methodology to analyse a
275 population-based cohort over thirty times larger than previous work. Our results are also consistent
276 with the findings from several other observational studies reporting improved survival among renin-
277 angiotensin system blockade medication users at other sites.^{26, 27} For example, one recent meta-
278 analysis found that mortality was 25% (95% CI: 1, 43) lower among cancer patients using ACE
279 inhibitors or ARBs, with particularly large decreases in urinary tract, colorectal, pancreatic, and
280 prostate cancer.²⁷

281

282 [Implications for practitioners and researchers](#)

283 Our results provide epidemiological evidence that the use of ARBs may be associated with improved
284 gastro-oesophageal cancer survival. Our conclusions are consistent with preclinical research which

285 has demonstrated that ARBs can slow tumour growth, stimulate cell apoptosis, reduce metastasis,
286 and inhibit angiogenesis.¹⁴⁻¹⁸ More specifically, ARBs have been shown to slow proliferation, inhibit
287 fibrosis, and prevent stress-induced injury in gastric cancer cell line and animal model studies.¹⁹⁻²³
288 Our finding of a slightly stronger association among gastric than oesophageal cancer patients
289 requires further exploration, however it could be due to higher renin-angiotensin system expression
290 among patients with *H.pylori* infection⁴⁸, the most important risk factor for gastric cancer. Likewise
291 our finding of a slightly stronger association for adenocarcinoma than squamous cell carcinoma
292 could be due to ARBs promoting healing of reflux oesophagitis among proton pump inhibitor users.⁴⁹
293
294 Our study suggests that it is worth further exploring the potential for ARBs to be repurposed as a
295 gastro-oesophageal cancer treatment, particularly as they are inexpensive (losartan costs £1.15
296 [\$1.48] per 28-tablet pack)⁵⁰, have no major safety concerns⁵¹, and are well tolerated by patients.⁵²
297 In this paper we have demonstrated that the association with gastro-oesophageal cancer mortality
298 adheres to several of Hill's criteria for causation including biological plausibility, experimental
299 evidence, temporality, biological gradient, consistency and specificity.⁵³ However, these findings
300 should be replicated in independent epidemiological studies with more complete information on
301 cancer stage.

302

303 Conclusions

304 In this large population-based cohort of patients with registry-confirmed gastro-oesophageal cancer,
305 we found a 17% reduction in cancer-specific mortality among ARB users. Although this association
306 adheres to several of Hill's criteria for causation, and is consistent with preclinical evidence, further
307 independent epidemiological studies with more complete stage data is required.

308 Disclosures

309 **Acknowledgements:** This study is based in part on data from the Clinical Practice Research Datalink
310 obtained under licence from the UK Medicines and Healthcare products Regulatory Agency.
311 However, the interpretation and conclusions contained in this study are those of the author/s alone.
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313 for AS from Cancer Research-UK [C54914/A20558].

314

315 **Abbreviations:** ACE: angiotensin converting enzyme; ARB: angiotensin receptor blocker; BMI: body
316 mass index; DDD: defined daily dose; HR: hazard ratio

317

318 **Authorship Statement:** CC, AS, BJ and CH conceived the study. JB conducted the analysis and drafted
319 the initial manuscript. All authors critically revised the article for intellectual content and approved
320 the final manuscript. JB acts as the study guarantor.

321

322 **Conflict of interest:** None to declare

323

324 **Figure Legends**

325 **Figure 1:** Red line represents the proportion of ARB users that are alive at a given time after
326 diagnosis. Blue line represents the proportion of non-ARB users that are alive at a given time after
327 diagnosis.

References

1. GLOBOCAN. Estimated Cancer Incidence, Mortality and Prevalence Worldwide in 2012.
2. Office for National Statistics. Cancer survival in England: Patients diagnosed between 2010 and 2014 and followed up to 2015. 2016; Available from: <http://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/cancersurvivalinenglandadultsdiagnosed/2010and2014andfollowedupto2015#5-year-survival>.
3. Viklund P, Wengstrom Y, Rouvelas I, et al. Quality of life and persisting symptoms after oesophageal cancer surgery. *Eur J Cancer*. 2006;42(10):1407-14.
4. Zieren HU, Jacobi CA, Zieren J, et al. Quality of life following resection of oesophageal carcinoma. *Br J Surg*. 1996;83(12):1772-5.
5. Lindholm LH, Ibsen H, Dahlöf B, et al. Cardiovascular morbidity and mortality in patients with diabetes in the Losartan Intervention For Endpoint reduction in hypertension study (LIFE): a randomised trial against atenolol. *Lancet*. 2002;359(9311):1004-10.
6. Pfeffer MA, Swedberg K, Granger CB, et al. Effects of candesartan on mortality and morbidity in patients with chronic heart failure: the CHARM-Overall programme. *Lancet (London, England)*. 2003;362(9386):759-66. Epub 2003/09/19.
7. National Institute for Health and Care Excellence (NICE). Hypertension in adults: diagnosis and management. 2016 [cited 2017 10/04/17]; Available from: <https://www.nice.org.uk/guidance/cg127/chapter/2-Research-recommendations>.
8. National Institute for Health and Care Excellence (NICE). Type 1 diabetes in adults: diagnosis and management. 2016 [cited 2017 10/04/17]; Available from: <https://www.nice.org.uk/guidance/ng17/chapter/1-Recommendations>.
9. Powell-Smith A, Goldacre B. OpenPrescribing.net. 2016. Available from: <https://openprescribing.net/>.
10. Volpe M, Azizi M, Danser AHJ, et al. Twisting arms to angiotensin receptor blockers/antagonists: the turn of cancer. *European Heart Journal*. 2011;32(1):19-22.
11. Deshayes F, Nahmias C. Angiotensin receptors: a new role in cancer? *Trends in endocrinology and metabolism: TEM*. 2005;16(7):293-9. Epub 2005/08/03.
12. Garg M, Angus PW, Burrell LM, et al. Review article: the pathophysiological roles of the renin-angiotensin system in the gastrointestinal tract. *Alimentary pharmacology & therapeutics*. 2012;35(4):414-28. Epub 2012/01/10.
13. George AJ, Thomas WG, Hannan RD. The renin-angiotensin system and cancer: old dog, new tricks. *Nat Rev Cancer*. 2010;10(11):745-59.
14. Rocken C, Lendeckel U, Dierkes J, et al. The number of lymph node metastases in gastric cancer correlates with the angiotensin I-converting enzyme gene insertion/deletion polymorphism. *Clinical cancer research : an official journal of the American Association for Cancer Research*. 2005;11(7):2526-30. Epub 2005/04/09.
15. Neo JH, Malcontenti-Wilson C, Muralidharan V, et al. Effect of ACE inhibitors and angiotensin II receptor antagonists in a mouse model of colorectal cancer liver metastases. *J Gastroenterol Hepatol*. 2007;22(4):577-84.

16. Gong Q, Davis M, Chipitsyna G, et al. Blocking angiotensin II Type 1 receptor triggers apoptotic cell death in human pancreatic cancer cells. *Pancreas*. 2010;39(5):581-94. Epub 2010/02/02.
17. Attoub S, Gaben AM, Al-Salam S, et al. Captopril as a potential inhibitor of lung tumor growth and metastasis. *Annals of the New York Academy of Sciences*. 2008;1138:65-72. Epub 2008/10/08.
18. Willis LM, El-Remessy AB, Somanath PR, et al. Angiotensin receptor blockers and angiogenesis: clinical and experimental evidence. *Clinical science (London, England : 1979)*. 2011;120(8):307-19. Epub 2011/04/14.
19. Huang MM, Guo AB, Sun JF, et al. Angiotensin II promotes the progression of human gastric cancer. *Mol Med Rep*. 2014;9(3):1056-60.
20. Okazaki M, Fushida S, Harada S, et al. The angiotensin II type 1 receptor blocker candesartan suppresses proliferation and fibrosis in gastric cancer. *Cancer letters*. 2014;355(1):46-53. Epub 2014/09/17.
21. Bregonzio C, Armando I, Ando H, et al. Anti-inflammatory effects of angiotensin II AT1 receptor antagonism prevent stress-induced gastric injury. *American journal of physiology Gastrointestinal and liver physiology*. 2003;285(2):G414-23. Epub 2003/04/11.
22. Kinoshita J, Fushida S, Harada S, et al. Local angiotensin II-generation in human gastric cancer: Correlation with tumor progression through the activation of ERK1/2, NF-kappa B and survivin. *Int J Oncol*. 2009;34(6):1573-82.
23. Wang L, Cai SR, Zhang CH, et al. Effects of angiotensin-converting enzyme inhibitors and angiotensin II type 1 receptor blockers on lymphangiogenesis of gastric cancer in a nude mouse model. *Chin Med J*. 2008;121(21):2167-71.
24. Bangalore S, Kumar S, Kjeldsen SE, et al. Antihypertensive drugs and risk of cancer: network meta-analyses and trial sequential analyses of 324,168 participants from randomised trials. *The Lancet Oncology*. 2011;12(1):65-82. Epub 2010/12/03.
25. Yoon C, Yang HS, Jeon I, et al. Use of angiotensin-converting-enzyme inhibitors or angiotensin-receptor blockers and cancer risk: a meta-analysis of observational studies. *Can Med Assoc J*. 2011;183(14):E1073-E84.
26. Mc Menamin UC, Murray LJ, Cantwell MM, et al. Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers in cancer progression and survival: a systematic review. *Cancer Causes Control*. 2012;23(2):221-30.
27. Song T, Choi CH, Kim MK, et al. The effect of angiotensin system inhibitors (angiotensin-converting enzyme inhibitors or angiotensin receptor blockers) on cancer recurrence and survival: a meta-analysis. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)*. 2017;26(1):78-85. Epub 2016/05/10.
28. Marthey L, Cadiot G, Seksik P, et al. Olmesartan-associated enteropathy: results of a national survey. *Alimentary pharmacology & therapeutics*. 2014;40(9):1103-9. Epub 2014/09/10.
29. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *International journal of epidemiology*. 2015;44(3):827-36. Epub 2015/06/08.
30. Khan NF, Perera R, Harper S, et al. Adaptation and validation of the Charlson Index for Read/OXMIS coded databases. *BMC family practice*. 2010;11:1. Epub 2010/01/07.

31. Joint Formulary Committee. Joint Formulary Committee. British National Formulary.[BNF online]. 2016 [cited 2017 13/04/17]; Available from: <https://www.medicinescomplete.com/mc/bnflegacy/current/PHP1219-losartan-potassium.htm>.
32. Tamim H, Monfared AA, LeLorier J. Application of lag-time into exposure definitions to control for protopathic bias. *Pharmacoepidemiology and drug safety*. 2007;16(3):250-8. Epub 2007/01/25.
33. Chubak J, Boudreau DM, Wirtz HS, et al. Threats to validity of nonrandomized studies of postdiagnosis exposures on cancer recurrence and survival. *J Natl Cancer Inst*. 2013;105(19):1456-62. Epub 2013/08/14.
34. Nielsen SF, Nordestgaard BG, Bojesen SE. Statin Use and Reduced Cancer-Related Mortality. *N Engl J Med*. 2012;367(19):1792-802.
35. Elwood PC, Morgan G, Pickering JE, et al. Aspirin in the Treatment of Cancer: Reductions in Metastatic Spread and in Mortality: A Systematic Review and Meta-Analyses of Published Studies. *PLoS One*. 2016;11(4):25.
36. Simon R, Makuch RW. A non-parametric graphical representation of the relationship between survival and the occurrence of an event: application to responder versus non-responder bias. *Statistics in medicine*. 1984;3(1):35-44. Epub 1984/01/01.
37. Lévesque LE, Hanley JA, Kezouh A, et al. Problem of immortal time bias in cohort studies: example using statins for preventing progression of diabetes. *BMJ (Clinical research ed)*. 2010;340.
38. Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Current epidemiology reports*. 2015;2(4):221-8.
39. Lipsitch M, Tchetgen ET, Cohen T. Negative Controls: A Tool for Detecting Confounding and Bias in Observational Studies. *Epidemiology (Cambridge, Mass)*. 2010;21(3):383-8.
40. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in medicine*. 2011;30(4):377-99. Epub 2011/01/13.
41. Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. *Journal of the American Statistical Association*. 1999;94(446):496-509.
42. Steele RJC, Brewster DH. Should we use total mortality rather than cancer specific mortality to judge cancer screening programmes? No. *BMJ (Clinical research ed)*. 2011;343.
43. Sarfati D, Blakely T, Pearce N. Measuring cancer survival in populations: relative survival vs cancer-specific survival. *International journal of epidemiology*. 2010;39(2):598-610. Epub 2010/02/10.
44. Shrank WH, Patrick AR, Alan Brookhart M. Healthy User and Related Biases in Observational Studies of Preventive Interventions: A Primer for Physicians. *Journal of General Internal Medicine*. 2011;26(5):546-50.
45. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. *Statistics in medicine*. 2011;30(4):377-99.
46. Chen YH, Huang CH, Lu HI, et al. Prognostic impact of renin-angiotensin system blockade in esophageal squamous cell carcinoma. *Journal of the renin-angiotensin-aldosterone system : JRAAS*. 2015;16(4):1185-92. Epub 2014/06/26.

47. Kim ST, Park KH, Oh SC, et al. How Does Inhibition of the Renin-Angiotensin System Affect the Prognosis of Advanced Gastric Cancer Patients Receiving Platinum-Based Chemotherapy? *Oncology*. 2012;83(6):354-60.
48. Sugimoto M, Yamaoka Y, Shirai N, et al. Role of renin-angiotensin system in gastric oncogenesis. *J Gastroenterol Hepatol*. 2012;27(3):442-51.
49. Miwa H, Hongo M, Kusano M. Combination of angiotensin II receptor blockers promotes proton pump inhibitor-based healing of reflux esophagitis. *Journal of gastroenterology*. 2012;47(3):249-55. Epub 2011/11/02.
50. Joint Formulary Committee. Losartan. In: Joint Formulary Committee. *British National Formulary*. [BNF online]. 2016 [cited 2017 13/04/17]; Available from: <https://www.medicinescomplete.com/mc/bnflegacy/current/PHP1219-losartan-potassium.htm>.
51. Sipahi I, Debanne SM, Rowland DY, et al. Angiotensin-receptor blockade and risk of cancer: meta-analysis of randomised controlled trials. *The Lancet Oncology*. 2010;11(7):627-36. Epub 2010/06/15.
52. Corrao G, Zambon A, Parodi A, et al. Discontinuation of and changes in drug therapy for hypertension among newly-treated patients: a population-based study in Italy. *Journal of hypertension*. 2008;26(4):819-24. Epub 2008/03/11.
53. Hill AB. The Environment and Disease: Association or Causation? *Proceedings of the Royal Society of Medicine*. 1965;58(5):295-300.

Tables and Figures

Table 1: Patient characteristics by ARB use at any time after diagnosis

	Non-user	User
Number of Patients	4,764	360
Year of Diagnosis		
1998-2002	1,163 (24.4%)	38 (10.6%)
2003-2007	1,651 (34.7%)	120 (33.3%)
2008-2012	1,950 (40.9%)	202 (56.1%)
Age at Diagnosis (SD)	69.5 (11.9)	71.9 (9.3)
0-49	268 (5.6%)	3 (0.8%)
50-59	684 (14.4%)	33 (9.2%)
60-69	1,284 (27.0%)	104 (28.9%)
70-79	1,512 (31.7%)	149 (41.4%)
80+	1,016 (21.3%)	71 (19.7%)
Gender		
Male	3,243 (68.1%)	216 (60.0%)
Female	1,521 (31.9%)	144 (40.0%)
Deprivation Quintile		
1 (Least Deprived)	949 (19.9%)	74 (20.6%)
2	1,182 (24.8%)	90 (25.0%)
3	951 (20.0%)	71 (19.7%)
4	955 (20.1%)	78 (21.7%)
5 (Most Deprived)	723 (15.2%)	47 (13.1%)
Missing	4	0
Comorbidities		
Diabetes	535 (11.2%)	101 (28.1%)
Chronic pulmonary disease	572 (12.0%)	57 (15.8%)
Renal disease	347 (7.3%)	65 (18.1%)
Cerebrovascular disease	242 (5.1%)	18 (5.0%)
Peptic ulcer disease	231 (4.8%)	18 (5.0%)
Peripheral vascular disease	218 (4.6%)	25 (6.9%)
Myocardial infarction	172 (3.6%)	26 (7.2%)
Congestive heart disease	168 (3.5%)	30 (8.3%)
Liver Disease	22 (0.5%)	4 (1.1%)
Confounder Medications		
Statin	1,149 (24.1%)	198 (55.0%)
Aspirin	931 (19.5%)	154 (42.8%)
Treatment		
Surgery	2,128 (44.7%)	186 (51.7%)
Chemotherapy	2,028 (42.6%)	160 (44.4%)
Radiotherapy	805 (16.9%)	64 (17.8%)
Grade		
1	183 (5.2%)	15 (5.9%)
2	1,398 (39.8%)	109 (42.7%)
3	1,900 (54.0%)	129 (50.6%)
4	35 (1.0%)	2 (0.8%)
Missing	1,248	105
Tumour type		
Adenocarcinoma	3,275 (68.7%)	265 (73.8%)
Squamous	804 (16.9%)	45 (12.5%)
Other	685 (14.4%)	49 (13.6%)
Stage		
1	73 (9.4%)	11 (16.9%)
2	147 (19.0%)	13 (20.0%)

3	280 (36.2%)	25 (38.5%)
4	274 (35.4%)	16 (24.6%)
Missing	3,990	295
Smoking		
Never	1,707 (39.4%)	156 (45.0%)
Former	1,557 (35.9%)	160 (46.1%)
Current	1,069 (24.7%)	31 (8.9%)
Missing	431	13
Alcohol (units per week)		
None	821 (30.1%)	71 (30.5%)
1-14	1,366 (50.0%)	117 (50.2%)
15-28	336 (12.3%)	31 (13.3%)
29-42	115 (4.2%)	10 (4.3%)
43+	94 (3.4%)	4 (1.7%)
Missing	2,032	127
BMI (kg/m²)		
Underweight (<18.5)	152 (4.4%)	2 (0.6%)
Normal (18.5-24.9)	1,239 (36.0%)	80 (25.4%)
Overweight (25-29.9)	1,352 (39.3%)	132 (41.9%)
Obese (≥30)	698 (20.3%)	101 (32.1%)
Missing	1,323	45

Table 2: Association between ARB use and gastro-oesophageal cancer mortality

	N	Person-Years	Deaths	Unadjusted HR	Adjusted HR ^a	Trend p-value
Gastro-oesophageal						
All ARBs Combined						
Never	4,764	9,241	3,175	Ref	Ref	0.003
Ever	360	786	170	0.80 (0.69,0.94)	0.83 (0.71,0.98)	
1-182 DDDs	146	263	92	0.87 (0.71,1.07)	0.91 (0.74,1.13)	
183-364 DDDs	67	130	40	0.92 (0.67,1.25)	0.97 (0.71,1.33)	
365-729 DDDs	57	109	24	0.82 (0.55,1.23)	0.83 (0.55,1.25)	
730+ DDDs	90	284	14	0.42 (0.25,0.71)	0.42 (0.25,0.72)	
Losartan						
Never	4,973	9,698	3,278	Ref	Ref	
Ever	151	330	67	0.82 (0.64,1.04)	0.82 (0.64,1.06)	
Candesartan						
Never	5,013	9,772	3,300	Ref	Ref	
Ever	111	255	45	0.72 (0.54,0.97)	0.71 (0.52,0.95)	
Oesophageal						
All ARBs Combined						
Never	2,565	4,499	1,776	Ref	Ref	0.135
Ever	168	338	91	0.89 (0.72,1.09)	0.89 (0.71,1.10)	
1-182 DDDs	68	100	47	0.87 (0.65,1.16)	0.89 (0.66,1.19)	
183-364 DDDs	31	53	24	1.21 (0.80,1.81)	1.21 (0.80,1.81)	
365-729 DDDs	30	53	13	0.95 (0.55,1.65)	0.92 (0.53,1.59)	
730+ DDDs	39	133	7	0.46 (0.22,0.97)	0.44 (0.21,0.94)	
Losartan						
Never	2,667	4,698	1,836	Ref	Ref	
Ever	66	139	31	0.82 (0.58,1.17)	0.84 (0.59,1.21)	
Candesartan						
Never	2,681	4,732	1,842	Ref	Ref	
Ever	52	105	25	0.76 (0.52,1.14)	0.73 (0.49,1.09)	
Gastric						
All ARBs Combined						
Never	2,199	4,743	1,399	Ref	Ref	0.009
Ever	192	448	79	0.75 (0.60,0.94)	0.79 (0.62,1.00)	
1-182 DDDs	78	163	45	0.89 (0.66,1.21)	0.95 (0.70,1.28)	
183-364 DDDs	36	78	16	0.70 (0.43,1.15)	0.75 (0.46,1.24)	
365-729 DDDs	27	56	11	0.74 (0.41,1.34)	0.76 (0.42,1.39)	
730+ DDDs	51	151	7	0.40 (0.19,0.85)	0.40 (0.19,0.84)	
Losartan						
Never	2,306	5,000	1,442	Ref	Ref	
Ever	85	191	36	0.85 (0.61,1.18)	0.81 (0.57,1.14)	
Candesartan						
Never	2,332	5,041	1,458	Ref	Ref	
Ever	59	150	20	0.68 (0.44,1.06)	0.67 (0.43,1.05)	

^a Adjusted for age, deprivation, year of diagnosis, cancer site, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (statins and aspirin, time-varying after diagnosis)

Figure 1: Association between ARB use and gastro-oesophageal cancer mortality

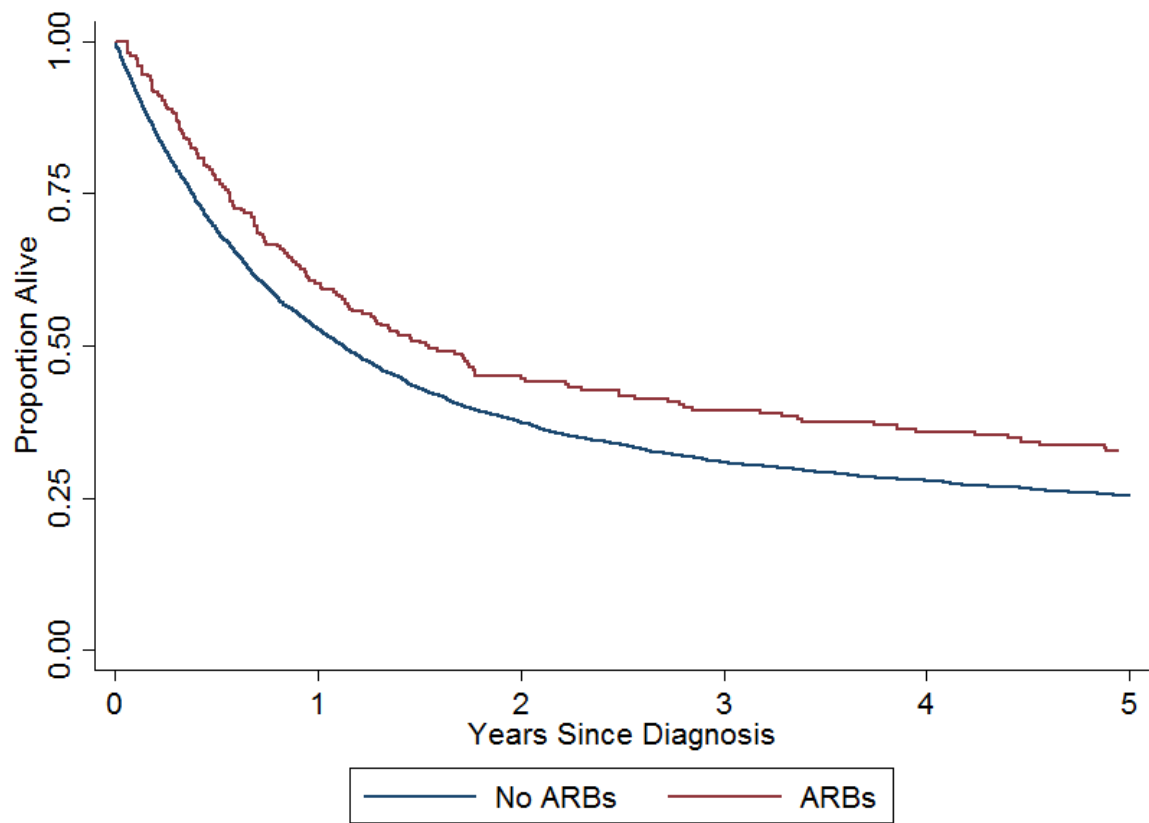


Table 3: Sensitivity and subgroup analysis for ARB use and gastro-oesophageal cancer mortality

	Non-Users ^a			Users			Unadjusted HR	Adjusted HR ^c
	N	Person-Years	Deaths ^b	N	Person-Years	Deaths		
Main analysis	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.83 (0.71,0.98)
Death definition								
All-cause	4,764	9,241	3,605	360	786	214	0.87 (0.76,1.00)	0.87 (0.75,1.00)
Primary or secondary GO cause	4,764	9,241	3,350	360	786	189	0.84 (0.73,0.98)	0.86 (0.74,1.00)
Exposure definition								
Year before diagnosis	4,757	11,733	3,130	367	821	215	0.91 (0.79,1.04)	0.91 (0.79,1.05)
Six months after diagnosis	4,804	9,447	3,167	320	581	178	0.82 (0.71,0.96)	0.85 (0.73,1.00)
Exposure lag								
None	4,731	11,579	3,149	393	976	196	0.82 (0.71,0.95)	0.85 (0.73,0.99)
12 months	4,870	7,314	1,722	254	629	94	0.81 (0.66,1.00)	0.82 (0.66,1.02)
Tumour type^d								
Adenocarcinoma	3,275	6,486	2,196	265	596	125	0.79 (0.66,0.94)	0.78 (0.65,0.94)
Squamous cell carcinoma	804	1,305	552	45	78	28	0.98 (0.67,1.43)	0.95 (0.63,1.43)
Surgical treatment	2,128	5,817	1,233	186	527	71	0.83 (0.66,1.06)	0.81 (0.63,1.05)
Hypertension diagnosis / treatment								
Pre-diagnosis hypertension diagnosis ^e	731	1,168	499	116	214	61	0.85 (0.65,1.12)	0.83 (0.62,1.09)
Pre-diagnosis antihypertensive medication users ^f	2,324	3,888	1,565	335	724	161	0.74 (0.63,0.87)	0.80 (0.67,0.94)
ARB vs. other antihypertensive medication ^g	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.83 (0.71,0.98)
Multiple Imputation								
Lifestyle factors ^h	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.85 (0.73,1.00)
Tumour prognostic factors ⁱ	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.87 (0.73,1.04)
Lifestyle & tumour prognostic factors ^j	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.94)	0.87 (0.73,1.03)
Competing risks regression^k	4,764	9,241	3,175	360	786	170	0.80 (0.69,0.93)	0.84 (0.72,0.99)

^a Non-users for each sensitivity analysis except for 'ARB vs. other antihypertensive medication' where patients who received a different antihypertensive medication serve as the non-user group

^b Deaths with an underlying cause of gastro-oesophageal cancer unless otherwise stated

^c Adjusted for age, deprivation, year of diagnosis, cancer site, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (statins, aspirin, time-varying after diagnosis)

^d P-value for interaction: 0.518

^e Restricted to patients with a hypertension diagnosis (Read code categories G20 and 662) in the year prior to diagnosis

^f Restricted to patients with a prescription of any antihypertensive medication (diuretics, vasodilator antihypertensive drugs, centrally acting antihypertensive drugs, alpha-adrenoceptor blocking drugs, beta-blockers, ACEIs, ARBs, renin inhibitors, and calcium channel blockers) in the year prior to cancer diagnosis

^g Using other antihypertensive medications as an active comparator

^h Additionally adjusted for smoking, BMI and alcohol consumption

ⁱ Additionally adjusted for stage and grade

^j Additional adjusted for smoking, BMI, alcohol consumption, stage and grade

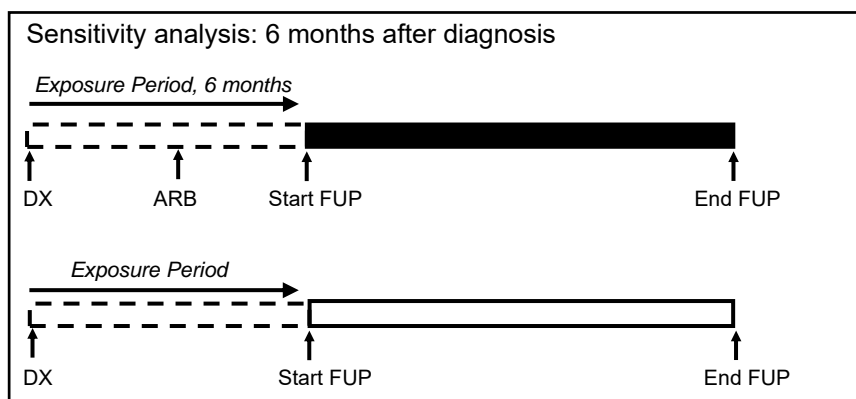
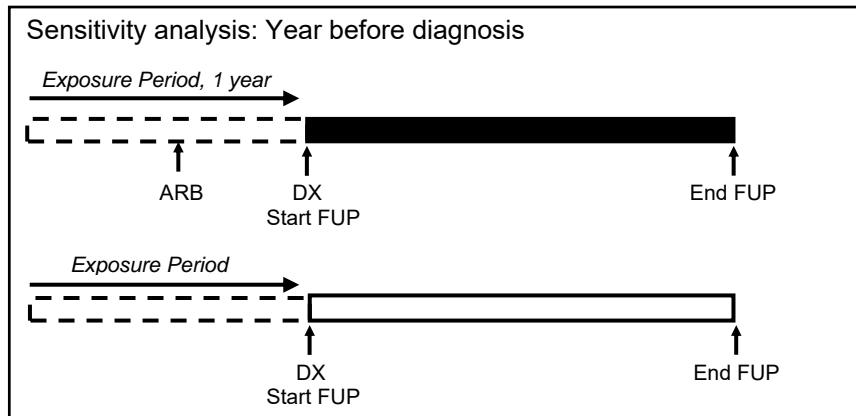
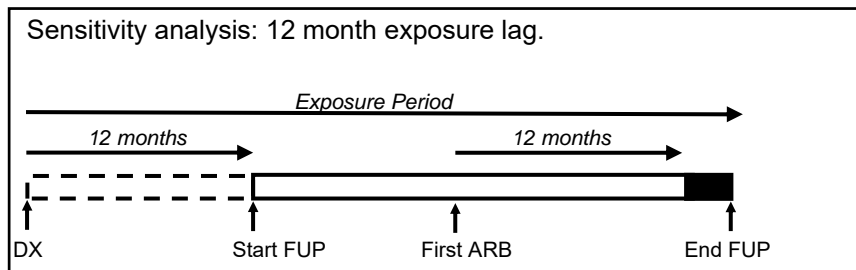
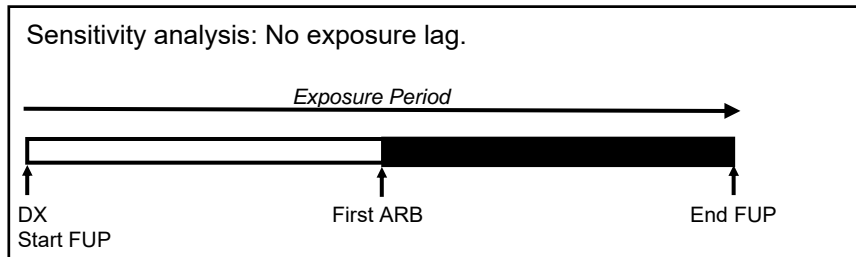
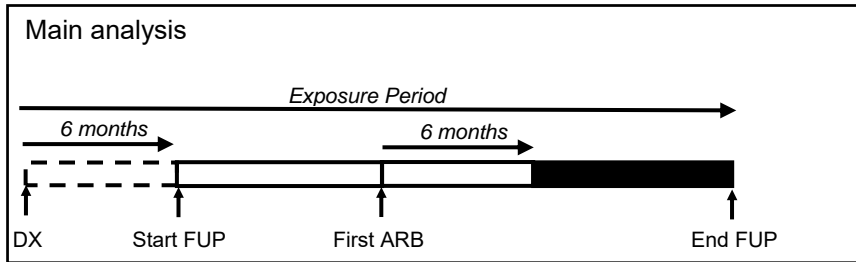
^k Using the Fine and Gray sub distribution hazard model with non-gastro-oesophageal cancer death as competing risk

Appendices

Appendix 1: List of generic and proprietary drug names used to identify ARBs

Substance	Medication
Azilsartan Medoxomil	Azilsartan, Edarbi (Takeda, High Wycombe, UK)
Candesartan Cilexetil	Candesartan, Amias (Takeda, High Wycombe, UK)
Eprosartan	Eprosartan, Teveten (Abbott Healthcare, Maidenhead, UK)
Irbesartan	Irbesartan, Aprovel (Bristol-Myers Squibb, New York, US & Sanofi-Aventis, Gentilly, France), Coaprovel (Bristol-Myers Squibb, New York, US & Sanofi-Aventis, Gentilly, France)
Losartan Potassium	Losartan, Cozaar (MSD, Hertfordshire, UK)
Olmesartan Medoxomil	Olmesartan, Olmetec (Daiichi Sankyo, Tokyo, Japan), Sevikar (Daiichi Sankyo, Tokyo, Japan)
Telmisartan	Telmisartan, Micardis (Boehringer Ingelheim, Rhein, Germany)
Valsartan	Valsartan, Diovan (Novartis, Basal, Switzerland), Entresto (Novartis, Basal, Switzerland)

Appendix 2: Illustration of study design for selected analyses^a



Legend: [Dashed line] Before FUP [Shaded box] ARB User [White box] ARB Non-user

^a FUP: follow-up period; DX: breast cancer diagnosis

Appendix 3: Complete model results for fully-adjust gastro-oesophageal analysis

Covariate	HR (95% CI)
ARB use	
Never	Ref
Ever	0.83 (0.71,0.98)
Age at Diagnosis	
	1.02 (1.01,1.02)
Deprivation Quintile	
1 (Least Deprived)	Ref
2	1.07 (0.96,1.18)
3	1.02 (0.92,1.14)
4	1.06 (0.95,1.18)
5 (Most Deprived)	1.11 (0.99,1.25)
Year of Diagnosis	
1998	Ref
1999	0.85 (0.66,1.11)
2000	0.96 (0.76,1.22)
2001	0.77 (0.62,0.97)
2002	0.81 (0.65,1.01)
2003	0.78 (0.62,0.97)
2004	0.69 (0.55,0.86)
2005	0.78 (0.62,0.97)
2006	0.72 (0.58,0.90)
2007	0.67 (0.54,0.84)
2008	0.72 (0.58,0.90)
2009	0.55 (0.43,0.69)
2010	0.54 (0.43,0.68)
2011	0.59 (0.46,0.74)
2012	0.64 (0.51,0.81)
2013	0.55 (0.42,0.71)
Treatment	
Surgery	0.54 (0.50,0.58)
Chemotherapy	1.36 (1.26,1.47)
Radiotherapy	1.10 (1.00,1.21)
Gender	
Male	Ref
Female	0.91 (0.85,0.98)
Site	
Oesophageal	Ref
Gastric	0.89 (0.83,0.96)
Comorbidities	
Cerebrovascular disease	0.99 (0.83,1.19)
Chronic pulmonary disease	0.91 (0.81,1.03)
Congestive heart disease	1.14 (0.94,1.40)
Diabetes	1.08 (0.97,1.22)
Myocardial infarction	1.05 (0.85,1.28)
Peptic ulcer disease	0.73 (0.61,0.89)
Peripheral vascular disease	1.06 (0.89,1.26)
Renal disease	1.15 (1.00,1.33)
Liver Disease	0.82 (0.44,1.53)
Other medication use	
Statin	Not shown ^a
Aspirin	Not shown

^a Hazard ratios for statin and aspirin use are not shown as our protocol states these are to be published separately.

Appendix 4: Negative control analysis for ACE inhibitor use and gastro-oesophageal cancer mortality

	N	Person-Years	Deaths	Unadjusted HR	Adjusted HR^a	Trend P-value
Gastro-oesophageal						
Never	4,061	7,916	2,746	Ref	Ref	0.343
Ever	1,063	2,111	599	0.96 (0.88,1.05)	0.98 (0.89,1.08)	
1-182 DDDs	384	668	234	0.86 (0.75,0.98)	0.86 (0.75,0.99)	
183-364 DDDs	189	321	131	1.03 (0.86,1.23)	1.05 (0.87,1.25)	
365-729 DDDs	188	330	119	1.15 (0.96,1.39)	1.20 (0.99,1.45)	
730+ DDDs	302	792	115	0.97 (0.80,1.17)	1.04 (0.85,1.27)	
Oesophageal						
Never	2,182	3,914	1,526	Ref	Ref	0.054
Ever	551	923	341	1.03 (0.92,1.16)	1.04 (0.91,1.18)	
1-182 DDDs	203	322	132	0.88 (0.73,1.05)	0.86 (0.71,1.03)	
183-364 DDDs	114	156	80	1.12 (0.89,1.40)	1.14 (0.91,1.45)	
365-729 DDDs	103	141	68	1.32 (1.03,1.68)	1.35 (1.05,1.73)	
730+ DDDs	131	304	61	1.10 (0.84,1.43)	1.16 (0.88,1.52)	
Gastric						
Never	1,879	4,002	1,220	Ref	Ref	0.679
Ever	512	1,188	258	0.89 (0.78,1.02)	0.92 (0.79,1.07)	
1-182 DDDs	181	347	102	0.84 (0.69,1.03)	0.85 (0.69,1.05)	
183-364 DDDs	75	165	51	0.91 (0.69,1.21)	0.93 (0.70,1.25)	
365-729 DDDs	85	189	51	1.01 (0.76,1.34)	1.06 (0.79,1.41)	
730+ DDDs	171	487	54	0.88 (0.67,1.16)	0.95 (0.71,1.26)	

^a Adjusted for age, deprivation, year of diagnosis, cancer treatment within 6 months (radiotherapy, chemotherapy, surgery), comorbidities (cerebrovascular disease, chronic pulmonary disease, congestive heart disease, diabetes, liver disease, myocardial infarction, peptic ulcer disease, peripheral vascular disease, renal disease) and other medication use (statins, aspirin, time-varying after diagnosis)