Chemistry 2001;47:1008-15.
5. Bertolaccini ML, Sanna G, Ralhan S, Gennari L, Merrill J, Khamashta M, et al. Antibodies directed to protein S in patients with systemic lupus erythematosus: prevalence and clinical significance. Thromb Haemost 2003;90:636-41.
6. Nojima J, Kuratsune H, Suehisa E, Kavasaki T, Machii T, Kitani T, et al. Acquired activated protein C resistance associated with anti protein S antibody as a strong risk factor for DVT in non-SLE patients. Throm Haemost 2002;88:716-22.
7. Galli M, Borrelli G, Jacobsen EM, Marfisi RM, Finazzi G, Marchioli R, et al. Clinical significance of different antiphospholipid antibodies in the WAPS (warfarin in the antiphospholipid syndrome) study. Blood 2007;110:1178-83.
8. Sorice M, Arcieri P, Griggi T, Circella A, Misasi R, Lenti L, et al. Inhibition of protein S by autoantibodies in patients with acquired protein S deficiency. Thromb Haemost 1996;75: 555-9.
9. Guermazi S, Regnault V, Gorgi Y, Ayed K, Lecompte T, Dellagi K. Further evidence for the presence of anti-protein S autoantibodies in patients with systemic lupus erythematosus. Blood Coagul Fibrinolylis 2000;11:491-8.
10. Regnault V, Boehlen F, Ozsahin H, Wahl D, de Groot P, Lecompte T, et al. Antiprotein S antibodies following a varicella infection: detection, characterisation and influence on thrombin generation. J Thromb Haemost 2005;3:1243-9.

Antiplatelet drugs and risk of venous thromboembolism: results from the EDITH case-control study

Previous studies suggested that aspirin provided some protection against VTE.[1,2] However, the role of antiplatelet agents in venous thrombus initiation or propagation is still discussed. With recent studies highlighting a possible link between arterial diseases and venous thrombosis,[3,4] new perspectives exist for the role of antiplatelet drugs in the management of VTE. We focused on the association between antiplatelet drug exposure and risk for a first venous thromboembolic event using a case-control study of hospitalized patients, and taking into account other potential associations.

Methods of the case-control study have been described in detail elsewhere.[5] Briefly, all patients ≥18 years hospitalized with a well-documented symptomatic VTE, were eligible for enrolment. For this report, we retained only outpatients, i.e. patients admitted for the VTE and selected those with a first venous thromboembolic event not related to major acquired risk factors, i.e. in the absence of surgery, plaster cast, pregnancy or delivery in the past three months, or active cancer. Controls were matched to the cases by age, gender and had no major acquired risk factors of VTE. Subjects with a previous episode of VTE or lifelong anticoagulant therapy were not eligible as controls. The protocol was approved by our institutional scientific and ethics board.

Cases and controls were interviewed during their hospital stay in a one-to-one standardized way. Atherothrombosis was defined as a past or recent history of either myocardial infarction or stroke or lower limb arteriopathy. For cases and controls drug exposure was defined as current use of drugs at the time of admission. All drugs recorded had to be taken at admission for more than one week. We retained as antiplatelet agents: aspirin (daily dose from 75 to 300 mg), dipyridamole and thienopyridines. We also recorded the use of lipid-lowering drugs, and the use of anti-inflammatory drugs: non steroidal anti-inflammatory drugs (NSAIDs) other than aspirin, and steroids. The reliability of our study database concerning drug exposure was validated by comparison to information provided by the National Health Service of France. A matched case control design was used to estimate relative risks of VTE according to drug exposure. Multivariate conditional logistic regression was performed to adjust for atherothrombosis and statin use, suspected as the main confounding factors, and for all other potential confounders detected through the univariate analysis.

Table 1. Characteristics of cases and matched controls.

Variables	*Cases n=402*	*Controls n=402*	*p value*
Mean age (±SD)	67.0 (±18.3)	67. 2 (±18.2)	0.91
Gender (% female)	232 (57.7)		
Pulmonary embolism (PE), n (%)	81 (20.1)		
Deep vein thrombosis (DVT), n (%)	162 (40.3)		
DVT+PE	159 (39.6)		
Mean Body Mass Index (± SD)	25.8 (±4.3)	24.8 (± 5.6)	<0.0001
Family history of VTE, n (%)	93 (23.1)	36 (9.0)	<0.0001
Chronic pulmonary disease, n (%)	14 (3.5)	30 (7.5)	0.02
Cardiac insufficiency, n (%)	20 (5.0)	28 (7.0)	0.29
Myocardial infarction, n (%)	25 (6.2)	40 (10.0)	0.05
Lower limb arteriopathy[a], n (%)	27 (7.7)	23 (7.2)	0.84
Stroke, n (%)	16 (4.0)	23 (5.7)	0.25
Atherosclerothrombosis[b], n (%)	60 (16.8)	75 (22.8)	0.05

[a]Lower limb arteriopathy was not evaluated in 49 cases and 84 controls; [b]atherosclerothrombosis was defined as history of myocardial infarction and/or stroke and/or lower limb arteriopathy.

Table 2. Matched conditional odds ratios and 95% confidence intervals for venous thromboembolism in relation to drugs of interest.

Exposure	*N. exposed patients among 402 cases n (%)*	*N. exposed patients among 402 controls n (%)*	*OR (95% CI)*
Aspirin*	51 (12.7)	88 (21.9)	0.50 (0.34-0.74)
Thienopyridine*	18 (4.5)	24 (6.0)	0.74 (0.40-1.38)
NSAID**	13 (3.2)	14 (3.5)	0.93 (0.44-1.98)
Steroid	36 (9.0)	33 (8.2)	1.12 (0.66-1.89)
Statin	32 (8.0)	55 (13.7)	0.52 (0.32-0.85)
Fibrate	48 (11.9)	30 (7.5)	1.72 (1.05-2.82)

**One control was current user of aspirin + thienopyridine. Two controls were current users of aspirin + dipyridamole. **NSAID: non steroidal anti-inflammatory drug.*

Four hundred and two cases were included in this analysis. Baseline characteristics are shown in Table 1.

Table 2 shows estimated risks for VTE in relation to the various drugs recorded for this report. One control used an association of aspirin + thienopyridine. None of the patients used dipyridamole alone, and 2 controls were current users of an association aspirin + dipyridamole. Aspirin use was associated with a significant 50% decreased risk of VTE (OR=0.50, 95% CI O.34-0.74). Neither thienopyridines, nor NSAIDs and steroids were associated with the risk of VTE.

The multivariate conditional logistic regression adjusting on statin use, atherothrombosis, chronic pulmonary disease, BMI, and family history of VTE did not alter the association between aspirin and VTE (OR=0.40, 95% CI 0.24-0.68). This association did not significantly differ across age groups or according to gender (Breslow-Day test values were 0.84 and 0.79 respectively).

Our data suggested that aspirin use was associated

with a significant decreased risk of a first VTE not related to major acquired risk factor, and this association remained significant after adjustment on statin use and atherothrombotic disease. No association was found with thienopyridines neither with NSAIDs nor with steroids, suggesting particular properties of aspirin in VTE.

Our results were consistent with those of the Antiplatelet Trialists' Collaboration meta-analysis and the Pulmonary Embolism Prevention (PEP) trial suggesting a risk reduction of VTE with aspirin of about 40%.[1,2] In the meta-analysis, the use of antiplatelet therapy significantly reduced the risk of VTE by 39% in high-risk medical patients or in patients undergoing orthopedic or general surgery.[1] Among the patients with hip fracture from the PEP trial, allocation to aspirin produced proportional reductions in PE of 43% (95% CI 18–60; p=0·002) and in symptomatic DVT of 29% (95% CI 3–48; p=0·03).[2] Recently Glynn *et al.* reported the results of a randomized study evaluating the effect of long-term low dose aspirin treatment on VTE occurrence in healthy women.[6] They found only a slight non-significant association between aspirin and unprovoked VTE (hazard ratio was 0.90, 95% CI 0.70-1.16). However, in the subgroup of older patients (≥65 years), more comparable with our population, the association was strengthened (hazard ratio 0.67, 95% CI 0.45-1.01).

Aspirin can be used as an anti-inflammatory drug, especially at high daily dose. Consequently, the association between aspirin and VTE could be explained, at least in part, by the anti-inflammatory properties of aspirin. However, in this report, aspirin was used at low dose and neither NSAIDs nor steroids were associated with a lower risk of VTE.

Antithrombotic properties of aspirin implies the inhibition of platelet cyclooxygenase 1 (*COX-1*) and consequently thromboxane A2 (*TXA2*) synthesis. Nevertheless, antithrombotic efficacy of aspirin is not limited to its antiplatelet effect and to *TXA2* synthesis inhibition, even if these effects are essential.[7] Aspirin could modulate the formation of thrombin, the key factor of blood coagulation. Szczeklik and colleagues have shown that aspirin, contrary to other antiplatelet drugs including ticlopidine, depressed thrombin formation in clotting blood.[8] Furthermore, they suggested that delay of thrombin generation by aspirin seemed unrelated to its inhibition of platelet COX.

The protective effect of aspirin as regards the risk of VTE remains questionable. The two ongoing studies, ASPIRE and WARFASA, that aim to determine the potential benefit of low-dose aspirin compared to placebo after initial anticoagulation to prevent recurrent symptomatic VTE could probably provide interesting data.[9]

Karine Lacut,[1] Jantien van der Maaten,[2] Grégoire Le Gal,[1] Géraldine Cornily,[1] Dominique Mottier,[1] Emmanuel Oger[1]

[1]Brest University, GETBO EA 3878, Epi-Pharm, Brest, F-29609 France; CHU Brest, Hôpital Cavale Blanche, Department of Internal Medicine and Chest Diseases, Brest, F-29609 France; [2]LUMC, Leiden, Netherlands.

Acknowledgments: the authors are indebted to all patients who agreed to participate in the study. They wish to express their gratitude to G Kermagoret who gathered all relevant information to locate eligible patients and performed data management. They also wish to thank all members of the research staff (L Gourant, ML Guennegues, MF Le Lay, P Logeais, G Meac'h, A Muniglia, I Pichon, M Renault, AM Roguedas, G Tréguer) for their valuable work. As a part of this study was conducted in partnership with Caisse Primaire d'Assurance Maladie from Brest district, France, the authors would like to thank Dr. Varnoux, MD and Dr. Nabbe, PharmD, for their fruitful collaboration.

Funding: the study was supported by grants from INSERM (Contrat de Recherche Stratégique 2001, CRES N° 4CR05G), from Région Bretagne (Programme 1044-04013235 n°1440) and Programme Hospitalier de Recherche Clinique 2000. The Centre Hospitalier Régional et Universitaire de Brest promoted the study. The funders of this study had no role in the design or conduct of the study; in the collection, analysis, or interpretation of the data; or in the preparation, review, or approval of the manuscript.

Key words: antiplatelet drugs; aspirin; thienopyridines; venous thromboembolism; case-control study.

Correspondence: Karine Lacut, MD, Department of Internal Medicine and Chest Diseases, Hôpital de la Cavale Blanche, F-29609 Brest Cedex, France. Phone: inernational +33.298347336. Fax: international +332.98347944. E-mail: karine.lacut@chu-brest.fr

Citation: Lacut K, van der Maaten J, Le Gal G, Cornily G, Mottier D, Oger E. Antiplatelet drugs and risk of venous thromboembolism: results from the EDITH case-control study. Haematologica 2008; 93:1117-1118. doi: 10.3324/haematol.12331

References

1. Antiplatelet Trialists' Collaboration. Collaborative overview of randomised trials of antiplatelet therapy: III. Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. BMJ 1994;308:235-46.
2. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) Trial. Lancet 2000;355:1295-302.
3. Prandoni P, Bilora F, Marchiori A, Bernardi E, Petrobelli F, Lensing AW, et al. An association between atherosclerosis and venous thrombosis. N Engl J Med 2003;348:1435-41.
4. Prandoni P, Ghiraduzzi A, Prins MH, Pergo V, Davidson BL, Sorensen H, et al. Venous thromboembolism and the risk of subsequent symptomatic atherosclerosis. J Thromb Haemost 2006;4:1891-6.
5. Oger E, Lacut K, Le Gal G, Couturaud F, Guenet D, Abalain J-H, et al. Hyperhomocysteinemia and low B vitamin levels are independently associated with venous thromboembolism: results from the EDITH study: a hospital-based case–control study. The EDITH Collaborative Study Group. J Thromb Haemost 2006;4:793-9.
6. Glynn RJ, Ridker PM, Goldhaber SZ, Buring JE. Effect of low-dose aspirin on the occurrence of venous thromboembolism: a randomized trial. Ann Intern Med 2007;147:525-33.
7. Undas A, Brummel-Ziedins KE, Mann KG. Antithrombotic properties of aspirin and resistance to aspirin: beyond strictly antiplatelet actions. Blood 2007;109:2285-92.
8. Szczeklik A, Krzanowski M, Gora P, Radwan J. Antiplatelet drugs and generation of thrombin in clotting. Blood 1992;80:2006-11.
9. Brighton TA, Eikelboom JW, Gallus A, Ockelford P, Becattini C, Agnelli G, et al. Low-dose aspirin for secondary prophylaxis of vein thrombosis – A prospectively planned meta-analysis. J Thromb Haemost 2005; 3 (Suppl 1):P2202[Abstract].