

Flexible diuretic regimens

Evidence check

14 August 2024

Rapid evidence checks are based on a simplified review method and may not be entirely exhaustive, but aim to provide a balanced assessment of what is already known about a specific problem or issue. This brief should not be a substitute for individual clinical judgement, nor is it an endorsed position of NSW Health.

Evidence check

Evidence check question

What is the ideal approach for furosemide titration for decongestion and prevention of dehydration in adults (over 18 years) with heart failure, in order to guide safe management by non-prescribing clinicians and patient self-management to stabilise symptoms?

Summary

- Flexible diuretic regimen refers to a pulmonary congestion management strategy in patients with chronic heart failure. It allows either the patient themselves or the healthcare provider to adjust the diuretic dosage based on change in body weight and relevant symptoms and signs, i.e. blood pressure and renal function, instead of having a fixed dosage.¹
- In this evidence check, the term 'diuretics' used throughout the document refers to loop diuretics only with a focus on furosemide; and is not inclusive of other types of diuretics such as mineralocorticoid receptor antagonists or thiazide diuretics.
- Evidence from clinical trials, observational studies and reviews suggest that flexible diuretic regimens in outpatient settings can be effective in reducing the rates of hospitalisation, readmission, emergency department visits, or clinical instability.¹⁻⁷
- Dosing optimisation strategies support individualised dosing regimens and using the lowest clinical effective dose to maintain the volume status.^{6, 8, 9}
- Several observational cohort studies and reviews suggest a dose-dependent association between diuretic use and worse outcomes such as worsened renal function, hospitalisation or mortality.¹⁰⁻¹⁴ In some studies, however, a direct cause-and-effect relationship is difficult to establish due to limitations in study designs.¹³⁻¹⁶

- Diuretic dosage intensification events are likely markers of disease severity rather than risk factors.^{6, 13, 15-17} Higher doses of diuretics may also lead to transient worsening of creatinine, but this does not lead to a long term reduction in kidney function.¹⁸
- Withdrawal of diuretics in clinically stable patients not at high risk of deterioration or on a lower baseline diuretic dose was found to be safe and feasible.^{5, 10, 13, 19, 20}
- Complementary tools to help monitor and guide the adjustment of the diuretic have also been experimented with and found to be useful in improving self-care behaviour.²¹

Flexible diuretic regimen

- In a 2021 randomised controlled trial, heart failure patients in the intervention group were instructed to follow a diuretic adjustment algorithm and received telephone support one to two times per week:
 - Compared to the control group whose diuretic dosage was adjusted at baseline only by a physician and who received no telephone support, the intervention group had reduced rates of readmission or emergency department visits for heart failure.²
- In another uncontrolled experimental study, a home diuretic protocol was found to be safe and feasible with high patient and clinical satisfaction.³ In this study, patients were instructed to double the oral diuretic dose if the patient gains two pounds overnight (~1kg) or five pounds (~2.3kg) over a week.³
- Implementation of a home-based tool for patients to adjust diuretic dosage and monitor symptoms has successfully reversed the weight gain in 45% cases after a sudden weight gain according to a retrospective chart review study from Sweden.⁴
- The National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand recommends that patients may increase the furosemide dose by 40mg daily if weight increases over 2kg in two days.²²
- The Heart Failure Association of the European Society of Cardiology position paper on self-care of heart failure (published in 2020) recommends that:
 - Patients who experience a sudden unexpected weight gain of >2kg in three days may adjust their diuretic dosage themselves or alert healthcare providers.⁵
 - Individualised information to support self-care management is warranted.⁵

Dose intensification

- A large-scale retrospective cohort study of 74,990 patients in Denmark found that intensification of oral diuretics was associated with a significantly increased mortality rate (at one-year: 18.0% after intensification event versus 10.4% in matched control).¹¹
- Similarly in a study from United States, oral diuretic dose intensification of any magnitude was associated with a higher number of heart failure hospitalisations, emergency department presentations and home visits, but not all-cause mortality.¹⁶
- In a small-scale retrospective cohort study of 560 patients, the dose-dependant crude association between higher doses of furosemide and mortality could be explained by patients' clinical

characteristics and disease severity. Therefore, the authors conclude the higher dose did not impair prognosis.¹⁵

Down-titration or withdrawal

- The European Society of Cardiology Heart Failure Long-Term (ESC-HF-LT) registry study of 8,130 outpatients found that outpatient loop diuretic increase (dose change = dose after index visit minus dose prior to visits; dose increase refers to when dose change is >0) was associated with a higher risk of worse outcomes. Dose decrease (dose change <0) was associated with better outcomes compared to the no change group.¹³ The following were associated with successful dose decrease:
 - Higher systolic blood pressure
 - Absence of:
 - sleep apnoea
 - peripheral congestion
 - moderate or severe mitral regurgitation¹³
- In a small sample sized study of 50 outpatients, loop diuretic down-titration was found to be feasible.²⁰
 - The patients had stable conditions without any sign of volume overload for three months.
 - Successful down-titration was defined “as a persistent dose reduction after 30 days without weight increase >1.5 kg or new-onset symptoms of worsening heart failure.”
 - Physical examination, transthoracic echocardiography and laboratory analysis had limited predictive capability to detect patients with down-titration success or failure.
 - Rather treating clinicians’ clinical judgement was reliable in predicting the down-titration success or failure.²⁰
- Similarly, a double-blind, multicentre, randomised controlled trial found that withdrawal of loop diuretics in clinically stable outpatients was safe and feasible.²³

Grey literature

- Guidelines included in this evidence check (see Table 2) generally recommend using the lowest diuretic dose to achieve and maintain euvolaemia in patients experiencing fluid congestion.^{22, 24-26}
- In outpatient settings, some guidelines recommend flexible diuretic regimens in which patients monitor their symptoms and weight change, and either adjust their oral diuretic dosage themselves based on a certain criterion or alert their healthcare providers.^{22, 26}
- The American College of Cardiology Expert Consensus Decision Pathway recommends a rescue dosing plan for heart failure patients discharged from the hospitals. It also recommends personalised triggers for increased diuretic therapy and prompts for contacting the clinician in the discharge regimen.¹⁸

Limitations

Only studies published since 2011 were included.

Background

Loop diuretics, such as furosemide, are the predominant choice of therapeutic diuretic agents in treating congestion (or fluid overload) in patients with heart failure.^{8, 9, 19}

Methods (see Appendix 1)

PubMed, Google and Google Scholar were searched on 30 August 2022. Key sources are detailed in the tables below.

Evidence tables

Table 1: Key peer-reviewed sources

Note some of the information is taken directly from the sources.

Source	Summary
Peer reviewed sources	
Effects of a diuretic adjustment algorithm protocol on heart failure admissions: A randomized clinical trial Feijo, et al. 2021 ²	• Study design: Randomised controlled trial • Intervention: The diuretic dose was adjusted according to the diuretic adjustment algorithm protocol and the patients received telephone calls for 30 days (see protocol below). • Protocol: The adjustment algorithm led to three differential pathways depending on daily weight change (≥ 1kg, expected weight, (≤ 1kg), incorporating assessment of signs and symptoms. • Conclusion: using the protocol improved the combined outcome in these outpatients, with favourable and significant results that included a reduction in heart failure (HF) admissions and in clinical instability.
Home diuretic protocol for heart failure: partnering with home health to improve outcomes and reduce readmissions Veilleux, et al. 2014 ³	• Study design: Uncontrolled interventional study • Intervention: A home-based tool designed to enhance self-care behaviour • Protocol: The protocol initiation criteria was a weight increase of two pounds (~ 1kg) overnight or five pounds in one week. • Conclusion: The MaineHealth Home Diuretic Program can be delivered effectively and safely to improve outcomes, reducing readmissions and allow patients to remain at home.

Table 2: Grey literature

Note: Some of the information is taken directly from the sources.

Source	Summary
Grey literature	
National Heart Foundation of Australia and Cardiac Society of Australia and New Zealand: Guidelines for the Prevention, Detection, and Management of Heart Failure in Australia 2018 Atherton, et al. 2018 ²²	• A diuretic should be considered in patients with heart failure and clinical symptoms, or signs of congestion, to improve symptoms and manage congestion. • Diuretics should be started at low dose and treatment adjusted according to clinical response. • Loop diuretics are generally favoured initially because they increase free water clearance and have a rapid onset of action. Start with oral furosemide (frusemide) 20–40mg daily or bumetanide (0.5–1.0mg daily). If more than 80mg daily furosemide (or >2mg daily bumetanide) is required, consider splitting doses (usually given as morning and midday doses). • Clinicians should regularly assess volume status and biochemistry (renal function, sodium and potassium) to adjust diuretic dose at 1–2 weeks and 6-monthly long term. Once a euvolaemic state has been achieved, aim to decrease the dose unless this has previously resulted in exacerbation of heart failure. • Patients may also be educated to adjust the dose of diuretic, e.g. increase furosemide (frusemide) dose by 40mg daily if weight increases over 2kg over two days.
2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure McDonagh, et al. 2021 ²⁶	• Loop diuretics are recommended to reduce the signs and/or symptoms of congestion in patients with Heart Failure reduced Ejection Fraction (HFrEF). • The quality of the evidence regarding diuretics is poor and their effects on morbidity and mortality have not been studied in randomised controlled trials. • The aim of diuretic therapy is to achieve and maintain euvolaemia with the lowest diuretic dose. • In some euvolaemic or hypovolaemic patients, the use of a diuretic drug might be reduced or discontinued. Patients should be trained to self-adjust their diuretic dose based on monitoring of symptoms and signs of congestion and daily weight measurements. • In the case of increasing dyspnoea or oedema or a sudden unexpected weight gain of >2kg in three days, patients may increase their diuretic dose and/or alert their healthcare team. • Practical guidance on the use of diuretics in patients with heart failure is provided in supplementary table 7 of this guideline.

Source	Summary
Grey literature	
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 Heidenreich, et al. 2022 ²⁵	- Diuretics should be prescribed to patients who have evidence of congestion or fluid retention. In any patient with a history of congestion, maintenance diuretics should be considered to avoid recurrent symptoms. - The treatment goal of diuretic use is to eliminate clinical evidence of fluid retention, using the lowest dose possible to maintain euvoemia. - With the exception of MRAs, the effects of diuretics on morbidity and mortality are uncertain. As such, diuretics should not be used in isolation but always combined with other Guideline Directed Medical Therapy for HF that reduces hospitalisations and prolongs survival. - In outpatients with HF, diuretic therapy is commonly initiated with low doses, and the dose is increased until urine output increases and weight decreases, generally by 0.5 to 1.0kg daily.
Chronic heart failure in adults: diagnosis and management NICE. 2018 ²⁷	- Diuretics should be routinely used for the relief of congestive symptoms and fluid retention in people with heart failure, and titrated (up and down) according to need following the initiation of subsequent heart failure therapies. - People who have heart failure with preserved ejection fraction should usually be offered a low to medium dose of loop diuretics (for example, less than 80mg furosemide per day). People whose heart failure does not respond to this treatment will need further specialist advice.
CCS/CHFS Heart Failure Guidelines Update: Defining a New Pharmacologic Standard of Care for Heart Failure With Reduced Ejection Fraction McDonald, et al. 2021 ²⁴	- Throughout the patient journey, nonpharmacologic therapies should be prescribed, along with judicious use of diuretics to maintain euvoemia. - If a drug with proven mortality or morbidity benefits does not appear to be tolerated (e.g. low blood pressure, low heart rate, or renal dysfunction), concomitant drugs (e.g. diuretics) with less proven benefit should be carefully reevaluated to determine whether their dose can be reduced or the drug discontinued. - Angiotensin receptor-neprilysin inhibitor (ARNI) might reduce diuretic requirements and diuretic dosing should be carefully evaluated when starting ARNI therapy. β-Blockers should be started at low doses and increased slowly (e.g. double the dose every 2-4 weeks). Transient fluid retention might occur with initiation or up titration of β-blockers and might require assessment of diuretic dosage (e.g. might consider deferring dosage reduction).

Source	Summary
Grey literature	
	- Careful attention to volume status is required when sodium glucose transport 2 (SGLT2) inhibitors, ARNIs, and loop diuretics are used in combination because of their concomitant effects to promote diuresis. Heart failure medication initiation and titration algorithm can be found on the Canadian Cardiovascular Society guideline resources webpage. guideline resources webpage.

Appendix 1: Methods

PubMed search terms

("heart failure"[MeSH Terms] OR "heart failure"[Title/Abstract]) AND ("patient education as topic"[MeSH Terms] OR "self management"[MeSH Terms] OR "self manag*" [Title/Abstract] OR "self monitor*" [Title/Abstract] OR "self-care"[Title/Abstract] OR "home"[Title/Abstract] OR "outpatient"[Title/Abstract]) AND ("diuretics"[Pharmacological Action] OR "diuretics"[MeSH Terms] OR "diuretics"[Title/Abstract] OR "furosemide"[Title/Abstract] OR "rescue dos*" [Title/Abstract] OR "flexible diuretic*" [Title/Abstract]) AND 2012/01/01:2022/12/31[Date - Publication] AND ("humans"[MeSH Terms] AND "english"[Language])

246 hits on 30 August 2022

Google search terms

Flexible diuretic regimen or protocol or algorithm

Inclusion and exclusion criteria

Inclusion	Exclusion
- Published in English - Published since 2011 Population: Adults (over 18 years) with heart failure Intervention: Oral furosemide titration Comparison: N/A or different regimen for titration Outcomes: decongestion and prevention of dehydration, hospitalisation, mortality or morbidity Study types: - Review studies with systematic search strategy and methods - Randomised or non-randomised controlled trials - Before and after studies, time series studies with or without a comparison group - Retrospective chart review studies - Interventional or evaluative studies presenting quantitative data - Evaluative studies with quantitative or qualitative	- Studies aimed to compare different diuretic agents and other supplementary agents - Not in English - Published prior to 2011 - Studies that do not meet Population, Intervention, Comparison, Outcomes and Study types (PICOS) criteria

Inclusion	Exclusion
assessment of outcomes with or without a comparison group ○ Grey literature such as guidelines and consensus statements	

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