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REVIEW ARTICLE

ABO blood group, hypercoagulability, and cardiovascular and cancer risk

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Abstract

The antigens of the ABO system (A, B, and H determinants, respectively) consist of complex carbohydrate molecules. It has been known for nearly half a century that the ABO blood group exerts a major influence on plasma levels of the von Willebrand factor (VWF)-factor VIII (FVIII) complex and that normal group O individuals have significantly lower levels of VWF and FVIII than do non-O individuals. As a consequence, several investigators have studied the association between ABO blood group and the risk of developing bleeding or thrombotic events. A number of epidemiological studies have also analyzed the biologic relevance of this interaction by assessing whether the ABO blood group could influence human longevity through the regulation of VWF-FVIII plasma levels. In this review, the molecular mechanisms by which the ABO blood group determines plasma VWF and consequently, FVIII levels, the possible clinical implications, and the current knowledge on the association between the ABO blood group and the risk of developing certain cancers will be reviewed.

Keywords: ABO blood group, von Willebrand factor, bleeding, thrombosis, longevity, cancer

Abbreviations: **CI**, confidence interval; **DVT**, deep vein thrombosis; **FACTORS**, Factors in Oral Anticoagulation Safety; **FV Leiden**, factor V Leiden; **FVIII**, factor VIII; **GH**, Group Health; **HR**, hazard ratio; **LETS**, Leiden Thrombophilia Study; **MARTHA**, Marseille Thrombosis Association; **MI**, myocardial infarction; **MTHFR**, methylenetetrahydrofolate reductase; **NSAIDs**, non-steroidal anti-inflammatory drugs; **OR**, odds ratio; **PCI**, percutaneous coronary intervention; **RR**, relative risk; **SCANDAT**, Scandinavian Donations and Transfusions; **SNP**, single-nucleotide polymorphism; **SPIRIT**, Stroke Prevention In Reversible Ischemia Trial; **TIMI**, thrombolysis in myocardial infarction; **VKA**, vitamin K antagonists; **VTE**, venous thromboembolism; **VWD**, von Willebrand disease; **VWF**, von Willebrand factor

Introduction

The antigens of the ABO system (A, B, and H determinants, respectively) consist of complex carbohydrate molecules. 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, and convert it into A- or B-antigens. The O alleles do not encode a functional enzyme and consequently OO carriers, who lack such transferase enzymes, continue to express the basic, unmodified, H structure, which has a solitary terminal fucose moiety attached[1].

The ABO blood group has a profound influence on hemostasis, as originally described by Preston and Barr in 1964[2], and confirmed by subsequent studies[3]. Indeed, it is well known that the ABO blood group exerts major

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quantitative effects on plasma levels of von Willebrand factor (VWF) and consequently of factor VIII (FVIII), since VWF acts as a specific carrier of FVIII and protects it from proteolytic degradation. It is also well established that, besides the *VWF* (12p12) and *FVIII* (Xq28) genes, the ABO blood group locus on chromosome 9q34 is the most important genetic determinant of plasma levels of the VWF-FVIII complex[4–9].

Several investigators have studied the clinical implications of this biological interaction and the influence of the ABO blood group on the risk of developing bleeding or thrombotic events, in an attempt to explain the difference in life span among individuals with different blood groups[2,10]. Current knowledge on these aspects, as well as the relationship between the ABO blood group and the risk of developing certain malignancies, will be summarized in this review.

Molecular biology of the ABO system

The three major alleles (A, B and O) in Caucasian individuals comprise 6 common ABO alleles (ABO*A101, ABO*A201, ABO*B101, ABO*O01, ABO*O02, and ABO*O03) and a larger number of rarer alleles[11]. A and B alleles are codominant, meaning that coexpression of an A and O allele gives rise to an A phenotype blood group, coexpression of a B and O allele gives rise to a B phenotype blood group, coexpression of an A and B allele gives rise to an AB phenotype blood group, and only when there is coexpression of two O alleles is an O phenotype blood group expressed (Figure 1). Naturally, coexpression of two A alleles gives rise to an A phenotype blood group, and coexpression of two B alleles gives rise to a B phenotype blood group. Many studies assessing ABO relationships are based on simplified phenotypes, whereby A, B and AB blood groups are grouped into a non-O blood group for data comparison.

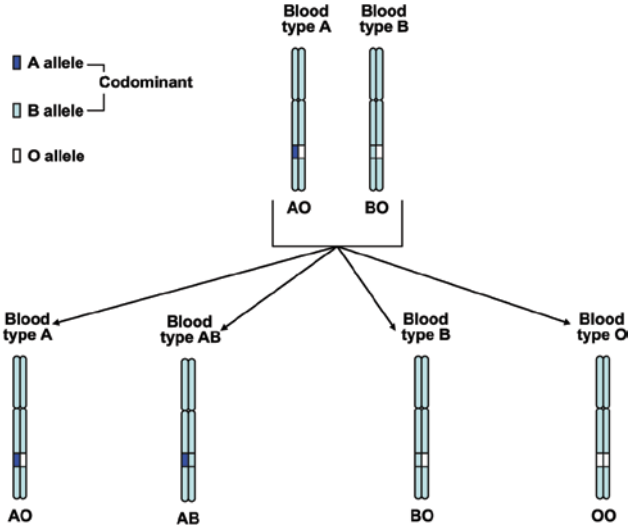

Figure 1. Simplified illustration of the genotype-phenotype relationship in the ABO blood group.

The effect of the ABO(H) blood group on VWF (non-O blood group individuals have VWF levels approximately 25% higher than O subjects) seems to be due to a direct effect of ABO rather than to a linkage disequilibrium to some other VWF regulatory genes[12,13]. Indeed, the ability to change the H-determinant to obtain the different antigens of the ABO blood group has been correlated with the capacity to modify N-linked glycosylation of VWF, which contains blood group A, B, and H(O) structures in its N-linked oligosaccharides[14]. Thus, changes in VWF glycan composition driven by different ABO allele products not only influence plasma VWF antigen levels, but may also have significant differential effects on VWF biologic activity[15], determining the rate of hepatic clearance and of VWF clearance rate of proteolysis by ADAMTS13[16].

Clinical implications of ABO system related to thrombosis and hemostasis

Thrombosis

The first study investigating the potential relationship between the ABO blood group and thrombosis was published by Bronte-Stewart *et al.* in 1962[17]. Briefly, 694 white and 98 black patients from the city of Cape Town were enrolled in a study undertaken within the teaching hospital of the University of Cape Town. Diagnosis of myocardial infarction (MI) was established according to the then available clinical and electrocardiography criteria. A deficiency of blood group O individuals among the patients with ischemic heart disease was observed and the degree of excess of groups A and B was similar (*i.e.* expressing these deviations in the form of relative incidence, the ratios were 1.34 for both A:O and A+B:O, and 1.31 for A+B+AB:O). Seven years later, Jick *et al.* published a cooperative study[18] that was prompted by an observation during a prospective drug-surveillance program of a deficit of patients with blood group O among those receiving anticoagulant therapy for venous thromboembolism (VTE); this cooperative study in the US and Europe enrolled young white women who developed VTE while taking oral contraceptives, during pregnancy or the puerperium (post-natal period), or in other circumstances. The authors confirmed the deficit of patients with blood type O in all the groups studied, and particularly in women who used oral contraceptives or were pregnant[18]. These preliminary findings, which were confirmed in further investigations by Westerholm *et al.*[19] and Mourant *et al.*[20], paved the way for a wide series of subsequent studies, the most relevant of which are described below and are summarized in Tables 1 and 2 (articles were retrieved from PubMed, Thomson and Google Scholar using the keywords "ABO", "blood group", "thrombosis" and "myocardial infarction").

Pooled risk of thrombosis

Among studies that have assessed the relationship between thrombosis in general and ABO blood groups, Jukic *et al.* found that the non-O blood group was associated with a higher probability of developing thrombosis as compared

Table 1. Summary of studies exploring the association between ABO blood group and venous thrombosis. Only studies in which the risk could be calculated are listed.

Study	End points	Outcome	First author, year [reference]
Case-control (301 cases and 301 controls)	VTE	Non-O versus O: – Phenotype; Crude OR 2.0 (95% CI 1.4–2.9) – Phenotype; Adjusted[1] OR 1.5 (95% CI, 1.0–2.2)	Koster, 1995[38]
Case-control in carriers of Factor V Leiden (147 cases and 32 controls)	VTE	Non-O versus O: – Phenotype; Crude OR 3.9 (1.7–8.8)	Robert, 2000[40]
Case-control (301 cases and 299 controls)	VTE	Non-O versus O: – Genotype; Crude OR 1.8 (95% CI 1.4–2.4) – Genotype; Adjusted[1] OR 1.4 (95% CI, 1.0–2.1)	Morelli, 2005[41]
Case-control (250 cases and 250 controls)	VTE	Non-O versus O: – Genotype; Crude OR 2.6 (95% CI, 1.8–3.8) – Genotype; Adjusted[1] OR 1.7 (95% CI, 1.1–2.6)	Tirado, 2005[42]
Case-control (510 cases and 364 asymptomatic controls)	VTE	O versus non-O: – Phenotype; Crude OR 0.62 (95% CI, 0.46–0.82) – Genotype; Crude OR 1.22 (95% CI, 0.80–1.86)	Mercier, 2005[37]
Nested case-control (126 cases and 255 controls)	VTE in pregnancy and puerperium	A versus O: – Phenotype; Crude OR 1.9 (95% CI, 1.2–3.1) AB versus O – Phenotype; Crude OR 1.6 (95% CI, 0.6–4.2) B versus O – Phenotype; Crude OR 1.1 (95% CI, 0.5–2.3)	Larsen, 2005[48]
Case-control in Factor V Leiden homozygotes (127 patients and 53 controls)	VTE	Non-O versus O:-OR 4.1 (95% CI, 1.9–8.9)	Procare-GEHT Group, 2006[45]
Nested case-control (492 cases and 1008 controls)	VTE	Non-O versus O: – Genotype; Crude OR 1.64 (95% CI, 1.32–2.05) – Genotype; Adjusted[1] OR 1.31 (95% CI, 1.02–1.68)	Ohira, 2007[43]
Case-control (609 cases and 198 controls)	VTE	Non-O versus O: – Genotype; FVL carriers: crude OR 1.76 (95% CI, 1.06–2.91) – Genotype; PT carriers: crude OR 2.17 (95% CI, 1.33–3.5)	Miñano, 2008[24]
Case-control (154 cases and 200 controls)	Thrombosis (VTE, CVD and arterial)	Non-O versus O: – Genotype; Crude OR 2.08 (95% CI, 1.32–3.27)	Jukic, 2009[21]
Case-control (504 cases and 2172 controls)	VTE	Non-O versus O: – Genotype; Crude OR 1.77 (95% CI, 1.43–2.18)	Wiggins, 2009[22]
Case-control (148 cases and 233 controls)	VTE	Non-O versus O: – Genotype; OR 4.28 (95% CI, 2.54–7.23)	Paiva, 2009[46]
Case-control (1150 cases and 801 controls)	VTE	O versus non-O: – Genotype; Crude 0.33 (95% CI, 0.26–0.42)	Trégouët, 2009[47]
Case-control (107 cases and 1825 controls)	Upper extremity DVT	Non-O versus O: – Genotype; Crude OR 2.1 (95% CI, 1.3–3.6) – Genotype; Adjusted[1] OR 1.7 (95% CI, 1.0–2.8)	Flinterman, 2010[49]

[1] Adjusted OR for von Willebrand factor (VWF) and/or factor VII.
CVD, chronic venous disease; FVL, factor V Leiden; PT, prothrombin 20210A allele.

with O (odds ratio [OR] 2.08; 95% confidence interval [CI], 1.32–3.27)[21]. Among the non-OO blood group, higher risk was observed for O^1A^1/O^2A^1 (OR 1.95; 95% CI, 1.15–3.31), $BB/O^1B/O^2B$ (OR 2.29; 95% CI, 1.25–4.21) and A^1B/A^2B genotypes (OR 2.73; 95% CI, 1.10–6.74). Wiggins *et al.* used data from the Group Health (GH), a large integrated health care system in western Washington State, to assess the association of the ABO genotype with MI, ischemic stroke, hemorrhagic stroke, and VTE[22]. The A^{11} (OR 1.56; 95%CI, 1.29–1.88) and B (OR 1.63; 95% CI, 1.25–2.14) haplotypes were associated with an increased risk of VTE compared with the reference haplotype O^{11}. These same haplotypes were also associated with an increased risk of both MI (A^{11} allele, OR 1.18; 95% CI, 1.04–1.35) and ischemic stroke (B allele, OR 1.47; 95% CI, 1.14–1.90). Moreover, the $A^{11}A^{11}$ genotype was associated with an increased risk of both VTE (OR 1.79; 95% CI, 1.41–2.26) and MI (OR 1.23; 95% CI, 1.05–1.44) compared with O^1O^1 genotype. Likewise, BB genotype was associated with an increased risk of VTE (OR 1.82; 95% CI, 1.29–2.57) and ischemic stroke (OR 1.59; 95% CI, 1–17–2.17) as compared with the O^1O^1 genotype. The AB genotype was associated with an increased risk of VTE (OR 2.70; 95% CI, 1.73–4.21). Globally, the comparison of O versus non-O genotypes was non-significant for the risk of MI, ischemic stroke or hemorrhagic stroke, but the non-O genotypes conferred an increased risk of VTE (OR 1.77; 95% CI, 1.43–2.18). In 2008, Wu *et al.* performed a systematic review and meta-analysis of clinical investigations that assessed the association of non-O blood groups with a variety of vascular disorders[23]. Among these pathologies,

Table 2. Summary of studies exploring the association between ABO blood group and arterial thrombosis. Only studies in which the risk could be calculated are listed.

Study	End points	Outcome	First author, year [reference]
Prospective (7662 males)	MI	O versus non-O: – Phenotype; RR 0.82 (95% CI 0.68–0.99)	Whincup, 1990[27]
Case-control (174 cases and 198 controls)	MI	Non-O versus O: – Genotype; FVL carriers: crude OR 1.35 (95% CI, 0.69–2.63) – Genotype; PT carriers: crude OR 1.06 (95% CI 0.58–1.93)	Miñano, 2008[24]
Case-control (154 cases and 200 controls)	Thrombosis (VTE, CVD and arterial)	Non-O versus O: – Genotype; Crude OR 2.08 (95%\ CI, 1.32–3.27)	Jukic, 2009[21]
Case-control (1063 cases and 3452 controls)	MI	Non-O versus O: – Genotype; Non significant A^{11} versus O: – Genotype; Crude OR 1.18 (95% CI, 1.04–1.35)	Wiggins, 2009[22]
Case-control (469 cases and 3452 controls)	Ischemic stroke	Non-O versus O: – Genotype; Non significant B versus O: – Genotype; Crude OR 1.47 (95% CI, 1.14–1.90)	Wiggins, 2009[22]
Case-controls (4901 cases and reference National population)	MI	Non-O versus O (all cause death): – Phenotype; HR 1.24 (95% CI, 1.01–1.52) Non-O versus O (cardiac mortality): – Phenotype; HR 1.53 (95% CI, 1.06–2.21)	Carpeggiani, 2010[33]
Nested case-control in patients with coronary artery disease (470 cases and 463 controls)	MI	Non-O versus O (all cause death): – Phenotype; OR 1.62 (95% CI, 1.23–2.13)	Reilly, 2011[32]

CVD, chronic venous disease; FVL, factor V Leiden; PT, prothrombin 20210A allele.

significant risk was observed for VTE (OR 1.79; 95% CI, 1.56–2.05), peripheral vascular disease (OR 1.45; 95% CI, 1.35–1.56), MI (OR 1.25; 95% CI 1.14–1.36) and ischemic stroke (OR 1.14; 95% CI, 1.01–1.27), whereas no increased risk was found for angina (OR 1.03; 95% CI, 0.89–1.19). The significance of the risk for MI drastically dropped after limiting the analysis to prospective studies (OR 1.01; 95% CI, 0.84–1.23). To establish the potential biological interactions of AB0 blood groups and thrombophilia, Miñano *et al.* assessed the risk of arterial and venous thromboses in carriers of FV Leiden (factor V Leiden) or the prothrombin 20210A allele in a Spanish multicenter collaborative case-control study[24], and reported that the prevalence of non-O genotypes was higher in symptomatic carriers of FV Leiden (71.1% versus 58.3%, p = 0.021; OR 1.76; 95% CI, 1.06–2.91) or the prothrombin 20210A allele (73.3% versus 55.9%, p = 0.001; OR 2.17; 95% CI, 1.33–3.53) than in asymptomatic carriers. Conversely, the risk of MI in non-O genotypes was non-significantly different from that of O-genotypes in patients with either FV Leiden (OR 1.35; 95% CI, 0.69–2.63; p = 0.234) or the prothrombin 20210A allele (OR 1.06; 95% CI 0.58–1.93; p = 0.842).

Arterial thrombosis

The results of numerous cross-sectional and prospective investigations demonstrate that patients with blood groups other than O have a higher risk of MI. In 1971, Medalie *et al.* conducted a 5-year prospective investigation involving 10,000 Israeli male government employees[25]. Subjects with blood groups A1, B, and A1B were found to have greater incidence rates of MI and angina pectoris than those with other blood groups. Conversely, subjects with blood type O tended to have lower incidence rates of MI and angina pectoris than those of other blood groups, although the differences were not significant. Identical results were obtained in the Framingham Heart Study cohort, in which a significant association was observed between blood type and intermittent claudication (such that blood group O had the lowest incidence rates). Additional but non-significant excesses for coronary heart disease events were also observed in non-O individuals[26]. A significant positive association (r = 0.58; p = 0.003) between the proportion of subjects carrying blood group O and the rate of first ischemic events was also reported by Whincup *et al.*, who prospectively followed 7,662 men with known ABO blood group selected from age-sex registers in general practices in 24 British towns[27]. The incidence of ischemic events in subjects carrying blood group A was also modestly higher than that of the other blood groups (relative risk [RR] 1.21; 95% CI, 1.01–1.46), whereas the RR of the first ischemic event in subjects carrying blood group O was also lower than in those who were non-O blood group carriers (RR 0.82; 95% CI, 0.68–0.99). Akhund *et al.* assessed the occurrence of MI and angina pectoris according to the ABO blood group among 300 Asian patients with coronary artery disease and found that blood group A was that most common among both MI and angina pectoris patients, whereas blood group O was the least frequent[28]. However, two subsequent investigations failed to find a significant difference in the frequency distribution of ABO blood groups in patients

undergoing primary on-pump coronary artery bypass surgery as compared with that of the general population[29,30]. Different results were however obtained by Ketch *et al.*[31], who studied 1,198 consecutive patients undergoing percutaneous coronary intervention (PCI) for MI and found that non-O blood group patients had larger infarcts, whereas O blood group patients displayed lower visible thrombus, a lower rate of stenting use and higher TIMI (thrombolysis in myocardial infarction) scores. No significant differences were however observed in procedural success, in-hospital blood transfusion or occurrence of major cardiac events at 1 year follow-up between non-O and O blood group carriers. Recently, Reilly *et al.* reported on two genome-wide association studies of coronary artery disease to address the hypothesis that genetic factors predisposing to MI in patients with coronary atherosclerosis might be distinct from those associated with the presence of coronary atherosclerosis[32]. The former case-control study (MedStar) was composed of 447 controls and 875 patients with angiographic coronary artery disease, with this latter group then divided between those with (n = 421) or without (n = 454) a previous history of MI. The latter hospital-based study (PennCath) included 3,815 consecutive patients undergoing cardiac catheterisation, which was followed by a nested case-control genome-wide association study on 1,401 white patients. The controls had no or minimum coronary artery disease (<10% stenosis of any vessel), whereas patients had angiographic coronary artery disease with at least one coronary vessel with 50% or more stenosis. Nearly half of these patients presented with, or had a history of, MI (n = 469). Interestingly, an increased risk in non-O blood group individuals was observed in coronary artery disease patients with MI versus those without MI (OR 1.62; 95% CI, 1.23–2.13) and in patients with angiographic coronary artery disease and MI versus controls (OR 1.44; 95% CI, 1.10–1.90), whereas the risk was not significant when comparing patients with angiographic coronary artery disease and without MI versus controls (OR 0.89; 95% CI, 0.68–1.17; p = 0.43), or all patients with angiographic coronary artery disease versus controls (OR 1.13; 95% CI, 0.90–1.43; p = 0.30). Nearly identical results were observed for the rs514659 SNP (single-nucleotide polymorphism). In a combined meta-analysis of 5,783 cases (patients with coronary artery disease with MI) and 3,644 controls (patients with coronary artery disease without MI), this SNP also displayed an OR of 1.21 (95% CI, 1.13–1.29). More recently, Carpeggiani *et al.* performed an observational study on patients with heart disease who received coronary angiography and in whom the ABO group was determined[33]; a significantly different distribution of ABO blood groups was observed in the study population (O 43.3%, A 41.4%, B 11.2%, AB 4.1%) as compared to the control population (O 40%, A 36%, B 17%, AB 7%). A significant association was also observed between non-O blood groups and family history of ischemic heart disease, hypercholesterolemia and presence of coronary atherosclerosis. Finally, an increased prevalence of A and B alleles was recorded in MI patients, and non-O blood groups were significant predictors of all-cause mortality (HR [hazard ratio] 1.24; 95% CI, 1.01–1.52) and cardiac mortality (HR 1.53; 95% CI, 1.06–2.21), especially in women. It is also noteworthy that in the 1,183 patients with"normal" coronary vessels, blood group O was prevalent (56%), while in the remaining 3,718 patients with significant coronary artery disease, a net prevalence of non-O blood groups was observed (61%; p < 0.001).

Some studies also sought to investigate whether the relationship between ABO blood group and risk of ischemic heart disease is independent of or dependent upon clinical and biochemical variables. In 1,393 men with ischemic heart disease, who experienced 178 first major episodes during an average follow-up period of 16.1 years, Meade *et al.* found that the incidence of ischemic 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 which was deemed independent from plasma FVIII and VWF levels[34]. Suadicani *et al.* reported that socioeconomic status was associated with a significant excess risk (RR 1.7; 95% CI, 1.1–2.7) among men carrying the O phenotype, which led the authors to conclude that the socioeconomic status might interplay with ABO blood groups in determining cardiovascular risk[35].

Venous thrombosis

Regardless of the previously reported associations in general thrombosis studies, further investigations provide additional support about the interplay between ABO blood groups and venous thrombosis. In a retrospective investigation, Wautrecht *et al.* assessed the phenotypic blood group distribution among ambulatory patients with a diagnosis of deep vein thrombosis (DVT) of the lower extremities over a period of 14 years[36] and reported that the frequency of DVT patients with non-O blood group was significantly higher than that of the healthy blood donors (70.6% versus 53.9%; p < 0.001). Similarly, Mercier *et al.*[37] found that phenotypic distribution of O blood group was lower in controls than in cases of venous thrombosis (31.4 versus 42.6%, OR 0.62; 95% CI, 0.46–0.82), but could not confirm these results with genotypic analysis, where no significant risk of VTE was observed in individuals carrying non-O blood groups (OR 1.22; 95% CI, 0.80–1.86; p = 0.33). It was hence concluded that the decreased risk of VTE might be more closely associated with the O phenotype than with the O allele.

Given this association, a large number of studies have investigated whether ABO blood groups are independent risk factors or increase the risk through interplay with other biological (especially, VWF and FVIII), clinical or demographical variables. Koster *et al.* performed a population-based, case-control study on 301 consecutive patients with a first, objectively-diagnosed episode of VTE and matched healthy controls[38], observing that

blood group O was less represented among VTE patients than in controls (25% versus 43%), and subjects carrying blood group O also had lower concentrations of both FVIII and VWF than those carrying non-O blood groups. The overall risk for VTE in non-O blood group individuals was significantly higher than in O blood group individuals even after adjustment for FVIII and VWF levels (adjusted OR 1.5; 95% CI 1.0–2.2). González Ordóñez *et al*. reported that the prevalence of FV Leiden mutation in carriers of O blood group was remarkably lower than in carriers of non-O blood groups (2.4% versus 19.9%; $p = 0.006$)[39]. Similarly, in a following investigation Robert *et al*. also found that the prevalence of non-O blood group was significantly higher in symptomatic carriers of FV Leiden than in asymptomatic carriers (82% versus 53%; OR 3.9; 95% CI, 1.7–8.8; $p < 0.001$), even after adjustment for pregnancy and use of oral contraceptives[40]. In the Leiden Thrombophilia Study (LETS) Morelli *et al*. reported that the crude OR of venous thrombosis for non-OO carriers as compared with OO carriers was 1.8 (95% CI 1.4–2.4), which only marginally decreased after adjustment for FVIII only (OR 1.5; 95% CI, 1.0–2.1), for VWF:Ag only (OR 1.6; 95% CI, 1.1–2.3) or both FVIII and VWF:Ag (OR 1.4; 95% CI, 1.0–2.1)[41]. The highest risk was reported for individuals with A^1A^1, (OR 2.1; 95% CI, 1.2–3.9), A^1B/A^2B (OR 2.1; 95% CI, 1.1–4.1) and A^1O^1/A^1O^2 (OR 2.0; 95% CI, 1.5–2.7) genotypes. It was thereby concluded that even after extensive adjustment for plasma VWF and FVIII levels, some risk-enhancing effect of blood group was still present. Thus, the presence of FV Leiden increased the risk of thrombosis in both OO carriers (OR 4.6; 95% CI, 2.0–10.1) and, to a much higher extent, in non-OO carriers (OR 23.2; 95% CI, 9.1–59.3). Nearly identical results were obtained by Tirado *et al*. in a case-control study[42], where the risk of venous thrombosis was found to be higher in non-O versus O blood individuals, both when expressed as crude OR (2.6; 95% CI, 1.8–3.8) and after adjustment for levels of FVIII and VWF (OR 1.7; 95% CI, 1.1–2.6). Patients with the A1 allele also showed an increased risk of thrombosis as compared with O blood group individuals (crude OR 3.1; 95% CI, 2.0–4.7; OR adjusted for FVIII and VWF levels 2.0; 95% CI, 1.3–3.3). The levels of both FVIII and VWF were higher in non-group O individuals; although the relative risk attributed to VWF disappeared after adjusting for the ABO group, patients with FVIII levels exceeding the 90th percentile were still associated with an increased risk of first thrombotic event (OR 3.7; 95% CI, 2.1–6.5) as well as of recurrence (OR 2.3; 95% CI: 1.3–4.1). Ohira *et al*. performed a nested case-control study that combined the Atherosclerosis Risk in Communities and the Cardiovascular Health Study cohorts[43], and found a significantly higher risk of VTE among non-O blood type carriers compared with O-blood type carriers (age-adjusted OR 1.64; 95% CI, 1.32–2.05); this risk remained significant even after adjustment for sex, race, body mass index, diabetes status and FVIII levels (OR: 1.31; 95% CI, 1.02–1.68). However, the risk was increased in non-O blood type individuals who were also carriers of FV Leiden (OR 6.77; 95% CI, 3.65–12.6). Schleef *et al*. studied ABO blood group genotype in patients with VTE and healthy controls[44], and found that the overall distribution of the ABO alleles was different ($p < 0.001$) with lower frequencies of O^1, O^2 and A^2 alleles being detected in the thrombosis group as compared with the control group. A higher frequency of the genotypes O^1O^1, O^1O^2 and O^1A^2 was also observed in the control group. As expected, higher plasma levels of FVIII and VWF were observed in non-O individuals. The Procare-GEHT Group carried out a retrospective multi-center cohort study on 127 patients with VTE and 53 asymptomatic subjects and concluded that non-O blood groups were more frequent in VTE patients as compared with controls (77% versus 46%; OR 4.1; 95% CI, 1.9–8.9) after adjustment for age, sex and other prothrombotic conditions including the prothrombin 20210A allele, the protein C promoter CG haplotype, the combination of A-1641G and C-1654T protein C polymorphisms, the FXIII Val34Leu polymorphism, the Thr325Ile, Ala147Thr polymorphisms of the thrombin-activatable fibrinolysis inhibitor, the polymorphisms –675 4G/5G, A-844G of plasminogen activator inhibitor-1, and the methylenetetrahydrofolate reductase (MTHFR) C677T polymorphism[45]. Following analysis of the genotypic and allelic frequencies of ABO blood groups in a group of young Brazilian patients with a confirmed history of VTE (n = 148) and 233 genetically unrelated healthy individuals without a history of VTE[46], Paiva *et al*. reported that, after adjustment for covariates (sex, age, and acquired risk factors), significant differences of alleles distributions were observed for the alleles A^1 (OR 1.54; 95% CI, 1.04–2.29), A^2 (OR 2.66; 95% CI, 1.46–4.85), and B (OR 3.24; 95% CI, 1.96–5.36). Conversely, the allele O^1 was associated with a decreased risk of VTE (OR 0.42; 95% CI, 0.30–0.58). Overall, the VTE risk of non-O blood groups carriers was more than 4-fold that of O-blood group (OR 4.28; 95% CI, 2.54–7.23). The most relevant protective effect against VTE was observed for the O^1O^1 genotype (OR 0.23; 95% CI, 0.13–0.37). Finally, the majority of carriers of FV Leiden and/or prothrombin G20210A polymorphism were in the non-O blood groups. Trégouët *et al*. carried out a genome-wide association analysis of VTE, by using a panel of approximately 317,000 SNPs in a case-control study that included 1,150 cases (unrelated, consecutively-recruited whites with a documented history of VTE and without strong known risk factors) and 801 controls of the MARseille THrombosis Association study (MARTHA)[47]. In line with previous findings, carriers of the O blood group were at lower risk of VTE than those carrying a non-O blood group (OR 0.33; 95% CI, 0.26–0.42). The A^2 blood group was also independently associated with a decreased VTE risk (OR 0.53; 95% CI, 0.38–0.74). Nevertheless, none of the SNPs tested remained significantly associated with VTE risk after adjustment for ABO blood group, which suggested that direct assessment of the ABO blood group may provide a stronger statistical association than the ABO SNPs

detected from the genome-wide association analysis. An additional interesting conclusion of this study was that although the relative risk associated with the ABO blood groups was significantly lower than that observed for FV Leiden (*i.e.* OR 2.01; 95% CI 1.63–2.48), its population-attributable fraction was calculated to be much higher (approximately 30% for the non-O status versus 17% for FV Leiden). To assess the potential association between ABO blood types and VTE in pregnancy and the puerperium, Larsen *et al*. carried out a nested case-control study on a cohort of 71,729 women[48]. The absolute rate of first-time VTE events during pregnancy and the puerperium per 1,000 births were 1.4 (95% CI, 1.1–1.8) for blood group A, 1.2 (95% CI, 0.5-2.3) for blood group AB, 0.8 (95% CI, 0.4–1.3) for blood group B and 0.7 (95% CI, 0.5–1.0) for blood group O. As compared with blood group O, carriers of blood group AB (OR during pregnancy 2.2; 95% CI, 0.4–12.5; OR during puerperium 2.7; 95% CI, 0.8–9.3) and A (OR during pregnancy 3.9; 95% CI, 1.5–9.7; OR during puerperium 2.4; 95% CI, 1.0–4.9), but not B (OR during pregnancy 1.5; 95% CI, 0.4–5.5; OR during puerperium 1.0; 95% CI, 0.3–3.3) were associated with an increased VTE risk. The risk remained unchanged after adjustment for potential confounding factors. Finally, blood groups A and AB were also associated with an increased risk of both DVT (adjusted ORs 2.4, 95% CI, 1.4–4.2; and 2.2, 95% CI, 0.8–6.3, respectively) and PE (adjusted ORs 2.3, 95% CI, 0.6–8.7; and 2.5, 95% CI, 0.2–27.2).

Additional manifestations of thrombosis

With regard to less frequent sites of venous thrombosis, Flinterman *et al*. assessed the levels of prothrombotic and anticoagulant factors as well as blood group as risk factors for venous thrombosis of the upper extremity in a case-control study[49]. The distribution of blood groups differed significantly between cases and controls; 68% of patients were blood group non-O as compared with 53% of controls. After adjustment for age and sex, blood group non-O was associated with an OR of 2.1 (95% CI, 1.3–3.6) for venous thrombosis as compared with blood group O. In a logistic regression model including ABO blood groups, VWF and FVIII levels, all effects were attenuated, particularly those of FVIII and VWF, while blood group non-O remained associated with an 1.7-fold risk (95% CI: 1.0–2.8). Rios *et al.*[50] carried out a cross-sectional study that included 195 patients with end-stage renal disease on hemodialysis for more than 6 months. Among prothrombotic risk factors, the G20210A mutation in the prothrombin gene was the only one that showed a significant association with vascular access thrombosis (OR 12.0; CI 95%, 1.8–83.5), whereas the FV Leiden mutation and ABO blood groups were not associated with vascular access thrombosis in univariate analysis. In particular, after pooling patients with A, B and AB blood groups as "non-O", their frequency in cases and controls was nearly identical (50% versus 49.7%).

Taken together these findings suggest that blood group O might be protective against MI in patients with angiographic coronary artery disease, although it would not be protective against coronary atherosclerosis (*i.e.* a principal association of non-O ABO glycotransferase activity with intracoronary thrombosis rather than atherosclerosis *per se*). Even more interesting were the findings that the leading ABO SNPs (rs657152 and rs505922) for VTE previously identified by Trégouët *et al.*[46] appeared to be strongly associated with MI in patients with angiographic coronary artery disease in this genome-wide association study and were in strong linkage disequilibrium with the leading ABO SNP (rs514659) for MI. As such, it can be hypothesized that common ABO genetic heterogeneity associated with blood group O might negatively influence the concentration of circulating VWF and FVIII and reduce the risk of MI in patients with coronary artery disease (Figure 2). They might also exert an even higher protection against thrombus formation and growth in the setting of VTE, whereby secondary hemostasis provides a greater contribution than in the setting of arterial thrombosis.

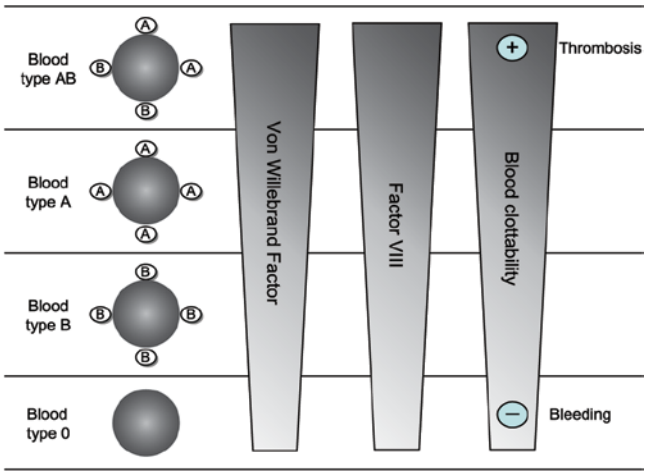

Figure 2. Potential pathogenetic mechanisms linking the different ABO blood groups with bleeding and thombotic events.

Bleeding

While a number of studies have analyzed the relationship between ABO blood groups and vascular thrombosis, only a few studies have been published on the association between ABO blood groups and hemorrhagic disorders (Table 3). However, as plasma VWF levels are 25–35% lower in subjects with O blood group than in non-O blood group individuals[12], the question of whether O blood group individuals have an increased bleeding tendency is reasonable to ask (Figure 2). Indeed, a higher rate of bleeding complications has been reported in patients belonging to group O in several old studies[51–55].

In the first study, in subjects with duodenal ulcers and healthy controls, Horwich *et al.*[51] found a significant increase of group O in subjects with bleeding duodenal ulcers over the normal controls. In addition, those with duodenal ulcers who bled had a significantly higher prevalence of blood group O over those with duodenal ulcers that did not. Similar results were also found in two subsequent studies[52,53]. A study by Habbick *et al.*[54] on 36 children with duodenal ulcers demonstrated an excess of group O patients in the ulcer group. Furthermore, Berg *et al.* found, in a series of patients who were admitted to hospital for bleeding duodenal ulcers, that the mean

Table 3. ABO blood group and bleeding tendency: summary of the literature.

First author, year [reference]	Population	Main results
Horwich, 1966[51]	5794 control subjects and 802 patients with duodenal ulcer	A higher prevalence of O blood group was found among patients with bleeding duodenal ulcer than normal controls and patients with non-bleeding duodenal ulcer.
Evans, 1968[52]	6510 control subjects and 649 patients with duodenal ulcers.	A higher prevalence of O blood group was found among patients with bleeding duodenal ulcer than normal controls and patients with non-bleeding duodenal ulcer.
Habbick, 1968[53]	36 children with duodenal ulcer and 5898 controls	The frequency of O blood group was significantly higher than control (72% versus 54%, $P < 0.05$).
Berg, 1969[55]	190 patients with duodenal ulcer hemorrhage and 5500 controls	The mean age at onset of hemorrhage in the group O patients was significantly lower than in group A (50.5 years versus 56.5 years, $P < 0.02$).
Northfield, 1971[57]	472 patients admitted with recurrent hemorrhage after acute gastrointestinal bleeding	ABO blood group did not affect the incidence of recurrent hemorrhage.
Viskum, 1972[53]	986 patients admitted for gastrointestinal hemorrhage	A significant excess of blood group O than expected was found among patients with hemorrhagic gastritis and duodenal ulcer ($P < 0.01$).
Ionescu, 1976[61]	482 patients died for cerebral hemorrhage and 20705 healthy controls	A non-statistically significant difference of ABO blood group distribution between patients with cerebral hemorrhage and controls was found.
Larsen, 1977[62]	121 patients with cerebral hemorrhage and 14304 healthy controls	A non-statistically significant difference of ABO blood group distribution between patients with cerebral hemorrhage and controls was found.
Gill, 1987[12]	1117 blood donors and 142 VWD patients	The frequency of O blood group in type I VWD patients (88/114 = 77%) was significantly higher than the expected frequency (45%, $P < 0.01$).
Halonen, 1987[66]	354 patients undergoing abdominal and pelvic surgery	ABO blood group was not associated with post-operative excessive bleeding.
Kuyvenhoven, 1999[65]	227 patients admitted for a bleeding gastric or duodenal ulcer	Only NSAID use emerged as a strong predictor (RR, 8.4) for hemorrhage caused by a peptic ulcer. Blood type was not significantly associated with bleeding (RR, 1.2).
Pruissen, 2007[63]	34 patients with non-fatal hemorrhage during OAC treatment for cerebral ischemia and 68 controls on OAC without bleeding	ABO blood group was not related with the risk of hemorrhage during oral anticoagulant treatment after cerebral ischemia (OR 1.3; 95% CI 0.6–1.9).
Welsby, 2007[64]	877 patients undergoing coronary artery bypass graft surgery	Patients with blood group O did not have increased bleeding after cardiac surgery compared with patients with other blood types ($P = 0.124$).
Reddy, 2008[59]	1261 Caucasians admitted with epistaxis and 1000 controls	Blood group O was over-represented in the group of Caucasian patients with epistaxis than control group (50.44% versus 45.10%, $P = 0.008$).
Wiggins, 2009[44]	91 patients with hemorrhagic stroke and controls	No association between ABO genotype and hemorrhagic stroke was found.
Bayan, 2009[56]	364 patients with upper gastrointestinal bleeding and 734 controls	Blood group O was found to have a higher frequency in the patient group than in the control group (46.2% versus 34.9%, $P = 0.004$).
Leonard, 2010[60]	303 patients with post-tonsillectomy hemorrhage and general Irish population	The prevalence of blood group O was higher in patients with post-tonsillectomy hemorrhage than in the general population (68% versus 55%, $P = 0.01$).

Abbreviations: OAC, oral anticoagulant.

age at onset for patients belonging to blood group O was lower than that for blood group A[55]. In a study analyzing the association between ABO groups and upper gastrointestinal bleeding, Bayan *et al.*[56] found that group O had a higher frequency in the patient group than in the control group. ABO blood groups did not appear to affect the incidence of recurrent hemorrhage after acute upper gastrointestinal bleeding in a study conducted by Northfield *et al.*[57]

Based on the previous observation of higher rates of admission for epistaxis among Caucasian compared with Asian individuals (*i.e.* Caucasians usually have a higher prevalence of blood group O)[58], Reddy *et al.*[59] analyzed retrospectively 1,261 Caucasian individuals admitted with epistaxis and found that blood group O patients were over-represented compared with control subjects. In addition, Leonard *et al.*[60] in a retrospective study on 303 patients suffering secondary post-tonsillectomy hemorrhages, observed a disproportionately high prevalence of blood group O compared with the general population and concluded that a non-causal blood group-related bleeding predisposition was present in this group of surgical patients.

By contrast, other studies did not confirm the higher bleeding tendency associated with blood group O. For instance, the evaluation by Ionescu *et al.*[61] of the ABO-blood group distribution in 482 patients who died of cerebral hemorrhage did not find a significant difference with the healthy population. These results were also confirmed by two subsequent studies[44,62]. Welsby *et al.*[63] found that patients with blood group O did not have increased bleeding after cardiac surgery compared with patients with other blood types. Kuyvenhoven *et al.*[64] analysed the interaction between the use of non-steroidal anti-inflammatory drugs (NSAIDs), *Helicobacter pylori* infection and the ABO blood group system in patients with peptic ulcer bleeding; among the parameters studied, only NSAID use emerged as a strong predictor for hemorrhage caused by a peptic ulcer. Similarly, in a study conducted by Halonen *et al.*[65] on patients undergoing abdominal and pelvic surgery, blood types were not associated with post-operative bleeding.

Other investigators analysed the relationship between ABO blood group and bleeding risk in patients with concomitant risk factors, such as the treatment with vitamin K antagonists (VKA), for hemorrhage[66,67]. A Dutch study that analysed ABO blood group genotypes using data from the FACTors in ORal anticoagulation Safety (FACTORS) case-control study showed that the risk for non-fatal major bleeding in non-OO blood group carriers was 30% lower than that of OO blood group carriers, although the difference was not statistically significant (OR 0.7; 95% CI: 0.4–1.1)[66]. Subsequently, Pruissen and colleagues[67], analysing 651 patients receiving oral anticoagulant treatment included in the Stroke Prevention In Reversible Ischemia Trial (SPIRIT), found that ABO blood group was not related to the risk of haemorrhage during oral anticoagulant treatment after cerebral ischemia.

Gill *et al.*[12] found firstly, that the ABO blood groups significantly influenced VWF:Ag (blood group O individuals had the lowest VWF:Ag levels), and secondly, that blood group O individuals were consistently over-represented in patients with the inherited bleeding disorder type I von Willebrand disease (now termed type 1 VWD). As this finding was not evident for the other forms of VWD (*i.e.* type II and type III [now termed type 2 and 3]), which had ABO blood group frequencies that did not differ from the expected distribution, the authors concluded that the type I VWD diagnosis could be influenced by the patient's ABO status. In epidemiological studies of VWD, in which a high frequency of type 1 VWD is typically identified[68], a relative predominance of O-blood group individuals has been reported[69,70].

In summary, the data in the literature are inconclusive, and only the results of large prospective trials will be able to assess whether the O blood group is associated with an increased bleeding tendency.

ABO blood groups and risk of cancer

Risk of gastric cancer

Many years ago, in a combined analysis of gastric cancer cases in 15 study locations in the United States, Europe and Australia, a significant positive association was reported between non-O blood group and risk of gastric cancer, with an OR of 1.24 (95% CI 1.18–1–30) for patients with blood group A compared to those with blood group O[71]. The recent large SCANDAT (Scandinavian Donations and Transfusions) study, involving more than one million donors who were followed for up to 35 years, demonstrated a similar magnitude of association with blood group A (OR 1.20, 95% CI 1.02–1.42)[72].

Risk of pancreatic cancer

Some early small case-control studies reported a significant association between the non-O blood group and increased risk of pancreatic cancer[73–75]. Recent large prospective, observational studies have renewed interest in this topic and confirmed an increased risk of pancreatic cancer with the non-O groups A, B, and AB compared to O. In the PanScan I genome-wide association study, 1,896 individuals with pancreatic cancer and 1,939 controls drawn from 12 cohort prospective studies and one hospital-based case-control study were genotyped using an Illumina 550K SNP panel and genome-wide significant evidence of association was reported to rs505922, a SNP in the ABO gene[76]. This association was also replicated in an independent sample of 2,457 affected individuals and 2,654 controls from eight case-control studies from the PanScan II study. Joint analyses of the two study phases yielded multiplicative per-allele OR of 1.20 (95% CI 1.12–1.28). Notably, the SNP rs505922 was in complete linkage disequilibrium with the O/non-O blood group allele, such that individuals with non-O blood groups are at higher risk of incident pancreatic cancer[76].

Among the participants of the Nurses' Health Study and the Health Professionals Follow-up Study, Wolpin *et al*. confirmed that compared with those with blood group O, participants with blood groups A, AB or B were more likely to develop pancreatic cancer (adjusted hazard ratios (HRs) for incident pancreatic cancer were 1.32 [95% CI 1.02–1.72], 1.51 [95% CI 1.02–2.23], and 1.72 [95% CI 1.25–2.38], respectively). Overall, approximately 20% of the pancreatic cancer cases were attributable to inheriting a non-O blood group. The age-adjusted incidence rates for pancreatic cancer per 100,000 person-years were 27 for participants with blood type O, 36 for those with blood type A, 41 for those with blood type AB, and 46 for those with blood type B, respectively[77].

Shortly after this Risch *et al*. reported that the increased risk of pancreatic cancer among the individuals with non-O blood group was even higher if they were also seropositive for CagA-negative *Helicobacter pylori* (OR 2.8, 95% CI 1.5–5.2)[78].

Finally, Petersen *et al*. conducted a genome-wide association study of pancreatic cancer in 3,851 affected individuals and 3,934 unaffected controls drawn from 12 prospective cohort studies and eight case-control studies. These investigators identified eight SNPs that map to three loci on chromosomes 13q22.1, 1q32.1 and 5p15.33 that warrant follow-up studies[79].

Risk of other types of cancer

Preliminary epidemiological evidence indicates that the ABO blood group may also be associated with an increased risk of developing other types of cancer. For instance, using two large prospective cohorts in the United States (70,650 female nurses and 24,820 male health professionals), Xie *et al*. reported that non-O blood group was significantly associated with a decreased risk of non-melanoma skin cancer. Compared with participants with blood group O, participants with non-O blood group had a 14% decreased risk of developing squamous cell carcinoma (adjusted HR 0.86, 95% CI 0.78–0.95) and a ~5% decreased risk of developing basal cell carcinoma[80]. In the Nurses' Health Study involving 49,153 women who were followed for 10 years, individuals with blood group B and AB combined were found to have an increased risk of developing ovarian cancer (adjusted HR 1.41, 95% CI 1.06-1.88) compared to those with blood group O[81]. Using the data from these two large prospective cohorts of US adults, no association was found between ABO blood groups and the risk of developing colorectal or breast cancers[82,83].

Finally, Lee *et al*. evaluated the prognostic value of immuno-histochemically-altered altered expression of ABO blood-group antigens in tumor samples from 164 patients who underwent curative surgery for non-small-cell lung cancer. They found that survival of the 28 patients with blood group A or AB who had primary tumors negative for blood group A was shorter than that of the 43 patients with antigen A-positive tumors and of the 93 patients with blood group B or O[84].

Putative underlying mechanisms linking ABO blood groups and cancer development

Although a number of observational studies have reported that non-O blood group is significantly associated with an increased risk of developing certain cancers, especially gastric and pancreatic cancers[85], the strength of this association is generally weak and the possibility of residual confounding cannot be excluded. To date, the underlying mechanisms by which the ABO blood group or the closely linked genetic variants of the ABO gene locus may influence cancer risk are still unclear and are the subject of intense research. One plausible hypothesis would be that the enzymatic activity of the ABO glycosyltransferase might affect both the processing and the clearance of molecules that may promote tumorigenesis[86]. This would be substantially analogous to the role played by the ABO glycosyltransferase in determining the levels of circulating VWF and the risk of VTE. However, some recent studies have also reported that genetic variants of the ABO gene locus are strong determinants of circulating levels of soluble E-selectin, P-selectin and intercellular adhesion molecule-1. All of these adhesion molecules are important mediators of chronic inflammation and immune cell recruitment that might also play a role in tumorigenesis related to the ABO blood group[87,88].

More research is urgently needed to confirm the relationship between the ABO blood groups and the risk of developing certain cancers and to further elucidate the underlying mechanisms by which this occurs.

Conclusions

The fact that ABO blood groups exert a major influence on hemostasis has been known for 50 years, and a great deal of clinical and experimental data has demonstrated that the non-O blood groups play an important role in the risk of developing both venous and arterial thrombosis, and especially VTE. This is plausibly due to the strict relationship existing between ABO blood groups and both FVIII and VWF, which are well known risk factor for VTE, whereas the pathogenetic role of these clotting factors in arterial thrombosis is still disputed because a large number of more "traditional" risk factors are more strongly linked with cardiovascular disease than FVIII or VWF *per se*[89,90]. It is also noteworthy that the incidence of VTE is higher in blacks than whites[91]. The former population carries a higher percentage of O blood type, a higher prevalence of several cardiovascular risk factors such as obesity and diabetes, as well as a very low prevalence of some common inherited thrombophilic mutations (e.g., FV Leiden and prothrombin G20210A)[39,91]; these findings provide further support to the stronger pathogenetic link between ABO blood groups and venous rather than arterial thrombosis. Finally it is important to mention that the different blood types tend to polarize with regard to their clotting tendencies, with blood types A and AB clotting more easily, and blood types O and B clotting less readily. Since secondary hemostasis plays a greater

role in venous than arterial thrombus formation,[90] this may explain the more substantial link between ABO blood groups and VTE. By contrast, the data available on the relationship between the O blood group and the increased risk of bleeding is limited. The O blood type is associated with lower VWF levels, and some studies suggest that it could be involved in the risk of development of more severe hemorrhages, especially in the presence of other concomitant bleeding risk factors (e.g., VKA therapy)[66,67]. However, the current data are contradictory, and only the results of large prospective trials will be able to assess whether such an association exists.

Finally, although recent prospective, observational studies have reported an association between non-O blood group and increased risk of developing certain cancers (especially gastric and pancreatic cancers), further larger follow-up studies are needed to confirm this association and to better elucidate the underlying mechanisms by which this occurs.

Declaration of interest

The authors state that there are no conflicts of interest regarding the publication of this article.

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