Indications of combined vitamin K antagonists and aspirin therapy

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Abstract Based on their mode of action, it is reasonable to expect that the combination therapy of aspirin and a vitamin K antagonist (VKA) may be more beneficial in preventing (athero) thrombotic complications in high-risk patients for cardiovascular events. However, there is no consensus about additional aspirin use in the most common indications for VKA or the use of VKAs to be added to the most common aspirin indications. The variation in clinical outcomes and bleeding complications suggests that extrapolating from one indication to another may not be appropriate. So far, decisions about the combined use of aspirin and VKA are individualized in the absence of adequate data. Only in patients with mechanical heart valves the benefits and safety of combining aspirin with VKA therapy seems obvious. In patients with peripheral artery disease no beneficial effect was noted for the combination therapy, perhaps with an exception of those with graft failure. For all other clinical situations, this is unclear and should be avoided.

Keywords: Antiplatelet therapy · Anticoagulant therapy · Vitamin K antagonists · Combination therapy · Atherosclerosis

Introduction

Platelets anti-aggregation drugs reduce cardiovascular events in nearly all groups of patients with clinical manifestations of atherosclerosis, including coronary artery, cerebrovascular and peripheral artery disease [1, 2]. However, the cardiovascular risk remains elevated even if patients are on optimal secondary preventive treatments [1]. On the other hand the use of vitamin K antagonists (VKAs) remains the most efficacious antithrombotic regimen for the primary and secondary prevention of cardioembolic stroke in high-risk patients with atrial fibrillation, prosthetic valves and for the prevention and treatment of venous thromboembolism. However, their safe use requires intensive dose monitoring.

The combination therapy of aspirin and VKAs is frequently considered in various clinical settings and is increasingly applied in high risk patients because of (a) the expected additional protection against coronary artery disease to stroke prevention among patients with atrial fibrillation who are exposed to a high risk for future coronary diseases, (b) additional further stroke-preventive efficacy to usual international normalized ratio (INR) targets for high-risk groups and (c) the supposed reduced risk of haemorrhage by using lower INR targets while preserving efficacy.

Methods

The purpose of this article is to discuss the efficacy and safety of the dual of aspirin and VKAs prescription in clinical settings of secondary prevention. We therefore performed a computerized search via PubMed/MedLine and the Cochrane database using the MeSH terminology. Keywords were: aspirin, anti platelet agent, warfarin,

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coumarin, anticoagulant, vitamin K antagonist, dual therapy, combination therapy, atrial fibrillation, myocardial ischemia, heart valve diseases, cerebrovascular disorders, peripheral artery disease, atherosclerosis and venous thromboembolism.

Results

Clinical settings with an indication for a VKA:
is adding aspirin beneficial?

Atrial fibrillation

The risk of stroke in people with atrial fibrillation (AF) is 3–5% per year, although this may vary according to other risk factors evaluated by the CHADS₂-score (a clinical prediction rule for estimating the risk of stroke in patients with AF) [3]. The risk of stroke in people with AF who have had a previous transient ischemic attack (TIA) may be as high as 12% per year. Anticoagulants have been proven to be more effective in prevention of ischemic stroke in people with AF than aspirin [4].

The current guideline recommends anticoagulation with a VKA in patients with persistent or paroxysmal AF at high risk of stroke (i.e., having any of the following features: prior ischemic stroke, transient ischemic attack, or systemic embolism, age > 75 years, moderately or severely impaired left ventricular systolic function and/or congestive heart failure, history of hypertension, or diabetes mellitus, corresponding to a CHADS₂-score of 3 or more). In patients between age 65 and 75 years, in the absence of other risk factors, who are at intermediate risk of stroke (i.e. CHADS₂-score ≤ 2) anti-thrombotic therapy with either a VKA or aspirin is recommended. In patients with persistent AF or paroxysmal AF below the age of 65 years who have no other risk factors (CHADS₂-score = 0), aspirin is recommended [5].

Although no additional benefit has been demonstrated from combining aspirin and a VKA for stroke prophylaxis in AF patients, concomitant conditions such as coronary artery disease (CAD), peripheral artery and cerebrovascular disease are indications for aspirin. However, there is insufficient evidence to justify the routine use of anti-platelet agents in addition to a VKA in these situations, primarily, because safety data of dual therapy are lacking: Table 1 shows the relative risk and the bleeding risk of the concomitant use of both aspirin and VKAs in patients with AF in different conducted studies. Lechat et al. found that there was no statistical difference between the groups for the primary endpoints, but haemorrhagic complications were significantly more frequent in the aspirin group [8]. Gullov et al. found in the AFASAK 2 trial that fixed-mini-dose warfarin and aspirin alone or in combination were

Table 1 Study characteristics comparing the benefits and risks of the combined aspirin and VKA in patients with atrial fibrillation

Study	Population (number)	Randomised comparisons (reached INR)	Primary endpoint(s)	Duration study (months)	RRR (%/y)	Minor bleeding (%/y)	Major bleeding (%/y)
SPAFI [6]	1,044	VKA (1.3) + A 325 mg VKA fixed-dose (2.4)	Stroke and systemic embolism	13	74	0.7	2.1
AFASAK [7]	677	VKA 1¼ mg VKA 1¼ mg + A 300 mg A 300 mg VKA (2.0–3.0)	Stroke or systemic embolism	36	NS	1.2 0.8 0.3 1.4	2.4 5.6 7.4 7.1
FFAACS [8]	157	VKA + placebo vs. VKA (2–2.6) + A 100 mg	Stroke, myocardial infarction, systemic arterial emboli or vascular death	10	NS, early termination of the study	1.1 1.4 15.8	11.8 1.4 4.8
Edvardsson et al. [9]	668	VKA 1¼ mg + A 75 mg vs. no treatment	Stroke	33	NS	N/A	2.1 0.4

RRR = relative risk reduction; VKA = vitamin K antagonist; A = Aspirin; N/A = not applicable

associated with both minor and major bleeding [7]. In a recent study with 3,566 patients with chronic AF, receiving warfarin therapy targeted to achieve an INR of 2.0–3.0, patients who were receiving concomitant aspirin (100 mg/day) had a more than 2-fold increased risk for major bleeding [10].

The trial conducted by Edvardsson et al. [9] on the effect of low-dose warfarin and aspirin vs. no treatment on stroke in a medium-risk population with AF was inconclusive, but consistent with a small beneficial effect of the combination therapy for reduction of stroke and major vascular events. However this slight advantage was accompanied with significantly increased risk of bleeding.

In the SPAFI trial [6] low-intensity, fixed-dose warfarin plus aspirin was insufficient for stroke prevention in patients with non-valvular AF at high-risk for thromboembolism; adjusted-dose warfarin (target INR 2.0–3.0) reduced stroke in high-risk patients importantly. In these highly selected high-risk patients with AF major bleeding occurred at comparable rates with both treatments.

In conclusion none of the conducted studies demonstrated a benefit of the antiplatelet and VKAs therapy combination. This combination therapy provides no better prophylaxis against stroke than a VKA alone while mild and severe haemorrhagic complications are significantly more frequent.

Valvular heart disease

Patients with prosthetic heart valves are at increased risk for valve thrombosis and valve related thromboembolism [11–13]. Life-long oral anticoagulation is considered to be essential for the prevention of thromboembolic events after implantation of a mechanical heart valve. Nevertheless, thromboembolic events occur after mechanical valve replacement in approximately 2–4% of patients per year despite the use of a VKA [14]. The addition of antiplatelet drugs to VKAs has been suggested and used to minimize this risk. An important issue is the effectiveness and safety of this strategy.

In 2003 The Cochrane Collaboration has published a review on the use of antiplatelet therapy and VKA in patients with prosthetic heart valves [15]. The authors reported that, compared to anticoagulation alone, the addition of an antiplatelet agent reduced the risk of thromboembolic events (odds ratio 0.39 (95% confidence interval (CI): 0.28–0.56; $P < 0.00001$)) and total mortality (odds ratio 0.55 (95% CI: 0.40–0.77; $P = 0.0003$)). The risk of major bleeding was increased when antiplatelet agents were added to VKAs (odds ratio 1.66 (95% CI: 1.18–2.34; $P = 0.003$)). They concluded that adding antiplatelet therapy to a VKA decreases the risk of systemic embolism or death among patients with prosthetic heart

valves while the risk of major bleeding is increased with antiplatelet therapy when added to a VKA.

The seventh ACCP conference on antithrombotic and thrombolytic therapy recommends the use of aspirin (75–100 mg/day) for patients who have mechanical heart valves and additional risk factors such as AF, myocardial infarction, left atrial enlargement, endocardial damage, and low ejection fraction and for patients with mechanical prosthetic heart valves who suffer from systemic embolism despite a therapeutic INR [16].

In two more recently published meta-analyses, it was definitely established that adding antiplatelet therapy, especially low-dose aspirin, to a VKA decreases the risk of systemic embolism or death among patients with prosthetic heart valves [17, 18]. The risk of major bleeding is slightly increased when adding antiplatelet therapy. Nonetheless, the risk of bleeding appears to be diminished with the lower doses of aspirin used in the more recent trials, resulting in a favourable risk-to-benefit profile. Older trials (Table 2) noted a significant increase in bleeding, particularly when high doses of aspirin were used (500 mg/day or more) in combination with high-intensity of a VKA.

In conclusion, the shown data demonstrate that the benefits of the combination of a VKA and aspirin outweighs the bleeding risks and that adding antiplatelet therapy to a VKA is more effective than anticoagulant therapy alone.

Venous thromboembolism

We found no trials evaluating the effects of Aspirin on top of a VKA indicated for venous thrombosis. Prospective randomised controlled clinical trials are therefore needed to disclose this clinical issue.

Clinical settings in which aspirin is indicated: is adding a VKA beneficial?

Non-cardioembolic stroke

Patients with limited cerebral ischemia of arterial origin are at risk of serious vascular events (4–11% annually) [26, 27]. Aspirin is generally recommended in patients with previous ischemic stroke or transient ischemic attack to reduce the risk of recurrence. In general, it reduces the incidence of major vascular events up to 20% [26–28].

VKAs are commonly recommended for the prevention of recurrent stroke in patients with AF, but to date it has no role in the prevention of non-cardioembolic ischemic stroke. No trials were found comparing the combination of aspirin and VKAs in combination to aspirin alone in the prevention of stroke of presumed arterial origin. The explanation for this may be that previous trials on VKA monotherapy in cerebrovascular disease were not more

Table 2 Studies comparing the benefits and risks of the combined aspirin and VKA in patients with prosthetic heart valves

Study	Population (number)	Comparisons (reached INR)	Primary endpoint(s)	Duration study (months)	RR (%)	Minor bleeding (%/y)	Major bleeding (%/y)
Dale [19]	Mechanical valves (148)	VKA (3) + A 1000 mg vs. VKA (3) + placebo	Any bleeding	24	66	8.5	2
Chesebro [20]	Mechanical valves (534)	VKA (1.5–2.5) + A 500 mg vs. VKA (1.5–2.5) + D 400 mg vs. VKA (1.5–2.5)	Bleeding and systemic thromboembolism	36	NS	N/A	2.4
Turpie [21]	Mechanical valves or tissue valves + AF (370)	VKA (3.0) + A 100 mg vs. VKA (3.1) + placebo	Death from vascular causes, major systemic embolism, valve thrombosis, and clinically important haemorrhage	48	77	8.75	4.7
Altman [22]	Mechanical valves (409)	VKA (2–3) + A 100 mg vs. VKA (2–3) + A 650 mg	Systemic embolism, death, and major haemorrhage	24	NS	4.3	1.3
Meschengieser [23]	Mechanical valves (503)	VKA (3.11) + A 100 mg vs. VKA (3.98) + A 100 mg	Thromboembolism and major haemorrhage	23	NS	7	1.7
Laffort [24]	Mechanical valves (229)	VKA (2.2) + A 200 mg vs. VKA (2.8)	Death, major thromboembolic events or major haemorrhage	12	NS	8.5	2.1
Casais [25]	Mechanical valves (121)	VKA (2.95) + A 100 mg vs. VKA (2.95)	Any bleeding	26	NS	10.5	4.7
						N/A	1
							0.5

RR = relative risk/year; A = Aspirin; D = dipyridamol; VKA = vitamin K antagonist; N/A = not applicable

efficacious than aspirin monotherapy, but were associated with higher bleeding rates. In an update of a Cochrane review in 2006, Algra et al. compared the efficacy and safety of VKAs and antiplatelet therapy in the secondary prevention of vascular events after cerebral ischemia of presumed arterial origin [29]. They found insufficient evidence to justify the routine use of medium intensity oral anticoagulants (INR 2.0–3.6); more intense anticoagulation (INR 3.0–4.5) was not safe because it yielded more major bleeding complications and should therefore not be used in this clinical setting. Even in the lowest intensity INR range, addition of warfarin had no benefit above aspirin alone. The WARSS study that compared the effect of aspirin (325 mg) to that of warfarin at a dose adjusted to produce an INR of 1.4–2.8 on recurrence of ischemic stroke or death from any cause within 2 years. This study showed no significant differences between the two modalities in any of the outcomes measured [30].

In patients with non-cardioembolic stroke, oral anticoagulants are no more effective than aspirin alone but cause more bleeding. However data on the safety and effectiveness of the dual therapy are lacking.

Myocardial infarction

Patients with a history of myocardial infarction are at increased risk for recurrent infarction, stroke and death [31, 32]. Although aspirin provides benefit preventing recurrent myocardial infarction, the rates of recurrent vascular events in patients with coronary artery disease remains high [26]. There is evidence that a marked thrombin generation persists for months after acute cardiac events. Such a persistent stimulus to thrombosis even in the presence of aspirin [33], may indicate a role for anticoagulation therapy in this condition. This hypothesis has led to the conduction of several trials testing the combination therapy of aspirin and VKAs at varying intensities. Although some studies have shown that addition of VKAs to aspirin decreases subsequent risk for cardiovascular events, most studies did not (Table 3). Because of the conflicting results of the trials so far, different meta-analysis have been conducted in an attempt to clarify this issue: Anand and Yusuf [2, 43] suggested that high-intensity oral anticoagulation (INR > 2.8) significantly reduced cardiovascular complications but increased bleeding rates compared with controls while the combination of moderate-intensity oral anticoagulation and aspirin was more effective and equally safe as aspirin alone. Low-intensity oral anticoagulation (INR < 2.0) in combination with aspirin did not reduce cardiovascular complications and increased bleeding compared to aspirin alone. The results of the meta-analysis guided by Rothberg et al. bolsters the finding that after an acute coronary

Table 3 Study characteristics comparing the benefits and risks of the combined aspirin and a VKA in patients with coronary artery disease

Study	Population (number)	Comparisons (reached INR)	Primary endpoint(s)	Duration study (months)	RR (%)	Minor bleeding (%/y)	Major bleeding (%/y)
ATACS [34]	NSTEMI/UA (214)	VKA (2.3) + A 162.5 mg vs. A 162.5 mg	Recurrent angina with ECG changes, myocardial infarction, and/or death	3	NS	11.2	11.6
CARS [35]	AMI (8803)	VKA 3 mg (<1.5) + A 160 mg 1 mg VKA (<1.5) + A 80 mg A 80 mg	Occurrence of reinfarction, non-fatal ischemic stroke, or cardiovascular death	14	NS	N/A	2.6 1.9
BAAS [36]	Angioplasty (1058)	VKA (3.0) + A 100 mg vs. A 100 mg	Death, myocardial infarction, target-lesion revascularisation, and stroke	12	71	0.4 4.0	3.2 0.2
OASIS-II [37]	ACS (3712)	VKA (2.1) + A 325 mg vs. A 325 mg	Cardiovascular death, MI or stroke	5	NS	6.5 11	6.5 3.1
Huynh [38]	NSTEMI, prior CABG (135)	VKA (2.0–2.5) + A 80 mg VKA (2–2) A 80 mg	Death or myocardial infarction or unstable angina	12	NS	1.5 9.8	2.4 0
WARIS-II [39]	AMI (3630)	VKA (2.2) + A 75 mg VKA (2.8) A 160 mg	Death, nonfatal reinfarction, or thromboembolic cerebral stroke	48	81	0.8 2.75	0.6 0.2
ASPECT-2 [40]	ACS (993)	VKA (2.4) + A 80 mg VKA (3.2) A 80 mg	Myocardial infarction, stroke, or death	26	55	N/A	1 0.5
CHAMP [41]	AMI (5095)	VKA (1.8) + A 81 mg vs. A 162 mg	All-cause mortality	32	NS	1.24 5.75	1.5 0.8
LoWASA [42]	AMI (3300)	VKA 1.25 mg + A (75 mg) vs. A 75 mg	Cardiovascular death, reinfarction stroke	60	NS	0.5 1.2	0.4 0.2

A = Aspirin; D = dipyridamol; VKA = vitamin K antagonist; N/A = not applicable; RR = relative risk

syndrome, VKAs plus aspirin decreases the rate of myocardial infarction or stroke more than aspirin alone [44]. Although the probability of major bleeding is also increased, the benefits would far outweigh the bleeding risks for many patients. On the other hand, the more recent performed meta-analysis by Dentali et al. has shown no benefits of combining aspirin and VKAs in patients with coronary artery disease: there was no difference in all-cause mortality with either treatment while the risk for major bleeding was higher in the combination group [17].

The data in Table 3 show that adding VKAs to aspirin in this patient category reduces ischemic events but increases the rates of bleeding complications.

Peripheral artery disease (PAD)

Aspirin therapy, while having no effect on walking distance or symptom status, seems to modify the clinical course of PAD. Large randomised trials have shown that aspirin monotherapy delays the progression of established PAD, as assessed by serial angiography, and decreases the need for surgical revascularisation [45, 46]. Among patients with AF and claudicatio intermittens, in whom there is a particular risk of acute embolic lower limb ischemia and stroke, randomised control trials and meta-analyses have clearly indicated that anticoagulation with a VKA (target INR 2.5–3.5) is superior to aspirin [47].

Previous data on dual therapy with aspirin and VKAs in patients with PAD and sinus rhythm are conflicting, small, heterogeneous and non-consistent. Many of these studies focused on peripheral artery patency after vascular reconstruction and were not designed to assess the potential benefit of a VKA to reduce future cardiovascular outcomes [36, 48–53]. As the rate of CV events is 5 times higher in patients with PAD compared to patients without PAD and moderate intensity VKA is effective in reducing CV events in patients with CAD, there is a strong rationale for testing the efficacy of long-term moderate intensity VKA (target INR between 2 and 3) in addition to antiplatelet therapy to prevent major vascular events in patients with PAD. The conducted WAVE (the Warfarin and Antiplatelet Vascular Evaluation)-trial [54], a large, international, randomised clinical trial of patients at a high risk for vascular diseases was designed to determine if moderate VKAs

anticoagulation (INR 2–3), in addition to antiplatelet therapy is superior to antiplatelet therapy alone. The conclusion was that a VKA (targeting an INR range of 2–3) added to antiplatelet therapy did not lower the rate of cardiovascular events or death, but causes a 3.5-fold increase in severe bleeding complications including cerebral haemorrhage. Life-threatening bleeding was seen in 4.0% on the combination therapy vs. 1.2% with aspirin alone ($P < 0.001$), effectively ruling out this dual approach in PAD (Table 4).

Discussion

There is no consensus about combining VKAs and aspirin in the most common indications for the use of anticoagulants and aspirin. Based on their mode of action, it is reasonable to expect that the combination therapy of aspirin and a VKA may be more beneficial in preventing (athero) thrombotic complications for cardiovascular events. Unfortunately, also bleeding complications may overweigh the potential advantage, so far the variations in outcomes suggest that extrapolating from one indication to another may not be appropriate.

Atrial fibrillation

The rationale for a dual therapy in AF is to reduce the risk of bleeding in patients with AF by using low dose of VKAs added to aspirin, to give additional stroke-preventive efficacy to usual anticoagulation in patients considered to be at high risk of thrombotic complications and the supposed additional protection against coronary artery disease to stroke prevention among patients with AF who are exposed to a high risk for future coronary diseases. However, there is insufficient evidence found to justify the concomitant use of aspirin and a VKA: none of the conducted studies demonstrated a benefit of the combination therapy. Therefore clinicians should be aware of the risks of combining aspirin and VKAs especially in our (ageing) population where the co-prevalence of atherosclerosis and AF escalates. Aspirin on top of a VKA provides no better prophylaxis against stroke than a VKA alone while haemorrhagic complications are significantly more frequent.

Table 4 Study characteristics comparing the benefits and risks of the combined aspirin and VKAs in patients with peripheral artery disease

Study	Population (number)	Comparisons (reached INR)	Primary endpoint(s)	Duration study (months)	RR (%)	Minor bleeding	Major bleeding
WAVE [54]	PAD (2161)	VKA (2–3) + A vs. A	Myocardial infarction, stroke, or death from cardiovascular causes	42	92	0.8%/y 0.3%/y	VKA + A (1.1%/y) A (0.3%/y)

RR = relative risk

Prosthetic valves

In case of prosthetic valves we can state that at present-day all the data analysing the combined use of aspirin and a VKA show a significantly lower risk for thromboembolism and that the benefits of the combination of a VKA and aspirin outweighs the bleeding risks and should be particularly useful in patients with established cardiovascular diseases, additional risk factors or recurrent embolism despite a therapeutic INR. In fact, mechanical heart valves remain the only clinical entity for which robust evidence is demonstrated in randomised trials that adding antiplatelet therapy to anticoagulant therapy is more effective than anticoagulant therapy alone.

Venous thromboembolism

We found no study evaluating the effects of adding aspirin to a VKA indicated for venous thromboembolism in case of concomitant aspirin indication. It is reasonable, based on their mode of action, to expect that the combination therapy of aspirin and a VKA may be more beneficial in preventing (athero) thrombotic complications in patients with venous thromboembolism. The onset of a venous thromboembolic event in patients who already take aspirin as a prophylaxis because they are at moderate to high risk for thromboembolic events, leads to the initiation of a VKA. At the time of VKA initiation, aspirin should be stopped because of the estimated higher risk of bleeding and the lack of evidence to support the combined use of aspirin and VKA in this patient category.

Non-cardioembolic stroke

Because of the lack of data from well-designed randomised trials assessing the combined therapy in patients with non-cardioembolic stroke and the finding that VKAs as monotherapy are not more efficacious than aspirin, antiplatelet agents remains nowadays the cornerstone of secondary prevention. VKAs are commonly recommended for the prevention of recurrent stroke in patients with AF, but it has a lesser or no role in the prevention of non-cardioembolic ischemic stroke. Given the risk/benefit ratio, costs of monitoring therapy, and difficulty in maintaining a therapeutic INR in a community setting, antiplatelet agents are preferred over VKAs for prevention of recurrent ischemic stroke. However VKAs should be considered in patients who cannot tolerate antiplatelet agents [55, 56].

Coronary artery disease

Conflicting results are found on this issue: in some studies clear reductions in total mortality, myocardial infarction,

and stroke occurred among patients treated with VKAs at high intensity, although this therapy was also associated with a significant increase in major bleeding. Conversely, low-intensity anticoagulation in the presence of aspirin does not confer any benefit over aspirin alone but still increases major bleeding episodes. Moderate-intensity anticoagulation reduced recurrent ischemic events and seems to be more effective than aspirin alone and to be relatively safe. This combination should be considered for high-risk patients with CAD, including those who suffer a CV event while receiving aspirin monotherapy. The potential benefits of VKA therapy in reducing serious clinical events should be weighed against life-threatening bleedings.

In a recent review Eijkelboom and Hirsh found that adding VKA to aspirin reduces recurrent ischemic events but does not reduce death and increases major bleeding [57]. This increase in bleeding appears to be outweighed by the reduction in recurrent myocardial infarction but the potential for an increase in intracranial bleeding with the combination of a VKA and aspirin is concerning.

Peripheral artery disease

Aspirin therapy is effective in preventing cardiovascular events and death in patients with peripheral artery disease [1]. No beneficial effect was noted for the combination therapy of aspirin and VKA. In the WAVE trial, adding a VKA to aspirin did not improve the clinical outcomes: the primary outcome, a composite of MI, stroke or death was not significantly different in the two groups but the rates of bleedings and life-threatening bleeding was significantly increased among patients treated with the combination of a VKA and antiplatelet therapy.

However, this dual approach could be beneficial in specific patient groups such as peripheral arterial reconstructive surgery, recurrent graft failure and in cases of limb salvage. Many randomised trials in patients with various vascular disorders have studied the efficacy of aspirin in the prevention of ischemic events. The Antiplatelet Trialists' Collaboration showed a beneficial effect of aspirin therapy with no clear differences between types of arterial disease. The efficacy of long-term treatment with aspirin in patient's who undergo infrainguinal bypass surgery, however, has been studied in only a few randomised trials [58–62]. The BOA (The Dutch Bypass Oral Anticoagulants or Aspirin) trial showed that VKAs were better for the prevention of infra-inguinal-vein-graft and for lowering the rate of ischemic events. Aspirin was better for the prevention of non-venous graft occlusion, and was associated with fewer bleeding episodes [36]. What the efficacy and safety of the combination therapy of aspirin and VKAs in such specific subgroups with peripheral artery diseases is not clear.

Conclusion

This overview makes clear that only for patients with mechanical heart valve the benefits and safety of combining aspirin with a VKA are clear. For patients with peripheral artery disease no beneficial effect was noted for the dual therapy. For other medical settings, there are no adequate data to guide this common clinical conclusion.

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