

ORIGINAL ARTICLE

Guideline-based audit of the hospital management of heart failure with reduced ejection fraction

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Key words

heart failure, systolic, guideline adherence, evidence-practice gap.

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Received 22 March 2022; accepted 26 May 2022.

Abstract

Background: Heart failure is a major burden in Australia in terms of morbidity, mortality and healthcare expenditure. Multiple evidence-based therapies are recommended for heart failure with reduced ejection fraction (HFrEF), but data on physician adherence to therapy guidelines are limited.

Aim: To compare use of HFrEF therapies against current evidence-based guidelines in an Australian hospital inpatient population.

Methods: A retrospective review of patients admitted with a principal diagnosis of HFrEF across six metropolitan hospitals in Sydney, Australia, between January 2015 and June 2016. Use of medical and device therapies was compared with guideline recommendations using individual patient indications/contraindications. Readmission and mortality data were collected for a 1-year period following the admission.

Results: Of the 1028 HFrEF patients identified, 39 were being managed with palliative intent, leaving 989 patients for the primary analysis. Use of beta-blockers (87.7% actual use/93.6% recommended use) and diuretics (88.4%/99.3%) was high among eligible patients. There were large evidence-practice gaps for angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB; 66.4%/89.0%) and aldosterone antagonists (41.0%/77.1%). In absolute terms, use of these therapies each increased by over 11% from admission. Ivabradine (11.5%/21.2%), automated internal cardiac defibrillators (29.5%/66.1%) and cardiac resynchronisation therapy (13.1%/28.7%) were used in a minority of eligible patients. Over the 1-year follow-up period, the mortality rate was 14.8%, and 44.2% of patients were readmitted to hospital at least once.

Conclusion: Hospitalisation is a key mechanism for initiation of HFrEF therapies. The large evidence-practice gaps for ACEI/ARB and aldosterone antagonists represent potential avenues for improved HFrEF management.

Introduction

There are over 400 000 Australians currently living with heart failure.¹ This condition is associated with profound

reductions in quality of life and significant healthcare expenditure.² Despite treatment advances, the estimated 5-year mortality rate for heart failure patients remains between 30% and 60%.^{3–5}

While limited evidence exists for the treatment of heart failure with preserved ejection fraction beyond supportive care, multiple evidence-based treatments exist for heart failure with reduced ejection fraction (HFrEF).^{1,3} Optimal use of multiple concomitant therapies has been shown to reduce mortality and rehospitalisation rates in HFrEF patients in clinical

Abbreviations: ACEI, angiotensin converting enzyme inhibitor; AICD, automated internal defibrillator; ARB, angiotensin II receptor blocker; CRT, cardiac resynchronisation therapy; HFrEF, heart failure with reduced ejection fraction; LVEF, left ventricular ejection fraction

Funding: RPAH Research Prize, NHMRC Program grant (AK).

Conflict of interest: None.



trial settings, leading to the formulation of prescribing guidelines to direct their use.^{6,7} Poor physician adherence to these guidelines in ‘real world’ international cohorts has been associated with increased mortality and rehospitalisation rates.^{7,8}

Data assessing physician adherence to HFrEF therapy guidelines in Australia are limited. Previous studies have described the prevalence of therapy use and been compared with other international cohorts to infer adherence.^{9,10} However, this approach is unable to account for differences in the indications and contraindications of therapies between individual patients. The true magnitude of evidence-practice gaps, the difference between guideline recommended and actual use of HFrEF therapies, therefore remains undefined in Australia.

Here, we describe the first comprehensive audit of HFrEF therapy use in Australia, which uses a combination of contemporary local and international guidelines, representing current best practice, to quantify potential treatment gaps in HFrEF therapy use across the inpatient population of several major metropolitan hospitals.

Methods

Ethics approval for this study was granted by the RPA Zone Human Research Ethics Committee (LNR/18/RPAH/184). All research was conducted in accordance with the Declaration of Helsinki.

The medical records of adult patients with a primary diagnosis of heart failure and admitted into one of six participating hospitals in Sydney, Australia, between January 2015 and June 2016 were reviewed for eligibility. The participating sites were Bankstown-Lidcombe, Canterbury, Concord, Liverpool, Royal Prince Alfred and Westmead Hospitals. Inclusion criteria were a left ventricular ejection fraction (LVEF) $\leq 40\%$ (or described as at least ‘mildly to moderately’ impaired). Patients were excluded if they did not survive the admission, were being managed with palliative intent or if a list of discharge medications was unavailable.

Data were obtained through patients’ electronic medical records. All collected parameters were the most recently available, prior to discharge. In the event of multiple admissions during the study entry period, data from the latest admission were used. Where patients did not have an echocardiogram performed during their stay, the most recent data were obtained from either a previous admission or report from an outpatient clinic. Follow-up data were obtained for patients who were admitted to any hospital within the Sydney or South Western Sydney local health districts within 1 year of

Table 1 Eligibility criteria for heart failure with reduced ejection fraction therapies

Therapy	LVEF (%)	Additional criteria
Beta-blocker	≤ 40	HR ≥ 50 b.p.m., no severe asthma
ACEI or ARB	≤ 40	eGFR ≥ 30 , serum $[K^+]$ ≤ 5.5 mM
Neprilysin inhibitor†	≤ 40	eGFR ≥ 30 , serum $[K^+]$ ≤ 5.4 mM‡ (must be stabilised on ACEI/ARB therapy)
Diuretic	–	Serum $[Na^+]$ ≥ 130 mM, serum $[K^+]$ ≥ 3.0 mM
Aldosterone antagonist	≤ 35	eGFR ≥ 30 , serum $[K^+]$ ≤ 5.0 mM
Ivabradine	≤ 35	HR ≥ 77 b.p.m., sinus rhythm, no heart block‡
AICD	≤ 35	‡
CRT	≤ 35	QRS > 150 ms or QRS > 120 ms with LBBB‡

†Currently available only in combination with valsartan.

‡Receiving beta-blocker and ACEI/ARB therapy (unless contraindicated). Eligibility criteria as per major society guidelines, adapted from Chia et al. (2016).

ACEI, angiotensin-converting enzyme inhibitor; AICD, automated internal cardiac defibrillator; ARB, angiotensin II receptor blocker; CRT, cardiac resynchronisation therapy; eGFR, estimated glomerular filtration rate; HR, heart rate; LBBB, left bundle branch block; LVEF, left ventricular ejection fraction.

discharge. These data included the principal diagnosis, the use of HFrEF therapies and patient survival.

Eligibility was assessed for the following HFrEF therapies: beta-blockers, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB), neprilysin inhibitors, diuretics, aldosterone antagonists, ivabradine, automated internal cardiac defibrillators (AICD) and cardiac resynchronisation therapy (CRT). Indications and contraindications for each therapy (Table 1) were based on Australian and international society guidelines, reviewed by Chia et al.⁶ Patients were also considered to be eligible for a therapy if they were already receiving it and regarded to be ineligible for a therapy where any additional contraindication was stated or identified in the records. Where LVEF was reported qualitatively, ‘mild to moderate’ impairment was taken to equate to a LVEF of 40%, ‘moderate’ impairment to 35% and ‘severe’ impairment to $<30\%$. An evidence-practice gap was defined as the absolute difference in proportion of patients receiving a particular therapy at discharge to that recommended by guidelines, based on individual patient indications and contraindications. Continuous variables are expressed as median (interquartile range (IQR)). Statistical comparisons are by Chi-squared or Mann–Whitney *U*-test, as appropriate.

Results

Between January 2015 and June 2016, a total of 3809 individual patients was admitted with a primary diagnosis of heart failure across the six participating hospitals. Three hundred and forty-eight patients did not survive the admission. Of the surviving patients, 2422 had heart failure with preserved ejection fraction and were ineligible for inclusion. Thirty-four of the remaining 1034 HFrEF patients were being managed with palliative intent and excluded. A total of 989 HFrEF patients was thus eligible for inclusion in the present study.

Table 2 Baseline and admission characteristics (*n* = 989)

Characteristic	<i>n</i> (%) or median (IQR)
Sex	
Male	728 (73.6)
Female	261 (26.4)
Age (years)	73 (63–82)
Index heart failure admission	235 (23.8)
Left ventricular ejection fraction (%)	
36–40	140 (14.2)
30–35	387 (39.1)
<30	462 (46.7)
Cardiovascular history	
Ischaemic heart disease	559 (62.3)
Percutaneous coronary intervention	272 (27.5)
Coronary artery bypass graft	298 (30.2)
Cerebrovascular accident	147 (14.9)
Peripheral vascular disease	154 (15.6)
Atrial fibrillation/flutter	503 (50.9)
Hypertension	723 (73.1)
Diabetes mellitus	523 (52.9)
Dyslipidaemia	58 (59.5)
Smoking status	
Non-smoker	159 (16.1)
Former smoker	261 (26.4)
Current smoker	124 (12.5)
Not recorded	445 (45.0)
Estimated glomerular filtration rate (mL/min/1.73 m ²)	
>90	91 (9.2)
60–90	295 (29.8)
30–59	443 (44.8)
<30	160 (16.2)
Admission pathway	
Emergency room	827 (83.6)
Interhospital transfer	72 (7.3)
Elective	47 (4.8)
Referred from consultant rooms	43 (4.3)
Length of stay (days)	6 (4–11)
Discharge destination	
Private residence	861 (87.1)
Interhospital transfer	65 (6.6)
Nursing home	53 (5.4)
Rehab	9 (0.9)

IQR, interquartile range.

Baseline characteristics of the study population are detailed in Table 2. Patients were predominantly male (73.6%), with a median age of 73 years (IQR 63–82). Approximately two-thirds (62.3%) of patients had ischaemic heart disease and 40.0% had a revascularisation procedure previously. Over one-fifth (23.8%) of patients did not have a documented prior history of heart failure. The majority (88.0%) of admissions were through the emergency department or urgent referral from consultant rooms. Median length of stay in hospital was 6 days (IQR 3–11), after which most (92.5%) patients were discharged back to the community.

Utilisation of evidence-based therapies

Utilisation of HFrEF therapies at admission and discharge is compared with guideline recommendations in Figure 1. The range of evidence-practice gaps between individual sites is shown in Figure 2. Hospitalisation resulted in large absolute increases in the use of beta-blockers, ACEI/ARB and diuretics, of between 16.5% and 20.8%. At discharge, the use of beta-blockers (87.7% actual/93.6% recommended) and diuretics (88.4%/99.3%) approximated that recommended by guidelines, whereas a large evidence-practice gap for ACEI/ARB (66.4%/89.0%) remained at discharge.

Patients not receiving one or more indicated mainstay medical therapies (beta-blockers, ACEI/ARB or aldosterone antagonists) were slightly older than those receiving all indicated therapies 75 (IQR 65–83) versus 72 years (IQR 61–82; *P* = 0.016). They were also more likely to be male (69.0% vs 60.6%; *P* = 0.005) and have an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m² (58.9% vs 48.7%; *P* = 0.001). There was a similar proportion of patients with an index heart failure admission in both groups (*P* = 0.123).

The majority (85.0%) of patients on beta-blocker therapy were receiving an agent with a demonstrated mortality benefit in HFrEF.⁶ A further 8.3% were receiving immediate-release metoprolol tartrate. The ratio of ACEI to ARB use was approximately five to one. Nearly all (99.5%) patients on a diuretic were receiving frusemide, with 4.0% of patients receiving multiple diuretics concurrently. Mean daily dosing of commonly used agents is shown in Table 3.

No patients were receiving a neprilysin inhibitor. Although approved for use, the drug did not yet qualify for government subsidy during the study entry period. A neprilysin inhibitor was indicated for 42.8% of patients at discharge. This would increase to 57.9% after the Pharmaceutical Benefits Scheme required stabilisation period on an ACEI/ARB.

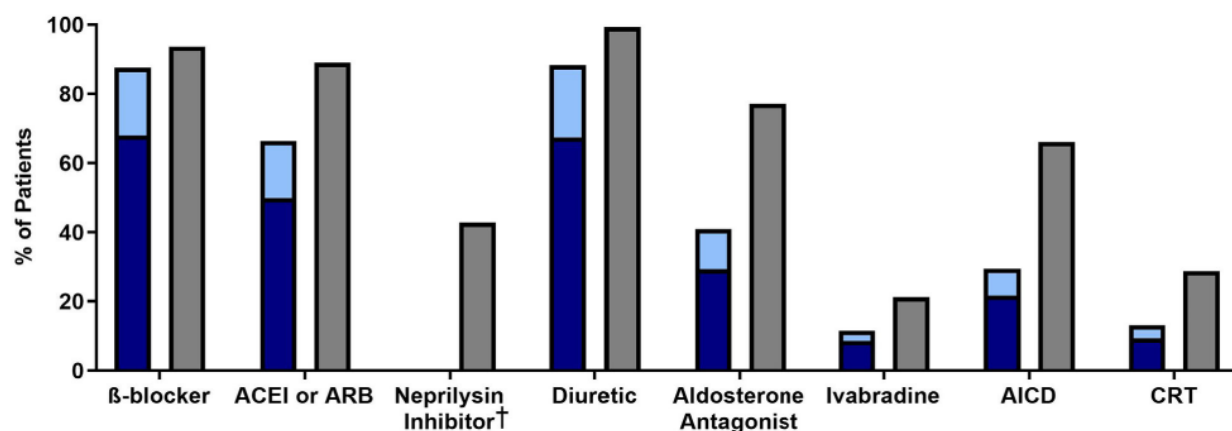


Figure 1 Comparison between actual and recommended (grey) use of therapies for heart failure with reduced ejection fraction ($n = 989$). Actual use of therapies is subdivided into use prior to admission (dark blue) and that initiated during the admission (light blue). (■), On therapy prior to admission; (▒), therapy commenced during admission; (■), recommended use of therapy. ACEI, angiotensin-converting enzyme inhibitor; AICD, automated internal cardiac defibrillator; ARB, angiotensin II receptor blocker; CRT, cardiac resynchronisation therapy.

Despite an absolute increase in the use of aldosterone antagonists of 11.6%, just over half of eligible patients were receiving this therapy at the time of discharge (41.0%/77.1%). Spironolactone accounted for nearly all (94.3%) of aldosterone antagonist use. Ivabradine use was uncommon and prescribed to approximately half of eligible patients (11.5%/21.2%).

Rates of both AICD (29.5%/66.1%) and CRT use (13.1%/28.7%) were less than half of that recommended by guidelines. Approximately two-thirds (67.2%) of AICD were in patients with an ischaemic cardiomyopathy. For patients with newly inserted devices, the median age was 68 years (IQR 57–77).

Documented contraindications for therapies beyond those covered already by our eligibility criteria (Table 1)

Table 3 Daily doses of common mainstay medical therapies at discharge

Agent	Mean daily dose (95% CI) (mg)
Beta-blocker	
Bisoprolol	5.2 (4.8–5.5)
Carvedilol	17.3 (15.0–19.5)
Metoprolol succinate	137.3 (93.5–181.2)
Nebivolol	4.6 (4.0–5.2)
ACEI	
Perindopril	4.4 (4.1–4.7)
Ramipril	3.9 (3.4–4.4)
ARB	
Candesartan	9.4 (7.4–11.5)
Irbesartan	194.5 (160.3–228.7)
Spironolactone	24.1 (22.6–25.7)

ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CI, confidence interval.

were rare, being noted for only 3.5% of all patients. They were most common for ACEI/ARB (2.1%), beta-blockers (0.9%) and loop diuretics (0.7%).

Patients with a new diagnosis of heart failure were more likely to not receive a beta-blocker despite an indication for one as compared with those with a pre-existing diagnosis (6.7% vs 3.3% of eligible patients; $P = 0.036$). For ACEI/ARB and aldosterone antagonists the trend was reversed, with those with a pre-existing heart failure diagnosis approximately twofold (15.5% vs 30%; $P < 0.001$) and sevenfold (5.5% vs 39.4%; $P = 0.002$) more likely to have not received the respective therapy despite guideline recommendation. There

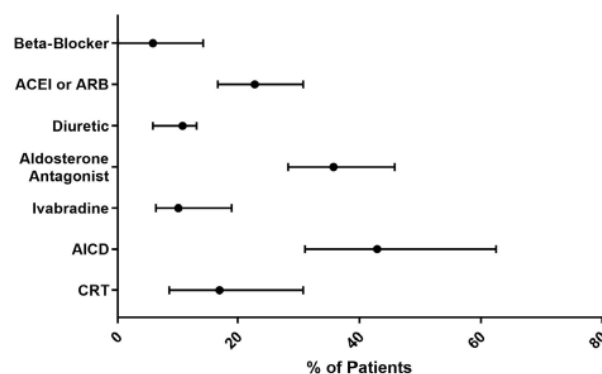
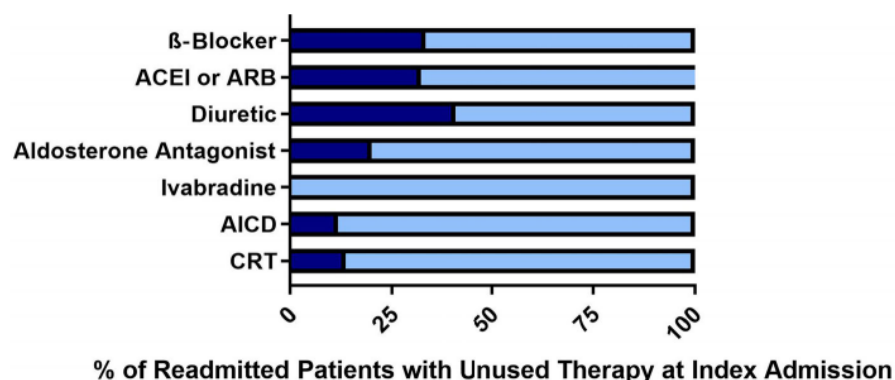


Figure 2 Variation in treatment gaps between sites by individual therapy. Graph shows treatment gap of all sites combined and error bars show the range of treatment gaps by each individual site. ACEI, angiotensin-converting enzyme inhibitor; AICD, automated internal cardiac defibrillator; ARB, angiotensin II receptor blocker; CRT, cardiac resynchronisation therapy.

Figure 3 Changes to therapeutic gaps in the year following discharge for readmitted patients. Patients who were readmitted and had been commenced on a previously unused therapy (dark blue) and patients readmitted and still not commenced on an unused therapy (light blue). (■), Commenced on therapy; (□), not commenced on therapy. ACEI, angiotensin-converting enzyme inhibitor; AICD, automated internal cardiac defibrillator; ARB, angiotensin II receptor blocker; CRT, cardiac resynchronisation therapy.



were few differences between the use of HFrEF therapies between patients with different ejection fractions. Those with a moderately reduced LVEF (30–35%) were more likely to have not received an aldosterone antagonist (56.5% vs 44.7% of eligible patients; $P = 0.002$), AICD (77.0% vs 57.3%; $P < 0.001$) or CRT (70.2% vs 52.7%; $P = 0.048$), compared with those with a severely reduced LVEF (<30%).

Follow-up period

In the year after patients were discharged, there was a mortality rate of 14.8%. Readmission was common, with 44.2% of patients returning to hospital. Multiple readmissions in the follow-up period was common, with one-fifth (19.6%) of all patients being readmitted twice or more. Over two-thirds (67.9%) of readmissions were due to heart failure. Despite readmission, the evidence-practice gaps identified in the study entry period tended to persist throughout the follow-up period (Fig. 3).

Discussion

The present study is the first comprehensive audit of physician adherence to HFrEF therapy guidelines in Australia, accounting for individual patient indications and contraindications. This enabled estimation of evidence-practice gap sizes for specific therapies, highlighting potential avenues to improve HFrEF management.

HFrEF therapy use across the six participating facilities was similar between sites and to the statewide trends reported previously in the NSW HF Snapshot study, suggesting generalisability to other inpatient HFrEF populations in Australia.¹⁰ Comorbidities were common in our study population, with a majority of patients having diabetes, atrial fibrillation/flutter and at least moderate kidney disease (eGFR <60 mL/min/1.73 m²). Reassuringly, a

similar burden of comorbidities has been reflected in the participants of clinical trials for HFrEF therapies.¹¹

Guideline adherence for beta-blockers was high, with an evidence-practice gap of less than 6%. However, of those receiving a beta-blocker, 15% were receiving an agent without a demonstrated benefit in HFrEF,⁶ of which immediate-release metoprolol tartrate was the most common. This is despite trial data showing statistical equivalence to placebo and inferiority to carvedilol in terms of mortality risk.^{12,13} This is in contrast to slow-release metoprolol succinate, which appears to have a similar mortality benefit to other heart failure-specific beta-blockers.¹⁴

The large evidence-practice gap in ACEI/ARB use of 22.6% may be partly explained by undocumented contraindications. Excepting cough, ACEI were not tolerated by approximately 9% of HFrEF patients in the prospective QUALIFY global survey, as compared with 2% in our retrospective cohort.¹⁵ However, this is unlikely to completely account for difference in ACEI/ARB use in our study (66%) as compared with international cohorts (78–90%).^{8,15,16} Other potential explanations might include a local reluctance to initiate an ‘antihypertensive therapy’ in normotensive HFrEF patients, despite guidelines recommending therapy without reference to blood pressure apart from symptomatic hypotension.⁶

At discharge, 36% of patients did not receive an aldosterone antagonist despite being recommended for one, the largest evidence-practice gap of the medical therapies. This is in contrast to the high utilisation rates, 65–69%, reported in some international cohorts.^{8,15,17} The evidence-practice gap was particularly pronounced for patients with a pre-existing heart failure diagnosis who were more than sevenfold more likely than those with newly diagnosed heart failure to not receive an aldosterone antagonist, despite a guideline recommendation for one. This disparity could be partly explained by patients with pre-existing HFrEF having trialled and not tolerated an aldosterone antagonist prior to the study admission,

with intolerance accounting for 15% of non-use of these agents in QUALIFY.¹⁵

Low overall use of these aldosterone antagonists may stem in part from a perception that these agents have similar indications to loop and thiazide diuretics, despite evidence of robust improvements in HFrEF outcomes independent of fluid overload or having been previously reserved for treatment of more severe heart failure.^{17,18} Given the magnitude of the evidence-practice gap and low treatment cost, aldosterone antagonists are a particularly attractive area of focus to improve HFrEF management. The IMPROVE HF study demonstrated this could be readily achieved through practice improvement initiatives, with nearly a doubling of aldosterone antagonists use in an American cohort of nearly 35 000 patients over a 2-year period.¹⁶

For mainstay medical therapies, hospitalisation resulted in a substantial increase in therapy use and this trend has also been noted statewide.¹⁰ While the remaining evidence-practice gaps may reflect a reluctance to begin multiple therapies in an acute setting, the persistence of evidence-practice gaps in the follow-up period suggests that outpatient initiation of therapies is uncommon. This is further supported by a recent retrospective study by Sindone *et al.*, which found low use of guideline-recommended therapies in a large Australian outpatient cohort.¹

The mean doses achieved for most medical therapies was approximately half of the recommended target doses of current guidelines, similar to that seen in Australian HFrEF patients in the outpatient setting.^{1,18,19} While dose up titration is important to maximise clinical efficacy, current local and international guidelines do not recommend that up titration be prioritised over the introduction of additional agents.^{18–20} This focus on combination therapy might partly explain the lower doses achieved with HFrEF patients outside clinical trials. The stepwise introduction of combination therapy, which remains recommended by Australian, but no longer American or European guidelines, might also explain some of the apparent evidence-treatment gaps.^{18–20} However, the persistence of such gaps in readmitted patients suggests the magnitude of this effect is modest.

Device therapy use was comparable with other international cohorts, although only half that recommended by current guidelines.^{15,16} Increased device implantation may be an important focus for improving HFrEF management in Australia. For AICD, increased utilisation may be limited to the two-thirds of patients with an underlying ischaemic aetiology for their HFrEF, a consequence of the DANISH study that found no all-cause mortality benefit of AICD in non-ischaemic cardiomyopathy.²¹ While their subgroup analysis did suggest a

benefit in patients aged <59 years, only one-quarter of new device insertion in our cohort occurred in patients of a similar age range.

The 14.8% mortality rate in our study was comparable with other heart failure cohorts internationally.^{4,17,22,23} However, it was less than half of the mortality rate reported in a recent retrospective study of over 12 000 heart failure patients from regional New South Wales.²⁴ This discrepancy may be partly explained by their use of more comprehensive national registry data to ascertain mortality status and the inclusion of palliative patients, but the disparity remains striking. The authors also noted no improvement in 1-year mortality over the decade-long study period, despite an improvement nationally over the same period. Whether this is due to lower utilisation of HFrEF therapies in regional settings remains unclear and will be an important aim of future research.

The main limitation of this study was its retrospective nature and the resultant risk of overestimating evidence-practice gaps as a consequence of undocumented contraindications. However, this overestimation would have been limited for medical therapies as our therapy eligibility criteria accounted for the most common contraindications.¹⁵ The contribution of undocumented transient contraindications, such as acute kidney injury is unclear, but infrequent introduction of relevant therapies in the outpatient setting suggests their effect is limited. Overestimation in evidence-practice gap for device therapies may be more substantial, as important factors, such as New York Heart Association class, frailty and overall prognosis were not captured.

Data for rehospitalisation and mortality were dependent on electronic records from hospitals within affiliated local health districts. Some deaths and readmissions to external hospitals may therefore have not been accounted for. This might have weakened our capacity to detect changes in HFrEF therapy use in readmitted patients. However, given that readmission data were available for nearly half of the patients, the impact on our estimates is likely limited.

Conclusion

Evidence-practice gaps exist for multiple HFrEF therapies, particularly for ACEI/ARB and aldosterone antagonists. Hospitalisation appears to be a major route of therapy initiation, with recommended therapies infrequently being commenced in the year after discharge. Ensuring appropriate use of recommended therapies in both inpatient and outpatient settings is therefore essential to improving HFrEF management.

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