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THE ROLE OF QUADRUPLE THERAPY IN PATIENTS WITH ISCHEMIC CARDIOMYOPATHY UNSUITABLE FOR REVASCULARIZATION: A CLINICAL CASE REPORT

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Abstract: *Coronary artery disease (CAD) is one of the most prevalent cardiovascular disorders and remains the leading cause of disability and mortality worldwide. In developed countries, CAD is the major cause of heart failure, accounting for nearly 60% of chronic heart failure cases.*

This clinical case demonstrates the management of a patient with ischemic cardiomyopathy and severe heart failure following myocardial infarction.

The treatment of patients with ischemic cardiomyopathy and the selection of optimal quadruple therapy remain a major clinical challenge for cardiologists. Considering the increasing number of patients with ischemic cardiomyopathy who are not candidates for coronary revascularization, this clinical case is of particular importance.

Quadruple therapy (ACE inhibitors/ARBs/ARNI, beta-blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors) represents the cornerstone of treatment in patients with ischemic cardiomyopathy who are not suitable for revascularization. This therapeutic strategy improves quality of life, enhances prognosis, prolongs survival, and reduces hospitalization and mortality associated with heart failure.

Keywords: *ischemic cardiomyopathy, quadruple therapy, revascularization, heart failure.*

Introduction: Coronary artery disease (CAD) is one of the most common cardiovascular diseases and remains the leading cause of disability and mortality worldwide. Approximately 200 million people globally suffer from CAD, corresponding to nearly 3,820 cases per 100,000 population. Each year, around 400 new cases per 100,000 population are diagnosed, most commonly presenting as acute myocardial infarction (AMI). Men are affected more frequently than women, although this difference decreases with age. According to the World Health Organization, CAD accounted for approximately 9.1 million deaths worldwide in 2021, representing 13% of all global deaths.[10]

Atherosclerosis is responsible for nearly 90% of CAD cases and represents the principal mechanism underlying acute coronary syndromes. Rupture of an atherosclerotic plaque within the epicardial coronary arteries triggers thrombosis, which may lead to sudden cardiac death or acute myocardial infarction.[1,2]

The development of myocardial ischemia is primarily associated with an imbalance between myocardial oxygen demand and oxygen supply. Impaired coronary blood flow initiates a sequence of pathophysiological events known as the “ischemic cascade.” Coronary blood flow at rest may remain preserved until luminal stenosis reaches approximately 90%. However, even less severe stenosis may reduce coronary flow reserve and provoke myocardial ischemia during increased oxygen demand.

Persistent ischemia leads to reduced myocardial perfusion, diastolic and systolic dysfunction, regional wall motion abnormalities, electrocardiographic changes, and eventually clinical symptoms. Because the subendocardial layer has a higher oxygen demand than the subepicardial layer, ischemia initially develops in the subendocardium and subsequently extends outward.

Temporary reduction of coronary blood flow may result in myocardial stunning, characterized by transient post-ischemic systolic dysfunction despite restored perfusion. Repeated ischemic episodes may also induce myocardial stunning.[5,7,9] In contrast, chronic reduction in coronary blood flow results in hibernating myocardium, a condition in which viable but dysfunctional myocardial tissue adapts to reduced perfusion and may recover contractility following successful revascularization.

If severe ischemia persists for a prolonged period, irreversible myocardial necrosis and scar formation develop, leading to permanent myocardial dysfunction.

Chronic heart failure (CHF) is a clinical syndrome characterized by symptoms such as dyspnea, fatigue, and peripheral edema, accompanied by structural and/or functional cardiac abnormalities resulting in reduced cardiac output and/or elevated intracardiac filling pressures.

In clinical practice, heart failure with reduced left ventricular ejection fraction secondary to CAD is commonly referred to as ischemic cardiomyopathy (ICM). ICM is considered a subtype of dilated cardiomyopathy caused by chronic myocardial ischemia due to coronary artery atherosclerosis.[4]

Although the term ischemic cardiomyopathy was introduced by G.E. Burch in 1970, earlier observations by E.B. Raftery in 1969 suggested a strong relationship between coronary artery disease and congestive heart failure. Later, Felker et al. proposed standardized diagnostic criteria for ischemic cardiomyopathy, including:

- Left ventricular ejection fraction (LVEF) below 40%;
- Increased left ventricular end-systolic volume index;
- Previous myocardial infarction or coronary revascularization;
- Significant coronary artery stenosis involving the left main coronary artery or multivessel disease.

Subsequently, Alshibaya and colleagues refined these criteria by including significant coronary stenosis, NYHA class II-IV heart failure, left ventricular dilatation, LVEF ≤35%, and significant mitral regurgitation.

Several pathological and neurohormonal mechanisms contribute to the development of ischemic cardiomyopathy. One of the principal mechanisms involves the coexistence of necrotic scarred myocardium and viable but dysfunctional myocardium. Scar tissue resulting from previous myocardial infarction is irreversible and does not recover after revascularization.[3] In contrast, hibernating myocardium represents an adaptive response to chronic hypoperfusion and may recover function after restoration of coronary blood flow.

Left ventricular remodeling is another key mechanism in ischemic cardiomyopathy. Remodeling occurs as an adaptive response to acute or chronic ischemia and is characterized initially by ventricular dilation and wall thinning, followed by progressive fibrosis and irreversible structural damage.

Transthoracic echocardiography plays a major role in risk stratification of patients with ischemic cardiomyopathy. Reduced LVEF is a well-established predictor of mortality and rehospitalization. Increased left ventricular dimensions also have important prognostic implications.

Natriuretic peptides are released by cardiomyocytes in response to ventricular stretch and pressure overload. These peptides counteract the renin-angiotensin-aldosterone system through vasodilation, natriuresis, and antifibrotic effects. Among them, NT-proBNP is widely used as a biomarker in heart failure due to its greater analytical stability.[7,9]

Elevated NT-proBNP levels have been consistently associated with poor prognosis in heart failure patients. Studies such as Val-HeFT and PRIDE demonstrated significantly increased mortality in patients with elevated NT-proBNP concentrations.

Management of ischemic heart failure includes guideline-directed medical therapy, coronary revascularization when feasible, and device therapy when indicated. Pharmacological treatment includes quadruple therapy consisting of:

- ACE inhibitors (ACEi), angiotensin receptor blockers (ARB), or angiotensin receptor-neprilysin inhibitors (ARNI);
- Beta-blockers;
- Mineralocorticoid receptor antagonists (MRA);
- Sodium-glucose cotransporter-2 (SGLT2) inhibitors.

Additional therapies may include ivabradine, digoxin, and diuretics when clinically indicated.

Clinical Case Presentation: A 36-year-old male patient presented to the outpatient department of the Aral Region Specialized Cardiology Center on June 11, 2025, with severe symptoms of chronic heart failure, including dyspnea during minimal

exertion (walking 15–20 meters), orthopnea, palpitations, cough aggravated in the supine position, dizziness, fatigue, and generalized weakness.

Medical History: The patient previously considered himself healthy and had no known chronic diseases. On May 1, 2025, he experienced severe retrosternal chest pain at rest associated with dyspnea and diaphoresis. However, he did not seek medical attention at that time. Subsequently, progressive exertional dyspnea and cough developed. Despite outpatient treatment at his local clinic, symptoms progressively worsened.

Physical Examination

General condition: moderately severe.
Consciousness: clear.
Position: semi-orthopneic.
Body temperature: 36.4°C.
Respiratory rate: 22/min.
Blood pressure: 80/60 mmHg.
Heart rate: 100 beats/min, regular rhythm.
Cardiac auscultation: gallop rhythm at the apex.
Pulmonary auscultation: diminished vesicular breath sounds at the lower lung fields bilaterally.
Peripheral edema: mild edema of the lower extremities.
Daily urine output: 600–800 mL.
Body mass index: 24.2 kg/m^2.

Kansas City Heart Failure Questionnaire (KCCQ) score: 9 points.
6-minute walk test distance: less than 100 meters.

Electrocardiography: ECG demonstrated sinus tachycardia (100 beats/min), pathological Q waves in leads I and aVL, QS complexes in leads V2–V6, nearly isoelectric ST segments, and negative T waves. These findings were consistent with extensive anterior, septal, apical, and lateral left ventricular myocardial scarring.

Echocardiography: Echocardiographic findings:

- Aortic root diameter: 22 mm
- LVEDD: 57 mm

- LVESD: 46 mm
- LVEDV: 213 mL
- LVESV: 98 mL
- LVEF: 33%
- Left atrial diameter: 38 mm
- Right ventricular diameter: 28 mm

Doppler examination revealed left ventricular diastolic dysfunction, moderate mitral regurgitation, and mild tricuspid regurgitation.

Conclusion: ischemic myocardial pathology with reduced global left ventricular contractility and left ventricular dilation.

Laboratory Investigations

- Hemoglobin: 122 g/L
- Platelets: 150×10^9/L
- Leukocytes: 4.5×10^9/L
- Blood glucose: 4.8 mmol/L
- Creatinine: 75 μmol/L
- Potassium: 3.8 mmol/L
- NT-proBNP: 12,500 pg/mL

Lipid profile:

- Total cholesterol: 6.0 mmol/L
- LDL cholesterol: 4.6 mmol/L
- Triglycerides: 1.9 mmol/L

Diagnosis

Primary Diagnosis

- Coronary artery disease

- Extensive anterior Q-wave myocardial infarction (May 1, 2025), scar formation stage
- Ischemic cardiomyopathy
- Dyslipidemia

Complications

- Chronic heart failure stage IIB with reduced ejection fraction
- NYHA functional class IV
- Functional mitral regurgitation grade II
- Functional tricuspid regurgitation grade I

Treatment and Clinical Course

The patient received the following treatment:

- Bisoprolol 1.25 mg/day
- Eplerenone 25 mg/day
- Empagliflozin 10 mg/day
- Aspirin 75 mg/day
- Rosuvastatin 20 mg/day

Because of severe hypotension (80/60 mmHg) and symptoms of hypoperfusion, ACEi/ARB/ARNI therapy was initially postponed.

After 3 days of treatment, the patient's condition improved moderately. Heart rate decreased to 80 beats/min. Ivabradine 10 mg/day was added for heart rate control and anti-ischemic therapy.

By day 5, blood pressure increased to 90/60 mmHg, and symptoms of hypotension significantly improved. Therefore, captopril 12.5 mg/day was initiated and gradually increased to 18.75 mg/day by day 8.

Following treatment optimization, the patient demonstrated substantial clinical improvement:

- Resolution of orthopnea

- Improved exercise tolerance
- Reduced dyspnea
- Heart rate decreased to 74 beats/min
- Blood pressure stabilized at 90/60 mmHg

Coronary Angiography

Coronary angiography demonstrated:

- Right coronary artery: no significant stenosis
- Left main coronary artery: no stenosis
- Left anterior descending artery (LAD): severe proximal and mid-segment stenoses (80–90%) with diffuse distal disease
- Circumflex artery: no significant stenosis
- OM1 branch: 40% stenosis

Myocardial Perfusion Scintigraphy (SPECT)

Myocardial scintigraphy demonstrated:

- Extensive ischemic changes in anterior, septal, and apical segments
- Nonviable myocardium in apical regions
- Small areas of dormant viable myocardium in the LAD territory
- Very high ischemic risk profile
- Evidence of pulmonary hypertension with right ventricular hypertrophy

After multidisciplinary discussion involving interventional cardiologists and cardiac surgeons, revascularization was considered technically impossible and unlikely to provide clinical benefit. Therefore, optimal medical therapy was recommended.

Follow-Up and Outcomes

After 10 days of quadruple therapy, significant improvement in intracardiac hemodynamics was observed.

Echocardiographic Changes

Parameter	Baseline	10 days	1 month	3 months	6 months
LVEDV (mL)	213	186	182	176	180
LVEF (%)	33	38	38	40	41
RV diameter (mm)	28	25	22	23	22
Left atrial diameter (mm)	38	35	33	35	35
Mitral regurgitation	++	+	+	+	+
Tricuspid regurgitation	+	-	-	-	-
NT-proBNP (pg/mL)	12500	7400	6300	2212	1220

At discharge, the patient's condition significantly improved:

- Blood pressure: 90/60 mmHg
- Heart rate: 70 beats/min
- KCCQ score: 2 points
- 6-minute walk distance: 250–300 meters

The patient was discharged with the following treatment regimen:

- Bisoprolol 1.25 mg/day
- Sacubitril/valsartan 50 mg/day
- Eplerenone 50 mg/day
- Empagliflozin 25 mg/day
- Ivabradine 10 mg/day
- Aspirin 75 mg/day
- Rosuvastatin/ezetimibe 20/10 mg/day

Discussion: This clinical case highlights the complexity of managing young patients with ischemic cardiomyopathy and severe heart failure following extensive

myocardial infarction. The case also demonstrates the clinical challenges encountered when coronary revascularization is not feasible.

In patients with ischemic cardiomyopathy, guideline-directed quadruple therapy remains the foundation of treatment. Combination therapy with ACEi/ARB/ARNI, beta-blockers, mineralocorticoid receptor antagonists, and SGLT2 inhibitors significantly improves survival, reduces hospitalizations, and enhances quality of life.

The observed reduction in NT-proBNP levels and improvement in left ventricular ejection fraction during follow-up support the effectiveness of comprehensive neurohormonal blockade in this patient.

This case further emphasizes the importance of myocardial viability assessment in determining treatment strategy. In patients with predominantly nonviable myocardium and diffuse coronary disease, revascularization may not provide significant benefit, making optimal medical therapy the primary therapeutic option.

Conclusion: This clinical case demonstrates that quadruple therapy can significantly improve clinical status, intracardiac hemodynamics, and biomarkers in patients with ischemic cardiomyopathy who are not suitable candidates for coronary revascularization.

Timely initiation and optimization of guideline-directed medical therapy remain essential for improving prognosis, reducing hospitalizations, and prolonging survival in patients with advanced ischemic heart failure.

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