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REVIEW

The role of aspirin in women's health

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Background: The aim of this review is to discuss the role of aspirin for various conditions in women.

Methods: A nonsystematic review of articles published on PubMed® that examines the role of aspirin in women.

Results: Aspirin is associated with a significant reduction of stroke risk in women, which may be linked to age. However, despite this evidence, underutilization of aspirin in eligible women is reported. In women of reproductive age, it may also have a role to play in reducing early-onset preeclampsia and intrauterine growth restriction, and in the prevention of recurrent miscarriage in women with antiphospholipid antibodies; it may also reduce cardiovascular risk in associated systemic conditions such as lupus. Aspirin may reduce colorectal cancer risk in women, but its role in breast cancer warrants further data from controlled trials.

Conclusions: The risk–benefit threshold for aspirin use in women has been established for several conditions. Reasons why women are less likely to be prescribed aspirin have not been established, but the overall underuse of aspirin in women needs to be addressed.

Keywords: CVD, cancer, menopause, preeclampsia

Introduction

Aspirin has been available for over a century,[1] and to date, over 100 randomized clinical trials (RCTs) have established its efficacy and safety in men and women for the prevention of vascular conditions including acute myocardial infarction (MI), ischemic stroke, and peripheral arterial disease.[2] RCTs have also shown that aspirin reduces the risk of colorectal cancer recurrence in high-risk subjects,[3,4] while observational studies have associated a decreased risk of colorectal adenomas with regular aspirin use.[5] A recently published, 20-year follow-up of randomized trials also found that low-dose aspirin reduced the incidence and mortality due to colorectal cancer in patients at no apparent increased risk for this malignancy.[6] Aspirin may also have a beneficial role in the prevention of breast, prostate, lung, stomach, and esophageal cancers.[7] Among women, aspirin may provide additional benefits in individuals at risk of preeclampsia, as was first postulated by Wallenburg et al[8] in 1986 and found in a number of RCTs thereafter,[9–11] and in postmenopausal individuals with or at risk of osteoporosis, rheumatoid arthritis, or breast cancer.[12]

Despite the compelling evidence that low-dose aspirin reduces morbidity and mortality in patients with cardiovascular disease (CVD), and numerous guidelines recommending its use,[13–15] many eligible patients, especially women, are not receiving aspirin for this indication.[16–18] Underutilization of aspirin may contribute to worsening

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morbidity, mortality, and health-related quality-of-life outcomes associated with vascular conditions in women compared with men.[18] The Women's Health Initiative Observational Study (WHIOS), for example, which examined 8928 postmenopausal women with CVD, found that only 46% were taking aspirin. After 6.5 years of follow-up, however, adjusted aspirin use was associated with a significantly lower all-cause mortality (hazard ratio [HR]: 0.86; $P = 0.04$) and cardiovascular-related mortality (HR: 0.75; $P = 0.01$) in those women taking aspirin.[17] In addition to recommendations regarding the use of aspirin for the prevention of CVD and associated complications, numerous guidelines also recommend low-dose aspirin for women at risk of preeclampsia;[19–21] but again, there is considerable variation in its use for this indication.[22]

Aims and methods

The aim of this review is to discuss key issues in the use of aspirin for various conditions in women. A literature search was performed in Medline (PubMed®) using the title/abstract search terms "aspirin AND cardiovascular AND women" (n = 343), "aspirin AND women's health study" (n = 29), "aspirin AND preeclampsia" (n = 14), "aspirin AND antiphospholipid syndrome" (n = 16), and "aspirin AND cancer AND women" (n = 88). Reviewed articles were limited to English-language publications, clinical trials, and meta-analyses, published within the last 5 years. All publications were manually searched. Articles of particular relevance known to the authors (including those earlier than 2005) have also been included. Although this approach may have introduced some bias, it ensured that key data published before 2005 were also included where relevant, such as the aspirin trials in CVD, but the focus of the article was the discussion of relatively recent data in women.

Cardiovascular disease

According to the American Heart Association, CVD was the cause of death in 432,709 US females in 2006, which was nearly twice that observed for death from all forms of cancer in women (N = 269,819).[23] Since 1984, the number of CVD deaths for females has exceeded those for males in the US.[23] The high incidence of CVD death among women has resulted in considerable interest in preventive interventions that have been evaluated specifically in women, and there is also increasing awareness among women about the impact of CVD, particularly in older women.[24,25] Key studies providing data on the role for aspirin in preventing CVD include the Women's Health study (WHS), The Nurses' Health Study (NHS), the WHIOS, and the Antithrombotic Trialists' (ATT) Collaboration.[17,26–29]

The WHS, a double-blind RCT, evaluated the benefits of aspirin in the primary prevention of CVD in 39,876 apparently healthy women health professionals. During a follow-up of around 10 years, 477 first major cardiovascular events were confirmed in the aspirin group compared with 522 in the placebo group. While this represented a nonsignificant trend toward lower risk of major events associated with CVD by 9% (relative risk [RR]: 0.91, 95% confidence interval [CI]: 0.80–1.03; $P = 0.13$) with aspirin in the overall group, analysis by age indicated that aspirin significantly reduced major events in women aged ≥ 65 years (RR: 0.74, 95% CI: 0.59–0.92] in women aged ≥ 65 years vs (RR: 1.01, 95% CI: 0.81–1.26 in women aged 45–54 years). There was also a 34% reduction in the risk of MI in women aged ≥ 65 years (RR: 0.66, 95% CI: 0.44–0.97; $P = 0.04$). In addition, women taking aspirin experienced an overall 17% decrease in the risk of stroke (RR: 0.83, 95% CI: 0.69–0.99; $P = 0.04$), mostly due to significant reductions in ischemic stroke (RR: 0.76, 95% CI: 0.63–0.93; $P = 0.009$). The RR for stroke reduction was comparable across all age groups.[26]

The NHS – a prospective study of 87,678 healthy female nurses in the age range 34–65 years and free of diagnosed CHD, stroke, and cancer at baseline – evaluated the association between regular aspirin use and the risk of a first MI and other cardiovascular events over 6 years. In this study, the use of 1–6 aspirin tablets per week was associated with a 32% reduced risk of a first MI among women (RR: 0.68, 95% CI: 0.52–0.89; $P = 0.005$).[27] Long-term, 24-year follow-up of this study showed that low-to-moderate doses of aspirin are associated with a 25% lower risk of all-cause mortality (RR: 0.75, 95% CI: 0.71–0.81) and a 38% reduced risk of CVD death (RR: 0.62, 95% CI: 0.55–0.71); these benefits were significant in older women and those with cardiac risk factors.[28] The WHIOS – an observational study to evaluate the relationship between aspirin use (81 or 325 mg) and clinical outcomes among postmenopausal women with stable CVD – found that aspirin use was associated with significantly lower risk of all-cause mortality, specifically cardiovascular mortality, among postmenopausal women with stable CVD.[17]

Data from some of these key trials have been included in meta-analyses. The ATT Collaboration[29] was a meta-analysis of individual participant data on serious vascular events (MI, stroke, or vascular death) and major bleeds in six primary prevention trials (95,000 individuals at low average risk [~50,000 were women], 660,000 person-years,

3554 serious vascular events) and 16 secondary prevention trials (17,000 individuals at high average risk, 43,000 person-years, 3306 serious vascular events) that compared long-term aspirin vs control. Among women, the RR for primary prevention of a major coronary event was 0.95 (95% CI: 0.77–1.17); for ischemic stroke, 0.77 (95% CI: 0.59–0.99); and for a serious vascular event, 0.88 (95% CI: 0.76–1.01). In the secondary prevention trials among women, the RR for risk reduction for a major coronary event was 0.73 (95% CI: 0.51–1.03); for ischemic stroke, 0.91 (95% CI: 0.52–1.57); and for a serious vascular event, 0.81 (95% CI: 0.64–1.02). These findings clearly show that low-dose aspirin has an important role to play in the prevention of stroke, particularly in older women. This is important, as age-related stroke incidence is likely to increase dramatically in women compared with men over the next 40 years.[30] Stroke may also be linked (albeit rarely) to multiple pregnancies, eclampsia, the postpartum period, and migraine.[31]

A number of cardiovascular studies have established the benefit–risk profile of aspirin use in a range of low-, medium- and high-risk patients, and in those with diabetes. The absolute benefit of treatment vs major bleeding risk in 1000 patients treated per year is illustrated in Figure 1,[32] which also indicates the position of the WHS[26] and in low-risk patients with diabetes enrolled in the Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD) study.[33] The vascular events avoided in women enrolled in the WHS vs major bleeds associated with aspirin treatment is in the bottom left-hand corner of the figure; this is largely due to the nonsignificant reduction of major cardiovascular events in this trial, but does not illustrate the benefits in terms of stroke reduction, where the threshold will be more favorable.[26] Largely as a result of the primary outcome of the WHS, the benefit–risk threshold and consequently the numbers needed to treat (NNT) to prevent one cardiovascular event is higher in women than in men when data are pooled in meta-analyses. In a meta-analysis of 95,456 subjects (51,342 women) from cardiovascular trials, the NNT to prevent one cardiovascular event was 333 for women and 270 men based on a mean follow-up of 6.4 years.[34]

Cost-effectiveness of CVD prophylaxis with aspirin in women

Cost analyses in women are few, and are usually restricted to those that include sex as a subgroup. In general, these cost analyses have shown that aspirin is cost-effective in older women.[35] In one analysis, which predicted the number of cardiovascular events prevented with treatment, quality-adjusted life-years and cost over a 10-year period using a standard model, aspirin was found to be cost-effective as primary prevention in women aged > 65 years with high cardiovascular risk (10-year cardiovascular risk > 10%) and

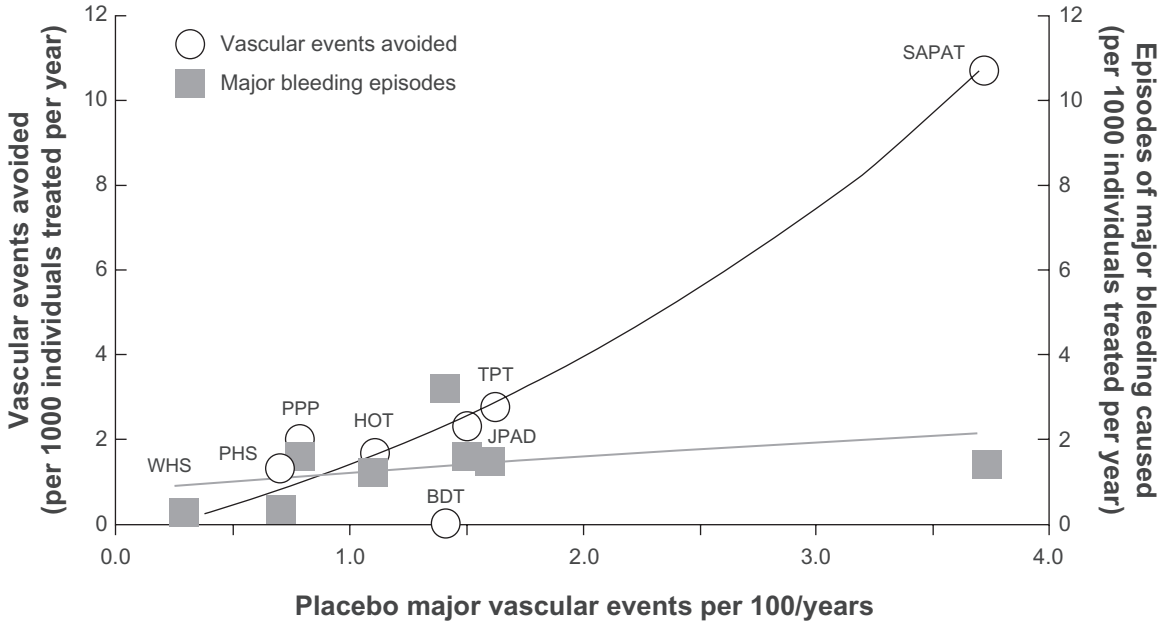

Figure 1 The absolute benefit (in terms of vascular events avoided/1000 treated/year) vs risks (major bleeds/1000 treated/year) associated with aspirin treatment in the key cardiovascular trials enrolling low-, medium-, and high-risk patients. Adapted with permission from the American College of Chest Physicians. Patrono C, et al. Platelet-active drugs: the relationships among dose, effectiveness, and side effects: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. *Chest.* 2004;126:234S–264S.
Abbreviations: BDT, British Doctors' Trial; HOT, Hypertension Optimal Treatment; JPAD, Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes; PHS, Physician's Health Study; PPP, Primary Prevention Project; SAPAT, Swedish Angina Pectoris Aspirin Trial; TPT, Thrombosis Prevention Trial; WHS, Women's Health Study.[32]

in women aged > 75 years with moderate cardiovascular risk (10-year cardiovascular risk > 15%).[36]

Findings from single trials and meta-analyses have yielded similar results. One cost analysis of aspirin for primary prevention of cardiovascular events based on the findings from a single trial indicated a favorable cost–utility ratio for older women with moderate cardiovascular risk.[37] Similar findings were observed when the ATT Collaboration meta-analysis data[29] were included in a model.[38]

Guideline recommendations for CVD prevention in women

Based on findings from trials in women, there are now specific guidelines recommending the use of aspirin, mainly in stroke prevention and in high-risk women. The US Preventive Services Task Force (USPSTF) calculated the risk threshold (ie, the potential benefit of a reduction in ischemic strokes outweighs the potential harm of an increase in gastrointestinal [GI] hemorrhage) for aspirin use in stroke primary prevention at a risk level of 1%–20%.[15] For women aged 55–59 years, the 10-year stroke risk is 3%, and the benefits of stroke prevention outweigh the risk of a GI bleed; this increases to 8% in women aged 60–69 years and to 11% in women aged 70–79 years. The USPSTF guidelines have been endorsed by a panel of experts from the American Diabetes Association, the American Heart Association, and the American College of Cardiology Foundation.

The AHA's *Effectiveness-Based Guidelines for the Prevention of Cardiovascular Disease in Women 2011 Update*[39] specifies that aspirin 75–325 mg/day is recommended in high-risk women with CHD and is reasonable in women with diabetes unless contraindicated; aspirin 81 mg/day or 100 mg every other day can be considered in women aged ≥ 65 years, if blood pressure is controlled and benefits in terms of ischemic stroke and MI prevention are likely to outweigh the risk of GI bleeding and hemorrhagic stroke, and it appears cost-effective in women ≥ 65 years with moderate-severe CVD risk. Aspirin is recommended in women aged < 65 years, when benefit for ischemic stroke prevention is likely to outweigh adverse effects of therapy. Several guidelines also recommend aspirin for the prevention of stroke in women. Low-dose aspirin is recommended in women aged > 45 years (or < 65 years) who are not at increased risk for intracerebral hemorrhage and who have good GI tolerance.[14,40] A number of other guidelines, including European guidelines, recommend the use of aspirin in patients with established CVD and in asymptomatic individuals at high risk of CVD, but do not specify different approaches for women.[41]

Some studies have observed that women have greater residual platelet activity after high-dose aspirin compared with men treated with a lower dose of aspirin, suggesting that female patients may benefit from higher maintenance dosages or the use of alternative antiplatelet medications.[42–44] Findings from the ATT Collaboration, however, show that the reduction in risk of major cardiovascular events is similar for men and women at similar doses, and thus, platelet reactivity may not justify differential dosing.[29]

The expanding role of aspirin in obstetric conditions

Preeclampsia

Preeclampsia is a potentially fatal pregnancy-specific hypertensive syndrome affecting around 2%–8% of pregnancies.[45] For the unborn child, it is linked to poor intrauterine growth, prematurity, and sometimes death,[10,45] and among mothers can lead to a spectrum of complications including eclampsia, stroke, (pulmonary) edema, and retinal problems. Preeclampsia/eclampsia is responsible for 10%–15% of direct maternal deaths, with intracranial hemorrhage as the most frequent cause. Reducing the occurrence of preeclampsia/eclampsia-related deaths is an important aspect of one of the World Health Organization Millennium Goals: to reduce the maternal mortality ratio by 75% between 1990 and 2015.[45,46]

In the long-term, preeclampsia among mothers is associated with an increased risk of developing CVD.[47] Indeed, a recent systematic analysis estimated that women with a history of preeclampsia/eclampsia have approximately double the risk of early cardiac, cerebrovascular, and peripheral arterial disease and cardiovascular mortality compared with women without such a history.[48] The reasons for this increased risk of CVD are unknown, but shared risk factors – including endothelial dysfunction, obesity, hypertension, hyperglycemia, insulin resistance, and dyslipidemia – have led to suggestions that metabolic syndrome may be an underlying mechanism common to CVDs and preeclampsia.[49] A recent systematic analysis of observational studies showed that women with a history of preeclampsia may also have an increased risk of microalbuminuria.[50]

Children born to pregnancies complicated by preeclampsia and intrauterine growth restriction (IUGR) can also have long-term sequelae including type 2 diabetes mellitus, hypertension, and CVD.[51,52] For example, the Helsinki Birth Cohort study, which examined 284 pregnancies complicated by preeclampsia and 1592 complicated by gestational hypertension, found that people born to mothers with these conditions were at increased risk of stroke (HR: 1.9; $P = 0.01$).[52]

Mechanisms underlying the effects of preeclampsia and IUGR and long-term sequelae have not been elucidated, but proposals include fetal undernutrition, genetic susceptibility, and postnatal accelerated growth.[53] A potential role of epigenetic modifications in the process has also been suggested.[51] A recent study comparing normotensive IUGR cases vs 31 IUGR cases with preeclampsia suggested that IUGR is the key factor affecting cardiac function, rather than the preeclampsia itself.[54]

The role of aspirin in preeclampsia

Causes of preeclampsia are not clear, but it is thought that individuals with preeclampsia have an imbalance of prostaglandin I2 (PG12) and thromboxane A2 (TXA2), which induces a vasoconstriction state. Aspirin is known to inhibit TXA2, a potent activator of platelet aggregation and vasoconstriction, thus reducing the balance between vasoconstriction and vasodilation. Findings from RCTs, observational studies and meta-analyses indicate that aspirin treatment initiated early in pregnancy is an efficient method of reducing the incidence of preeclampsia and its consequences (Table 1);[9,10,55–60] only aspirin and calcium in a low-intake diet have been shown to have effects for the prevention of preeclampsia. Heparin or dalteparin and aspirin, however, may be superior to aspirin alone in women with inherited thrombophilias.[55]

The most recent meta-analysis, which examined 27 studies involving 11,348 women, showed that low-dose aspirin was effective in reducing preeclampsia (RR: 0.47), severe preeclampsia (RR: 0.09), and IUGR (RR: 44) when used in early pregnancy (<16 weeks' gestation) (Figure 2).[61–71] These findings support the results of earlier studies, including a meta-analysis of 14 trials involving 12,416 women, which showed that aspirin was beneficial in reducing perinatal death and preeclampsia, and increasing birth weight.[72] The benefits of aspirin in reducing blood pressure in pregnant women may also be linked to time of administration, with bedtime administration being more effective than at other times of day.[73] Findings from the Cochrane group, which have analyzed 59 trials to date (37,560 women), also suggest that the benefits of aspirin are greater in women at high risk of developing preeclampsia compared with low-risk women.[10] It may be important to develop a risk–benefit threshold in pregnant women based on risk factors for preeclampsia, safety issues (such as previous GI ulcers, *Helicobacter pylori* infection, etc), aspirin dose and timing, and duration of treatment. Preeclampsia could also be used to predict future increased risk of CVD, particularly hypertension, later in life,[74,75] and could be introduced into risk calculation scores for women.

Despite the data supporting the use of aspirin in high-risk pregnancy, considerable variation in its use for this condition is observed.[22] To date, there are no accurate tests that are suitable for use in routine clinical practice to predict the likelihood of preeclampsia in women not at high risk.[76]

Prevention of miscarriage in women with antiphospholipid syndrome

The antiphospholipid syndrome can lead to thrombosis, pregnancy loss, and pre-term delivery, particularly in patients with preeclampsia.[77] It has been postulated that a procoagulant state is induced in the antiphospholipid syndrome, which is mediated by TXA2 (Figure 3).[77] Reduction of this thrombogenic state could explain the benefits associated with aspirin use in these patients. A number of studies (summarized in Table 2)[78–85] have demonstrated that aspirin, either alone or in combination with heparin, prevents recurrent miscarriage in patients with antiphospholipid antibodies (APLAs); these studies suggest that aspirin plus unfractionated heparin is associated with better outcomes than aspirin alone or aspirin plus low-molecular-weight heparin.

Based on these findings, the American College of Chest Physicians guidelines recommend aspirin plus heparin (unfractionated or low molecular weight) in pregnant patients with APLAs and a history of more than two early pregnancy losses or more than one late pregnancy loss, preeclampsia, IUGR, or abruption.[86] Aspirin in combination with heparin is also recommended in pregnant individuals without recurrent miscarriage and/or fetal loss if they are positive for APLAs and have a history of thromboembolism (Table 3).[77]

Prevention in women with idiopathic recurrent miscarriage

Recurrent miscarriage (≥3 consecutive losses < 20 weeks postmenstruation) is a distressing problem that can affect as many as 0.5%–3% of fertile couples of reproductive age.[87] In many cases, no underlying cause (such as antiphospholipid syndrome) can be identified, and there is currently no treatment for this problem. A recently completed prospective study comparing patients with unexplained recurrent first-trimester pregnancy loss with matched control subjects found that those with unexplained recurrent miscarriage have significantly increased platelet aggregation in response to arachidonic acid.[87] The enhanced response to this agonist provides a strong rationale for the use of aspirin in management of this clinical condition. Small-scale trials investigating the use of aspirin in the prevention of recurrent

Table 1 Trials investigating the effects of aspirin on incidence of preeclampsia and fetal growth restriction

Study	Study design	Study treatment	Patient population and number	Primary outcome	Result of primary outcome in women	Conclusion
Bujold et al[56]	Meta-analysis (9 RCTs)	Aspirin vs control	1317 women at increased risk of preeclampsia, (abnormal uterine artery Doppler)	Incidence of preeclampsia	Aspirin reduced the risk of preeclampsia: • Started at ≤16 weeks' gestation (RR: 0.48, 95% CI: 0.33–30.68) • Started at 17–19 weeks' gestation (RR: 0.55, 95% CI: 0.17–11.76) • Started at ≥20 weeks' gestation (RR: 0.82, 95% CI: 0.62–61.09)	Aspirin treatment initiated early in pregnancy reduces the incidence of preeclampsia and its consequences in women at increased risk
Lambers et al[57]	RCT	Aspirin (low dose) for the first trimester vs placebo	54 women undergoing IVF	Incidence of pregnancy complications	Hypertensive pregnancy complications were lower in the aspirin group (3.6%) vs the placebo group (28.9%) ($P < 0.05$)	Low-dose aspirin during IVF and first trimester may reduce the incidence of hypertensive pregnancy complications
Askie et al[9]	Meta-analysis (31 preeclampsia primary prevention trials)	Antiplatelet agents vs control	32,217 women and 32,819 babies	Incidence of preeclampsia	Antiplatelet agents reduced the RR of developing preeclampsia (RR:0.90, 95% CI: 0.84–0.97)	Antiplatelet agents during pregnancy are associated with moderate but consistent reductions in the RR of preeclampsia, of birth before 34 weeks' gestation, and of having a pregnancy with a serious adverse outcome
Urban et al[58]	Retrospective cohort study	Low-dose aspirin, LMWH, aspirin and heparin or control	84 multiparous patients with a previous history of severe preeclampsia and IUGR	Adverse pregnancy outcome	Low-dose aspirin plus LMWH significantly reduced the risk of developing IUGR (OR: 0.16, 95% CI: 0.03–0.98). Among women with previous severe preeclampsia, combined treatment reduced adverse pregnancy outcome in the index pregnancy (OR: 0.08, 95%CI: 0.01–0.96), IUGR (OR: 0.02, 95% CI: <0.01–0.46), and IUGR with severe preeclampsia (OR: 0.08, 95% CI: 0.01–0.96)	Combined treatment with low-dose aspirin alone or in combination with LMWH is protective against the development of adverse pregnancy outcome in a cohort of women with antecedent adverse pregnancy outcome

Leduc et al[55]	Retrospective analysis	Dalteparin and low-dose aspirin	43 women with inherited thrombophilia	Obstetric complications	Combined dalteparin and aspirin significantly decreased the risk of preeclampsia (OR: 0.80, 95% CI: 0.70–0.91; $P = 0.001$) and IUGR (OR: 0.70, 95% CI: 0.60–0.82; $P = 0.001$). Dalteparin or aspirin alone showed equivalent effects in preventing preeclampsia and IUGR	Combined treatment with dalteparin and aspirin decreases the risk of preeclampsia by 20% and the risk of IUGR by 30% in women with inherited thrombophilia
Duley et al[10]	Systematic review (59 trials)	Antiplatelet agents vs control	37,560 pregnant women at risk of developing preeclampsia	Incidence of preeclampsia and complications	Antiplatelet agents were associated with reduction in risk of: • Preeclampsia (RR: 0.83, 95% CI: 0.77–0.89) • Preterm birth (RR: 0.92, 95% CI: 0.88–0.97) • Fetal or neonatal deaths (RR: 0.86, 95% CI: 0.76–0.98) • Small-for-gestational age babies (RR: 0.90, 95% CI: 0.83–0.98)	Antiplatelet agents, largely low-dose aspirin, have moderate benefits when used for prevention of preeclampsia and its consequences
Ruano et al[59]	Meta-analysis (22 studies)	Low-dose aspirin vs placebo	33,498 pregnant women at risk of developing preeclampsia	Incidence of preeclampsia	Low-dose aspirin had no statistically significant effect on the incidence of preeclampsia in the low-risk group (RR: 0.95, 95% CI: 0.81–1.11), but did have a small beneficial effect in the high-risk group (RR: 0.87, 95% CI: 0.79–0.96)	Low-dose aspirin is mildly beneficial in terms of reducing the incidence of preeclampsia in women at high risk of developing preeclampsia
Ebrashy et al[60]	RCT	Low-dose aspirin	139 pregnant women at risk of preeclampsia or IUGR (abnormal uterine artery Doppler)	Incidence of preeclampsia	• Preeclampsia developed in 35% of women receiving aspirin vs 62% of women in the control group ($P = 0.003$) • Severe preeclampsia developed in 8% of women receiving aspirin vs 23% of women in the control group ($P = 0.215$) • Preeclampsia before 37 weeks of gestation occurred in 4% of women receiving aspirin vs 83% of controls ($P < 0.001$)	Low-dose aspirin administered as early as 14–16 weeks of gestation to pregnant women at high risk of preeclampsia may reduce or modify the course of severe preeclampsia

Abbreviations: CI, confidence interval; HR, hazard ratio; IUGR: intrauterine growth restriction; IVF, in-vitro fertilization; LMWH, low-molecular-weight heparin; MI, myocardial infarction; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

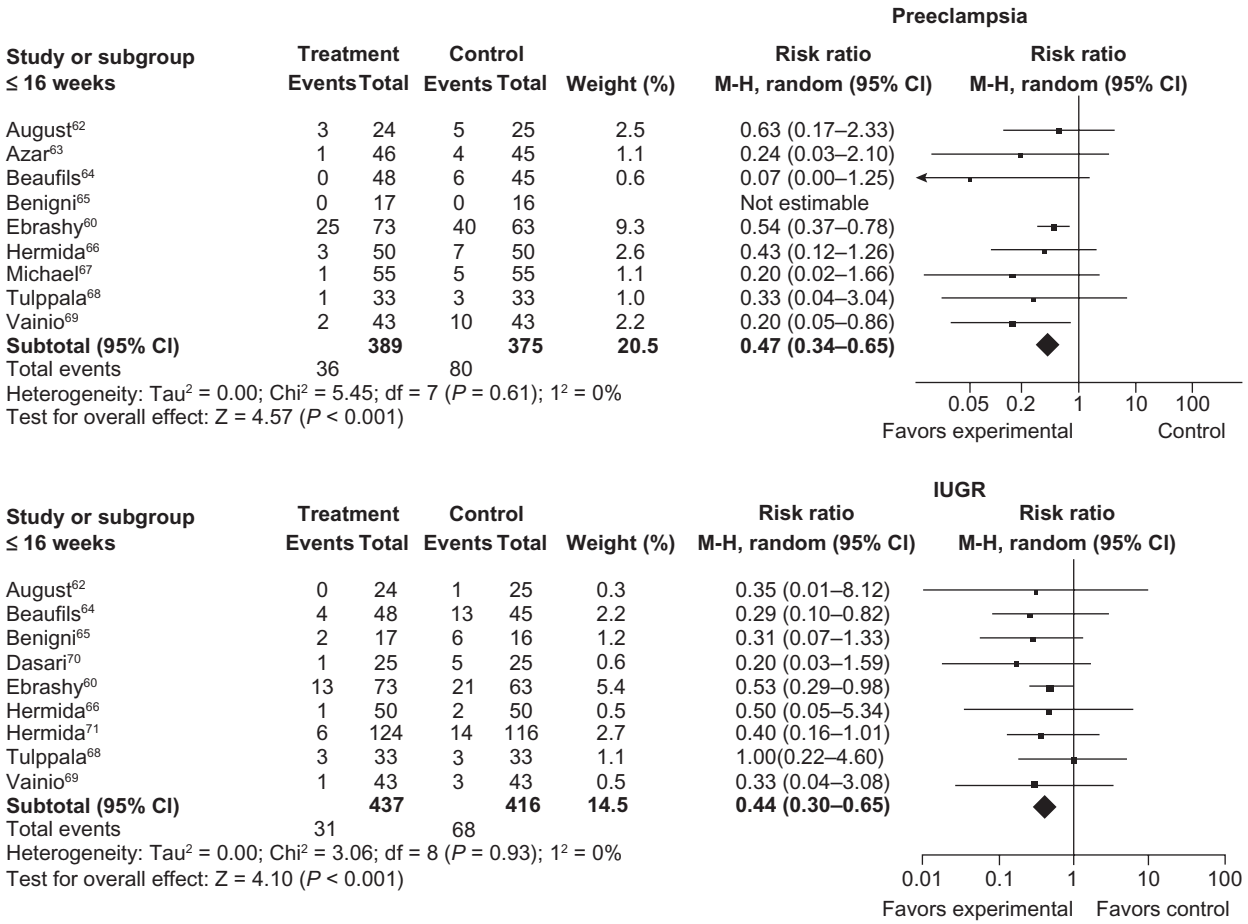

Figure 2 The effect of aspirin treatment on preeclampsia (**A**) and IUGR (**B**) in pregnant women (≤16 weeks' gestation). Adapted with permission from Bujold E, et al. Prevention of preeclampsia and intrauterine growth restriction with aspirin started in early pregnancy *Obstet Gynecol*. 2010;116:402–414, with permission from LWW.
Abbreviations: CI, confidence interval; df, degrees of freedom; IUGR, intrauterine growth restriction; M-H, Mantel-Haentszel.[61–71]

miscarriage in women without antiphospholipid syndrome have so far found little benefit;[88] however, the findings regarding aggregation response to arachidonic acid lend support to reevaluating the benefit of aspirin in larger trials with a clearly defined cohort of individuals with recurrent miscarriage.

The expanding role of aspirin in chronic inflammatory disorders

Systemic lupus erythematosus

Systemic lupus erythematosus (SLE) – an inflammatory rheumatic disease of immunologic origin characterized by autoantibody production, polyarthritis, and protean clinical manifestations – affects considerably more women than men.[89] Cardiovascular morbidity and mortality is a frequent complication of SLE, particularly in females aged 35–44 years, in whom the risk of MI is raised 50-fold.[90] Traditional cardiac risk factors – including hyperlipidemia, hypertension, and sedentary lifestyle – are all prevalent in patients with SLE, but cannot fully account for the magnitude of this increased risk, suggesting that SLE itself may also confer increased risk.[91] Conventional wisdom in the field is that cardiac risk factors should be aggressively treated in SLE, although there are limited data on the effectiveness of individual interventions. The benefits observed with aspirin in the reduction of cardiovascular events in non-SLE populations suggest that it may also benefit women affected by the condition, although further investigation is warranted; however, as APLAs may also be involved in the development of SLE, it is likely that aspirin could prevent the thrombogenic state, as described previously.[77]

The potential role of aspirin in cancer

The potential role of aspirin in cancer prevention is based on more than 30 years of research, with beneficial effects being mainly observed in colorectal adenoma and cancer

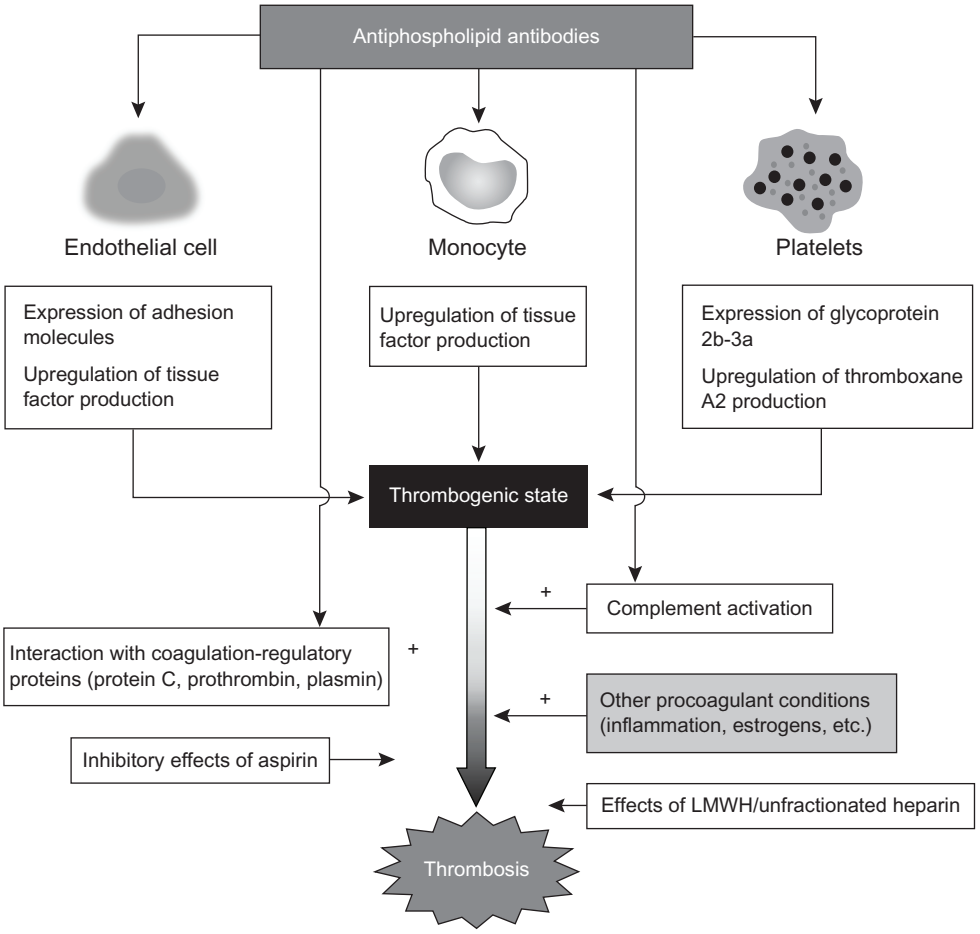

Figure 3 Pathogenesis of thrombosis in antiphospholipid syndrome and the mode of action of aspirin and heparin.[77]
Adapted from The Lancet, Published online September 6, 2010, Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. Copyright (2011), with permission from Elsevier.
Abbreviation: LMWH, low-molecular-weight heparin.

prevention.[7] Aspirin may exert its beneficial anticancer effects through inhibition of cyclooxygenase (COX)-1 in platelets or COX-1 and/or COX-2 in nucleated cells.[92] This will result in the inhibition of COX-derived products that are involved in angiogenesis (TXA2) or apoptosis (PGE2/PGE2 receptors). Non-COX-dependent pathways may include modulation of oncogenic factors (eg, NFκB), other pathways (eg, β-catenin), genetic alterations (eg, DNA), or energy depletion of tumor cells by phosphorylation.[93]

Colorectal cancer

Colorectal cancer is a serious concern among both men and women. It is estimated that in 2010, there will be 102,900 new cases of colorectal cancer (49,470 in men and 53,430 in women) and 39,670 new cases of rectal cancer (22,620 in men and 17,050 in women).[94] A recent analysis of studies in primary and secondary prevention of vascular events, involving > 14,000 patients, found that low-dose aspirin (75 mg/day) reduced the long-term incidence and mortality due to colorectal cancer.[6] In this analysis, the reductions in incidence and death due to colorectal cancer were greater for proximal colon tumors than for distal colon or rectal tumors. This is an important finding, as regular screening with sigmoidoscopy or colonoscopy is not effective in preventing tumors in this location.[6] A further study using participants from the NHS (n = 83,767) showed that aspirin use was associated with 29% reduction in the risk of colorectal cancer in women.[95]

Breast cancer

Breast cancer is a significant concern among many women. In the US in 2006, breast cancer claimed the lives of 40,821 females.[23] Nonsteroidal anti-inflammatory drugs (NSAIDs), including aspirin, inhibit COX and thereby reduce prostaglandin synthesis. The observation that abnormally upregulated COX and prostaglandins

Table 2 Trials investigating the effect of aspirin on pregnancy outcomes in women with antiphospholipid syndrome

Study	Study design	Study treatment	Patient population and number	Primary outcome	Result of primary outcome in women	Conclusion
Mak et al[78]	Meta-analysis (5 trials)	Aspirin plus heparin vs aspirin	334 women with recurrent pregnancy loss and positive antiphospholipid antibodies	Live birth rates	Patients who received heparin and aspirin had significantly higher live birth rate (RR: 1.301, 95% CI: 1.040–1.629) than aspirin alone	The combination of heparin and aspirin is superior to aspirin alone in achieving more live births in patients with recurrent pregnancy loss and positive antiphospholipid antibodies
Bramham et al[79]	Observational study	Aspirin, and LMWH	67 women with antiphospholipid syndrome (83 pregnancies)	Pregnancy outcome	Women with thrombotic antiphospholipid syndrome had higher rates of preterm delivery (26.8% vs 4.7%, $P = 0.05$) than women with recurrent miscarriage and more small-for-gestational-age babies than women with placental dysfunction (39.5% vs 4.8%, $P = 0.003$) Women with placental dysfunction had significantly longer gestations compared with their pretreatment pregnancies (38.4 [28.4–41.4] vs 24.0 [18–35] weeks, $P < 0.0001$) and 100% live birth rate after treatment with aspirin and LMWH	Treatment with aspirin and LMWH is associated with improved outcomes for women with previous late fetal loss or early delivery due to placental dysfunction
Ziakas et al[80]	Meta-analysis (5 trials)	Unfractionated heparin or LMWH heparin plus aspirin	398 women with antiphospholipid syndrome	Live-birth rate	Unfractionated heparin plus aspirin had a significant effect on pregnancy loss (OR: 0.26) whereas the effect of LMWH plus aspirin was insignificant (OR: 0.70)	Unfractionated heparin and aspirin have a significant benefit in reducing pregnancy loss
Cohn et al[81]	Prospective observational study	Aspirin plus heparin vs aspirin	176 pregnant women with antiphospholipid antibodies and recurrent miscarriage	Live-birth rate	79% of women who received aspirin and heparin had a live birth compared with 62% who received aspirin only	Aspirin and heparin is associated with higher live birth rate than aspirin alone
Laskin et al[82]	RCT	Aspirin plus LMWH vs aspirin	88 women with recurrent pregnancy loss and antiphospholipid antibodies or inherited thrombophilia or antinuclear antibodies	Live-birth rate	• 77.8% had a live birth in the LMWH plus aspirin group compared with 79.1% in the aspirin only group • No difference with respect to pregnancy outcome and presence of APLAs and treatment group	LMWH plus aspirin was not superior to aspirin alone in preventing recurrent pregnancy loss
Dendrinos et al[83]	RCT	LMWH plus aspirin IV immunoglobulin	78 pregnant women with antiphospholipid antibodies and recurrent miscarriage	Live-birth rate	72.5% had a live birth in the LMWH plus aspirin group compared with 39.5% in the IV immunoglobulin group	LMWH plus aspirin was superior to IV immunoglobulin in preventing pregnancy loss

Goel et al[84]	RCT	Aspirin vs aspirin plus unfractionated heparin	72 pregnant women with antiphospholipid antibodies and recurrent miscarriage	Live-birth rate	Women treated with aspirin plus unfractionated heparin had a higher live-birth rate compared with those treated with aspirin (84.8% vs 61.5%; $P < 0.05$)	Aspirin and heparin is associated with higher live-birth rate than spirin alone
Empson et al[85]	RCT	Aspirin vs unfractionated heparin or LMWH and aspirin	849 pregnant women with history of pregnancy loss and antiphospholipid antibodies	Pregnancy loss	Aspirin plus heparin significantly reduced pregnancy loss by 54% compared with aspirin alone Aspirin plus LMWH reduced pregnancy loss by 22% compared with aspirin alone (this was not significant)	Aspirin and heparin may reduce pregnancy loss compared with aspirin alone, but more trials are needed to explore differences between heparin and LMWH

Abbreviations: APLAs, antiphospholipid antibodies; CI, confidence interval; IUGR, intra-uterine growth restriction; IV, intravenous; LMWH, low molecular weight heparin; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

Table 3 Suggested treatment regimens (involving aspirin) for conditions associated with antiphospholipid syndrome[77]

Patient	Treatment (primary thromboprophylaxis)
Patients with systemic lupus erythematosus and lupus anticoagulant and/or persistently positive anticardiolipin	Hydroxychloroquine and consider low-dose aspirin
Patients with obstetric antiphospholipid syndrome (outside pregnancy)	Low-dose aspirin or no therapy
Asymptomatic carriers of antiphospholipid antibodies	No therapy or low-dose aspirin
Pregnant patient	**Treatment (prophylactic or therapeutic)**
Antiphospholipid syndrome without previous thrombosis and with recurrent early miscarriage	Low-dose aspirin alone or with unfractionated heparin
Antiphospholipid syndrome without previous thrombosis and with fetal death (≥10 weeks' gestation) or severe early-onset preeclampsia	Low-dose aspirin plus unfractionated heparin or LMWH
Antiphospholipid syndrome with previous thrombosis	Low-dose aspirin plus unfractionated heparin or LMWH

Adapted from *The Lancet*, Published online September 6, 2010, Ruiz-Irastorza G, Crowther M, Branch W, Khamashta MA. Antiphospholipid syndrome. Copyright (2011), with permission from Elsevier.
Abbreviation: LMWH, low-molecular-weight heparin.

are features of breast cancer suggests that aspirin may have potential value in treatment and prevention of the disease. Results investigating effects of aspirin on incidence of breast cancer are inconsistent, with some studies identifying reduced incidence of breast cancer in women taking aspirin vs those not taking aspirin, and others finding no effect (Table 4);[96–103] given this lack of consistent findings, further investigation is warranted. A recent prospective observational study based on responses from 4164 female registered nurses in the NHS who were diagnosed with stages I–III breast cancer has indicated that among women living ≥ 1 year after a breast cancer diagnosis, aspirin use was associated with a decreased risk of distant recurrence and breast cancer death.[96]

Endometrial cancer

Although no prospective studies to date have explored the relationship between the use of aspirin, other NSAIDs, and acetaminophen and endometrial adenocarcinoma, data from a prospective cohort study suggest that while use of aspirin or other NSAIDs do not play important roles in endometrial cancer risk overall, risk is significantly lower for current aspirin users who are obese or who were postmenopausal and had never used postmenopausal hormones.[104] The potential effects of aspirin in these subgroups warrant further investigation.

Table 4 Trials investigating the effects of aspirin on breast cancer

Study	Study design	Study treatment	Patient population and number	Primary outcome	Result of primary outcome in women	Conclusion
Bardia et al[97]	Prospective observational study	Aspirin or NSAID use vs nonuse	26,580 postmenopausal women	Breast cancer	• Aspirin was associated with a lower risk of breast cancer (RR: 0.80) compared with nonusers • Use of NSAIDs did not reduce breast cancer risk	Aspirin was associated with a 20% reduction in breast cancer risk, which was unaffected by hormone receptor status
Holmes et al[96]	Prospective observational study	Aspirin vs nonuse	4164 women diagnosed with breast cancer	Breast cancer mortality	Aspirin use was associated with a decreased risk of breast cancer death. The adjusted RRs for 1, 2–5, and 6–7 days of aspirin use per week compared with no use were 1.07 (95% CI: 0.70–1.63), 0.29 (95% CI: 0.16–0.52), and 0.36 (95% CI: 0.24–0.54), respectively (test for linear trend, $P < 0.001$). Results were similar for distant recurrence	Among women living $\geq$ 1 year after a breast cancer diagnosis, aspirin use was associated with a decreased risk of distant recurrence and breast cancer death
McTiernan et al[98]	RCT	Aspirin 325 mg/day vs placebo	143 postmenopausal women	Total mammographic breast density	Geometric mean baseline percent density was 17.6% (95% CI: 14.8–20.9) in women randomized to aspirin and 19.2% (95% CI: 16.3–22.7) in women randomized to placebo. Percent density decreased in women randomized to aspirin by an absolute 0.8% vs an absolute decrease of 1.2% in controls ($P = 0.84$). Total breast area and dense area decreased to a similar degree in women assigned to aspirin and in those assigned to placebo, with no statistically significant differences between trial arms	Aspirin has no effect on mammographic density in postmenopausal women
Zhao et al[99]	Meta-analysis (26 studies)	NSAIDs	528,705 women	Breast cancer risk	The RR of NSAIDs use and the incidence of breast cancer was 0.94 (95% CI: 0.88–1.00) with random-effects model. A slight reduction of breast cancer in patients taking aspirin and ibuprofen was observed with pooled RR of 0.91 (95% CI: 0.83–0.98) and 0.81 (95% CI: 0.67–0.97), respectively	NSAIDs use is associated with a slight decrease in risk for the development of breast cancer

Takkouche et al[100]	Meta-analysis (38 studies)	NSAIDs (ibuprofen or aspirin) vs nonuse	2,788,715 women	Breast cancer risk	NSAID use was associated with reduced risk for breast cancer (RR: 0.88, 95% CI: 0.84–0.93). Specific analyses for aspirin (RR: 0.87, 95% CI: 0.82–0.92) and ibuprofen (RR: 0.79, 95% CI: 0.64–0.97) yielded similar results	NSAID use is associated with reduced risk for breast cancer
Zhang et al[101]	RCT	Low-dose aspirin vs placebo	39,876 women with no history of cancer or CVD	Breast cancer incidence and tumor characteristics	Low-dose aspirin had no significant effect on risk of total, invasive or in-situ breast cancers	Findings suggest that low-dose aspirin does not have a preventive effect on breast cancer
Mangiapane et al[102]	Meta-analysis (10 studies)	Aspirin (varying doses and durations)	> 200,000 pre- and postmenopausal women	Breast cancer risk	The combined estimate of the RR was 0.75 (95% CI: 0.64–0.88) using the random-effects model. Heterogeneity between the studies could not be explained by the covariates study-type and study-population. The combination of frequency and duration of aspirin use resulted in a significant dose–response relationship between aspirin use and breast cancer risk. Each additional pill/year reduced the breast cancer risk to ~2%	Findings support evidence that aspirin may reduce breast cancer risk. Moreover, a dose–response relationship seems to exist
Cook et al[103]	RCT	Aspirin 100 mg (alternate days) vs placebo	19,934 women aged 45 years	Cancer risk and cancer mortality	Low-dose aspirin had no effect on the RR for: • Total cancer (RR: 1.01, 95% CI: 0.94–1.08; $P = 0.87$) • Breast cancer (RR: 0.98, 95% CI: 0.87–1.09; $P = 0.68$) • Colorectal cancer (RR: 0.97, 95% CI: 0.77–1.24; $P = 0.83$) A trend toward reduction in risk (RR: 0.78, 95% CI: 0.59–1.03; $P = 0.08$) was observed for lung cancer There was also no reduction in cancer mortality either overall (RR:0.95, 95% CI: 0.81–1.11; $P = 0.51$) or by site, except for lung cancer (RR: 0.70, 95% CI: 0.50–0.99; $P = 0.04$)	Low-dose aspirin (100 mg on alternate days) for an average 10 years of treatment does not lower risk of total, breast, colorectal, or other site-specific cancers

Abbreviations: CI, confidence interval; NSAID, nonsteroidal anti-inflammatory drug; OR, odds ratio; RCT, randomized controlled trial; RR, relative risk.

Conclusion

Aspirin has a clear role in the secondary prevention of CVD in individuals. Although initial trials with aspirin had limited representation of women, subsequent large-scale, long-term studies have confirmed the relevance of the findings in women. RCTs and cohort studies show that aspirin is also consistent in reducing the risk of first events in appropriate patients and support the benefit–risk profile of aspirin in primary prevention. Beyond CVD, however, aspirin may provide additional benefits in women. Numerous trials have indicated the benefits of aspirin for preeclampsia, in reducing IUGR, and in preventing miscarriage in pregnant women with APLAs. Trials also suggest that there may be benefits for individuals diagnosed with breast cancer, although these findings require confirmation in larger, long-term studies. The low rates of uptake of aspirin among women in whom it is indicated remains a concern given the role of CVD in death among women. Reasons why women are less likely to have been prescribed aspirin have not been established, but the overall underuse of aspirin in women needs to be addressed. Although aspirin use in women is recommended in a number of CVD prevention guidelines, it is possible that the development of more extensive guidelines specific to women's issues could address some of these concerns. A number of ongoing trials are looking at the role of aspirin in women only studies; these include breast cancer (in women on tamoxifen therapy), in preeclampsia (in combination with enoxaparin or progesterone), and in recurrent miscarriage (in combination with folic acid, steroids, or heparin).

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Disclosure

The authors report no conflicts of interest in this work.

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