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REVIEW

Prothrombin G20210A Mutation and Lower Extremity Peripheral Arterial Disease: A Systematic Review and Meta-analysis

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WHAT THIS PAPER ADDS

The role of thrombophilia in patients with peripheral arterial disease (PAD) remains controversial. In this comprehensive systematic review, an association between prothrombin G20210A and those with PAD presenting with critical limb ischemia is shown. The role of prothrombin G20210A as a future predictor of critical limb ischemia in patients with PAD should be evaluated in prospective cohort studies.

Objective/Background: Despite being an important risk factor for venous thromboembolism, the role of the prothrombin G20210A mutation in patients with arterial disease remains unclear. The aim of this review was to evaluate the association of prothrombin G20210A and lower extremity peripheral arterial disease (PAD).

Methods: This was a systematic review and meta-analysis of case–control studies. A systematic review of electronic databases, including MEDLINE and Embase, was conducted to assess the prevalence of prothrombin G20210A in patients with lower extremity PAD. The main outcome was the prevalence of prothrombin G20210A in patients with lower extremity PAD. The random effects model odds ratio (OR) was used as the primary outcome measure.

Results: The initial electronic search identified 168 relevant abstracts of which five studies evaluating 1,524 cases of PAD and 1,553 controls were included. Prothrombin G20210A was found in 70 of 1,524 patients with lower extremity PAD and 44 of 1,553 of the controls (random effects OR 1.68, 95% confidence interval [CI] 0.8–3.2). In those with critical limb ischemia (CLI), the prevalence of prothrombin G20210A was 23 of 302 compared with 31 of 1,253 of the controls (OR 3.2, 95% CI 1.6–6.1).

Conclusion: Despite finding no significant association between lower extremity PAD and prothrombin G20210A, the meta-analysis suggests that the prevalence of prothrombin G20210A is significantly elevated in those with atherosclerotic occlusive disease of the lower extremities presenting with CLI. Well-designed prospective cohort studies evaluating the role of prothrombin G20210A as a predictor of disease progression or adverse vascular events are highly needed.

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INTRODUCTION

Prothrombin G20210A is a common genetic mutation that increases the concentration of prothrombin, and affects 0.7–4.0% of the general population.[1] Despite being an important risk factor for venous thromboembolism (VTE),[2] its role in the pathogenesis of atherosclerotic disease

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(especially peripheral arterial disease [PAD]) remains unclear.[3] Recent studies and systematic reviews have suggested an association between prothrombin G20210A and stroke (in young patients) or acute coronary syndrome. Multiple studies providing conflicting results have evaluated the prevalence of the prothrombin G20210A gene in patients with lower extremity PAD,[4] and some studies have suggested that prothrombin G20210A is more likely to affect those with critical limb ischemia (CLI).[4,5] To address this issue, the prevalence of prothrombin G20210A in patients with lower extremity PAD and in controls was examined.

METHODS

A systematic review of electronic databases, including MEDLINE, PubMed, and Embase, was conducted to assess the prevalence of prothrombin G20210A in patients with lower extremity PAD. (The search strategies and a Preferred Reporting Items for Systematic Reviews and Meta-Analyses checklist are presented as Appendices 1 and 2, respectively.) The search was conducted for the period January 1995—October 2014. The search was designed with the support of a librarian from the Ottawa Hospital Health Services, and was supplemented by a hand-search of relevant articles, abstract books from international meetings, and published reviews.

Study selection

Case—control studies were included if they reported the prevalence of prothrombin G20210A in patients with lower extremity PAD. The authors of relevant papers were contacted to ensure that all the relevant data were captured. All potentially relevant articles were reviewed in full in order to ensure that they satisfied the inclusion criteria: (i) enrolment of patients with symptomatic lower extremity PAD defined as the presence of signs and symptoms typical of lower extremity PAD (Fontaine II or higher); (ii) had confirmatory testing (including ankle—brachial index [ABI], Doppler ultrasound, digital subtraction angiography, or computed tomography angiography); (iii) prothrombin G20210A genotyping was available for all participants; (iv) the numbers of cases and controls with and without prothrombin G20210A were provided in the article. Studies were excluded if the participants did not receive objective testing for the prothrombin G20210A mutation, or included patients with self-reported lower extremity PAD without objective testing.

Data extraction and quality assessment

Two reviewers (FV and EG) independently assessed the eligibility of all articles identified via the initial search strategy. A third reviewer adjudicated all discrepancies if

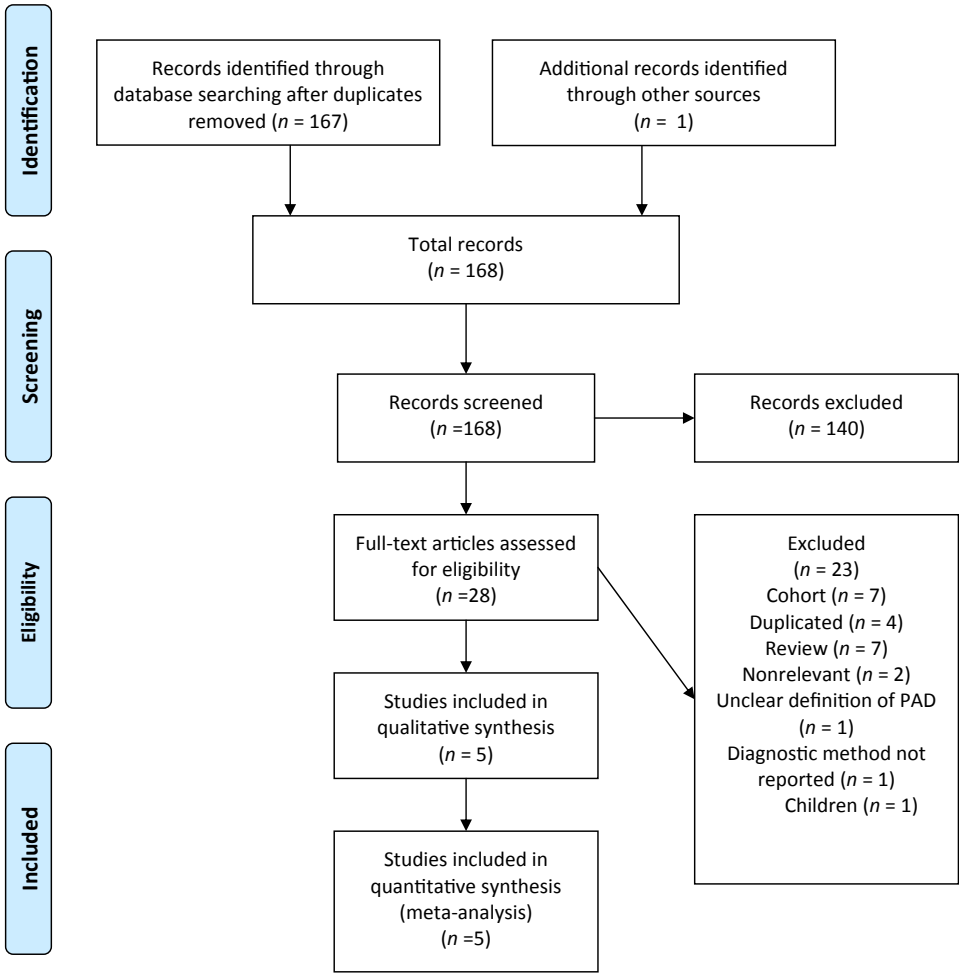

Figure 1. Flow diagram. *Note*. PAD = lower extremity peripheral arterial disease.

Table 1. Characteristics of the studies included.

Study	Definition of PAD	Country	PAD (*n*)	Controls (*n*)	Matched	Ethnicity	Males, cases/controls (%)	Smokers, cases/controls (%)	Hypertension, cases/controls (%)	Diabetes, cases/controls (%)	CLI (%)[a]
Mueller et al. (2005)[10]	ABI at index < 1, angiography	Austria	433	433[b]	Yes	White	71/71	45/12	58/41	27/27	17
Renner et al. (2000)[9]	Clinical symptoms, ABI at index < 1, confirmation by Doppler or angiography	Austria	336	300[c]	No	[d]	54/48	42/23	65/29	34/13	22
Reny et al. (2004)[5]	Clinical symptoms, and ABI at index < 0.90 or prior revascularization	France	184	330[e]	Yes	White	[e]	97/55	52/31	24/8	14
Sartori et al. (2010)[4]	Clinical symptoms, ABI at index < 0.90, confirmation by Doppler	Italy	291	210[d]	No	White	64/58	33/10	79/37	27/4	38
Sofi et al. (2005)[11]	Clinical symptoms, ABI at index < 0.90	Italy	280	280[f]	Yes	—	77/77	70/20	54/15	17/2	32

Note. Quality was assessed using the Newcastle–Ottawa scale. PAD = lower extremity peripheral arterial disease; CLI = critical limb ischemia; ABI = ankle–brachial index.

[a] CLI defined as Fontaine stages III or IV.

[b] No clinical indication of PAD by history and physical examination; systolic brachial blood pressure equal to or less than the blood pressure in of each of the right and left anterior tibial and posterior tibial arteries (i.e., ABI = 1.0); no pathologic pattern of pulse waves in lower limbs by continuous-wave spectral analysis; no coronary artery disease; no cardiovascular disease; no previous vascular surgery or stenting of the internal carotid arteries; no stenosis of the internal carotid artery $> 50\%$ by color duplex ultrasound scans; no history of venous thromboembolism; and no history or presence of any malignancy.

[c] Only Austrian participants without any known arterial or venous disease served.

[d] Age-matched controls had no history of arterial disease (stroke, myocardial infarction, angina, or PAD) and were randomly selected from 703 white men of a previously described control group used to study genetic risk factors for vascular thrombosis.

[e] Only men included.

[f] Unrelated participants without PAD, matched for age and sex, who were recruited from the staff of the University of Florence and from partners or friends of patients.

Table 2. Quality assessment by the Newcastle—Ottawa scale.

Study	Is the case definition adequate?	Representativeness of the cases	Selection of controls	Definitions of controls	Comparability of cases and controls	Ascertainment of exposure	Same method of ascertainment for cases and controls	Nonresponse rate
Mueller et al. (2005)[10]	*	*		*	*	*	*	*
Renner et al. (2000)[9]	*	*		*	*	*	*	*
Reny et al. (2004)[5]	*	*	*	*	*	*	*	*
Sartori et al. (2010)[4]	*	*		*	*	*	*	*
Sofi et al. (2005)[11]	*	*	*		*	*	*	*

needed (GLG). Two independent reviewers used the Newcastle—Ottawa Scale (NOS) for observational studies to assess the methodological quality of the selected studies.[6]

Outcome measure

The primary outcome measure was the odds ratio (OR) for the prevalence of patients with prothrombin G20210A with lower extremity PAD. A prespecified subgroup analysis was conducted based on the severity of the disease, defined as intermittent claudication (defined as patients with Fontaine stage IIa/IIb) or CLI (defined as patients with Fontaine III/IV).

Data synthesis and analysis

The random effects model OR was used as the primary outcome measure, along with the corresponding 95% confidence intervals (CIs). Pooled proportions were calculated as the back-transformation of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian—Laird weights for the random effects model. Transformation of proportions into a quantity using the Freeman—Tukey variant of the arcsine square root method is suitable for the usual fixed and random effects summaries. The I^2 statistic was used to quantify heterogeneity among the pooled estimates across studies. An I^2 value $< 25\%$ was considered low-level heterogeneity, 25—50% as moderate-level heterogeneity, and $> 50\%$ as high-level heterogeneity. Homozygote and heterozygote carriers of prothrombin G20210A were analyzed as one group. The statistical analysis was performed using RevMan 5.3 (The Cochrane Collaboration, Copenhagen, Denmark) and the **Grading of Recommendations, Assessment, Development and Evaluations** (GRADE) analysis was conducted using GradePRO (www.gradepro.org).

RESULTS

The initial electronic search identified 168 relevant abstracts (after the removal of duplicates), of which 140 were considered nonrelevant to the search and therefore excluded; 28 were selected for full text review. Twenty-two were excluded for the reasons described in Fig. 1 (two studies evaluated the prevalence of prothrombin G20210A in patients with PAD but did not satisfy the inclusion criteria[7,8]). Of the five studies selected, two were conducted in Austria,[9,10] one in France,[5] and two in Italy.[4,11] The prevalence of patients with CLI varied between 14% and 38% across studies. Two of the studies, both from Austria, included patients with an ABI < 1 (one confirmed the disease with digital subtraction angiography,[10] and the other with Doppler ultrasound or angiography[9]), whereas the rest of the studies included patients with an ABI < 0.9. Baseline characteristics of cases and controls included in the studies are presented in Table 1. The quality scores using the NOS) are presented in Table 2.

In total, the five studies evaluated 1,524 cases of lower extremity PAD and 1,553 controls (see Table 3 for a more

comprehensive review of the number of patients included in each study and individual OR). Prothrombin G20210A was found in 70 of 1,524 patients with lower extremity PAD (random effects pooled proportion 4.7%, 95% CI 3.3—6.3; $I^2 = 47\%$) and 44 of 1,553 of the controls (random effects pooled proportion 2.9%, 95% CI 1.8—4.15; $I^2 = 43.9\%$) (random effects OR 1.68, 95% CI 0.8—3.2 [$P = 0.11$); $I^2 = 61.3\%$; see Fig. 2).[7,8]

Using data from four studies the prevalence of prothrombin G20210A in those with claudication (Fontaine IIa or IIb) or CLI (Fontaine III/IV) as separate subgroups was analyzed.[4,5,10,11] The number of patients with CLI was not obtained for one study (no response was received to an email sent to the authors[9]). The prevalence of prothrombin G20210A was 38 of 886 in those with claudication (random effects pooled proportion 4%, 95% CI 3.1—5.9; $I^2 = 5.2\%$) and 31 of 1,253 in the healthy controls (random effects pooled proportion 2.6%, 95% CI 1.6—3.7; $I^2 = 31.5\%$) (random effects OR 1.8, 95% CI 0.8—3.8; $I^2 = 55.4\%$; see Fig. 3). In those with CLI the prevalence of prothrombin G20210A was 23 of 302 (random effects pooled proportion 8%, 95% CI 3.9—13.4; $I^2 = 55.3\%$) compared with 31 of 1,253 (random effects pooled proportion 2.6%, 95% CI 1.6—3.7; $I^2 = 31.5\%$) in the healthy controls (random effects OR 3.2, 95% CI 1.6—6.13; $I^2 = 19.5\%$; see Fig. 4). Further, analysis restricting by the use of matched case—controls did not modify the association of prothrombin G20210A and CLI.

Table 4 presents an analysis of the evidence using a **GRADE** approach.

DISCUSSION

Despite finding no association between lower extremity PAD and prothrombin G20210A, the meta-analysis suggests that the prevalence of prothrombin G20210A is significantly elevated in those with atherosclerotic occlusive disease of the lower extremities presenting with CLI.

The association of prothrombin G20210A with atherosclerotic disease remains a matter of debate.[12,13] Despite the widespread belief that prothrombin G20210A is essentially a risk factor for VTE,[3,14] some meta-analyses and

Table 3. Total number of prothrombin G20210A (PTGM) carriers included in each study and individual odds ratios (OR).

Prevalence of PTGM in patients with PAD defined vs. controls				
Study	PTGM carriers/PAD cases (*n*)	PTGM carriers/controls (*n*)	OR	95% CI
Mueller et al. (2005)[10]	16/433	12/433	1.34	0.6—2.8
Renner et al. (2000)[9]	9/336	13/300	0.60	0.2—1.4
Reny et al. (2004)[5]	12/184	6/330	3.76	1.3—10.2
Sartori et al. (2010)[4]	18/291	9/210	1.47	0.6—3.3
Sofi et al. (2005)[11]	15/280	4/280	3.90	1.2—11.9
Prevalence of PTGM in those with claudication (Fontaine IIa/IIb) vs. controls				
Study	PTGM carriers/PAD cases	PTGM carriers/controls	OR	95% CI
Mueller et al. (2005)[10]	12/359	12/433	1.21	0.5—2.7
Reny et al. (2004)[5]	8/158	6/330	2.88	0.9—8.4
Sartori et al. (2010)[4]	6/181	9/210	0.76	0.2—2.1
Sofi et al. (2005)[11]	12/190	4/280	4.65	1.4—14.6
Prevalence of PTGM in those with CLI (Fontaine III/IV) vs. controls				
Study	PTGM carriers/PAD cases	PTGM carriers/controls	OR	95% CI
Mueller et al. (2005)[10]	4/74	12/433	2.00	0.6—6.3
Reny et al. (2004)[5]	4/26	6/330	9.81	2.5—37.3
Sartori et al. (2010)[4]	12/110	9/210	2.73	1.1—6.7
Sofi et al. (2005)[11]	3/90	4/280	2.37	0.52—10.8

Note. PAD = lower extremity peripheral arterial disease; CI = confidence interval; CLI = critical limb ischemia.

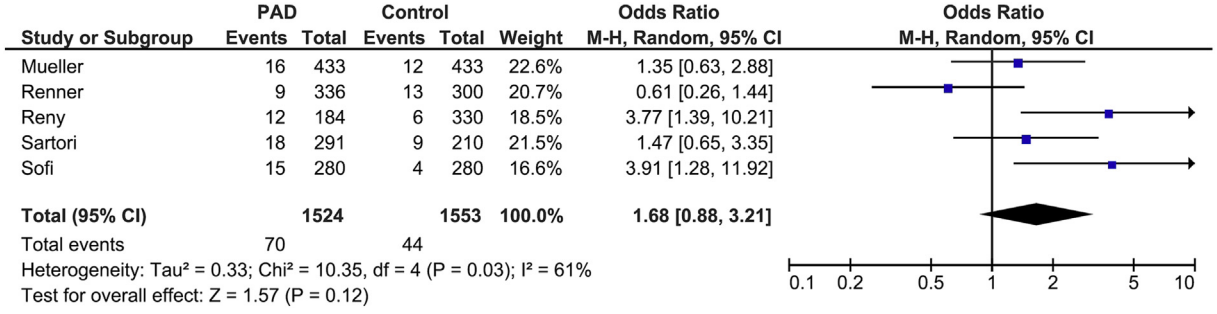

Figure 2. Forest plot prevalence of Prothrombin G20210A in patients with lower extremity peripheral arterial disease (PAD) vs. controls. *Note*. CI = confidence interval; Mueller = Mueller et al. (2005)[10]; Reny = Reny et al. (2004)[5]; Sartori = Sartori et al. (2010)[4]; Sofi = Sofi et al. (2005).[11]

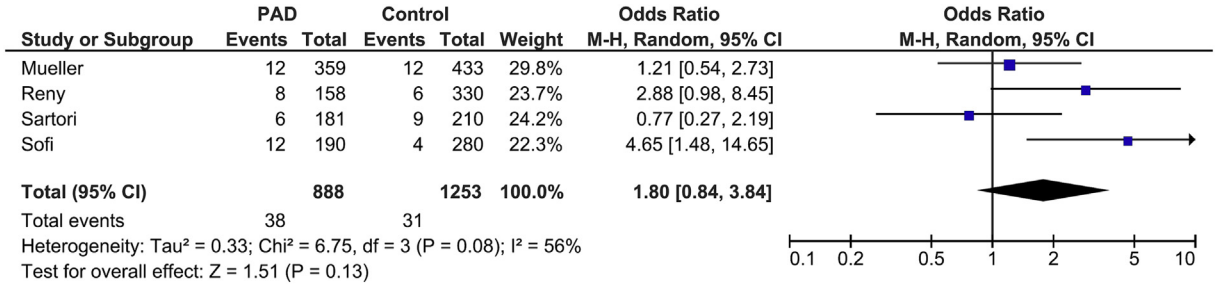

Figure 3. Forest plot prevalence of prothrombin G20210A in patients with lower extremity claudication vs. controls. *Note*. PAD = lower extremity peripheral arterial disease; CI = confidence interval; Mueller et al. (2005)[10]; Reny = Reny et al. (2004)[5]; Sartori = Sartori et al. (2010)[4]; Sofi = Sofi et al. (2005).[11]

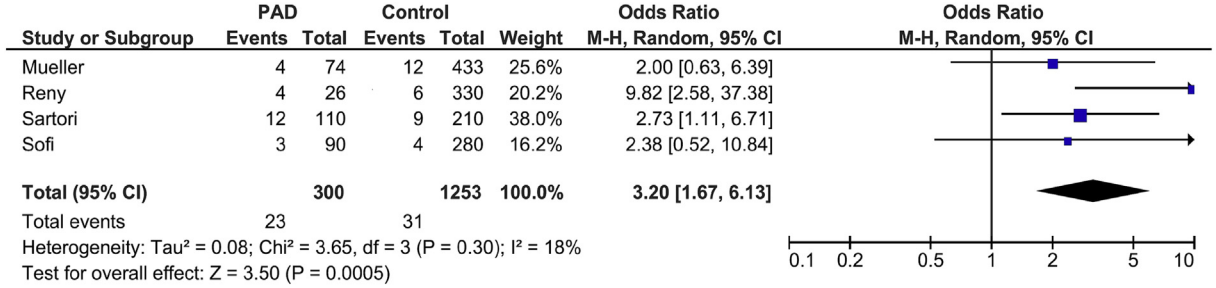

Figure 4. Forest plot prevalence of prothrombin G20210A in patients with lower extremity critical limb ischemia vs. controls. *Note*. PAD = lower extremity peripheral arterial disease; CI = confidence interval; Mueller et al. (2005)[10]; Reny = Reny et al. (2004)[5]; Sartori = Sartori et al. (2010)[4]; Sofi = Sofi et al. (2005).[11]

large population studies have suggested that prothrombin G20210A either alone or in combination with other genetics variants increases the risk of stroke or coronary disease.[2,15–17] To the knowledge of the authors, only one systematic review, conducted in 2003, identified a study addressing the association between G20210A and atherosclerotic occlusive disease of the lower extremities.[18] The present study identified four additional studies that show this association and is the first meta-analysis to show an association between prothrombin G20210A and CLI secondary to atherosclerotic occlusive disease of the lower extremities (as suggested by the case–control studies of Reny et al.[5] in 2004 and Sartori et al.[4] in 2010).

The activation of the coagulation cascade appears to increase the risk of disease progression and vascular events in patients with PAD,[19–24] via multiple mechanisms.[25–27] Thrombin has multiple effects. Following thrombus formation it remains abundant in mural thrombi subsequent to vascular injury and may be important for vessel repair processes as it appears to regulate inflammatory processes.[23,28,29] It also directly stimulates vascular smooth muscle cell proliferation and migration.[28,29] The prothrombin G20210A mutation is located at the 3′-untranslated polyadenylation cleavage site and is associated with increased plasma prothrombin levels.[30] Others have suggested prothrombin G20210A could lead to higher levels of thrombin formation should triggering of the coagulation cascade occurs (measured by endogenous thrombin potential).[31]

As with patients with VTE and those with other forms of arterial disease, the utility of screening for prothrombin G20210A in patients with PAD to guide prognostic or therapeutic decisions is uncertain.[3,12] Based on the data presented herein, whether prothrombin G20210A increases the risk of progression from claudication to CLI remains speculative. One cohort suggested that all carriers of prothrombin G20210A showed disease progression compared with 67% of the noncarriers (this difference was nonsignificant, possibly owing to the small sample size). In order to provide more definite answers regarding the role of prothrombin G20210A in patients with PAD, large prospective cohort studies are required.

The present study has limitations. First, given that the prevalence of prothrombin G20210A varies between different ethnicities and geographical areas,[1] and that the majority of study participants were white, the results do not apply to ethnic groups other than the one represented in this study (white people from Germanic and Latin European countries). Second, the association between CLI and prothrombin G20210A was based on only four studies, as it was not possible to retrieve information from all studies. Third, by including case–control studies, it cannot be estimated if the presence of prothrombin G20210A is associated with progression from claudication to CLI, or an increased risk of future vascular events (especially in patients with CLI[32]), or following vascular procedures. The number of studies addressing the outcome after procedures is limited, to the authors' knowledge, to three small studies with < 10

Table 4. Grading of the evidence.

Quality assessment							Effect	Quality	Importance
No. of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Relative (95% CI) Absolute (95% CI)		
Prevalence of PTGM in patients with PAD									
5	Observational	Serious	Serious [a–c]	Serious	Serious	High heterogeneity Large variations in associations all plausible residual confounding would reduce the effect	OR 1.68 (0.80–3.20) 19 more per 1,000 (6–58 more)	Low	Moderate
Prevalence of PTGM in patients CLI									
4	Observational	Not serious	Not serious[a]	Not serious	Not serious	Very strong association, all plausible residual confounding would reduce the effect	OR 3.19 (1.60–6.10) 49 more per 1,000 (14–106 fewer)	Moderate	Important

Note. CI = confidence interval; PTGM = prothrombin G20210A; PAD = lower extremity peripheral arterial disease; OR = odds ratio; CLI = critical limb ischemia. [a] Different controls. [b] Different inclusion criteria. [c] Different countries/ethnicities.

patients, all of whom were carriers of prothrombin G20210A.[31–33] Fourth, except for the analysis of CLI, all the analyses had high heterogeneity. Fifth, claudicants and patients with CLI were divided using Fontaine stage alone. Sixth, not all the studies used matching and, as such, potentially introduced bias. However, the two studies that did not use initial matching adjusted the results for relevant characteristics. Seventh, the types of controls selected varied across studies, although all of them excluded patients with clinically overt vascular or thrombotic disease. Eight, the selection of cases varied across studies. Two of the studies, both from Austria, included patients with an ABI < 1 (one confirmed the disease with digital subtraction angiography,[10] and the other with Doppler ultrasound or angiography[9]), whereas the rest of the studies included patients with an ABI < 0.9. Finally, homozygous prothrombin G20210A could not be assessed owing to the small number of patients affected, and the potential for potential high-risk interactions with prothrombin G20210A, such as blood type, could not be investigated.

CONCLUSION

This meta-analysis could not find an association between prothrombin G20210A and PAD, but suggests that the prevalence of prothrombin G20210A is elevated in those with CLI secondary to PAD. Well-designed prospective cohort studies evaluating the role of prothrombin G20210A as a predictor of disease progression to CLI or adverse vascular events are highly needed.

CONFLICT OF INTEREST

None.

FUNDING

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejvs.2015.04.033

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COUP D'OEIL

Cementing the Vena Cava

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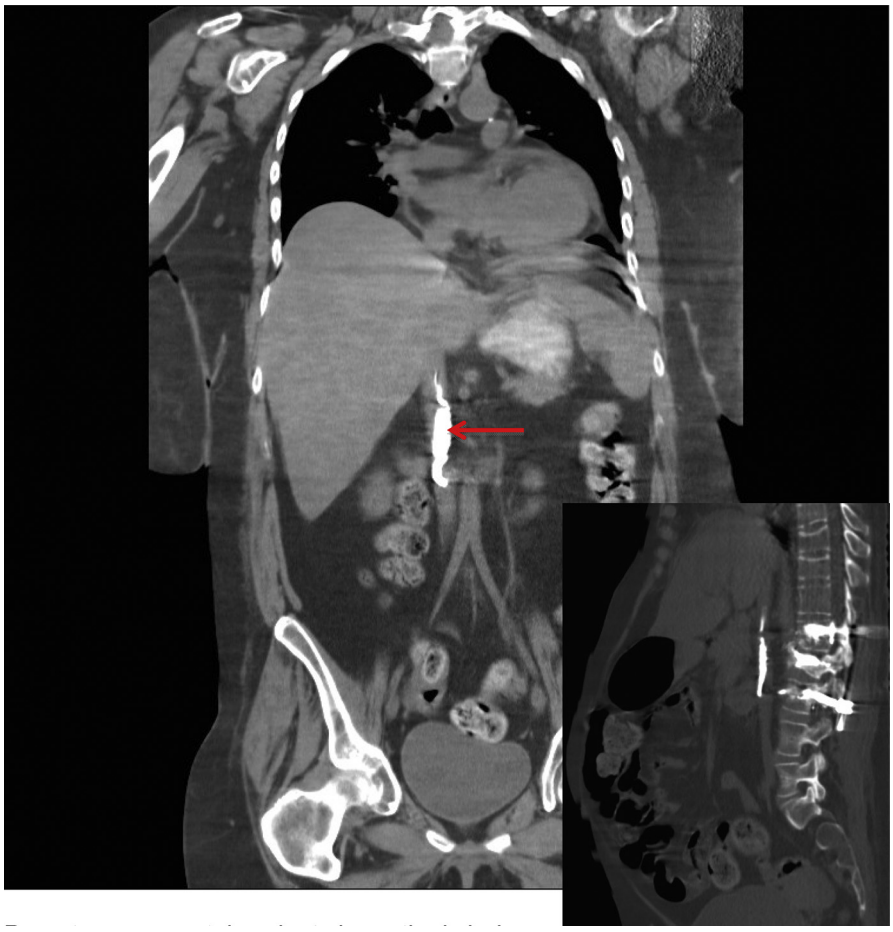

Percutaneous vertebroplasty is routinely being performed in patients with vertebral compression fractures using polymethylmetaacrylate cement. The cement commonly leaks into the perivertebral tissues, but only around 1% of patients develop any clinical symptoms. The computed tomography image shows extrusion of cement into the vena cava (arrow) in a 24-year-old female treated for steroid-induced osteoporotic vertebral fracture. This was only discovered 1 week after the procedure when the patient complained of persistent backache, which prompted the imaging. She had no lower limb symptoms and in view of this, conservative management was pursued with anticoagulation therapy.

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