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Inge Heim, Mirjana Jembrek-Gostović

POLYCLINIC FOR THE PREVENTION OF CARDIOVASCULAR DISEASES AND REHABILITATION, ZAGREB

REVIEW OF HOSPITAL MORTALITY FROM THE CLINICAL AND EPIDEMIOLOGICAL POINT OF VIEW

During the year 2005, 4000 people died of cardiovascular diseases in the City of Zagreb. This data is collected in Central Bureau of Statistics and it can also be found in the Croatian Health Service Yearbook 2005. Unfortunately, it only refers to mortality rate and it does not include the incidence of those diseases. In order to gather data about the incidence, Mile Majačić, MD, chief physician and the head of Srčana Polyclinic, initiated in 1979 a register for the area of the City of Zagreb. This register was done on the model of other towns in the world where World Health Organization (WHO) has initiated the organization of acute myocardial infarction register. The register was in use after questionnaires from WHO were taken as samples and directions and instructions accepted. All

As new treatments and new knowledge appeared so was the questionnaire filled with new information. In time, it was obvious that the concept of the register should be altered and so in 2003 the Register of Acute Coronary Syndrome was formed. This Register was based on numerous clinical data. It was also found out, from the number of different discussions on cardiac meetings, that there is certain inapprehension in keeping the Register and its results among epidemiologists and clinicians. That made us clear things up, which is the basic point of this presentation.

It is well known fact that clinicians deal with individuals and epidemiologists with the whole population and such try to find the solution to the problem. We don't need to mention that our final and the most important interest is patients' well being. However, team work is very important here, and sometimes it is more and sometimes less successful. In this presentation we will talk about the problem of mortality rate from acute myocardial infarction (AMI) or from acute coronary syndrome (ACS) from cardiologist and epidemiologist's point of view. Since the results don't match, it is understandable that some distrust has occurred from clinician's side, so some problems should be discussed, clarified and the facts should be put where they belong. Primarily, the problem is that population register includes all cases of AMI or ACS in the City of Zagreb, while the cardiologist takes into consideration only an individual who is situated in coronary unit in cardiac department. Cardiologist is the one who saves and treats the patient, while epidemiologist tries to clear some problems in population with his or her information and in that way help clinician and the patient.

The importance of statistics, which is kept by clinicians, is to see the effect of invasive and conservative therapy in order to help the patient and to lower down mortality. It is also forgotten that hospital registers keep track of all hospitalized patients no matter in which hospital department they are, because patients don't die from infarction only on cardiology but on other departments as well. Population register contains all patients in certain population as well as dead in hospitals in the first 24 hours for whom there is not enough data to state diagnoses. Such cases epidemiologists put in the group called "possible" infarction. Sudden death is also noted in the Register.

Our population register for the City of Zagreb uses protocol from MONICA project [1], from which we use articles 1, 2, and 9.

1. Safe AMI – clinical criteria is satisfied
2. Possible AMI – the word itself states that all criteria is not satisfied, but there is reasonable doubt that it was AMI among patients who survived and those who end up fatal (suddenly or not), and there are no other evidences that some other disease was present.
3. Ischemic cardiac arrest – not provoked with an intervention or something like that (we see it rarely in hospitals)
9. Mortalities with insufficient data are rarely seen in hospitals.

According to the research results in the world, which have shown the same differences, it was concluded that they occur due to wider definition of AMI in the case of population registers. That is quite understandable because by epidemiological approach we are trying to include all cases in certain population. Kuch et al [1] have analyzed hospital mortality from AMI from the point of view of clinicians and epidemiologists and they have confirmed those differences.

Other differences in statistical data of hospital mortality belong to the fact that only people

from Zagreb are included in the Register, and in our hospitals patients from Zagreb surroundings (Samobor, Velika Gorica, Zaprešić, Dugo Selo, Vrbovec etc) are also treated. Thanks to organization "Croatian network primary PCI" [2] other patients from other towns in Croatia like Bjelovar, Čakovec etc, are coming to hospitals. We are all familiar with the fact that for the last decade the coronary heart disease mortality has been lowered. It is interesting to see how much the prevention and how much all therapeutic procedures have contributed to it. According to some authors [3, 4] primary prevention contributed for 23%, secondary prevention for 29% and therapeutic procedures for 49% have lowered AMI mortality rate. According to this, it is quite understandable that cardiologist, who treats the patient, and epidemiologist, who deals with prevention, should work in team in order to lower the coronary heart disease mortality rate or to prevent the beginning of the disease itself. From the all above mentioned it is clear that epidemiological and clinical data about hospital mortality do not match because of the different approach and view of the population for which data are gathered and wider approach towards AMI problem.

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COURAGE – NEW ASPECT ON THE TREATMENT OF STABLE CORONARY DISEASE

"Percutaneous coronary intervention (PCI) or optimal pharmacological treatment of patients with chronic stable coronary disease doesn't necessarily differ in the outcome of the disease. PCI among those patients doesn't lower the death risk, myocardial infarction or other big cardiovascular events". This is the conclusion of the COURAGE study which was emphasized as one of the most important news in cardiovascular medicine on just finished annual meeting of American College of Cardiology in New Orleans. The study raised dust and in addition sat on fire the debate between interventional and non interventional cardiologists. The results of the study were published on the Internet pages New England Journal of Medicine magazine (www.nejm.org 27th March 2007). This study included 2287 patients in 50 American and Canadian centers who have proved symptomatic stable coronary disease. The basic criteria which have to be fulfilled among patients are proved stenosis (at least 70%) in proximal segment of at least one epicardial coronary artery and that ischemia is observed with non invasive techniques (electrocardiogram, stress testing and similar). After that patients were put in two groups in random order. The first group of patients (1149 of them) included patients with medical therapy who underwent PCI, while other group included patients (1138 of them) who were treated only with medical (optimal) therapy. Patients were monitored for approximately 4.6 years. Cumulative rate of unwanted cardiovascular outcomes (death, infarction and stroke) was 19% among patients treated with PCI, while among those who were treated only with medical therapy was 18.5%. There are several reasons for these results but, as experts in this field state, the main reason is that coronary artery which has chronic atherosclerotic stenosis is usually not the cause of acute coronary happenings. Without any doubt PCI is superior and irreplaceable mean in acute coronary syndrome treatment (unstable angina, myocardial infarction with or without ST elevation). Acute coronary syndrome is the reason of more than a half of PCI in the USA. Researches in

COURAGE study advice not to hurry with PCI in stable coronary disease, because identical results can be achieved by using optimal medical therapy (aspirin, nitrates, beta blockers, ACE inhibitors, statin, calcium antagonists).

The results of COURAGE study had a great effect in American medical but in non medical public too. Even daily newspapers (USA Today and other) reported about them. In fact, 1.2 millions of angioplasty is done in USA a year and their price is about 40.000 USD per intervention (according to USA Today). On the other hand, optimal medical therapy is multiple cheaper because generic parallels have occurred in all groups of medicaments. Stent manufacturers, who haven't accepted sponsorship of COURAGE study, are already running their business with negative trend. The worth of stock of Boston Scientific in New York has decreased for 6.6%. Another thing worth mentioning here is very live debate in cardiac association about the safety of using so-called "drug-eluting" stents, or in other words risks of late thrombosis.

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CONTROVERSY ABOUT SAFE USAGE OF DES (DRUG ELUTING STENT)

56th Congress ACC (American College of Cardiology) was held from 24th to 27th March 2007 in New Orleans. One of the topics was passionate debate about advantages of drug eluting stents (DES) as opposed to bare metal stents (BMS).

The same dispute started on the World Cardiac Congress in Barcelona in 2006, when the LATE study and meta-analyses CAMENZIND results were published. These results shown 38% increase of infarction and death rate among patients with DES compared to those with BMS. As the main reason for these unwanted effects was frequent appearance of late thrombosis in stent (3.3%), which is really surprising since described mortality is doubled than in earlier published studies. All doubts were finally cleared by Danish study of University hospital Aarhus. Their results were commented within all important sections on congress in New Orleans. The study included 5422 patients with DES and 11.730 patients with BMS. Monitoring of the patients lasted for 15 months. The results of the study are undoubtedly in favor of DES stents: 43% of restenoses reduction and TLR (target lesion revascularization) compared to BMS, with non significant increase of thromboses frequency (with 1.9% in BMS to 2.2% in DES). It was emphasized that in order to achieve optimal result in using DES the most important thing is to have good patient selection (on-label indication). These are the ones with long lesions (15-30 mm) on smaller veins (2.5-3.5 mm). Patients with complex coronary pathologies (diabetes, bundled vein disease, in-stent restenoses, ostial stenoses and similar) undoubtedly benefit from this therapy. That is the reason why Ministry of Health and Social Welfare of the Republic of Croatia has approved the use of DES stent (Narodne Novine 11/2007). The initial enthusiasm in using DES, especially among patients who suffer from off-label indications, was shattered by the fact of late thromboses in DES stents which can be explained by uncontrolled use of the same (for example in Switzerland only DES is implanted in all patients). Today it is considered that DES stent therapy is justified within 50% of well chosen patients, and that positive outcome can be expected from them. The results of BASKET LATE study prove that patients with implanted DES stent should undergo strict and long dual anti aggregation therapy.

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ANNOUNCEMENT

II INTERNATIONAL CONGRESS OF ECHOCARDIOGRAPHY OPATIJA, 11th till 13th October 2007 II. International Congress of Echocardiography "Cardiovascular Ultrasound – from Imaging to Knowledge in the Practice of Clinical Cardiology" will be held in hotel Adriatic,

Opatija for 11th till 13th October 2007.

The first notice is available on Kardio.hr portal.

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Kardio list Online 2007; 2(4): 30-32.

Mario Ivanuša

BJELOVAR GENERAL HOSPITAL

NEW PROOFS CONCERNING SAFETY IN USING STATIN AND CLOPIDOGREL

A quarter of a century has passed since the first evidence about usefulness of stent usage among patients with hypercholesterolemia appeared. As the number of patients have risen throughout years so have the number of proofs about usefulness and safety of the use of statin in secondary prevention of the patients with proved coronary heart disease (CHD), peripheral vascular disease, recovery after stroke, as in primary prevention of the high risk patients who have main causes of risk (diabetes, arterial hypertension, smoking). Recently published studies (PROVE IT-TMI 22, Phase Z of the A to Z, TNT, IDEAL) have proven decrease of a risk among patients with CHD so far as higher doses of statin are used instead of moderate doses.

In spite of the fact that the use of statin has 40% more prevalence of side effects compared to placebo, the prevalence of important muscular side effects and toxic liver effect is rare while using moderate and high doses of statin. Mild side effects, like myalgia (pain in a muscle along with normal creatine kinase) and higher value of some of liver enzymes make two thirds of registered side effects [1, 2].

Meta-analyses of 18 random, placebo controlled studies, that include 71.108 patients who are under statin primary or secondary prevention from the year 2006, has confirmed well known fact that the treatment with statin is safe [1]. So, in order to prevent one cardiovascular event (myocardial infarction, revascularization, stroke, cardiovascular death, death from other cause) it is needed to treat 27 patients, with the risk of one side effect on 197 patients treated with statin. Occurrence of serious side effects such as the increase of creatine kinase more than 10-fold from the highest normal value or rhabdomyolysis is rare and it can occur in one on 3400 treated patients. Only rhabdomyolysis can occur more rarely – on one in 7428 patients on statin. According to the results of the above mentioned meta-analyses, where 85.8% exposure to statin made simvastatin, pravastatin and lovastatin, the same occurrence of side effects was noticed among patients on simvastatin, pravastatin and lovastatin. The occurrence of side effects was the biggest among patients who were on atorvastatin, but fluvastatin had the lowest occurrence of side effects.

In the new review article about the safety of statins [2] Davidson and Robinson select older maternal age, body mass index and the glomerular filtration rate as prediction of muscular and liver toxicity of statin. Concurrent use of fibrates, nicotinic acid or cyclosporine increases the possibility of toxic muscular effect. Since some statins (lovastatin, simvastatin, atorvastatin) are metabolized through enzyme system of cytochrome (CYP) p450 3a4, drugs which inhibit CYP 3A4 (erythromycin, clarithromycin, ketoconazole, itraconazole, antiviral from protease inhibitor) increase the risk of myopathy and rhabdomyolysis. Antidepressants (fluoxetine, fluvoxamine, sertraline) can also potentially increase statin toxicity, and concurrent usage of diltiazem, verapamil or amiodarone with high dosage of simvastatin can increase the risk of myopathy. Among patients with CHD, statin is used frequently together with clopidogrel, antiplatelet drug from thienopyridine group. After oral usage clopidogrel is in vivo from inactive pre drug activated by enzyme system CYP P450 mainly with CYP 3A4. Therefore there is an assumption for potential interaction of clopidogrel with atorvastatin, simvastatin and lovastatin. This observation, which was described for the first time in 2002 in ex vivo study of Leo et al, has not only raised many dilemmas about the safety of the therapy, but it has resulted in the change of chronic therapy [3]. Mach et al in their study researched ex vivo interaction of platelets function during concurrent use of statin [4]. They have proved that that simvastatin and fluvastatin obstruct the impact of clopidogrel in healthy volunteers, and they didn't reach that conclusion for atorvastatin, pravastatin or rosuvastatin. Just published study has confirmed that in healthy volunteers the concurrent use of fluvastatin and clopidogrel doesn't have more significant influence on pharmacokinetics of fluvastatin or platelet inhibition caused by clopidogrel [5]. It didn't take long to get answers to these important ex vivo interactions. In 2003 analyses started [6] and after that debate about data from MITRA PLUS register which haven't proved undesired clinical interaction between clopidogrel and atorvastatin among patients with acute coronary syndrome (ACS). Interaction study [7] among patients with angina pectoris or acute

myocardial infarction that underwent percutaneous coronary intervention with stent implantation has proven that statin, and most of all atorvastatin, doesn't inhibit antiplatelet effect of clopidogrel. Results of the study from 2005 haven't confirmed more significant undesired clinical interaction of statin and clopidogrel among 1651 patients with ACS [8], and the same conclusion was reached in the study with 66 patients who have stable clinical features of ACS [9]. The data analyses of the patients with ACS without elevation of ST-segment from GRACE register has proven favorable, synergistic effect of clopidogrel and statin on a disease outcome [10]. Prof. Bassand in his article on the same topic [11] concludes that there are no clinical proofs that concurrent use of clopidogrel and statin causes partial or complete inactivation of antiplatelet activity and clinically more significant effects.

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