### REVIEW

### from

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External member of the Medical University - Sofia of the Scientific Jury on the basis of order № 68 / 28.02.2020 of the Chairman of the Supervisory Board at MHAT "NKB" EAD-Sofia

on the dissertation on the topic: "Study of renal function in patients undergoing invasive angiographic examination with a new biomarker-neutrophilgelatinase associated lipocalin (NGAL)"

for awarding the educational and scientific degree "Doctor" in the scientific specialty "Cardiology" (code 03.01.47) to Dr. Iliana Hristova Petrova-Stoyanova, PhD student in self-study in the field of higher education 7. Health and Sports, in the professional field 7.1. Medicine and doctoral program Cardiology at MHAT "NKB" EAD - Sofia

As an appointed member of the jury for this competition, I have no conflicts of interest to be declared.

The dissertation is written on 282 standard pages and includes 95 figures and 82 tables. An additional appendix includes 28 tables and 13 figures. The bibliography contains 407 literature sources, of which 4 in Cyrillic and 403 in Latin.

# **Relevance of the topic**

With the development of medicine and the improvement of the diagnostic process in modern clinical practice, the use of highly specialized imaging techniques that use a contrast agent (CA) is increasingly necessary. Many of these diagnostic tests also become therapeutic by performing various microvascular techniques. Along with the invariable benefits of extending the scope and application of interventional procedures, it undoubtedly raises the question of the possible adverse effects of the application of CA on renal function. One of the most widely used definitions of this effect is contrast-induced nephropathy (CIN).

Timely diagnosis of CIN and adequate behavior in its development is extremely important. The presence of a number of risk factors leads not only to post-procedural impairment of renal function in subjects with contrast, but also to a worsened prognosis in the form of increased mortality, the need for hemodialysis treatment and the occurrence of adverse cardiovascular events.

For these reasons, a number of authors are focusing their efforts on developing predictive models and risk scales to predict the occurrence of CIN in a timely manner. Determining the individual risk and the respective approach in each individual patient is among the main goals of these point systems. Adequate selection of the high-risk patient population would also contribute to the development of new therapeutic approaches in the future, such as adequate hydration, pre-delineation of the strategy for the specific intervention. imaging, the use of alternative techniques such as intravascular ultrasound (IVUS) or coronary blood flow (FFR) assessment, which may reduce the amount of contrast agent.

From the data published so far, it can be said that there is still a need to develop sufficiently good risk models that meet both the conditions - to be easily applicable in clinical practice, to facilitate clinical decision-making and to have proven causal relationship with subsequent complications in patients

The research is focused on patients undergoing invasive angiography and assessment of renal function before and after the administration of the contrast agent.

According to the literature, the incidence of CIN after coronary interventions varies between 11.3% and 14.5 %.63 On the other hand, it should be noted that in many clinical situations, CIN may remain clinically unrecognized due to its asymptomatic course, untimely monitoring of renal function after contrast examination or early discharge of patients. The likelihood that the frequency of this complication will be underestimated in these situations remains possible.

Millions of doses of contrast agents are currently used worldwide in various radiological studies6

The expansion of the range of these studies and their use among the elderly population, many of whom have CKD and diabetes mellitus, the main risk factors for CIN, necessitates adequate screening of all patients to assess the true incidence of this complication.

Given the above, I find the topic of this dissertation unquestionably relevant and with great practical potential. It can also be used as a basis for future research research.

### Structure of the dissertation

The dissertation is in accordance with the standards for preparation of scientific work for obtaining a scientific and educational degree "Doctor". Includes the following separate parts: literature review - 88 pages, purpose and tasks - 2 pages, material and methods - 16 pages, results - 118 pages, summaries and conclusions - 12 pages, contributions - 1 page, appendices - 1 page, bibliography - 17 pages and publications related to the dissertation - 18 pages.

The proportion between the structuring departments of the work is observed.

### Knowledge of the problem and scientific formulation

The literature review is very well structured, detailed and comprehensive. It deeply touches on various aspects of the topic: etiology, pathogenesis, pathophysiology and hemodynamic changes involved in the development of CIN. The methods of prevention and the different therapeutic regimens for the treatment of CIN are analyzed., the risk factors of the studied patient population as well as the role of NGAL as a new biomarker for the diagnosis of OBU are considered in detail.

The results of a large number of author groups working in this field are correctly quoted. The clarity of the exposition is also contributed by the appropriate illustration with 4 tables and 8 figures.

The conclusions from the literature review are meaningfully formulated and logically argue the purpose and tasks of the dissertation.

**The aim** is clearly and specifically defined: "The aim of the study was to examine renal function in a group of patients who underwent routine invasive angiographic examination using a new biomarker, Neutrophil Gelatinase Associated Lipocaline (NGAL) and its comparison to serum crenania. and GF ".

Fully in accordance with the formulated goal, 8 specific tasks are correctly identified.

The dissertation included and examined 145 patients, of which a total of 135 patients were included in the final analysis (seven had violated the study protocol at different stages; two required emergency surgery after the end of the angiographic examination, and one patient has withdrawn its informed consent for conducting SCAG, as the patients are selected with clearly formulated

criteria for inclusion and exclusion in full compliance with the set goals and objectives.

The research is prospective which makes the dissertation especially valuable

The classification of patients was performed according to criteria determining the initial values of biomarkers and according to criteria defining the dynamic changes in biomarkers.

Based on these criteria, patients are classified into several main groups and respective subgroups. In cases where the same cohort of patients met several criteria simultaneously, a subgroup distribution was made at several levels and additional analysis was performed.

The research methods used are modern and meet the goals and objectives set by the dissertation. Follow-up indicators are well formulated and patients are closely monitored

The results of the dissertation are described in detail on 118 standard pages and very well illustrated with overview figures and tables, analyzed in detail in the text. They strictly follow the purpose and tasks of the dissertation. The own results are discussed in depth and competently and are compared with those of other teams

Statistical methods are appropriate for the purposes of the study and allow reliable data to be obtained.

In accordance with the obtained results, 11 contributions were formulated - 3 original and 8 confirmatory. They are semantically and factually substantiated by the results and the discussion and prove the scientific and clinical-applied value of the work of Dr. Petrova.

# Contributions of original character

1. For the first time, the incorporation of functional and structural biomarker data into the new conceptual framework for acute renal impairment proposed by the Working Group on Quality Initiative in Acute Dialysis (ADQI) is described in the field of invasive cardiology.

2. For the first time in Bulgaria the use of NGAL in contrast angiographic examinations is demonstrated

3. The scientific relevance of the classification of a standard sample to the new NGAL biomarker is determined and an own scale is proposed to assess the degree of renal impairment.

# **Contributions of confirmative character**

1. A detailed approach is presented, according to which the assessment of renal function in patients undergoing contrast angiography is performed simultaneously on the basis of the registered baseline levels and the reported dynamic changes in two types of biomarkers.

2. The possibilities of a new approach for integration of plasma NHAL in the risk stratification of patients are demonstrated, by applying it in a risk scale for assessment of serious renal dysfunction.

3. A comparative model on the independent role of each of the two types of biomarkers (functional and structural) in the assessment of renal function and the level of risk among patients undergoing contrast angiographic examination is presented.

# Contributions of scientifically applied character

1. The role of NGAL as an early biomarker for the diagnosis of CIN has been demonstrated, both in patients with preserved renal function and in the conditions of chronic kidney disease.

2. The presence of groups with subclinical acute renal impairment, regardless of the degree of baseline renal function, has been demonstrated in patients undergoing contrast angiography.

3. Different reference limits of plasma NHAL are established according to the stage of chronic kidney disease.

4. The influence of the accompanying diseases and risk factors on the reported levels of NGAL is demonstrated.

5. The classical scale for risk assessment of development of contrastinduced nephropathy is supplemented by comparing it with the structural biomarker.

**The summary report** is designed according to the requirements and reflects the main results, their discussion, conclusions and scientific contributions of the dissertation.

On the topic of the dissertation the candidate has published 7 articles as the first author, accepted and published in journals: "Health bg", "Medicart", Science Cardiology "," "Cardiovascular diseases" "Comptes rendus de l'Academie bulgare des Sciences", "Bulgarian Cardiology", two chapters from books, and has presented 7 reports at scientific conferences. The required publications on the topic, as well as the participation in international scientific forums are correctly quoted.

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#### Conclusion

The dissertation contains scientific, scientific-applied and applied results, which represent an original contribution to science and meet all the requirements of the Law for development of the academic staff in the Republic of Bulgaria (RASRB), the Rules for application of ZRASRB EAD. The presented materials and dissertation results fully comply with the specific requirements of MHAT "NKB" EAD.

The dissertation shows that the doctoral student Dr. Iliana Hristova Petrova-Stoyanova has in-depth theoretical knowledge and professional skills in the scientific specialty "Cardiology" (code 03.01.47.). demonstrating qualities and skills for independent research.

Due to the above, I **CONVINCEDLY** give my **POSITIVE** assessment of the study, presented by the above reviewed dissertation, abstract, results and contributions, and I offer the esteemed JURY to award the educational and scientific degree "**DOCTOR**" to **Dr. Iliana Hristova Petrova Stoyanova** in a doctoral program in Cardiology.

Review prepared :

21.05.2020

Prof. Dr. Diana Krumova Trendamova-Lazarova, MD