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THE INTERACTION OF STATINS AND CLOPIDOGREL, MYTH OR REALITY?

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Clopidogrel and statins have usually been prescribed to the patients who have been diagnosed coronary heart disease at the same time. It is specially prescribed to the patients who have already undergone through percutaneous intervention with stent implantation or will go under one. The interindividual variability of clopidogrel effect on blocking platelet P2Y receptors is well known [1]. There has been an attempt to explain a part of this phenomenon by possible interactions of statins with clopidogrel, specially with statins that just like clopidogrel are being metabolized in liver with cytochrome P450 3A4 (CYP3A4-MET) isoenzyme (atorvastatin, simvastatin) as opposed to those that have completely different metabolic path (non-CYP3A4-MET) like pravastatin and fluvastatin. The first study that talks about it was published in 2003 [2]. It was about ex vivo study done on 44 examinees that has shown attenuation of antiplatelet effect of clopidogrel while taking atorvastatin at the same time. Afterwards there was similar study with simvastatin with the same conclusion [3]. Despite the fact that that was ex vivo study done on small number of examinees and without any proof of clinical consequences, the

number of patients that needed simultaneous use of statin and clopidogrel was shifted from CYP3A4-MET to non-CYP3A4-MET statin. This kind of approach has raised suspicion since there was, at the same time, clinically proven superiority of CYP3A4-MET statin in relation to non-CYP3A4-MET statin in order to lower frequency of undesirable cardiac event in coronary patients [4]. Subsequently, the big numbers of smaller clinical studies have appeared where most of them have refused hypothesis of statin and clopidogrel interaction.

The final answer to this question would be given by big randomized, prospective study that would compare CYP3A4-MET with non-CYP3A4 statin in patients on clopidogrel. Apart from monitoring the effect on inhibition of platelet aggregation it is necessary to monitor clinical effects. Since this kind of study would require certain material and human sources, it is not likely that it would appear in near future, if it appears at all. In order to get a proper answer to this question the secondary analyses on 15.603 examinees was done from CHARISMA study (Clopidogrel for High Atherothrombotic Risk and Ischemic Stabilization, Management and Avoidance) [5]. From the total amount of examinees, 7.802 of them were randomized on clopidogrel, and 7801 on placebo. The use of statins was non randomized and was left on discretion of working cardiologist. The total amount of 10.748 (64,6%) patients was on statin before randomization. From that amount, 8.245 on CYP3A4-MET statin and 1748 on non-CYP3A4-MET statin. In this study the big cardio-vascular events were monitored (myocardial infarction, stroke and cardio-vascular death). The analyses have shown that some important different statistical analyses were not shown in major cardio-vascular events among patients who have taken:

- clopidogrel (5.9%) or placebo (6.7%) with any other type of statin
- clopidogrel (5.9%) or placebo (6.6%) with CYP3A4-MET statin
- clopidogrel (5.7%) or placebo (7.2%) with non-CYP3A4-MET statin

So, in spite of the theoretical assumptions and the results of ex vivo study, the negative interactions of clopidogrel and CYP3A4-MET statin were not proven with the help of clinical study on the big number of examinees. Hence, in conclusion there should be pointed out that it is not necessary to choose the type of statin according to its way of metabolism in liver, but according to its clinical effects proved in big clinical studies, even when it is necessary to apply long-term usage of clopidogrel.

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30 YEARS OF ANGIOPLASTY – IN THE MEMORY OF ANDREAS GRUENTZIG

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The big part of Congress on transcatheter cardiovascular treatment (TCT), which was held from 20th till 25th October 2007 in Washington, was dedicated to the 30 years of coronary angioplasty. The memory of angioplasty pioneer doctor Andreas Gruentzig was revived. He was the first one who did the first "non-surgical dilatation of stenoses of coronary artery" on the 16th September 1977 [1-3].

Since 1972 in Zurich, Gruentzig had developed the technology for percutaneous coronary angioplasty, which could be seen as primitive for today's notions. The technology was all about blown balloon which was placed on the top of catheter, which was without possibility of "navigation". The first researches that were done on animals were really encouraging for Gruentzig himself, but his colleagues were not as enthusiastic as he was. For example, after successful percutaneous coronary dilatation on dog, the pathologist's written report stated that Gruentzig should "stop with whatever he is doing", and that he would definitely never apply this technology on people. However, as further researches had shown the safety and credibility of the technique, Gruentzig had successfully convinced his superiors that the thing had to "work" among people.

The search for the first patients had begun and it was shown that it was more difficult than they had thought it would.

Through more than a year Gruentzig had been looking for a patient with simple isolated lesion and angina difficulties refracted on triple therapy. In those times coronary disease was not indication for coronography. The patients with the above mentioned clinical picture had most frequently suffered from triplex coronary heart disease, and the only way of treatment, even among isolated lesions was cardio-surgical procedure. Accidentally, in 1977 the patient presented himself. He was 38 years old, with angina pectoris and coronography of 85% isolated stenosis of LAD. He was willing to listen to a doctor. Gruentzig had explained the technique in details. He had also stated all side effects and seriousness of the situation, nevertheless he gave the chance to the patient to evade sternotomy. Accidentally or not, there was a patient in the same room who had just arrived with the aortocoronary bypass, with the big cut after sternotomy, number of drains that could be seen under gauze and painful grimace on his face. Of course, the 38 year old patient had consented only on the basis of talk with the doctor without the informed consent, ethical commission and internal control.

Gruentzig, of course, didn't know what would happen when he blew the balloon and occludes LAD for a moment. Nobody did that before. Cardio-surgical team was ready in the back under Doctor Marko Turina as a leader. Cardio-surgeons didn't see this method as possible competition. They were curious, and they believed if this method was in use, it would solve only isolated, short-term stenoses, that were only 10-15% of casuistic.

Gruentzig easily pressed balloon into place of stenosis of a conscious patient, blew balloon, and nothing wrong happened, and stenosis disappeared on the next angiogram. It remained like that on the following control coronarographies after a month, 10 years, 23 years...

Gruentzig overshadowed and outplayed everybody. Of course, there were some failures also, but everybody knew that the method would live. However, superior's support was not given, and human interrelations in his team were getting worse. As it is usually happening. Gruentzig ended up in 1980 in the University of Emory in Atlanta with his laboratory team and technology. The rest is a history, or to better put it the present time. The technique hasn't slowed down its development. Its pioneer, doctor Gruentzig died in 1985 in a plane crash. He will be remembered as the revolutionist in medicine.

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ASPIRIN IN THE 21ST CENTURY

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On the 6th October 2007 I attended the 6th International Expert Forum, in Rome. The Forum was dedicated to the role of aspirin in the 21st century. On this gathering the leading experts from the different parts of the world have debated about the role and the use of aspirin in the prevention of initial and repetitive vascular events. They stressed out the big importance of cardiovascular diseases and stroke in morbidity and mortality throughout the world. Safety and efficacy of an aspirin in primary prevention of cardiovascular and cerebrovascular diseases have been shown in many studies. Despite the possibility of cheap intervention, as it is aspirin and guidelines that support its clinical usage, many patients with the risk of the above mentioned diseases are still being unrecognized and untreated.

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THE RECORD TAKEN ON THE MEETING ON STEMI TRANSPORT

- the area that is covered by Clinical Hospital Center Zagreb

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The meeting was held on the 22nd October 2007 in Clinical Hospital Center Zagreb. All interested participants from PCI hospital attended the meeting (the hospital that has possibility to treat with percutaneous coronary intervention) and all other interested participants from the area that cover non-PCI hospital (the hospitals that have no ability to treat patients with the method of percutaneous coronary intervention) that in STEMI network (management of acute myocardial infarction with ST-segment elevation in the National program of intervention cardiology) are transporting patients to Clinical Hospital Center Zagreb, and those are Varaždin and Bjelovar.

After short plenary, (Professor Miličić, MD, PhD & Strozzi, MD, PhD) some data about transporting in STEMI were shown (Professor Ernst, MD, PhD), procedures in acute myocardial infarction non ST-segment elevation (NSTEMI) (Margetić, MD, MS), the report on the results in non-PCI hospitals (Ivanuša, MD, PhD, chief physician), and short suggestion on how to make a form that would equalize the procedure (Skorić, MD).

After that there was a discussion where all participants stated their problems and suggestions, after which some conclusions were reached:

1. If the time of ischemia is shorter than three hours, and fibrinolysis could be done immediately, while the time of mechanical opening of the artery would be longer than 90 minutes, the same should be applied. If fibrinolysis is successful, the patients should be transported the day after to Clinical Hospital Center Zagreb because of coronography and possible intervention of aimed lesion – phone contact with the physician in CCU (coronary care unit) in the morning at 9 o'clock. This kind of procedure could be left as possibility to non-PCI hospital in case some problems with the transport occur.
2. In case that fibrinolysis was unsuccessful (persistence of pain, ST-elevation, complication); the patients should immediately be transported (rescue PCI).
3. If the pain occurred three or more hours before, and lasted till six hours (12 hours if doctor in charge thinks it is necessary), or the time of ischemia is longer than three hours at the moment of presenting, the patient should be transported to PCI as soon as possible. The same procedure should be done for cardiogenic shock or some other more serious complications, where the outcome after PCI could be much better.
4. In NSTEMI infarction, that is stabilized, the patient should be sent the following day with prior agreement with the doctor

in CCU. This category of the patients doesn't include those that have minimal increase of troponin, but those who belong to high risk patients within the meaning of persistence or pain relapse, ECG-changes and clinical impression. There was also a talk of giving inhibitors of Gp IIb/IIIa (eptifibatide), and it was concluded that non-PCI hospitals don't have authority for it. There was also stressed out that the right of every hospital depends on their financial plan. This topic was left for the discussion on the next meeting.

5. There was also discussion about the patients, for which is difficult to get a date, who have so called unstable or newly-appeared angina with minimal increase of troponin, stabilization but induced ischemia. This will be discussed in Clinical Hospital Center Zagreb and it will try to be solved for mutual satisfaction.

6. The new form, which was suggested by Clinical Hospital Center Zagreb, was adopted. It is attached to this record and in contains phone numbers for a contact. This form includes the demands that were accepted by colleagues from non-PCI hospitals: taking blood type and Rh factor, vein path if possible not in cubital vein, shaved groin, medicaments, signed consent etc. It is also agreed that the doctors from transport contact directly CCU when they approach Zagreb, so they would be told where to take the patient, and possibilities are:

a. directly to cath lab (Catheterization Laboratory), which would be the best,
b. in CCU in case cath lab is not ready,
c. patients are taken to the emergency internal service, but the nurse is asked to give all documentation when going to the emergency intervention service, since he/she has to go there to endorse documentation for transport. The department will collect documentation after.

7. Physicians from non-PCI hospitals are asked to plan transporting back till 12 o'clock or to shift it for the following day, which means that the contact from non-PCI hospital with CCU will be made between 9-10 in the morning and get the information, if return transport of the patient could start.

8. The question of giving heparin (fractionated) remained. The recommendation for now is that the patients with STEMI before transport to PCI hospital is not given fractionated heparin but only loading dosage of clopidogrel and aspirin, in order to avoid the combination of heparins (UFH with LMWH), especially in the present phase when our laboratory hasn't got the possibility of measuring ACT. This is the topic for the discussion for the next meeting.

9. The main part of this register is (apart from suggested algorithm and form) an informative consent from PCI hospital (Clinical Hospital Center Zagreb) which should be signed by the patient in non-PCI hospital.

10. It is possible that it will take some time so that planned algorithm is implemented without any problems, so some patience is also needed.

11. The new meeting is being planned in 3-4 months in order to discuss the results of this agreement and once again to make an evaluation of some problems.

ALGORITHM OF PATIENT'S PREPARATION THAT IS SENT TO PRIMARY PCI ON THE AREA COVERED BY CLINICAL HOSPITAL CENTER ZAGREB

1. STEMI diagnosis – 12-lead ECG ± right-sided chest leads

2. the time of ischemia

- primary decision PCI vs. thrombolytic therapy (within 3 hours)
- the possibility of organizing safe transport within 90 minutes from the first contact with the health service

3. informing the patient and patient's consent for primary PCI

4. phone contact to the network center in Clinical Hospital Center Zagreb (**+385-1-236-7467** – Coronary Care Unit)

- the basic data about the patient (age, gender, blood pressure, pulse, 12-lead ECG...),
- the time of ischemia
- did he sign the informed consent
- does he have palpable femoral pulse

5. accepted indications for primary PCI

6. to ensure:

- setting up IV path (if possible not in cubital vein) - monitoring of the patient who needs the constant physician's surveillance

- giving agreed therapy (aspirin plus clopidogrel)

- taking out the test tube for blood type and Rh (name, surname, date of birth plus name and surname of the person who has taken the specimen)

- shaved groin

7. the patient while leaving regional institution should have:

- IV path

- 12-channel EKG from regional institution,

- written history of a disease,

- filled patient's form that is sent to primary PCI in Clinical Hospital Center Zagreb,

- signed informative consent,

- marked test tube for defining blood type and Rh,

- in case the time of transport to PCI hospital is not prolonged - shaved groin.

8. Call the network center while approaching Zagreb from the emergency vehicle (**+385-1-236-7476** – Coronary Care Unit or **+385-1-238-8164** Catheterization Laboratory).

9. while entering Clinical Hospital Center Zagreb:

- physician, patient (monitored on defibrillator) and all documentation goes to the Catheterization Laboratory or to Coronary Care Unit depending on the agreement on the phone,

- after admission it is necessary to go to Emergency internal service and notify staff on duty about the admission.

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THE FORM OF A PATIENT WHO IS SENT TO PRIMARY PCI
IN CLINICAL HOSPITAL CENTER ZAGREB

Name and surname of a patient: _____

Gender: M / F

The year of birth: _____

The beginning of chest pain: _____

The time of arrival in the Emergency of regional institution: _____

The time of contact with the Internal service of regional institution: _____

Present therapy: _____

Allergies: _____

Confirmed STEMI: YES NO

Given 300mg of aspirin: YES NO

Given 600 mg (8 pills a 75mg) of clopidogrel: YES NO

NOT given heparin: YES NO

Made vein path: YES NO

Signed informative consent: YES NO

Given and according to the directions marked test tube for blood type and Rh: YES NO

Shaved groin: YES NO

Complications during transport: YES _____ NO

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GUIDELINES FOR THE DIAGNOSIS AND TREATING OF ARTERIAL HYPERTENSION IN 2007.
WORKING GROUP OF THE EUROPEAN SOCIETY FOR HYPERTENSION AND THE EUROPEAN SOCIETY OF CARDIOLOGY

Bojan Jelaković, Vice President of Croatian Society for Hypertension

When these two European expert societies published the guidelines for diagnosis and treatment of arterial hypertension 4 years ago, nobody thought that it would become one of the most cited articles in the recent period. That evidently point out the importance of the problem that arterial hypertension represents today in the world, but it also stresses out the quality of the guidelines, i.e., the approach of those two societies towards the hypertension since there were other American guidelines JNC-7 published at the same time but they were not as cited as much. The thing that makes European guidelines from the year 2003 special, and the same thing was stressed in the guidelines this year is, that they are firstly consultative, flexible and as much as it is possible in such article, focused on individual patient. That is the reason, why are they gladly read although they are rather long. As opposed to the guidelines from the year 2003 that in their content had included the results of many studies, new guidelines from 2007 do not give as much recommendations based on the results of the big

studies (that were not in as big number as in earlier times, except for ASCOT study) but they are directed to even more precise estimation of total cardiovascular risk.

The definition and classification of arterial hypertension has not drastically changed in relation to before, although it is once again mentioned that the border is arbitrary and that there is a continuum of risks till the value even below optimal ones. The new borders are mentioned only for continued (ambulatory care) and home measured blood pressure as shown in the Table 1.

Table 1. Border (middle) values of blood pressure in relation with the different way of measuring

	SYSTOLIC BLOOD PRESSURE	DIASTOLIC BLOOD PRESSURE
Dispensary or clinic	140	90
24-hours	125-130	80
Day	130-135	85
Night	120	70
Home measurement	130-135	85

Considering the big amount of results of different epidemiological projects, but also the observation from some interventional studies, in the evaluation of total risk and stratification of the patients, metabolic syndrome was introduced. The presence of components of metabolic syndrome can considerably influence on the decision on faster and more aggressive introduction of medical therapy. In the last couple of years the conscious of the importance of kidney disease has dramatically risen. So in new guidelines bigger value and importance was given to kidney damage so that even the small increase of serum creatinin and the presence of microalbuminuria increase the risk and speed up the decision of medical treatment. On the Picture 1 stratification of cardiovascular risk is shown, and introduced curve shows how the definition of hypertension, i.e. the decision on starting with the medicament treatment, could significantly change which is confirmed that the border value is artificial and mostly based on certain (short term) pharmaco-economical criteria.

The absolute risk should be defined among most of the patients. But, absolute risk is partly defined by age, so these guidelines recommend that among young patients should relative risk be defined, since absolute risk could be falsely low (because of the younger age) although they could have big total risk (smoking, obesity, dyslipidemia).

In estimating sub clinical damages the first place belongs to microalbuminuria, i.e. mild kidney function damage, and left ventricular hypertrophy. Both damages should be assessed to all people who suffer from hypertension, and methods are cheap and available (test strip and EKG). The new procedures suggest measuring the index of ankle-upper arm in order to assess atherosclerotic changes, as well as measuring the speed of pulse wave which is precise measure of the height of arterial pressure in big arteries that are unavailable to conventional measurement. It seems they are better indicators of clinical procedure.

In therapeutic procedure the first thing that is mentioned, is the importance of changing bad living habits, but it is also mentioned that the suggestions should not be given to the patients only in a declarative way and by the way, but they need to be institutionalized and prepared with the help of experts. That definitely increases the price of such treatment, the same as the fact that the patients who are treated with this kind of non pharmacological procedures should be called for the check up more often. While calculating the price of treatment this is usually not included. The basic part of medicaments includes the group of five antihypertensives. Since patients who suffer from hypertension use more medicaments it is of minor importance with which medicament the treatment will start. The choice of medicament or the combination depends on the total amount of cardiovascular risk of the patient, prolonged damages in patients, and on the Picture 2 all possible combinations are shown. As opposed to earlier guidelines, the combination of beta-blockers and thiazide diuretics is not recommended because of pro diabetogenic effect. Although beta-blockers are left as the possibility of initial way of treating through the guidelines text, and on the couple of tables it is evident that they should be preferred only among patients with coronary heart disease or old myocardial infarction. It is also stressed out that we should be very careful while using thiazide diuretics in patients who have higher risk of diabetes. The combination that should be given the advantage in general hypertensive population is marked with solid lines. Borders mark the group of antihypertensive that has been proved as useful in interventional researches.

These guidelines as all others have some weaknesses and imperfections. But globally they will improve the way of taking care of people who suffer from hypertension. As the last ones, these will also be translated in Croatian and they will be available to all interested people in extenso (supplement of Hineka) and in short version. I believe that the big part of them will be used in our environment, and soon as the review of the group of Croatian experts will be published considering their usage in our country. We hope that many will find them useful, and that they will motivate responsible institutions and insurance companies to promote the measures of primary prevention, but also to grant more time that a physician will dedicate to a patient during each check up, because the good physician-nurse-patient relationship is the basis of a successful treatment.

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Arterijski tlak (mmHg)					
Rizični čimbenici, SOO ili bolest	Normalan ST 120-129 ili DT 80-84	Visoko normalan ST 130-139 ili DT 85-89	Stupanj 1 AH ST 140-159 ili DT 90-99	Stupanj 2 AH ST 160-179 ili DT 100-109	Stupanj 3 AH ST ≥180 ili DT ≥110
Bez rizičnih čimbenika	Prosječan rizik	Prosječan rizik	Nizak dodatni rizik	Umjereni dodatni rizik	Visok dodatni rizik
1-2 rizična čimbenika	Nizak dodatni rizik	Nizak dodatni rizik	Umjereni dodatni rizik	Umjereni dodatni rizik	Vrlo visok dodatni rizik
3 ili više rizičnih čimbenika, MS, SOO ili ŠB	Umjereni dodatni rizik	Visok dodatni rizik	Visok dodatni rizik	Visok dodatni rizik	Vrlo visok dodatni rizik
Razvijena KV ili bubrežna bolest	Vrlo visok dodatni rizik	Vrlo visok dodatni rizik	Vrlo visok dodatni rizik	Vrlo visok dodatni rizik	Vrlo visok dodatni rizik

Slika 1. Stratifikacija kardiovaskularnoga rizika u četiri kategorije, tj. "prava" klasifikacija arterijske hipertenzije
 ST: sistolički arterijski tlak; DT: dijastolički arterijski tlak; KV: kardiovaskularni; AH: arterijska hipertenzija; ŠB: šećerna bolest. Nizak, umjeren, visok i vrlo visok rizik se odnosi na 10-godišnji rizik ne fatalnog ili fatalnog KV događaja. Termin "dodatni" u svim kategorijama označava da je rizik veći od prosječnog; SOO: subkliničko oštećenje organa; MS: metabolički sindrom. Isprekidana linija označava kako definicija hipertenzije može biti varijabilna s obzirom na stupanj ukupnog KV rizika.

Picture 1. Stratification of cardiovascular risk in four categories, i.e. "real" classification of arterial hypertension
 SBP: systolic blood pressure; DBP: diastolic blood pressure; CV: cardiovascular; AH: arterial hypertension; Low, moderate, high and very high risk implies on 10 year risk of non-fatal or fatal CV event. The term "extra" in all categories marks that risk is higher than the average; SAP: sub-clinical damage of organs; MS: metabolic syndrome. Broken line marks how the definition of hypertension could be variable in connection with the percentage of total CV risk.

Picture 2. Possible combination of antihypertensive therapy

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OPEN LABORATORY FOR INVASIVE CARDIOLOGY IN CLINICAL HOSPITAL MERKUR

Damir Kozmar

Clinical Hospital Merkur, Zagreb

We would like to inform you that from the beginning of October 2007 in Clinical Hospital Merkur, Zagreb the new Laboratory for invasive cardiology has been opened. Since all of you probably have patients that need reasonable diagnoses or treatment with that method, we invite you to send us your patients for which you suspect that they need medical services of the above mentioned laboratory. At this very moment we are able to offer services of diagnostics and intervention coronography. In case our service is expanded to the emergency invasive treatment you will be informed.

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THE RESULTS OF KARDIO.HR WEB QUESTIONNAIRE

From the period from 10th October till 5th December 2007 we have received only 38 answers on the question whether you use one-dimensional echocardiography method during routine echocardiography examinations. Although, since recently, it can not be charged, the most of the answers indicate that we use one-dimensional echocardiography every day (43 answers; 89,5%). We received 2 answers (5,3%) stating they don't use it, and

two more (5,3%) don't know whether they use it.

Kardio list Online 2007;2(12):82. KARDIO LIST – SPONZOR'S PAGE

EFFICACY AND SAFETY OF ATORIS IN A WIDE POPULATION OF PATIENTS

Barbara Guštin

Marketing, Krka, d. d., Novo Mesto, Slovenia

Cardiovascular diseases (CVDs) represent a big medical and economic burden in Europe. They are the major cause of premature death and disability in the middle-aged and elderly in Europe. In clinical practice the priorities for CVD prevention

are patients with established atherosclerotic CVD, diabetes as well as asymptomatic individuals who are at increased risk of CVD due to multiple risk factors or a markedly increased single risk factor. Among the objectives of cardiovascular disease prevention a more rigorous risk factor control is needed, including control of cholesterol levels[1].

The ATOP study was designed to establish the efficacy and safety of Atoris (Krka's atorvastatin) in wide population of patients with primary hypercholesterolemia and combined hyperlipidemia: primary prevention (high-risk patients without confirmed atherosclerotic CVD classified according to SCORE tables), patients with metabolic syndrome, patients with diabetes, patients with coronary heart disease and patients with occlusive disease of non-coronary arteries. This international, multicentre, prospective trial was performed in 4 countries (Croatia, Slovenia, Hungary, Ukraine). Patients were treated with 10 mg to 40 mg of Atoris for a period of 12 weeks. The initial dose was 10 mg and in cases where the concentration of LDL-cholesterol had to be lowered for more than 45% it was initiated with 20mg. If, after first 6 weeks of the treatment target levels of LDL-c were not reached, the dose was titrated to 20 mg or 40 mg. A total of 334 patients were included in the statistical analysis. The average age was 60.5 years. An almost equivalent number of males and females was included (49.2% and 50.8% respectively). Arterial hypertension and smoking were present in 56.9% and 27.9 % of the patients. 32.3% of the patients were at high risk without established atherosclerotic CVD and 67.7% of the patients had established atherosclerotic disease. The average daily dose of Atoris at the end of the study was 21.3 mg. The treatment with Atoris resulted in a statistically significant reduction in LDL-cholesterol by 36% and total cholesterol by 26% ($p < 0.001$). There was also a statistically significant reduction in triglycerides, total cholesterol/HDL ratio and LDL cholesterol with HDL cholesterol ratio. A separate analysis showed a similar beneficial effect of Atoris in lipid parameters in different

groups of patients: patients with coronary disease, patients with diabetes, patients with metabolic syndrome or patients in primary prevention (Figure 1). Eleven patients (3.3%) discontinued the treatment due to side effects. In none of the patients was there an increase in alanine aminotransferase above 3 times the upper limit of normal levels. ($>3x$ UNL). Only in one patient there was an increase in aspartate aminotransferase above 3 times the upper limit of normal levels. ($>3x$ UNL). In none of the patients was there an increase in creatine kinase above 10 times the upper limit of normal levels. The prospective ATOP study confirmed the therapeutic efficacy and good safety profile of Atoris. Similar beneficial effects of Atoris were seen in wide population of patients.

Picture 1. Relative changes of total cholesterol and LDL in different groups of patients treated with Atoris

LITERATURE

1. Graham I, Atar D, Borch-Johansen K, et al European guidelines on cardiovascular disease prevention in clinical practice: executive summary. Fourth joint Task Force of the European Society of Cardiology and other societies on cardiovascular disease prevention in clinical practice (constituted by representatives of nine societies and by invited experts). Eur J Cardiovasc Prev Rehabil 2007; 14 (Suppl 2):E1-40.

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Kardio list Online 2007;2(12):83. KARDIO LIST – SPONZOR'S PAGE

10 years of Krka's statins

5 years of Atoris

Doctors appreciate it,
patients trust them.

ATORIS atorvastatin
Pills of 10mg, 20mg and 40mg

Indications: Hyperlipidemia. Prevention of cardiovascular disease.

Dosage and ways of taking pills: Recommended daily dosage is 10mg. The ultimate daily dosage is 80mg.

Contraindications: Hypersensitivity to any drug ingredients. Active liver disease.

Inexplicable permanent elevation of transaminase level in serum. Skeletal muscles disease. Pregnancy and breast feeding.

Interactions: Taking Atoris and cyclosporine, antibiotics (erythromycin, klarythromycin, kinupristine and dalfoprisitne), protease inhibitors, derivatives of fibric acid, niacin, azole antimicotic or nefazodone at the same time can cause myopathy with rhabdomyolysis and kidney insufficiency. There is a need for caution when atrovastatine is taken together with digoksin and varfarine

Side effects: Most patients can tolerate atrovastatine well. Side effects that can occur are: gastrointestinal disorder, headache, muscular pain and sleeping disorder. Significant, but rare group of side effects represent muscular disorder (myopathy) which is manifested as pain and muscular weakness and higher level of muscular fraction of creatine-kinaze (CK).

Over dosage: Constant monitoring is needed as well as keeping work of vital functions and preventing further drug absorption.

Medicine distribution: only on medical reference

Package: 30 atrovastatine film-pills of 10mg and 20mg or 40mg; 60 film-pills of 40mg.

Date of text preparation: November 2007.

The main part of this sponsor's material belongs to the approved summary of the drug ingredients and the complete approved instructions, all in accordance with the Article 16. and 22. of the Regulations of marketing and informing about drugs, homeopathic and medical products. ('Narodne novine' number 62/05).

You can get all information from the company:
Krka-farma d.o.o., Radnička 48/II, p.p. 205, Zagreb 10002,
Phone **(01) 63 21 100** , Fax (01) 61 76 739,
E-mail:krka-farma@zg.tel.hr, www.krka-farma.hr

KRKA

Our innovations and knowledge is dedicated to health. That is the reason why our determines, persistence and experience contribute to one goal – and that is the development of useful and safe products of the top quality.

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AN INVITATION FOR THE GENERAL MEETING AND CHRISTMAS BANQUET OF CROATIAN CARDIAC SOCIETY

Zagreb, Hotel Westin, "Opera", 20th December 2007

General Assembly, beginning at 6 pm
Christmas Banquet from 8 – 10 pm

Dear colleagues, members and associates of Croatian Cardiac Society!

Croatian Cardiac Society (CCS) prepares traditional Christmas Banquet this year too. Christmas Banquet has always been an occasion for working, scientific and expert discussion. The discussion is usually prepared immediately before solemnization of Christmas gathering of CCS.

This year we plan to organize annual meeting of CCS, where activity and business of the Society will be discussed, Statute, the preparation of the Election Assembly, national congress and main symposium and meetings throughout the following year. In the working part of the meeting we will try to implement one expert lecture as it has been our practice for the last years.

The General meeting Assembly will be held on Thursday 20th December 2007 on the upper floor of Hotel Westin in Zagreb, with the beginning at 6 pm. All members of CCS are invited to the General Assembly. Christmas banquet will follow the Assembly. This is also chance for mingling with other CCS members as with our associates.

I would like to invite all members of CCS on the General Assembly with the beginning at 6 pm, and all members, associates, sponsors and friends of CCS to join us on Christmas Banquet with the beginning at 8 pm.

I send you warm regards and wish you all the best wishes for Christmas and a New Year.

Sincerely yours,

Professor Davor Miličić, MD, PhD
The president of Croatian Cardiac Society