ABO blood group and thrombotic vascular disease

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Summary
ABO blood group antigens are complex carbohydrate molecules expressed on red blood cells and a variety of tissues. The ABO blood type is implicated in the development of a number of human diseases and there is increasing evidence regarding its involvement in the pathogenesis of cardiovascular disorders, mainly through its effect on von Willebrand factor levels. In this review, after a brief analysis of the potential molecular mechanisms by which the blood group influences haemostasis, we focus on the clinical implications of such interaction. Overall, the literature data document the close relationship between venous thromboembolism (VTE) and non-O blood type, which is associated with an approximately two-fold increased risk of venous thrombosis. A supra-additive effect on VTE risk is observed when an inherited thrombophilic condition is associated with non-O blood group. A weaker association exists between non-O blood type and arterial thrombosis, which needs to be further investigated.

Keywords
ABO blood group, thrombosis, venous thromboembolism, arterial thrombosis, coronary heart disease

Introduction
After its first description by the Austrian Nobel Prize Karl Landsteiner in 1901 (1), the ABO blood group system has been the subject of intensive research over more than a century, with great improvements in the understanding of its biology and physiology (2). The antigens of the ABO blood group system (A, B and H determinants) consist of complex carbohydrate molecules placed on the extracellular surface of the red blood cell (RBC) membranes (3). The A and B alleles encode slightly different glycosyltransferases that add N-acetylgalactosamine and D-galactose, respectively, to a common precursor side chain, the H determinant, converting it into A- or B-antigens. The O alleles encode no functional enzyme and hence in OO carriers the H antigen remains unmodified, with a fucose moiety attached to the precursor oligosaccharide chains (4).

The ABH antigens are not confined to RBCs but are widely expressed in a variety of human cells and tissues, including the epithelium, sensory neurons, platelets and the vascular endothelium (3). Thus, ABO matching is critical not only in blood transfusion but also in cell/tissue/organ transplantation (5). Accordingly, the clinical significance of the ABO blood group system extends beyond transfusion medicine and several reports have suggested an important involvement in the susceptibility to infectious, neoplastic and cardiovascular disorders (6–8). The actual knowledge on the mechanistic and clinical role of ABO blood type in cardiovascular diseases is summarised in this review.

Biological background
The ABO blood group exerts a profound influence on haemostasis, documented by the close relationship between ABO blood type and von Willebrand factor (VWF) and hence factor VIII (FVIII) plasma levels (9–11). Individuals with blood group O have approximately 25% lower VWF plasma levels compared with those with blood group non-O (12, 13). Among the non-O groups, AB individuals have the highest VWF levels, followed by group B and group A (12). A2 blood group, which accounts for approximately 20% of the A-type blood and is characterised by a partially non-functioning glycosyltransferase (14), has the lowest VWF and FVIII levels of all non-O blood types (15). Moreover, plasma VWF levels are even lower in subjects with the rare Bombay blood group phenotype, that is lacking the capacity to produce the H-antigen via fucosylation of the penultimate galactose residue (16).

The presence of ABO blood group determinants on VWF N-glycans provides the molecular basis of the connection between ABO blood type and VWF levels (17). However, the exact mechanism whereby ABH antigens affect the plasma levels of VWF remains partially unclear, the most plausible mechanism being that the ABH-bearing carbohydrate moiety of VWF influences VWF levels by affecting plasma clearance (18–20). Although this hypothesis is supported by the finding that VWF plasma half-life is significantly shorter in group O versus non-O individuals (10.0 vs 25.5 hours, respectively) (21), the molecular mechanism underlying the enhanced clearance of group O VWF remains unknown. According to recent investigations, macrophages...
may be involved in this accelerated uptake via LR1 (low-density lipoprotein receptor-related protein 1) or other receptors (Fig. 1B) (22, 23). The role of LR1 is particularly intriguing, considering also the reports documenting the influence of LR1 polymorphisms on FVIII levels and hence on the risk of venous thromboembolism (VTE) (24, 25). Another important role for VWF ABO carbohydrate structures relates to their potential to regulate VWF susceptibility to proteolysis by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) (26). Several groups that had studied plasma VWF purified from individuals of different ABO blood groups consistently observed significantly higher proteolysis for group O VWF versus non-O (26). This effect on the rate of VWF cleavage by ADAMTS13 has also been demonstrated in experimental studies, where the alteration of VWF glycosylation significantly affected ADAMTS13-dependent VWF proteolysis (27–29). The study by McKinnon et al. (30) showed that the removal of the majority of N-linked glycans of VWF and the N1574 VWF mutation preventing VWF glycosylation, which resembled a condition similar to that occurring in group O subjects, were characterised by an increased susceptibility of VWF to ADAMTS13 proteolysis. Unlike plasma-VWF, platelet VWF does not express AB blood group antigens, thus exhibiting a peculiar resistance to ADAMTS13 proteolysis (28). This phenomenon has relevant biological implications, because it may explain why platelet activation at the sites of vascular injury leads to the release of high-molecular-weight multimers (HMWM) of VWF are particularly resistant to ADAMTS13 proteolysis, thus facilitating platelet plug formation.

All in all, these studies suggest that the carbohydrate determinants of VWF (ABH-bearing structures) protect this moiety from proteolytic degradation by ADAMTS13. Other studies have evidenced the capacity of specific N-linked glycosylation to modulate synthesis and secretion of VWF (27). However, additional mechanisms have been proposed to explain the association between ABO blood group and thrombotic vascular disease. A series of genome-wide association studies (GWAS) have linked the ABO locus to the serum levels of soluble intercellular adhesion molecule-1 (sICAM-1), tumour necrosis factor α (TNF-α), P-selectin (sP-selectin) and E-selectin (sE-selectin) (31–33), which are implicated in the atherosclerotic process (34, 35).

Clinical implications

On the basis of the large amount of data documenting the positive association between high levels of VWF and thrombosis (36), a
number of epidemiologic studies have assessed whether or not ABO blood type influences the risk of developing venous or arterial thrombotic events (6).

**ABO blood group and venous thromboembolism**

**a) Single studies**

The first observation on the association between ABO blood type and VTE was made in 1963 by Dick et al., who found a statistically significant predominance of group A in 461 VTE patients (37). Several single studies have since analysed whether or not the different ABO blood groups carry different risks of developing VTE: the most relevant are summarised in Table 1. In the Leiden Thrombophilia Study, Koster et al. (38) observed that blood group O was less frequent (25% vs 43%) in 301 consecutive VTE patients than in 301 healthy matched controls. The VTE risk of non-O blood group carriers remained significantly higher after adjustment for FVIII and VWF levels. Wautrecht et al. (39) retrospectively analysed the blood group distribution among 369 patients with a diagnosis of deep-vein thrombosis (DVT) of the lower extremities over a period of 14 years. The frequency of DVT patients with non-O blood group was definitely higher than that of 49,373 healthy blood donors (70.6% vs 53.9%; p<0.001). More recently, Tirado et al. (40) investigated the prothrombotic role of FVIII, FVIII and ABO and found that the risk of VTE was higher in non-O versus O blood type individuals, even after adjustment for FVIII and VWF levels. In the Longitudinal Investigation of Thrombophilia Etiology (LITE) study (41), which analysed the ABO genotype in 492 participants who subsequently developed VTE and 1,008 participants who remained free of VTE, a significantly higher risk of VTE (odds ratio [OR] 1.64; 95% confidence interval [CI] 1.32–2.05) was observed among non-O blood type carriers than among those with O-blood type. This risk decreased but remained statistically significant after adjustment for a number of variables including sex, race, body mass index, diabetes and FVIII levels (OR 1.31; 95% CI 1.02–1.68). Interestingly the risk increased by more than five folds in non-O blood type individuals who were also carriers of factor V (FV) Leiden (OR 6.77; 95% CI 3.65–12.6) (41).

The fact that the combination of FV Leiden and non-ABO blood type was associated with VTE more strongly than expected from a simple additive model of individual risks was confirmed by a number of subsequent studies (see Table 1) (42, 43). Wolpin et al. (44) prospectively examined the association of ABO blood type and the risk of incident pulmonary embolism (PE) in two large cohort studies, the Nurses’ Health Study and the Health Professionals Follow-up Study. Compared to those with O-blood type, participants with non-O blood type were at increased risk for both idiopathic and non-idiopathic PE. In a large prospective Danish study Sode et al. found that the population attributable risk of VTE was 20% for ABO blood type, 10% for FV Leiden and 1% for prothrombin G20210A, thus making ABO blood type as the most important risk factor for VTE in the general population (45). Very recently, non-O blood type has been suggested to play an important role also in the risk of VTE recurrence (46). In the REVERSE study, Gandara et al. (47) prospectively followed a cohort of 509 patients with unprovoked VTE who discontinued oral anticoagulation after 5–7 months of therapy and found an impressive difference in the rate of recurrent VTE according to the different ABO blood types. Indeed, during 1,552 patient years, 101 events occurred in 380 non-O patients (6.5 events per 100 patient years; 95% CI 5.3–7.7) compared to 14 events in 129 O patients (2.4 per 100 patient years; 95% CI 1.3–3.7). This important difference persisted after adjustment for possible confounders such as sex, FVIII and post-thrombotic syndrome (adjusted hazard ratio [HR] 2.0; 95% CI 1.2–3.8).

The association between ABO blood type and VTE has also been explored by a number of GWAS. For instance, in the GWAS conducted by Tregouet et al. (48), the single nucleotide polymorphisms (SNPs) rs8176750, rs8176746 and rs8176719, which tag the A2, B, and O blood groups showed that blood type O was associated with a 67% lower risk of VTE than non-O blood groups. Additionally, the A2 blood group had a 47% lower risk of VTE when compared to the other non-O blood group phenotypes. Blood type A2 was also shown to be associated with 22% lower VTE risk in a recently published GWAS involving 1,503 VTE patients in which rs8176704 was used to tag the A2 blood group (49).

**b) Systematic reviews and meta-analyses**

A systematic review and meta-analysis on the association between ABO blood group and all vascular diseases was published by Wu et al. in 2008 (50). The 21 studies analysed, including 4,709 VTE cases, gave a pooled OR of 1.79 (95% CI 1.56–2.05) for non-O status, which was replicated by a more recent meta-analysis carried out on a larger number of studies and VTE cases (38 studies with 10,305 VTE cases) (51). Indeed, the prevalence of non-O blood group was significantly higher in VTE patients compared to controls, with a resulting pooled OR of 2.08 (95% CI: 1.83–2.37; p<0.00001). Of note, also the supra-additive effect on the VTE risk of the association between non-O status and the factor V Leiden mutation (OR: 7.60; 95% CI: 3.21–17.99) found in our meta-analysis was in accordance with the previous observations by Wu et al. (50), who calculated a pooled OR of 3.88 (95% CI: 2.51–6.00) in non-O VTE subjects who also carried factor V Leiden.

All in all, the literature data stemming from single studies and meta-analyses clearly show that non-O blood group is associated with a moderately increased risk (approximately two-fold) of VTE (52, 53).

**ABO blood group and arterial thrombosis**

**a) Single studies**

The causative role of non-O blood type has also been explored in the setting of arterial thrombosis (see Table 1 for the main studies). In 1971, Medalie et al. (54) published a five-year prospective study involving 10,000 males from Israel, showing that O blood type subjects had a non-statistically significant lower incidence of myocardial infarction and angina pectoris, than those
### Table 1: Summary of the main studies on the association between ABO blood group and thrombosis.

<table>
<thead>
<tr>
<th>First author, year (ref.)</th>
<th>Study design</th>
<th>Endpoint</th>
<th>Patients/controls</th>
<th>O blood group distribution (cases vs controls)</th>
<th>Non-O blood group-associated thrombotic risk (adjusted OR)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Venous thromboembolism</strong></td>
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<tr>
<td>Koster, 1995 (38)</td>
<td>Case-control</td>
<td>VTE</td>
<td>301/301</td>
<td>25 % vs. 43 %</td>
<td>1.5 (95 % CI, 1.0–2.2)</td>
</tr>
<tr>
<td>Wauthrecht, 1998 (39)</td>
<td>Case-control</td>
<td>DVT</td>
<td>367/49,373</td>
<td>29.4 % vs. 46.1 % (P&lt; 0.001)</td>
<td>NA</td>
</tr>
<tr>
<td>Tirado, 2005 (40)</td>
<td>Case-control</td>
<td>VTE</td>
<td>250/250</td>
<td>23.3 % vs. 44.3 % (P&lt; 0.0001)</td>
<td>1.7 (95 % CI, 1.1–2.6)</td>
</tr>
<tr>
<td>Ohira, 2007 (41)</td>
<td>Case-control</td>
<td>VTE</td>
<td>492/1008</td>
<td>35.6 % vs. 47.5 % (P&lt; 0.001)</td>
<td>1.31 (95 % CI, 1.01–1.68) FVL carriers: 6.77 (95 % CI, 3.65–12.6)</td>
</tr>
<tr>
<td>Trégouët, 2009 (48)</td>
<td>Case-control</td>
<td>VTE</td>
<td>453/1327</td>
<td>-</td>
<td>0.33 (95 % CI, 0.26–0.42)</td>
</tr>
<tr>
<td>Heit, 2012 (49)</td>
<td>Case-control</td>
<td>GWAS</td>
<td>1503/1459</td>
<td>-</td>
<td>0.52 (95 % CI, 0.44–0.60)</td>
</tr>
<tr>
<td>El-Galaly, 2012 (42)</td>
<td>Case-cohort</td>
<td>VTE</td>
<td>578/1733</td>
<td>NA</td>
<td>1.85 (95 % CI, 1.37–2.50) FVL carriers: 5.12 (95 % CI, 3.05–8.59)</td>
</tr>
<tr>
<td>Spiezia, 2013 (43)</td>
<td>Case-control</td>
<td>VTE</td>
<td>712/712</td>
<td>30.9 % vs. 49.7 %</td>
<td>2.21 (95 % CI, 1.78–2.75) FVL carriers: 3.67 (95 % CI, 2.45–5.48)</td>
</tr>
<tr>
<td>Wolpin, 2011 (44)</td>
<td>Prospective</td>
<td>PE</td>
<td>499/-</td>
<td>-</td>
<td>1.46 (95 % CI, 1.22–1.76)</td>
</tr>
<tr>
<td><strong>Myocardial infarction/coronary artery disease</strong></td>
<td></td>
<td></td>
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<tr>
<td>Whincup, 1990 (55)</td>
<td>Prospective</td>
<td>MI</td>
<td>7662/-</td>
<td>-</td>
<td>1.22 (95 % CI, 1.04–1.43)</td>
</tr>
<tr>
<td>Roest, 2007 (57)</td>
<td>Prospective</td>
<td>MI</td>
<td>200/1532</td>
<td>-</td>
<td>1.8 (95 % CI, 1.0–3.0)</td>
</tr>
<tr>
<td>Carpeggiani, 2010 (59)</td>
<td>Case-control</td>
<td>MI mortality</td>
<td>4901/NA</td>
<td>43.3 % vs. 40 %</td>
<td>1.53 (95 % CI, 1.06–2.21)</td>
</tr>
<tr>
<td>Jager, 2010 (62)</td>
<td>Prospective</td>
<td>CV mortality</td>
<td>631/-</td>
<td>-</td>
<td>2.08 (95 % CI, 0.85–5.07)</td>
</tr>
<tr>
<td>Reilly, 2011 (66)</td>
<td>Case-control</td>
<td>GWAS</td>
<td>470/463</td>
<td>-</td>
<td>1.62 (95 % CI, 1.23–2.13)</td>
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<tr>
<td><strong>Ischaemic stroke</strong></td>
<td></td>
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<tr>
<td>Hanson, 2012 (73)</td>
<td>Case-control</td>
<td>IS</td>
<td>600/600</td>
<td>-</td>
<td>0.9 (95 % CI, 0.7–1.2)</td>
</tr>
<tr>
<td>Williams, 2012 (69)</td>
<td>Case-control</td>
<td>GWAS</td>
<td>8900/55000</td>
<td>-</td>
<td>1.07 (95 % CI, 1.03–1.11)</td>
</tr>
<tr>
<td><strong>Multiple endpoints</strong></td>
<td></td>
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<td></td>
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</tr>
<tr>
<td>Wiggins, 2009 (58)</td>
<td>Case-control</td>
<td>VTE MI IS</td>
<td>5042172 10633452 4693452</td>
<td>-</td>
<td>1.77 (95 % CI, 1.43–2.18) 1.23 (95 % CI, 1.05–1.44) 1.59 (95 % CI, 1.17–2.17)</td>
</tr>
<tr>
<td>Sode, 2013 (45)</td>
<td>Prospective</td>
<td>VTE MI</td>
<td>66010</td>
<td>-</td>
<td>1.4 (95 % CI, 1.3–1.5) 1.1 (1.0–1.1)</td>
</tr>
</tbody>
</table>

VTE, venous thromboembolism; PE, pulmonary embolism; OR, odds ratio; CI, confidence intervals; NA, not available; FVL, factor V Leiden; VTE, venous thromboembolism; DVT, deep-vein thrombosis; MI, myocardial infarction; CV, cardiovascular; IS, ischaemic stroke; GWAS, genome wide association study. 1O blood group vs non-O blood group. 2Adjusted hazard ratio. A11 allele. B allele. Relative risk. ABO single nucleotide polymorphism rs505922.
with other blood groups. A slightly higher incidence of ischaemic heart disease in subjects carrying blood group A was subsequently reported in a British study which prospectively followed 7,662 men (55). In 1,393 men followed for an average period of 16.1 years, Meade et al. found that the incidence of ischaemic heart disease was significantly higher in carriers of blood group AB than in those of groups O, A or B, especially for fatal events; an effect independent from plasma FVIII and VWF levels (56). In the prospective study conducted by Roest et al. (57) in 200 post-menopausal women, an excess of blood group genotypes A and B was observed in cases with acute ischaemic heart disease. In a population-based case-control study, Wiggins et al. (58) used data from Group Health (GH), a large integrated health care system in the western Washington State, in order to assess the association of ABO genotype with arterial thrombosis, and found a significant association between A and B alleles and myocardial infarction and ischaemic stroke, respectively. Interestingly, an observational study on 4,901 patients with suspected or documented ischaemic heart disease who underwent coronary angiography observed a significant association between non-O blood group and family history of ischaemic heart disease, hypercholesterolaemia, presence of coronary atherosclerosis and, ultimately, cardiac mortality (59). A positive association between non-O blood type and circulating cholesterol levels in coronary heart disease was also found by others (60, 61). In particular, Chen et al. (61) recently showed that approximately 10% of the effect of non-O type on coronary artery disease (CAD) and myocardial infarction susceptibility was mediated by its influence on low-density lipoprotein (LDL) cholesterol level. A two-fold increased cardiovascular mortality in non-O compared with O blood type was also observed in the Hoorn study (62). Furthermore, three recent studies analysed the link between ABO blood type and coronary heart disease with conflicting results (45, 63, 64).

As observed for VTE, recent GWAS have revealed associations between the ABO locus and CAD (65). One of the most relevant was the GWAS conducted by Reilly et al. (66), who identified at the ABO locus a novel association protective against myocardial infarction, attributable to the glycosyltransferase-deficient enzyme that encodes the group O phenotype. In particular, an increased risk in non-O blood group individuals was observed in patients with myocardial infarction versus those without myocardial infarction, suggesting that the primary relationship of ABO to clinical CAD is through modulation of coronary thrombosis or plaque rupture in established coronary atherosclerosis rather than through primary promotion of atherosclerosis per se (66).

A meta-analysis of 14 GWAS studies of CAD comprising 22,233 cases and 64,762 controls followed by validation of the association signals in 56,682 additional individuals, identified 23 loci (10 confirmed and 13 new) as established risk factors for CAD (67). The authors identified the rs579459 SNP in the ABO locus as having the fifth highest association, with an OR of 1.10 (95% CI 1.09–2.95) (68). A number of GWAS have also analysed the association between the ABO locus and ischaemic stroke. For instance, the EuroCLOT study identified the genetic variant rs505922 in the ABO locus as independently associated with ischaemic stroke, and in particular the subtypes large-vessel and cardioembolic stroke, but not small-vessel disease (69). Notably, in a genome-wide analysis conducted by Dichgans et al. (70), in order to evaluate the extent of shared genetic susceptibility to both ischaemic stroke and CAD, the rs579459 variant at the ABO locus significantly correlated with CAD and ischaemic stroke, particularly the large artery stroke subtype, thus demonstrating a substantial overlap among genetic risk factors for these conditions.

### b) Systematic reviews and meta-analyses

The link between ABO blood type and arterial thrombosis was also assessed by a number of systematic reviews and meta-analyses. Wu et al. (50), beside the association with VTE, also observed a consistent positive relation with peripheral vascular disease (OR: 1.45; 95% CI: 1.35–1.56), ischaemic stroke (OR: 1.14; 95% CI: 1.01–1.27) and myocardial infarction (OR: 1.25; 95% CI: 1.14–1.36). However, the latter disappeared when the analysis was restricted to prospective studies only (OR: 1.01; 95% CI: 0.84–1.23). More recently, He et al. (71) performed a meta-analysis of data from the Health Professionals Follow-up Study (HPFS), Nurses’ Health Study (NHS) and five other prospective cohort studies that had enrolled several thousands of participants, to conclude that individuals with non-O blood group had an 11% increased risk of developing coronary heart disease as compared with O blood group individuals. The association between ABO blood type and arterial thrombotic events was also explored by some of us through a systematic analysis of 28 published studies: the prevalence of non-O blood group was significantly higher in patients with myocardial infarction (pooled OR 1.28, 95% CI 1.17 to 1.40; p < 0.001) and ischaemic stroke (pooled OR 1.17, 95% CI 1.01 to 1.35; p = 0.03) than in controls (72). However, the restriction of this analysis to high quality studies confirmed the association with myocardial infarction (pooled OR 1.17, 95% CI 1.03 to 1.32) but not that with ischaemic stroke (pooled OR 1.28, 95% CI 0.94 to 1.74). The latter finding was in keeping with the results of a recent case-control on 600 cases and controls conducted by Hanson et al. (73), who found no association between ABO phenotype or genotype and stroke.

Overall, the evidence from the literature on the association between non-O blood type and arterial thrombosis is less robust than that documenting the link with VTE and any increased risk appears to be rather modest (74). Perhaps the reason for this discrepancy lies in the fact that arterial thrombosis encompasses a wider array of clinical conditions than VTE.
Evolutionary implications

The hypothesis that a greater propensity for blood clot formation in non-O subjects conferred a survival advantage to early humans by protecting them from haemorrhages is intriguing. A similar argument has been raised for the occurrence of the gain-of-function prothrombotic mutations factor V Leiden and prothrombin G20210A, which have been surmised to reduce the bleeding-related risk of death during pregnancy (75, 76). Indeed, there are a number of examples documenting that the blood type distribution among different populations in different times is driven by an evolutionary selective pressure, which acts by modifying susceptibility to various diseases. The best example is that of infectious diseases: the fact that O blood type provides a selective advantage against severe malaria probably explains the higher prevalence of this blood group in areas (i.e. Africa) in which malaria is endemic (77). Similarly, other authors have hypothesised that the relatively high prevalence in India of B blood group, which has been shown to protect against severe cholera, could be related to the selective pressure from this infectious disease endemic in that area (78). Analysing this argument from another point of view, and thus considering the association found by some between non-O blood type and cardiovascular mortality (the first cause of death in men) (59, 62), it could be of interest to ascertain whether or not ABO blood group correlates with life expectancy. This specific issue was tackled by Coppola et al. (79) in a case-control study which compared VWF levels and ABO blood group distribution in 74 centenarians and 110 controls. Surprisingly, the antigenic and functional (ristocetin cofactor) plasma levels of VWF were significantly higher in centenarians than in controls without significant difference between blood group O or non-O, suggesting that mechanisms different from these play a key role in successful aging.

Conclusions

The recent elucidation of the biologic mechanisms underlying the link between ABO blood group and VWF has renewed the interest towards the study of the clinical implications of this interaction. In particular, recent findings have strengthened the belief in the close link between VTE and non-O blood type, which nowadays should be considered the most frequent genetic risk factor for venous thrombosis. In contrast, less certainty exists on the relationship between non-O blood group and arterial thrombosis, particularly myocardial infarction, probably because this positive association is weaker, reaching statistical significance in some studies but not in others. The aim of future research in this field should be also directed to explore the interaction of ABO blood type with other genetic or environmental risk factors for thrombosis and to determine whether or not knowledge of ABO blood type is clinically helpful in order to define the individual thrombotic risk profile.

Conflicts of interest

None declared.

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