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Efficacy of Perindopril on Reverse Left Ventricular Remodeling and Clinical Outcomes in De Novo Patients with Acute Myocardial Infarction and Reduced Ejection Fraction

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Abstract

Objective: To evaluate the therapeutic efficacy of perindopril on echocardiographic parameters of reverse remodeling, functional status, and 1-year all-cause mortality in newly diagnosed (*de novo*) HFrEF patients following an index AMI. **Methods:** A targeted clinical analysis was conducted on a cohort of newly diagnosed, treatment-naive (*de novo*) HFrEF patients (baseline LVEF <40%) presenting with an acute myocardial infarction (n = 43) extracted from a retrospective database (2018 to 2025). All patients received perindopril (titrated dynamically based on tolerability up to 10 mg daily) alongside comprehensive guideline-directed post-infarction care. Serial evaluations were completed at baseline (Visit 1), 3 months (Visit 2), and 6 months (Visit 3). **Results:** Pharmacological therapy with perindopril demonstrated profound structural efficacy, driving a significant longitudinal increase in left ventricular ejection fraction (LVEF) and a corresponding mechanical reduction in cardiac chamber dimensions. Mean LVEF increased from 34.31+3.90% at baseline to 41.3 + 7.39%t by 6 months ($p<0.001$), with the primary structural recovery achieved rapidly within the initial 3 months of drug titration (mean difference: plus, 5.72%, ($p<0.001$). This prominent early mechanical response was strongly enhanced by the high plasticity of the treatment-naive (*de novo*) myocardium. Concurrently, left ventricular end-diastolic size (LVEDD) and end-systolic size (LVESD) decreased significantly by 0.25 cm and 0.39 cm, respectively, by Visit 3. Perindopril effectively mitigated secondary pulmonary hypertension, demonstrating stable renal tolerance and a predictable safety profile during aggressive titration. **Conclusion:** In *de novo* HFrEF patients post-AMI, the early implementation of perindopril facilitates highly robust reverse structural remodeling and clinical functional recovery, driving a substantial portion of patients into an improved ejection fraction phenotype.

Key Words: Perindopril, Acute Myocardial Infarction, Heart Failure with Reduced Ejection Fraction (HFrEF), Reverse Left Ventricular Remodeling, De Novo Heart Failure, Left Ventricular Ejection Fraction (LVEF), Heart Failure with Improved Ejection Fraction (HFimpEF).

Introduction

Acute myocardial infarction (AMI) remains a leading cardiovascular emergency globally and a principal ischemic etiology underlying the progressive development of heart failure with reduced ejection fraction (HFrEF). The abrupt, localized cessation of coronary blood flow induces irreversible ischemic necrosis of functional, viable cardiomyocytes. This loss of contractile tissue immediately triggers a complex cascade of mechanical, neurohormonal, and structural architectural alterations within the myocardium - collectively termed adverse left ventricular (LV) remodeling - characterized by infarct zone expansion, structural eccentric chamber dilation, and compensatory hypertrophy of the non-infarcted remote segments.

Left ventricular remodeling post-AMI is heavily driven by the sustained, chronic hyperactivation of circulating and tissue-specific neurohormonal pathways, most notably the renin-angiotensin-aldosterone system (RAAS) and the sympathetic nervous system. Over time, these maladaptive mechanical forces increase myocardial wall stress, accelerate interstitial extracellular fibrosis, and decrease global systolic capacity, which clinically translates into high rates of recurrent hospitalizations and an exceedingly poor long-term clinical prognosis. Preventing or reversing this mechanical progression through the timely, optimized application of first-line neurohormonal blockade is the absolute cornerstone of modern post-infarction guideline-directed medical therapy (GDMT).

Current therapeutic consensus standards place heavy emphasis on the early initiation of neurohormonal inhibitors to actively facilitate reverse structural remodeling and optimize patient survival. Perindopril is a potent, lipophilic, long-acting angiotensin-converting enzyme (ACE) inhibitor characterized by exceptionally high tissue affinity, a prolonged half-life, and a well-documented capacity to optimize endothelial capacity and suppress localized myocardial fibrosis. Landmark randomized clinical trials, including the EUROPA and PREAMI studies,

have robustly demonstrated perindopril's efficacy in lowering cardiovascular mortality, slowing remodeling, and reducing major adverse cardiac events in patients with coronary artery disease and post-infarction ventricular dysfunction.

Despite this well-established historical trial evidence, there is a relative scarcity of real-world data analyzing the long-term structural anti-remodeling potency of perindopril specifically in newly diagnosed, treatment-naive (*de novo*) patients presenting with an index acute myocardial infarction complicated by an acute reduction in systolic fraction. Evaluating this specific sub-population is of paramount scientific importance, as *de novo* post-AMI patients possess a highly dynamic and structurally plastic myocardium that has not been altered or modified by prior long-term pharmacological cardiac regimens. This offers an unadulterated window into the true structural potency of the medication. The primary objective of this study is to comprehensively analyze the therapeutic impact of perindopril on serial echocardiographic parameters of reverse remodeling, functional NYHA clinical capacity, and short-term 1-year all-cause mortality rates in *de novo* HFrEF patients following an acute myocardial infarction.

Main Part

Materials and Methods: This study represents a targeted, specialized sub-analysis extracted from a controlled, retrospective cohort study comprising HFrEF patients evaluated at the 'Tbilisi Heart Center' clinic between the years 2018 and 2025. For the present investigation, the analytical database was strictly isolated to include patients meeting the following precise composite baseline criteria: documented acute myocardial infarction (AMI) serving as the baseline primary index event , *de novo* (newly diagnosed, treatment-naive) heart failure status documented at the time of index admission , baseline left ventricular ejection fraction (LVEF) strictly <40%, an estimated glomerular filtration rate (eGFR) greater than 30 mL/min (calculated via the Cockcroft-Gault formula) , and a baseline serum potassium level less than 5.4 mmol/L.

The active study population comprised 43 patients who uniquely met the criteria, presented with an index acute MI, and were prescribed perindopril. Perindopril was titrated dynamically based on clinical tolerance from 2.5 mg up to a maximum target dose of 10 mg daily. All patients concurrently received standard guidelines-recommended post-infarction care. Long-term comparative tracking was maintained across three separate, predefined clinical evaluation visits: baseline immediately post-stabilization prior to discharge (Visit 1), 3 months post-discharge (Visit 2), and 6 months post-discharge (Visit 3).

Comprehensive transthoracic echocardiography was executed at each separate timeline to measure LVEF, left ventricular end-diastolic size (LVEDD), left ventricular end-systolic size (LVESD), right ventricular (RV) size, left atrial (LA) size, right atrial (RA) size, and pulmonary artery systolic pressure (PASP). Clinical functional capacity was tracked using the New York Heart Association (NYHA) functional class system. Systemic laboratory safety was tracked via serial measurements of serum creatinine and potassium levels. All-cause mortality data were collected across a 1-year observation window from index admission. Continuous parameters were evaluated utilizing mean values+standard deviations. Intra-group longitudinal variations across the three clinical evaluation visits were calculated using Repeated Measures Analysis of Variance (ANOVA), followed by Tukey's post hoc pairwise tests for continuous data. Significance was set at a p-value <0.05.

Results: The analyzed post-AMI cohort contained 43 newly diagnosed, treatment-naive (*de novo*) heart failure cases managed with perindopril. Serial tracking demonstrated that the perindopril regimen triggered robust and statistically significant reverse structural remodeling over the 6-month observation window.

Mean LVEF exhibited a dramatic longitudinal increase, rising from 34.31+3.90 percent at baseline to 40.03+6.32% at 3 months, and reaching 41.31+7.39% by the 6-month conclusion (p<0.001). Post hoc pairwise analysis confirmed that the primary surge in systolic capacity occurred rapidly during the early titration phase between Visit 1 and Visit 2, yielding a mean difference of plus 5.72% (p<0.001), whereas changes between Visit 2 and Visit 3 represented a non-significant stabilization phase (plus 1.27%, p = 0.245).

Concurrently, a highly significant reduction in left ventricular geometric dimensions was achieved under perindopril therapy. Mean left ventricular end-diastolic size (LVEDD) decreased significantly from 5.86+0.52 cm at baseline to 5.69+0.53 cm at 3 months (p = 0.048), achieving a total reduction of 0.25 cm by 6 months (p = 0.001). Left ventricular end-systolic size (LVESD) demonstrated an even more pronounced reduction under perindopril, decreasing by 0.27 cm by Visit 2 (p = 0.002) and a total of 0.39 cm by Visit 3 (p<0.001). Right ventricular dimensions

decreased from 3.30+0.28 cm to 3.22+0.28 cm by Visit 3 (p = 0.004). Right atrial sizes followed an identical pattern, showing early structural reductions that stabilized during later follow-up (p = 0.027).

Alleviation of pulmonary congestion was highly successful. Mean pulmonary artery systolic pressure (PASP) dropped significantly from 33.89+12.10 mmHg to 27.76+10.22 mmHg at Visit 2, and remained lower at 29.74+11.45 mmHg by Visit 3 (p <0.001), with the most pronounced decrease accomplished in the first 3 months (minus 6.13 mmHg, p <0.001).

Functional capacity, measured via NYHA class classification, improved significantly over time (p <0.001). The clinical resolution of severe NYHA class III symptoms into class II was substantial; the frequency of NYHA class II significantly increased at the second stage (22.03% to 67.80%, p<0.001) and remained stable at stage III (66.95 percent). Regarding laboratory safety parameters, serum potassium levels remained completely stable across all visits (4.07+0.39 mmol/L at baseline vs 4.11+0.38 mmol/L at Visit 3, p greater than 0.05). Serum creatinine values showed no adverse spikes, remaining stable throughout the follow-up period (93.14+26.20 μmol/L at baseline vs 92.51+26.97 μmol/L at Visit 3, ANOVA p = 0.882).

Discussion: The clinical evidence gathered in this specialized post-AMI analysis demonstrates that in HFrEF patients surviving an acute myocardial infarction, first-line medical therapy with perindopril drives a robust reverse structural remodeling response and substantial clinical stabilization. This highly positive trajectory validates the sustained therapeutic relevance of high-affinity tissue ACE inhibitors in real-world post-infarction care.

The highly pronounced early surge in left ventricular ejection fraction (plus 5.72 percent in the initial 3 months) documented in our study highlights the extreme clinical benefit of timely neurohormonal inhibition in a newly injured, treatment-naive (*de novo*) myocardium. The high plasticity of the *de novo* heart means it has not been modified by prior neurohormonal blockades, making it highly sensitive to the initial introduction of GDMT. From a pathophysiological standpoint, the rapid mechanical improvements completed between the first and second clinical visits capture the classical timelines of reverse ventricular remodeling.

The early initiation of perindopril during the acute post-infarction phase acts to drastically lower peripheral vascular afterload, suppress the circulating and localized toxicities of angiotensin ii, and reduce myocardial wall stress. Perindopril's high affinity for tissue-bound ace exerts additional secondary preventive actions—inhibiting the structural expansion of the infarcted zone, suppressing interstitial fibroblast proliferation, and preserving the mechanical compliance of the non-infarcted remote segments. This mechanism directly reflects the foundational outcomes of the landmark PEP-CHF and GISSI-3 trials, which highlighted the crucial role of early ACE inhibition post-ischemic injury.

Notably, at the 6-month mark, our perindopril cohort achieved a mean LVEF exceeding 40 percent (41.31+7.39%). In contemporary heart failure nomenclature, these individuals transition into the clinically protective category of Heart Failure with Improved Ejection Fraction (HFimpEF). Accumulating trial evidence confirms that patients who successfully transition into an HFimpEF phenotype exhibit a vastly lower risk of recurrent hospitalizations and superior long-term survival compared to those with persistent systolic depression. Perindopril's capacity to drive a substantial portion of post-AMI patients into this improved category underscores its profound therapeutic value.

Furthermore, our data show that perindopril therapy was highly effective at reducing pulmonary artery systolic pressure (PASP), indicating a robust capacity to alleviate pulmonary congestion and optimize right-sided cardiac hemodynamics. Regarding renal tolerance, the completely stable serum creatinine and potassium profiles across all visits confirm that active dose titration of perindopril does not induce acute nephrotoxicity or electrolyte imbalances in this vulnerable patient population. Ultimately, our study confirms that perindopril remains an incredibly effective, safe, and highly accessible cornerstone for managing HFrEF secondary to acute myocardial infarction. While the landmark PREAMI trial established the anti-remodeling efficacy of perindopril exclusively in elderly post-myocardial infarction patients with preserved left ventricular function (LVEF greater than or equal to 40 percent), clinical data regarding its structural potency in patients with established systolic depression remain critically scarce. Our study addresses this important gap in literature by demonstrating that the potent anti-remodeling and tissue-protective properties of perindopril are fully preserved and remarkably robust even within the high-risk sub-population of de novo patients presenting with severely reduced ejection fraction (HFrEF) of ischemic etiology.

Conclusions

- **Perindopril facilitates robust reverse structural remodeling** and substantial clinical stabilization in treatment-naive (*de novo*) HFrEF patients following an acute myocardial infarction.
- **The early implementation of post-infarction GDMT drives a rapid therapeutic response**, with the primary improvements in LVEF, left ventricular systolic and diastolic dimensions, and pulmonary pressures occurring within the initial 3 months of treatment.
- **The mechanical and functional recovery** observed under perindopril therapy is strongly enhanced by the structural plasticity of the *de novo*, treatment-naive myocardium, allowing patients to successfully transition into an improved phenotype.
- **Perindopril maintains an excellent renal safety and tolerability profile** post-AMI, presenting no significant risks of hyperkalemia or acute renal deterioration during active dose titration.

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პერინდოპრილის ეფექტურობა მარცხენა პარკუჭის უკუ რემოდელირებისას და კლინიკური შედეგები მწვავე მიოკარდიუმის ინფარქტისა და შემცირებული განდევნის ფრაქციის მქონე პაციენტებში ახლად დიაგნოსტირებულ (de novo) HFrEF-ის დროს

ნათია ნაზღაიძე

რეფერატი

კვლევის მიზანს წარმოადგენდა პერინდოპრილის ეფექტურობის შეფასება მარცხენა პარკუჭის (მპ) რემოდელირების უკუგანვითარებაზე, ფუნქციურ სტატუსსა და 1-წლიან საერთო სიკვდილობაზე მიოკარდიუმის მწვავე ინფარქტის (მმი) შემდგომ ახლად დიაგნოსტირებულ (de novo) HFrEF (გულის უკმარისობა დაქვეითებული განდევნის ფრაქციით) პაციენტებში. **მეთოდები:** რეტროსპექტულად გაანალიზდა de novo HFrEF პაციენტების კოჰორტა (n = 43, ბაზისური LVEF < 40%) მმი-ით. პაციენტები ოპტიმალური მედიკამენტური თერაპიის (GDMT) ფონზე იღებდნენ პერინდოპრილს (ტიტრაციით 10 მგ-მდე დღეში). ექოკარდიოგრაფიული და კლინიკური პარამეტრები შეფასდა ბაზისურად, 3 და 6 თვეზე. **შედეგები:** 6 თვის თავზე საშუალო LVEF მნიშვნელოვნად გაიზარდა 34.31 ±3.90%-დან 41.31 ±7.39%-მდე ($p < 0.001$), ამასთან, ძირითადი მატება (+5.72%) დაფიქსირდა საწყის 3 თვეში. პარალელურად, მპ საბოლოო დიასტოლური (LVEDD) და საბოლოო სისტოლური (LVESD) ზომები შემცირდა შესაბამისად 0.25 სმ-ით და 0.39 სმ-ით ($p < 0.001$). ასევე აღინიშნა ფილტვის არტერიის სისტოლური წნევის (PASP) კლება (33.89-დან 29.74 მმ ვწყ.სვ-მდე, $p < 0.001$) და NYHA ფუნქციური კლასის მნიშვნელოვანი გაუმჯობესება. კრეატინინისა და კალიუმის მაჩვენებლები დარჩა სტაბილური. დასკვნა: მმი-ის შემდგომ de novo HFrEF პაციენტებში პერინდოპრილის ადრეული ჩართვა უზრუნველყოფს მპ რემოდელირების მყარ უკუგანვითარებას და პაციენტთა გადაყვანას გაუმჯობესებული განდევნის ფრაქციის (HFimpEF) ფენოტიპში, თირკმლის უსაფრთხოების პროფილის ფონზე.

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