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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

GEORGIAN MEDICAL NEWS

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GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board since 1994. GMN carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

GMN is indexed in MEDLINE, SCOPUS, PubMed and VINITI Russian Academy of Sciences. The full text content is available through EBSCO databases.

GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения. Журнал индексируется в MEDLINE, отражён в базе данных SCOPUS, PubMed и ВИНИТИ РАН. Полнотекстовые статьи журнала доступны через БД EBSCO.

GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

ჟურნალი ინდექსირებულია MEDLINE-ის საერთაშორისო სისტემაში, ასახულია SCOPUS-ის, PubMed-ის და ВИНИТИ РАН-ის მონაცემთა ბაზებში. სტატიების სრული ტექსტი ხელმისაწვდომია EBSCO-ს მონაცემთა ბაზებიდან.

WEBSITE

www.geomednews.com

К СВЕДЕНИЮ АВТОРОВ!

При направлении статьи в редакцию необходимо соблюдать следующие правила:

1. Статья должна быть представлена в двух экземплярах, на русском или английском языках, напечатанная через **полтора интервала на одной стороне стандартного листа с шириной левого поля в три сантиметра**. Используемый компьютерный шрифт для текста на русском и английском языках - **Times New Roman** (**Кириллица**), для текста на грузинском языке следует использовать **AcadNusx.** Размер шрифта - **12**. К рукописи, напечатанной на компьютере, должен быть приложен CD со статьей.

2. Размер статьи должен быть не менее десяти и не более двадцати страниц машинописи, включая указатель литературы и резюме на английском, русском и грузинском языках.

3. В статье должны быть освещены актуальность данного материала, методы и результаты исследования и их обсуждение.

При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

5. Таблицы необходимо представлять в печатной форме. Фотокопии не принимаются. **Все цифровые, итоговые и процентные данные в таблицах должны соответствовать таковым в тексте статьи**. Таблицы и графики должны быть озаглавлены.

6. Фотографии должны быть контрастными, фотокопии с рентгенограмм - в позитивном изображении. Рисунки, чертежи и диаграммы следует озаглавить, пронумеровать и вставить в соответствующее место текста **в tiff формате**.

В подписях к микрофотографиям следует указывать степень увеличения через окуляр или объектив и метод окраски или импрегнации срезов.

7. Фамилии отечественных авторов приводятся в оригинальной транскрипции.

8. При оформлении и направлении статей в журнал МНГ просим авторов соблюдать правила, изложенные в «Единых требованиях к рукописям, представляемым в биомедицинские журналы», принятых Международным комитетом редакторов медицинских журналов - http://www.spinesurgery.ru/files/publish.pdf и http://www.nlm.nih.gov/bsd/uniform_requirements.html
В конце каждой оригинальной статьи приводится библиографический список. В список литературы включаются все материалы, на которые имеются ссылки в тексте. Список составляется в алфавитном порядке и нумеруется. Литературный источник приводится на языке оригинала. В списке литературы сначала приводятся работы, написанные знаками грузинского алфавита, затем кириллицей и латиницей. Ссылки на цитируемые работы в тексте статьи даются в квадратных скобках в виде номера, соответствующего номеру данной работы в списке литературы. Большинство цитированных источников должны быть за последние 5-7 лет.

9. Для получения права на публикацию статья должна иметь от руководителя работы или учреждения визу и сопроводительное отношение, написанные или напечатанные на бланке и заверенные подписью и печатью.

10. В конце статьи должны быть подписи всех авторов, полностью приведены их фамилии, имена и отчества, указаны служебный и домашний номера телефонов и адреса или иные координаты. Количество авторов (соавторов) не должно превышать пяти человек.

11. Редакция оставляет за собой право сокращать и исправлять статьи. Корректура авторам не высылается, вся работа и сверка проводится по авторскому оригиналу.

12. Недопустимо направление в редакцию работ, представленных к печати в иных издательствах или опубликованных в других изданиях.

При нарушении указанных правил статьи не рассматриваются.

REQUIREMENTS

Please note, materials submitted to the Editorial Office Staff are supposed to meet the following requirements:

1. Articles must be provided with a double copy, in English or Russian languages and typed or compu-ter-printed on a single side of standard typing paper, with the left margin of **3** centimeters width, and **1.5** spacing between the lines, typeface - **Times New Roman** (**Cyrillic**), print size - **12** (referring to Georgian and Russian materials). With computer-printed texts please enclose a CD carrying the same file titled with Latin symbols.

2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

Accurately numbered subtitles for each illustration must be listed on a separate sheet of paper. In the subtitles for the microphotographs please indicate the ocular and objective lens magnification power, method of coloring or impregnation of the microscopic sections (preparations).

7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

8. Please follow guidance offered to authors by The International Committee of Medical Journal Editors guidance in its Uniform Requirements for Manuscripts Submitted to Biomedical Journals publication available online at: http://www.nlm.nih.gov/bsd/uniform_requirements.html
http://www.icmje.org/urm_full.pdf
In GMN style for each work cited in the text, a bibliographic reference is given, and this is located at the end of the article under the title "References". All references cited in the text must be listed. The list of references should be arranged alphabetically and then numbered. References are numbered in the text [numbers in square brackets] and in the reference list and numbers are repeated throughout the text as needed. The bibliographic description is given in the language of publication (citations in Georgian script are followed by Cyrillic and Latin).

9. To obtain the rights of publication articles must be accompanied by a visa from the project instructor or the establishment, where the work has been performed, and a reference letter, both written or typed on a special signed form, certified by a stamp or a seal.

10. Articles must be signed by all of the authors at the end, and they must be provided with a list of full names, office and home phone numbers and addresses or other non-office locations where the authors could be reached. The number of the authors (co-authors) must not exceed the limit of 5 people.

11. Editorial Staff reserves the rights to cut down in size and correct the articles. Proof-sheets are not sent out to the authors. The entire editorial and collation work is performed according to the author's original text.

12. Sending in the works that have already been assigned to the press by other Editorial Staffs or have been printed by other publishers is not permissible.

Articles that Fail to Meet the Aforementioned Requirements are not Assigned to be Reviewed.

ავტორთა საყურადღებოდ!

რედაქციაში სტატიის წარმოდგენისას საჭიროა დავიცვათ შემდეგი წესები:

1. სტატია უნდა წარმოადგინოთ 2 ცალად, რუსულ ან ინგლისურ ენებზე,დაბეჭდილი სტანდარტული ფურცლის 1 გვერდზე, 3 სმ სიგანის მარცხენა ველისა და სტრიქონებს შორის 1,5 ინტერვალის დაცვით. გამოყენებული კომპიუტერული შრიფტი რუსულ და ინგლისურენოვან ტექსტებში - **Times New Roman (Кириллица)**, ხოლო ქართულენოვან ტექსტში საჭიროა გამოვიყენოთ **AcadNusx.** შრიფტის ზომა – 12. სტატიას თან უნდა ახლდეს CD სტატიით.

2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

3. სტატიაში საჭიროა გაშუქდეს: საკითხის აქტუალობა; კვლევის მიზანი; საკვლევი მასალა და გამოყენებული მეთოდები; მიღებული შედეგები და მათი განსჯა. ექსპერიმენტული ხასიათის სტატიების წარმოდგენისას ავტორებმა უნდა მიუთითონ საექსპერიმენტო ცხოველების სახეობა და რაოდენობა; გაუტკივარებისა და დაძინების მეთოდები (მწვავე ცდების პირობებში).

4. სტატიას თან უნდა ახლდეს რეზიუმე ინგლისურ, რუსულ და ქართულ ენებზე არანაკლებ ნახევარი გვერდის მოცულობისა (სათაურის, ავტორების, დაწესებულების მითითებით და უნდა შეიცავდეს შემდეგ განყოფილებებს: მიზანი, მასალა და მეთოდები, შედეგები და დასკვნები; ტექსტუალური ნაწილი არ უნდა იყოს 15 სტრიქონზე ნაკლები) და საკვანძო სიტყვების ჩამონათვალი (key words).

5. ცხრილები საჭიროა წარმოადგინოთ ნაბეჭდი სახით. ყველა ციფრული, შემაჯამებელი და პროცენტული მონაცემები უნდა შეესაბამებოდეს ტექსტში მოყვანილს.

6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

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HEMOSTASIS DISORDERS IN CORONARY ARTERY DISEASE: A PROSPECTIVE COMPARATIVE STUDY OF 130 PATIENTS

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Abstract.

Background: The laboratory detection of factors that participate in coagulation mechanisms in patients with coronary heart disease may lead to important findings regarding the contribution of endothelial function to atherosclerotic lesions of coronary arteries. The main purpose of this study was to investigate the role of high-sensitivity C-reactive protein (hs-CRP), von Willebrand factor (vWF) activity, thrombomodulin (TM), ADAMTS13 activity and myeloperoxidase (MPO) in patients undergoing coronary angiography due to non-ST-elevation myocardial infarction (NSTEMI), unstable angina (UA) and stable angina pectoris with positive stress testing-induced myocardial ischemia (controls). Furthermore, the measured biomarkers were examined among patients with classical cardiovascular risk factors.

Methods: 50 NSTEMI patients, 50 UA patients and 30 controls referred to coronary angiography were included in the study. The blood samples were collected before the catheter procedure. MPO, TM and ADAMTS13 activity were measured by enzyme-linked immunosorbent assay (ELISA), while vWF activity was calculated with INNOVANCE vWF Ac.

Results: When the laboratory results were compared between the three study groups, hs-CRP was found to be higher in NSTEMI patients compared to UA patients ($p=0.0015$) and controls ($p<0.0001$). ADAMTS13 activity was higher in NSTEMI ($p=0.0035$) and UA patients ($p=0.0102$) compared to controls and TM was lower in NSTEMI patients compared to UA patients ($p=0.0307$) and controls ($p=0.0002$). Moreover, MPO was higher in UA patients compared to the control group ($p=0.0227$). Finally, each of the aforementioned biomarkers was compared in the presence of the following cardiovascular risk factors: smoking, diabetes mellitus, arterial hypertension, dyslipidemia, chronic kidney disease (CKD) and peripheral artery disease (PAD).

Conclusion: The results of this study add more data to the current medical literature concerning the role of coagulation disorders, endothelial damage and immunothrombosis in patients with coronary artery disease and their correlation with traditional risk factors for cardiovascular disease.

Key words. Coronary artery disease, endothelial dysfunction, hemostasis disorders.

Abbreviations.

ACS: Acute Coronary Syndrome; **ADAMTS13:** A Disintegrin and Metalloproteinase with a Thrombospondin type 1 Motif, Member 13; **CKD:** Chronic Kidney Disease; **CRP:** C-reactive Protein; **CS:** Controls; **ELISA:** Enzyme-Linked Immunosorbent Assay; **FVIII:** Factor VIII; **FRET:** Fluorescence Resonance Energy Transfer; **GPIb:** Glycoprotein Ib; **HDL:** High-Density Lipoprotein; **hs-CRP:** High-Sensitivity CRP; **LDL:** Low-Density Lipoprotein; **MPO:** Myeloperoxidase; **NETs:** Neutrophil Extracellular Traps; **NO:** Nitrogen Monoxide; **NSTEMI:** Non-ST-Elevation Myocardial Infarction; **PAD:** Peripheral Artery Disease; **PAI-1:** Plasminogen Activator Inhibitor-1; **PCI:** Percutaneous Coronary Intervention; **PGI2:** Prostaglandin I_2; **ROS:** Reactive Oxygen Species; **SD:** Standard Deviation; **SGOT:** Serum Glutamic Oxaloacetic Transaminase; **SGPT:** Serum Glutamic Pyruvic Transaminase; **STEMI:** ST-Elevation Myocardial Infarction; **TAFI:** Thrombin-Activatable Fibrinolysis Inhibitor; **TF:** Tissue Factor; **TM:** Thrombomodulin; **vWF:** von Willebrand Factor; **UA:** Unstable Angina; **XPO:** Haloperoxidases

Introduction.

Atherosclerosis is a chronic and progressive vascular disease. It commences in adolescence and early adulthood and usually has a long asymptomatic phase, while its progression can be accelerated by various cardiovascular risk factors. The most common include arterial hypertension, dyslipidemia, diabetes mellitus, smoking and obesity, which can lead to oxidative stress and endothelial dysfunction [1]. Under normal circumstances the endothelial cells of the blood vessels release a variety of substances that participate in the pathways of inflammation, thrombosis, angiogenesis, and vascular tone regulation [2]. The endothelial dysfunction disrupts the balance of these mechanisms, causing decrease in the bioavailability of nitrogen monoxide (NO), increase in the endovascular concentration of reactive oxygen species (ROS), release of inflammatory cytokines and amplification of the mechanisms of thrombosis and adhesion of platelets and leukocytes [3]. The thrombotic mechanisms in the damaged endothelium are activated by the increased production of prothrombotic agents, such as von Willebrand factor (vWF), tissue factor (TF) and thrombomodulin (TM), as well as the inhibition of fibrinolysis, due to increased plasminogen activator inhibitor-1 (PAI-1) [4,5]. Additional factors that contribute to thrombosis are the reduced levels of prostaglandin I_2 (PGI_2), which induce platelet accumulation and the decreased circulating metalloproteinase ADAMTS13 (a disintegrin and metalloproteinase with a thrombospondin type 1 motif, member 13), which is normally responsible for the

cleavage of vWF multimers into small, inactive fragments [6].

Elevated plasma myeloperoxidase (MPO) levels have been associated with a variety of clinical conditions including systemic inflammation, risk of cardiovascular events and vascular endothelial dysfunction [7-9]. The quantification of TM in the circulation provides insight into the extent of vascular endothelial cell damage. It has been documented that patients suffering from cardiovascular diseases, such as acute coronary syndrome, have increased circulating TM concentrations, while ADAMTS13 activity is found to be mildly or moderately decreased [10,11]. Furthermore, elevated levels of vWF have been reported in response to stress, inflammation, and endothelial lesions, and have been related to thrombotic complications such as myocardial infarction [12].

Recent data highlight the presence of neutrophil extracellular traps (NETs) in the intraluminal part of human atherosclerotic vessels, as well as the coronary arteries of patients undergoing acute myocardial infarction [13-15]. Moreover, the role of prothrombotic molecules, such as vWF, TF and TM has been examined in the pathophysiology of ST- elevation myocardial infarction (STEMI) [16-18]. The main purpose of this study was to investigate the role of hemostasis disorders, endothelial dysfunction and immunothrombosis in patients with non-ST-elevation myocardial infarction (NSTEMI) and unstable angina (UA) and their correlation with traditional risk factors for cardiovascular disease.

Materials and Methods.

Sample collection:

This study was approved by the Institutional Review Boards of the Athens Hellenic Red Cross Hospital and Aretaieion University Hospital and was performed in accordance with the principles of the Declaration of Helsinki. The methodology of the study was approved by the Human Research Ethics Committee of the Medical University of Athens. Written informed consent was obtained from all individual participants included in the study. A total of 130 patients were included in the study, of which 50 suffered from NSTEMI, 50 had UA and 30 had stable angina pectoris with positive stress testing-induced myocardial ischemia (controls). None of them had a prior history of thrombosis or malignancy. Blood samples were collected before the coronary angiography and were tested for: (1) complete blood count; (2) biochemistry panel (glucose, blood urea nitrogen, creatinine, sodium, potassium, serum glutamic oxaloacetic transaminase-SGOT, serum glutamic pyruvic transaminase-SGPT); (3) lipidemic profile (total cholesterol, high-density lipoprotein-HDL, low-density lipoprotein-LDL, triglycerides); (4) biomarkers of myocardial injury (troponin I, creatine kinase-MB); (5) high sensitivity C-reactive protein (hs-CRP); (6) vWF activity, ADAMTS13 activity, TM and MPO as markers of endothelial damage and factors of immunothrombosis. MPO, TM and ADAMTS13 activity were measured by enzyme-linked immunosorbent assay (ELISA), while vWF activity was calculated with INNOVANCE vWF Ac.

MPO, TM, ADAMTS13 activity: Principle of Elisa:

MPO was calculated using the Quantikine® Human MPO Immunoassay (R&D Systems®, a Bio- Techne® brand, Minneapolis, MN, USA), which is a 4.5 hour solid-phase ELISA designed to measure human MPO in serum. TM was measured by the use of the Quantikine® Human Thrombomodulin/BDCA-3 Immunoassay, which is also a 4.5 hour solid-phase ELISA designed to measure human TM in serum and plasma. It contains NS0-expressed recombinant human TM. These assays employ the quantitative sandwich enzyme immunoassay technique. A monoclonal antibody specific for human MPO/TM was pre-coated onto a microplate. Standards and samples were pipetted into the wells and any MPO/TM present was bound by the immobilized antibody. After washing away any unbound substances, an enzyme-linked polyclonal antibody specific for human MPO/TM was added to the wells. Following a wash to remove any unbound antibody-enzyme reagent, a substrate solution was added to the wells and color developed in proportion to the amount of MPO/TM bound in the initial step. The color development was then stopped, and the intensity of the color was measured. MPO and TM measurements were made with the use of Thermo Scientific Wellwash® Versa Microplate Washer.

ADAMTS13 activity was calculated with the use of the ATS-13 Activity Assay (Immucor GTI Diagnostics, Inc., Waukesha, WI, USA). This procedure is based on fluorescence resonance energy transfer (FRET) technology. A synthetic fragment of the vWF protein was used as the substrate. Cleavage of this peptide between two modified residues released the fluorescence quenching capabilities. This assay is based on quantifying the cleavage of a small fragment of vWF by the ADAMTS13 protease. The cleavage of this synthetic substrate was detected by reading the fluorescence that resulted when the substrate was cleaved. Thermo Scientific Fluoroskan Immucor® was used for the measurement of ADAMTS13 activity.

VWF activity: Innovance Ac assay:

VWF activity was calculated with the Innovance® VWF Ac Assay (Siemens Healthcare Diagnostics Products GmbH, Marburg, Germany), which is a particle enhanced assay for the automated determination of vWF activity in human citrated plasma. The assay principle makes use of the binding of vWF to its receptor glycoprotein Ib (GPIb). GPIb is the main vWF receptor on platelets. Polystyrene particles were coated with an antibody against GPIb. Recombinant GPIb (two gain-of-function mutations included) was added and binded to the antibody as well as to the vWF of the sample. Due to the gain-of-function mutations, vWF binding to GPIb does not require ristocetin. This vWF binding induced a particle agglutination which was measured as an increase in extinction by turbidimetric measurements. VWF activity was measured with the use of BCSxP Siemens.

Data analysis:

The statistical analysis was performed using the SAS for Windows 9.4 software platform (SAS Institute Inc., NC, U.S.A.; DiMaggio, 2013; SAS Institute, 2014). Descriptive values were expressed as median and Quartile 1 (Q1) to Quartile 3 (Q3) range and for completeness reasons the mean ± standard deviation (SD) was reported. Comparisons between groups for the qualitative parameters were made using the chi-square test (and if required a Fisher exact test was performed).

For the continuous parameters normality was not possible to be ensured (via the Kolmogorov Smirnov test), therefore non parametric tests were applied, specifically the Mann Whitney U test and the Kruskal-Wallis test. For the laboratory measured data, statistical tests were applied both for the arithmetic values and for the same parameters categorized as normal, high, and low. Statistical significance was determined by $p<0.05$. During study design it was decided that 50 patients would be adequate for the UA group, 50 additional patients for the NSTEMI group and 30 patients for the control group, since we expected large effect sizes for most of the coagulation characteristics. However, irrelevant of the study design, p values are reported along with their power (stated as 1-β) and higher power (i.e., near 1 indicates less probability for error, while smaller values towards 0 indicate higher probability). Power of the results was calculated using the G*Power version 3.1.9.7 software and for two sided tests. Finally, to adjust for multiplicity of tests the false discovery rate method was applied. However, these methods assume that all the hypothesis tests are statistically independent, and such independence cannot be guaranteed, especially in this study that there may be interrelation among the variables. For convenience the adjusted and not adjusted p-values are also reported.

Results.

Demographic characteristics:

In total 130 patients participated in the study. Of these 50 (38.46%) had NSTEMI, 50 (38.46%) suffered from UA and 30 (23.08%) had stable angina pectoris with positive stress testing-induced myocardial ischemia (controls). The female patients were 28 (21.54%) and the median age of the study population was 62 years (Q1-Q3=54-71 years old). The baseline characteristics of the medical history of the study population were examined in each group separately (Table 1).

Endothelial factors and patient groups:

Each endothelial factor was examined and compared between three patient groups: NSTEMI, UA and controls. Hs-CRP was found to be higher in NSTEMI patients compared to UA patients ($p=0.0015$, $1-\beta=0.34$) and controls ($p<0.0001$, $1-\beta=0.90$). ADAMTS13 activity was higher in NSTEMI ($p=0.0035$, $1-\beta=0.81$) and UA patients ($p=0.0102$, $1-\beta=0.80$) compared to controls and TM was lower in NSTEMI patients compared to UA ($p=0.0307$, $1-\beta=0.56$) and controls ($p=0.0002$, $1-\beta=0.95$). Finally, MPO was higher in UA patients compared to the control group ($p=0.0227$, $1-\beta=0.62$) (Figure 1 and Table A1 in the appendix).

According to the statistical results for the endothelial factors as categorical data, hs-CRP was high in all NSTEMI cases, in 98% of UA cases and in 63% of controls ($p<0.0001$, $1-\beta=0.99$), without significant difference between the NSTEMI and UA groups. Similar to the arithmetic data comparisons, the percentage of NSTEMI and UA cases that ADAMTS13 was low was lower in NSTEMI and UA groups than controls and the percentage of cases that had low levels of TM was higher in NSTEMI and UA groups than controls. No differences in MPO were confirmed when studying the endothelial factors categorized (Table A2 in the Appendix).

NSTEMI and UA versus controls:

In order to make a comparison between patients with acute coronary syndrome and those with stable coronary artery disease, NSTEMI and UA patients were combined in one group (acute coronary syndrome- ACS, N=100) and the controls in a separate group (CS, N=30). The comparison depicted that ACS patients had higher hs-CRP ($p<0.0001$, $1-\beta=0.66$), higher ADAMTS13 activity ($p=0.0021$, $1-\beta=0.80$) and lower TM ($p=0.0016$, $1-\beta=0.60$) compared with the control group. VWF activity and MPO measurements did not show statistically significant difference (Table 2). When the normal range cut-off values were used (and the arithmetic variables were converted to categorical), Fisher exact test was applied to evaluate for statistical significance. The results were similar to the arithmetic. Specifically, 99% of the ACS cases had high hs-CRP compared to 63% of the CS that had high hs-CRP (OR: 57, 95% CI: 7-470, $p<0.0001$, $1-\beta=1$), similarly a higher percentage of ACS patients had normal ADAMTS13 activity ($p=0.0042$, $1-\beta=0.89$) and low TM ($p=0.0007$, $1-\beta=0.97$) (Table A3 in the appendix).

Endothelial biomarkers and cardiovascular risk factors:

The endothelial biomarkers were compared in the presence of the following cardiovascular risk factors: smoking, diabetes mellitus, arterial hypertension, dyslipidemia, chronic kidney disease (CKD) and peripheral artery disease (PAD). MPO was significantly higher in smokers than non-smokers ($p=0.02$, $1-\beta=0.62$), patients with diabetes mellitus had significantly higher TM ($p=0.040$, $1-\beta=0.56$) compared to non-diabetic patients and patients with PAD had lower MPO levels than patients without peripheral arteriopathy ($p=0.04$, $1-\beta=0.63$). Furthermore, patients with CKD had higher hs-CRP ($p=0.007$, $1-\beta=0.21$), higher TM ($p=0.01$, $1-\beta=0.83$), lower MPO ($p=0.03$, $1-\beta=0.31$) and lower ADAMTS13 activity (marginally, $p=0.097$, $1-\beta=0.42$) than those without nephropathy (table 3). There were no statistically significant results when comparing the endothelial biomarkers in the groups of arterial hypertension while for dyslipidemia hs-CRP was lower in patients with dyslipidemia ($p=0.0014$, $1-\beta=0.82$), however this was not reflected when comparing hs-CRP for patients within normal or abnormal levels.

Discussion.

Under physiological conditions, the endothelium plays a protective role as it prevents adhesion of circulating blood cells, keeps the vasculature in a vasodilated state and inhibits vascular smooth muscle proliferation. However, when endothelial dysfunction occurs in cases such as coronary artery disease, it contributes to enhanced vasoconstriction responses, adhesion of platelets and monocytes and proliferation of vascular smooth muscle cells [19-21]. Decreased levels of NO and prostacyclin lead to local vasospasm, generalized increase in vascular tone and facilitated thrombus formation [22-25]. The function of the endothelium is further aggravated in the presence of the traditional risk factors, such as arterial

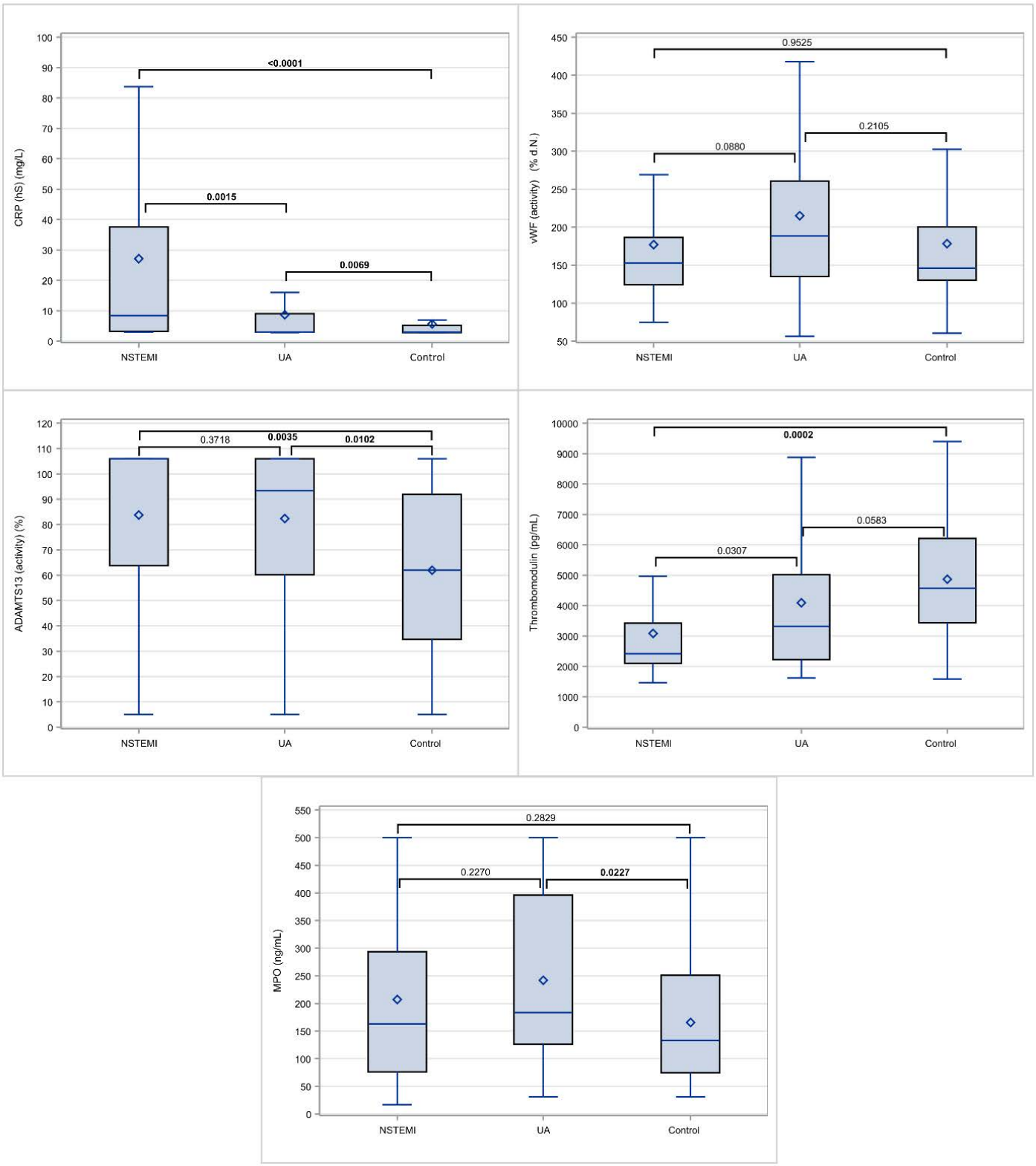

Figure 1. *Box and whisker plots of the endothelial factors for the three study groups (NSTEMI, UA and controls). Box limits indicate the Q1 and Q2 limits, whisker limits show the minimum and maximum value after outlier exclusion (outliers not shown), lines within boxes indicate the median value and rhomboid symbols the mean value. The p values (bold when significant) between the groups are shown above or below the horizontal lines.*

Table 1. *Demographic characteristics of the study population.*

Characteristic	Study population (N-130) (%)	NSTEMI patients (N-50) (%)	UA patients (N-50) (%)	Control group (N-30) (%)
Age median (Q1-Q3)	62 (54-71)	67.5 (54-75)	61.5 (55-69)	59 (53-68)
Gender (female)	28 (21.5%)	9 (18%)	10 (20%)	9 (30%)
Smoker (current)	47 (36.1%)	22 (44%)	18 (36%)	7 (23.3%)
Smoker (ex)	56 (43.1%)	21 (42%)	21 (42%)	14 (46.7%)
Diabetes mellitus	37 (28.5%)	14 (28%)	17 (34%)	6 (20%)
Dyslipidemia	70 (53.9%)	24 (48%)	22 (44%)	24 (80%)
Arterial hypertension	76 (58.5%)	27 (54%)	30 (60%)	19 (63.3%)
Peripheral artery disease	9 (6.9%)	4 (8%)	4 (8%)	1 (3.3%)
Renal disease	14 (10.8%)	9 (18%)	4 (8%)	1 (3.3%)
Family history of coronary artery disease	19 (14.6%)	8 (16%)	6 (12%)	5 (16.6%)

Table 2. *Endothelial status in ACS and CS cases (arithmetic variables).*

Characteristic	ACS (N=100)	CS (N=30)	p value	Adjusted p value
	Median (Q1-Q3)	Median (Q1-Q3)		
hs-CRP (mg/L)	5 (3-15.5)	3 (2.9-5.3)	**<0.0001**	**0.0005**
vWF activity (% d.N.)	166.1 (131.5-225.3)	146.3 (130.3-200.4)	0.4657	0.4657
ADAMTS13 activity (%)	97.3 (62.2-106)	62 (34.7-91.9)	**0.0021**	**0.0035**
TM (pg/mL)	2741 (2103-4338.5)	4574 (3436-6212)	**0.0016**	**0.0035**
MPO (ng/mL)	177.3 (100-334.9)	133.3 (74.7-250.9)	0.0623	0.0779

Table 3. *Endothelial status compared to smoking, diabetes mellitus, PAD, CKD, hypertension and dyslipidemia.*

Characteristic	Smokers (N=47)	Non-smokers (N=83)	p (Adjusted p)	Diabetics (N=37)	Non-diabetics (N=93)	p (Adjusted p)
	Mean±SD	Mean±SD		Median (Q1-Q3)	Median (Q1-Q3)	
hs-CRP (mg/L)	14.1±22.4	15.7±29.7	**0.75 (0.8114)**	5.8 (3-13.4)	3.5 (3-10.9)	**0.5206 (0.6508)**
vWF activity (% d.N.)	198.5±100	188.2±96.8	**0.5649 (0.8114)**	191.5 (137-287)	156.2 (129.6-197.4)	**0.1683 (0.2947)**
ADAMTS13 activity (%)	77.3±32	78.7±31.3	**0.8114 (0.8114)**	84.9(56.9-106)	91.9 (59.4-106)	**0.8082 (0.8082)**
TM (pg/mL)	3571.3±1753.8	4059.3±2806	**0.2831 (0.7078)**	4179 (2284-5699)	2935 (2118-4447)	**0.04 (0.2)**
MPO (ng/mL)	251.9±167.6	187.7±137.9	**0.02 (0.1)**	138.8 (74.7-276.1)	178 (102.5-298.8)	**0.1768 (0.2947)**
Characteristic	**PAD (N=9)**	**No PAD (N=121)**	**p (Adjusted p)**	**CKD (N=14)**	**No CKD (N=116)**	**p (Adjusted p)**
	Median (Q1-Q3)	**Median (Q1-Q3)**		**Median (Q1-Q3)**	**Median (Q1-Q3)**	
hs-CRP (mg/L)	6.8 (4.9-8.7)	3.6 (3-13.4)	**0.2776 (0.4627)**	9.8 (5.8-20.8)	3.4 (3-11)	**0.0071 (0.0355)**
vWF activity (% d.N.)	135.4 (119.2-154.1)	162.9 (133.4-222.3)	**0.1095 (0.2738)**	174.1 (133.4-255.6)	157.5 (130-218.7)	**0.6174 (0.6174)**
ADAMTS13 activity (%)	79.4 (58.9-106)	92 (56.9-106)	**0.8421 (0.8652)**	57.9 (35.9-106)	92.1 (59.8-106)	**0.0966 (0.1208)**
TM (pg/mL)	3883 (2118-4553)	3147 (2133-4891)	**0.8652 (0.8652)**	4627.5 (2995-8882)	2950 (2118-4587)	**0.0149 (0.0373)**
MPO (ng/mL)	65.1 (54-150.8)	164.5 (97.5-293.9)	**0.0439 (0.2195)**	88.6 (46.7-150.8)	174.5 (99.1-304)	**0.0327 (0.0545)**
Characteristic	**Hypertension (N=76)**	**No Hypertension (N=54)**	**p (Adjusted p)**	**Dyslipidemia (N=70)**	**No Dyslipidemia (N=60)**	**p (Adjusted p)**
	Median (Q1-Q3)	**Median (Q1-Q3)**		**Median (Q1-Q3)**	**Median (Q1-Q3)**	
hs-CRP (mg/L)	4.6 (3-12.4)	3.8 (3-14.2)	**0.9769 (0.9769)**	3.1 (3-6.8)	6.7 (3-22.5)	**0.0014 (0.007)**
vWF activity (% d.N.)	156.6 (134.9-220.4)	173.6 (121.8-235.5)	**0.9135 (0.9769)**	151.2 (130.3-218.9)	175.9 (132-228.9)	**0.3443 (0.7032)**
ADAMTS13 activity (%)	91.9 (55.6-106)	90.7 (60.1-106)	**0.8990 (0.9769)**	90.7 (55.2-106)	92.8 (61-106)	**0.6344 (0.7032)**
TM (pg/mL)	3412.5 (2178.5-5011)	2800 (2103-4319)	**0.1281 (0.6405)**	3494 (2118-5020)	2851.5 (2178.5-4520.5)	**0.4606 (0.7032)**
MPO (ng/mL)	141 (76.3-304)	185.6 (104.8-276.6)	**0.2614 (0.6535)**	161.9 (90.2-315.9)	161.6 (89.4-262.5)	**0.7032 (0.7032)**

hypertension, diabetes mellitus and dyslipidemia [26-28]. Oxidized low-density lipoproteins, the renin-angiotensin axis and insulin resistance play important roles in the pathogenesis of impaired endothelial function, characterized by impairment of endothelium-dependent vasodilation and by pro-coagulant and pro-inflammatory endothelial activities [29-32]. The laboratory detection and measurement of factors that contribute to coagulation mechanisms in endothelial dysfunction in patients with coronary heart disease is important in regard to the contribution of endothelial function to atherosclerotic lesions of coronary arteries. The correlation of these molecules to the classical cardiovascular risk factors may lead to better comprehension of the mechanisms and pathophysiology of atherosclerosis and coronary artery disease.

C-reactive protein (CRP) is a normal pentameric plasma protein which belongs to the pentraxin family of calcium-dependent ligand-binding proteins. It is secreted by the liver in response to a variety of inflammatory cytokines, thus serving as a marker of inflammation. Levels of CRP increase rapidly in response to trauma, inflammation, and infection [33,34]. It has also been observed that hs-CRP levels are increased in patients with ACS and a growing number of studies have determined that high hs-CRP levels consistently predict recurrent coronary events in patients with unstable angina and acute myocardial infarction [35,36]. In addition, elevated hs-CRP levels are associated with lower survival rates in these patients with cardiovascular disease [37]. Parameters for hs-CRP are as follows: (1) hs-CRP lower than 1.0mg/L indicates a low risk of developing cardiovascular disease; (2) hs-CRP between 1.0 and 3.0mg/L indicates an average risk; and (3) hs-CRP higher than 3.0mg/L indicates a high risk [38-40]. In our study, ACS patients had higher hs-CRP levels than CS ($p<0.0001$) and hs-CRP was found to be higher in NSTEMI patients compared to UA patients ($p=0.0015$) and CS ($p<0.0001$).

VWF is a multimeric, high-molecular glycoprotein involved in primary hemostasis, supporting platelet adhesion and aggregation via binding to the platelet GPIb receptor under shear stress at the site of injury. Furthermore, vWF is the specific carrier protein of factor VIII (FVIII), protecting FVIII against inactivation and rapid clearance. Elevated levels of vWF have been reported in response to stress, inflammation and endothelial lesions and have been related to thrombotic complications such as venous thromboembolism and myocardial infarction [12]. Several studies show that plasma levels of vWF are increased in patients with acute myocardial infarction [16,41,42]. The laboratory method that we used in our study measured the activity of vWF, instead of the quantitative detection of the protein. According to our results, ACS patients had higher vWF activity (median: 166 vs. 146) than CS, however without confirmed statistical significance ($p=0.46$).

ADAMTS13 is a zinc-containing metalloprotease enzyme responsible for cleaving vWF multimers into small, inactive fragments. The lack of ADAMTS13 activity results in the accumulation of multimers of vWF in the plasma and ultimately intravascular platelet aggregation [43,44]. Decreased ADAMTS13 activity has been found in patients with STEMI, as far as coronary and systemic regulation is concerned [45-47]. In our study, ADAMTS13 activity was higher in NSTEMI and UA patients compared to controls, implying the possibility that its activity may be lower in the coronary circulation but not the systemic circulation in these patient groups. However, this hypothesis requires further research, since there are no studies in the literature measuring the levels of ADAMTS13 activity in the coronary circulation of NSTEMI and UA patients. Furthermore, patients with CKD had lower ADAMTS13 activity (marginally, $p=0.097$) than those without nephropathy.

TM, also known as BDCA-3 and CD141, is a transmembrane protein mainly expressed by vascular endothelial cells. TM is an important component in the anti-coagulation and fibrinolysis system. When the coagulation cascade is activated, prothrombin is converted to thrombin by coagulation factors Va and VIIIa, ultimately leading to fibrin clot formation. TM functions as a cell surface receptor for thrombin. The TM-thrombin complex activates protein C to degrade coagulation factors Va and VIIIa, thereby reducing the amount of thrombin generated and inhibiting coagulation [48,49]. TM-thrombin complex also activates thrombin-activatable fibrinolysis inhibitor (TAFI), creating a carboxypeptidase that inhibits fibrinolysis. It has been documented that patients suffering from cardiovascular diseases, such as ACS and pulmonary thromboembolism, have increased circulating TM concentrations [10,50]. We found that TM was lower in NSTEMI patients compared to UA patients ($p=0.0307$) and controls ($p=0.0002$). Patients with diabetes mellitus had significantly higher TM ($p=0.040$) compared to non-diabetic patients and patients with CKD had higher TM ($p=0.01$) than those without nephropathy. Various studies have shown elevated plasma concentrations of TM in disorders with endothelial dysfunction, such as inflammation, diabetes mellitus, sepsis, autoimmune diseases, and renal diseases [51-53].

MPO is a heme- containing enzyme belonging to the haloperoxidases (XPO) subfamily of peroxidases. It is an abundant neutrophil and monocyte glycoprotein that catalyzes the hydrogen peroxide dependent formation of hypochlorous acid and other reactive species [54,55]. Reaction of these compounds with macromolecules results in the nitrosylation, chlorination and oxidation of tyrosine residues, lipids and cholesterol and the intermolecular crosslinking of proteins and DNA [56-58]. MPO binds albumin, the macrophage mannose receptor, cytokeratin 1 on vascular endothelial cells, high molecular weight kininogen and the integrin CD11b/CD18 on neutrophils. These interactions promote MPO clearance, reduce the levels of nitric oxide and bradykinin and inhibit vasodilation [59,60]. Elevated plasma MPO levels have been associated with a variety of clinical conditions including systemic inflammation, eclampsia, risk of cardiovascular events and vascular endothelial dysfunction [7-9,61,62]. In our study, MPO was higher in UA patients compared to the control group ($p=0.0227$) and was significantly higher in smokers than non-smokers ($p=0.02$). Smoking is one of the most important risk factors for coronary artery disease. It has been found that MPO contributes to the development and progression of coronary artery disease in smokers [63,64]. Patients with PAD had lower MPO levels than patients without peripheral arteriopathy ($p=0.04$) and patients with CKD had

lower MPO (p=0.03) than those without nephropathy. Plasma MPO levels could be used for risk stratification of major adverse cardiovascular events, such as myocardial infarction and heart failure, in patients with PAD [65]. Finally, it has been shown that MPO plays an important role not only in oxidant-mediated antimicrobial defense by granulocytes, but also in the progression of degenerative and immunologic diseases of the kidney [66,67].

Conclusions.

The results of this study add more data to the current medical literature concerning the role of coagulation disorders, endothelial damage and immunothrombosis in patients with coronary artery disease and their correlation with traditional risk factors for cardiovascular disease.

Declarations of interest.

None.

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Table A1. *Endothelial status among NSTEMI, UA and CS groups.*

Characteristic	NSTEMI (N=50)	UA (N=50)	CONTROL (N=30)	p (NSTEMI vs. UA)	Adjusted p (NSTEMI vs. UA)	p (NSTEMI vs. CS)	Adjusted p (NSTEMI vs. CS)	p (UA vs. CS)	Adjusted p (UA vs. CS)
	Median (Q1-Q3)	Median (Q1-Q3)	Median (Q1-Q3)						
hs-CRP (mg/L)	8.4 (3.3-37.6)	3 (3-9)	3 (2.9-5.3)	**0.0015**	**0.0075**	**<0.0001**	**<0.0001**	**0.0069**	**0.0255**
vWF activity (% d.N.)	152.7 (124.3-186.7)	188.4 (135.4-260.7)	146.3 (130.3-200.4)	0.0880	0.1467	0.9525	0.9525	0.2105	0.2105
ADAMTS13 activity (%)	106 (63.8-106)	93.3 (60.1-106)	62 (34.7-91.9)	0.3718	0.3718	**0.0035**	**0.0058**	**0.0102**	**0.0255**
TM (pg/mL)	2413 (2103-3423)	3320 (2224-5020)	4574 (3436-6212)	**0.0307**	0.0768	**0.0002**	**0.0005**	0.0583	0.0729
MPO (ng/mL)	163.1 (76.4-293.9)	183.8 (126.2-396.1)	133.3 (74.7-250.9)	0.2270	0.2838	0.2829	0.3536	**0.0227**	**0.0378**

Table A2. *Endothelial activity categorized comparisons among NSTEMI, UA and CS.*

Description	Contingency table	NSTEMI vs. UA			NSTEMI vs. CS			UA vs. CS		
		p	Adjusted p	OR and 95% CI	p	Adjusted p	OR and 95% CI	p	Adjusted p	OR and 95% CI
hs-CRP categorized	CS vs. high (19/63.33%) CS vs. normal (11/36.67%) NSTEMI vs. high (50/100%) NSTEMI vs. normal (0/0%) UA vs. high (49/98%) UA vs. normal (1/2%)	1	1	N/A	**<0.0001**	**0.0002**	N/A	**<0.0001**	**0.0003**	0 (0-0.3)
vWF categorized	CS vs. high (11/36.67%) CS vs. normal (19/63.33%) NSTEMI vs. high (20/40%) NSTEMI vs. normal (30/60%) UA vs. high (28/56%) UA vs. normal (22/44%)	0.1609	0.4843	0.5 (0.2-1.2)	0.8162	1	0.9 (0.3-2.2)	0.1104	0.138	0.5 (0.2-1.2)
ADAMTS13 categorized	CS vs. low (18/60%) CS vs. normal (12/40%) NSTEMI vs. low (13/26%) NSTEMI vs. normal (37/74%) UA vs. low (16/32%) UA vs. normal (34/68%)	0.6598	1	0.7 (0.3-1.8)	**0.0041**	**0.0068**	4.3 (1.6-11.2)	**0.0197**	**0.0493**	3.2 (1.2-8.2)
TM categorized	CS vs. high (10/33.33%) CS vs. low (5/16.67%) CS vs. normal (15/50%) NSTEMI vs. high (4/8%) NSTEMI vs. low (30/60%) NSTEMI vs. normal (16/32%) UA vs. high (9/18%) UA vs. low (22/44%) UA vs. normal (19/38%)	0.1937	0.4843	N/A	**0.0002**	**0.0005**	N/A	**0.0315**	0.0525	N/A
MPO categorized	CS vs. high (9/30%) CS vs. low (0/0%) CS vs. normal (21/70%) NSTEMI vs. high (18/36%) NSTEMI vs. low (1/2%) NSTEMI vs. normal (31/62%) UA vs. high (18/36%) UA vs. low (0/0%) UA vs. normal (32/64%)	1	1	N/A	0.7680	1	N/A	0.6326	0.6326	0.8 (0.3-2)

Table A3. *Endothelial status in ACS and CS cases (categorical variables).*

Description	Contingency table	p value	Adjusted p	OR & 95% CI
hs-CRP categorized	ACS vs. high (99/99%), ACS vs. normal (1/1%) CS vs. high (19/63.33%), CS vs. normal (11/36.67%)	**<0.0001**	**0.0003**	57.3 (7-470.5)
vWF categorized	ACS vs. high (48/48%), ACS vs. normal (52/52%) CS vs. high (11/36.67%), CS vs. normal (19/63.33%)	0.3026	0.3783	1.6 (0.7-3.7)
ADAMTS13 categorized	ACS vs. low (29/29%), ACS vs. normal (71/71%) CS vs. low (18/60%), CS vs. normal (12/40%)	**0.0042**	**0.007**	0.3 (0.1-0.6)
TM categorized	ACS vs. high (13/13%), ACS vs. low (52/52%), ACS vs. normal (35/35%) CS vs. high (10/33.33%), CS vs. low (5/16.67%), CS vs. normal (15/50%)	**0.0007**	**0.0018**	N/A
MPO categorized	ACS vs. high (36/36%), ACS vs. low (1/1%), ACS vs. normal (63/63%) CS vs. high (9/30%), CS vs. low (0/0%), CS vs. normal (21/70%)	0.7405	0.7405	N/A