

## Tromboembolijske bolesti kao biološki i klinički sindrom – uloga Mediteranske lige za prevenciju tromboembolijskih bolesti

### Thromboembolic diseases as biological and clinical syndrome – Role of the Mediterranean League against Thromboembolic Diseases

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**Ključne riječi:** venska tromboembolija; duboka venska tromboza; arterijska tromboza; tromboembolijske bolesti; Mediteranska liga za prevenciju tromboembolijskih bolesti

Još je prije 150 godina ustanovljeno da do patološkog nastanka ugruška ili tromboze dolazi zbog promjena na stijenkama krvnih žila, promjena protoka krvi, kao i njezinog sastava. Unatoč tome, kroz povijest je bilo potrebno uložiti znatan napor kako bi se tromboza prihvatila kao specifični entitet koji zahjeva istraživanja i kliničke studije. Do 60-tih godina znanstvenici su uglavnom bili zaokupljeni istraživanjem hemoragije, te je zabilježen vrlo mali broj istraživanja o čimbenicima i mehanizmima odgovornim za nastanak tromboze, koja je bila složenija i manje poznata (1-3). Shodno tome, u svijetu gotovo da nije postojalo društvo koje bi okupljalo znanstvenike koji su se bavili istraživanjem ovog entiteta.

U ovakvom ozračju, 1967. godine, nakon povratka sa staža iz Nacionalnog centra za transfuziju (engl. *National Blood Transfusion Centre*) u Parizu, doktorica Jasone Monasterio u Bilbaou je organizirala prvi španjolsko-francuski simpozij o Hemoragijskim sindromima i tromboembolijskim bolestima, uz podršku doktora Jose Antonia Iriarte sa Kardiološkog instituta (engl. *Institute of Procardiacos*). Osnovna je ideja bila okupljanje vodećih francuskih i španjolskih stručnjaka u hemostazi, angiologiji i kardiologiji te drugim disciplinama koje su vezane za trombozu. Na simpoziju se raspravljalo o hiperkoagulabilnosti kao biološkom i kliničkom sindromu, kao potencijalnom uzroku venske tromboembolije, rizičnim čimbenicima za infarkt miokarda i njegovim sociološkim posljedicama, kontroli protuzgrušavajuće terapije i stanjima hiperfibrinolize. Ustanovljen je protokol za dijagnozu i liječenje tromboembolizma te je dogovorena organizacija okupljanja stručnjaka iz ovoga i vezanih područja svake druge godine. Također je dogovoreno da će se na slijedeće sastanke pozvati stručnjaci iz ostalih mediteranskih zemalja.

**Keywords:** venous thromboembolism; deep vein thrombosis; thromboembolic diseases; arterial thrombosis; Mediterranean League against Thromboembolic Diseases (MLTD)

As early as 150 years ago, it was established that pathological occurrence of blood clot or thrombosis is due to changes in vascular wall, blood flow and blood content. Still, considerable effort had to be made through history in order for the thrombosis to be accepted as a specific entity that entails investigations and clinical studies. Until 1960's, scientists were chiefly focused on investigating hemorrhage, with very few studies of the factors and mechanisms responsible for the occurrence of thrombosis that was actually more complex and less known (1-3). Accordingly, there was practically no society worldwide to gather researchers investigating this entity.

In such circumstances, after her return in 1967 from internship at the National Blood Transfusion Center in Paris, dr. Jasone Monasterio organized in Bilbao the first Spanish-French symposium on hemorrhagic syndromes and thromboembolic diseases with support of dr. Jose Antonio Iriarte, Institute of Procardiacos. The principal idea was to gather leading French and Spanish scientists in hemostasis, angiology and cardiology, and other fields related to thrombosis. The symposium discussed hypercoagulability as a biological and clinical syndrome, as a potential cause of venous thromboembolism, then risk factors for myocardial infarction and its sociological effects, control of anticoagulant therapy, and conditions of hyperfibrinolysis. A protocol for diagnosis and treatment of thromboembolism was established and agreement was reached to organize biannual gatherings of scientists in this and related fields. It was also agreed that experts from other Mediterranean countries should be invited to future meetings.

The symposium was actually the beginning of the idea about founding the Mediterranean League against

Simpozij je zapravo bio začetak ideje o osnivanju Mediteranske lige za prevenciju tromboembolijskih bolesti (engl. *Mediterranean League against Thromboembolic Diseases*, MLTD), jedne od prvih organizacija koja je okupljala znanstvenike bazičnih znanosti i specijaliste, kliničare koji se zanimaju za trombozu i hemostazu.

Slijedeći se sastanak održao ponovno u Bilbaou, u listopadu 1969. godine kao Prvi mediteranski kongres o tromboembolizmu (engl. *The First Mediterranean Congress on Thromboembolism*), gdje je Liga službeno i osnovana. Tijekom kongresa održana je Glavna skupština i usvojen je Statut Lige, a za prvog Glavnog tajnika Lige postavljen je Dr. Jose Antonio Iriarte, jedan od inicijatora njezinog osnutka. Prve države članice bile su Bugarska, Francuska, Grčka, Italija, Izrael, Španjolska i Turska. Prema svom statutu, Liga je osnovana u znanstvene i edukacijske svrhe, s ciljem promocije istraživanja patogeneze tromboembolijskih bolesti, njihove prevencije, dijagnoze i liječenja, a sve kako bi se postigla što bolja skrb za oboljele. Kako bi se osigurala razmjena rezultata i iskustava, dogovoreno je da će se svake druge godine organizirati Međunarodni kongres o trombozi (engl. *International Thrombosis Congress*, ITC) u jednoj od zemalja članica, a u godini između dva kongresa simpoziji. Shodno tome, slijedeća tri kongresa održana su u zemljama koje su sudjelovale u osnivanju Lige i to redom kako su njihovi članovi postajali Savjetnici: 1971. u Istanbulu (Turska), 1973. u Tel Avivu (Izrael) i 1976. godine u Ateni (Grčka). Tijekom prvog desetljeća djelovanja, u rad Lige su se uključile još 4 zemlje sa različitih mediteranskih područja i to 1971. Egipat, Tunis i Jugoslavija, a 1973. godine Rumunjska (3,4).

Nakon petog Međunarodnog kongresa o trombozi održanog 1978. godine u Bologni, u slijedećih deset godina Liga je učvrstila poziciju kao Internacionalno znanstveno društvo u području tromboembolijskih bolesti. Zbog velikog interesa za pohađanje ovih susreta i njihovog visokog znanstvenog stupnja, savjetnici-osnivači su predložili da se MLTD registrira kao znanstveno društvo u Nacionalnom registru udruženja u Španjolskoj, što je i učinjeno 1980. godine. Na sljedećim ITC kongresima, organiziranim redom u Monte Carlu (1980.), Valenciji (1982.), Istanbulu (1984.), Jeruzalemu (1986.) i Ateni (1988.), zabilježen je sve veći broj posjetitelja iz zemalja cijelog svijeta, kao i vodećih međunarodnih stručnjaka iz područja tromboze kao predavača. U navedenom razdoblju ostvarena je suradnja sa svjetskim udrugama koje djeluju na sličnim znanstvenim i kliničkim poljima, kao što su npr., Latinamerička udruga za hemostazu i trombozu (španj. *Grupo Cooperativo Latino Americano de Hemostasia y Trombosis*, CLAHT), Europska udruga za istraživanje tromboze (engl. *European Thrombosis Research Organisation*, ETRO), Dunavska liga za prevenciju tromboze i hemoragije (engl. *Danubian League against Thrombosis and Haemorrhagic Disorders*), kao i nacionalnim društvima za trombozu i hemostazu

Thromboembolic Diseases (MLTD), one of the first organizations to bring together basic scientists and specialists, clinicians interested in thrombosis and hemostasis.

The following meeting was held again in Bilbao in October 1969 as the 1<sup>st</sup> Mediterranean Congress on Thromboembolism where the League was officially founded. During the Congress, General Assembly was held and the League by-laws were adopted, while Dr. Jose Antonio Iriarte, one of its founding members, was appointed the first General secretary of the League. The following countries were original members of the League: Bulgaria, France, Greece, Italy, Israel, Spain and Turkey. According to its Statute, the League was established for scientific and educational purposes, with the goal of promoting research of the pathogenesis of thromboembolic diseases, their prevention, diagnosis and treatment, and thus of providing overall better care of patients. In order to ensure exchange of results and experience, it was agreed that International Thrombosis Congress (ITC) was to be organized every other year in one of the member countries, with symposia in years in between. Accordingly, the following three congresses were held in countries that were among the League founders, and in the same order that their members were appointed as Councillors: in 1971 in Istanbul, Turkey, in 1973 in Tel Aviv, Israel, and in 1976 in Athens, Greece. During the first decade of its activity, another four countries from different Mediterranean regions became members of the League: Egypt, Tunisia, and Yugoslavia in 1971, and Rumania in 1973 (3,4).

After the 5<sup>th</sup> ITC that was held in Bologna in 1978, the League strengthened its position during the following ten years as an international scientific society in the field of thromboembolic diseases. Based on intense interest in attending such meetings and on their high scientific rating, the founding Councillors suggested that MLTD be registered as a scientific society in the National Registry of Associations in Spain, which was implemented in 1980. At the ITC congresses to follow, organized in Monte Carlo (1980), Valencia (1982), Istanbul (1984), Jerusalem (1986) and Athens (1988), an ever increasing number of attendees was recorded from all over the world, as well as of leading international experts in the field of thrombosis as lecturers. In that period, collaboration was established with associations worldwide that were active in similar scientific and clinical fields as, for instance, Latin-American cooperative association for hemostasis and thrombosis (*Grupo Cooperativo Latino Americano de Hemostasia y Trombosis*, CLAHT), European Thrombosis Research Organisation (ETRO), Danubian League against Thrombosis and Haemorrhagic Disorders, and with national societies for thrombosis and hemostasis in countries that were the League members. Particularly intense collaboration was achieved with International Society on Thrombosis and Haemostasis (ISTH). ISTH participates in organization of

država članica Lige. Osobito snažna suradnja ostvarena je sa Međunarodnim društvom za trombozu i hemostazu (engl. *International Society on Thrombosis and Haemostasis*, ISTH). ISTH sudjeluje u organizaciji MLTD tečajeva, a godišnji sastanci Glavnog odbora MLTD održavaju se tijekom ISTH kongresa (3,4).

Zbog značajnog rasta međunarodnog uspjeha u trećoj dekadi nakon osnutka, Liga je morala osvježiti originalni statut, kako bi držala korak sa porastom broja članica i znanstvenim aktivnostima. Tijekom tog razdoblja, radu Lige su se pridružile Slovenija, Portugal i Maroko. Također, 1996. Statut je preveden na engleski jezik, a iste godine časopis *Haemostasis* (danas *Pathophysiology of Haemostasis and Thrombosis*) prihvaćen je kao službeni časopis MLTD-a (3,4).

Pozitivan trend razvoja nastavljen je i u ovom desetljeću. Na ITC kongresima u Portu 2000., Bologni 2002., Ljubljani 2004. i Tel Avivu 2006. sudjelovao je izuzetno veliki broj polaznika iz cijeloga svijeta, a radu Lige su se pridružile Saudijska Arabija i Cipar. U travnju 2004. kreirana je web stranica Lige ([www.medleague-thrombosis.org](http://www.medleague-thrombosis.org)) kao moderno oružje za efikasnu i globalnu difuziju aktivnosti, dok je 2006. osnovana i Zaklada MLTD. Cilj Zaklade je prikupljanje neophodnih financijskih sredstava putem akcija i/ili donacija privatnih i javnih institucija zainteresiranih za razvoj mediteranske regije. Predviđeno je da će se prikupljena sredstva utrošiti na uključivanje u rad Lige mediteranskih zemalja koje još nisu njezine članice, a zatim na formiranje nagrada za najbolja istraživanja na ovom polju. Aktivnosti Zaklade biti će usmjerene na članove Lige, znanstvenu zajednicu mediteranskih zemalja kao i na bolesnike koji su oboljeli ili su pod rizikom razvitka arterijske ili venske tromboze kroz njihova udruženja na području mediteranske zajednice (3,4).

Tijekom dvadesetog Međunarodnog kongresa o trombozi, koji je održan krajem lipnja 2008. u Ateni, istraživači i kliničari iz Hrvatske pozvani su da aktiviraju svoj rad u MLTD, izmjene svoja saznanja sa kolegama iz ostalih zemalja, kako bi zajedno doprinjeli unaprijeđenju istraživanja na ovom polju.

Hrvatska mediteranskom podneblju pripada zemljopisno i klimatski, a kao i u većini tranzicijskih europskih zemalja, tromboembolijske bolesti veliki su javnozdravstveni problem i jedan od glavnih uzroka povećanja troškova u zdravstvu (5,6). 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 ishemične bolesti srca s udjelom od 36,5% te cerebrovaskularne bolesti s udjelom 31,4% (7,8). Epidemiološki podatci o udjelu venske tromboembolije u pobolu i smrtnosti za Hrvatsku tek trebaju biti utvrđeni. U Europi, venska tromboembolija je treći po redu uzrok smrtnosti sa preko 500.000 smrtnih slučajeva godišnje. Gotovo 60% svih slučajeva venske tromboembolije čine hospitalizira-

MLTD courses, and annual meetings of the MLTD Executive Board are held during ISTH congresses (3,4).

Due to increased international success in the third decade after its foundation, the League had to update the original bylaws in order to keep pace with the increasing number of its member countries and scientific activities. Slovenia, Portugal and Morocco joined the League during that period. Also, the bylaws were in 1996 translated in English and in the same year the journal *Haemostasis* (today: *Pathophysiology of Haemostasis and Thrombosis*) was accepted as the official journal of MLTD (3,4).

Positive developing trend has continued in this decade as well. An exceptionally high number of participants attended IT congresses in Porto in 2000, Bologna in 2002, Ljubljana in 2004, and in Tel Aviv in 2006, while Saudi Arabia and Cyprus became new members of the League. In April 2004, the League web pages ([www.medleague-thrombosis.org](http://www.medleague-thrombosis.org)) were created as a modern tool for efficient and global diffusion of activities, and also MLTD Foundation was established in 2006. The aim of the Foundation is to gather necessary financial resources through drives and/or donations from private and public institutions interested in development of the Mediterranean region. The plan is to spend the collected funds to include in the League activities those Mediterranean countries that have not as yet become its members, and to design awards for best studies in this scientific field. Activities of the Foundation will be focused on the League members, scientific community of Mediterranean countries, and on the patients affected or at risk of developing arterial or venous thrombosis and their associations in Mediterranean community (3,4).

During the 20<sup>th</sup> ITC that was held in Athens at the end of June 2008, researchers and clinicians from Croatia were invited to become active in MLTD, exchange their insights with colleagues from other countries and thus contribute together to advancement of research in the field.

Croatia belongs to the Mediterranean region both geographically and by its climate and in Croatia, as in most transitional European countries, thromboembolic diseases are major public health problem and one of the main causes of increased healthcare costs (5,6). The rate of deaths due to cardiovascular diseases in Croatia with regard to overall mortality was 50.6% in year 2007; the leading diagnostic subgroups were ischemic cardiac diseases and cerebrovascular disease with mortality rates of 36.5% and 31.4%, respectively (7,8). Epidemiologic data on morbidity and mortality rates for venous thromboembolism (VTE) in Croatia are yet to be estimated. In Europe, VTE is the third cause of death with over 500,000 death cases per year. Almost 60% of all VTE cases are hospitalized patients, with the proportion of pulmonary embolism (PE) of 5-10%, which means that VTE is the most preventable cause of death of hospital patients. Major orthopedic

ni bolesnici, s udjelom oboljelih od plućne embolije od 5-10%, što znači da je venska tromboembolija „najprevenabilniji“ uzrok smrti bolesnika u bolnici. Velike ortopedske operacije bez profilakse nose ozbiljan rizik od razvoja venske tromboembolije, a bez preventivnog tretmana i do 60% kirurških bolesnika može razviti duboku vensku trombozu, tj. 0,2-10% ih može razviti plućnu emboliju (9). Stoga nije neobično da je napredak u razvoju novih antitrombotika i antitrombocitnih lijekova, kao i dijagnostičkih testova za slijed liječenja oboljelih, glavna tema slijedećeg, 21. Internacionalnog kongresa o trombozi u organizaciji MLTD-a i međunarodno priznatog hematologa prof. Mannuccija, koji će se održati u Milanu u Italiji tijekom srpnja 2010. godine (10,11).

Unatoč tome što je strategija prevencije, dijagnoze i liječenja znatno unaprijeđena tijekom proteklih 20 godina, visoka prevalencija tromboembolijskih događaja stavlja naglasak na istraživanje novih čimbenika rizika za razvoj bolesti s ciljem razjašnjenja patogeneze te brzog i točnog prepoznavanja uzroka tromboze (11,12). Jedan od osnovnih ciljeva Lige u budućnosti je stvaranje mreže radnih skupina koje bi činile osovinu MLTD, kao i postavljanje međunarodnih projekata uz suradnju članova Lige s međunarodnim stručnjacima u svrhu unapređenja istraživanja epidemiologije, dijagnoze i liječenja tromboze, kako bi se smanjio rizik za razvoj bolesti, njezino širenje i poboljšala skrb o oboljelima.

surgeries without prophylaxis carry a serious risk of VTE, while even 60% of surgical patients may develop deep vein thrombosis (DVT) without preventative treatment, i.e. 0.2-10% of them may develop PE (9). It is therefore not surprising that the progress in development of new antithrombotics, antiplatelet drugs, and diagnostic tests for therapy of patients is the major topic of the forthcoming 21<sup>st</sup> International Congress on Thrombosis which is organized by MLTD and by an internationally recognized hematologist prof. Mannucci and will take place in Milan, Italy, during July 2010 (10,11).

Although the strategy of prevention, diagnosis and treatment have significantly advanced during the past twenty years, high prevalence of thromboembolic events places emphasis on investigation of new risk factors of the disease with a view to explaining pathogenesis and achieve fast and accurate recognition of the causes of thrombosis (11,12). One of the main future objectives of the League is establishment of a network of working groups that should make the axis of MLTD, and initiation of international projects involving cooperation of the League members with international experts with the purpose of promoting research of epidemiology, diagnosis and treatment of thrombosis and thus reducing the risk of disease, its spread and improving patient care.

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