Chapter

Are ABO Gene Alleles Responsible for Cardiovascular Diseases and Venous Thromboembolism and Do They Play a Role in COVID?

Dennis J. Cordato, Wissam Soubra, Sameer Saleem and Kaneez Fatima Shad

Abstract

Cardiovascular diseases (CVD) including coronary heart disease and stroke are leading causes of death and disability globally. Studies of the association between ABO blood groups and CVD have consistently demonstrated an increased risk of coronary heart disease, myocardial infarction, cerebral ischaemic stroke, peripheral arterial disease and venous thromboembolism (VTE) including deep vein thrombosis and pulmonary thromboembolism in patients who possess a non-O blood group type. The most likely mechanism is thought to be the increase in von Willebrand Factor (vWF) and factor VIII levels seen in patients with a non-O blood group. Other postulated mechanisms include elevations in circulating inflammatory markers such as endothelial cell and platelet adhesion molecules in subjects with a non-O blood group. More recently, it has also been recognised that individuals with a non-O blood group type carry a higher risk of SARS-C0V-2 infection and COVID-19 related complications. The increased levels in vWF and factor VIII amongst individuals with a non-O blood group who have contracted SARS-CoV-2 infection may result in an additive thrombophilic effect to that caused by the SARS-CoV-2 virus. Another postulated mechanism is that individuals with an O-blood group are protected by anti-A and B antibodies which possibly inhibit the binding of the SARS-CoV-2 spike protein to lung epithelium angiotensin converting enzyme-2 receptors. There are over 35 minor blood groups on red blood cells, some of which such as Kidd, Lewis and Duffy have been associated with CVD either alone or in combination with a non-O blood group allele(s). However, their role in SARS-CoV-2 infection and mechanism of action for an association with CVD remain unknown. This review explores the relationship between ABO and minor blood groups with CVD and VTE, with a focus on potential mechanisms underlying this relationship and the potential role of ABO blood group types in COVID.

Keywords: cardiovascular diseases, venous thromboembolism, ABO blood group, von Willebrand Factor, COVID

1. Introduction

Cardiovascular diseases (CVD) including coronary heart disease and stroke are the global leading cause of death and a major contributor to disability [1].

Traditional modifiable risk factors include hypertension, dyslipidaemia, diabetes mellitus, current smoking, obesity and physical inactivity and non-modifiable risk factors include age, gender, family history and ethnic background [2]. Amongst the non-modifiable risk factors, genetic variations in conjunction with traditional modifiable risk factors may significantly influence the trajectory of an individual's CVD risk [3]. Studies on the association between ABO blood group and CVD have consistently demonstrated that possession of the O blood group, the most common phenotype in most populations [4], confers protection against an individual developing a cardiovascular event [5–11]. The A and B blood groups are most frequently seen in Caucasian and Asian populations, respectively [4]. However, the magnitude of the association between CVD and ABO blood grouping across different ethnic populations is controversial in part due to the higher population attributable risk of traditional modifiable vascular risk factors [9, 10, 12].

There is also a well-documented interaction between ABO blood group and venous thromboembolism (VTE) [7, 13–15]. The A2 blood subgroup, which is less common than A1 and rare in Asian populations [5], has been reported to be associated with a modest VTE risk (Odds Ratio 1.2) whereas the A1 and B subgroups confer a 1.8-fold increased risk [7]. The non-O blood groups are associated with ~25–30% higher plasma levels of factor VIII and von Willebrand Factor (vWF) which are felt to be the major contributing factors to the increased risk of VTE [7, 16]. ABO blood grouping has been reported to influence activated protein C resistance [8], plasma lipid levels [11] and markers of inflammation including soluble intercellular adhesion molecule 1 (ICAM1), plasma soluble E-selection and P-selectin and tumour necrosis factor-alpha [11]. An additive effect on VTE risk and ABO blood group has also been described in association with factor V Leiden and prothrombin gene mutations [10, 17]. Finally, ABO blood grouping has more recently been reported to influence

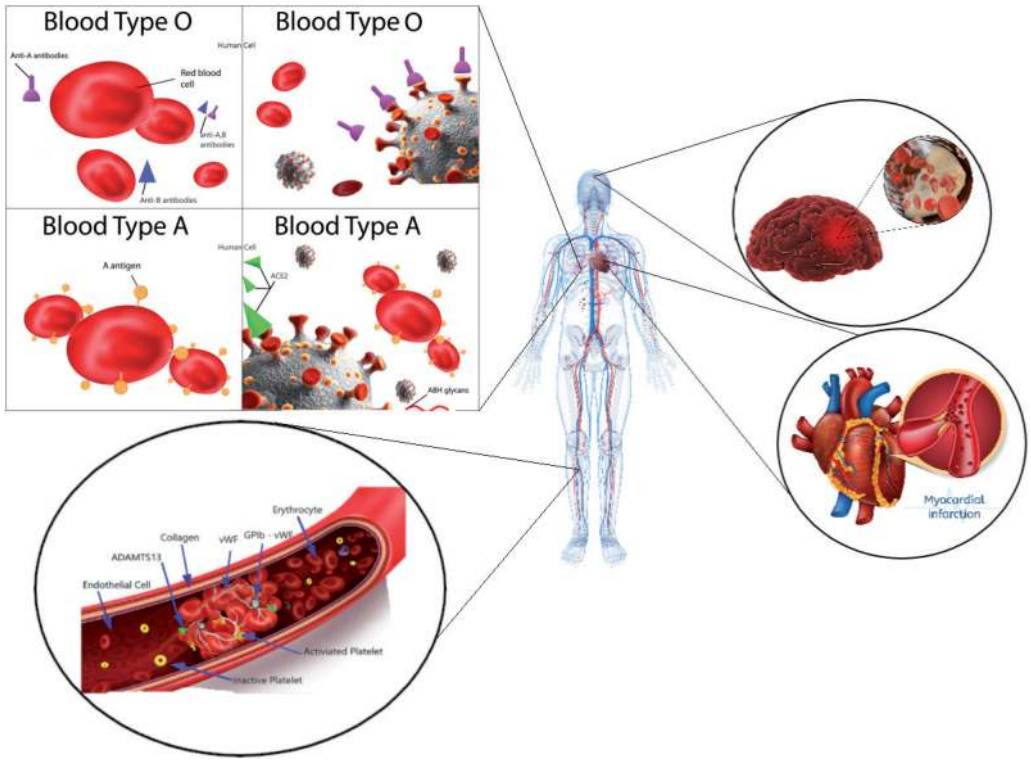

Figure 1.
ABO gene and their potential role in COVID-19, cerebral ischaemic disease, peripheral arterial disease, and myocardial infarction.

susceptibility to SARS-CoV-2 infection and an individual's propensity to more severe disease [18–20]. Proposed mechanisms include an additive risk of COVID-19 related thrombophilic complications in patients with a non-O blood group and a protective role of the O-blood group against the binding of the SARS-CoV-2 spike protein to lung epithelium angiotensin converting enzyme-2 receptor [18–20].

There are at least 35 minor blood group antigens in addition to ABO including Kidd, MNS, Duffy and Lewis [21] for which some, including Kidd and Lewis, have also been associated with CVD although the mechanisms of the associations are unclear [22–24].

This review will focus on the relationship between ABO blood types and CVD including coronary artery disease, ischaemic stroke, peripheral arterial disease and VTE (**Figure 1**). The contemporary relationship between SARS-CoV-2 infection, CVD and ABO blood grouping and the role of minor blood group antigens in the pathogenesis of CVD will also be discussed.

2. The ABO blood group system

The discovery of the ABO blood group system in 1900 by Austrian physician Karl Landsteiner saw him awarded of a Nobel Prize in physiology and medicine thirty years later [25]. The ABO blood group system consists of three main alleles A, B and O with codominant A and B alleles resulting in an inheritance pattern consisting of six genotypes and four major blood types [4, 25]. The ABO locus is found on chromosome 9 (9q34.1-q34.2) and codes for 2 glycosyltransferases A and B that transfer N-acetyl-D-galactosamine and D-galactose to a H antigen acceptor site on red blood cells (RBC) producing A and B surface antigens and blood group types, respectively (**Figure 2**) [26]. Lack of glycosyltransferase activity results in an unmodified ABO H antigen precursor and an O blood group type (O standing for 'Ohne', the German word for 'without') [25, 26]. Although ABO blood group antigens are RBC antigens, they are also expressed on human tissue including epithelial and endothelial cells [4].

The four basic ABO blood groups are O, A, B and AB. The ABO blood phenotypes have multiple subtypes, including A1, A2 and A3, in which 80% of blood group A cases are A1 in subtype, and O1, O2 and O3, in which O1 accounts for 95% of blood group O cases (**Table 1**) [4, 26]. From an evolutionary perspective, the oldest blood groups are A and O with A1 subtype considered the ancestral blood group [4, 7]. Single nucleotide polymorphisms (SNPs) of the ABO gene define the major haplotypes of European ancestry populations [7]. A substitution from proline to leucine at amino acid 156 results in a change from A1 to the less common A2 allele [5, 7]. Substitutions from glycine to serine at amino acid 235, leucine to methionine at amino acid 266 and glycine to alanine at amino acid 268 results in B allele subtypes [7, 27]. In contrast, the O1 type is a consequence of a frameshift deletion of guanine (cdel261G, p88fs118Stop) which translates to a protein without enzymatic activity [4, 5, 7].

There are significant geographic and racial variations in the distribution of blood groups across the world [4, 25]. Contributing factors include migration over the time of humankind's existence and processes of natural selection influenced by environmental factors such as climate and major diseases including malaria for which the O blood group confers protection [25]. Blood group A is predominant in Northern and Central Europe, B in Central Asia and O in Africa, South America, and Australia [4, 5, 25]. However, there are isolated populations within each continent that have a completely different blood group [4]. For example, the O blood group is common in different areas of Europe including Scandinavia and Switzerland [10, 25]. The most recent blood group, AB, appears to have arisen when A blood group populations in Europe migrated and mixed with B blood group populations of Asia [4].

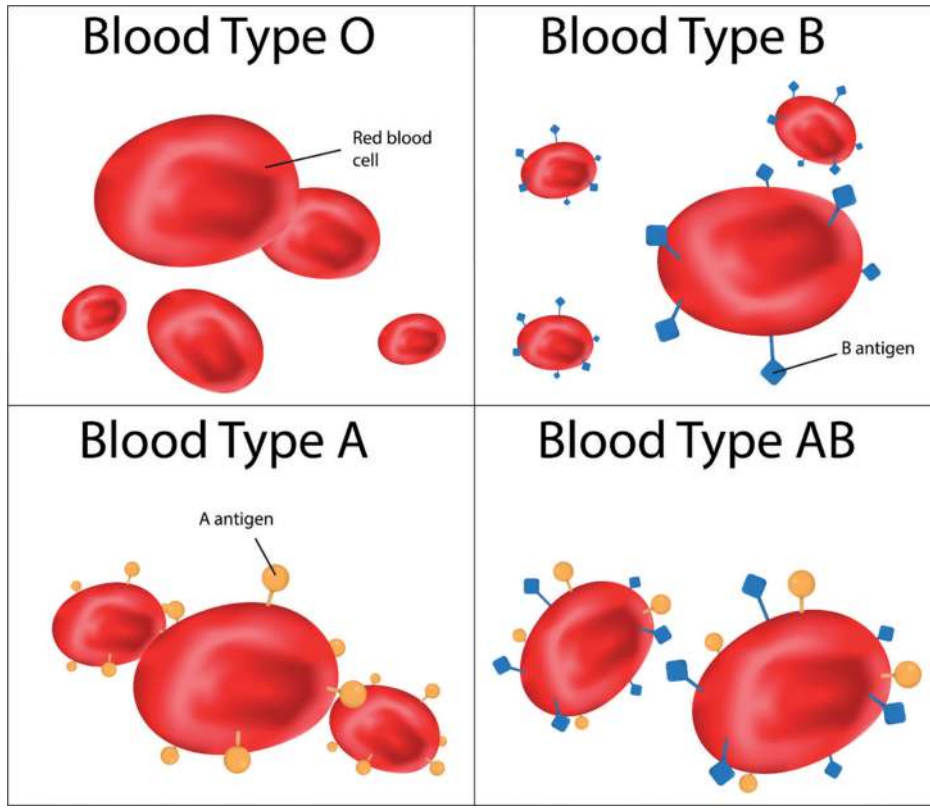

Figure 2.
Transfer of N-acetyl-D-galactosamine and D-galactose to a H antigen acceptor site on red blood cells (RBC) produces A and B surface antigens and blood group types, respectively. Lack of such a transfer result in an unmodified ABO H antigen precursor and the O blood group type.

ABO blood groups [25]	
A	A1, A2, A3 and other rare types including A4, A5, A6, Z, X, End, Boutu, g and i
B	B1, B2, B3 and rare types w, x, v and m
Other subtypes	O1, O2, O3 and other types including Yy, Hh, Xx and Bombay

Table 1.
The main ABO groups and their subtypes.

Due to the association between clotting and ABO blood group, these geographic and racial differences may contribute to ethnic differences seen in rates of CVD.

3. ABO blood groups and arterial diseases

There have been numerous retrospective and prospective studies and meta-analyses demonstrating an association between non-O blood groups and CVD events [5, 8–12, 24]. These studies have consistently demonstrated an association between non-O blood groups and an increased risk of arterial disease including myocardial infarction, coronary heart disease, peripheral arterial disease, and ischaemic stroke (**Table 2**). Possible mechanisms for an association with CVD include vWF-related thrombosis and modulation of platelet function through other platelet proteins which also express ABO antigens such as glycoprotein IIb [5]. The following two sections discuss the relationship between ABO blood groups and arterial diseases.

Study and year	Type of study	Subjects	Age range	Country	Findings (non-O versus O)
Medalie et al. 1971 [24]	5-year prospective observational	10,000 males	>40 y	Israel	↑ MI and angina pectoris in A1, B, $A1Jk^{a-}$, BJk^{a-}
Wu et al. 2007 [8]	Meta-analysis	45 arterial studies with 9720 subjects	Multiple ages	Multiple countries	↑ MI (OR 1.25), PAD (OR 1.45) & cerebral arterial ischaemia (OR1.14) in non-blood O
Wiggins et al. 2009 [30]	Case control study (10 y follow-up)	1063 MI, 469 ischaemic & 91 haemorrhagic stroke vs. 3462 C	Age range 30–79	United States	↑ MI in blood group A^{11} & ↑ ischaemic stroke in blood group B compared to O1O1
He et al. 2012 [11]	26-year prospective observational	62,073 female nurses	30–55 y at baseline	United States	↑ coronary heart disease in A, B and AB blood groups
He et al. 2012 [11]	20-year prospective observational	27,428 males	40–75 y at baseline	United States	↑ coronary heart disease in blood groups A, B & AB
Zakai et al. 2014 [12]	Case cohort study (median 5.8 y follow-up)	646 stroke & 989 non-stroke controls (REGARD study)	Mean ages 63.6–66.8 y	United States	↑ stroke risk in blood group AB versus O with hazard ratio greater in those without diabetes mellitus
Vasan et al. 2016 [10]	SCANDAT2 (12.6 y median follow-up)	1112072 blood donors	Mean age 33 y at baseline	Sweden and Denmark	↑ MI & stroke in non-O blood group
Capuzzo et al. 2016 [6]	> 2-year observational (median 5.3 y)	249 blood donors with Cardiorisk score > 20	35–55 y	Italy	↑ clinical or subclinical CVD events including ACS, cerebral ischaemia, cardiac arrhythmia & PAD in non-O group
Chen et al. 2016 [9]	Meta-analysis	17 studies of 225,810 participants	Multiple ranges	Multiple countries	↑ coronary heart disease in blood group A (OR 1.14) vs. O (OR 0.89)
Lin et al. 2017 [28]	Acute observational	1209 ST-elevation MI patients	Mean age 55 y	China	↑ post-MI spontaneous recanalization in O group
Fu et al. 2020 [29]	Case control study	61 HR & 600 randomly selected MI C	75.6 y (HR) v 66.2 y C	China	↑ HR following MI in blood group A

ACS = acute coronary syndrome; C = control subjects; CVD = cardiovascular disease; HR = heart rupture; MI = myocardial infarction; OR = Odds Ratio; PAD = peripheral arterial disease; SCANDAT = Scandinavian Donations and Transfusions; y = years.

Table 2.
Subject characteristics and non-O versus O blood group findings for the studies presented in the ABO blood groups and arterial diseases section (by year of publication).

4. ABO and coronary artery disease

In 1971, Medalie et al. reported the findings of a five-year prospective study of 10,000 Israeli male government employees aged ≥40 years who were born in six different regions (Eastern, Central and South-eastern Europe, Israel, Asia, and North Africa) [24]. The study found that subjects with blood groups A1, B, and A1B tended to have higher rates of myocardial infarction and those with A1 and B had higher rates of angina pectoris when compared to other blood groups [24]. Further, subjects who were negative for the Kidd glycoprotein (JK^{a-}), a red blood cell urea transporter, had the highest rates of myocardial infarction and angina pectoris and adding this group to the ABO system ($A1Jk^{a-}$, BJk^{a-} and, particularly, $A1BJk^{a-}$) was associated with very high incidence rates [24].

A pooled analysis of two large prospective United States (US) cohort studies, the Nurses' Health Study (NHS) which included 62,073 women and the Health Professionals Follow-up Study (HPFS) which included 27,428 men, both of which had >20 years follow-up, also found that the ABO blood group was significantly associated with an increased risk of coronary heart disease for men and women [11]. A limitation of these two patient cohorts was the self-reporting of ABO and Rh factor status. However, a validation analysis of a subsample of 98 subjects found a 93% serologically confirmed ABO consistency for NHS and 90% consistency for HPFS. The combined analysis found that those with blood group A, B or AB were more likely to develop coronary heart disease and this risk was independent of age, level of physical activity, alcohol or smoking consumption or diabetes history [5, 11]. A meta-analysis, performed by the same authors, of 7 cohort studies including NHS and HPFS which combined a total of 114,648 individuals and 5,741 coronary heart disease cases found a significant pooled relative risk for coronary heart disease in patients with a non-O blood group of 1.1 (95% CI 1.05–1.18, $p = 0.0001$). Subjects with an O blood group had a lower risk for coronary heart disease when compared to B or AB with a trend seen for blood group A [5, 11].

ABO blood group status may be clinically relevant in subjects with concurrent cardiovascular risk factors. A study of 289 Italian blood donors with a high cardiovascular risk score (≥20) found that those with a non-O blood group had an increased risk of CVD events (including acute coronary syndrome, cerebral ischaemia, cardiac arrhythmias and supraaortic trunk or iliac artery stenosis) during a median follow-up of 5.3 years [6]. ABO blood group status may also influence CVD-related patient outcomes. In a study of 1209 patients with acute myocardial infarction, Lin et al. found a higher rate of spontaneous recanalization following myocardial infarction in association with the O blood group whereas the rate of spontaneous recanalization was lower in subjects with an A blood group [28]. Blood group A type has also been associated with an increased risk of heart rupture following myocardial infarction [29]. Hence, ABO blood type may not only predispose susceptible individuals to an increased risk of CVD events but may also influence post-myocardial infarction outcomes.

5. ABO, stroke, and arterial disease in general

ABO blood group status has been shown to influence stroke risk. An association of AB blood group with stroke (adjusted Hazards Ratio [aHR] 1.83, 95% CI 1.01–3.30) was found in the (Reasons for Geographic And Racial Differences in Stroke [REGARDS]) study which involved 30,239 US participants followed up over 5.8 years [12]. This finding remained significant after adjustment for age, gender, race region and Framingham stroke risk factors (systolic blood pressure, taking

antihypertensive medication, diabetes, current smoking, atrial fibrillation and left ventricular hypertrophy). The association was greater in those participants without diabetes mellitus (aHR 3.33 95% CI, 1.61–6.88). Factor VIII levels accounted for 60% of the AB associated stroke risk [12]. Another study by Wiggins et al. identified an increased risk of ischaemic stroke in subjects with a B blood group (OR 1.59, 95% CI 1.17–2.17) [30].

Meta-analysis studies have also demonstrated associations between non-O blood groups and arterial diseases in general. Chen et al. performed a meta-analysis of 17 studies involving 225,810 participants and found that blood group A was associated with an increased risk of coronary artery disease (OR 1.14, 95% CI 1.03–1.26, $p = 0.01$) and blood group O a lower risk (OR 0.85, 95% CI 0.78–0.94, $p < 0.001$) [9]. These results remained significant after cases of myocardial infarction were excluded. Wu et al. conducted a systematic review and meta-analysis of 59 studies, both retrospective and prospective, reporting associations of ABO blood groups and arterial disease [8]. They found significant ORs of 1.25 (95% CI 1.14–1.36) for myocardial infarction (n = 22 studies), 1.45 (95% CI 1.35–1.46) for peripheral arterial disease (n = 8 studies) and 1.14 (95% CI 1.01–1.27) for cerebral ischaemia of arterial origin (n = 7 studies) in subjects with a non-O blood group [8].

6. ABO blood groups and venous thromboembolism

The relationship between the ABO blood groups and VTE is most probably stronger than that seen in arterial diseases [5]. The association between blood group subtypes and VTE has been well documented in a few genome-wide association (GWAS) [5, 31, 32], meta-analyses and/or case–control studies [7, 8, 10, 13] (**Table 3**). A French GWAS study involving 419 patients with early age onset of first deep vein thrombosis (DVT) who were compared to 1228 controls found that participants with blood type O had a 67% lower risk of VTE compared to n those with a non-O blood group [5, 31]. Relative to other non-O groups, subjects with the uncommon A2 subtype had a 47% lower risk [5, 31]. In the same study, Factor V Leiden mutations were also associated with increased risk of VTE although the authors did not investigate the potential for an additive risk in those having both a non-O blood group and a Factor V Leiden mutation [31]. A similar association of non-O blood group with VTE was found in another GWAS study comparing 1503 VTE subjects to 1459 age and gender matched controls [32]. In this study, the population attributable risk for VTE was highest for the non-O blood group, followed by blood type A, Factor V Leiden, and prothrombin G20210A [32].

There is evidence that the A2 subtype of blood group A is associated with a lower VTE risk when compared to the A1 allele [5, 33]. The A2 allele possesses a single base deletion near its carboxyl terminal (1061delC) which results in 30 to 50-fold less A-transferase activity than its A1 counterpart which suggests a correlation between the degree of H antigen glycosylation and VTE risk [33]. Data from 2 population-based case control studies that included 504 post-menopausal women with non-fatal VTE found that the B and AB blood groups were both associated with an increased risk of VTE (OR 1.82, 95% CI 1.29–2.57, and OR 2.7, 95% CI 1.73–4.21, respectively) when compared to O1O1 subjects [30]. Participants with A11, a subtype of the A1 allele, also carried a 79% increased risk of VTE (OR 1.79, 95% CI 1.41–2.26) [30]. An increased VTE risk was also identified in a population-based case control study of venous thrombosis (Leiden Thrombophilia Study) [34]. In this study, an increased thrombotic risk was found for non-O blood groups apart from those with genotypes homozygous to A2 or possession of any A2/O combination. Subjects with A1B/A2B and A1A1/A1A2 blood group genotypes had a 90–110%

Study and year	Type of study	Subjects	Age range	Country	Findings (non-O versus O)
Morelli et al. 2005 [34]	Case control study (LETS study)	471 patients & 471 C	Not reported	Nether-lands	↑ VTE for all non-O blood group except A2A2 or any A2O combination
Wu et al. 2007 [8]	Meta-analysis	21 VTE studies with 6720 subjects	Multiple	Multiple	↑ VTE in A1A2/A1B/BB (OR 2.44) & A!O/BO/ A2B (OR 2.11) blood groups
Lima et al. 2009 [17]	Case control study	65 VTE patients & 51 C	Mean age 34 y (range 6–67 y)	Brazil	↑ VTE for FVL (OR 10.1) and double ↑ risk if also AB (OR 22.3)
Trégouët et al. 2009 [31]	Case control study (GWAS screening)	419 VTE patients & 1228 healthy C	Age at onset<50 y	France	↑ VTE in non-O blood group, relative lower risk VTE of A2 amongst non-O subjects and additive risk of FVL mutation
Wiggins et al. 2009 [30]	Case control study (10 y follow-up)	Peri/ post-MP women 504 VTE & 2172 C	Age range 30–89 y	United States	↑ VTE in B (OR 1.82), AB (OR 2.7) & A11 (OR 1.79) compared to O1O1 blood group
Heit et al. 2012 [32]	Case control study (GWAS analysis)	1503 VTE & 1459 age & gender matched C	Mean age for VTE & C 55 y	United States	↑ VTE population attributable risk for non-O blood group followed by A blood group, FVL & prothrombin G20210A
Vasan et al. 2016 [10]	SCANDAT2 (12.6 y median follow-up)	1112072 blood donors	Mean age 33 y at baseline	Sweden and Denmark	↑ VTE including pregnancy-related VTE & DVT in non-O blood group
Sun et al. 2017 [13]	Retrospective observational (7 y)	1412 VTE & 199,248 C	Mean 57.3 y VTE & 47.5 C	China	↑ VTE in non-O blood group (OR 1.35)
Goumidi et al. 2021 [7]	Pooled analysis of 6 studies	5425 VTE & 8445 C	Not reported	Multiple countries	↑ VTE for A2 (OR 1.2), A1 & B (OR 1.8) & ↓ VTE for O2 (OR 0.8) compared to O1

C = control subjects; DVT = deep vein thrombosis; FVL = Factor V Leiden; GWAS = genome-wide association study; LETS = Leiden Thrombophilia Study; MP = menopausal; OR = Odds Ratio; PTE = pulmonary thromboembolism; SCANDAT = Scandinavian Donations and Transfusions; VTE = venous thromboembolism; y = years.

Table 3.
A summary of subject characteristics and non-O versus O blood group findings for the studies presented in the ABO blood groups and VTE section (by year of publication).

increased risk and those with BB/BO1/B02 genotypes had a 60% increased risk when compared to the OO genotype [34].

In a pooled analysis of 6 case–control/prospective studies of VTE, the A2 subgroup was found to be associated with a modest increase in VTE risk (OR 1.2) whereas the A1 and B subgroups had a 1.8-fold increased risk compared to the O1 subgroup. In contrast, O2 had a relative protective effect (OR 0.8) [7]. Both the A1

and B subgroups were associated with increased vWF and factor VIII plasma levels whereas only the A1 subgroup was associated with increased ICAM levels [7]. A meta-analysis of 21 VTE studies, 18 of which were retrospective in design, found a pooled OR of 1.79 (95% CI 1.56–2.05) for non-O blood group and VTE [7]. The combination of A1A1/A1B/BB genotypes had an OR of 2.44 (95% CI 1.79–3.33) and A1O/BO/A2B an OR of 2.11 (95% CI 1.66–2.68) for VTE [8].

The presence of a non-O blood group has been found to correlate with unprovoked PTE, provoked including pregnancy induced and recurrent VTE. In a Scandinavian 25-year follow-up study of >1.6 million blood donors, those with a non-O blood group had higher rates of pregnancy-related VTE events, DVT and pulmonary embolism [10]. The risks of recurrent pulmonary embolism and DVT provoked by comorbid illness were also higher in subjects with a non-O blood group [10]. A large hospital-based retrospective study of 200,660 Han Chinese patients including 1412 VTE subjects (600 with DVT, 441 with pulmonary embolism and 371 with both conditions) conducted between 2010 and 2016 found a significant association of non-O blood group with VTE (OR 1.35, 95% CI 1.21–1.54) [13]. Interestingly, subgroup analysis found a relatively greater non-O blood group risk for those with an unprovoked VTE (OR 1.86) compared to provoked VTE (OR 1.22). The OR for having a non-O blood group also appeared to decrease with age [13]. Finally, a Brazilian case control study comparing 65 subjects with a history of DVT to 51 controls showed a significant increased risk of VTE in the presence of Factor V Leiden mutation (OR 10.1) which doubled in those in whom the AB allele of the ABO blood group was also present (OR 22.3) [17].

Future research into the role of developing risk stratification models or algorithms, for example, by combining ABO and other genetic variables with patient comorbidity and arterial risk factors to identify individuals at higher risk of VTE is warranted. This may translate to improved cardiovascular disease management including decision making for VTE prophylaxis at the hospital and outpatient setting.

7. Von Willebrand factor, factor VIII and other factors associated with ABO blood group and CVD

The majority of studies that have been presented in this review implicate an increase in plasma levels of vWF and factor VIII by non-O blood group types as the likely mechanism for an increased risk of thromboembolic events [5–13]. VWF/factor VIII are important in the acute phase response to vessel injury [8]. VWF is a carrier of factor VIII, protects it from inactivation, can also recruit platelets to a site of vessel injury to induce a coagulation cascade responsible for clot formation [5]. VWF can also bind to the platelet receptor glycoprotein Iba, to form a bridge between platelets and the endothelium and participate in a thrombo-inflammatory response (**Figure 3**) [35, 36].

ABO blood groups may have a direct functional effect on circulating vWF and thereby modulate both vWF and factor VIII levels [5]. The mechanism by which the presence of an N-acetyl-D-galactosamine or D-galactose residue on glycans expressed on the H antigen acceptor site of a RBC influences plasma levels and/or bioactivity of vWF is unclear [16]. A plausible mechanism is that ABO glycans on vWF itself influence its release into plasma and/or its clearance [16]. VWF is derived from a pre-pro-polypeptide (ppvWF) synthesized in endothelial cells and megakaryocytes [16]. The expression of blood antigen A on vWF correlates with decreased ppvWF to vWF ratios as well as longer half-life and increased plasma levels of vWF [16].

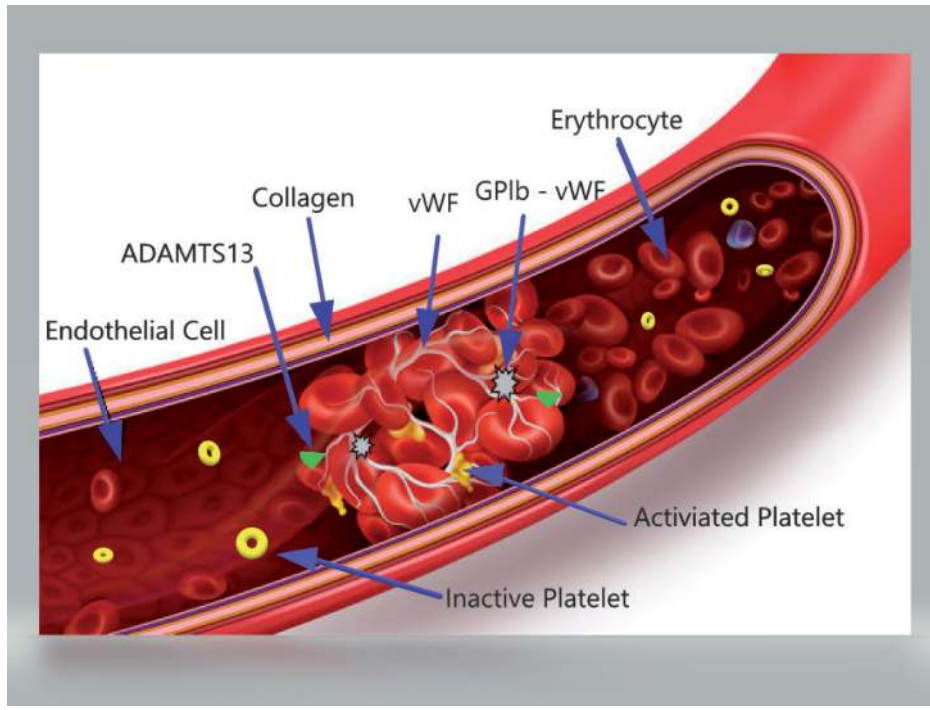

Figure 3.
*Von Willebrand factor (vWF) can bind to the platelet receptor glycoprotein Ib (GPIb) to form a bridge between platelets and the endothelium and a thrombo-inflammatory response. The protease ADAMTTS13 (***a** **d***isintegrin* **a***nd* **m***etalloproteinase with a* **t***hrombo***s***pondin type 1 motif, member* **13***) is responsible for the proteolysis and clearance of vWF from the circulation.*

It has been postulated that the presence of A and B terminal carbohydrate antigens influence the proteolysis of vWF by its major protease ADAMTTS13 (**a** **d**isintegrin **a**nd **m**etalloproteinase with a **t**hrombo**s**pondin type 1 motif, member **13** - also known as von Willebrand factor-cleaving protease [VWFCP]) [5]. Individuals lacking glycosyltransferase activity (O blood group) have higher levels of ADAMTS13 activity suggesting that ABO glycosyltransferase activity can indirectly modify, for example, inhibit proteolytic activity and reduce vWF clearance from the circulation [5]. However, there are studies which have not supported this as the underlying mechanism [37]. Future research into other, yet to be determined, ABO blood group and VWF-related associations may unravel the underlying mechanism of a non-O blood group increased risk of thrombosis.

Blood group antigens are also associated with elevated plasma levels of markers of inflammation including endothelial cell and platelet-derived adhesion molecules [5]. Elevated plasma levels of adhesion molecules including soluble P-selectin, soluble ICAM-1 and tumour necrosis factor-alpha are associated with ABO genotype, which may result in arterial and venous thrombosis and an increased CVD risk [5, 11]. However, in studies reporting the circulating expression levels of sICAM-1 and soluble P-selectin, the blood group A has paradoxically been found to be associated with lower circulating expression levels of sICAM-1 and soluble P-selectin when compared to the O blood group [38, 39]. This contradictory finding has been described in healthy Chinese populations and a study of Caucasian women without a history of chronic disease [38, 39]. A postulated explanation for why blood group A, in general, may be associated with lower circulating inflammatory markers despite carrying a higher CVD risk is that higher levels of sICAM-1 or soluble P-selectin expression are limited to those with significant CVD risk factors and/or symptomatic CVD. The concentrations of membrane forms of these adhesion

molecules may also higher and thereby still mediate leucocyte migration and adhesion at an endothelial level [39]. It is also possible that reduced levels of sICAM-1 increase the adhesion of leukocytes on endothelial surfaces which may result in increased arterial inflammation [40].

Platelet glycoproteins including GPIIb, and platelet endothelial cell adhesion molecule are known to carry ABO blood group antigens and may be involved in thrombosis through modulation of the GPIIb-GPIIIa fibrinogen receptor complex [5]. A relationship between ABO blood group and angiotensin converting enzyme activity has also been reported which implicates a role for ABO blood group in the regulation of arterial risk factors such as hypertension [41].

Epidemiological studies have demonstrated an association between an elevated serum cholesterol including low-density lipoprotein cholesterol and non-O blood groups [5, 42]. These findings implicate ABO genotypes in the modulation of plasma lipids. ABO blood groups are also associated with phytosterol levels which have also been reported to modify cardiovascular risk [5].

8. ABO blood group, COVID-19, and CVD

There is growing evidence that ABO blood groups may play a role in the susceptibility to and severity of SARS-CoV-2 infection [18–20]. Individuals with blood group O have a lower risk and those with blood group A carry a higher risk of SARS-CoV-2 infection [18]. A systematic review by the International Society of Blood Transfusion (ISBT) COVID-19 working group recently reported that subjects with blood group A had a higher rate of SARS-CoV-2 infection as well as an increased risk of requiring mechanical ventilation, continuous renal replacement therapy and prolonged intensive care unit stay [18]. Postulated mechanisms include an increase in angiotensin converting enzyme-1 levels in blood group A patients and an increased risk of cardiovascular, thromboembolic, and inflammatory complications [18]. It is plausible that possession of a non-O blood group and associated increase in vWF and factor VIII levels have an additive effect to the thrombophilia caused by SARS-CoV-2 and results in an increased risk of COVID-related CVD complications [18–20]. A recent hypothesis for an association between non-O blood group type and risk of SARS-CoV-2 infection is that anti-A and/or anti-B antibodies, which are present in patients with blood group O bind to a corresponding antigen, for example the angiotensin-converting-enzyme-2-receptor, on the SARS-CoV-2 viral envelope which then inhibits viral entry into lung epithelium (**Figure 4**) [18]. Although ABH antigen structures are yet to be described on the SARS-CoV-2 protein, the spike protein has been reported to possess N-glycans and N-glycosylation sites which could potentially interact with anti-A and anti-B antigens and thus confer protection against infection in individuals with the blood group O type [18]. The possibility that blood group A patients also have higher rates of underlying comorbidities which significantly contribute to COVID-related complications cannot be excluded [18].

A single-centre study from Bangladesh which evaluated 438 patients with SARS-CoV-2 infection also found a significantly higher rate of blood group A amongst COVID-19 patients compared to the general population [20]. However, ABO blood groups were not associated with type of presentation or recovery from infection [20]. Conversely, an observational study of 14,112 individuals tested for SARS-CoV-2 in the New York Presbyterian hospital system found that risk of intubation was increased for AB and B blood groups but decreased for A when compared to O blood group and risk of death was increased for those with AB blood group and decreased for A and B blood groups [19]. Interestingly, Rhesus status, which is not implicated

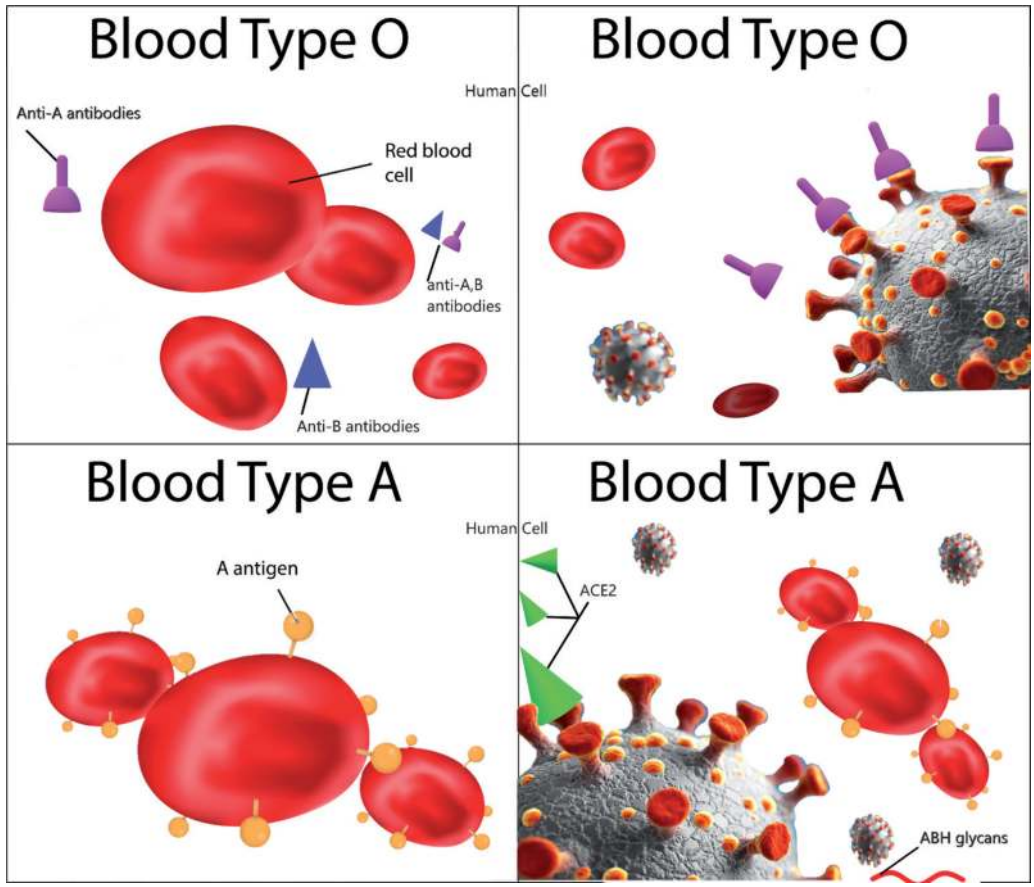

Figure 4.
A hypothesis for an association between non-O blood group type and risk of SARS-CoV-2 infection is that anti-A and/or anti-B antibodies may bind to the angiotensin-converting-enzyme-2-receptor on the SARS-CoV-2 viral envelope and thereby inhibit viral entry into lung epithelium. Top left shows blood group O with anti-A and anti-B antibodies in the plasma. Top right illustrates anti-A antibodies of blood group O which potentially competitively bind to the spike protein of SARS-CoV-2 and thus inhibit infection. Lower left shows blood group A with A-antigens on the membranes of red blood cells. Lower right depicts ABH glycans on the SARS-CoV-2 spike protein which potentially competitively bind to angiotensin converting enzyme 2 (ACE2) receptors.

in CVD risk, correlated with COVID-19 risk [19]. Rhesus-negative subjects had a lower risk of SARS-CoV-2 infection, intubation, and death [19]. The mechanism of the relationships of ABO blood group, Rhesus status and SARS-CoV-2 infection is unknown. Further research into the relationship between blood groups and risk of SARS-CoV-2 infection and COVID-19 related complications is warranted.

9. Minor blood group antigens and CVD

There are over 35 minor blood group antigens on red blood cells [21], some of which including P and Lewis, are widely distributed in other human cells and body fluids [43, 44]. Minor blood groups have been associated with several diseases ranging from malignancy to peptic ulcer disease, infection and CVD [43, 44]. As discussed previously, subjects with a combination of blood groups A or B and the Kidd antigen Jk^{a-} status have been shown to be at increased risk of myocardial infarction [24]. Sialyl-Le^x (sLe^x), an antigen of the Lewis blood group system, is a major ligand for the cellular adhesion molecules E, P and L-selectin which are involved in the adhesion of leucocytes to endothelium [44]. The Duffy blood group glycoprotein is a chemokine receptor on RBCs that is involved in the recruitment

of leucocytes to sites of inflammation [44]. Although the exact mechanisms are unclear, these biological characteristics offer explanation why the Lewis and Duffy blood group antigens may be associated with an increased risk of CVD.

The Lewis blood group system, which was first discovered by Mourant in 1946, is classified into four phenotypes [Le(a-b-), Le(a + b-), Le(a-b+), Le(a + b+)] determined by two genetic systems closely related on the short arm of chromosome 19 [45]. In a study of 3385 Danish males, the Le(a-b-) phenotype was associated with an increased risk of mortality from ischaemic heart disease [46]. In another Danish study involving 702 participants (72% male), the Le(a-b-) was associated with self-reported non-fatal stroke [47]. However, a North Indian cross-sectional study that compared 161 patients with angiographically-proven coronary artery disease with 71 control subjects with normal angiography, found that the lack of Lewis antigen expression was associated with coronary artery disease in female subjects only [48]. A lack of Lewis antigen expression has also been associated with a higher body mass index, weight gain over time, a lower level of physical activity, type 2 diabetes mellitus and hypertriglyceridemia all of which associated with an increased risk of CVD [49–52].

The Duffy antigen, located on the long arm of chromosome 1 [53], has also been implicated in CVD risk [54]. There are four Duffy phenotypes [Fy(a-b-), Fy(a + b-), Fy(a-b+), Fy(a + b+) [53]. A study of 5301 African American participants found that Duffy negative subjects with a neutrophil: lymphocyte ratio ≥ 1.77 were more likely to have coronary artery disease and stroke [54]. Lack of Duffy expression has also been associated with chronic organ damage, in particular renal dysfunction, in subjects with sickle-cell disease [55].

To the best of our knowledge, there have been no studies to date addressing the relationship of minor blood groups and COVID-19.

The limitations of studies evaluating the role of minor blood groups in CVD include their observational cohort design, case selection, outcome definitions, cohort sizes and influence of population attributable factors.

10. Conclusion

Subjects with non-O blood group type have an increased risk of arterial and venous thromboembolism. Blood groups A1, B and AB are at particularly increased risk of CVD events whereas blood group O confers a protective effect. Postulated mechanisms of underlying the relationship between ABO blood group and CVD include vWF and factor VIII activity and elevations in circulating inflammatory markers and plasma lipids. Comorbidities including arterial risk factors and predisposing factors to VTE such as concomitant Factor V Leiden mutations may have an additive effect to thromboembolic risk. Minor blood group types including Kidd, Lewis and Duffy are also been associated with CVD. The relationship of non-O blood group type and SARS-CoV-2 infection warrants further research. Future directions include the development and implementation of risk stratification algorithms for thromboembolic risk such as ABO blood group and other factors associated with arterial or venous disease in a hospital or outpatient setting.

Author details

Dennis J. Cordato[1,2,3], Wissam Soubra[3,4,5], Sameer Saleem[1,2,3] and Kaneez Fatima Shad[3,5,6*]

1 Department of Neurophysiology, Liverpool Hospital, NSW, Australia

2 South Western Sydney Clinic School, University of New South Wales, Sydney, NSW, Australia

3 Ingham Institute for Applied Medical Research, Liverpool, NSW, Australia

4 A Healthy Step Clinic, NSW, Australia

5 School of Life Sciences, University of Technology Sydney, NSW, Australia

6 School of Behavioural and Health Sciences, Faculty of Health Sciences, Australian Catholic University, NSW, Australia

*Address all correspondence to: kaneez.fatimashad@uts.edu.au; ftmshad@gmail.com

IntechOpen

References

[1] Roth GA, Mensah GA, Johnson CO, Addolorato G, Ammirati E, Baddour LM, Barengo NC, Beaton AZ, Benjamin EJ, Benziger CP, Bonny A, Brauer M, Brodmann M, Cahill TJ, Carapetis J, Catapano AL, Chugh SS, Cooper LT, Coresh J, Criqui M, DeCleene N, Eagle KA, Emmons-Bell S, Feigin VL, Fernández-Solà J, Fowkes G, Gakidou E, Grundy SM, He FJ, Howard G, Hu F, Inker L, Karthikeyan G, Kassebaum N, Koroshetz W, Lavie C, Lloyd-Jones D, Lu HS, Mirijello A, Temesgen AM, Mokdad A, Moran AE, Muntner P, Narula J, Neal B, Ntsekhe M, Moraes de Oliveira G, Otto C, Owolabi M, Pratt M, Rajagopalan S, Reitsma M, Ribeiro ALP, Rigotti N, Rodgers A, Sable C, Shakil S, Sliwa-Hahnle K, Stark B, Sundström J, Timpel P, Tleyjeh IM, Valgimigli M, Vos T, Whelton PK, Yacoub M, Zuhlke L, Murray C, Fuster V; GBD-NHLBI-JACC Global Burden of Cardiovascular Diseases Writing Group. Global burden of cardiovascular diseases and risk factors, 1990-2019: update from the GBD 2019 Study. J Am Coll Cardiol 2020; 76(25):2982-3021

[2] European Association for Cardiovascular Prevention & Rehabilitation, Reiner Z, Catapano AL, De Backer G, Graham I, Taskinen MR, Wiklund O, Agewall S, Alegria E, Chapman MJ, Durrington P, Erdine S, Halcox J, Hobbs R, Kjekshus J, Filardi PP, Riccardi G, Storey RF, Wood D; ESC Committee for Practice Guidelines (CPG) 2008-2010 and 2010-2012 Committees. ESC/EAS Guidelines for the management of dyslipidaemias: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS). Eur Heart J 2011; 32(14):1769-818.

[3] Inouye M, Abraham G, Nelson CP, Wood AM, Sweeting MJ, Dudbridge F, Lai FY, Kaptoge S, Brozynska M, Wang T, Ye S, Webb TR, Rutter MK, Tzoulaki I, Patel RS, Loos RJF, Keavney B, Hemingway H, Thompson J, Watkins H, Deloukas P, Di Angelantonio E, Butterworth AS, Danesh J, Samani NJ; UK Biobank CardioMetabolic Consortium CHD Working Group. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. J Am Coll Cardiol 2018; 72(16):1883-1893.

[4] Dean L. Blood Groups and Red Cell Antigens [Internet]. Bethesda (MD): National Center for Biotechnology Information (US); 2005. Chapter 5. The ABO blood group. Available from: https://www.ncbi.nlm.nih.gov/books/NBK2267/

[5] Zhang H, Mooney CJ, Reilly MP. ABO blood groups and cardiovascular diseases. Int J Vasc Med 2012; 2012:641917.

[6] Capuzzo E, Bonfanti C, Frattini F, Montorsi P, Turdo R, Previdi MG, Turrini E, Franchini M. The relationship between ABO blood group and cardiovascular disease: results from the Cardiorisk program. Ann Transl Med 2016; 4(10):189.

[7] Goumidi L, Thibord F, Wiggins KL, Li-Gao R, Brown MR, van Hylckama Vlieg A, Souto JC, Soria JM, Ibrahim-Kosta M, Saut N, Daian D, Olaso R, Amouyel P, Debette S, Boland A, Bailly P, Morrison AC, Mook-Kanamori DO, Deleuze JF, Johnson A, de Vries PS, Sabater-Lleal M, Chiaroni J, Smith NL, Rosendaal FR, Chasman DI, Trégouët DA, Morange PE. Association between ABO haplotypes and the risk of venous thrombosis: impact on disease risk estimation. Blood 2021; 137(17):2394-2402.

[8] Wu O, Bayoumi N, Vickers MA, Clark P. ABO(H) blood groups and

vascular disease: a systematic review and meta-analysis. J Thromb Haemost 2008; 6(1):62-69.

[9] Chen Z, Yang SH, Xu H, Li JJ. ABO blood group system and the coronary artery disease: an updated systematic review and meta-analysis. Sci Rep 2016; 6:23250.

[10] Vasan SK, Rostgaard K, Majeed A, Ullum H, Titlestad KE, Pedersen OB, Erikstrup C, Nielsen KR, Melbye M, Nyrén O, Hjalgrim H, Edgren G. ABO blood group and risk of thromboembolic and arterial disease: a study of 1.5 million blood donors. Circulation 2016; 133(15):1449-1457.

[11] He M, Wolpin B, Rexrode K, Manson JE, Rimm E, Hu FB, Qi L. ABO blood group and risk of coronary heart disease in two prospective cohort studies. Arterioscler Thromb Vasc Biol 2012; 32(9):2314-2320.

[12] Zakai NA, Judd SE, Alexander K, McClure LA, Kissela BM, Howard G, Cushman M. ABO blood type and stroke risk: the REasons for Geographic And Racial Differences in Stroke Study. J Thromb Haemost 2014; 12(4):564-570.

[13] Sun X, Feng J, Wu W, Peng M, Shi J. ABO blood types associated with the risk of venous thromboembolism in Han Chinese people: A hospital-based study of 200,000 patients. Sci Rep 2017; 7:42925.

[14] Sun Y, Mao P, Lu J, Dai J, Teng H, Jiang Q. ABO blood type and ABO gene with susceptibility to deep vein thrombosis following orthopedic surgery: a case-control study in Chinese Han population. Sci China Life Sci 2015; 58(4):390-391.

[15] Samama MM; for the Sirius Study Group. An epidemiologic study of risk factors for deep vein thrombosis in medical outpatients: the Sirius study. Arch Intern Med 2000; 160(22):3415-3420.

[16] Stowell CP and Stowell SR. Biologic roles of the ABH and Lewis histo-blood group antigens Part I: infection and immunity. Vox Sang 2019; 114(5):426-442.

[17] Lima MB, de Oliveira-Filho AB, Campos JF, Melo FC, Neves WB, Melo RA, Lemos JA. Increased risk of venous thrombosis by AB alleles of the ABO blood group and Factor V Leiden in a Brazilian population. Genet Mol Biol 2009; 32(2):264-267.

[18] Goel R, Bloch EM, Pirenne F, Al-Riyami AZ, Crowe E, Dau L, Land K, Townsend M, Jecko T, Rahimi-Levene N, Patidar G, Josephson CD, Arora S, Vermeulen M, Vrielink H, Montemayor C, Oreh A, Hindawi S, van den Berg K, Serrano K, So-Osman C, Wood E, Devine DV, Spitalnik SL; ISBT COVID-19 Working Group. ABO blood group and COVID-19: a review on behalf of the ISBT COVID-19 working group. Vox Sang 2021 Feb 12:10.1111/vox.13076. doi: 10.1111/vox.13076. Epub ahead of print.

[19] Zietz M, Zucker J, Tatonetti NP. Associations between blood type and COVID-19 infection, intubation, and death. Nat Commun 2020; 11(1):5761.

[20] Mahmud R, Rassel MA, Monayem FB, Sayeed SKJB, Islam MS, Islam MM, Yusuf MA, Rahman S, Islam KMN, Mahmud I, Hossain MZ, Chowdhury AH, Kabir AKMH, Ahmed KGU, Rahman MM. Association of ABO blood groups with presentation and outcomes of confirmed SARS CoV-2 infection: A prospective study in the largest COVID-19 dedicated hospital in Bangladesh. PLoS One 2021; 16(4):e0249252.

[21] Holt SG, Kotagiri P, Hogan C, Hughes P, Masterson R. The potential role of antibodies against minor blood

group antigens in renal transplantation. Transpl Int 2020; 33(8):841-848.

[22] Ellison RC, Zhang Y, Myers RH, Swanson JL, Higgins M, Eckfeldt J. Lewis blood group phenotype as an independent risk factor for coronary heart disease (the NHLBI Family Heart Study). Am J Cardiol 1999; 83(3):345-348.

[23] Enevold C, Nielsen CH, Molbo D, Lund R, Bendtzen K, Fiehn N-, Holmstrup P. Lewis and AB0 blood group-phenotypes in periodontitis, cardiovascular disease, obesity and stroke. Sci Rep. 2019; 9(1):6283.

[24] Medalie JH, Levene C, Papier C, Goldbourt U, Dreyfuss F, Oron D, Neufeld H, Riss E. Blood groups, myocardial infarction and angina pectoris among 10,000 adult males. N Engl J Med 1971; 285(24):1348-1353.

[25] Farhud DD, Zarif Yeganeh M. A brief history of human blood groups. Iran J Public Health 2013; 42(1):1-6.

[26] Ségurel L, Thompson EE, Flutre T, Lovstad J, Venkat A, Margulis SW, Moyse J, Ross S, Gamble K, Sella G, Ober C, Przeworski M. The ABO blood group is a trans-species polymorphism in primates. Proc Natl Acad Sci U S A 2012; 109(45):18493-18498.

[27] Yamamoto F. Molecular genetics of the ABO histo-blood group system. Vox Sang 1995; 69(1):1-7.

[28] Lin XL, Zhou BY, Li S, Li XL, Luo ZR, Li JJ. Correlation of ABO blood groups with spontaneous recanalization in acute myocardial infarction. Scand Cardiovasc J 2017; 51(4):217-220.

[29] Fu Y, Chen M, Sun H, Guo Z, Gao Y, Yang X, Li K, Wang L. Blood group A: a risk factor for heart rupture after acute myocardial infarction. BMC Cardiovasc Disord 2020; 20(1):471.

[30] Wiggins KL, Smith NL, Glazer NL, Rosendaal FR, Heckbert SR, Psaty BM, Rice KM, Lumley T. ABO genotype and risk of thrombotic events and hemorrhagic stroke. J Thromb Haemost 2009; 7(2):263-269.

[31] Trégouët DA, Heath S, Saut N, Biron-Andreani C, Schved JF, Pernod G, Galan P, Drouet L, Zelenika D, Juhan-Vague I, Alessi MC, Tiret L, Lathrop M, Emmerich J, Morange PE. Common susceptibility alleles are unlikely to contribute as strongly as the FV and ABO loci to VTE risk: results from a GWAS approach. Blood 2009; 113(21):5298-5303.

[32] Heit JA, Armasu SM, Asmann YW, Cunningham JM, Matsumoto ME, Petterson TM, De Andrade M. A genome-wide association study of venous thromboembolism identifies risk variants in chromosomes 1q24.2 and 9q. J Thromb Haemost 2012; 10(8):1521-1531.

[33] Yamamoto F, McNeill PD, Hakomori S. Human histo-blood group A2 transferase coded by A2 allele, one of the A subtypes, is characterized by a single base deletion in the coding sequence, which results in an additional domain at the carboxyl terminal. Biochem Biophys Res Commun 1992; 187(1):366-374.

[34] Morelli VM, De Visser MC, Vos HL, Bertina RM, Rosendaal FR. ABO blood group genotypes and the risk of venous thrombosis: effect of factor V Leiden. J Thromb Haemost 2005; 3(1):183-185.

[35] Buchtele N, Schwameis M, Gilbert JC, Schörgenhofer C, Jilma B. Targeting von Willebrand Factor in ischaemic stroke: focus on clinical evidence. Thromb Haemost 2018; 118(6):959-978.

[36] Denorme F, Vanhoorelbeke K, De Meyer SF. von Willebrand Factor and platelet glycoprotein Ib: A

thromboinflammatory axis in stroke. Front Immunol 2019; 10:2884.

[37] Badirou I, Kurdi M, Rayes J, Legendre P, Christophe OD, Lenting PJ, Denis CV. von Willebrand factor clearance does not involve proteolysis by ADAMTS-13. J Thromb Haemost 2010; 8(10):2338-2340.

[38] Zhang W, Xu Q, Zhuang Y, Chen Y. Novel association of soluble intercellular adhesion molecule 1 and soluble P-selectin with the ABO blood group in a Chinese population. Exp Ther Med 2016; (2):909-914.

[39] Paré G, Chasman DI, Kellogg M, Zee RY, Rifai N, Badola S, Miletich JP, Ridker PM. Novel association of ABO histo-blood group antigen with soluble ICAM-1: results of a genome-wide association study of 6,578 women. PLoS Genet. 2008; 4(7):e1000118.

[40] Libby P, Ridker PM, Maseri A. Inflammation and atherosclerosis. Circulation. 2002; 105(9):1135-1143.

[41] Cídl K, Strelcová L, Znojil V, Váchi J. Angiotensin I-converting enzyme (ACE) polymorphism and ABO blood groups as factors codetermining plasma ACE activity. Exp Hematol 1996; 24(7):790-794.

[42] Garrison RJ, Havlik RJ, Harris RB, Feinleib M, Kannel WB, Padgett SJ. ABO blood group and cardiovacular disease: the Framingham study. Atherosclerosis 1976; 25(2-3):311-318.

[43] Garratty G. Relationship of blood groups to disease: do blood group antigens have a biological role? Rev Med Inst Mex Seguro Soc 2005; 43 (Suppl 1):113-121.

[44] Garratty G. Blood groups and disease: a historical perspective. Transfus Med Rev 2000; 14(4)291-301.

[45] Combs MR. Lewis blood group system review. Immunohematology 2009; 25(3):112-118.

[46] Hein HO, Sørensen H, Suadicani P, Gyntelberg F. The Lewis blood group--a new genetic marker of ischaemic heart disease. J Intern Med 1992; 232(6):481-487.

[47] Enevold C, Nielsen CH, Molbo D, Lund R, Bendtzen K, Fiehn N-, Holmstrup P. Lewis and AB0 blood group-phenotypes in periodontitis, cardiovascular disease, obesity and stroke. Sci Rep 2019; 9(1):6283.

[48] Natarajan R, Dhawan HK, Choudhury S, Vijayvergiya R, Marwaha N. Lewis blood group phenotype vis-a-vis biochemical and physiological parameters of coronary artery disease: A study in North Indian population. Asian J Transfus Sci 2020;14(1):9-12.

[49] Suadicani P, Hein HO, Gyntelberg F. Weight changes and risk of ischaemic heart disease for middle aged and elderly men. An 8-year follow-up in the Copenhagen Male study. J Cardiovasc Risk 1997; 4(1):25-32.

[50] Hein HO, Sørensen H, Suadicani P, Gyntelberg F. Alcohol consumption, Lewis phenotypes, and risk of ischaemic heart disease. Lancet 1993; 341(8842):392-396.

[51] Hein HO, Suadicani P, Gyntelberg F. Lewis phenotypes, leisure time physical activity, and risk of ischaemic heart disease: an 11 year follow up in the Copenhagen male study. Heart 2001; 85(2):159-164.

[52] Petit JM, Morvan Y, Mansuy-Collignon S, Viviani V, Vaillant G, Matejka G, Aho S, Guignier F, Brun JM. Hypertriglyceridaemia and Lewis (A-B-) phenotype in non-insulin-dependent diabetic patients. Diabetes Metab 1997;23(3):202-204.

[53] Höher G, Fiegenbaum M, Almeida S. Molecular basis of the Duffy blood group system. Blood Transfus 2018; 16(1):93-100.

[54] Kim S, Eliot M, Koestler DC, Wu WC, Kelsey KT. Association of Neutrophil-to-Lymphocyte Ratio With Mortality and Cardiovascular Disease in the Jackson Heart Study and Modification by the Duffy Antigen Variant. JAMA Cardiol 2018; 3(6):455-462.

[55] Afenyi-Annan A, Kail M, Combs MR, Orringer EP, Ashley- expression is associated with organ damage in patients with sickle cell disease. Transfusion 2008; 48(5):917-924.