Synergism between non-O blood group and oral estrogen in the risk of venous thromboembolism among postmenopausal women: The ESTHER study

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Dear Sir,

Numerous studies have reported an association between ABO blood type and venous thromboembolism (VTE). Most of them have found a higher prevalence of non-O blood type among VTE patients than control (1–6). Recent data have emphasized the synergism between non-O blood type and factor V Leiden mutation in VTE risk (7, 8). Other VTE risk factors, such as hormone therapy (HT) among postmenopausal women, may also modify the association between ABO blood type and VTE risk. Therefore, we investigated the association of VTE with ABO blood type and the potential effect modifiers for this association in a case-control study of VTE among postmenopausal women.

We used the final data of the EStrogen and THromboEmbolism Risk (ESTHER) study performed in France between 1998 and 2006. Study design has been described (9, 10). Briefly, the population consisted of postmenopausal women aged 45 to 70 years with neither a personal history of VTE nor contra-indication to hormone therapy (HT), nor predisposing factors for VTE. Cases had to have presented a first documented episode of idiopathic VTE. One to three controls were matched to each case for age, center and admission date. Data including information on ABO blood group were self-reported during a direct interview from the same standardized questionnaire. Prothrombotic mutations (factor V Leiden and G20210A prothrombin mutation) were determined by standard methods (11).

Odds ratios (OR) for VTE and 95% confidence intervals (CI) were estimated using an unconditional logistic regression adjusted for the matching variables (age, center and admission date). Stratified analyses were used to assess the effect modifiers of several risk factors for the association between ABO blood type (non-O versus O) and VTE. Interactions between ABO blood type and VTE risk factors were assessed on an additive scale using the relative excess risk due to interaction (RERI) as described (12). The proportion of disease burden caused by two factors that could be attributed to their interaction (RERI%) was also used.

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A total of 271 cases and 610 controls were included in the ESTHER study. Most current users of estrogen therapy received 17β-estradiol (except for two cases who used conjugated equine estrogens). Mean dose of oral estrogen was 1.5 mg per day ranging from 0.5 to 2 mg, and the most common daily dose of transdermal estrogen was 50 μg or less (9–11). Information on blood group was missing for 56 cases and 96 controls. Overall, participants with non-O blood type had a two-fold higher VTE risk than participants with O blood type (OR=2.0 and 95% CI: 1.4–2.9 after adjustment for age, center, and admission date). ORs associated with blood type by levels of VTE risk factors are given in Table 1. The adjusted OR for a user of oral estrogen with a non-O blood type compared with a non-user with a O blood type was 8.9 (95% CI: 4.4–17.8; $p<0.001$) and it was larger than the sum of effects related to each factor alone. The RERI statistic was 5.4 ($p<0.05$), indicating that 68% of the VTE risk excess for non-O blood type and oral estrogen use was due to the interaction of both factors. By contrast, transdermal estrogen use was not significantly associated with VTE risk and did not modify the association of VTE with ABO blood type. Obesity, family history of VTE, varicose veins and prothrombotic mutations (factor V Leiden mutation and G20210A prothrombin mutation) all increased VTE risk. However, none of these VTE risk factors significantly modified the association of blood type with VTE.

Our results show that non-O blood type is a VTE risk factor among postmenopausal women. These data are consistent with those from several other studies regarding the increased VTE risk among non-O blood type compared with O blood type (1–3, 7, 8). Previous data provided evidence that self-reported information on ABO blood type was highly valid for epidemiologic studies (13). It is therefore unlikely that misclassification of blood group type due to self-reported information can result in an important bias in the present analysis. The ESTHER study fails to provide evidence for a significant positive interaction between non-O blood type and factor V Leiden mutation in producing VTE risk as previously reported (7, 8). Relatively low sample size may, in part, explain this negative finding. Alternatively, this interaction could be gender specific and further data are needed to test this hypothesis. The finding of a synergism between oral but not transdermal estrogen use and non-O blood group type has the potential to advance the prevention of VTE among women. While women with non-O blood type treated by oral estrogen define a subgroup at high risk for VTE, transdermal estrogen does not confer an additional risk on women with non-O blood type. Therefore, taking into account the blood group type, together with the other VTE risk factors, could benefit women in the management of their menopausal symptoms.

Table 1: Odds ratios (OR), 95% confidence intervals (CI) and RERI for venous thromboembolism in relation jointly to blood type and other factors.

Variable	Blood type	Cases	Controls	OR	95% CI[#]	RERI[$], RERI%[£]
-	O	63	232	1.0	Reference	-
	Non-O	152	282	2.0	1.4–2.9	
Oral Estrogen use						
Non-use	O	32	133	1.0	Reference	5.4*, 68%
Non-use	Non-O	75	172	1.8	1.1–2.9	
Use	O	10	19	2.7	1.1–6.6	
Use	Non-O	38	25	8.9	4.4–17.8	
Transdermal Estrogen use						
Non-use	O	32	133	1.0	Reference	0.1, 7%
Non-use	Non-O	75	172	1.8	1.1–2.9	
Use	O	21	80	1.3	0.7–2.6	
Use	Non-O	39	85	2.2	1.3–3.9	
BMI (kg/m^2)						
< 30.0	O	48	203	1.0	Reference	1.7, 46%
< 30.0	Non-O	119	252	2.0	1.4–3.0	
>= 30.0	O	14	28	2.0	1.0–4.0	
>= 30.0	Non-O	33	30	4.7	2.6–8.6	
Varicose veins						
No	O	25	142	1.0	Reference	–0.2, …
No	Non-O	63	146	2.6	1.5–4.4	
Yes	O	37	89	2.5	1.4–4.6	
Yes	Non-O	89	136	3.9	2.3–6.5	
Family history of VTE						
No	O	42	187	1.0	Reference	0.1, 4%
No	Non-O	105	208	2.2	1.4–3.3	
Yes	O	20	44	2.1	1.1–4.0	
Yes	Non-O	47	64	3.4	2.1–5.8	
Factor V Leiden						
GG	O	43	208	1.0	Reference	–4.0, …
GG	Non-O	177	233	2.4	1.6–3.9	
AA/AG	O	11	6	8.1	2.8–23.7	
AA/AG	Non-O	18	16	5.5	2.6–11.7	
G20210A polymorphism						
GG	O	50	212	1.0	Reference	–2.1, …
GG	Non-O	120	240	2.1	1.5–3.1	
AG	O	5	2	7.8	1.4–44.0	
AG	Non-O	15	9	6.8	2.8–16.7	

[#]Adjusted for age, center and admission date; ET: Estrogen Therapy; [$]RERI : relative excess risk due to interaction; [£]RERI% means the proportion of disease burden caused by two factors that can be attributed to their interaction. RERI%=RERI/[RR(AB)-1]*100
*p<0.05.

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