

Inherited and Acquired Thrombophilia in Adults with Retinal Vascular Occlusion: A Systematic Review and Meta-Analysis.

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Key Words:	Retinal Vein Occlusion, Retinal Artery Occlusion, Thrombophilia, Systematic Review, Meta-Analysis

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3 **Inherited and Acquired Thrombophilia in Adults with Retinal Vascular**
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5 **Occlusion: A Systematic Review and Meta-Analysis.**
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ESSENTIALS:

- The prevalence of thrombophilias in patients with retinal vascular occlusion is unclear.
- Systematic Reviews and Meta-Analysis of 95 studies were performed.
- Similar prevalences were observed in retinal vascular occlusion and the general population.
- Routine thrombophilia screening may not be useful in patients with retinal vascular occlusion.

ABSTRACT

Background: Retinal vascular occlusion is a leading cause of sight loss. Both retinal artery occlusion (RAO) and retinal vein occlusion (RVO) have been associated with hypercoagulable states; however, the burden of thrombophilia in these patients is unclear.

Objectives: This study aims at estimating the prevalence of inherited and acquired thrombophilias in adults with RAO or RVO, through a systematic review and meta-analysis of the literature.

Patients/Methods: Pubmed and EMBASE were systematically searched from inception to 29th February 2020. All studies reporting prevalences of Factor V Leiden (FVL) and Prothrombin (F-II) G20210A mutations, MTHFR C677T and PAI 4G polymorphisms, Antithrombin III (AT-III), Protein C (PC) and Protein S (PS) activity deficiencies, hyperhomocysteinemia and antiphospholipid (APL) antibodies in adults with RAO or RVO were included. Pooled prevalences and 95% Confidence Intervals (CI) were calculated.

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3 **Results:** Ninety-five studies were included; FVL and F-II mutations were found in 6%
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5 (95%CI: 5-8%) and 3% (95%CI: 2-4%) of individuals with RVO, respectively, while
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7 AT-III, PC and PS activity deficiencies were found in less than 2%. The MTHFR
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9 C677T and PAI 4G homozygous polymorphism were observed in 13% (95%CI: 10-
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11 17%) and 23% (95%CI: 16-31%) of RVO, respectively; 8% presented APL
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13 antibodies. Similar findings were observed in individuals with RAO.
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17 **Conclusions:** Compared to healthy subjects, patients with retinal vascular occlusion
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19 showed similar prevalences of inherited and acquired thrombophilias. These findings
20
21 do not support routine thrombophilia screening in individuals with RAO or RVO.
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26 **Key Words:** Retinal Vein Occlusion, Retinal Artery Occlusion, Thrombophilia,
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28 Systematic Review, Meta-Analysis.
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INTRODUCTION

Vascular occlusion of the retina is one of the major causes of vision loss throughout the world.[1] Vascular occlusion may occur as Retinal Artery Occlusion (RAO) or Retinal Vein Occlusion (RVO); both conditions are also categorized based on the anatomic site of the obstruction as central RAO (CRAO), branch RAO (BRAO), central RVO (CRVO) and branch RVO (BRVO).

The pathophysiology of retinal vascular occlusion is multifactorial, with a wide range of modifiable and non-modifiable risk factors[2] including aging, hypertension, diabetes and dyslipidemia.[3,4] Even hypercoagulable states - which may predispose subjects to a higher risk of blood clot formation - has been associated with a higher incidence of both RAO and RVO in several population-based cohorts. Several gene variants have been already identified and linked to an increased risk of thrombosis (especially venous thromboembolism [VTE]), including mutations in genes encoding coagulation factors (e.g. Factor V and Factor II) or natural anticoagulants (Antithrombin III, Protein C, Protein S).[5,6] Unusual form of VTE, i.e. thrombosis occurring at different sites than lower limbs, have been linked to genetic variants of hemostasis traits;[7] however, clinical studies have provided conflicting findings on the clinical significance of both inherited (e.g. Factor V Leiden (FVL) Mutation, Prothrombin (F-II) G20210A mutation) and acquired (i.e. Antiphospholipid (APL) antibodies syndrome) thrombophilias in the pathogenesis of retinal vascular occlusions.[8,9] Beyond well-known acquired and inherited thrombophilia, casual VTE risk factors, other conditions including PAI-1 and MTHFR variants, as well as hyperhomocysteinemia, failed in explaining a higher risk of VTE;[10,11] nevertheless, they have been linked to a higher incidence of retinal vascular occlusion with conflicting results, and their assessment is sometimes part of the

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3 diagnostic work-up of these patients. A better understanding of the strength of the
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5 association between hypercoagulability and retinal vascular occlusion may inform on
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7 the management of patients with both RAO and RVO, with important consequences
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9 on diagnostic work-up and treatment.
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12 This study aims to provide a systematic review and meta-analysis of studies
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14 reporting the prevalence of several inherited and acquired thrombophilias in adults
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16 with RAO or RVO.
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21 **METHODS**

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23 This systematic review was performed according to the Preferred Reporting
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25 Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and
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27 recommendations (<http://www.prisma-statement.org>).
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32 *Search Strategy*

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34 A systematic and comprehensive literature search was performed on Pubmed
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36 and EMBASE databases, from inception to 29th of February 2020. Keywords used
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38 and combined in the search strategy comprised a combination of terms relevant to
39
40 the research question, including 'Retinal Vein Occlusion', 'Retinal Artery Occlusion',
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42 'Thrombophilia', and terms related to the hypercoagulable states investigated. The
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44 full search strategy is listed in the supplementary materials.
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51 *Studies Selection*

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53 According to PRISMA guidance, all records retrieved from the search were
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55 systematically screened in parallel and independently by two authors (BC and MB),
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57 according to their titles and abstracts. Each record included after the first phase was
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3 then independently evaluated for full-text eligibility by two authors (BC and MB);
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5 conflicts were resolved by collegial discussion, with a third author when necessary
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7 (GFR). Inclusion criteria were: i) studies on adults with RAO, RVO or their specific
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9 forms (CRAO, BRAO, CRVO, BRVO); ii) studies reporting the prevalence of
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11 following thrombophilias: F-V Leiden mutation (rs6025); F-II G20210A mutation
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13 (rs1799963); Antithrombin III (AT-III) deficiency; Protein C (PC) deficiency; Protein S
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15 (PS) deficiency, hyperhomocysteinemia, methylenetetrahydrofolate reductase
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17 (MTHFR) C677T mutation (rs1801133), plasminogen activator inhibitor-1 (PAI) 4G
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19 mutation (rs1799889), and antiphospholipid antibodies (APL). Exclusion criteria
20
21 were: i) studies with less than <20 patients for each disease (RAO or RVO); ii)
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23 studies that did not report data on the aforementioned thrombophilic conditions; iii)
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25 studies that investigated highly selected cohorts, i.e. only adults presenting with
26
27 retinal vascular occlusion and no existing comorbidities or predisposing conditions,
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29 or cohort composed of only very young patients (<40 years old); iv) conference
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31 abstracts, comments, editorials, case reports, systematic reviews and meta-analysis;
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33 v) article written in languages other than English. In the case of two or more studies
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35 based on the same cohort of subjects and exploring the same outcome(s), only the
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37 most recently published was selected and included in the systematic review and
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39 meta-analysis.
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49 *Data Extraction and Quality Assessment*

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51 Data from the studies included were extracted independently by two co-
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53 authors (BC and MB), under the supervision of a third author (GFR). Data on sample
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55 size, type of retinal vascular occlusion, mean or median age, and percentage of
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3 males adults were collected, along with the number of patients presenting with each
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5 thrombophilia.
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8 All studies included were independently evaluated by two co-authors (GFR
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10 and BC) to assess the risk of bias, according to recommendations of the Agency for
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12 Healthcare Research and Quality.[12] The screening was performed for five main
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14 bias domains (selection bias, performance bias, attrition bias, detection bias and
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16 reporting bias). An overall, synthetic grade was produced for each study.
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20 21 *Outcomes Definition*

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23 Primary outcomes were the prevalence of the inherited and acquired
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25 thrombophilias, i.e. F-V Leiden, F-II G20210A, MTHFR C677T, and PAI 4G
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27 mutations, AT-III, PC and PS activity deficiency, hyperhomocysteinemia and APL
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29 antibodies. For F-V and F-II mutations, only a small proportion of patients were
30
31 described as homozygous; also, in several studies, no clear distinction between
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33 heterozygous and homozygous mutations was made, so that we computed
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35 homozygous patients together with heterozygous carriers. AT-III, PC, and PS activity
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37 deficiencies, as well as hyperhomocysteinemia, were defined according to the
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39 definition used in the original studies. Patients with heterozygous (CT) or
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41 homozygous (TT) MTHFR C677T and PAI 4G polymorphisms were analyzed
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43 separately. APL antibodies were defined as positivity for both anticardiolipin (ACA)
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45 and anti- β 2 glycoprotein-I antibodies, where available, or the positivity of the only
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47 one reported; several studies reported data only on ACA antibodies and were
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49 included as well in the analysis.
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58 *Statistical Analysis*

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3 Prevalences from original studies were pooled and compared using a
4 random-effects model as for primary analysis; as a secondary analysis, fixed-effect
5 models were also computed.
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10 When pooling prevalences which tend to extreme ranges (i.e. 0% or 100%),
11 the variance of the study may be overestimated, so we conducted our analysis
12 transforming prevalence estimated with the Freeman-Tukey double arcsine method,
13 as previously reported.[13,14] Pooled estimates were reported as pooled prevalence
14 and 95% confidence intervals (CI).
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21 The inconsistency index (I^2) was calculated to measure heterogeneity.
22 According to pre-specified cut-offs, low heterogeneity was defined as an I^2 of <25%,
23 moderate heterogeneity when I^2 falls between 25 and 75%, and high heterogeneity
24 when I^2 was >75%.
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30 In patients with RVO, we also performed two additional secondary analyses: i)
31 we stratified studies according to the localization of the occlusion (CRVO vs. BRVO);
32 ii) we stratified studies according to the risk of bias (low vs. medium/high overall risk
33 of bias). Statistical analysis was performed using Stata 16 (StataCorp, USA).
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42 **RESULTS**

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44 A total of 2,856 articles were retrieved (2,042 from Pubmed and 814 from
45 EMBASE). After the titles and abstracts screening, a total of 161 full-texts were
46 assessed, of which 66 were subsequently excluded. A total of 95 articles were
47 included in the analysis (Figure S1). Table 1 summarizes the main characteristics
48 and findings of the studies included: 89 reported data on RVO and 11 on RAO. Most
49 of the studies (n=54, 57%) were conducted in Europe; 22 in Middle East or North
50 Africa, 9 in North America, 6 in Asia, and 2 in South America and Oceania.
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3 According to the type of thrombophilia, 50 studies explored FVL mutation; 38
4 reported about F-II G20210A mutation, 35 on hyperhomocysteinemia, 31 on MTHFR
5 C677T mutation, 28 on APL antibodies presence, 24 on PC activity deficit, 22 on AT-
6 III activity deficit and 20 on PS activity deficit, while only six reported about PAI 4G
7 mutation.
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15 The risk of bias was assessed for each study as reported in Table S1: 63
16 studies were rated at low risk, 24 at medium risk, and 8 at high risk of bias.
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20 21 *Factor V Leiden mutation*

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23 Among 3,981 patients with RVO, the pooled prevalence of FVL mutation was 6%
24 (95% CI: 5-8%; $I^2=80%$; figure 1A). Significant heterogeneity was found between
25 geographical groups ($p=0.016$), with the higher prevalence reported in middle
26 east/north African studies (pooled prevalence: 13%, 95% CI: 6-22%). The pooled
27 prevalence of FVL mutation was lower in European (6% [95% CI 4-7%]) and north-
28 American cohorts (5% [95% CI 3-8%]). Similar results were obtained with the fixed-
29 effect model (figure S2A).
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40 Only six studies explored the association between FVL mutation and RAO, with a
41 similar pooled prevalence to that of RVO (7%, 95% CI: 2-13%, $I^2=62%$, figure 1,
42 panel B), regardless of the model applied (figure S2B).
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49 *F-II G20210A mutation*

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51 Across 34 studies, a pooled prevalence of 3% (95% CI: 2-4%; $I^2=54%$; figure 2A)
52 was computed with no significant heterogeneity across geographical groups. Five
53 studies reported on the association between RAO and F-II G20210A mutation, with a
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3 pooled prevalence of 3% (95% CI: 1-6%, $I^2=13\%$; figure 2B). Similar results were
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5 shown using a fixed-effect model (Figure S3A-B).
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10 *AT-III, PC and PS activity deficiencies*

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12 Among the twenty studies reporting on the AT-III deficit in patients with RVO had
13 large heterogeneity in the thrombophilia definition (i.e. cut-off AT-III activity): <100%
14 of normal reference activity (n=1); [Supplementary Reference 7, S7] <81-89%
15 (n=3), [S51, S55, S67] <80% (n=7). [S15, S34, S44, S49, S65, S73, S86] An even lower
16 cut-off was used (n=2), [S74, S75] and in eight studies no clear definition was
17 provided. [S1, S3, S6, S10, S57, S58, S60, S85]
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26 Pooled estimates showed a low prevalence of AT-III deficiency (1%; 95% CI: 0-2%;
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28 $I^2=68\%$, Figure 3A), with significant heterogeneity across geographical group
29 (p=0.023) and the higher prevalence in middle-east/north-Africans (5%, 95% CI: 1-
30 10%).
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35 Twenty-two studies looked at PC activity deficiency, with a total of 1,738 RVO
36 patients. Nine studies used a definition of <70% of normal reference
37 activity; [S7, S15, S20, S44, S49, S51, S74, S75, S86] two studies included patients with
38 higher cut-offs (<73% [S34] and <85% [S67]) and only one study adopted lower level
39 (<60% [S40]). For 10 studies, a clear definition was not
40 identifiable. [S1, S3, S6, S10, S57, S58, S60, S78, S81, S85] Pooled estimates showed a
41 prevalence of 2% (95% CI 0-3%, $I^2=75\%$, figure 3B), with significant heterogeneity
42 (p<0.001) between geographical groups: European-based cohorts showed a lower
43 prevalence (0%, 95% CI: 0-1%, $I^2=15\%$) than middle-east and north-African studies,
44 (pooled prevalence: 13%, 95% CI: 6-22%, $I^2=13\%$).
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3 Seventeen studies reported data about PS activity deficiency in RVO adults, for a
4 total of 1276 patients. As for the definitions used, five studies adopted a cut-off of
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6 total of 1276 patients. As for the definitions used, five studies adopted a cut-off of
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8 <70% of normal reference activity,[S7,S15,S20,S67,S75] and 4 studies used a
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10 lower-cut-off (ranging from <65% to <60%).[S40,S44,S49,S86] For eight studies a
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12 clear definition of PS activity deficit was not
13
14 found.[S1,S3,S10,S57,S58,S60,S78,S85] A pooled prevalence of 2% (95% CI:0-4%;
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16 $I^2=74%$, figure 3C) was calculated with no significant heterogeneity was across
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18 geographical groups and a higher prevalence in middle-east and north-Africans.
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20 Similar findings were observed in the fixed-effect models (Figure S4A-C
21
22 respectively).

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26 Only 4 studies investigated RAO patients.[S34,S48,S59,S65] Pooled prevalence for
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28 AT-III activity deficit in adults with RAO was 3% (95% CI: 0-9%, $I^2=57%$, figure S5-
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30 A), higher as compared with that observed in RVO; PC and PS activity deficiencies
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32 were similarly prevalent in RAO to those in RVO (2%, 95% CI 0-10%, $I^2=61%$ and
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34 1%, 95% CI: 0-4, $I^2=24%$, respectively, figure S5B-C). Fixed-effect models for AT-III,
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36 PC, and PS activity deficits in RAO are reported in figure S6A-C respectively.
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42 *Hyperhomocysteinemia and MTHFR C677T polymorphism*

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44 Thirty studies reported data about hyperhomocysteinemia in patients with RVO, for a
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46 total of 2,656 patients. High grade of heterogeneity was found according to the
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48 definition of hyperhomocysteinemia, based on different cut-offs of homocysteine
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50 level: between 15 and 16 $\mu\text{mol/L}$:[S20,S28,S30,S56,S62,S73,S87,S93] above 16
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52 $\mu\text{mol/L}$:[S3,S16,S60,S85] and above 15 $\mu\text{mol/L}$.[S2,S12,S15,S46,S49
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54 S67,S70,S72,S88,S94] Furthermore, five studies reported data based on sex-
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56 specific cut-off [S13,S25,S53,S61,S82] and one study according to different cut-offs
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3 by sex and age.[S40] Finally, the definition was unclear in 2 studies.[S78,S79]
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5 Pooled prevalence of 24% (95% CI: 19-30%, $I^2=89%$, figure 4A) was found across
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7 studies included. Non-significant heterogeneity was observed across different
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9 geographical areas, but higher pooled prevalences were found in middle-east/north-
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11 African and North-American studies, as compared with European and Asian cohorts.
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13 The fixed-effect model showed a slightly lower prevalence (22%, 95% CI: 20-24%,
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15 figure S7A).
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19 Overall, 30 studies reported about MTHFR C677T mutations, although several
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21 explored only CT or TT mutations. As for heterozygous mutation, a pooled
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23 prevalence of 44% (95% CI: 39-48%, $I^2=77%$, Figure 4B) was computed, without
24
25 significant heterogeneity between geographical groups; middle east and north-
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27 African cohorts contributes for the most of the heterogeneity. As for the homozygous
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29 C677T mutation, a pooled prevalence of 13% (95% CI: 10-17%, $I^2=79%$, figure 4C)
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31 was found, with non-significant heterogeneity between geographical locations
32
33 ($p=0.124$): European and Asian-based cohorts showed slightly higher pooled
34
35 prevalences (15% and 13%, respectively), while south-American and middle-
36
37 east/North African studies yielded lower estimates (9% and 10%, respectively).
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39 Fixed-effect models showed similar results for both CT and TT mutation (Figure
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41 S7B-C, respectively).
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47 In patients with RAO, a pooled prevalence of 27% (95% CI: 14-42%, $I^2=93%$, figure
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49 5A) was found for hyperhomocysteinemia across 6 studies. However, when
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51 performing a fixed-effect model, pooled prevalence drops to 17% (95% CI: 16-18%,
52
53 figure S8A) due to the higher weight of an Australian-based population study.[S17]
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55 As for the MTHFR C677T mutation, the prevalence of the heterozygous and
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57 homozygous mutation in patients with RAO was respectively 48% (95% CI: 39-56%)
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3 and 23% (95% CI 7-43%) across 2 studies (figure 5B-C respectively). Fixed-effect
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5 models for both MTHFR C677T heterozygous and homozygous mutation in patients
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7 with RAO are reported in figure S8B-C respectively.
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10 11 12 *PAI 4G mutation*

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14 Overall, six studies report about the association between RVO and PAI 4G mutation.
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16 As for the heterozygous 4G mutation, a pooled prevalence of 50% (95% CI: 43-57%,
17
18 $I^2=58%$, Figure 6A) was found across the study included, five of which were from
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20 Europe; a pooled prevalence of 25% (95% CI: 16-31%, $I^2=74%$, Figure 6B) was
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22 calculated for homozygous 4G mutation. Fixed-effect models produced comparable
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24 results (Figure S9A-B).
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28 Since only one study reported data on the prevalence of PAI 4G mutation in patients
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30 with RAO, pooled prevalence estimate for this thrombophilia was not computed.
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33 34 35 *APL Antibodies*

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37 Across 24 studies and a total of 2130 patients, a pooled prevalence of 8% (95% CI
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39 5-12%, $I^2=86%$; Figure 6C) was found for the presence of APL antibodies. Non-
40
41 significant heterogeneity was found between geographical groups ($p=0.051$), with
42
43 Asian and European-based cohorts showing lower prevalence (2% and 7%,
44
45 respectively). Similar results were observed with fixed-effect models (Figure S9C).
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47 In patients with RAO, across 4 studies, the pooled prevalence of APL antibodies was
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49 equal to 13% (95% CI: 4-26%, $I^2=77%$, figure S10A) when using a random-effect
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51 model, and resulted higher with a fixed-effect model (17%, 95% CI: 12-23%, figure
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53 S10B).
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Comparison in the Prevalence of Thrombophilias between RAO and RVO

Overall, similar prevalences for all thrombophilias were shown with random-effect models (Table S2). However, such findings were not confirmed by the fixed-effect models, for hyperhomocystenemia more prevalent in RVO patients (22% [95% CI: 20-24%] vs. 17% [95% CI: 16-18%], p for heterogeneity: <0.001), while APL antibodies resulted more associated with RAO (pooled prevalence 17% [95% CI: 12-23%] vs. 7% [95% CI: 6-8%], p for heterogeneity: <0.001).

Sensitivity Analysis

In a first sensitivity analysis, we compared pooled estimates in patients with CRVO and BRVO using a random-effect model (Figure 7A). No significant heterogeneity was observed between the two groups in terms of pooled prevalence for each thrombophilia explored. BRVO patients showed a non-significant trend of higher FVL mutation and PS deficiency prevalences, while in CRVO a non-significantly higher prevalence of APL antibodies was observed.

In a second sensitivity analysis, we analyzed pooled prevalences according to the overall risk of bias of the studies (low vs. medium or high risk of bias; Figure 7B). Pooled prevalences of APL antibodies resulted lower in studies with low risk of bias (5%, 95% CI: 3-8% vs. 14%, 95% CI: 7-23% of studies with a medium-high risk of bias, p for heterogeneity=0.018); on the other side, pooled estimate for hyperhomocystenemia was higher in low-risk of bias studies (29% 95% CI: 23-35% vs. 17%, 95% CI: 10-25%, p for heterogeneity=0.016). Non-significant trends were also observed for MTHFR C677 homozygous mutation and PC activity deficiency.

DISCUSSION

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3 In this systematic review and meta-analysis, we reported the pooled
4 prevalence of inherited and acquired thrombophilia in over 10.000 patients with
5 retinal vascular occlusion, across 95 studies. Overall, congenital AT-III, PC, and PS
6 activity deficiencies were the least represented inherited thrombophilia in patients
7 with RAO or RVO, while FVL and APL antibodies were the most represented.
8 Moreover, hyperhomocysteinemia, MTHFR C677T, and PAI 4G polymorphism were
9 also highly prevalent. Of note, the distribution of thrombophilias is very similar to that
10 observed in generally healthy populations (Table S3). The only significant
11 differences were observed for AT-III, PC, and PS deficiencies, which were found
12 more prevalent in subjects with RAO and RVO, and also the prevalence of APL
13 antibodies, slightly higher in patients with RAO. Nevertheless, such differences
14 observed might be due to heterogeneity in the definition of these thrombophilic
15 conditions in the original studies, both for the anticoagulant deficiencies and for the
16 presence of APL antibodies.
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35 The total prevalence of inherited thrombophilia in patients with retinal vascular
36 occlusion varies according to the site of the obstruction and geographical setting.
37 When stratifying our results according to geographical locations of the original
38 studies, we found a higher prevalence of FVL mutation in middle-east and north-
39 African cohorts as compared with both European and north-American studies as well
40 as compared with healthy populations from the same regions (13% vs. 0-2%,[15,16]
41 respectively). Similar findings were observed for F-II G20210A mutation, with higher
42 prevalence in patients with RVO from middle-east and north African countries
43 compared to similar general populations (4% vs. approximately 0.5%[17,18] for F-II
44 G20210A, respectively). While our findings may suggest a different degree of
45 association between retinal vascular occlusion and thrombophilic conditions across
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3 different ethnicities, we cannot exclude that these results may be driven by few
4 studies, which may have inflated the pooled prevalence in some groups. These
5 findings, however, should be taken carefully into account by treating physicians,
6 since they might have implications in the management of those ethnicities at higher
7 risk of presenting with thrombophilic conditions.
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12 To our knowledge, our study is the first to comprehensively evaluate the
13 burden of a broad spectrum of thrombophilic conditions in patients with retinal
14 vascular occlusion. The Association between thrombophilia and risk of both RAO
15 and RVO has long been speculated,[19] but with great uncertainty according to
16 existing evidence. Our findings showed that the overall prevalences of inherited and
17 acquired hemostatic disorder in patients with retinal vascular occlusion are broadly
18 similar to those observed in general, unaffected populations. Although younger
19 patients may present a higher prevalence of these thrombophilic
20 conditions,[S48,S51,S87] our study does not demonstrate a higher prevalence of
21 thrombophilia in the overall cohort of patients with RAO and RVO. The vast majority
22 of retinal vascular occlusion, in fact, affects elderly patients, in which traditional
23 cardiovascular risk factors may have a more important underlying role in the onset of
24 the disease. Most of the cohorts included in this analysis, indeed, were mainly
25 composed of elderly, and this may contribute to the overall prevalence of the
26 thrombophilias tested. A potential bias in the pooled prevalence observed, and
27 limited generalizability of the findings to younger patients cannot be excluded. In fact,
28 a greater prevalence of inherited or acquired thrombophilias could be present among
29 young adults with retinal vascular occlusion, since in this subgroup of patients the
30 contribution of other cardiovascular risk factors may be less important. Therefore, the
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3 results of this meta-analysis may not apply to all patients with retinal vascular
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5 occlusion, especially those with a younger age.
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8 These results are also consistent with previously published studies, that
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10 reported no association between retinal vascular occlusion and familiar history of
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12 VTE.[20] suggesting that inherited thrombophilias, which are strong and well-known
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14 causative factors for familiar susceptibility to VTE, are unlikely of primary importance
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16 in the pathogenesis of retinal vascular occlusion.
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19 As for the comparison between RAO and RVO, according to our primary
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21 analysis, we did not find any significant differences in terms of prevalence of any of
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23 the explored thrombophilic conditions. This may reinforce the hypothesis that RAO
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25 and RVO share similar risk factors, including cardiovascular and metabolic
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27 comorbidities (hypertension, dyslipidemia, diabetes) and hemostatic disorders. Also,
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29 retinal artery and retinal vein present close anatomical relation, since they share a
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31 common adventitia sheath, and this may influence the pathogenesis of vascular
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33 occlusions. Particularly, CRVO was associated with compression from the central
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35 retinal artery at the lamina cribrosa, where the two vessels are strongly bond. [21–
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37 23] However, most of the studies investigated RVO, and evidence regarding RAO is
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39 scarce and limited. Actual differences may exist, and further studies may be required
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41 to draw definitive conclusions. Similarly, our analysis did not show any significant
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43 differences between BRVO and CRVO, supporting the hypothesis that potential
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45 pathogenesis differences between these forms of RVO may be sustained by other
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47 factors.
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54 The key message and implication of our study may affect the diagnostic work-
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56 up of patients presenting with RAO or RVO. Based on our findings, there is no clear
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58 evidence to support a mass screening for thrombophilia in the overall cohort of
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3 patients with retinal vascular occlusion. Some patients may benefit from a thorough
4 and comprehensive haematological investigation: i) young patients at higher risk of
5 being carriers of thrombophilic conditions, especially in the absence of other risk
6 factors for retinal vascular occlusion; ii) individuals of selected geographical areas,
7 with a higher prevalence of certain thrombophilia; iii) individuals with a family or
8 personal history of venous or arterial thrombotic events, mainly when recurrent or
9 occurring at a younger age; iv) the presence of autoimmune diseases, known to be
10 associated with higher thrombotic risk. Although the identification of specific
11 categories at higher risk of thrombophilia was beyond the scope of this analysis, we
12 do support a careful screening on a case-by-case basis, considering the pre-test
13 probability, the cost-benefit ratio and the potential psychological implication for
14 patients. This approach is consistent with the actual guidance on the management of
15 patients with retinal vascular occlusion.[24]
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35 *Limitations*

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37 Our analysis has several limitations. First, our review protocol did not include
38 a screening of gray literature; however, given the research question, this is unlikely
39 to have significantly limited the comprehensiveness of our analysis. Second high
40 heterogeneity between studies (both in terms of the definition of thrombophilic
41 conditions and methods used for their assessment) may have influenced our results.
42 Particularly, a high grade of heterogeneity was found for the definition of AT-III, PC
43 and PS deficiencies, and the presence of APL antibodies, and this might have been
44 responsible for the higher prevalence observed. This definition bias has to be
45 considered in the careful interpretation of our findings. Also, studies exploring the
46 association of F-V and F-II mutations with retinal vascular occlusion barely reported
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3 data disaggregated according to the heterozygosity or homozygosity of the genetic
4 variants. A relatively low number of patients with homozygous mutations were
5 computed along with heterozygous carriers. Given that not all studies reported
6 clearly about homozygous individuals, we were not able to produce reliable
7 estimates for these prevalences. Nevertheless, we did not exclude these subjects
8 from the analysis, since this would have led to an underestimation of the actual
9 prevalence of the conditions. Second, most of the studies were based on small
10 cohorts, with a potentially high risk of selection bias, especially for those studies
11 which include only relatively young patients or adults referred for thrombophilia
12 screening by their ophthalmologists. Moreover, a substantial grade of heterogeneity
13 was also found across the studies included, for several thrombophilic conditions.
14 However, we performed our primary analysis with the use of random-effect models,
15 to mitigate heterogeneity and the potential impact of a single study on the overall
16 estimates. We also provide a sensitivity analysis according to the overall risk of bias,
17 to exclude the contribution of studies with a medium or high risk of bias. Finally,
18 relatively few studies investigated the association between thrombophilia and RAO,
19 thus limiting our ability to explore this association.
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45 CONCLUSIONS

46 In patients with retinal vascular occlusion, pooled prevalences of inherited and
47 acquired thrombophilias were estimated and resulted similar to what observed in the
48 general population. No significant differences were observed in the primary analysis
49 between RAO and RVO patients, nor according to the localization of RVO (i.e.
50 CRVO vs. BRVO). Our findings are consistent with current recommendations, which
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3 do not support thrombophilia screening in the diagnostic workup of all patients
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5 presenting with retinal vascular occlusion.
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14 **Addendum:** GFR conceived and designed the study, performed the search,
15 performed the statistical analysis, interpreted data and produced the first draft of the
16 manuscript; BC and MB performed studies selection, extracted the data, performed
17 the bias assessment, contributed to data interpretation and critically revised the
18 manuscript; GV contributed to data interpretation and to the drafting of the
19 manuscript; EP, RC, MP, SB and VR contributed to conception and design of the
20 study and critically revised the manuscript for important intellectual content. All gave
21 final approval and agree to the submission of the manuscript.
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58 **Conflict of interest disclosure:** The authors declare no competing financial interests.
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Supporting Information: See Supplementary Materials

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FIGURE LEGENDS**Figure 1: Pooled Prevalence for Factor V Leiden mutation in RVO and RAO**

Legend: Panel A: RVO, Random-Effects model; Panel B: RAO, Random-Effects model

Figure 2: Pooled Prevalence for Factor II G20210A mutation in RVO and RAO

Legend: Panel A: RVO, Random-Effects model; Panel B: RAO: Random-Effects model

Figure 3: Pooled Prevalence for Antithrombin III, Protein C and Protein S Activity Deficit in patients with RVO

Legend: Panel A: Antithrombin III deficit, Random-Effects model; Panel B: Protein C deficit, Random-Effects model; Panel C: Protein S deficit, Random-Effects model

Figure 4: Pooled Prevalence for Hyperhomocysteinemia, MTHFR C677T Heterozygous mutation and MTHFR C677T Homozygous mutation in patients with RVO

Legend: Panel A: Hyperhomocysteinemia, Random-Effects model; Panel B: MTHFR C677T Heterozygous, Random-Effects model; Panel C: MTHFR C677T Homozygous, Random-Effects model

Figure 5: Pooled Prevalence for Hyperhomocysteinemia, MTHFR C677T Heterozygous mutation and MTHFR C677T Homozygous mutation in patients with RAO

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3 **Legend:** Panel A: Hyperhomocysteinemia, Random-Effects model; Panel B: MTHFR
4 C677T Heterozygous, Random-Effects model; Panel C: MTHFR C677T
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7 Homozygous, Random-Effects model
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12 **Figure 6: Pooled Prevalence for PAI 4G Heterozygous mutation, PAI 4G**

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14 **Homozygous mutation and Antiphospholipid antibodies in patients with RVO**

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17 **Legend:** Panel A: PAI 4G Heterozygous, Random-Effects model; Panel B: PAI 4G
18 Homozygous, Random-Effects model; Panel C: Antiphospholipid antibodies,
19 Random-Effects model
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26 **Figure 7: Sensitivity analysis according to RVO localization and overall risk of**
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28 **bias**

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30 **Legend:** Panel A: CRVO vs. BRVO; Panel B: Low vs. High Risk of Bias
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Table 1: Main Characteristics of the Studies Included in the Systematic Review²¹

AUTHOR	Year	Type of Study	Geographical Location	N of pts	Type of RVO/RAO	Age (Mean \pm SD)	Males (n, %)	Thrombophilic conditions Reported
El-Asrar et al.[S1]	1998	Single Center Cohort	Middle East/North Africa	57	CRVO: 35 BRVO: 22	48 \pm 11.5	44 (77%)	APL antibodies, AT-III, PC, PS deficit
El-Asrar et al.[S2]	2002	Single Center Cohort	Middle East/North Africa	56	CRVO: 36 BRVO: 12	43.9 \pm 11.4 49.5 \pm 7.7	44 (79%)	HyperHcys
Adamczuk et al.[S3]	2002	Single Center Cohort	South America	37	CRVO: 37	49 ^a	17 (46%)	APL antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys, MTHFR, PAI
Albisinni et al.[S4]	1998	Single Center Cohort	Europe	36	RVO: 36	53	16 (44%)	F-V, F-II
Aras et al.[S5]	2001	Single Center Cohort	Middle East/North Africa	40	CRVO: 19 BRVO: 21	59 \pm 10	21 (53%)	F-V, F-II
Arsène et al.[S6]	2005	Single Center Cohort	Europe	234	CRVO: 153 BRVO: 81	62 \pm 14	149 (64%)	F-V, F-II, AT-III, PC
Ates et al.[S7]	2006	Single Center Cohort	Middle East/North Africa	54	CRVO: 27 BRVO: 27	22-86	-	AT-III, PC, PS
Biancardi et al.[S8]	2007	Single Center Cohort	South America	55	RVO: 55	17-83	23 (42%)	F-V, F-II, MTHFR
Birinci et al.[S9]	2003	Single Center Cohort	Middle East/North Africa	24	CRVO: 24	59.0 \pm 3.5	-	APL Antibodies
Bombeli et al.[S10]	2002	Single Center Cohort	Europe	68	RVO: 68	51.6	39 (57%)	F-V, F-II, AT-III, PC, PS
Boyd et al.[S11]	2001	Single Center Cohort	Europe	66	CRVO: 66	60.3 \pm 16.2	-	F-II, MTHFR
Brown et al.[S12]	2002	Single Center Cohort	North America	20	RVO: 20	69.1 \pm 10.7	12 (60%)	HyperHcys
Bucciarelli et al.[S13]	2017	Single Center Cohort	Europe	313	RVO: 313	54 [41-63]	147 (47%)	F-V, F-II, HyperHcys
Cahill et al.[S14]	2001	Single Center Cohort	Europe	61	RVO: 61 RAO: 26	-	-	MTHFR
Chapin et al.[S15]	2015	Two Centers Cohort	South America	37	RVO: 20	51	7 (35%)	APL antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys
Cho et al.[S16]	2019	Single Center Cohort	Asia	1928	CRVO: 417 BRVO: 1511	61.2 \pm 16.7 62.0 \pm 13.1	217 (52%) 680 (45%)	HyperHcys
Chua et al.[S17]	2006	Population-based Cohort	Oceania	3409	RAO: 3409	66.7	1463 (43%)	HyperHcys
Ciardella et al.[S18]	1998	Single Center Cohort	North America	30	RVO: 30	66 \pm 13	-	F-V
Coniglio et al.[S19]	1996	Single Center Cohort	Europe	48	RVO: 48	46.5	26 (54%)	APL antibodies

Cruciani et al.[S20]	2003	Single Center Cohort	Europe	29	RVO: 29	39.3	15 (52%)	APL Antibodies, F-V, F-II, PC, PS, HyperHcys, MTHFR
De Polo et al.[S21]	2015	Single Center Cohort	Europe	37	RVO: 37	74.5 ± 8.8	17 (46%)	F-V, F-II, MTHFR
Demirci et al.[S22]	1999	Single Center Cohort	Middle East/North Africa	50	CRVO: 25	46.7	8 (32%)	F-V
					BRVO: 25	53.0	9 (36%)	
Di Capua et al.[S23]	2010	Single Center Cohort	Europe	110	CRVO: 62	47 ± 15	29 (47%)	APL Antibodies, F-V, F-II, MTHFR.
					BRVO: 48	55 ± 9	22 (54%)	
Dodson et al.[S24]	2003	Single Center Cohort	North America	40	RVO: 40	66.1	21 (52%)	F-V, F-II, MTHFR
Dong et al.[S25]	2014	Single Center Cohort	Asia	36	CRVO: 36	60.6 ± 6.3	17 (47%)	HyperHcys, MTHFR.
Fernandez-Vega et al.[S26]	2019	Single Center Cohort	Europe	172	CRVO: 38	62.7 ± 13.2	19 (50%)	MTHFR
					BRVO: 134	63.0 ± 10.1	63 (47%)	
Ferrazzi et al.[S27]	2005	Single Center Cohort	Europe	69	RVO: 69	64.1 ± 14.6	40 (58%)	MTHFR
Gao et al.[S28]	2006	Single Center Cohort	Asia	64	CRVO: 64	59.5 ± 3.8	33 (52%)	HyperHcys
Gao et al.[S29]	2008	Single Center Cohort	Asia	64	CRVO: 64	59.5 ± 3.8	33 (52%)	MTHFR
Ghaznavi et al.[S30]	2016	Single Center Cohort	Middle East/North Africa	73	RVO: 73	52.7 ± 16.2	35 (48%)	HyperHcys
Giannaki et al.[S31]	2013	Single Center Cohort	Europe	51	RVO: 51	70	22 (43%)	F-V, F-II, MTHFR, PAI.
Giordano et al.[S32]	1998	Single Center Cohort	Europe	30	CRVO: 18	48 ± 4.3	14 (47%)	APL Antibodies
					BRVO: 10	53 ± 2.1		
Glacet-Bernard et al.[S33]	1994	Single Center Cohort	Europe	75	CRVO: 44	57	28 (64%)	APL Antibodies
					BRVO: 24	67	12 (50%)	
Glueck et al.[S34]	2012	Single Center Cohort	North America	164	CRVO: 132	57 ± 14	55 (42%)	APL Antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys, MTHFR, PAI
					CRAO: 32	52 ± 16	13 (41%)	
Gori et al.[S35]	2004	Single Center Cohort	Europe	112	RVO: 112	60 ^a	52 (46%)	PAI
Gottlieb et al.[S36]	1998	Single Center Cohort	North America	21	CRVO: 21	42.1	15 (71%)	F-V
Graham et al.[S37]	1996	Single Center Cohort	Oceania	23	CRVO: 23	60.2 ± 16.2	-	F-V
Greiner et al.[S38]	1999	Single Center Cohort	Europe	116	CRVO: 48	24-91	65 (56%)	F-V
					BRVO: 33			
					CRAO: 21			
					BRAO: 14			
Gumus et al.[S39]	2006	Single Center Cohort	Middle East/North Africa	82	CRVO: 26	57.7 ± 9.4	36 (44%)	F-V, F-II.
					BRVO: 56			
Hansen et al.[S40]	2000	Single Center Cohort	Europe	54	RVO: 54	56 ^a	32 (57%)	APL Antibodies, F-V, PC, PS, HyperHcys

Hvarfner et al.[S41]	2003	Single Center Cohort	Europe	166	CRVO: 166	64 ± 15	86 (52%)	F-V
Incorvaia et al.[S42]	2001	Single Center Cohort	Europe	100	CRVO: 50	70.5 ± 8.7	27 (54%)	F-II
					BRVO: 50	68.7 ± 7.8	23 (46%)	
Johnson et al.[S43]	2001	Single Center Cohort	North America	44	CRVO: 44	66.6	30 (68%)	F-V
Kadayifcilar et al.[S44]	2001	Single Center Cohort	Middle East/North Africa	54	CRVO: 22	59.7 ± 12	30 (55%)	APL Antibodies, AT-III, PC
					BRVO: 32			
Kalayci et al.[S45]	1999	Single Center Cohort	Middle East/North Africa	52	CRVO: 25	64 ± 15	15 (60%)	F-V, F-II
					BRVO: 27	57 ± 13	16 (59%)	
Koylu et al.[S46]	2017	Single Center Cohort	Middle East/North Africa	49	RVO: 49	52.1 ± 17.4	39 (80%)	F-V; F-II, HyperHcys, MTHFR
Kuhli et al.[S47]	2002	Single Center Cohort	Europe	142	RVO: 142	52.1	74 (52%)	F-V
Kuhli-Hattenbach et al.[S48]	2016	Two centers Cohort	Europe	25	RAO: 25	42.8 ± 10.8	7 (28%)	APL Antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys
Lahey et al.[S49]	2002	Single Center Cohort	North America	55	CRVO: 55	44	25 (45%)	APL Antibodies, F-V, AT-III, PC, PS, HyperHcys
Larsson et al.[S50]	1999	Single Center Cohort	Europe	129	CRVO: 129	59	74 (57%)	F-II
Larsson et al.[S51]	1999	Single Center Cohort	Europe	37	CRVO: 37	40.5	21 (57%)	AT-III, PC
Larsson et al.[S52]	2000	Single Center Cohort	Europe	116	CRVO: 116	60.1	67 (58%)	MTHFR
Lattanzio et al.[S53]	2006	Single Center Cohort	Europe	58	CRVO: 58	39.8 ± 9.6	38 (66%)	HyperHcys
Linna et al.[S54]	1996	Single Center Cohort	Europe	46	CRVO: 28	40.5	24 (52%)	F-V
					BRVO: 18			
Loewenstein et al.[S55]	1999	Single Center Cohort	Middle East/North Africa	59	RVO: 59	61.4 ± 12.9	29 (49%)	F-V, AT-III
Manaviat et al.[S56]	2006	Single Center Cohort	Middle East/North Africa	21	RVO: 21	52.5 ± 12.7	14 (67%)	HyperHcys
Marcucci et al.[S57]	2001	Single Center Cohort	Europe	100	RVO: 100	59 ^a	54 (54%)	AT-III, PC, PS
Marcucci et al.[S58]	2003	Single Center Cohort	Europe	55	CRVO: 26	57 ^a	24 (44%)	AT-III, PC, PS
					BRVO: 29			
Marcucci et al.[S59]	2007	Single Center Cohort	Europe	41	CRAO: 25	69.6 ± 12.8	20 (49%)	APL, F-V, F-II, AT-III, PC, PS, HyperHcys
					BRAO: 16			
Martinez et al.[S60]	2014	Single Center Cohort	Europe	100	CRVO: 26	60.0 ± 13.5	18 (69%)	F-V, F-II, AT-III, PC, PS, HyperHcys
					BRVO: 74	59.0 ± 12.4	40 (54%)	
Minniti et al.[S61]	2014	Single Center Cohort	Europe	91	RVO: 91	57 ± 12	51 (56%)	HyperHcys, MTHFR
Moghimi et al.[S62]	2008	Single Center Cohort	Middle East/North Africa	54	CRVO: 54	59.8 ± 12.7	32 (59%)	HyperHcys

Mrad et al.[S63]	2014	Single Center Cohort	Middle East/North Africa	88	CRVO: 20 BRVO: 68	51.5 ± 18.5 49.5 ± 17.7	62 (70%)	F-V, F-II
Mrad et al.[S64]	2014	Single Center Cohort	Middle East/North Africa	72	RVO: 72	48.5 ± 17.4	50 (69%)	MTHFR
Nagy et al.[S65]	2008	Single Center Cohort	Europe	28	RAO: 28	61.1 ± 12.3	16 (57%)	F-V, F-II, AT-III, PC, PS
Nalcaci et al.[S66]	2019	Single Center Cohort	Middle East/North Africa	40	CRVO: 18 BRVO: 22	41.6 ± 10.0	22 (55%)	F-V, F-II, MTHFR
Napal et al.[S67]	2016	Single Center Cohort	Europe	170	RVO: 170	68 ± 11	93 (55%)	APL Antibodies, F-V, F-II, AT-III, PC, PS, HyperHcys
Nema et al.[S68]	2018	Single Center Cohort	Asia	50	RVO: 50	54.6 ± 13.9	18 (36%)	F-V, MTHFR
Paccalin et al.[S69]	2006	Single Center Cohort	Europe	68	RVO: 68	32-90	30 (44%)	APL Antibodies
Palmowski-Wolfe et al.[S70]	2005	Single Center Cohort	Europe	253	CRVO: 93 BRVO: 70 CRAO: 41 BRAO: 49	-	-	HyperHcys
Palmowski-Wolfe et al.[S71]	2007	Single Center Cohort	Europe	254	CRVO: 93 BRVO: 67 CRAO: 41 BRAO: 53	66.5 ± 11.2	-	APL Antibodies
Pianka et al.[S72]	2000	Single Center Cohort	Middle East/North Africa	21	CRVO: 21	58.6 ± 2.7	-	HyperHcys
Ponto et al.[S73]	2019	Single Center Cohort	Europe	92	CRVO: 61 BRVO: 31	64 63	34 (56%) 17 (55%)	APL Antibodies, F-V, F-II, AT-III, HyperHcys
Rehak et al.[S74]	2010	Single Center Cohort	Europe	121	CRVO: 79 BRVO: 42	63.5	57 (47%)	F-V, AT-III, PC
Risse et al.[S75]	2014	Single Center Cohort	Europe	139	CRVO: 88 BRVO: 51	67.3 ± 12.9 65.9 ± 11.7	50 (57%) 26 (51%)	APL Antibodies, F-V, F-II, AT-III, PC, PS, MTHFR
Russo et al.[S76]	2015	Single Center Cohort	Europe	113	RVO: 113	18-77	57 (50%)	F-V, F-II, MTHFR, PAI
Salomon et al.[S77]	1998	Single Center Cohort	Middle East/North Africa	102	RVO: 102	59.9 ± 16.1 64.0 ± 12.9	58 (57%)	F-V, F-II, MTHFR
Sartori et al.[S78]	2013	Single Center Cohort	Europe	132	RVO: 132	53.6 ± 16.7	77 (58%)	APL Antibodies, F-V, F-II, PC, PS, HyperHcys.
Schockman et al.[S79]	2015	Single Center Cohort	North America	191	CRVO: 172 BRVO: 19	57 ± 15	75 (39%)	APL Antibodies, F-V, F-II, HyperHcys
Scott et al.[S80]	2001	Single Center Cohort	Europe	45	CRVO: 24 BRVO: 21	38.7 ^a 46.8 ^a	11 (46%) 8 (38%)	APL Antibodies, F-V
Sinawat et al.[S81]	2017	Single Center Cohort	Asia	100	CRVO: 70	36.5 ± 8.7	32 (46%)	APL Antibodies, PC, PS.

					BRVO: 30	43 ± 8.2	17 (57%)	
Sodi et al.[S82]	2011	Single Center Cohort	Europe	103	CRVO: 103	67.4 ± 7.7	54 (52%)	APL Antibodies, F-V, F-II, HyperHcys, MTHFR
Sofi et al.[S83]	2008	Single Center Cohort	Europe	127	BRVO: 127	65 ^a	53 (42%)	MTHFR
Soltanpour et al.[S84]	2013	Single Center Cohort	Middle East/North Africa	73	RVO: 73	52.7 ± 16.2	35 (48%)	MTHFR
Sottilotta et al.[S85]	2010	Single Center Cohort	Europe	105	RVO: 105	-	46 (43%)	F-V, F-II, AT-III, PC, PS, HyperHcys, MTHFR
Tekeli et al.[S86]	1999	Single Center Cohort	Middle East/North Africa	45	CRVO: 31 BRVO: 14	56 ± 2	25 (56%)	AT-III, PC, PS
Vieira et al.[S87]	2019	Single Center Cohort	Europe	60	CRVO: 35 BRVO: 25	64.0 ± 13.5	35 (58%)	APL, F-V, F-II, HyperHcys, MTHFR, PAI
Vine et al.[S88]	2000	Single Center Cohort	North America	74	CRVO: 74	69.8	29 (39%)	HyperHcys
Weger et al.[S89]	2003	Single Center Cohort	Europe	136	RAO: 136	69.8 ± 10.1	78 (57%)	F-V, F-II
Weger et al.[S90]	2005	Single Center Cohort	Europe	294	BRVO: 294	67.0 ± 11.4	128 (44%)	F-V, F-II
Weger et al.[S91]	2002	Single Center Cohort	Europe	105	RAO: 105	69.1 ± 10.6	59 (56%)	HyperHcys, MTHFR
Weger et al.[S92]	2002	Single Center Cohort	Europe	84	BRVO: 84	68.1 ± 11.1	37 (44%)	MTHFR
Weger et al.[S93]	2002	Single Center Cohort	Europe	78	CRVO: 78	68.7 ± 11.4	33 (42%)	HyperHcys, MTHFR.
Yildirim et al.[S94]	2004	Single Center Cohort	Middle East/North Africa	33	RVO: 33	61	15 (45%)	HyperHcys
Yioti et al.[S95]	2013	Single Center Cohort	Europe	48	RVO: 48	64 [53-70]	34 (71%)	F-V, F-II

Legend: AT-III: Antithrombin-III Activity Deficiency, F-V: Factor V Leiden Mutation; F-II: Factor II G20210A Mutation, HyperHcys: Hyperhomocysteinemia; MTHFR: MTHFR C677T Mutation; PAI: PAI 4G Mutation; PC: Protein C Activity Deficiency; PS: Protein S Activity Deficiency

Figure 1

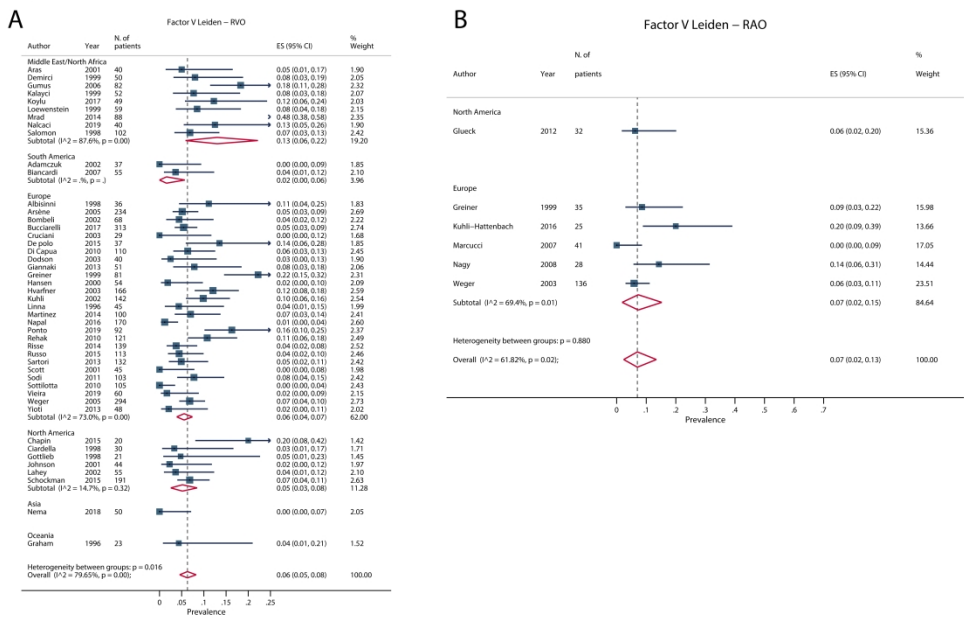


Figure 1: Pooled Prevalence for Factor V Leiden mutation in RVO and RAO
Legend: Panel A: RVO, Random-Effects model; Panel B: RAO, Random-Effects model

Figure 2

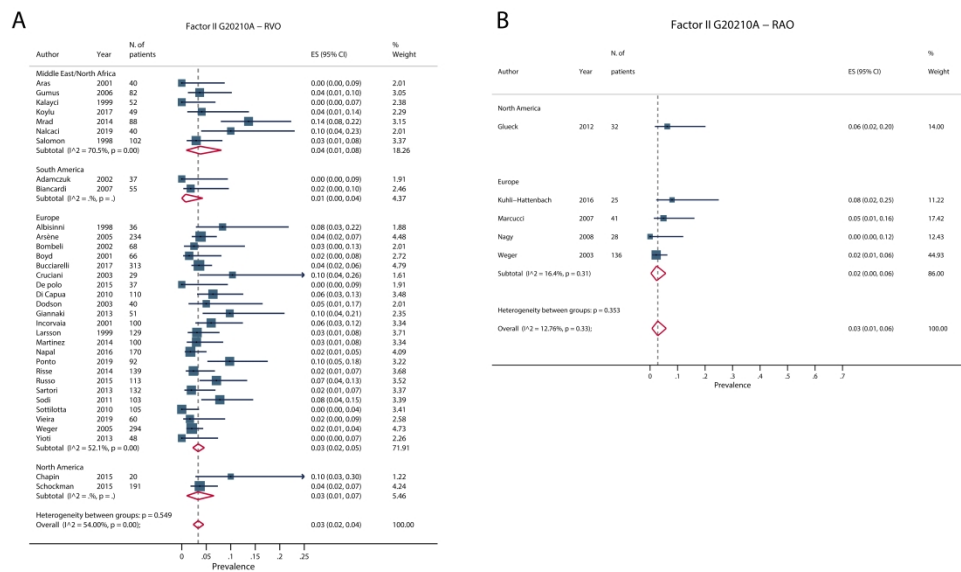


Figure 2: Pooled Prevalence for Factor II G20210A mutation in RVO and RAO
 Legend: Panel A: RVO, Random-Effects model; Panel B: RAO: Random-Effects model

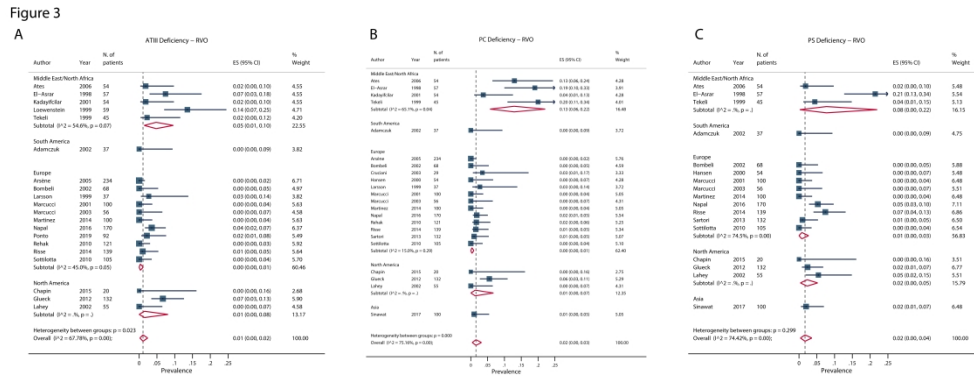


Figure 3: Pooled Prevalence for Antithrombin III, Protein C and Protein S Activity Deficit in patients with RVO
 Legend: Panel A: Antithrombin III deficit, Random-Effects model; Panel B: Protein C deficit, Random-Effects model; Panel C: Protein S deficit, Random-Effects model

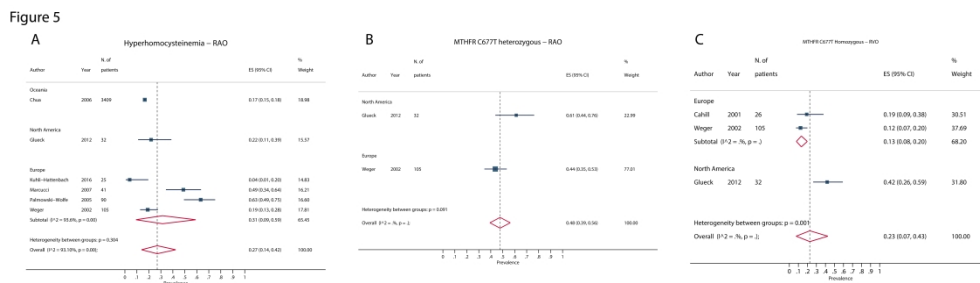


Figure 5: Pooled Prevalence for Hyperhomocysteinemia, MTHFR C677T Heterozygous mutation and MTHFR C677T Homozygous mutation in patients with RAO
 Legend: Panel A: Hyperhomocysteinemia, Random-Effects model; Panel B: MTHFR C677T Heterozygous, Random-Effects model; Panel C: MTHFR C677T Homozygous, Random-Effects model

Figure 6

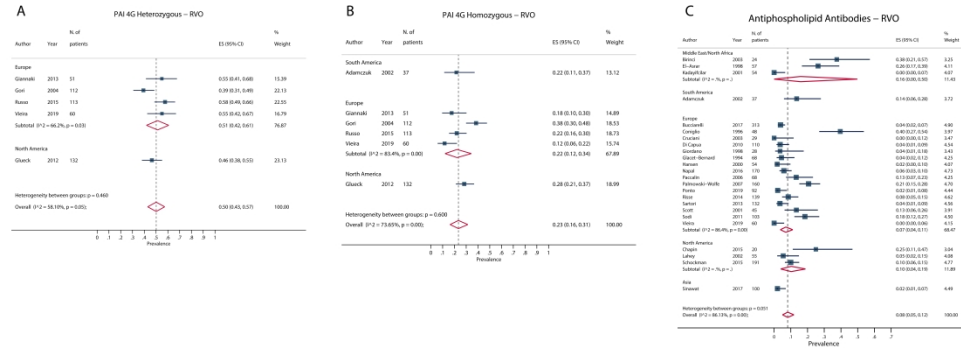


Figure 6: Pooled Prevalence for PAI 4G Heterozygous mutation, PAI 4G Homozygous mutation and Antiphospholipid antibodies in patients with RVO
 Legend: Panel A: PAI 4G Heterozygous, Random-Effects model; Panel B: PAI 4G Homozygous, Random-Effects model; Panel C: Antiphospholipid antibodies, Random-Effects model

Figure 7

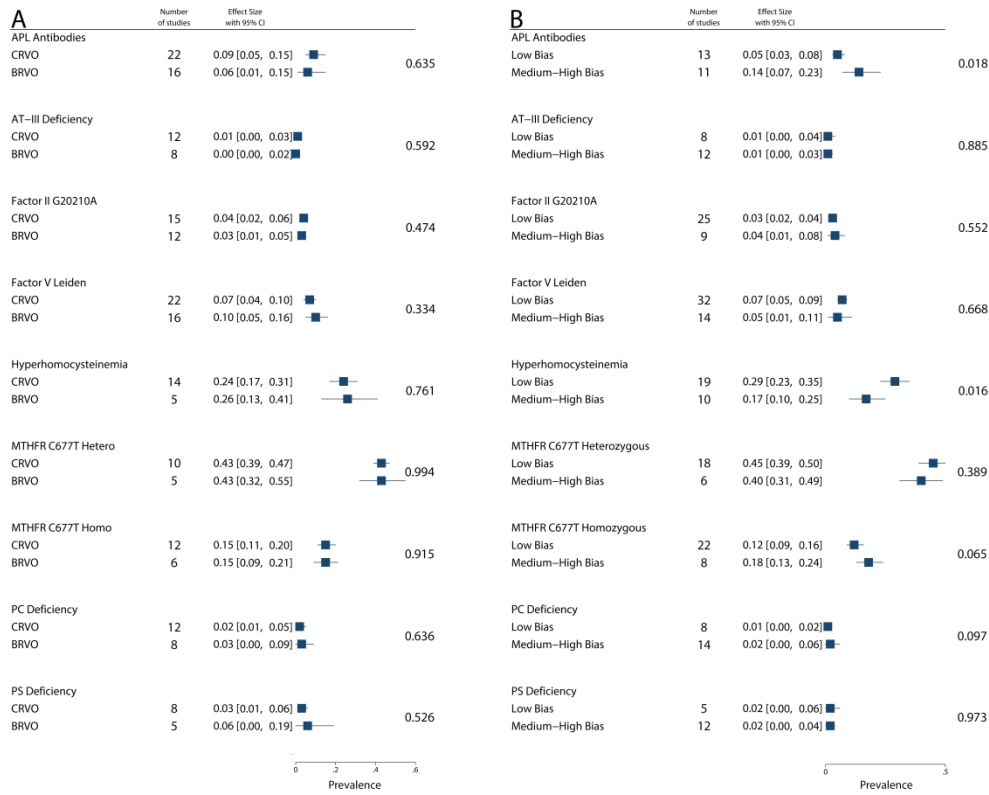


Figure 7: Sensitivity analysis according to RVO localization and overall risk of bias
 Legend: Panel A: CRVO vs. BRVO; Panel B: Low vs. High Risk of Bias



PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	3-4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	3-4
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	5-8
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	5-8
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	5-8
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	5-8
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	5-8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	5-8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	5-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	5-8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	5-8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	5-8



PRISMA 2009 Checklist

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Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	5-8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	5-8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	8
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	8
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	8
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	8-14
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	8-14
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	8
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	8-14
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	14-17
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	14-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	14-17
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	18

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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List of Supplementary References

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Full Search Strategy

PUBMED

("Retinal Vein Occlusion"[Mesh] OR "Retinal Vein Occlusion" OR "Retina vein occlusion" OR RVO OR BRVO OR CRVO OR "Retinal Vein Thrombosis" OR "Retina Vein Thrombosis" OR "Retinal Artery Occlusion" OR "Retina Artery Occlusion" OR RAO OR CRAO OR BRAO OR "Retinal Artery Thrombosis" OR "Retina Artery Thrombosis" OR "Retinal Artery Occlusion"[Mesh]) AND (Thrombophilia OR "Thrombophilia"[Mesh] OR Thrombophili* OR hypercoagul* OR prothrombot* OR "Factor V" OR "blood clotting factor 5" OR "Factor V"[Mesh] OR Leiden OR "activated Protein C Resistance" OR "Activated Protein C Resistance"[Mesh] OR "Protein C" OR "Protein C"[Mesh] OR "Protein S" OR "Protein S"[Mesh] OR "Protein S Deficiency"[Mesh] OR "Protein C Deficiency"[Mesh] OR prothrombin* OR "Prothrombin"[Mesh] OR "Factor II" OR "G20210A" OR MTHFR OR Hyperhomocysteinemia OR Homocystein* OR Antithrombin OR ATIII OR "Antithrombin III Deficiency"[Mesh] OR Plasminogen OR PAI OR "Antiphospholipid Syndrome"[Mesh] OR "Lupus anticoagulant" OR LAC OR Antiphospholipid OR "anti-cardiolipin" OR "cardiolipin antibody" OR "anti-apolipoprotein" OR "glycoprotein I" OR "glycoprotein 1")

EMBASE

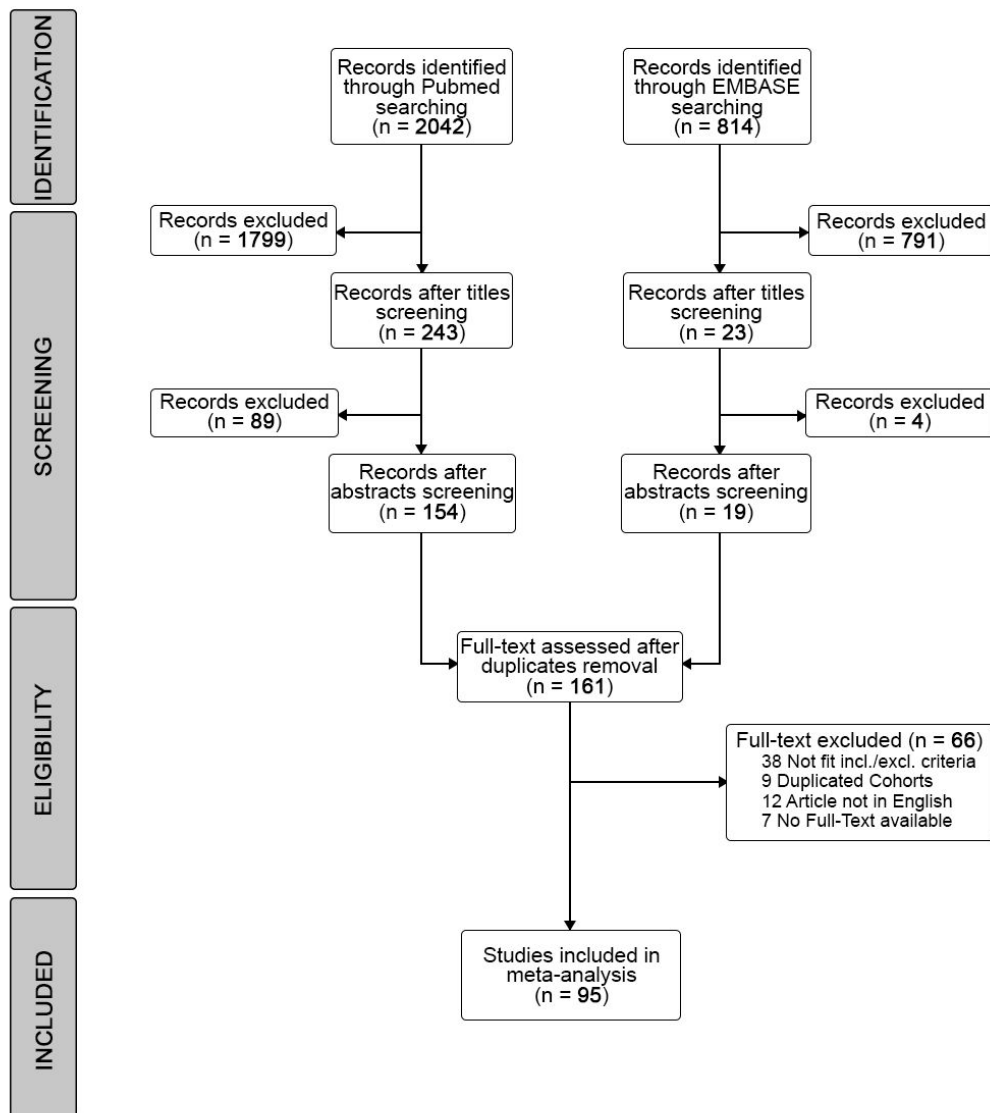
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2. 'thrombophilia'/exp OR 'thrombophili*' OR 'hypercoagul*' OR 'prothrombot*' OR 'factor v' OR 'blood clotting factor 5'/exp OR 'leiden' OR 'activated protein c resistance'/exp OR 'protein c'/exp OR 'protein s'/exp OR 'prothrombin'/exp OR 'factor ii' OR 'g20210a' OR 'mthfr' OR 'hyperhomocysteinemia'/exp OR 'homocystein*' OR 'antithrombin'/exp OR 'atiii' OR 'antithrombin deficiency'/exp OR 'plasminogen' OR 'pai' OR 'antiphospholipid syndrome'/exp OR 'lupus anticoagulant'/exp OR 'lac' OR 'antiphospholipid' OR 'anti-cardiolipin' OR 'cardiolipin antibody'/exp OR 'anti-apolipoprotein' OR 'glycoprotein i' OR 'glycoprotein 1'

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4. #3 AND [embase]/lim NOT ([embase]/lim AND [medline]/lim)

Figure S1: PRISMA Flow-Chart of the screening and selection phases.

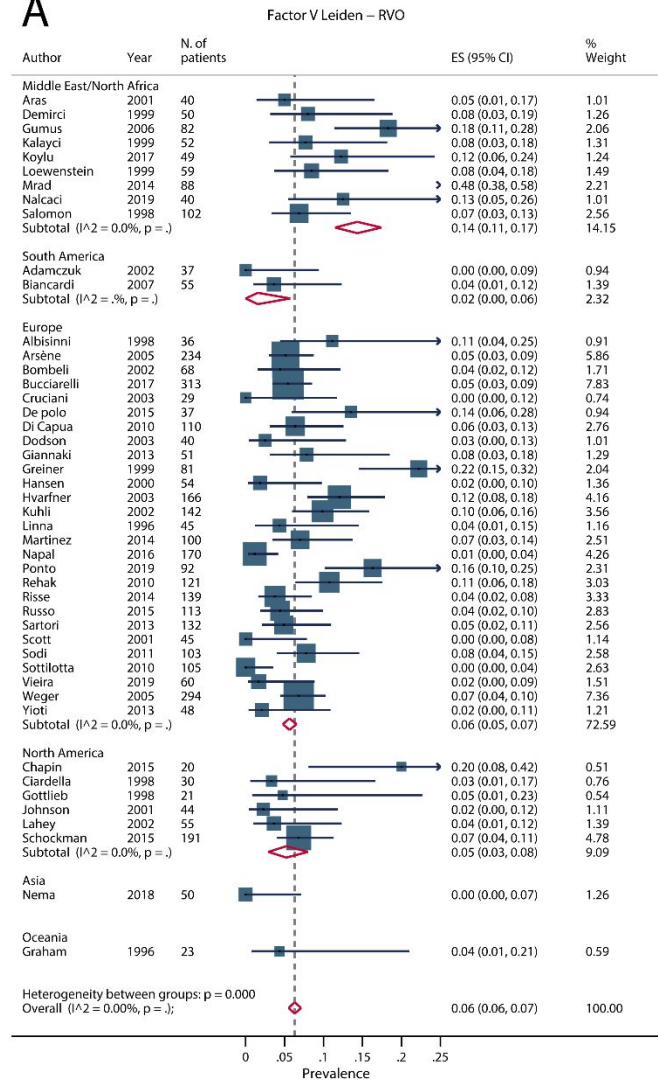


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Figure S2: Pooled Prevalence for Factor V Leiden mutation in RVO and RAO (Legend: i) Panel A: RVO, Fixed-Effects model; ii) Panel B: RAO: Fixed-Effects model)

For Peer Review

A



B

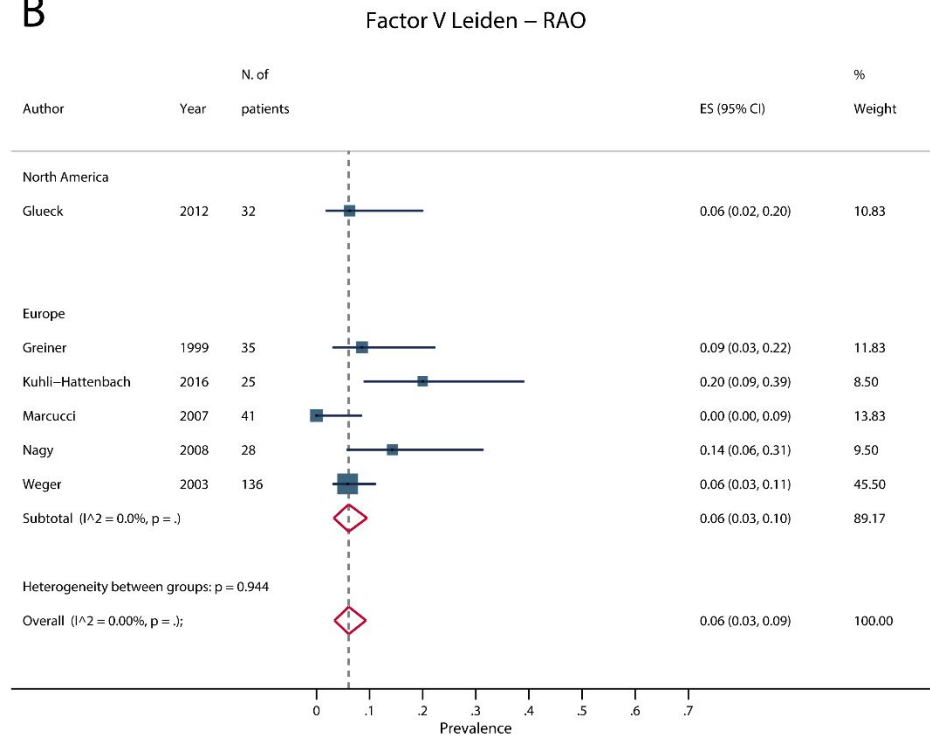


Figure S3: Pooled Prevalence for Factor II G20210A mutation in RVO and RAO (Legend: i) Panel A: RVO, Fixed-Effects model; ii) Panel B: RAO: Fixed-Effects model)

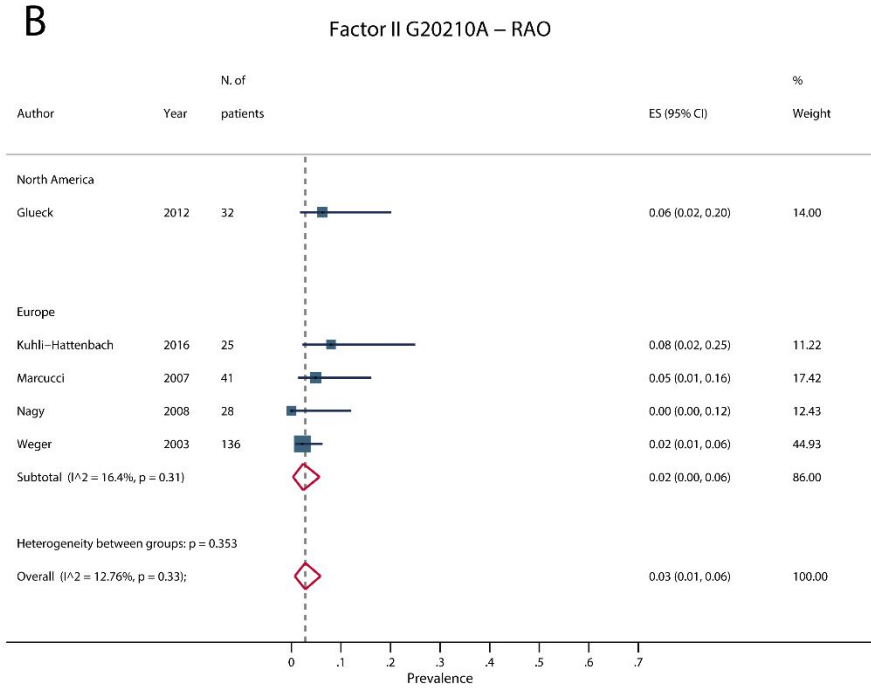
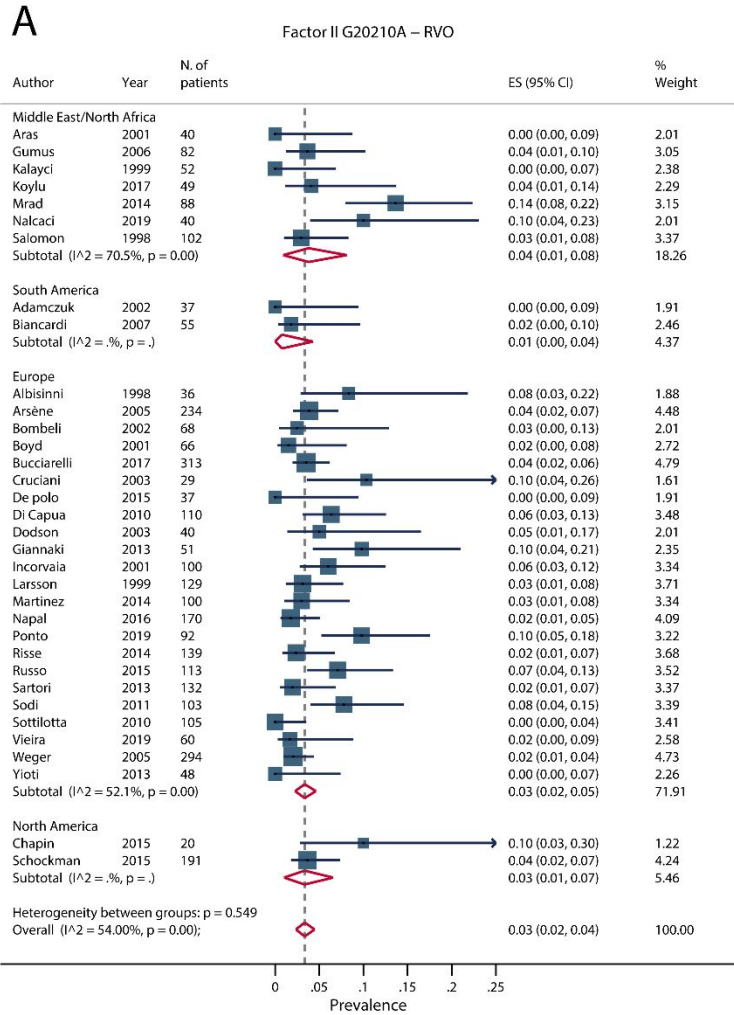


Figure S4: Pooled Prevalence for Antithrombin III, Protein C and Protein S Activity Deficit in patients with RVO – Fixed-Effects models (Legend: i)

Panel A: Antithrombin III deficit; ii) Panel B: Protein C deficit; iii) Panel C: Protein S deficit)

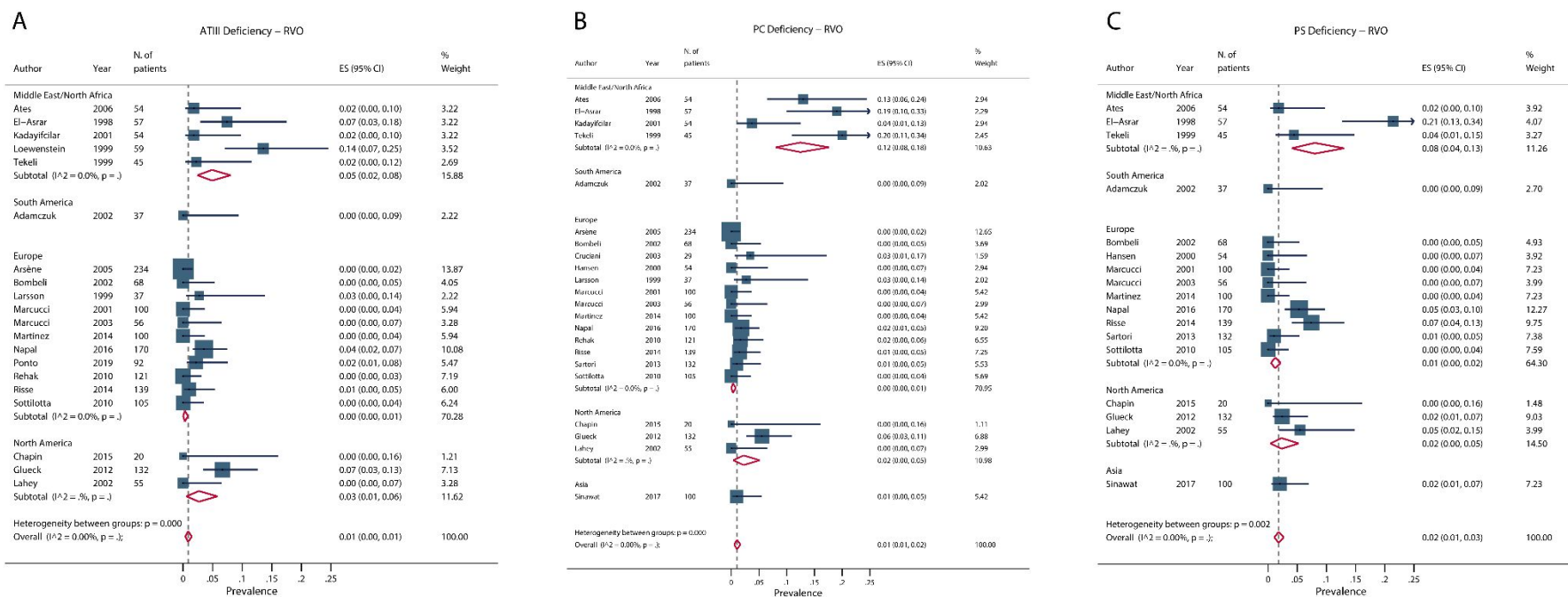
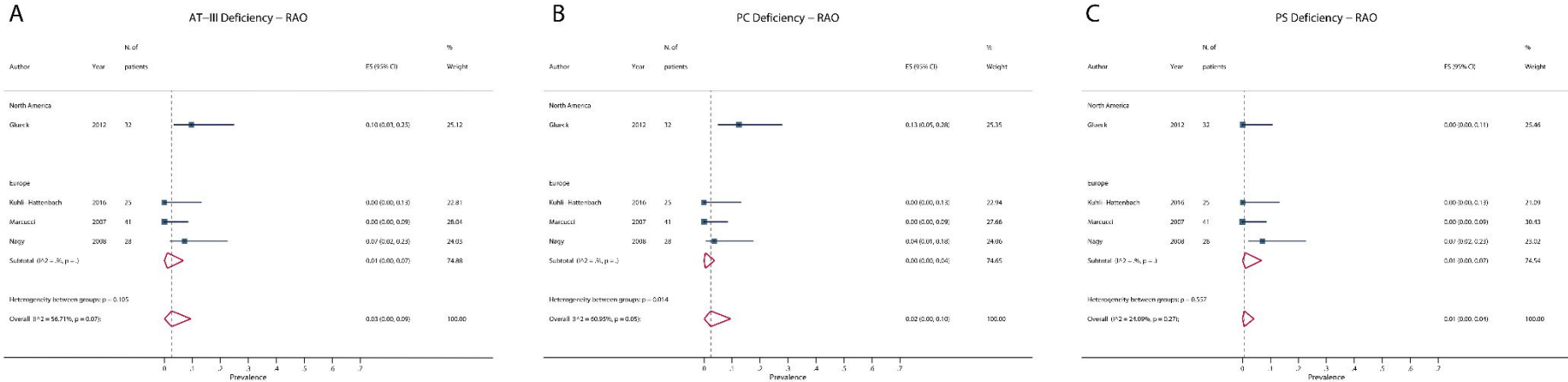


Figure S5: Pooled Prevalence for Antithrombin III, Protein C and Protein S Activity Deficit in patients with RAO – Fixed-Effects models (Legend: i)

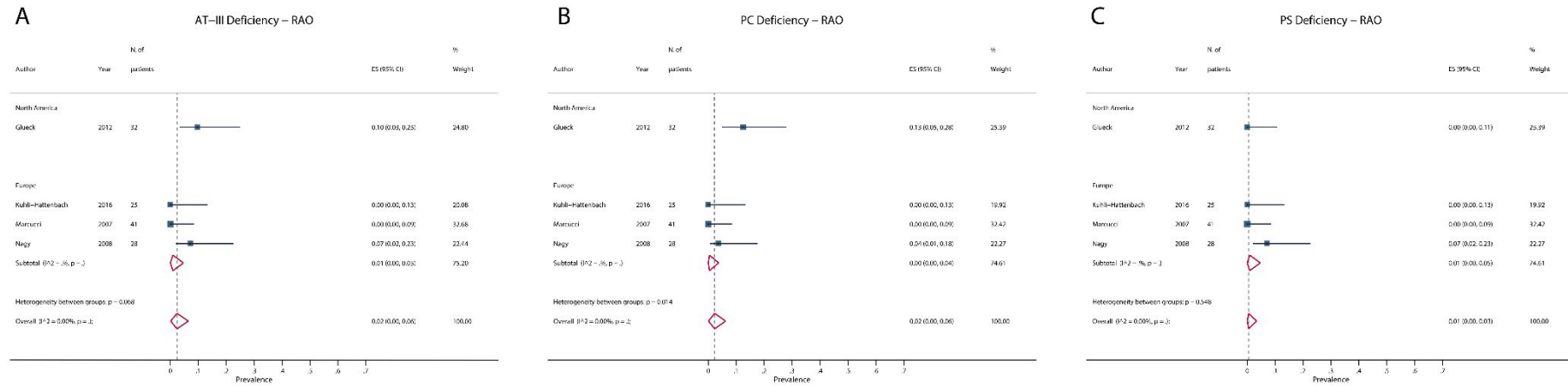
Panel A: Antithrombin III deficit ii) Panel B: Protein C deficit; iii) Panel C: Protein S deficit)



Review

Figure S6: Pooled Prevalence for Antithrombin III, Protein C and Protein S Activity Deficit in patients with RAO – Fixed-Effects models (Legend: i)

Panel A: Antithrombin III deficit; ii) Panel B: Protein C deficit; iii) Panel C: Protein S deficit)



Review

Figure S7: Pooled Prevalence for Hyperhomocysteinemia, MTHFR C677T Heterozygous mutation and MTHFR C677T Homozygous mutation in patients with RVO – Fixed-Effects models (Legend: i) Panel A: Hyperhomocysteinemia; ii) Panel B: MTHFR C677T Heterozygous; iii) Panel C: MTHFR C677T Homozygous

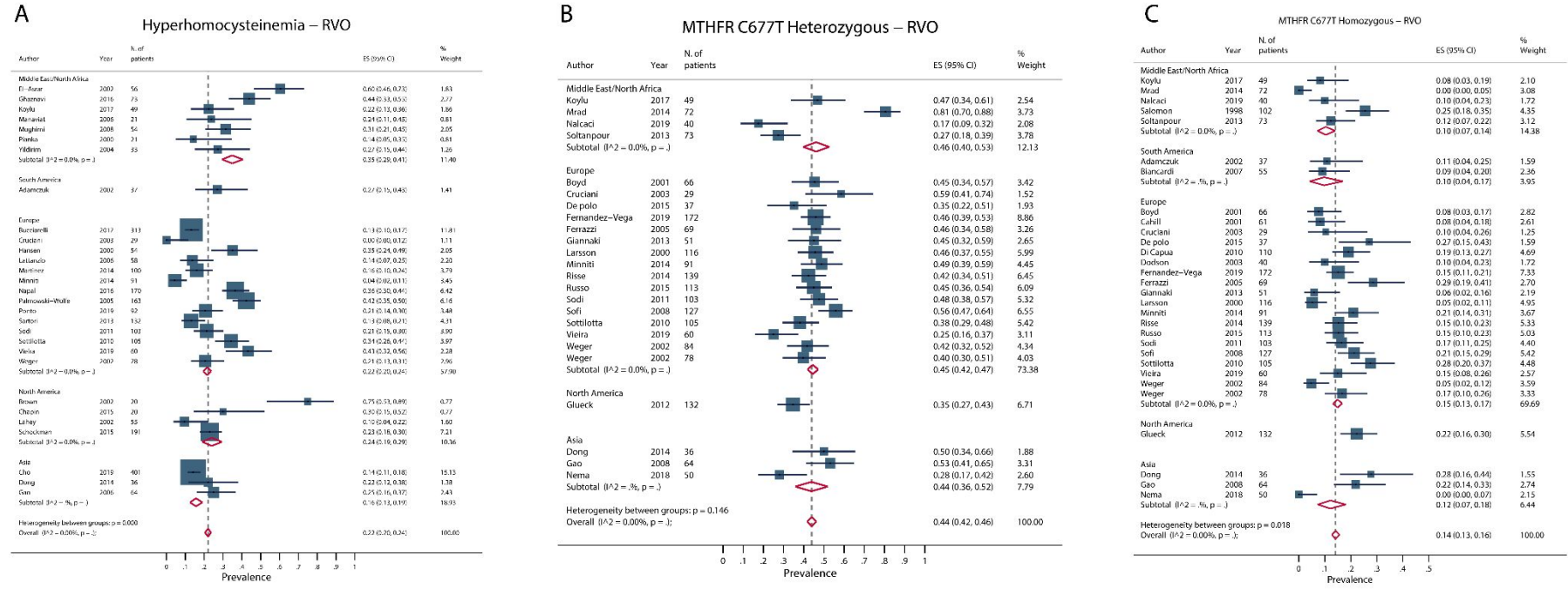


Figure S8: Pooled Prevalence for Hyperhomocysteinemia, MTHFR C677T Heterozygous mutation and MTHFR C677T Homozygous mutation in patients with RAO – Fixed-Effects models (Legend: i) Panel A: Hyperhomocysteinemia; ii) Panel B: MTHFR C677T Heterozygous; iii) Panel C: MTHFR C677T Homozygous

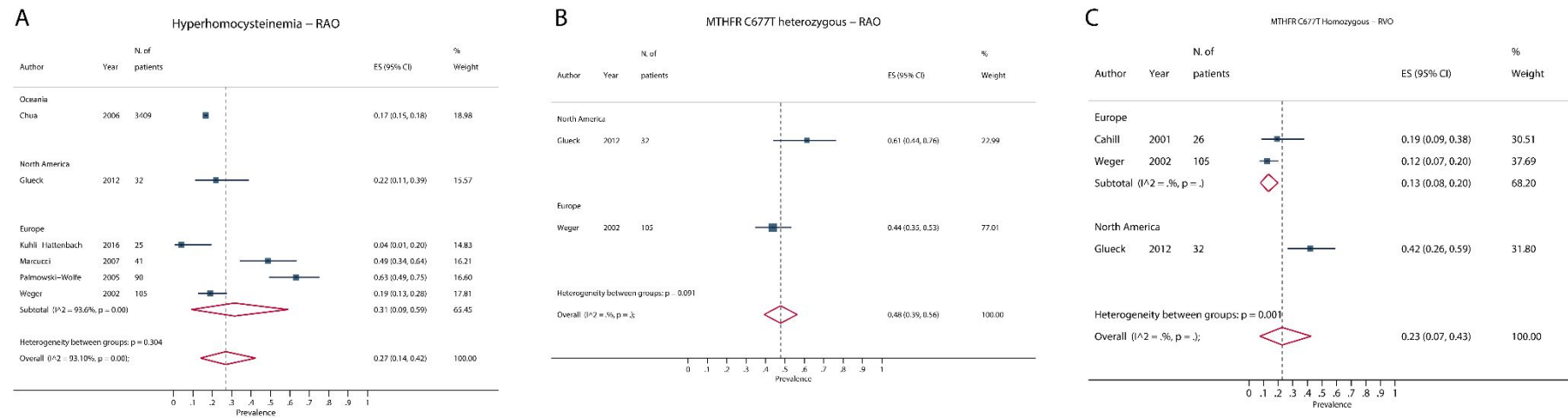


Figure S9: Pooled Prevalence for PAI 4G Heterozygous mutation, PAI 4G Homozygous mutation and Antiphospholipid antibodies in patients with RVO – Fixed-Effects models (Legend: i) Panel A: PAI 4G Heterozygous; ii) Panel B: PAI 4G Homozygous; iii) Panel C: Antiphospholipid antibodies

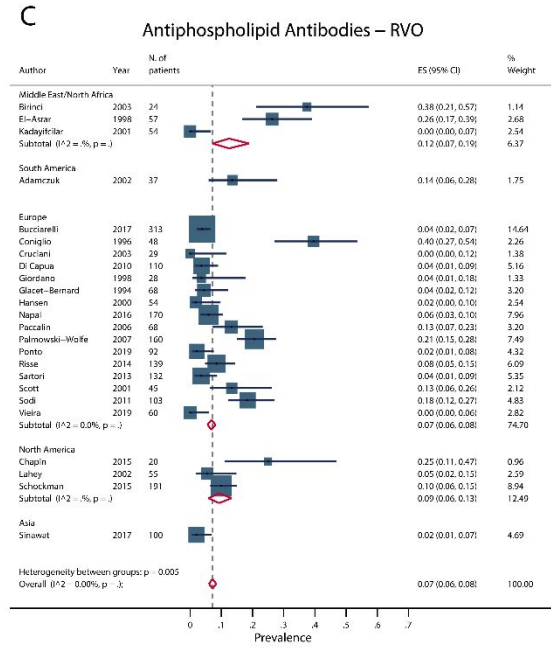
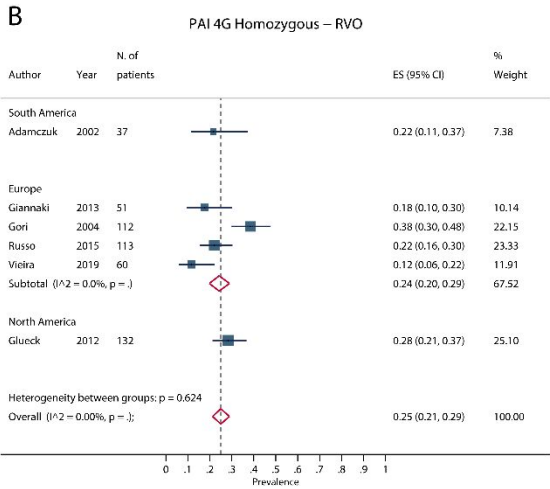
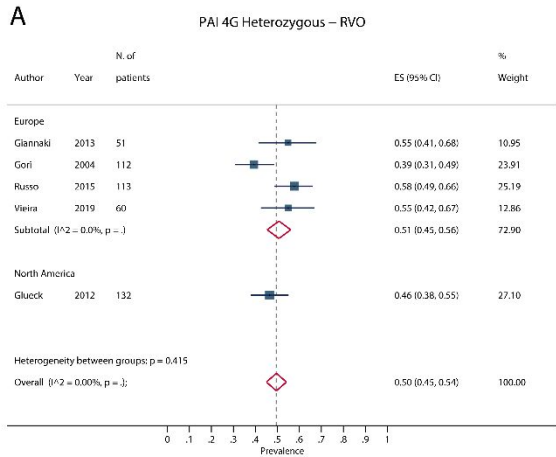


Figure S10: Pooled Prevalence for Antiphospholipid antibodies in patients with RAO

Legend: i) Panel A: Random-Effects model ii) Panel B: Fixed-Effects model

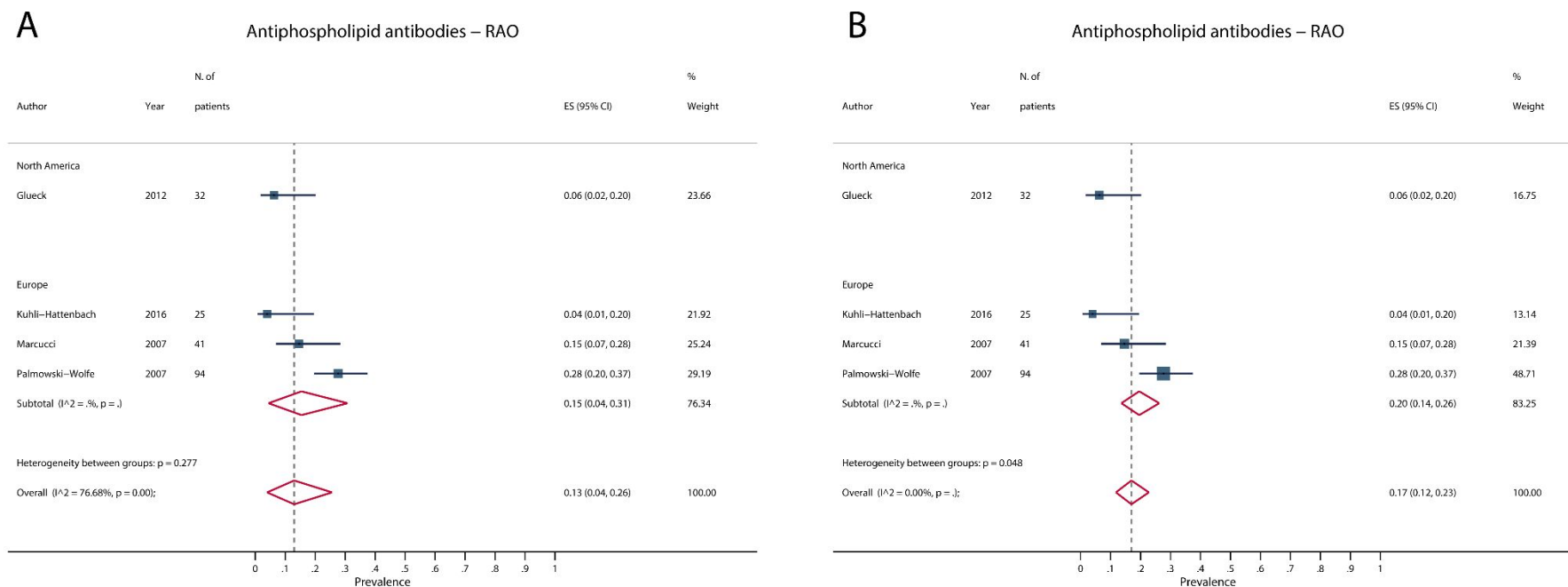


Table S1: Evaluation of bias for the studies included in the Systematic Review.

STUDY	YEAR	SELECTION BIAS	PERFORMANCE BIAS	ATTRITION BIAS	DETECTION BIAS	REPORTING BIAS	OVERALL BIAS
El-Asrar et al.	1998	Low Risk	Low Risk	High Risk ^a	High Risk ^a	Low Risk	Medium Risk
El-Asrar et al.	2002	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

1								
2								
3	Adamczuk et al.	2002	High Risk ^b	Medium Risk ^b	Low Risk	High Risk ^c	Medium Risk ^d	High Risk
4								
5	Albisinni et al.	1998	Low Risk	Medium Risk ^e	Low Risk	Low Risk	Medium Risk ^e	Low Risk
6								
7	Aras et al.	2001	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
8								
9	Arsène et al.	2005	Low Risk	Low Risk	Low Risk	Medium Risk ^c	Low Risk	Low Risk
10								
11	Ates et al.	2006	High Risk ^f	Medium Risk ^f	Low Risk	Low Risk	Low Risk	High Risk
12								
13	Biancardi et al.	2007	High Risk ^b	Medium Risk ^b	Low Risk	Low Risk	Low Risk	Medium Risk
14								
15	Birinci et al.	2003	Low Risk	Low Risk	Low Risk	Medium Risk ^g	Low Risk	Medium Risk
16								
17	Bombeli et al.	2002	High Risk ^b	Medium Risk ^b	Low Risk	High Risk ^c	Medium Risk ^e	High Risk
18								
19	Boyd et al.	2001	Low Risk	Medium Risk ^e	Low Risk	Low Risk	Medium Risk ^e	Low Risk
20								
21	Brown et al.	2002	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
22								
23	Bucciarelli et al.	2017	High Risk ^b	Medium Risk ^b	Low Risk	Low Risk	Medium Risk ^d	Medium Risk
24								
25	Cahill et al.	2001	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk ^{d,e}	Low Risk
26								
27	Chapin et al.	2015	High Risk ^b	Medium Risk ^b	Low Risk	Low Risk	Low Risk	Medium Risk
28								
29	Cho et al.	2019	Low Risk	Low Risk	Low Risk	High Risk ^a	Low Risk	Medium Risk
30								
31	Chua et al.	2006	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk ^e	Low Risk
32								
33	Ciardella et al.	1998	Low Risk	Low Risk	Medium Risk ^g	Medium Risk ^g	Low Risk	Medium Risk
34								
35	Coniglio et al.	1996	Low Risk	Low Risk	Low Risk	Medium Risk ^g	Medium Risk ^e	Medium Risk
36								
37	Cruciani et al.	2003	High Risk ^f	Medium Risk ^f	Low Risk	Low Risk	Low Risk	Medium Risk
38								
39	De Polo et al.	2015	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk ^e	Low Risk
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Demirci et al.	1999	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Di Capua et al.	2010	Medium Risk ^f	Low Risk	Low Risk	Low Risk	Medium Risk ^g	Low Risk	Low Risk
Dodson et al.	2003	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Dong et al.	2014	Medium Risk ^f	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Fernandez-Vega et al.	2019	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Ferrazzi et al.	2005	Low Risk	Low Risk	High Risk ^a	Medium Risk ^a	Low Risk	Low Risk	Medium Risk
Gao et al.	2006	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Gao et al.	2008	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Ghaznavi et al.	2016	High Risk ^b	Medium Risk ^b	Low Risk	Low Risk	Medium Risk ^e	Low Risk	High Risk
Giannaki et al.	2013	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Giordano et al.	1998	Low Risk	Low Risk	Low Risk	Medium Risk ^g	Low Risk	Low Risk	Low Risk
Glacet-Bernard et al.	1994	Low Risk	Low Risk	Low Risk	Medium Risk ^g	Low Risk	Low Risk	Low Risk
Glueck et al.	2012	Low Risk	Low Risk	High Risk ^a	Medium Risk ^a	Medium Risk ^e	Low Risk	Medium Risk
Gori et al.	2004	High Risk ^{b, f}	Medium Risk ^f	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk
Gottlieb et al.	1998	High Risk ^h	Medium Risk ^h	Low Risk	Low Risk	Medium Risk ^e	Low Risk	Medium Risk
Graham et al.	1996	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk ^e	Low Risk	Low Risk
Greiner et al.	1999	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
Gumus et al.	2006	Medium Risk ^f	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk

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3	Risse et al.	2014	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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5	Russo et al.	2015	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk ^e	Low Risk
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7	Salomon et al.	1998	Low Risk	Low risk	Low Risk	Low Risk	Low Risk	Low Risk
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9	Sartori et al.	2013	Low Risk	Low Risk	Low Risk	Medium Risk ^c	Low Risk	Low Risk
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11	Schockman et al.	2015	Medium Risk ⁱ	Low Risk	Low Risk	Medium Risk ^c	Medium Risk ^e	Low Risk
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13	Scott et al.	2001	High Risk ^h	Medium Risk ^h	Low Risk	Low Risk	Low Risk	Medium Risk
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15	Sinawat et al.	2017	High Risk ^h	Medium Risk ^h	Low Risk	Medium Risk ^c	Low Risk	High Risk
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17	Sodi et al.	2011	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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19	Sofi et al.	2008	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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21	Soltanpour et al.	2013	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk ^e	Low Risk
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23	Sottilotta et al.	2010	High Risk ^h	Medium Risk ^h	Low Risk	Low Risk	Medium Risk ^e	Medium Risk
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25	Tekeli et al.	1999	High Risk ^a	Medium Risk ^a	High Risk ^a	Low Risk	Low Risk	High Risk
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27	Vieira et al.	2019	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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29	Vine et al.	2000	High Risk ^a	Medium Risk ^a	High Risk ^a	Low Risk	Low Risk	Low Risk
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31	Weger et al.	2003	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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33	Weger et al.	2005	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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35	Weger et al.	2002	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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37	Weger et al.	2002	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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39	Weger et al.	2002	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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3	Yildirim et al.	2004	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk	Low Risk
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5	Yioti et al.	2013	Low Risk	Low Risk	Low Risk	Low Risk	Medium Risk ^d	Low Risk
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7 **Legend:** a: several thrombophilic conditions were searched only in a subset of patients; b: patients referred for thrombophilic screening; c: No data about definition of one or
8 more thrombophilic condition(s) explored; d: Only partial reporting for one or more thrombophilic conditions; e: Incomplete data on population characteristics; f: Excluded
9 patients with several medical conditions which may predispose to retinal vascular occlusion; g: thrombophilic condition(s) was/were explored in a partial or outdated way; h:
10 Selected only young patients (below a certain cut-off of age); i) studied only a subset of patients of an overall cohort
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For Peer Review

Table S2: Comparison between pooled prevalences in patients with RAO and RVO

Condition	Model	RVO Prevalence (95% CI)	RAO Prevalence (95% CI)	Overall Prevalence (95% CI)	P for subgroup heterogeneity
F-V Leiden Mutation	Random Effect	6% (5-8%)	7% (2-13%)	6% (5-8%)	0.700
F-V Leiden Mutation	Fixed Effect	6% (6-7%)	6% (3-9%)	6% (6-7%)	0.913
F-II G20210A Mutation	Random Effect	3% (2-4%)	3% (1-6%)	3% (2-4%)	0.955
F-II G20210A Mutation	Fixed Effect	3% (3-4%)	3% (1-5%)	3% (2-4%)	0.932
AT-III Activity Deficit	Random Effect	1% (0-2%)	3% (0-9%)	1% (0-2%)	0.355
AT-III Activity Deficit	Fixed Effect	1% (0-1%)	2% (0-6%)	1% (0-1%)	0.124
PC Activity Deficit	Random Effect	2% (0-3%)	2% (0-10%)	2% (0-3%)	0.572
PC Activity Deficit	Fixed Effect	1% (1-2%)	2% (0-6%)	1% (1-2%)	0.202
PS Activity Deficit	Random Effect	2% (0-4%)	1% (0-4%)	1% (0-3%)	0.720
PS Activity Deficit	Fixed Effect	2% (1-3%)	1% (0-3%)	2% (1-2%)	0.576
Hyperhomocysteinemia	Random Effect	24% (19-30%)	27% (14-42%)	25% (21-29%)	0.746
Hyperhomocysteinemia	Fixed Effect	22% (20-24%)	17% (16-18%)	19% (18-20%)	<0.001
MTHFR C677T Heterozygous mutation	Random Effect	44% (39-48%)	48% (39-56%)	44% (40-49%)	0.392
MTHFR C677T Heterozygous mutation	Fixed Effect	44% (42-46%)	48% (39-56%)	44% (42-46%)	0.394
MTHFR C677T Homozygous mutation	Random Effect	13% (10-17%)	23% (7-43%)	14% (11-17%)	0.265
MTHFR C677T Homozygous mutation	Fixed Effect	14% (13-16%)	18% (12-24%)	14% (13-16%)	0.183
APL Antibodies	Random Effect	8% (5-12%)	13% (4-26%)	9% (6-12%)	0.343
APL Antibodies	Fixed Effect	7% (6-8%)	17% (12-23%)	8% (7-9%)	<0.001

Legend: APL: Antiphospholipid; AT-III: Antithrombin III; F-V: Factor V; F-II: Factor II; PC: Protein C; PS: Protein S; MTHFR: Methylene tetrahydrofolate reductase

Table S3: Prevalence of explored conditions in general population compared to pooled estimates in RAO and RVO patients.

Condition	Prevalence in general population	RVO Prevalence (95% CI)	RAO Prevalence (95% CI)
F-V Leiden Mutation	5%[8]	6% (5-8%)	7% (2-13%)
F-II G20210A Mutation	2-3%[8]	3% (2-4%)	3% (1-6%)
AT-III Activity Deficit	<0.2%[8,74]	1% (0-2%)	3% (0-9%)
PC Activity Deficit	0.2%[8]	2% (0-3%)	2% (0-10%)
PS Activity Deficit	0-1%[8]	2% (0-4%)	1% (0-4%)
MTHFR C677T Heterozygous mutation	33%[126]	44% (39-48%)	48% (39-56%)
MTHFR C677T Homozygous mutation	7-12%[74]	13% (10-17%)	23% (7-43%)
PAI 4G Heterozygous mutation	50-54%[127,128]	50% (43-57%)	-
PAI 4G Homozygous mutation	24-26%[127,128]	23% (16-31%)	-
APL Antibodies	1-10%[8,74]	8% (5-12%)	13% (4-26%)