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Novosti s 21. internacionalnog kongresa o trombozi

Novelties from the 21st International Congress on Thrombosis

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U razdoblju od 6. do 9. srpnja 2010. god. u organizaciji Mediteranske lige za prevenciju tromboembolijskih bolesti (MLTD) održan je 21. internacionalni kongres o trombozi (ICT) u Milanu. MLTD ima dugu tradiciju i definiranu ulogu u okupljanju bazičnih znanstvenika i kliničara koji se bave trombozom kao zasebnim entitetom[1]. Prema mišljenju prof Mannucci, predsjednika 21. ICT, kraj prve dekade 21. stoljeća bio je pravi trenutak da se sumiraju najvažniji koraci napravljeni na ovom području.

U najvećem dijelu predavanja opisani su potencijal i primjena novih molekula u liječenju tromboembolijskih bolesti. Nove spoznaje o pojedinim čimbenicima u sustavu hemostaze rezultirale su razvojem novih protuzgrušavajućih lijekova. Presudan korak napravljen je početkom primjene direktnih inhibitora trombina (DTI), oralnih pripravaka koji se daju u fiksnim dozama, a koji se ne vezuju za proteine plazme što rezultira predvidljivijim protuzgrušavajućim odgovorom. Inhibiraju trombin vezan na fibrin ili aktivaciju čimbenika zgrušavanja uključenih u nakupljanje trombina, što znači da rutinski koagulacijski testovi nisu praktični za njihov slijed. Stoga je izveden zaključak da je neophodno razviti nove dijagnostičke testove i unaprijediti istraživanja na ovom polju. Odabir prikladne farmakoterapije, usmjerene na inhibiciju agregacije trombocita i čimbenike koagulacijske kaskade u svrhu sprječavanja nastanka ugruška ili njegovog proširenja u krvnim žilama zahtjeva veliku pažnju, a rizik od krvarenja mora biti sveden na minimum. Većina istraživanja je pokazala da je primjena novih strategija liječenja efikasnija uz slične ili nešto slabije nuspojave.

Korist i rizik primjene acetilsalicilne kiseline (ASK) u primarnoj i sekundarnoj prevenciji akutnog koronarnog sindroma (ACS) i dalje su predmet brojnih istraživanja i debata. Godine 2009. meta-analiza randomiziranih studija je utvrdila da je efikasnost primjene ASK nešto manja nego što se to do sada mislilo. Međutim, nedavna istraživanja su pokazala da istovremena primjena ASK s novijim antitrombocitnim lijekovima poput tienopiridina (klopidogrela, tiklopidina i prasugrela), P2Y12 antagonista (ticagrelor i cangrelor), inhibitora glikoproteina IIb-IIIa (abciximab, eptifibatide, tirofiban) uzimajući u obzir individualne faktore rizika, vrijeme terapije i dozu, minimalizira rizik i optimizira ishod bolesti. Primjena klopidogrela uz ASK u ACS, pokazala je poboljšanje ishoda kod pacijenata i u slučaju potrebe za trombolizom ili primarnom perkutanom koronarnom intervencijom. Kao efikasan derivat tienopiridina pokazao se i prasugrel, čija primjena poboljšava klinički ishod i stanje pacijenata s infarktom miokarda s elevacijom ST-segmenta.

During the period from 6th to 9th July 2010, the 21st International Congress on Thrombosis (ICT) was held organized by the Mediterranean League Against Thromboembolic Diseases (MLTD) in Milan. The MLTD has a long tradition and a defined role in gathering basic scientists and clinicians who deal with thombosis as a special entity[1]. In opinion of Prof. Mannucci, the President of the 21st ICT, the end of the first decade of then 21st century was the right moment to sum up the most important steps taken in this area.

In the largest number of lectures, the potential and application of new molecules in treatment of thromboembolic diseases were described. The new information about specific factors in the system of haemostasis has resulted in the development of new anticoagulation drugs. The crucial step was taken at the beginning of the application of direct thrombin inhibitor (DTI), oral medicines administered in fixed doses that are not bound to plasma proteins, resulting in foreseeable anticoagulation response. They inhibit the thrombin bound to fibrin or activation of the factors of coagulation included in gathering thrombins which means that the routine coagulation tests are not practical for their sequence. Therefore, the conclusion is that it is necessary to develop some new diagnostic tests and improve researches in this field. The selection of appropriate pharmacotherapy focused on the inhibition of the aggregation of trombocytes and factors of coagulation cascade for the purpose of prevention of occurrence of clot or its spreading in blood vessels requires our due attention, while the risk of bleeding must be reduced to minimum. Most of the researches showed that the application of new strategies is more efficient with similar or somewhat less significant side-effects.

The benefit and risk of application of aspirin in the primary and secondary prevention of acute coronary syndrome (ACS) are still the subject of a number of researches and debates. In 2009 the meta-analysis of randomized studies determined that the efficiency of application of aspirin is somewhat less than what it was believed to be. However, the recent researches showed that the simultaneous application of aspirin with new antiplatelet drugs such as thyenopiridine (clopidogrel, ticlopidine and prasugrel), P2Y12 antagonists (ticagrelor and cangrelor), glycoprotein IIb-IIIa inhibitors (abciximab, eptifibatide, tirofiban) considering individual risk factors, time of therapy and dose, minimizes the risk and optimizes the outcome of the disease. The application of clopidogrel along with aspirin in ACS has showed the improvement of the outcome in a patient and in the case of a need for thrombolysis or primary percutaneous coronary intervention. Prasugrel proved to be an efficient thyenopiridine derivate, the application of which

Za sve pacijente s fibrilacijom atrija te visokim rizikom kardioembolijskog moždanog udara, neovisno o dobi trenutne smjernice preporučuju produženu terapiju s varfarinom ili u slučaju kontraindikacije ASK. Prema novijim podacima primjena umjerenih doza DTI dabigatrana u sekundarnoj prevenciji moždanog udara (MU) se pokazala efikasna poput varfarina, uz nešto manje nuspojava. Obzirom da se dabigatran primjenjuje u fiksnim dozama te je smanjena potreba za njegovim monitoringom obećava u prevenciji ponovnih embolijskih događaja kod pacijenata s kardioembolijskim MU.

Tkivni aktivator plazminogena (rt-PA) dokazan je trombolitik, međutim istraživanja djela individualnih komponenti fibrinolitičkog sustava poput plazminogena, inhibitora plazmina i TAFI-a dala su oprečne rezultate. Razlog nekonzistentnosti je najvjerovatnije posljedica njihovih nefibrinolitičkih karakteristika npr. uloge u upali i angiogenezi. Novije pretkliničke studije su pokazale da neke metaloproteinaze (MMPs) primjenjene s malim dozama rt-PA mogu biti efikasan trombolitik, a bez izazivanja sistemskog litičkog stanja kod arterijske tromboze. Kako bi se definirale skupine pacijenata koje bi od navedenog najviše profitirale neophodna su dodatna istraživanja.

Kao relativno nova i potentna tehnologija u liječenju predstavljena je i tvz. antisense tehnologija inhibicije proteina. Terapija se bazira na hibridizaciji mRNA putem visokospecifičnih oligonukleotida. Posljedica je selektivno oslobađanje ciljane mRNA što vodi odgovarajućoj redukciji i selektivnoj inhibiciji ciljanog proteina. Studije na životinjama podržale su ovaj koncept, međutim neophodna su dodatna istraživanja i njezina daljnja evaluacija.

Istraživanja o novim antikoagulansima pokazala su značajne rezultate, međutim, čitav niz pitanja ostao je otvoren. Antidoti, monitoring, utjecaj na laboratorijske testove te eventualne nuspojave tek se trebaju istražiti, a konačni zaključci biti će poznati nakon što se objave rezultati 3. i 4. faze kliničkih studija. Više novosti, kao i detalja o navedenim istraživanjima, može se pronaći u specijalnom izdanju časopisa *Pathophysiology of thrombosis and haemostasis* objavljenom na stranicama MLTD-a[2].

Nove spoznaje i smjernice zasigurno će biti prikazane na 22. ICT koji će se održati tijekom listopada 2012. god. u Nici u Francuskoj[3].

Istraživači i kliničari iz Hrvatske pozvani su da aktiviraju svoj rad u MLTD još tijekom 20. ICT koji je održan krajem lipnja 2008 god. u Ateni. U radu 21. ICT kongresa sa posterskim radovima sudjelovalo je nekoliko kolega. Hrvatska mediteranskom podneblju pripada zemljopisno i klimatski, a kao i u većini tranzicijskih europskih zemalja tromboembolijske bolesti su joj veliki javnozdravstveni problem. Udio osoba umrlih zbog bolesti srca i krvnih žila u Hrvatskoj u ukupnom mortalitetu 2007. godine iznosio je 50,6%, a vodeće dijagnostičke podskupine bile su ishemijske bolesti srca s udjelom od 36,5% te cerebrovaskularne bolesti s udjelom 31,4%. Epidemiološki podaci o udjelu VTE u pobolu i smrtnosti za Hrvatsku tek trebaju biti utvrđeni[4-6]. Jedan od osnovnih ciljeva MLTD-a u budućnosti je stvaranje mreže radnih skupina i postavljanje internacionalnih projekata sa svrhom istraživanja epidemiologije, dijagnoze i liječenja tromboze. Kako bi se to moglo ostvariti, neophodno je da se u rad Lige uključi što veći broj stručnjaka iz svih zemalja članica, pa tako i iz Hrvatske.

improves the clinical outcome and condition of a patient with myocardial infarction with ST-segment elevation.

For all patients with atrial fibrillation and a high risk of cardioembolic stroke, regardless of age, the current guidelines suggest extended therapy with varfarin or aspirin in the case of contraindication. According to the most recent data, the application of moderate DTI doses of dabigatran in the secondary prevention of stroke has proved to be more efficient such as varfarin with a fewer number of side-effects. Since dabigatran is applied in fixed doses and the need for its monitoring has been reduced, it is promising in the prevention of recurring embolic events in patients with cardioembolic stroke.

The tissue plasminogen activator (rt-PA) is a proved thrombolytic drug, the researches of the part of individual components of fibrinolytic system such as plasminogen, plasmin inhibitor and TAFI have provided opposite results. The reason for inconsistency may be a consequence of their non-fibrinolytic characteristics, such as the role in inflammation and angiogenesis. The latest preclinical studies have showed that some metalloproteinases (MMPs) applied in small doses rt-PA may be an efficient thrombolytic agent without causing systemic lytic state in the arterial thrombosis. In order to define the groups of patients that would mostly benefit from the above mentioned, some additional researches need to be conducted.

The so-called antisense technology of protein inhibition is a relatively new and potent technology. The therapy is based on hybridization of mRNA through highly specific oligonucleotides. The consequence is a selective release of the target mRNA which leads to reduction and selective inhibition of the target protein. The studies on animals have supported this concept, but some additional researches and its new evaluation are required.

The researches on new anticoagulation agents have showed some significant results, but there are a great number of open issues. Antidotes, monitoring, the impact on the laboratory tests and any potential side-effects need to be researched and the final conclusions will be known after the results of the 3rd and 4th stage of clinical studies have been published. More news and details about the above researches may be found in special issue of the journal *Pathophysiology of thrombosis and haemostasis* publicized on the website of MLTD[2].

Some new information and guidelines will be certainly presented at the 22nd ICT that will be held during October 2012 in Nice in France[3].

The researches and clinicians from Croatia were invited to activate their work in MLTD at the 20th ICT that was held by the end of June 2008 in Athens. There are several colleagues who participated in their poster presentations in the work at the 21st ICT. Croatia has Mediterranean climate with regard to geographical and climatic features and as in the most of transitional European countries thromboembolic diseases are a great public and health problem. The share of persons who died as a consequence of cardiovascular diseases in Croatia in total mortality in 2007 was 50.6% and the leading diagnostic sub-groups were the ischemic heart diseases with a share of 36.5% and cerebrovascular diseases with a share of 31.4%. The epidemiologic data on the share of VTE in morbidity and mortality are only to be

Godine 2006. osnovana je i Zaklada MLTD čija će aktivnosti biti usmjerena na članove Lige, znanstvenu zajednicu mediteranskih zemalja kao i na pacijente koji su oboljeli ili su pod rizikom oboljenja od arterijske ili venske tromboze kroz njihova udruženja na području mediteranske zajednice.

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determined for Croatia[4-6]. One of the basic goals of MLTD in the future is the creation of the network of work groups and preparation of the international projects with a purpose of researching epidemiology, diagnosis and treatment of thrombosis. As to be able to accomplish that objective, it is necessary to have greater number of experts involved in the work of the League from all member states and Croatia as well. In 2006 the MLTD Foundation was established whose activity will be focused on the League members, scientific community of the Mediterranean countries and patients who suffer or are at risk to suffer from arterial or venous thrombosis through their associations in the region of the Mediterranean community.

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