СРПСКИ АРХИВ
ЗА ЦЕЛОКУПНО ЛЕКАРСТВО
SERBIAN ARCHIVES
OF MEDICINE

Address: 1 Kraljice Natalije Street, Belgrade 11000, Serbia
☏ +381 11 4092 776, Fax: +381 11 3348 653
E-mail: office@srpskiarhiv.rs, Web address: www.srpskiarhiv.rs

Paper Accepted* **ISSN Online 2406-0895**

Original Article / Оригинални рад

Milena Kostić[1,♣], Marina Fišeković-Kremić[2], Mira Kiš-Veljković[3]

Recognition and treatment of mild cognitive impairment in Serbian general practice

Препознавање и лечење благог когнитивног поремећаја у пракси лекара опште медицине Србије

[1]Dr Đorđe Kovačević Health Center, Lazarevac, Serbia;
[2]Novi Beograd Health Center, Belgrade, Serbia;
[3]Bel Medic Healthcare center, Belgrade, Serbia

Received: June 20, 2021
Revised: January 2, 2023
Accepted: January 10, 2023
Online First: January 20, 2023
DOI: https://doi.org/10.2298/SARH210620007K

*__Accepted papers__ are articles in press that have gone through due peer review process and have been accepted for publication by the Editorial Board of the *Serbian Archives of Medicine*. They have not yet been copy-edited and/or formatted in the publication house style, and the text may be changed before the final publication.
Although accepted papers do not yet have all the accompanying bibliographic details available, they can already be cited using the year of online publication and the DOI, as follows: the author's last name and initial of the first name, article title, journal title, online first publication month and year, and the DOI; e.g.: Petrović P, Jovanović J. The title of the article. Srp Arh Celok Lek. Online First, February 2017.
When the final article is assigned to volumes/issues of the journal, the Article in Press version will be removed and the final version will appear in the associated published volumes/issues of the journal. The date the article was made available online first will be carried over.

♣**Correspondence to:**
Milena KOSTIĆ
Dr Đorđe Kovačević Health Center, Dr Đorđa Kovačevića 27, 11550 Lazarevac, Serbia
E-mail address: kmilena22@yahoo.com

Recognition and treatment of mild cognitive impairment in Serbian general practice

Препознавање и лечење благог когнитивног поремећаја у пракси лекара опште медицине Србије

SUMMARY

Introduction/Objective Mild cognitive impairment (MCI) is a state of progressive cognitive decline, rarely recognized by general practitioners (GPs), which is a reason of late treatment and fast progression towards more serious conditions. The main obstacles for the timely treatment of MCI are lack of diagnostic protocols and clinical guidelines as well as lack of knowledge and disbelief in the pharmacological therapeutic possibilities.
The aim of this investigation was to assess level of recognition of MCI symptoms by general practitioners (GPs), and to estimate their perception of distinct risk factors significance for MCI development.

Methods Participants (general practitioners) of the "Days of General Medicine" Conference (Serbia, March 2018), n = 340, completed 12 items questionnaire about recognition and treatment of the MCI patients. We have used descriptive statistics, Chi-square, Mann–Whitney U tests, binary logistic regression analysis for results presentation, sub-groups comparison, to assess predictors of drug therapy selection, respectively.

Results Study showed GPs recognize diabetes as most important factor for MCI, then hypercholesterolemia, smoking and sedentary behavior, while hypertension and obesity are perceived as less important. Those GPs who estimated diabetes and hypercholesterolemia as more important for all patients are significantly more prone to prescribe symptomatic therapy (pentoxifylline and vinpocetine), $p < 0.05$ according to Chi-square test. Logistic regression analysis regarding therapy predictions showed that years of GP experience is the most important predictor of drug therapy selection ($p < 0.01$).

Conclusion Results of this investigation pointed a need for MCI education for young physicians, in order to improve diagnosis and treatment of these patients.

Keywords: mild cognitive impairment; diagnosis; pharmacological therapy; general practice physicians

САЖЕТАК

Увод/Циљ Благо когнитивно оштећење (БКО) је стање прогресивног когнитивног опадања, које лекари опште медицине ретко препознају, што је разлог касног лечења и брзог напредовања ка озбиљнијем стању. Главне сметње правовременом лечењу БКО су недостатак дијагностичких протокола и клиничких смерница, као и недостатак знања и неповерење у фармаколошке терапијске могућности.
Циљ овог истраживања био је да се процени ниво препознавања симптома БКО од стране лекара опште медицине и да се процени њихова перцепција значајних фактора ризика за развој овог обољења.

Методе Учесници конференције „Дани опште медицине", лекари опште медицине (Србија, март 2018.), $n = 340$, попунили су упитник са 12 питања о препознавању и лечењу пацијената са БКО. За приказ резултата је коришћена дескриптивна статистика, χ^2, Ман–Витни U тест, бинарна логистичку регресиона анализу, да бисмо проценили предикторе избора терапије лековима.

Резултати Показано је да лекари опште медицине препознају дијабетес као најважнији фактор за БКО, затим хиперхолестеролемију, пушење и седентарно понашање, док се хипертензија и гојазност сматрају мање важним. Они лекари опште медицине који су дијабетес и хиперхолестеролемију проценили као важније за све пацијенте, знатно су склонији прописивању симптоматских лекова (пентоксифилин и винпоцетин), $p < 0,05$ према χ^2 тесту. Логистичка регресиона анализа у вези са предвиђањима примене симптоматске терапије показала је да су године искуства лекара најважнији предиктор избора терапије лековима ($p < 0,01$).

Закључак Резултати овог истраживања указали су на потребу едукације везане за БКО за младе лекаре, како би се побољшала дијагноза и лечење ових пацијената.

Кључне речи: благо когнитивно оштећење; дијагноза; фармаколошка терапија; лекари опште медицине

INTRODUCTION

Mild cognitive impairment (MCI) is defined as mental decline which is not severe enough to cause dependence in daily functioning [1]. The main obstacle in MCI defining and, thus, diagnosis is its similarity with dementia and also lack of appropriate and sufficiently sensitive diagnostic (psychometric) tests. MCI is frequently evolved as secondary consequence of several diseases such as neurologic, neurodegenerative, psychiatric or vascular, but also could be a manifestation of Alzheimer disease [2]. Regarding sub-typisation of this disease there are two main types: amnestic (the basic problem is related to memory loss) and non-amnestic where the focus is on other cognitive problems such as visuo-spatial skills, language and/or executive functions [3]. Of particular interests are reversible MCIs caused by metabolic, vascular, systemic or psychiatric conditions which could be controlled and cured; along with that, the MCI also has a chance to be alleviated [4]. According to some definitions, MCI is patients' mental status placed between normal ageing and dementia [5]. Because of that, it is of crucial importance to enable primary care physicians more information about signs, symptoms and clinical tools for its recognition and diagnostics. Moreover, if we are aware that Alzheimer's or non-Alzheimer's dementia will develop in 10-15% of patients 12 months after the MCI diagnosis [6], we should make every effort to broaden the window of possible disease postponement or even eradication. Neurobehavioral MCI estimation relies on several tests: mini mental state examination (MMSE), clock drawing test (CDT) and frontal function tests [7]. Modern clinical practice recommended several biomarkers as a part of regular diagnostic procedure, but also imaging techniques [4]. Selection of neuropsychological tests for MCI diagnosis is challenging, because too simple tests are lacking sensitivity and too complicated tests could not resolve disease development. MCI diagnosis obviously depends upon primary healthcare practitioners' judgment; therefore, it is important to prepare powerful tools and assure MCI awareness for those physicians dealing

with susceptible population in everyday practice.

The aim of this investigation was to assess the regular practice of Serbian physicians, and increase their awareness about the risk factors (RF) and signs and symptoms of cognitive impairment (CI).

METHODS

This survey is conceptualized as cross-sectional and performed by using specifically constructed questionnaire for the "General Medicine Days" conference (Belgrade, Serbia March 2018; http://www.opstamedicina.org/default.asp?ID=1368), by several members of the Serbian Medical Society, Section of General Practice (SGP). The Scientific Committee of the SGP has approved the questionaries' structure, content and purpose of the investigation. The subjects of the survey were medical doctors, general practitioners and general medicine specialists (n=340) taking a part in the Conference. All participants were voluntarily filled the questionnaire and thus have taking a part in the investigation. The study was conducted in accordance with the principles of the Declaration of Helsinki, regarding participants' name and identity protection. The questionnaire consisted of 12 questions. This questionnaire analysis gives us an opportunity to compare opinions, attitudes and common practice of general practitioners involved in medical treatment of MCI patients, as a first line "warriors" of any healthcare system. Questionnaires' analysis leads to several conclusions, which could serve for real life practice overview and improvement. The integral version of the questionnaire is uploaded as supplementary file.

Questionnaire structure description

In total, 30 medical doctors selected by study organizers (random sample selection method), filled the questionnaire to test its comprehension, readability and questions

formatting. Questionnaire equivalence reliability is estimated by using Cronbach's alpha analysis. After this preliminary analysis, slight modifications were performed to make the questions more understandable and better formatted. This questionnaire included 12 items classified into four key domains. The first domain consisted of three study subjects (physicians) related items: number of years of service, data about specialization, and total number of patients per physician.

The first three questions were formatted as gaped sentences formats (1 and 3) and second question was of multiple-choice type. Second domain (4-5th question) addressed items regarding patients' age and percentage distribution of number of risk factors related to cardiovascular disease (CVD) (both formatted as gaped sentences). Third domain was a core section comprising questions about cognitive decline related issues (questions 6-11th queried whether physicians notice cognitive symptoms in their patients, whether patients are aware of the existence of cognitive decline symptoms, at which frequency do physicians perceive cognitive symptoms as normal ageing, at which frequency do physicians use cognitive decline tests, physicians' estimation of cardiovascular risk factors importance in cognitive decline development and percent of cognitive declined patients who were directed to neurologist, respectively. Questions 6, 7, and 10 were multiple-choice and 8, 9, and 11 gaped sentences type. Last, 4th part of questionnaire was devoted to the choice of cognitive decline therapy (12th question, multiple choice type). Data from all completed questionnaires were entered in primary excel database, coded and statistically analyzed using the descriptive and inferential methods and IBM SPSS Statistics for Windows software Version 21.0. (IBM Corp., Armonk, NY, USA).

Questionnaire's validation analysis

Cronbach's analysis showed acceptable reliability of the questionnaire (Cronbach alpha

= 0,726). Not any item if deleted didn't produce significantly higher reliability index, which means that all items are consistent with the main topic. The intraclass correlation coefficient (single measures) was 0.525 (95% confidence interval 0.438–0.642; F = 12.5, df1 = 28, df2 = 243, $p < 0.01$). Average inter-item correlation coefficient was 0.311±0.040 which suggested relatively strong correlation between items (the average correlation coefficient is acceptable if it is larger than 0.300). Test–retest analysis showed good correlation between different items in two time points (average Spearman's $\rho = 0.875$ (0.700–0.983; $p < 0.01$).

Statistical analysis

Data are presented as frequencies (%) for categorical variables and median values (interquartile range, IQR) in the case of continuous variables and graphically with pie and bar charts. χ^2 test for categorical variables were used for relation between variables estimation because the data are presented as Likert scale. Mann–Whitney U test was used for continuous variables comparison. Binary logistic regression analysis was used in order to test predictive capability of different factors for a. physicians' CVD risk factors importance for MCI awareness and b. drug prescription *vs.* supplements and/or without therapy attitude. Criterion for low and high CVD risk factors awareness was determined from sum of all six risk factors marks given by physicians, where tertile values (1^{st} tertile = 22, and 2^{nd} tertile =27 points) were cut-offs for low, medium and high awareness. For binary logistic regression analysis, we used only low and high awareness subjects. For all tests p value < 0.05 was considered as statistically significant.

RESULTS

Physicians' data

Physicians, participants in this current study have broad level of experience (1 to 41

years) with majority of them having 21–30 years in medical service. Average number of patients per doctor according to practice protocol was about 1800 patients (range: 5–5000). Usual number of medical check-ups per physician per day is about 40. Almost half of participants were without medical specializations (44.7%) and other half had specialization in general medicine (Table 1).

Physicians' estimation of patient's population characteristics regarding age and risk factors numbers

Higher number of different comorbidities (arterial hypertension, diabetes mellitus, hyperlipidemia, obesity) and risk social habits (smoking and physical inactivity) assumes higher probability of cognitive declines being observed in patients, by either themselves or by their physicians. Results indicate that according to physicians estimation high percent of patients (about 40%) had 3 and more conditions connected with changes in cognition, which is expected because about 50% of physicians reported that they have more than 50% of patients older than 65y. (Figure 1).

The majority of physicians (80%) noticed MCI symptoms in less than 30% of their patients. Physicians reported that less than 30% of patients averagely have complained about MCI symptoms (Figure 2; A and B).

The highest proportion of physicians (73.2%) estimated MCI symptoms as normal ageing in low percent of their patients (below 30%). Almost 28% of physicians referred more than 50% of their patients to neurologist for more specialized diagnostics and therapy, while 54% of physicians send 30%-50% of patients to the neurologist (Figure 2C).

The most important MCI risk factor assumed by almost 85% of physicians is diabetes mellitus (sum of opinions "important for older" and "for all" patients), in smaller percent as important risk factors are estimated hypercholesterolemia (76%), smoking (76%) and physical

inactivity (76%), and arterial hypertension (73%), with slightly less percent. Obesity was obviously underscored and considered as important CI factor for 56% responders (Table 2).

Comparison between general practitioners' and general medicine specialists' perception of mild cognitive impairment and related risk factors

CVD related RF were estimated as more important by specialists compared to general practitioners ($p<0.05$). Accordingly, specialists noticed significantly lower percent of patients without CI RF, and also assumed less frequently cognitive decline signs and symptoms as "normal aging" consequence ($p<0.05$, 0.01, respectively). Subsequent analysis of possible factors determining patients' referral to neurologist revealed physicians who estimated diabetes mellitus as important factor for all patients are more prone to cooperate with neurologist to provide better diagnostics and treatment for potentially CI jeopardized patients (Table 3). Table 3 also presents data about therapy practice of GPs/GMSs regarding MCI patients, revealing more specialist are likely to prescribe the symptomatic therapy ($p<0.05$).

Comparing the physicians who dealt with less than 35% of patients older than 65 years and those with more than 70% of older ones, we found that those who dealt with younger patient population, in significantly lower percent referred patients to neurologist to diagnose their cognitive decline (data not shown here). As expected, more experienced physicians (more than 30 years of medical service) considered hypercholesterolemia, obesity and physical inactivity as more important inductors of cognitive disturbances, than less experienced participants (supplementary Table S1). In contrast to expectations, results of the questionnaire showed that physicians with larger number of patients (>2000 according to medical protocol registration) performed some of the functional tests (one or more) on a larger number of patients, compared to colleagues with less than 2000 patients (15% (10-30) *vs*. 10% (5-28), $p=0.049$ by Mann-Whitney U test).

Physicians MCI treatment attitude and practice

Only 5% of physicians did not advice any medication to patients with CI symptoms. For this indication physicians usually use two kinds of drugs (pentoxifylline, vinpocetine), many different supplements or different combinations which are commonly used in clinical practice in Serbia. The most popular supplement for this treatment area is *ginkgo biloba* preparation, recommended from 20.6% of physicians, and the most frequently in combination with antioxidants (33.2%). Prescription drugs indicated for circulatory disorders (pentoxifylline and vinpocetine) were given from 104 (30.6%) physicians, while the use of dietary supplements was advised from 64.4% physicians. Pentoxifylline was prescribed from 62 (18.2%) physicians, alone or in combination with other preparations; 7 physicians (2.0%) prescribed it as the only therapy. Vinpocetine, alone or in combination with other preparations was prescribed from 56 (16.4%) physicians, while only in 4,7% of cases as the only drug, according to data gathered in this current study. Circulatory system disorders related drugs was prescribed significantly more by specialists than by general practitioners (21% *vs.* 9%, $p<0.01$). Detailed data regarding MCI therapy practice are presented at the supplementary Table 2.

Results of this investigation enabled therapy modality choice analysis and its dependence from physicians' attitude or judgment of distinct CVD RF as triggers of patients' CI (Figure 3). Diabetes mellitus and hypercholesterolemia rating as significant factors for CI occurrence, regardless of patients age, leads to significantly higher proportion of any of the two prescription drugs (pentoxifylline and/or vinpocetine); $p<0.05$ for both RF according to Chi-square test.

Logistic regression analysis was performed to assess possible factors (predictors) for physicians' awareness of CV risk factors importance and also for providing prescription drugs (pentoxifylline and/or vinpocetine) among this study group (Tables 4 and 5, respectively). This analysis was a surrogate quantitative measure of physicians' MCI recognition. After the primary univariate analysis of all possible factors from the questionnaire, we have selected all

predictors with $p \leq 0.100$ and included it in multivariate logistic regression analysis with backward selection to get the best Models of physicians' awareness of CV risk factors importance and therapy prescription predictors, respectively (Table 4, Table 5).

The most significant predictors of risk factors recognition were relate to physicians' experience, number of patients per protocol, number of their CVD-CI RF and percent of physicians who assumed MCI as normal ageing, while predictors of drugs' prescription were years of experience, number of their CVD-CI RF and number of physicians who performed cognitive tests.

DISCUSSION

Worldwide absolute number of people with dementia was estimated to 35.6 million in 2010, and it is predicted to 115.4 million people by 2050 [8].

Epidemiological studies revealed MCI prevalence in people older than 65 y. about 5-10% [9,10]. MCI is difficult to predict because diagnosis depends on the precise definitions/subtypisation [11]. One half of the physicians taking a part in this study were general practitioner with specialization in general medicine and other half was without specialization (basic data about study participants are presented in the Table 1). General insight in regular medical practice showed a large work load of the Serbian physicians with about 40 patients per day. Majority of the participants were experienced physicians with more than 20 years of service. They reported about 70% of patients had 2 or more CVD RF which could be predisposing indicators of MCI (Figure 1). Detailed physicians' categorization of 6 traditional CVD risk factors' importance for cognitive impairment progression is presented at the Table 2. In the last decade is recognized that CVD RF like arterial hypertension, diabetes mellitus, dyslipidemia and obesity could cause brain alterations, hence problems in cognition, especially in older patients became evident. RF are clustered with ageing, so intellectual problems in

elderly are not incidental. This relation between number of RF and cognition impairment are also a part of normal ageing and this is a main obstacle for appropriate MCI diagnosis [12]. Even subclinical cognitive changes could seriously disturbed patients' daily activities and many important aspects of their general well-being like medication adherence, comorbidity recognition and overall safety [13]. Majority of general practitioners noticed forgetfulness, decreased concentration, walking instability, thought slowness (symptoms of damage to small blood vessels in the brain) in 5% to 30% of their patients, while 5-20% of their patients complained on forgetfulness, mood swings, walking instability or a feeling of blurry mind themselves (Fig. 2). These data are in accordance with other studies which reported MCI in about 16-20% of patients older than 65 y [6]. Number of patients with MCI is certainly in positive correlation with proportion of older patients (older population is defined as subjects older than 65, which is in agreement with period of retirement for working population).

Recommendation from American Academy of Neurology (AAN) [4] is decisive regarding assuming cognitive symptoms as normal ageing, late diagnosis will lead to failure to recognize reversible CI symptoms. This in turn may affect patients' life quality, course of disease, progression to dementia, cost increase for the healthcare system. Serbian physicians generally reported cognitive impairment symptoms as "normal ageing" in less than 25% of their patients (Fig. 2).

Undiagnosed MCI in older population ranged from 50-75% according to results of different studies and is a consequence of various backgrounds [14]. GP listed several reasons: lack of time, early symptoms unrecognition, insufficient knowledge about screening methods, discomfort between physician, patients and their family caused by coping with this issue, lack of disease-specific biomarker and limitation of treatment options [15]. Although the physicians generally don't ignore MCI symptoms, they rarely proceed to perform regular cognitive functional tests. Physicians responded that in most of the cases they perform CI functional tests

in less than 25% of patients suspected to have MCI. The reasons could be patients related, as in Judge et al. study [15], as patients frequently not disclosed symptoms and related cognitive impairment symptoms, assuming it as normal ageing; long waiting list and insufficient time for patients' examination hinder GP to act and make patients to refuse further checkup. Higher percent of physicians (38%) referred more patients to neurologist for specialized diagnostics and therapy (Figure 4.), and this, while more encouraging, is still a low percent of intervention for MCI suspected patients. According to Serbian National Guideline for Good Clinical Practice – Alzheimer disease [16] every patient with cognitive symptoms and suspicion of cognitive impairment must be tested and referred to neurologist. GP estimated DM as the most important RF, then hypercholesterolemia, smoking and physical inactivity. This part of investigation could explain general position of these CVD RF as significant predictors of universal cognitive health determinant (Fig. 3). Diabetes, smoking and physical activity were rated as equally important as CI predisposing RF by 50% or more GP. Physicians rated diabetes as important RF are more likely to cooperate with neurologist. Hypertension and especially obesity were rated as less important RF, which is surprising finding of this study. It is worrisome, that arterial hypertension so as hypercholesterolemia are perceived as important RF only for older people, by significantly large percent of GPs (31%, 37%, respectively). CVD-related pathology alters brain structure, leading to gray matter atrophy, white matter lesions, and damage of subcortical white matter pathways [17]. Current neurophysiological literature reports significance of hypertension directed to memory, attention, complex activities and meaning, appropriate behavior [18]. Regular testing of cognitive abilities, even from middle age, and CVD risk factors screening is essential, because adequate control of these factors could prevent CI progression to dementia [12]. The results we obtained have shown urgent need for increasing the awareness of GPs on the connection between CVD risk factors, especially hypertension, and cognitive impairment and the basic CI testing recommendations and relevant

therapeutic approaches for this condition. In the light of current COVID-19 pandemic situation, we must ask a question - what will be the consequences of subordinating all domains of healthcare system to this infectious disease and what will be the destiny of MCI patients if left undiagnosed and without therapeutic and/or lifestyle intervention?

General practitioners and general medicine specialists' comparison, underlined more experience and broader view of later study participants. The main results refer to more cautious stance of specialists towards CI phenomenon among patients (Table 3). Also 4 important CVD risk factors were estimated as more important by specialists compared to general practitioners. The similar result was evident when comparing GPs experience: physicians with more than 30 years of service rated hypercholesterolemia, obesity and physical inactivity as more important RF for MCI than participants with less than 30 years of service. This is surplus evidence that the amount of knowledge and experience is crucial in forming the physicians' attitude towards CI and their clinical decisions. Physicians with higher workload are more diligent towards CI test performance. We suppose that GPs with more patients are in fact "popular" physicians, maybe because of their professionalism and assiduity (Serbian general practice is based on a "chosen physician" model). There are attempts to develop simple diagnostic screening tool rely on verbal fluency, which is recently confirmed by McDonnell [19] and Nguyen [20], but Abdivalievna [21] emphasized significance of emotional state of the patients for the proper diagnosis of MCI.

One of the discouraging reasons for GP s' hesitation apropos MCI diagnosis is lack of appropriate therapy options, the data shown in Judge et al. paper [15]. Therapy for MCI is AD indicated therapy, like donepezil (acetyl-choline esterase inhibitor), with proofed ability to postpone dementia [22]. Majority of GPs suggest different antioxidants as therapeutic choice. Ginkgo biloba supplement alone or in combination with antioxidants are the most frequently used, while small percent of GPs prescribe pentoxifylline or vinpocetine as the only two

substances categorized as medicinal products approved for the circulatory disorders in Serbia. GPs' prescribed combination of pentoxifylline or vinpocetine with antioxidants or ginkgo biloba in low percent of cases. Physicians are more prone to providing therapy if they perceive arterial hypertension and/or hyperlipidemia as highly important RF for all patients, regardless of age. Physicians who estimate diabetes mellitus and/or hyperlipidemia as important RF for MCI development are likely to prescribe pentoxifylline and/or vinpocetine (Fig. 3).

Pentoxifylline activity depends on its positive hemorheological characteristics that affects microcirculation, its main indication is in the treatment of intermittent claudication [23]. McCarty's review [24] revealed positive pentoxifylline influence at reducing dementia progress in patients with documented cerebrovascular disease, which was confirmed in Rasyid's study [25], Khan's [26] and Sha's [27] review. Vinpocetine is the active ingredient of a drug registered for the treatment of symptoms of chronic cerebrovascular disorders. Vinpocetine has complex mechanism of action, involving brain circulation augmentation, oxygen utilization, increasing tolerance of neural tissue towards hypoxia/ischemia, anticonvulsive activity, inhibition of the phosphodiesterase enzyme, enhancement of blood rheological properties and anti-aggregatory activity [28]. Study dealt with geroprotectors development presented vinpocetine as potential anti-ageing agent, even its activity in AD has not been confirmed [29]. Multiple regression analysis of predictors model of factors which are connected with CV risk factors recognition so as commitment to symptomatic therapy for MCI prescription stressed importance of more years of work experience and more specialized medical education. Experienced clinicians use sophisticated diagnostic techniques, because of awareness about different therapeutic possibilities. Lee and associates documented the need for continuing medical education, which is in line with our own results [30]. We want to emphasize that the answer about prescribing practice could have been significantly influenced by the fact that GPs were asked about prescribing drugs for symptoms of small vessel disease in the brain,

which affects not only cognitive functions, but also other brain functions.

CONCLUSION

Results of this study revealed physicians' working experience and specialization as main factors for MCI diagnosis and treatment. General medicine specialists showed better recognition of MCI, so as CVD RF appreciation. The target group for education are younger physicians with less experience/without specialization. New age demands about faster and more focused education revealed short courses or educational workshops devoted to MCI diagnostics and therapy as acceptable option. Therapeutic approach should be grounded on evidence-based prescription treatment, instead of *per inertia* dietary supplements use, due to the lack of valid clinical evidence for the latter. Current recommendations include different cognitive exercises and physical activity for older people. Although we don't have a direct question about this kind of practice among Serbian GPs, according to our experience, this is regular real-life practice also in Serbia, as a potential measure for dementia prevention. Implementation of these interventions has a proven beneficial effect in slowing down MCI progression and when combined with adequate control of RF, even leading to its reversal in certain number of affected subjects. Future investigation should be more patients-oriented in order to estimate their real-life behavior and to suggest these simple, but potent life-style measures.

ACKNOWLEDGEMENTS

This study was designed in accordance with the principles of Helsinki Declaration and was approved by the Scientific Board of Section of General Practice of Serbian Medical Society.

Initial version of the manuscript was prepared by medical writer, Prof. dr. Jelena Kotur-

Stevuljević, and sponsored by Gedeon Richter, Representative Office Belgrade, Serbia.

Conflict of interest: None declared.

REFERENCES

1. Gillis C, Mirzaei F, Potashman M, Ikram MA, Maserejian N. The incidence of mild cognitive impairment: A systematic review and data synthesis. Alzheimers Dement (Amst). 2019;11:248-256. doi: 10.1016/j.dadm.2019.01.004. PMID: 30911599; PMCID: PMC6416157.
2. Cheng YW, Chen TF, Chiu MJ. From mild cognitive impairment to subjective cognitive decline: conceptual and methodological evolution. Neuropsychiatr Dis Treat. 2017;13:491-498. doi: 10.2147/NDT.S123428. PMID: 28243102; PMCID: PMC5317337.
3. Subramanyam A, Singh S. Mild cognitive decline: Concept, types, presentation, and management. J Geriatr Ment Health. 2016;3:10–20. doi: 10.4103/2348-9995.181910
4. Petersen RC, Lopez O, Armstrong MJ, Getchius TSD, Ganguli M, Gloss D, et al. Practice guideline update summary: Mild cognitive impairment: Report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. Neurology. 2018;90(3):126-135. doi: 10.1212/WNL.0000000000004826. Epub 2017 Dec 27. PMID: 29282327; PMCID: PMC5772157.
5. Pavlović DM, Pavlović AM. Blago kognitivno oštećenje. Srp Arh Cel Lek. 2009; 137(7-8):434-439.
6. Pais R, Ruano L, P Carvalho O, Barros H. Global cognitive impairment prevalence and incidence in community dwelling older adults-a systematic review. Geriatrics (Basel). 2020;5(4):84. doi: 10.3390/geriatrics5040084. PMID: 33121002; PMCID: PMC7709591.
7. Berg L. Clinical Dementia Rating (CDR). Psychopharmacol Bull. 1988;24(4):637-9. PMID: 3249765.
8. McDonald WM. Overview of neurocognitive disorders. Focus (Am Psychiatr Publ). 2017;15(1):4-12. doi: 10.1176/appi.focus.20160030. Epub 2017 Jan 11. PMID: 31975834; PMCID: PMC6519631.
9. Mohd Safien A, Ibrahim N, Subramaniam P, Shahar S, Din NC, Ismail A, et al. Randomized controlled trials of a psychosocial intervention for improving the cognitive function among older adults: a scoping review. Gerontol Geriatr Med. 2021;7:23337214211025167. doi: 10.1177/23337214211025167. PMID: 34395815; PMCID: PMC8361523.
10. McCollum L, Karlawish J. Cognitive impairment evaluation and management. Med Clin North Am. 2020;104(5):807-825. doi: 10.1016/j.mcna.2020.06.007. PMID: 32773047; PMCID: PMC7416715.
11. Gillis C, Mirzaei F, Potashman M, Ikram MA, Maserejian N. The incidence of mild cognitive impairment: A systematic review and data synthesis. Alzheimers Dement (Amst). 2019;11:248-256. doi: 10.1016/j.dadm.2019.01.004. PMID: 30911599; PMCID: PMC6416157.
12. Stephan BCM, Harrison SL, Keage HAD, Babateen A, Robinson L, Siervo M. Cardiovascular disease, the nitric oxide pathway and risk of cognitive impairment and dementia. Curr Cardiol Rep. 2017;19(9):87. doi: 10.1007/s11886-017-0898-y. PMID: 28801790; PMCID: PMC5554286.
13. Tuch G, Soo WK, Luo KY, Frearson K, Oh EL, Phillips JL, et al. Cognitive assessment tools recommended in geriatric oncology guidelines: a rapid review. Curr Oncol. 2021;28(5):3987-4003. doi: 10.3390/curroncol28050339. PMID: 34677257; PMCID: PMC8534877.
14. Liss JL, Seleri Assunção S, Cummings J, Atri A, Geldmacher DS, et al. Practical recommendations for timely, accurate diagnosis of symptomatic Alzheimer's disease (MCI and dementia) in primary care: a review and synthesis. J Intern Med. 2021;290(2):310-334. doi: 10.1111/joim.13244. Epub 2021 Mar 31. PMID: 33458891; PMCID: PMC8359937.
15. Judge D, Roberts J, Khandker R, Ambegaonkar B, Black CM. Physician perceptions about the barriers to prompt diagnosis of mild cognitive impairment and Alzheimer's disease. Int J Alzheimers Dis. 2019;2019:3637954. doi: 10.1155/2019/3637954. PMID: 31263595; PMCID: PMC6556253.
16. Ministry of Health of the Republic of Serbia (2013). National guideline to good clinical practice for the diagnosis and treatment of Alzheimer's disease. Republic Expert Commission for the development and implementation of guidelines to good clinical practice [ed. Nadežda Čoviković Šternić] Belgrade.
17. Gorelick PB, Sorond F. Vascular risk burden, brain health, and next steps. Neurology. 2018;91(16):729-730. doi: 10.1212/WNL.0000000000006346. Epub 2018 Sep 19. PMID: 30232249.
18. Forte G, Casagrande M. Effects of blood pressure on cognitive performance in aging: a systematic review. Brain Sci. 2020;10(12):919. doi: 10.3390/brainsci10120919. PMID: 33261205; PMCID: PMC7760512.
19. McDonnell M, Dill L, Panos S, Amano S, Brown W, Giurgius S, et al. Verbal fluency as a screening tool for mild cognitive impairment. Int Psychogeriatr. 2020;32(9):1055-1062. doi: 10.1017/S1041610219000644. Epub 2019 Jul 1. PMID: 31258101.
20. Nguyen AT, Lee GJ. Cognitive screening for early detection of mild cognitive impairment. Int Psychogeriatr. 2020;32(9):1015-1017. doi: 10.1017/S1041610219000991. PMID: 33025873.
21. Abdivalievna, A. N., & Rahmonkul qizi, B. H. Features of cognitive disorders. Innovative Society: Problems, Analysis and Development Prospects 2022; 101–105. Retrieved from http://www.openconference.us/index.php/ISPADP/article/view/177

22. Emrani S, Arain HA, DeMarshall C, Nuriel T. APOE4 is associated with cognitive and pathological heterogeneity in patients with Alzheimer's disease: a systematic review. Alzheimers Res Ther. 2020;12(1):141. doi: 10.1186/s13195-020-00712-4. PMID: 33148345; PMCID: PMC7643479.
23. Broderick C, Forster R, Abdel-Hadi M, Salhiyyah K. Pentoxifylline for intermittent claudication. Cochrane Database of Systematic Reviews 2020, Issue 10. Art. No.: CD005262. DOI: 10.1002/14651858.CD005262.pub4.
24. McCarty MF, O'Keefe JH, DiNicolantonio JJ. Pentoxifylline for vascular health: a brief review of the literature. Open Heart. 2016;3(1):e000365. doi: 10.1136/openhrt-2015-000365. PMID: 26870389; PMCID: PMC4746528.
25. Rasyid A, Harris S, Nurhayati E, Prihartono J. Pentoxifylline in acute ischemic stroke patients with blood hyperviscosity. Int J Appl Pharm. 2018;10(Special Issue 1):307-310. https://doi.org/10.22159/ijap.2018.v10s1.68
26. Khan A, Kalaria RN, Corbett A, Ballard C. Update on vascular dementia. J Geriatr Psychiatry Neurol. 2016;29(5):281-301. doi: 10.1177/0891988716654987. PMID: 27502303.
27. Sha MC, Callahan CM. The efficacy of pentoxifylline in the treatment of vascular dementia: a systematic review. Alzheimer Dis Assoc Disord. 2003;17(1):46-54. doi: 10.1097/00002093-200301000-00006. PMID: 12621319.
28. Zhang YS, Li JD, Yan C. An update on vinpocetine: New discoveries and clinical implications. Eur J Pharmacol. 2018;819:30-34. doi: 10.1016/j.ejphar.2017.11.041. Epub 2017 Nov 26. PMID: 29183836; PMCID: PMC5766389.
29. Moskalev A, Chernyagina E, Tsvetkov V, Fedintsev A, Shaposhnikov M, Krut'ko V, et al. Developing criteria for evaluation of geroprotectors as a key stage toward translation to the clinic. Aging Cell. 2016;15(3):407-15. doi: 10.1111/acel.12463. Epub 2016 Mar 11. PMID: 26970234; PMCID: PMC4854916.
30. Lee L, Weston WW, Hillier LM. Education to improve dementia care: impact of a structured clinical reasoning approach. Fam Med. 2018;50(3):195-203. https://doi.org/10.22454/FamMed.2018.221401.

Table 1. Physicians' related data: working experience, number of patients per physician and proportion of general medicine specialist *vs.* general practitioner

Variable	**Minimum–Maximum**	**Median (25^{th} – 75^{th} percentile)**
Physicians' years of service (n = 340)	1–41	24 (13–30)
Frequencies, number (%) < 10 y. 11–20 y. 21–30 y. 31–40 y.	 72 (21.2) 69 (20.3) 128 (37.6) 60 (17.6)	
Number of patients in physician's protocols	5–5000	1800 (1400–2000)
Distribution of frequencies, number (%) < 1000 1001–1500 1501–2000 2001–2500 > 2500	 28 (8.2) 74 (21.8) 138 (40.6) 65 (19.1) 18 (5.3)	
Physicians' specialization *vs.* general practitioner number (%)	186 (54.7) *vs.* 152 (44.7)	

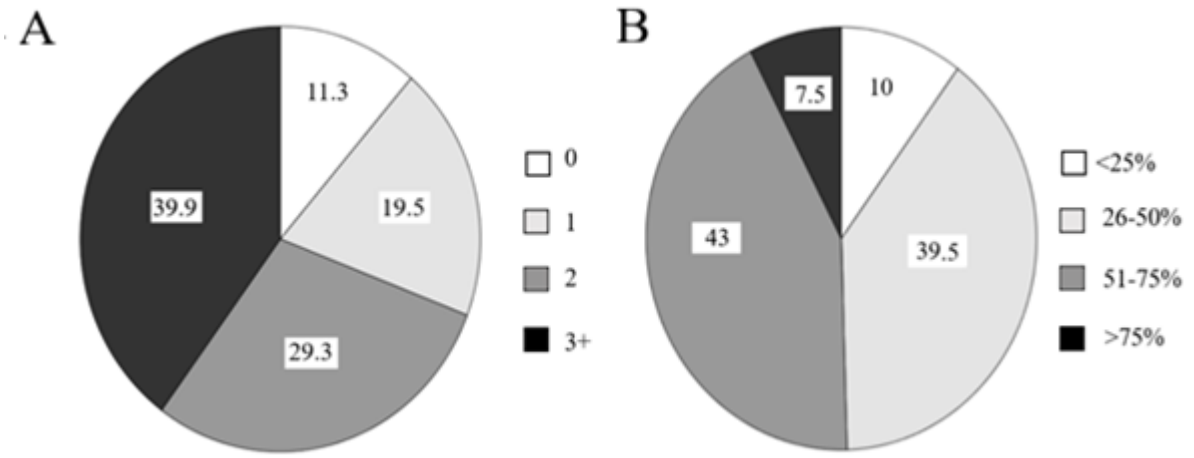

Figure 1. Percent of physicians' estimation of: A – proportion of patients with different risk factors (arterial hypertension, diabetes mellitus, hypercholesterolemia, obesity, smoking, physical inactivity) in their practice, (%); B – proportion of patients older than 65 (%)

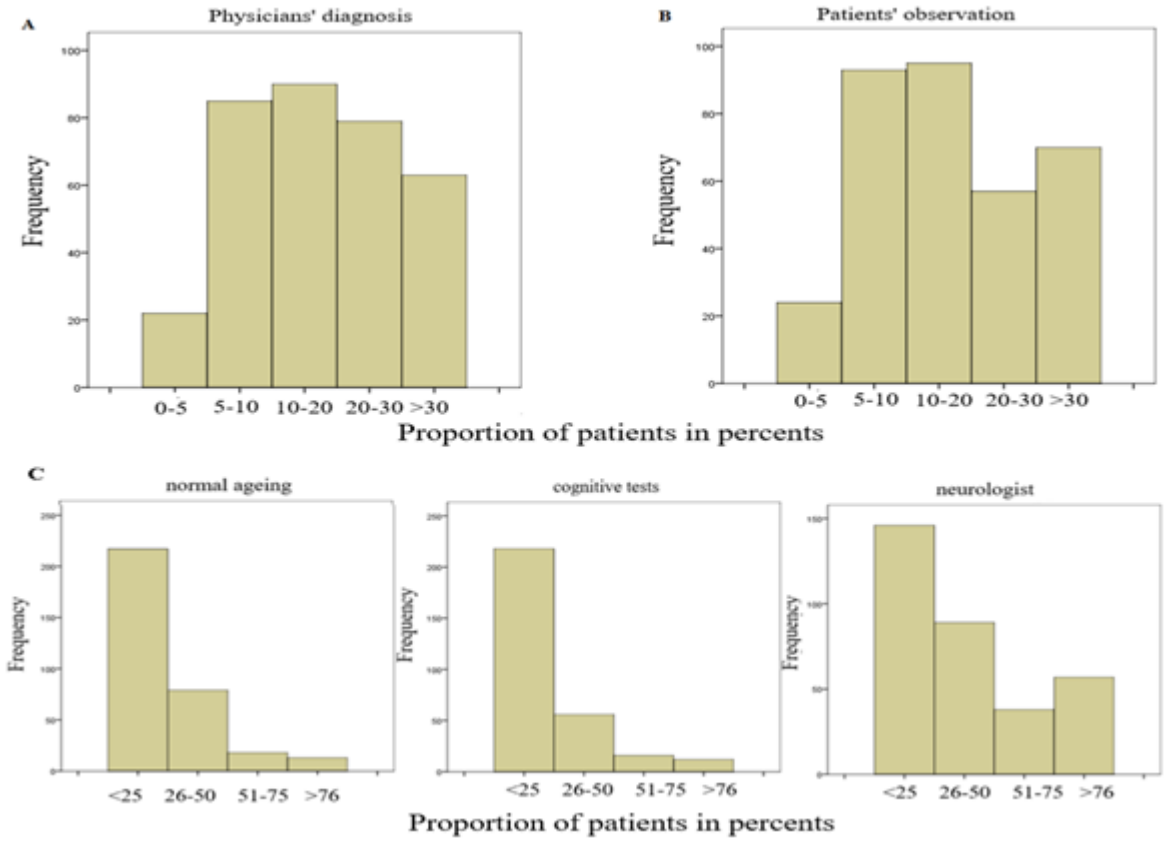

Figure 2. Distribution of physicians' estimation of patients proportion whose cognitive deterioration was noticed by physicians (A) or patients themselves (B); proportion of three characteristics of physicians' attitude towards patients' cognitive decline signs and symptoms: perceiving as normal ageing, cognitive tests performance and referring to neurologist (C); A – distribution of frequency of physicians noticed patients' forgetfulness, decreased concentration, walking instability, thought slowness (symptoms of brain's small blood vessels damage); B – distribution of frequency of patients complains about forgetfulness, mood swings, walking instability, or a "blurred" mind; A and B data expressed in % (0–5, 5–10, 10–20, 20–30, > 30); C – distribution of frequency of physicians opinion about MCI as normal ageing, cognitive tests implementation and neurologist inclusion (results are presented in %: < 25, 26–50, 51–75, > 76)

Table 2. Average physicians' categorization (in %) of six traditional cardiovascular disease risk factors importance for cognitive impairment development

Disease/life style-importance	Unimportant	Low importance	Undefined /unspecified attitude	Important for older patients	Important for all patients
Arterial hypertension	3.9	7.0	16.6	30.8	41.7
Diabetes mellitus	0.9	5.1	9.6	28.8	55.6
Hypercholesterolemia	1.8	6.0	15.9	37.4	38.9
Obesity	1.8	17.6	25.1	22.7	32.7
Smoking	1.8	8.4	14.1	21.9	53.8
Physical inactivity	2.4	6.4	15.2	25.9	50.0

Table 3. General practitioners' and general medicine specialists' comparison regarding cardiovascular diseases risk factors perception and mild cognitive impairment therapy practice

Variable	General practitioner	General medicine specialist	p
Risk factors for cognitive impairment – physicians' perception#			
Arterial hypertension 0/1/2	47/53/49 (31.5/35.6/32.9%)	44/48/88 (24.4/26.7/48.9%)	0.014
Hypercholesterolemia 0/1/2	47/60/44 (31.1/39.7/45.5%)	32/64/85 (17.7/35.4/54.5%)	0.001
Smoking 0/1/2	45/37/68 (30.0/24.7/45.3%)	36/35/110 (19.9/19.3/60.8%)	0.017
Physical inactivity 0/1/2	41/45/62 (27.7/30.4/41.9%)	38/39/101 (21.3/21.9/56.7%)	0.028
Patients without risk factors (%)*	10.0 (5.0-20.0)	10.0 (5.0-15.0)	0.048
Cognitive symptoms assumed as normal ageing (%)*	20.0 (10.0-30.0)	10 (6.0-30.0)	<0.01
Therapy			
Prescription drug (pentoxifylline or vinpocetine alone or in any combination with different supplements) no/yes	112/40 (74%/26%)	120/66 (64%/36%)	0.045

***** p – Mann–Whitney U test; otherwise χ^2 test for categorical variables
# – level of risk factor estimation: 0 – unimportant; 1 – important only for old patients; 2 important for all patients

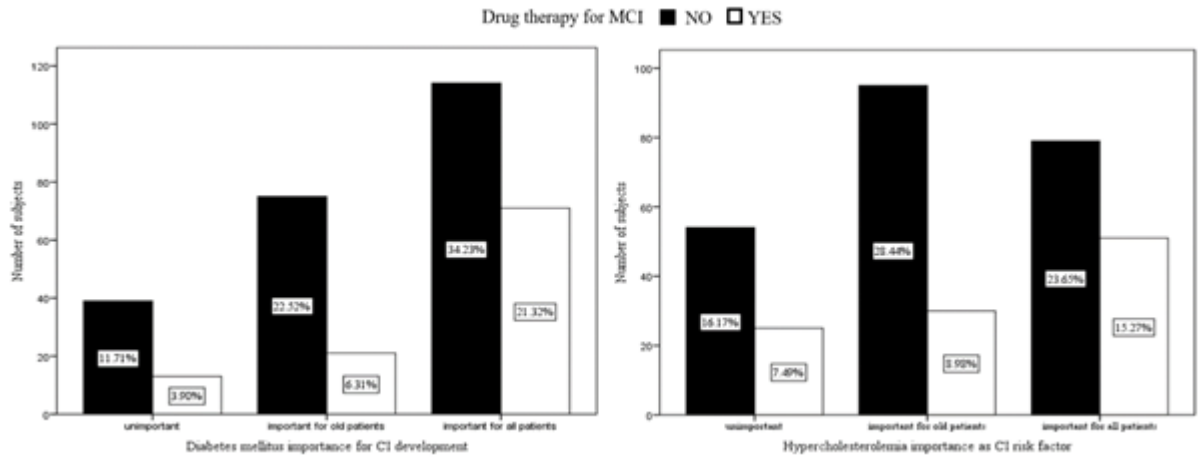

Figure 3. Distribution of physicians with different attitude towards hypercholesterolemia and diabetes mellitus importance as CI risk factor who prescribed drug therapy *vs*. supplements for cognitive impairment; χ^2 test for proportion comparison is used; $p < 0.05$ *vs*. physicians' stance estimated distinct risk factor as less important for both risk factors, respectively

Table 4. Univariate and multivariate logistic regression analysis of predictors for physicians' awareness of cardiovascular risk factors importance for CI development

Predictor	B (SE)	Wald coefficient	OR (95th CI)	p
Years of physicians' experience	-0.043 (0.013)	10.30	0.958 (0.934–0.983)	**0.001**
Physicians' specialization *vs.* general practitioner	-0.763 (0.265)	8.30	0.466 (0.277–0.784)	**0.004**
Number of patients in physician's protocols	0.000 (0.000)	3.40	1.000 (0.999–1.00)	**0.066**
Percent of patients older than 65 years	0.004 (0.007)	0.30	1.004 (0.990–1.018)	0.573
Percent of patients without CVD risk factors	0.003 (0.014)	0.03	1.003 (0.976–1.030)	0.854
Percent of patients with 1 CVD risk factor	0.023 (0.013)	3.20	1.023 (0.998–1.048)	**0.072**
Percent of patients with 2 or more CVD risk factors	-0.015 (0.007)	4.00	0.985 (0.971–1.000)	**0.046**
Percent of physicians perceiving MCI symptoms as normal ageing	0.011 (0.006)	3.40	1.011 (0.999–1.023)	**0.065**
Percent of physicians who perform MCI tests	-0.006 (0.006)	0.90	0.994 (0.983–1.006)	0.341
Percent of physicians who referred MCI suspected patients to neurologist	-0.006 (0.004)	2.00	0.994 (0.986–1.002)	0.153
Multivariant analysis – the best model*				
Years of physicians' experience	**-0.051 (0.015)**	**11.9**	**0.950 (0.923–0.978)**	**0.001**
Number of patients in physician's protocols	-0.001 (0.000)	2.8	0.999 (0.998–1.000)	0.094
Percent of patients with 2 or more CVD risk factors	-0.020 (0.008)	6.2	0.980 (0.964–0.996)	**0.013**
Percent of physicians perceiving MCI symptoms as normal ageing	0.013 (0.007)	4.0	1.013 (1.000–1.027)	**0.047**

CVD – cardiovascular disease; MCI – mild cognitive impairment;
*Variables selected for multivariant analysis according to p from the univariant analysis ≤ 0.100
B (SE) – beta coefficient (standard error); OR – odds ratio with 95th confidence interval, p – significance

Table 5. Univariate and multivariate logistic regression analysis of predictors for providing prescription drugs (pentoxifylline and/or vinpocetine) by physicians

Predictor	B (SE)	Wald coefficient	OR (95th CI)	p
Years of physicians' experience	0.037 (0.012)	9.2	1.038 (1.013–1.064)	**0.002**
Physicians' specialization *vs.* general practitioner	0.432 (0.240)	3.247	1.54 (0.96–2.46)	**0.072**
Number of patients in physician's protocols	0.000 (0.000)	0.885	1.00 (0.99–1.00)	0.347
Percent of patients older than 65 years	-0.001 (-0.006)	0.014	0.99 (0.99–1.01)	0.906
Percent of patients without CVD risk factors	0.004 (-0.012)	0.136	1.00 (0.98–1.03)	0.712
Percent of patients with 1 CVD risk factor	0.008 (-0.010)	0.652	1.01 (0.99–1.03)	0.419
Percent of patients with 2 or more CVD risk factors	-0.024 (0.011)	4.607	0.98 (0.96–0.99)	**0.032**
Percent of physicians perceiving MCI symptoms as normal ageing	-0.002 (0.006)	0.137	0.99 (0.98–1.01)	0.711
Percent of physicians who perform MCI tests	0.012 (0.005)	5.686	1.01 (1.00–1.02)	**0.017**
Percent of physicians who referred MCI suspected patients to neurologist	0.006 (0.001)	2.640	1.01(0.99–1.02)	**0.100**
Physicians' estimation of arterial hypertension importance	0.113 (0.110)	1.058	1.12 (0.90–1.39)	0.304
Physicians' estimation of diabetes mellitus importance	0.300 (0.143)	4.373	1.35 (1.02–1.79)	**0.037**
Physicians' estimation of hypercholesterolemia importance	0.182 (0.126)	2.077	1.20 (0.94–1.54)	0.150
Physicians' estimation of obesity importance	0.011 (0.102)	0.011	1.01 (0.83–1.23)	0.918
Physicians' estimation of smoking importance	0.121 (0.114)	1.139	1.13 (0.90–1.41)	0.286
Physicians' estimation of physical inactivity importance	0.184 (0.119)	2.392	1.20 (0.95–1.52)	0.122
Multivariant analysis – the best model*				
Years of physicians' experience	0.039 (0.014)	7.8	1.04 (1.01–1.07)	**0.005**
Percent of patients with 2 or more CVD risk factors	-0.029 (0.013)	5.1	0.97 (0.95–0.99)	**0.024**
Percent of physicians who perform MCI tests	0.013 (0.005)	5.8	1.03 (1.01–1.05)	**0.016**

CVD – cardiovascular disease; MCI – mild cognitive impairment;
*Variables selected for multivariant analysis according to p from the univariant analysis ≤ 0.100
B (SE): Beta coefficient (standard error), OR- odds ratio with 95th confidence interval, p - significance

