Regionalne razlike između trendova standardiziranih stopa mortaliteta od periferne arterijske bolesti od 2011. do 2020. u Republici Hrvatskoj

Regional Differences in Standardized Mortality Rate Trends for Peripheral Artery Disease from 2011 to 2020 in the Republic of Croatia

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SAŽETAK: Periferna arterijska bolest (PAB), uz ishemijsku bolest srca i moždani udar, među trima je najznačajnijim dijagnostičkim podskupinama kardiovaskularnih bolesti. Prema procjenama, prevalencija u mlađih od 50 godina je <1 %, a u starijih od 65 godina 6 %. Analiza dinamike kretanja PAB-a upućuje na smanjenje incidencije u EU15+ državama posljednjih 27 godina, ali uz povećanje mortaliteta. Republika Hrvatska ističe se među mediteranskim zemljama po visokom kardiovaskularnom opterećenju, ali nema sustavnih epidemioloških istraživanja dinamike kretanja mortaliteta od PAB-a. U ovom su istraživanju regresijskom analizom dobno standardiziranih stopa mortaliteta od PAB-a prema regijama od 2011. do 2020. godine prikazani trendovi i vremenske točke s promjenama. Iz bolničkih informacijskih sustava dviju ustanova odabrane su dijagnoze primijenjene u kodiranju PAB-a te interventnih i dijagnostičkih postupaka i dopunjene dijagnozama iskorištenima u prethodnim istraživanjima. Iz Baze umrlih Hrvatskog zavoda za javno zdravstvo dobiveni su podatci po petogodišnjim dobnim skupinama, spolu i županijama. Za regionalnu podjelu uporabljena je Nacionalna klasifikacija statističkih regija iz 2019., a dobno standardizirane stope izračunate su na temelju Revidirane europske standardne populacije 2013. Mortalitet je u porastu u muškaraca (3,09 %) i žena (2,94 %), a prisutne su značajne regionalne razlike u trendu kod muškaraca u Jadranskoj Hrvatskoj i kod obaju spolova u Sjevernoj Hrvatskoj. Kod muškaraca najveći porast ima Grad Zagreb, 3,71 %, dok je najmanja i ujedno jedina negativna vrijednost zabilježena u Sjevernoj Hrvatskoj, −0,24 %. Kod žena najveći porast ima Grad Zagreb, 3,57 %, a najmanji Sjeverna Hrvatska 1,67 %. Ovo istraživanje trendova mortaliteta, uz podizanje svjesnosti, pomaže boljem razumijevanju epidemiološke dinamike ove nedostatno dijagnosticirane i liječene kompleksne kronične bolesti. Poboljšanja kliničke skrbi za bolesnike oboljele od PAB-a moguće je ostvariti sustavnim probirom individualnih i klinički značajnih podataka u medicinskim ustanovama i njihovim ujedinjavanjem u regionalnim i nacionalnim registrima.

SUMMARY: Peripheral artery disease (PAD) is, along with ischemic heart disease and stroke, one of the three most significant diagnostic subgroups of cardiovascular diseases. According to prevalence estimates, the prevalence of PAD is <1% in persons aged <50 and 6% in persons aged >65. Analysis of

the dynamics of PAD in the population has indicated a reduction of its incidence in EU15+ countries in the last 27 years, but with increasing mortality. The Republic of Croatia stands out among other Mediterranean countries due to its high cardiovascular burden, but there have been no systematic epidemiological studies on the dynamics of mortality from PAD. In the present study, regression analysis of age-standardized mortality rates due to PAD were used to show trends and timepoints with changes over time by region for the period from 2011 to 2020. The hospital information systems of two institutions were searched for diagnoses that are applied for coding PAD and related interventional and diagnostic procedures, supplemented by diagnoses used in previous studies. Data were obtained from the Croatian Institute of Public Health Mortality Database and were categorized five-year-interval age groups, by sex, and by county. The National Classification of Statistical Regions from 2019 was used for regional classification, and age-standardized rates were calculated based on the Revised European Standard Population from 2013. Mortality increased in both men (3.09%) and women (2.94%), and there were significant regional differences in this trend for men in Adriatic Croatia and for both sexes in Northern Croatia. In men, the greatest increase was observed in the City of Zagreb, namely 3.71%, whereas the lowest and also the only negative value was found in Northern Croatia, namely -0.24%. In women, the greatest increase was in the City of Zagreb, i.e. 3.57%, and the lowest in Northern Croatia at 1.67%. In addition to raising awareness, this study on mortality trends facilitates improving our understanding of the epidemiological dynamics of this insufficiently diagnosed and treated, complex, and chronic disease. Improving clinical care for patients with PAD can be achieved by systemic screening of individual and clinically relevant data at medical institutions and merging this data in regional and national registries.

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Uvod

Kardiovaskularne bolesti (KVB) vodeći su uzrok smrti u Europi.[1] Periferna arterijska bolest (PAB), uz ishemijsku bolest srca (IBS) i moždani udar, jedna je od tri najznačajnije dijagnostičke podskupine KVB-a. Danas se pod tim pojmom u kliničkoj praksi razumijeva djelomična ili kompletna opstrukcija jedne ili više perifernih arterija donjih ekstremiteta.[2] Morbiditetu i mortalitetu od te kompleksne kronične bolesti najviše pridonose tradicionalni čimbenici rizika za KVB kao što su primjerice pušenje, dijabetes i hiperlipidemija.[3] U svijetu od nje boluje 230 milijuna ljudi, pri čemu oba spola podjednako obolijevaju, dok žene češće imaju klinički asimptomatski oblik bolesti.[4]

Perifernu arterijsku bolest obilježava kontinuum kliničke prezentacije, koji uključuje početne asimptomatske oblike bolesti i krajnju za život ugrožavajuću kritičnu ishemiju.[3] U kliničkoj praksi intermitentne klaudikacije najčešći su oblik bolesti i njihova prevalencija raste s dobi. Procjenjuje se da je prevalencija u populaciji mlađoj od 50 godina <1 %, dok u starijih od 65 godina iznosi 6 %.[5] Stvarna prevalencija procijenjena na temelju pedobrahijalnog indeksa (ABI) upućuje na to da u općoj populaciji asimptomatski klinički oblik učestalošću višestruko nadmašuje intermitentne klaudikacije.[6]

Introduction

Cardiovascular diseases (CVDs) are the leading cause of death in Europe.[1] Peripheral artery disease (PAD) is, along with ischemic heart disease (IHD) and stroke, one of the three most significant diagnostic subgroups of CVDs. Today, the term PAD is used in clinical practice to denote partial or complete obstruction of one or more peripheral arteries of the lower extremities.[2] Morbidity and mortality from this disease is primarily influenced by traditional risk factors for CVDs such as for example smoking, diabetes, and hyperlipidemia.[3] Globally, 230 million people suffer from PAD, with both sexes represented approximately equality, although the clinically asymptomatic form of the disease is more common in women.[4]

Peripheral artery disease is characterized by a continuum of clinical presentations that includes the initial asymptomatic forms of the disease and ultimately life-threatening critical ischemia.[3] In clinical practice, intermittent claudication is the most common form of the disease, and its prevalence increases with age. It is estimated that the prevalence is <1% in the population aged <50, whereas it is 6% in those aged >65.[5] The true prevalence, estimated based on the ankle brachial index (ABI), indicates that the asymptomatic clinical form of the disease in the general population is several times more common than intermittent claudication.[6]

Hrvatska akademija znanosti i umjetnosti i Hrvatsko društvo za aterosklerozu još su 2015. godine na znanstvenom skupu o prevenciji ateroskleroze prepoznali kliničku važnost asimptomatske ateroskleroze. Tada je naglašena potreba personalizirane prevencije PAB-a i češće primjene dijagnostičkih metoda poput ABI, brzine pulsnoga vala i dilatacije ovisne o protoku koje u Republici Hrvatskoj (RH) još uvijek nisu u rutinskoj kliničkoj primjeni kod asimptomatske bolesti.[7,8]

Periferna arterijska bolest među važnijim je uzrocima amputacija u svijetu, ali, osim toga, izrazito narušava kvalitetu života oboljelih i povećava rizik od velikih kardiovaskularnih (KV) događaja i smrti. Treba istaknuti da je u Europi od 80-ih godina prošlega stoljeća smanjen mortalitet od vodećih KVB-a – IBS-a i moždanog udara. Ipak, analiza dinamike kretanja PAB-a u populaciji upućuje na smanjenje incidencije u EU15+ državama posljednjih 27 godina, ali se unatoč tomu mortalitet povećao.[9]

Prema KV opterećenju, RH se ističe među drugim mediteranskim zemljama članicama EU-a, kao što su primjerice Italija, Španjolska i Portugal, po visokom morbiditetu i mortalitetu. Njezini obrasci mortaliteta od KVB-a više nalikuju na tranzicijske zemlje srednje i istočne Europe.[10] Ipak, unatoč vodećoj ulozi koju KVB imaju u ukupnom morbiditetu i mortalitetu, nisu provedena sustavna epidemiološka istraživanja dinamike kretanja glavnih dijagnostičkih podskupina, uključujući i PAB.[11] Valja pretpostaviti da je u Hrvatskoj, kao i u drugim zemljama, u usporedbi s IBS-om i moždanim udarom, PAB suboptimalno dijagnosticirana i liječena bolest. Osim pojedinih bolničkih registara, u medicinskim centrima sustavno se ne prate ishodi liječenja bolesnika s uznapredovanim stadijima bolesti liječenih endovaskularnim i kirurškim zahvatima.[12,13] Budući da su od epidemioloških podataka raspoloživi samo agregirani podatci vitalne mortalitetne statistike, uzimajući u obzir sva ograničenja takvih podataka, moguće je jedino prikazati njihove trendove kako bi se identificirale regije u kojima je mortalitet od ove bolesti u porastu.

U ovom je istraživanju načinjena regresijska analiza dobno standardiziranih stopa mortaliteta od PAB-a prema NUTS-2 regijama od 2011. do 2020. godine kako bi se prikazali trend i vremenske točke u kojima su zabilježene promjene.

Materijali i metode

IZVORI PODATAKA

Periferna arterijska bolest u kliničkoj praksi obuhvaća širok spektar dijagnoza te su i unutar i između zemalja zamijećene velike razlike. Zbog mogućnosti sustavno pogrešne klasifikacije među bolnicama u smislu odabira dijagnoza i radi veće kliničke utemeljenosti, dva liječnika specijalista, interventni radiolog iz Kliničke bolnice Dubrava i internist kardiolog iz Kliničkog bolničkog centra Zagreb, iz bolničkih informacijskih sustava navedenih ustanova odabrali su dijagnoze koje se primjenjuju u kodiranju PAB-a te interventnih i dijagnostičkih postupaka u takvih bolesnika.[14] Navedene su dijagnoze dopunjene dijagnozama koje su iskorištene u drugim istraživanjima.[15] U konačnici, iz Baze umrlih Hrvatskog zavoda za javno zdravstvo za razdoblje od 2011. do 2020. godine dobiveni su podatci po petogodišnjim dobnim skupinama od 0 do 85+, spolu i županijama za sljedeće dijagnoze[16,17] (**tablica 1**).

Popis stanovnika po županijama preuzet je s mrežnih stranica Državnog zavoda za statistiku na temelju procjena načinjenih sredinom svake od navedenih godina.[18]

As early as 2015, the Croatian Academy of Sciences and Arts and the Croatian Society for Atherosclerosis recognized the clinical significance of asymptomatic atherosclerosis at a scientific congress on the prevention of atherosclerosis. They emphasized the need for personalized PAD prevention and more frequent application of diagnostic methods such as the ABI, pulse wave velocity, and flow-mediated dilatation, which have still not entered routine clinical application for asymptomatic disease in the Republic of Croatia.[7,8]

Peripheral artery disease is one of the more significant causes of amputation worldwide, but it also severely impacts quality of life in patients and increases risk of severe cardiovascular (CV) events and death. It should be emphasized that, starting with the 1980s, a reduction in mortality from leading CVDs – IHD and stroke – was achieved in Europe. However, despite the analysis of population dynamics for PAD indicating reduced incidence in EU15+ countries in the last 27 years, mortality has nevertheless increased.[9]

The CV burden in Croatia stands out in comparison with other Mediterranean EU member countries, such as for example Italy, Spain, and Portugal, due to high morbidity and mortality found in Croatia. Croatian CVD mortality patterns are more similar to transitional countries in central and eastern Europe.[10] However, despite the leading role held by CVDs in total morbidity and mortality, no systematic epidemiological studies have been performed on the dynamics of the main diagnostic subgroups in Croatia, which includes PAD.[11] It is to be assumed that in Croatia, as in other countries, PAD represents a suboptimally diagnosed and treated disease in comparison with IHD and stroke. Other than the existence of individual hospital registries, medical centers do not systematically track treatment outcomes in patients with advanced stages of the disease treated with endovascular and surgical procedures.[12,13] Given that the only data available are aggregate vital statistics on mortality, and considering all the limitations of such data, it is only possible to describe their trends in order to identify regions in which mortality from this disease is increasing.

This study was based on a regression analysis of age-standardized mortality rates due to PAD according to NUTS-2 regions in Croatia from 2011 to 2020 in order to determine existing trends and timepoints in which trend changes could be noted.

Materials and methods

DATA SOURCES

In clinical practice, PAD encompasses a whole spectrum of diagnoses, and large differences have been observed both within and between different countries. Due to systemic misclassification bias between hospitals with regard to choosing the diagnosis and in order to achieve higher clinical reliability, two specialist physicians, namely an interventional radiologist from the Dubrava Clinical Hospital and an internist cardiologist from the University Hospital Centre Zagreb, were engaged to examine hospital information systems and choose the diagnoses that are applied in coding PAD as well as the interventional and diagnostic procedures used in these patients.[14] These diagnoses were supplemented by diagnoses used in other studies.[15] Finally, the Mortality Database of the Croatian Institute of Public Health was used to collect data for the period from 2011 to 2020, stratified by five-year age groups for patients between the ages of 0 and 85+, as well as by sex and by county (**Table 1**).[16,17]

The population census by county was taken from the webpages of the Croatian Bureau of Statistics and was based on

TABLE 1. Diagnoses used in peripheral artery disease coding in interventional and diagnostic procedures.

E10.5 Insulin-dependent diabetes with peripheral circulatory complications

E10.7 Insulin-dependent diabetes with multiple complications

E11.5 Non-insulin-dependent diabetes mellitus with peripheral circulatory complications

E11.7 Non-insulin-dependent diabetes mellitus, with multiple complications

E13.7 Other specified diabetes, with multiple complications

E14.5 Diabetes mellitus, unspecified, with peripheral circulatory complications

E14.7 Diabetes mellitus, unspecified, with multiple complications

I70.0 Atherosclerosis of the aorta

I70.1 Atherosclerosis of renal artery

I70.2 Atherosclerosis of arteries of limbs

I70.8 Atherosclerosis of other arteries

I70.9 Generalized and unspecified atherosclerosis

I73.9 Disease of peripheral blood vessels, unspecified

I74.2 Embolism and thrombosis of the arteries of the hand

I74.3 Embolism and thrombosis of leg arteries

I74.4 Embolism and thrombosis of arteries of limbs, unspecified

I74.5 Embolism and thrombosis of iliac artery

I74.8 Embolism and thrombosis of other arteries

I74.9 Embolism and thrombosis of unspecified arteries

Za dobno standardizirane stope mortaliteta od IBS-a i cerebrovaskularne bolesti (CVB) prema NUTS-2 regijama podatci su preuzeti iz baze EUROSTAT.[19]

DEFINICIJA ZEMLJOPISNIH REGIJA

U ovome je radu iskorištena Nacionalna klasifikacija statističkih regija iz 2019., kojom se utvrđuje podjela Hrvatske na četiri statističke regije druge razine (NUTS-2): (i) Grad Zagreb, (ii) Sjeverna Hrvatska, koju čine: Koprivničko-križevačka županija, Međimurska županija, Varaždinska županija, Krapinsko-zagorska županija i Zagrebačka županija, (iii) Panonska Hrvatska, koju čine: Virovitičko-podravska županija, Bjelovarsko-bilogorska županija, Požeško-slavonska županija, Brodsko-posavska županija, Osječko-baranjska županija, Vukovarsko-srijemska županija, Karlovačka županija i Sisačko-moslavačka županija i (iv) Jadranska Hrvatska, koju čine: Primorsko-goranska županija, Ličko-senjska županija, Zadarska županija, Šibensko-kninska županija, Splitsko-dalmatinska županija, Istarska županija i Dubrovačko-neretvanska županija.[20]

IZRAČUN DOBNO STANDARDIZIRANIH STOPA

Opće i dobno specifične stope za 2020. godinu izračunate su kao ukupan broj umrlih od navedenih dijagnoza na 100 000 stanovnika opće populacije i stanovnika određenih dobnih skupina. Dobno specifične stope primijenjene su za izračun dobno standardiziranih stopa na temelju Revidirane europske standardne populacije (RESP) 2013 tako da su dobno specifične stope (od 0 do 85+) pomnožene s ponderima stan-

estimates made at the middle point of each of the examined years.[18]

Data for age-standardized mortality rates from IHD and cerebrovascular disease (CBVD) according to NUTS-2 regions were taken from the Eurostat database.[19]

DEFINING GEOGRAPHICAL REGIONS

This study used the National Classification of Statistical Regions from 2019 that divides the Republic of Croatia into four second-level statistical regions (NUTS-2), namely (i) the City of Zagreb, (ii) Northern Croatia, comprising: Koprivnica-Križevci County, Međimurje County, Varaždin County, Krapina-Zagorje County, and Zagreb County, (iii) Pannonian Croatia, comprising: Virovitica-Podravina County, Bjelovar-Bilogora County, Požega-Slavonia County, Brod-Posavina County, Osijek-Baranja County, Vukovar-Srijem County, Karlovac County, and Sisak-Moslavina County, and (iv) Adriatic Croatia, comprising: Primorje-Gorski Kotar County, Lika-Senj County, Zadar County, Šibenik-Knin County, Split-Dalmatia County, Istria County, and Dubrovnik-Neretva County.[20]

CALCULATING AGE-STANDARDIZED RATES

General and age-specific mortality rates for 2020 were calculated as the total number of deaths from the examined diagnoses per 100 000 inhabitants in the general population and inhabitants in specific age groups. Age-specific rates were applied to the calculation of age-standardized rates based on the Revised European Standard Population (RESP) from 2013 by multiply-

dardnih populacija. RESP 2013 je utemeljena na projekcijama populacija zemalja članica EU-27 i članica Europskog udruženja slobodne trgovine za razdoblje od 2011. do 2030. godine i podijeljena u petogodišnje dobne skupine, uz iznimku prve dobne skupine s dobnom kategorijom 0, dok je najstarija dobna skupina 95+.[21,22]

STATISTIČKA OBRADA

Za analizu podataka i prikaza mape uporabljen je računalni program za tabličnu pohranu i obradu podataka Microsoft Excel 365 (Microsoft Corporation, Redmond, Washington, SAD). U statističkoj su analizi primjenjivane metode deskriptivne i analitičke statistike. Kontinuirane varijable uspoređene su t-testom i Pearsonovim testom korelacije, a kao razina statističke značajnosti uzeta je vrijednost p <0,05. Statističke su analize napravljene primjenom statističkog programa *SPSS Statistics 26* (IBM, Amonk, New York, SAD) i *JASP 0.16.1*.[23]

Za analizu trenda smrtnosti od PAB-a primijenjena je *joinpoint* analiza, koja prepozna i kvantificira značajne točke promjena trenda, tzv. joinpointovi. Takva se analiza često primjenjuje u epidemiološkim istraživanjima, osobito u analizama trendova incidencije i smrtnosti kod različitih bolesti.[24,25] Pretpostavka *joinpoint* analiza jest da trend podataka ima linearnu funkciju sa segmentima gdje se mijenja brzina trenda. Preciznije rečeno, *joinpointovi* su vremenske točke u kojima se mijenja smjer ili brzina trenda podataka. Podatci se prvo prikažu grafički, a potom se primjenjuje matematički model kako bi se identificirale značajne promjene trendova. Nakon identifikacije točaka prijeloma trenda, analiza procjenjuje koeficijente nagiba i razinu statističke značajnosti segmenta, što omogućuje kvantifikaciju brzine trendova.[26] Prednosti su *joinpoint* analize u tome što je to objektivna metoda za identifikaciju značajnih promjena u trendovima i što pruža kvantitativne podatke o brzinama promjena.[27,28]

Rezultati

U **tablici 2** prikazane su dobno standardizirane stope prema NUTS-2 regijama za tri dijagnostičke podskupine KVB-a. U

ing age-specific rates (from age 0 to 85+) with weighted standard population averages. RESP 2013 is based on population projections for EU-27 member states and members of the European Free Trade Association for the period from 2011 to 2030 and is divided into five-year age groups, with the exception of the first group with the age category of 0, and with the oldest age group being 95+.[21,22]

STATISTICAL ANALYSIS

Data analysis and mapping were performed in the Microsoft Excel 365 computer program for spreadsheeting and data analysis (Microsoft Corporation, Redmond, Washington, USA). Statistical analysis employed descriptive and analytic statistical methods. The T-test and Pearson correlation test were used for comparing continuous variables, and statistical significance was set at p<0.05. Statistical analyses were performed using the SPSS Statistics 26 program (IBM, Amonk, New York, USA) as well as JASP 0.16.1.[23]

PAD mortality trends were analyzed using joinpoint analysis, which recognizes and quantifies significant points in trend changes, i.e. the so-called joinpoints. This analysis is often applied in epidemiological studies, especially in analyzing trends in incidence and mortality for different diseases.[24,25] The assumption of joinpoint analysis is that the data trend has a linear function with segments with changes in the speed of the trend. More precisely, joinpoints are timepoints in which the direction or speed of the data trend changes. The data are first shown graphically, followed by the application of a mathematical model in order to identify significant trend changes. After identifying trend joinpoints, the analysis estimates slope coefficients and the level of statistical significance of individual segments, which allows the quantification of trend speed.[26] The advantages of joinpoint analysis are that it is an objective method for the identification of significant changes in trend and that it provides quantitative data on the speed of the changes.[27,28]

Results

Table 2 shows the age-standardized rates according to NUTS-2 regions for three CVD diagnostic subgroups. In both sexes, the

TABLE 2. Age-standardized mortality rates per 100,000 inhabitants from peripheral arterial disease, cerebrovascular disease, and ischemic heart disease by sex and geographical regions for the year 2020.

NUTS-2 regions	Sex	PAD	CVD*	IHD*
City of Zagreb	Men	74.07	111.98	194.69
	Women	71.00	90.20	115.91
Northern Croatia	Men	73.00	165.82	240.75
	Women	69.65	121.48	136.12
Pannonian Croatia	Men	61.13	183.42	288.29
	Women	50.81	134.64	202.53
Adriatic Croatia	Men	50.14	106.33	236.30
	Women	40.37	92.68	156.50

NUTS-2 = french: *Nomenclature des unités territoriales statistiques* = engl. National classification of statistical regions, PAD = Peripheral arterial disease, CVD = cerebrovascular disease, IHD = Ishemic heart disease, *data from Eurostat

obaju spolova najveći mortalitet od CVB-a i IBS-a zabilježen je u Panonskoj Hrvatskoj, a od PAB-a u Gradu Zagrebu. Muškarci imaju veće stope mortaliteta od žena za sve tri dijagnostičke skupine KVB-a.

GRAD ZAGREB

U muškaraca u Gradu Zagrebu nije zabilježena promjena trenda, za razliku od žena, u kojih je zabilježena jedna točka prijeloma između dvaju razdoblja od 2011. do 2018. i od 2018. do 2020. (**slika 1**). Kod muškaraca nije bilo promjene trenda, dok je u žena zabilježena jedna točka prijeloma. U razdoblju od 2011. do 2018. kod žena je zabilježen negativan trend od −3,12 %, a od 2018. do 2020. izrazito pozitivan trend od 30,85 %.

highest mortality was reported in Pannonian Croatia for CVDs and IHD and in the City of Zagreb for PAD. Men had higher mortality rates in comparison with women for all three CVD diagnostic subgroups.

THE CITY OF ZAGREB

No trend change in mortality rates was observed in men in the City of Zagreb, as opposed to women, in whom one joinpoint was observed between two periods, namely from 2011 to 2018 and from 2018 to 2020 (**Figure 1**). There were no trend changes in men, and one joinpoint was observed in women. In the period from 2011 to 2018, a negative trend of -3.12% was found in women, and an extremely positive trend of 30.85% was observed from 2018 to 2020.
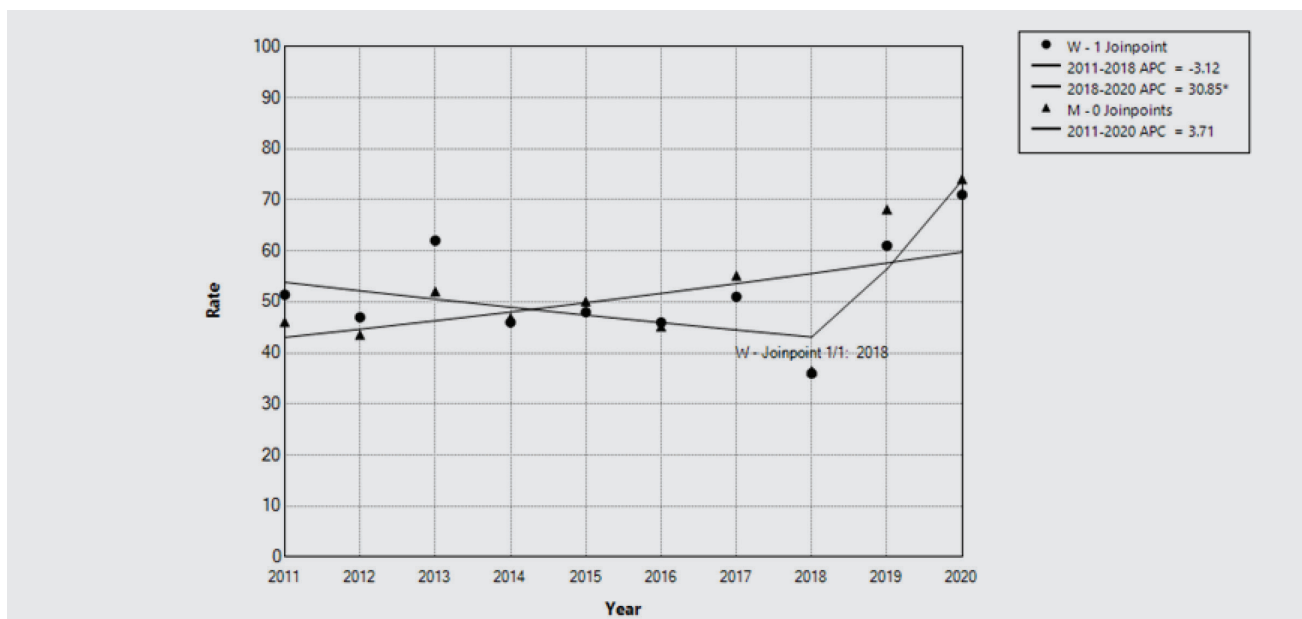

FIGURE 1. The City of Zagreb – joinpoint analysis of mortality from peripheral artery disease in men and women in the period from 2011 to 2020.
▲ Men, ● Women

SJEVERNA HRVATSKA

U Sjevernoj Hrvatskoj zamijećene su značajne točke prijeloma u muškaraca i u žena između razdoblja 2011. do 2018. i 2018. do 2020. (**slika 2**). Kod muškaraca je nakon značajnoga negativnog trenda od −7,58 % u razdoblju od 2011. do 2018. uslijedio značajan pozitivan trend od 30,38 %. Slična je dinamika zamijećena i u žena te nakon negativnog trenda od −6,91 % (2011. do 2018.) slijedi značajan pozitivan trend od 38,45 %, od 2018. do 2020. godine (**tablica 3**).

PANONSKA HRVATSKA

Kod muškaraca u Panonskoj Hrvatskoj trend je bio konstantan, dok je u žena zabilježena jedna točka prijeloma između razdoblja 2011. do 2018. i 2018. do 2020. (**slika 3**). Kod muškaraca je trend bio pozitivan 1,14 %, dok je u žena od 2011. do 2018. bio negativan (−3,78 %), nakon čega je došlo do pozitivnog trenda, 28,71 % od 2018. do 2020., no razlike nisu bile značajne.

NORTHERN CROATIA

For Norther Croatia, significant joinpoints were observed both in men and in women between the periods from 2011 to 2018 and from 2018 to 2020 (**Figure 2**). In men, a significant negative trend of -7.58% in the period from 2011 to 2018 was followed by a positive trend of 30.38%. A similar dynamic was also observed in women, in whom a negative trend of -6.91% (2011 to 2018) was followed by a positive trend of 38.45% from 2018 to 2020 (**Table 3**).

PANNONIAN CROATIA

The trend was constant for men in Pannonian Croatia, whereas one joinpoint was observed in women between the periods from 2011 to 2018 and from 2018 to 2020 (**Figure 3**). Men had a positive trend of 1.14%, while women had a negative trend (-3.78%) from 2011 to 2018, followed by a positive trend of 28.71% from 2018 to 2020, but the differences were not significant.
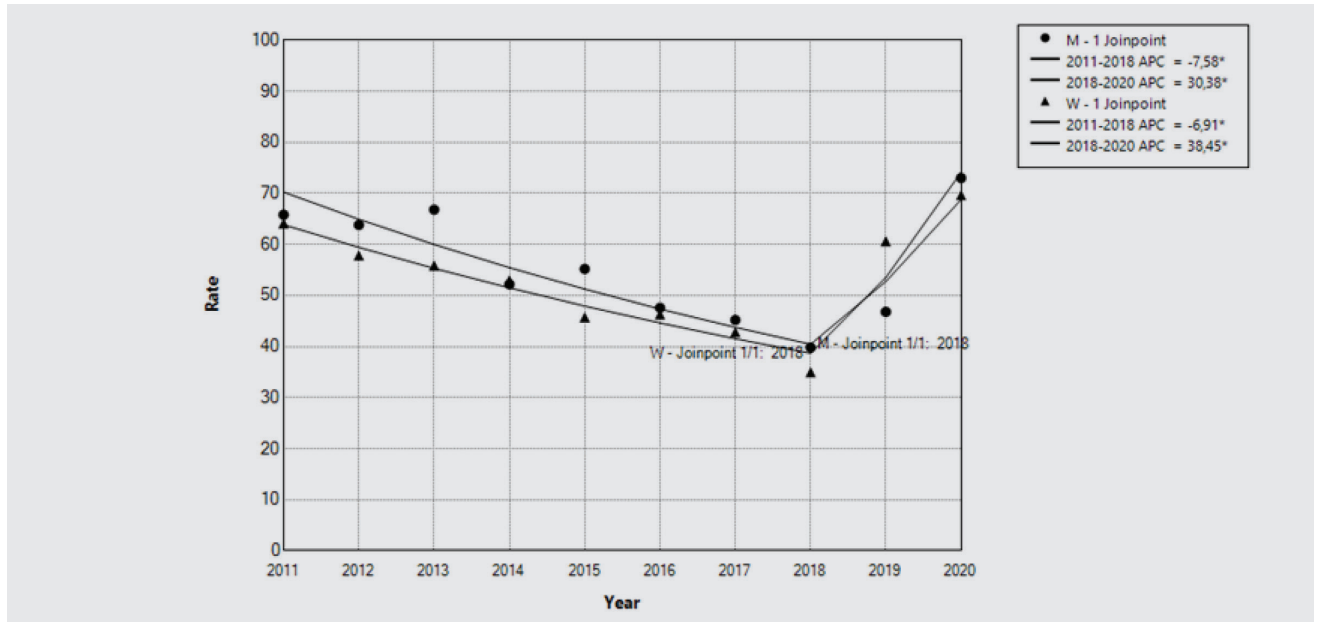
FIGURE 2. Northern Croatia – joinpoint analysis of mortality from peripheral artery disease in men and women in the period from 2011 to 2020.
▲ Men, ● Women

TABLE 3. Northern Croatia – annual percentage change in the age-standardized mortality rate from peripheral arterial disease by sex.

	Sex	Period	APC	95 % confidence interval	Value t statistics	p
Northern Croatia	Men	2011-2018	-7.58*	[-10.52, -4.54]	-6.26	0.002*
	Men	2018-2020	30.38*	[2.33, 66.13]	2.81	0.037*
	Women	2011-2018	-6.91*	[-8.36, -5.45]	-11.78	<0.001*
	Women	2018-2020	38.45*	[23.17, 55.63]	7.15	0.001*

JADRANSKA HRVATSKA

Kod muškaraca u Jadranskoj Hrvatskoj zabilježena je jedna točka prijeloma između dvaju razdoblja: od 2011. do 2014. i od 2014. do 2020, dok u žena nema točaka prijeloma trenda **(slika 4)**. Kod muškaraca u Jadranskoj Hrvatskoj od 2011. do 2014. zabilježen je negativan trend uz prosječnu godišnju postotnu promjenu −9,14 %, međutim, u sljedećem razdoblju od 2014. do 2020. dolazi do značajnog prijeloma i pozitivnog trenda od 7,67 %. Kod žena nije bilo značajne promjene trenda i on je od 2011. do 2020. iznosio 2,43 % **(tablica 4)**.

REPUBLIKA HRVATSKA

Vrijednosti prosječnih godišnjih postotnih promjena za Republiku Hrvatsku i za NUTS-2 regije tijekom cijelog istraživanoga razdoblja od 2011. godine do 2020. godine nisu bile značajne. U istraživanom razdoblju za Republiku Hrvatsku kod obaju spolova prisutna je jedna točka prijeloma između razdoblja 2011. do 2018. i 2018. do 2020. godine, ali ona nije značajna. Od 2011. do 2018. trend mortaliteta bio je negativan

ADRIATIC CROATIA

One joinpoint was observed between two periods in men in Adriatic Croatia, namely between 2011 to 2014 and from 2014 to 2020, whereas there were no joinpoints in women (**Figure 4**). From 2011 to 2014, men in Adriatic Croatia had a negative trend with an average annual percentage change of -9.14%, but there was a significant joinpoint in the following period between 2014 and 2020 and a positive trend of 7.67%. There were no significant trend changes in women, with the trend being 2.43% from 2011 to 2020 (**Table 4**).

THE REPUBLIC OF CROATIA

Average annual percentage change (AAPC) values for the Republic of Croatia and the NUTS-2 regions during the whole study period from 2011 to 2020 were not significant. In the study period, there was one joinpoint between the periods from 2011 to 2018 and from 2018 to 2020 for both sexes in the Republic of Croatia as a whole, but it was not significant. From 2011 to 2018, the mortality trend was negative both in men and in women, namely -2.51%
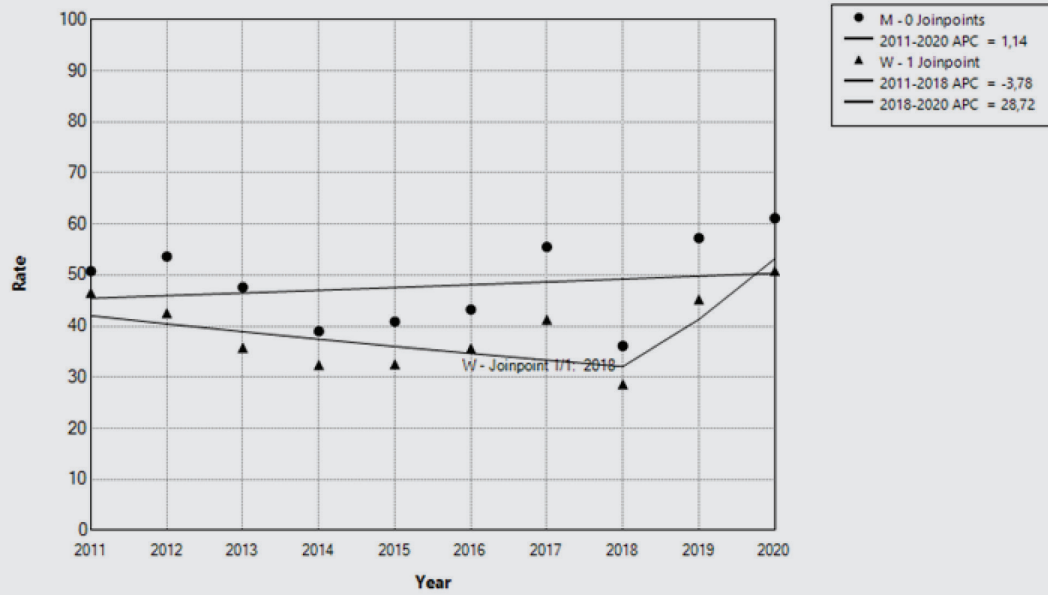
FIGURE 3. Pannonian Croatia – joinpoint analysis of mortality from PAD in men and women in the period from 2011 to 2020.
▲ Men, ● Women

TABLE 4. Adriatic Croatia – annual percentage change in the age-standardized mortality rate from peripheral arterial disease by sex.

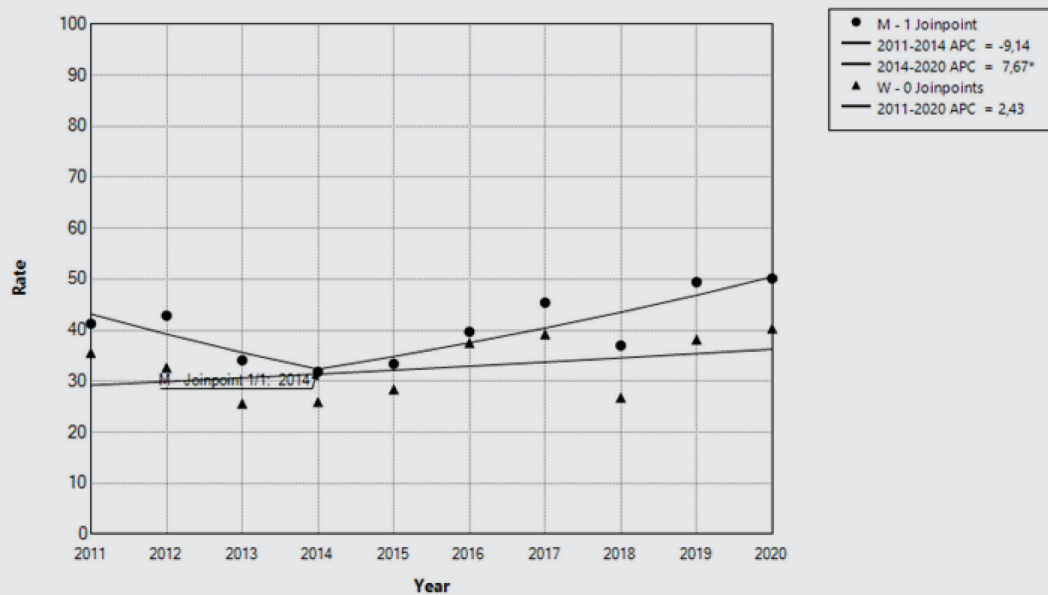| Sex	Period	APC	95 % confidence interval	Value t statistics	p
Men	2011-2014	-9.14	[-25.46, 10.75]	-1.25	0,268
Men	2014-2020	7.67*	[0.70, 15.12]	2.84	0,036*
Women	2011-2020	2.43	[-2.07, 7.14]	1.23	0,253

FIGURE 4. Adriatic Croatia – joinpoint analysis of mortality from peripheral artery disease in men and women in the period from 2011 to 2020.
▲ Men, ● Women

za muškarce i za žene, −2,51 % i −3,69 %, nakon čega je u razdoblju od 2018. do 2020. došlo do povećanja od 25,36 % i 29,94 %, a razlike nisu statistički značajne.

Diskusija

U ovom smo istraživanju s pomoću odabranih dijagnoza na temelju mortalitetne statistike po NUTS-2 regijama izračunali trendove dobno standardiziranih stopa mortaliteta od PAB-a od 2011. do 2020. godine. Mortalitet je porastao za 3,09 % u muškaraca i 2,94 % u žena, a prisutne su velike regionalne razlike u trendu koje su značajne u muškaraca u Jadranskoj Hrvatskoj i u obaju spolova u Sjevernoj Hrvatskoj.

Kada se govori o KVB-u, treba istaknuti da se među EU članicama RH ubraja u skupinu tranzicijskih zemalja visoko opterećenih mortalitetom i morbiditetom od KVB-a.[29] Razlike po spolu upućuju na veću smrtnost muškaraca u svim trima dijagnostičkim podskupinama KVB-a. Rezultati također potvrđuju regionalne razlike pa je tako, primjerice, za oba spola najveći mortalitet od CVB-a i IBS-a u Panonskoj Hrvatskoj, dok je najveći mortalitet od PAB-a u Gradu Zagrebu. To je u skladu s prijašnjim istraživanjima, prema kojima je kontinentalni dio više opterećen KVB-om u usporedbi s mediteranskom regijom.[30] Budući da Grad Zagreb uz Jadransku Hrvatsku ima niže stope mortaliteta od IBS-a i CVB-a, valja očekivati da mortalitet od PAB-a slijedi isti gradijent.[30,31] Međutim, Grad Zagreb ističe se najvećim mortalitetom od PAB-a u obama spolovima (**tablica 2**).

Regionalne razlike u trendu mortaliteta od PAB-a, premda izražene, prema prosječnoj godišnjoj postotnoj promjeni dobno standardiziranih stopa nisu statistički značajne. Kod muškaraca najveći je porast u Gradu Zagrebu, 3,71 %, dok je najmanja i ujedno jedina negativna vrijednost zabilježena u Sjevernoj Hrvatskoj, −0,24 %. Kod žena Grad Zagreb ima najveći porast, a Sjeverna Hrvatska najmanji, 3,57 % prema 1,67 %. Opažene razlike u mortalitetu, sukladno prijašnjim istraživanjima, najvećim su dijelom objašnjive distribucijom čimbenika rizika i zdravstvenom skrbi.[32-34] Ipak, pritom ne treba zanemariti ulogu prepoznavanja ove bolesti od medicinskih djelatnika i samih bolesnika, kao i važnu ulogu socioekonomskih odrednica u distribuciji zdravlja i bolesti. Dobivene je rezultate teško precizno objasniti zbog izostanka sustavnih i metodološki zahtjevnijih epidemioloških istraživanja koja omogućuju uzročno-posljedično objašnjenje međuregionalnih razlika u morbiditetu i mortalitetu od KVB-a. Naime, kako su za incidenciju i prevalenciju dostupni podatci utemeljeni na procjenama, u konačnici je zakonski obvezna mortalitetna statistika, usprkos ograničenjima, temelj ovakvim i drugim javnozdravstvenim istraživanjima.[35] Unatoč izostanku nacionalnih istraživanja, istraživanja provedena u svijetu u velikoj su mjeri poopćiva i na našu populaciju. Prema njima, mortalitetu od KVB-a u najvećoj mjeri pridonose čimbenici rizika, dok je preostali udio, manji od 50 %, određen dostupnošću i kvalitetom medicinske skrbi. Dostupnost/jednakost i kvaliteta zdravstvene skrbi, uz sredstva koja se izdvajaju za zdravstvo, ključne su domene za procjenu uspješnosti zdravstvenog sustava. Treba istaknuti da su izdvajanja za zdravstvo u RH *per capita* treća najmanja u EU-u te su, prilagođena kupovnoj moći, 2016. godine iznosila 1.272 US$, što je 52 % prosjeka EU-a i 85 % prosjeka EU-a 13.[10,36] Osim malih sredstava, podatci o kvaliteti zdravstvene skrbi i učinkovitosti primijenjenih zdravstvenih tehnologija nisu dostupni na razini me-

and -3.69%, respectively, after which there was an increase of 25.36% and 29.94%, respectively, in the period from 2018 to 2020, but the differences were not statistically significant.

Discussion

In this study, we used a selected set of diagnoses to calculate age-standardized mortality rates from PAD from 2011 to 2020 by NUTS-2 regions based on mortality statistics. Mortality increased by 3.09% in men and 2.94% in women, and there were large regional differences in trend, which were statistically significant in men in Adriatic Croatia and in both sexes in Northern Croatia.

When discussing CVDs, it should be emphasized that the Republic of Croatia is among the EU member states that are considered transitional countries with a high burden of CVD mortality and morbidity.[29] Differences by sex indicate higher mortality in men in all three CVD diagnostic subgroups. Our results also confirm regional differences, with, for example, the highest mortality from CVD and IHD for both sexes being found in Pannonian Croatia, whereas the highest mortality from PAD was found in the City of Zagreb. This is in agreement with previous studies, according to which the continental part of Croatia has a greater CVD burden in comparison with the Mediterranean region.[30] Since the City of Zagreb, along with Adriatic Croatia, has lower mortality rates for IHD and CVD, we would expect PAD mortality to be along the same gradient.[30,31] However, the City of Zagreb stands out with the highest mortality from PAD for both sexes (**Table 2**).

Regional differences in PAD mortality trends, although pronounced, were not statistically significant based on the average annual percentage change of age-standardized rates. In men, the greatest increase was in the City of Zagreb, 3.71%, while the lowest and also the only negative value was found in Northern Croatia, namely -0.24%. In women, the increase was highest in the City of Zagreb and lowest in Northern Croatia: 3.57% and 1.67%, respectively. These differences in mortality, in line with previous studies, are largely explainable by the distribution of risk factors and healthcare.[32-34] However, we should not ignore the role played by correct identification of this disease both by medical professionals and the patients themselves, as well as the significant role of socioeconomic determinants in the distribution of health and disease. The results obtained in the present study are difficult to explain precisely, due to the lack of systematic and methodologically more challenging epidemiological studies that provide causal explanations of interregional differences in CVD morbidity and mortality. Namely, since the data available on incidence and prevalence are based on assessments, it is ultimately statistics on mortality, the provision of which is obliged by law, that represents the foundation of such public health research, despite its limitations.[35] Despite the lack of national studies, studies conducted globally are largely generalizable to our population as well. According to these studies, CVD mortality is primarily influenced by risk factors, with the rest of the mortality rate, less than 50%, being determined by the availability and quality of medical care. Availably/equality and quality of healthcare are, along with the funds allocated to healthcare, key domains for assessing the successfulness of a healthcare systems. It should be emphasized that the funds allocated to healthcare in the Republic of Croatia are the third lowest per capita in the EU, reaching 1 272 USD (adjusted for purchasing power parity) in 2016, which was 52% of the EU average and 85% of the EU13 average.[10,36] In addition to low funding, data on healthcare quality and the effectiveness of the applied medical

dicinskih ustanova, pa stoga njihov doprinos u mjerenju ishoda liječenja nije moguće procijeniti.[37] Ipak, u bazi EUROSTAT dostupni su metodološki standardizirani i agregirani pokazatelji kliničkih ishoda za infarkt miokarda i moždani udar koji omogućuju usporedbu među državama. Tako, primjerice, standardizirana tridesetodnevna bolnička smrtnost od infarkta miokarda nekoliko puta nadmašuje navedenu smrtnost u susjednoj Sloveniji, pri čemu je omjer navedenog mortaliteta među medicinskim ustanovama deset puta.[36]

Slijedom navedenoga, mortalitet od PAB-a u ovom istraživanju moguće je objasniti isključivo istodobnim razmatranjem nedostatnosti i ograničenja epidemioloških i kliničkih podataka, kao i pokazatelja o kvaliteti liječenja. U analizi medicinske skrbi strukturu zdravstva, koju čine troškovi i dostupnost medicinskih ustanova i liječnika specijalista, svakako treba razlikovati od samoga procesa pružanja vaskularne skrbi, među kojim treba istaknuti godišnji volumen intervencija. Usprkos manjku podataka, razlike između ishoda liječenja na razini institucija u kliničkoj su praksi razvidne i treba pretpostaviti da veći medicinski i akademski centri imaju bolju kvalitetu liječenja.[38] Isto tako, pri analizi dostupnosti endovaskularnih i kirurških intervencija svakako treba istaknuti nekoliko centara visokog volumena u Gradu Zagrebu, što može utjecati na rezultate istraživanja ponajprije u smislu boljeg registriranja PAB-a kao uzroka smrti. Takva centralizacija ljudskih i tehnoloških potencijala nije ekskluzivno obilježje pripisivo liječenju PAB-a, već je takav trend zamijećen i kod drugih specijalnosti.[38]

Republika Hrvatska izrazito je opterećena čimbenicima rizika povezanima sa životnim stilom, koji su uzrok više od polovine smrti.[10] Među čimbenicima rizika koji najviše utječu na mortalitet od PAB-a po učinku se ističu povišena razina glukoze u krvi natašte, arterijska hipertenzija (AH), pušenje i prehrana bogata solju.[33] Na njihovu važnost u mortalitetu upućuju stope mortaliteta više od prosjeka EU-a među uzrocima smrti koji se mogu spriječiti i liječiti.[10,39] Isto tako, pušenje je u RH velik javnozdravstveni problem. Usprkos prevalenciji od 20 % u odraslih osoba koja je među najvišima u Europi, nisu provedene učinkovite mjere smanjenja toga nepoželjnog trenda.[10] Svakako treba istaknuti vodeću poziciju u EU-u po ukupnoj prevalenciji AH-a od 37 %, a prosječan sistolički tlak od 137,5 mmHg (95 % CI 131,2 – 143,8) 2015. godine bio je najveći u svijetu.[40] Ipak, usprkos velikoj javnozdravstvenoj važnosti nije utemeljen sustavan program probira za AH, a recentna stopa nedijagnosticirane AH iznosi 7,1 %.[41,42] Budući da je AH, dijagnosticirana i nedijagnosticirana, među važnijim čimbenicima rizika za nastanak PAB-a, valja pretpostaviti da sinergističko djelovanjem s ostalim tradicionalnim čimbenicima rizika, ponajprije pušenjem i dijabetesom, objašnjava velik udio mortaliteta.[3,43] Istraživanja provedena 2000-ih godina pokazala su mnogo veću prevalenciju AH-a u kontinentalnoj Hrvatskoj nego u Jadranskoj Hrvatskoj, dok je prevalencija pušenja bila veća u Jadranskoj Hrvatskoj.[44] Zamjetna je podudarnost niže stope mortaliteta od PAB-a u ovom istraživanju s nižom prevalencijom AH-a u Jadranskoj Hrvatskoj iz ranijih istraživanja, međutim, s druge strane, stopa nedijagnosticirane AH znatno je povezana sa životom u Jadranskoj Hrvatskoj. Gubitak mediteranskog obrasca prehrane u Jadranskoj Hrvatskoj koji je pokatkad povezan i s većim unosom soli već je prije opisan u nekim istraživanjima.[45] Isto tako, osobe s nedijagnosticiranom AH češće su pušači i više konzumiraju alkohol u usporedbi s dijagnosticiranim hipertoničarima.[42]

technologies are not available at the level of medical institutions, and thus their contribution to the measurement of treatment outcomes cannot be evaluated.[37] However, the Eurostat database provides methodologically standardized and aggregated indicators for clinical outcomes in myocardial infarction and stroke, which allows comparisons between countries. For example, standardized 30-day hospital mortality from myocardial infarction is several times higher than this mortality statistic in the neighboring country of Slovenia, with a tenfold difference in mortality ratio between medical institutions.[36]

Given the above, mortality due to PAD in the present study can be explained only by simultaneously considering the inadequacy and limitations of epidemiological and clinical data as well as indicators on treatment quality. Analysis of medical care should certainly differentiate between the healthcare structure, determined by expenses and the availability of specialist physicians, and the process of providing vascular care, where the annual volume of interventions should be emphasized. Despite the lack of data, the differences in treatment outcomes in clinical practice are clear, and it can be assumed that larger medical and academic centers provide higher quality treatment.[38] Additionally, when analyzing the availability of endovascular and surgical interventions, the presence of several high-volume centers in the City of Zagreb should certainly be emphasized, as they may have influenced the study results, primarily in the sense of better registration of PAD as the cause of death. Such centralization of human and technological potential is not a characteristic exclusive to the treatment of PAD, and such trends have been observed for other specialties as well.[38]

The Republic of Croatia is severely burdened by lifestyle-related risk factors, which are the cause of more than half of deaths.[10] Among risk factors that have the highest influence on mortality from PAD, elevated fasting blood glucose values, arterial hypertension (AH), smoking, and a diet rich in salt stand out as those with the greatest effect.[33] Their significance for mortality is indicated by the high Croatian mortality rates from causes that can be prevented and treated, which are above the EU average.[10,39] Furthermore, smoking represents a large public health issue in Croatia. Despite a prevalence of 20% in adults, which is among the highest in Europe, no effective measures for reducing this unwanted trend have been implemented.[10] The leading position of Croatia among EU countries with an overall prevalence of AH of 37% should also certainly be emphasized, and the Croatian average systolic pressure of 137.5 mmHg (95 % CI 131.2.143.8) in 2015 was the highest in the world.[40] However, despite its great significance for public health, no systematic screening programs for AH have been implemented, and the recent rate of undiagnosed AH is 7.1%.[41,42] Given that AH, both diagnosed and undiagnosed, is one of the major risk factors for the development of PAD, it is to be assumed that its synergistic effect together other traditional risk factors, primarily smoking and diabetes, explains the large mortality ratio.[3,43] Studies conducted in the 2000s showed a significantly higher prevalence of AH in continental Croatia in comparison with Adriatic Croatia, whereas the prevalence of smoking was higher in Adriatic Croatia.[44] There was a notable correspondence with lower mortality rates due to PAD in the present study with the lower prevalence of AH in Adriatic Croatia in earlier studies, but, on the other hand, the rate of undiagnosed AH is significantly associated with living in Adriatic Croatia. The loss of the Mediterranean diet pattern in Adriatic Croatia, which is sometimes also associated with higher salt intake, has been previously described in some studies.[45] Furthermore, persons

Iako za RH nisu izračunate populacijske atributivne frakcije za pojedine tradicionalne čimbenike rizika, kao ni njihov pojedinačni utjecaj na KV smrtnost, zamjetna je podudarnost AH-a s višom smrtnošću od PAB-a u kontinentalnoj Hrvatskoj. Usprkos tomu, i neovisno o dobi i spolu bolesnici s dijagnosticiranim PAB-om mnogo su češće dugogodišnji pušači i dodatno hipertoničari u usporedbi s koronarnim bolesnicima bez PAB-a.[46]

Veće stope mortaliteta u Gradu Zagrebu također se mogu djelomično objasniti boljim prepoznavanjem PAB-a od zdravstvenih djelatnika (**tablica 2**). Naime, prepoznavanje bolesti utječe na pokazatelje morbiditeta i mortalitete i izgledno je da su naši liječnici opće medicine, kao i liječnici u drugim zemljama, vjerojatno slabo upoznati s ovom kroničnom bolešću.[47] Dijabetes, koji često uzrokuje polivaskularnu zahvaćenost u bolesnika s PAB-om, u dosadašnjim je istraživanjima imao znatan utjecaj na veću smrtnost bilo kojeg uzroka, a kod simptomatskih bolničkih pacijenata zamijećena je i veća stopa neželjenih kardijalnih događaja tijekom duljeg vremena praćenja.[12,48] Međutim, među poznatim koronarnim bolesnicima gotovo je isti udio onih koji imaju PAB u odnosu prema onima u kojih se na osnovi kliničkih simptoma sumnja na PAB, a koji nemaju još postavljenu dijagnozu PAB-a (6,4 % prema 6,3 %).[46] Podatci o tome koliko su liječnici opće medicine upoznati s koordiniranjem kliničkog procesa i dijagnostičkim i terapijskim postupcima oboljelih od PAB-a bili bi izuzetno korisni, ali nisu dostupni. Oni bi pridonijeli boljem probiru PAB-a u koronarnih bolesnika. Isto tako, ne postoje podatci na temelju kojih bi se jasno mogla utvrditi kvaliteta primarne zdravstvene zaštite, ali su u praksi razvidni njezina fragmentiranost, kao i nedostatno prepoznavanje i liječenje PAB-a.[10]

Ekonomski razvoj i njegova neujednačenost utječe na distribuciju KV mortaliteta svih dijagnostičkih podskupina (**tablica 2**). Psihosocijalni čimbenici rizika smatraju se podjednako značajnima jer je njihov rizik sličan tradicionalnim KV čimbenicima rizika.[49,50] Hrvatska je država s izraženim regionalnim razlikama, a treba istaknuti 2,5 puta veće prihode Grada Zagreba u usporedbi s Panonskom Hrvatskom.[51,52] Društveno raslojavanje vidljivo je u visokim i rastućim ekonomskim nejednakostima građana i raspodjeli zdravlja, zdravstvenog ponašanja i bolesti.[10] Ipak, izraženoj društvenoj podjeli, nejednakostima pri dostupnosti zdravstvene zašite i razlikama u kliničkim ishodima posvećuje se malo pozornosti, pa je stoga teško procijeniti uzročno-posljedičnu povezanost zbog dostupnosti uglavnom agregiranih podataka.[53,54] Isto tako, nije moguće usporediti razinu medicinske skrbi među ustanovama jer nema sustavnog prikupljanja kliničkih ishoda na temelju pokazatelja specifičnih za bolest.[55]

Rezultati upućuju na porast trenda mortaliteta koji je izraženiji u muškaraca, a to je u skladu s trendovima zabilježenima u svijetu posljednjih 20 godina.[56] Prema razdobljima, pad mortaliteta prisutan je u obaju spolova od 2011. do 2018., nakon čega je u razdoblju od 2018. do 2020. došlo do izrazitog, ali neznačajnog povećanja od 25,36 % i 29,94 %.

Trendovi po pojedinim razdobljima i različite točke prijeloma razlikuju se prema NUTS-2 regijama i prema spolu. Značajne promjene trenda zabilježene su u Jadranskoj Hrvatskoj kod muškaraca (**slika 4**, **tablica 4**) i u Sjevernoj Hrvatskoj u obaju spolova (**slika 2, tablica 3**).

Trend mortaliteta kod žena u Jadranskoj Hrvatskoj stabilan je i iznosio je 2,43 %. Za razliku od njih, kod muškaraca

with undiagnosed AH are more often smokers and consume alcohol more often in comparison with diagnosed hypertonic patients.[42] Although population attributable fractions for individual traditional risk factors and their individual influence on CV mortality have not been calculated for the Republic of Croatia, there was a notable correspondence between AH and higher mortality due to PAD in continental Croatia. Despite that, and regardless of age and sex, patients with diagnosed PAD are significantly more frequently long-term smokers and hypertonic in comparison with coronary patients without PAD.[46]

The higher mortality rates in the City of Zagreb can also be partially explained by better identification of PAD on part of healthcare professionals (**Table 2**). Correctly recognizing this disease affects morbidity and mortality indicators, and it is likely that our family physicians, like physicians from other countries, are probably poorly acquainted with this chronic disease.[47] Diabetes, which often causes polyvascular involvement in patients with PAD, had a significant effect on all-cause mortality in previous studies, and a higher rate of unwanted cardiac events was also observed in symptomatic hospital patients during long-term follow-up.[12,48] However, diagnosed coronary patients had almost the same ratio of PAD prevalence in comparison with those in whom there was suspicion of PAD based on clinical symptoms, but no currently established PAD diagnosis (6.4% vs. 6.3%).[46] Data showing how familiar family medicine physicians are with coordinating the clinical process and the diagnostic and treatment procedures for patients suffering from PAD would be extremely useful, but are not available. Such data would contribute to improved screening for PAD in coronary patients. Furthermore, there are no data based on which a clear determination of the quality of primary healthcare could be made, but its fragmentation is clear in practice, as is the inadequate identification and treatment of PAD.[10]

Economic development and its inequality contribute to the distribution of CV mortality for all diagnostic subgroups (**Table 2**). Psychosocial risk factors are considered to be of approximately equal significance since their risk is familiar to traditional CV risk factors.[49,50] The Republic of Croatia is a country with pronounced regional differences, and the 2.5 times higher income in the City of Zagreb in comparison with Pannonian Croatia must be emphasized.[51,52] Social stratification can be clearly seen in the high and increasing economical inequalities of among inhabitants, as well as in the distribution of health, health-related behavior, and disease.[10] However, despite pronounced social stratification, inequalities regarding the availability of healthcare and differences in clinical outcomes are given little attention, and it is thus difficult to assess the causal relationship between the two due to the availability of mostly aggregated data.[53,54] Furthermore, the level of medical care in different institutions also cannot be compared since there is no systematic data gathering on clinical outcomes based on indicators specific to the disease.[55]

Our results indicate an increase in mortality trends that is more pronounced in men, which is in agreement with globally reported trends in the last 20 years.[56] By time period, a drop in mortality was present is both sexes from 2011 to 2018, after which the period from 2018 to 2020 had a pronounced, but non-significant increase of 25.36% and 29.94%.

Trends by time period and various joinpoints differed by NUTS-2 region and by sex. Significant trend changes were observed in Adriatic Croatia in men (**Figure 2**, **Table 4**) and in Northern Croatia in both sexes (**Figure 2**, **Table 3**).

The mortality trend in women in Adriatic Croatia was stable at 2.43%. In contrast, a negative trend was observed in men from 2011 to 2014, with an average annual percentage change

je od 2011. do 2014. zabilježen negativan trend, uz prosječnu godišnju postotnu promjenu od −9,14 %, ali u sljedećem razdoblju, od 2014. do 2020., dolazi do značajnog prijeloma i pozitivnog trenda od 7,67 % (**slika 4**, **tablica 4**). Ova mediteranska regija tradicionalno ima niže stope mortaliteta od KVB-a, što je pripisivo čimbenicima rizika, ali i protektivnom učinku mediteranskog načina života i prehrane.[31,57] Treba svakako istaknuti bolji ekonomski status županija iz te regije, koje ju ubrajaju u najrazvijenije, primjerice Istarska, Zadarska, Dubrovačko-neretvanska.[30] Naime, primanja su uz razinu stupnja edukacije pojedinca bitna odrednica zdravlja populacije te je zamijećena pozitivna korelacija između razine samoprocijenjenog zdravlja i prihoda.[36] Ipak, upravo ta regija ima visok rizik od nedijagnosticirane AH, što se u literaturi objašnjava smanjenim mjerenjem tlaka kod liječnika opće medicine.[34]

U Gradu Zagrebu u muškaraca je tijekom cijelog razdoblja trend stabilan, 3,71 %, za razliku od žena, u kojih je zabilježena točka prijeloma između dvaju razdoblja, od 2011. do 2018. i od 2018. do 2020. U razdoblju od 2011. do 2018. u žena je zabilježen negativan trend od −3,12 %, a od 2018. do 2020. ističe se izrazito pozitivan trend od 30,85 % (**slika 1**).

U Panonskoj Hrvatskoj nema značajnih promjena trenda. U muškaraca je bio konstantan 1,14 %, dok je u žena zabilježena točka prijeloma između razdoblja. Tako je od 2011. do 2018. trend negativan (−3,78 %), nakon čega je došlo do pozitivnog trenda od 28,71 %, od 2018. do 2020. (**slika 3**).

Sjeverna Hrvatska među svim regijama bilježi najveće promjene trenda mortaliteta. U muškaraca se ističe značajan negativan trend od −7,58 % u razdoblju od 2011. do 2018., koji je prethodio također značajnom, ali pozitivnom trendu od 30,38 %. Slična je dinamika zamijećena i u žena − nakon negativnog trenda od −6,91 % (2011. – 2018.) slijedi značajan pozitivan trend od 38,45 %, od 2018. do 2020. godine (**slika 2**, **tablica 3**).

Pri interpretaciji epidemioloških pokazatelja PAB-a, ponajprije prevalencije i mortaliteta, treba istaknuti da su takve procjene, i u nas i u svijetu, izrazito podcijenjene. Prema iskustvima iz kliničke prakse, primjena ABI-ja u općoj populaciji nije dostatna i udio je asimptomatskih slučajeva uz klinički značajne vrijednosti ABI-ja velik.[58] Klinički značajan ABI ≤0,9 utječe na mortalitet i 3 − 6 puta povećava rizik od smrti u usporedbi sa zdravim osobama.[4] Isto tako, morbiditet i mortalitet nakon dijagnoze PAB-a pokazao se većim od onoga nakon infarkta miokarda.[42] U općoj se populaciji rijetko provodi probir na PAB s pomoću ABI-ja, a uloga PAB-a u povećanju rizika od smrti i komplikacija u bolesnika s drugim KVB-om, poput IBS-a i CVB-om, često se zanemaruje. Usprkos naporima Radne skupine za angiologiju i periferne vaskularne bolesti Hrvatskoga kardiološkog društva (HKD), a po uzoru na inicijativu Radne skupine za perifernu cirkulaciju Europskoga kardiološkog društva (ESC) u RH je mjerenje ABI-ja u procjeni KV rizika, ali i u funkcijskoj procjeni statusa perifernih arterija donjih udova još uvijek zanemarena pretraga.[7] Naime, među liječnicima koji aktivno sudjeluju u dijagnostičkom procesu i procjeni PAB-a, njih samo 7 % primjenjuje ABI kao metodu probira i inicijalnu metodu za procjenu težine bolesti. Isto tako, čak 78 % kardiologa smatra je da potrebna dodatna edukacija iz angiologije u liječenju i dijagnostici PAB-a. Sve prije navedeno upućuje na nužnost pridržavanja ESC smjernica za dijagnostiku i liječenje PAB-a koje je predstavio HKD.[59] Potrebu osvješćivanja bolesnika u vezi prevencije i ranom dijagnostikom prepoznala je i Sekcija za intervencijsku

of -9,14%, but in the following period, from 2014 to 2020, there was a significant joinpoint and a positive trend of 7.67% (**Figure 4**, **Table 4**). This Mediterranean region traditionally has lower CVD mortality rates, which is ascribable to risk factors, but also to the protective effect of the Mediterranean lifestyle and diet.[31,57] It is certainly important to note the superior economic status of counties in this region, which are among the most highly developed, for example Istria County, Zadar County, and Dubrovnik-Neretva County.[30] Income, together with individual education levels, are significant determinants of population health, and a positive correlation has been reported between self-assessed health and income.[36] However, this region has a high risk of undiagnosed AH, which is explained in the literature as due to reduced blood pressure measurements on part of family physicians.[34]

The trend for men in the City of Zagreb was stable at 3.71% during the whole study period, as opposed to women, in whom a joinpoint was observed between two periods, namely from 2011 to 2018 and from 2018 to 2020. In the period from 2011 to 2018, a negative trend of -3.12% was found in women, whereas the trend from 2018 to 2020 was extremely positive at 30.85% (**Figure 1**).

There were no significant trend changes in Pannonian Croatia. The trend in men was constant at 1.14%, while a joinpoint was found in women between different periods. The trend was negative (-3.78%) from 2011 to 2018, followed by a positive trend of 28.71% from 2018 to 2020 (**Figure 3**).

Among all the regions, the largest changes in mortality trends were found in Northern Croatia. In men, a significant negative trend of -7.58% was found for the period between 2011 to 2018, which was followed by a significant but positive trend of 30.38%. Similar dynamics were observed in women − after a negative trend of -6.91% (2011-2018) there was a significant positive trend of 38.45% from 2018 to 2020 (**Figure 2**, **Table 3**).

When interpreting the epidemiological indicators of PAD, primarily prevalence and mortality, it should be emphasized that such estimates, both in Croatia and globally, are substantially undervalued. According to experience from clinical practice, the application of ABI in the general population is insufficient and the ratio of asymptomatic cases with clinically significant ABI values is large.[58] Clinically significant ABI of ≤0.9 affects mortality and causes a 3- to 6-fold increased risk of death in comparison with healthy persons.[4] Furthermore, morbidity and mortality after PAD diagnosis have been shown to be higher than after myocardial infarction.[42] ABI screening for PAD is rarely conducted in the general population, and the role of PAD in increasing the risk of death and complications in patients with other CVDs, such as IHD and CVI, is often neglected. Despite the efforts of the Working Group on Angiology and Peripheral Vascular Diseases of the Croatian Cardiac Society (CCS), which are based on the initiative of the Working Group on Peripheral Circulation of the European Society of Cardiology (ESC), measuring ABI in the assessment of CV risk and the functional assessment of the peripheral arteries of the lower limbs is still a neglected test in the Republic of Croatia.[7] Among physicians actively participating in the diagnostic process and assessment of PAD, only 7% apply ABI as a screening method and the initial method of assessing disease severity. Furthermore, as many as 78% of cardiologists believe additional education in angiology is needed for the treatment and diagnosis of PAD. All the above indicates the necessity of adhering to ESC guidelines for the diagnosis and treatment of PAD that have been presented by the CCS.[59] The need to increase patient awareness regarding prevention and early

radiologiju Hrvatskoga društva radiologa i objavljen je Priručnik za pacijente oboljele od bolesti perifernih arterija namijenjen ponajprije općoj populaciji.[60]

U konačnici, podjednako je važno istaknuti kliničko značenje rane dijagnostika PAB-a i povezanosti tromboza arterija donjih ekstremiteta s povećanim rizikom od raka. Rizik za nastanak bilo kojeg sijela raka iznosi 2,5 % unutar 6 mjeseci praćenja nakon postavljanja dijagnoze i ostaje povećan i do 17,9 % nakon 20 godina, pri čemu je povezanost s rakom pluća osobito izražena.[61,62] Potonja činjenica nije nezanemariva u zemljama visoko opterećenim onkološkim bolestima.

Ovo istraživanje ima prednosti i nedostatke. Među prednostima treba istaknuti primjenu nove Nacionalne klasifikacije statističkih regija iz siječnja 2019., koja RH dijeli na četiri već navedene statističke regije druge razine (NUTS-2), dok je u prethodnome razdoblju bila podijeljena na dvije takve regije – Panonsku i Jadransku Hrvatsku. Na ovaj su način slabije razvijene županije kontinentalne Hrvatske bile svrstane u istu kategoriju kao i Grad Zagreb, a koji ima mnogo viši BDP po stanovniku. Novom su podjelom sve NUTS-2 regije, osim Grada Zagreba, klasificirane u kategoriju slabije razvijenih regija jer je njihov BDP manji od 75 % prosječnog BPD-a EU-a. Izdvajanja po stanovniku u RH u apsolutnim su terminima treća najmanja u EU-u i 2016. godine, prilagođena kupovnoj moći iznosila 1.272 US$, što je 52 % prosjeka EU-a i 85 % prosjeka EU-a 13.[43,47] Grad Zagreb treba u epidemiološkim istraživanjima zasebno analizirati zbog većih prihoda i dostupnosti i kvalitete zdravstvene zaštite koja utječe na pokazatelje morbiditeta i mortaliteta. Osim aktualne NUTS-2 klasifikacije, među prednostima istraživanja svakako treba istaknuti primjenu javno dostupnoga statističkog programa *joinpoint*, koji se ističe učinkovitošću provođenja linearne i *joinpoint* analize trenda.[63] Ograničena mogućnost otkrivanja manjih promjena trenda u razdoblju između *joinpointova* jest nedostatak toga programa. Ipak, *joinpoint* analiza je statistička metoda koja se primjenjuje za identifikaciju i kvantificiranje značajnih promjena u trendovima podataka, što je izuzetno korisno u epidemiološkim istraživanjima i donošenju odluka o javnom zdravlju. Ekološki dizajn istraživanja također je nedostatak jer izrazito otežava donošenje zaključaka o uzročno-posljedičnoj povezanosti. Međutim, nema jedinstvenoga nacionalnog registara niti usklađenog prikupljanja na razini bolnica na temelju kojih bi se pratili ishodi liječenja pacijenata s pomoću odabranih pokazatelja. Osim toga, nije moguće utvrditi točnost pri kodiranju uzroka smrti između NUTS-2 regija, a treba istaknuti i to da bolesnici oboljeli od PAB-a imaju brojne komorbiditete koji, zasigurno, otežavaju kodiranje uzroka smrti. Usporedivost istraživanja ograničena je i zbog velikih međudržavnih razlika u praksi samoga kodiranja u bolesnika s PAB-om u kojih je indicirana revaskularizacija.[64] Naime, MKB-10 nije prikladna za razlikovanje pojedinih kliničkih stadija PAB-a, zbog čega je samo kodiranje ove bolesti, za razliku od IBS-a i moždanog udara, izrazito podložno sustavnoj pogrešci klasifikacije. Neke zemlje, kao što su, primjerice, Njemačka ili Sjedinjene Američke Države, u kliničkoj se praksi koriste proširenom MKB-10, koja mnogo bolje odgovara kliničkoj prezentaciji PAB-a. Ipak, odabrane dijagnoze u ovom istraživanju primjenjuju se u dvama velikim kliničkim bolničkim centrima u kojima se provode endovaskularni i kirurški zahvati za liječenja bolesnika s PAB-om i mogu se smatrati reprezentativnim za kliničku praksu. U literaturi se ističu nedostatci MKB-10 i prednosti MKB-11 koja nudi veće moguć-

diagnosis has also been recognized by the Section for Interventional Radiology of the Croatian Society of Radiology, which published a Handbook for patients suffering from peripheral artery disease that is primarily aimed at the general population.[60]

Finally, it is equally important to emphasized the clinical significance of early PAD diagnosis and the association between thrombosis of the arteries in the lower extremities and increased risk of cancer. The risk for the development of cancer from any site is 2.5% within 6 months of follow-up after the establishment of the diagnosis and remains elevated by up to 17.9% after 20 years, with an especially pronounced association with lung cancer.[61,62] The latter fact is not negligible in countries with a high burden of oncological diseases.

The present study had both advantages and limitations. An advantage that should be emphasized is the application of the new National Classification of Statistical Regions from January 2019, which divides the Republic of Croatia into the four second-level statistical regions (NUTS-2) we have described above, whereas the country was previously divided into only two such regions – Pannonian and Adriatic Croatia. In the earlier classification, less-developed counties in continental Croatia were in the same category as the City of Zagreb, which has significantly higher GPD per capita. The new classifications places all NUTS-2 regions except the City of Zagreb in the category of less-developed regions, since their GDP is below 75% of the EU average. Funds allocated to healthcare per capita are the third lowest in the EU in absolute terms, reaching 1 272 USD (adjusted for purchasing power parity) in 2016, which was 52% of the EU average and 85% of the EU13 average.[43,47] The City of Zagreb must be analyzed separately in epidemiological studies due the higher average income and availability and quality of healthcare, which affects morbidity and mortality indicators. In addition to the use of the current NUTS-2 classification, one advantage of the present study that should certainly be emphasized is the use of the publicly available joinpoint program, which excels at effective performance of linear and joinpoint trend analysis.[63] The limited capacity to discover smaller trend changes in the period between joinpoints is the weakness of this program. However, joinpoint analysis is a statistical method used for the identification and quantification of significant changes in data trends, which is extremely useful in epidemiological research and making decisions on public health. The ecological design of the study also represents a limitation, since it makes it very difficult to reach conclusions on causal relationships. However, there is no unified national registry or coordinated data gathering at the hospital level that could be used to monitor treatment outcomes in patients using the chosen indicators. Additionally, it was not possible to ascertain the accuracy of the coding of causes of death between the NUTS-2 regions, and it should also be emphasized that patients with PAD have numerous comorbidities that certainly make it more difficult to correctly code the cause of death. The comparability of the study was also limited by the large differences between different countries in the practice of the coding for patients with PAD in whom revascularization is indicated.[64] ICD-10 is not appropriate for differentiating the individual clinical stages of PAD, leading to the coding of this disease, as opposed to IHD and stroke, being very prone to misclassification bias. Some countries, such as for example Germany or the United States, use the expanded ICD-10 classification in clinical practice, which is much better suited to the clinical presentation of PAD. However, the diagnoses selected for this study are applied in two large clinical hospital centers that perform endovascular and surgical procedures for the treatment of patients with PAD and can be considered representative of clinical practice. The literature emphasizes the

nosti registriranja pojedinih kliničkih stadija PAB-a jer sadržava dijagnoze koje se odnose na Klasifikaciju po Rutherfordu i Fontainu.[64] Međutim, treba naglasiti da RH nema ujednačen i ujedinjen sustav prikupljanja podataka na razini sekundarne zdravstvene zaštite. Svaki medicinski centar u RH ima vlastiti bolnički informacijski sustav i ne mogu se isključiti postojanja drukčijih dijagnoza i drukčije prakse kodiranja ni eventualne promjene računalnih sustava (i dostupnih MKB kodova) zdravstvenih ustanova tijekom analiziranog razdoblja. Ipak, vitalna mortalitetna statistika u Europi među boljima je u svijetu te su takvi rutinski prikupljeni podatci često osnova za epidemiološka istraživanja. Republika Hrvatska ima visoku cjelovitost podataka o smrtnosti, koja se procjenjuje većom od 65 %.[65,66] U prijašnjim je znanstvenim istraživanjima navedena dobra praksa kodiranja uzroka smrti za IBS i CVB tako da usprkos manjku istraživanja možemo pretpostaviti istu razinu kvalitete i kod PAB-a.[67] U hrvatskome zdravstvenom sustavu nema administrativnih ograničenja za korištenje zdravstvenom zaštitom izvan mjesta boravka i velik broj bolesnika liječi se u velikim medicinskim i akademskim centrima, što povećava liste čekanja.[68] Takva praksa opterećuje zdravstveni sustav, ali ne utječe na mortalitetnu statistiku jer se uzroci smrti registriraju prema mjestu boravka. Različiti trendovi mortaliteta između muškaraca i žena upozoravaju da nije bilo promjene načina kodiranja uzroka smrti koji se odnose na PAB jer bi u tom slučaju trendovi među spolovima bili slični. Premda prijašnja istraživanja upućuju na prednost muškaraca za određene terapijske postupke, dizajn ovoga istraživanja i prikupljeni podatci ograničavaju donošenje takvoga zaključka.[69] Unatoč svim već navedenim nedostatcima, ovim su istraživanjem kvantificirane regionalne razlike u mortalitetu i naglašena je potreba za daljnjim kliničkim i epidemiološkim istraživanjima PAB-a.

Periferna arterijska bolest visoko je prevalentna, ali istodobno dijagnostički i terapijski složena i kompleksna kronična bolest, zahtjevna za kodiranje. Obilježava je velik broj asimptomatskih slučajeva, koji imaju izrazito povećan rizik od neželjenih KV događaja. Njezin je mortalitet, premda nedvojbeno podcijenjen, u RH od 2011. do 2020. u porastu. Grad Zagreb se među NUTS-2 regijama ističe porastom mortaliteta za oba spola, a Panonska i Sjeverna Hrvatska znatnim promjenama trenda. Epidemiološka i klinička istraživanja o PAB-u u RH izrazito su nedostatna, unatoč velikoj kliničkoj i javnozdravstvenoj važnosti koju ona ima unutar skupine KVB-a. Premda veći medicinski centri raspolažu tehnološki naprednim endovaskularnim i kirurškim metodama za liječenje oboljelih od PAB-a, sustavna istraživanja o primjeni dijagnostičkih i terapijskih smjernica i mjerenja kliničkih ishoda liječenja ovakvih pacijenata nisu provedena. Neovisno o manjku individualnih podataka o oboljelima, ovo regionalno istraživanje trendova mortaliteta, uz podizanje svjesnosti, pomaže boljem razumijevanju epidemiološke dinamike ove nedostatno dijagnosticirane i liječene kompleksne kronične bolesti. Sustavan probir te prikupljanje individualnih i klinički značajnih podataka u medicinskim ustanovama koje se skrbe o pacijentima s PAB-om i njihovo ujedinjavanje u regionalnim i nacionalnim registrima jedini su načini poboljšanja kliničke skrbi za bolesnike oboljele od PAB-a u budućnosti. Rana dijagnoza i smanjenje čimbenika rizika te sekundarna prevencija iz epidemiološke perspektive imaju najveće značenje u smanjenju mortaliteta.

shortcoming of ICD-10 and the advantages of ICD-11, which provides more opportunities for registering the individual clinical stages of PAD since it includes diagnoses that use the Rutherford and Fontaine classification for PAD.[64] However, it should be emphasized that the Republic of Croatia does not have a consistent and unified system for gathering data at the level of secondary healthcare. Every medical center in Croatia has its own hospital information system, and the existence of different diagnoses and different coding practices cannot be excluded, nor can possible changes in computer systems (and the available ICD codes) in healthcare institutions during the study period be ruled out. However, vital statistics on mortality in Europe are among the best in the world, and such routinely gathered data often form the basis of epidemiological studies. The Republic of Croatia has a high completeness in mortality data, estimated to be above 65%.[65,66] Previous scientific studies have reported good practices for coding causes of death for IHD and CVD, and we may therefore assume the same level of quality for PAD, despite the lack of specific studies.[67] In the Croatian healthcare system, there are no administrative limitations for the use of healthcare outside the place of residence, and many patients are treated in the larger medical and academic centers, which increases waiting lists.[68] This practice causes a burden on the healthcare system, but does not effect mortality statistics since the causes of death are registered by place of residence. The difference in mortality trends between men and women indicate that there was no change in the way causes of death related of PAD were coded, as that would have led to similarities in the trends for both sexes. Although previous studies indicate an advantage for men for certain treatment procedures, the design of this study and the obtained data limit reaching such a conclusion.[69] Despite the limitations listed above, this study quantified the regional differences in mortality and emphasized the need for further clinical and epidemiological research on PAD.

Peripheral artery disease has a high prevalence, but it also represents a complex chronic disease that is challenging to diagnose and treat, and difficult to code. It is characterized by a large number of asymptomatic cases that have a highly increased risk of unwanted CV events. Its mortality, although undoubtedly underestimated, has been increasing in the Republic of Croatia from 2011 to 2020. The City of Zagreb stands out among the NUTS-2 regions as having increased mortality in both sexes, and Pannonian and Northern Croatia had significant trend changes. Epidemiological and clinical studies on PAD in Croatia are severely lacking, despite the great clinical and public health significance it has among CVDs. Although larger medical centers use technologically advanced endovascular and surgical methods for treating patients with PAD, systematic studies on the application of diagnostic and treatment guidelines and the measurement of clinical treatment outcomes for these patients have not been conducted. Regardless of the lack of individual patient data, this regional study on mortality trends, in addition to raising awareness, facilitates a better understanding of the epidemiological dynamics of this insufficiently diagnosed and treated, complex, and chronic disease. Systematic screening and gathering individual and clinically significant data in medical institutions that treat patients with PAD and their unification in regional and national registries are the only way to improve the clinical care for patients with PAD in the future. From an epidemiological perspective, early diagnosis and reducing risk factors as well as secondary prevention are of the highest importance in reducing mortality.

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