https://doi.org/10.31925/farmacia.2025.1.9 **ORIGINAL ARTICLE**

AGE AS IMPORTANT FACTOR IN TREATMENT OF PERIPHERAL ARTERIAL DISEASE: MONTE CARLO NUMERICAL ANALYSIS APPLICATION

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Abstract

Peripheral arterial disease (PAD) is a growing global health concern, with age being the strongest non-modifiable risk factor for its progression. Despite various therapeutic options, the chronic nature of PAD makes achieving optimal treatment outcomes challenging. This study aimed to identify a mathematical correlation using a hypothetical patient cohort to assess the impact of age on claudication distance (CD) improvement after six months of pharmacological therapy. A total of 82 PAD patients were treated with dual therapy: pentoxifylline + acetyl-salicylic acid (ASA/PEN) or cilostazol + acetyl-salicylic acid (ASA/CIL). Results showed a significant increase in CD after six months in the ASA/CIL group ($p = 0.042$). Age was also significantly associated with both initial CD ($p < 0.001$) and CD improvement after treatment ($p < 0.013$). Monte Carlo (MC) simulation highlighted the benefit of early ASA/CIL therapy, particularly in patients aged 55 - 65 years, for maximizing walking distance improvements. Our findings suggest that MC numerical analysis is a valuable tool for PAD treatment optimization, demonstrating strong predictive ability. Further studies with larger cohorts are needed to validate this approach and refine individualized treatment strategies.

Rezumat

Boala arterială periferică (BAP) este o problemă de sănătate globală în creștere, vârsta fiind cel mai puternic factor de risc pentru progresia acesteia. Deși există diferite opțiuni terapeutice, natura cronică a BAP face dificilă obținerea unor rezultate optime ale tratamentului. Acest studiu a urmărit să identifice o corelație matematică folosind o cohortă ipotetică de pacienți pentru a evalua impactul vârstei asupra îmbunătățirii distanței până la claudicație (DC), după șase luni de tratament farmacologic. Un total de 82 de pacienți cu BAP au fost tratați cu terapie dublă: pentoxifilină + acid acetil-salicilic (AAS/PEN) sau cilostazol + acid acetil-salicilic (AAS/CIL). Rezultatele au arătat o creștere semnificativă a DC după șase luni în grupul AAS/CIL ($p = 0,042$). Vârsta a fost, de asemenea, asociată semnificativ atât cu DC inițială ($p < 0,001$), cât și cu îmbunătățirea DC după tratament ($p < 0,013$). Simularea Monte Carlo (MC) a evidențiat beneficiul tratamentului AAS/CIL precoce, în special la pacienții cu vârsta cuprinsă între 55 - 65 de ani, pentru maximizarea îmbunătățirii distanței de mers. Constatările noastre sugerează că analiza numerică MC este un instrument valoros pentru optimizarea tratamentului BAP, demonstrând o capacitate predictivă puternică. Sunt necesare studii suplimentare cu cohorte mai mari pentru a valida această abordare și pentru a rafina strategiile de tratament individualizate.

Keywords: peripheral arterial disease, age, Monte Carlo analysis

Introduction

Peripheral arterial disease (PAD), primarily driven by progressive atherosclerosis, is a global public health problem owing to its high and rising prevalence and association with functional decline, immobility, cardiovascular events, and negative impact on an individual's quality of life [1]. It is common in both men and women, whereas prevalence increases with age, in such a manner that more than 10% of those aged 65 and older will have intermittent claudication in the lower limbs as the hallmark of PAD clinical presentation [2, 3]. In addition to numerous modifiable factors (smoking, hypertension, hyperlipidaemia, obesity, diabetes, physical inactivity), age is considered the strongest non-modifiable determinant for the development and progression of PAD [4]. Younger age at PAD diagnosis may require more aggressive interventions focused on cardiovascular event prevention and treatment. Therefore, early diagnosis, timely initiation of pharmacotherapy, and consideration of the present risk factors are very important to improve walking ability and avoid severe complications [5]. Despite the large number of therapeutic modalities, chronic and progressive

characteristics of PAD make it difficult to achieve optimal therapeutic goals [1]. Antiplatelet therapy is recommended to reduce the cardiovascular risk in patients with symptomatic PAD, while cilostazol and pentoxifylline may be effective therapeutic options to improve symptoms and increase walking distance in patients with claudication [6].

The present study is the continuation of the research published by Damnjanović *et al*. [7], whose results showed that the female gender, dyslipidaemia, and hypertension had a significant effect on the applied pharmacotherapy in patients with PAD. In our study, we focused on age as an important factor in the treatment of PAD. In order to overcome a small study population, lack of power, and risk of causing statistical errors, we performed Monte Carlo (MC) simulation. Therefore, the aim of this study was the identification of mathematical correlation using a large hypothetical cohort of patients to demonstrate the impact of the patient's age in improving the claudication distance after six months of medication therapy in patients with PAD.

Materials and Methods

This prospective study was conducted at the Clinic of Vascular surgery, University Clinical Centre of Nis, Serbia. Data was collected over a 12-month period, from January 2020 to December 2020. The research included respondents diagnosed with lower extremity peripheral artery disease for the first time. The criteria applied for inclusion in the study involved: patients with stage IIa and IIb disease according to Fontaine, in whom PAD of the lower extremities had been verified using Doppler sonography or MSCT angiography [8].

The research protocol was approved by the Ethics Committee of the Faculty of Medicine, University of Niš (12-15637-2/5 dated 12/24/2019). The research was fully adapted to the Declaration of Helsinki on ethical behaviour and conducted according to the principles of Good Clinical Practice (GCP). All patients were informed about the purpose of the study and voluntarily signed the consent. The research was designed as a prospective cross-sectional study comprising a survey. The survey included questions with close answers and different variants from dichotomous to combined ones, as well as additional open questions. In order to protect patient data, each patient was assigned a code at the beginning of the study. The following data were collected: demographic characteristics (gender, age, body mass index (BMI)); therapy characteristics (medicine and administered dose); the presence of risk factors (smoking, obesity, diabetes, dyslipidaemia and hypertension), measured initial claudication distance before medicine administration (CD0) and claudication distance 6 months after treatment was applied (CD6). Claudication distance is defined as the walking distance after which the patient is forced to stop because of severe pain and muscle cramps. In order to adequately analyse the data, the subjects were divided into groups according to gender, age, applied dual therapy modalities, pentoxifylline 1200 mg/day + acetyl-salicylic acid 100 mg/day (ASA/PEN) or cilostazol 200 mg/day + ASA 100 mg/day (ASA/CIL). The detailed protocol of research is described in the paper written by Damnjanović *et al.* [7]. It is unusual for PAD to manifest in those aged < 55 years, but its prevalence increases sharply with age [4]. According to this, the patients were divided into three age categories (55 - 64 years, 65 - 75, ≥ 75 years).

Statistical analysis

The characteristics of the study group were expressed as the median and interquartile range or mean and standard deviation or frequency (with or without percentages). Student's t-test (for normally distributed data) or the Kruskal-Wallis Test and Mann–Whitney U test (non-normally distributed data) were employed for the comparison of two or more (Kruskal-Wallis Test) independent samples. Univariate and multivariable linear regression analysis was conducted in order to estimate factors influencing CD6 values after six months of medication therapy. Confounding factors can influence both the dependent and independent variables, potentially distorting the true relationship between them. In the case of linear regression, confounders were controlled by including them as independent variables. Therefore, we adjusted our model for confounders. The multivariate regression included all covariates that were significant in the univariate models. Regression equation was created, which served as a basis for MC simulation, performed by Matlab software.

Numerical analysis using Monte Carlo simulation method

This chapter presents a numerical analysis of previously experimentally obtained results and a derived regression model using the MC simulation method. This method is very useful and has found its application in almost every field of research [9, 10].

Results and Discussion

The study involved 82 patients, 59.76% males and 40.24% females. Descriptive data, demographic information, and pharmacotherapy characteristics of the respondents are presented as absolute and relative numbers, mean values ± standard deviations (SD), centre (median) values, and interquartile difference (Table I).

Table I

Descriptive, demographic and pharmacotherapy characteristics of the respondents

Gender	**N**	**%**
Male	49	59.76
Female	33	40.24
Age (years)	Mean: 67.62 ± 8.22 Median: 69 Interquartile range: 62 - 73	
55-64	29	35.37
65-74	36	43.90
≥ 75	17	20.73
BMI (kg/m^2)	Mean: 30.82 ± 3.21 Median: 31.45 Interquartile range: 28.7 - 32.8	
< 30	23	28.05
≥ 30	59	71.95
Claudication distance	**N**	**%**
CD0	Mean: 201.71 ± 64.17 Median:185 Interquartile range: 155 - 245	
CD6	303.03 ± 167.17 Median: 295 Interquartile range: 220 - 395	
Risk factor	**N**	**%**
Obesity	59	71.95
Smoking	63	76.82
Diabetes	57	69.51
Dyslipidaemia	52	63.71
Hypertension	62	75.60
Pharmacotherapy	**N**	**%**
ASA/PEN	40	48.78
ASA/CIL	42	51.22

The median age was 69 years (interquartile range 62 - 73 years old). The body mass index ≥ 30kg/m^2 was recorded in 71.95% of respondents. Smoking was the most prevalent risk factor (76.82%), while dyslipidaemia was the least prevalent (63.71%). In the conducted research, 48.78% of subjects received the combination of ASA/PEN, while the therapeutic regimen of ASA/CIL was administered to 51.22%. The median CD0 was 185 m, while median CD6 therapy was 295 m.

Table II shows CD0 and CD6 values in relation to the applied therapeutic modality (ASA/CIL or ASA/PEN).

Table II

Values of CD0 and CD6 in relation to the therapeutic regimen

Treatment	**CD0**	**CD6**
ASA/CIL	203.10 ± 57.66 182.55 (110)	367.98 ± 168.28 310 (192.50)
ASA/PEN	200.25 ± 71.09 185 (80)	310.13 ± 162.82 267.50 (196.25)
Mann-Whitney U test	Z = -0.474 (p = 0.636)	Z = -2.032 (**p = 0.042**)

The results of the conducted research show a statistically significant prolongation of CD6 in the group of patients who applied ASA/CIL (p = 0.042). The management of PAD varies depending on the disease severity and symptom status, but the major goals of treatment strategies are to lower cardiovascular risk and to improve walking ability [11]. Options are limited for pharmacologic management of intermittent claudication symptoms. The backbone of modern pharmacotherapy for PAD consists of antiplatelet drugs (ASA or inhibitors of P2Y12 receptors) and peripheral vasodilators [12, 13]. Pentoxifylline and cilostazol are the most commonly used vasoactive drugs to increase walking distance, in addition to walking exercise and the management of risk factors [6]. Improvements in blood viscosity and erythrocyte

deformability have been cited as potential mechanisms of action for pentoxifylline [14]. Cilostazol is a phosphodiesterase-III inhibitor, which has vasodilatory, antiplatelet, and antithrombotic actions, and available guidelines for the treatment of PAD favour its use [12].

The obtained results are in accordance with a large number of already conducted studies that confirm the importance of the use of peripheral vasodilators in PAD treatment [15, 16]. The efficacy of pentoxifylline in treating PAD and improving claudication distance was investigated in a large number of studies, but their results are not coherent [15, 16]. Randomised multicentre studies examining the effects of pentoxifylline differed significantly in both design and by the final effects on improving intermittent claudication symptoms. In the therapy of intermittent claudication, cilostazol occupies the most important place. The results of clinical trials show that cilostazol significantly improves blood perfusion in the lower extremities, which consequently leads to a significant prolongation [17, 18]. Also, the synergistic effect of the administration of cilostazol and acetylsalicylic acid is confirmed, justifying the simultaneous administration of these drugs [19]. The results of the conducted research show a statistically significant prolongation of CD6 in the group of patients who applied ASA/CIL (Table II), and they are in line with the existing results on the importance of using cilostazol in PAD therapy [17, 18, 20]. A comprehensive approach to treating PAD as a chronic condition may be impacted by variations in adherence levels. Poor adherence to medication is a global challenge, particularly in long-term therapies [21]. Therefore, ensuring high adherence should be a priority for healthcare professionals to enhance therapeutic outcomes in the long-term management of PAD [22].

In order to analyse the detailed influence of the age of the patients on the prolongation of the claudication distance, the patients were divided into three age categories. Table III shows CD0 and CD6 values in relation to the age categories of respondents.

Table III

Values of CD0 and CD6 in relation to the age of respondents

Age (years)	**CD0**	**CD6**
55 - 64 (group 1)	239.66 ± 77.86 245.00 (112.50)	432.76 ± 210.49 360.00 (375.00)
65 - 74 (group 2)	181.39 ± 40.91 172.50 (60)	295.42 ± 88.10 292.50 (153.75)
> 75 (group 3)	180.00 ± 50.37 165.00 (30)	275.00 ± 149.41 230.00 (110)
Kruskal Wallis Test	Chi-Square = 13.444 (**p = 0.001**)	Chi-Square = 8.696 (**p = 0.013**)
Mann-Whitney U test, post hoc	1 *vs*. 2, Z = -3.285 (**p = 0.001**) 1 *vs*. 3, Z = -2.895 (**p = 0.004**) 2 *vs*. 3, Z = -0.449 (p = 0.654)	1 *vs*. 2, Z = -2.178 (**p = 0.029**) 1 *vs*. 3, Z = -2.493 (**p = 0.013**) 2 *vs*. 3, Z = -1.545 (p = 0.122)

In relation to the age of the subjects, the results of the conducted research indicate the existence of a statistically significant difference in the value of the initial claudication distance (CD0) between groups with a significance of $p < 0.001$, as well as within groups ($p = 0.001$ (group 1 *vs*. group 2); $p = 0.004$ (group 1 *vs*. group 3)). When it comes to the value of CD6, a statistically significant difference was noted between the examined groups ($p < 0.013$), as well as within the groups ($p = 0.029$ (group 1 *vs*. group 2); $p = 0.013$ (group 1 *vs*. group 3)). Diseases that disproportionately affect the elderly, such as PAD, have special significance for a variety of reasons. In order to promote healthy ageing, it is imperative to improve outcomes of diseases that affect the elderly [23]. Understanding the relationship between risk factors and disease prevalence may contribute to achieving optimal therapeutic goals. Increasing age is a well-known risk factor for atherosclerosis and therefore for the development and progression of PAD. Moreover, vascular dysfunction has been shown to increase with age because of decreased compliance, angiogenesis, endothelial antithrombotic properties, and increased inflammation [24]. A large number of factors that contribute to the progression of PAD are positively correlated with the age of the patient. While recommendations for the prevention and treatment of PAD do not vary based on age, elderly patients with PAD may be less likely to receive the recommended therapy [25]. In accordance, the effectiveness of treatments may differ according to the age of patients. In our study, the walking distance decreased with increasing age of the patients. The obtained results can be explained by the fact that with age, distinct changes occur at the level of each blood layer vessel, and the resulting changes trigger a cascade of events that lead to stiffness, thickening the arteries, and reducing the availability of nitric oxide [26, 27].

Table IV shows CD0 and CD6 values in relation to the age of respondents and the applied therapeutic modality.

Table IV

Values of C0 and C6 in relation to the age of respondents and the applied therapeutic modality

Age group (years)	Treatment	CD0	CD6
55 - 64	ASA/CIL	238.93 ± 62.52 265.00 (130)	486.79 ± 200.86 522.50 (350)
	ASA/PEN	240.33 ± 92.17 195 (115)	382.33 ± 213.32 295.00 (122.50)
	Mann-Whitney U test	Z = -0.022 (p = 0.983)	Z = -1.506 (p = 0.132)
65 - 74	Treatment	CD0	CD6
	ASA/CIL	180.00 ± 42.43 172.50 (57.50)	309.00 ± 83.36 300.00 (102.50)
	ASA/PEN	183.13 ± 40.24 175 (61.25)	278.44 ± 94.02 267.50 (186.25)
	Mann-Whitney U test/Student t test	Z = -0.367 (p = 0.713)	t = 1.033 (p = 0.309)
> 75	Treatment	CD0	CD6
	ASA/CIL	198.13 ± 56.63 175 (86.25)	307.50 ± 172.44 247.50 (92.50)
	ASA/PEN	163.89 ± 40.60 155 (50)	246.11 ± 128.96 215.00 (180.00)
	Mann-Whitney U test	Z = -1.690 (p = 0.910)	Z = -1.301 (p = 0.193)

Analysing the obtained results, no statistically significant difference was noticed for the values of CD0 and CD6 in relation to the age of the subjects and the therapy they applied. In relation to the therapeutic modalities, there was no statistically significant difference in CD0 and CD6 in relation to the age subgroups of the subjects (Table 4). In general, the pharmacokinetic profile of cilostazol is not influenced by age or gender [28].

Based on the previously obtained results, regression analysis was conducted in order to assess the factors that might affect the value of CD6. Table V shows the results of the univariate regression analysis of the CD6-dependent variable adjusted for CD0 (base model).

Table V

Univariate regression analysis of the CD6-dependent variable adjusted for CD0

Model	Covariate	B (95% CI)	Beta	Sig.	R^2 (%) *
Base	CD_0	2.002 (1.631 - 2.373)	0.768	< 0.001	59.1 (< 0.001)
Base+Gender	Gender (female)	-7.190 (-57.279 - 42.889)	-0.021	0.776	59.1 (< 0.001)
Base+Age	Age (years)	-2.783 (-5.961 - (-0.396))	-0.137	0.085**	60.6 (< 0.001)
Age (years)	Age (years)	-9.064 (-13.118 - (-5.011))	-0.445	< 0.001	19.8 (< 0.001)
Base+BMI	BMI (absolute values)	-10.310 (-17.827 - (-2.792))	-0.198	0.008	62.6 (< 0.001)
Base+Smoking	Smoking	-60.420 (-119.766 - (-1.074))	-0.153	0.046	61.1 (< 0.001)
Base+DM	DM	-2.414 (-59.410 - 54.582)	-0.007	0.933	59.1 (< 0.001)
Base+DYS	DYS	-71.782 (-122.515 - (-21.050))	-0.208	0.006	62.8 (< 0.001)
Base+HTA	HTA	-58.143 (-113.443 - (-2.842))	-0.150	0.040	61.2 (< 0.001)
Base+risk factors	Risk factors (> 3)	-55.269 (-105.552-(- 5.017))	-0.163	0.032	61.4 (< 0.001)
Base+treatment	ASA/CIL *vs.* ACA/PEN	52.181 (5.996 - 98.367)	0.157	0.027	61.5 (< 0.001)

Significance of the whole model; **significant negative correlation with CD0 (r = -4.3); B-unstandardized coefficient; CI-confidence interval; Beta-standardized coefficient; Sig.-significance of the present covariate; R^2-proportion of the variance explained by the present model; BMI-body mass index; CD0-claudication distance at the beginning of the treatment (the first examination); CD6-claudication distance at 6th month after treatment. DM-diabetes mellitus; DYS-dyslipidemia; HTA-arterial hypertension; ASA-acetylsalicylic acid; CIL-cilostazol; PEN-pentoxifylline.

Univariate analysis identified age, BMI, smoking, DYS, HTA and the number of risk factors > 3 and applied therapeutic modalities as potential covariates that influence the values of the claudication distance 6 months after the applied therapy. Individual models were fitted to CD0. The influence of potential covariates from univariate analysis was additionally analysed by multivariate regression analysis (Table VI).

Finally, results of multivariate regression indicated that CD0, age, BMI and applied therapeutic modalities do represent significant predictors for CD6 values. Further validation of the obtained model was carried out by MC numerical analysis, where the basis for the simulation model was the regression equation obtained from the multivariate model.

Table VI

Multivariate regression analysis of CD6-dependent variable adjusted for CD0

Model: Base+Age+BMI+Smoking+DYS+HTA+Risk factors+Treatment				
Covariate	**B (95% CI)**	**Beta**	**Sig.**	**R^2 (%)***
Constant	725.145 (351.238 - 1099.051)	/	< 0.001	**73 (< 0.001)**
Base (CD_0)	1.326 (0.912 - 1.739)	0.509	< 0.001	
Age (years)	-3.599 (-6.527 - (-0.671))	-0.177	0.017	
BMI (apsolute values)	-12.587 (-21.418 - (-3.757))	-0.242	0.006	
ASA/CIL *vs*. ASA/PEN	65.923 (24.735 - 107.111)	0.198	0.002	
Smoking	-64.935 (-134.747 - 4.877)	-0.165	0.068	
DYS	-52.300 (-111.577 - 6.977)	-0.152	0.083	
HTA	-24.308 (-86.031 - 37.416)	-0.063	0.435	
Risk factors (> 3)	28.866 (-44.940 - 102.673)	0.085	0.438	

The obtained model better explains the variability of CD6 (r^2 = 73%) compared to the basic model *(r^2 = 59%).

Numerical analysis using Monte Carlo simulation method

This chapter presents a numerical analysis of previously experimentally obtained results and a derived regression model using MC simulation method. According to the regression model, a simulation scheme is constructed (Figure 1a). The Simulink regression model scheme implies: a0 = 725.145, a1 = -12.587, a2 = 1.326, a3 = -3.599, a4 = 65.923. Blocks BMI, CD0 and AGE are the input signals and present body mass index, claudication distance at the first check-up and patient's years respectively. If the therapy is included block ASA takes value 1, and 0 when there is no therapy. The output block of this scheme (CD6) presents the estimated claudication distance after 6 months of treatment.

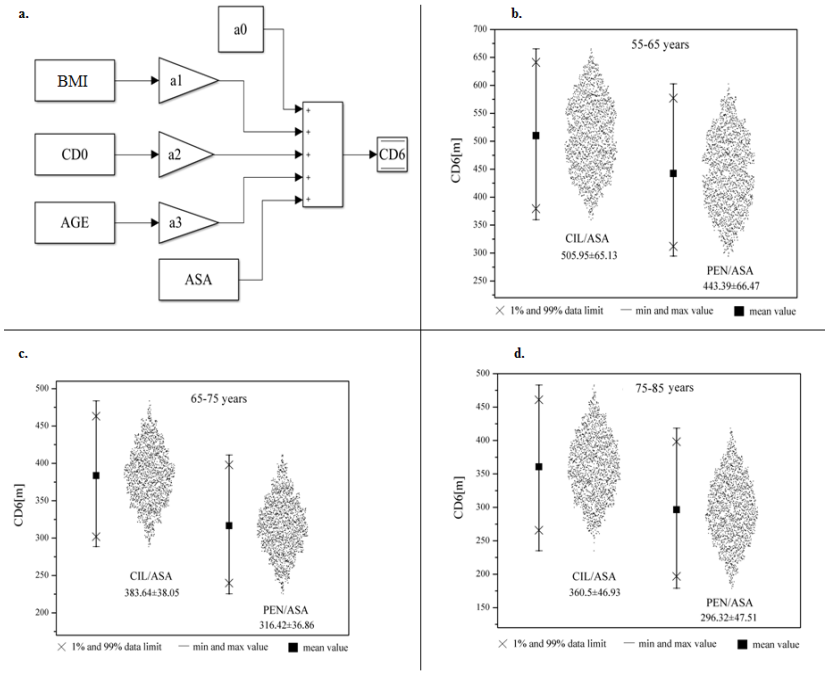

Figure 1.

Simulink regression model scheme

According to BMI and CD0 measured values, the ranges for different age groups of these parameters are calculated as mean values and their standard deviations (Table I). The data from these ranges were further used as an input parameter in the MC simulation scheme from Figure 1a. Now, after 2000 simulations for different combinations of BMI and CD0 parameters and replacing in the regression model, according to the simulation model from Figure 1a, 2000 different values for CD6 are obtained and presented in Figures 1b - 1d. This procedure was repeated for different age groups (age: 55 - 65, age: 65 - 75, age: 75 - 85).

Figure 2 compares the regression model with the basic one, which includes only one variable (CD6 = - 64.044 + 2.002 x CD0).

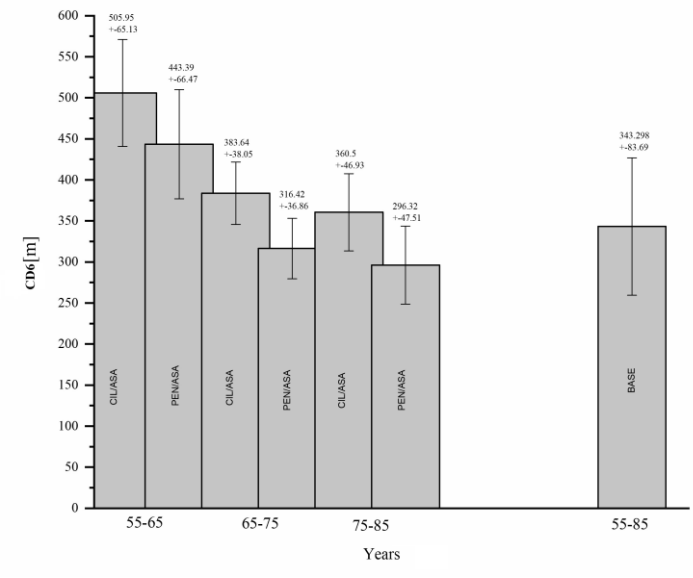

Figure 2.
Comparation of the regression model with the basic one

As we can see in this figure, the base model presents a significantly wider picture of output results compared to regression model outputs analysed in this work, especially if we compare the standard deviation values of both models, where the reduction in standard deviations goes from 22.17% to 55.95%. In addition, regression models showed a reduced coefficient of variation, 10 - 16% compared to the base model (24%). This figure also shows that the basic model does not consist of expected values for the age of 55 - 65 years. Finally, considering more patient parameters (age and treatment) with an MC generation of 1000 numerical patients significantly impacts model optimisation by reducing the expected output range. The Monte Carlo model is an influential statistical method that uses random sampling to simulate various potential outcomes and uncertainties. In clinical settings, it plays a crucial role in advancing precision medicine by helping clinicians and researchers navigate the complexities of individualised patient care. It allows for optimising drug efficacy and treatment strategies across a range of clinical scenarios [29]. The model's flexibility also enables the assessment of uncertainties, offering valuable insights for resource allocation, cost-effectiveness evaluations, and strategic healthcare planning. Through simplified examples and applications, healthcare practitioners can enhance their understanding and use of the MC method to improve decision-making, refine analytical accuracy, and contribute to better healthcare outcomes [29,30]. Literary data indicate that until now, MC modelling is used to assess the cost-effectiveness of various therapeutic agents in patients with PAD [31, 32] or to estimate the lifetime risk of PAD [33]. To our knowledge, this is the first application of MC simulations to estimating the influence of age in improving the claudication distance in patients with PAD. We used an MC simulation to investigate the impact of age on improving the claudication distance and measurement variability on treatment outcomes for different age patient subgroups. The results of the conducted research indicate dominance for the application of the CIL/ASA therapeutic modality, with the best results achieved in patients aged 55 - 65 years. So, in accordance with vascular ageing, timely detection of the disease and early introduction of therapy can significantly affect the improvement of the claudication distance in patients with PAD.

This study has several limitations. First, a short time of monitoring of the medication therapy and the relatively small sample size make it difficult to allow identifying relationships among patients' characteristics and the long-term improvement of claudication distance. Possibly, additional influence from covariates could be identified if the sample size was larger and if medication therapy was used for a longer period.

Conclusions

In conclusion, the patient's age is positively associated with the improvement of the claudication distance after six months of medication treatment in patients with PAD. Although classical statistical methods did not confirm a statistically significant difference in the application of the analysed therapeutic modalities in relation to age categories, the application of MC simulation indicates the need for early use of CIL/ASA, especially in patients aged 55 - 65, in order to effectively improve the claudication distance in patients with PAD. According to our study, the application of MC numerical analysis may be a useful tool in the treatment of PAD because the

reliance on this analysis is a compelling vision that shows high prediction ability. The findings of this study might provide basic scientific and theoretical support for an individual therapeutic approach that is aligned with the age of the patient. More prospective and multi-centre studies with large sample sizes should be conducted to develop certain predictive models, which can be widely accepted in the field of PAD treatment in order to improve symptoms and increase walking distance in patients with claudication in appropriately aged populations.

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Conflict of interest

The authors declare no conflict of interest.

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