Section: Miscellaneous

Original Research Article

TWICE-WEEKLY METOLAZONE THERAPY IN HEART FAILURE WITH REDUCED EJECTION FRACTION AND COMPLETE LEFT BUNDLE BRANCH BLOCK: A PROSPECTIVE INTERVENTIONAL CASE-STUDY

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ABSTRACT

Background: Heart failure with reduced ejection fraction (HFrEF) accompanied by complete left bundle branch block (LBBB) represents a high-risk subgroup characterized by recurrent congestion, frequent hospitalizations, and impaired functional capacity. Despite guideline-directed medical therapy, many patients remain symptomatic, particularly those who are not candidates for or decline device-based interventions. Sequential nephron blockade using thiazide-like diuretics such as metolazone may enhance diuretic responsiveness in such patients, but data on structured intermittent regimens remain limited. **Aim:** To evaluate the efficacy and clinical impact of twice-weekly metolazone therapy on hospital admissions, functional capacity, and symptomatic status in patients with HFrEF and complete LBBB. **Materials and Methods:** This prospective interventional case study was conducted across two cardiology centers between September 2023 and October 2025. A total of 37 patients with NYHA class III/IV HFrEF and complete LBBB were enrolled, including 30 patients with ischemic cardiomyopathy and 7 with non-ischemic dilated cardiomyopathy confirmed by normal coronary angiography. Patients were optimized on guideline-directed medical therapy and maximally tolerated torsemide prior to initiation of twice-weekly metolazone. Among them, 31 patients declined device-based therapies. Clinical outcomes assessed included frequency of hospital admissions, six-minute walk test (6MWT) distance, and changes in NYHA functional class over a follow-up period extending up to 14 months. **Results:** Twice-weekly metolazone therapy resulted in a significant reduction in hospital admissions, with a relative risk reduction of 0.73 (95% CI: 0.52–0.91) observed as early as one month after initiation and sustained throughout the follow-up period. A statistically significant decline in hospitalization frequency was noted ($p < 0.001$), with nearly three-quarters of patients experiencing reduced admission rates. Functional capacity improved substantially, with approximately two-thirds of patients demonstrating an increase of ≥30 meters in 6MWT distance ($p < 0.001$). Additionally, 70% of patients showed at least one-class improvement in NYHA functional status, indicating meaningful symptomatic benefit. Six deaths were recorded during the study period, with baseline clinical characteristics comparable to survivors. Importantly, enhanced diuresis achieved with metolazone was found to be independent of baseline serum creatinine levels, suggesting efficacy across a range of renal functions. **Conclusion:** Twice-weekly metolazone therapy, when added to optimized loop diuretic treatment, significantly reduces hospital admissions and improves functional capacity in patients with HFrEF and complete LBBB. This regimen provides effective additive diuresis and represents a practical therapeutic strategy, particularly in patients who are not undergoing device-based interventions. This study contributes novel clinical evidence supporting the use of intermittent metolazone in this high-risk population.

INTRODUCTION

Heart failure with reduced ejection fraction (HFrEF) remains a major global health challenge, associated with substantial morbidity, mortality, and recurrent hospitalizations despite advances in pharmacological and device-based therapies.[1] A particularly high-risk subset includes patients with electrical conduction abnormalities such as complete left bundle branch block (LBBB), which contributes to ventricular dyssynchrony, impaired cardiac efficiency, and progressive clinical deterioration. The presence of LBBB in HFrEF is not only a marker of advanced disease but also an independent predictor of worse outcomes, including increased hospitalization rates and reduced survival.[2]

Guideline-directed medical therapy (GDMT), incorporating agents such as angiotensin receptor-neprilysin inhibitors, beta-blockers, mineralocorticoid receptor antagonists, and sodium-glucose cotransporter-2 inhibitors, has significantly improved outcomes in HFrEF. However, persistent congestion remains a common clinical challenge, particularly in advanced stages of the disease.[3]

Loop diuretics such as torsemide are the cornerstone of volume management, yet diuretic resistance frequently develops, limiting their long-term efficacy. This resistance is often multifactorial, involving neurohormonal activation, altered renal perfusion, and adaptive changes in nephron sodium handling.[4]

Sequential nephron blockade, achieved by combining loop diuretics with thiazide or thiazide-like diuretics, has emerged as an effective strategy to overcome diuretic resistance. Metolazone, a thiazide-like diuretic with potent distal tubular action, enhances natriuresis when used in conjunction with loop diuretics, even in patients with impaired renal function. While its use is well recognized in acute decompensated heart failure, there is limited structured evidence regarding its role in chronic, intermittent dosing regimens aimed at reducing long-term morbidity.[5,6]

In patients with HFrEF and LBBB, cardiac resynchronization therapy (CRT) offers substantial symptomatic and prognostic benefits. However, a significant proportion of patients either decline device therapy, are not suitable candidates, or lack access due to socioeconomic constraints. In such scenarios, optimizing medical management becomes critically important to reduce symptom burden and prevent recurrent hospitalizations.[7]

Metolazone, when administered intermittently rather than daily, may offer a balanced approach by enhancing diuretic efficacy while minimizing the risks of electrolyte imbalance and renal dysfunction associated with continuous use. However, prospective clinical data evaluating such dosing strategies in stable yet symptomatic HFrEF populations remain sparse.[8]

The present prospective interventional case study was therefore designed to evaluate the clinical efficacy of twice-weekly metolazone therapy in patients with HFrEF and complete LBBB who remained symptomatic despite optimal medical therapy. The study specifically aims to assess its impact on hospitalization frequency, functional capacity as measured by the six-minute walk test, and overall symptomatic improvement reflected by changes in NYHA functional class.

MATERIALS AND METHODS

Study Design and Setting: This prospective interventional case study was conducted across two dedicated cardiology centers over a study period extending from September 2023 to October 2025. The study was designed to evaluate the clinical effectiveness of a structured intermittent diuretic strategy using metolazone in patients with advanced heart failure. All participants were followed longitudinally with predefined clinical and functional outcome assessments.

Study Population: A total of 37 patients diagnosed with heart failure with reduced ejection fraction (HFrEF) and complete left bundle branch block (LBBB) were enrolled in the study. The cohort included patients with both ischemic and non-ischemic etiologies of cardiomyopathy. Specifically, 30 patients had ischemic cardiomyopathy, while 7 patients were diagnosed with non-ischemic dilated cardiomyopathy confirmed by normal coronary angiography. The study population primarily consisted of patients with advanced symptomatic disease corresponding to New York Heart Association (NYHA) functional class III or IV.

Inclusion Criteria: Patients were included if they met the following criteria:

- Age ≥18 years
- Established diagnosis of HFrEF with reduced left ventricular ejection fraction
- Presence of complete LBBB on electrocardiography
- NYHA functional class III or IV despite optimal guideline-directed medical therapy
- Persistent symptoms of congestion requiring escalation of diuretic therapy

Exclusion Criteria: Patients were excluded if they had:

- Acute decompensated heart failure requiring immediate hospitalization at baseline
- Severe renal impairment requiring dialysis
- Significant electrolyte imbalance at baseline
- Known hypersensitivity to metolazone
- Inability to comply with follow-up protocol

Baseline Evaluation: All patients underwent detailed clinical evaluation at baseline, including demographic profiling, comorbidity assessment, and etiology classification of cardiomyopathy. Baseline functional status was assessed using NYHA classification. Exercise capacity was quantified using

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the six-minute walk test (6MWT). Laboratory investigations included renal function tests and serum electrolytes. Prior to intervention, all patients were stabilized on maximally tolerated doses of loop diuretic therapy (torsemide) along with standard guideline-directed medical therapy.

Intervention Protocol: Following optimization of baseline therapy, patients were initiated on metolazone administered twice weekly as an adjunct to ongoing loop diuretic treatment. This intermittent dosing strategy was chosen to enhance diuretic response while minimizing the risk of adverse effects such as electrolyte disturbances and renal dysfunction. The dosing schedule was standardized across participants, and adherence was reinforced through regular follow-up.

Among the study cohort, 31 patients declined device-based therapy, including cardiac resynchronization therapy (CRT), despite being eligible, thereby emphasizing the need for alternative therapeutic strategies in this subgroup.

Follow-up and Outcome Measures: Patients were followed up regularly over a period of up to 14 months. The primary outcome measure was the frequency of hospital admissions due to heart failure exacerbation. Secondary outcome measures included:

- Change in functional capacity as assessed by six-minute walk test (6MWT)
- Change in NYHA functional class
- Clinical response in terms of symptom improvement
- Safety parameters including renal function and electrolyte status

Statistical Analysis: Data were analyzed to assess changes in clinical and functional parameters following initiation of twice-weekly metolazone therapy. Continuous variables such as 6MWT distance were compared over time, while categorical variables such as NYHA class were analyzed for distribution shifts. The relative risk reduction in hospital admissions was calculated with corresponding confidence intervals. Statistical significance was determined using appropriate tests, with a p-value of less than 0.05 considered significant.

Ethical Considerations: The study was conducted in accordance with ethical principles governing clinical research. Informed consent was obtained from all participants prior to inclusion in the study. Patient confidentiality was strictly maintained, and all interventions were performed as part of standard clinical care with additional structured monitoring.

RESULTS

The study evaluated 37 patients with advanced HFrEF and complete LBBB who were initiated on twice-weekly metolazone in addition to optimized background therapy. The cohort predominantly consisted of patients with severe symptomatic limitation (NYHA class III/IV), reflecting a high-risk population with frequent hospitalizations and reduced functional capacity at baseline. Over a follow-up period extending up to 14 months, a consistent and clinically meaningful improvement was observed across multiple outcome domains. There was a marked reduction in hospital admission frequency, accompanied by significant gains in exercise tolerance as measured by the six-minute walk test (6MWT), and a favorable shift in NYHA functional class. Importantly, these benefits were observed early after initiation of therapy and were sustained throughout the follow-up period. The intervention demonstrated a favorable safety profile, with effective diuresis achieved irrespective of baseline renal function.

Table 1: Baseline demographic and clinical characteristics of study population

Parameter	Value
Total patients	37
Ischemic cardiomyopathy	30 (81.1%)
Non-ischemic dilated cardiomyopathy	7 (18.9%)
NYHA Class III	Majority
NYHA Class IV	Remaining subset
Presence of complete LBBB	100%

Table 1 outlines the baseline profile of the enrolled patients, highlighting the predominance of ischemic etiology and advanced functional class.

Table 2: Device therapy acceptance among eligible patients

Parameter	Value
Eligible for CRT/device therapy	31
Declined device therapy	31 (100%)
Accepted device therapy	0

Table 2 demonstrates the proportion of patients declining device-based therapy despite eligibility.

Table 3: Change in hospital admissions following metolazone therapy

Parameter	Value
Relative risk (RR) of admissions	0.73
95% Confidence Interval	0.52 – 0.91
p-value	<0.001
Reduction observed from	1 month onward
Sustained effect duration	Up to 14 months

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Table 3 shows a statistically significant reduction in hospital admission rates after initiation of twice-weekly metolazone.

Table 4: Proportion of patients with reduced hospitalization frequency

Outcome	Number (%)
Reduced hospital admissions	~75%
No significant change	Remaining subset

Table 4 highlights the proportion of patients benefiting from reduced admissions.

Table 5: Change in six-minute walk test (6MWT) distance

Parameter	Outcome
Patients with ≥30 m improvement	~66%
Statistical significance	$p < 0.001$
Overall trend	Significant improvement

Table 5 summarizes improvement in functional exercise capacity following intervention.

Table 6: Change in NYHA functional class

Outcome	Number (%)
Improvement by ≥1 NYHA class	70%
No change	Remaining patients
Worsening	None reported

Table 6 demonstrates symptomatic improvement following therapy.

Table 7: Mortality outcomes during follow-up

Parameter	Value
Total deaths	6
Survivors	31
Baseline characteristic difference	No significant difference

Table 7 presents mortality data observed during the study period.

Table 8: Renal function and diuretic response

Parameter	Observation
Diuretic response	Effective
Dependence on serum creatinine	None observed
Renal safety	Maintained

Table 8 evaluates the relationship between renal function and diuretic efficacy.

Table 9: Duration of sustained clinical benefit

Parameter	Value
Early response onset	Within 1 month
Duration of sustained benefit	Up to 14 months

Table 9 outlines the persistence of therapeutic effects over time.

Table 10: Overall clinical response profile

Outcome Domain	Observation
Hospital admissions	Significantly reduced
Functional capacity	Improved
NYHA class	Improved
Safety	Acceptable

Table 10 summarizes combined clinical outcomes following intervention.

Table 1 demonstrates that the study population predominantly comprised patients with ischemic cardiomyopathy (30 out of 37; 81.1%), with all patients exhibiting complete LBBB and the majority presenting in advanced NYHA class III/IV, indicating a severely symptomatic cohort.

Table 2 shows that all 31 patients (100%) who were eligible for device therapy declined it, highlighting a critical therapeutic gap and the clinical relevance of alternative medical strategies in such populations.

Table 3 reveals that twice-weekly metolazone therapy resulted in a significant reduction in hospital admissions, with a relative risk of 0.73 (95% CI: 0.52–0.91) and strong statistical significance ($p < 0.001$), with benefits evident as early as one month and sustained over 14 months.

Table 4 indicates that approximately three-quarters of patients (~75%) experienced a reduction in hospitalization frequency, reflecting a robust and clinically meaningful response to the intervention.

Table 5 demonstrates that nearly two-thirds of patients (~66%) achieved an improvement of at least 30 meters in 6MWT distance, with a statistically significant overall improvement ($p < 0.001$), confirming enhanced functional capacity.

Table 6 shows that 70% of patients experienced an improvement of at least one NYHA class, indicating

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substantial symptomatic relief and improved quality of life.

Table 7 reports that 6 out of 37 patients died during follow-up, with no significant baseline differences compared to survivors, suggesting that mortality outcomes were likely influenced by disease severity rather than intervention-related factors.

Table 8 highlights that the diuretic effect of metolazone was independent of serum creatinine levels, demonstrating its efficacy across varying degrees of renal function without compromising safety.

Table 9 confirms that the therapeutic benefits of metolazone were not only rapid in onset (within one month) but also sustained over a prolonged period of up to 14 months.

Table 10 consolidates the overall findings, showing consistent improvement across key clinical domains including hospitalization rates, functional capacity, and symptomatic status, with an acceptable safety profile, thereby reinforcing the effectiveness of the intervention in this high-risk patient population.

DISCUSSION

The present prospective interventional case study demonstrates that a structured intermittent diuretic strategy using twice-weekly metolazone provides significant clinical benefit in patients with heart failure with reduced ejection fraction (HFrEF) and complete left bundle branch block (LBBB). The findings highlight meaningful reductions in hospital admissions, improvement in functional capacity, and favorable symptomatic shifts, particularly in a cohort characterized by advanced disease and limited uptake of device-based therapies.

A central observation of this study is the substantial reduction in hospitalization frequency following initiation of metolazone. Recurrent hospital admissions in HFrEF are largely driven by persistent congestion and inadequate diuretic response. Loop diuretics, although foundational, often become less effective over time due to adaptive mechanisms such as distal tubular sodium reabsorption and neurohormonal activation.[9] The addition of metolazone, a thiazide-like diuretic acting at the distal convoluted tubule, facilitates sequential nephron blockade, thereby enhancing natriuresis and overcoming diuretic resistance. The observed early onset of benefit within one month and its sustained effect over 14 months underscore the durability of this therapeutic approach.[10]

Improvement in functional capacity, as evidenced by significant gains in six-minute walk test (6MWT) distance, further reinforces the clinical utility of this regimen. Functional limitation in HFrEF is multifactorial, arising from reduced cardiac output, elevated filling pressures, and skeletal muscle deconditioning.[10] By effectively reducing volume overload and improving hemodynamic status, metolazone likely contributes to enhanced exercise tolerance. The finding that a substantial proportion of patients achieved clinically meaningful improvements (≥30 meters) reflects not only statistical significance but also real-world functional benefit.[11]

The improvement in New York Heart Association (NYHA) functional class observed in the majority of patients aligns with the improvements in both congestion status and exercise capacity. Symptomatic relief remains a key therapeutic goal in advanced heart failure, particularly in patients who are not candidates for advanced interventions. In this study, approximately 70% of patients experienced at least one-class improvement, suggesting that intermittent metolazone can meaningfully alter disease burden and daily functioning.[12]

An important clinical context of this study is the presence of complete LBBB in all patients, a condition associated with mechanical dyssynchrony and poorer outcomes. While cardiac resynchronization therapy (CRT) remains the standard of care for eligible patients, a notable proportion of patients either decline or lack access to such interventions. In this cohort, all eligible patients declined device therapy, highlighting a significant real-world limitation. The observed benefits of metolazone in this subgroup emphasize the importance of optimizing pharmacological strategies when device therapy is not pursued.[13]

Another noteworthy finding is the independence of diuretic efficacy from baseline renal function. Diuretic therapy in heart failure is often limited by concerns regarding worsening renal function and electrolyte imbalance. Metolazone, however, demonstrated effective diuresis without apparent dependence on serum creatinine levels, suggesting that it can be safely utilized across a range of renal profiles when appropriately monitored. The intermittent dosing strategy likely contributed to minimizing adverse effects while preserving therapeutic efficacy.[14]

Mortality observed in the study (6 patients) appeared consistent with the severity of underlying disease rather than being attributable to the intervention itself. Given the advanced stage of heart failure in this population, such outcomes are not unexpected. Importantly, there were no signals indicating increased risk associated with the use of metolazone in this regimen.[15]

The findings of this study contribute to the evolving understanding of diuretic optimization in chronic heart failure. While metolazone is traditionally used in acute settings or as rescue therapy, this study supports its role as part of a planned, intermittent regimen aimed at long-term disease control. This approach may offer a practical and cost-effective alternative in resource-limited settings or in patients unwilling to undergo invasive procedures.[16]

However, certain limitations must be acknowledged. The study is limited by its relatively small sample size and lack of a control group, which may affect the generalizability of the findings. Additionally, as a

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case-study design, the potential for selection bias cannot be excluded. Despite these limitations, the consistency of observed benefits across multiple clinically relevant endpoints strengthens the validity of the conclusions.

Overall, twice-weekly metolazone emerges as a valuable adjunctive therapy in advanced HFrEF with LBBB, particularly in patients with persistent congestion and limited therapeutic options. The strategy of intermittent dosing appears to balance efficacy and safety, offering a feasible pathway to improve outcomes in a challenging patient population.

Limitations

This study has several important limitations that should be considered while interpreting the findings. First, the sample size was relatively small, comprising only 37 patients, which may limit the statistical power and generalizability of the results to broader heart failure populations. Second, the study was conducted as a prospective interventional case study without a parallel control group or randomization, making it difficult to definitively attribute observed benefits solely to the intervention and raising the possibility of confounding factors.

Third, the study population was highly selected, consisting exclusively of patients with advanced HFrEF and complete LBBB who were symptomatic despite optimal medical therapy and who declined device-based interventions. This may introduce selection bias and limit applicability to patients with less severe disease or those undergoing cardiac resynchronization therapy. Fourth, the follow-up duration, although extending up to 14 months, may still be insufficient to evaluate long-term outcomes such as sustained mortality benefit or progression of heart failure.

Additionally, while clinical outcomes such as hospital admissions, 6-minute walk distance, and NYHA class were assessed, more objective hemodynamic parameters and biomarker-based evaluations were not included. The absence of detailed electrolyte trend analysis and standardized adverse event reporting may also limit comprehensive safety assessment. Finally, adherence to therapy and lifestyle modifications, which can influence outcomes in heart failure, were not formally quantified.

Despite these limitations, the study provides valuable real-world insights into a practical and potentially effective therapeutic strategy in a high-risk and often underrepresented patient population.

CONCLUSION

Twice-weekly metolazone therapy, when added to optimized loop diuretic treatment, demonstrates significant clinical benefit in patients with heart failure with reduced ejection fraction and complete left bundle branch block. The intervention is associated with a marked reduction in hospital admissions, meaningful improvement in functional capacity, and favorable symptomatic progression as reflected by NYHA class improvement.

The strategy of intermittent dosing appears to effectively enhance diuretic response while maintaining an acceptable safety profile, even in patients with varying degrees of renal function. These findings are particularly relevant for patients who are not candidates for or decline device-based therapies, where optimizing pharmacological management becomes essential.

This study contributes novel clinical evidence supporting the role of structured, twice-weekly metolazone as an adjunctive therapy in advanced heart failure. Larger, controlled studies are warranted to validate these findings and to further establish its role in long-term heart failure management.

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