

Review

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PCSK9 inhibitors and their use in advanced heart failure and heart transplant recipients

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Abstract

The use of proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors has garnered widespread attention in the medical community over the past ten years. A number of landmark trials have demonstrated the efficacy of PCSK9 inhibitors in lowering low-density lipoprotein (LDL) levels dramatically when added to background statin therapy. Importantly, their use has led to a significant reduction in adverse events in patients at risk and with established cardiovascular diseases. Published evidence is sparse in the heart failure (HF) population, especially in those with Stage D disease. While the use of PCSK9 inhibitors has not been reported in patients with durable mechanical circulatory support devices, limited data exist in heart transplant recipients. Management of dyslipidemia is critically important in post-heart transplant population as it contributes to the development of cardiac allograft vasculopathy (CAV). However, most 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors (statins) interfere with the metabolism of commonly used immunosuppressant agents, such as tacrolimus. Case studies in post-heart transplant patients demonstrated significant LDL reduction with PCSK9 inhibitor use, without significant drug-drug interactions or adverse events. Two trials are currently underway examining their efficacy in reducing CAV progression. This paper aims to review the available clinical evidence for PCSK9 inhibitor use in HF patients, with specific focus on the advanced heart failure group.

Keywords: PCSK9 inhibitors, left ventricular assist device, heart transplant, heart failure



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INTRODUCTION

The association between dyslipidemia and the risk of atherosclerotic cardiovascular diseases (ASCVD) is well established. Numerous clinical studies have documented the strong correlation of elevated serum low-density lipoprotein cholesterol (LDL-C) levels with plaque development and progression over the past decades^[1-3]. This has led to a surge in research aimed at identifying new molecules with more profound cholesterol lowering effect. The 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitors were developed in the mid-1980's, and lovastatin was the first statin approved by the Food and Drug Administration (FDA) in 1987. Several more potent drugs in this class have been more recently developed and introduced into clinical practice, as their routine use has been widely endorsed by both the American College of Cardiology/American Heart Association (ACC/AHA) and European guidelines for many years^[4,5]. For the past few decades, statins have served as the backbone for LDL-C reduction and have revolutionized cardiovascular prevention^[1,4]. However, it became evident that medications in this class may not be well tolerated by many, may be contraindicated, or may provide suboptimal lipid control in some patients. Therefore, research in the field of cardiovascular prevention continued and several novel agents in multiple drug classes have been developed with profound lipid lowering effect. Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors are one of those new classes.

THE BIOLOGY OF PCSK9

LDL-C receptors (LDL-R) are transmembrane proteins that function primarily to attract, bind to, and remove circulating LDL-C particles from the blood. While a limited number of LDL-R are present on the surface of most cells of the human body, their expression is abundant on hepatocytes^[6]. After binding to a target LDL-C particle, the receptor complex enters the hepatocyte through endocytic clathrin-coated pit formation. Subsequently, the ligand separates, the LDL-R is recycled and is transported back to the cell surface to bind additional LDL-C particles^[6]. This cycle may repeat several times per hour, up to 150 times total, which is thought to be the lifecycle of the LDL-R^[7]. PCSK9 is a proteolytic enzyme secreted by the liver that regulates the number of LDL-R expressed on the cellular surface. It interferes with the release of the LDL-C particle from its receptor following endocytosis, ultimately prompting proteolysis of the entire complex^[1,6]. Premature degradation leads to the reduced expression of LDL-R on the hepatocyte surface and therefore decreased LDL-C clearance. On the contrary, inhibiting the PCSK9 enzyme leads to increased LDL-R recovery and a significant reduction in circulating LDL-C^[1].

In addition to hepatocytes, PCSK9 is expressed in cardiac myocytes and vascular smooth muscle cells in response to pro-inflammatory mediators such as lipopolysaccharide, TNF alpha, ox-LDL, reactive oxygen species (ROS) and damaged mitochondrial DNA^[8-12]. In turn, PCSK9 increases the expression of various scavenger receptors, particularly LOX-1, through a positive feedback loop. This facilitates ox-LDL uptake by macrophages promoting the development and progression of atherosclerosis^[13]. In addition, it mediates the further release of pro-inflammatory cytokines from macrophages, hepatocytes and other tissues^[9,13].

Myocardial ischemia and elevated ROS levels during reperfusion promote mitochondrial stress, cardiomyocyte apoptosis, autophagy, and increase PCSK9 expression in the zone bordering the infarction^[14-16]. Animal models demonstrate that pre-treatment with PCSK9 inhibitors reduces the infarct size by attenuating mitochondrial dysfunction, mitochondrial fission and the apoptotic process. However, administration following the ischemic injury was not protective^[17]. Further studies are needed to determine the possible protective role of PCSK9 inhibitors in reducing infarct size following coronary occlusion.

ESTABLISHED AND EMERGING PCSK9 INHIBITORS

Soon after discovery of the PCSK9 enzyme, inhibiting its function became a target of intense research. This led to the development of a novel class of agents with prominent cholesterol lowering effect, the

PCSK9 inhibitors. Two subcutaneous products, evolucumab (Amgen Inc, Thousand Oaks, CA, USA) and alirocumab (Sanofi SA, Paris, France; and Regeneron Pharmaceutical Inc, Eastview, New York, USA), are currently approved by the FDA, both of which are human monoclonal antibodies with identical mechanism of action. Three landmark clinical trials have evaluated these medications with their results transforming the landscape of lipid management. OSLER, ODYSSEY, and FOURIER have been recently published. These were randomized, controlled, outcome trials that explored the impact of evolucumab or alirocumab on serum LDL-C reduction, risk of cardiovascular events and safety outcomes^[18-20]. All enrolled patients were at high risk or had documented ASCVD when entering the clinical studies. PCSK9 inhibitors were used on top of moderate or high-intensity background statin therapy in the treatment groups. The three trials confirmed a sustained, approximately 60% reduction in serum LDL-C level when compared to placebo. This was accompanied by a significant reduction in adverse clinical outcomes, including death, unstable angina, myocardial infarction and ischemic stroke. Importantly, progressively lower serum LDL-C levels, even below previously reported target values, were not associated with worse outcomes^[21]. The drugs are well-tolerated in general with injection-site reactions, mild influenza-like illness and self-limiting myalgias as the most frequently reported side effects in real-world experience^[22]. However, they are quite expensive. Their role may be of greater importance in patients with familiar hypercholesterolemia and in post-heart transplant population where long-term treatment is necessary.

In addition to the monoclonal antibodies already in clinical practice, small interfering RNAs (siRNAs) are also under investigation with the aim to reduce circulating PCSK9 levels. SiRNAs interfere with the expression of specific genes by promoting mRNA degradation prior to translation. Inclisiran is a long-acting siRNA that targets hepatic PCSK9 synthesis and has been shown to significantly reduce circulating LDL-C levels. It has the distinct advantage of twice per year dosing and acting at the intracellular level of hepatocytes^[23]. It is currently awaiting FDA approval that is expected by the end of 2020. Vaccination aiming to develop PCSK9-specific antibodies are also under investigation. DSPE-PEG-maleimide lipid (L-IFPT) adsorbed to Alhydrogel® (L-IFPTA+) administration has shown to induce a high IgG antibody response, specific against the PCSK9 peptide in hypercholesterolemic mice^[24]. This was paralleled by a 42% reduction in circulating LDL-C levels. This approach could provide safe and long lasting PCSK9 inhibition, as well as decrease the cost and frequency of administration^[24,25].

CURRENT GUIDELINES ON THE USE OF PCSK9 INHIBITORS

The 2018 ACC/AHA/NLA (American College of Cardiology/American Heart Association/National Lipid Association) cholesterol guidelines for clinical practice utilize the ASCVD risk calculator to determine if a patient would benefit from interventions reducing LDL-C levels. Two large meta-analyses have confirmed that ASCVD risk declines progressively as serum LDL-C is lowered using statin therapy^[26,27]. Guidelines now define cholesterol-lowering goals in terms of absolute LDL-C level and percentage LDL-C reduction. The calculated 10-year ASCVD risk is classified into “low risk” < 5%, “borderline risk” 5%-7.5%, “intermediate risk” 7.5%-20% and “high risk” > 20% groups^[4], which determines the recommended intensity of statin therapy (low, moderate, or high). The guidelines also identify a group of patients who are thought to benefit from additional lower levels of LDL-C, with target levels below 70 mg/dL. At times, this goal may only be achieved when prescribing a high-intensity statin combined with a medication from a different drug class. Ezetimibe is currently the first line adjuvant agent, and PCSK9 inhibitors are considered second line adjunctive agents^[4]. Current guidelines also identify additional groups of patients who should be initiated on a PCSK9 inhibitor given their high ASCVD risk. These include individuals with heterozygous familial hypercholesterolemia with an LDL-C of 100 mg/dL or higher, patients with LDL-C level exceeding 220 mg/dL, and persistently elevated serum LDL-C above 130 mg/dL despite a combination of high-intensity statin and ezetimibe^[4].

PCSK9 INHIBITORS IN PATIENTS WITH HEART FAILURE

The medical management of patients with heart failure has become increasingly more complex over the past decades with several new drug classes added to the treatment pool. Diuretics are the most commonly used agents aiming to achieve euvolemia. Medications that reduce sympathetic nervous system activity or block the renin-angiotensin-aldosterone axis have been shown to improve outcomes significantly and are recommended by all guidelines^[28,29]. In contrast, the routine use of lipid lowering agents remains controversial in this population. Statins may be indicated for patients with ischemic cardiomyopathy or with high 10-year ASCVD risk score. However, their use is not established in individuals with non-ischemic heart failure etiology. In two randomized controlled trials (CORONA and GISSI-HF), moderate dose rosuvastatin administration was not associated with improved mortality or a decrease in adverse cardiovascular events in patients with heart failure of any cause, despite significant reduction in LDL-C^[30,31]. The possible benefit of targeting the PCSK9-LDL-R pathway in this population also remains uncertain. In a recent sub-study of BIOSTAT-CHF (Biology Study to Tailored Treatment in Chronic Heart Failure), frozen serum samples obtained from patients with worsening heart failure were analyzed for circulating levels of PCSK9 and LDL-R^[32]. Authors described an independent and significant association between the activity of this axis and adverse clinical outcomes. However, it remains unclear if elevated circulating PCSK9 level is merely a marker or possibly a contributor to increased mortality. New evidence suggests a possible additional benefit of PCSK9 inhibitors stemming from their anti-inflammatory properties^[11,33]. However, as of today, no randomized controlled trials have been published assessing the efficacy of PCSK9 inhibitors in patients with heart failure. Further studies are warranted to establish their benefit in this population.

PCSK9 INHIBITOR USE IN PATIENTS WITH DURABLE MECHANICAL CIRCULATORY SUPPORT DEVICES

The use of durable mechanical circulatory support (MCS) devices has been steadily rising over the past decade in patients with advanced heart failure. Despite the technological advancements and dramatic improvement in clinical outcomes with newer generation devices, neurological complications remain relatively high in these patients^[34,35]. With the newest generation Heart Mate 3 LVAD (Abbott Laboratories, Minneapolis, MN), the cumulative rate of stroke remains at around 10% at two years^[36]. Many of these ischemic and hemorrhagic cerebrovascular events are related to hypertension, micro embolization, infection and changes in cerebral autoregulation, owing to the continuous flow profile. Although many patients supported with MCS have underlying ischemic cardiomyopathy and diffuse atherosclerotic vascular disease, there is limited evidence for statin therapy to improve survival in this population. Vieira and colleagues found that statin use after LVAD implantation is associated with lower rates of ischemic, but not hemorrhagic strokes^[37]. On further evaluation, it was hypothesized that the pleiotropic effects of statins, including their anti-inflammatory, immunologic and anti-thrombotic effects, are primarily responsible for these clinical benefits^[37]. No specific guidelines currently address statin use in patients receiving LVAD, and providers often rely on risk calculators and consider other indications when prescribing statins. Similarly, there are no published data or guidelines on PCSK9 inhibitor use in this population. More studies are needed to evaluate how these novel lipid lowering agents are tolerated in patients supported with an LVAD and how these may affect long-term clinical outcomes, including stroke.

PCSK9 INHIBITORS IN HEART TRANSPLANT RECIPIENTS

Heart transplantation is the most definitive treatment option for patients with end stage heart failure. Advances in post-transplant care has led to significant reduction in rejection rates, infections, and the incidence of malignancies. The improvement in graft and patient survival unmasked cardiac allograft vasculopathy (CAV) as the leading cause of morbidity and mortality a few years following transplantation. With the prevalence of CAV rising to 47% at 10 years, effective and early prevention are critically important^[38,39]. The predominant histological feature of CAV is the progressive, diffuse thickening of the

coronary intima affecting all large epicardial vessels, intramuscular arteries as well as the microvascular bed^[40,41]. The initial, immune-mediated arteritis is followed by the diffuse deposition of cholesterol particles within the intima. Risk factors include the host-mediated immunological response towards the graft as well as non-immune factors, such as dyslipidemia, hypertension, smoking, CMV infection and ischemia-reperfusion injury^[42,43]. Dyslipidemia is extremely common in heart transplant recipients. Many patients have long-standing hyperlipidemia prior to transplantation, and it is also a well-established side effect of immunosuppressive agents, including corticosteroids, rapamycin and calcineurin inhibitors (e.g., tacrolimus, cyclosporine)^[44]. As such, statin therapy is a Class I recommendation in current guidelines for heart transplant recipients, irrespective of serum cholesterol levels^[38]. Despite being the standard of care, many statins have significant interactions with immunosuppressants, may cause myositis, rhabdomyolysis or myalgias, and may provide suboptimal lipid control^[45].

Due to the above limitations and the unfavorable side effect profile of statin therapy in the post-transplant population, there are ongoing investigations to test therapeutic alternatives for lipid management, such as PCSK9 inhibitors. Agents in this class bind specifically to an extracellular target and do not interact with the cytochrome P450 system. Therefore, they have low risk for significant drug-drug interactions, including with immunosuppressants, and their properties render them well tolerated overall^[46,47]. Interestingly, Simha and colleagues reported that mammalian target of rapamycin (mTOR) inhibition with sirolimus increases PCSK9 expression in both humans and *in-vitro* cell culture studies; however, the increased PCSK9 levels did not correlate with sirolimus-induced hypercholesterolemia. It is postulated that sirolimus may cause hyperlipidemia via multiple pathways and further studies are under-way^[48]. Although no large, randomized clinical trials have yet been completed, several case series reported single center experiences on the use of PCSK9 inhibitors in statin-intolerant heart transplant recipients [Table 1]. The reduction in serum LDL-C in response to PCSK9 initiation averaged between 40% and 70%^[44,49]. Both drugs in the class demonstrated a favorable safety profile with adverse reactions limited to injection site erythema, rhinorrhea, nausea and clinically insignificant transaminitis^[49,50]. These case series reported no increase in the risk of graft rejection, infections or fluctuation in serum immunosuppressant levels^[44,49,51,52]. In addition to their direct benefit on circulating LDL-C levels, the anti-inflammatory properties of PCSK9 inhibitors may also reduce the activation of the innate immune system encountered after solid organ transplantation^[33,53]. While the results of current observational data on the use of PCSK9 inhibitors in heart transplant recipients are promising, most reports are limited by the number of patients and short-term follow-up, highlighting the need for additional studies in the field.

A recent paper by Bjerre and colleagues reported elevated levels of PCSK9 in patients with macrovascular CAV, as detected by coronary angiography and optic coherence tomography^[54]. In addition, the authors found a trend towards higher circulating PCSK9 levels in the subgroup taking mTOR inhibitors. Note, however, that it is routine practice to initiate patients on an mTOR inhibitor once CAV is established, and therefore this observation might be unrelated to the immunosuppressant used. Nevertheless, further larger scale randomized studies are needed to establish the possible benefit of PCSK9 inhibition in de novo heart transplant recipients to prevent CAV development and progression.

FUTURE DIRECTION

Given their clinical efficacy in reducing serum LDL-C, limited side effect profile, and the lack of interactions with immunosuppressants, it is imperative to further explore the idea of PCSK9 inhibitor use in heart transplant recipients for CAV prevention. Two clinical trials are currently open and are actively enrolling patients. EVOLVD is a multicenter, randomized, controlled, double-blind study aiming to determine whether the addition of evolocumab on top of background statin therapy, can ameliorate CAV in de novo heart transplant patients at 12 months, as assessed by coronary intravascular ultrasound^[55]. First results are expected to be published in 2022. The PCSK9 Inhibition After Heart Transplantation trial lead

Table 1. Published reports on PCSK9 inhibitor use in heart transplant recipients

Author	Title/PMID	Drug used and number of patients	Outcome	Adverse effects
Warden <i>et al.</i> ^[49]	Use of PCSK9 inhibitors in solid organ transplantation recipients	alirocumab <i>n</i> = 2; evolocumab <i>n</i> = 9; sequential <i>n</i> = 1	60% median LDL-C decrease	25% mild and self-limiting injection site reactions, nausea and rhinorrhea
Di Nora <i>et al.</i> ^[57]	Safety and efficacy of pcsk9 inhibitor treatment in heart transplant patients PMID: 30399127	evolocumab <i>n</i> =1	87% decrease in LDL	None
Jennings <i>et al.</i> ^[52]	PCSK9 inhibitor use in heart transplant recipients: a case series and review of the literature PMID: 31478991	evolocumab <i>n</i> = 7	45% decrease in LDL	None
Kühl <i>et al.</i> ^[44]	Treatment of hypercholesterolemia with PCSK9 inhibitors in patients after cardiac transplantation PMID: 30650126	evolocumab <i>n</i> = 8; alicumab <i>n</i> = 2	40% decrease in LDL; 30% decrease in cholesterol	alirocumab patient developed HCC and Hep E
Moayed <i>et al.</i> ^[45]	Safety and efficacy of PCSK9 inhibitors after heart transplantation PMID 30595172	evolocumab <i>n</i> = 6	> 70% reduction in LDL	None
Groba-Marco <i>et al.</i> ^[51]	Treatment of hypercholesterolemia with PCSK9 inhibitors in heart transplant recipients. first experience in Spain. PMID 31474577	alirocumab <i>n</i> = 5	45%-76% reduction in LDL	None
Sandesara <i>et al.</i> ^[50]	PCSK9 inhibition in patients with heart transplantation: a case series PMID 31353230	alirocumab <i>n</i> = 1; evolocumab <i>n</i> = 2	64% reduction in LDL; 49% reduction in total cholesterol	None

PCSK9: proprotein convertase subtilisin/kexin type 9; LDL: lowering low-density lipoprotein

by Fearon^[56] from Stanford University (NCT03537742) aims to determine alirocumab's safety, efficacy, and impact on CAV when administered early after heart transplantation. The expected study completion date is in September 2023. Further, long-term outcome trials will be needed to establish the safety and efficacy of PCSK9 inhibitors in heart transplant recipients.

CONCLUSION

With the discovery of PCSK9 inhibitors, cardiologists are given a novel but expensive tool to manage hyperlipidemia in patients at high risk for ASCVD, and those intolerant to more conventional therapies. Several large, randomized, outcome trials have established their safety, efficacy and favorable side effect profile. Trials are ongoing for heart transplant recipients, yet current evidence is lacking for advanced heart failure patients and those with durable mechanical circulatory support. New PCSK9 inhibitors are on the horizon with a more patient-friendly administration schedule. When evaluated and introduced into clinical practice, these will hopefully reduce the overall cost burden, thereby enabling a more widespread utilization.

DECLARATIONS

Authors' contributions

Literature review, manuscript preparation, review, editing: Agdamag ACC, Maharaj VR, Fraser M, Edmiston JB, Charpentier V, Francis GS, Alexy T

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Ethical approval and consent to participate

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Consent for publication

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