Chapter 12
Medical and Invasive Management of Coronary Artery Disease in Patients on Anticoagulants

Ryan Berg and Nabil Shafi

Abstract The management of coronary artery disease in patients on anticoagulants represents a difficult clinical scenario. As more intense therapy is given, patients are expected to have less ischemic/thrombotic events, but they will have increased bleeding risks. In this chapter we examine the evidence base of the risks and benefits of combining antiplatelet therapy and anticoagulant therapy in both the primary and secondary prevention settings. While most of these data concern warfarin as the primary anticoagulant, we will review any data on the novel oral anticoagulants (NOACs) as well.

Keywords Aspirin • Clopidogrel • Warfarin • Coronary artery disease • Triple therapy • Novel oral anticoagulants

Introduction

The management of coronary artery disease (CAD) in patients on anticoagulants represents a difficult clinical scenario. This has been previously described as a "Yin-Yang" paradigm of balancing anti-ischemic efficacy and bleeding risk when combining more potent antithrombotic/anticoagulant therapy [1]. As more intense therapy is given, patients are expected to have less ischemic/thrombotic events, however, in return they are at risk for increased bleeding. There is further potential risk when a recent coronary stent is placed in a patient on an anticoagulant due to the concern for stent thrombosis with early discontinuation of antiplatelet therapy if a bleeding episode occurs. To further complicate the matter, there are now multiple antiplatelet agents available (ticagrelor, clopidogrel, prasugrel, ticlopidine, aspirin) as well as multiple oral anticoagulants (warfarin, dabigatran, rivaroxaban, and

R. Berg, MD (✉) • N. Shafi, MD
UCSF Fresno Department of Cardiology, Community Regional Medical Center, Fresno, CA, USA
e-mail: medrberg@hotmail.com

J.A. Ambrose, A.E. Rodríguez (eds.), *Controversies in Cardiology*,
DOI 10.1007/978-3-319-20415-4_12

apixaban). This chapter examines the evidence base in both primary and secondary prevention and considers the controversies and unresolved issues surrounding the use of triple therapy. While most of these data utilized warfarin as the primary anticoagulant, we will review any data on the novel oral anticoagulants (NOACs) as well.

Aspirin for Primary Prevention of Cardiovascular Disease in addition to anticoagulation

Aspirin (ASA) has been the mainstay of pharmacotherapy for the secondary prevention of cardiovascular events by reducing mortality and decreasing subsequent cardiac events [2]. Aspirin's antithrombotic effect is through the irreversible inhibition of COX-1 and 2, which prevents the generation of prostaglandins including thromboxane A2 that induce platelet aggregation. Consequently, the principle effect of ASA is the inhibition of platelet-mediated thrombus formation in the arterial circulation [2–4]. The prophylactic use of ASA for the primary prevention of coronary artery disease (CAD) events has been extensively investigated over the last 25 years and the data are less certain than the secondary prevention data. Questions remain regarding the efficacy, safety and the degree of cardiovascular risk associated with the most favorable benefit: risk ratio for its use in primary prevention of CAD.

A meta-analysis carried out by the Anti-Thrombotic Trialists (ATT) Collaboration in 2009 [5] included the first six primary prevention trials [6–11] (n = 95,000) and demonstrated ASA significantly reduced the incidence of serious vascular events, defined as a combined end point of MI, death from a vascular cause or stroke (0.51 versus 0.57 %/year). This significant reduction was attributable principally to a significant reduction in the first non-fatal MI (0.18 versus 0.23 %/year). ASA therapy was associated with six fewer myocardial infarctions (MI) per 1000 low-risk persons treated over a 10 year period (5 % CAD risk at 10 years according to the Framingham risk categories). For persons at moderate (15 %) and high (25 %) CVD risk, ASA led to a reduction of 19 and 31 MIs per 1000 patients treated, respectively [12]. However, this benefit came at the expense of a bleeding event rate that was higher as a function of cardiovascular risk. Compared with placebo, the high risk population would experience 22 more bleeds per 1000 persons treated with ASA versus 4 more bleeds per 1000 persons treated with ASA in the low-risk population [12]. The meta-analysis by the ATT Collaboration found that allocation to ASA increased major GI and other extracranial bleeds (defined as a bleed requiring transfusion or resulting in death) by about 50 % (0.10 %/year vs. 0.07 %/year; risk ratio: 1.54 [95 % CI: 1.30–1.82], $p < 0.0001$). Furthermore, ASA also increased the risk of hemorrhagic stroke. A meta-analysis of 16 placebo-controlled RCTs, comprising a total of 55,462 patients, showed that treatment with aspirin was associated with a relative risk of hemorrhagic stroke of 1.84 ($p < 0.001$) [13].

With respect to mortality, the ATT Collaboration showed aspirin compared with placebo did not reduce all-cause mortality, cardiovascular mortality, non-vascular

mortality or deaths of unknown cause [4]. Four more recent meta-analyses have been performed by other groups, and published in 2011–2012 [14–17]. In all of them, three additional trials were included: the JPAD (Japanese Primary Prevention of Atherosclerosis With Aspirin for Diabetes), POPADAD (Prevention of Progression of Arterial Disease and Diabetes), and AAA (Aspirin for Asymptomatic Atherosclerosis) trials [18–20]. These meta-analyses had the same unified message that ASA use did not reduce cardiovascular related death or overall mortality. However, ASA use was associated with a 12 % proportional reduction in major vascular events, translating to a number needed to treat (NNT) of about 2000 in low risk individuals to prevent one non-fatal myocardial infarction [21]. In the 2012 meta-analysis, the net cardiovascular benefit exceeded the bleeding risk at higher baseline CAD events rates [17]. In summary, ASA use in the primary prevention of CAD events has been shown to reduce the risk of a first MI (particularly in high risk patients), but coming at a significant expense of an increased risk of both gastrointestinal bleeding and hemorrhagic stroke [7]. As a result, current guidelines differ substantially in their recommendations for ASA's use in primary prevention of CAD, reflecting the uncertainty of a clear risk/benefit ratio in this population [12, 22–24] (see Table 12.1).

As there is already a concern of increased bleeding with aspirin alone for primary prevention, it is no surprise that combining with an anticoagulant in primary prevention leads to even further increases in bleeding. There are limited data that assess combination therapy in the primary prevention cohort. One meta-analysis of ten randomized controlled trials performed by Dentali et al. assessed the treatment of combination warfarin-ASA compared to warfarin alone primarily in patients where the indication for aspirin was the primary prevention of cardiovascular disease (both CAD and stroke) [25]). Six of the trials used low dose aspirin (<100 mg), and four of the trials had higher doses of aspirin. The risk for cardiovascular events

Table 12.1 Summary of major society recommendations for aspirin use in primary prevention of CVD

American Heart Association (AHA)/American College of Cardiology (ACC)/American Diabetes Association (ADA) [22]
1. Aspirin is reasonable in diabetic patient whose 10 year risk of events is >10 % and who are not at increased risk of bleeding 2. Aspirin may be considered for diabetic patients with intermediate risk of cardiovascular events (younger patients with at least risk factor, older patients with no risk factors, or patients with a 10-year risk of 5–10 %)
American College of Chest Physicians (ACCP) [12]
Aspirin (75–100 mg daily) for persons age 50 years or older without symptomatic CVD (Grade 2B)
US Preventative Services Task Force [23]
Low dose Aspirin for men 45–79 years and women 55–79 years when the potential benefit due to reduction of MI outweighs the potential harm due to increase in gastrointestinal hemorrhage (Grade A). Risk factor calculator for available at http://cvdrisk.nhlbi.nih.gov/calculator.asp
European Society of Cardiology [24]
Aspirin is not recommended in individuals without cardiovascular or cerebrovascular disease due to increased risk of major bleeding (Class III, Level of Evidence: B)

was significantly reduced by combination warfarin-ASA therapy (OR = 0.66; 95 % CI: 0.52–0.84). However, this therapeutic benefit was driven by five studies involving patients with mechanical heart valves (OR = 0.27; 95 % CI: 0.15–0.49). There was no statistically significant cardiovascular event reduction in the other studies where the warfarin was given for other indications. The aforementioned meta-analysis also assessed the risk for major bleeding associated with combination warfarin-ASA compared with warfarin alone. There was an increased risk for major bleeding with warfarin-ASA over warfarin alone, with an annual risk of 2.3 % vs. 1.3 %, a difference that was clinically relevant, although it was of borderline statistical significance (OR = 1.43; 95 % CI: 1.00–2.02).

In the ORBIT AF registry, it was found that despite this known evidence, it is common in up to 35 % of patients in atrial fibrillation in modern practice to be on combination therapy with an antiplatelet on top of an anticoagulant [26]. A significant proportion of this population (39 %) was on the antiplatelet agent for primary prevention only. As this was a more modern study, most (89 %) patients were on an 81 mg dose of aspirin. This study also confirmed what was postulated in the prior meta-analysis: combination therapy was associated with more major bleeding (adjusted hazard ratio, 1.53; 95 % confidence interval, 1.20–1.96 p = 0.0006) with no benefit in preventing ischemic outcomes leading toward a trend in increased mortality in the dual therapy group (adjusted hazard ratio 1.26 (0.98–1.63) p = .08).

Overall, there does not appear to be compelling evidence that warfarin-ASA combination therapy is more effective than warfarin alone for the prevention of cardiovascular events in patients with atrial fibrillation. There is, however, consistent evidence that warfarin-ASA therapy increases serious bleeding, irrespective of the patient population studied. As stated above, the group of patients with mechanical heart valves should be considered separately as combination therapy has shown net clinical benefit. Patients with mechanical valve prostheses require long-term anticoagulation and aspirin administration due to the inherent risk of thromboembolism. This is primarily due to abnormal flow conditions (stagnation and shear stress flow) imposed by the prosthetic heart valves, increasing both the risk of thrombosis and thromboembolism [27]. In a Cochrane report, 13 studies involving 4122 patients were reviewed [28]. Compared with anticoagulation alone, the addition of an antiplatelet agent (either dipyridamole or ASA) reduced the risk of thromboembolic events (odds ratio (OR) 0.43, 95 % confidence interval (CI) 0.32–0.59; P < 0.00001). This came at the expense of an increase in major bleeding (OR 1.58, 95 % CI 1.14–2.18; P = 0.006), despite the fact that low dose aspirin (<100 mg) was used in a majority of the trials that included aspirin as the antiplatelet agent. However, the net clinical benefit favored the combination of an anticoagulant plus an antiplatelet, as there was shown to be decreased mortality (OR 0.57, 95 % CI 0.42–0.78; P = 0.0004). In summary, patients with mechanical heart valves derive a net therapeutic benefit with warfarin-ASA as the reduction in thromboembolic events outweighs the increase in the risk for serious bleeding and this combination is endorsed by the latest American College of Cardiology (ACC) 2014 guidelines on Valvular heart disease [29].

Secondary Prevention

While it is fairly clear from primary prevention that the risk of bleeding outweighs the benefit of a combination of antiplatelet therapy and anticoagulation, there is much more controversy in the realm of secondary prevention. There are many different secondary prevention scenarios (stable CAD, acute coronary syndromes, patients after recent coronary artery bypass surgery (CABG), and patients after recent stenting) each of which have different ischemic risk profiles in which to balance the bleeding risk. As we make our decision as to what regimen to give, we are always balancing a risk/benefit ratio of ischemic efficacy vs bleeding risk. The ischemic benefit of the antiplatelet therapy on top of the anticoagulants is quite different in each of those secondary prevention scenarios. Unfortunately, there are not enough data available to cover every different drug in every different clinical scenario. However, we must examine these clinical scenarios separately and review the data that are available and the subsequent guideline recommendations from the major medical societies.

Secondary Prevention of Stable CAD

The ACC guidelines on secondary prevention in stable ischemic heart disease state that aspirin monotherapy (or other antiplatelet if allergic) is a Class I indication to continue lifelong [30]. For a patient on anticoagulation for thrombotic disease, the anticoagulants are more efficacious as compared to antiplatelet agents in preventing a thrombotic event in the common clinical scenarios of deep vein thrombosis (DVT), pulmonary embolism (PE), and atrial fibrillation [31]. It is common in up to 11 % of the population with stable coronary artery to have an indication for anticoagulation [32]. In this situation, it is common for practitioners to combine an antiplatelet agent with an anticoagulant with the thought that they are treating two separate diseases with two separate targeted therapies. However, recent real world registries have shown that the combination can lead to serious bleeding which is an independent predictor of mortality [32, 33]. In the CORONOR trial, over 4000 patients with stable CAD (at least 1 year out from any acute coronary syndrome or revascularization procedure) were prospectively studied over a 2 year period [32]. Patients on an anticoagulant in addition to an antiplatelet had a 7.3 times increased risk of bleeding in comparison to antiplatelet monotherapy. This trial only assessed significant (Bleeding Academic Research Consortium (BARC) 3 or higher) bleeding, and indeed the bleeding events were an independent predictor of mortality in this stable CAD population. There was no downside (no increased ischemic stroke, myocardial infarction or cardiovascular death) to being on a single anticoagulant alone as compared to being on an anticoagulant plus an antiplatelet agent. Therefore, this study clearly shows the benefit of only taking anticoagulation alone (without the addition of any antiplatelet agent) in a stable coronary artery disease patient that is

at least 1 year out from an acute coronary syndrome or any type of revascularization that has a definite indication for anticoagulation. One limitation of this study was that the dosing of aspirin was not reported. A larger observational cohort study of 8700 Danish patients with both atrial fibrillation and stable coronary artery disease backs up this hypothesis as well [33]. They showed that relative to warfarin monotherapy, there was no decrease in the risk of MI or coronary death associated with the use of warfarin plus an antiplatelet agent. In fact, if triple combination therapy was used, there was actually an increase in this ischemic risk. There was also comparative benefit in all of these groups in terms of preventing thromboembolism. On the flip side, bleeding risk hazard ratios were significantly (50–80 %) higher on dual therapy and up to 100 % higher with triple therapy as compared with monotherapy with warfarin alone. Bleeding was also shown to be an independent predictor of mortality in this study as well. What about trying antiplatelet therapy alone in this population? This population had over 95 % of the patients with a $CHADS_2VASC_2$ score of ≥ 2. Antiplatelet therapy alone did have decreased bleeding risks, but in exchange there was increased MI, cardiovascular death, thromboembolism and mortality. Therefore, this is not an acceptable alternative. One limitation of this large data set was that the exact aspirin dosing was not reported and broken down to the individual endpoints, although it was stated that all doses were <150 mg i.e. a relatively low dose. A second limitation was that there were no patients on NOACS or new antiplatelet agents in this trial. However, the combination of dual or single antiplatelet therapy in addition to NOACs has been shown to have a similarly increased bleeding risk without additional stroke prevention benefit [34, 35]. Current guidelines do not provide guidance on combination therapy in this stable ischemic heart disease population.

Secondary Prevention after Acute Coronary Syndrome (ACS) or Percutaneous Coronary Intervention (PCI)

Most ACS patients will undergo an early invasive strategy which frequently leads them to revascularization by CABG or stenting. It is clear from the early stent trials that antiplatelet therapy is more efficacious in preventing stent thrombosis than warfarin alone or with warfarin with a single antiplatelet agent [36–39]. However, these trials involved early generation bare metal stents that were not necessarily deployed appropriately and would be expected to be at a higher risk of thrombosis than current stent deployment techniques with thin strut bare metal stent systems or second /third generation drug eluting stent (DES) systems. On the other hand, it is also clear that dual antiplatelet therapy alone is not a substitute for anticoagulation in those patients at risk of stroke [40]. Therefore, it is important to assess newer trials in the DES area to see where the net clinical benefit of multiple pharmacologic regimens lie.

Initial registry data (n = 239) showed the combination of warfarin plus clopidogrel as having no stent thrombosis compared to a 15 % rate with warfarin plus

aspirin, as well as a higher MI rate of 18.2 % vs 11 % [41]. This was followed by the large Danish registry assessing over 12,000 patients with atrial fibrillation that had a recent MI or PCI on various anticoagulant regimens [42]. This registry showed no increased risk of an ischemic coronary event in double therapy (anticoagulant plus single antiplatelet) vs triple therapy (dual antiplatelet plus anticoagulant). On the other hand, the bleeding risk was lower with dual therapy as compared to triple therapy. When clopidogrel was the antiplatelet agent, this lower bleeding risk was not statistically significant, compared to aspirin which did have statistically significant lower bleeding. One limitation of this trial was that aspirin dosing was not reported. All-cause mortality was statistically significantly lower with the combination of an oral anticoagulant plus clopidogrel in comparison to an oral anticoagulant plus aspirin. As a whole, these registry data are hypothesis-generating suggesting that a combination of clopidogrel plus an oral anticoagulant alone might be the best combination when a stent is placed and both an anticoagulant and an antiplatelet is needed.

The warfarin and clopidogrel combination was more definitively tested in the multicenter, randomized WOEST trial [43]. The WOEST trial studied 573 patients who were on long term anticoagulation for multiple clinical indications (majority of patient had atrial fibrillation) and who were undergoing PCI (25–30 % with acute coronary syndromes). Patients were randomized to receive triple therapy (aspirin at a dose of 80–100 mg, clopidogrel 75 mg, and warfarin) versus dual therapy with warfarin plus clopidogrel. The primary endpoint was any bleeding which occurred more in the triple therapy group (44.4 %) as compared to the double therapy group (19.4 % $p < .0001$). Severe bleeding (BARC 3) was twice as high with triple therapy as compared to double therapy and this was statistically significant. There was no difference in ischemic/thrombotic outcomes in either of the groups. However, there was lower mortality with double therapy (2.5 %) vs triple therapy (6.3 % $p = .027$). While these data are impressive, the study was not powered to consider the ischemic and mortality endpoints and must only be considered hypothesis-generating.

One limitation of these studies was that warfarin was used as the anticoagulant and not the NOACS. However, based on other evidence, it is reasonable to expect similar increased bleeding risk with NOACS as part of a triple therapy combination. For example, in post ACS patients, triple therapy with apixaban was associated with worsening bleeding but no better thromboembolic protection leading to premature discontinuation of the APPRAISE-2 clinical trial [44]. When all studies of NOACs in ACS were included in multiple meta-analyses, a similar trend was seen with at least a doubling of bleeding rate with triple therapy as compared to dual antiplatelet therapy with only a very mild decrease in ischemic events [45, 46].

The newest 2014 ACC guidelines on atrial fibrillation give a IIb recommendation for choosing bare metal stents to minimize the duration of dual antiplatelet therapy in atrial fibrillation patients as compared to DES [47]. There is also a IIb recommendation to use clopidogrel alone plus an oral anticoagulant for those with a $CHADS_2VASC_2$ scores ≥ 2. This is in contrast to the European guidelines on revascularization [48] and their consensus document on atrial fibrillation in the setting of PCI or ACS [49]. These provide more detail depending on the patient's

Recommendations	Class[a]	Level[b]
In patients with a firm indication for oral anticoagulation (e.g. atrial fibrillation with CHA_2DS_2-VASc score ≥2, venous thromboembolism, LV thrombus, or mechanical valve prosthesis), oral anticoagulation is recommended in addition to antiplatelet therpay.	I	C
New-generation DES are preferred over BMS among patients requiring oral anticoagulation if bleeding risk is low (HAS-BLED ≤2).	IIa	C
In patients with SCAD and atrial fibrillation with CHA_2DS_2-VASc score ≥2 at low bleeding risk (HAS-BLED ≤2), inital triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of at least one month after BMS or new-generation DES followed by dual therapy with (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C
DAPT should be considered as alternative to initial triple therapy for patients with SCAD and atrial fibrillation with a CHA_2DS_2-VASc score ≤1.	IIa	C
In patients with ACS and atrial fibrillation with low bleeding risk (HAS-BLED ≤2), inital triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of 6 months irrespective of stent type followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) continued up to 12 months.	IIa	C
In patients requiring oral anticoagulation at high bleeding risk (HAS BLED ≥3), triple therapy of (N)OAC and ASA (75–100 mg/day) and clopidogrel 75 mg/day should be considered for a duration of one month followed by (N)OAC and aspirin 75–100 mg/day or clopidogrel (75 mg/day) irrespective of clinical setting (SCAD or ACS) and stent type (BMS or new-generation DES).	IIa	C
Dual therapy of (N)OAC and clopidogrel 75 mg/day may be considered as a alternative to initial triple therapy in selected patients.	IIb	B
The use of ticagrelor and prasugrel as part of initial triple therapy is not recommended	III	C

Fig. 12.1 2014 European Guideline recommendations for antithrombotic treatment in patients undergoing PCI who require oral anticoagulation. *a* class of recommendation, *b* level of evidence, *DAPT* dual antiplatelet therapy, *SCAD* stable coronary artery disease (Modified from Windecker et al. [48], with permission of Oxford University Press)

$CHADS_2VASC_2$ score and HAS BLED score (see Fig. 12.1). Triple therapy was the preferred strategy for at least 1 month. These recommendations were based mostly on expert opinion. Like the ACC guidelines, they endorsed the WOEST strategy of dual therapy right away as only a IIb indication. They do clarify that prasugrel or ticagrelor should not be used as a part of triple therapy because of the greater risk of major bleeding [50].

Conclusion

Based on the current guidelines and the data presented above, in a patient with an indication for anticoagulation, we recommend the following:

1. No additional antiplatelet regimen should be used for primary prevention of coronary artery disease or for secondary prevention in stable coronary artery disease patients (at least 1 year out from revascularization or ACS). Anticoagulation alone should be given.
2. In a patient with a recent acute coronary syndrome or a recently placed stent, we endorse the individualized approach of the ESC guidelines in which the exact regimen should be based on weighing their thrombotic risk ($CHADS_2VASC_2$ score) vs the bleeding risk (HAS BLED) score (Fig. 12.1).
3. In patients with mechanical heart valves, combination therapy of both aspirin and warfarin should be given, regardless of cardiovascular disease status.
4. It is important to realize the limitations of most of the data that have been presented. First, it is important to realize that most of the data comes from patients

with the indication for anticoagulation being atrial fibrillation. When considering atrial fibrillation, the risk of stroke using the $CHADS_2VASC_2$ risk algorithm might be low (score = 0 or 1) and these patients could benefit from antiplatelet therapy alone. This was shown convincingly in the MUSICA prospective registry. Low risk atrial fibrillation patients (CHADS of 0 or 1) had no adverse cardiovascular events, including stroke, on dual antiplatelet therapy alone whereas any combination with an anticoagulant showed more bleeding and worsening cardiovascular events in this low risk subset [51]. Another limitation is that the exact dosing of aspirin wasn't known in many of the large registries and meta-analyses that make up a bulk of the data. Also, when considering bleeding risk, there are multiple definitions of bleeding that vary from minor nuisance bleeding to a major intracranial bleed that could be life threatening. Therefore, all bleeding "endpoints" don't carry the same clinical weight within and between trials. It is important for the physician to make sure they are comparing "major" ischemic events that they are trying to prevent (like stroke and myocardial infarction) to "major" bleeding events. It is sometimes necessary to go back to the individual clinical trial to sort this out. Therefore, even with the current evidence and guideline recommendations, it is always necessary for a physician to individualize care to their particular patient, and it is often necessary to go outside of the guidelines when the evidence base that made up the guidelines didn't include that particular demographic in their trials.

5. Clearly, there is currently an incomplete evidence base and we look forward to the publication of further trials Redual PCI (looking at dabigatran in various combination regimens), Pioneer AF-PCI (examining rivaroxaban in various combination regimens, Isar Triple (looking at 6 weeks of triple therapy vs 6 months of triple therapy after DES implantation)) and the creation of new larger randomized trials to help further guide best practices in this controversial area.

References

1. Lardizabal J, Joshi B, Ambrose J. The balance between anti-ischemic efficacy and bleeding risk of antithrombotic therapy in percutaneous coronary intervention: a Yin-Yang paradigm. J Invasive Cardiol. 2010;22:284–92.
2. Collaborative meta-analysis of randomised trials of antiplatelet therapy for prevention of death, myocardial infarction, and stroke in high risk patients. BMJ. 2002;324:71–86.
3. Hamberg M, Svensson J, Samuelsson B. Thromboxanes: a new group of biologically active compounds derived from prostaglandin endoperoxides. Proc Natl Acad Sci. 1975;72:2294–8.
4. Fitzgerald GA. Mechanisms of platelet activation: thromboxane A2 as an amplifying signal for other agonists. Am J Cardiol. 1991;68:11B–5.
5. Baigent C, Blackwell L, Collins R, et al. Aspirin in the primary and secondary prevention of vascular disease: collaborative meta-analysis of individual participant data from randomised trials. Lancet. 2009;373:1849–60.
6. Peto R, Gray R, Collins R, et al. Randomised trial of prophylactic daily aspirin in British male doctors. Br Med J. 1988;296:313–6.
7. 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;352:1293–304.

8. 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;357:89–95.
9. 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;321:129–35.
10. The Medical Research Council's General Practice Research Framework. 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. Lancet. 1998;351:233–41.
11. Hansson L, Zanchetti A, Carruthers SG, 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. Lancet. 1998;351:1755–62.
12. Vandvik PO, Lincoff AM, Gore JM, et al. Primary and secondary prevention of cardiovascular disease: antithrombotic Therapy and Prevention of Thrombosis, 9th edition: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest. 2012;141: e637S–68.
13. He J, Whelton PK, Vu B, et al. Aspirin and risk of hemorrhagic stroke: a meta-analysis of randomized controlled trials. JAMA. 1998;280:1930–5.
14. Bartolucci AA, Tendera M, Howard G. Meta-analysis of multiple primary prevention trials of cardiovascular events using aspirin. Am J Cardiol. 2011;107:1796–801.
15. Raju N, Sobieraj-Teague M, Hirsh J, et al. Effect of aspirin on mortality in the primary prevention of cardiovascular disease. Am J Med. 2011;124:621–9.
16. Berger JS, Lala A, Krantz MJ, et al. Aspirin for the prevention of cardiovascular events in patients without clinical cardiovascular disease: a meta-analysis of randomized trials. Am Heart J. 2011;162:115–24.
17. Seshasai SR, Wijesuriya S, Sivakumaran R, et al. Effect of aspirin on vascular and nonvascular outcomes: meta-analysis of randomized controlled trials. Arch Intern Med. 2012;172:209–16.
18. 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;300:2134–41.
19. Fowkes FG, Price JF, Stewart MC, et al. Aspirin for prevention of cardiovascular events in a general population screened for a low ankle brachial index: a randomized controlled trial. JAMA. 2010;303:841–8.
20. Belch J, MacCuish A, Campbell I, et al. The prevention of progression of arterial disease and diabetes (POPADAD) trial. BMJ. 2008;337:a1840.
21. Patrono C. Low-dose aspirin in primary prevention: cardioprotection, chemoprevention, both, or neither? Eur Heart J. 2013;34:3403–11.
22. Pignone M, Alberts MJ, Colwell JA, et al. Aspirin for primary prevention of cardiovascular events in people with diabetes: a position statement of the American Diabetes Association, a scientific statement of the American Heart Association, and an expert consensus document of the American College of Cardiology Foundation. Circulation. 2010;121:2694–701.
23. Wolff T, Miller T, Ko S. Aspirin for the primary prevention of cardiovascular events: an update of the evidence for the US Preventative Services Task Force. Ann Intern Med. 2009;150:405–10.
24. Perk J, De Backer G, Gohlke H, et al. European Guidelines on cardiovascular disease prevention in clinical practice (version 2012). The Fifth Joint Task Force of the European Society of Cardiology and Other Societies on Cardiovascular Disease Prevention in Clinical Practice (constituted by representatives of nine societies and by invited experts). Eur Heart J. 2012;33:1635–701.
25. Dentali F, Douketis JD, Lim W, Crowther M. Combined aspirin-oral anticoagulant therapy compared with oral anticoagulant therapy alone among patients at risk for cardiovascular disease. Arch Intern Med. 2007;167:117–1241.

26. Steinberg B, Kim S, Piccini J, et al. Use and associated risks of concomitant aspirin therapy with oral anticoagulation in patients with atrial fibrillation: insights from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation (ORBIT-AF) Registry. Circulation. 2013;128:721–8.
27. Butchart EG. Prosthetic heart valves. Cardiovascular thrombosis. 2nd ed. 1998. p. 395–414.
28. Massel D, Little S. Antiplatelet and anticoagulation for patients with prosthetic heart valves. Cochrane Database Syst Rev. 2013 (7):CD003464.
29. Nishimura RA, Otto CM, Bonow RO, et al. 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;63(22): e57–185.
30. Fihn S, Gardin J, Abrams J, et al. 2012 ACCF/AHA/ACP/AATS/PCNA/SCAI/STS guideline for the diagnosis and management of patients with stable ischemic heart disease. J Am Coll Cardiol. 2012;60:e44–164.
31. Hart R, Pearce L, Aguilar M. Meta-analysis: antithrombotic therapy to prevent stroke in patients who have nonvalvular atrial fibrillation. Ann Intern Med. 2007;146:857–67.
32. Hamon M, Lemesle G, Tricot O, et al. Incidence, source, determinants, and prognostic impact of major bleeding in outpatients with stable coronary artery disease. J Am Coll Cardiol. 2014;64:1430–6.
33. Lamberts M, Gislason G, Lip G, et al. Antiplatelet therapy for stable coronary artery disease in atrial fibrillation patients taking an oral anticoagulant. Circulation. 2014;129:1577–85.
34. Dans A, Connolly S, Wallentin L, et al. Concomitant use of antiplatelet therapy with dabigatran or warfarin in the Randomized Evaluation of Long-Term Anticoagulation Therapy (RE-LY) trial. Circulation. 2013;127:634–40.
35. Alexander J, Lopes R, Thomas L, et al. Apixaban vs. warfarin with concomitant aspirin in patients with atrial fibrillation: insights from the ARISTOTLE trial. Eur Heart J. 2014;35:224–32.
36. Schömig A, Neumann FJ, Kastrati A, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334:1084–9.
37. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. N Engl J Med. 1998;339:1665–71.
38. Bertrand ME, Legrand V, Boland J, et al. Randomized multicenter comparison of conventional anticoagulation versus antiplatelet therapy in unplanned and elective coronary stenting. The Full Anticoagulation Versus Aspirin and Ticlopidine (FANTASTIC) Study. Circulation. 1996;98:1597–603.
39. Urban P, Macaya C, Rupprecht H, et al. Randomized evaluation of anticoagulation versus antiplatelet therapy after coronary stent implantation in high-risk patients. The Multicenter Aspirin and Ticlopidine Trial after Intracoronary Stenting (MATTIS). Circulation. 1998;98:2126–32.
40. Connolly S, Pogue J, Hart R, et al. Clopidogrel plus aspirin versus oral anticoagulation for atrial fibrillation in the Atrial fibrillation Clopidogrel Trial with Irbesartan for prevention of Vascular Events (ACTIVE W): a randomised controlled trial. Lancet. 2006;367:1903–12.
41. Karjalainen PP, Porela P, Ylitalo A, et al. Safety and efficacy of combined antiplatelet-warfarin therapy after coronary stenting. Eur Heart J. 2007;28:726–32.
42. Lamberts M, Gislason G, Olesen J, et al. Oral anticoagulation and antiplatelets in atrial fibrillation patients after myocardial infarction and coronary intervention. J Am Coll Cardiol. 2013;62:981–9.
43. Dewilde W, Oirbans T, Verheugt F, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomized, controlled trial. Lancet. 2013;381:1107–15.
44. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. N Engl J Med. 2011;365:699–708.

45. Oldgren J, Wallentin L, Alexander J, et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. Eur Heart J. 2013;34:1670–80.
46. Komocsi A, Vorobcsuk A, Kehl D, et al. Use of new-generation oral anticoagulant agents in patients receiving antiplatelet therapy after an acute coronary syndrome: systematic review and meta-analysis of randomized controlled trials. Arch Intern Med. 2012;172:1537–45.
47. January C, Wann L, Alpert J, et al. AHA/ACC/HRS guideline for the management of patients with atrial fibrillation. J Am Coll Cardiol. 2014;64(21):e1–76.
48. Windecker S, Kolh P, Alfonso F, et al. 2014 ESC/EACTS guideline on myocardial revascularization. Eur Heart J. 2014;35(37):2541–619. doi:10.1093/eurheartj/ehu278. Epub 2014 Aug 29.
49. Lip G, Windecker S, Hubert K, et al. Management of antithrombotic therapy in atrial fibrillation patients presenting with acute coronary syndrome and/or undergoing percutaneous coronary or valve interventions: a joint consensus document of the European Society of Cardiology Working Group on Thrombosis, European Heart Rhythm Association (EHRA), European Association of Percutaneous Cardiovascular Interventions (EAPCI) and European Association of Acute Cardiac Care (ACCA) endorsed by the Heart Rhythm Society (HRS) and Asia-Pacific Heart Rhythm Society (APHRS). Eur Heart J. 2014;35(45):3155–79.
50. Sarafoff N, Martischnig A, Wealer J, et al. Triple therapy with aspirin, prasugrel, and vitamin K antagonists in patients with drug-eluting stent implantation and an indication for oral anticoagulation. J Am Coll Cardiol. 2013;61:2060–6.
51. Sambola A, Ferreira-Gonzalez I, Angel J, et al. Therapeutic strategies after coronary stenting in chronically anticoagulated patients: the MUSICA study. Heart. 2009;95:1483–8.