Editorial

European and American guidelines for the management of patients with heart failure - different recommendations based on the same research results?

Currently, the main reasons for significant changes in medical guidelines are new results of randomized clinical trials. In addition to the direct impact on the treatment of individual patients, the solutions proposed in the guidelines correlate with the decisions of health care payers in individual countries, and this largely translates into the overall quality of medical care. Considering the importance of guidelines of scientific societies, they must be comprehensive, objective, and at the same time, due to the constant technological and pharmacological progress, it is necessary to develop mechanisms thanks to which these guidelines can be regularly updated as new clinical data become available. The guidelines of the European Society of Cardiology (ESC) (1) and the joined guidelines of the American College of Cardiology Foundation (ACCF)/ American Heart Association (AHA)/ Heart Failure Society of America (HFSA) (2) for the management of patients with heart failure are particularly important due to their global reach.

The authors of both documents restated both the definition of HF itself and novel pharmacological and non-pharmacological interventions. While the definition of the disease entity and general assumptions seem universal, the detailed treatment regimens differ (Table 1). The current classification of HF is as follows: HFrEF (HF with reduced ejection fraction (EF)): LVEF ≤40%; HFmrEF (HF with mildly reduced EF): LVEF 41-49%; HFpEF (HF with preserved EF): LVEF ≥50%. According to American guidelines we can distinguish also HFimpEF (HF with improved EF): previous LVEF ≤40% and follow-up measurement of LVEF >40%; and four stages of progression HF from A to D (At risk for HF -> Pre-HF -> symptomatic HF -> Advanced HF), with independent recommendations for each of them.

Both publications indicate in the group of patients with HFrEF a 4-drug treatment regimen based on: 1) drugs affecting the renin-angiotensin-aldosterone system (RAAS): angiotensin converting enzyme inhibitor (ACEI), angiotensin II receptor blocker (ARB), angiotensin receptor neprilysin inhibitor (ARNI), 2) B-blockers (BB), 3) mineralocorticoid receptor antagonists (MRA), 4) sodium glucose cotransporter-2 inhibitors (SGLT2i), which is becoming a major player in the treatment of heart failure.

The ACCF/AHA/HFSA guidelines strongly identify ARNI as the preferred RAAS modulator with a class Ia recommendation and state that the use of ACEI or ARB may be used "when the use of ARNI is not possible." The ESC guidelines appear to be more conservative, establishing the strength of the recommendations for the use of ARNI as Ib, stating that ARNI is recommended "as a replacement for angiotensin converting enzyme inhibitors" in suitable patients who remain symptomatic despite optimal treatment, although ARNI can be considered a first-line drug (class IIb).

There is no differences in recommendation of loop diuretics (class I), ivabradine (class IIa), verciguat (class IIb) or digoxin (class IIb). The most significant difference in the proposed treatment regimens of this group of patients concerns the use of hydralazine-isosorbide dinitrate.

The ACCF/AHA/HFSA indicates recommendation class Ia for African-Americans, while the ESC provides a class IIa recommendation, citing the lack of "clear evidence to suggest the use of this fixed-dose combination therapy in all patients with HFrEF." In the remaining groups of patients with heart failure (preserved and mildly reduced EF value), the differences in recommendations are even more pronounced.

The European guidelines did not issue recommendations for the use of SGLT2i in patients with HFmrEF or for any of the drug in patients with HFpEF in contrast to the ACCF/AHA/HFSA guidelines, which support the use of ARNI, mineralocorticoid receptor antagonists, and SGLT2i in the treatment of HF with preserved EF with recommendation class IIb, IIb and IIa respectively.

Address for Correspondence: Adam Stanczyk, Department of Clinical Pharmacology, Medical University of Lodz, Poland
Email: astanzykpl@yahoo.com
Received: 28.05.2022 **Accepted:** 29.05.2022

Table 1. Selected differences in the approach to pharmacotherapy in patients with HF according to ESC and ACCF/AHA/HFSA guidelines

Topic	ACCF/AHA/HFSA recommendation	ESC recommendation	Discrepancies between guidelines
HFrEF			
First-line therapy	-ARNI/SGLT2i/BB/MRA (class I) -Use of ACEI/ARB when the use of ARNI is not feasible (class I)	-ACEI/ARNI/SGLT2i/BB/MRA (class I) -ARNI as a replacement for ACEI in patients who remain symptomatic on ACEI/BB/MRA (class I)	According to ACCF/AHA/HFSA ARNI is the preferred RAAS modulator, including patients hospitalized with de novo HF
Other	-H-ISDN in self-identified Black patients with NYHA III/IV symptoms despite standard therapy (class I) or in patients who cannot tolerate first -line agents (class IIb)	-H-ISDN (class IIa)	Lower level of recommendation according to ESC as a result of difficulties in translation to patients of other race-ethnic group
Economical value of therapy	-High: ACEI/ARB/ARNI/BB/MRA/H-ISDN -Intermediate: SGLT2i -Low: tafamadis	No recommendation	Lack of recommendation of the value of therapies in ESC guidelines
HFmrEF			
First-line therapy	-SGLT2i (class IIa) -ARNI/ACEI/ARB/BB/MRA (class IIb)	-ARNI/ACEI/ARB/BB/MRA (class IIb)	Lack of recommendation for SGLT2i in ESC guidelines
Economical value of therapy	-High: ACEI/ARB/ARNI/BB/MRA/H-ISDN -Intermediate: SGLT2i -Low: tafamadis	No recommendation	Lack of recommendation of the value of therapies in ESC guidelines
HFpEF			
First-line therapy	-SGLT2i (class IIa) -ARNI/ARB/MRA (class IIb)	No recommendation	Lack of recommendation in ESC guidelines
Economical value of therapy	-Low: tafamadis	No recommendation	Lack of recommendation of the value of therapies in ESC guidelines
HFimpEF			
First-line therapy	Continue therapy	Continue therapy (class I)	Lack of level of recommendation in ESC guidelines

ACCF- American College of Cardiology Foundation, ACEI- angiotensin converting enzyme inhibitor, AHA- American Heart Association, ARB- angiotensin II receptor blocker, ARNI- angiotensin receptor neprilisin inhibitor, BB- B-blockers, EF- ejection fraction, ESC- European Society of Cardiology, HF- heart failure, HFimpEF- HF with improved EF, HFmrEF- HF with mildly reduced EF, HFpEF- HF with preserved EF, HFrEF - HF with reduced EF, HFSA- Heart Failure Society of America, H-ISDN- hydralazine-isosorbide dinitrate, MRA- mineralocorticoid receptor antagonists, SGLT2i- sodium glucose cotransporter-2 inhibitors

The authors of the ESC guidelines confirm the Food and Drug Administration support for ARNI and MRA in the treatment of heart failure with preserved ejection fraction (HFpEF), however, they do not provide a class or level of recommendation for any of these pharmacotherapies, mainly because the benefits of these drugs were only seen in pre-defined subgroups (women and participants with the EF <57% for ARNI) and post hoc analyses (i.e., participants with EF <55% and participants recruited in the Americas for MRA).

The indicated differences in guidelines, despite the same results of research that are the basis for making therapeutic decisions, do not result from a different clinical picture of HF on both continents. They are caused, among other things, by population differences taking into account the greater share of the black anon-Hispanic patients, justifying a higher level of recommendations for hydralazine-isosorbide dinitrate in this subgroup, taking into account its impact on morbidity and mortality. The second parameter indicated directly in the ACCF/AHA/HFSA guideline is the economic value statement of the intervention. This is absent in the European guidelines, but it is very important step that should be widely disseminated on all guidelines.

Due to continuous progress, it is imperative to have mechanisms for this guidance document to become documents that are regularly updated as new clinical data become available. I believe that the expected results of ongoing clinical trials with SGLT2i in various groups of patients with heart failure will soon force to update the current guidelines.

Adam Stanczyk
Department of Clinical Pharmacology,
Medical University of Lodz, Poland

Peer-review: internal
Conflict of interest: None to declare
Authorship: A.S
Acknowledgement and funding: None to declare

References

1.McDonagh TA, Metra M, Adamo M, Gardner RS, Baumbach A, Böhm M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) With the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J 2021; 42: 3599–726. doi:10.1093/eurheartj/ehab368

2.Heidenreich PA, Bozkurt B, Aguilar D, Allen LA, Byun JJ, Colvin MM, et al. 2022 AHA/ACC/HFSA guideline for the management of heart failure: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. J Am Coll Cardiol 2022; doi:10.1016/j.jacc.2021.12.012

Dunes at Kop van Schouwen, North Sea coast, The Netherlands. Photography by Christiaan Vrints, Antwerp, Belgium