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OPTIMIZATION OF PHARMACOTHERAPY IN CHRONIC HEART FAILURE: CLINICAL PHARMACOLOGICAL ASPECTS OF CONTEMPORARY FOUNDATIONAL THERAPY AND ASSESSMENT OF MEDICATION SAFETY

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ABSTRACT

Contemporary treatment of heart failure with reduced ejection fraction rests on four foundational drug classes, each of which independently reduces mortality. This article provides a clinical pharmacological assessment of foundational therapy, the sequence and speed of its initiation, and the safety issues that arise in real-world practice. Rapid in-hospital initiation and up-titration reduced the 180-day composite of heart failure readmission or death from 23.3% to 15.2%, whereas registry data show that only a small minority of eligible patients receive target doses of all classes. Monitoring of potassium and renal function, the management of hypotension and the avoidance of prognosis-worsening co-medication are examined.

Keywords: *chronic heart failure; reduced ejection fraction; foundational therapy; sacubitril/valsartan; SGLT2 inhibitors; up-titration; hyperkalaemia; medication safety.*

ОПТИМИЗАЦИЯ ФАРМАКОТЕРАПИИ ХРОНИЧЕСКОЙ СЕРДЕЧНОЙ НЕДОСТАТОЧНОСТИ: КЛИНИКО-ФАРМАКОЛОГИЧЕСКИЕ АСПЕКТЫ БАЗИСНОЙ ТЕРАПИИ И ОЦЕНКА ЛЕКАРСТВЕННОЙ БЕЗОПАСНОСТИ

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АННОТАЦИЯ

Современное лечение сердечной недостаточности со сниженной фракцией выброса основано на четырёх базисных классах препаратов, каждый из которых независимо снижает смертность. В статье проведена клинико-фармакологическая оценка базисной терапии, последовательности и скорости её начала, а также вопросов безопасности в реальной практике. Быстрое начало и титрование в стационаре снизили 180-дневную композитную точку с 23,3% до 15,2%, тогда как данные регистров показывают, что целевые дозы всех классов получает лишь незначительная доля подходящих пациентов. Рассмотрены контроль калия и функции почек, ведение гипотензии и исключение препаратов, ухудшающих прогноз.

Ключевые слова: *хроническая сердечная недостаточность; сниженная фракция выброса; базисная терапия; сакубитрил/валсартан; ингибиторы SGLT2; титрование доз; гиперкалиемия; лекарственная безопасность.*

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) is one of the few chronic conditions in which pharmacotherapy changes prognosis rather than merely relieving symptoms. Over three decades the treatment paradigm has evolved from sequential addition of drugs to the concept of four foundational classes — renin–angiotensin system inhibitors (preferably an angiotensin receptor–neprilysin inhibitor), beta-blockers, mineralocorticoid receptor antagonists and sodium–glucose cotransporter 2 inhibitors — each of which reduces mortality independently of the others [1, 2].

The clinical problem has therefore shifted from what to prescribe to how quickly and how completely the regimen can be implemented in an individual patient. This shift places clinical pharmacology at the centre of heart failure care: the limiting factors are now hypotension, renal dysfunction, hyperkalaemia, polypharmacy and adherence. The aim of this article is to assess foundational therapy from the standpoints of efficacy, implementation and medication safety.

MATERIALS AND METHODS

This is an analytical review. Searches were performed in PubMed/MEDLINE, the Cochrane Library and Scopus using the terms “heart failure reduced ejection fraction”, “guideline-directed medical therapy”, “sacubitril valsartan”, “SGLT2 inhibitor heart failure”, “up-titration”, “hyperkalaemia heart failure”. Priority was given to pivotal randomized controlled trials, contemporary clinical practice guidelines and registry data reflecting real-world implementation.

RESULTS AND DISCUSSION

Evidence base for the four foundational classes

Each foundational class rests on a dedicated outcome trial. PARADIGM-HF established the superiority of sacubitril/valsartan over enalapril for cardiovascular death and heart failure hospitalization [3]. EMPHASIS-HF demonstrated benefit from eplerenone in patients with mild symptoms [4]. DAPA-HF and EMPEROR-Reduced independently established the benefit of SGLT2 inhibition irrespective of diabetes status [5, 6], and DELIVER subsequently extended this benefit to mildly reduced and preserved ejection fraction [7]. Modelling of the combined effect indicates that comprehensive therapy with all classes yields a substantially longer event-free survival than conventional treatment [8]. A comparative summary is given in Table 1.

Table 1

Foundational drug classes in heart failure with reduced ejection fraction

Class	Principal mechanism	Key safety issues	Practical notes
ARNI (sacubitril/valsartan) or ACE inhibitor / ARB	Blockade of the renin–angiotensin system with concurrent potentiation of natriuretic peptides	Symptomatic hypotension, hyperkalaemia, decline in renal function, angio-oedema	A 36-hour washout is mandatory when switching from an ACE inhibitor; never combine ARNI with an ACE inhibitor
Beta-blockers (bisoprolol, carvedilol, metoprolol succinate, nebivolol)	Attenuation of sympathetic overactivity and reverse remodelling	Bradycardia, transient worsening of symptoms at initiation, bronchospasm	Start at a low dose in a euvolaemic patient; double the dose at intervals of no less than two weeks
MRA (spironolactone, eplerenone)	Blockade of aldosterone-mediated fibrosis and sodium retention	Hyperkalaemia, deterioration of renal function, gynaecomastia (spironolactone)	Contraindicated if potassium exceeds 5.0 mmol/L; check potassium and creatinine at 1 and 4 weeks
SGLT2 inhibitors (dapagliflozin, empagliflozin)	Natriuresis, improved myocardial energetics and renal protection	Genital mycotic infection, volume depletion, rare euglycaemic ketoacidosis	No dose titration required; may be started early irrespective of diabetes status
Additional agents (ivabradine, vericiguat, digoxin, iron)	Heart-rate reduction, stimulation of soluble guanylate cyclase, symptom control	Bradycardia, hypotension, digoxin toxicity in renal impairment	Considered only after the four foundational classes have been implemented

Speed of implementation: from sequential to rapid initiation

The 2023 focused update reaffirmed that all four classes should be established as early as possible rather than sequentially over months [9]. The decisive evidence comes from STRONG-HF, in which high-intensity care with rapid up-titration and close follow-up after an acute heart failure admission reduced the 180-day composite of heart failure readmission or all-cause death from 23.3% to 15.2% [10]. These results are shown in Figure 1.

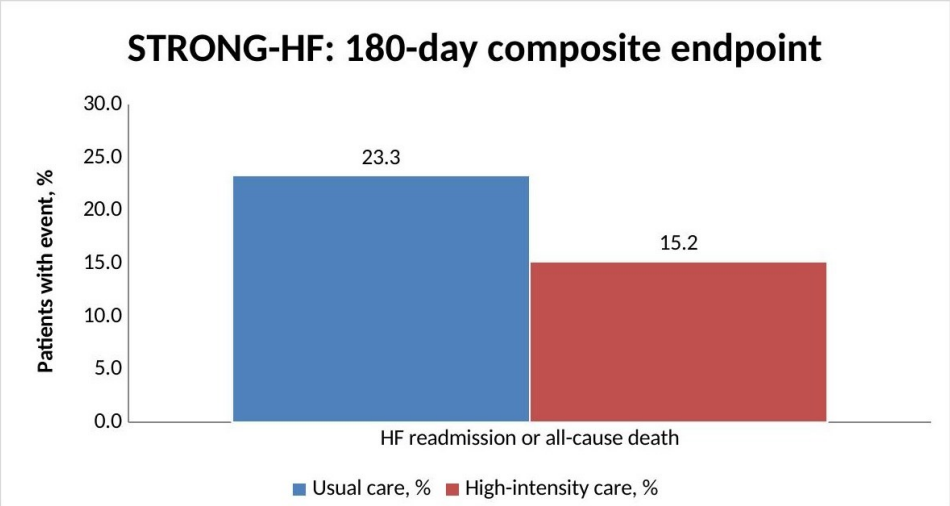

Figure 1. Primary composite endpoint at 180 days in the STRONG-HF trial.

The contrast with routine practice is striking. In the CHAMP-HF registry only a small minority of eligible outpatients received target doses of all indicated classes simultaneously, and a substantial proportion received no dose of one or more classes at all [11]. The bottleneck is therefore implementation rather than evidence, and the principal levers are structured follow-up, protocol-driven titration and explicit documentation of the reason whenever a class is omitted.

Medication safety and monitoring

Three safety domains dominate. The first is potassium and renal function: the combination of a renin–angiotensin system inhibitor with an MRA increases the risk of hyperkalaemia, which is the commonest reason for premature discontinuation of prognostically important therapy. A modest early rise in creatinine after initiation is expected and should not by itself prompt withdrawal. The second is blood pressure: asymptomatic hypotension is not an indication to stop foundational therapy, whereas symptomatic hypotension should first prompt reduction of diuretics and of drugs prescribed for other indications. The third is heart rate and rhythm, particularly during beta-blocker titration.

Equally important is what must not be co-prescribed. Non-steroidal anti-inflammatory drugs promote sodium retention and renal dysfunction; non-dihydropyridine calcium channel blockers are negatively inotropic; thiazolidinediones and certain antiarrhythmic agents worsen outcomes. Because patients with heart failure are typically older and multimorbid, the burden of potentially serious drug–drug interactions is high in this population [12], and several commonly used agents are listed as potentially inappropriate in older adults [13].

Practical recommendations

All four foundational classes should be initiated during the index hospitalization or at the first outpatient contact, starting at low doses rather than delaying initiation for the sake of higher doses of a single class. An SGLT2 inhibitor requires no titration and can be started immediately. Potassium and creatinine should be checked one and four weeks after initiation or dose change of a renin–angiotensin system inhibitor or MRA. Follow-up visits should be scheduled at short intervals during the titration phase, in line with the STRONG-HF model. Every omitted class should be documented with its reason, and the omission should be revisited at each subsequent visit. Finally, the whole medication list should be reviewed for agents that worsen prognosis, consistent with the principles of the global medication safety agenda [14].

CONCLUSION

Foundational therapy for heart failure with reduced ejection fraction is now defined, and its components act additively on mortality. The decisive clinical question has moved from selection to implementation: rapid, protocol-driven initiation and up-titration reduced the 180-day risk of readmission or death by approximately one third, whereas registry data demonstrate that most eligible patients remain undertreated. Safe implementation depends on a small number of concrete practices — early initiation of all four classes at low doses, scheduled biochemical monitoring, tolerance of asymptomatic hypotension and modest creatinine rise, reduction of diuretics before foundational drugs, and systematic removal of co-medication that worsens prognosis. Clinical pharmacology thus determines not whether the evidence is applied, but how completely.

REFERENCES

1. McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Böhm, M., Burri, H., Butler, J., Čelutkienė, J., Chioncel, O., Cleland, J. G. F., Coats, A. J. S., Crespo-Leiro, M. G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A. W., Jaarsma, T., Jankowska, E. A., … Skibelund, A. K. (2021). 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal, 42(36), 3599–3726. https://doi.org/10.1093/eurheartj/ehab368

2. Heidenreich, P. A., Bozkurt, B., Aguilar, D., Allen, L. A., Byun, J. J., Colvin, M. M., Deswal, A., Drazner, M. H., Dunlay, S. M., Evers, L. R., Fang, J. C., Fedson, S. E., Fonarow, G. C., Hayek, S. S., Hernandez, A. F., Khazanie, P., Kittleson, M. M., Lee, C. S., Link, M. S., … Yancy, C. W. (2022). 2022 AHA/ACC/HFSA guideline for the management of heart failure. Circulation, 145(18), e895–e1032. https://doi.org/10.1161/CIR.0000000000001063

3. McMurray, J. J. V., Packer, M., Desai, A. S., Gong, J., Lefkowitz, M. P., Rizkala, A. R., Rouleau, J. L., Shi, V. C., Solomon, S. D., Swedberg, K., & Zile, M. R. (2014). Angiotensin–neprilysin inhibition versus enalapril in heart failure. New England Journal of Medicine, 371(11), 993–1004. https://doi.org/10.1056/NEJMoa1409077

4. Zannad, F., McMurray, J. J. V., Krum, H., van Veldhuisen, D. J., Swedberg, K., Shi, H., Vincent, J., Pocock, S. J., & Pitt, B. (2011). Eplerenone in patients with systolic heart failure and mild symptoms. New England Journal of Medicine, 364(1), 11–21. https://doi.org/10.1056/NEJMoa1009492

5. McMurray, J. J. V., Solomon, S. D., Inzucchi, S. E., Køber, L., Kosiborod, M. N., Martinez, F. A., Ponikowski, P., Sabatine, M. S., Anand, I. S., Bělohlávek, J., Böhm, M., Chiang, C.-E., Chopra, V. K., de Boer, R. A., Desai, A. S., Diez, M., Drozdz, J., Dukát, A., Ge, J., … Langkilde, A. M. (2019). Dapagliflozin in patients with heart failure and reduced ejection fraction. New England Journal of Medicine, 381(21), 1995–2008. https://doi.org/10.1056/NEJMoa1911303

6. Packer, M., Anker, S. D., Butler, J., Filippatos, G., Pocock, S. J., Carson, P., Januzzi, J., Verma, S., Tsutsui, H., Brueckmann, M., Jamal, W., Kimura, K., Schnee, J., Zeller, C., Cotton, D., Bocchi, E., Böhm, M., Choi, D.-J., Chopra, V., … Zannad, F. (2020). Cardiovascular and renal outcomes with empagliflozin in heart failure. New England Journal of Medicine, 383(15), 1413–1424. https://doi.org/10.1056/NEJMoa2022190

7. Solomon, S. D., McMurray, J. J. V., Claggett, B., de Boer, R. A., DeMets, D., Hernandez, A. F., Inzucchi, S. E., Kosiborod, M. N., Lam, C. S. P., Martinez, F., Shah, S. J., Desai, A. S., Jhund, P. S., Belohlavek, J., Chiang, C.-E., Borleffs, C. J. W., Comin-Colet, J., Dobreanu, D., Drozdz, J., … Langkilde, A. M. (2022). Dapagliflozin in heart failure with mildly reduced or preserved ejection fraction. New England Journal of Medicine, 387(12), 1089–1098. https://doi.org/10.1056/NEJMoa2206286

8. Vaduganathan, M., Claggett, B. L., Jhund, P. S., Cunningham, J. W., Pedro Ferreira, J., Zannad, F., Packer, M., Fonarow, G. C., McMurray, J. J. V., & Solomon, S. D. (2020). Estimating lifetime benefits of comprehensive disease-modifying pharmacological therapies in patients with heart failure with reduced ejection fraction: A comparative analysis of three randomised controlled trials. The Lancet, 396(10244), 121–128. https://doi.org/10.1016/S0140-6736(20)30748-0

9. McDonagh, T. A., Metra, M., Adamo, M., Gardner, R. S., Baumbach, A., Böhm, M., Burri, H., Butler, J., Čelutkienė, J., Chioncel, O., Cleland, J. G. F., Crespo-Leiro, M. G., Farmakis, D., Gilard, M., Heymans, S., Hoes, A. W., Jaarsma, T., Jankowska, E. A., Lainscak, M., … Rosano, G. M. C. (2023). 2023 focused update of the 2021 ESC guidelines for the diagnosis and treatment of acute and chronic heart failure. European Heart Journal, 44(37), 3627–3639. https://doi.org/10.1093/eurheartj/ehad195

10. Mebazaa, A., Davison, B., Chioncel, O., Cohen-Solal, A., Diaz, R., Filippatos, G., Metra, M., Ponikowski, P., Sliwa, K., Voors, A. A., Edwards, C., Novosadova, M., Takagi, K., Damasceno, A., Saidu, H., Gayat, E., Pang, P. S., Celutkiene, J., & Cotter, G. (2022). Safety, tolerability and efficacy of up-titration of guideline-directed medical therapies for acute heart failure (STRONG-HF): A multinational, open-label, randomised trial. The Lancet, 400(10367), 1938–1952. https://doi.org/10.1016/S0140-6736(22)02076-1

11. Greene, S. J., Butler, J., Albert, N. M., DeVore, A. D., Sharma, P. P., Duffy, C. I., Hill, C. L., McCague, K., Mi, X., Patterson, J. H., Spertus, J. A., Thomas, L., Williams, F. B., Hernandez, A. F., & Fonarow, G. C. (2018). Medical therapy for heart failure with reduced ejection fraction: The CHAMP-HF registry. Journal of the American College of Cardiology, 72(4), 351–366. https://doi.org/10.1016/j.jacc.2018.04.070

12. Guthrie, B., Makubate, B., Hernandez-Santiago, V., & Dreischulte, T. (2015). The rising tide of polypharmacy and drug-drug interactions: Population database analysis 1995–2010. BMC Medicine, 13, 74. https://doi.org/10.1186/s12916-015-0322-7

13. American Geriatrics Society Beers Criteria Update Expert Panel. (2023). American Geriatrics Society 2023 updated AGS Beers Criteria for potentially inappropriate medication use in older adults. Journal of the American Geriatrics Society, 71(7), 2052–2081. https://doi.org/10.1111/jgs.18372

14. World Health Organization. (2017). Medication without harm: WHO global patient safety challenge. World Health Organization. https://www.who.int/initiatives/medication-without-harm