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CLINICAL RESEARCH

Aspirin for primary prevention of vascular events in women: individualized prediction of treatment effects

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Aims To identify women who benefit from aspirin 100 mg on alternate days for primary prevention of vascular events by using treatment effect prediction based on individual patient characteristics.

Methods and results Randomized controlled trial data from the Women's Health Study were used to predict treatment effects for individual women in terms of absolute risk reduction for major cardiovascular events (i.e. myocardial infarction, stroke, or cardiovascular death). Predictions were based on existing risk scores, i.e. Framingham (FRS), and Reynolds (RRS), and on a newly developed prediction model. The net benefit of different aspirin treatment-strategies was compared: (i) treat no one, (ii) treat everyone, (iii) treatment according to the current guidelines (i.e. selective treatment of women >65 years of age or having >10% FRS), and (iv) prediction-based treatment (i.e. selective treatment of patients whose predicted treatment effect exceeds a given decision threshold). The predicted reduction in 10-year absolute risk for major cardiovascular events was <1% in 97.8% of 27 939 study subjects when based on the refitted FRS, in 97.0% when based on the refitted RRS, and in 90.0% when based on the newly developed model. Of the treatment strategies considered, only prediction-based treatment using the newly developed model and selective treatment of women >65 years of age yielded more net benefit than treating no one, provided that the 10-year number-willing-to-treat (NWT) to prevent one cardiovascular event was above 50.

Conclusion Aspirin was ineffective or even harmful in the majority of patients. Age was positively related to treatment effect, whereas current smoking and baseline risk for cardiovascular events were not. When the NWT is 50 or lower, the aspirin treatment strategy that is associated with optimal net benefit in primary prevention of vascular events in women is to treat none.

Trial registration information: Clinicaltrials.gov identifier number: NCT00000479.

Keywords Aspirin • Primary prevention • Treatment effect prediction • Net benefit

Introduction

In primary prevention of cardiovascular disease, aspirin is of uncertain net value as the reduction in vascular events needs to be weighed against any increase in major bleeds.[1,2] Meta-analyses have shown that long-term aspirin treatment yields a 12% [95% confidence interval (CI) 6–18%] relative risk reduction in major cardiovascular events (i.e. myocardial infarction, stroke, or vascular death).[1,3] The average absolute risk reduction in ischaemic events in patients without a history of cardiovascular disease, however, was only 0.08% per year, corresponding with a 10-year number needed to treat (NNT) to prevent one ischaemic cardiovascular

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event of well over 100. In addition, aspirin use is associated with 0.01% increased yearly absolute risk for haemorrhagic stroke, 0.03% increased yearly absolute risk for major extracranial bleeds, and more frequent occurrence of minor bleeding complications, such as epistaxis, easy bruising, and haematuria.[1,3,4]

Although subgroup analyses so far have been unsuccessful in identifying patient characteristics that are associated with a higher than average treatment effect,[1] it is widely acknowledged that the aforementioned average absolute risk reductions may not apply to each individual patient. Heterogeneity of treatment effect may be overlooked by conventional subgroup analyses, because the effect of treatment is presented according to the presence or absence of one patient characteristic at the time (e.g. presence of diabetes, age below or above a certain limit, or gender), while treatment effect of the individual patient may rather be determined by multiple patient characteristics together.[5] Moreover, subgroup analyses still result in relative, rather than absolute, treatment effect estimates. Because in general, absolute treatment effect is larger in high-risk patients, primary prevention guidelines currently recommend considering aspirin treatment in patients whose 10-year risk for coronary heart disease (CHD) is $\geq$10%,[6,7] and in patients $\geq$65 years of age.[8] Yet, the precise point at which the benefits exceed the risks remains to be established.[2]

In this study, we aim to identify individual women who benefit from aspirin treatment using data from the Women's Health Study (WHS).[4] We develop methods for the prediction of 10-year absolute treatment effect for individual patients based on multiple patient characteristics. Moreover, we show how predicted reduction in vascular events can be weighed against treatment harm and calculate the net benefit of the following treatment strategies: (i) treat no one, (ii) treat everyone, (iii) treatment according to the current guidelines (i.e. selective treatment of women $\geq$65 years of age or having $\geq$10% 10-year risk for CHD), and (iv) prediction-based treatment (i.e. selective treatment of patients whose predicted treatment effect exceeds a decision threshold).

Methods

The design, rationale, and outcomes of the WHS are described in detail elsewhere.[4,9] In brief, the WHS evaluated the effect of 100 mg of aspirin on alternate days when compared with placebo on the occurrence of major cardiovascular events (i.e. non-fatal myocardial infarction, non-fatal stroke, or death from cardiovascular causes) among 39 876 initially healthy women of 45 years of age or older. After a mean follow-up of 10.1 years (range 8.2–10.9), the hazard ratio for occurrence of the primary endpoint was 0.91 (95% CI 0.80–1.03), favouring aspirin treatment.[4] Importantly, aspirin treatment was associated with increased risk for gastrointestinal bleeding (RR 1.22, 95% CI 1.10–1.34), peptic ulcer (RR 1.32, 95% CI 1.16–1.50), haematuria (RR 1.06, 95% CI 1.01–1.12), easy bruising (RR 1.40, 95% CI 1.37–1.45), and epistaxis (RR 1.16, 95% CI 1.11–1.22).

Women eligible for the current analysis were those who provided an adequate baseline plasma sample ($n = 27\,939$). Covariate data were missing on 1% or less of participants and were reduced using single imputation methods, since complete case analysis leads to loss of statistical power and possibly to bias (Online Supplementary 1).[10]

Prediction of treatment effect for individual patients

To identify individual women who benefit from aspirin treatment, three models for prediction of 10-year absolute treatment effect were developed using previously described methods (*Box 1*).[5] The first two models are based on the assumption that the absolute treatment effect is larger in patients at high baseline risk for the outcome. Average baseline risk for major cardiovascular events of each individual participant was estimated using existing risk scores, i.e. the Framingham risk score (FRS)[11] and the Reynolds risk score (RRS).[12] The FRS and RRS were recalibrated to optimize prediction of major cardiovascular event risk by adjusting the mean survival and mean linear predictor to the study population, but not the model coefficients. On-treatment and off-treatment risks for major cardiovascular events of each individual participant were estimated by multiplying the individual's average refitted FRS and refitted RRS by 0.953 and 1.047, respectively, so that the mean survival reflected that in the cohort, and the ratio between on-treatment and off-treatment risks was equal to the overall hazard ratio between the aspirin-treated group and the control group (HR 0.91, 95% CI 0.80–1.03). Subsequently, the predicted 10-year absolute treatment effect (i.e. the absolute risk reduction achieved by aspirin treatment during 10 years) was defined as the difference between on-treatment and off-treatment risks of each individual patient.

Alternatively, a new prediction model for estimating aspirin treatment effect was developed based on the WHS trial data (*Box 1*, Online Supplementary 1). A theoretical advantage of this model over the first two models is that it is not based on the assumption that treatment effect increases linearly with baseline risk: modification of the treatment effect by patient characteristics was tested and, if significant, included in the model. A theoretical disadvantage of this model is potential over-fitting, limiting its value in clinical practice. Hence, we refer to this conceptual prediction model as the 'optimal fit' model. The effect of aspirin treatment was embedded in this 'optimal fit' model as one of the explanatory variables. The on-treatment and off-treatment risks for major cardiovascular events for each individual patient were predicted, setting the '*aspirin*' term in the model to 'TRUE' and 'FALSE', respectively. Again, the predicted 10-year absolute treatment effect was defined as the difference between on-treatment and off-treatment risks for each individual patient.

Calibration of the predictions based on the refitted FRS, the refitted RRS, and the 'optimal fit' model was assessed by plotting the observed Kaplan–Meier 10-year survival for major cardiovascular events within deciles of the predicted survival against the mean predicted 10-year survival of each decile and by the Hosmer–Lemeshow test *P*-value. Discrimination was assessed by calculation of the c-statistic.

Net benefit assessment

The net benefit of the aspirin use for prevention of major cardiovascular events in women without a history of vascular disease was determined using the net benefit assessment method described by Vickers *et al.*[13] This method enables weighing treatment benefit against treatment harm and can be used to compare the potential impact of different treatment strategies, based on the observed event rates and treatment rates in study participants. The following treatment strategies were considered: (i) treat no one, (ii) treat everyone, (iii) treatment according to the current guidelines (i.e. selective treatment of women $\geq$65 years of age or having $\geq$10% 10-year risk for CHD), and (iv) prediction-based treatment (i.e. selective treatment of patients whose predicted absolute treatment effect exceeds a

decision threshold). A detailed explanation of the net benefit assessment method, including a calculation example, is provided in Online Supplementary 2.

Box 1 Three methods for prediction of aspirin treatment effect for individual patients

Predicted 10-year absolute treatment effect = Off-treatment risk − On-treatment risk

Off-treatment absolute 10-year risk for major cardiovascular events (%):

(1) 1.047 × refitted Framingham Risk Score estimate.†
Based on the Framingham Risk Score as published in the ATP-III guidelines.[11]

(2) 1.047 × refitted Reynolds Risk Score estimate.†
Based on the Reynolds Risk Score as derived from the WHS.[12]

(3) 'Optimal fit' model risk estimate, when *aspirin* treatment is set to FALSE.

On-treatment absolute 10-year risk for major cardiovascular events (%):

(1) 0.953 × refitted Framingham Risk Score estimate.†
Based on the Framingham Risk Score as published in the ATP-III guidelines.[11]

(2) 0.953 × refitted Reynolds Risk Score estimate.†
Based on the Reynolds Risk Score as derived from the WHS.[12]

(3) 'Optimal fit' model risk estimate, when *aspirin* treatment is set to TRUE.

'Optimal fit'-model: ‡

$[1-0.9865445^{\exp[B]}] \times 100\%$, where:

$B = 0.0941 \times$ age in years $- 0.0166 \times$ age in years [if using *aspirin*] $+ 0.8334$ [if current smoker] $+ 0.3310$ [if current smoker and using *aspirin*] $+ 3.0856 \times$ log(systolic blood pressure in mmHg) $+ 0.7960 \times$ natural logarithm (total cholesterol in mmol/L $\times$ 0.02586) $- 0.8501 \times$ natural logarithm (HDL cholesterol in mmol/L $\times$ 0.02586) $+ 0.0341 \times$ natural logarithm (high-sensitivity C-reactive protein in mg/dL) $+ 0.1601 \times$ natural logarithm (high-sensitivity C-reactive protein in mg/dL) [if using *aspirin*] $+ 0.2794$ [if using blood pressure lowering medication] $+ 0.2545$ [if positive family history for premature myocardial infarction] $+ 0.1709 \times$ haemoglobin A_{1c} in % [if diabetic] $+ 1.2530$ [if using *aspirin*] $- 0.0219 \times$ body mass index in kg/m^2 [if using *aspirin*] $- 21.06314$.

† The refitted risk scores estimate mean 10-year risk for major cardiovascular events for women with and without aspirin treatment. The ratio between the multipliers (1.047 and 0.953) is equal to the overall hazard ratio for the occurrence of major cardiovascular events in the aspirin-treated group vs. the control group [i.e. the relative treatment effect; HR 0.91 (95% CI 0.80–1.03)].

‡ Aspirin treatment effect is expressed in the 'Optimal fit' model as coefficients for aspirin treatment and for interaction terms between aspirin and age, smoking, high-sensitivity C-reactive protein, and body mass index.

See Online Supplementary 1 for further detail.

The calculation of net benefit is in part based on assumptions about the severity of treatment harm. Harms associated with aspirin treatment include excess risk for adverse reactions (i.e. major and minor bleeding events), monetary costs, and discomfort of sustaining treatment. The severity of treatment harm could be expressed as the maximum acceptable NNT to prevent one major cardiovascular event. For example, if the severity of a major cardiovascular event is assumed to be 50 times worse than the harms of aspirin treatment for 10 years, the maximum acceptable NNT is 50. The NNT that is associated with clinical equipoise is referred to as the number willing to treat (NWT).[5] A large NWT indicates that small treatment gain is already sufficient to outweigh treatment harm, whereas a small NWT indicates the need for larger gain before initiating treatment. Notably, the appropriate NWT is subjective and may differ between countries, between patients, between doctors, and over time. For this reason, we refrained from making any assumptions about the severity of treatment harm, but calculated the net benefit for every value of NWT between 30 and 250. To facilitate choosing the appropriate NWT level, we calculated the number of treatment-induced incident cases of gastrointestinal bleeding/peptic ulceration, haematuria, epistaxis, and easy bruising that are associated with aspirin treatment of, in example, 30, 50, and 100 women <65 years and ≥ 65 years of age during 10 years. Calculations were based on the difference in observed survival (Kaplan–Meier estimates) between the aspirin- and placebo-treated groups. Aspirin has also been associated with increased risk for iron deficiency anaemia, but this was not recorded in the WHS.[14]

Prediction-based treatment is defined as selective treatment of patients whose predicted treatment effect exceeds a certain decision threshold.[13,15] Notably, this decision threshold is inversely related to the NWT. For example, when the NWT is 50, this means that patients whose predicted treatment effect exceeds 2% (1 divided by 50) absolute risk reduction for major cardiovascular events are supposed to benefit from treatment. Thus, for NWT equal to 50, the decision threshold was set to 2% predicted absolute treatment effect. The net benefit results were presented graphically in a decision curve after locally weighted scatter plot smoothing (LOWESS).[13,15]

Analyses were conducted using open source statistical software, R version 2.13.0 (R Foundation for Statistical Computing, http://www.R-project.org), including the add-on package Design.

Results

The baseline characteristics of the WHS participants are shown in *Table 1*. On average, women were at low baseline risk for cardiovascular disease, because the mean 10-year risk for cardiovascular events was 2.9%. However, high-risk groups such as women ≥ 65 years of age ($n = 2968$), women with diabetes mellitus ($n = 687$), and women having $\geq 10\%$ 10-year risk for CHD ($n = 1068$) were also represented. In the aspirin-treated group (13 976 women), 312 major cardiovascular events were observed, while in the placebo-treated group (13 963 women), 340 major cardiovascular events were observed. Similar to the RRS, the final 'optimal fit' model contains coefficients for age, current smoking, systolic blood pressure, total cholesterol, HDL cholesterol, high-sensitivity C-reactive protein, blood pressure lowering medication use, family history of premature myocardial infarction, and haemoglobin A_{1c} (for women with diabetes mellitus only). The treatment effect of aspirin is expressed in the 'optimal fit' model as coefficients for aspirin treatment and for interaction terms for aspirin treatment and age, smoking, hs-C-reactive protein, and body mass index (BMI), meaning that these patient characteristics determined variations in relative treatment effect. Discrimination of the refitted FRS (c-statistic 0.78, 95% CI 0.76–0.80), the refitted RRS (c-statistic

Table 1 Baseline characteristics of the total study population and of women having <2% vs. ≥2% predicted absolute treatment effect based on the 'optimal fit' model

Characteristic		Total study population, *n* = 27 939	<2% predicted ARR, *n* = 26 712	≥2% predicted ARR, *n* = 1227
Age (years)	Mean (SD)	54.7 (7)	54.0 (6)	69.4 (4)
	% >65	10.6	7.2	84.4
Ethnicity	% Caucasian	95.3	95.3	96.1
Current smoking	%	11.7	12.1	2.7
Family history of premature CHD	%	14.4	14.4	13.3
HDL cholesterol (mmol/L)	Mean (SD)	1.40 (0.39)	1.40 (0.39)	1.22 (0.34)
Total cholesterol (mmol/L)	Mean (SD)	5.5 (1.0)	5.5 (1.0)	5.9 (1.0)
Hs-C-reactive protein (mg/L)	Median (IQ range)	2.0 (0.8–4.4)	2.0 (0.8–4.4)	1.9 (0.9–3.6)
Systolic blood pressure (mmHg)	Mean (SD)	124 (14)	123 (13)	141 (14)
Blood pressure lowering medication use	%	13.4	11.9	45.1
Lipid lowering medication use	%	3.2	2.9	10.8
Diabetes mellitus	%	2.5	1.9	15.6
Body mass index (kg/m^2)	Mean (SD)	25.9 (5)	25.8 (5)	28.0 (5)
Menopausal status	% post-menopausal	54.4	52.3	98.8
Hormone replacement therapy use	%	48.6	48.2	55.3
10-year risk for cardiovascular events (%)[a]	≤5.0%	84.8	88.3	8.7
	5.0–9.9%	10.0	8.6	41.3
	≥10.0%	5.2	3.1	50.0

CHD, coronary heart disease; HDL cholesterol, high-density lipoprotein cholesterol.
[a]Based on the Reynolds Risk Score.[12]

0.79, 95% CI 0.77–0.81), and the 'optimal fit' model (c-statistic 0.80, 95% CI 0.78–0.81) was generally good. As shown in Online Supplementary 3, although all three calibration plots were well balanced, the refitted FRS slightly overestimated the risk in the two highest risk deciles, as evidenced by the Hosmer–Lemeshow statistic (*P*-value 0.02).

Identification of women who benefit from aspirin treatment

For each individual WHS participant, the 10-year absolute treatment effect was predicted using all three models. The predicted reduction in 10-year absolute risk for major cardiovascular events was ≤1% in 97.8% of the study subjects when based on the refitted FRS, in 97.0% when based on the refitted RRS, and in 90.0% when based on the newly developed model (*Figure 1*). Characteristics of 1227 women (4.4%) having ≥2% predicted absolute treatment effect based on the 'optimal fit' model are shown in *Table 1*. Most strikingly, these women were older, rarely current smokers, and more often had a history of diabetes mellitus. Notably, almost all women younger than 65 years of age (99.2%) had ≤2% predicted absolute treatment effect. Of the women >65 years old, only 35% had a ≥2% predicted absolute treatment effect. Women having ≥2% predicted absolute treatment effect based on the 'optimal fit' model were on average at higher risk for cardiovascular events (mean 12.3% absolute 10-year risk) compared with the total WHS population (mean 2.9% absolute 10-year risk). Still, 50.0% was at low risk (<10% absolute 10-year risk).

Net benefit of aspirin treatment

A net benefit calculation example is provided in Online Supplementary 2. The net benefit of treating no one serves as a reference and is equal to zero. The net benefit of the other strategies represents the change (usually decrease) in the event rate minus the harm of treatment which would have been achieved if that aspirin treatment strategy was actualized instead of treating no one. In the example (Online Supplementary 2), we arbitrarily set the appropriate 10-year NWT at 50 and we calculated the net benefit of treating everyone, and the net benefit of prediction-based treatment using the 'optimal fit' model. Similar calculations were performed for every other NWT value between 30 and 250 and for the other proposed treatment strategies (i.e. treatment according to current guidelines and prediction-based treatment using the refitted FRS and refitted RRS) as well.

The net benefit assessment results are presented in decision curves (*Figure 2*). As expected, aspirin treatment of all patients yields negative net benefit unless the NWT to prevent one major cardiovascular event in 10 years is unrealistically large (i.e. much higher than 250; *Figure 2A*). This means that treating everyone does not improve clinical outcome compared with treating no one, regardless of how the harms of treatment are rated. Noteworthy, selective treatment of women having ≥10% 10-year risk for CHD, as is advocated by most guidelines, was not associated with net benefit for any value of NWT either (*Figure 2B*). Selective treatment of women ≥65 years of age, as recommended in the most recent AHA guideline, is associated with positive net

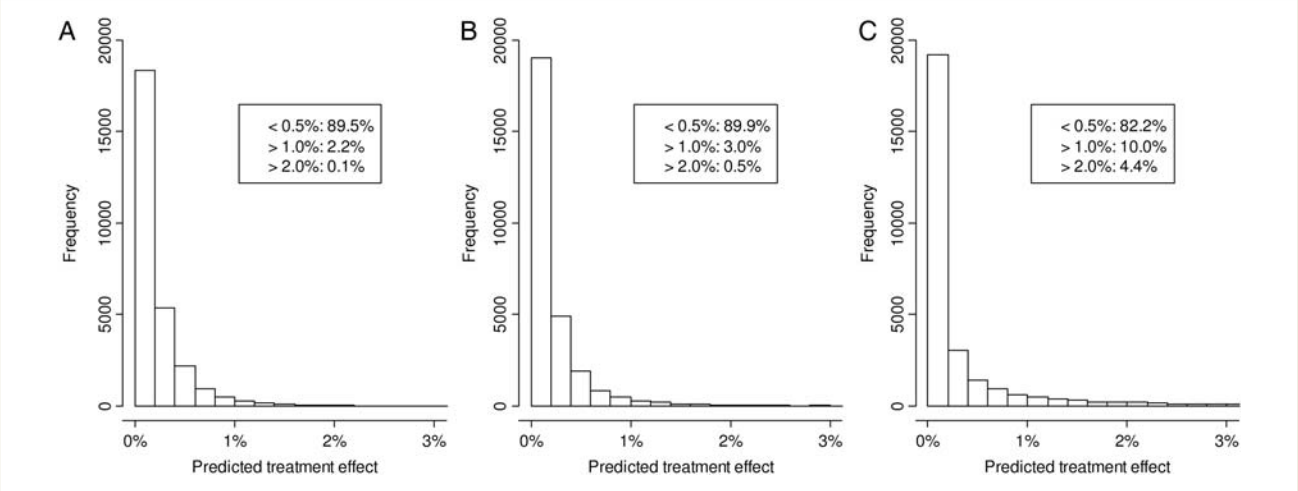

Figure 1 Distribution of predicted absolute 10-year treatment effect for participants of the Women's Health Study. Treatment effect is expressed as predicted 10-year absolute risk reduction in major cardiovascular events. (*A*) Predictions based on the Refitted Framingham Risk Score method. (*B*) Predictions based on the Refitted Reynolds Risk Score method. (*C*) Predictions based on the 'Optimal Fit'-model method.

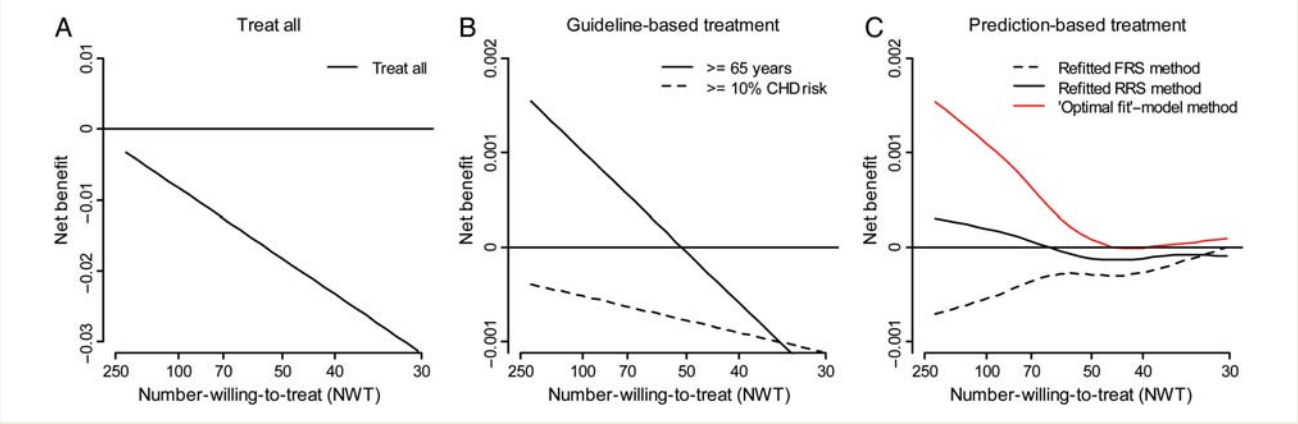

Figure 2 Decision curves. The net benefit of treating no one serves as a reference and is equal to zero. Positive net benefit means that the treatment strategy concerned led to a more favourable trade-off between benefits (observed decrease in event rate) and harms (represented by the corresponding number-willing-to-treat; NWT). (*A*) Aspirin treatment of all women results in negative net benefit for every value of NWT between 30 and 250. (*B*) Selective treatment of women having >10% 10-year risk for CHD does not result in positive net benefit either. Selective treatment of women ≥65 years of age is associated with positive net benefit if the NWT is >50, but not if the NWT is <50. (*C*) Prediction-based treatment using the 'optimal fit'-model method was associated with more net benefit compared with using the refitted FRS and the refitted RRS method for every value of NWT between 30 and 250.

benefit if the NWT is >50, but not if the NWT is ≤50. This means that selective treatment of women ≥65 years of age may improve clinical outcome, but only if the severity of one major cardiovascular event is thought to outweigh the total harms associated with aspirin treatment of 50 women ≥65 years of age during 10 years.

Treatment harm associated with treatment of 30, 50, and 100 women ≥65 years and <65 years of age during 10 years is summarized in *Table 2*. Harm of aspirin treatment of 50 women ≥65 years of age during 10 years comprises 1.1 incident cases of gastrointestinal bleeding/peptic ulceration, 1.6 incident cases of haematuria, 2.2 incident cases of epistaxis, 3.9 incident cases of easy bruising, and, not unimportantly, 500 person-years inconvenience of adhering to daily medication. When the total burden of these adverse treatment effects is considered to be equal to or lower than the disease burden of one cardiovascular event, the 10-year NWT of women ≥65 years of age is ≥50. Otherwise, the 10-year NWT of women ≥65 years of age is <50. Notably, the risk for haemorrhagic stroke, the most severe complication of aspirin treatment, is already incorporated in the main effect

Table 2 Relationship between the number-willing-to-treat (NWT) and treatment harm

	NWT 30		NWT 50		NWT 100	
	<65 years	≥65 years	<65 years	≥65 years	<65 years	≥65 years
Treatment-induced GI-bleeds/peptic ulcers	0.2	0.7	0.4	1.1	0.7	2.2
Treatment-induced haematuria	0.2	0.9	0.3	1.6	0.6	3.2
Treatment-induced epistaxis	0.7	1.3	1.1	2.2	2.2	4.4
Treatment-induced easy bruising	3.4	2.3	5.7	3.9	11.5	7.7

Number of extra incident adverse events caused by treatment of 30, 50, and 100 women (<65 years or ≥65 years) with 100 mg aspirin on alternate days during 10 years.

measure (i.e. major cardiovascular events) and does not need to be taken into account separately.

Finally, *Figure 2C* shows the net benefit of prediction-based treatment (i.e. selective treatment of patients whose predicted absolute treatment effect exceeds a certain decision threshold). Prediction-based treatment using the 'optimal fit'-model method resulted in positive net benefit if the NWT was higher than approximately 50. Prediction-based treatment using the refitted FRS method and the refitted RRS method, however, resulted in negative or less positive net benefit for all NWT values. Taken together, *Figure 2B* and *C* shows that absolute aspirin treatment effect does not increase linearly with baseline risk for major cardiovascular events, but rather is dependent on individual patient characteristics, most importantly age (*Table 1*).

Discussion

In this *post hoc* analysis of the WHS, clinical trial data were used to demonstrate which individual women might benefit from aspirin treatment for primary prevention of vascular events. Absolute treatment effect for individual subjects was predicted based on existing risk scores (i.e. FRS and RRS), and on a newly developed prediction model, showing that aspirin treatment during 10 years results in less than 1% absolute risk reduction in the majority of patients (>90% of study participants). Age was the strongest determinant of treatment effect as women having ≥2% predicted absolute treatment effect were much older on average (mean 69.4 years vs. 54.7 years in the total study population) and almost all women younger than 65 years of age (99.2%) had ≤2% predicted absolute treatment effect.

The net benefit of prediction-based treatment (i.e. selective treatment of patients whose predicted treatment effect exceeds a decision threshold) was calculated on the basis of the observed event rates and treatment rates in study participants, and compared with the net benefit of treating no one, treating everyone, and with guideline-based treatment (i.e. selective treatment of women ≥65 years of age or women having ≥10% 10-year risk for CHD). Selective treatment of women on the basis of baseline 10-year risk for CHD or predicted absolute treatment effect by the refitted FRS or refitted RRS did not result in positive net benefit compared with treating no one. Using baseline risk for cardiovascular events for identification of women who benefit from aspirin was, thus, not successful. Although the FRS was developed at a time when the use of now widely available medication (e.g. statins) was scarce, potential misclassification of baseline risk was avoided by recalibrating the mean survival and mean linear predictor to the study population. A more plausible explanation for these observations is that current smoking, a characteristic that is associated with considerably higher baseline risk for cardiovascular events, was associated with lower aspirin treatment effect in this study (*Box 1*, *Table 1*). Importantly, meta-analyses of aspirin trials in the primary prevention setting have also failed to demonstrate the effectiveness of aspirin treatment in current smokers and patients at high risk for CHD.[1] In contrast, selective treatment of women ≥65 years old and selective treatment on the basis of predicted absolute treatment effect by the 'optimal fit' model resulted in more net benefit than treating no one, provided that the 10-year NWT was above 50.

Although paucity of evidence for the effectiveness of aspirin for primary prevention of cardiovascular disease is well recognized, the American Heart Association (AHA) and European Society of Cardiology (ESC) currently recommend that aspirin treatment could be considered in patients whose 10-year risk for CHD is ≥10%.[6,7] In addition, the most recent guideline of the AHA is appended with the statement that aspirin can be useful in women ≥65 years of age.[8] Because older age is also associated with higher risk for adverse bleeding events, the United States Preventive Services Task Force recommends to take both age and 10-year risk for CHD into account when taking aspirin treatment decisions.[16] Yet, the indications for aspirin in these guidelines are under discussion.[14] Also, the United States Food and Drug Administration (FDA) have not yet approved the use of aspirin for primary prevention of cardiovascular events.

The current study, being an ultimate attempt to identify individual patients that benefit from aspirin treatment in primary prevention, confirms that the place for aspirin in primary prevention in women is limited. Despite higher effectiveness in women ≥65 years of age, the 10-year NWT still needs to be well above 50 for the benefits to outweigh the harm of treatment. Several trials evaluating the effects of aspirin in primary prevention are still ongoing. The results of the ARRIVE trial, a randomized controlled trial comparing aspirin 100 mg daily vs. placebo in patients at moderate risk of developing cardiovascular disease (approximately 10–20% 10-year CHD risk), are expected in 2014. The effectiveness of aspirin in patients ≥65 years of age, which was also suggested by *post hoc* analyses of the Physician's Health

Study,[17] is currently being evaluated by two other ongoing randomized trials (i.e. the JPPP and ASPREE).

Limitations

The main limitation of this study is that it is a *post hoc* analysis. Yet, the risk of chance findings was minimized by using existing risk scores and pre-specified candidate covariates for the prediction of absolute treatment effect. Moreover, chance findings usually lead to false positive results, whereas this study mainly shows lack of effect. Secondly, trial participants are usually at much lower risk than the general population, even given the same Framingham risk, which could have resulted in underestimation of the absolute risk reduction that can be achieved by aspirin treatment. Treatment adherence, however, is usually more optimal in a trial setting, meaning that the absolute aspirin treatment effect in the general population could also be lower. Thirdly, although it has been suggested that aspirin may change the presentation of vascular events rather than prevent them,[14] we expressed the treatment effect as the reduction in absolute risk for major cardiovascular events, which was the predefined primary endpoint of the WHS. Effect estimates were mainly driven by a reduction in non-fatal strokes, whereas overall no significant differences in the occurrence of myocardial infarction and death from cardiovascular causes were observed.[4] Finally, it should be stressed that the findings in this study apply to women only. Although the overall effect of aspirin for prevention of major cardiovascular events is similar in both sexes, aspirin was shown to prevent coronary events rather than ischaemic strokes in men.[1,3] Due to this inconsistency, we cannot automatically assume study results in women to apply to men also.

Conclusions

Individual patient characteristics predict absolute treatment effect of aspirin in primary prevention of vascular events in women. Absolute treatment effect from aspirin is most importantly determined by age and not by baseline risk for major cardiovascular events. Aspirin was ineffective or even harmful in the majority of study participants. When the NWT to prevent one major cardiovascular event in 10 years is 50 or lower, the aspirin treatment strategy that is associated with optimal net benefit in primary prevention of vascular events in women is to treat none.

Contributions of the authors

J.A.N.D.: conception of the research question, design, and execution of data analyses, interpretation of the results, drafting of the manuscript. F.L.J.V.: conception of the research question, design of data analyses, interpretation of the results, revision of the manuscript for important intellectual content. P.M.R.: conception of the research question, collection of the data, design of data analyses, interpretation of the results, revision of the manuscript for important intellectual content. N.P.P.: conception of the research question, design of data analyses, interpretation of the results, revision of the manuscript for important intellectual content. A.M.J.W.: conception of the research question, design of data analyses, interpretation of the results, revision of the manuscript for important intellectual content. J.E.B.: conception of the research question, collection of the data, interpretation of the results, revision of the manuscript for important intellectual content. Y.G.: conception of the research question, design of data analyses, interpretation of the results, revision of the manuscript for important intellectual content. N.R.C.: conception of the research question, collection of the data, design of data analyses, interpretation of the results, revision of the manuscript for important intellectual content.

Details of ethical approval

Written informed consent was obtained from all participants. The trial was approved by the institutional review board of Brigham and Women's Hospital, Boston, and was monitored by an external data and safety monitoring board.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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