PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	NSAIDs, statins, low-dose aspirin and PPIs and the risk of oesophageal adenocarcinoma among patients with Barrett's oesophagus, a population based case-control study
AUTHORS	Masclee, Gwen; Coloma, Preciosa; Spaander, Manon; Kuipers, Ernst; Sturkenboom, Miriam

VERSION 1 - REVIEW

REVIEWER	Ian Beales Norfolk and Norwich University Hospital Norwich, United Kingdom
REVIEW RETURNED	25-Sep-2014

GENERAL COMMENTS	Thank you for asking me to review this well written and presented paper. The questions regarding drugs, especially PPI, COX-inhibitors and statins in relation to oesophageal cancer remain important and this paper adds more data to what is still somewhat confusing literature. The authors are quite correct in that previous studies have demonstrated associations and possibly important protective effects of COX-inhibitors and statins but all those papers have some methological issues. The authors have attempted to address these associations with a novel nested case-control method. Whilst the approach is sound, the major and probably critical weakness of he study are the absolute low numbers of cancers studied. The overall negative results of the study, but the wide confidence intervals are completely compatible with the previous studies, and two separate metaanalyses that have suggested an odds ratio of 0.5 for statins and a combination effect with COX-inhibitors. Neither of these meta-analyses are cited in the paper which seems an oversight? The general aims of the paper are outlined but the specific primary aims do need to be much more explicit: this needs to be used to inform a pre-study power and sample size estimation which should be included in the methods. Was the primary outcome PPIs, NSAIDs or Statins, or all 3, in which case the design should be clearly stated. The overall incidence of cancer in these Barrett's oesophagus cohorts does seem very low, much lower than even the most recent pooled estimates of cancer risk in Barrett's, what is the explanation for this? How accurate are the original diagnoses of Barrett's oesophagus? The major flaw that the diagnosis of Barrett's oesophagus was not verified against a pre-defined standard needs even more emphasis. It seems quite possible that not only a majority of low risk Barrett's patients were included but some may not have actually had Barrett's oesophagus (by current definitions) at all (a mixture of intestinal metaplasia at the cardia or misidentified hiatus hernias). The positive association with PPI use could be taken to reflect intrinsic differences in the two groups as baseline, those with

	more severe reflux required more PPI and where actually at higher risk of cancer because they actually had already developed a significant (>3 cm) Barrett's segment, whilst an unknown percentage of the non cancer controls actually had "ultra-short segment" to use one term and no significant reflux symptoms? The lack of data about length of Barrett's and low grade dysplasia on entry, as well as the lack of data on visceral obesity are major issues, that cannot be corrected for in the analysis. It is also notable that this study has failed to find the other positive associations with BMI that have usually been reported. Whilst studies that are negative, even if they contradict prevailing wisdom are always welcome, there are significant weaknesses in this study that influence whether this study significantly influences the current body of knowledge. The abstract cites that statins use > 3 years was inversely associated with cancer progression, this is not statistically significant and the abstract should acknowledge this uncertainty, where in fact the data in this small sample could be negative or associated with a protective effect. Throughout there seems to be confusion as to what exactly is being measured by NSAIDs. It seems this is cyclo-oxygenase inhibitors including high dose aspirin and COX-2 selective agents? Whilst this seems reasonable, the exclusion of low-dose cardioprotective aspirin seems slightly strange? Other studies have shown that low dose aspirin is associated with a lower incidence of cancer progression and indeed this effect may be additive to statins. Whilst the available literature are confusing as to what have been classified as COX-inhibitors in each study, the failure to explore or even discuss aspirin separately does seem rather amiss, presumably the prescribing data for this is just as accessible as all other drugs? The authors have pointed out some of the failings of the previous case control data, in terms of accuracy of drug exposure, but the current methodology is unable to measure non-prescribed, over-the-counter NSAID use which may confound the results. There are so additional unusual results that the authors do not discuss, which may mark out these cohorts as being slightly atypical. I must admit that I do find it hard to believe that only 2.5 % of one of the Barrett's cohorts had oesophagitis at the time of diagnosis of Barrett's oesophagitis, this seems very low compared to clinical experience. This along with the diagnoses of hiatus hernia and gastritis (which is a particularly vague term at best) must be regarded as potentially very inaccurate data, without verification of the original data as likely these were reported and collected in a very ad hoc manner. This paper is of interest, but the inadequate cancer sample size does severely limit the interpretation of the results and the authors have rather played down this limitation and overstated the benefits of the design (which I agree with are substantial) but this design has failed to deliver an adequate sample size.

REVIEWER	Hashem El-Serag Baylor College of Medicine Houston USA
REVIEW RETURNED	03-Oct-2014

GENERAL COMMENTS	This study was designed to address worthy question. The retrospective cohort design within BE cohorts is appropriate. However, the number of outcome events is too small to make any

	meaningful sense of the findings (a negative study with a trend). The NL cohort in particular has too few events which necessitated expanding the outcome to BO and HGD thus adding to the heterogenrity of the study. Introduction Several places “esophageal cancer” is mentioned; need to specify if OAC or otherwise I don’t think the statement about incidence of BO is correct; prevalence is a more likely descriptor Not sure what the reference for all GI cancer does, or the sentence following that. Methods What about OAC diagnosed at the same time of BO diagnosis; have you excluded those? I recommend trying and presenting sensitivity analyses where the matching period is changed. It seems like for exposures (medications) and cancers that are very age sensitive and therefore tighten matching by age to 1 or max 2 years (not 5). On the other hand, the date of BO diagnosis is an artificial date that does not coincide with the date of BE onset but rather with date of BO diagnosis and therefore you need to relax the matching for that to more than one year. Given the few outcome events, the analyses using multiple categories of duration and medications are way underpowered Along the same lines Table 5; most cells have few or no observations

REVIEWER	Tusar K Desai William Beaumont Hospital Michigan USA
REVIEW RETURNED	12-Oct-2014

GENERAL COMMENTS	Interesting approach to difficult problem. the number of OAC cases is very low only 45. the authors acknowledge this problem repeatedly. the low number of OAC cases limits the significance of the findings and so the trend toward lower OAC incidence in statin users is not statistically significant. because of this I would soften the statement that chemoprevention with nsaids or statins is not justified. the reason that such a low proportion of BO patients developed OAC is probably because the overwhelming majority of the BO patients in their database had short segment BO. in the US it is estimated that > 80% of patients undergoing BO surveillance have short segment BO. the OAC risk in this population is very very low < 0.2% annually. the authors acknowledge that they do not have data on length of BO and is it possible that they obtain this data for future studies. The main problem is the very low incidence of OAC in the study population 1/341. I suspect this is because the majority of the BO patients have short segment BO; a sub group of patients whose cancer risk is very low (<0.2% annually in 1 large meta analysis.) This large population of SS BO represents background noise that obscures the important

	data which is the drug use history of the long segment BO population. It would be very helpful to present data limited to long segment BO population. It is worth noting that in a pooled analysis of 6 studies published in Gastroenterology in 2012(Liao et. al.) there were 1226 OAC cases compared to 45 in this study. The Liao study showed a benefit to NSAID use. therefore perhaps the authors could soften their statement regarding nsaids being not beneficial. the trend toward a lower risk of OAC in statin users for more than 3 years might also be encouraging I would soften the statement that chemoprevention trials are not warranted. I would particularly emphasize that we have far better data to support nsaid and statin use in BO than we do to support RFA ablation for non dysplastic BO and yet RFA ablation is used widely in the for profit US health care system.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1
Reviewer Name Ian Beales
Institution and Country Norfolk and Norwich University Hospital
Norwich, United Kingdom
Please state any competing interests or state 'None declared': None declared

Thank you for asking me to review this well written and presented paper. The questions regarding drugs, especially PPI, COX-inhibitors and statins in relation to oesophageal cancer remain important and this paper adds more data to what is still somewhat confusing literature. The authors are quite correct in that previous studies have demonstrated associations and possibly important protective effects of COX-inhibitors and statins but all those papers have some methodological issues. The authors have attempted to address these associations with a novel nested case-control method. Whilst the approach is sound, the major and probably critical weakness of the study are the absolute low numbers of cancers studied. The overall negative results of the study, but the wide confidence intervals are completely compatible with the previous studies, and two separate meta-analyses that have suggested an odds ratio of 0.5 for statins and a combination effect with COX-inhibitors. Neither of these meta-analyses are cited in the paper which seems an oversight?
We have included in the revised manuscript two more recent meta-analyses1-2 on the use of statins and COX-inhibitors and the risk of esophageal cancer and esophageal adenocarcinoma.

The general aims of the paper are outlined but the specific primary aims do need to be much more explicit: this needs to be used to inform a pre-study power and sample size estimation which should be included in the methods. Was the primary outcome PPIs, NSAIDs or Statins, or all 3, in which case the design should be clearly stated.
The primary aim of the current study was to look at the effects of all three drugs (NSAIDs, PPIs and statins) as all three were reported independently often in different studies to affect the risk of oesophageal adenocarcinoma in Barrett's oesophagus patients. In addition, on request of the reviewer we have also included low-dose aspirin as exposure to the manuscript.
We have clarified this now in the Methods Section:
- page 11: "Two nested case-control studies were conducted assessing the risk of OAC for use of four drugs (NSAIDs, PPIs, statins and low-dose aspirin)."
- on page 12 under subheading 'Drug exposure': "Drug exposures of interest included four drug groups: NSAIDs, PPIs, statins and low-dose aspirin."
Also, we have moved the section on power calculation from the Discussion Section to the Methods Section:

- page 13: “Given an exposure prevalence of NSAIDs of 30%, of statins of 22% or 36%, of PPIs of 87% or 52% and of low-dose aspirin of 25% among controls and a correlation of 0.5 between exposed and unexposed subjects, we have 80% power (with a type 1 error of 5%) to detect a true odds ratio of OAC of 0.34 for NSAIDs, around 0.38-0.40 for statins, around 0.32-0.45 for PPIs and 0.29 for low-dose aspirin which would be in concordance with previous studies.”

The overall incidence of cancer in these Barrett's oesophagus cohorts does seem very low, much lower than even the most recent pooled estimates of cancer risk in Barrett's, what is the explanation for this? How accurate are the original diagnoses of Barrett's oesophagus? The major flaw that the diagnosis of Barrett's oesophagus was not verified against a pre-defined standard needs even more emphasis. It seems quite possible that not only a majority of low risk Barrett's patients were included but some may not have actually had Barrett's oesophagus (by current definitions) at all (a mixture of intestinal metaplasia at the cardia or misidentified hiatus hernias).

The incidence of oesophageal adenocarcinoma (OAC) in BO patients has been studied extensively in various cohort studies. These were mostly based on BO patients from referral centers. A systematic review and meta-analysis of their data reported an annual OAC incidence in the order of 0.3-0.5%.3-5 However, recent population-based studies reported an annual incidence of 0.12-0.14%6-8 of OAC among BO patients, which is in line with the 0.09% annual incidence of OAC with the OAC diagnosis at least 1 year after BO diagnosis from the current study.9 However, we agree with the reviewer that misclassification of Barrett’s oesophagus may have occurred, resulting in a dilution of the cases with patients who were at low risk to develop OAC. We have added the following to the

- Discussion section, page 31: “This may have resulted in misclassification of BO and OAC. However, the 1-year risk of OAC after BO diagnosis, excluding OAC cases within 1 year after BO diagnosis, was 0.086% (95% CI: 0.04–0.17) in the current study, which is similar to other population-based studies. Because we could not verify the diagnosis of Barrett’s oesophagus against a clinical pre-specified standard and did not review biopsy specimens, it is also possible that we inadvertently included patients at very low risk of developing OAC.”

The positive association with PPI use could be taken to reflect intrinsic differences in the two groups as baseline, those with more severe reflux required more PPI and where actually at higher risk of cancer because they actually had already developed a significant (>3 cm) Barrett's segment, whilst an unknown percentage of the non cancer controls actually had "ultra-short segment" to use one term and no significant reflux symptoms?

The lack of data about length of Barrett's and low grade dysplasia on entry, as well as the lack of data on visceral obesity are major issues, that cannot be corrected for in the analysis.

It is also notable that this study has failed to find the other positive associations with BMI that have usually been reported. Whilst studies that are negative, even if they contradict prevailing wisdom are always welcome, there are significant weaknesses in this study that influence whether this study significantly influences the current body of knowledge. The abstract cites that statins use > 3 years was inversely associated with cancer progression, this is not statistically significant and the abstract should acknowledge this uncertainty, where in fact the data in this small sample could be negative or associated with a protective effect.

The incidence of newly diagnosed OAC within the BO cohort is somewhat lower compared to the annual incidence of OAC as reported by a systematic review and meta-analysis of observational studies on primarily cohort studies performed in referral centers.3-5 We observed an 0.09% annual incidence of OAC among BO subjects9, which is similar to estimates from other population-based studies.6-8 However, the difference could be due to the design since we were interested in newly diagnosed BO subjects who subsequently developed OAC at least 1 year after BO diagnosis. On the other hand it could indeed be due to the fact that we have included subjects with BO whom in fact may have had a short segment of BO. These subjects may have indeed a very low annual risk of developing OAC, which could have contributed to the fact that no chemopreventive effect was observed.

Regarding the length of Barrett’s oesophagus segment, we could not verify this in the UK database. In

the Netherlands we were able to retrieve information on the length of Barrett's segment. This showed that 8% of Barrett's oesophagus subjects (controls) had a segment length < 2cm; 13.7% of subjects a segment length between 2 and 3 cm and 11.8% of BO subjects a segment length longer than 3 cm. Unfortunately, for 60% of Barrett's oesophagus controls the length was not mentioned in the medical record. Regarding the grade of dysplasia at time of Barrett's oesophagus diagnosis, 45% of controls had no dysplasia, there was low-grade dysplasia in 6% of controls, and no information available on dysplasia grade in 46% of controls. Of the cases that developed HGD or EAC, 24% had a prior histology report of low-grade dysplasia.
We have added the following to
- The Methods Section, page 10: "In IPCI we could utilize free text from the medical record to assess the Barrett segment length and grade of dysplasia."
- The Discussion Section, page 31: "Because we could not verify the diagnosis of Barrett's oesophagus against a clinical pre-specified standard and did not review biopsy specimens, it is also possible that we inadvertently included patients at very low risk of developing OAC. In the Dutch database we could search through the medical records and noted that 8% had a segment length < 2cm, 13.7% between 2 and 3 cm, 11.8% longer than 3 cm, whereas for 60% of BO controls the length was not mentioned. Regarding the grade of dysplasia at time of Barrett's oesophagus diagnosis, 45% of controls had no dysplasia, there was low grade dysplasia in 6% of BO subjects, indefinite for dysplasia in 1.8%, whereas no information on dysplasia grade was available in 46% of controls. Of the cases that developed HGD or EAC, 24% had a prior histology report of low-grade dysplasia.

Throughout there seems to be confusion as to what exactly is being measured by NSAIDs. It seems this is cyclo-oxygenase inhibitors including high dose aspirin and COX-2 selective agents? Whilst this seems reasonable, the exclusion of low-dose cardioprotective aspirin seems slightly strange? Other studies have shown that low dose aspirin is associated with a lower incidence of cancer progression and indeed this effect may be additive to statins. Whilst the available literature are confusing as to what have been classified as COX-inhibitors in each study, the failure to explore or even discuss aspirin separately does seem rather amiss, presumably the prescribing data for this is just as accessible as all other drugs?
NSAIDs included the traditional non selective NSAIDs and also COX-2 selective inhibitors. High-dose aspirin is considered as a traditional NSAID. We did not consider low-dose aspirin in the primary analysis, however have now included this in the current study. We have added this accordingly in the Methods, Results and Discussion Section.

The authors have pointed out some of the failings of the previous case control data, in terms of accuracy of drug exposure, but the current methodology is unable to measure non-prescribed, over-the-counter NSAID use which may confound the results.
We agree with the reviewer, that over-the-counter NSAIDs cannot be retrieved in an observational study using prescription data. However, as this is a general issue and the fact that we know that overt-the-counter use of NSAIDs is often for short duration, we expect the potential effect on the drug use to be minor. In a previous study it was shown that even though NSAIDs may be available OTC, prescription data give valid estimates of an association.10 Also during the study period prescription NSAIDs were reimbursable in the United Kingdom and the Netherlands. We have added the following to the Discussion Section, page 29: "During the study period NSAIDs and PPIs were reimbursable in the Netherlands and United Kingdom, and thus we assume that over-the-counter use of NSAIDs and PPIs did not confound the results to a great extent."

There are so additional unusual results that the authors do not discuss, which may mark out these cohorts as being slightly atypical. I must admit that I do find it hard to believe that only 2.5 % of one of the Barrett's cohorts had oesophagitis at the time of diagnosis of Barrett's oesophagitis, this seems very low compared to clinical experience. This along with the diagnoses of hiatus hernia and gastritis (which is a particularly vague term at best) must be regarded as potentially very inaccurate data,

without verification of the original data as likely these were reported and collected in a very ad hoc manner.
The limitation of the UK database is that we cannot utilize free text from the medical records. In the Dutch database, we have access to all medical history documented by the GP in the medical record of the patient. A database that is rich in free text is more likely able to provide information on comorbid diseases as well as other clinical findings that support the diagnosis. However this also means that manual validation is necessary. Due to space constraints in the manuscript we could not discuss these results in detail, but we have added the following to the Discussion Section acknowledging the limitation as mentioned above:
- Page 31-32: “In the Dutch database we could utilize all free text entered in the medical record, enabling to look for more detailed information in clinical letters, resulting in higher proportion of risk factors, such as presence of oesophagitis and a hiatal hernia at time of BO diagnosis as compared to the UK database in which we relied on diagnosis codes.”

This paper is of interest, but the inadequate cancer sample size does severely limit the interpretation of the results and the authors have rather played down this limitation and overstated the benefits of the design (which I agree with are substantial) but this design has failed to deliver an adequate sample size.
We recognize the point of the reviewer and have modified:
- The conclusion of the abstract, page 4-5: “In this population-based nested case-control study, use of NSAIDs, PPIs, low-dose aspirin or statins did not reduce the risk of HGD and OAC among BO patients. These findings indicate that for an unselected group of BO patients chemoprevention by use of drugs to reduce progression to HGD and OAC should not be considered directly as routine care.”
- The conclusion of the manuscript as follows, page 32: “In conclusion, in this population-based nested case-control study use of NSAIDs, PPIs, low-dose aspirin or statins did not reduce the risk of high-grade dysplasia and oesophageal adenocarcinoma among patients with Barrett’s oesophagus. These findings indicate that for an unselected group of patients with Barrett’s oesophagus chemoprevention by use of drug to reduce progression should not be considered directly as routine care.”

Reviewer: 2
Reviewer Name Hashem El-Serag
Institution and Country Baylor College of Medicine
Houston
USA
Please state any competing interests or state ‘None declared’: None

This study was designed to address worthy question. The retrospective cohort design within BE cohorts is appropriate. However, the number of outcome events is too small to make any meaningful sense of the findings (a negative study with a trend). The NL cohort in particular has too few events which necessitated expanding the outcome to BO and HGD thus adding to the heterogeneity of the study.

Introduction
Several places “esophageal cancer” is mentioned; need to specify if OAC or otherwise
We have specified the following in the Introduction Section (page 7):
- Death rates of most cancers decreased in recent years in contrast to the 3% increase in death rates of all oesophageal cancer (both squamous cell as adenocarcinoma) among males.11 The age-standardized mortality rate for oesophageal cancer overall is 5.1 per 100,000 persons.12 The need for effective prevention of oesophageal cancer in general is therefore warranted, particularly given the low 5-year survival rate of 13%-17%.13
I don’t think the statement about incidence of BO is correct; prevalence is a more likely descriptor

We appreciate the suggestion, indeed at a certain time point the prevalence is a good descriptor of the frequency of disease. However, we believe that when assessing the frequency of disease over time, the incidence (newly diagnosed subjects) may be a more relevant one in order to see the disease behaviour and disease pattern across countries and over time.

Not sure what the reference for all GI cancer does, or the sentence following that.

We have used the WHO Global Health Observatory Data Repository11 to assess the cause-specific mortality by country; and thus burden and the mortality by gastrointestinal cancers in the United Kingdom and the Netherland for instance. We have maintained the text as it was, but would of course be most willing to make changes if the editor should wish so.

Methods
What about OAC diagnosed at the same time of BO diagnosis; have you excluded those?
Oesophageal adenocarcinoma occurring at time of BO diagnosis or within 1 year of BO diagnosis was excluded in the current study. We have added the following to the Methods section page 11: "We only considered incident HGD or OAC cases: i.e. if the date of diagnosis occurred after inclusion into the BO cohort and was at least 12 months after BO diagnosis. Cases occurring within 1 year from BO diagnosis were considered to be already existent at BO diagnosis date and in relation to the BO diagnostic work-up."

I recommend trying and presenting sensitivity analyses where the matching period is changed. It seems like for exposures (medications) and cancers that are very age sensitive and therefore tighten matching by age to 1 or max 2 years (not 5). On the other hand, the date of BO diagnosis is an artificial date that does not coincide with the date of BE onset but rather with date of BO diagnosis and therefore you need to relax the matching for that to more than one year.
We appreciate the suggestion. However, we were able to verify the date of BO diagnosis as the earliest date of start of symptoms leading to BO diagnosis, in order to approximate the date of BO onset as good as possible. Although the exact date on which the first aberrant Barrett's cell is formed is almost impossible to determine. Matching on sex and year of BO diagnosis makes the groups of cases and controls comparable and exchangeable regarding basic characteristics. We chose to match age by ±5-years because a more restricted matching would have resulted in less control subjects, and subsequently, lower statistical power.

Given the few outcome events, the analyses using multiple categories of duration and medications are way underpowered

Along the same lines Table 5; most cells have few or no observations

We appreciate the remark. Rather than excluding the table we have added the following to the Results and Discussion section in order to provide the context of the Table. Also, according to suggestion of reviewer 1 we have included low-dose aspirin as exposure in the manuscript:
- Page 19, "Concomitant use of drugs of interest did not decrease the risk of OAC (Table 5) compared to use of PPIs only, probably due to the smaller number of cases."
- Page 28, "This however, also limited the analyses by creating multiple exposure categories."

Reviewer: 3
Reviewer Name Tusar K Desai
Institution and Country William Beaumont Hospital
Michigan USA
Please state any competing interests or state 'None declared': None declared

interesting approach to difficult problem.
the number of OAC cases is very low only 45.
the authors acknowledge this problem repeatedly.
the low number of OAC cases limits the significance of the findings and so the trend toward lower OAC incidence in statin users is not statistically significant.
because of this I would soften the statement that chemoprevention with nsaids or statins is not justified.
We agree with the reviewer and have changed the
- Abstract as follows, page 4-5: “Conclusion: In this population-based nested case-control study use of NSAIDs, PPIs, low-dose aspirin and statins did not reduce the risk of HGD and OAC among BO patients. These findings indicate that for an unselected group of BO patients chemoprevention by use of drugs to reduce progression to HGD and OAC should not be considered directly as routine care.”

- Conclusion of the manuscript as follows, page 32: “In conclusion, in this population-based nested case-control study use of NSAIDs, PPIs, low-dose aspirin or statins did not reduce the risk of high-grade dysplasia and oesophageal adenocarcinoma among patients with Barrett’s oesophagus. These findings indicate that for an unselected group of patients with Barrett’s oesophagus chemoprevention by use of drug to reduce progression should not be considered directly as routine care.”

The reason that such a low proportion of BO patients developed OAC is probably because the overwhelming majority of the BO patients in their database had short segment BO. in the US it is estimated that > 80% of patients undergoing BO surveillance have short segment BO. the OAC risk in this population is very very low < 0.2% annually. the authors acknowledge that they do not have data on length of BO and is it possible that they obtain this data for future studies. the main problem is the very low incidence of OAC in the study population 1/341.
I suspect this is because the majority of the BO patients have short segment BO; a sub group of patients whose cancer risk is very low (<0.2% annually in 1 large meta analysis.) This large population of SS BO represents background noise that obscures the important data which is the drug use history of the long segment BO population. It would be very helpful to present data limited to long segment BO population.
The incidence of oesophageal adenocarcinoma (OAC) in BO patients has been studied extensively in various cohort studies. These were mostly based on BO patients from referral centers. A systematic review and meta-analysis of their data reported an annual OAC incidence in the order of 0.3-0.5%.3-5 However, recent population-based studies reported an annual incidence of 0.12-0.14%6-8 of OAC among BO patients, which is in line with the 0.09% annual incidence of OAC with the OAC diagnosis at least 1 year after BO diagnosis from the current study.9 However, the difference could be due to the design since we were interested in newly diagnosed BO subjects who subsequently developed OAC at least 1 year after BO diagnosis. On the other hand it could indeed be due to the fact that we have included subjects with BO whom in fact may have had a short segment of BO. These subjects may have indeed a very low annual risk of developing OAC, which could have contributed to the fact that no chemopreventive effect was observed.
Regarding the length of Barrett’s oesophagus segment, we could not verify this in the UK database. In the Netherlands we were able to retrieve information on the length of Barrett’s segment. This showed that 8% of Barrett’s oesophagus subjects (controls) had a segment length < 2cm; 13.7% of subjects a segment length between 2 and 3 cm and 11.8% of BO subjects a segment length longer than 3 cm. Unfortunately, for 60% of Barrett’s oesophagus subjects (controls) the length was not mentioned in the medical record. Regarding the grade of dysplasia at time of Barrett’s oesophagus diagnosis, 45% of controls had no dysplasia, there was low-grade dysplasia in 6% of controls, and no information available on dysplasia grade in 46% of controls. Of the cases that developed HGD or EAC, 24% had a prior histology report of low-grade dysplasia.
We have added the following to

- The Article Summary, page 6: “We did not have detailed pathology information on the Barrett segment length or grade of dysplasia at cohort entry for all BO cohort members in both countries. This may have resulted by including subjects with a short segment BO whom may be at lower risk of developing HGD and OAC at start.”
- The Methods Section, page 10: “In IPCI we could utilize free text from the medical record to assess the Barrett segment length and grade of dysplasia.”
- Discussion section, page 31: “This may have resulted in misclassification of BO and OAC. However, the 1-year risk of OAC after BO diagnosis, excluding OAC cases within 1 year after BO diagnosis, was 0.086% (95% CI: 0.04–0.17) in the current study, which is similar to other population-based studies. Because we could not verify the diagnosis of Barrett’s oesophagus against a clinical pre-specified standard and did not review biopsy specimens, it is also possible that we inadvertently included patients at very low risk of developing OAC. In the Dutch database we could search through the medical records and noted that 8% had a segment length < 2cm, 13.7% between 2 and 3 cm, 11.8% longer than 3 cm, whereas for 60% of BO controls the length was not mentioned. Regarding the grade of dysplasia at time of Barrett’s oesophagus diagnosis, 45% of controls had no dysplasia, there was low grade dysplasia in 6% of BO subjects, indefinite for dysplasia in 1.8%, whereas no information on dysplasia grade was available in 46% of controls. Of the cases that developed HGD or EAC, 24% had a prior histology report of low-grade dysplasia.

It is worth noting that in a pooled analysis of 6 studies published in Gastroenterology in 2012(Liao et. al.) there were 1226 OAC cases compared to 45 in this study. The Liao study showed a benefit to NSAID use. therefore perhaps the authors could soften their statement regarding nsaids being not beneficial.
We appreciate the suggestion. Indeed in a selected group of BO patients with longer BO segment, the use of NSAIDs has been shown to prevent OAC development. However, since we included an unselected group of BO subjects from the general population and with differing BO segment length, regular treatment to prevent OAC among BO subjects does not seem to be including NSAID use. We have rephrased the statement to:
- Abstract, page 4-5: “In this population-based nested case-control study use of NSAIDs, PPIs, low-dose aspirin and statins did not reduce the risk of HGD and OAC among BO patients. These findings indicate that for an unselected group of BO patients chemoprevention by use of drugs to reduce progression to HGD and OAC should not be directly considered as routine care.”
- Discussion section, page 27: “In this unselected group of BO patients use of low-dose aspirin or NSAIDs was not associated with a decrease in risk of OAC.”
The trend toward a lower risk of OAC in statin users for more than 3 years might also be encouraging I would soften the statement that chemoprevention trials are not warranted. I would particularly emphasize that we have far better data to support nsaid and statin use in BO than we do to support RFA ablation for non dysplastic BO and yet RFA ablation is used widely in the for profit US health care system.
Before NSAIDs, low-dose aspirin and statins are used in clinical routine practice and prescribed to all patients with BO, more knowledge on the benefit-risk balance with the use of drugs as routine treatment is needed. For instance, in a selected subgroup of patients, whom are at low risk of developing upper gastrointestinal bleeding, for instance, younger patients, and not taking any other ulcerogenic drugs, use of NSAIDs as chemoprevention may be appropriate. However, the duration before a chemopreventative effect would be established may not be feasible or considered appropriate in comparison to the direct effect of RFA ablation or mucosal resection.

References

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