

## USE OF BETA BLOCKERS IN ACUTE CORONARY SYNDROME IN SERBIA IN THE PERIOD 2000 – 2005

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The approaches in prevention and therapy of acute coronary syndrome (ACS) are different ways of conservative and invasive procedures which have contributed to reduction of mortality of ischemic heart disease (IHD) by 20 %, approximately, in many parts of the world in the recent 20 years. Beta blockers (BBs) have given significant contribution to prevention and therapy of ACS, especially their use in ACS and in the first years of secondary prevention of IHD. The aim of the study was the estimation of patients with ACS in Serbia in the period 2000 – 2005, as well as the evaluation of BB use in ACS and resolving dilemma concerning their prescription.

The data about patients were obtained from the National Register for ACS in Serbia. Lately, there has been a marked increase in the number of coronary units (CU) and patients with ACS. In admission diagnoses, there was the largest number of patients with AMI or 69,7%, with the highest total mortality of 11,7 %. In addition, higher rates of male patients than female ones, as well as an increase of male patients in the age group of 50-59 years, and an increase of female patients in the age group of 70-79 years were reported. It is interesting that the rate of female patients is higher than presented in literature. It is noted that the rate of AMI with ST segment elevation (STEMI) is more frequent than AMI without ST elevation (NSTEMI). STEMI is more frequent in younger patients and male ones. Case-fatality of STEMI patients is significantly higher compared with NSTEMI patients ( $p < 0,000$ ). The percentage of patients with ACS treated with BB is still low and it has not been changed significantly in recent years. *Acta Medica Medianae* 2008;47(3):28-34.

**Key words:** beta blockers (BBs), acute coronary syndrome (ACS), secondary prevention of ischemic heart disease (IHD)

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### Introduction

The term ACS is an expression used in recent years for a diagnosis of acute coronary disease, occurring within first hours or in the first days of the beginning of symptoms of the disease. Unstable angina pectoris, STEMI, NSTEMI and sudden death stand for the acute forms of coronary disease.

In order to select an appropriate therapeutic approach, there is a need for precise diagnosis and risk evaluation of future cardiac events, so that evaluation should be done early, based on available clinical electrocardiographic and sensitive and specific biomarkers (17). New cardiospecific markers, troponin I and troponin T enabled better diagnosis of myocardial necrosis, and the use of thrombolytic therapy (TT) and percutaneous coronary intervention (PCI) as a standard therapy in STEMI. The use of antithrombotic drugs and PCI

in NSTEMI and in unstable AP have helped to define the importance of ACD, first of all because of appropriate therapy whose efficiency is mainly determined by fast drug application (1).

Early BB application in AMI has given objective evidences of the favourable effect, because it reduces intensity of chest pain, reduces ST segment elevation on ECG in transmural infarction and reduces the concentration of creatine kinase. The use of BBs reduces the heart volume, arterial blood pressure and retards pulse, the result of which is the reduction of oxygen consumption and lactic acid creation (2).

It is considered that continuation of BB therapy after acute phase is important in reducing possible extension of infarctional zone. The prophylactic use of BBs after AMI has an excellent effect, first of all in patients with uncomplicated infarction. Those patients with heart insufficiency (HI), ischemia or serious arrhythmia must have individual therapy depending on complete clinical status. It is considered that 50% of patients after AMI can be treated with BBs, following the indications.

All BBs are efficient in treating AP, although some groups of BBs have some specific characteristics, which are important for some groups of patients with AP (3).

Convincing evidences of reduction on mortality achieved by BBs in patients with AMI in postinfarction monitoring at the beginning of the '80s, have brought to presumption that this way of treatment has to improve the result in angina on exertion and in unstable angina. Unfortunately, there have not been done yet good studies which could support this presumption.

Exhaustive controlled clinical studies affirm beta-blockers as drugs that reduce mortality in secondary prevention of ischemic heart disease (7,8).

The analysis of 14-year follow-up showed that the therapy with aspirin, BB and coronary revascularisation is successful when it comes to intermediary goals, i.e. infarction relapse, anginal attacks and repeated revascularisation, but the cumulative effect on mortality is not clear (12).

### Aims

The aim of the research was the estimation of patients with ACS in Serbia in the period from 2000 to 2005, and also the estimation of BB use in ACS and resolving dilemma related to their prescription.

### Material and methods

The method of analysis means the estimation of patients with ACS in CU and UIC in Serbia in the period from 2000 to 2005.

The research summarizes the results of six-year-long study which are presented in tables and graphs. Descriptive and analytical methods were used in the research. The groups of examinees were divided according to sex, age and structural forms of ACS.

The results were obtained during one year based on data processing of the number of patients with ACS in Serbia collected for the first time in 2003 by the team of ACS experts in the Ministry of Health. The data from National Register for ACS in Serbia were compared to the data for ACS from European countries-Euro Heart Survey ACS II (EHS ACS II) from 2004, which included 6,356 patients from 32 countries. Unique epidemic data were collected by means of coronary reports containing minimal necessary data about all patients treated in CU and UIC in Serbia.

The unpublished data from Public Health Institute „Dr Milan Jovanovic Batut“ in Belgrade were used for the estimation of BBs in ACS in Serbia and they were compared to the data from EHS ACS II from 2004. The data about estimation of BB consumption in the world were taken from the site [www.legemiddelforbruket.no](http://www.legemiddelforbruket.no).

The analysis enabled resolving the existing therapeutic dilemma and more exact estimation of successful treatment. The analysis was a help to doctors to decide about therapy procedure (Evidence-based medicine), shape science-based instructions for clinical practice (Evidence-based practice) and gives contribution for further research.

### Results

The patients of both sexes and different ages with ACS in CU and UIC care in Serbia were involved in the six-years-long period from 2000 to 2005.

We noticed that the data about the number of patients with ACS in 2000 and 2001 in Serbia were missing or incomplete (Tables 1,2).

Table 1. Data of ACS in Serbia for the year 2000

unchanged number of beds for 15 years (the number of patients has increased in the City of Belgrade by 50 %)
inadequate access, inadequate keeping of medical documentation

Table 2. Data of ACS in Serbia for 2001

28 CU and UIC (incomplete data)
mortality from AMI: 18 %

According to incomplete data for November 2002 and based on the results from 48 CU and UIC in Serbia, 786 patients were treated, average age  $63 \pm 1$  years (20-87 years of age). According to sex it was registered that 59 % were men with ACS,  $61 \pm 12$  (70% -  $62 \pm 12$ , EHS ACSII) years and 41% were women,  $66 \pm 10$  (30%  $70 \pm 12$ , EHS ACSII) years. TT was used in a significantly low percentage of patients i.e. in 15.1% of patients (Table 3).

Table 3. Data of ACS in Serbia for November, 2002

48 CU	
786 patients, 20-87 years of age ( $63 \pm 11$ )	
M: 59 %, $61 \pm 12$ , Serbia	W: 41 %, $66 \pm 10$ , Serbia
70 %, $62 \pm 12$ , EHS ACS II	30 %, $70 \pm 12$ , EHS ACS II
with TT: patients	15,1 %

Analyzing the results obtained from 50 CUs and UICs in 2003 in Serbia, we noted that 12.739 of patients were treated, of which 8.883 patients had AMI diagnosis. Further analysis indicated that according to sex, 62.7% of patients were men and 37.3% were women. The average age of men was  $61.06 \pm 11.7$  years, and of women  $65.76 \pm 10.46$  years. The youngest patient was 19 years old and the oldest was 93 years old. During hospital admissions, ST segment changes on ECG were observed in patients with STEMI and NSTEMI. In 6.716 patients or 75.6%, ST segment elevation was registered, while in 2.167 patients or 24.4%, ST segment elevation was not registered. ST segment elevation was statistically significantly more frequent in younger patients

than in older ones. Women were more numerous in NSTEMI group than in STEMI group. TT was given to 1,965 patients or 29,26% of 6,716 patients in total.

It should be noted that the number of patients treated with TT in 2003 was significantly lower in relation to the European recommendations.

In the group of patients treated with TT, case fatality was 7,5%, i.e. 147 patients of 1,965 deceased. TT was not applied in 4,751 cases. In this group of patients, case fatality was 15,3%, i.e. 726 patients deceased. The difference in the prognosis of patients, with and without applied TT, was statistically very high ( $P < 0,000$ ). The total mortality for STEMI was 13,0%, and for NSTEMI 7,6% (Table 4).

Table 4. Data of ACS in Serbia for 2003

50 KJ (12739 patients)	males	62,7 %, 61,06±11,7
	females	37,3 %, 65,76±10,46
AIM (8883 patients)	STEMI	6 716 patients, 75,6 % 35% females, total mortality 13%
	NSTEMI	2 167 patients, 24,4 % 38% females, total mortality 7,6%
with TT: 1 965 patients, 29,26 % case fatality: 147 patients, 7,5 %		
without TT: 4 751 patients case fatality: 726 patients, 15,3 %		

In 2003, in the admission diagnoses, the most of the patients were diagnosed with AMI (69,7%). In this group of patients, the highest total mortality of 11,7% was reported (Table 5).

Table 5. Structure in the form of ACS and total mortality in the course of 2003

Year 2003:
AMI: 8 883 patients, 69,7 %
unstable AP: 3 856 patients, 30,27 %
total mortality from AMI: 11,7 %, hospital mortality of AMI: 8,9 %, total mortality of unstable AP: 1,6 %

In 2004, in CU and UIC in Serbia (CU of the Institute of Cardiovascular Diseases Sremska Kamenica, CU of the Health Care Centre in Leskovac and the Health Care Centre in Vranje were not included), 19.859 patients were treated, of which 12.351 or 62.2% had ACS diagnosis.

Also, an increase in the number of patients with ACS for previous year was reported. According to sex, 63,1% were men and 36,9 % were women. The average age of men was 61,53±11,32 years, and of women 66,05±10,62 years. The statistical data related to sexes and the average age were not significantly different compared to data from 2003. From the total number of patients with AMI, of which 8.360 were registered in 2004, there were 6,393 patients with STEMI or 76,5%, and 1,967 patients with NSTEMI or 23,5%. The number of patients with STEMI and NSTEMI did not differ much statisti-

cally in regard to 2003. It is confirmed that ST segment elevation was statistically significantly more frequent in younger patients than in older ones. Of 6,393 STEMI patients, 1,972 patients or 30,8% were treated with TT. Case-fatality was 7,6%, i.e. 150 patients of this group died. 4,421 patients or 69,2% were not treated with TT. In this group, case-fatality was 14,5%, i.e. 642 patients died. The difference in the prognosis of patients treated or not with TT in 2004 was statistically very significant. The number of patients treated with TT in 2004 was significantly smaller in regard to the European recommendations. It was noted that, thanks to TT and better diagnostics, the mortality of patients with AMI was significantly reduced during the last 3 years in Serbia. Case fatality of patients with AMI and ST elevation and patients treated with TT statistically was significantly lower ( $p < 0,000$ ) compared to the group which was not treated with TT (Table 6).

Table 6. Data of ACS in Serbia for 2004

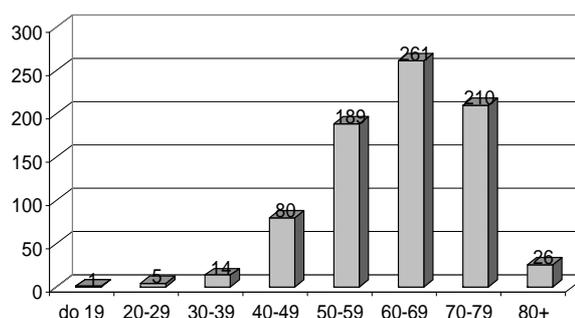
50 CU	19 859 patients
ACS 12 351 patients, 62,2 %	
M:	W:
63,1 %, 61,53±11	36,9 %, 66,05±10,62
AMI: 8 360 patients	
STEMI:	NSTEMI:
6 393 patients, 76,5 %	1 967 patients, 23,5 %
with TT: 1 972 patients, 30,8 %	
case fatality: 150 patients, 7,6 %	
without TT: 4 421 patients, 69,2 %	
case fatality: 642 patients, 14,5 %	

We registered that, according to sex, the results for 2005 were similar to the data of the year before (Table 7).

Table 7. Data on ACS in Serbia for December 1 -31, 2005

51 CU	
12 739 patients, age adjusted rate 61 ± 11; 19-93 years of age	
M:	60,9 %, 61±11
W:	39,1 %, 65±8
with TT: 36,4 %	

The most numerous age group of patients with ACS was from 50 to 79 years in 2005 (Graph 1)



Graph 1. Patients of ACS presented by age groups in the course of 2005

Table 8. Registration year, number of patients with ACS and therapy in the period from 2002 to 2005

Year	Patients (%)			
	2002	2003	2004	2005
Number of patients	4 202	12739	12 351	12 598
Aspirine	86,0	88,1	89,9 EHS ACS II 97	85,8
Heparine	77,2	77,1	83,4 EHS ACS II 94	82,1
Nitroglycerine	72,1	77,3	81,8 EHS ACS II 75	73,5
Beta blockers	52,8	52,3	56,1 EHS ACS II 83	56,5
ACE inhibitors	51,3	51,5	55,7 EHS ACS II 71	53,1
Diuretics	9,1	29,9	33,6	33,6

\*Source: unpublished data of the Public Health Institute Serbia "Dr Milan Jovanovic Batut", in October, 2007

In the period from 2002 to 2005, we registered that the percentage of patients with ACS treated with BB was still low and it has not changed significantly in recent years (Table 8).

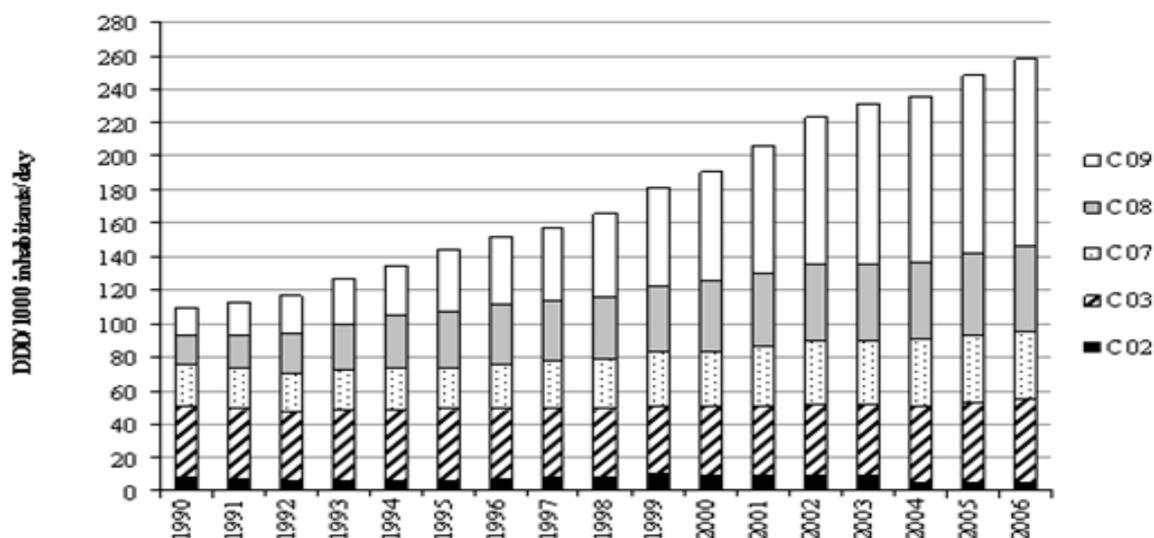
The following data are from Norwegian site which has regular and very detailed data processing about drug consumption and it is often an indicator how certain drug is ranked in Europe.

According to the sales in million of NOK, BB were ranked 3<sup>rd</sup> (CV system) in the period from 2002 to 2006 (Table 9).

Also, the continual increase of BB consumption according to DDD can be noted in the period from 1990 to 2006 (Graph 2). In the following tables you can see the 10 most sold POMs (prescription only medicine) in 2006. According to the sales in million of NOK, metoprolol is ranked 7<sup>th</sup>, and according to DDD it is ranked 6<sup>th</sup> (Table 11,12).

Table 9. Sales per ATC 3rd level for ATC group C - Cardiovascular system

ATC	ATC level name	mill NOK (AUP)				
		2002	2003	2004	2005	2006
C01A	Cardiac glycosides	6,9	6,6	7,6	7,2	8,6
C01B	Antiarrhythmics, class I and III	24,5	22,7	18,7	19,8	20,1
C01C	Cardiac stimulants excl. cardiac glycosides	12,1	13,5	15,4	18,4	20,0
C01D	Vasodilators used in cardiac diseases	102,6	85,6	81,5	73,2	65,5
C01E	Other cardiac preparations	1,3	1,2	1,2	1,2	1,0
C02A	Antiadrenergic agents, centrally acting	8,5	9,4	9,8	10,1	10,7
C02C	Antiadrenergic agents, peripherally acting	87,5	76,5	45,3	38,6	29,6
C02D	Arteriolar smooth muscle, agents acting on	0,2	0,3	0,3	0,3	0,3
C02K	Other antihypertensives		4,9	15,0	22,1	21,9
C03A	Low-ceiling diuretics, thiazides	5,6	6,8	11,3	15,9	19,9
C03C	High-ceiling diuretics	51,8	51,9	60,0	59,7	56,2
C03D	Potassium-sparing agents	8,7	8,9	8,9	9,3	10,4
C03E	Diuretics and potassium-sparing agents in combination	7,8	7,8	8,5	7,3	7,3
C04A	Peripheral vasodilators	6,0	5,2	4,7	3,7	2,3
<b>C07A</b>	<b>Beta blocking agents</b>	<b>257,3</b>	<b>255,7</b>	<b>268,5</b>	<b>259,2</b>	<b>258,5</b>
<b>C07B</b>	<b>Beta blocking agents and thiazides</b>		<b>0,9</b>	<b>2,7</b>	<b>4,4</b>	<b>4,6</b>
C08C	Selective calcium channel blockers with mainly vascular effect	320,0	289,3	243,5	149,0	142,2
C08D	Selective calcium channel blockers with direct cardiac effects	47,8	42,6	39,8	35,8	31,9
C09A	ACE-inhibitors, plain	206,9	177,3	135,9	77,3	80,2
C09B	ACE-inhibitors, combinations	78,5	67,8	57,1	35,2	29,8
C09C	Angiotensin II antagonists, plain	248,5	267,3	293,5	324,5	330,0
C09D	Angiotensin II antagonists, combinations	215,4	247,7	301,1	364,6	390,1
C10A	Lipid modifying agents, plain	1105,1	1091,3	970,4	807,4	646,5
C10B	Lipid modifying agents, combinations					0,02



Graph 2. Sales of antihypertensives (C02), diuretics (C03), beta blocking agents (C07) calcium channel blockers (C08) and ACE-inhibitors + angiotensin II antagonists (C09) 1990 - 2006

Table 10. Sales of 10 most sold POMs ranked according to the sales in million of AUK in 2006

ATC kode ATC code	Virkestoff Active ingredient	Bruksområde Indication	Million DDD Million DDD	Million kr (AUP) Million NOK (AUP)
L04AA11	Etanercept	Leddgikt m.m.	1	434
C10AA05	Atorvastatin	Kolesterolsenkende	86	377
R03AK06	Salmeterol og flutikason	Astma/KOLS	21	350
A02BC05	Esomeprazol	Spiserørsbetennelse m.m.	28	349
L04AA12	Infliximab	Leddgikt m.m.	1	260
N05AH03	Olanzapin	Psykiske lidelser	5	208
C07AB02	Metoprolol	Hjerte/kar sykdom	40	199
R03AK07	Formeterol og budesonid	Astma/KOLS	11	194
C10AA01	Simvastatin	Kolesterolsenkende	144	180
C09DA01	Losartan og hydroklortiazid	Hjerte/kar sykdom	21	168

Table 11. Sales of the 10 most sold POMs ranked according to the sales in million of DDDs (Includes only drugs with DDDs) in 2006

ATC kode ATC code	Virkestoff Active ingredient	Bruksområde Indication	Million DDD Million DDD	Million kr (AUP) Million NOK (AUP)
C10AA01	Simvastatin	Kolesterolsenkende	144	180
B01AC06	Acetylsalisylsyre	Blodpropp forebyggende	108	110
C10AA05	Atorvastatin	Kolesterolsenkende	86	377
N05CF01	Zopiklon	Sovemiddel	52	99
C08CA01	Amlodipin	Hjerte/kar sykdom	51	60
C07AB02	Metoprolol	Hjerte/kar sykdom	40	199
C09AA05	Ramipril	Hjerte/kar sykdom	40	41
C03CA01	Furosemid	Hjerte/kar sykdom	37	34
H03AA01	Levothyroksinnatrium	Thyroksintilskudd	36	50
R06AE07	Cetirizin	Pollenallergi	36	43

## Discussion

In our country, as in many countries in transition, an increase of mortality and incidence in ACS has been reported. The mortality in AMI is about 30%, of which more than half of all deaths occur before a sick person arrives to hospital.

Although survival after hospitalization has improved in the last 20 years, additional 5-10% of survived patients die in the first year after infarction (9). There is a continual risk of increased mortality and new infarctions in recovered patients (10).

There is no country in which data collection about the incidence of CV diseases is regular. In

observing morbidity, MONICA study data were mainly used. The City of Novi Sad in Serbia was included in the MONICA study. Heart diseases represent a leading cause of premature death in most developed countries of the world as well (11). On the scale of the countries ranked according to the rates, Serbia is placed in the upper third for female population and a little above the middle for male population. In Serbia, without Kosovo and Metohia, the rate of mortality in 1996 was 800 for men and 600 for women, from 45 to 70 years of age, which puts our country on the top of the ranked countries (13). The aim of this study was to emphasize the importance of regular collection of epidemic data about the number of patients with ACS in Serbia, during one year and also, to emphasize the importance of BB use in ACS, particularly in secondary prevention of IHD, which was confirmed by numerous clinical trials. The study confirmed the facts that, besides strong arguments and numerous recommendations, BBs have not been accepted enough as an integral part of treatment of ACS in Serbia. Consequently, there have been many deceased despite favorable pharmacoeconomic condition.

On the other hand, in the world, BBs represent a standard treatment for angina on exertion, mixed angina on exertion and at rest, as well as unstable AP. BB reduces case-fatality in acute phase of infarction and in postinfarction phase, which contributed to prolongation of life in CV patients. The data about monitoring of postinfarction phase are particularly convincing (14).

The analysis of medical documentation of over 200.000 patients shows that, even in states which are often considered CI for BBs, such as heart failure, pulmonary diseases, patients without transmural infarction and old-aged population, have all benefits of BB (15).

According to the results of the Euro Heart Survey Acute Coronary Syndrome II (EHS II), BBs are being applied in 83% of patients, and according to the multicontinental study GRACE, in 79% of patients (4,5). In RIKS-HIA, the Swedish register with 26.000 subjects suffering from AIM with ST elevation, it has been stated that BBs applied from 1999 to 2004 in 84,7 % of patients treated with in-hospital thrombolysis, and in 88,9% of patients treated with prehospital thrombolysis (6). In our conditions, BBs have been applied considerably less frequently; according to the data from 2002 in 52,8% of patients, in 2003 in 52,3%, in 2004 in 56,1%, and in 2005 in 56,5% of patients with ACS. It would be interesting to mention that every year the use of BB in the treatment of patients with ACS considerably increases, which was especially noticeable in 2004 and 2005, though it is still less present in comparison with the data of the European regions.

The working group ACC/AHA considers that early i.v. beta-blockade is induced for patients without CI. It is interesting that retrospective analysis of National Infarction Register in USA which shows that intracranial hemorrhage with immediately applied i.v. beta-blockade has been reduced by 31%. Intracranial hemorrhage is the major threat for plasminogen activation.

In the postinfarction phase, the use of BB reduces case-fatality by 35-40% in different kinds of patients (16). Without going into details about advantages of certain groups of drugs' application or invasive procedure, the place of BBs in therapy protocols, either for STEMI or NSTEMI, is undoubtedly very important (18). The first studies showed that in the prethrombolytic era, as well as the combined use of thrombolysis and BBs in TIMI II study in patients with complete infarction. The recent CP study shows that intense BB therapy is of vital importance for the most of NSTEMI patients (19).

BBs reduce morbidity and mortality immediately after infarction, but also weeks, months and years after infarction (20,21). According to the recommendations of the European Society of Cardiology, in the treatment of patients with NSTEMI and STEMI, as primarily anti-stress medications, BB find their place in infarction therapy, if they are not contraindicated (22).

BBs are the most efficient antianginal drugs for reduction of ischemia in ambulatory patients. They reduce the needs of the myocardium for oxygen, reducing heart frequency, contractility and systolic blood pressure during exertion. They are highly efficient as a monotherapy for AP and are the drugs of choice for angina after infarction (2). It is considered that BBs are effective alone or with other drugs in 70-80% of patients with classic angina. Timely diagnosis and treatment with modern methods (like a PCI superior method) have significantly improved the prognosis of patients with ACS (23,24).

Therefore, the application of BBs in ACS should be considered seriously by changing prescription habits and overcoming groundless fear in some of the doctors. Unmistakably, the benefit of prescribing overcomes possible risks.

## Conclusion

The results show that Serbia is at the top of the list of countries with average yearly increase of morbidity and mortality of CV disease.

In Serbia, the drug choice does not significantly influence the prescription and consumption of BB, which should be proportional to their clinical significance and therapy possibilities. It is interesting that this is all happening when great controlled clinical trials confirm BBs as medicines which reduce mortality in primary and secondary prevention of IHD and congestive heart failure.

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## PRIMENA BETA BLOKATORA U AKUTNOM KORONARNOM SINDROMU U SRBIJI U PERIODU OD 2000. DO 2005. GODINE

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Pristupi u prevenciji i terapiji akutnog koronarnog sindroma (AKS) su razni modaliteti konzervativnih i invazivnih procedura, koji su doprineli da se poslednjih 20 godina, u mnogim delovima sveta, mortalitet od ishemijske bolesti srca (IBS) smanjio za oko 20%. Značajan doprinos tome dali su beta blokatori (BB), naročito njihova primena u AKS i prvim godinama sekundarne prevencije IBS. Cilj rada bila je procena bolesnika sa AKS u Srbiji u periodu od 2000. do 2005. godine, kao i procena primene BB u AKS i otklanjanje nedoumica vezanih za njihovo propisivanje.

Podaci o obolelima dobijeni su iz Nacionalnog registra za AKS (REAKS) u Srbiji. U proteklom periodu zapažen je porast broja koronarnih jedinica (KJ) i porast obolelih od AKS. U prijemnim dijagnozama bilo je najviše bolesnika sa AIM ili 69,7%, gde je zabeležen i najveći ukupan mortalitet od 11,7%. Uočena je veća zastupljenost obolelih muškaraca u odnosu na obolele žene i to porast obolelih muškaraca u starosnoj grupi od 50 do 59 godina i porast obolelih žena u starosnoj grupi od 70 do 79 godina. Interesantna je velika zastupljenost ženskog pola, veća nego što se navodi u literaturi. Zapaženo je da se registruje značajno češća zastupljenost AIM sa elevacijom ST segmenta (STEMI), u odnosu na AIM bez ST elevacije (NSTEMI). STEMI je češći kod mladih bolesnika i kod muškaraca. Letalitet bolesnika sa STEMI je značajno veći u odnosu na bolesnike NSTEMI ( $P < 0,000$ ). Procenat bolesnika sa AKS koji je primao BB i dalje je mali i nije se značajno menjao poslednjih godina. *Acta Medica Medianae* 2008;47(3):28-34.

**Ključne reči:** beta blokatori (BB), akutni koronarni sindrom (AKS), sekundarna prevencija ishemijske bolesti srca (IBS)