PHARMACIA

Pharmacia 71: 1–6
DOI 10.3897/pharmacia.71.e115952

Research Article

Cost-effectiveness of cardiomyopathy ambulatory care with sacubitril/valsartan vs standard therapy after COVID-19 in Kazakhstan

Dana Dadanbekova[1], Kairat Zhakipbekov[1], Almat Kodasbayev[1], Ubaidilla Datkhayev[1], Guenka Petrova[2], Konstantin Tachkov[2]

1 *NPJSC "S. D. Asfendiyarov Kazakh National Medical University", Almaty, Kazakhstan*
2 *Medical University of Sofia, Faculty of Pharmacy, Sofia, Bulgaria*

Corresponding author: Guenka Petrova (gpetrova@pharmfac.mu-sofia.bg)

Received 18 November 2023 ♦ **Accepted** 11 January 2024 ♦ **Published** 8 February 2024

Citation: Dadanbekova D, Zhakipbekov K, Kodasbayev A, Datkhayev U, Petrova G, Tachkov K (2024) Cost-effectiveness of cardiomyopathy ambulatory care with sacubitril/valsartan vs standard therapy after COVID-19 in Kazakhstan. Pharmacia 71: 1–6. https://doi.org/10.3897/pharmacia.71.e115952

Abstract

The aim of this study is to evaluate the cost-effectiveness of 2 different therapies of cardiomyopathy (CM) after COVID -19. The focus of the study is fixed dose combination (FDC) of sacubitril/valsartan and standard therapy in Kazakhstan. This is written from the point of view of the health insurance institution.

Information for the age, gender, CM therapy, number of hospitalizations, COVID-19 infection, and past cardiovascular surgeries of 237 patients with incidents of CM which required a hospitalization after a COVID-19 infection was collected. Selected patients were divided into two groups: the cost of FDC and standard therapy and the annual cost of their therapy was calculated. The incremental cost-effectiveness ratio was calculated by dividing the cost of medication therapy by the number of hospitalizations between the two compared groups. Robustness of the results was tested with deterministic and probabilistic sensitivity analyses. The study was performed in City cardiology centre of Almaty in Kazakhstan during 2020–2022.

Results show that FDC is more costly but more effective, leading to fewer hospitalizations. ICER accounts for €-2,743.08 per hospitalization saved in the group on FDC vs standard of therapy.

Sacubitril/valsartan is cost-effective in ambulatory conditions in comparison with standard therapy of cardiomyopathy after COVID-19 leading to savings due to the decrease in the number of hospitalizations.

Keywords

Cardiomyopathy, cost-effectiveness, pharmacotherapy, sacubitril/valsartan, COVID-19

Introduction

Cardiomyopathies (CMs) are a heterogeneous group of pathologies characterized by structural and functional alterations of the heart described in the MOGE(S) classification of the American College of Cardiology/American Heart Association stage and New York Heart Association. (Ciarambino et al. 2021). There are around 620 million people living with heart and circulatory disease worldwide and this number has been rising due to changing lifestyles, an ageing and growing population, and improved survival rates from heart attacks and

strokes. Globally, it's estimated that 1 in 13 people are living with a heart or circulatory disease (British Heart Foundation 2023).

Medication for the treatment of CM involves a variety of therapeutic classes. Fixed dose combination (FDC) of sacubitril/valsartan is one of the most recommended choices, as well as a combination of mono products such as ACE inhibitors, diuretics, ca-channel antagonists, sartans, and beta blockers, depending on the involvement of different functions and concomitant diseases (Cooper et al. 2023). The cost-effectiveness of sacubitril/valsartan is studied in different settings for different population groups but rarely in low-income countries (Ramos et al. 2017; McMurray et al. 2018).

The main reason for hospital admission is heart failure diagnosed by signs and symptoms and demonstrated by at least one objective sign, such as pulmonary rales, peripheral oedema, congestion in a chest radiograph, or a third heart sound. Cost-effective management involves patients' education (Cline et al. 1998).

The Center for Disease Control (CDC 2023) in the United States has published a list of concomitant diseases associated with severe COVID-19 infections. These include cancer, chronic kidney disease, cardiovascular diseases (coronary heart disease, heart failure and/or cardiomyopathy) (Centers for Disease Control and Prevention 2023). A systematic review of the relation between CM and COVID-19 concluded that cardiac injury and cardiomyopathy were common conditions in patients with COVID-19. Authors suggested that cardiac damage should be considered in managing patients with COVID-19. (Omidi et al. 2021). Therefore, medication treatment of CM after COVID-19 should be as effective as possible to prevent further patient deterioration and for low-income countries should also be cost-effective.

In the large, randomized, double-blind PARADIGM-HF trial, sacubitril/valsartan resulted in a significant improvement in morbidity and mortality in patients with CM, and reduced the risk of CV death or heart failure, hospitalization, as well as all causes of death McMurray et al. (2014). These results situated sacubitril/valsartan as a safe and effective therapy, especially for patients in the high risk category such as COVID-19 patients.

In Kazakhstan sacubitril/valsartan was relatively newly introduced in the practice, and up until that point, standard therapy involved a combination of mono products from different classes. To date, there haven't been studies in Kazakhstan on the cost-effectiveness of ambulatory therapy of patients with cardiomyopathy after COVID-19 and it was this that provoked our interest in this study (Schreiber et al. 2022).

The objective of this study is to evaluate the cost-effectiveness of 2 different therapies of CM after COVID -19. It compares the FDC of sacubitril/valsartan and standard therapy in Kazakhstan. This paper is written from the point of view of the health insurance institution.

Materials and methods

Design of the study

This is an ambispective, observational study of 237 patients with CM which required hospitalization after COVID-19 infection. The prospective part of the study encompasses the recording of patients' characteristics and therapy during their admittance and hospital stay, while the retrospective part was performed when hospital records were revised, and matching patients were further analyzed. The prospective part covers the period 2018–2022 and the retrospective part covers the period 2020–2022.

Hospital records of all patients admitted into the hospital between 2018–2022 were systematized and out of them were extracted those admitted after COVID-19 announcement with CM and proven or suspicious COVID-19 infection. This study is part of a larger project and covers a period longer than COVID-19 infection, but for the purposes of the current manuscript we extracted records only for the period of COVID-19 infection (2020–2022).

For the selected patients in question information was systematized on admittance date, hospital stay, ambulatory therapy, age, gender, CM therapy, the number of hospitalizations during 2020–2022, COVID-19 infection, and past cardiovascular surgeries. A history of previous cardiac surgery was only noted as a patient's characteristic.

Records of selected patients were separated into two groups: on standard therapy and on FDC therapy with newly introduced sacubitril/valsartan.

The study was performed in City cardiology center of Almaty in Kazakhstan. The Ethical committee of the Kazakh national medical university approved the retrospective part of the study (decision № 1365 from 27.04.2022) and the selection and analysis of records started at the end of 2022.

Cost analysis

For every patient we calculated the yearly cost of medication for ambulatory therapy after their discharge. The standard therapy includes the following medicines: captopril, ramipril, carvedilol, bisoprolol, spironolactone, digoxin, furosemide in different combinations. The FDC therapy includes the sacubitril/valsartan combined with either carvedilol, bisoprolol, spironolactone, digoxin, or furosemide.

The cost of therapy was calculated by multiplying the average daily prescribed dose for every patient with the number of days on therapy.

Prices of medicines were derived from the national positive drug list in 2021 at reimbursement level (Order of the Minister of Health of the Republic of Kazakhstan 2021). The prices of medicines did not change during 2018–2022 which allows us to use the latest issued order.

The cost of medication therapy was calculated in national currency (Tenge) at the exchange rate of 508 Tenge = 1€.

Cost-effectiveness analysis (CEA)

The number of hospitalizations, appearing as consequence of a patient's status worsening, was chosen as the outcome measure. It is a short-term outcome reflecting the hospital as source of data.

The incremental cost-effectiveness ratio (ICER) was calculated by dividing the cost of medication therapy by the number of hospitalizations between the two compared alternatives following the formula (Drummond et al. 2005).

ICER = ((Cost of FDC – Cost of standard therapy)/(Average number of hospitalizations per patients on FDC – Average number of hospitalizations per patients on standard therapy)).

One-way sensitivity analysis was performed by varying the cost and results within +/-30% interval. A probabilistic Monte-Carlo sensitivity analysis was also conducted. Since both costs and results were expected to have negative values, a gamma distribution was used for both. 1000 simulations were conducted, analyzing the incremental cost-effectiveness ratio, as well as the percentage of simulations, where FDC reduced number of hospitalizations.

Results

Patients' characteristics

Both groups differ in terms of patient number (Table 1). A majority of patients received FDC therapy, which could be attributed to the physicians' attempt to provide better therapy. This is also probably due to the fact that almost half of the patients in both groups survived cardiac surgery. The proportion of male to female is almost 3 to 1, with average age between 57 and 65 years of age. Although during hospitalization most of the patients declared that they had signs of COVID-19 infection, only 12% to 29% presented clinical proof during that time.

Table 1. Patient demographic.

Characteristic	FDC group	Standard therapy group
N (%)	207 (87.34%)	30 (12.66%)
Male (%)	66.2%	76.7%
Female (%)	33.8%	23.3%
Average age (SD)	58 (13.6)	65 (15.3)
Clinically proven COVID-19	12%	29%
Surgery (n and %)	76 (36.7%)	15 (50%)

Cost analysis

Medication therapy and its cost are described in Table 2.

Patients on FDC therapy are using one or 2 additional medicines. When there are 2 diuretics, spironolactone is prescribed as salvaging therapy in case of severe hypertension and furosemide was used as maintenance therapy. Patients on standard therapy received on average four medicines. Depending on the additional medicines the cost of FDC group varies between 263,234.35 and 301,274.65 tenge (518–593 €). The cost of standard therapy is nearly five times lower.

Table 2. Yearly medication therapy cost.

Prescribed medicines	N of patients	Yearly cost of FDC group in national currency (€)	Yearly cost of standard therapy group national currency (€)
Bisoprolol Spironolactone, Digoxin, Furosemide	17		60,254.2 (118.61 €)
Captopril Carvedilol Spironolactone, Digoxin, Furosemide	6		90,228 (117.61 €)
Ramipril Carvedilol Spironolactone, Digoxin, Furosemide	7		97,214.1 (191.37€)
Sacubitril/Valsartan Bisoprolol, Eplerenone, Digoxin	6	266,968.3 (525.53 €)	
Sacubitril/Valsartan, Bisoprolol, Spironolactone	33	263,234.35 (518.18 €)	
Sacubitril/Valsartan, Bisoprolol, Spironolactone, Furosemide	60	280,126.55 (551.43 €)	
Sacubitril/Valsartan, Carvedilol, Spironolactone, Furosemide	75	301,274.65 (593.06 €)	
Sacubitril/Valsartan, Spironolactone, Furosemide	33	274,987.35 (541.31 €)	
Average yearly cost (SD)		283,895.3 (558.85€) (12,533.22)	74 872,9 (147.38 €) (16,033.5)

Cost-effectiveness analysis

Patients on FDC therapy have fewer hospitalizations, although the difference is minimal. The incremental cost-effectiveness ratio is negative since patients on FDC save hospitalization costs to health insurance institutions (Table 3). The additional cost saved from hospitalizations accounts for 1,393,483Tenge (2,743€). We can conclude that the FDC is a cost-effective therapy because the GDP per capita in Kazakhstan accounts for 10 380 $US [12].

Table 3. Incremental cost-effectiveness analysis.

Group	Yearly cost (Tenge) (SD)	Average number of post COVID-19 hospitalizations (SD)	Δ C	Δ E	ICER (ΔC/ΔE)
Standard	74,872.9 (16,033.5)	3.25 (0.84)			
FDC	283,895.3 (12,533.22)	3.1 (0.75)	209,022.4	-0.15	- 1,393,482.7

The sensitivity analysis identifies that the cost of therapy is the key variable in CEA that might influence the incremental cost-effectiveness ration (ICER) (Fig. 1).

The probabilistic sensitivity analysis shows that for most of the time, FDC combinations will reduce the number of hospitalizations after COVID-19. Approximately 60.4% of the point-estimate results show negative results, which means a lower number of hospitalizations. In 39.6% of the cases, the standard therapy will have lower costs, but also better results (i.e reduce the number of hospitalizations). There are approximately 3 results, where the FDC therapy

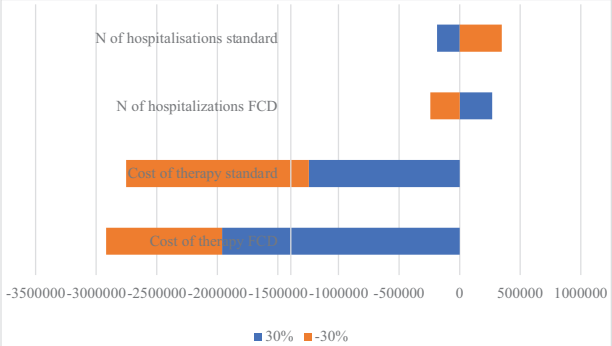

Figure 1. Deterministic cost-effectiveness analysis.

will have lower costs, but also lower results (Fig. 2). Almost always the FDC result will have higher costs; however all ICER estimates are below the threshold value of 5 080 000 Tenge (10 000€), with the average ICER being 208 122.7 Tenge (410€) (WHO 2023).

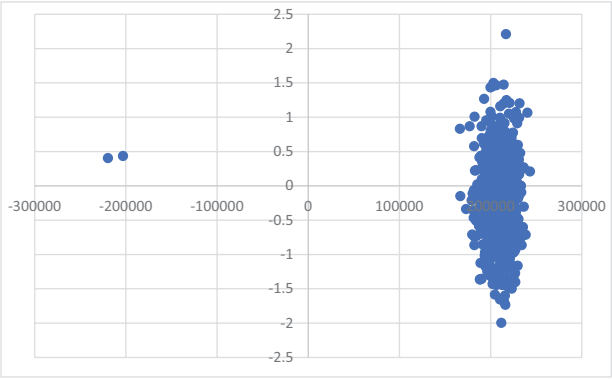

Figure 2. Probabilistic analysis.

Discussion

In this study we attempt to analyze the cost-effectiveness of including FDC sacubitril/valsartan to the MC therapy after COVID-19 for patients in Kazakhstan. To the best of our knowledge this is the first study from a national perspective exploring the cost effectiveness of FDC sacubitril/valsartan for the patients with CM in Kazakhstan. It shows that the therapy of patients with CM is cost-effective and saves hospitalizations. The strength of our study lies in the fact that it is observing hospitalized patients with clinically proven COVID-19 infection, or with symptoms after their discharge from hospital. Cline et al. analyzed the cost-effectiveness of an educational program for 190 patients with heart failure and found out that education and self-management reduce hospitalizations.

Several cost-effectiveness analyses of the FDC sacubitril/valsartan have been performed in different country settings. According to McMurrey in the UK settings, the cost per quality-adjusted life-year (QALY) gained for sacubitril/valsartan, was £17 100 (€20 400) in comparison with enalapril for a prevented death; in Denmark, the ICER for sacubitril/valsartan was Kr 174 000 (€22 600), while in Colombia, the ICER was COP$39.5 million (€11 200) per QALY gained in preventing one death case in comparison with enalapril. (McMurray et al. 2018). In the same study was also compared the hospitalization rate for enalapril (n = 3.5) and sacubitril/valsartan (between n = 3.2 and n = 3.01) which resembles our study.

Ramos et al. found out that the incremental cost-effectiveness ratio was €17,600 per quality adjusted life-year (QALY) in the Netherlands. The comparison was made between sacubitril/valsartan and enalapril (Ramos et al. 2017).

Ademi et al. assessed the cost-effectiveness of sacubitril/valsartan compared to ACEIs for the treatment of individuals with chronic heart failure from the perspective of the Swiss health care system (Ademi et al. 2017). They found out that the sacubitril/valsartan strategy showed a decrease in the number of hospitalizations (and lifetime hospital costs thus leading to an ICER of CHF 25 684 per QALY).

The study by Thomas A. et al. compared sacubitril/valsartan and enalapril for treating patients with heart failure and reduced ejection fraction (Gaziano et al. 2016). They chose as main treatment outcomes hospitalizations, and quality-adjusted life-years (QALYs) and calculated the costs, and incremental costs per QALY gained. They modelled that there would be 220 fewer hospital admissions per 1000 patients with HF treated with sacubitril/valsartan vs enalapril over a period of 30 years, thus leading to incremental cost-effectiveness ratio (ICER) of $45 017 per QALY. Results for the same study performed by Jordan B King produced similar results, finding that ICER of $50,959 per QALY over a 40-year period (King et al. 2016). The same methodology for Singapore health care setting led to ICER of SGD 41,019 (USD 30,354) to SGD 1,447,103 (USD 1,070,856) per QALY gained (Liang et al. 2018). Evidently, the FDC combination reduces the number of hospitalizations, which has also been noted in our study, and although the differences might be minimal, the evidence supports this conclusion.

Two other studies performed systematic reviews (Rezapour A.) involving 15 studies comparing sacubitril/valsartan and enalapril in terms of reduced mortality and hospitalization rate. Sacubitril/valsartan produced higher annual and total lifetime costs for all countries under consideration (Thailand, Germany, and USA) and was considered a cost-effective alternative (Proudfoot et al. 2013). The second systematic review was performed by Proudfoot (Rezapour et al. 2022) and focused on modelling studies. It included 44 cost-effectiveness models and 5 HTAs from European decision makers, n = 20; North and South Americas, n = 14; Asia and Australia, n = 10]. Authors concluded sacubitril/valsartan to be a cost-effective therapy in 37/41 models in chronic heart failure patients and 2/3 models in hospitalized patients.

Similar to other studies, we also found that sacubitril/valsartan is a cost-effective therapy in comparison for standard of care in Kazakhstan. The difference is that we focused on patients with CM, and right across the spectrum of diseases involving heart failure. Although the cost of therapy is not reimbursed, our analysis shows that in

the majority of cases, the FDC combination will result in fewer hospitalizations, and this will always be under the estimated Threshold for Kazakhstan.

The already pointed systematic review on the relation between CM and COVID-19, which concluded that cardiac injury and cardiomyopathy were common conditions in patients with COVID-19, proves our suggestion that the observed patients are at high risk, and it is worth investing in their therapy (Omidi et al. 2021).

The limitation of our study is in the small sample size of the patients on standard therapy. We can assume that physicians prefer to prescribe sacubitril/ valsartan, as more effective therapy to as many patients as possible because of persistent or past COVID-19 infection. We attempted to reduce this limitation by applying a probabilistic sensitivity analysis, to further strengthen the evidence. The other limitation is in the lack of information about the patients' adherence to therapy which might have deteriorated due to high co-payment.

The system of compulsory social health insurance (CSHI) in Kazakhstan has been in effect since January 1, 2020. Basic principles of the CSHI system are social orientation. The state pays contributions for 11 million citizens from 15 preferential categories. There is joint responsibility shared between the state, employers, and citizens responsible for the health of the population and providing equal access to medical care. Every insured person has the right to the necessary amount of medical care, regardless of the number of paid contributions, and the money goes to the patient. The patient can express a preference for a particular medical establishment to receive medical services as long as it is a provider of the Fund. The Fund pays medical establishments for medical services only after monitoring the quality and volume of medical care provided, as well as medicines included in the Positive drug list (Katsaga et al. 2012).

Conclusion

Sacubitril/valsartan is cost-effective in ambulatory conditions in comparison with standard therapy of cardiomyopathy after COVID-19, leading to savings due to the decrease in the number of hospitalizations.

Acknowledgements

This study was funded by the European Union Next-Generation EU, through the National Recovery and Resilience Plan of the Republic of Bulgaria, project N BG-RRP-2.004-0004-C01.

References

Ademi Z, Pfeil A, Hancock E, Trueman D, Haroun R, Deschaseaux C, Schwenkglenks M (2017) Cost-effectiveness of sacubitril/valsartan in chronic heart-failure patients with reduced ejection fraction. Swiss Medical Weekly 147: w14533. https://doi.org/10.4414/smw.2017.14533

British heart foundation (2023) Global heart and circulatory diseases factsheet. https://www.bhf.org.uk/-/media/files/for-professionals/research/heart-statistics/bhf-cvd-statistics-global-factsheet.pdf?rev=-e61c05db17e9439a8c2e4720f6ca0a19&hash=6350DE1B2A19D-939431D876311077C7B

CDC [Centers for Disease Control and Prevention] (2023) People who are at higher risk for severe illness. https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/people-at-higher-risk.html

Ciarambino T, Menna G, Sansone G, Giordano M (2021) Cardiomyopathies: An overview. International Journal of Molecular Sciences 22(14): e7722. https://doi.org/10.3390/ijms22147722

Cline C, Israelsson B, Willenheimer R (1998) Cost effective management programme for heart failure reduces hospitalisation. Heart 80(5): 442–446. https://doi.org/10.1136/hrt.80.5.442

Cooper L, McKenna W, Dardas T (2023) Definition and classification of the cardiomyopathies. UpToDate. https://www.uptodate.com/contents/definition-and-classification-of-the-cardiomyopathies?-source=mostViewed_widget

Drummond M, Sculpher M, Torrance G, O'Brien BJ, Stoddart GL (2005) Methods for the economic evaluation of health care programmes (3rd edn.). Oxford University Press. https://doi.org/10.1093/oso/9780198529446.001.0001

Gaziano TA, Fonarow GC, Claggett B, Chan WW, Deschaseaux-Voinet C, Turner SJ, Rouleau JL, Zile MR, McMurray JJ, Solomon SD (2016) Cost-effectiveness analysis of sacubitril/valsartan vs enalapril in patients with heart failure and reduced ejection fraction. JAMA Cardiol 1(6): 666–672. https://doi.org/10.1001/jamacardio.2016.1747

Katsaga A, Kulzhanov M, Karanikolos M, Rechel B (2012) Kazakhstan: Health system review. Health Systems in Transition 14(1): 1–154.

King J, Shah R, Bress A, Nelson R, Bellows B (2016) Cost-effectiveness of sacubitril-valsartan combination therapy compared with enalapril for the treatment of heart failure with reduced ejection fraction. JACC Heart Failure 4(5): 392–402. https://doi.org/10.1016/j.jchf.2016.02.007

Liang L, Wu D, Aziz M, Wong R, Sim D, Leong K, Wei Y, Tan D, Kwong Ng (2018) Cost-effectiveness of sacubitril/valsartan versus enalapril in patients with heart failure and reduced ejection fraction. Journal of Medical Economics 21(2): 174–181. https://doi.org/10.1080/13696998.2017.1387119

McMurray JJV, Packer M, Desai, Akshay S, Gong J, Lefkowitz MP, Rizkala AR, Rouleau JL, Shi VC, Solomon SD, Swedberg K, Zile MR (2014) Angiotensin–neprilysin inhibition versus enalapril in heart failure. New England Journal of Medicine 371(11): 993–1004. https://doi.org/10.1056/NEJMoa1409077

McMurray J, Trueman D, Hancock E, Cowie M, Briggs A, Taylor M, Mumby-Croft J, Woodcock F, Lacey M, Haroun R, Deschaseaux C (2018) Cost-effectiveness of sacubitril/valsartan in the treatment of heart failure with reduced ejection fraction. Heart 104(12): 1006–1013. https://doi.org/10.1136/heartjnl-2016-310661

Omidi F, Hajikhani B, Kazemi SN, Tajbakhsh A, Riazi S, Mirsaeidi M, Ansari A, Ghanbari Boroujeni M, Khalili F, Hadadi S, Nasiri MJ (2021) COVID-19 and cardiomyopathy: A systematic re-

view. Frontiers in Cardiovascular Medicine 8: e695206. https://doi.org/10.3389/fcvm.2021.695206

Order of the Minister of Health of the Republic of Kazakhstan (2021) No. KR DSM -77 "About the approval of marginal prices for the trade name of medicines and medical devices within the guaranteed volume of free medical care and (or) in the system of compulsory social health insurance". https://adilet.zan.kz/rus/docs/V2100023886

Proudfoot C, Gautam R, Cristino J, Agrawal R, Thakur L, Tolley K (2023) Model parameters influencing the cost-effectiveness of sacubitril/valsartan in heart failure: evidence from a systematic literature review. The European Journal of Health Economics 24(3): 453–467. https://doi.org/10.1007/s10198-022-01485-3

Ramos I, Versteegh M, de Boer R, Koenders J, Linssen G, Meeder J, Rutten-van Mölken M (2017) Cost effectiveness of the angiotensin receptor neprilysin inhibitor Sacubitril/Valsartan for patients with chronic heart failure and reduced ejection fraction in the Netherlands: A country adaptation. Value in Health 20(10): 1260–1269. https://doi.org/10.1016/j.jval.2017.05.013

Rezapour A, Azari S, Arabloo J, Kolivand P, Behzadifar M, Omidi N, Asiabar A, Saberian P, Pourasghari H, Bragazzi NL, Mehrani M, Shahi S, Tajdini M (2022) Cost-effectiveness of sacubitril/valsartan compared with enalapril in patients with heart failure with reduced ejection fraction: A systematic review. The Journal of Tehran University Heart Center 17(4): 168–179. https://doi.org/10.18502/jthc.v17i4.11603

Schreiber A, Elango K, Soussu C, Fakhra S, Asad S, Ahsan C (2022) COVID-19 induced cardiomyopathy successfully treated with tocilizumab. Case Reports in Cardiology 2022: e9943937. https://doi.org/10.1155/2022/9943937

Spertus J, Jones P, Sandhu A, Arnold S (2020) Interpreting the Kansas City cardiomyopathy questionnaire in clinical trials and clinical care: JACC state-of-the-art review. Journal of the American College of Cardiology 76(20): 2379–2390. https://doi.org/10.1016/j.jacc.2020.09.542

WHO (2023) New cost-effectiveness updates from WHO-CHOICE. https://www.who.int/news-room/feature-stories/detail/new-cost-effectiveness-updates-from-who-choice