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Mortality rate related to peripheral arterial disease: A retrospective analysis of epidemiological data (years 2008–2019)

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Abstract *Background and aims:* Peripheral arterial disease (PAD) is one of the most prevalent cardiovascular diseases with more than 230 million people being affected worldwide. As highlighted by the recent European Society of Cardiology guidelines, data on the epidemiology of PAD is urgently needed.

Methods and results: We accessed the vital registration data of the Veneto region (Northern Italy, approximately five millions inhabitants) covering the period 2008–2019. We computed annual age-standardized rates for PAD reported as the underlying cause of death (UCOD) or as one of multiple causes of death (MCOD). Age-adjusted odds ratios (OR) served to study the association between PAD and cardiovascular comorbidities.

The age-standardized mortality rate for PAD as MCOD slightly declined from 19.6 to 17.8 in men and from 10.8 to 9.1 deaths per 100,000 population-years in women. The age-standardized PAD-specific mortality rate (UCOD) remained stable: 3.1 to 3.7 per 100,000 person-years in women (Average Annual Percent Change 1.3, 95% CI -0.8; 3.4%) and 4.4 to 4.3 per 100,000 person-years (Average Annual Percent Change -0.2, 95% CI -3.6; 3.4%) in men. PAD contributed to 1.6% of all deaths recorded in the region. Ischemic heart disease, diabetes mellitus and neoplasms were the most prevalent UCOD among PAD patients. PAD was associated with diabetes mellitus (OR 3.79, 95%CI 3.55–4.06) and chronic kidney diseases (OR 2.73, 95%CI 2.51–2.97) in men, and with atrial fibrillation (OR 2.26, 95%CI 2.10–2.44) in women.

Conclusion: PAD remains a substantial cause of death in the general population of this high-income region of Western Europe with marked sex-specific differences.

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1. Introduction

Peripheral arterial disease (PAD) is one of the most prevalent cardiovascular diseases in aging societies, which are characterized by a high prevalence of diabetes, dyslipidemia, arterial hypertension, obesity, and smoking [1,2]. Its clinical presentation ranges from the absence of any symptoms to leg pain, intermittent claudication, and, in the most severe cases, critical limb ischemia [3]. The goal of medical treatment is to prevent the progression of the disease, whereas that of invasive therapies is to restore adequate blood flow, relieve symptoms, and reduce the risk of amputation.

A recent review has estimated that more than 230 million individuals suffer from PAD worldwide [2]. Changes in the prevalence of risk factors in ageing societies and in countries transitioning to a Western lifestyle influence the incidence and prognosis of PAD [4]. Indeed, patients with PAD are at a high risk for myocardial infarction and stroke, and largely contribute to healthcare costs and burdens [5]. As highlighted by the recent guidelines of the European Society of Cardiology [6] and the analysis of PAD prevalence from the Global Burden of Disease [2], more information is urgently needed on the epidemiology of PAD. Reliable estimates of PAD-related mortality are currently outdated or lacking [7–9]. In contrast, registry data showed that PAD patients are characterized by an excess fatality of about 60% [10]. Also in light of recent advances in the management of PAD [10–12], an improved understanding of contemporary trends in mortality rates would add to our knowledge of the disease. Furthermore, it may contribute to increase the awareness of this condition, which is often characterized by underdiagnosis and a low adherence to medical treatment [1,13].

In this study, we investigated time trends in age-standardized PAD-related mortality rates in a high-income region of Italy with a homogeneous healthcare system, geography, and population structure as a proxy for other Western regions with similar characteristics.

2. Methods

Located in north-eastern Italy, Veneto had approximately 5 million inhabitants as of 2019. Death certificates are forwarded to the regional epidemiology department. Causes of death are coded according to the International Classification of Diseases, 10th edition (ICD-10).

Standard mortality statistics follow international rules that identify one single underlying cause of death (UCOD) among all conditions reported in the certificate. Usually, the UCOD chosen by the physician who fills in the certificate is confirmed, but in some cases a different UCOD may be selected from those listed on the death certificate if considered more appropriate according to rules set by the World Health Organization. To standardize the UCOD assignment, automated procedures are commonly used. In Veneto, the Automated Classification of Medical Entities software was used until 2018, and the IRIS software, already adopted in most European countries, from 2018 onwards. In addition to UCOD, the database also includes all other comorbidities of each person listed on the death certificate as concomitant causes of death and thus can provide information on multiple causes of death (MCOD, defined as either underlying or concomitant causes of death).

All death certificates from January 1st, 2008 to December 31st, 2019 were examined. Death certificates were considered to be PAD-related, if the following ICD-10 codes were present in any position (underlying or concomitant cause of death): I70.2 (Atherosclerosis of native arteries of the extremities), I73.9 (Peripheral vascular disease, unspecified), I74.3 (Embolism and thrombosis of arteries of the lower extremities), I74.4 (Embolism and thrombosis of arteries of extremities, unspecified). The ICD-10 codes were chosen based on the previous epidemiological studies on PAD [14–16]. For each year, the number of deaths with PAD in any position (MCOD) and the number of deaths with PAD selected as the underlying cause (PAD as UCOD) were calculated first.

In addition, the age- and sex-specific mortality rates, age-standardized rates (direct standardization, 2013 European standard population), and the proportional mortality (share of PAD-related deaths out of all deaths) were calculated. Using the Joinpoint software, we estimated the Average Annual Percent Change (AAPC) in age-standardized rates throughout the study period with the corresponding 95% confidence intervals (95%CI). The underlying causes of death (UCOD) were also identified among certificates that presented PAD in any position. Finally, the association of the presence of PAD in any position on death certificates with the presence of each of the main cardiovascular risk factors and diseases (diabetes, atrial fibrillation, hypertension, chronic kidney disease, chronic obstructive pulmonary disease) in any position was investigated using age-adjusted odds ratios (OR) with 95%CI estimated by conditional logistic regression stratified by age. To assess whether variations by sex in OR estimates for PAD were statistically significant, interaction terms between sex and risk factors were added in regression models. Since cardiovascular diseases, in particular myocardial infarction and cerebrovascular diseases, are the main cause of death in developed countries, we removed ischemic heart diseases (IHD) and cerebrovascular diseases (CVD) from the reference group of patients who died without PAD to avoid dilution of the association between the risk factors and PAD, and we tested the association of IHD and CVD (vs. those with no PAD, IHD, or CVD) as well with each risk factor for comparison.

Data was analyzed with Stata (version 15.0) and RStudio (version 1.4). The analysis of causes of mortality is included among mandatory activities of the Regional Epidemiology Department according to regional and national law. The data serving for this analysis was anonymized and their use did not require ethics or institutional review board approval.

3. Results

Between 2008 and 2019, the average annual number of deaths from all causes was 46,494, for a total of 557,932 deaths. Of these, 4485 men and 4654 women died from

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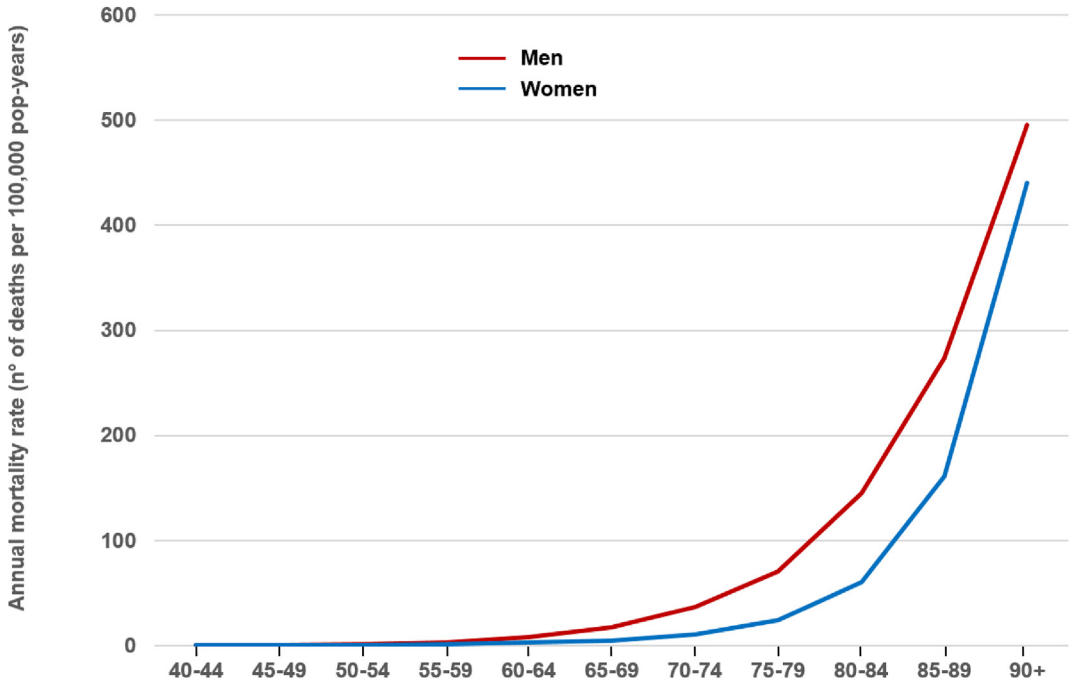

Figure 1 Exponential increase of PAD-related mortality across age groups and age-specific differences between sexes. Values are expressed as number of PAD-related deaths in any position of the death certificate per 100,000 population-years over the entire study period.

PAD or its complications, corresponding to 1.6% of all deaths recorded in the region. The corresponding crude PAD-related mortality was 15.6 per 100,000 person-years (2008–2019): 15.7 per 100,000 person-years in men and 15.5 per 100,000 person-years in women. The age-adjusted mortality rate for the whole population was 13.8 per 100,000 person-years for PAD as MCOD, and 3.9 per 100,000 person-years for PAD as UCOD. Fig. 1 shows the exponential increase of PAD-related mortality across age groups and age-specific differences between sexes. Data on the place of death show that the majority of PAD patients died in hospital (56.7%): a comprehensive overview for deaths with and without PAD is provided in Supplementary Table 1.

3.1. Trends in PAD-related mortality

Between 2008 and 2019, the age-standardized PAD-related mortality (MCOD) showed a slight decrease from 19.6 to 17.8 per 100.000 person-years in men and from 10.8 to 9.1 per 100,000 person-years in women. The age-standardized PAD-specific mortality (UCOD) remained stable: 3.1 to 3.7 per 100,000 person-years in women (AAPC 1.3, 95% CI -0.8; 3.4%) and 4.4 to 4.3 per 100,000 person-years (AAPC -0.2, 95% CI -3.6; 3.4%) in men; Fig. 2. Table 1 illustrates the trends in PAD-related proportionate mortality, suggesting a small increase over time.

3.2. Prevalence of concomitant diseases in patients with and without PAD

PAD was listed as the UCOD in 2613 patients (28.6% of all PAD deaths): 1043 men (23.3%) and 1570 women (33.7%). The other UCODs recorded in death certificates of PAD patients are listed in Table 2. In men, ischemic heart disease (17.3%), diabetes mellitus (14.2%) and neoplasms (13.6%) were the other most prevalent conditions listed that initiated the pathological progression to death among PAD patients. In women, these were diabetes mellitus (13.6%), ischemic heart disease (12.8%) and neoplasms (5.7%).

We calculated the odds of presenting with specific cardiovascular risk factors and related conditions for deaths with mention of the main cardiovascular conditions (PAD, ischemic heart disease, cerebrovascular disease) versus those without mention of any of them; Table 3. Diabetes was strongly associated with PAD, especially in men. PAD and CKD were frequently mentioned in the same death certificate, with a pattern similar to diabetes: estimated ORs were higher among males and decreased from PAD to IHD to CVD. Hypertensive diseases appeared to be less strongly associated to PAD than to other cardiovascular syndromes. Variation by sex in OR estimates for PAD was highly significant for all risk factors ($p < 0.001$ for interaction, data not shown); in contrast with other investigated conditions, the OR for atrial fibrillation was higher among females. Lastly, COPD, sharing a common risk factor (smoke) with cardiovascular syndromes, was significantly associated in death certificates to IHD, and to PAD only among men.

4. Discussion

The recent European Society of Cardiology guidelines on PAD highlighted that epidemiological data on PAD is needed and called for better disease-specific estimates. The present study is one of the first focused analyses of

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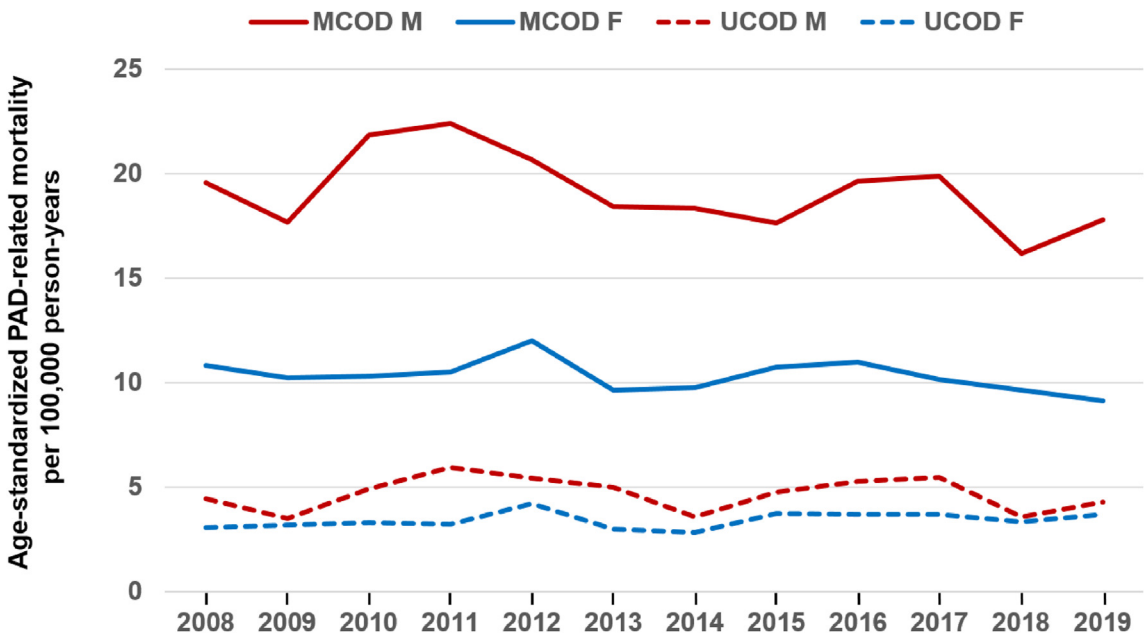

Figure 2 Annual age-standardized PAD-related mortality rate for multiple cause of death (MCOD) and underlying cause of death (UCOD) per 100.000 person-years in men (M) and women (F).

Table 1 Trends in PAD-related mortality rates in women and men, Veneto region, Italy.

	Years 2008–2011	Years 2012–2015	Years 2016–2019
Men			
UCOD, n	295	354	394
UCOD, Standardized mortality rate[a]	4.7	4.7	4.6
MCOD, n	1389	1479	1617
Proportionate mortality, %[a]	1.6%	1.7%	1.8%
MCOD, Standardized mortality rate[a]	20.4	18.7	18.3
Women			
UCOD, n	420	529	621
UCOD, Standardized mortality rate[a]	3.2	3.4	3.6
MCOD, n	1377	1606	1671
Proportionate mortality, %[a]	1.5%	1.6%	1.6%
MCOD, Standardized mortality rate[a]	10.4	10.5	10.0

PAD-related mortality rates are expressed as the number of PAD-related deaths per 100,000 population-years (pop-yrs). Proportionate mortality is expressed as the number of PAD-related deaths per 100 all-cause deaths in the general population.
Abbreviations: PAD, peripheral arterial disease; UCOD, underlying cause of death; MCOD, multiple causes of death
[a] Deaths per 100,000 pop-yrs

Table 2 List of the selected underlying causes of death from death certificates in patients with peripheral arterial disease (PAD).

Underlying cause of death	ICD-10 code	Men		Women	
		n	%	*n*	%
Peripheral arterial disease	I70.2, I73.9, I74.3, I74.4	1043	23.3%	1570	33.7%
Ischemic heart diseases	I20–I25	777	17.3%	595	12.8%
Diabetes mellitus	E10-E14	635	14.2%	631	13.6%
Neoplasms	C00-D48	611	13.6%	263	5.7%
Cerebrovascular diseases	I60–I69	191	4.3%	264	5.7%
Hypertensive diseases	I10–I15	172	3.8%	279	6.0%
COPD	J40-J44, J47	117	2.6%	57	1.2%
Dementia/Alzheimer disease	F01–F03, G30	83	1.9%	157	3.4%
Atrial fibrillation and flutter	I48	35	0.8%	98	2.1%
Total		4485		4654	

Abbreviations: COPD, Chronic Obstructive Pulmonary Disease

PAD-related mortality using individual patient level data. It illustrates that PAD substantially contributes to overall deaths (1.6% of total) in this Italian region of approximately five millions. In contrast to other cardiovascular conditions, the age-standardized PAD-related mortality (MCOD) showed only a slight decrease in both sexes, whereas it remained stable if PAD was considered as UCOD. Our study also emphasizes the interactions between PAD and specific cardiovascular risk factors or co-morbidities, including diabetes, chronic kidney disease, and atrial fibrillation, which exhibited a higher prevalence in PAD vs. non-PAD-related deaths. In ageing populations, it is foreseeable that the impact of PAD on the global burden of cardiovascular mortality will increase in the years to come.

Mortality from PAD as the underlying cause of death decreased between 1990 and 2017 in most high-income countries, as illustrated in an analysis of aggregated data from the Global Burden of Disease initiative [17]. In contrast, mortality related to PAD as a concomitant cause

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Table 3 Age-adjusted Odds ratios for the presence of selected conditions in the death certificates of individuals who died with peripheral arterial disease, ischemic heart disease or cerebrovascular diseases (vs. none of these conditions), by gender.

	OR for PAD (vs no PAD, IHD, CVD)	OR for IHD (vs no PAD, IHD, CVD)	OR for CVD (vs no PAD, IHD, CVD)
Men			
Diabetes mellitus	3.79 (95% CI 3.55; 4.06)	2.50 (95% CI 2.43; 2.56)	1.77 (95% CI 1.71; 1.83)
Atrial fibrillation	1.75 (95% CI 1.61; 1.91)	1.57 (95% CI 1.52; 1.62)	1.89 (95% CI 1.83; 1.96)
Hypertensive disease	1.52 (95% CI 1.41; 1.64)	1.84 (95% CI 1.79; 1.88)	1.78 (95% CI 1.73; 1.83)
COPD	1.26 95% CI 1.15; 1,38)	1.30 (95% CI 1.26; 1.34)	0.83 (95% CI 0.79; 0.86)
Chronic kidney diseases	2.73 (95% CI 2.51; 2,97)	1.94 (95% CI 1.87; 2.00)	1.10 (95% CI 1.05; 1.15)
Women			
Diabetes mellitus	2.86 (95% CI 2.67; 3.07)	2.05 (95% CI 2.00; 2.11)	1.47 (95% CI 1.43; 1.51)
Atrial fibrillation	2.26 (95% CI 2.10; 2.44)	1.60 (95% CI 1.55; 1.64)	1.99 (95% CI 1.94; 2.05)
Hypertensive diseases	1.15 (95% CI 1.07; 1.23)	1.55 (95% CI 1.51; 1.58)	1.55 (95% CI 1.51; 1.58)
COPD	0.89 (95% CI 0.78; 1.01)	1.29 (95% CI 1.24; 1.34)	0.71 (95% CI 0.68; 0.75)
Chronic kidney diseases	1.94 (95% CI 1.75; 2.15)	1.66 (95% CI 1.60; 1.73)	0.91 (95% CI 0.87; 0.96)

PAD: peripheral arterial disease; IHD: Ischemic Heart Disease; CVD: Cerebrovascular disease; COPD: Chronich Obstructive Pulmonary Disease; OR: odds ratio; CI: 95% confidence interval.

of death in the US showed a decline from 1999 to 2017 in both sexes [18]. To the best of our knowledge, analyses on the association between PAD and other conditions mentioned in death certificates are lacking. Our data show that PAD contributed as either underlying or concomitant cause to approximately 16 deaths per 100,000 general population in the period 2008–2019, corresponding to 1.6% of all deaths, which is in line with estimates from other countries. This mortality rate is similar to that of other major cardiovascular causes of death, like pulmonary embolism or chronic obstructive pulmonary disease. We could not find a significant trend in age-adjusted PAD-related mortality: this finding is at odds with the general decline in the mortality rate of cardiovascular diseases in high-income countries, which has been explained by improvement in medical and endovascular treatment, as well as a control of major risk factors [19]. An explanation could be that better awareness for PAD led to more diagnoses been made, therefore increasing the overall prevalence of the disease and, indirectly, mortality rates. Indeed, mortality for cardiovascular diseases remains high and shows an increasing trend in the low- and middle-income countries. Late diagnosis from lack of awareness on signs and symptoms, insufficient preventive care, inadequate control of blood pressure, and decreased physical activity are the underlying reasons for this increase [20]. Additional studies should dissect if there are time trends concerning the severity of the disease, namely more “low-risk” PAD cases being diagnosed over time. This information would have clinical implications concerning pharmacological prevention, the quality of which is still falling short in real life [21], and endovascular treatments.

The higher proportion of PAD-specific mortality both as MCOD and UCOD in men as compared to women may reflect the sex-specific distribution of smokers [22–24]. Interestingly, PAD-specific mortality (UCOD), remained constant over the decade in the male population, whereas in women it showed a tendency towards a slight increase. There are several possible reasons for the difference in trends. First, smoking rates among women in their teens converged with those among men during the 1980ss and 1990s; women who were in their teens in those decades reached the age at which clinically relevant PAD complications typically occur in the past decade. Indeed, current or former tobacco use is strongly associated with mortality in patients with PAD [25], and PAD patients with COPD have a higher risk of cardiovascular death, MI, or ischemic stroke compared with those without COPD in the EUCLID trial [26]. COPD was not associated with PAD-related mortality among women in our study.

The clear association of PAD-specific mortality with diabetes mellitus in our study indicates that these two conditions are mutually responsible for progression to terminal stages of the disease. Progression of PAD was shown to be associated with increased mortality in diabetic patients [27]. In another study of patients with symptomatic PAD, mortality rates were twice as high in the presence of diabetes mellitus and five times as high in diabetic patients with advanced age [28]. These findings are consistent with the direction and magnitude of the association we observed.

Conditional logistic regression showed that the association between PAD and specific comorbidities, like diabetes mellitus, hypertensive diseases, and chronic kidney disease, was stronger in men than in women. The opposite was the case for atrial fibrillation. The complex interactions between cardiovascular risk factors, sex-specific scoring systems, drug compliance, and genetic differences alone could hardly explain this difference [29]. Efforts are being done to tailor primary and secondary cardiovascular prevention, and acute treatment, in men and women to take into account these differences [30–32].

Our data integrates existing information on the prevalence, risk factors, and fatality of peripheral vascular disease [2]. Because peripheral vascular disease does not rank in the top 10 causes of death worldwide, apart from representing a component of cardiovascular diseases, its importance may have been so far underestimated. A recent systematic review that investigated survival and morbidity in contemporary PAD cohorts showed pooled event rates for all-cause mortality and mortality from cardiovascular causes of 113 and 39 per 1000 person-years, respectively [4].

Our study has limitations. First, the cause of death was derived using ICD-10 coding in death certificates and was not based on autopsy results. Second, in some cases UCOD may have been based on subjective judgement of a treating physician and does not necessarily reflect the true cause of death. Third, not all pathologies are listed on

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death certificates. Finally, our analysis was restricted to the Veneto region in Italy only and may not necessarily be generalizable to other populations, specifically from low and middle-income countries.

In conclusion, PAD contributed to 16 deaths per 100,000 general population in the period 2008–2019 in Veneto with a non-significant decrease in the overall age-standardized PAD-related mortality (MCOD). PAD-specific mortality (UCOD) was higher in men than in women. PAD is still characterized by marked sex-specific differences in the prevalence of risk factors, also if accounting for their sex-specific distribution in the general population without PAD.

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Author contributions

Stefano Barco, Ugo Fedeli: concept and design, analysis, and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published. Davide Voci, Marc Righini, David Spirk, Luca Valerio, Elena Schievano, Nils Kucher: analysis and/or interpretation of data; critical writing or revising the intellectual content; and final approval of the version to be published.

Declaration of competing interest

Stefano Barco has received congress and travel payments from Daiichi-Sankyo, Boston Scientific, and Bayer HealthCare; institutional grants from Sanofi, Boston Scientific, Bard, and Bayer HealthCare; and personal fees and honoraria from Bayer HealthCare, LeoPharma, Boston Scientific, and Daiichi-Sankyo, outside the present work. David Spirk reports employment by Sanofi-Aventis. Nils Kucher reports grants from Concept Medical, Bard, and Bayer; and personal fees from Bayer, Bard, Medtronic, Boston Scientific, BTG, and Pfizer, outside the submitted work. Marc Righini has received speaker's honoraria from Bayer, Daïchi Sankyo, Pfizer/BMS, and Biomérieux. The other authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2022.11.020.

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