ABSTRACT

Aspirin's antithrombotic effects have a long-established place in the prevention of cardiovascular disease (CVD), and its traditional use as a core therapy for secondary prevention of CVD is well recognized. However, with the advent of newer antiplatelet agents and an increasing understanding of aspirin's bleeding risks, its role across the full spectrum of modern CVD prevention has become less certain. As a consequence, recent trials have begun investigating aspirin-free strategies in secondary prevention. For example, a contemporary metanalysis of trials that assessed P2Y\textsubscript{12} inhibitor monotherapy versus prolonged (≥ 12 months) dual antiplatelet therapy (which includes aspirin) after percutaneous coronary intervention reported a lower risk of major bleeding and no increase in stent thrombosis, all-cause mortality, myocardial infarction (MI), or stroke in the P2Y\textsubscript{12} monotherapy group.

In contrast to secondary prevention, aspirin's role in primary prevention has always been more controversial. While historical trials reported a reduction in MI and stroke, more contemporary trials have suggested diminishing benefit for aspirin in this setting, with no reduction in hard outcomes, and some primary prevention trials have even indicated a potential for harm. In this review, we discuss how changing population demographics, enhanced control of lipids and blood pressure, changes in the definition of outcomes like MI, evolution of aspirin formulations, and updated clinical practice guidelines have all impacted the use of aspirin for primary and secondary CVD prevention.
INTRODUCTION

Studied in one of the first randomized clinical trials in medical history, aspirin is one of the oldest and most well-known medications in Western medicine. Due to its proven efficacy, aspirin has been called a “wonder drug.” Irreversibly inhibiting cyclooxygenase and thereby decreasing platelet aggregation, aspirin’s antithrombotic effects quickly established it as a staple in the prevention of cardiovascular disease (CVD). However, with advances in other treatment areas and changing population demographics, its role in cardiovascular disease prevention is evolving. In this focused review, we provide an update of aspirin’s role in the primary and secondary prevention of CVD, with some insights into where the field of CVD prevention might be heading next. The role of aspirin in the treatment and secondary prevention of stroke is not discussed. As such, our focus is on aspirin use among patients at risk for, or with a history of, either acute coronary syndrome (ACS) or chronic coronary syndrome (CCS).

SECONDARY PREVENTION

Aspirin is a generally unquestioned core therapy in the secondary prevention of CVD because it inhibits platelet aggregation, thereby reducing the risk for recurrent arterial thrombosis. With a strong evidence base confirmed by the Antithrombotic Trialists’ Collaboration, international guidelines recommend lifelong aspirin as secondary prevention for the majority of adults at risk for recurrent CVD. Even so, the advent of newer and more potent antiplatelet drugs, such as the P2Y₁₂ inhibitors, have expanded antithrombotic options for secondary prevention beyond aspirin.

Aspirin’s association with an increased bleeding risk is also well established, particularly with respect to gastrointestinal bleeding events (Figure 1). While many of these events are not fatal, bleeding linked to antiplatelet use after percutaneous coronary intervention (PCI) has been associated with an increased risk of all-cause mortality. Therefore, recent trials have increasingly tested so-called “aspirin-free” strategies in selected secondary prevention patients. We note here that the term “aspirin-free strategy” is technically a misnomer when applied to persons undergoing PCI since no outcomes trial to date has tested the efficacy and safety of PCI without providing aspirin and another antiplatelet agent at the time of PCI and immediately afterwards. Rather, almost all of these “aspirin-free strategy” trials tested discontinuing aspirin 1 or more months after PCI, with only one trial studying PCI with aspirin loading provided at the time of the procedure but no aspirin provided afterwards. As such, we are not aware of any trial in which patients undergoing PCI received no periprocedural aspirin at all.

ASPIRIN IN PATIENTS WITH RECENT PERCUTANEOUS CORONARY INTERVENTION

As noted above, aspirin’s role in the immediate period (1–3 months) after recent PCI remains unquestioned to date. The traditional approach was to continue a regimen of oral dual antiplatelet therapy, or DAPT (such as aspirin plus another platelet inhibitor), for a period of 6 or 12 months after PCI in CCS and ACS, respectively. Following that, guidelines recommend lifelong aspirin therapy. However, the ubiquitous requirement for post-PCI aspirin beyond the 1- to 3-month mark has recently been challenged. Recent trials have started to examine both shorter durations of DAPT as well as monotherapy with P2Y₁₂ inhibitors in place of aspirin, particularly in the setting of triple therapy.

Two recent meta-analyses including 32,145 patients who underwent PCI in the setting of either CCS or ACS concluded that early aspirin discontinuation (1–3 months after PCI) was associated with a significant reduction in major bleeding by almost 40%, without increasing the ischemic risk or patient mortality. While statistically inconclusive, the meta-analyses do suggest that 3 months of DAPT might be better than 1 month in terms of balancing bleeding and ischemic risks in these post-PCI patients. A detailed discussion of the individual trials can be found in recent reviews by Jacobsen et al. and Cao et al., with an overview in Figure 2.

These findings are now reflected in the most recent guidelines (Table 1), which recommend a shortened duration of DAPT, followed by clopidogrel monotherapy without aspirin, as the treatment of choice for those at very high risk of bleeding following PCI. In patients with a concurrent indication for oral anticoagulation (OAC), guidelines also recommend complete discontinuation of all antiplatelets at 12 months while continuing lifelong OAC monotherapy, effectively removing aspirin from the long-term secondary prevention plan in these patients.

PRIMARY PREVENTION

The use of aspirin in primary prevention was motivated by its initial antithrombotic successes in trials of secondary prevention of CVD. However, aspirin’s role in primary prevention has always been controversial. Aspirin’s first appearance in a major primary prevention guideline was based on five major trials conducted between 1988 and 2001. Further trials followed in the early 2000s. These older trials, summarized in Table 2, were collated in meta-analyses reporting that primary prevention aspirin did not reduce nonfatal MI, with a trend to lower mortality, especially in persons with increased CVD risk (eg, 10-yr risk > 10%). However, the trials conducted in the 2000s suggested that there may be some temporal reduction in aspirin’s efficacy in the primary prevention.
A recent study showed no difference in the primary end point of a composite outcome of time to first occurrence of confirmed MI, stroke, CV death, unstable angina, or transient ischemic attack between the two groups (HR 0.96; 95% CI, 0.81–1.13; \( P = .6038 \)). However, on a (less causally valid) per protocol analysis, the hazard ratios for both combined fatal/nonfatal MI and nonfatal MI were lower in the aspirin group (HR 0.53; 95% CI, 0.36–0.79; \( P = .0014 \) for total MI and HR 0.55; 95% CI, 0.36–0.84; \( P = .0056 \) for nonfatal MI).

The ASCEND (A Study of Cardiovascular Events in Diabetes) trial included 15,480 participants \( \geq 40 \) years of age, most of whom were considered low (\(< 5\%\) to moderate (5–10\%\) risk for a cardiovascular event in 5 years. The occurrence of the primary outcome of a first vascular event (a composite of nonfatal MI, nonfatal stroke, or transient ischemic attack, or death from any vascular cause excluding confirmed intracranial hemorrhage) was lower in the aspirin group than the placebo group (8.5\% vs 9.6\%, respectively; rate ratio 0.88; 95% CI, 0.79–0.97; \( P = .01 \)). There was no significant difference between groups in the mortality rate from all combined vascular causes. The aspirin group had a significantly higher incidence of major bleeding compared with the placebo group (4.1\% vs 3.2\%; rate ratio 1.29; 95% CI, 1.09–1.52; \( P = .003 \)). Most of these were a result of gastrointestinal bleeding (41.3\%).

Aspirin in Reducing Events in the Elderly (ASPREE) was the final and largest of the trials published in 2018. Relevantly, it targeted an older population with a median age of 74 years. The trial found no significant difference in cardiovascular events (including fatal and nonfatal MI and stroke) between the aspirin versus control groups (HR 0.95; 95% CI, 0.83–1.08), and the rates of fatal CVD were also similar. Significant for this age group, aspirin
Figure 2 Recent trials assessing aspirin-free strategies following primary percutaneous coronary intervention in patients with and without a dual indication for oral anticoagulation. NR: not reported; HR: hazard ratio; CI: confidence interval; CV: cardiovascular; ISTH: International Society of Thrombosis and Haemostasis; MI: myocardial infarction; BARC: bleeding academic research consortium; TIMI: thrombosis in myocardial infarction.

Allocated antiplatelet therapy was continued for at least 1 month, up to 1 year in those with stable coronary disease who received a bare metal stent. The decision on duration was at the discretion of the attending physician. In patients with an acute coronary syndrome or those who received a drug-eluting stent, clopidogrel was continued for at least 1 year.

* Aspirin was continued for 1 month in those with a bare metal stent and 3 months in those with a drug-eluting stent.

# Aspirin was continued for a minimum of 1 month and up to 12 months at the investigator’s discretion.

Very-low-dose rivaroxaban = 2.5 mg twice daily.
also did not reduce the risk of incident disability. In addition, there was a substantially higher rate of major hemorrhagic events in the aspirin group (HR 1.38; 95% CI, 1.18–1.62; \(p < .001\)) as well as a suggestion of increased mortality (HR 1.14; 95% CI, 1.01–1.29). Following the publication of ASPREE, the American College of Cardiology/American Heart Association recommended aspirin only in select patients and recommend against routine use in primary prevention among adults over age 70.

The most recent study, TIPS-3 (The International Polycap Study 3), was published in 2020. Participants were randomized in a two-by-two factorial fashion to receive aspirin plus placebo, polypill (simvastatin, atenolol, hydrochlorothiazide, and ramipril) plus placebo, double placebo, or double active treatment. In a direct comparison of aspirin to placebo, the aspirin group showed no difference regarding death from cardiovascular causes, MI, or stroke (HR 0.86; 95% CI, 0.67–1.10). When comparing polypill plus aspirin to double placebo, the primary outcome (a composite of death from cardiovascular causes, MI, stroke, heart failure, resuscitated cardiac arrest, or arterial revascularisation) occurred in 59 (4.1%) of those in the polypill-plus-aspirin group versus 83 (5.8%) in the double-placebo group (HR 0.69; 95% CI, 0.50–0.97). However, given the null finding when comparing aspirin to placebo, this benefit of polypill plus aspirin over double placebo was driven by the polypill component of the intervention. Notably, there were no reported increases in bleeding events in TIPS-3 participants who received aspirin versus placebo. Given the consistency of excess bleeding risks documented across similar previous aspirin trials, this raises questions as to (A) the validity of bleeding outcomes in the TIPS-3 trial, which do not appear to have been adjudicated, and (B) how well participants adhered to the trial regimen. With regard to A, while the aspirin dose was low in TIPS-3 (75 mg), the HOT (Hypertension Optimal Treatment) trial used the same dosing regime in a much larger population and found a significant increase in nonfatal bleeding risks.
| STUDY                | BMD | PHS | TPT | HOT | PPP | WHS | POPAD | JPAD | AAA | JPP | ARRIVE | ASCEND | ASPREE | TIPS-3 |
|---------------------|-----|-----|-----|-----|-----|-----|-------|------|-----|-----|--------|--------|--------|-------|
| Year                | 1988| 1989| 1998| 1998| 2001| 2005| 2008  | 2008 | 2010| 2014| 2018   | 2018   | 2018   | 2020  |
| Participants        | 5,139| 2,071| 5,085| 18,790| 4,495| 39,876| 12,76 | 2,539| 3,350| 14,464| 12,546| 15,460| 11,914| 5,713 |
| Design              | Randomized (control), blinded (2:1 randomization in favor of the aspirin group) | Prospective, randomized double-blind placebo-controlled trial | Randomized, double-blind, placebo-controlled trial, 2 x 2 factorial design | Randomized, double-blind placebo-controlled trial, 2 x 2 factorial design | Randomized, open-label trial (blinded end point assessment) | Randomized double-blind, placebo-controlled trial, parallel group | Randomized, double-blind, placebo-controlled trial | Randomized, double-blind, placebo-controlled trial, factorial design |
| Aspirin Dose        | 300 mg or 500 mg daily aspirin | 75 mg controlled-release aspirin | 100 mg enteric-coated aspirin | 75 mg aspirin | 100 mg enteric-coated aspirin | 100 mg enteric-coated aspirin | Enteric-coated aspirin | 100 mg enteric-coated aspirin | 100 mg enteric-coated aspirin | Enteric-coated aspirin 75 mg daily |
| Comparator          | Placebo | No aspirin | Placebo | Placebo | Placebo | No aspirin | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo | Placebo |
| Population          | Healthy male doctors in US ages 40-84 years | Healthy male doctors in US ages 40-84 years | Men and women aged 50-80 years with diastolic BP ≥ 100 mmHg and 115 mmHg to two occasions | Men and women aged 50-80 years with diastolic BP ≥ 100 mmHg and 115 mmHg to two occasions | Healthy female health professionals ≥ 45 years | Men and women aged 30-85 years with diabetes and A1C ≤ 0.99 | Men and women aged 60-85 years w/ hyper tension, hyperlipidemia or diabetes | Men and women aged 50-75 years w/ A1C ≤ 0.95 | Men aged ≥ 55 years w/ 2-4 CV risk factors; women aged ≥ 60 years w/ ≥ 3 CV risk factors | Men and women aged ≥ 70 years | Men aged > 50 years and women aged ≥ 55 years with an elevated INTERHEART score (intermediate or high risk) |
| BMI (kg/m2)         | 22.4 (5-25) | 27.4 | 28.4 | 27.6 | 26 | 29.3 | 24 | - | 24.2 | 28.4 | 30.7 | 28.1 | 25.8 |
| Smoker              | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) | Yes (11%) |
| Hypertension        | Mean BP 135.6 mm Hg (39%) | Mean BP 139 mm Hg (39%) | Mean BP 170/105 mm Hg (39%) | Mean BP 145/85 mm Hg (39%) | Mean BP 135/77 mm Hg (39%) | Mean BP 148/84 mm Hg (39%) | Mean BP 137/78 mm Hg (39%) | Mean BP 145 mm Hg (39%) | Mean BP 145 mm Hg (39%) | Mean BP 145 mm Hg (39%) | Mean BP 145 mm Hg (39%) |
| Hyperlipidemia      | Cholesterol ≥ 6.7 mmol/L (4%) | Mean cholesterol 6.4 mmol/L | Mean cholesterol 6.1 mmol/L | Mean cholesterol 6.1 mmol/L | Mean cholesterol 5.5 mmol/L | Mean cholesterol 5.2 mmol/L | Mean cholesterol 5.2 mmol/L | Mean cholesterol 5.2 mmol/L | Mean cholesterol 5.2 mmol/L | Mean cholesterol 4.2 mmol/L | Mean cholesterol 5.2 mmol/L | Mean cholesterol 3.1 mmol/L |

KOND}
| STUDY | BMD | PHS | TPT | HOT | PPP | WHS | POPAD | JPAD | AAA | JPPP | ARRIVE | ASCEND | ASFREE | TIPS-3 |
|-------|-----|-----|-----|-----|-----|-----|-------|------|-----|------|--------|--------|--------|-------|
| Diabetes | 2% | 2% | – | 8% | 17% | 3% | 100% | 100% | 3% | 34% | 0% | 100% | 100% | 36.7% |
| Statin use (%) | – | – | – | – | 16% | – | – | 26% | – | – | – | 43% | 75% | 34% |

Potential interaction with warfarin arm, so may have been avoided

- Lipid-lowering agents (including statins)
  4% at start, increased to 25% at 5 years

PPI (%)

- Approx. 25% at trial completion

25% at trial entry

### OUTCOME DATA

| Follow-up (years) | Median 5.5 | Median 5 | Median 6.8 | Mean 3.8 | Mean 3.6 | Mean 10.1 | Median 6.7 | Mean 4.4 | Mean 8.2 | Median 5 | Median 5 | Median 7.4 | Mean 4.6 |
|-------------------|------------|---------|------------|---------|---------|---------|------------|---------|---------|---------|---------|---------|---------|
| **Primary end point (aspirin vs control)** | Definite MI or stroke resulting in death (63.2 vs 62.3 per 1,000 person-years; P = NS) | CV mortality (81 vs 83; RR 0.96; CI 0.6–1.54) | Excluding warfarin arm (83 vs 107 events; P = NS) | Major CV events excluding silent MI (315 vs 368; RR 0.85; CI 0.73–0.99; P = 0.03) | Major CV events (45 vs 64; RR 0.71; 95% CI 0.48–1.04) | Major CV events (477 vs 522; RR 0.91; 95% CI 0.80–1.03; P = 0.13) | Major CV (116 vs 117; RR 0.98; 95% CI 0.76–1.26; P = 0.86) | Major CV events (68 vs 86; RR 0.80; 95% CI 0.58–1.10; P = 0.16) | Major CV (193 vs 207; RR 0.96; 95% CI 0.87–1.15; P = 0.34) | Major CV events (269 vs 281; RR 0.98; 95% CI 0.79–0.97; P = 0.01) | Death, dementia, or persistent physical disability (21.5 vs 21.2 per 1,000 person-years; HR 1.01; 95% CI 0.92–1.11; P = 0.79) |
| **Secondary end point (aspirin vs control)** | Nonfatal stroke (32.4 vs 28.5 per 1,000 person-years; P = NS) | MI (139 vs 239; RR 0.56; 95% CI 0.45–0.70; P < 0.0001) | Stroke (119 vs 98; RR 1.22; 95% CI 0.93–1.60; P = 0.15) | MI (82 vs 127; RR 0.64; 95% CI 0.49–0.85; P = 0.002) | Stroke (146 vs 148; RR 0.98; 95% CI 0.78–1.24; P = 0.88) | Total CV events (141 vs 187; RR 0.77; 95% CI 0.62–0.95) | CV death (17 vs 31; RR 0.56; 95% CI 0.31–0.99) | All-cause mortality (62 vs 68; RR 0.81; 95% CI 0.58–1.13) | CV mortality (1 vs 10; RR 0.01; 95% CI 0.01–0.79; P = 0.0037) | Composite of primary end point or angina, claudication, or TIA | Composite of primary end point or other ischaemia (280 vs 319; RR 0.89; 95% CI 0.75–1.04; P = 0.14) | Composite of major vascular event (83 vs 93; RR 0.88; 95% CI 0.80–0.97; | Death from CV causes, MI, or stroke (116 vs 134; RR 0.86; 95% CI 0.67–1.10) |
| | | | | | | | | | | Composite of individual outcomes of the time to CV death, MI, or stroke; time to UA, time to TIA, and time to death (P = NS for all end points) | | | |

(Knd.)
Table 2 Summary of major primary prevention trials to date. Baseline characteristics represent an average of the complete trial population (ie, both control and treatment arms). BMD: British Male Doctors; PHS: Physicians Health Study; TPT: Thrombosis Prevention Trial; HOT: Hypertension Optimal Treatment; PPP: Primary Prevention Project; WHS: Women’s Health Study; POPADAD: Progression of Arterial Disease and Diabetes; JPAD: Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes; AAA: Aspirin for Asymptomatic Atherosclerosis; JPPP: Japanese Primary Prevention Project; ARRVIE: Aspirin to Reduce Risk of Initial Vascular Events; ASCEND: A Study of CV Events in Diabetes; ASPREE: Aspirin in Reducing Events in the Elderly; TIPS-3: The International Polycap Study-3; BP: blood pressure; CI: confidence interval; CV: cardiovascular; CVD: cardiovascular disease; BP: blood pressure; ABI: ankle brachial index; GI: gastrointestinal; IHD: ischemic heart disease; LDL-c: low density lipoprotein cholesterol; MI: myocardial infarction; NS: nonsignificant; PPI: proton pump inhibitor; SBP: systolic blood pressure; TIA: transient ischemic attack; UA: unstable angina; UK: United Kingdom; US: United States; BMI: body mass index.
(70 vs 129; RR 1.8; P < .001). With regard to B, there was higher-than-anticipated discontinuation of the trial regime (39.7% for the aspirin vs placebo comparison, whereas expected incidence was 20%). This was partially due to significant trial interruptions from the COVID-19 pandemic, which led to barriers regarding drug delivery, access for in-person follow-up, and overall completion of trial visits. The trial also included a 3- to 4-week run-in period, during which 9.5% of potentially eligible patients were excluded from the randomization process due to intolerance of the trial medications.

**SO, WHAT HAS CHANGED?**

One of the main theories explaining the potential change in aspirin’s efficacy in CVD prevention focuses on the changing context in which aspirin is being tested. While the most recent aspirin trials attempted to select patients at higher risk, the observed event rates were often lower than expected, likely due to better CVD risk factor management and contemporary treatments. Consequently, the argument has been made that statin use in primary prevention has shown far greater consistent benefit, without the drawbacks of bleeding, and may offer a better “bang for your buck” compared with widespread aspirin use.

In addition, the introduction of newer high-sensitivity troponins has changed the way we define MIs. Synchronously, expedited mechanical reperfusion with PCI has now become the standard of care, which means there is a lower likelihood of a fatal outcome after an MI than when original primary prevention trials were conducted. Both of these factors may have changed the influence of aspirin on ischemic outcomes in modern patients. Dosing regimens of aspirin have also changed significantly, with earlier trials including doses of up to 500 mg compared with 75 mg used in the most recent TIPS-3 trial. Whereas historical trials used “plain” aspirin, newer trials have started to include enteric-coated (EC) aspirin. It is possible that EC aspirin may be less effective than regular aspirin, with suggestions of increased aspirin resistance in those receiving EC aspirin formulations and even reduced oral bioavailability at increased body weights. All of these factors may be contributing to differences we are seeing in contemporary trial outcomes testing the efficacy of aspirin in primary prevention.

**WHERE TO NEXT?**

**WHAT’S NEXT IN SECONDARY PREVENTION?**

The recurrent theme from recent secondary prevention trials is that earlier cessation of the aspirin component of DAPT and continuation with a more potent P2Y₁₂ inhibitor alone does not translate into an increased ischemic risk in the short term, although it adds the benefit of reduced bleeding risks. However, most of the trials in this area had a limited follow-up period. Therefore, the question remains as to what should happen once a patient meets the 12-month mark. Is continuation with lifelong P2Y₁₂ inhibitors the way forward, or is a switch back to lifelong aspirin and discontinuation of the P2Y₁₂ inhibitor the more appropriate choice? Given the increased bleeding risk in the aging population, the question also remains as to whether complete discontinuation of all antiplatelet therapy at 12 months, with focus on maintaining other secondary prevention targets, may also be a worthwhile option.

There are currently several ongoing trials aiming to further elucidate these questions. As it stands, in the absence of a concurrent indication for OAC, aspirin remains the antiplatelet of choice for long-term secondary prevention of ACS/CCS.

**WHAT’S NEXT IN PRIMARY PREVENTION?**

The next frontier for aspirin in the primary prevention space is identifying those individuals considered at high risk of CVD who may benefit from aspirin use as a primary preventive strategy. There are several heterogeneous risk scores available, and while they have traditionally performed well in the population in which they were validated, we know that they are imperfect at an individual level.

Addition of a coronary artery calcium (CAC) score to personalize a patient’s risk assessment has also been gaining traction, with the 2018 Cholesterol Clinical Practice Guidelines supporting its use in decision making in relation to statin use. One of the drawbacks of traditional risk factor scores is that patients with higher scores, and therefore considered at higher risk of CVD, are often also at higher risk of bleeding. This is in part based on the heavy reliance on age as a prediction variable, where increasing age confers both an increased risk of CVD and bleeding. While a high CAC also has been correlated with an increased bleeding risk, this correlation is weaker than the association between age and bleeding. Therefore, calculation of a CAC score in those with a borderline or high CV risk score but a lower bleeding risk may help to identify those who will benefit from aspirin therapy. Specifically, CAC scores ≥ 100 and ≥ 400 have been shown to identify those likely to experience a net benefit from aspirin therapy. Conversely, a CAC score equal to 0 may be a useful way of identifying patients with high calculated CVD risk scores who are in fact low risk and in turn should avoid aspirin.

**CONCLUSION**

With rapidly evolving novel antithrombotic and preventive therapies, our ability to modify cardiovascular risk factors has improved. With that, the role of aspirin in
both primary and secondary prevention in the modern era also continues to evolve. In secondary prevention, use of P2Y₁₂ inhibitors has modified the need for aspirin in patients with higher bleeding risks. Further trials with direct comparisons between the different P2Y₁₂ inhibitors and with longer follow-up periods are needed, as are trials truly testing whether PCI can be performed without administering aspirin. In the primary prevention of CVD, newer trials have affirmed that aspirin has a limited role, perhaps best conserved for a select group of primary prevention patients who are at higher risk of CVD but low risk of bleeding. Our task is to identify who exactly these patients are. Furthermore, patients and providers must acknowledge that primary prevention aspirin is only proven to reduce nonfatal CVD events, with no impact on mortality and thus patient longevity. While the landscape is changing, the chapter on aspirin is far from over.

KEY POINTS

- Rapidly evolving novel antithrombotic and preventive therapies have transformed our ability to modify cardiovascular risk factors. As a result, aspirin’s role in primary and secondary prevention of cardiovascular disease (CVD) is evolving.
- Availability of alternative antiplatelet agents, such as P2Y₁₂ inhibitors, mean that aspirin is no longer a ubiquitous requirement beyond the 1-month period following percutaneous coronary intervention (PCI).
- Guidelines now recommend complete discontinuation of aspirin 12 months after PCI in patients with a concurrent indication for oral anticoagulation therapy.
- The use of aspirin for primary prevention may be considered in a select group of patients who are at high risk of incident CVD but have a low bleeding risk.

COMPETING INTERESTS

The authors have completed and submitted the Methodist DeBakey Cardiovascular Journal Conflict of Interest statement and none were reported.

AUTHOR AFFILIATIONS

Ella Murphy, MB BCh BAO, MSc
National University of Ireland, Galway, Ireland

James M. G. Curneen, MB BCh BAO orcid.org/0000-0002-6414-9803
National University of Ireland, Galway, Ireland

John W. McEvoy, MB BCh BAO, MEd, MHS orcid.org/0000-0001-6530-5479
National University of Ireland, Galway, Ireland

REFERENCES

1. Fuster V, Sweeney Joseph M. Aspirin: a historical and contemporary therapeutic overview. 2011 Feb 22;123(7):768-78. doi: 10.1161/CIRCULATIONAHA.110.963843
2. Jeffreys D. Aspirin: The Remarkable Story of a Wonder Drug. New York, NY: Bloomsbury Publishing Inc.; 2004. 352 p.
3. Collaborative overview of randomised trials of antiplatelet therapy—1: Prevention of death, myocardial infarction, and stroke by prolonged antiplatelet therapy in various categories of patients. Antiplatelet Trialists’ Collaboration. BMJ. 1994 Jan 8;308(6921):81-106.
4. Baigent C, Blackwell L, Collins R, et al.; Antithrombotic Trialists’ (ATT) Collaboration. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009 May 30;373(9678):1849-60. doi: 10.1016/S0140-6736(09)60503-1
5. Jacobsen AP, Rabe I, McCarthy CP, et al. Lifelong Aspirin for All in the Secondary Prevention of Chronic Coronary Syndrome: Still Sacrosanct or Is Reappraisal Warranted? Circulation. 2020 Oct 20;142(16):1579-90. doi: 10.1161/CIRCULATIONAHA.120.045695
6. Antiplatelet Trialists’ Collaboration. Secondary prevention of vascular disease by prolonged antiplatelet treatment. Antiplatelet Trialists’ Collaboration. Br Med J (Clin Res Ed). 1988;296(6168):320-331.
7. Antithrombotic Trialists Collaboration. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002 Jan 12;324(7329):71-86. doi: 10.1136/bmj.324.7329.71
8. CAPRIE Steering Committee. A randomised, blinded, trial of clopidogrel versus aspirin in patients at risk of ischaemic events (CAPRIE). Lancet. 1996 Nov 16;348(9038):1329-39. doi: 10.1016/s0140-6736(96)09457-3
9. Coo D, Chandiramani R, Chiarito M, Claessen BE, Mehran R. Evolution of antithrombotic therapy in patients undergoing percutaneous coronary intervention: a 40-year journey. Eur Heart J. 2021 Jan 21;42(4):339-51. doi: 10.1093/eurheartj/ehaa824
10. Généreux P, Giustino G, Witzenbichler B, et al. Incidence, Predictors, and Impact of Post-Discharge Bleeding After Percutaneous Coronary Intervention. J Am Coll Cardiol. 2015 Sep 1;66(9):1036-45. doi: 10.1016/j.jacc.2015.06.1323
11. Kogame N, Guimarães Patricia O, Modolo R, et al. Aspirin-Free Prasugrel Monotherapy Following Coronary Artery Stenting in Patients With Stable CAD. JACC: Cardiovascular Interventions. 2020;13(19):2251-2262. doi: 10.1016/j.jcin.2020.06.023
12. Knuuti J, Wijns W, Saraste A, et al.; ESC Scientific Document Group. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J. 2020 Jan 14;41(3):407-477. doi: 10.1093/eurheartj/ehz425
13. Giacoppo D, Matsuda Y, Fovino LN, et al. Short dual antiplatelet therapy followed by P2Y12 inhibitor monotherapy vs. prolonged dual antiplatelet therapy after percutaneous coronary intervention with second-generation drug-eluting stents: a systematic review and meta-analysis of randomized clinical trials. Eur Heart J. 2021 Jan 21;42(4):308-319. doi: 10.1093/eurheartj/ehaa739

14. O'Donoghue ML, Murphy SA, Sabatine MS. The Safety and Efficacy of Aspirin Discontinuation on a Background of a P2Y 12 Inhibitor in Patients After Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis. Circulation. 2020 Aug 11;142(6):538-45. doi: 10.1161/CIRCULATIONAHA.120.046251

15. Kumbhani DJ, Cannon CP, Beavers CJ, et al. 2020 ACC Expert Consensus Decision Pathway for Antiagulant and Antiplatelet Therapy in Patients With Atrial Fibrillation or Venous Thromboembolism Undergoing Percutaneous Coronary Intervention or With Atherosclerotic Cardiovascular Disease: A Report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol. 2021 Feb 9;77(5):629-58. doi: 10.1016/j.jacc.2020.09.011

16. Hindricks G, Potpara T, Dogres N, et al. 2020 ESC Guidelines for the diagnosis and management of atrial fibrillation developed in collaboration with the European Association for Cardio-Thoracic Surgery (EACTS). Eur Heart J. 2021 Feb 1;42(5):373-498. doi: 10.1093/eurheartj/ehaa412

17. Raber I, McCarthy CP, Vaduganathan M, et al. The rise and fall of aspirin in the primary prevention of cardiovascular disease. 2019 May 25;393(10186):2155-67. doi: 10.1016/j.s0140-6736(19)30541-0

18. Levine GN, Bates ER, Bittl JA, et al. 2016 ACC/AHA Guideline Focused Update on Duration of Dual Antiplatelet Therapy in Patients With Coronary Artery Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines: An Update of the 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention, 2011 ACCF/AHA Guideline for Coronary Artery Bypass Graft Surgery, 2012 ACC/AHA/ACP/AATS/PCNA/SCAI/STS Guideline for the Diagnosis and Management of Patients With Stable Ischemic Heart Disease, 2013 ACCF/AHA Guideline for the Management of ST-Elevation Myocardial Infarction, 2014 AHA/ACC Guideline for the Management of Patients With Non-ST-Elevation Acute Coronary Syndromes, and 2014 ACCF/AHA Guideline on Perioperative Cardiovascular Evaluation and Management of Patients Undergoing Noncardiac Surgery. Circulation. 2016 Sep 6;134(10):e123-55. doi: 10.1161/CIR.0000000000000404

19. Petro R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J (Clin Res Ed). 1988 Jan 30;296(6618):313-6. doi: 10.1136/bmj.296.6618.313

20. 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 Jul 20;321(3):129-35. doi: 10.1056/NEJM198907203210301

21. Thrombosis prevention trial: randomised trial of low-intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease in men at increased risk. The Medical Research Council’s General Practice Research Framework. Lancet. 1998 Jan 24;351(9098):233-41.

22. Hansson L, Zanchetti A, Carruthers S, et al. Effects of intensive blood-pressure lowering and low-dose aspirin in patients with hypertension: principal results of the Hypertension Optimal Treatment (HOT) randomised trial. HOT Study Group. Lancet. 1998 Jun 13;351(9118):1755-62. doi: 10.1016/s0140-6736(98)04311-6

23. de Gaetano G, Collaborative Group of the Primary Prevention Project. Low-dose aspirin and vitamin E in people at cardiovascular risk: a randomised trial in general practice. Collaborative Group of the Primary Prevention Project. Lancet. 2001 Jan 13;357(9250):89-95. doi: 10.1016/s0140-6736(00)03539-x

24. Ridker PM, Cook NR, Lee IM, et al. A randomized trial of low-dose aspirin in the primary prevention of cardiovascular disease in women. N Engl J Med. 2005 Mar 31;352(13):1293-304. doi: 10.1056/NEJMoa050613

25. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial: factorial randomised placebo controlled trial of aspirin and antioxidants in patients with diabetes and asymptomatic peripheral arterial disease. BMJ. 2008 Oct 16;337:a1840. doi: 10.1136/bmj.a1840

26. Ogawa H, Nakayama M, Morimoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in patients with type 2 diabetes: a randomized controlled trial. JAMA. 2008 Nov 12;300(18):2134-41. doi: 10.1001/jama.2008.623

27. Fowkes FGR, Price JF, Stewart MCW, et al.; Aspirin for Asymptomatic Atherosclerosis Trialists. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010 Mar 3;303(9):841-8. doi: 10.1001/jama.2010.221

28. Ikeda Y, Shimada K, Teramoto T, et al. Low-dose aspirin for primary prevention of atherosclerotic events in Japanese patients 60 years or older with atherosclerotic risk factors: a randomized controlled clinical trial. JAMA. 2014 Dec 17;312(23):2510-20. doi: 10.1001/jama.2014.15690

29. Guirguis-Blake JM, Evans CV, Senger CA, O’Connor EA, Whitlock EP. Aspirin for the Primary Prevention of Cardiovascular Events: A Systematic Evidence Review for the U.S. Preventive Services Task Force. 2016 Jun 21;164(12):804-13. doi: 10.7326/M15-2113

30. Mora S, Manson JE. Aspirin for Primary Prevention of Atherosclerotic Cardiovascular Disease: Advances in Diagnosis and Treatment. JAMA Intern Med. 2016 Aug 1;176(8):1195-204. doi: 10.1001/jamainternmed.2016.2648
31. Gaziano JM, Brotons C, Coppolecchia R, et al.; ARRIVE Executive Committee. Use of aspirin to reduce risk of initial vascular events in patients at moderate risk of cardiovascular disease (ARRIVE): a randomised, double-blind, placebo-controlled trial. Lancet. 2018 Sep 22;392(10152):1036-46. doi: 10.1016/S0140-6736(18)31924-X

32. Bowman L, Mafham M, Wallendszus K, et al.; ASCEND Study Collaborative Group. Effects of Aspirin for Primary Prevention in Persons with Diabetes Mellitus. N Engl J Med. 2018 Oct 18;379(16):1509-1518. doi: 10.1056/NEJMoa1805819

33. Yusuf S, Joseph P, Dans A, et al.; International Polycap Study 3 Investigators. Polypill with or without Aspirin in Persons without Cardiovascular Disease. N Engl J Med. 2018 Oct 18;379(16):1509-1518. doi: 10.1056/NEJMoa1805819

34. Woods RL, Espinoza S, Thao LTP, et al.; ASPREE Investigator Group. Effect of Aspirin on Activities of Daily Living Disability in Community-Dwelling Older Adults. J Gerontol A Biol Sci Med Sci. 2020 Dec 26;glaa316. doi: 10.1093/gerona/glaa316

35. Arnett DK, Blumenthal RS, Albert MA, et al. 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. 2019 Jun 18;139(25):e1162-e1177. doi: 10.1161/CIR.0000000000000638

36. Cainzos-Achirica M, Miedema MD, McEvoy JW, et al. Coronary Artery Calcium for Personalized Allocation of Aspirin in Primary Prevention of Cardiovascular Disease in 2019: The MESA Study (Multi-Ethnic Study of Atherosclerosis). Circulation. 2020 May 12;141(19):1541-53. doi: 10.1161/CIRCULATIONAHA.119.045010

37. Ajufo E, Ayers CR, Vigen R, et al. Value of Coronary Artery Calcium Scanning in Association With the Net Benefit of Aspirin in Primary Prevention of Atherosclerotic Cardiovascular Disease. JAMA Cardiol. 2021 Feb 1;6(2):179-87. doi: 10.1001/jamacardio.2020.4939