ABO(H) blood groups and vascular disease: a systematic review and meta-analysis

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Summary. *Background:* Associations between vascular disease and ABO(H) blood groups have a long history, but no consensus exists regarding its magnitude and significance, or whether it relates to all disorders equally. An accurate calculation of risk would allow direct assessment of whether the effects of non-O status on thrombosis risk are of the magnitude predicted by its effect on von Willebrand factor/FVIII levels. *Methods and results:* We conducted a systematic review and meta-analysis of studies reporting associations with non-O blood groups. This gave pooled odds ratios of 1.25 [95% confidence interval (CI) 1.14–1.36] for myocardial infarction (MI), 1.03 (95% CI 0.89–1.19) for angina, 1.45 (95% CI 1.35–1.56) for peripheral vascular disease, 1.14 (95% CI 1.01–1.27) for cerebral ischemia of arterial origin, and 1.79 (95% CI 1.56 to 2.05) for venous thromboembolism (VTE). However, restriction to prospective MI studies only did not confirm the association (OR 1.01; 95% CI 0.84–1.23), although these studies may have failed to capture early-onset disease. For VTE, using a combined group of OO/A_2A_2/A_2O as index, the combination of A_1A_1/A_1B/BB gave an OR of 2.44 (95% CI 1.79–3.33) and A_1O/ BO/A_2B an OR of 2.11 (95% CI 1.66–2.68). *Conclusions:* This study confirms the historical impression of linkage between some vascular disorders and non-O blood group status. Although the odds ratios are similar to those predicted by the effect of ABO(H) on von Willebrand factor levels, further work is required to assess risk prospectively and to refine the effect of reducing O(H) antigen expression on thrombosis. However, as non-O and particularly A_1A_1, A_1B, BB constitute a significant proportion of the population attributable fraction of VTE, there may be a role for more widespread adoption of ABO(H) typing in testing strategies.

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Introduction

The association between thrombosis and ABO(H) blood groups has a long history suggesting that non-O blood groups confer a higher risk of myocardial infarction (MI), angina, peripheral vascular disease (PVD), cerebral ischemia of arterial origin (CIAO), and venous thromboembolism (VTE) than group O. However, no consensus exists regarding whether these associations are real, what its magnitude is, whether such associations affect all vascular disease equally, whether they result from a protection by O(H) (or a deleterious effect of group A), whether the association is causal and what utility there is in including ABO(H) as part of testing to identify those at risk.

Such a link is plausible as ABO(H) determinants occur on factor (F) VIII and von Willebrand factor (VWF), with the lowest VWF levels seen in those of genotype OO and the highest in those with the least O(H) antigen expression (i.e. AA, AB and BB) [1]. Although ABO(H) may also influence activated protein C resistance [2], no consistent relationship with cholesterol [3,4] or other coagulation markers [4–7] has been proven. Thus, estimating whether the strength of association between ABO(H) type and thrombosis is similar to that predicted by the known relationship between VWF/FVIIIc levels and disease would add considerable weight to the hypothesis that these factors are causal. We have therefore performed a systematic review and meta-analysis of the studies reporting associations between ABO(H) blood group and MI, angina, PVD, CIAO and VTE.

Methods

Search strategy and selection criteria

An extensive search was performed on all major electronic data bases from inception to May 2007: MEDLINE, EMBASE, the Cumulative Index to Nursing and Allied Health Literature print index (CINAHL), and Ovid OLDMEDLIINE (1950–1965). Relevant keywords and permutations of search terms

relating to blood group were combined with those relating to vascular disease (Table S1). This was supplemented by using the Web of Science data base to generate a list of articles that cited identified original studies. In addition, we also carried out hand searching of reference lists and recent thrombosis conference proceedings (including the British Society for Haematology, the British Society for Haemostasis and Thrombosis, The European Haematology Association and the International Society for Haemostasis and Thrombosis).

All prospective and retrospective studies meeting the following criteria were included: (i) a population that included those who had been ABO(H) typed; (ii) clinical outcomes included measures of incidences of MI, angina, PVD, CIAO and VTE; and (iii) extractable data that defined the blood groups as either A, B, AB and O, group O and non-O, or group A and non-A. Although we focused on English language studies, studies were not excluded on the basis of language.

Data abstraction and study quality assessment

One author (PC) screened abstracts and excluded irrelevant references and the remaining studies were retrieved in full (Fig. S1). Subsequently, two authors independently reviewed and extracted data on study design, patient characteristics and outcome definitions from these studies according to a predefined protocol. In addition, the quality of the studies included in the review was also assessed using a validated generic checklist designed for quantitative studies [8]. This checklist included 14 criteria, which are consistent with the recommendations from the Centre for Reviews and Dissemination (CRD), and the consensus statement of meta-analysis reporting observational studies in epidemiology [9,10]. Any disagreement relating to study inclusion, data extraction or quality assessment was resolved by discussion.

Statistical analysis

Meta-analysis was carried out and pooled risks of blood group non-O relative to group O were calculated for all five outcomes based on the random effects model [11]. All the results were expressed as odds ratios (ORs), with values >1.0 indicating an increased risk of the outcome associated with group non-O. Where possible, secondary analysis was conducted to determine the risk of group A relative to O and relative to non-A (data not shown). A_2 cells have higher O(H) antigen expression than A_1 [12] and A_2O and A_2A_2 groups have the lowest of all non-O FVIII levels [13]. Correspondingly, to determine the effect of the least expression of the O(H) antigen (and potentially the highest FVIII/VWF levels) on thrombotic risk we also analyzed available data coding A_2 with O. Thus, the risk associated with carriage of a combined group of OO, A_2O and A_2A_2 relative to heterozygote 'O' genotypes (A_1O, BO and A_2B) and also relative to a combined group of A_1A_1, A_1B and BB was determined for all primary outcomes.

Heterogeneity between studies was examined with standard chi-square tests. In addition, the I^2 statistic was also calculated [14]. Where appropriate, the extent of study variables influencing the heterogeneity in the effects was explored by fitting meta-regression models [15]. The variables considered in the model were: the year of publication, retrospective or prospective study design, the presence of objective diagnosis of clinical outcome and whether the control group was selected from a similar population to the group with events. The association between study size and results was examined in funnel plots by plotting odds ratios against their standard error and asymmetry was measured by the asymmetry coefficient [16]. Sensitivity/influence analysis was performed by repeating the meta-analysis, but omitting one study at a time to exclude dominance of any one study. Analyses were performed in Rev Man (Cochrane Collaboration) and Stata version 9.0 (StataCorp LP, College Station, TX, USA).

Results

Of 256 studies retrieved from the initial search, 59 met the inclusion criteria and were included. Variation in the methodological quality of the studies was observed (Fig. S2). The key limitations to MI/angina studies were not reporting result uncertainty (12 studies) [17–28] and a lack of control for potential population stratification (12 studies) [17,22–24,26–33]. For PVD, no study reported result uncertainty and/or provided detailed demographic data [21,34–40]. Studies on CIAO were generally of good quality, although four did not define CIAO using modern imaging [21,41–43]. For VTE studies, the majority did not report detailed demographic data [44–57], whilst others failed to comprehensively adjust for potential population stratification [13,44–58], or employed an insufficient sample size [46,50,54,55].

Myocardial infarction and angina

Of the 22 MI studies included, 5 were conducted prospectively; 11 employed objective diagnosis and 14 used controls from a comparable population (Table S2). Nine reported a significant increase in the risk of MI with non-O [17,18,22,23,25,30,32,33, 59], whilst one reported a reduced risk [60]. Overall (Fig. 1), non-O was associated with an increased risk in MI (pooled OR 1.25; 95% CI 1.14–1.36); however, there was evidence of heterogeneity ($P < 0.0001$), with a moderate proportion of the total variation in the estimated effect due to between-study heterogeneity (I^2 67%). Meta-regression revealed that the effect of blood group non-O on MI risk was influenced by whether the studies were conducted retrospectively or prospectively ($P = 0.04$), with separate analysis showing that retrospective studies are associated with a greater risk estimate than prospective ones (OR 1.33, 95% CI 1.21–1.46 vs. OR 1.01, 95% CI 0.84–1.23). The funnel plot appeared asymmetric, but analysis did not show any significant bias due to study size. Using group O as an index, based upon 19 studies, group A was associated with a similar increase in MI risk (OR 1.29, 95% CI 1.16–1.45) to that observed with non-O (Fig. 2).

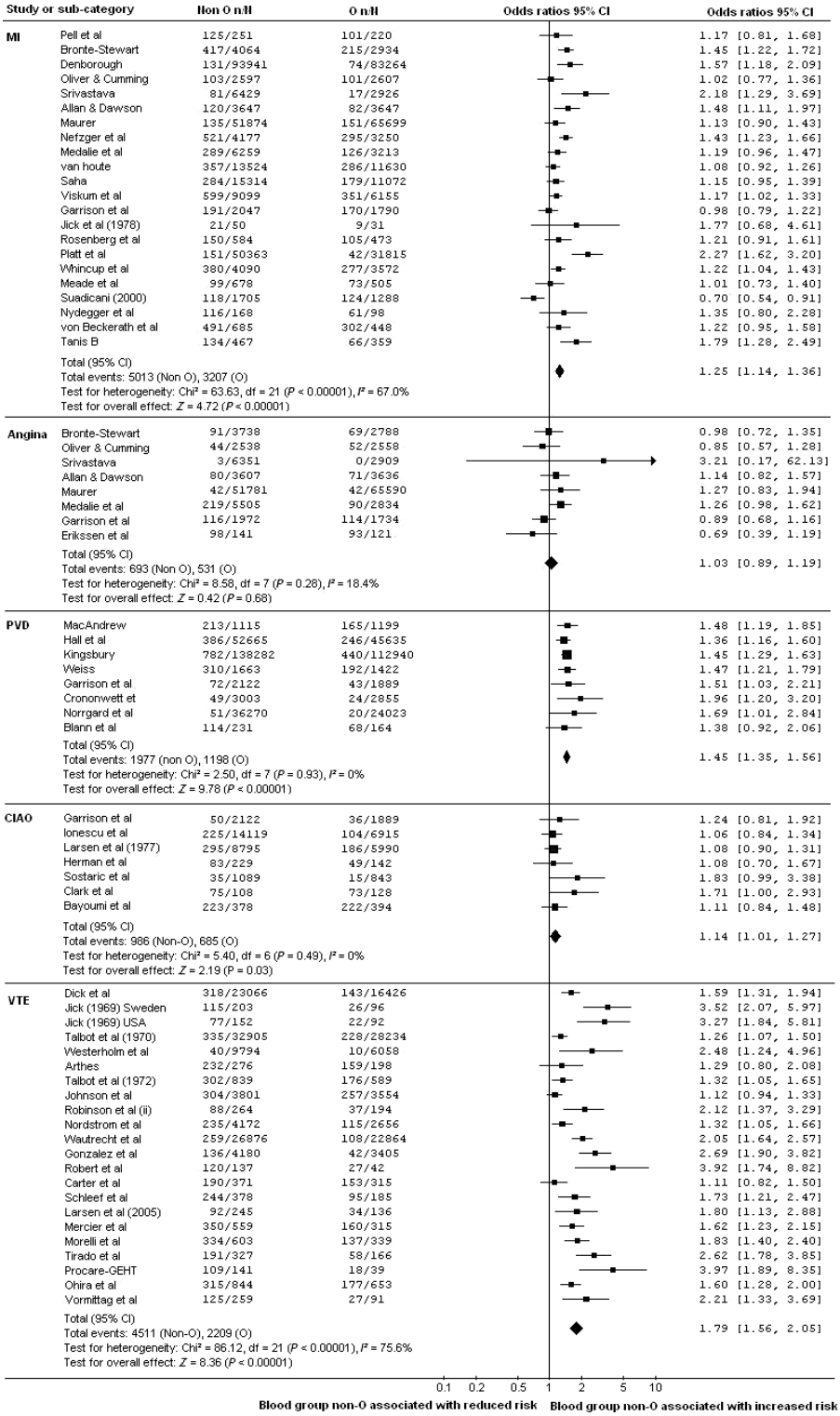

Fig. 1. The individual study odds ratios (with 95% confidence intervals) and the results of the meta-analysis of blood groups non-O relative to O for myocardial infarction (MI), angina, venous thromboembolism (VTE), peripheral vascular disease (PVD) and cerebral ischemia of arterial origin (CIAO) are shown.

For angina, three of the eight studies were prospective [20,21,31], four employed objective diagnosis [20,26,32,33] and three [20,21,60] compared cases with similar controls. None reported significant findings, and no overall effect was found when the study findings were pooled (Fig. 1, OR 1.03, 95% CI 0.89–1.19). There was no evidence of heterogeneity ($P = 0.28$) and the individual study estimates were relatively consistent (I^2 18%). Due to the small number of studies meta-regression

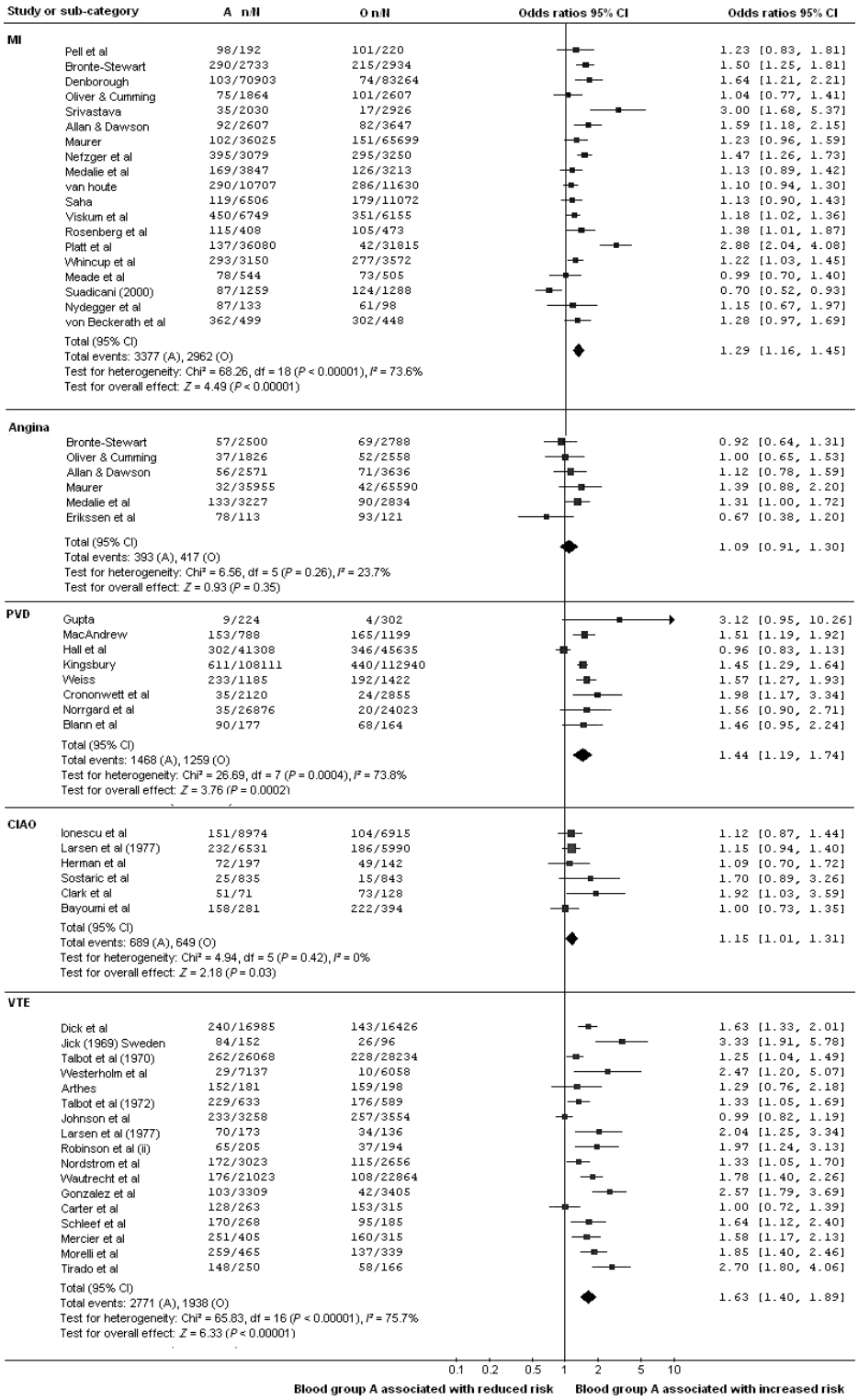

Fig. 2. The individual study odds ratios (with 95% confidence intervals) and the results of the meta-analysis of blood group A relative to O for myocardial infarction (MI), angina, venous thromboembolism (VTE), peripheral vascular disease (PVD) and cerebral ischemia of arterial origin (CIAO) are shown.

was not performed to avoid data over-fitting. Data on group A were available in six studies and, with the exception of one [20], none reported statistically significant findings (Fig. 2), with no overall effect of group A relative to O observed in pooled analysis (OR 1.09, 95% CI 0.91–1.30).

Peripheral vascular disease

Eight studies reported an increased risk of PVD with non-O (Fig. 1), with 4 employing an objective diagnosis [35,36,39,40] and three [21,35,38] using similar controls (Table S3). The

pooled OR for the risk of PVD for non-O relative to O was 1.45 (95% CI 1.35–1.56). There was no evidence of heterogeneity ($P = 0.93$) and the findings of the individual studies were highly consistent (I^2 0%). Meta-regression was not performed due to the small number of studies. All 8 studies provided data on group A (Fig. 2), and a similar increase in PVD risk was found in group A relative to O (OR 1.44; 95%CI 1.19–1.74).

Cerebral ischemia of arterial origin

Four of the seven studies with CIAO data employed an objective diagnosis [21,41–43] (Table S4). However, although only one reported statistically significant findings, all reported an increased risk of CIAO. Pooling the studies (Fig. 1) showed that non-O significantly increased the risk of CIAO (OR 1.14, 95% CI 1.01–1.27). There was no evidence of heterogeneity ($P = 0.49$) and the findings of the individual studies were highly consistent (I^2 0%). Meta-regression was not carried out to explore heterogeneity further due to the small number of studies. Only one of the seven did not provide data on group A (Fig. 2). The pooled OR for group A relative to O was similar to that for non-O (OR 1.15, 95% CI 1.01–1.31).

Venous thromboembolism

Of the 21 studies included in the VTE analysis, 3 were carried out prospectively [49,50,61], 10 employed objective diagnosis [13,44,47–49,58,61–64] and 14 [13,45,46,50–52,54,57,58,61,63–66] used controls from a comparable population (Table S5). With the exception of three [45,52,57], all reported a significant increase in VTE risk with non-O, with ORs from 1.26 to 3.92. Overall, the pooled OR was 1.79 (95% CI 1.56–2.05), indicating a significant increase in VTE risk associated with non-O. However, significant heterogeneity was present ($P < 0.0001$) and the findings of the individual studies were highly inconsistent (I^2 76%). Meta-regression showed that none of the study-level variables had a significant influence on the risk estimate. However, the funnel plot was asymmetric and there was evidence of bias based on both the Egger weighted regression method ($P = 0.000$) and Begg's rank correlation method ($P = 0.004$). Based on 17 studies [13,44,45,47–58,63,65], similar results to that for non O/O comparisons were observed for group A relative to O (Fig. 2, pooled OR 1.63, 95% CI 1.40–1.89).

When the data were restricted to VTE subjects who also carried factor V Leiden (FVL) [13,46,61,66], a greater impact of non-O on VTE risk was observed, giving a pooled OR of 3.88 (95% CI 2.51–6.00).

Blood group genotypes were available from three studies [13,44,63]. A combined group of $A_1O/BO/A_2B$ was associated with a 2.11 increased VTE risk (95% CI 1.66–2.68) when compared with the combined $OO/A_2A_2/A_2O$ group. There was no evidence of heterogeneity ($P = 0.23$) and the findings of the studies were relatively consistent (I^2 33%). The VTE risk when those with the least O(H) antigen expression (a combined group of $A_1B/A_1A_1/BB$) were compared with the OO/A_2A_2,/A_2O group was 2.44 (95% CI 1.79–3.33). Similarly, there was no evidence of heterogeneity ($P = 0.58$) and the findings of the studies were highly consistent (I^2 0%).

Sensitivity analysis

For each of the primary outcomes, sensitivity/influence analysis showed that the results remained consistent and no individual study appeared to significantly influence any of the findings.

Discussion

In this study we compared non-O with group O, as groups AA, BB and AB have a similar effect on circulating VWF [67], which might indicate protection by the O(H) antigen, rather than a thrombotic effect of a particular non-O group. However, as some studies have found a particular effect of group A [18,20,22], analysis of A compared with both O and non-A (data not shown) was also performed. In both cases and for all disorders, remarkably similar ORs were observed to that of non-O/O comparisons, with a considerable overlap in the 95% confidence intervals.

For MI, the non-O risk is restricted to retrospective studies, with no overall effect observed in prospective cohorts. Although ABO(H) is determined at birth, retrospective studies can only be performed on survivors, which could potentially indicate a survival advantage of non-O groups after MI. However, prospective studies may have excluded early-onset disease, as four of the five excluded those with pre-existing ischemic heart disease at inception [20,21,60,68]. Interestingly, in the one study that did not [30], a significant increase in MI was associated with non-O (OR 1.22, 95% CI 1.04–1.43). That no increase in the risk of angina was observed either individually, or in meta-analysis, may indicate that ABO(H) has no effect on the pathogenesis of atheroma, but only influences thrombus formation. The results observed may, however, reflect the poor or relatively non-specific clinical diagnostic criteria employed in many studies [21,25,28,33].

Despite heterogeneity between studies, the majority of VTE investigations reported an increased VTE risk associated with non-O, giving a pooled OR of 1.75 (95% CI 1.51–2.03). This heterogeneity, however, was not explained by study variables, although there is insufficient information from available studies to exclude an effect of ethnicity. Restricting the data to those carrying FVL [13,46,61,66], gave a greater pooled OR of 3.88 (95% CI 2.51–6.00). However, as yet, no study has reported any similar interaction with the prothrombin 20210A mutation [47,61]. The studies of VTE also gave an opportunity to study whether there might be a 'dose-response' effect of the O(H) antigen on VTE occurrence. Using 'OO' genotypes (classifying A_2 with O) as a baseline, the combined group of $A_1A_1/A_1B/BB$ (the lowest O(H) expression), was associated with a slightly higher VTE risk (OR 2.44, 95% CI 1.79–3.33) than heterozygote O genotypes (the combination of

$A_1O/BO/A_2B$; OR 2.11, 95% CI 1.66–2.68). However, perhaps resulting from the small amount of available data, no significant increase in the risk from the $A_1O/BO/A_2B$ to the $A_1A_1/A_1B/BB$ group was observed (OR 1.17, 95% CI 0.86–1.58).

For PVD, we observed a pooled OR of 1.45 (95% CI 1.35–1.56) for non-O relative to O. Interestingly, whilst only some used objective diagnosis [35,36,39,40], or comparable controls [21,35,38], the findings were highly consistent. For CIAO, pooling of the small number of available studies revealed that blood group non-O produces a small, but significant, increased risk of CIAO (OR 1.14, 95% CI 1.01–1.27).

Arterial and venous thrombosis share a number of risk factors/risk markers. In particular, higher levels of VWF/FVIII are both risk markers and effectors of thrombus formation and progression [69,70]. That ABO(H) status has a stronger influence on VTE seems, at first, surprising, as VWF is a recognized risk factor/effector for coronary heart disease [71–73]. However, a number of more 'classical' risk markers/effectors are more strongly linked with the disease than VWF [74]. Moreover, although generally associated with increasing age, VTE occurs (and more importantly is often reported) in younger subjects in association with pregnancy, hormonal therapy and surgery. A stronger genetic influence on younger-onset disease is intuitive and, as noted above, a number of the prospective cardiovascular risk studies excluded younger-onset disease at inception. The more marked effect of MI and CIAO on immediate survival (and therefore the distribution of subjects available for recruitment to retrospective studies) may also more markedly affect VTE than MI studies. The finding of a similar degree of risk of PVD to that of VTE is, however, compatible with the known association of increasing levels of VWF and the presentation and progression of PVD [75].

Although it seems likely that FVIII levels carry an additional risk to that explained by ABO(H) and indeed not all ABO(H) VTE risk is explained by FVIIIc levels [44,76], to be causal the observed difference in risk between O and non-O types should at least be in keeping with differences in the plasma levels of VWF/FVIII between the groups and with the degree of thrombosis risk that these plasma levels predict. As VWF/FVIII is part of the acute phase response, the best estimates of the effect of ABO(H) on VWF will be obtained from subjects sampled before disease onset. Blood group O in normal subjects is associated with VWF antigen levels of 65.4–102.8 IU/dL [44,76], with most studies reporting mean levels <90 IU/dL. In group A, B and AB subjects mean values ranging from 90–139 IU/dL [[44,76] have been reported, with a mean for the combined non-O group of 133.9 IU/dL reported in one study [44]. Whincup and colleagues [77] have shown that disease-free subjects with a VWF antigen of 90–126 IU/dL have a 1.29-fold (95% CI 0.92–1.80) increased risk of non-fatal MI/coronary artery disease death on follow-up when compared with those with levels of <90 IU/dL. Although a crude comparison, this result is consistent with the above effect of non-O on VWF and on the odds ratio of non-O and MI observed in the current study. For VTE, good prospective data using SI units are lacking. One retrospective study has shown that VWF antigen levels of 100–124.9 IU/dL are associated with a 1.5-fold increased risk of VTE when compared with levels <100 IU/dL [69]. Although this is consistent with the OR for VTE and non-O that we have observed, prospective examination of VWF/FVIIIc levels in SI units would be required to confirm a causal relationship between non-O groups and VTE. The fact that we have observed a greater risk in those with the least O(H) antigen expression would, however, be consistent with causality.

Currently, ABO(H) determination is not universally included as part of the suite of tests used to identify those considered at particular risk of VTE. Although FVL and the prothrombin 20210A mutation carry a higher relative risk than non-O subjects, their population-attributable fraction (PAF) in the UK is considerably smaller than that for non-O subjects. By way of illustration, if the incidence of FVL [2], non-O [78] and the combination group $A_1A_1/A_1B/BB$ [12] is taken as 3.4%, 55.0% and 7.3%, respectively, and a 7-fold increase in VTE risk in heterozygote FVL carriers is assumed, then the PAF for FVL would be 16.9%. By comparison, from the current study non-O status would give a PAF of 30.3%, with a PAF associated with the combined group of $A_1A_1/A_1B/BB$ of 9.5%. This latter figure contrasts with the prothrombin 20210A mutation, which occurs in at most 2% of UK subjects [79] and carries a 2–5-fold relative risk of VTE, resulting in a PAF of between 1.96 and 7.4%. Although universal screening may not be cost- [80] or clinically-effective, the addition of ABO(H) typing to selective screening programmes to identify those at risk with a view to antithrombotic intervention (perhaps particularly $A_1A_1/A_1B/BB$ subjects) may give useful information, both in isolation and in combination with other routine thrombophilia testing.

The data included in this review span the last 45 years. Interestingly, despite the general improvements in study execution over that time, the publication year, the presence or absence of objective diagnoses and the use of comparable controls did not have significant effects on the overall conclusions of the review. However, further work is required to refine the risks observed, with more information from prospective studies of MI/angina required. Moreover, the potential for those with the least expression of the O(H) antigen to have the highest VTE risk needs to be confirmed, with similar genotyping studies needed to assess any parallel effect in MI, CIAO or PVD.

Disclosure of Conflict of Interests

The authors state that they have no conflict of interest.

Supplementary Material

The following supplementary material is available for this article:

Table S1. Keywords used in the search.
Table S2. Characteristics of studies on myocardial infarction (MI) and angina.
Table S3. Characteristics of studies on peripheral vascular disease.
Table S4. Characteristics of studies on cerebral ischemia of arterial origin.
Table S5. Characteristics of studies on venous thromboembolism.
Fig. S1. Selection of studies for review.
Fig. S2. Results of quality assessment for all studies included in the review.

This material is available as part of the online article from: http://www.blackwell-synergy.com/doi/abs/10.1111/j.1538-7836.2007.02818.x (This link will take you to the article abstract).

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