A SYSTEMATIC REVIEW: MODEL-BASED COST-EFFECTIVENESS ANALYSES OF GUIDELINE-DIRECTED DISEASE-MODIFYING MEDICAL THERAPIES FOR HEART FAILURE WITH REDUCED EJECTION FRACTION

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BACKGROUND

- The four pillars of heart failure (HF) therapeutics, which comprised angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), angiotensin receptor neprilysin inhibitor (ARNI), beta-blocker (BB), mineralocorticoid receptor agonist (MRA) and sodium-glucose co-transporter-2 inhibitor (SGLT-2i), have come to the forefront for the management of heart failure with reduced ejection fraction (HFrEF) due to their proven benefits in reducing mortality and hospitalisation.[1-2]
- However, timely initiation of novel therapeutics such as ARNI and SGLT-2i in routine clinical practice remains a clear gap worldwide and the barriers include limited access and high drug costs.[3]
- To understand the value of HF therapeutics and assist decision-making in the management of HFrEF, many cost effectiveness analyses (CEAs) have been conducted using economic models with varying structures and assumptions.

OBJECTIVE

This systematic review aims to critically appraise and summarise the model-based CEAs of guideline-directed medical therapies (GDMT) for HFrEF.

METHODS

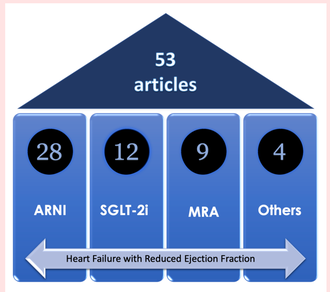
- A systematic search was performed on MEDLINE, Embase, Scopus, NHSEED, HTA and the Cochrane Library. Grey literature was searched using INAHTA, ProQuest and Informit. Backward citation tracking was conducted.
- The key inclusion criteria were all economic evaluations published from Jan 2010 - April 2022 that compared the costs and outcomes of GDMT for HFrEF using a decision-analytic model.
- The primary outcome was the incremental cost-effectiveness ratios (ICER) in terms of cost/quality-adjusted life year.
- Articles that reported cost-effectiveness estimates in several countries and against different comparators were disaggregated to better reflect the ICERs when different model structures and assumptions are applied in different healthcare settings and allow comparison.

RESULTS

- A total of 53 articles comparing the costs and outcomes of GDMT for HRrEF were identified in this review.
- While 45 were published articles in journals, 8 were health technology assessment (HTA) reports.
- When the studies that reported ICERs for multiple countries were disaggregated, 67 CEAs were retrieved.
- When the studies that reported ICERs of studied drugs against different comparators were disaggregated, 76 CEAs were retrieved.

76 ECONOMIC EVALUATIONS COMPARED THE COST-EFFECTIVENESS OF

- ARNI (sacubitril/valsartan) against ACEI (n=26)
- ARNI (sacubitril/valsartan) against ARB (n= 6)
- ARNI (sacubitril/valsartan) early initiation against late initiation (n=3)
- ARNI (sacubitril/valsartan) against implantable cardioverter defibrillator (n=1)
- ARNI (sacubitril/valsartan) against SGLT-2i (n=2)
- SGLT-2i (dapagliflozin) against standard of care (n=16)
- SGLT-2i (empagliflozin) against standard of care (n=8)
- MRA (eplerenone) against standard of care (n=10)
- Others* (n=4)



*Others include 1) ACEI+BB+MRA vs ACEI+BB therapy and diuretics only; 2) RAASi vs without RAASi; 3) Patiromer, spironolactone, and ACEI vs ACEI only; 4) Genetically targeted treatment with bucindolol vs carvedilol

MODEL STRUCTURES

- Markov model (44/53, 83%) was the most commonly used model, followed by discrete-event simulation (8/53, 15%) and decision tree (1/53, 2%).
- 70% (36/53) models specified the use of a lifetime horizon, with a monthly cycle length (31/53, 59%).
- 92% (49/53) of the included studies evaluated the cost-effectiveness of HF therapeutics from the healthcare system and payers' perspectives and only 3% (2/53) included indirect costs such as productivity loss in the analyses.
- While most economic evaluations were conducted in high-income countries (56/67, 84%), there has been an increasing number of studies from upper-middle-income countries (3/67, 4%) and lower-middle-income countries (8/67, 12%) since 2015.

FIGURE 1: TYPES OF DECISION-ANALYTICAL MODELS FOR HEART FAILURE WITH REDUCED EJECTION FRACTION

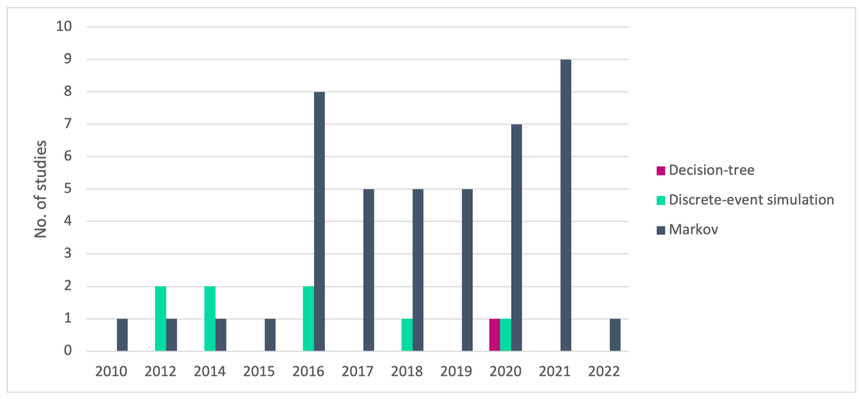
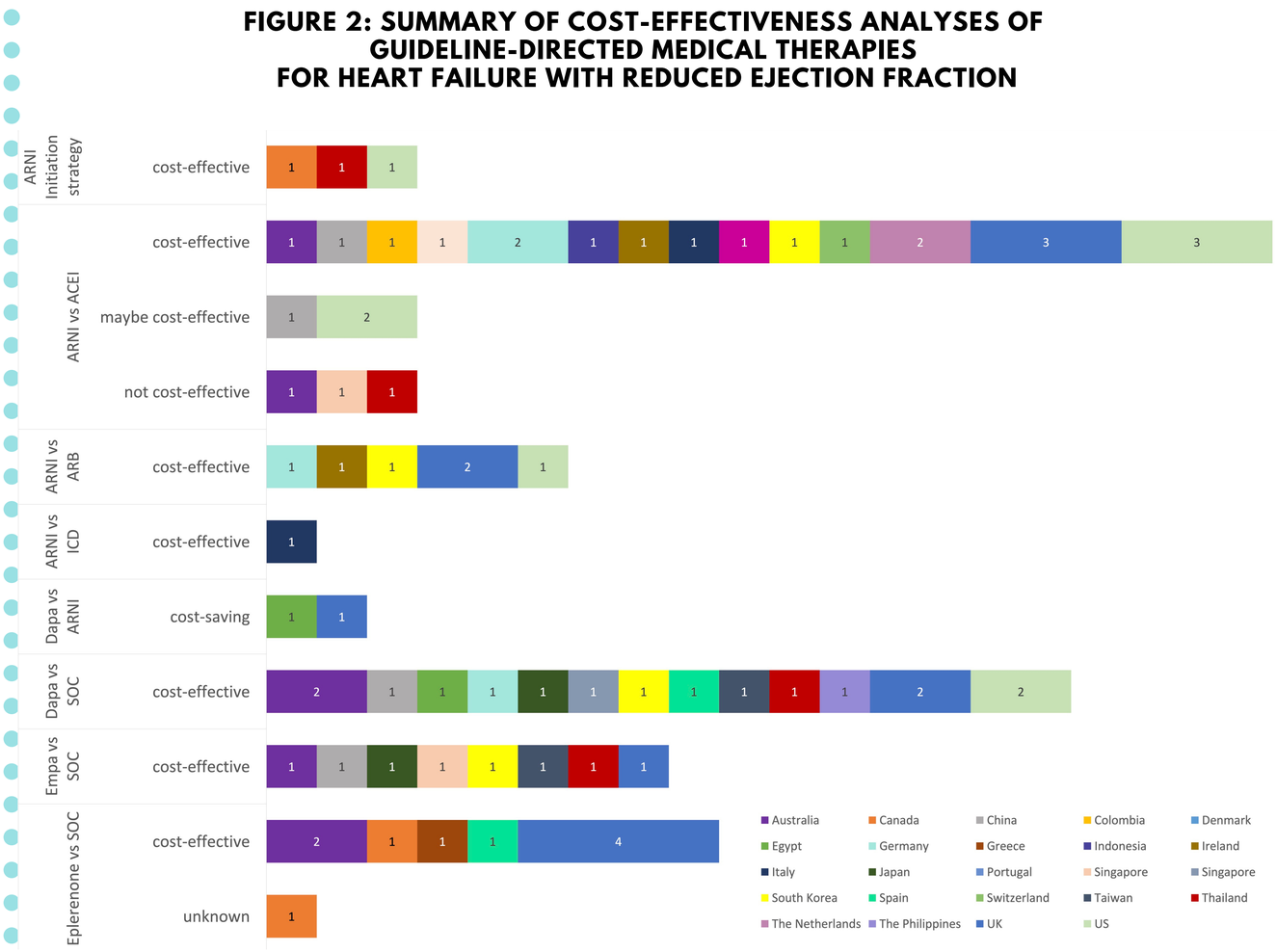


FIGURE 2: SUMMARY OF COST-EFFECTIVENESS ANALYSES OF GUIDELINE-DIRECTED MEDICAL THERAPIES FOR HEART FAILURE WITH REDUCED EJECTION FRACTION



ARNI

- Compared with ACEI, 22 CEAs (77%) demonstrated that ARNI was cost-effective. The 3 countries that reported ARNi being not cost-effective were Asia-Pacific countries, namely Singapore, Thailand and Australia.
- Compared with ARB, all 6 CEAs showed that ARNI was cost-effective.
- Comparing de novo and late initiation of ARNI, 3 studies showed that de novo initiation of ARNI was more cost-effective.
- Lastly, one CEA reported that ARNI dominates implantable cardioverter defibrillator (ICD) in HFrEF.

SGLT-2I

- Dapagliflozin and empagliflozin were more cost-effective compared to the standard of care from different healthcare settings.
- The ICERs for SGLT-2i were generally smaller compared to ARNI due to its lower drug costs.
- This is consistent with two cost-minimisation analyses that demonstrated SGLT-2i (dapagliflozin) being more cost-saving compared to ARNI, assuming similar benefits of both therapeutics.

MRA

- 90% (9/10) CEAs reported that eplerenone was cost-effective compared to the standard of care (SOC).

DISCUSSION

- Most CEAs demonstrated that the newer therapeutics (ARNI, SGLT-2i and eplerenone) are more cost-effective compared to the standard of care for HFrEF from different healthcare systems and payer's perspective.
- Given the differences in model structures and assumptions, variations in population characteristics and uncertainties surrounding the input parameters, the cost-effectiveness estimates are highly heterogeneous and the transferability of the study conclusions to individual countries is questionable.
- Also, the conclusion of whether the intervention is more cost-effective compared to the comparator often relies on the willingness-to-pay threshold (WTP) of the payers.
- There is a need to conduct country-specific CEAs to inform resource allocation, particularly in low and upper-middle-income countries where the WTP threshold in these countries is often lower than the high-income countries.
- A transparent and explicit WTP threshold is important to allow the valuation of innovative therapeutics and assist price negotiation between the pharmaceutical industries and the payers, improving access to HFrEF therapeutics with proven clinical effectiveness.

CONCLUSION

Despite most CEAs demonstrating that the newer therapeutics (ARNI, SGLT-2i and eplerenone) are cost-effective for HFrEF, there is a need to conduct country-specific CEAs to inform resource allocation in the local context. A transparent and explicit WTP threshold is important for the valuation of innovative therapeutics.

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CONFLICT OF INTEREST:

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ABBREVIATIONS:

CEA: cost-effectiveness analyses; ACEI: angiotensin-converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor neprilysin inhibitor; BB: beta-blocker; MRA: mineralocorticoid receptor agonist; SGLT-2i: sodium-glucose co-transporter-2 inhibitor; Dapa: dapagliflozin; Empa: empagliflozin; ICD: implantable cardioverter defibrillator; SOC: standard of care; HF: heart failure; HFrEF: heart failure with reduced ejection fraction, GDMT: guideline-directed medical therapies; HTA: health technology assessment; WTP: willingness-to-pay threshold