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RESEARCH ARTICLE

Correlation of LV Mass Index and Its Parameters with Vitamin D Levels in Essential Hypertension Nanocarrier-Based Gene Therapy and Gene Editing for Valvular Heart Disease and Other Rare Cardiac Disorders

Dr. Akshaya Viswanathan, Dr Deepika A, Dr Vimal S
Department of Biochemistry, Saveetha Medical College, Saveetha Institute of Medical and Technical Sciences, Saveetha University, Chennai, Tamil Nadu, India.

*Corresponding Author
Dr Vimal S

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Abstract: ***Background***: Valvular heart disease (VHD) and rare hereditary cardiac disorders are complex conditions that often lead to significant morbidity and mortality due to their progressive nature and lack of curative therapies. Conventional treatments including valve repair or replacement, primarily address symptoms without correcting the molecular or genetic root causes, leaving patients susceptible to long-term complications such as valve degeneration, calcification, and arrhythmias. The advent of gene therapy and precise gene-editing technologies, delivered via advanced nanocarrier platforms, offers a promising avenue to overcome these limitations. Nanocarriers including lipid nanoparticles, polymeric nanoparticles, inorganic nanostructures, extracellular vesicles, and hybrid systems enable targeted, efficient, and minimally immunogenic delivery of therapeutic nucleic acids or genome-editing components to cardiac tissues. This review provides a comprehensive overview of current nanocarrier strategies for cardiovascular gene therapy, highlighting their design, mechanisms of action, preclinical efficacy, and potential for clinical translation. We also discuss safety considerations, translational challenges, and future perspectives, emphasizing the potential of integrating nanotechnology with gene editing to create patient-specific, durable treatments for VHD and rare genetic cardiac disorders.

Keywords: CRISPR-Cas9; valvular heart disease; rare cardiac disorders; lipid nanoparticles; extracellular vesicles

INTRODUCTION

Cardiovascular diseases (CVDs) remain the leading cause of mortality worldwide, accounting for more than 17 million deaths annually [1]. Within this spectrum, valvular heart disease (VHD) represents a significant subset characterized by structural and functional impairment of one or more cardiac valves, leading to stenosis, regurgitation, or combined dysfunction [2].

Although surgical interventions, such as valve replacement or repair, provide symptomatic relief and improve survival, they fail to correct the molecular alterations responsible for disease progression. Postoperative complications, including valve thrombosis, prosthetic degeneration, and chronic inflammation, highlight the unmet need for therapies targeting the disease's underlying mechanisms [3].

Gene therapy and genome-editing strategies offer such precision interventions by introducing functional copies of defective genes, silencing pathogenic alleles, or directly correcting mutations [4].

However, efficient delivery to cardiac tissues especially the dense and avascular valvular ECM remains a critical barrier. Nanocarriers provide an elegant solution by protecting genetic cargo, facilitating tissue-specific delivery, enhancing cellular uptake, and minimizing immune activation [5].

The recent success of lipid nanoparticle-based mRNA vaccines has catalyzed the translation of these technologies to cardiovascular applications, supporting the development of gene replacement, silencing, and editing therapies for VHD and rare cardiac disorders [6]. The current state of nanocarriers as gene therapy vectors for the treatment of cardiovascular disorders is thoroughly reviewed in this paper, with particular attention to coronary heart disease, pulmonary hypertension, hypertension, and valvular heart disease. We will also discuss aiming to give these new therapeutic treatment approaches a solid foundation and support, as well as the related difficulties and opportunities for the future. Information about nanocarrier-based gene therapy for valvular heart disease is compiled in a unique way in this review.

2. CATEGORIES AND DESIGN OF NANOCARRIERS FOR CARDIAC GENE DELIVERY

Nanocarrier systems have revolutionized gene therapy by enabling efficient delivery of nucleic acids and genome-editing machinery to specific tissues [7]. In cardiac applications, they must overcome several physiological barriers, including the dense valvular ECM, high hemodynamic shear forces, and rapid clearance by the reticuloendothelial system [8] (Figure 1).

2.1 LIPID-BASED NANOCARRIERS

Lipid nanoparticles (LNPs) are widely recognized for their biocompatibility, tunable physicochemical properties, and clinical feasibility. Ionizable lipids facilitate nucleic acid encapsulation and endosomal escape, while helper lipids stabilize particle structure [9].

PEGylation improves circulation time, reducing opsonization and renal clearance. LNPs can deliver mRNA encoding therapeutic proteins, siRNA targeting pathogenic transcripts, or CRISPR-Cas components for genome editing [10]. Targeting can be enhanced through surface modifications with peptides, antibodies, or aptamers that recognize inflamed or diseased valvular endothelium. For example, VCAM-1-targeted LNPs have shown selective accumulation in aortic valve tissues in preclinical models, highlighting their potential to achieve high local efficacy with minimal systemic exposure [11].

Recent developments include stimuli-responsive LNPs that release cargo in response to oxidative stress, enzymatic activity, or pH changes typical of diseased cardiac tissues. Such smart systems enable controlled temporal and spatial gene modulation, potentially reducing off-target effects and enhancing therapeutic outcomes [12].

2.2 POLYMERIC NANOCARRIERS

Polymeric nanoparticles, constructed from materials such as PLGA, PEG-PLA, or chitosan, is tunability for size, surface charge, and degradation kinetics. They protect nucleic acids from enzymatic degradation, permit sustained release, and can be functionalized with targeting ligands for VICs or valve endothelial cells (VECs) [13]. Dendrimers like PAMAM provide high nucleic acid loading efficiency and precise surface chemistry for conjugation with bioactive molecules [14]. Polymeric systems can also incorporate stimuli-responsive features, enabling cargo release in response to mechanical strain or enzymatic triggers within the valvular microenvironment [15]. Biodegradable polymers minimize long-term toxicity by degrading into non-immunogenic metabolites, which is particularly important for chronic cardiovascular conditions requiring repeated dosing [16].

2.3 INORGANIC NANOCARRIERS

Inorganic nanomaterials, including gold, silica, and iron oxide nanoparticles, are notable for their stability, surface modifiability, and theranostic capabilities. Mesoporous silica nanoparticles (MSNs), for instance, offer high surface area and tunable pore sizes, enabling co-delivery of multiple therapeutic agents [17]. Gold nanoparticles can be functionalized with CRISPR ribonucleoproteins or siRNA and can be tracked in vivo due to their optical properties [18].

2.4 EXTRACELLULAR VESICLES (EVS) AND EXOSOMES

Exosomes and other EVs are naturally occurring nanocarriers secreted by various cell types, including stem cells and cardiomyocytes. Their endogenous origin confers low immunogenicity and inherent tissue-homing capabilities. Engineered EVs can carry mRNA, siRNA, DNA, or CRISPR components to cardiac cells. Surface proteins facilitate receptor-mediated uptake by VICs and VECs, enhancing delivery efficiency [19].

2.5 HYBRID AND BIOMIMETIC NANOCARRIERS

Hybrid nanocarriers integrate the advantages of multiple materials, such as lipid polymer combinations or cell membrane-coated systems. Biomimetic coatings, including platelet or red blood cell membranes, extend circulation time, evade immune clearance, and promote tissue-specific targeting [20]. In VHD, platelet membrane-coated nanoparticles have demonstrated selective homing to inflamed valve tissue, enabling localized delivery of anti-calcific or anti-fibrotic nucleic acids [21]. Hybrid approaches also allow co-delivery of multiple therapeutics, including gene editing machinery and immunomodulatory factors, supporting combination strategies for complex diseases like calcific aortic valve disease (CAVD) [22].

3. Mechanisms of Gene Therapy and Gene Editing in Cardiovascular Systems

Gene therapy and editing strategies aim to correct or modulate disease-causing molecular abnormalities at the cellular and genomic levels. Gene replacement therapy involves delivering functional copies of genes to restore normal protein expression [23]. For instance, delivery of wild-type NOTCH1 or FBN1 can correct deficiencies in congenital valve disorders or connective tissue syndromes [24]. Gene silencing strategies, using siRNA, shRNA, or antisense oligonucleotides, reduce pathogenic gene expression. Silencing pro-calcific genes such as RUNX2, BMP2, or SMAD3 can prevent VIC osteogenic differentiation and calcification [25].

Gene editing technologies, including CRISPR Cas9, base editors, and prime editors, enable precise genomic modifications. Nanocarrier-mediated delivery enhances cytoplasmic or nuclear entry, reduces immunogenicity, and allows repeated dosing a key advantage over viral vectors [26].

4. Nanocarrier Applications in Valvular Heart Disease

4.1 TARGETING CALCIFIC AORTIC VALVE DISEASE (CAVD)

CAVD is driven by endothelial dysfunction, chronic inflammation, and osteogenic differentiation of VICs. Nanocarrier-mediated delivery of siRNA against RUNX2, BMP2, or SMAD3 has shown promise in preclinical models, effectively reducing calcification and preserving valve function [27]. Hybrid lipid polymer nanocarriers carrying shRNA against SMAD3 have reversed endothelial-to-mesenchymal transition (EndoMT) and attenuated calcific progression in diabetic mouse models [28] (Table 1). Similarly, MSNs loaded with anti-calcific siRNA improved endothelialization in tissue-engineered valve constructs, demonstrating dual regenerative and anti-calcific potential [29] [30].

4.2 ANTI-INFLAMMATORY AND REGENERATIVE GENE THERAPY

Chronic inflammation accelerates valvular fibrosis and calcification. Exosome-mediated delivery of transcription factors such as CEBPA and Spi1 can

promote anti-inflammatory macrophage polarization, mitigating local tissue injury [31]. LNP-based mRNA therapies encoding VEGF or matrix metalloproteinase inhibitors stimulate endothelial repair, promote neovascularization, and prevent further ECM degeneration. These approaches demonstrate the potential to combine anti-inflammatory and regenerative therapies in a single platform [32].

4.3 PRECISION TARGETING OF VALVE ENDOTHELIAL CELLS

VECs regulate valve homeostasis and matrix remodeling. Nanocarriers functionalized with VCAM-1 or collagen IV ligands enable selective delivery to diseased valvular tissue [33]. Collagen IV-binding peptide-conjugated lipid polymer nanoparticles carrying shRNA successfully localized to valve leaflets, suppressed osteogenic differentiation, and reduced calcium deposition. Such precision targeting reduces systemic exposure and enhances therapeutic efficacy [34] (Figure 2).

5. GENE EDITING IN RARE CARDIAC DISORDERS

In Marfan syndrome, FBN1 correction via CRISPR-loaded nanoparticles in patient-derived induced pluripotent stem cells restored fibrillin-1 synthesis and normalized ECM structure [35]. For congenital valve defects linked to NOTCH1 or TBX5, lipid polymer hybrid nanoparticles enabled targeted gene editing with minimal off-target effects. Similarly, polymeric nanoparticles delivering mRNA encoding TGF-β pathway inhibitors mitigated aortic dilation in connective tissue disorders [36].

Integration with patient-specific iPSC-derived cardiac tissues supports personalized therapy and autologous tissue engineering, offering a model for screening, optimizing, and validating therapeutic strategies before clinical application [37].

6. FUTURE OUTLOOK AND CLINICAL TRANSLATION

The future of nanocarrier-mediated gene therapy and gene editing for valvular heart disease (VHD) and rare cardiac disorders lies in the convergence of precision medicine, advanced biomaterials, and genome engineering [38]. Emerging strategies are increasingly focused on disease- and tissue-specific targeting, such as developing ligands, aptamers, or peptide conjugates that recognize inflamed or calcified valve endothelium, thereby enhancing therapeutic specificity while minimizing systemic exposure [39]. Multifunctional nanocarriers that integrate therapeutic delivery, real-time imaging, and responsive release mechanisms are likely to play a pivotal role in translating preclinical successes to human applications [40] [41]. Furthermore, the refinement of catheter-based and minimally invasive delivery techniques will allow localized administration of gene therapy agents directly to valve leaflets or myocardium, reducing off-target effects and improving clinical feasibility [42]. On the genome-editing front, the evolution of base editors, prime editors, and epigenome modulators holds promise for safer, reversible, and highly precise correction of pathogenic mutations, particularly in pediatric patients or in rare congenital disorders [43]. In parallel, integration with patient-specific iPSC-derived models enables personalized therapeutic screening and optimization, providing a platform for predicting efficacy, reducing adverse effects, and advancing autologous tissue engineering for regenerative purposes [44]. The establishment of robust safety and regulatory frameworks will be crucial, encompassing immunogenicity assessment, long-term genomic stability, and standardized manufacturing protocols for scalable nanocarrier production [45]. Collectively, these advances suggest that in the coming decade, nanocarrier-mediated gene therapies could evolve from experimental interventions into clinically viable, precision-guided treatments for a wide spectrum of valvular and rare cardiac diseases [46] [47].

7. CONCLUSION

Nanocarrier-based gene therapy and gene editing represent a transformative paradigm in cardiovascular medicine, offering the potential to address the underlying molecular and genetic drivers of valvular heart disease and rare cardiac disorders rather than merely alleviating symptoms. By enabling precise delivery of nucleic acids, RNA therapeutics, or genome-editing machinery, nanocarriers overcome key biological barriers, including the dense extracellular matrix of valve tissue and the immune clearance mechanisms that limit conventional therapies. The integration of targeted, multifunctional nanocarriers with advanced gene-editing technologies allows for personalized, durable, and minimally invasive interventions, with the potential to correct pathogenic mutations, modulate dysregulated signaling pathways, and promote tissue regeneration. As research progresses, continued interdisciplinary collaboration across nanotechnology, molecular cardiology, and regenerative medicine will be essential to optimize safety, efficacy, and scalability, ultimately translating these innovations into next-generation, precision therapies that can significantly improve outcomes and quality of life for patients with complex cardiovascular diseases. The horizon for nanocarrier-based cardiac gene therapy is promising, with the prospect of moving from preclinical breakthroughs to real-world clinical applications that redefine the management of valvular and rare genetic heart disorders.

FIGURE 1. Schematic representation of various nanocarrier platforms for therapeutic delivery, including inorganic, lipid-based, polymeric, and protein-based systems. The illustration summarizes their structural features, drug loading capacities, and comparative benefits and limitations.

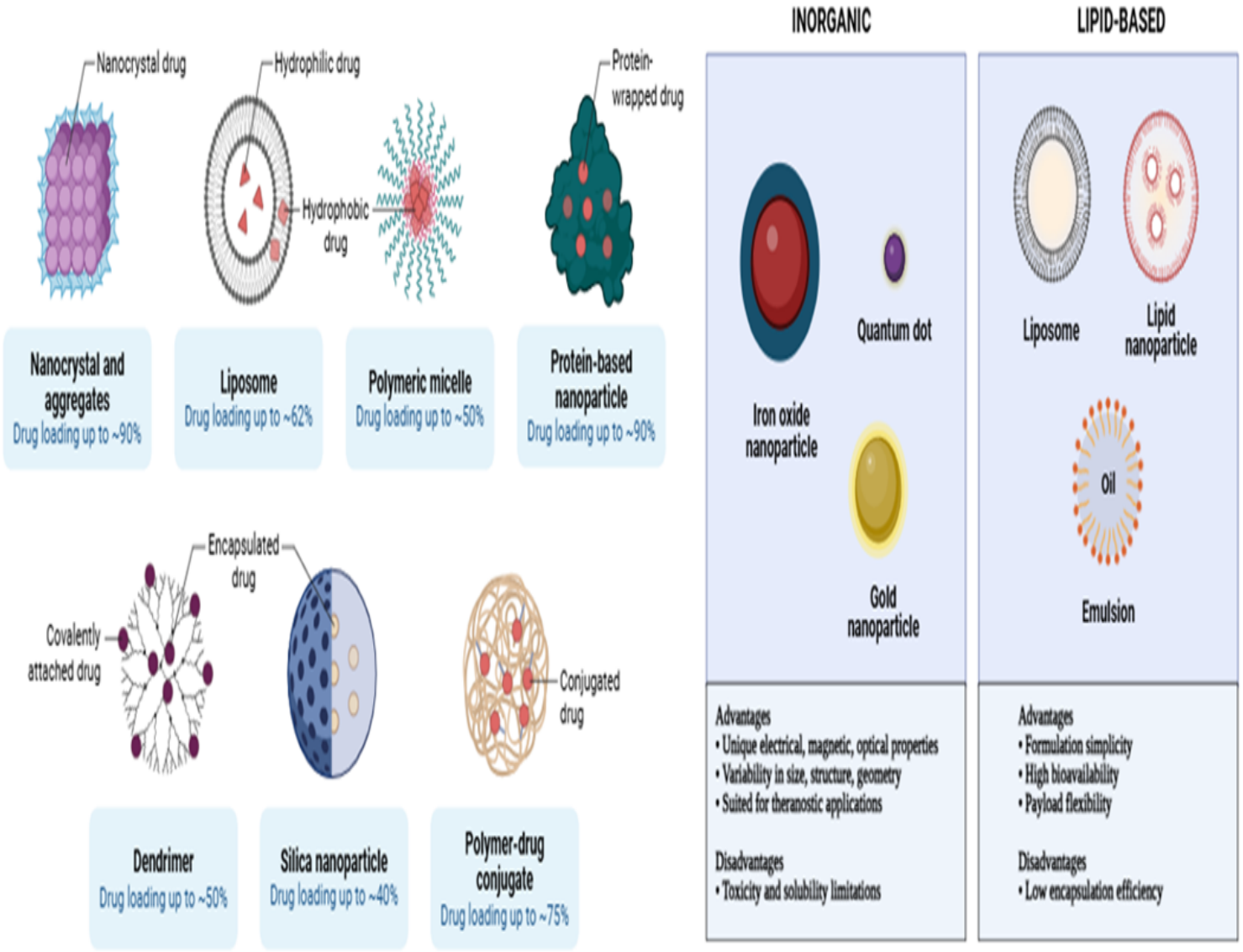

FIGURE 2. the diagram represent the way endothelial failure causes inflammatory and fibrotic pathways to be activated, ROS to be produced in excess, and nitric oxide to be reduced. The combination of these molecular changes leads to cardiac dysfunction, hypertrophy, and myocardial injury.

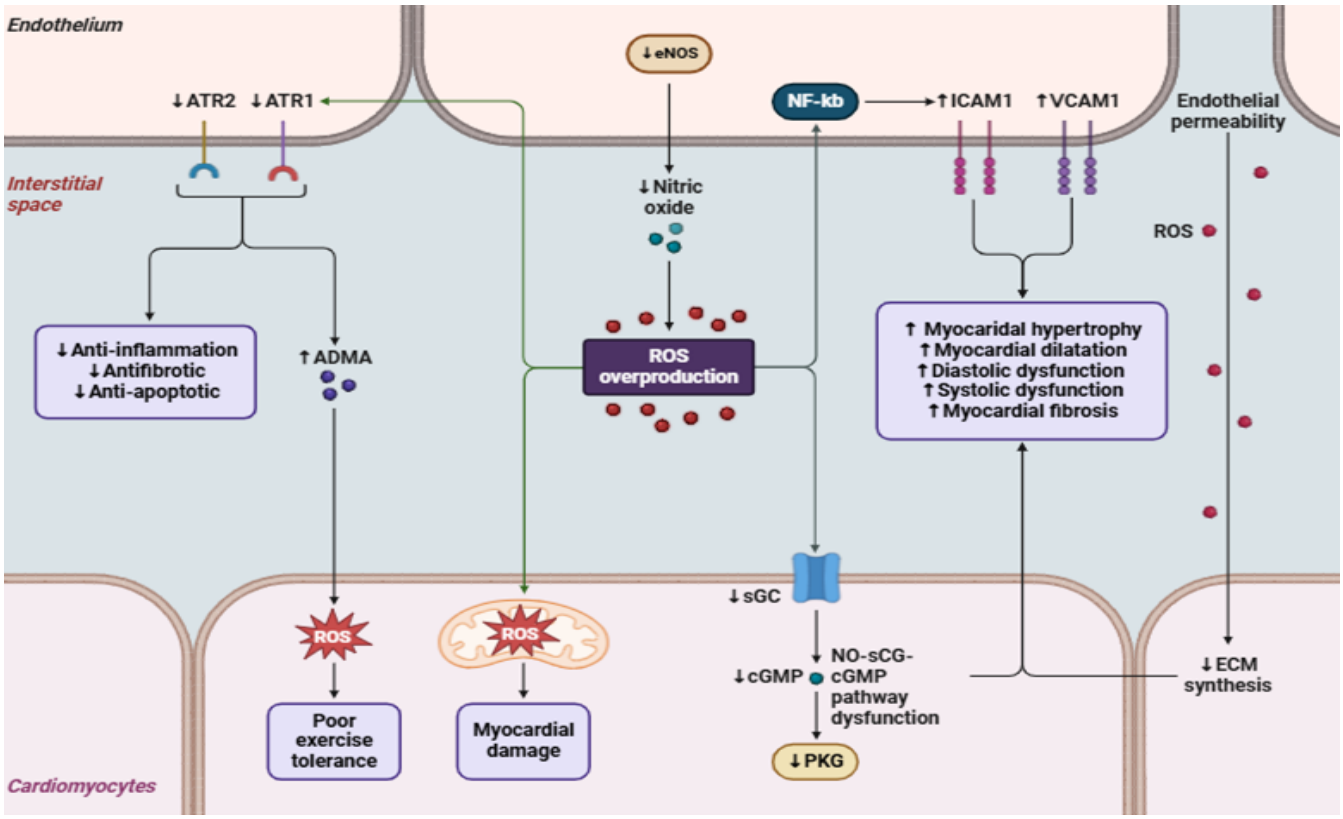

TABLE 1. The molecular mechanisms by which endothelial dysfunction promotes ROS overproduction, inflammation, and fibrosis, leading to myocardial damage and cardiac dysfunction. The studies highlight interconnected oxidative, inflammatory, and fibrotic pathways contributing to disease progression.

Mechanistic Component	Molecular/Cellular Events	Physiological Consequence	References
Endothelial Dysfunction	Reduced eNOS activity, impaired NO bioavailability, and increased VCAM-1 expression	Loss of vasodilation, endothelial activation, and inflammation	[8], [11], [33], [39]
Reactive Oxygen Species (ROS) Overproduction	Activation of NADPH oxidase, mitochondrial oxidative stress, and xanthine oxidase activity	Oxidative damage to lipids, proteins, and DNA within cardiomyocytes	[12], [27], [28], [31]
Inflammatory Pathway Activation	NF-κB signaling, cytokine release (IL-6, TNF-α), macrophage polarization	Chronic inflammation, endothelial mesenchymal transition (EndoMT)	[31], [33], [39]
Fibrotic Remodeling	Upregulation of TGF-β and SMAD3 signaling, increased collagen synthesis	Myocardial stiffness, extracellular matrix (ECM) remodeling	[25], [28], [29]
Reduced Nitric Oxide (NO)	Decreased NO synthesis and increased NO scavenging by ROS	Impaired vasorelaxation, vascular constriction, and hypoxia	[8], [11], [39]
Cardiac Structural Damage	Cardiomyocyte hypertrophy, fibrosis, and necrosis due to oxidative and inflammatory stress	Cardiac dysfunction, heart failure progression	[27], [28], [31], [33]

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