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Arguments favoring low versus high dose aspirin in the prophylaxis of venous thromboembolism

The use of aspirin in the prevention of venous thromboembolism (VTE) is still controversial. In a profound review on the use of aspirin for primary and secondary prevention of venous thromboembolism and other cardiovascular disorders Cohen et al. [1] conclude that the benefits of aspirin are well documented for conditions like myocardial infarction, coronary heart disease, and stroke, but less clearly for prevention of VTE after orthopedic surgery. The latter indistinctness has been a matter of concern in many earlier reviews and meta-analyses, and has even led to non-uniform guidelines on VTE prevention from the American College of Chest Physicians (ACCP), American Academy of Orthopaedic Surgeons (AAOS), the UK National Institute for Health and Care Excellence (NICE), and the Scottish Intercollegiate Guidelines Network (SIGN). The lack of clarity on this topic has been ascribed to methodological limitations of published trials, with moderate quality evidence. However, little attention has been paid to the dose of aspirin used in the separate trials. The use of differing doses of aspirin in the prophylaxis of VTE might have different results just as in the prevention of arterial thrombotic diseases, which are effectively reduced by a dose between 75 and 150, but not by a lower or higher dose [2]. In fact, a high dose may decrease its effectiveness, as shown by the Aspirin and Carotid Endarterectomy Trial, where the risk of stroke, myocardial infarction, and death was significantly greater for patients taking higher doses of aspirin (650–1300 mg) compared to those taking lower doses (81–325 mg) [3].

One might object that the dose-dependent prevention by aspirin will differ for venous and arterial thromboses because venous thrombi, primarily driven by the clotting pathway in a low-flow, low-shear condition, comprise predominantly red blood cells and fibrin, whereas arterial thrombi, thought to be more platelet driven under high flow and high shear, mainly consist of platelets and fibrin. However, both embolism formations depend on the presence of platelets [4], [5] and share similar risk factors (e.g. smoking, diabetes, hypertension). Furthermore, each of these disorders is a marker of increased risk of the other [6].

We therefore performed a literature search on PubMed and EMBASE for prospective, randomized controlled trials (RCT) in preventing VTE (deep-vein thrombosis and pulmonary embolism) after orthopedic or general surgery, which investigated the effect of daily aspirin given alone or when added to anticoagulants. We noted for each trial how much aspirin was given. Only those studies were selected in which the control group (placebo or no prophylaxis) or the anticoagulant group not only had the same risk profile as the aspirin group but also was treated in the same period, by the same surgeons, and in the same institutions. This yielded 24 studies (Tables 1–3). For each study the effectiveness of aspirin was quantified by the relative risk (RR) on VTE and its 95% confidence interval (95% CI) [7]. In contrast to the VTE-incidence itself, which is substantially influenced by medical developments (including mobilization, more or less traumatic surgery, use of regional anesthesia, pneumatic compression devices, and use of anticoagulants), the RR is not or much less sensitive to changes over the years in clinical practice. For subgroups varying in aspirin dose weighted means of RR (and 95% CI) were calculated by the inverse variance method [8].

Table 1 summarizes the trials which compared aspirin to control. As shown, the mean weighted relative risks went from 1.12 for the highest dose (2000 mg/d), via 0.89 for the medium dose range (600–1300 mg/d) to 0.65 for the lowest dose (160–250 mg/d). The low-dose group had a 95% confidence interval of RR entirely below unity, indicating a significant reduction in VTE. However, it should be noted that in most of the high and medium dose studies the numbers of patients evaluated are too few by today's standards of RCT's. Hence, the RR-data in this table only provide preliminary evidence favoring a low versus high dose of aspirin for VTE.

Table 1 additionally suggests a similar picture even when only one kind of surgery is taken into account. For example, the two hip-fracture studies with an aspirin-dose of 1300 and 900 mg/d, respectively, had a mean weighted relative risk of 0.92 (95% CI 0.70–1.21), while the one which used 160 mg/d had a RR of 0.64 (0.50–0.81).

Of note, regarding the results of Harris et al. [9], the relatively low VTE-incidence in the aspirin group (1200 mg/d) of that study (25%) could not been reproduced in later studies (without controls) from the same center (incidences of 44 and 60% [10, 11]).

A contrast between the effect of high and low dose aspirin is also suggested when single use of aspirin after operation is compared to single use of anticoagulants (Table 2). Aspirin was inferior to heparins and coumarins in studies that used a high or medium dose, (weighted mean RR: 1.89 and 1.74, respectively; the latter being statistically significant), but not in studies that used an aspirin-dose smaller than or equal to 250 mg/d (weighted mean RR close to unity).

Table 3 indicates that additional use of aspirin in treatments with unfractionated heparin further decreases the incidence of VTE only at a lower aspirin-dose (80 mg/d).

Low dose aspirin seems to prevent VTE better than high dose aspirin not only after surgery but also in other conditions. After acute ischemic stroke, for example, the effect of 160 mg of aspirin daily was not inferior to LMWH treatment [37], whereas a higher dose (300 mg/d) was less protective (RR 6.43; 1.46–28.36) than LMWH [38]. A favorable effect of low dose aspirin was also noticed when given after chemotherapy: aspirin in doses between 80 and 100 mg/d reduced the incidence of VTE compared to control (RR 0.33; 95% CI 0.17–0.63) [34], and the effectiveness of these doses did not significantly differ from treatment with warfarin [35] or LMWH [35], [36]. In addition, long-term use of 100 mg/d diminished the risk for recurrence of unprovoked VTE (RR 0.71; 0.55–0.93 [40]), (0.63; 0.41–0.97 [41]), and (0.58; 0.42–0.79 [42]). In contrast, prevention of VTE during long-distance traveling with 400 mg of aspirin was not better than control, and less effective than LMWH [39].

A dose of 50 mg/d might be the lower limit because this amount was insufficient to significantly decrease the risk for unprovoked VTE and other cardiovascular events in a 10 years study on participants of the Women's Health Study (RR 0.95; 0.80–1.14 [43]), be it that during this long period only 67% of the women reported taking at least two thirds of their aspirin.

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Table 1
Incidence of postoperative venous thromboembolism (VTE) after high, medium or low dose aspirin versus control.

Study	Aspirin			Control		Surgery	Relative risk (95% CI)
	mg/d	(%) VTE	n/N	(%) VTE	n/N		
Soreff [12]	2000	48	10/21	36	5/14	Hip replacement or AP	1.33 (0.58–3.07)
Schöndorf [13]	2000	63	19/30	60	9/15	Hip replacement	1.06 (0.64–1.73)
						Weighted mean RR	***1.12 (0.73–1.72)***
Powers [14]	1300	41	27/66	46	29/63	Hip fracture	0.89 (0.60–1.32)
Clagett [15]	1300	16	9/56	22	11/49	Thoracic or abdominal	0.72 (0.32–1.58)
Hume [16]	1300	33	7/21	50	10/20	Hip reconstruction	0.67 (0.32–1.41)
Harris [9]	1200	25	11/44	45	23/51	Hip replacement	0.55 (0.31–1.00)
Schöndorf [13]	1000	58	19/33	60	9/15	Hip replacement	0.96 (0.58–1.59)
Alfaro [17]	1000	3.3	1/30	30	9/30	Hip replacement	0.11 (0.01–0.82)
Encke [18]	990	28	9/32	38	12/32	Abdominal	0.75 (0.37–1.53)
Morris [19]	900	63	20/32	66	21/32	Hip fracture	0.95 (0.66–1.38)
Steering [20]	600	27	2/153	22	3/150	Thoracic or abdominal	1.25 (0.84–1.85)
						Weighted mean RR	***0.89 (0.74–1.06)***
Alfaro [17]	250	3.3	1/30	30	9/30	Hip replacement	0.11 (0.01–0.82)
PEP [21]	160	1.6	105/6679	2.5	165/6677	Hip fracture	0.64 (0.50–0.81)
PEP [21]	160	1.1	22/2047	1.3	26/2041	Hip or knee AP	0.84 (0.48–1.48)
						Weighted mean RR	***0.65 (0.52–0.81)***

Abbreviations: VTE (venous thromboembolism) = deep venous thrombosis and pulmonary embolism; n = number of patients with VTE; N = total number of patients; AP = arthroplasty; 95% CI = 95% confidence interval of relative risk.

An explanation for the ineffectiveness of high dose aspirin in the prophylaxis of arterial and, likely, venous thrombosis might be found in aspirin's twofold action: aspirin inhibits platelet aggregation by irreversibly blocking COX-1 mediated thromboxane formation in platelets, but may enforce aggregation when it also inhibits COX-2 mediated synthesis of platelet inhibiting prostacyclin (PGI_2) in endothelial cells. Since platelets are anucleate, without de novo protein synthesis, a low dose of aspirin is sufficient to inhibit COX-1 activity for the rest of platelet life (7–10 days). The nucleated endothelial cells can, however, perform protein resynthesis, and resume PGI_2 production soon after ingestion of low dose aspirin, but not when higher doses are used. Since PGI_2 potently depresses most forms of platelet activation, a reduction of plasma PGI_2 by high dose aspirin will enhance platelet aggregability despite COX-1 blockade.

Due to the short half-life of PGI_2 (6–10 min in blood [44]) the effect of high dose aspirin on platelet aggregability in-vivo is difficult to demonstrate in-vitro. In the usual clinical settings, where measurements are often delayed by transport of the blood samples to a local laboratory, both control and aspirin samples will be measured when PGI_2 has already been metabolized and has lost its platelet inhibiting activity. The enhancing effect of high dose aspirin can be observed only if aggregation in whole blood is measured immediately after sampling, or when aggregation is continuously measured photometrically in blood flowing from a cannulated vein, so nearly in-vivo. Using this method it has been found that the intake of 500 or 1000 mg of aspirin by 16 healthy volunteers increased ADP-induced in-vitro platelet aggregation in venous blood by resp. 176 and 204%, as compared to placebo, whereas a dose of 80 mg did not [45]. In the same study venous plasma concentrations of PGI_2 (measured as its stabile metabolite 6-keto-PGF1α) were lowered by resp. 24 and 30% after the high doses, with no change after the low dose, which strongly suggests that the enhanced platelet aggregability after intake of high dose aspirin was caused by inhibition of endothelial PGI_2 release.

Table 2
Incidence of postoperative venous thromboembolism (VTE) after high, medium or low dose aspirin versus heparins or coumarins.

Study	Aspirin			Anticoagulant		Surgery	Anti-coagulant	Relative risk (95% CI)
	mg/d	(%) VTE	n/N	(%) VTE	n/N			
Josefsson [22]	3000	23	9/40	12	5/42	Hip replacement	DHEH	***1.89 (0.69–5.16)***
Graor [23]	1300	44	30/68	20	13/67	Hip or knee AP	LMWH	2.27 (1.30–3.97)
Powers [14]	1300	41	27/66	20	13/65	Hip fracture	Coumarin	2.05 (1.16–3.60)
Loew [24]	1000	30	19/63	19	11/57	Thorac. or abdom.	UH	1.56 (0.82–2.99)
Alfaro [17]	1000	3.3	1/30	17	5/30	Hip replacement	DHEH	0.20 (0.02–1.61)
Woller [25]	650	8	12/152	0.7	1/129	Hip or knee AP	Coumarin	10.18 (1.34–77.27)
Westrich [26]	650	18	23/129	14	19/135	Total knee AP	LMWH	1.27 (0.73–2.21)
							Weighted mean RR	***1.74 (1.31–2.32)***
Alfaro [17]	250	3.3	1/30	17	5/30	Hip replacement	DHEH	0.20 (0.02–1.61)
Tian [27]	100	13	13/100	7.1	10/140	Hip or knee AP	LMWH	1.82 (0.83–3.98)
Zou [28]	100	16	18/110	13	14/102	Total knee AP	LMHW	1.19 (0.63–2.27)
Jiang [29]	100	17	10/60	18	11/60	Total knee AP	LMWH[a]	0.91 (0.42–1.98)
Anderson [30]	81	0.3	1/380	1.3	5/398	Total hip AP	LMWH	0.21 (0.02–1.78)
							Weighted mean RR	***1.09 (0.73–1.63)***

Abbreviations: see notes in Table 1; DHEH = dihydroergotamine-heparin; UH = unfractionated heparin; LMWH = low molecular weight heparin, which includes dalteparin, ardeparin, and enoxaparin.

[a] Aspirin or dalteparin given after an initial 10 days of dalteparin.