The Role of ABO Blood Type in Thrombosis Scoring Systems

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Abstract

In addition to their major role in transfusion medicine, there is increasing evidence that ABO blood group antigens (complex carbohydrate molecules widely expressed on the surface of red blood cells and several other cell types) are implicated in the development of a wide array of pathologic conditions. In particular, intense research has been dedicated over the last 50 years to the study of the association between non-O blood type and the risk of developing cardiovascular disorders. Several pathways have been hypothesized to explain this relationship, the most reasonable implying the influence of the ABO blood group on circulating plasma levels of von Willebrand factor, factor VIII, and several inflammatory cytokines. This narrative review summarizes the current knowledge on the role of ABO antigens in both venous and arterial thromboses, focusing on their association with clinical scoring systems evaluating thrombotic risk.

Keywords
- ABO blood group
- arterial thrombosis
- venous thromboembolism
- scoring systems

The ABO blood group system, which consists of three main alleles (two codominant A and B and one recessive O), is controlled by a single gene located on the terminal portion of the long arm of chromosome 9 (9q34.2).[1,2] The A and B alleles encode slightly different glycosyltransferases (transferase A, α 1-3-N-acetylgalactosaminyltransferase; transferase B, α 1-3-galactosyltransferase) that add N-acetylgalactosamine and D-galactose, respectively, to a common precursor side chain, the H substance, converting it into A or B antigens. The O allele does not encode a functional enzyme and consequently OO carriers, who lack these transferase enzymes, continue to express the basic, unmodified H structure constituting a solitary terminal fucose moiety attached to the precursor oligosaccharide chain.[3]

Besides their presence on red blood cells, ABO antigens are also expressed on the surface of a variety of human cells and tissues, including epithelial cells, sensory neurons, platelets, and the vascular endothelium.[4] It is, therefore, plausible from a biological point of view that the clinical significance of ABO blood type may not be limited only to transfusion medicine; indeed, there is a large amount of data from the literature consistently documenting the involvement of ABO blood group antigens in the development of a wide array of human diseases.[5–13] This narrative review will summarize the main biologic and clinical evidence of the interaction between hemostasis and ABO blood type focusing on its role in clinical scoring systems assessing thrombotic risk.

ABO Blood Type and Thrombosis

As previously mentioned, several studies have reported over the past 50 years the primary relation of ABO blood type with thrombosis,[14–22] and the recent discovery of the *ABO* gene as the most involved locus for both primary and recurrent venous thromboembolism (VTE) and arterial thrombosis (i.e., myocardial infarction, coronary artery disease, and ischemic stroke) has further corroborated this

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hypothesis.[23–26] Several systematic reviews and meta-analyses have performed pooled analyses of the published studies with the aim of quantifying the ABO-related residual thrombotic risk. In a meta-analysis, Wu et al[27] reported odds ratios (ORs) for non-O relative to O blood group of 1.45 (95% confidence interval [CI], 1.35–1.56) for peripheral vascular disease, 1.14 (95% CI, 1.01–1.27) for ischemic stroke, 1.25 (95% CI, 1.14–1.36) for myocardial infarction, and 1.79 (95% CI, 1.56–2.05) for VTE. Another meta-analysis, collecting data from the Health Professionals Follow-up Study, Nurses' Health Study, and five other prospective cohort studies in which several thousand participants were enrolled, was published recently by He et al.[28] They concluded that subjects with non-O blood group had a slight but significant increased relative risk (RR, 1.11; 95% CI, 1.05–1.18; $p < 0.001$) of developing coronary heart disease as compared with O blood group individuals. The ABO-associated venous and arterial thrombotic risk was analyzed separately by our group in two meta-analyses.[29,30] In the first meta-analysis, which included 38 studies with 10,305 VTE cases, we noted that having a non-O blood group carries an approximately twofold increased risk of venous thrombosis (OR, 2.08; 95% CI, 1.83–2.37).[29] In a subsequent systematic review of 28 studies assessing the association between ABO blood type and arterial thrombotic events, we found that the prevalence of non-O blood group was significantly higher in patients with myocardial infarction (OR, 1.28; 95% CI, 1.17–1.40; $p < 0.001$) and ischemic stroke (OR, 1.17; 95% CI, 1.01–1.35; $p = 0.03$) than in controls.[30] In another meta-analysis by Takagi and Umemoto[31] of 10 studies with a total of 174,945 participants, non-O blood group appeared to be an independent risk factor for both coronary artery disease (OR, 1.14; 95% CI, 1.04–1.25; $p = 0.006$) and myocardial infarction (OR, 1.16; 95% CI, 1.02–1.31; $p = 0.02$). An updated systematic review and meta-analysis by Chen et al[32] combining results from 17 case–control and cohort studies covering 225,810 participants showed that the risk of coronary artery disease was significantly higher in blood group A (OR, 1.14; 95% CI, 1.03–1.26; $p = 0.01$) and lower in blood group O (OR, 0.85; 95% CI, 0.78–0.94; $p = 0.0008$). Finally, a meta-analysis of 14 genome-wide association studies of coronary artery disease, including 22,233 cases and 64,762 controls, identified 23 loci as established risk factors for coronary artery disease.[33] Notably, the authors identified the rs579459 variant (which tags the A1 allele) in the ABO locus as having the fifth highest association, with an OR of 1.10 (95% CI, 1.07–1.13).

The profound influence exerted on hemostasis by ABO antigens, demonstrated by their close relationship with von Willebrand factor (VWF) and, consequently, coagulation factor VIII (FVIII) plasma levels, has been proposed to explain the association between ABO blood group and thrombotic vascular disease.[34] Indeed, while it has been established that the ABO system is responsible for approximately 15 and 10% of overall VWF and FVIII interindividual variability, respectively,[35,36] it is equally well known that subjects with non-O blood group have VWF and FVIII circulating levels that are approximately 25% higher than O blood group subjects.[33] The presence of ABO blood group determinants on VWF N-glycans provides the molecular basis of the connection between ABO blood group and VWF levels.[34] In individuals with O blood group, VWF is cleaved by ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13) and undergoes enhanced clearance through low-density lipoprotein receptor-related protein 1 (LRP1), resulting in a reduced VWF activity compared with those with non-O blood group. Conversely, in individuals with non-O blood group, the A/B/AB antigen-related VWF glycosylation protects it from proteolysis and clearance by ADAMTS13 and LRP1, respectively, resulting in increased VWF levels compared with those with O blood group.[37–39] Beyond the association with levels of circulating VWF, recent investigations have been focused on the capacity of ABO blood group antigens to influence serum levels of several inflammatory cytokines (i.e., tumor necrosis factor-α, soluble intercellular adhesion molecule 1, E-selectin, P-selectin, and interleukin 6), whose higher concentrations have been associated with an increased risk of cardiovascular thrombotic events.[40–43] Finally, the observations of the association between the ABO locus and plasma lipoprotein concentrations[44] and between non-O blood types and increased circulating cholesterol levels[45,46] add another important contribution to the understanding of the pathogenic mechanisms underlying the correlation between ABO blood group and coronary heart disease susceptibility. All in all, these data document that the relation between the ABO blood group system and cardiovascular diseases is more complex than the simple modulation of hemostasis.

Interaction between ABO Blood Type and Other Thrombotic Risk Factors

Besides the consistent experimental and clinical observations of the close relationship between ABO blood group and thrombotic vascular disease, several studies have also investigated the interaction between ABO antigens and other known thrombotic risk factors.[20,47–52] In the Longitudinal Investigation of Thromboembolism Etiology (LITE) study,[49] which analyzed the ABO genotype in 492 participants who subsequently developed VTE and 1,008 participants who remained free of VTE, the authors observed that the VTE risk in non-O blood type individuals increased more than fivefold (ORs from 1.31 [95% CI, 1.02–1.68] to 6.77 [95% CI, 3.65–12.6]) when they were also carriers of factor V (FV) Leiden. The fact that the combination of FV Leiden and non-O blood type was associated with VTE more strongly than expected from a simple additive model of individual risks was confirmed in further studies. For instance, in a Danish case cohort study[51] of 56,104 participants with 641 incident VTE episodes, the presence of FV Leiden heterozygosity conferred a hazard ratio (HR) for VTE of 2.84 (95% CI, 2.15–3.76), but when present in persons with non-O blood type, the adjusted HR for VTE became 5.12 (95% CI, 3.05–8.59), exceeding the sum of separate effects. In a retrospective case–control study conducted in Italy on a large number of patients with deep vein thrombosis (DVT) and controls (712 cases and 712 controls), the investigators found

Table 1 Characteristics of the main studies on the association between ABO blood group and other thrombotic risk factors

First author (year)[ref.]	Study design	Cases/controls	Non-O vs. O blood group-associated thrombotic risk
Morelli (2005)[48]	Case–control	471 with VTE/471 without VTE	OR, 1.7 (95% CI, 1.3–2.3) FVL carriers: OR, 23.2 (95% CI, 9.1–59.3)[a]
Ohira (2007)[49]	Case–control	492 with VTE/1,008 without VTE	aOR, 1.31 (95% CI, 1.01–1.68) FVL carriers: aOR, 6.77 (95% CI, 3.65–12.6)
Miñano (2008)[50]	Case–control	807 FVL/PT 20210A carriers: 609 with VTE/198 without VTE	FVL carriers: OR, 1.76 (95% CI, 1.06–2.91) PT 20210A carriers: OR, 2.17 (95% CI, 1.33–3.53)
El-Galaly (2012)[51]	Case–control	578 with VTE/1,733 without VTE	aHR, 1.84 (95% CI, 1.50–2.27) FVL carriers: aHR, 5.12 (95% CI, 3.05–8.59)
Spiezia (2013)[20]	Case–control	712 with DVT/712 without DVT	OR, 2.21 (95% CI, 1.78–2.75) FVL carriers: OR, 3.67 (95% CI, 2.45–5.48)
Sode (2013)[52]	Prospective	66,001 participants with 2,279 VTE	aHR, 1.4 (95% CI, 1.3–1.5) FVL carriers: aHR, 2.2 (95% CI, 2.0–2.2)
Streiff (2004)[54]	Retrospective	28 with VTE/102 without VTE[b]	A vs. O: HR, 2.7 (95% CI, 1.0–7.0) AB vs. O: HR, 9.4 (95% CI, 2.7–32)
Larsen (2005)[55]	Case–control	129 with VTE/258 without VTE[c]	A vs. O: aOR, 2.4 (95% CI, 1.3–4.3) AB vs. O: aOR, 2.0 (95% CI, 0.7–5.8)
Canonico (2008)[56]	Case–control	271 with VTE/610 without VTE[d]	aOR, 8.9 (95% CI, 4.4–17.8)[e]

Abbreviations: aHR, adjusted hazard ratio; aOR, adjusted odds ratio; CI, confidence interval; DVT, deep vein thrombosis; FVL, factor V Leiden; OR, odds ratio; PT, prothrombin; VTE, venous thromboembolism.
[a]Versus O blood group and FVL (−).
[b]Patients with malignant glioma.
[c]Women during pregnancy or puerperium.
[d]Women under postmenopausal hormone therapy.
[e]Non-O oral estrogen users versus O nonusers.

that the non-O blood group increased the risk of DVT 2.2 times (OR, 2.21; 95% CI, 1.78–2.75) over group O. A sevenfold greater increase in the DVT risk (OR, 7.06; 95% CI, 4.85–10.28) was observed when an inherited thrombophilic condition (FV Leiden, prothrombin G20210A mutation, deficiencies of natural anticoagulants) was combined with non-O group.[20] Pertaining to the pooled analyses of data, the synergistic effect on VTE risk of the association between non-O status and FV Leiden observed in the meta-analysis by Wu et al[27] (OR, 7.60; 95% CI, 3.21–17.99) was subsequently replicated in the meta-analysis performed by our group[29] (OR, 3.88; 95% CI, 2.51–6.00). In addition to the interaction with inherited thrombophilic risk factors, there are also increasing amounts of data documenting a synergistic hypercoagulable effect of ABO blood group antigens in several physiological or clinical conditions characterized by increased thrombotic potential, such as pregnancy and the puerperium, postmenopausal hormone replacement therapy, trauma, and cancers.[53–57] The main results of the most important studies assessing the link between ABO blood type and inherited and/or acquired thrombotic conditions are summarized in ►**Table 1**.

ABO Blood Type and Cardiovascular Scoring Systems

As previously described, there is a large body of evidence consistently demonstrating that ABO blood type is not only an important genetic determinant of venous and arterial thromboses but it is also able to interact with other genetic and nongenetic factors in the modulation of thrombotic risk. As a result, with the aim of better quantifying the ABO attributable thrombotic risk, some investigators have assessed the association of ABO blood group with scores evaluating arterial thrombotic risk. Yang et al[58] investigated ABO blood group in 1,311 young Chinese adults with acute ischemic cerebral stroke by using the National Institutes of Health Stroke Scale (NIHSS) score, a valid, reliable, and reproducible neurological severity scale performed at admission and associated with chronic functional outcome. Notably, the authors demonstrated the utility of the score as a predictor of clinical outcomes in ABO blood group, since stroke patients with non-O blood group have a higher probability of an unfavorable outcome at discharge than O blood type patients with the same NIHSS scores. In addition, Gong et al[59] investigated the relation of ABO blood type and the severity of coronary atherosclerosis assessed by the Gensini score, a useful angiographic system to assess fatal and nonfatal cardiovascular events. The results of this large Chinese cohort study, which enrolled 2,919 consecutive patients undergoing coronary angiography, showed that while blood group A was an independent risk factor (OR, 1.44; 95% CI, 1.16–1.80; $p = 0.001$), group O was a protective factor (OR, 0.77; 95% CI, 0.65–0.92; $p = 0.004$) for serious coronary atherosclerosis. Finally, the relationship

between ABO blood type and cardiovascular disease was assessed by our group using the Cardiorisk score.[60] During the decade 2005 to 2015, 17,197 Italian blood donors were enrolled in the Cardiorisk program, derived from the Framingham risk profile algorithm,[61] which included the assessment of eight variables (sex, age, total cholesterol, high-density lipoprotein cholesterol, glycemia, arterial blood pressure, antihypertensive therapy, and smoking) which were used to generate a score. The 249 individuals with a resulting score $\geq$ 20, considered at high cardiovascular risk, underwent additional tests (chest X-ray, stress electrocardiogram, and Doppler ultrasound of supra-aortic trunks) and were closely monitored clinically for at least 2 years of follow-up. Among these, 36 (14.5%) had abnormal tests and 23 of them developed adverse cardiovascular events (10 acute coronary syndrome, 2 cerebral ischemia, 3 cardiac arrhythmia, 8 stenosis of supra-aortic trunks or iliac arteries) during a median follow-up of 5.3 years. A subanalysis of ABO blood group in this cohort of 249 high-risk individuals found a statistically significant association between the non-O blood type and the risk of developing subclinical or clinical cardiovascular events (OR, 3.3; 95% CI, 1.1–10.1).

Conclusion

Overall, a large body of evidence from experimental and clinical studies documents the close link between the ABO blood group system and hemostasis, and several lines of research indicate that ABO blood group antigens might modulate various distinct pathways related to cardiovascular risk factors, atherosclerosis, and thrombosis. Thanks to intense research in this field, today, it is possible to conclude that non-O blood type is an independent risk factor for both venous and arterial thromboses. In addition, investigation of the association between ABO antigens and traditional cardiovascular risk factors in the context of thrombotic score assessments has identified non-O blood type as an important cardiovascular prognostic biomarker. However, research in this field is in its early stages and further studies are needed to better clarify the interaction of the ABO antigens with other acquired and inherited thrombotic risk factors. In particular, considering that non-O blood type is associated with an approximately twofold increased VTE risk, it could be very interesting to analyze its relation with scores assessing the risk of primary and recurrent vein thrombosis.[62]

Conflict of Interest

The authors declare they do not have any conflict of interest or affiliation with any organization whose financial interest may be affected by material in the article.

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