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VASCUNET / ICVR REPORT

Editor's Choice – International Variations and Sex Disparities in the Treatment of Peripheral Arterial Occlusive Disease: A Report from VASCUNET and the International Consortium of Vascular Registries

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WHAT THIS PAPER ADDS

This is the first international comparison of population based data from 11 countries participating in the VASCUNET and International Consortium of Vascular Registries, highlighting the invasive treatment of symptomatic peripheral arterial occlusive disease. Patient selection and choice of treatment differed widely between countries. The proportion of patients receiving treatment for claudication varied between 6% and 69%, and endovascular techniques were used between 24% and 88%. Although females represent 40% of the target population, they were older and more frequently presented with chronic limb threatening ischaemia than males. These sex and procedure selection differences present opportunities for deeper studies.

Objective: The aim of this study was to determine sex specific differences in the invasive treatment of symptomatic peripheral arterial occlusive disease (PAOD) between member states participating in the VASCUNET and International Consortium of Vascular Registries.

Methods: Data on open surgical revascularisation and peripheral vascular intervention (PVI) of symptomatic PAOD from 2010 to 2017 were collected from population based administrative and registry data from 11 countries. Differences in age, sex, indication, and invasive treatment modality were analysed.

Results: Data from 11 countries covering 671 million inhabitants and 1 164 497 hospitalisations (40% women, mean age 72 years, 49% with intermittent claudication, 54% treated with PVI) in Europe (including Russia), North America, Australia, and New Zealand were included. Patient selection and treatment modality varied widely for the proportion of female patients (23% in Portugal and 46% in Sweden), the proportion of patients with claudication (6% in Italy and 69% in Russia), patients' mean age (70 years in the USA and 76 years in Italy), the proportion of octogenarians (8% in Russia and 33% in Sweden), and the proportion of PVI (24% in Russia and 88% in Italy). Numerous differences between females and males were observed in regard to patient age (72 *vs.* 70 years), the proportion of octogenarians (28% *vs.* 15%), proportion of patients with claudication (45% *vs.* 51%), proportion of PVI (57% *vs.* 51%), and length of hospital stay (7 days *vs.* 6 days).

Conclusion: Remarkable differences regarding the proportion of peripheral vascular interventions, patients with claudication, and octogenarians were seen across countries and sexes. Future studies should address the underlying reasons for this, including the impact of national societal guidelines, reimbursement, and differences in health maintenance.

Keywords: Administrative data, Diabetic foot syndrome (DFS), Epidemiology, Lower extremity artery disease, Peripheral arterial occlusive disease (PAOD), Registries

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INTRODUCTION

Peripheral arterial occlusive disease (PAOD) is the major cause of limb loss and is further associated with functional disability and impaired quality of life.[1] To date, an estimated 200 million patients are known to be affected, and the ageing demographics have led to a rapidly increasing prevalence in Western countries.[2,3] As in other vascular diseases, rapid adoption of less invasive revascularisation techniques has occurred, with possible impacts on patient selection and short term outcomes.[4] In prior VASCUNET reports on PAOD related lower limb amputations and bypass surgery, marked variations between countries were observed.[5,6] These reports subsequently generated numerous hypotheses concerning possible differences between countries in case selection and interventional treatment patterns for peripheral vascular disease.

Previous large scale observational studies on PAOD treatment also revealed marked sex disparities in patient selection and practice.[7–9] However, cross border comparisons of different healthcare systems remain sparse.

International comparisons of real world evidence from both clinical and administrative registries and health insurance claims can help to better understand the impact of reimbursement systems and geographical factors on patient selection and treatment patterns. Furthermore, these data can complement high level evidence from randomised clinical trials and guide physicians, regulators, and politicians to improve healthcare systems in the interests of patients.[10]

The current study aimed to determine the scope of practice of invasive treatment for symptomatic PAOD in a global real world setting. It further aimed to describe case selection in terms of the patient's age and sex between countries participating in the International Consortium of Vascular Registries (ICVR) and the VASCUNET committee of the European Society for Vascular Surgery (ESVS).

MATERIALS AND METHODS

The VASCUNET collaboration and the International Consortium of Vascular Registries

VASCUNET (www.vascunet.org) is a collaboration of vascular registries from Europe, South America, and Australasia administered and partly funded by the ESVS. It was founded in 1997, and numerous contributions have been published since that time. VASCUNET aims to increase knowledge and understanding of vascular diseases, and to promote excellence in vascular surgery, using an international vascular audit. In 2014, the VASCUNET collaboration and the Society for Vascular Surgery's Vascular Quality Initiative (VQI) mutually founded the ICVR as a transatlantic framework for registry based research and quality improvement.[11,12]

A data extraction and study protocol were developed (see Supplementary Material), based on expert consensus. For this study, national statistics, administrative data, and health insurance claims were used to determine in hospital treatments for symptomatic PAOD comprising patients with intermittent claudication (IC) or chronic limb threatening ischaemia (CLTI) using the World Health Organization International Classification of Diseases (ICD-9 or ICD-10). The Scandinavian registries have specifically designed operative procedure codes, according to the Nordic Medico-Statistical Committee (NOMESCO) Classification of Surgical Procedures. The study included procedures conducted between 1 January 2010 and 31 December 2017.

Dichotomised by sex, data were collected for the number of patients undergoing either open surgical revascularisation (OSR; bypass or endarterectomy) or peripheral vascular intervention (PVI). Hybrid procedures were included in the OSR group. For all subgroups, data were collected regarding mean age and the proportion of octogenarians, the proportion of patients with IC *vs.* CLTI, and the mean length of hospital stay. Additional population data were accessed through the Statistical Office of the European Union (EUROSTAT) or the Organisation for Economic Co-operation and Development (OECD). In addition, a comprehensive survey was performed, and additional interviews conducted when necessary (see Supplementary Material). Data were requested by the VASCUNET and ICVR representatives. The first author (C.-A. B.) collected and coordinated the anonymised data set.

Statistical analysis

The data were primarily analysed using descriptive statistics, mean and range for continuous variables and relative frequencies (%) and 95% confidence interval (CI) for categorical variables. Quantitative data were further visually displayed in figures and tables. Adobe Illustrator (Adobe Systems Software Ireland Limited, Dublin, Republic of Ireland) was used to create the diagrams.

Ethical considerations

Several review boards and national guidelines concerning research on routinely collected data determined that retrospectively using aggregated data from national statistics is not human subject research, as de-identified data sets were used. Thus, patient informed consent was not obtained for this study.[13]

RESULTS

Aggregated study data from 11 countries comprising a total of 1 164 497 hospitalisations between 2010 and 2017 (mean 145 562 per year) were included in the comparisons (Table 1). The USA submitted data from national hospital episode statistics (Centers for Medicare & Medicaid Services [CMS]), including patient level data from the VQI registry. The entire cohort included 39.8% female patients (95% CI 39.7—39.9) (Fig. 1). The mean age was 71.9 years (range 70.0—74.1 years). Of all patients, 48.5% (95% CI 48.4—48.6) were treated for IC *vs.* CLTI (Fig. 2), and 53.6% (95% CI 53.6—53.7) were treated with PVI *vs.* OSR (Fig. 3).

Table 1. Baseline characteristics of the general population and the patients receiving invasive treatment by open surgical revascularisation (OSR) or peripheral vascular intervention (PVI) in the 11 countries participating in the VASCUNET and International Consortium of Vascular Registries from 2010 to 2017 to determine sex specific differences in the management of symptomatic peripheral arterial occlusive disease

Country	Health spending in 2017 − USD per capita	Inhabitants			Procedures or patients					
		Total − *n*	Females − %	Life expectancy in women *vs* men − y	Total − *n**	Age − y	Women − %	IC *vs* CLTI − %	PVI *vs* OSR − %	LOS − d
Australia	5005	24.98 million	50.2	84.9 *vs* 80.7	64 332	71.8	32.5	56.7	75.8	9.0
Germany	5848	82.91 million	50.7	83.4 *vs* 78.7	135 272	72.8	43.3	60.0	66.2	8.5
Iceland	4154	352 721	49.8	84.3 *vs* 81.1	1611	72.2	40.8	51.3	78.6	3.2
Italy	3376	60.42 million	51.2	85.2 *vs* 80.8	68 744	75.8	41.1	5.9	87.7	5.6
Malta	3715	493 559	49.0	84.6 *vs* 80.4	2674	72.9	40.5	14.6	68.4	7.0
New Zealand	3742	4.84 million	50.8	83.6 *vs* 80.2	6621	71.0	36.8	38.5†	28.4†	4.7
Norway	6064	5.31 million	49.5	84.4 *vs* 81.3	23 461	72.3	43.5	63.4	71.4	2.5
Portugal	2759	10.28 million	52.7	84.9 *vs* 78.7	12 410	70.0	23.1	29.8	56.6	9.9
Russia	1514	143.67 million	53.5	77.8 *vs* 67.8	240 045	70.0	33.3	68.8	24.0	8.5
Sweden	5264	10.18 million	49.9	84.1 *vs* 81.0	41 710	74.2	46.4	34.77	68.3	NA
USA	10 207	326.69 million	50.5	81.1 *vs* 76.1	414 368 (Medicare) 153 249 (VQI)	72.4 (Medicare) 67.0 (VQI)	43.0 (Medicare) 39.2 (VQI)	39.2 (Medicare) 45.3 (VQI)	46.4 (Medicare) 77.5 (VQI)	3.8 (Medicare) 2.8 (VQI)

USD = United States Dollars; IC = intermittent claudication; CLTI = chronic limb threatening ischaemia; LOS = length of stay (in hospital); NA = not available; VQI = Vascular Quality Initiative.
* Completeness of data was >95% for all.
† Adjusted for exclusion.

Indication for treatment (intermittent claudication vs. chronic limb threatening ischaemia)

The lowest proportion of patients treated for IC *vs.* CLTI was observed in Italy (5.9%, 95% CI 5.7—6.0) and the highest proportion in Russia (68.8%, 95% CI 68.6—69.0) (Fig. 2). There were small differences between the CMS and VQI databases in the USA. A higher proportion of revascularisation for patients with IC was noted in countries where physician payment was within a fee for service model (54% *vs.* 38%).

Peripheral vascular interventions vs. open surgery

The proportion of PVI varied widely between 24.0% (95% CI 23.8—24.1) in Russia and 87.7% (95% CI 87.4—87.9) in Italy (Fig. 3). There was substantial difference between the two US data sources, with a higher rate of PVI in the VQI database reflecting the increase in PVI in participating VQI centres.

Proportion of ageing patients and octogenarians

The mean age of the patients ranged from 70 years in the USA (Medicare beneficiaries) to 76 years in Italy (Table 1). The proportion of octogenarians among all patients varied from 7.6% (95% CI 7.5—7.7) in Russia to 33.0% (95% CI 32.5—33.4) in Sweden (Fig. 4).

Sex disparities

Of the entire dataset, 463 745 female patients (40%) were included in the sex specific analyses. The proportion of female *vs.* male patients in the national samples varied from 23.1% (95% CI 22.4—23.9) in Portugal to 46.4% (95% CI 45.9—46.9) in Sweden (Fig. 1). At the time of treatment, female patients were between 2.1 years (USA) and 10.1 years (Russia) older than their male counterparts, except for Italy, where women were 0.9 years younger than men (Fig. 1). Female patients more often underwent invasive treatment for the management of IC in Iceland (53.7% *vs.* 49.5% in males, gender gap +4.26 percentage points [p.p.]) and Russia (69.3% *vs.* 68.5%, gender gap +0.77 p.p.) when compared with male patients. By contrast, the proportion of female patients with IC was lower in Portugal (18.4% *vs.* 33.3%, gender gap − 14.87 p.p.), Malta (9.7% *vs.* 18.0%, gender gap − 8.31 p.p.), USA (in Medicare beneficiaries: 36.0% *vs.* 41.7%, gender gap − 5.69 p.p.; in VQI: 43.3% *vs.* 46.6%, gender gap − 3.20 p.p.), New Zealand (35.1% *vs.* 40.6%, gender gap − 5.47 p.p.), Norway (60.3% *vs.* 65.7%,

gender gap − 5.40 p.p.), Australia (53.3% *vs.* 58.4%, gender gap − 5.06 p.p.), Sweden (32.4% *vs.* 36.7%, gender gap − 4.23 p.p.), Italy (5.3% *vs.* 6.3%, gender gap − 1.05 p.p.), and Germany (57.3% *vs.* 62.1%, gender gap − 4.85 p.p.), when compared with male patients (Fig. 2). While 57.3% (95% CI 57.2−57.4) of females were treated by PVI, their male counterparts were treated by PVI in 48.8% (95% CI 48.7−48.9). Except for Italy (87.6% *vs.* 87.8%, gender gap − 0.12 p.p.), females were more frequently treated by PVI in all other countries with sex differences in favour of females from +2.40% (72.8% *vs.* 70.4%) in Norway and +14.90% (68.1% *vs.* 53.2%) in Portugal (Fig. 3).

DISCUSSION

In this largest international comparison of real world data on the treatment of symptomatic PAOD, including >1 million procedures from 11 countries, a wide variation in practice was observed between countries. The proportion of treatment for IC varied from 6% in Italy to 69% in Russia, while the preferred treatment choice varied inversely (24% PVI in Russia to 88% in Italy). Striking sex based differences were observed, where females were less often intervened upon and even when there was an intervention, it was at a more advanced stage, with substantial regional variation. These findings hint at external factors, with a possible impact on guideline adherence and patient selection (Supplementary Material).

The Reduction of Atherothrombosis for Continued Health (REACH) Registry previously reported cardiovascular outcomes in nearly 65 000 outpatients across the world but did not focus on invasive treatments.[14] In a previous VASCUNET report on infrainguinal bypass surgery, the authors included registry data from nine countries comprising 32 087 cases between 2005 and 2009. In line with the current study, significant variations in practice between countries were demonstrated.[6] As in the current study, the proportion of females varied from 25% to 44%, and the proportion of patients with claudication ranged from 16% to 41%. That first VASCUNET report led to a heated discussion regarding the underlying reasons for the remarkable discrepancies between treatment standards and clinical reality.[15] The current study confirmed these findings by Lees *et al.*,[6] while adding a larger sample over an updated study period. For practical reasons, the merely descriptive approach of the current study does not allow determination of causal relationships behind the interesting findings. Nevertheless, several hypotheses could be generated that should be addressed with future research.

At first glance, the high proportion of patients with claudication, with very few undergoing PVI, in Russia contrasts with the situation in Italy. Although these may appear to be outliers in a large data set, between both extremes, the treatment reality was homogeneously distributed among all other participating countries and all representatives verified that the current study reflects treatment reality in the corresponding healthcare system. Patient selection and choice of treatment are known to be affected by the underlying reimbursement system and the available healthcare infrastructure. A trend towards increasing numbers of elective revascularisations and PVI has been previously reported in Western countries.[3] Certainly, the necessary technical equipment and medical devices generate high capital expenditures with limited availability in countries with low healthcare expenditures. With only $1514 USD per capita in 2017, the total annual health spending in Russia amounts to only 15% of the health spending in the USA ($10 207 USD) and approximately 40% of the OECD average ($3857 USD).[16] Interestingly, the

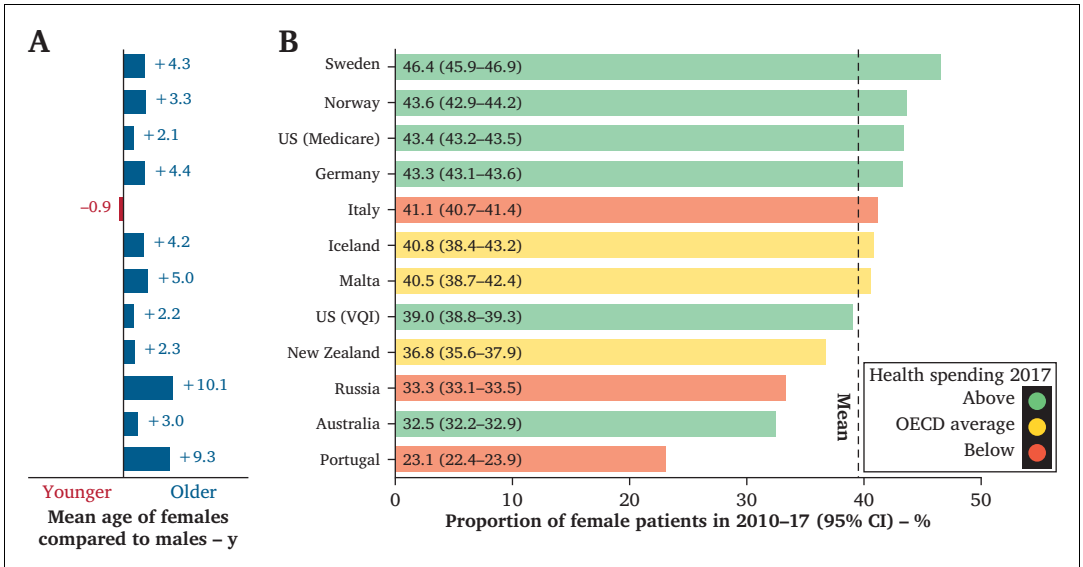

Figure 1. (A) Differences in mean age between women and men (y) and (B) mean proportion (95% confidence interval) of female patients among all hospitalisations between 2010 and 2017 in 11 countries participating in the VASCUNET and International Consortium of Vascular Registries. US = United States; VQI = Vascular Quality Initiative; OECD = Organisation for Economic Co-operation and Development.

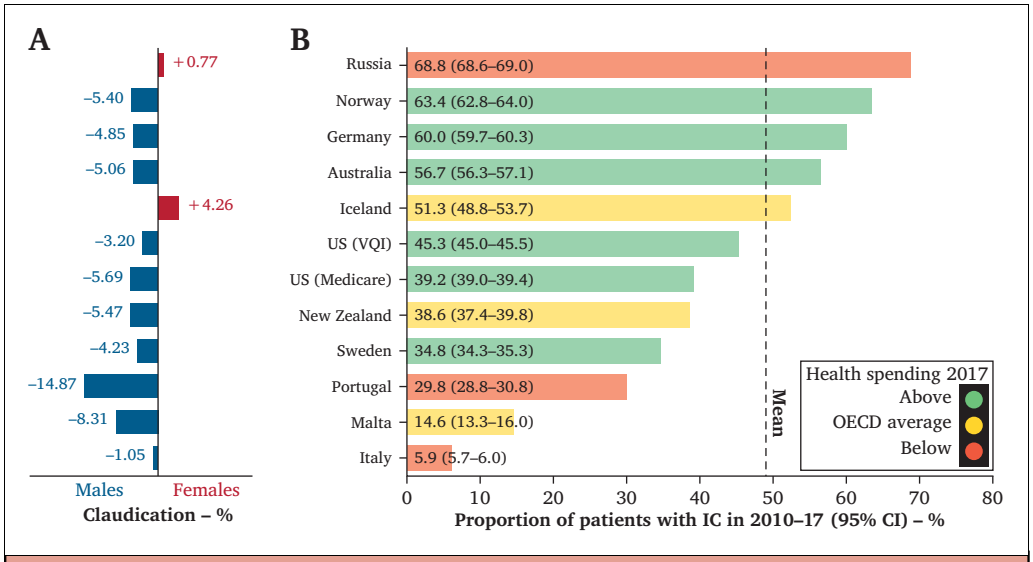

Figure 2. (A) Differences in the proportion of women and men with intermittent claudication (IC) and (B) mean proportion (95% confidence interval) of patients presenting with IC vs. chronic limb threatening ischaemia between 2010 and 2017 in 11 countries participating in the VASCUNET and International Consortium of Vascular Registries. US = United States; VQI = Vascular Quality Initiative; OECD = Organisation for Economic Co-operation and Development.

number of hospital beds per 1000 inhabitants in Russia was the third highest among all the OECD countries (8.1 in 2017) and Russia has the sixth highest rate of doctor consultations per year among all OECD countries (9.7 per capita in 2018).[17,18]

Indications for treatment have previously been suggested to be influenced by healthcare reimbursement models. Previous VASCUNET reports have shown a larger proportion of asymptomatic carotid stenosis (0% *vs.* 60%), minor *vs.* major amputations (14% *vs* 18%), and small abdominal aortic aneurysm (5% *vs.* 39%) selected for treatment in countries with fee for service *vs.* population based reimbursement.[5,19,20] The results of the current study indicate a higher proportion of elective revascularisation for patients with IC in countries where physician payment was, to some degree, dependent on the number of performed procedures (Supplementary Material). The wide overall regional variation for case selection is probably multifactorial. In

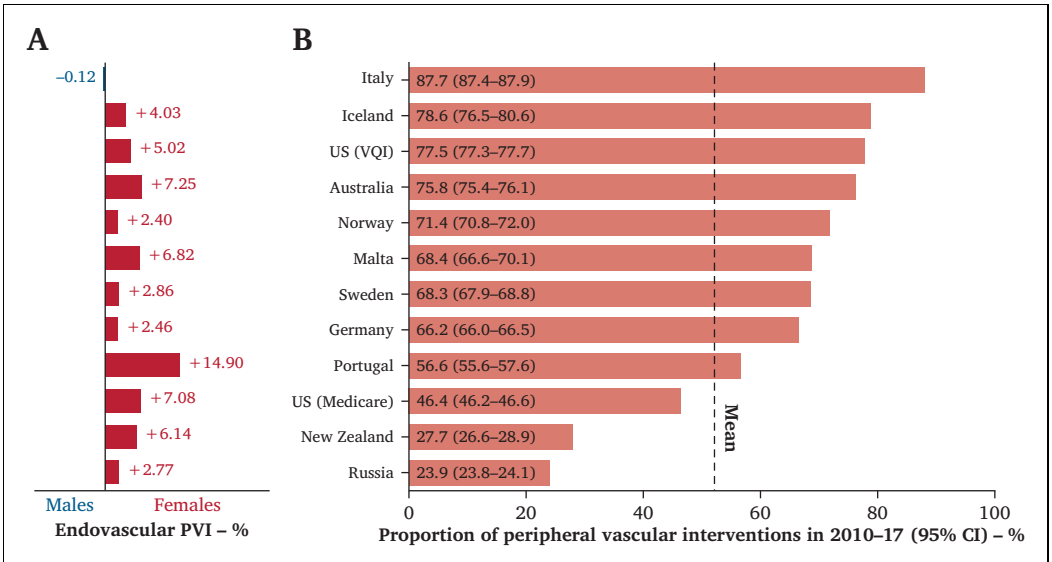

Figure 3. (A) Differences in the proportion of endovascular peripheral vascular interventions (PVI) between women and men, and (B) mean proportion (95% confidence interval) of patients being treated by endovascular peripheral vascular interventions vs. open surgery between 2010 and 2017 in 11 countries participating in the VASCUNET and International Consortium of Vascular Registries. US = United States; VQI = Vascular Quality Initiative.

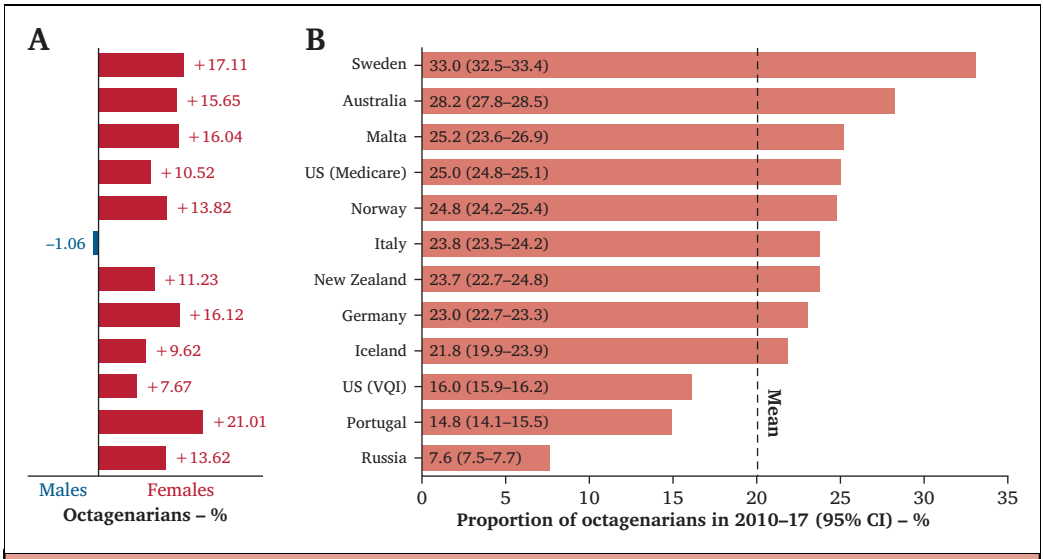

Figure 4. (A) Differences in the proportion of octogenarians between females vs. males and (B) mean proportion (95% confidence interval) of octogenarians among all hospitalisations between 2010 and 2017 in 11 countries participating in the VASCUNET and International Consortium of Vascular Registries. US = United States; VQI = Vascular Quality Initiative.

Norway, almost twice as many patients with IC were treated invasively compared with Sweden, despite Nordic countries having comparable population based reimbursement systems. Explanatory factors may be attitude towards quality of life and adherence to guidelines. Diverging regional systems for social security when there is loss of autonomy could be another influencing factor.

In the current study, a relatively high proportion of octogenarians was treated. The high proportion registered in Sweden may probably be related to the high proportion of patients with CLTI when compared with Russia, which had a lower life expectancy.

Other observational studies addressed the research topic of sex disparities in PAOD treatment. Hess *et al.* included some 400 000 patients (42% females) from the multicentre Premier Healthcare Database in the United States treated between 2009 and 2014.[21] Of these patients, 77% had endovascular treatment, and the authors reported improved outcomes for females regarding one year major adverse limb events.[21] Women are known to present at a later stage of the disease and often exhibit different or even atypical symptoms.[22,23]

The current study confirmed findings from prior publications and highlighted important sex disparities that may have implications for both patients and healthcare systems. Women were approximately three years older and underwent treatment at a more advanced disease stage, which is in agreement with other studies.[9,22–24] In a cohort study using Swedish national health care registries (2008–2013), the authors identified 18 742 revascularised patients with PAOD. When compared with females, males were more often revascularised for IC, which was also confirmed by the current study. In a multivariable model, the authors also identified male sex as independent predictor for a composite end point, including myocardial infarction, stroke, or cardiovascular death.[24] Another national Swedish audit of all hospitalised patients with PAOD revealed a similar prevalence between sexes. Further, men, although younger (73.3 *vs.* 76.6 years), had a significantly higher burden of cardiovascular related comorbidities and diabetes compared with females.[25] Ramkumar *et al.* used registry data from the VQI (2010–2013) comprising 26 750 procedures.[23] Although the authors found that women were less often current or former smokers, both the TransAtlantic Inter-Society Consensus classification and lesion characteristics were similar among men and women. Furthermore, although females presented more frequently with ischaemic rest pain, the authors concluded that treatment modalities did not vary by sex. Egorova *et al.* used 2.4 million inpatient discharge records (500 000 with PAOD) from New York, New Jersey, and Florida (1998–2007) to determine sex related differences.[9] When compared with their male counterparts, female patients were persistently three years older, more likely to be emergency admissions, and less often underwent invasive vascular procedures. The authors also observed that women were consistently less likely to undergo OSR throughout the entire period. While there were several differences regarding the methodology and cohort, the current study revealed diametrically opposed PVI rates for females *vs.* males in the USA using VQI registry data and Medicare claims. Besides other hypotheses, this indicates that the various registries used in observational studies are probably affected by marginal differences regarding the corresponding target population. Confirming previous reports, in the current study, women were less often treated by OSR. The reason for this is incompletely understood. A more advanced disease at later onset, smaller vessels and worse surgical outcomes have been proposed.[9,22–24] Differences in clinical presentation and PAOD awareness may also

contribute to these contrasts in procedural management.[26] Supporting these hypotheses, a previous claims analysis by Peters *et al.* recently revealed that females admitted with symptomatic PAOD at German hospitals were less often diagnosed with PAOD and more often received painkillers and antidepressants in the year before admission.[27]

In Portugal, fewer than one in four patients selected for revascularisation were women, despite making up 53% of the total population. In line with that, the proportion of IC was 15% higher in male patients, while the proportion of octogenarians was 21% higher in female patients, pointing to a rigorous selection of female patients.

Since the first VASCUNET report was published in 2012, several guidelines from international societies have been released concerning the diagnosis and treatment of PAOD.[28–30] Because half of all guideline recommendations were based on expert consensus due to a paucity of high level evidence, the treatment decision and preferred invasive procedure is often based on individual experience. Therefore, the observed variations do not necessarily imply worse adherence to the guidelines. The extent to which environmental factors, and physician and patient behaviours explain treatment patterns is not established. It seems likely, however, that male sex and procedural indication play an important role of delivery of care, a gap that may need to be reduced. Thus, future studies should aim to better understand the relationship between sex, treatment modalities, and outcomes. Large clinical and administrative registries can help to approximate to real world evidence that is generalisable to nationwide populations. However, possible selection bias and residual confounding should be addressed appropriately.

Limitations

This study has several limitations. Despite using a clear and detailed study protocol and search algorithm to permit comparable data extraction from governmental databases, there are still significant differences in coding practices, collection of administrative data, and availability of data. Owing to data privacy regulations, patient level data were not uniformly available for this study. Therefore, some procedures (e.g., bypass surgery, endarterectomy, and PVI) were collected and analysed as an individual event. Secondly, this study did not aim to adjust for comprehensive information regarding comorbidities. While the ICVR has previously published consensus recommendations for PAOD registry data collection, broader adoption is required for true harmonisation of data elements and their definitions. Robust data on diabetes or lifestyle factors such as smoking habits and physical activity were difficult to obtain.[31,32] Against that backdrop, it is possible that women exhibit a later onset of cardiovascular disease, and sex differences in smoking habits or diabetes have an impact on patient selection and practice. It is assumed that the practice of coding and registration has remained rather stable over time in each country, making the results more robust than the head to head comparisons between countries. While different healthcare reimbursement strategies may impact coding of comorbid conditions it is unlikely to impact coding of the procedure performed and the diagnosis associated with the procedure.

Conclusion

Remarkable differences were seen in the real world treatment of PAOD between both countries and sexes. Future studies should address the underlying reasons, including the impact of national societal guidelines and vascular health maintenance. It is hoped that this report will stimulate conversation between vascular specialists about the factors underlying these differences in practice.

CONFLICT OF INTEREST

None.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ejvs.2020.08.027.

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