## THE ROLE OF MESENCHYMAL STEM CELL-DERIVED EXTRACELLULAR VESICLES IN CARDIAC REPAIR

## Bogdanov Alan<sup>1</sup>, Badalyan Albert<sup>1</sup>, Babuci Angela<sup>1</sup>

<sup>1</sup>Department of Anatomy and Clinical Anatomy, *Nicolae Testemitanu* State University of Medicine and Pharmacy, Chisinau, Republic of Moldova.

**Introduction:** Cardiovascular diseases remain the predominant cause of global morbidity and mortality. Traditional treatments, including therapeutical and surgical approaches, primarily address symptoms rather than myocardial tissue regeneration. Mesenchymal stem cells (MSCs) with extracellular vesicles (EVs) emerging as key mediators of their therapeutic effects, are widely used in regenerative medicine. This review aims to comprehensively synthesize existing systematic reviews and meta-analyses on MSC-EVs for cardiac repair.

**Materials and Methods:** A comprehensive search of PubMed, Scopus, Web of Science, and Embase identified systematic reviews and meta-analyses (2015–2024) evaluating MSC-EV efficacy in preclinical and clinical cardiac repair. A total of 25 references were included in this umbrella review. **Results:** Findings show that MSC-EVs exert cardioprotective effects through multiple mechanisms. For instance, they have anti-apoptotic effects by modulating pro-survival signaling pathways, such as PI3K/Akt and ERK. An increased expression of VEGF and other pro-angiogenic factors improved vascularization in infarcted tissue. Furthermore, MSC-EVs regulate inflammatory responses by reducing pro-inflammatory cytokines like TNF- $\alpha$  and IL-6, while promoting anti-inflammatory mediators such as IL-10 and TGF- $\beta$ . Additionally, MSC-EVs downregulate fibrotic markers, limiting pathological scar formation after myocardial infarction (MI). Despite promising preclinical findings, several limitations must be addressed before clinical application. The standardization of MSC-EV production is crucial, as variability in isolation methods, including intravenous, intracoronary, or direct myocardial injection, require further investigation. Lastly, long-term safety remains a concern, as potential risks like immune reactions and off-target effects necessitate additional clinical evaluation.

**Conclusion:** MSC-EVs represent a prospective area in regenerative medicine, offering a cell-free therapeutic strategy for myocardial repair. Current evidence supports their efficacy in preclinical models, yet clinical translation requires standardized protocols, larger trials, and long-term safety assessments. Future research focused on optimizing biomanufacturing techniques and conducting well-controlled human studies will bring MSC-EV therapy closer to clinical reality.

**Keywords:** mesenchymal stem cells, extracellular vesicles, cardiovascular diseases, myocardial infarction, regenerative medicine, angiogenesis, immunomodulation.