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Aspirin in primary cardiovascular prevention: the two faces of the coin and the importance of the Number Needed to Treat: a systematic review and meta-analysis.

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Keywords: aspirin; cardiovascular disease; primary prevention; bleeding risk; number needed to treat.

Abstract. Aspirin has been an essential treatment for the primary prevention of cardiovascular diseases (CVD). Several randomized controlled studies do not support the routine use of aspirin, mainly due to its association with bleeding risk. This systematic review aims to advocate aspirin prescription based on the Number Needed to Treat (NNT) and the Number Needed to Harm (NNH). This combination provides a good measure of the effort to avoid an unfavorable outcome, weighed against possible associated risks. A search of randomized studies on aspirin treatment was conducted in two separate periods. Four studies from 1988-1998 and six from 2001-2018 were included in the analysis (157,060 participants). The primary endpoint was a composite outcome of Non-fatal Myocardial Infarction (NFMI), Non-fatal Ischemic Stroke (NFIS), and CV mortality. Major bleeding was a safety endpoint. We calculated the Absolute Risk Reduction (ARR%), NNT, and NNH, alongside the Relative Risk (RR) and 95% CI of each primary endpoint. The results of all included studies (10) showed a net benefit with aspirin treatment for NFMI (NNT= 259) and the composite outcome (NNT=292) with a significant relative risk reduction of 20% ($p=0.003$; $I^2= 0\%$) and 10% ($p<0.001$; $I^2= 0\%$), respectively. There was a relevant 60% increase in the bleeding risk ($p<0.0001$, NNH=208; $I^2= 3\%$). The NNT and NNH may constitute measures of efficacy and risk in clinical shared decision-making. However, it is essential to consistently establish that patients' benefit-risk should be individualized and not represent a clinical guide for everyone.

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Aspirina en prevención cardiovascular primaria. Las dos caras de la moneda y la importancia del número necesario a tratar. Revisión sistemática y metanálisis.

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Palabras clave: aspirina; enfermedad cardiovascular; prevención primaria; riesgo hemorrágico; número necesario a tratar.

Resumen. La aspirina ha sido un tratamiento esencial para la prevención primaria de las enfermedades cardiovasculares (ECV). Varios estudios controlados aleatorizados no apoyan el uso rutinario de la aspirina principalmente debido a su asociación con el riesgo de sangrado. Esta revisión sistemática tiene como objetivo evaluar la prescripción de aspirina basada en el Número Necesario para Tratar (NNT) y el Número Necesario para Dañar (NNH). Esta combinación proporciona una buena medida del esfuerzo para evitar un resultado desfavorable, sopesado frente a los posibles riesgos asociados. Se realizó una búsqueda de estudios aleatorios sobre el tratamiento con aspirina en dos períodos separados. En el análisis se incluyeron cuatro estudios de 1988 a 1998 y seis de 2001 a 2018 (157 060 participantes). El criterio principal de valoración fue un resultado compuesto de infarto de miocardio no mortal (NFMI), accidente cerebrovascular isquémico no mortal (NFIS) y mortalidad cardiovascular. La hemorragia mayor fue el punto final de seguridad. Se calculó la reducción del riesgo absoluto (RAR), el NNT y el NNH, junto con el riesgo relativo (RR) y el IC del 95% de cada criterio principal de valoración. Los resultados de todos los estudios incluidos (10) mostraron un beneficio neto con el tratamiento con aspirina para NFMI (NNT= 383) y el resultado compuesto (NNT=445) con una reducción significativa del riesgo relativo del 20% (p=0,003; I^2= 0%) y 10% (p<0,001; I^2= 0%), respectivamente. Hubo un incremento relevante del 60% en el riesgo de sangrado (p<0,0001, NNH=208; I^2= 3%). El NNT y el NNH pueden constituir medidas de eficacia y riesgo en la toma de decisiones clínicas compartidas. Sin embargo, es importante establecer consistentemente que el riesgo-beneficio de los pacientes debe ser individualizado, y no una guía clínica para todos.

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INTRODUCTION

More than 30 years have passed since the Physician´s Health Study was published. This painstaking work demonstrated a 44% risk reduction of myocardial infarction (MI) with aspirin (RR: 0.56; 95 %CI, 0.45 to 0.70; p<0.0001) [1]. This effect was more pronounced in the group of individuals older than 50 years, while the presence of ulcer and transfusion demand as secondary events were not significant compared with the placebo group (RR: 1.22; 95%CI,0.98 to 1.53; p = 0.08 for ulcer). The conclusion of this work was a recommendation for the use of aspirin in the primary prevention of a first MI in healthy individuals. However, the US Food and Drug Administration (FDA) did not approve the professional labeling of aspirin for the prevention of MI because another

similar trial, The British Doctor´s Trial, did not show benefit from aspirin administration for cardiovascular prevention [2]. In 2003, the use of aspirin was updated in the primary prevention of cardiovascular disease [3]. In addition to the two mentioned trials, three more trials were also analyzed: The Thrombosis Prevention Trial [4], The Hypertension Optimal Treatment Study [5], and The Primary Prevention Project [6], including 55.580 randomized participants (11.466 women). The studies mentioned above revealed a 32% reduction in the risk of a first MI and a 15% reduction in the risk of all important vascular events following aspirin´s treatment, demonstrating strong evidence of the use of aspirin in the primary prevention of MI. At that time, the US Preventive Services Task Force (USPTF) [7] and the American Heart Association recommended aspirin for men and women whose 10-year risk of a first coronary event was 10% or greater [8] since the benefits of a reduction of cardiovascular (CV) events outweighed the risks in most of the patients presenting this sort of cardiovascular risk.

Additionally, there are gender-specific differences in platelet function and response to aspirin [9,10]. Women under 65 years old without known CVD have a minor response to aspirin therapy in the primary prevention of coronary artery disease [11]; the dose recommended was 81-100 mg every other day [12].

The net benefits for persons who have started taking aspirin continue accumulating over time without a bleeding event. The net benefits, however, generally become progressively smaller with advancing age because of an increased risk for bleeding, and modeling data suggest that it may be reasonable to consider stopping aspirin use at around age 75 [13] for primary prevention. Despite this, there is a gap in understanding the benefits and risks of giving aspirin to patients at moderate risk of CVD. Aspirin has been a primary preventive drug for cardiovascular and cerebrovascular diseases for years. What has happened recently to change the concept and the prescription for the use of aspirin in the primary prevention of CVD? Today, the use of aspirin for primary prevention has been a subject of debate. Based on well-conducted studies, organizations such as the European Society of Cardiology, European Association for Cardiovascular Prevention & Rehabilitation, and the USPSTF, have delivered an almost uniform verdict that substantially changed the aspirin prescription for primary CV prevention [13,14].

The Number Needed to Treat (NNT), calculated as the reciprocal of the absolute risk reduction percentage, is a concise, clinically useful parameter that provides quantitative information on the efficacy of therapeutic interventions. Moreover, NNT allows clinicians to understand how much effort is needed to prevent a given event. The NNT and its opposite, the Number Needed to Harm (NNH), can be helpful in medical decision-making, then the use of NNT or NNH could be the likelihood of obtaining a benefit or harm [15]. This systematic review aims to study the effect of aspirin in the primary prevention of CVD, under the scope of fundamental trials that have been an essential guide in the prescription or not of aspirin throughout decades till nowadays. Based on this premise, we believe that using the NNT and NNH could guide physicians in deciding whether aspirin could be prescribed to prevent primary CV events.

METHODOLOGY

Search Strategy

The present review exclusively focuses on aspirin as a preventive drug for primary CVD treatment. The search was divided into two periods to differentiate the times when the aspirin prescription was relevant (from 1988 to 1999, Table 1a) to the one where aspirin was questioned for primary prevention (from 2000 to 2018, Table 1b). The later period has been considered the modern era of cardiovascular primary prevention [16].

Table 1a.
Features of randomized controlled studies on the aspirin primary prevention in cardiovascular diseases (1989-1999).

Study	Number of individuals/ follow-up (years)	Intervention design	Primary events	Secondary events	Outcomes in primary events	Outcomes in secondary events:
The British Doctor´s Trial (1988)[2]	5139 (3429 vs 1710) 6	Aspirin 500 mg/d/ vs no aspirin	NFMI:	Not specified	NFMI: 1.03 (0.71-1.49), p=0,96. Stroke: 1.377 (0.72-2.60), p=0.40	Not specified
Physician´s health study (PHS)(1989)[1]	22071 (11037 vs 11034)/ 5	Aspirin 325 mg/beta-carotene every other day vs placebo	NFMI, non-fatal stroke, and death for CVD	Ulcer, hemorrhage of any cause, and transfusion	For non-fatal MI: 0.56 (CI:0.45-0.70), p<0,0001. For Stroke: 1.22 (0.93-1.60), p=0.15. For CV Mortality: 0.96 (0.60-1.54), p=0.87	Hemorrhage of any cause: 2979 (27%) in aspirin group vs 2248 (20,3%) RR=1.32 (1.25-1.40). p<0,0001
The Thrombosis Prevention Trial (TPT) (1998)[4]	5085 (2545 vs 2540)/ 6	Aspirin 75 mg/d vs placebo	Ischemic Heart Disease: Coronary death, fatal and NFMI	Major, intermediate and minor hemorrhage	For NFMI: 0.69 (0.53-0.89), p<0,0049. For fatal MI: 1.13 (0.78- 1.63), p= 0,57. For coronary death: 0.81 (0.66-0.99), p<0,048	Hemorrhage of any cause: 1.24 (1.12-1.37), p<0.0001. Major bleeding: 1.52 (1.01-2.28), p<0.055. Intermediate: 2,00 (0.61-6.65),p=0.38
The Hypertension Optimal Treatment (HOT) Study(1998)[5]	18790 (9399 vs 9391)/ 4	Aspirin 75 mg/d vs placebo	Major CV events: fatal and NFMI, stroke, and other CV deaths	Major fatal, non-fatal hemorrhage, and minor hemorrhage	Major CV events, 0·85 (0·73–0·99), p<0.03. Fatal and NFMI: 0·64 (0·49–0·85) p<0,002. Stroke: 0·98 (0·78–1·24), p=0.88 CV death: 0·95 (0·75–1·20), p= 0.65	Any type of hemorrhage: 1.74 (1.44-2.09), p<0,0001. Major hemorrhage: 1.84 (1.38-2.46), p<0,0001

NFMI: Non-fatal Myocardial Infarction; CV: Cardiovascular; CVD: Cardiovascular disease.

Table 1b
Features of randomized controlled studies on the aspirin primary prevention in cardiovascular diseases (2001-2018).

Study	Number of individuals/ follow up (years)	Intervention design	Primary events	Secondary events	Outcomes in primary events :	Outcomes in secondary events:
The Primary Prevention Project (PPP) (2001)[6]	4495 (2226 vs 2269)/ 3.6	Aspirin 100 mg/ d/vitamin E vs no aspirin	CV Death, NFMI, and non-fatal stroke.	Major fatal /non-fatal hemorrhage	CV deaths: 0·56 (0·31–1.00), p=0.06. All MI: 0·69 (0·38–1·23), p=0,27. Stroke: 0·67 (0·36–1·27), p=0,29	Any type of hemorrhage: 4.07 (1.67-9.96), p<0,0015 Major hemorrhage: 1.74 (1.32-2.30), p<0,0001
The Primary Prevention of Cardiovascular Disease in Women (WHS) (2005) [19]	39876 (19934 vs 19942) 10	Aspirin 100mg every other day vs placebo Patients; >45 year old	NFMI, non-fatal stroke, or death from cardiovascular causes	GI bleeding requiring transfusion	Major CV events: (RR, 0.91; (0.80 to 1.03); p=0.13. Stroke: RR;0.83; (0.69-0.99); p=0.04). Fatal or NFMI: RR: 1.02; (0.84-1.25); p=0.83, or death from cardiovascular causes RR 0.95; (0.74-1.22); p=0.68)	Major bleeding: RR, 1.40; (1.07- 1.83); p=0.02
The Japanese Primary Prevention Project (JPPP) (2014)[20]	14 464 (7220 vs 7244)/ 6.5	Aspirin 100mg daily vs no aspirin	Composite primary outcome was death from CV causes (MI, stroke, and other CV causes), non-fatal stroke (ischemic or hemorrhagic, including undefined cerebrovascular events), and NFMI	Secondary outcomes included in divide endpoints.	Composite outcome: HR:0.94 (0.77-1.15); p= 0.54. NFMI: HR:0.53 (0.31-0.91), p= 0.02. TIA:HR: 0.57 (0.32-0.99);p =0.04	Extracranial (major) hemorrhage: HR:1.85 (1.22-2.81); p = 0.004).

Table 1b.
CONTINUACIÓN

Study	Number of individuals/ follow up (years)	Intervention design	Primary events	Secondary events	Outcomes in primary events :	Outcomes in secondary events:
The ASPREE Trial (2018)[21]	19114 (9525 vs 9589)/ 4.7	Aspirin 100mg daily vs placebo	Endpoints included major hemorrhage and cardiovascular disease (fatal coronary heart disease, NFMI, fatal or non-fatal stroke, or hospitalization for heart failure).	Major Hemorrhage as secondary endpoint	For CVD: HR: 0.95; (0.83-1.08), p=NS. Fatal, NFMI: HR:0.93 (0.76-1.15). Stroke: HR: 0.89 (0.71-1.11)	Major Hemorrhage: HR: 1.38; (1.18-1.62); p<0.001
The ARRIVE Trial (2018)[22]	12546 (6270 vs 6276)/ 5 years	Aspirin vs placebo Eligible patients were aged 55 years (men) or 60 years (women) and older and had an average cardiovascular risk	The primary efficacy endpoint was a composite outcome of cardiovascular death, MI, unstable angina, stroke, or TIA.	Safety endpoints were hemorrhagic events and incidence of other adverse events	HR:0·96; (0·81–1·13), p=0·6038).; NFMI: HR 0·90, (0·67–1·20); p=0·4562	
The ASCEND Trial (2018)[23]	15,480 (7740 vs 7740)/ 7.4	Aspirin 100mg vs placebo in diabetic patients	The primary efficacy outcome (MI., stroke or TIA, or death from any vascular cause, excluding any confirmed intracranial hemorrhage)	The primary safety outcome was the first major bleeding event	Serious vascular events: 0.88; (0.79-0.97), p=0.01. NFMI: 0.98 (0.80–1.19). Stroke: 0.88 (0.73–1.06)	Major bleeding events:1.29 (1.09 -1.52); p=0.003

NFMI: Non-Fatal Myocardial Infarction; CV: Cardiovascular; TIA: Transient ischemic attack; HR: Hazard ratio; RR: Relative risk.

The bibliography search was conducted in PUBMED by MEDLINE and Google Scholar under the following MESH (Medical Subject Headings) terminology: *aspirin in primary prevention, aspirin in myocardial infarction, aspirin in stroke, aspirin in cardiovascular death or mortality, aspirin in bleeding or hemorrhage; those terms were connected thru a Boolean "and" with randomized controlled trials* (Fig. 1). Additionally, the term *number needed to treat* was used for the complementary bibliography. The primary endpoint to report was a composite of non-fatal myocardial infarction (NFMI), non-fatal ischemic stroke (NFIS), and cardiovascular mortality (CVM). The primary bleeding outcome was major bleeding, as stated by the studies. The exclusion criteria were: a) studies with less than 4000 participants, b) systematic reviews on aspirin treatment because there are good reviews about it [16-18], c) a combination of antiplatelet or anticoagulants treatments with aspirin (The Thrombosis Prevention Trial assessed warfarin and aspirin alone and in combination but data for participants who received warfarin were excluded from the analysis), d) duplicate publications and e) those works that do not contain the composite as the endpoint.

Finally, four studies from 1988-1998 [1,2,4,5] and six studies from 2001-2018 [6,19-23] were included in the analysis (Tables 1a and 1b). This article has been assessed according to the PRISMA 2020 statement and checklist [24]. The bias risk in each study was assumed according to a systematic review published previously [16], following the Cochrane risk of bias assessment, and the Jadad scale was used to evaluate the quality of the randomized controlled studies (< 3: high risk of bias, ≥ 3: low risk of bias) [25]. Ethical approval was not required for conducting this study.

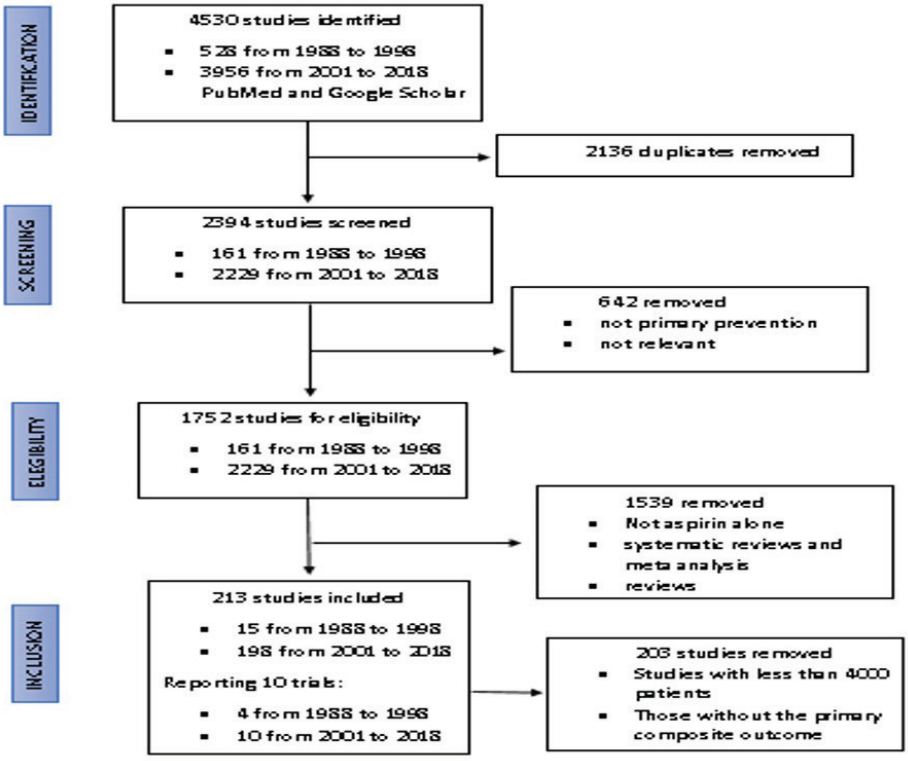

Fig. 1. Flow chart of literature search strategy according to the MESH terminology. Note: some data might be lost in the early stages of the search.

Statistical approach

NNT and NNH

NNT or NNH would be the number of patients to be treated to obtain one benefit or one harm in a predefined period [26]. The number needed to treat is simply the reciprocal of the absolute risk difference obtained from the percentage of events in the control group minus the percentage of events in the experimental group (also named as absolute difference). Depending on the treatment, when the difference in the two groups proportions is significant, the NNT is small, and vice versa. NNT is a concise, clinically helpful presentation of the effect of an intervention. The NNT and the NNH are calculated as the inverse of the absolute reduction (ARR) or absolute increment of the risk (ARI). A 95% CI for NNT can be constructed by simply inverting and exchanging the limits of a 95% CI from the ARR. When the result shows an ARR or ARI with 95% CI extended from negative to positive values, it means that the zero is included, and the NNT is infinity thus, we need to separate two intervals using via infinity (∞) and indicate that the treatment may be helpful or harmful [27].

As Altman has mentioned [27], the terms NNT and NNH may not be appropriate to denote benefit and harm. He proposes the abbreviations of NNTB (benefit) and NNTH (harm). However, we maintain the conventional abbreviations of NNH and NNT to refer to benefit or harm, respectively. We also constructed an arbitrary classification of the NNT or NNH effect as follow: Net benefit, Uncertain benefit (treatment could be harmful), Uncertain harm (treatment could be helpful), and net harm.

Because the included studies have different follow-up periods, we have to make assumptions about it and make a "time adjustment" because if we want to be able to compare these NNTs, it is necessary to adjust all of them to refer to the same tracking time. So it is necessary to uniform the time of these studies to obtain the same relative interpretation of the results regarding benefit and harm. For this purpose, we have to use the following formula:[28,29]

$$NNT_{(hypothetic)} \div Time_{(hypothetic)} = NNT_{(observed)} \div Time_{(observed)}$$

Rearranging the terms, we have;

$$NNT_{(hypothetic)} = NNT_{(observed)} \times [Time_{(hypothetic)} / Time_{(observed)}]$$

In the present study, we have adjusted five years as a hypothetical time for all the included studies to calculate NNT and NNH. We used a computer program for ARR, NNT, and NNH to obtain the data and their 95% CI (https://www.graphpad.com/quickcalcs/NNT1/). Additionally, as an effect measure, a Relative Risk and its 95% CI were estimated using the Comprehensive Meta-Analysis program (Biostat, Englewood, NJ) alongside the relative weight and random effect. As statistical parameters, the consistence for heterogeneity (I^2) was determined as low (<25%), moderate (25% to 75%,), and high (>75%) by testing the chi-square calculation of each meta-analysis (Cochrane Q) according to the Higgins formula[30]; and statistical significance was fixed as $p<0.05$.

The forest plot for meta-analysis of each primary effective endpoint and safety was constructed under NNT and NNH parameters, with all included studies performing a logarithmic scale with infinity value in the middle of the scale according to previous reference[30], the NNT 95%CI (benefit) values are shown to the left and NNH 95% CI (harm) values on the right with the overall estimate.

RESULTS

Table 2a shows the total results of the endpoints in the trials made in the last year of the 20th century (four trials with a total of 51,085 participants), with a net benefit for NFMI (NNT= 156) confirmed by a significant relative risk reduction of 31% [RR,95%CI: 0.69(0.61-0.79); p<0,0001; I^2= 10.5%].

Table 2a. Summarized results of the endpoints in the included studies, period 1988-1998 (n= 4).

ENDPOINTS	Aspirin events (%) n: 26410	No Aspirin events (%) n:24675	RR(95%CI), p value; I^2	ARR% (95%CI)	ARI% (95%CI)	NNT (95%CI)	NNH (95%CI)*	Observations
NFMI	385 (1.46)	518 (2.10)	0.69 (0.61-0.79) <0.0001; 10.5%	0.64 (0.41-0.87)		156 (115 - 244)		Net benefit of aspirin treatment
NFIS	338 (1.28)	300 (1.22)	1.02 (0.83-1.25) 0.87; 11.5%		0.06 (-0.13 to 0.26)		1667 (770 to ∞ to 390)	Uncertain harm (aspirin could be helpful)
CV Mortality	463 (1.75)	383 (1.55)	1.12 (0.99-1.30) 0.08 ; 0%		0.20 (-0.02 to 0.42)		500 (4986 to ∞ to 237)	Uncertain harm (aspirin could be helpful)
Composite Outcome	1186 (4.49)	1201 (4.87)	0.92 (0.85-0.99) 0.046; 0%	0.38 (0.01-0.74)		266 (135 - 10158)		Net benefit of aspirin treatment
Major bleeding	205 (0.78)	109 (0.44)	1.79 (1.42-2.26) <0.0001; 0%		0.33 (0.20 -0.47)		299 (213 - 500)	Net harm of aspirin treatment

The composite outcome shows an NNT of 266 and an 8% relative risk reduction [RR,95%CI: 0.92(0.85-0.99); p=0.046; I^2= 0%]. The major bleeding revealed a 79% increase in the relative risk [RR,95%CI; 1.79(1.42-2.26); p<0.0001; I^2= 0%, NNH=299;].

Table 2b points out the same elements of the previous table with 105,975 participants and six trials made in two decades of the 21st century. The result of the studies carried out showed a benefit with the treatment for NFIS (NNT= 553) with a 12% in relative risk reduction [RR,95%CI: 0.88 (0.80-0.98); p<0.01; I^2= 0%]. The composite outcome presented an NNT of 288 with a significant relative risk reduction of 9% [RR,95%CI: 0.91 (0.86-0.97); p<0.003; I^2= 0%], and for major bleeding, there was a 57% increase of the relative risk [RR,95%CI: 1.57 (1.30-1.91); p<0.0001; I^2= 0%, NNH= 175;].

The total of the results in the combined and separate primary endpoints of all studies are shown in Table 2c. From a total of 157,060 participants, there was a net benefit of 20% and 10% on the relative risk reduction for NFMI [RR= 0.80 (0.69 to 0.93); p=0.003; I^2= 0%; NNT= 259] and Composite outcome [RR= 0.90 (0.85 to 0.99); p<0.001; I^2= 0%; NNT= 292] respectively. Major bleeding presents a 60% increase in the relative risk [RR: 1.60 (1.38 to 1.85); p<0.0001; I^2= 3%; NNH= 208]. The rest of the endpoints showed an uncertain result because the aspirin treatment could be harmful or helpful compared with the control.

Forest plots of the meta-analysis of aspirin treatment in the total included studies are shown in terms of NNT (benefit) or NNH (harm) for each primary endpoint.

Table 2b. Summarized results of the endpoints in the included studies, period 2001-2018 (n= 6).

ENDPOINTS	Aspirin events (%) n: 52915	No Aspirin events (%) n: 53060	RR (95%CI) p value; I^2	ARR% (95%CI) r	ARI% (95%CI)	NNT (95%CI)	NNH (95%CI)	Observations
NFMI	669 (1.26)	718 (1.35)	0.93 (0.82-1.05) 0.21; 9.6%	0.09 (-0.05 to 0.23)		1112 (435 to ∞ to2086)		Uncertain benefit (aspirin could be harmful)
NFIS	721 (1.36)	819 (1.54)	0.88 (0.80-0.98) <0.01; 0%	0.18 (0.04 -0.33)		553 (303- 2500)		Net benefit of aspirin treatment
CV Mortality	508 (0.96)	551 (1.04)	0.92 (0.82-1.04) 0.20; 0%	0.08 (-0.04 to 0.20)		1250 (505 to ∞ to 2419)		Uncertain benefit (aspirin could be harmful)
Composite Outcome	1898 (3.59)	2088 (3.94)	0.91 (0.86- 0.97) 0.003; 0%	0.35 (0.12 - 0.58)		288 (174- 839)		Net benefit of aspirin treatment
Major bleeding	964 (1.82)	662 (1.25)	1.57 (1.30-1.91) <0.0001; 0%		0.57 (0.43 -0.72)		175 (139- 233)	Net harm of aspirin treatment

The overall estimate points out that concerning aspirin treatment revealed a net benefit for NFMI (Fig. 2a), an uncertain benefit for NFIS (Fig. 2b), and uncertain harm for CV mortality (Fig. 2c). As we expected, net harm was associated with major bleeding (Fig. 2d)

DISCUSSION

The light of the results of this systematic review, we argued that aspirin has an ambiguous place in the prescription for primary CV prevention. NFMI from studies of the 20th century and NFIS in this century showed a net benefit with the aspirin treatment. In some instances, the treatment could be harmful, given negative ARR 95% CI values. The composite outcome results also reported benefits in the two groups of studies. Globally there was a net benefit of aspirin treatment for NFMI and the composite outcome but also a significant bleeding risk. This study demonstrates that the absolute risk reduction for cardiovascular events and absolute risk increase for major bleeding associated with aspirin use were of similar magnitude. In terms of NNT and NNH, this represents notable data on the aspirin prescription despite some evidence that indicates the efficacy of aspirin could be uncertain in the NNT/NNH ratio since all of the studies and the combined results have shown a relevant bleeding risk. These findings have similarities with a recent meta-analysis [31]. A systematic review [32] revealed an ARR of 0.41% in the composite cardiovascular outcome with an NNT of 241 and an ARI of 0.47% for major bleeding risk, representing an NNH of 210. This confirmed a possible adverse effect of aspirin due to bleeding risk. Another systematic review [33] showed a reduction of 10% of MCE (major cardiovascular events) (0.90, 95% CI 0.85-0.96, p<0.001) with an

Table 2c
Summarized results of the endpoints in all included studies (n=10).

ENDPOINTS	Aspirin events (%) n: 79325 n:	No aspirin events% n:77735	RR (95%CI) p value; I^2	ARR% (95%CI)	ARI% (95%CI)	NNT (95%CI)	NNH (95%CI)	Observations
NFMI	954 (1.20)	1236 (1.59)	0.80 (0.69-0.93) 0.003; 0%	0.39 (0.27-0.50)		259 (199-369)		Net benefit of aspirin treatment
NFIS	1059 (1.34)	1119 (1.44)	0.93 (0.83-1.01) 0.09; 0%	0.10 (-0.01 to 0.22)		958 (454 to ∞ to 8910)		Uncertain benefit (aspirin could be harmful)
CV. Mortality	971 (1.22)	934 (1.20)	0.96 (0.88-1.05) 0.39; 0%	0.02 (-0.09 to 0.13)			4433 (1167 to ∞ to 765)	Uncertain harm (aspirin could be helpful)
Composite Outcome	3084 (3.89)	3289 (4.23)	0.90 (0.85-0.99) <0.001; 0%	0.34 (0.15-0.54)		292 (186-676)		Net benefit of aspirin treatment
Major bleeding	1169 (1.47)	771(1.00)	1.60 (1.38-1.85) <0.0001;3%		0.48 (0.37-0.59)	208 (269-170)		Net harm of aspirin treatment

NFMI: Non-fatal Myocardial Infarction, NFIS: Non-fatal Ischemic Stroke, CV: Cardiovascular, RR: Relative Risk, ARR: Absolute Risk Reduction, ARI: Absolute Risk Increase, NNT: Number Needed to Treat, NNH: Number Needed to Harm, CI: Confidence Interval. Note: In the present study, each individual study was adjusted to 5 years a hypothetical time to calculate NNT and NNH: NNT(hypothetic) = NNT(observed) X [Time(hypothetic) / Time (observed)].

When the result shows an ARR with 95%CI positive values means a net benefit (NNT); when the result shows an ARI with 95%CI means net harm (NNH). When the result shows an ARR or ARI with 95%CI extended from negative to positive values means that the zero is included thus we need to separate two intervals using via infinity (∞) and indicates that the treatment may be helpful or harmful [27].

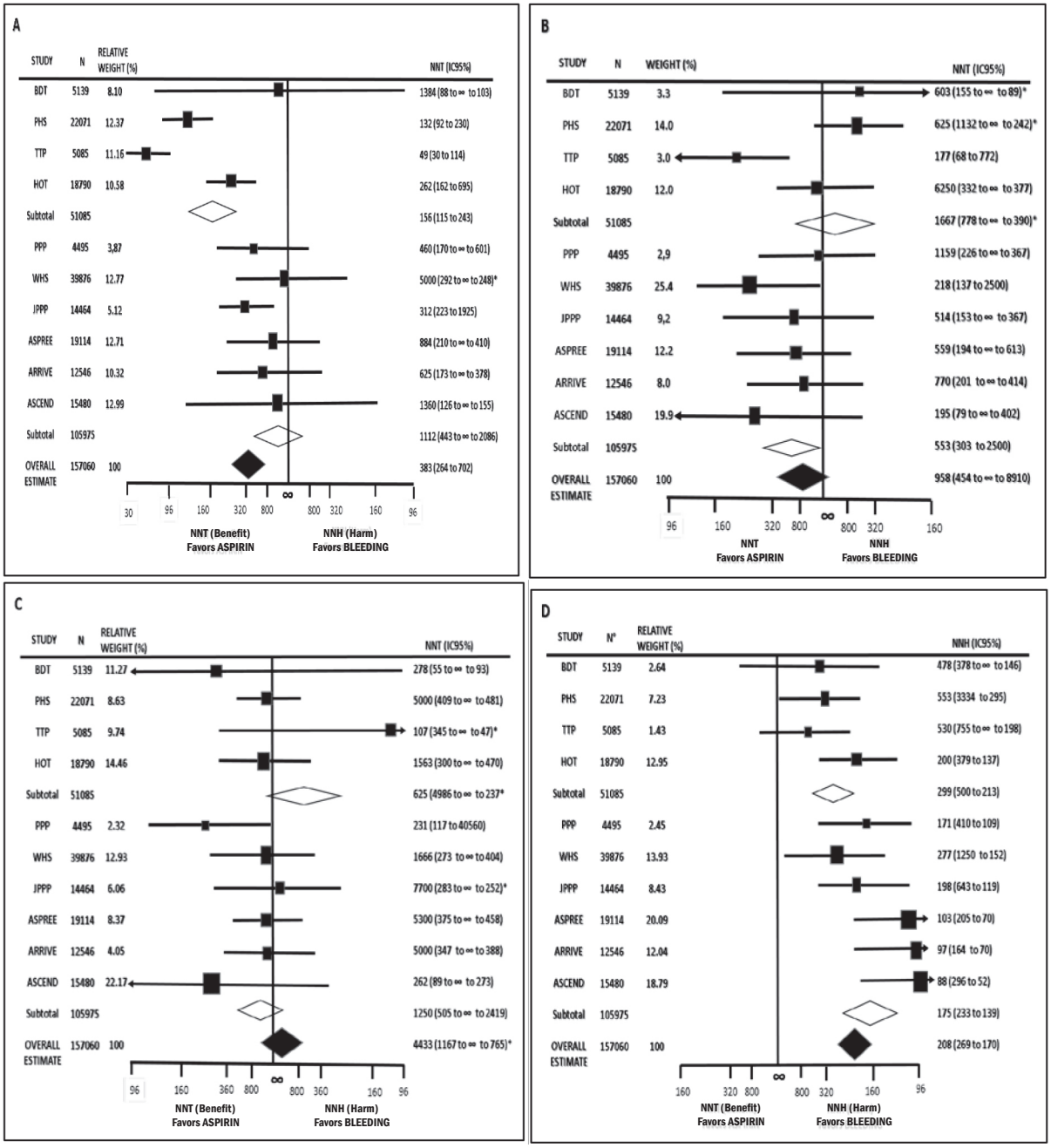

Fig. 2. Forest plot of meta-analysis of the included studies calculating from ARR95%CI as effect measure the NNT or NNH with their respective 95%CI. Non-fatal myocardial infarction (A), Non-fatal ischemic stroke (B), Cardiovascular mortality (C), and Major bleeding (D) as endpoints. *Denotes Absolute Risk Increase (ARI). When the ARR95%CI includes zero we need to separate two intervals using via infinity (∞) in the middle of the scale [27].

ARR of 0.39% (95%CI: 0.18-0.61), which correspond to NNT of 253 (95%CI: 163-568) to prevent one single MCE, and the NNH (major bleeding) was 306. These results are similar to our work, indicating potential harm in aspirin use due to increased bleeding risk. Abdelaziz *et al*. [34] showed in an illustration the NNT for MI (357), ischemic stroke (500), TIA (370), and MACE (263) with the NNH for major bleeding (222), hemorrhagic stroke (1000), and GI bleeding (385), based on pooled data from 15 randomized controlled trials. Therefore, it was deduced that bleeding risk is present when calculating the NNTs over NNH with major bleeding. These findings suggest that the decision to use aspirin for primary prevention should be tailored to the individual patient based on the estimated CV risk. Another approach to evaluate aspirin treatment in the primary prevention of CV events is to compare benefits (prevention of MI and stroke) and harms (major GI bleeds and hemorrhagic stroke) using relative weights in the assessment of systematic reviews of the NNT and NNH as the number of person-years with treatment need to prevent one adverse event [35]. This approach demonstrated a net benefit for aspirin; nevertheless, in the sensitivity analysis, aspirin was harmful due to greater relative weight for GI bleeds.

We tried to give a better scope of aspirin as a primary preventive treatment for CV events, but unfortunately, the controversy persists. To treat or not to treat with aspirin is the question, and this situation is under debate. To better understand this complex scenario, we follow the timing of the declarations of the USPSTF about the statements on aspirin prevention in CVD [7,36-38].

In this contemporary period, aspirin passed from being a good prescription for primary prevention of CVD at any age to a restriction for its use only in 40-59 years old individuals, with a strong recommendation against its use in older people. The last decision came from another six studies, whose results regarding the therapy with aspirin in primary prevention for CVD were unfavorable for its recommendation (Table 1b). Additionally, in an analysis of 17 RCT (164.862 participants) [39], aspirin did not show any significant reduction in all-cause mortality compared with placebo (RR:0.97;95%CI:0.93-1.01; p=0.13). However, when ≥ 65 years old patients were excluded, it significantly reduced all-cause mortality (RR 0.94; 95% CI 0.90–0.99; p = 0.01) in the aspirin group. These results concord with the age arguments recently expressed by the USPSTF. The European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice colleagues and other systematic reviews share the same opinion since its guidelines do not recommend aspirin for the primary prevention of CVD at all [14,40]. However, those agreements can lead to misinterpretation or confusion for patients in whom aspirin therapy may be essential: such as those on primary or secondary prevention with an established CV risk of more than 10% [41].

The only explanation for this change is attributed to the bleeding risk that increases with age. However, there is a debate about this new scenario, and doubts must be cleared. For example, should they stop taking aspirin for people who have been using aspirin for years and do not have evidence of bleeding? If yes, what could we probably expect? So we could expect an increase in CV events in this particular group unless there is an indication of another alternative surrogate for aspirin prescription.

A comment arises regarding the different conduct over time on aspirin prescription, during the last decades of the 20th century and then the change of opinion in the two decades of the 21st century. The first studies on aspirin and prevention of cardiovascular risk focused mainly on the significant relative reduction of the risk of myocardial infarction (44% PHS, 31% TPT, and 36% HOT, only the BDT showed a non-significant 3%). Perhaps this finding eluded the atten-

tion to the side effects of bleeding caused by the administration of aspirin, which was barely mentioned in those papers, but was not given its due importance, despite the relevant relative increase in the risk of major bleeding (71% PHS, 52% TPT, and 84% HOT). On the contrary, the trials that were performed in the two decades of the 21st century addressed with great interest the risk of bleeding with aspirin prescription in the prevention of CVD. For this reason, these papers highlighted the relevance of major hemorrhage as a contraindication to aspirin intake. They concluded that serious but no fatal bleeding [42] is frequent with aspirin administration compared with the benefit achieved in CV prevention. As a representative example, the myocardial infarction in terms of RRR (Relative Risk Reduction for efficacy) vs. major bleeding as RRI (Relative Risk Increase for safety) is shown as follows: PPP (31% vs. 74%), WHS (2% vs. 40%), JPPP (47% vs. 85%), ASPREE (7% vs. 38%), ASCEND (2% vs. 29%) and the ARRIVE (10% vs 110%), all of them favoring the bleeding risk. The different points of view above about aspirin treatment changed the opinion of doctors and their patients regarding the routine use of aspirin as a primary preventive drug in CV events.

Another point of view of this conflictive situation is that the prescription of aspirin is unnecessary in some instances because it is an over-a-counter (OTC) drug that can be freely purchased, and patients have been buying the drug without considering the potential bleeding risk [41].

Although there are relevant evidence and guidelines as instruments for shared decision-making to help clinicians in the use of aspirin in primary prevention [43-46] and the search for a benefit versus risk prediction tool, we propose the NNT and NNH as valuable measures in the balancing benefit-risk with aspirin in the therapy of the effective primary prevention of CV events. Knowing or estimating NNT and NNH for an individual patient's risk could be a guide for the overall or net value of a prophylactic intervention [47]. This combination provides a good measure of the effort in avoiding an unfavorable outcome, weighed against possible associated risks. The calculation of these measures is straightforward, and also its interpretation so that physicians could make an individual clinical decision based on the results of the interventions for CV primary prevention guided by the calculation of how many patients can be treated to avoid one adverse event, counterbalancing with the collateral side effects of the aspirin prescription. However, although the calculation of the NNT is simple, we need to consider the treatment time to ensure its correct interpretation [48]. An essential limitation of NNT and NNH is that these metrics are limited to dichotomous (rather than continuous) outcomes [16].

Limitations

The present study has several limitations: first, the dose of aspirin was different in the studies, oscillating between 75mg and 500mg with six trials using 100mg daily. Second, there were some difficulties in classifying endpoints (MI and Stroke are sometimes not defined as non-fatal, and several studies did not specify major bleeding as a safety endpoint). On the other hand, one crucial point that is missing is the evolution of the definition of non-fatal MI: in the "modern era", the use of troponin captures minor MIs which were previously missed by ECG and/or CPK only, and on the other hand, we did not include total mortality as an outcome, and this could probably be a significant cause of bias. Third, in the studies made in the 20th century, particularly bleeding events were poorly reported despite the apparent evidence. Fourth, the studies were not analyzed, separating participants from high and low cardiovascular risk. Fifth, The NNT and NNH were calculated in hypothetical results that were expressed as five years of tracking time as a standard

unit for all studies and their calculations, thus the results of this review need to be interpreted with prudence. Sixth, the forest plots for meta-analysis for NNT and NNH were constructed with a scale including infinity (∞) and quoting to separate in two confidence intervals when there were negative values.

CONCLUSION

Recent studies have demonstrated that aspirin should not be recommended in the primary prevention of CVD, although it has a place in the secondary prevention of CVD [17,45,49]. The use of aspirin in primary cardiovascular disease was associated with a lower risk of cardiovascular events and an increased risk of major bleeding. NNT as a measure of effect and NNH to determine harm could be helpful in clinical share decision-making. However, as the "two faces of the coin" (not determined by a coin flip), it is essential to establish consistently that the benefit-risk for patients should be individualized and not be a clinical practice guide for everyone.

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Author's contribution

GV was responsible for the study rationale, manuscript drafting, and statistical analysis. JWM performed the literature search and made the final review of the manuscript. All authors were involved in the conception and the design of the study and interpretation of the data, revised the manuscript critically for important intellectual content, and finally approved the manuscript submitted.

REFERENCES

1. **Steering Committee of the Physicians' Health Study Research Group**. Final report on the aspirin component of the ongoing Physicians' Health Study. N Engl J Med 1989;321(3):129-135. *doi: 10.1056/nejm198907203210301.*
2. **Peto R, Gray R, Collins R, Wheatley K, Hennekens C, Jamrozik K, Warlow C, Hafner B, Thompson E, Norton S, Gilliland J, Doll R.** Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed) 1988;296(6618):313-6. *doi:1136/bmj.296.6618.313.*
3. **Eidelman RS, Hebert PR, Weisman SM, Hennekens CH**. An update on aspirin in the primary prevention of cardiovascular disease. Arch Intern Med 2003;163(17):2006-10. *doi: 10.1001/archinte.163.17.2006.*
4. **The Medical Research Council's General Practice Research Framework**. **Thrombosis prevention trial**: a randomized trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischemic heart disease in men at increased risk Lancet 1998;351(9098):233-241. *https://doi.org/10.1016/S0140-6736(97)11475-1.*

5. **Hansson L, Zanchetti A, Carruthers SG, Dahlöf B, Elmfeldt D, Julius S, Ménard J, Rahn KH, Wedel H, Westerling S, for the HOT Study Group.** Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomized trial. Lancet 1998;351:1755-1762. *https://doi.org/10.1016/s0140-6736(98)04311-6.*
6. **Collaborative Group of the Primary Prevention Project**. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomized trial in general practice. Lancet 2001;357:89- 95. *https://doi.org/10.1016/S0140-6736(00)03539-X.*
7. **US Preventive Services Task Force**. Aspirin for the primary prevention of cardiovascular events: recommendation and rationale. Ann Intern Med 2002;136:157- 160. *doi: 10.7326/0003-4819-136-2-200201150-00015.*
8. **Pearson TA, Blair SN, Daniels SR, Eckel RH, Fair JM, Fortmann SP, Franklin BA, Goldstein LB, Greenland P, Grundy SM, Hong Y, Miller NH, Lauer RM, Ockene IS, Sacco RL, Sallis Jr JF, Smith Jr SC, Stone NJ, Taubert KA.** AHA Guidelines for Primary Prevention of Cardiovascular Disease and Stroke: 2002 Update: Consensus Panel Guide to Comprehensive Risk Reduction for Adult Patients Without Coronary or Other Atherosclerotic Vascular Diseases. American Heart Association Science Advisory and Coordinating Committee. Circulation 2002;106(3):388-391. *doi: 1161/01.cir.0000020190.45892.75.*
9. **Diez-Ewald M, Arocha F, Vizcaíno G**. Effect of low-dose of aspirin on platelet function from patients at risk of myocardial infarction (Spanish). Invest Clín 1984;25:125-137.
10. **Berger JS, Roncaglioni MC, Avanzini F, Pangrazzi I, Tognoni G, Brown DL**. Aspirin for the primary prevention of cardiovascular events in women and men: a sex-specific meta-analysis of randomized controlled trials. JAMA 2006;295:306–313. *doi: 10.1001/jama.295.3.306.*
11. **Zuern CS, Lindemann S, Gawaz M.** Platelet function and response to aspirin: gender-specific features and implications for female thrombotic risk and management. Semin Thromb Hemost 2009;35(3):295-306. *doi:10.1055/s-0029-1222608.*
12. **Mosca L, Benjamin EJ, Berra K, Bezanson JL, Dolor RJ, Lloyd-Jones DM, Newby LK, Piña IL, Roger VL, Shaw LJ, Zhao D, Beckie TM, Bushnell C, D'Armiento J, Kris-Etherton PM, Fang J, Ganiats TG, Gomes AS, Gracia CR, Haan CK, Jackson EA, Judelson DR, Kelepouris E, Lavie CJ, Moore A, Nussmeier NA, Ofili E, Oparil S, Ouyang P, Pinn VW, Sherif K, Smith SC Jr, Sopko G, Chandra-Strobos N, Urbina EM, Vaccarino V, Wenger NK.** Effectiveness-based guidelines for the prevention of cardiovascular disease in women–2011 update: a guideline from the American Heart Association. Circulation 2011;123:1243–1262. *doi: 10.1161/CIR.0b013e31820faaf8.*
13. **US Preventive Services Task Force, Davidson, KW, Barry MJ, Mangione CM, Cabana M, Chelmow D, Coker TR, Davis EM, Donahue KE, Jaén CR, Krist AH, Kubik M, Li L, Ogedegbe G, Pbert L, Ruiz JM, Stevermer J, Tseng CW, Wong JB.** Aspirin Use to Prevent Cardiovascular Disease: US Preventive Services Task Force Recommendation Statement. JAMA 2022;327(16):1577–1584. *https://doi.org/10.1001/jama.2022.4983.*
14. **Piepoli MF, Hoes AW, Agewall S, Albus C, Brotons C, Catapano AL, Cooney MT, Corrà U, Cosyns B, Deaton C, Graham I, Hall MS, Hobbs FDR, Løchen ML, Löllgen H, Marques-Vidal P, Perk J, Prescott E, Redon J, Richter DJ, Sattar N, Smulders Y, Tiberi M, van der Worp HB, van Dis I, Verschuren WMM, Binno S.** 2016 European Guidelines on cardiovascular disease prevention in clinical practice: The Sixth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of 10 societies and by invited experts) Developed with the special contribution of the

European Association for Cardiovascular Prevention & Rehabilitation (EACPR). Eur Heart J 2016;37:2315–2381. *doi: 1093/eurheartj/ehw106.*

15. **Citrome L, Ketter TA**. When does a difference make a difference? Interpretation of number needed to treat, number needed to harm, and likelihood to be helped or harmed. Int J Clin Pract 2013;67(5):407-411. *doi:10.1111/ijcp.12142.*
16. **Zheng SL, Roddick AJ**. Association of aspirin use for primary prevention with cardiovascular events and bleeding events: a systematic review and meta-analysis. JAMA 2019;22;321(3):277-287. *doi: 1001/jama.2018.20578.*
17. **Antithrombotic Trialists' (ATT) Collaboration**. Aspirin in the primary and secondary prevention of vascular disease: a collaborative meta-analysis of individual participant data from randomized. Lancet 2009; 373:1849–1860. *doi: 1016/S0140-6736(09)60503-1.*
18. **Mahmoud AN, Gad MM, Elgendy AY, Elgendy IY, Bavry AA**. Efficacy and safety of aspirin for primary prevention of cardiovascular events: a meta-analysis and trial sequential analysis of randomized controlled trials. Eur Heart J 2019;40(7):607-617. *doi:10.1093/eurheartj/ehy813.*
19. **Ridker PM, Cook NR, Lee IM, Gordon D, Gaziano JM, Manson JE, Hennekens CH, Buring JE.** A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med 2005;352(13):1293-1304. *doi:10.1056/NEJMoa050613.*
20. **Ikeda Y, Shimada K, Teramoto T, Uchiyama S, Yamazaki T, Oikawa S, Sugawara M, Ando K, Murata M, Yokoyama K, Ishizuka N.** Low-dose aspirin for primary prevention of cardiovascular events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized clinical trial. JAMA 2014;312(23):2510-2520. *doi:10.1001/jama.2014.15690.*
21. **McNeil JJ, Wolfe R, Woods RL, Tonkin AM, Donnan GA, Nelson MR, Reid CM, Lockery JE, Kirpach B, Storey E, Shah RC, Williamson JD, Margolis KL, Ernst ME, Abhayaratna WP, Stocks N, Fitzgerald SM, Orchard SG, Trevaks RE, Beilin LJ, Johnston CI, Ryan J, Radziszewska B, Jelinek M, Malik M, Eaton CB, Brauer D, Cloud G, Wood EM, Mahady SE, Satterfield S, Grimm R, Murray AM; ASPREE Investigator Group.** Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. N Engl J Med 2018;379(16):1509-1518. *doi: 10.1056/NEJMoa1805819.*
22. **Gaziano JM, Brotons C, Coppolecchia R, Crichelli C, Darius H, Gorelick PB, Howard G, Pearson TA, Rothwell PM, Ruilope LM, Tendera M, Tognoni G; ARRIVE Executive Committee**. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomized doubled-blind, placebo-controlled trial. Lancet 2018;392(10152):1036-1046. *doi:10.1016/S0140-6736(18)31924-X.*
23. **ASCEND Study Collaborative Group, Bowman L, Mafham M, Wallendszus K, Stevens W, Buck G, Barton J, Murphy K, Aung T, Haynes R, Cox J, Murawska A, Young A, Lay M, Chen F, Sammons E, Waters E, Adler A, Bodansky J, Farmer A, McPherson R, Neil A, Simpson D, Peto R, Baigent C, Collins R, Parish S, Armitage J.** Effects of aspirin for primary prevention in persons with diabetes mellitus. N Engl J Med 2018;379(16):1529-1539. *doi:10.1056/NEJMoa1804988.*
24. **Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, Shamseer L, Tetzlaff JM, Akl EA, Brennan SE, Chou R, Glanville J, Grimshaw JM, Hróbjartsson A, Lalu MM, Li T, Loder EW, Mayo-Wilson E, McDonald S, McGuinness LA, Stewart LA, Thomas J, Tricco AC, Welch VA, Whiting P, Moher D.** The PRISMA 2020 statement: An updated guideline for reporting systematic reviews. BMJ 2021;372:n71. *doi: 1036/bmj.n71.*
25. **Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan D, McQuay HJ.** Assessing the quality of reports of randomi-

zed clinical trials: ¿is blinding necessary? Control Clin Trials 1996;17:1–12. *https://doi.org/10.1016/0197-2456(95)00134-4.*

26. **Barratt A, Wyer PC, Hatala R, McGinn T, Dans AL, Keitz S, Moyer V, For GG; Evidence-Based Medicine Teaching Tips Working Group.** Tips for learners of evidence-based medicine: 1. Relative risk reduction, absolute risk reduction, and, number needed to treat. CMAJ 2004;171(4):353-358. *doi:10.1503/cmaj.1021197.*
27. **Altman DG**. Confidence intervals for the number needed to treat. BMJ 1998; 317(7168):1309-1312. *doi:10.1136/bmj.317.7168.1309.*
28. **Hull RD, Liang J, Bergqvist D, Yusen RD**. Benefit-to-harm ratio of thromboprophylaxis for patients undergoing major orthopaedic surgery. A systematic review. Thromb Haemost 2014;111(2):199-212. *doi:10.1160/TH13-08-0654.*
29. **Evidence Based Medicine**: How to practice and teach EBM. Editors: Sharon Straus, Paul Glasziou, W. Scott Richardson, R. Brian Haynes (Spanish) 5th Edition Copyright: © Elsevier 2019, Published: April 7, 2019, eBook ISBN: 9788491135579, pp 360.
30. **Higgins JPT, Thompson SG, Deeks JJ, Altman DG**. Measuring inconsistency in meta-analysis. BMJ 2003;327:557-560.
31. **Zhao B, Wu Q, Wang L, Liao C, Dong Y, Xu J, Wei Y, Zhang W.** Pros and cons of aspirin for the primary prevention of cardiovascular events: a secondary study of trial sequential analysis. Front Pharmacol 2021;11:592116. *doi:10.3389/fphar.2020.592116*
32. **Antiplatelet Trialists' Collaboration**. Collaborative overview of randomised trials of antiplatelet therapy--I: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. BMJ 1994;308(6921):81-106.
33. **Berger JS, Lala A, Krantz MJ, Baker GS, Hiatt WR**. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. Am Heart J 2011;162(1):115-124. *doi:10.1016/j.ahj.2011.04.006.*
34. **Abdelaziz HK, Saad M, Pothineni NVK, Megaly M, Potluri R, Saleh M, Kon DLC, Roberts DH, Bhatt DL, Aronow HD, Abbott JD, Mehta JL.** Aspirin for primary prevention of cardiovascular events. J Am Coll Cardiol 2019;73(23):2915-2929. *doi:10.1016/j.jacc.2019.03.501.*
35. **Puhan MA, Singh S, Weiss CO, Varadhan R, Sharma R, Boyd CM**. Evaluation of the Benefits and Harms of Aspirin for Primary Prevention of Cardiovascular Events: A Comparison of Quantitative Approaches. Rockville (MD): Agency for Healthcare Research and Quality (US); November 2013. Nov. Report No.: 12(14)-EHC149-EF.
36. **US Preventive Services Task Force**. Aspirin for the prevention of cardiovascular disease: US Preventive Services Task Force recommendation statement. Ann Intern Med 2009;150(6):396-404. *doi:10.7326/0003-4819-150-6-200903170-00008*.
37. **US Preventive Services Task Force**. Seeks Comments on Draft Recommendation Statement on Aspirin to Prevent Cardiovascular Disease and Cancer, September 15, 2015. www.uspreventiveservicestaskforce.org.
38. **US Preventive Services Task Force**. Publishes Final Recommendation Statement on Aspirin Use for the Primary Prevention of Cardiovascular Disease and Colorectal Cancer. April 12, 2016.www.uspreventiveservicestaskforce.org.
39. **Barbarawi M, Kheiri B, Zayed Y, Gakhal I, Al-Abdouh A, Barbarawi O, Rashdan L, Rizk F, Bachuwa G, Alkotob ML.** Aspirin efficacy in primary prevention: a meta-analysis of randomized controlled trials. High Blood Press Cardiovasc Prev 2019;26(4):283-291. *doi:10.1007/s40292-019-00325-5*
40. **Pallikadavath S, Ashton L, Brunskill NJ, Burton JO, Gray LJ, Major RW**. Aspirin for the primary prevention of cardiovascular disease in individuals with chronic kidney disease: a systematic review and meta-analysis. Eur J Prev Cardiol 2022;28(17):1953-1960. *doi:10.1093/eurjpc/zwab132.*

41. **Rawal A, Cave B, Ardeshna D, Hana D, Ibebuogu UN, Khouzam RN**. The death of aspirin for primary prevention ċshould aspirin be changed to a prescription only medication? Ann Transl Med 2019;7(17):402. *doi:10.21037/atm.2019.07.05.*
42. **Elwood PC, Morgan G, Galante J, Chia JW, Dolwani S, Graziano JM, Kelson M, Lanas A, Longley M, Phillips CJ, Pickering J, Roberts SE, Soon SS, Steward W, Morris D, Weightman AL.** Systematic review and meta-analysis of randomised trials to ascertain fatal gastrointestinal bleeding events attributable to preventive low-dose aspirin: no evidence of increased risk. PLoS One 2016;11(11):e0166166. *doi:10.1371/journal.pone.0166166.*
43. **ACC/AHA Clinical Practice Guideline.** 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines**.** Circulation;140(11):e596-e646. *https://doi.org/10.1161/CIR.0000000000000678.*
44. **Visseren FLJ, Mach F, Smulders YM, Carballo D, Koskinas KC, Back M, Benetos A, Biffi A, Boavida JM, Capodanno D, Cosyns B, Crawford C, Davos CH, Desormais I, Angelantonio ED, Franco OH, Halvorsen S, Richard Hobbs FD, Hollander M, Jankowska EA, Michal M, Sacco S, Sattar N, Tokgozoğlu L, Tonstad S, Tsioufis KP, van Dis I, van Gelder IC, Wanner C, Williams B; ESC Scientific Document Group**. 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. Developed by the Task Force for cardiovascular disease prevention in clinical practice with representatives of the European Society of Cardiology and 12 medical societies. With the special contribution of the European Association of Preventive Cardiology (EAPC). Eur J Prev Cardiol 2022; 29, 5-115. *doi:10.1093/eurjpc/zwab154.*
45. **Marquis-Gravel G, Roe MT, Harrington RA, Muñoz D, Hernandez AF, Jones WS**. Revisiting the role of aspirin for the primary prevention of cardiovascular disease. Circulation 2019;140(13):1115-1124. *doi:10.1161/CIRCULATIONAHA.119.040205.*
46. **Seidu S, Kunutsor SK, Sesso HD, Gaziano JM, Buring JE, Roncaglioni MC, Khunti K.** Aspirin has potential benefits for primary prevention of cardiovascular outcomes in diabetes: updated literature-based and individual participant data meta-analyses of randomized controlled trials. Cardiovasc Diabetol 2019;18(1):70. *doi:10.1186/s12933-019-0875-4.*
47. **McQuay HJ, Moore RA**. Using numerical results from systematic reviews in clinical practice. Ann Intern Med 1997;126(9):712-720. *doi:10.7326/0003-4819-126-9-199705010-00007.*
48. **Suissa S**. The Number Needed to Treat: 25 Years of Trials and Tribulations in Clinical Research. Rambam Maimonides Med J 2015;6(3):e0033. Published 2015 Jul 30. *doi:10.5041/RMMJ.10218.*
49. **Vizcaíno G, Montalvo Herdoiza JP, Siteneski A, Tauriz Navarro W**. Secondary prevention in minor ischemic stroke with antiplatelet treatment. systematic review and meta-analysis of comparative studies with aspirin under non-inferiority criteria. Invest Clin 2020;61(3):265-282. *https://doi.org/10.22209/IC.v61n3a06.*