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Interaction Between Aspirin and ACE Inhibitors

Resolving Discrepancies Using a Meta-Analysis

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Abstract

Background: Recently, studies have attempted to explore the interaction between ACE inhibitors and aspirin (acetylsalicylic acid) when both drugs are used concomitantly to reduce mortality in patients with coronary artery disease. Results have been conflicting due, in part, to sub-optimal methods used to explore this interaction.

Methods: We reviewed systematically all studies on mortality in patients treated with ACE inhibitors and aspirin and conducted a meta-analysis in order to explore the interaction between both drugs and resolve discrepancies. To be included, each study had to provide data on mortality of patients who received both drugs, either drug and no drug. These data were necessary to calculate the synergy index (S) and its 95% confidence interval (CI) that we used to quantify the effect due to interaction between ACE inhibitors and aspirin. After testing for heterogeneity of effects, we pooled the S values from the individual studies into one summary measure.

Subsequently, we compared our results with those obtained through the most common but incorrect method of evaluating interaction. This method uses significance testing of the relative risk of mortality when a 'product term' between ACE inhibitors and aspirin is entered in a logistic regression model.

Results: Eight studies met the inclusion criteria. The pooled synergy index S indicates slight but precise antagonism between ACE inhibitors and aspirin (S = 0.91; 95% CI 0.80 to 1.03). In contrast, the pooled 'product term' is not significant and would have lead to the conclusion of absence of interaction (p = 0.15).

Conclusion: There seems to be an antagonistic interaction between ACE inhibitors and aspirin. Former discrepancies were due to inadequate assessment of interaction. Results from the Studies on Left Ventricular Dysfunction (SOLVD) and Heart Outcome Prevention Evaluation (HOPE) trials that assessed the effect of combined administration of ACE inhibitors and aspirin were not included in

this meta-analysis because those trials did not provide enough data to compute the S statistic. It is possible that results from on-going trials such as Women's Atovarstatin Trial on Cholesterol (WATCH) will shed more light on ACE inhibitor and aspirin interaction in the future.

ACE inhibitors have been shown to reduce mortality in patients with congestive heart failure and coronary artery disease.[1,2] Aspirin (acetylsalicylic acid) is also recommended in the prevention of ischaemic events.[3] Recent studies have raised the possibility of a negative interaction between ACE inhibitors and aspirin.[4,5] As a result, some clinicians have been reluctant in prescribing both agents concomitantly to their patients.

Several studies have attempted to explore the interaction between ACE inhibitors and aspirin with conflicting results.[5,6] The major limitation of these studies is the method by which interaction is quantified. Interaction was explored by: (i) reporting the risk of mortality among patients taking both drugs; or (ii) including a 'product term' (ACE inhibitors, aspirin), inappropriately called 'interaction term', in a regression model (generally a logistic regression) and drawing conclusions from its p-value. Although widely used in cardiovascular epidemiology, none of these methods measures interaction correctly, and thus, their use has been discouraged.[7,8] Both practices may produce results that lead to uninformative conclusions since neither of them measures biological interaction, which should be understood as the cooperation at a cellular level of two substances in producing an effect.[8,9] This means that the presence of one substance influences the effect of the other. If the effect is enhanced, there is positive interaction or synergism, and if it is reduced, there is negative interaction or antagonism.[7]

In other words, the biological approach implies that the outcome of interest in patients exposed to both drugs is compared with patients taking each drug alone. If the reduction of mortality among patients exposed to both drugs is greater than the sum of mortality reductions among those patients exposed to either drug alone, there is then synergy between the two drugs. Similarly, if the magnitude of the mortality reduction in patients exposed to ACE inhibitors and aspirin is smaller than the sum of the mortality reduction of those patients exposed to either drug alone, there is then antagonism.

The 'p-value method of the product term' is incorrect in essence because the logistic model is additive on a logarithmic scale, which means that it is actually a multiplicative model. Therefore, assessing interaction of two causes based on the significance of a product term is not equivalent to assessing the departure of the model from additivity.

Some narrative reviews have attempted to answer the question of whether there is interaction between ACE inhibitors and aspirin.[10,11] However, we are not aware of any published quantitative review that has specifically explored this issue. We, therefore, undertook this meta-analysis to quantify the interaction between ACE inhibitors and aspirin using the biological approach. As a secondary analysis, in order to compare results derived from both methods, we explored interaction using statistical testing of the relative risk of a product term between ACE inhibitors and aspirin.

Methods

We searched MEDLINE from 1966 to 2001, EMBASE, International Pharmaceutical Abstracts and the Cochrane Library for studies that examined mortality in patients taking aspirin and ACE inhibitors. We used MESH terms and free text words, including the words aspirin, acetylsalicylic acid, ASA, angiotensin converting enzyme, ACE inhibitors, captopril, enalapril, fosinopril, lisinopril, ramipril, quinapril, trandolapril, and zofenopril. From the studies that we retrieved through this search, we selected only those that examined mortality as an outcome. We also examined the reference list of each article retrieved. To be included in the meta-analysis, a study had to meet the following criteria: (i) be a randomised controlled trial

or an observational study in any patient group of all ages and diagnoses; (ii) measures mortality as the primary outcome and; (iii) provide relative risk (or enough data to calculate it) together with a confidence interval of mortality in patients receiving both drugs, either drug and placebo.

When a study was published more than once, we excluded the oldest publications and included the most recent publication only.

We used two methods to quantify interaction. The first method is the correct approach and its use should be encouraged. The second method is shown as an illustrative example of an approach that should be abandoned. In the first method, we used the synergy index (S) to quantify interaction using the biological approach.[8] For preventive exposures as is the case of two drugs, S is calculated as follows:

$$S = \frac{1 - RR_{11}}{1 - RR_{01}\,RR_{10}}$$

where RR_{11} is the relative risk of those patients exposed to both drugs, RR_{01} the relative risk of those exposed to aspirin only and RR_{10} the relative risk of patients exposed to ACE inhibitors only. An S index greater than one indicates a positive interaction or synergism and antagonism is indicated when its value is less than one. For each study we calculated the S statistic. We then pooled the S values obtained through studies in one summary weighted measure with its corresponding 95% confidence interval (CI).[12] We used the reciprocals of the estimated variances of the S values as a weight. As the total number of studies was relatively small, in order to check for heterogeneity between synergy measures across studies, we used a parametric bootstrap version of the DerSimonian and Laird's test statistic (Q*), with 1000 replications.[13]

In the second (and incorrect) analysis, for each study, we calculated through a logistic regression model the relative risk of mortality of a product term between ACE inhibitors and aspirin, together with its p-value. We then pooled the relative risk estimates of each study thus obtained into one summary measure.

Results

We found eight studies that met our inclusion criteria.[6,14-20] Table I shows the main characteristics of these studies. A total of 121 760 patients were followed-up and the average number per study was 15 220 (range 1556 to 58 050). The total number of deaths was 12 718. Follow-up through studies ranged between 4 weeks and 5 years. Five additional studies were not included in the meta-analysis because they did not provide sufficient data to calculate the S statistic.[2,4,5,21,22]

Table I. General characteristics of eight studies included in the meta-analysis of interaction between aspirin (acetylsalicyclic acid) and ACE inhibitors (ACE) in patients with heart failure

Study	Total no. of patients	Proportion of patients taking aspirin (%)	No. of deaths	ACE inhibitor	Duration of follow-up
CONSENSUS II[15]	6090	79	598	Enalapril	6mo
CCS-1[17]	13 634	73	1271	Captopril	4wk
ISIS-4[14]	58 050	94	4319	Capropril	5wk
TRACE[20]	6676	37	673	Trandolapril	24 to 50mo
SMILE[18]	1556	11	138	Zofenopril	6wk
SAVE[19]	2231	20	503	Captopril	24 to 60mo
Krumholz et al.[6]	14 129	26	3946	Captopril, enalapril	1y
GISSI[16]	19 394	89	1270	Lisinopril	6wk
Total	**121 760**		**12 718**		

CCS-1 = Chinese Cardiac Study-1; **CONSENSUS II** = Cooperative New Scandinavian Enalapril Survival Study II; **GISSI** = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; **ISIS-4** = Fourth International Study of Infarct Survival; **SAVE** = Survival and Ventricular Enlargement study; **SMILE** = Survival of Myocardial Infarction Long-Term Evaluation; **TRACE** = Trandolapril Cardiac Evaluation.

Whenever complete data were not available in the original publication, we used figures obtained from a re-analysis of studies where raw data for each study were presented.[23] Data for seven of the studies came from large randomised controlled trials of ACE inhibitors in post myocardial infarction patients.[14-20] One study was a cohort study of geriatric patients.[6]

Despite differences in their design, the results of the individual studies are consistent. We did not detect any heterogeneity between the S estimates of the individual studies (p-value of Q* = 0.53). The pooled synergy index S indicates slight antagonism between ACE inhibitors and aspirin, and its 95% CI is narrow (S = 0.91, 95% CI 0.80 to 1.03).

As part of the secondary analysis, in seven out of eight studies, the p-values of the 'product term' are large and consistent with absence of interaction. The p-value of the pooled 'product term' is also large (p = 0.15) and would lead to the same conclusion of absence of interaction between both drugs (table II).

Discussion

The results of our meta-analysis, based on a large number of patients, show that ACE inhibitors and aspirin have antagonistic effects on mortality among patients with coronary artery disease. This antagonistic effect is small but precise.

So far, individual studies have not provided sufficient evidence of a possible interaction between these drugs and their results were contradictory. These results ranged from a slight positive interaction (or synergism), and the claim that combined prescription is superior to monotherapy,[6] to moderate or strong antagonism.[4,5,24] Between these two extreme results, there are studies or re-analyses of previous studies that did not find any evidence of an interaction between ACE inhibitors and aspirin.[23]

With the exception of one study that measured biological interaction,[24] all other studies based their conclusion and recommendations on the p-value significance ($p < 0.05$) of a product term between aspirin and ACE inhibitor entered in a multivariate model, or on the magnitude of the relative risk of patients exposed to both drugs. In the latter case, some studies calculated this relative risk using those patients who received ACE inhibitors only at baseline, while others used those patients exposed to aspirin only at baseline. These differences in the computations were responsible, at least partly, for the controversial results regarding

Table II. Relative risk of mortality among patients exposed to aspirin (acetylsalicyclic acid) and ACE inhibitors (ACE) or both, and interaction measures between both drugs

Study reference	RR aspirin (95% CI)[a]	RR ACE (95% CI)[a]	RR aspirin + ACE (95% CI)[a]	S[b] (95% CI)	OR product term[c] (95% CI)	p-Value OR product term
CONSENSUS II[15]	0.71 (0.54-0.93)	1.00 (0.73–1.40)	0.80 (0.61-1.05)	0.68 (0.18-2.55)	1.13 (0.77-1.65)	0.53
CCS-1[17]	0.47 (0.40-0.56)	0.91 (0.75-1.09)	0.45 (0.38-0.53)	0.96 (0.70-1.30)	1.05 (0.83-1.32)	0.68
ISIS-4[14]	0.37 (0.32-0.42)	0.92 (0.77-1.12)	0.34 (0.30-0.39)	0.99 (0.78-1.24)	1.00 (0.82-1.23)	0.95
TRACE[20]	0.45 (0.29-0.71)	0.55 (0.29-1.04)	0.34 (0.21-0.54)	0.88 (0.38-2.01)	1.37 (0.70-2.66)	0.36
SMILE[18]	0.56 (0.35-0.89)	0.55 (0.34-0.90)	0.43 (0.26-0.71)	0.82 (0.29-2.30)	1.39 (0.68-2.85)	0.37
SAVE[19]	0.66 (0.50-0.87)	0.85 (0.64-1.14)	0.48 (0.36-0.64)	1.19 (0.69-2.01)	0.85 (0.57-1.28)	0.44
Krumholz et al.[6]	0.55 (0.49-0.62)	0.82 (0.73-0.92)	0.64 (0.57-0.71)	0.67 (0.49-0.87)	1.40 (1.21-1.63)	0.00
GISSI[16]	0.36 (0.29-0.44)	0.88 (0.69-1.14)	0.31 (0.25-0.38)	1.01 (0.71-1.41)	0.97 (0.73-1.30)	0.84
Pooled values	**0.47 (0.44-0.50)**	**0.85 (0.79-0.92)**	**0.48 (0.45-0.51)**	**0.91 (0.80-1.03)**	**1.11 (0.96-1.28)**	**0.15**

a Reference category: patients unexposed to any drug.

b S: Synergy index. $S = 1 - RR_{aspirin+ACE} / 1 - RR_{aspirin} \times RR_{ACE}$.

c Product term: ACE × aspirin term, entered in a logistic regression model.

CCS-1 = Chinese Cardiac Study-1; **CONSENSUS II** = Cooperative New Scandinavian Enalapril Survival Study II; **GISSI** = Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico; **ISIS-4** = Fourth International Study of Infarct Survival; **OR** = odds ratio; **RR** = relative risk; **SAVE** = Survival and Ventricular Enlargement study; **SMILE** = Survival of Myocardial Infarction Long-Term Evaluation; **TRACE** = Trandolapril Cardiac Evaluation. **95% CI** = 95% confidence interval.

interaction. A recent pooled analysis of three studies found no difference in mortality among patients treated with ACE inhibitors with and without aspirin at baseline.[25] However, no specific assessment of interaction was carried out in this study.

Hence, the majority of the studies used a purely statistical definition of interaction when a biological definition would have been more accurate. Conclusions based on this statistical approach are often misleading if not incorrect as the magnitude or the statistical significance of a 'product term' is by no means a proof of the presence or absence of drug interaction.[7,9]

Our meta-analysis has some limitations. As in every meta-analysis, the quality of the individual studies may influence largely the results of the review. Publication bias cannot be ruled out since we could not find raw data for all the studies that have explored this interaction.[1,2,4,5,21,22] It is a clear drawback that important trials [e.g. Studies of Left Ventricular Dysfunction (SOLVD)[1,4] and Heart Outcome Prevention Evaluation (HOPE)[2]] that assessed the effect of ACE inhibitors and aspirin were not included in our analysis because they did not provide enough data to compute the S statistic. If these data had been available, the results might have been different. However, a funnel plot did not provide any evidence of publication bias (data not shown). The studies included in our meta-analysis were post hoc analyses of randomised controlled trials as well as a cohort study.[6] The data made available in the individual studies did not allow adjustment for potential confounders. In the clinical trials, although patients were randomised to either ACE inhibitors or placebo, confounding by indication cannot be ruled out. Patients receiving aspirin at the time of the heart failure may have been at a more severe stage of disease, and thus, may have had a higher risk of death than those patients who were not taking aspirin. However, this hypothesis is unlikely since patients who received both ACE inhibitors and aspirin in the combined population of patients from the four large randomised controlled trials [Chinese Cardiac Study (CCS)-1, Cooperative New Scandinavian Enalapril Survival Study (CONSENSUS)-II, Gruppo Italiano per lo Studio della Sopravvivenza nell'Infarto Miocardico (GISSI)-3, International Study of Infarct Survival (ISIS)-4], which formed more than 90% of the patients in our meta-analysis, were generally healthier, hence, at a lower risk of mortality than those taking ACE inhibitors alone.[23] Our results do not confirm the hypothesis suggesting that the difference in baseline risk between patients groups introduces bias.

Measuring in a straightforward fashion the biological interaction between aspirin and ACE inhibitors requires a clinical trial with four randomisation arms (placebo, ACE inhibitor only, aspirin only, and both drugs). This hypothetical trial is unlikely to be carried out as the use of placebo in patients with heart failure would be unethical. However, it is probable that individual on-going studies will shed more light on this issue in the near future. The Women's Atovarstatin Trial on Cholesterol (WATCH) trial is a good example of these studies as it tests specifically the interaction between warfarin and aspirin in patients with chronic heart failure.[26]

In summary, this study provided evidence of a slight antagonism between ACE inhibitors and aspirin in their effect on mortality. However, this study was not carried out to with the purpose of recommending to practitioners any attitude related to the prescription of these drugs. For any recommendation, several other issues have to be discussed (cost/benefit, adverse effects, etc.) and these are beyond the scope of this study.

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