**Critical Appraisal: Blood Pressure Effects of Intravenous Furosemide in Acute Decompensated Heart Failure**

**Introduction to the Clinical Dilemma**

For any clinician in a busy UK Emergency Department, the management of Acute Decompensated Heart Failure (ADHF) is a daily reality. A core component of this management is intravenous (IV) diuretic therapy, with furosemide being the cornerstone. However, a common clinical uncertainty arises, particularly in patients with borderline or low-normal blood pressure: will giving a necessary dose of IV furosemide precipitate dangerous hypotension? This fear can lead to clinical inertia, under-dosing, and potentially incomplete decongestion, which is associated with a **three- to sixfold increase in short-term readmission or death**.

This document provides a critical appraisal of a key paper that directly addresses this dilemma: **"Blood Pressure Effects and Risk of Hypotension due to Intravenous Furosemide in Acute Decompensated Heart Failure" by Harrison et al., published in *Academic Emergency Medicine***. The purpose of this appraisal is to systematically evaluate the paper's methodology, analyse its results, and translate its findings into practical, evidence-based implications for UK Emergency Medicine practice.

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**1.0 PICO Breakdown**

To understand the core question of the study, we can break it down using the PICO (Population, Intervention, Comparison, Outcome) framework.

| Component | Description |
|---|---|
| **P**opulation | 253 adult patients prospectively enrolled from five US hospital emergency departments (EDs) with diagnostically adjudicated Acute Decompensated Heart Failure (ADHF). |
| **I**ntervention | Administration of intravenous furosemide at doses determined by the treating physician. |
| **C**omparison | The study compared blood pressure measurements before and after IV furosemide administration. It also used multivariable modelling to compare the effect of furosemide against the effects of other confounders. |
| **O**utcomes | The primary outcome was Systolic Blood Pressure (SBP) as a continuous variable. A key secondary outcome was hypotension, defined as SBP < 90 mmHg. |

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### 2.0 Critical Appraisal using the CASP Cohort Study Checklist

The CASP (Critical Appraisal Skills Programme) checklist is a systematic tool designed to evaluate the validity, results, and relevance of research. By applying its framework to this cohort study, we can assess the trustworthiness of the paper's findings and determine their clinical value.

### 2.1 Did the study address a clearly focused issue?

**Yes.** The study had a very clear and clinically relevant objective: to quantify the magnitude of SBP changes and the risk of hypotension that is specifically attributable to IV furosemide. Crucially, the aim was to distinguish this effect from the many other confounding factors present during the acute management of ADHF, such as patient characteristics and co-administered treatments.

### 2.2 Was the cohort recruited in an acceptable way?

The cohort was recruited prospectively from five hospital EDs across two US states, which enhances its generalisability. The inclusion criteria were pragmatic and reflected real-world presentations: ED physician suspicion of ADHF with supporting evidence such as dyspnoea, pulmonary oedema on chest X-ray, or a BNP > 300 pg/mL. Key exclusion criteria appropriately removed patients whose haemodynamics would be confounded by other acute processes (e.g., sepsis, STEMI). A major strength was that the final diagnosis of ADHF was adjudicated by two experienced authors, **blinded to one another's assessment**, to ensure the cohort was well-defined.

### 2.3 Was the exposure accurately measured to minimise bias?

**Yes.** The exposure of interest was the administration of IV furosemide. The study meticulously recorded the timing and dose of all interventions. To ensure accuracy and harmonise the clinical data with the haemodynamic data, all event timings were based on the internal clock of the continuous monitoring device (the ClearSight monitor).

### 2.4 Was the outcome accurately measured to minimise bias?

**Yes.** The outcome (blood pressure) was measured using a continuous, non-invasive ClearSight finger-cuff monitor. This device recorded SBP, DBP, MAP, and heart rate at 20-second intervals, providing an incredibly granular dataset. This high-frequency measurement is a significant strength, as it can detect transient hypotension that would be missed by standard, intermittent cuff measurements. The device has also been previously validated, showing a high correlation ($R^2 = 0.96$) with invasive arterial monitoring, though it should be noted this was for a prior version of the device. A more recent meta-analysis found the average difference between this type

of finger-cuff monitor and an invasive arterial line was only 4.2 mmHg, confirming its utility for high-frequency monitoring.

**2.5 Have the authors identified all important confounding factors?**

The authors identified and adjusted for a comprehensive list of potential confounders. This included baseline vital signs, patient demographics (age, BMI), extensive medical history (hypertension, diabetes, heart failure, renal disease), home medications, key laboratory results (troponin, BNP), ejection fraction, and a wide array of co-administered ED therapies (e.g., nitroglycerin, NIPPV, beta-blockers, ACE inhibitors). This robust approach to identifying confounders is central to the study's validity.

**2.6 Was the follow-up of subjects complete and long enough?**

Patients were monitored continuously for a period of 3-6 hours. This duration is clinically relevant and was justified by the authors based on the pharmacokinetics of IV furosemide. The time to peak effect is approximately 2 hours, with a duration of action of up to 6 hours. Furthermore, the "braking phenomenon," where diuretic effectiveness wanes, begins around the 6-hour mark, making this a logical and sufficient observation window for the initial ED dose.

**2.7 What are the results of this study?**

The core finding was that IV furosemide had a much smaller effect on blood pressure than commonly believed. After accounting for all other factors, IV furosemide accounted for only **1.4% of the variance in SBP** and **1.7% of the variance in hypotension risk**. In practical terms, an 80mg dose of IV furosemide was associated with a multivariable-adjusted average SBP drop of just **-11.9 mmHg**.

**2.8 How precise are the results?**

The results are highly precise. For example, the authors calculated that for a patient with a baseline SBP ≥ 120 mmHg, an 80mg dose of IV furosemide was associated with a risk of hypotension of ≤ 2%. For a 40mg dose, the risk was < 1% for patients with an SBP ≥ 110 mmHg. These precise, dose- and baseline-dependent risk estimates are a key strength.

**2.9 Do you believe the results?**

**Yes.** The results are highly believable due to the study's significant methodological strengths. The combination of a prospective design, high-frequency continuous monitoring (which minimises measurement bias), and, most importantly, robust multivariable statistical adjustment for a wide range of clinical confounders makes the findings credible and trustworthy.

**2.10 Can the results be applied to the local population?**

The study was conducted in a US population. While the fundamental pathophysiology of ADHF is universal, there may be differences in local prescribing habits, patient demographics (e.g., baseline medication use), or healthcare systems in the UK. However, the biological effect of furosemide and the haemodynamic principles are the same. Therefore, the findings are likely to be broadly applicable to the UK patient population, though this context should be kept in mind.

### 2.11 Do the results of this study fit with other available evidence?

The authors note that while popular clinical references and textbooks ubiquitously warn of furosemide-induced hypotension, there is a striking lack of prior literature specifically evaluating this risk in the ADHF population. Previous reports in *chronic, compensated* heart failure patients have suggested a higher risk. The authors plausibly reason that the acute volume overload characteristic of ADHF is likely protective against significant blood pressure drops, explaining why their findings differ from those in other populations.

This systematic appraisal confirms the study is of high quality, setting the stage for a deeper analysis of its methods and results.

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## 3.0 Deep Dive: Methodology and Study Design

A study's conclusions are only as strong as its methodology. To fully appreciate the findings of Harrison et al., it is essential to deconstruct its design, particularly the sophisticated measurement and statistical techniques that set it apart.

### 3.1 Study Design

This was a **multicenter, prospective observational cohort study**. It was conducted as a pre-planned secondary analysis of a larger study (the CLEAR-AHF study). The prospective nature is a key strength, as it allows for planned, systematic data collection, reducing the risk of recall and measurement bias common in retrospective studies.

### 3.2 Measurements and Data Collection

The cornerstone of the data collection was the **ClearSight finger-cuff monitor**. This device non-invasively reconstructs an arterial pressure waveform, providing continuous haemodynamic data recorded every 20 seconds. This generated a massive, high-fidelity dataset of 91,210 observations. All other clinical data, from patient demographics to the precise timing of ED treatments, were meticulously recorded in a dedicated research database (REDCap).

### 3.3 An Interesting Technique: Statistical Modelling

The study's most significant strength lies in its statistical approach. The researchers employed **mixed effects regression modelling** (specifically, a Linear Mixed Model for continuous SBP and a Generalized Linear Mixed Model for binary hypotension).

For the non-specialist, this advanced statistical technique can be understood as a powerful tool for untangling complex clinical scenarios. It allowed the researchers to statistically **isolate the very small, independent effect of furosemide** from the much larger haemodynamic effects caused by:

1. **Between-subject variation:** Differences between patients (e.g., age, comorbidities, ejection fraction).
2. **Within-subject confounders:** Other treatments given over time to the same patient (e.g., nitrates, NIPPV).

By using Nagelkerke's adjusted $R^2$ statistic, they were able to quantify precisely what proportion of the change in blood pressure was explained by their entire model, and—most importantly—how much of that change was attributable *specifically* to the administration of IV furosemide. This rigorous separation of effect from confounding is what makes the study's conclusions so powerful.

This robust methodology lends high credibility to the results, which we will now explore in detail.

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### 4.0 Summary and Analysis of Results

This section synthesises the main results, focusing on the patient population, the raw incidence of hypotension, and the crucial multivariable-adjusted effects of IV furosemide that form the paper's central conclusion.

### 4.1 Patient Characteristics

The study included 253 patients with a median age of 60 years. The cohort represented a typical ADHF population, with a median ejection fraction of 40% and a median BNP of 1070 pg/mL. A history of heart failure was present in 92% of patients, and 61% were already on home loop diuretics, suggesting a population with established disease. The median SBP at the time of diuretic administration was 148 mmHg, indicating that most patients were normotensive or hypertensive at the point of treatment.

### 4.2 Primary Findings: SBP and Hypotension

Before statistical adjustment, the raw data showed a small but statistically significant decrease in average SBP after IV furosemide administration, from 140 mmHg to 134 mmHg ($p < 0.001$).

However, the crucial unadjusted finding related to safety: the overall incidence of hypotension (SBP < 90 mmHg) was virtually identical before and after the diuretic was given (6.1% vs 6.0%, p=0.7). Furthermore, any episodes of hypotension that did occur were transient; **no patient experienced sustained hypotension lasting 30 minutes or more**.

### 4.3 Multivariable-Adjusted Effects

The full statistical model was powerful, explaining **79.6% of the overall variance in SBP** and **58.1% of the variance in hypotension risk**. The central conclusion is that after adjusting for all other clinical factors, IV furosemide *itself* explained only a tiny fraction of this: **1.4% of the SBP variance** and **1.7% of the hypotension risk variance**, respectively. The vast majority of the predictable change in blood pressure was attributable to other factors.

The specific, adjusted effect of an **80 mg IV furosemide dose** was an average SBP drop of **-11.9 mmHg**. This effect had a clear time course, reaching its lowest point (nadir) of **-15.2 mmHg at 147 minutes** before partially recovering to **-8.5 mmHg by the 6-hour mark**.

The risk of hypotension was highly dependent on the baseline SBP and the dose given:

- For an **80 mg dose**, the risk of hypotension was ≤ 2% in patients with a baseline SBP of 120 mmHg or higher.
- For a **40 mg dose**, the risk was even lower, at < 1% for patients with a baseline SBP of 110 mmHg or higher.

### 4.4 Impact of Co-administered Drugs

The analysis revealed that other common ED treatments had a much more profound impact on blood pressure. Co-administration of furosemide with **NIPPV** (mean difference -24.9 mmHg) and, most strikingly, **oral diltiazem** (-33.2 mmHg) was associated with a significantly greater, multiplicative reduction in SBP.

These results clearly demonstrate that while IV furosemide has a modest, predictable, and transient effect on blood pressure, it is not the primary driver of haemodynamic instability in the vast majority of ADHF patients.

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## 5.0 Evaluation of Strengths and Weaknesses

Every study has inherent strengths and limitations. A balanced appraisal requires acknowledging both to correctly interpret and apply the findings.

### Strengths vs. Weaknesses

| Strengths | Weaknesses |
|---|---|
| **Prospective, Multicenter Design:** Enhances generalisability and reduces bias compared to single-centre, retrospective data. | **Observational Design:** Cannot definitively infer causality. Despite robust adjustment, the risk of unmeasured confounders remains. |
| **High-Frequency Continuous Monitoring:** Provided a granular dataset (91,210 observations), allowing for precise analysis of haemodynamic trends and detection of transient events. | **Specific Population:** Excluded the sickest patients (cardiogenic shock, STEMI, Stage D heart failure), so results are not applicable to these cohorts. |
| **Robust Statistical Analysis:** The use of mixed effects modelling to rigorously control for a large number of clinical confounders is a major methodological strength. | **Non-Invasive Monitoring:** While validated, the ClearSight monitor is not the absolute gold standard of invasive arterial monitoring. |
| **Real-World Data:** The observational design reflects actual clinical practice regarding dosing and co-administered treatments, increasing its relevance. | **Limited High-Dose Data:** Few patients received doses above 80-100 mg, making the effect estimates for higher doses less precise. |
| | **Initial ED Dosing Only:** Did not evaluate the cumulative haemodynamic effects of subsequent diuretic doses given during hospitalisation. |

Despite the limitations inherent in an observational study, the methodological rigour and powerful statistical analysis mean the strengths significantly outweigh the weaknesses, making the conclusions robust.

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### 6.0 Authors' Conclusions and Critical Assessment

This section presents the authors' own summary of their findings and provides a critical verdict on whether their conclusion is justified by the evidence presented in the paper.

### 6.1 Stated Conclusion

The authors conclude in their abstract: *"Blood pressure reductions after IVFu during ADHF treatment are modest, and hypotension is rare and transient. Most variance in SBP during ADHF treatment is due to other factors."*

### 6.2 Critical Verdict

**The authors' conclusion is well-supported and fully justified by their data.**

This verdict is based on the powerful, quantitative evidence produced by their robust methodology. The key findings that support this conclusion are:

- The extremely small proportion of SBP variance attributable solely to furosemide (1.4%).
- The modest mean drop in SBP (-11.9 mmHg for an 80mg dose) that is predictable.
- The clear relationship showing that risk is dependent on baseline SBP and dose, allowing for risk stratification.
- The transient nature of the effect, which resolves by 6 hours, with no episodes of prolonged hypotension (≥30 minutes) observed.

This study provides compelling evidence to challenge the long-held clinical fear that guideline-recommended doses of IV furosemide are a primary driver of haemodynamic instability in the majority of ADHF patients. It effectively reframes the conversation, suggesting that our concern should be directed more toward baseline haemodynamics and the impact of co-interventions.

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### 7.0 Applicability and Clinical Implications for UK Emergency Medicine

The final and most important step of any critical appraisal is to determine the "so what?" factor for our local practice. This section translates the study's findings into practical implications for a UK Emergency Department.

1. **Reassurance in Normotensive/Hypertensive Patients:** For the majority of ADHF patients who present with a normal or elevated SBP (≥120 mmHg), this study provides strong reassurance that standard IV furosemide doses carry a very low risk of causing clinically significant hypotension. For a patient with an SBP ≥ 120 mmHg, an 80mg dose has a risk of ≤2%, while a 40mg dose has a risk closer to 1%.
2. **Quantified Risk in Borderline Patients:** For patients with a borderline SBP (e.g., 90-110 mmHg), this study does not eliminate risk, but it *quantifies* it. This allows for a more informed risk-benefit discussion. It shows that the risk, while higher, remains low for initial doses (e.g., <1% for a 40mg dose in a patient with an SBP ≥110 mmHg). This evidence supports a strategy of starting with a lower dose (e.g., 40mg) in these patients and closely monitoring the response.

3. **Vigilance with Co-medications:** A major practical takeaway is that other interventions, particularly **NIPPV** and **diltiazem**, have a much greater, and at times multiplicative, effect on SBP. Clinicians should be far more vigilant about the haemodynamic impact of these co-interventions than of furosemide itself. A patient's blood pressure dropping after receiving both NIPPV and furosemide is more likely attributable to the NIPPV.
4. **Challenging Under-dosing:** The authors note that fear of hypotension can lead to under-dosing. This is supported by previous survey data cited in the paper, where nearly 20% of ED physicians reported withholding IV furosemide due to this fear. This evidence should empower UK clinicians to adhere more closely to guideline-recommended diuretic doses. Achieving effective decongestion early is crucial for improving symptoms and preventing readmission, and this paper suggests that the haemodynamic risk of doing so has been overestimated.

In summary, this paper is a valuable contribution to the evidence base. It provides a robust, quantitative framework that allows for more nuanced and confident decision-making when administering one of the most common drugs in emergency medicine.

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**8.0 FRCEM OSCE Style Questions**

This section provides a practical educational tool based on the key findings of the paper, framed as typical exam-style questions.

**Question 1: Clinical Scenario (Management Station)**

**Prompt:** *"You are an Emergency Medicine registrar. A 72-year-old man presents with a two-day history of increasing shortness of breath and swollen legs. He has a history of heart failure with an ejection fraction of 35%. His observations are: RR 24, SpO2 93% on room air, HR 98 (irregularly irregular), and a blood pressure of 112/76 mmHg. His chest X-ray shows pulmonary oedema. The junior doctor is concerned about giving IV furosemide because the patient's SBP is 'on the lower side'. Discuss your immediate management plan, specifically justifying your approach to diuretics based on recent evidence."*

**Model Answer:**

- **Immediate Actions (ABC approach):**
    - Sit the patient upright to reduce preload.
    - Provide supplemental oxygen to target saturations of 94-98%.

    - Establish IV access and obtain bloods including FBC, U&Es, and troponin. Request a 12-lead ECG.
    - I would consider non-invasive ventilation (NIPPV) if there are signs of respiratory failure, but I would be mindful of its own potential to lower blood pressure and monitor closely if initiated.

- **Diuretic Management and Justification:**
    - I would proceed with administering intravenous furosemide. The junior doctor's concern is valid and reflects common clinical caution, but high-quality evidence from the Harrison et al. study helps us quantify this risk.
    - That study was a **prospective observational cohort study** using continuous blood pressure monitoring in ADHF patients.
    - Its key finding was that IV furosemide itself accounts for a very small amount of blood pressure variation—less than 2%. The risk of hypotension is primarily dependent on the baseline SBP and the dose.
    - For a patient with an SBP of around 110 mmHg, the study showed the risk of hypotension from a **40mg IV dose of furosemide was less than 1%**.
    - Furthermore, any effect is transient, peaking around 2 hours and resolving within 6 hours.
    - Therefore, I would confidently start with **40mg of IV furosemide** and closely monitor the patient's blood pressure and clinical response. This evidence suggests the benefits of achieving decongestion significantly outweigh the minimal and predictable haemodynamic risk in this specific scenario.

**Question 2: Critical Appraisal Station**

**Prompt:** *"You are presented with the abstract of the paper by Harrison et al. on the blood pressure effects of IV furosemide in ADHF. The examiner asks you: 'Based on the methods described in this abstract, what is the single most important methodological strength of this study, and why does it make the findings more trustworthy than previous knowledge on this topic?'"*

**Model Answer:**

- **Identify the Strength:** The single most important methodological strength is the use of **multivariable-adjusted mixed effects regression modelling**.
- **Explain 'Why':**

- The emergency treatment of ADHF is complex. Patients receive multiple simultaneous treatments (like oxygen, nitrates, or NIPPV) and have numerous underlying characteristics (like comorbidities or a low EF) that all affect blood pressure. This creates significant confounding.
- Simply observing that a patient's blood pressure drops after they receive furosemide doesn't prove furosemide was the cause.
- The statistical technique used in this study—mixed effects modelling—allowed the researchers to mathematically account for dozens of these confounders simultaneously.
- This allowed them to statistically **isolate and quantify the *independent* effect of furosemide** on blood pressure. By doing this, they could demonstrate that furosemide's own contribution to blood pressure changes was tiny (1.4% of the total variance), while other factors were much more significant.
- This rigorous approach to managing confounding is what makes the findings more trustworthy than anecdotal experience or simple pre-post observations, which cannot separate the drug's true effect from everything else happening to the patient.