

# The relationship between ABO blood group and cardiovascular disease: results from the Cardiorisk program

Enrico Capuzzo<sup>1</sup>, Carlo Bonfanti<sup>1</sup>, Francesco Frattini<sup>1</sup>, Paolo Montorsi<sup>1</sup>, Rosalia Turdo<sup>1</sup>, Maria Grazia Previdi<sup>1</sup>, Elisa Turrini<sup>2</sup>, Massimo Franchini<sup>1</sup>

<sup>1</sup>Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, Mantova, Italy; <sup>2</sup>AVIS Provinciale, Mantova, Italy

*Contributions:* (I) Conception and design: E Capuzzo, C Bonfanti, M Franchini; (II) Administrative support: E Turrini; (III) Provision of study materials or patients: P Montorsi, MG Previdi; (IV) Collection and assembly of data: F Frattini, P Montorsi, R Turdo; (V) Data analysis and interpretation: E Capuzzo, C Bonfanti, M Franchini; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

*Correspondence to:* Massimo Franchini, MD. Department of Hematology and Transfusion Medicine, Carlo Poma Hospital, Mantova, Italy. Email: massimo.franchini@aopoma.it.

**Background:** The ABO blood group exerts a profound influence on hemostasis, and it has hence been associated with the development of thrombotic cardiovascular adverse events. In this study, we evaluated the relationship between the ABO blood group and the risk of cardiovascular disease assessed with the Cardiorisk score.

**Methods:** All blood donors aged between 35 and 65 years were enrolled in the Cardiorisk program, which included the assessment of 8 variables (sex, age, total cholesterol, high-density lipoprotein (HDL) cholesterol, plasma glucose, arterial blood pressure, anti-hypertensive therapy and smoking) which were used to generate a score. Individuals with a resulting score  $\geq 20$ , considered at high cardiovascular risk, underwent additional instrumental tests (chest X-ray, stress electrocardiogram and Doppler ultrasound of supra-aortic trunks) and were closely clinically monitored.

**Results:** Between January 2005 and December 2015, 289 blood donors with Cardiorisk  $\geq 20$  were identified, 249 of whom were included in the study with at least 2 years of follow-up. Among these, 36 (14.5%) had instrumental abnormality tests and developed adverse cardiovascular events (10 acute coronary syndrome, 2 cerebral ischemia, 3 cardiac arrhythmia, 8 stenosis of supra-aortic trunks or iliac arteries) during a median follow-up of 5.3 years. In this group of 249 high risk individuals, a statistically significant association ( $P=0.02$ ) was found between the non-O blood type and the risk of developing subclinical or clinical cardiovascular events (odds ratio, 3.3; 95% CI, 1.1–10.1;  $P=0.033$ ).

**Conclusions:** The results of this study underline the both key role of ABO blood group for the risk of developing arterial thrombotic events and the need for including such unmodifiable variable on the scores assessing the thrombotic risk.

**Keywords:** ABO blood group; cardiovascular disease; Cardiorisk score; blood donors

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## Introduction

The ABO blood group system consists of three main alleles [two co-dominant (A and B) and one recessive (O)] (1,2). The A and B alleles of the ABO locus encode A and B glycosyltransferase activities, which convert precursor H antigen into either A or B determinants, the A and B

antigens having an extra saccharide unit to the O unit (N-acetylgalactosamine and galactose, respectively). Group O individuals lack such transferase enzymes and express basic, unchanged H-antigen (3). Notably, the ABO antigens are expressed not only on the surface of red blood cells but also on a variety of human cells and tissues, including epithelia, platelets, vascular endothelia

and neurons (4). Therefore, it is reasonable to hypothesize that such carbohydrate moieties are of importance not only for transfusion and transplantation medicine, but also for the pathogenesis of various systemic diseases (5-9). Among these pathologies, the best clinical evidence emerged from the association between ABO antigens and cardiovascular disorders, as documented by a number of systematic reviews and meta-analyses (6,10-12). In this study, we assessed whether the ABO blood group correlates with the risk of developing clinical or subclinical cardiovascular disease in a homogeneous population of blood donors at the Department of Transfusion Medicine and Haematology (DMTE) of Mantova.

## Materials and methods

Since January 2005, all blood donors aged between 35 and 65 years belonging to the Italian Association of Volunteers Blood Donors (AVIS) and donating at the DMTE of Mantova were enrolled in the program of cardiovascular primary prevention named Cardiorisk. This program, which was initially developed by the Transfusion and Immunohematology Center of the Polyclinic of Milan (13,14) on the basis of the CUORE project from the Italian National Institute of Health (15-17), was designed to calculate the risk of developing cardiovascular disease within subsequent 10 years. Eight parameters [sex, age, total cholesterol >200 mg/dL (5.17 mmol/L), high-density lipoprotein (HDL) cholesterol <40 mg/dL (1.03 mmol/L), plasma glucose >100 mg/dL (5.56 mmol/L), arterial systolic blood pressure >140 mm/Hg, anti-hypertensive therapy and smoking] were annually collected for each enrolled blood donor to generate a score which identified individuals at low-moderate (score <20) or high cardiovascular risk (score ≥20). Clinical and laboratory data collection as well as the calculation of the Cardiorisk score were performed using the regional software EmoNet (Insiel Mercato, Udine, Italy) for global management of transfusion services. Only blood donors with a minimum follow-up of at least 2 years were included in this study. All blood donors with a Cardiorisk score ≥20 were suspended from blood donation and underwent additional instrumental tests (chest X-ray, stress electrocardiogram and Doppler ultrasound of supra-aortic trunks). Those with normal results were readmitted, whereas the others were withdrawn from blood donation and referred to the treating physicians for follow-up or further specialist (cardiologist, vascular surgeon) evaluation for most appropriate treatment. Their follow-up was

updated every 3 months in the software for the management of blood donors (EmoNet). The ABO blood group of all blood donors with a Cardiorisk score ≥20 during the period 2005–2015 was recorded and the distribution was compared with that of the group of blood donors with a Cardiorisk score >20. Statistical analysis was performed using Fischer's Exact Test. A P value less than 0.05 was considered statistically significant. Descriptive data were presented as medians with range.

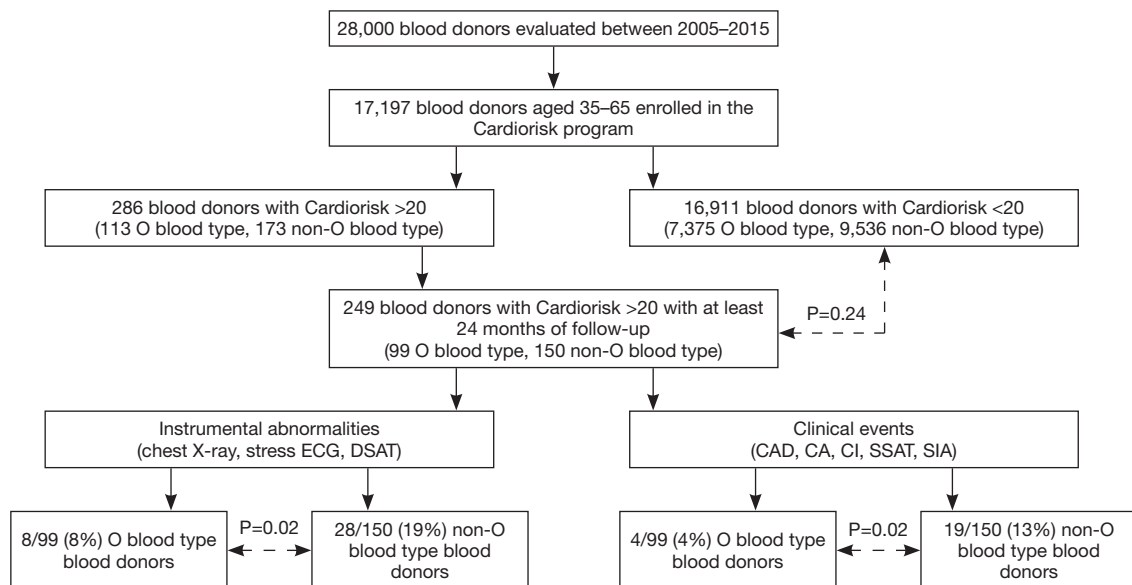
## Results

Among the 17,197 blood donors aged 35–65 years included in Cardiorisk program during the period 2005–2015, 286 had a Cardiorisk score >20, and 249 of them were evaluated having a follow-up of at least 24 months (median follow-up, 5.3 years; range, 2–10 years). All blood donors with Cardiorisk score ≥20 were males and their median age was 55 years (range, 35–65 years). Of these, 99 (39.8%) had O blood type while the remaining 150 (60.2%) had non-O blood type. Among the control group, represented by 16,911 consecutive blood donors with a Cardiorisk <20 (10,321 males and 6,590 females; median age at evaluation 47 years, range, 35–65 years), the ABO blood group distribution was the following: 7,375 (43.6%) O blood type and 9,536 (56.4%) non-O blood type. No statistically significant difference in ABO blood group distribution was present between the two groups of blood donors with Cardiorisk ≥ and <20 (P=0.2) (Table 1). Thirty-six of the 249 (14.5%) blood donors with a score ≥20 had at least one abnormal instrumental test result and their ABO status significantly differed from control group showing an excess of non-O blood types (77.8% in donors with Cardiorisk ≥20 and instrumental test abnormalities *vs.* 56.4% in blood donors with Cardiorisk <20, P=0.01) (Table 1). In addition, the prevalence of such abnormalities was markedly higher in non-O *vs.* O blood type subjects [28/150 (18.7%) *vs.* 8/99 (8.1%), P=0.02]. Twenty-three (9.2%) individuals developed also clinical cardiovascular events during the follow-up period (10 acute coronary syndrome, 2 cerebral ischemia, 3 cardiac arrhythmia, 8 stenosis of supra-aortic trunks or iliac arteries). Again, the non-O blood group distribution in such patients significantly differed from that of the control group with Cardiorisk <20 (82.6% *vs.* 56.4%, P=0.01), having non-O blood type subjects an increased risk of developing cardiovascular events compared with O blood type [19/150 (12.7%) *vs.* 4/99 (4.0%), P=0.02]. Accordingly, non-O blood type subjects had a nearly 3-fold higher risk

**Table 1** Comparison of ABO blood group distribution between blood donors with Cardiorisk score  $\geq 20$  and  $< 20$ 

Blood donors (35–65 years)	N	O blood group, N (%)	Non-O blood group, N (%)				P value*
			A	B	AB	Total	
A: Cardiorisk $\geq 20$ (all individuals)	249	99 (39.8)	116 (46.6)	21 (8.4)	13 (5.2)	150 (60.2)	A vs. D =0.24
B: Cardiorisk $\geq 20$ (with instrumental test abnormalities)	36	8 (22.2)	21 (58.3)	5 (13.9)	2 (5.6)	28 (77.8)	B vs. D =0.01
C: Cardiorisk $\geq 20$ (with clinical symptoms)	23	4 (17.4)	13 (56.5)	4 (17.4)	2 (8.7)	19 (82.6)	C vs. D =0.01
D: Cardiorisk $< 20$ (controls)	16,911	7,375 (43.6)	7,209 (42.6)	1,620 (9.6)	707 (4.2)	9,536 (56.4)	

\* , O blood group vs. non-O blood group. The statistical analysis was performed using Fischer's exact test.



**Figure 1** Flow chart with the results of the study. ECG, electrocardiogram; DSAT, doppler of supra-aortic trunk; CAD, coronary artery disease; CA, cardiac arrhythmia; CI, cerebral ischemia; SSAT, stenosis of supra-aortic trunks; SIA, stenosis of iliac arteries.

of developing cardiovascular events on follow-up compared to O blood type (crude odds ratio, 3.3; 95% CI, 1.1–10.1;  $P=0.033$ ). *Figure 1* summarizes the results of the study.

## Discussion

The ABO blood group exerts a profound influence on hemostasis, being a key determinant of plasma concentrations of von Willebrand factor (VWF) and, consequently, of coagulation factor VIII (FVIII) (18,19). It is well known, indeed, that individuals with non-O blood group have circulating levels of both VWF and FVIII that are approximately 25% higher than O blood group subjects, and the underlying mechanism resides in the positive influence on VWF levels and activity of the addition of A and B antigens, by the specific glycosyltransferase enzymes,

on the existing VWF H oligosaccharides (20). The non-O related increased levels of VWF and FVIII, in addition with those of several inflammatory cytokines (i.e., tumor necrosis factor- $\alpha$ , soluble intercellular adhesion molecule 1, E-selectin, P-selectin and interleukin-6) and cholesterol levels, have been suggested as the most likely mechanisms for explaining the association between ABO blood group and cardiovascular diseases (21–24). The close link between non-O blood type and cardiovascular risk emerges also from our study, which assessed for the first time the clinical impact of the Cardiorisk program in a large population of Italian blood donors. Indeed, while previous publications (13,14,25) limited their analysis to the epidemiological characteristics of blood donors stratified according to the Cardiorisk score, in the present study we followed such population to clinically validate the predictive risk of this

program. Notably, all the blood donors with Cardiorisk  $\geq 20$  were males and their median age was higher than that of the general blood donor population (55 vs. 47 years), thus outlining the key role of sex and age in the atherosclerosis process. Since the distribution of the O and AB blood groups was found to have no association with the gender at our latitude (26), the prevalence of males observed in the population with Cardiorisk  $\geq 20$  has not seemingly influenced the outcome of our analysis. In addition, the observation that 14.5% and 9.2% of high-risk blood donors had a subclinical or clinical evidence of an underlying cardiovascular disease, respectively, further validates the utility of this primary cardiovascular prevention program in a large population such as that of blood donors. However, the most striking finding of our study was the strong correlation between the ABO status and the cardiovascular risk: indeed, among the blood donors identified as high risk by the Cardiorisk program (i.e., those with a score  $\geq 20$ ), those belonging to non-O blood type had a significantly increased incidence of cardiovascular adverse events compared with O blood type subjects. Our data are thus in keeping with previous investigations documenting the importance of ABO blood type in the pathogenesis not only of venous thromboembolism but also of arterial thrombotic process (10-12).

## Conclusions

In conclusion we believe that, similarly to other scores evaluating the risk of developing acute occlusive arterial events (27,28), the ABO status should be incorporated also in the Cardiorisk score in order to better identify blood donors at higher risk of developing cardiovascular adverse events, and thus implementing preventive measures on modifiable risk factors.

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## Footnote

*Conflicts of Interest:* The authors have no conflicts of interest to declare.

*Ethical Statement:* This study was approved by the institutional ethic review board and informed consent was obtained from all patients.

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