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ORIGINAL ARTICLE

Gastroprotection in Low-Dose Aspirin Users for Primary and Secondary Prevention of ACS: Results of a Cost-Effectiveness Analysis Including Compliance

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Abstract
Purpose Low-dose aspirin (ASA) increases the risk of upper gastrointestinal (GI) complications. Proton pump inhibitors (PPIs) reduce these upper GI side effects, yet patient compliance to PPIs is low. We determined the cost-effectiveness of gastroprotective strategies in low-dose ASA users considering ASA and PPI compliance.
Methods Using a Markov model we compared four strategies: *no medication*, *ASA monotherapy*, *ASA+PPI* co-therapy and a *fixed combination* of ASA and PPI for primary and secondary prevention of ACS. The risk of acute coronary syndrome (ACS), upper GI bleeding and dyspepsia was modeled as a function of compliance and the relative risk of developing these events while using medication. Costs, quality adjusted life years and number of ACS events were evaluated, applying a variable risk of upper GI bleeding. Probabilistic sensitivity analyses were performed.
Results For our base case patients using ASA for primary prevention of ACS *no medication* was superior to *ASA monotherapy.* PPI co-therapy was cost-effective (incremental cost-effectiveness ratio [ICER] €10,314) compared to *no medication*. In secondary prevention, *PPI co-therapy* was cost-effective (ICER €563) while the *fixed combination* yielded an ICER < €20,000 only in a population with elevated risk for upper GI bleeding or moderate PPI compliance. *PPI co-therapy* had the highest probability to be cost-effective in all scenarios. PPI use lowered the overall number of ACS.
Conclusions Considering compliance, PPI co-therapy is likely to be cost-effective in patients taking low dose ASA for primary and secondary prevention of ACS, given low PPI prices. In secondary prevention, a fixed combination seems cost-effective in patients with elevated risk for upper GI bleeding or in those with moderate PPI compliance. Both strategies reduced the number of ACS compared to ASA monotherapy.

Keywords Cost-effectiveness · QALY · Aspirin · Proton pump inhibitor · Dyspepsia · Gastrointestinal bleeding · Compliance

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Introduction

The beneficial effects of low-dose aspirin (ASA) (75–325 mg) in the prevention of acute coronary syndrome (ACS) are well recognized, especially in patients with

established cardiovascular (CV) disease (secondary prevention) [1–3]. Guidelines recommend that ASA needs to be administered as soon as possible after an ACS and this should be continued for the remaining lifetime of the patient [4]. The effectiveness of low-dose ASA for primary prevention is less certain. The reduction in CV events needs to be weighed against an increased risk for gastrointestinal (GI) side effects including bleeding, particularly in the upper GI tract, and dyspepsia [5, 6]. Randomized placebo controlled trials as well as observational studies have shown that low-dose ASA approximately doubles the risk of GI bleeding compared to placebo [7, 8]. Nonetheless, a recent study demonstrated that low-dose ASA for primary prevention is likely to be cost-effective even in patients at moderate risk for CV disease [9], thereby indicating that the CV benefits might outweigh the GI risks.

In order to prevent GI complications in ASA-users, proton pump inhibitors (PPIs)—which reduce the production of gastric acid—are often used as prophylactic therapy. PPI therapy has proven to reduce the risk of dyspeptic symptoms, gastroduodenal ulcers and upper GI bleeding in patients taking low-dose ASA [10–13]. However previous studies showed that the cost-effectiveness of PPI co-therapy in the primary and secondary prevention of CV disease depends on the baseline risk for upper GI bleeding and PPI prices [9, 14]. But due to generic availability PPI prices have plummeted in the last several years, which may have enhanced the cost-effectiveness of PPI co-therapy.

To attain the effect of both ASA and PPI, patient compliance is important. Yet it is unclear how patient compliance influences the cost-effectiveness of these therapies. It is known that discontinuation of ASA entails a three-fold higher risk of atherothrombotic events in patients with moderate to high risk for developing an ACS event [15]. The most important reason for ASA discontinuation is the occurrence of GI side effects [16–18].

Also, patient compliance to PPI co-therapy is suboptimal. Herlitz et al. showed that of all patients who were prescribed a daily PPI concomitant to low-dose ASA, less than half took >75 % of the prescribed PPIs and almost one-third did not take their PPI at all [19]. The relation between the risk of upper GI complications, CV complications and PPI compliance in low-dose ASA users is not clear, but among non-steroidal anti-inflammatory drug (NSAID) users it was shown that the risk of upper GI complications increased by 9 % for every 10 % decrease in PPI compliance [20]. Therefore, an important goal in the prevention of an ACS event and upper GI complications is to improve patient compliance to both ASA and PPI. One way to achieve better compliance to PPI, is to combine PPI with low-dose ASA in a fixed combination. The effectiveness of such a fixed combination has already been demonstrated in chronic NSAID users [21].

In this study, we evaluated the cost-effectiveness of four competing strategies for the primary and secondary prevention of ACS—including the fixed combination of ASA+PPI and its separate components—when GI and CV outcomes and patient compliance are considered.

Materials and Methods

A Markov model was developed to compare the costs and outcomes of competing strategies for the primary and secondary prevention of ACS. We performed two separate analyses using different baseline situations; one in which no previous CV events had occurred, and one in which all subjects had a history of ACS. In the primary prevention analysis we compared 1) *no medication*, 2) low-dose *ASA monotherapy* (enteric coated acetylsalicylic acid 81 mg), 3) low-dose ASA with concomitant PPI therapy [*ASA+PPI*](omeprazole 20 mg) and 4) a *fixed combination* of low-dose ASA and PPI (enteric coated acetylsalicylic acid 81 mg + omeprazole 20 mg). In the secondary prevention model, only the latter three strategies were incorporated.

In this study the primary outcome was incremental cost per quality adjusted life year (QALY) gained. Using this outcome measure we accounted for both the quantity of a person's life as well as the quality. The third-party payer perspective was applied for the analyses. As a secondary outcome, we looked at the number of ACS events occurring with the different treatment strategies. Additionally, we studied the correlation between PPI compliance and the number of ACS events in 10.000 simulated patients.

Patient Population

Primary Prevention

The base-case cohort for the primary prevention analysis consisted of 60-year old males with no history of ACS, yet an increased risk (10 %) to develop ACS within the next 10 years. This reflects patients with one or more risk factors for ACS (e.g. high blood pressure, high cholesterol, smoker) for whom primary CV prevention with low-dose ASA may be indicated.[22]

Secondary Prevention

In order to evaluate the outcome for a patient group taking low-dose ASA for secondary prevention of ACS, we adjusted the baseline situation and created a second base-case cohort that consisted of 60-year old males with a history of ACS and a 10-year risk of recurrence of 23 % (based on annual risk estimates [23–25]), which we also followed over a lifetime horizon. In this model, the treatment strategy *no*

medication was eliminated, since these patients have a clear indication to receive at least *ASA monotherapy*. All patients started in the 'ACS' health state from which they could transfer to all other relevant health states as depicted in Fig. 1.

Model Structure

The cohort was followed through one-year Markov cycles over a lifetime horizon. All patients started in a health state in which they were free of CV and GI complications. At the end of a cycle patients could either stay in this health state or develop dyspepsia, upper GI bleeding, ACS or die (Fig. 1). Patients could return to the "no complications" health state only after dyspepsia. After an ACS or upper GI bleeding, patients transferred to a 'post' health state in which they remained at higher risk for a recurrent event, had a different utility and higher health care costs compared to "no complications". In a "post" health state, the patient could still develop other complications, yet they could never return to a "non-post" health state.

To derive reliable cost approximations, we attempted to reflect a patient's treatment course—within a health state—according to what happens in clinical practice. Therefore, some assumptions regarding clinical practice were incorporated in the model, based on both clinical guidelines and clinical experts' experience (See Technical Appendix).

Clinical Efficacy

Clinical probability estimates and treatment effectiveness data were primarily derived from the published literature (Table 1). We performed a structured search using PubMed and Embase databases, and we created a panel of 4 expert gastroenterologists and 1 cardiologist who provided expert opinions if no published literature was available, or if available information was conflicting.

In order to derive annual transition probabilities, we multiplied baseline risks on the development of ACS, upper GI bleeding and dyspepsia by the relative risks of ASA use and, if appropriate, PPI use. Age-dependent probabilities were used for the development of an ACS and GI bleeding. In addition, we used a risk multiplier to increase the baseline probability of upper GI bleeding to a maximum of three times the average risk. In this way we simulated an additional patient population with a higher GI bleeding risk as compared to the average population to experience more or less benefit from the treatment strategies under evaluation.

Mortality

Annual, age-dependent probabilities of death (Fig. 7) were applied throughout the model, extracted from life tables in The Netherlands[26]. However, in the health states "GIB" and "ACS" event specific mortality estimates (Table 1 & Fig. 7) were applied.

Compliance Assumptions

We introduced a method to include compliance in our Markov model, by which the probability of an event (e.g. dyspepsia, upper GI bleeding or ACS) was dependent on a patient's compliance. An equation was built into the model as such that every event probability was calculated through this equation;

$$\text{Risk placebo} * (1 - (C(1 - RR)/100))$$

where C stands for compliance rate (0–100 %) and RR is the relative risk of developing an event while using medication. The equation can be applied to all individual therapies, as well as to a combination of therapies, in which case the equation should be applied in sequence. The equation implies that patients who are 0 % compliant to low-dose ASA/PPI do not experience the benefits nor side effects of ASA or PPI. For example, if a 60-year old patient were

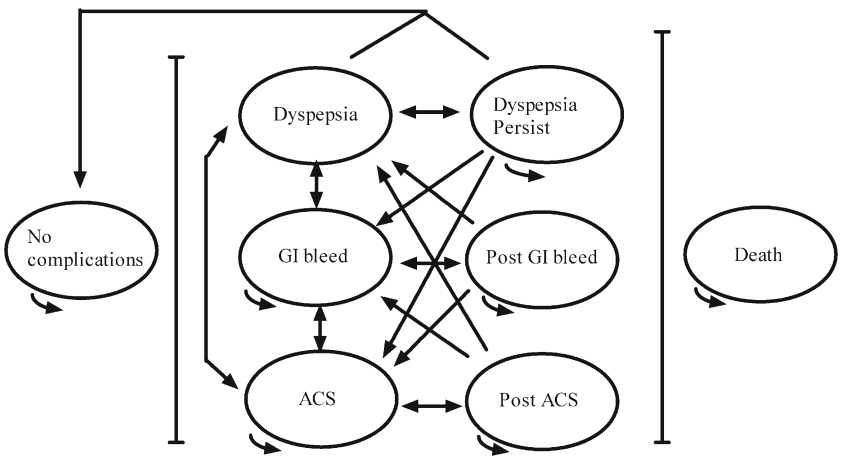

Fig. 1 Markov model structure; the cohort was followed through one-year Markov cycles over a lifetime horizon. All patients started in a health state in which they were free of cardiovascular and GI complications. At the end of a cycle patients could either stay in this health state or develop dyspepsia, upper GI bleeding, ACS or die. Patients with upper GI bleeding, ACS or in a post-state on these two and who are developing dyspepsia could not transfer to no complications

Table 1 Input parameters

Variable	Base case estimate	Sensitivity range	Source
Baseline probabilities	Probability	Probability	
Dyspepsia	0.17	0.05–0.25	[12]
GIB (post GIB)	0.023	0.02–0.08	[34]
GIB (after ACS)	0.007	0.003–0.025	[35, 36]
GIB (after ACS and post GIB)	0.095	0.04–0.10	Assumed
ACS (post ACS)	0.04	0.006–0.056	[23–25]
Mortality GIB	0.08	0.04–0.14	[25, 32, 37, 38]
Mortality ACS	0.09	0.05–0.12	[22, 39–43]
Relative risks[a]	Relative risk	Relative risk	
ASA; dyspepsia	1.09	1–1.22	[7]
ASA; GIB	2.07	1.61–2.66	[7, 24]
ASA; ACS			
Primary prevention	0.80	0.54–0.91	[1–3, 5, 27]
Secondary prevention	0.78		
PPI; dyspepsia	0.58	0.4–0.85	[12]
PPI; GIB	0.32	0.11–0.65	[11, 13, 28, 29]
Annual placebo risks	Probability		
Death	Age dependent[b]		[26]
ACS	Age dependent (0.0089+0.000336 per year)		[3, 26, 30]
GIB	Age dependent (0.0014+0.00015 per year)		[7, 31–33]
Medication costs (€ per daily dose)	€ per daily dose	€ per daily dose	
81 mg aspirin	€0.02	€ 0.01–0.05	[44]
20 mg omeprazole	€0.022	€ 0.01–0.33	[44]
40 mg omeprazole	€0.044	€ 0.02–0.66	[44]
Fixed combination	€0.45	€ 0.2–0.7	[44]
Annual utilities[c]	Utility	Utility	
Dyspepsia	0.94	0.90–0.98	[45, 46]
Dyspepsia persist	0.88	0.87–0.93	[45, 46]
GI bleeding	0.94	0.88–0.97	[45, 46]
Post GIB	0.98	0.95–1	[47]
ACS	0.86	0.75–0.90	[48, 49]
Post ACS	0.90	0.85–0.95	[47, 49]
Compliance	Percentages	Percentages	
ASA, no complications	75 %	0–100	[50]
ASA, GI complications	60 %	0–100	[16]
ASA, post ACS	90 %	0–100	[51, 52]
ASA, post ACS, GI complications	70 %	0–100	[16, 17, 53]
Fixed combination, no complications	75 %	0–100	Assumed
Fixed combination, post ACS/ GI complications	90 %	0–100	Assumed
PPI, no GI complications	62 %	0–100	[54, 55]
PPI, GI complications	76 %	0–100	[19, 56]

ASA low-dose aspirin; *PPI* proton pump inhibitor; *GIB* upper GI bleeding; *ACS* acute coronary syndrome; *GI* gastrointestinal

[a]Annual transition probabilities can be calculated by multiplying baseline probabilities*relative risks; e.g. *P*(dyspepsia|ASA) = 0.17*1.09

[b]Figure in appendix

[c]References refer to the studies that reported event utilities, which were used as input for the disutility calculations (see Appendix). These were performed to derive the annual utilities as reported here, thereby accounting for the duration of the event

100 % compliant to both low-dose ASA and PPI, his risk of GI bleeding equals:

$$\begin{aligned}\text{Risk placebo} &* (1 - ((100(1 - \text{RR ASA}))/100)) \\ &* (1 - ((100(1 - \text{RR PPI}))/100)) = \\ \text{Risk placebo} &* \text{RR ASA} * \text{RR PPI} = 0.0014 * 2.07 \\ &* 0.32 = 0.0009\end{aligned}$$

We assumed a linear relationship between the compliance rate of both ASA and PPI and their effect, based on a relation which was found for PPI compliance and the risk of upper GI bleeding in NSAID users[20]. Using this method, we were able to model different compliance rates at different health states, thereby emulating reality as a patient's compliance to low-dose ASA and PPIs is dependent on the previous

occurrence of GI or CV side effects [16, 17]. Based on the available literature we estimated base-case compliance rates as shown in Table 1. Patients using the fixed combination of ASA and PPI are by definition 100 % compliant to the PPI. Compliance for the fixed combination was assumed equal to compliance for ASA as a single component.

Utilities

Utility values were derived from the literature (Table 1). Utility calculations (Table 4) were made in order to derive annual health utilities, thereby accounting for the duration of the event (Technical Appendix). All utilities are discounted at an annual rate of 3 %.

Costs Calculations

Health care costs were estimated from a third-party payer perspective, considering only direct costs. The costs of the medications studied (Table 1) were primarily derived from the Dutch Health Care Insurance Board (HCIB) and include cost prizes, claw-back (deduction applied to pharmacies' reimbursement) and taxes [42]. In the model these prizes were increased by a dispensing fee assuming four prescriptions per year. Standardized cost prizes were used for general practitioner (GP) consultations, emergency department and outpatient visits and inpatient hospital stay, following the HCIB guidelines [57]. Specific costs of diagnostic and therapeutic interventions were derived from the Dutch Healthcare Authority (Table 5). We used 2011 prices in euros and discounted all costs at a rate of 3 %. The total costs for each health state are displayed in Table 2.

Sensitivity Analyses

We performed one way sensitivity analyses to get an overview of the most influential variables on the results (Table 1). Plausible ranges were determined by employing the variability that was found in the literature. Applying a willingness to pay (WTP) threshold of €20,000 per QALY, parameter threshold values were obtained at which the relative order between strategies changed. This WTP-threshold is relatively arbitrary as there is no official threshold in the Netherlands. It is, however, the most conservative threshold out of a range of thresholds (€20,000–€80,000) that have been suggested for the Netherlands

Additionally, we performed a probabilistic sensitivity analysis, for which we included probability distributions around all transition probabilities (beta distributions), relative risks (log normal distributions), costs (gamma distributions) and utilities (beta distributions) (Table 6). Furthermore, we wanted to simulate non-compliance as well as partial and full-compliance. We therefore created compliance distributions with a probability to be non-compliant as well as probabilities for partial and full-compliance (Fig. 8). These compliance distributions were based on assumptions verified with our expert panel. A detailed overview of all input parameters for the probabilistic sensitivity analyses is provided in the Technical Appendix. We conducted a Monte Carlo simulation with 10,000 samples, which resulted in scatter plots and cost-effectiveness acceptability curves for both primary and secondary prevention of ACS and for patients with average and elevated (three-fold) risk of upper GI bleeding.

Table 2 Annual costs per state of health

Health state	Costs[a] (€)
No complications	37.89
Dyspepsia	356.77
Dyspepsia persist	104.36
GI bleed	6389.11
Post GI bleed	84.39
ACS	8836.95
Post ACS	174.57

[a]Costs include medication costs. Costs displayed are from the treatment strategy "ASA monotherapy"

Results

Primary Prevention

Average GI Bleeding Risk

In a cohort of 60-year old males taking low-dose ASA for primary prevention of ACS the treatment strategies *no medication* as well as *ASA+PPI* were likely to be cost-effective, with the latter strategy yielding an incremental cost effectiveness ratio (ICER) of €10,314 per QALY gained compared to *no medication*. *ASA monotherapy* was not cost-effective, as the ICER of this strategy was higher than the ICER of the next, more effective alternative (*ASA+PPI;* extended dominance). The incremental cost of the *fixed combination* compared to *ASA+PPI* was €35,832 per additional QALY. Table 3 shows the results of our base case analyses.

Elevated GI Bleeding Risk

In a cohort of 60-year old patients with a 3-fold increased risk for upper GI complications taking low-dose ASA for primary prevention of ACS, *ASA monotherapy* was dominated since it was more costly and less effective than *no medication* (Table 3). *ASA+PPI* yielded an ICER of €10,449 per QALY gained compared to *no medication*. Compared to *ASA+PPI*, the *fixed combination* yielded an ICER of €24,825 per QALY gained.

Table 3 Base case results

Analysis	Strategy	Costs (€)	QALYs	Incremental cost-effectiveness ratio (€/QALY gained)
Primary prevention Average GI bleeding risk	*No medication*	3409.60	15.91	–
	ASA monotherapy	3932.90	15.90	(Dominated)
	ASA+PPI	4108.60	15.97	€10,314
	Fixed combination	5909.60	16.03	€35,832
Primary prevention Elevated GI bleeding risk	*No medication*	4004.80	15.85	–
	ASA monotherapy	4855.40	15.80	(Dominated)
	ASA+PPI	4682.40	15.91	€10,449
	Fixed combination	6335.40	15.98	€24,825
Secondary prevention Average GI bleeding risk	*ASA monotherapy*	16,877.70	13.02	–
	ASA+PPI	16,924.90	13.10	€563
	Fixed combination	18,953.40	13.17	€22,927
Secondary prevention Elevated GI bleeding risk	*ASA monotherapy*	17,844.20	12.92	(Dominated)
	ASA+PPI	17,532.50	13.03	–
	Fixed combination	19,353.80	13.12	€14,682

Sensitivity Analyses

We performed one-way sensitivity analyses to assess the influence of individual parameters on the model. The results were most sensitive to 1) compliance of PPI and 2) cost of the fixed combination and the PPI and 3) the probability of developing dyspepsia. A tornado diagram of the full one-way sensitivity analysis for average and high risk patients, comparing the *fixed combination* to *ASA+PPI*, is presented in the Technical Appendix.

Threshold analysis for the average risk patient showed that if PPI compliance drops below 40 %, the *ASA+PPI* strategy was no longer cost-effective when a WTP threshold of €20,000 was applied. The *fixed combination* then yields an ICER of €21,430 per QALY gained, making *no medication* the only cost-effective strategy. In an average risk population the *fixed combination* was cost-effective only if it costs less than €0.32 per day. In a high risk population the *fixed combination* was cost-effective when it costs less than €0.40 per day, PPI compliance falls below 55 %, or PPI costs more than €0.07 per day.

Cost-effectiveness acceptability curves (Fig. 2) point out that the treatment option *ASA+PPI* has the highest probability of being cost-effective for primary prevention if we hold on to a WTP threshold of €20,000 per QALY gained.

Secondary Prevention

Average GI Bleeding Risk

In a cohort of 60-year old males with an average GI bleeding risk profile taking low-dose ASA for secondary prevention *ASA+PPI* was likely to be cost-effective, yielding an ICER of €563 per QALY gained (Table 3). Compared to *ASA+PPI*, the *fixed combination* was less cost-effective with an ICER of €22,927 per QALY gained.

Elevated GI Bleeding Risk

When accounting for a higher GI-complication risk, the treatment option *ASA monotherapy* was dominated by *ASA+PPI*. *ASA+PPI* and the *fixed combination* both seemed acceptable strategies, as the *fixed combination* yielded an ICER of €14,682 per QALY gained compared to *ASA+PPI*.

Sensitivity Analyses

One-way sensitivity analyses showed that the results were sensitive to 1) compliance to PPI, 2) cost of PPI and 3) cost of the fixed combination. A tornado diagram of the full one-way sensitivity analysis for average risk patients, comparing the *fixed combination* to *ASA+PPI*, is presented in the Technical Appendix.

Threshold analysis for the average risk patient showed that if PPI compliance drops below 56 %, the *fixed combination* becomes the most effective strategy below the willingness to pay threshold of €20,000 per QALY. If the compliance rate is very low (<21 %), the *fixed combination* is the only cost-effective strategy. Should the cost of PPI exceed €0.05 per day or should the *fixed combination* cost less than €0.42, the *fixed combination* becomes cost-effective. In high risk patients, the *fixed combination* was no longer cost-effective at a cost beyond €0.54 or compliance to PPI before GI complications exceeds 72 %.

In the probabilistic sensitivity analyses the cost-effectiveness of the *fixed combination* is again not confirmed for average risk patients (Fig. 3). *ASA+PPI* has the highest probability of being

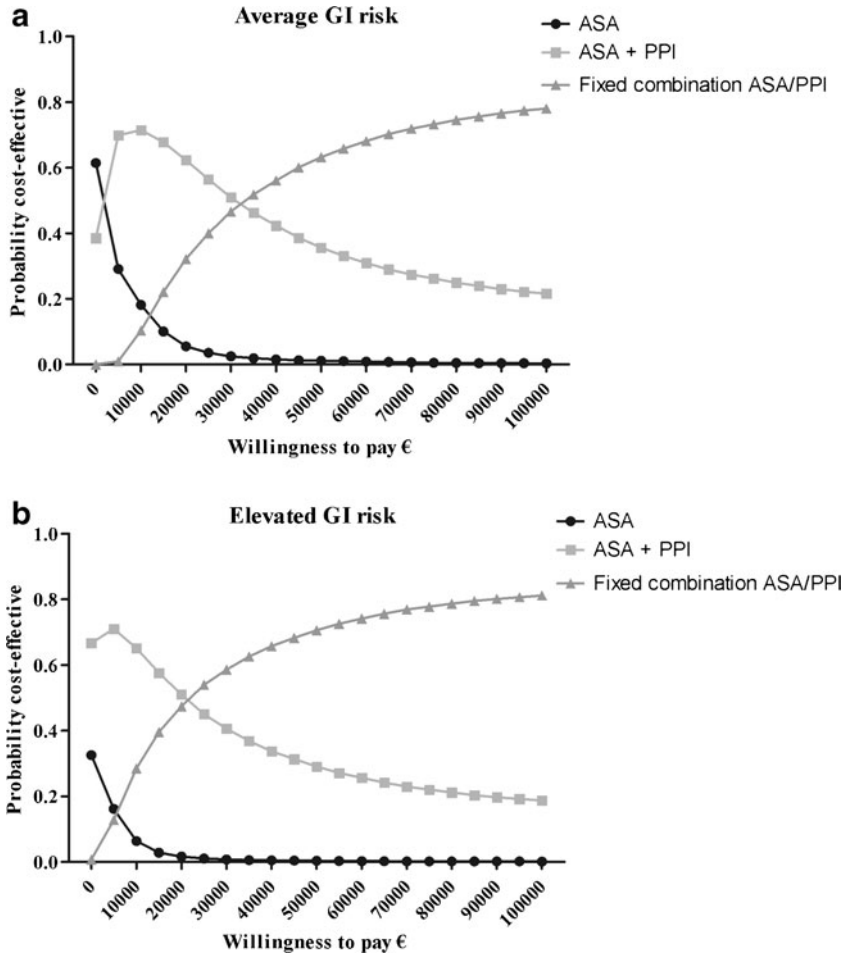

Fig. 2 Cost-effectiveness acceptability curves of the primary prevention cohort. a average GI bleeding risk, b elevated GI bleeding risk. WTP = Willingness to pay. This figure illustrates the probability that a strategy is cost-effective at various WTP thresholds

cost-effective at a willingness to pay threshold of €20,000 per QALY. For high risk patients, the probabilities of being the preferred strategy are equal for *ASA+PPI* and the *fixed combination* at a WTP threshold of €20,000 per QALY, yet are higher for *ASA+PPI* at lower thresholds.

Acute Coronary Syndrome Risk

In both primary and secondary prevention, patients treated with the *fixed combination* had the lowest risk of an (recurrent) ACS compared to the other strategies (Figs. 4 and 5, $p<0.01$). Notably, patients treated with *ASA+PPI* also had a lower risk of an ACS compared to patients taking *ASA monotherapy* ($p< 0.01$).

In primary prevention, one ACS could be prevented if 435 patients are treated with *ASA+PPI* co-therapy instead of *ASA monotherapy* (NNT [number needed to treat] = 435)). The NNT for the *fixed combination* (compared to ASA monotherapy) is even lower; only 124 patients have to be treated with the *fixed combination* instead of *ASA monotherapy* to prevent one ACS. For secondary prevention the preventive effect of PPIs was stronger; with a NNT of 385 and 74, respectively. The GI bleeding risk did not influence the risk of an ACS among different treatment groups.

Higher patient compliance to ASA is the main driver of the lower ACS risk in patients taking the PPI co-therapy or the fixed combination. Since PPIs reduce GI side effects of ASA, PPI co-therapy indirectly increases ASA compliance. To study the influence of PPI compliance on the risk of an ACS, we plotted the patient compliance to PPI against the number of ACS events (Fig. 6). Especially in patients treated with *ASA+PPI* for secondary prevention we found that with every 20 % decrease in PPI compliance the risk of an ACS increased by 0.12 %. Again, GI bleeding risk did not influence these results.

Discussion

The results of our cost-effectiveness study suggest that use of low-dose ASA for primary prevention is only cost-effective when a PPI is co-administered. *ASA monotherapy* was not cost-effective: we found that both *no medication* and *ASA+PPI* were better treatment options over *ASA monotherapy* for patients with both average and high GI

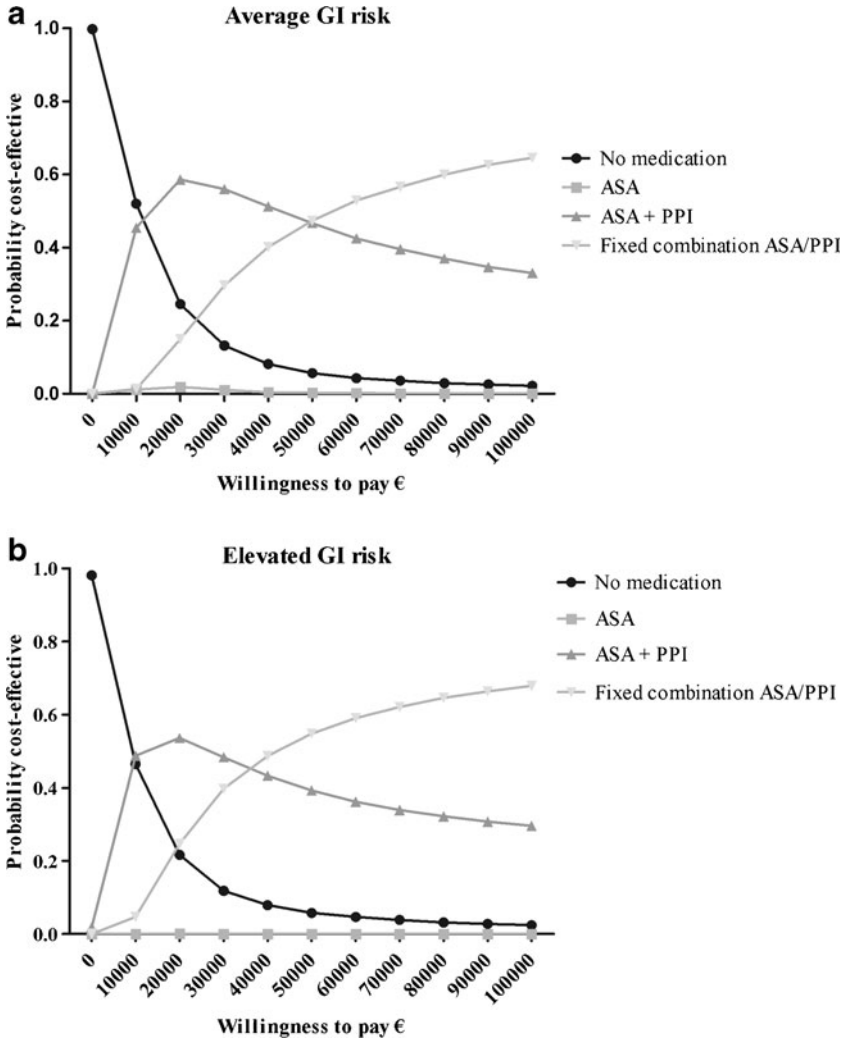

Fig. 3 Cost-effectiveness acceptability curves of the secondary prevention cohort. **a** average GI bleeding risk, **b** elevated GI bleeding risk. WTP = Willingness to pay. This figure illustrates the probability that a strategy is cost-effective at various WTP thresholds

bleeding risk. Our results were however dependent on the costs of PPIs and PPI compliance. For patients with average GI bleeding risk and low compliance to PPI, *no medication* was the best treatment option. For patients with an elevated GI bleeding risk and low compliance to PPI the *fixed combination* of ASA and PPI was likely to be cost-effective. In

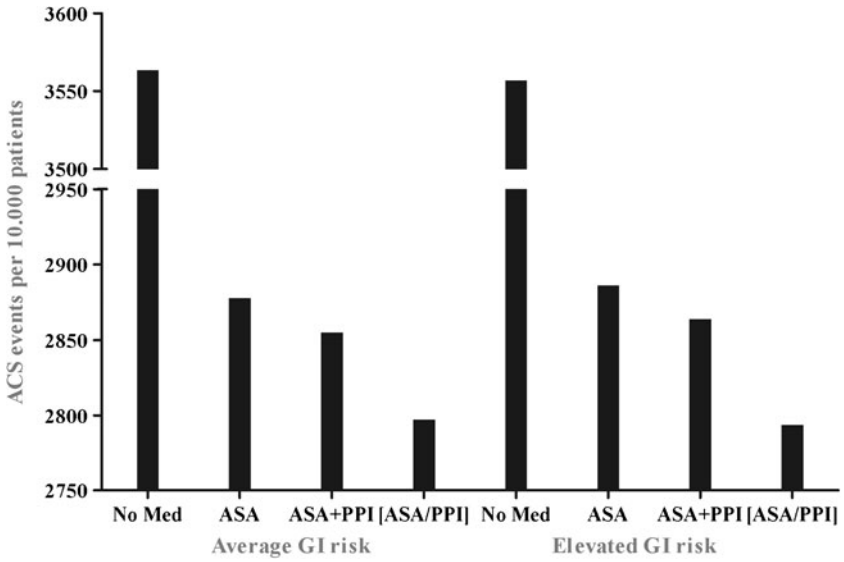

Fig. 4 Total number of ACS events during follow-up in 10,000 patients treated with the different treatment strategies for primary prevention. All strategies differed statistically significant $p<0.01$

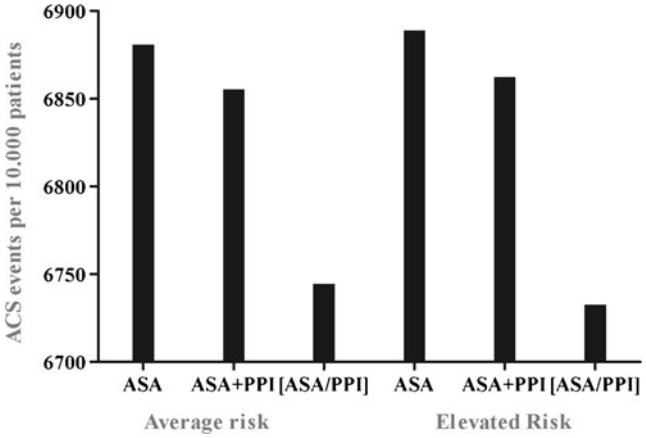

Fig. 5 Total number of ACS events during follow-up in 10,000 patients treated with the different treatment strategies for secondary prevention. All strategies differed statistically significant $p<0.01$

secondary prevention of ACS, *ASA+PPI* co-therapy was the preferred treatment strategy in all patients taking low-dose ASA and it was even cost-saving for patients with increased GI bleeding risk when it was compared to *ASA monotherapy*. In patients with increased GI bleeding risk, the *fixed combination* seemed an additional cost-effective option.

Prior studies have investigated the cost-effectiveness of low-dose ASA in the prevention of coronary heart disease. Greving et al. concluded that ASA is only cost-effective for men with a 10-year CV disease risk of >10 %[58], while Earnshaw et al. concluded that ASA monotherapy is cost-effective in middle-aged men across a range of CV and GI bleeding risk factors[9]. The contrasting results between

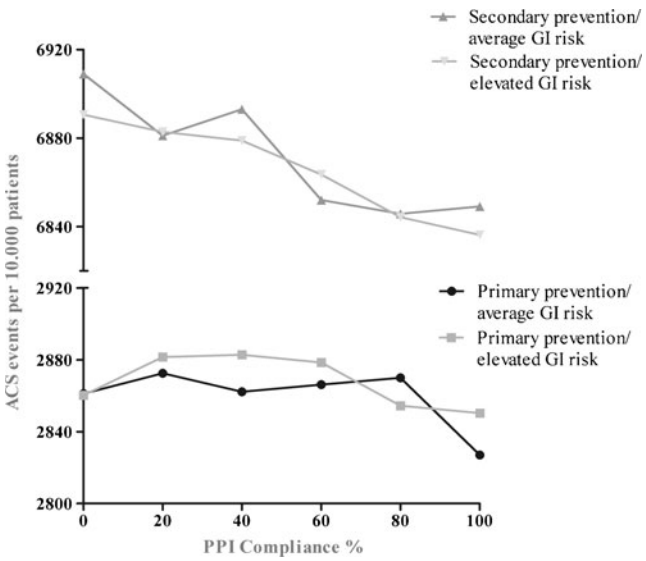

Fig. 6 PPI compliance plotted against the total number of ACS events in 10.000 simulated patients

these studies and our results are mainly due to the effect of structural and parameter model differences. Most importantly, in our model dyspepsia is included as a separate health state, as well as the chronic condition of persisting dyspepsia. Chronic or recurrent dyspepsia is a common GI complication, affecting 20–37 % of adults and impacting many domains of health related quality of life [45, 59, 60]. The risk of developing dyspepsia is increased in patients taking low-dose ASA [7, 61, 62]. On the other hand, PPI therapy increases the proportion of patients with resolution of dyspeptic symptoms [12, 13, 63]. The inclusion of dyspepsia in our model impairs the cost-effectiveness of ASA monotherapy but favors the cost-effectiveness of PPI co-therapy. The cost-effectiveness of PPI co-therapy is also favored by the low (generic) costs of PPIs in the Netherlands, where a single dose of 20 mg omeprazole is available at a price of €0.02. Another study on the cost-effectiveness of PPI co-therapy in secondary CV prevention was in line with our results, as PPI co-therapy was regarded cost-effective at PPI prices below $250 per year [14]. Yet, we are the first to report PPI co-therapy to be potentially cost-saving.

The analyses were performed from a third-party payer perspective. If we had included costs associated with productivity loss in our analysis, this would have led to more favorable cost-effectiveness outcomes for the strategies ASA+PPI co-therapy and the fixed combination, as these strategies are associated with less events compared to the other strategies, resulting in less incremental costs. Using a third-party payer perspective can therefore be regarded more conservative compared to using a societal perspective.

A secondary outcome of this study was the association between the different treatment strategies and the absolute risk of developing an ACS and the effect of PPI compliance on the absolute ACS risk. We found that patients treated with PPI co-therapy or the fixed combination had a significantly lower ACS-risk compared to patients treated with ASA monotherapy or no medication. This underlines the hypothesis that concomitant prescription of PPI reduces GI side effects and thereby increases patients' compliance to ASA, which in turn reduces the probability of developing an ACS. A recent study by Saini et al. also suggested that PPI co-therapy has the potential to improve CV outcomes [64].

Our study had several important strengths. First, we included patient compliance in our model using a method that enabled us to model partial patient compliance as well as alterations in compliance rates depending on a patient's medical history. Additionally, we modeled both PPI compliance and ASA compliance and included the effect of compliance on the occurrence of GI events and ACS. Many studies evaluating the cost-effectiveness of low-dose ASA

mainly looked at CV outcomes, and therefore often concluded that low-dose ASA is cost-effective in primary prevention of ACS [65]. We also included dyspepsia in our model as well as an age dependent risk of GI bleeding; included both primary and secondary prevention of ACS, and varied the GI bleeding risk to cover a wide patient population. We increased the risk of GI complications up to a 3-fold higher risk which corresponds to patients who, for example, use anticoagulants or NSAIDs concomitantly [31].

This study had some limitations. First, this study is limited by its hypothetical design. Our base case parameter estimates were derived from literature including studies with heterogeneous designs, populations and follow up periods. In order to correct for that, we used systematic reviews and meta-analyses where possible and to account for uncertainties we performed probabilistic sensitivity analyses across a wide range for each key variable in the model. We chose a 60-year old men as base case patient, as this corresponded with the average patient in clinical trials [2, 3, 5, 25]. Little data is available on primarily women. Possibly, women do not benefit to the same extent from ASA for primary prevention of ACS compared to men, yet results are conflicting and recommendations by guidelines are comparable for males and females [2, 66]. A second limitation might have been the generalizability of our results to healthcare systems that differ from the Netherlands. We are aware of higher medication costs in other countries (e.g. USA), especially PPI costs. We therefore included a figure (Fig. 9) which shows the cost-effectiveness estimates for a range of PPI prices. Moreover the WTP may vary between different countries. We applied a WTP-threshold of €20,000 for our threshold analyses, although this threshold is relatively arbitrary as there is no official threshold in the Netherlands. Third, if no published literature was available for input for our model, estimates were based on expert opinion, but were then tested over a wide range in one-way and probabilistic sensitivity analyses. Moreover, we assumed a linear relation between compliance rates and effectiveness of ASA and/or PPI, which might not reflect reality: the antiplatelet effect of ASA is known to last several days after intake, so the influence of compliance on the effectiveness of ASA might have been overestimated. The relation between PPI compliance and the occurrence of GI side effects is unclear in patients using low-dose ASA as well as the exact association between low-dose ASA use and the development of dyspepsia, and we therefore tested a wide range of relative risk values. Last, in order to prevent the model from becoming too cumbersome, we did not include other CV outcomes in our model, nor did we include the preventive effect ASA is thought to have on the development of GI cancer [67]. We did also not include side effects of PPI therapy. Existing data about the potential association between PPI and adverse outcomes such as vitamin and mineral deficiencies, pneumonia and osteoporosis vary and are based on observational studies; moreover the absolute incidences of these side effects are low [68, 69].

In conclusion, this cost-effectiveness study suggest that PPI co-therapy is the preferred treatment strategy in patients taking low-dose ASA for the prevention of ACS, given that PPIs are available at low prices. A fixed combination may be cost-effective in patients who are at increased risk for GI bleeding and who are poorly compliant to PPI. Both PPI co-therapy and the fixed combination were found to be more effective in reducing the ACS risk compared to ASA monotherapy, due to a reduction in dyspepsia and consequent increase in compliance with ASA therapy. These results suggest that the current guidelines may need to be expanded, recommending PPI co-therapy for all low-dose ASA users if generic PPIs can be purchased for relatively low prices. Future clinical trials are needed to assess the effect of PPI and ASA compliance on the occurrence of GI events and ACS.

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Conflicts of Interest The salary of N.L. de Groot is paid by an unrestricted grant from AstraZeneca. HGM van Haalen reports no conflicts of interest during the conduction of this research project. She currently works for AstraZeneca. BMR Spiegel has received unrestricted research grant support from Movetis and serves as an advisor for AstraZeneca. L. Laine serves as a consultant for AstraZeneca, Eisai, Horizon, and Pfizer and joins the Safety Monitoring Board for Bayer, Merck and BMS. A. Lanas serves as an advisor for AstraZeneca and Bayer. J. Jaspers Focks reports no conflicts of interest. PD Siersema received unrestricted research grant support from AstraZeneca, Movetis and Janssen, and serves as an advisor for Pfizer, Janssen and Movetis. MGH van Oijen received unrestricted grant support from AstraZeneca and Janssen, and serves as an advisor for AstraZeneca and Pfizer.

Contributorship Statement HGM van Haalen: study concept and design, analysis and interpretation of data, drafting of the manuscript, statistical analysis; NL de Groot: study concept and design, analysis and interpretation of data, drafting of the manuscript, statistical analysis; BMR Spiegel: analysis and interpretation of data, critical revision; L Laine: interpretation of data, critical revision; A Lanas: interpretation of data, critical revision; J Jaspers Focks: interpretation of data, critical revision; PD Siersema: interpretation of data, critical revision, study supervision; MGH van Oijen: study concept and design, analysis and interpretation of data, drafting of the manuscript, statistical analysis, study supervision

By Dutch law, this protocol did not need approval by the Ethical Review Board as no identifiable patient data were used.

Technical Appendix

Input Parameters

We performed a structured search using PubMed and Embase databases limiting our results to English language and using combinations of relevant entry terms *(aspirin, proton pump inhibitor, gastrointestinal, acute coronary syndrome, prevention, compliance, adherence, incidence, risk, relative risk, cost-effectiveness)*. Where available, we used meta-analyses or systematic reviews reporting intention-to-treat summary estimates. In order to derive annual transition probabilities, we multiplied placebo risks (on the development of ACS, upper GI bleeding and dyspepsia) by the relative risks of aspirin and, if necessary, PPI. In case placebo risks were unknown, we divided the risk with aspirin monotherapy by the relative risk of aspirin. Utility values of the combined health states for which no data was available (e.g. Post ACS+dyspepsia) were derived by multiplying the separate utilities of the involved health states (Table 4).

Model Assumptions

1) A patient who develops dyspepsia visited his/her primary care provider and received a 4 week trial of PPI therapy (omeprazole 20 mg daily). Patients previously treated with PPIs were assumed to be given a dose of 40 mg/day. Should this be ineffective (approximately 45 % of patients), the patient is referred to a gastroenterologist. The patient receives diagnostic endoscopy including a *H.pylori* test. *H.Pylori* eradication therapy is given if appropriate, and eradication is confirmed by a breath test. Patients receive another 8 weeks of PPI therapy and are assumed to visit their primary care provider a total of three times per year.
2) All patients with persistent dyspepsia receive PPI therapy. Patients who were allocated to *no medication* or *aspirin monotherapy* receive 20 mg PPI daily during the complete cycle, whereas patients who were allocated *aspirin+PPI* or a *single tablet formulation* receive additional PPI (40 mg omeprazole daily in total). All patients are assumed to visit their primary care provider annually.
3) Patients who develop an upper GI bleeding are admitted to the hospital after reporting to the emergency department. Sixty percent of patients need a blood transfusion and all receive endoscopic therapy, intravenous PPI, *H.pylori* testing and *H.pylori* eradication therapy plus breath test confirmation if necessary. A second therapeutic endoscopy is performed in case of therapy failure, followed by percutaneous embolization if therapeutic endoscopy remains unsuccessful. A second look endoscopy is

Table 4 Derivation of health state utilities

Health state	Percentage of patients	Utility	Duration (days)	Disutility[a]
Dyspepsia	55 %	0,88	28	0.005
	45 %	1	337	0
	45 %	0.88	365	0.054
				0.059
Dyspepsia persist	100 %	0.88	365	0.12
GI bleeding	100 %	0.49	31	0.043
	100 %	0.98	334	0.019
				0.062
Post GIB	100 %	0.98	365	0.02
ACS	100 %	0.49	31	0.043
	100 %	0.90	334	0.092
				0.135
Post ACS	100 %	0.90	365	0.1

Duration of events were based on assumptions

[a] Disutility = Percentage (1-utility) duration ÷ 365

Table 5 Health care costs

Activities	Costs (€)	Source
GP consult	28	Health Care Insurance Board
GP home visit	43	Health Care Insurance Board
Emergency department visit	151	Health Care Insurance Board
Day In hospital (normal)	457	Health Care Insurance Board
Day In hospital (IC)	2183	Health Care Insurance Board
Blood transfusion	204,35	Sanquin blood bank
Endoscopy (diagnostics)	397,86	Dutch Healthcare Authority
Endoscopy+intervention	850	Hospital tariff
Surgical/radiological intervention after GIB	1329,47	Dutch Healthcare Authority
H.Pylori diagnostics (biopsy)	3,5	Dutch Healthcare Authority
H.Pylori diagnostics (breathtest)	63,92	Dutch Healthcare Authority
H.Pylori eradication	11,39	Medicijnkosten.nl
ECG	19,02	Dutch Healthcare Authority
Biomarkers (troponin)	8,03	Dutch Healthcare Authority
PCI	4246,32	Dutch Healthcare Authority
CABG	11429	Dutch Healthcare Authority
Angiocardiography	348,6	Dutch Healthcare Authority
Stress test	38,2	Hospital tariff
Outpatient visit	72	Health Care Insurance Board
Trombolysis	209,06	Medicijnkosten.nl

Table 6 Distributions of the probabilistic sensitivity ananlyses

Variable	Base case estimate	Distribution	Input	
Baseline probabilities			Alpha	Beta
Probability of recurrent dyspepsia	0.62	Beta	897.22	549.91
Probability of recurrent dyspepsia on ASA	0.55	Beta	212.87	174.17
Probability of recurrent dyspepsia in ASA and PPI	0.7	Beta	229.77	98.47
Probability of ACS postACS	0.031	Beta	5.72	178.66
Probability of death after an ACS	0.09	Beta	21.16	214.00
Probability of death after GIB	0.08	Beta	8.97	103.13
Probability of dyspepsia after an ACS	0.25	Beta	17.76	53.27
Probability of dyspepsia on ASA	0.19	Beta	11.04	47.08
Probability of GIB after an ACS	0.015	Beta	7.02	461.07
Probability of GIB postACS	0.007	Beta	15.25	2163.58
Probability of GIB postGIB after an ACS	0.063	Beta	15.81	235.16
Probability of GIB postGIB on ASA	0.048	Beta	9.31	184.74
Relative risks			Log mean	SE
ASA; dyspepsia	1.09	Log normal	0.09	0.04
ASA; GIB	2.07	Log normal	0.73	0.12
ASA; ACS		Log normal	−0.22	0.10
Primary prevention	0.80			
Secondary prevention	0.78			
PPI; dyspepsia	0.58	Log normal	−0.54	0.18
PPI; GIB	0.32	Log normal	−1.14	0.40
Costs			Alpha	Beta
Dyspepsia	€ 313.00	Gamma	25	0.08
Dyspepsia persist	€28.00	Gamma	25	0.89
GIB	€6.168.00	Gamma	25	0.004
Post GIB	€ -	Gamma		
Post GIB+dyspepsia	€594.00	Gamma	25	0.04
Post GIB+dyspepsia persist	€28.00	Gamma	25	0.89
Post GIB+ACS	€8.799.00	Gamma	25	0.003
ACS	€8.799.00	Gamma	25	0.003
Dyspepsia persist+ACS	€8.827.00	Gamma	25	0.003
Post GIB+dyspepsia persist+ACS	€8.827.00	Gamma	25	0.003
Post ACS	€137.00	Gamma	25	0.18
Post ACS+dyspepsia	€450.00	Gamma	25	0.06
Post ACS+dyspepsia persist	€165.00	Gamma	25	0.15
Post ACS+GIB	€6.305.00	Gamma	25	0.004
Post ACS+Post GIB	€137.00	Gamma	25	0.18
Post ACS+Post GIB+Dyspepsia	€730.00	Gamma	25	0.03
Post ACS+Post GIB+dyspepsia pers	€165.00	Gamma	25	0.15
Annual utilities			Alpha	Beta
Dyspepsia	0.94	Beta	55.14	8.98
Dyspepsia persist	0.88	Beta	23.06	1.47
GI bleeding	0.94	Beta	47.12	6.43
Post GIB	0.98	Beta	23.06	1.47
ACS	0.86	Beta	39.10	4.34
Post ACS	0.90	Beta	21.24	0.43

ASA low-dose aspirin; *PPI* Proton Pump Inhibitor; *GIB* (upper) Gastrointestinal bleeding; *ACS* Acute coronary syndrome; *GI* gastrointestinal

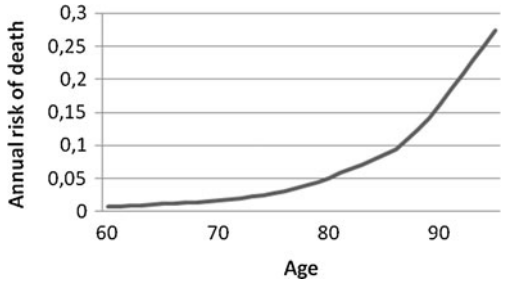

Fig. 7 (Risk of death all causes) by age

performed in patients with an ulcus ventriculi. The average duration of hospitalization is 10 days. At discharge all patients receive PPI therapy for the remainder of the time horizon: 20 mg omeprazole in case the patient was allocated to *no medication* or *aspirin monotherapy* and 40 mg omeprazole in case the patients was allocated *aspirin+PPI* or a *single tablet formulation*. Patients allocated to the *single tablet formulation* continue their assigned medication and are prescribed an additional 20 mg

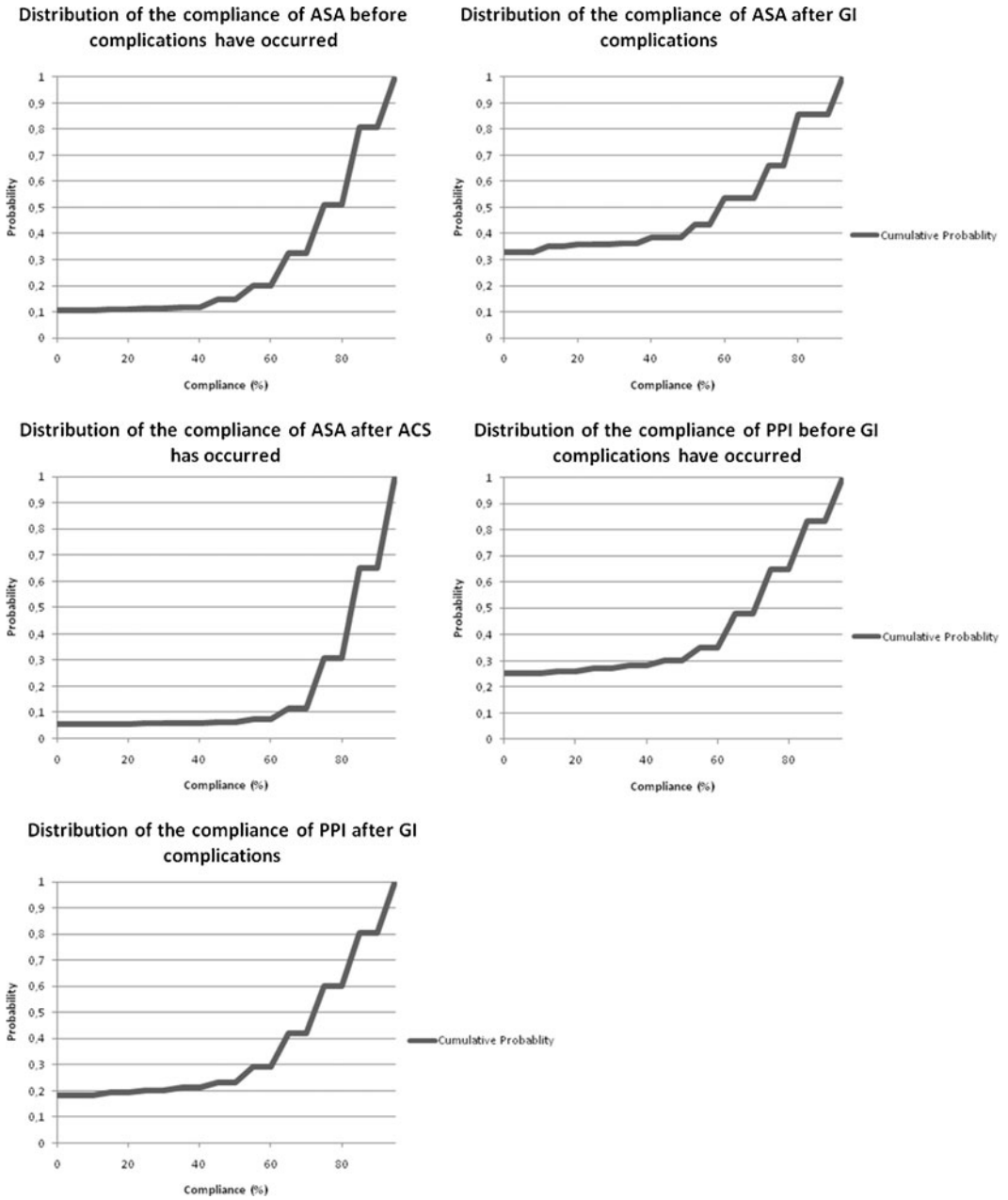

Fig. 8 Probability distributions of compliance. N.B. The compliance to the single tablet formulation before complications have occurred, was assumed to equal the compliance to aspirin before complications have occurred. The compliance to the single tablet formulation after ACS or GI complications, was assumed to equal the compliance to aspirin after an ACS

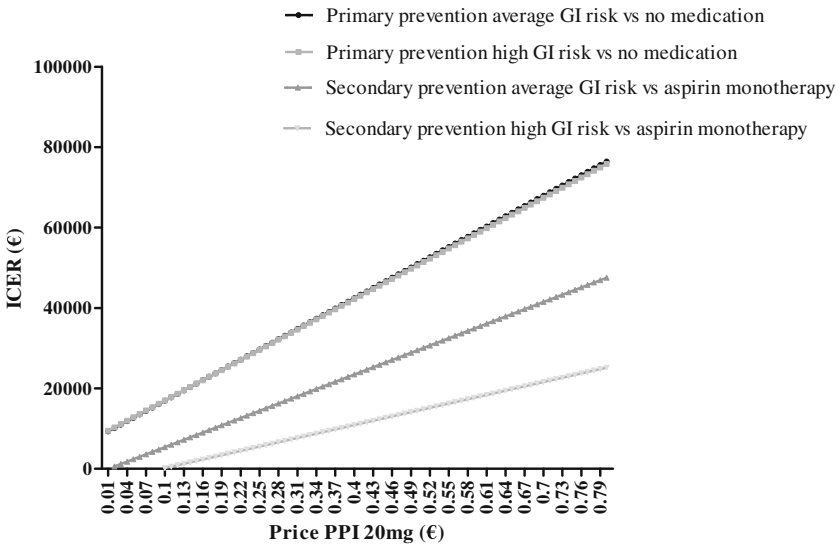

Fig. 9 Cost-effectiveness of PPI co-therapy for a range of PPI prices

PPI (instead of changing to 40 mg PPI concomitant to low-dose aspirin). In case of primary prevention of ACS, low-dose aspirin therapy is interrupted for 1 year. Patients are assumed to visit the outpatient clinic once in the following year. During the first year, 6.7 % of patients experiences a rebleeding.

4) Patients experiencing an ACS report to the emergency department where an ECG is made and cardiac marker levels (including troponin) are determined. We assumed that coronary angiography is performed in 90 % of patients, whereas 70 % of patients receive an additional percutaneous intervention and 5 % of patients require coronary artery bypass grafting surgery. In hospital, all patients receive low-dose aspirin and β-blockers, and some patients receive clopidogrel (60 %), ACE-inhibitors (55 %), nitroglycerin (70 %) and heparin (35 %). The average duration of hospitalization is 5 days. At discharge, all patients receive low-dose

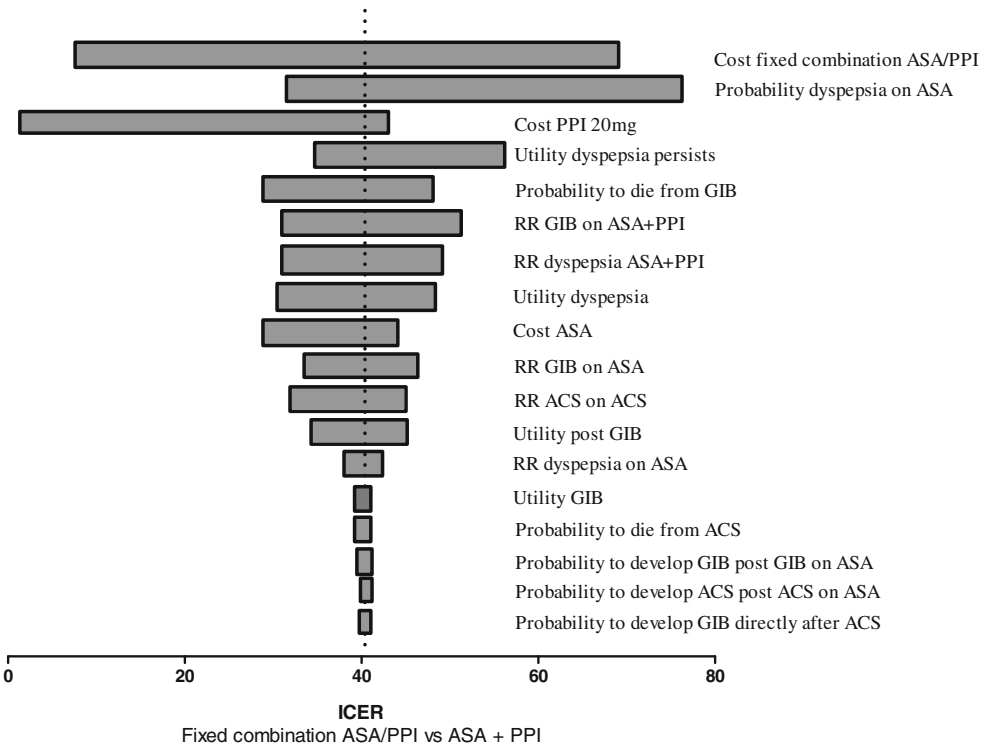

Fig. 10 Tornado diagram of one way sensitivity analyses comparing the fixed combination with ASA+PPI co-therapy for average risk patients using aspirin for primary prevention

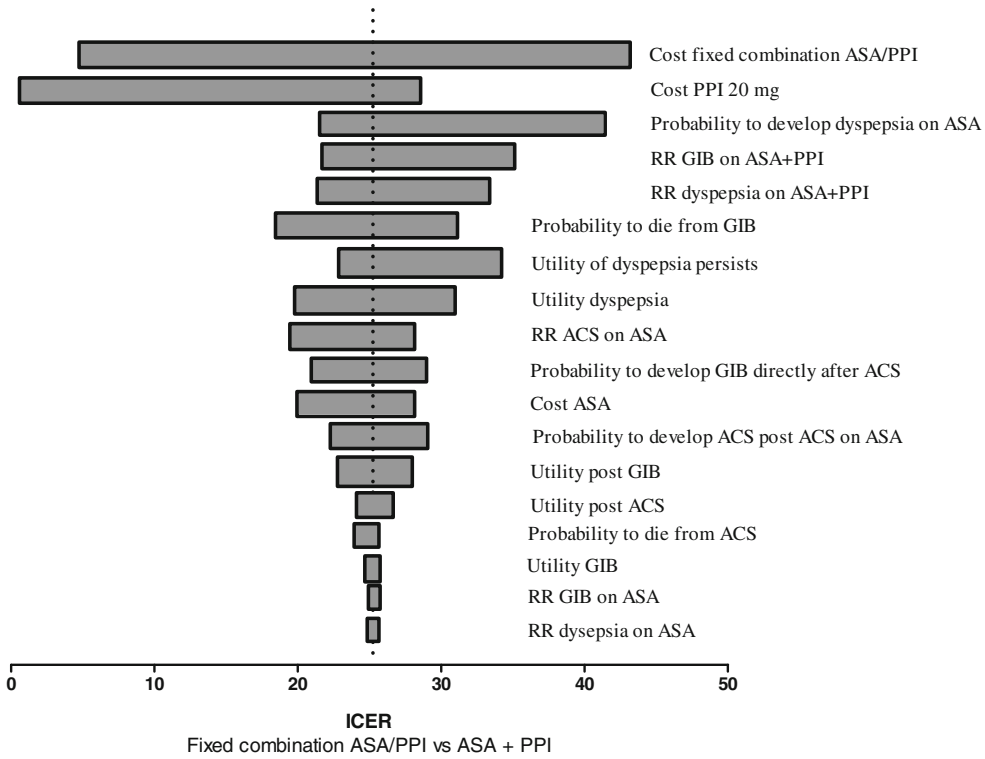

Fig. 11 Tornado diagram of one way sensitivity analyses comparing the fixed combination with ASA+PPI co-therapy for average risk patients using aspirin for secondary prevention

aspirin. In addition, patients receive β-blockers, statins and ACE-inhibitors for the remainder of the time horizon, whereas 80 % also receive clopidogrel for 1 year. During the first year rehospitalization is necessary in 30 % of patients. Patients are assumed to visit the outpatient clinic four times during the first year and once annually thereafter

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