EDITORIAL

STEMI in 2019 - European and Romanian Evidences

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Editorial comment to

L. Anghel et al., "Arrhythmic complications in women with STEMI"

and

A. Ceamburu et al., "Gender equality applies (partially) to ST-segment elevation myocardial infarction too"

The present article is based, partly on current data from the Romanian STEMI registry, an experience that is beginning to gain increased contour, partly on original papers published in this current number by colleagues working in coronary care units and invasive cardiology laboratories, papers that are taking into account a subject considered „taboo" until recently - the gender related post-STEMI patient evolution, but also on the editorial „The year in cardiology 2018: acute coronary syndromes", published by Petr Widimsky, Filippo Crea, Ronald K. Binder and Thomas F. Luscher in this January number of *European Heart Journal*[1].

Current statistics (2018) from the Romanian STEMI registry are counting over 12.000 primary PCI or post-thrombolysis invasive procedures, a considerable number that is allowing interesting conclusions and considerations for the European cardiology community. Beyond a great number of problems concerning management algorithms of acute coronary syndromes, statistics are demonstrating a real progress. In my opinion, the latest STEMI diagnostic and treatment guideline is not that opened in motivating a medical system still seeking optimal logistic and organizing standards, due to the exclusion of the classical „time to balloon" and the introduction of the „time from first medical contact", a time that may also account a significant delay of time and that is presented as a somehow „negative" patient feature and not a responsibility of the UPU - SMURD – catheterization laboratory system[2]. Regardless of that fact, the current guideline is presenting the more coherent proposal of the pharmaco-invasive attitude, that is half – dose thrombolysis facilitated angioplasty and complete antithrombotic pre-PCI treatment, an attitude that may be suited not only for patients older than 70 years (we salute the entrance of some Romanian cardiology centers in the European trial STREAM-2). Moreover, one essential fact underlined by the current guideline is the reinforcement of the use of thrombolysis, as soon as possible after the onset of symptoms, when the patient cannot reach a 24/24, 7/7 PCI capable center during the first 90 minutes delay of time. Confusions related to this timing started with the 2017 STEMI guideline, with the exclusion of the time from first ischemia related symptoms. Beyond this, another questionable proposal of the above mentioned guideline is the usefulness of PCI after 24 and up to 48 hours after onset of symptoms, including inn asymptomatic patients after the first 12 hours. This new class II indication should not lead to an increased delay of time regarding the revascularization procedure. New data emerged over the last year of global and also European experience need to be highlighted. Although some may seem theoretical, they are based, without doubt, on evaluation and treatment principles that need to be taken in consideration, like adaptive immunity alterations that may trigger inflammation of atherosclerotic plaque, as well as prevalence of erosion in the atheroma poor in aggressive lipids[3]. This process is most commonly encountered in non ST elevation (NSTEMI) acute co-

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ronary syndromes mostly in women, a process that is being four times more frequent than the classical dissection, hemorrhage and plaque thrombosis, well defined by P. Libby and G. Pasterkamp in an already famous *European Heart Journal* article – „Requiem for the vulnerable plaque"[4]. This process is the result of almost 3 decades of statins and aspirin use by a great amount of population, both in primary as well as in secondary cardiovascular prevention. The new (the fourth) acute myocardial infarction definition is clearly underlying these complex mechanisms in acute coronary syndromes and it is also emerging as a result of the year 2018 in cardiology. The evidence of changes in early mortality after STEMI, starting with the years 1950 when coronary care units emerged (45%) to approximately 11-12% in the primary PCI, reperfusion and antithrombotic attitude era, recently underlined by the SWEDEHEART Registry shouldn't be seen out of the picture in which, the same registry demonstrated in the late years a total 4 years mortality of 40%[5]!

New observations related to myocardial remodeling and recent studies that analyzed its positive influence (some using osteocrin and some, on-going using ARNI) seem to have promising results, but further evidences are needed. Great effort was put in order to achieve early acute myocardial infarction diagnosis, but the use of new evaluating procedures of high sensitive troponins and biomarkers like cysteine-rich angiogenic inducer 61 Cyr61 or CCN1 have not fulfilled safety reasons yet[6].

The new STEMI entity, MINOCA- myocardial infarction with non-obstructive coronary artery disease lead to new clinical and decisional situations, but also to testing some classical provocative agents like acetylcholine and ergonovine administered soon after coronary angiography in order to certify active ischemia[7].

Regarding ST elevation segment acute coronary syndromes in women, some well-known facts are established related to prothrombogenic versus fibrinolytic factors: decreased plasminogen and increased antithrombogenic factors like Protein C, antithrombin and tissue factor pathway inhibitor, especially in older women. Beyond these classical findings, recent data demonstrated a clear advantage related to hemorrhagic risk in women when radial approach is preferred. However, pre-procedural maximum statin dose administration has not proved the same benefit as in men[8]. Another finding is that, Takotsubo syndrome, a clinical entity more and more often found in general statistics as an apparently benign form of STEMI, was more frequently encountered in women and, starting with last year, there is a clear etiopathogenic classification of that syndrome[9].

The experience of our colleagues from Iasi and respectively Cluj-Napoca/Targu Mures regarding gender related differences in acute coronary syndromes evolution have demonstrated, in a similar manner with other current foreign studies, a more severe evolution in women following primary PCI in STEMI, both in what concerns the frequency of complications as well as the increased of in-hospital mortality. An explanation may be represented by the higher risk score and multiple comorbidities of women analyzed in compare to men, a situation commonly encountered in clinical studies („GENDER EQUALITY APPLIES (PARTIALLY) TO ST-SEGMENT ELEVATION MYOCARDIAL INFARCTION TOO" – Alexandru Ceambur, Razvan Constantin Serban, Ioana Sus, Eva Katalin Lakatos, Zoltan Demjen, Paul Ciprian Fisca, Laszlo Hadadi, Cristina Somkereki, Alina Scridon). On the other hand, arrhythmogenic risk, especially in anterior localization STEMI was greater, both for ventricular fibrillation as well as for atrial fibrillation, thus leading to an increased relative mortality and early post myocardial infarction complications („ARRHYTHMIC COMPLICATIONS IN WOMEN WITH STEMI"- L. Anghel, Cristina Prisacariu, Amin Bazyani, Liviu Macovei). Results are demonstrating that, in older women, the frailty and vulnerability may lead to an increased short and long term mortality after an invasive revascularized STEMI. Also, a recent Scandinavian study also found gender differences and significant delay related to first medical contact and optimal reperfusion time, much more frequent in women patients in compare to male ones, due to confusion in diagnostic[10].

Another controversy is related to primary PCI in elderly patients, especially patients older than 80 years. This is also a sensitive issue in Romanian hospitals, not only for economical and logistic reasons. A recent American Heart Association paper published an evaluation of over 470.000 elderly patients, during 16 years of follow-up, patients that benefit from primary PCI in STEMI. The decrease for the risk of death of any cause was 53% for patients with age between 75 and 79 years, 49% for patients with age between 80 and 84 years and 42% for patients older than 85. This data should determine the use of an unequivocal attitude regarding the efficacy and morality of the preferred revascularization method.

Beyond new data in the field, another debated subject is represented by the optimal antithrombotic treatment. When taking into account older women, thrombotic risk has an unacceptable increase after prolonged antiplatelet aggressive therapy (including anticoagulants) - prasugrel, ticagrelor, thus underlying the need for a closer monitoring of this category of patients and the consideration of more „softer" molecules like clopidogrel, especially after the first month of DAPT - double antiplatelet therapy (TROPICAL ACS, CHANGE DAPT, TOPIC etc.).[11] An interesting issue is represented by non-valvular atrial fibrillation patients with the need for PCI, including STEMI, with the option for double antiplatelet antithrombotic therapy (direct oral anticoagulant - DOAC plus aspirin or Clopidogrel/Ticagrelor) certified by at least three clinical studies - PIONEER AF-PCI, RE-DUAL and AUGUSTUS, versus triple antithrombotic therapy (anticoagulant plus double antiplatelet treatment), all studies with results that demonstrated lower hemorrhagic risks and antithrombotic benefits for the DOAC plus aspirin or Clopidogrel/Ticagrelor combination. However, recent data from the VALIDATE-SWEDEHEART trial and MATRIX trial did not confirm the use of bivalirudine versus unfractionated heparin in the pre-procedural setting, in order to decrease hemorrhagic risk[12].

Promising study results with decreased mortality rate after two years of follow-up were found using a new generation of hypolipemiant medication – PCSK-9 inhibitors - ODYSSEY OUTCOMES using alirocumab and FOURIER using evolocumab[13]. However, beyond the fact that further studies are needed, in the setting of a restrictive economic Romanian environment, the increased price of that medication represents an important issue.

Another important controversy is represented by multivascular approach, beyond culprit coronary lesion, in acute coronary syndromes patients, an approach that may be considered during index hospitalization or in a staged procedure. For patients with STEMI and cardiogenic shock, the CULPRIT-SHOCK trial demonstrated, despite previous results, lower early and medium-term mortality rates when using culprit lesion approach only in compare to multivascular approach during the same procedure[14].

Another issue of controversy was verified by the VERDICT trial, with results that demonstrated the fact that, in the case of a NSTEMI acute coronary syndrome with a GRACE score inferior to 140, there is no sufficient need for early revascularization procedure (mean time 4,7 hours) versus delayed revascularization approach (61,6 hours)[15].

Regarding percutaneous revascularization of left main lesions in acute coronary syndromes, the results of DELTA-2 registry brought optimism of investigators and medical specialized community. Gender differences in STEMI/NTEMI patients were evaluated by a Canadian registry – SCAD Cohort study that also demonstrated the prevalence of spontaneous coronary dissection in average age with overt stress factors women patients[16].

An unsolved issue, associated with high mortality rate is represented by the approach of patients with unstable hemodynamic status following cardiac resuscitation after ventricular fibrillation in STEMI, with mortality rates up to 60% during the first year and irreversible cerebral damage, despite the use of ventricular mechanical devices like IMPELLA or ECMO. Unfortunately, these devices are rarely used in our country, with an even higher mortality rate in these situations. The door-to-balloon-time is another deficient indicator in many areas, including our country, due to logistical and organization issues that are well known in the few PCI capable centers across Romania. Concerning novel anti-inflammatory therapies (CANTOS) and the use of stem cells in order to replace necrotic myocardial tissue, a reasonable amount of time must elapse before routine use.

Despite progress but also deficiencies that were highlighted in this article, my opinion is that we are witnessing an increased trend regarding the improvement in morbidity- mortality rates after STEMI/NSTEMI acute coronary syndromes patients, but, even more important, of primary prevention measures implemented in order to avoid these severe pathology with irreversible consequences over the quality and duration of patients life.

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