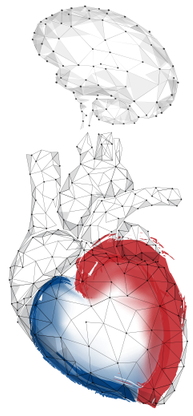
Cardiovascular Prevention and Pharmacotherapy



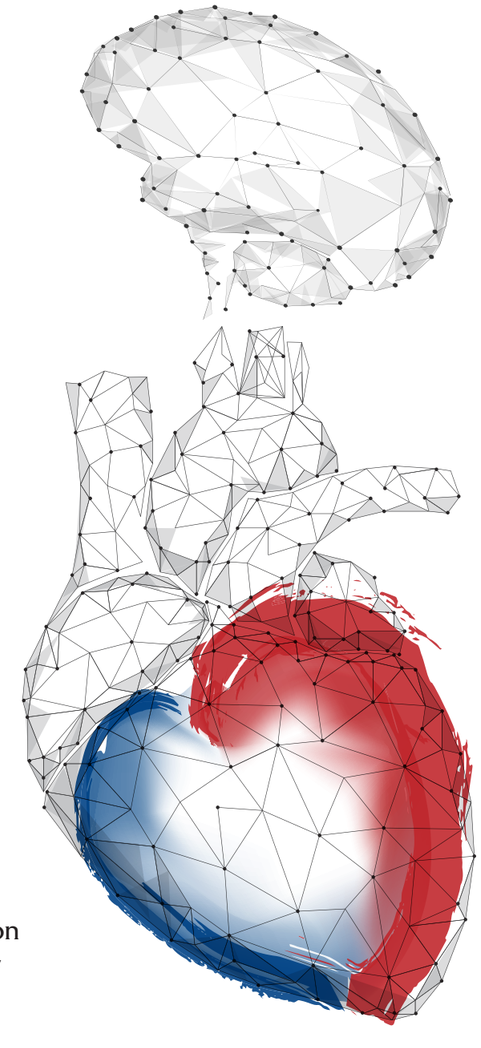
Korean Society of Cardiovascular Disease Prevention
Korean Society of Cardiovascular Pharmacotherapy

Vol. 5 • No. 4 • October 2023
Pages 99–150
https://e-jcpp.org

Vol. 5 • No. 4 • October 2023

https://e-jcpp.org
eISSN 2671-700X

Cardiovascular Prevention and Pharmacotherapy



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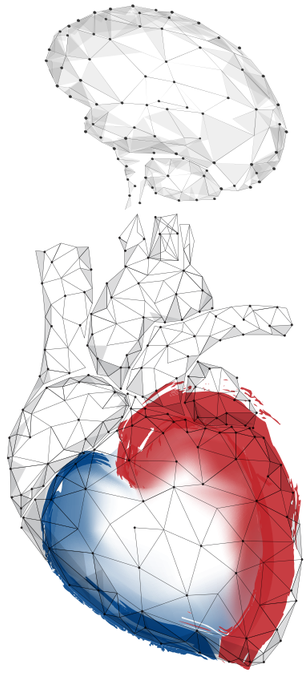
Vol. 5 • No. 4 • October 2023 eISSN 2671-700X



Aims and Scope

Cardiovascular Prevention and Pharmacotherapy (CPP) is an open access, peer-reviewed, online-only journal. CPP is the official journal of the Korean Society of Cardiovascular Disease Prevention (KSCP) and the Korean Society of Cardiovascular Pharmacotherapy Korea Chapter (KSCVP). The journal is published four times a year (on the last day of January, April, July, and October).

CPP covers all clinical and basic research on cardiovascular, cerebrovascular, and metabolic diseases including epidemiology, pathophysiology, treatments, and preventive activity. CPP publishes original research articles, review articles, editorials, and letters to the editor in English. Educational content will be published in English or Korean in various formats.

Publisher

Korean Society of Cardiovascular Disease Prevention, Korean Society of Cardiovascular Pharmacotherapy

Editor-in-Chief

Junghyun Noh, Inje University, Korea

Editorial Office

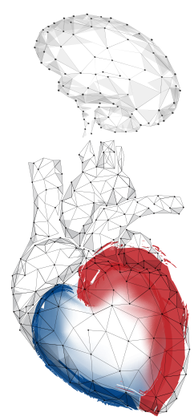
Cardiovascular Prevention and Pharmacotherapy
#243, Yongwon Building, 31, Seochojungang-ro 18-gil, Seocho-gu, Seoul 06634, Korea
Tel +82-70-8873-6030 **Fax** +82-2-587-2066 **Email** cpp1@e-jcpp.org **Website** https://e-jcpp.org

Publishing Office

M2PI
#805, 26 Sangwon 1-gil, Seongdong-gu, Seoul 04779, Korea
Tel +82-2-6966-4930 **Fax** +82-2-6966-4945 **Email** support@m2-pi.com **Website** https://m2-pi.com

Published on 31 October, 2023

Cardiovascular Prevention and Pharmacotherapy



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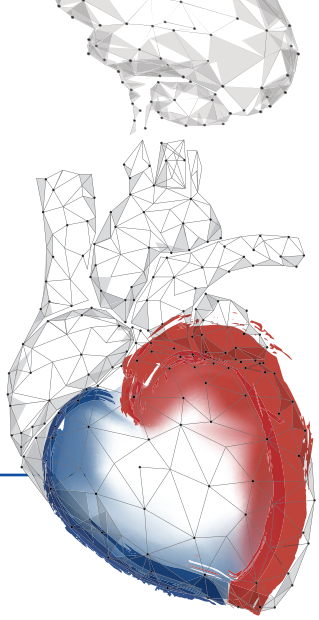
Cardiovascular Prevention and Pharmacotherapy

Vol. 5 • No. 4 • October 2023 eISSN 2671-700X



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Cardiovasc Prev Pharmacother 2023;5(4):99-101
eISSN 2671-700X
https://doi.org/10.36011/cpp.2023.5.e13

Cardiovascular Prevention and Pharmacotherapy

Cardiovascular-related health behavior changes: lessons from the COVID-19 pandemic and post-pandemic challenges

Inha Jung[1], Won-Young Lee[2]

[1]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Korea University Ansan Hospital, Ansan, Korea*
[2]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, Seoul, Korea*

Cardiovascular disease (CVD) is the leading cause of death worldwide, and its substantial healthcare costs are a global public health concern [1]. Hypertension, diabetes, dyslipidemia, cigarette smoking, physical inactivity, obesity, and unhealthy diets are well-known modifiable risk factors for CVD [2]. Considering that nearly a quarter of CVD-related deaths can be avoided through effective behavioral interventions [3], evidence-based guidelines propose behavioral counseling as the initial treatment approach to encourage cardiovascular-related health behaviors, including regular exercise and a balanced diet [4,5].

COVID-19, which emerged in September 2019 in Wuhan, China, quickly escalated into a global pandemic [6]. After the World Health Organization (WHO) declared COVID-19 a public health emergency on January 30, 2020, it had a profound impact on public health and prompted significant changes in health behaviors, particularly among individuals with chronic health conditions such as diabetes and obesity [7–9]. Throughout the pandemic, many countries and territories imposed mandatory lockdown restrictions to curb the rapid spread of the virus. The temporary closure of public venues, including restaurants and fitness facilities, led to changes in health-related behaviors, such as regular exercise and maintaining a balanced, healthy diet [8,10]. A study investigating behavioral changes in Japanese patients with diabetes during the COVID-19 pandemic [11] found that decreased physical activity levels adversely affected glycemic control and contributed to weight gain. Furthermore, studies have shown that the social isolation resulting from stay-at-home orders had detrimental effects on mental health and eating habits [12]. A study conducted in Spain [13] noted an increase in emotional eating in response to boredom or anxiety during the pandemic, leading to weight gain.

The observed changes in health-related behaviors during the COVID-19 pandemic may vary based on ethnicity, race, or country. Therefore, it is essential to understand the sociodemographic factors that influence individuals' health-related behaviors in order to develop effective public health policies. In a previous issue of *Cardiovascular Prevention and Pharmacotherapy*, Kim et al. [14] conducted a study investigating the changes in CVD-related health behaviors during the COVID-19 pandemic and associated sociodemographic factors among the Korean population.

Received: September 2, 2023; **Accepted:** September 19, 2023
Correspondence to Won-Young Lee, MD
Division of Endocrinology and Metabolism, Department of Internal Medicine, Kangbuk Samsung Hospital, Sungkyunkwan University School of Medicine, 29 Saemunan-ro, Jongno-gu, Seoul 03181, Korea
Email: drlwy@hanmail.net

Interestingly, the study noted positive changes in smoking habits, alcohol consumption, and healthcare service utilization. However, negative changes were observed in diet, exercise, and stress levels. This contrasts with other studies that reported an increase in alcohol consumption and tobacco use [15,16]. Unlike previous research demonstrating a correlation between higher income and engagement in health-protective behaviors during the COVID-19 pandemic [17], the authors did not find any significant associations between negative changes in health behaviors and household income, with the exception of smoking.

The study highlights that patients with cardiometabolic diseases, including coronary heart disease, cerebrovascular disease, hypertension, diabetes, and dyslipidemia, are more likely to exhibit aggravated health behaviors, except for smoking and alcohol consumption [14]. The study, therefore, provides valuable insights. Numerous studies have shown that the COVID-19 pandemic has brought about substantial changes in health-related behaviors, with several unfavorable shifts that could potentially contribute to elevated rates of CVD. Even as quarantine policies change and the prevalence of COVID-19 decreases, the negative changes in cardiovascular-related health behaviors established during the pandemic may persist, potentially leading to an increased CVD prevalence.

Long-term, large-scale studies with longitudinal designs are required to evaluate the impact of unhealthy health-related behaviors during the COVID-19 era on the development of CVD. Furthermore, a more robust approach to public education and targeted promotional campaigns is crucial for populations at high risk. The goal of these efforts is to promote the re-establishment of healthy lifestyle habits and the maintenance of beneficial health adjustments after the pandemic.

ARTICLE INFORMATION

Ethics statements
Not applicable.

Conflicts of interest
Won-Young Lee is the Consulting Editor of *Cardiovascular Prevention and Pharmacotherapy*, but was not involved in the peer reviewer selection, evaluation, or decision process of this article. The authors have no other conflicts of interest to declare.

Funding
None.

Author contributions
Conceptualization: all authors; Supervision: WYL; Writing–original draft: IJ; Writing–review & editing: all authors. All authors read and approved the final manuscript.

ORCID
Inha Jung, https://orcid.org/0000-0001-8561-8544
Won-Young Lee, https://orcid.org/0000-0002-1082-7592

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Review Article

Cardiovasc Prev Pharmacother 2023;5(4):102-112
eISSN 2671-700X
https://doi.org/10.36011/cpp.2023.5.e15

Cardiovascular Prevention and Pharmacotherapy

Decision-making for recurrent atrial fibrillation after catheter ablation

Jum Suk Ko[1], Sung Soo Kim[2], Hyung Ki Jeong[1], Nam Ho Kim[1]

[1]*Division of Cardiology, Department of Internal Medicine, Wonkwang University Hospital, Wonkwang University School of Medicine, Iksan, Korea*
[2]*Department of Cardiovascular Medicine, Chosun University College of Medicine, Gwangju, Korea*

Catheter ablation for atrial fibrillation (AF), especially pulmonary vein (PV) isolation, is widely used for rhythm control. However, AF recurrence remains a challenge, affecting 20% to 50% of cases. This review focuses on AF recurrence after catheter ablation. AF recurrence can be categorized into early recurrence (ER) within 3 months after index procedure, late recurrence (LR) within 1 year, and very LR (VLR) occurring beyond 1 year. ER has emerged as a significant predictor of LR, contrary to the traditional understanding. LR is primarily caused by PV reconnection, while VLR more involves non-PV triggers or substrates. Managing AF recurrence includes antiarrhythmic drugs, steroids, colchicine, and repeat ablation. Antiarrhythmic drugs reduce ER but have a limited impact on LR. Steroids have been shown to reduce ER, but not long-term recurrence. Colchicine, an anti-inflammatory agent, shows promise in reducing both ER and LR, although further research is necessary. Whether to perform early repeat ablation after ER remains uncertain, as not all patients require immediate intervention. In conclusion, AF recurrence after ablation remains a complex issue. Understanding the underlying mechanisms is essential for personalized management. Tailored approaches, considering individual characteristics, are crucial for long-term success. Future research should focus on improving therapeutic strategies for AF recurrence.

Keywords: Atrial fibrillation; Catheter ablation; Recurrence

INTRODUCTION

Atrial fibrillation (AF) is the most common arrhythmia; it requires sustained treatment and is a leading cause of a variety of morbidities. The mainstream of AF management is the "ABC pathway," as outlined in a recent guideline [1,2]. In particular, the importance of rhythm control for improved symptoms has been increasingly emphasized. The EAST-AFNET 4 (Early Therapy of Atrial Fibrillation for Stroke Prevention Trial) Study [3] demonstrated that early rhythm control significantly improved composite cardiovascular outcomes compared to the usual care group. Those results have justified active attempts for rhythm control. Currently, catheter ablation for effective rhythm control is widely utilized. Stemming from the pioneering work of Haissaguerre et al. [4], pulmonary vein (PV) isolation by radiofrequency (RF) catheter ablation has become a cornerstone of AF ablation. Furthermore, other than RF energy, cryoablation and pulsed field ablation are also effectively employed for PV isolation. Numerous previous studies have

Received: August 16, 2023; **Revised:** October 7, 2023; **Accepted:** October 10, 2023
Correspondence to Hyung Ki Jeong, MD
Division of Cardiology, Department of Internal Medicine, Wonkwang University Hospital, Wonkwang University School of Medicine, 895 Muwang-ro, Iksan 54538, Korea
Email: jhk30334@hanmail.net

confirmed that catheter ablation for rhythm control is more effective than medical rhythm control [5–7]. However, a persistent issue is the recurrence of AF. AF recurrences after catheter ablation are common, with estimates ranging from 20% to 50% after 5 years [8]. There is limited guidance available for decision-making or for managing AF recurrence after catheter ablation. Therefore, we present a review of the etiology of AF recurrence after catheter ablation, the characteristics of atrial electrical remodeling in the redo procedure, and management options for AF recurrence.

DEFINITION OF AF RECURRENCE

Early recurrence

Early recurrence (ER) refers to the recurrence of AF within 3 months after ablation, and it is known to occur in approximately 50% of patients postprocedure. In an expert consensus on catheter and surgical ablation of AF, ER is defined as recurrence of atrial tachyarrhythmia—comprising AF, atrial flutter (AFL), and atrial tachycardia (AT)—within 3 months after ablation [8]. This period is often referred to as the blanking period, a term that has been defined differently across various studies, with durations ranging from 1 week to 3 months [9–13]. This diversity in blanking periods has made it challenging to standardize the definition. In the expert consensus statements, the task force team agreed to define the blanking period as the first 3 months postprocedure, during which any recurrence of AF should not be considered a treatment failure. If a blanking period of less than 3 months is chosen, it should be prespecified and clearly stated. Previous studies have often attributed ER occurring shortly after the procedure to acute inflammatory reactions caused by RF energy application, transient imbalances in the autonomic nervous system, or the need for lesions created by RF energy to stabilize over time [14–16]. All of these factors were once thought to be reversible.

Recent studies have consistently provided evidence that ER can be a significant predictor of late recurrence (LR) beyond 1 year, challenging the traditional understanding of ER. Kim et al. [17] conducted a retrospective analysis and found that 24.1% of patients experienced ER. In a multivariate analysis, ER was identified as an independent predictive factor for LR following a single procedure, with a hazard ratio (HR) of 2.76. This trend was consistent regardless of whether the AF type was paroxysmal or nonparoxysmal. Several substudies of large randomized trials have also reported similar findings. In a substudy of the ADVICE (Adenosine Following Pulmonary Vein Isolation to Target Dormant Conduction Elimination) Trial [18], 49.1% of patients who underwent RF catheter ablation experienced ER of atrial tachyarrhythmia, including AF/AT, and among these patients, those who experienced ER had a significantly higher incidence of LR (HR, 4.80). Andrade et al. [19] analyzed a subgroup of the STAR-AF (Substrate and Trigger Ablation for Reduction of Atrial Fibrillation) Trial and found that 49% of patients experienced ER. During a 1-year follow-up period, the group of patients who experienced ER had a significantly higher incidence of LR (66.7%) than the group that did not experience ER (28.6%). Not only RF catheter ablation, but also cryoablation has shown a considerable rate of ER, which was a strong predictor for LR. Park et al. [20] analyzed 406 patients who underwent cryoablation at two tertiary institutions. Of these patients, 161 (39.7%) had paroxysmal AF, and 104 (25.6%) experienced ER. The group of patients with ER had a significantly higher incidence of LR at 1 year.

The timing of ER appears to influence the incidence of LR in distinct ways. In a study of paroxysmal AF [21], it was noted that patients who experienced their first recurrence within the first 3 months had a lower incidence of LR. Similarly, other studies have shown that patients who had a recurrence within the first month exhibited fewer instances of LR than those who experienced recurrence in the second or third month [18,22]. Conversely, in a study of persistent AF, this temporal difference seemed to have less of an impact. The authors of that study speculated that this might be due to variations in the underlying mechanisms of recurrence. They suggested that paroxysmal AF might be more influenced by transient factors, while persistent AF might be more closely associated with substrate-related factors, leading to recurrence [23].

Late recurrence

LR is defined as recurrence within 1 year, excluding the first 3 months following the index procedure (referred to as the blanking period) [8]. Recurrence after ablation usually occurs within 1 year, especially within 6 months, and the annual recurrence rate ranges from 5% to 9% [24,25]. LR

has been reported to occur in 25% to 40% of cases, and this rate seems to vary among studies because of differences in patient population (paroxysmal vs. persistent, monitoring methods, follow-up duration, and study designs) [26,27]. PV reconnection is a main mechanism in many cases [26]. Numerous studies have reported factors predicting LR, with advanced age, male sex, left atrium size, and ER being commonly recognized as influential factors [28–33].

Very late recurrence

Very LR (VLR), defined as recurrence occurring 1 year or more after the index procedure, has an annual rate of 7.6% [8]. It has been noted that the recurrence rate tends to increase as the follow-up period extends [24,34]. While PV reconnection remains the primary cause, accounting for approximately 50% to 70% of cases, this cause is less common than it is for LR [24,35–37]. Sotomi et al. [35] compared the electrophysiologic characteristics in redo procedures for recurrent AF between LR and VLR. In that study, 124 with LR and 26 with VLR, PV reconnection was significantly lower in the VLR group (90% vs. 69%, P<0.01). Moreover, among the reconnected PV, the trigger that initiated the atrial tachyarrhythmia was significantly lower in the VLR group. The authors suggested that not only PV reconnection, but also the progression of the AF substrate, might be an important mechanism explaining VLR. Similar findings were also observed in Korean data. Choi et al. [38] reported that during a follow-up period of more than 5 years, the extra-PV trigger significantly increased in a patient group who experienced AF recurrence after 5 years from the initial procedure.

One intriguing study [39] suggests that in instances where sinus rhythm is sustained for an extended period, there tends to be a more favorable response to direct current (DC) cardioversion or antiarrhythmic drugs, even without the necessity for repeat ablation. It is worth noting that repeat ablation has also demonstrated improved response rates in these patients. In another study [40], a considerable proportion of patients with PV reconnection have been observed to remain AF-free, suggesting that factors beyond PV triggers may influence AF occurrence in patients with long-term maintenance of sinus rhythm.

Baseline characteristics for recurrence

Previous studies have analyzed various risk factors for the recurrence of AF. Although there may be minor differences across studies, the most notable risk factors include the size of the left atrium (LA), the duration of AF, age, and epicardial fat [1]. In one meta-analysis [41], LA size >50 mm was a strong predictor of LR (odds ratio, 5.10; 95% CI, 2.00–12.9), and another research [42] also emphasized the significance of LA size and hypertension as important factors associated with recurrence. LA size and volume, especially when measured using computed tomography, were found to be associated with recurrence in studies with over 2 years of follow-up (VLR) [43–45]. Additionally, epicardial fat was found to impact both LR and VLR [46]. Other factors, such as prolonged P wave duration, high body mass index, extended interatrial conduction time, and social factors like low educational attainment, low family income, and living alone, were also associated with AF recurrence following ablation [47–49].

Type of recurrence: AF, AFL, and AT

The definition of recurrence varies across studies. Some studies consider only AF as recurrence, while others include all forms of atrial tachyarrhythmia, such as AFL or AT. For instance, the current expert consensus statement defines atrial tachyarrhythmia, including AF, AT and AFL, as recurrence. The reported frequency of recurrence ranges from 4.7% to 31%, reflecting the impact of different ablation methods and extents during the index procedure [50–52].

The mechanism of AFL and AT recurrence is primarily related to PV reconnection or conduction delay/conduction block occurring in previously ablated lesions, leading to reentry. In prior studies, it appeared to be more favorable clinical course if the recurrence was as AFL and AT. One study involving 341 ablation cases [53], AFL and AT recurrence was reported in 10 individuals (3%), mostly associated with PV reconnection, and curative outcomes were achieved during redo procedures. Choi et al. [52] analyzed 133 redo procedure patients and found that 50 (37.6%) experienced AT recurrence and 83 (62.4%) experienced AF recurrence. The frequency of PV reconnection did not show significant differences between the two groups, while atrial arrhythmia-free survival was significantly better in

the AT recurrence group. The main mechanisms of AT were predominantly related to perimitral flutter, followed by roof flutter and cavotricuspid isthmus flutter, with the exception of PV-related flutter. In addition, there were cases of focal AT from the vein of Marshal, septum, coronary sinus, and superior vena cava (SVC).

In most cases of AFL and AT recurrence, the initial treatment typically involves DC cardioversion or antiarrhythmic drugs, which have often demonstrated favorable outcomes. However, these tachyarrhythmias may lead to worsening symptoms due to an increased mean ventricular rate (often a 2:1 ventricular response) compared to AF. Therefore, if the arrhythmia persists or frequently recurs, it may be reasonable to consider repeated ablation as a treatment option.

MEDICAL MANAGEMENT FOR AF RECURRENCE

Antiarrhythmic drugs

The association between ER and LR has led some researchers to investigate the potential effectiveness of reducing ER through antiarrhythmic drug therapy. Among these studies, the 5A Study [54] focused on 110 patients with paroxysmal AF who had undergone postprocedural antiarrhythmic drug therapy for 6 weeks. This resulted in a significant reduction in ER (13% vs. 28%), but no significant difference in LR was observed (72% vs. 68%). Similar trends were noted in the AMIO-CAT (Short-term Amiodarone Treatment after Catheter Ablation for Atrial Fibrillation) Trial [55] and the EAST-AF (Efficacy of Antiarrhythmic Drugs Short-Term Use After Catheter Ablation for Atrial Fibrillation) Trial [56], suggesting that while postablation antiarrhythmic drugs may have some effect in decreasing ER, their impact on recurrence beyond 3 months seems minimal. Even the meta-analysis data [57] did not show any statistically significant benefits. Therefore, the prescription of postprocedural antiarrhythmic drugs should be approached with caution, taking into account both the potential benefits and side effects, rather than being prescribed routinely.

Steroids

Given that acute inflammatory reactions are a key mechanism contributing to ER, it has been hypothesized that administering anti-inflammatory steroids immediately postprocedure could reduce such recurrences. Numerous studies have been undertaken to test this theory. According to research by Kim et al. [58], steroids were found to be significant in reducing ER, but they did not significantly impact recurrences at the 24-month mark. Recent data [59] has indicated that while steroids can decrease the inflammatory marker, they do not improve recurrence rates, regardless of whether the recurrence is early or late. Therefore, the routine prescription of steroids following an ablation procedure is not currently recommended.

Colchicine

The concept that AF recurrence is due to inflammatory reactions has led to the investigation of the anti-inflammatory agent colchicine. Two studies [60,61] have yielded promising results, demonstrating a reduction in ER and potential for reducing LR as well. Colchicine also decreased inflammatory markers. According to Deftereos et al. [61], early AF recurrence is mediated by an inflammatory process, and colchicine exerts its anti-inflammatory effect by inhibiting microtubule depolymerization. This inhibition simultaneously negatively impacts the phosphorylation of calcium channels, ultimately reducing calcium overload-induced tachyarrhythmia. Thus, colchicine appears to have a protective effect against AF recurrence. In an animal study [62], colchicine was associated with reduced myocardial fibrosis, which could potentially influence long-term AF recurrence. However, due to the relatively small sample size, varying dosing strategies, and diverse study endpoints, the current expert consensus has not issued a definitive recommendation regarding colchicine. A recent meta-analysis [63] indicated that colchicine not only tends to inhibit ER, but may also inhibit LR, as suggested by some previous studies. However, a significant number of patients taking colchicine were unable to maintain adherence to the prescribed duration as planned in the study, and discontinued use due to adverse effects of the drug. Given the adverse effects of colchicine, careful consideration is necessary before its administration. Moreover, due to the absence of large-scale studies, further research is needed to establish its efficacy and safety.

DC cardioversion

DC cardioversion is frequently used to restore patients' rhythm to normal sinus rhythm following a recurrence after ablation. O'Donnell et al. [64] reported that clinical recovery post-PV isolation typically takes around 3 months, and there has been a documented delay effect of RF energy following ablation [16]. Animal studies have shown that during persistent AF, the atrial effective refractory period decreases, heart rate accelerates, and AF induction rates increase [65]. Therefore, it has been observed that electrical and structural changes continue during sustained AF, adversely affecting the atrial myocardium at both cellular and inflammatory levels [66]. In this scenario, a vicious cycle ensues, leading to further persistence of AF and contributing to significant fibrosis and chamber enlargement in the LA. Specifically, during the acute inflammatory phase postablation, the environment is thought to be particularly conducive to AF induction. There is a viewpoint that maintaining sinus rhythm until atrial lesion healing occurs could be beneficial for long-term outcomes [67]. However, the optimal timing for DC cardioversion remains unclear. Some studies suggest that early DC cardioversion during the ER phase is associated with better long-term outcomes [66,67]. In contrast, other research findings suggest that the impact of early cardioversion on LR may not be significantly correlated [68,69]. Current expert opinions performing DC cardioversion within 30 days if recurrence occurs postablation [8].

REDO PROCEDURE

Early period

The primary mechanism of ER is PV reconnection, as illustrated in Fig. 1. Electrophysiological testing conducted during early repeat ablation revealed that 88.2% of patients with ER exhibited PV reconnection. In contrast, PV reconnection was observed in only 41.7% of patients without ER [70].

Whether to perform early repeat ablation in cases of ER remains unclear. In a study involving 302 patients [71], 158 experienced ER, with 151 of these included in the analysis. Of these, 61 patients underwent early repeat ablation within a month following the initial procedure, while the remaining 90 patients received standard care. All patients were given antiarrhythmic therapy for a month. If ER was present, the antiarrhythmic therapy was extended beyond a month. If symptoms persisted at the 3-month mark, antiarrhythmic therapy was continued until further ablation was performed. The group that underwent early repeat ablation demonstrated significantly lower recurrence rates during follow-up, but this was also linked to a significant increase in the total number of procedures. In a substudy of the STOP-AF (Sustained Treatment of Paroxysmal Atrial Fibrillation) Trial [72], out of 163 patients, 84 experienced ER, with 30 of them (36%) undergoing early repeat ablation during the blanking period. The use of antiarrhythmic drugs post–blanking period was discouraged. When compared

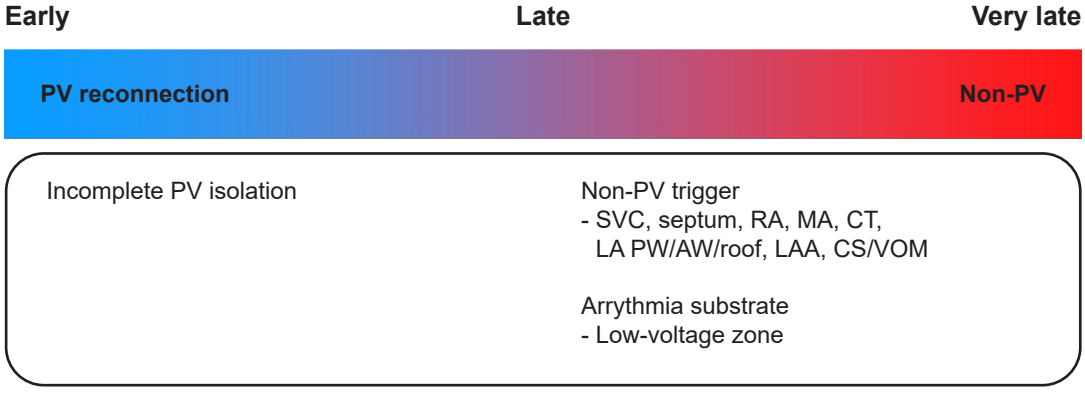

Fig. 1. Mechanism of recurrence of atrial tachyarrhythmias according to the recurrence period. PV, pulmonary vein; SVC, superior vena cava; RA, right atrium; MA, mitral annulus; CT, crista terminalis; LA, left atrium; PW, posterior wall; AW, anterior wall; LAA, left atrium appendage; CS, coronary sinus; VOM, vein of Marshal.

to patient groups without ER, the AF-free survival rate was significantly higher in the early ablation group. The group with ER but without repeat ablation demonstrated the least favorable outcome. However, the authors noted that 55.6% of patients who experienced ER later had LR, while the remaining 44.4% did not experience LR despite having ER in this study. Therefore, they emphasized that not all patients with ER necessarily require immediate ablation. Instead, they suggested that considering the cost, the patient's disease burden, and the risks associated with ablation, it might be more prudent to follow the expert consensus recommendation of waiting for 3 months before considering repeat ablation. Similar trends were observed in another study [21], where 51% had early atrial tachyarrhythmia and developed LR later, while the remaining 49% did not experience LR, a finding the authors considered noteworthy.

If a recurrence happens during the blanking period, the decision to proceed with an immediate repeat ablation should be thoughtfully considered. This decision should take into account the ongoing presence of atrial arrhythmia, the patient's perceived disease burden, and potential mechanisms as indicated by the records from the initial procedure.

Late period

PV reconnection is also widely recognized as a primary mechanism of LR. A study involving 149 patients undergoing repeat procedures [73] found that electrophysiological testing during the first repeat ablation revealed PV reconnection in all patients. However, in subsequent procedures (second or third), the incidence of PV reconnection decreased, with a particularly notable reduction observed in persistent AF cases. Another study [74] reported PV reconnection in 73.2% of cases during repeat ablation. The importance PV reconnection as a contributing factor to recurrence appears to diminish as the timing of recurrence becomes more delayed (Fig. 1). Nevertheless, since PV reconnection plays a substantial role in a significant number of recurrence cases, it is crucial to assess the status of PV during repeat ablation.

Very late period

While PV reconnection is a widely recognized primary mechanism, non-PV triggers or substrates appear to be increasingly significant in the very late period (Fig. 1). Consequently, key predictive factors for VLR include nonparoxysmal forms of AF or underlying structural heart diseases (such as valvular or myocardial diseases), and advanced age at the time of the first ablation.

In a study [36] that analyzed 137 patients who experienced recurrences after 36 months, electrophysiological testing during repeat ablation revealed PV reconnection in 81% of cases. However, a significant percentage of non-PV triggers were also discovered, including 35% from SVC, 45.9% from the posterior wall, and 51.82% from the roof. Other research [35] has also shown a trend towards a numerical decrease in PV triggers in the VLR group compared to non-VLR cases, although this was not statistically significant (77% vs. 82%). A recent study by Choi et al. [38], which had a 5-year follow-up, found that in patients who maintained sinus rhythm for more than 5 years, extra-PV triggers were more prevalent than PV reconnection. This suggests that while PV triggers may be crucial in the early stages of AF, as atrial cardiomyopathy progresses over time, the importance of extra-PV triggers increases.

While PV reconnection is a significant factor, with potential causes such as gaps or a lack of transmural ablation lines during the index procedure, the coexistence of many PV reconnection cases with long-term sinus rhythm maintenance suggests that our understanding of the mechanisms underlying AF initiation and long-term maintenance is still uncertain. Therefore, it seems that the substrate plays a crucial role in VLR. In the study of Kim et al. [75], voltage mapping was performed during the index procedure. Based on these results, the authors divided the patients into four groups according to the extent of the low-voltage zone. They demonstrated that a higher prevalence of low-voltage zones was associated with a higher recurrence rate of AF at 3 years.

Redo procedure vs. antiarrhythmic drugs

A comparative study [76] was conducted to investigate the management of recurrent AF following the initial procedure, with a particular focus on the comparison between repeat ablation and antiarrhythmic drug therapy. The study scrutinized a cohort of 1,230 patients who underwent repeat procedures from a total of 4,913 patients who ex-

perienced AF recurrence in China. The primary endpoint, which included cardiovascular mortality, stroke, and major bleeding, showed significant improvement in the group that underwent repeat procedures. This result aligns with data from Swedish health registries [77]. However, it contrasts with previous findings from the ORBIT-AF (Outcomes Registry for Better Informed Treatment of Atrial Fibrillation) Trial [78], which did not demonstrate similar improvements in hard endpoints.

Temporal trends

An analysis of healthcare data from the United States [79] examined the decision-making process and timing of repeat ablation. Roughly 14.6% of patients with recurrent conditions underwent repeat ablation, with 12.1% of these patients receiving a second ablation within 1 year of the recurrence. Of this group, 20.6% underwent repeat ablation during the blanking period. Interestingly, social factors such as income level and residence in the southern United States had a more substantial influence on the decision to undergo repeat ablation than any particular clinical characteristics.

A survey [80] was conducted to examine the current treatment trends for ER among contemporary physicians, specifically targeting 436 members of the European Heart Rhythm Association (EHRA). The survey sought information on the strategies used to manage ER. Of those who responded, 58% indicated that they did not adhere to the expert consensus guidelines for ER, choosing not to perform repeat ablation. When faced with the first AF recurrence during the blanking period, 62% of physicians opted for a combination of antiarrhythmic drugs and DC cardioversion, 17% employed rate control strategies, 20% performed only DC cardioversion, and a mere 1% selected repeat ablation. In instances of AFL/AT recurrence, there was a marked preference for repeat ablation, particularly when typical flutter was detected, with 51% of physicians choosing this treatment approach.

In another survey study [81], 107 EHRA members were queried about their management strategies following a recurrence. The responses varied based on whether the recurrence was paroxysmal or persistent. PV isolation-only redo procedures were notably more prevalent in paroxysmal cases, while substrate modification was more frequently attempted in nonparoxysmal cases. There was also a difference in the rate control treatment approach, with 7% for paroxysmal cases and 21% for nonparoxysmal cases. The management strategies also exhibited slight variations. In paroxysmal AF cases, PV isolation was deemed the most critical, while for persistent AF, additional procedures such as low-voltage area ablation, complex fractionated atrial electrograms, empirical lines, and non-PV trigger ablation were also performed during redo procedures. Interestingly, a significant proportion of physicians adopted a conservative approach, either modifying or adding antiarrhythmic drugs. This indicates that a considerable number of clinicians prefer a less invasive, conservative therapeutic approach. Furthermore, the relatively low emphasis (paroxysmal AF, 33%; persistent AF, 29%) on lifestyle improvements and risk factor management suggests that these aspects warrant more attention. In terms of antiarrhythmic drugs, 73% of physicians utilized class Ic drugs, while 22% chose amiodarone. The use of colchicine was reported by 13% of the physicians.

CONCLUSIONS

Although AF recurrence is a prevalent and complex problem, there are few guidelines for its management. This paper reviews past literature, recent studies, and trends concerning the mechanisms and management of AF recurrences. While PV reconnection is indeed a significant mechanism that triggers and sustains AF recurrence, it does not account for all instances of recurrence. Consequently, personalized management strategies, tailored to individual characteristics, are crucial for successful long-term outcomes in AF patients following catheter ablation. Further research is required to optimize therapeutic approaches for AF recurrence.

ARTICLE INFORMATION

Ethics statements
Not applicable.

Conflicts of interest
The authors have no conflicts of interest to declare.

Funding
None.

Author contributions

Conceptualization: HKJ; Supervision: NHK, JSK, SSK; Writing–original draft: HKJ; Writing–review & editing: all authors. All authors read and approved the final manuscript.

ORCID

Jum Suk Ko, https://orcid.org/0000-0002-8573-0066
Sung Soo Kim, https://orcid.org/0000-0002-5190-227X
Hyung Ki Jeong, https://orcid.org/0000-0001-5749-9525
Nam Ho Kim, https://orcid.org/0000-0003-4559-5493

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Review Article

Cardiovasc Prev Pharmacother 2023;5(4):113-125
eISSN 2671-700X
https://doi.org/10.36011/cpp.2023.5.e16

Cardiovascular Prevention and Pharmacotherapy

Calcium channel blockers for hypertension: old, but still useful

Eun Mi Lee

Division of Cardiology, Department of Internal Medicine, Wonkwang University Sanbon Hospital, Gunpo, Korea

Calcium channel blockers (CCBs) constitute a heterogeneous class of drugs that can be divided into dihydropyridines (DHPs) and non-DHPs. DHP-CCBs are subcategorized into four generations based on the duration of activity and pharmacokinetics, while non-DHP-CCBs are subcategorized into phenylethylamine and benzodiazepine derivatives. DHP-CCBs are vascular-selective and function as potent vasodilators, whereas non-DHP-CCBs are cardiac-selective and are useful for treating tachyarrhythmia, but reduce cardiac contractility and heart rate. Traditional DHP-CCBs (nifedipine) mainly block L-type calcium channels, whereas novel CCBs block N-type (amlodipine) and/or T-type channels (efonidipine) in addition to L-type channels, leading to organ-protective effects. DHP-CCBs have a potent blood pressure–lowering effect and suppress atherosclerosis and coronary vasospasm. Diltiazem, a non-DHP-CCB, is highly effective for vasospasm control. CCBs reduce left ventricular hypertrophy and arterial stiffness. Amlodipine, a DHP-CCB, reduces blood pressure variability. L/N- and L/T-type CCBs combined with renin-angiotensin system blockers reduce proteinuria and improve kidney function compared with L-type CCBs. According to large-scale trials, DHP-CCBs reduce cardiovascular events in patients with isolated systolic hypertension, as well as in elderly and high-risk patients. Accordingly, CCBs are indicated for hypertension in elderly patients, isolated systolic hypertension, angina pectoris, and coronary vasospasm. Non-DHP-CCBs are contraindicated in high-grade heart block, bradycardia (<60 beats per minute [bpm]), and heart failure with reduced ejection fraction (HFrEF). DHP-CCBs should be used with caution in patients with tachyarrhythmia, HFrEF, and severe leg edema, and non-DHP-CCBs should be used carefully in those with constipation. Each CCB has distinct pharmacokinetics and side effects, underscoring the need for meticulous consideration in clinical practice.

Keywords: Hypertension; Anti-hypertensive drugs; Calcium channel blockers; Dihydropyridine

INTRODUCTION

Calcium channel blockers (CCBs) play a crucial role in the treatment of hypertension, either as an initial monotherapy or in combination with other classes of antihypertensive drugs in Korea [1]. Beyond blood pressure (BP) control, they are also utilized for conditions such as angina pectoris, coronary vasospasm, and arrhythmias [2]. These medications constitute a heterogeneous class of drugs that can be divided into dihydropyridines (DHPs) and non-DHPs according to the main site of action, each with distinct pharmacokinetic profiles and side effects [3–6].

This review provides an overview of CCBs: (1) their classification and pharmacokinetic profiles; (2) the underlying mechanism of action; (3) their efficacy in lowering BP and reducing BP variability; (4) their role in protecting against

Received: August 29, 2023; **Revised:** October 9, 2023; **Accepted:** October 10, 2023
Correspondence to Eun Mi Lee, MD
Division of Cardiology, Department of Internal Medicine, Wonkwang University Sanbon Hospital, 327 Sanbon-ro, Gunpo 15865, Korea
Email: mdemlee@naver.com

target organ damage; (5) their potential for preventing cardiovascular events; and (6) the indications, contraindications, and side effects associated with CCBs.

CLASSIFICATION AND PHARMACOKINETIC PROFILES

CCBs are categorized into DHP-CCBs and non-DHP-CCBs based on their chemical structure (Fig. 1) [3–6]. DHP-CCBs primarily act on vascular smooth muscles, promoting vasodilation without significantly affecting cardiac function (vascular selectivity). These drugs are further divided into four generations based on their discovery time, onset of drug effect, and duration of activity. Long-acting CCBs are characterized by higher vascular selectivity, increased lipophilicity, and reduced sympathetic excitation. Conversely, non-DHP-CCBs exert a more pronounced effect on the conduction system and ventricular muscle, but are less effective in promoting vasodilation (cardiac selectivity). These drugs are subcategorized as phenylethylamine (PAA) and benzodiazepine (BTZ) derivatives based on their chemical structure. Each category of non-DHP-CCBs is further divided into two generations according to the duration of action. Representative DHP-CCBs include the following: first-generation CCBs such as short-acting nifedipine and nicardipine, which have a rapid onset and short duration of vasodilating activity; second-generation drugs such as extended-release nifedipine, felodipine, benidipine, and efonidipine, which have a slow release and short duration of activity; third-generation drugs such as amlodipine and azelnidipine, which exhibit stable pharmacokinetics (e.g.,

CCB Classes	Dihydropyridine	Non-dihydropyridine	
		Phenylalkylamine (PAA)	Benzodiazepine (BTZ)
Main action site	***Vascular*** selectivity Vascular smooth muscle	***Cardiac*** selectivity Impulse conduction system, ventricular muscle	Act in both heart and blood vessel ***Intermediate effect*** between the DHP and PAA type
	First generation of Non-DHP	Verapamil	Diltiazem
	Second generation of Non-DHP	Verapamil SR	Diltiazem SR
Coronary artery vasodilation	↑↑↑	↑↑	↑↑↑
Peripheral vessel vasodilation	↑↑↑	↑↑	↑
Cardiac contraction	↑	↓↓	↓
Heart rate	↑→	↓↓	↓
Atrioventricular conduction	↑→	↓↓	↓

Generation of DHP-CCB	First generation	Second generation	Third generation	Fourth generation
Drugs	Short acting nifedipine	Extended release nifedipine, Felodipine, Benidipine, Efonidipine	Amlodipine, Azelidipine	Lacidipine Lercanidipine, Cilnidipine
Onset	Rapid	Gradual	Slow	Slow
Duration	Slow acting	Moderate	Long acting	Long acting
Vasodilation	↑↑↑	↑↑↑	↑↑	↑↑↑
Sympathoexcitation	↑↑↑	↑↑	↑	→
Renal protection	→	→	↑	↑↑
Lipophilicity	↑	↑	↑↑	↑↑↑
Side effects				
Tachycardia	↑↑↑	↑↑	↑/→	↑/→
Headache	↑↑↑	↑↑	↑	↑/→
Flushing	↑↑↑	↑↑	↑	↑/→
Edema	↑↑	↑↑	↑	→

Slow onset, longer duration, higher vascular selectivity, higher lipophilicity, lesser sympathoexicitation

Fig. 1. Classification and pharmacological actions of calcium channel blockers (CCBs). DHP, dihydropyridine; PAA, benzodiazepine; Non-DHP, non-dihydropyridine; SR, sustained release; ↑↑↑, strongest; ↑↑, very strong; ↑, strong positive action; →, neutral action; ↓, negative action.
Based on data from Sueta et al. [3], and Wang et al. [4], Elliott et al. [5], Wang et al. [6].

slow action and long duration of activity), higher vascular selectivity, and less sympathoexcitation, resulting in less cardiac selectivity and thus, better tolerance in patients with heart failure (HF); and fourth-generation drugs including lacidipine, lercanidipine, and cilnidipine, which have stronger lipophilicity, leading to stable activity, reduction in peripheral edema, and a broad therapeutic spectrum, especially for myocardial ischemia and HF [4,7]. The first-generation short-acting nifedipine was associated with increased mortality and myocardial ischemia due to rebound activation of sympathetic activity caused by its short duration and rapid onset of vasodilating activity [4]. Therefore, it is currently not recommended by the 2022 Korean Society of Hypertension (KSH) Guideline [2] and is not commercially available in Korea. Among non-DHP-CCBs, PAA derivatives, such as verapamil, exhibit higher cardiac selectivity, acting on the impulse conduction system (ICS) including the sinoatrial (SA) node and atrioventricular (AV) node, and ventricular muscle. As a result, it has negative inotropic, chronotropic, and dromotropic effects; thus, it is useful for arrhythmia treatment, but it should be avoided in cases of HF and bradycardia [2,3,8]. BTZ derivatives, such as diltiazem, have an intermediate effect between DHP-CCBs and PAA derivatives, acting on the myocardium and ICS, particularly in the AV node. These drugs have a very strong effect on coronary vasodilation, making them useful for treating coronary vasospasm [3]. Representative non-DHP-CCBs are as follows: first-generation, verapamil and diltiazem; and second-generation, verapamil sustained release and diltiazem sustained release [3]. The pharmacokinetic profile of each CCB is presented in Table 1 [3,4,6,7,9–17].

MECHANISMS

The first study of CCBs was reported by Fleckenstein et al. [18] in 1969. CCBs disrupt the inward movement of extracellular calcium (Ca2+) through the calcium channel, leading to a decrease in peripheral vascular resistance and, consequently, reduced BP [4]. Additionally, CCBs induce coronary vasodilation and inhibit ventricular contraction and the intracellular signaling system (ICS), leading to anti-anginal and anti-arrhythmic effects (Fig. 2) [3]. Voltage-gated Ca^{2+} channels are composed of four subunits: α1 and α2, δ, β, and γ. These channels are pharmacologically classified into different subtypes (Fig. 3A) [19,20]: high voltage–activated (L- and N-type), low voltage–activated (T-type), and P/Q- and R-types. The characteristics of these channels are determined by the pore-forming α1 subunit. Traditional CCBs, such as nifedipine and felodipine, primarily affect L-type channels, acting as potent vasodilators. In contrast, novel CCBs influence N-type (cilnidipine, amlodipine) and/or T-type channels (efonidipine) in addition to L-type channels. N-type channels are associated with decreased norepinephrine release at sympathetic nerve endings, while T-type channels are linked to improved renal microcirculation (Fig. 3B) [11,12,21]. Therefore, it is hypothesized that the combined blocking of N- or T- channels, in addition to L-type channels by CCBs, may exert organ-protective actions in the treatment of hypertension, beyond just lowering BP. Furukawa et al. [10] demonstrated the selectivity of DHP-CCBs for calcium channel subtypes, suggesting that these properties could provide different pharmacological information and influence the adverse effects of DHP-CCBs.

EFFICACY OF BP REDUCTION

Wang et al. [6] found that DHP-CCBs demonstrated a superior 24-hour BP reduction compared to other classes of antihypertensive drugs, including renin-angiotensin system (RAS) blockers, β-blockers, and diuretics. The weighted mean difference was 5 mmHg for systolic BP and 3 mmHg for diastolic BP. Furthermore, in the DHP-CCB group, both daytime and nighttime systolic BP reductions were significantly and positively correlated with the BP value at baseline. This correlation was weak and not statistically significant in other drug classes. A Cochrane review [22] also revealed a relatively consistent BP-lowering effect at each hour over a 24-hour period among six DHP-CCBs, nifedipine, felodipine, manidipine, amlodipine, lercanidipine, and nicardipine. Lorimer et al. [23] reported that amlodipine had better BP reduction than lisinopril (supine systolic/diastolic BP reduction 24-hour after dosing, –12%/–14% decrease in amlodipine group vs. –7%/–7% decrease in lisinopril group). Additionally, amlodipine provided more consistent control of BP over 24 hours compared to lisinopril, due to the significantly longer half-life of amlodipine (35–50 hours) compared to lisinopril (12.6 hours). Thus, DHP-CCBs have a potent BP-lowering effect.

Table 1. Pharmacokinetics of calcium channel blockers

Class	Generation	Drug	Ca^{2+} channel	Terminal half-life (hr)	Dose (mg)	No. of doses/day	Indication	Affect LV function[b]	Renal protection[b]	Pregnancy[a]
PAA	First	Verapamil	L-type	6–8	40–80	3	HTN, AP, atrial dysarrhythmia	↓↓↓	→/↑	Category C
					80–480	1				
	Second	Verapamil SR	L-type	12–24	180–240	1	HTN, AP, atrial dysarrhythmia	↓↓↓	→/↑	Avoided for the first two trimesters of pregnancy (IV form)
BTZ	First	Diltiazem	L-type	6–8	30–90	3	HTN, AP, atrial dysarrhythmia	↓↓	→	Category C
	Second	Diltiazem SR	L-type	18–24	90–540	1	HTN, AP, atrial dysarrhythmia	↓↓	→	Category C
DHP	First	Short-acting nifedipine	L-type	2–4	-	-	HTN	↓	→	Category C
		Nicardipine	L-type	6–8	20–30	3	HTN		→	Category C
	Second	Nifedipine	L-type	24	30–120	1	HTN, AP	↓/→	→/↓	Category C Second-line antihypertensive drug in pregnancy
		Nicardipine	L-type	14.4	30–60	2	HTN	↓/→	→/↑	Category C
		Felodipine	L-type	11–16	2.5–10	1	HTN	↓/→	→	Category C
		Isradipine SR	L-type	8	2.5–5	2	HTN	↓/→	→	Category C
				12–18	5–10	1			→	Limited data
		Nimodipine	L-type	8–10			Subdural hemorrhage	↓/→	→	
		Benidipine	L/N/T-type	30–50	2–8	1	HTN, AP, renal parenchymal HTN	↓/→	→	Not recommended
		Efonidipine	L/T-type	4	20–40	1	HTN	↓	↑↑	Category C
		Manidipine	L/T-type	4–8	5–20	1	HTN	↓	↑/→	No clinical data
	Third	Amlodipine	L/N-type	35–50	2.5–10	1	HTN, AP	↓/→	↑↓	Category C Breastfeeding is not recommended
		Azelnidipine	L/T-type	16–28	8–16	1	HTN	↓/→	↑↑	Not recommended
	Fourth	Cilindipine	L/N-type	24	5–10	1	HTN	↓/→	↑↑	None confirmed safe
		Lacidipine	L-type	30–50	2–6	1	HTN	↓/→	→	Limited human data
		Lercadipine	L/T-type	8–10	5–20	1	HTN	↓/→	↑↑	No evidence

LV, left ventricular; PAA, phenylalkylamine; HTN, hypertension; AP, angina pectoris; SR, sustained release; IV, intravenous route; BTZ, benzothiazepine; DHP, dihydropyridine.
[a]Based on the US Food and Drug Administration (FDA) category. Category C is defined as a risk category where there have been no satisfactory studies in pregnancy women, but animal studies have demonstrated a risk to the fetus; the potential benefits of the drug may outweigh the risk. [b]Downward arrow indicate negative action, upward arrow indicate positive action, and the degree is presented by the number of arrows; rightward arrow indicate neural or no effect.
Based on data from Wang et al. [6], Chandra and Ramesh [7], Ram [14], Packer et al. [15], Thamcharoen et al. [16], and Ferri et al. [17].

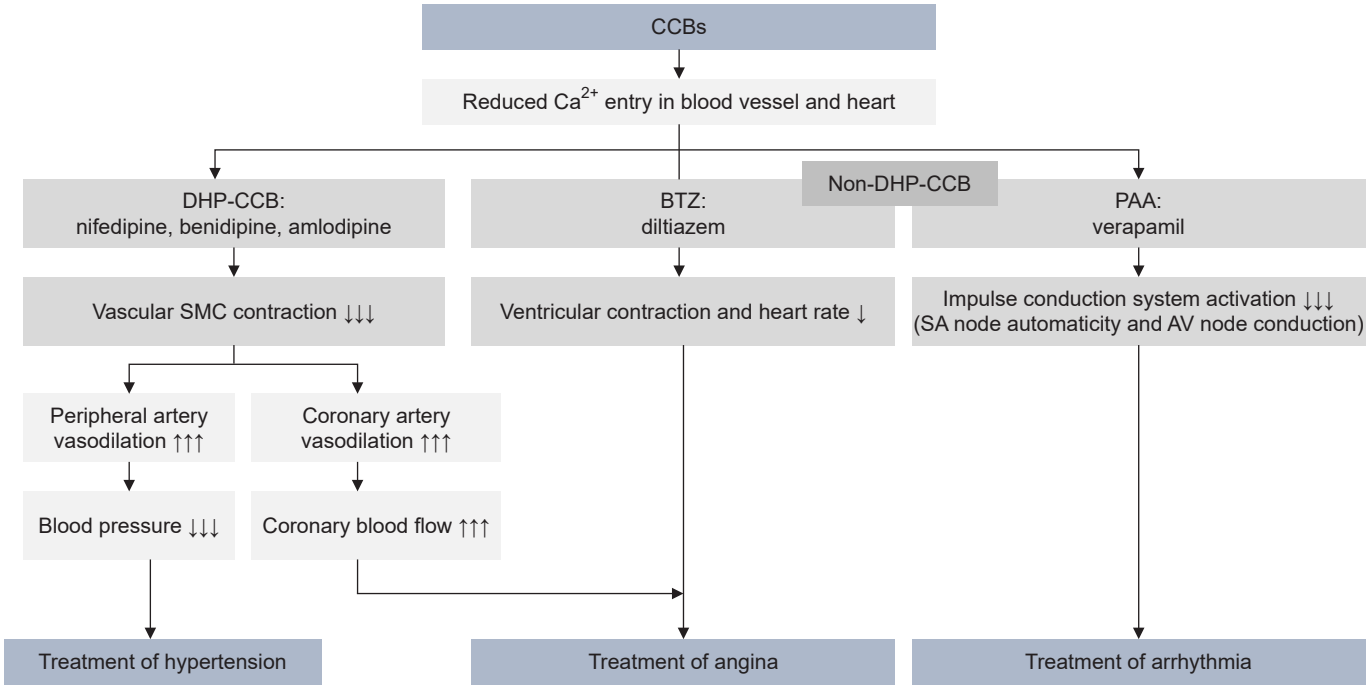

Fig. 2. Three main pharmacological mechanisms of calcium channel blockers (CCBs): treatment of hypertension through peripheral vasodilation; treatment of angina pectoris through coronary artery vasodilation and decreased ventricular contraction and heart rate; and arrhythmia treatment through decreased impulse conduction system excitation. Downward arrow indicate negative action, upward arrow indicate positive action (the degree is presented by the number of arrows). DHP, dihydropyridine; BTZ, benzothiazepine; PAA, phenylalkylamine; SMC, smooth muscle cell; SA node, sinoatrial node; AV node, atrioventricular node.
Based on data from Sueta et al. [3].

BP VARIABILITY

Rothwell et al. [24] found that in patients with treated hypertension, variability in systolic BP was linked to vascular events, independent of the mean systolic BP. In the ASCOT-BPLA (Anglo-Scandinavian Cardiac Outcomes Trial Blood Pressure Lowering Arm) Study [25], the variability of systolic BP was lower in the group treated with amlodipine compared to the group treated with atenolol. Furthermore, subsequent trends in BP variability during follow-up in the atenolol group were associated with trends in stroke risk. This finding partially explains the reduced risk of vascular events observed in the amlodipine group. In a meta-analysis [26], it was found that CCBs and nonloop diuretics reduced interindividual systolic BP variability, while RAS blockers and β-blockers increased it. The ALLHAT (Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial) Study [27] suggests that chlorthalidone and the DHP-CCB amlodipine are associated with lower systolic BP variability than lisinopril.

PROTECTION FOR HMOD

LVH and HF

CCBs provide protective effects against hypertension-mediated organ damage (HMOD). Different classes of antihypertensive drugs have varying impacts on the reduction of left ventricular hypertrophy (LVH) [28]. Klingbeil et al. [29] reported that LVH decreased by 13% with angiotensin receptor blockers (ARBs), 11% with CCBs, 10% with angiotensin-converting enzyme inhibitors (ACEIs), 8% with diuretics , and 6% with β-blockers. Therefore, CCBs serve as an intermediate-range solution for LVH reduction and are recommended for treating hypertensive patients with LVH. However, CCBs are less effective than other first-line antihypertensive drugs in protecting against HF [30]. The ALLHAT Study [31] aimed to determine whether treatment with

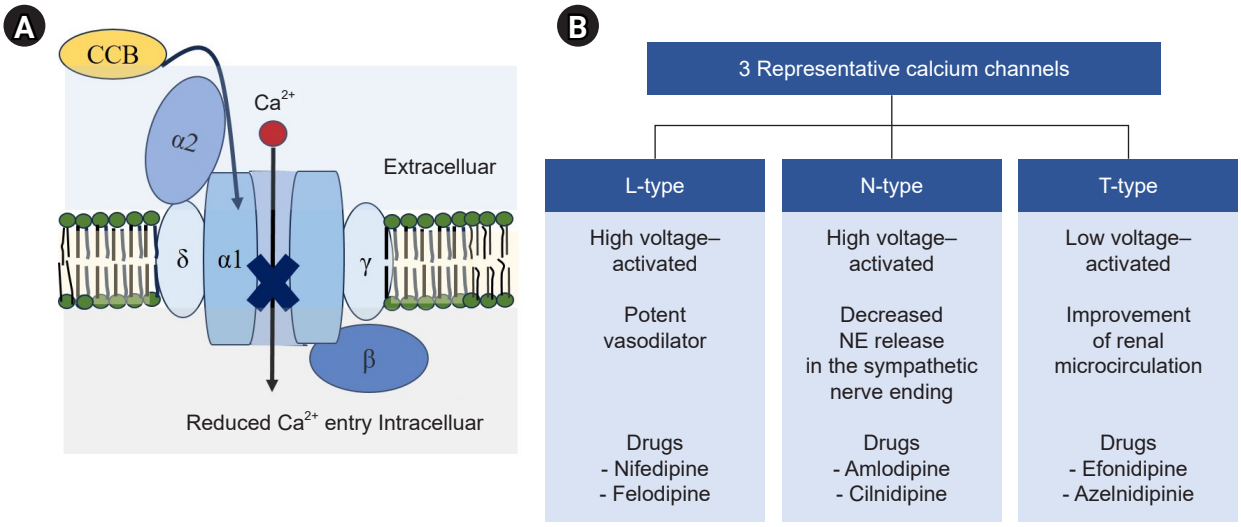

Fig. 3. Voltage-gated calcium channels and three representative types. (A) Voltage-gated calcium channels. Voltage-gated extracellular calcium (Ca^{2+}) channels consist of four subunits, α1 and α2, δ, β, and γ, and they are pharmacologically classified into different subtypes; the characteristics of which are determined by the pore-forming α1 subunit. Calcium channel blockers (CCBs) disrupt the inward movement of Ca^{2+} through the calcium channel. (B) Three representative types of calcium channel. Calcium channels are pharmacologically classified into different subtypes: high voltage–activated (L- and N-type) and low voltage–activated (T-type). L-type channels act as potent vasodilators, N-type channels have decreased norepinephrine (NE) release in the sympathetic nerve ending, and T-type channels have improvement of renal microcirculation. It is speculated that the combined blocking of N- or T-channels in addition to traditional L-type blocking in CCBs leads to different pharmacologic impacts and adverse effects of dihydropyridine CCBs.

CCBs or ACEIs reduces the incidence of coronary artery disease (CAD) or other cardiovascular disease (CVD) events compared to treatment with diuretics. The study found no difference in primary outcomes between treatment groups, but HF was higher in the amlodipine group. Conversely, the PRAISE-2 (Prospective Randomized Amlodipine Survival Evaluation 2) Study [15] showed that amlodipine had a neutral effect on mortality based on ejection fraction. According to the 2023 Guidelines from the European Society of Hypertension (ESH) [8], in patients with hypertension and HF with reduced ejection fraction (HFrEF), the initial recommendation is to combine drugs with sacubitril/ valsartan, RAS blockers, β-blockers, aldosterone inhibitors, and sodium-glucose cotransporter 2 (SGLT2) inhibitors. If control is not achieved, a DHP-CCB can be added for BP control. The use of non-DHP-CCB is not recommended in HFrEF due to their negative inotropic effects. For patients with hypertension and HF with preserved ejection fraction, the treatment of hypertension with all major antihypertensive drugs, including CCBs, is recommended.

Arterial stiffness

Increased arterial stiffness, as measured by pulse wave velocity (PWV), is a potent independent predictor of cardiovascular morbidity and mortality in patients with hypertension [32]. Therefore, reducing arterial stiffness can lower cardiovascular risk. However, the data on the impact of CCBs on arterial stiffness is limited, though some studies suggest beneficial outcomes. For instance, Hayoz et al. [33] reported that treatments with amlodipine and valsartan for 38 weeks similarly reduced carotid-femoral PWV in postmenopausal women with hypertension. Takami and Shigemasa [34] found that ARBs resulted in the most significant reductions in pulse pressure and brachial PWV. This was followed by ACEIs and L- and N-type CCBs, while L-type CCBs showed no improvement. Matsui et al. [35] demonstrated that a combination of ARB (olmesartan, 20 mg) and DHP-CCB (azelnidipine, 16 mg) had a more beneficial effect on central systolic BP and arterial stiffness than the combination of ARB and diuretic, despite similar reductions in brachial systolic BP between the two treatments.

Thus, DHP-CCB monotherapy or combination therapy with a DHP-CCB and ARB might protect against arterial stiffness

Atherosclerosis and coronary vasospasm

Henry and Bentley [36] conducted an experiment to test the impact of nifedipine on atherosclerosis in rabbits fed a cholesterol diet. Their findings showed that aortic lesions stainable with Sudan IV covered 40%±5% of the intimal surface in animals in the placebo group versus 17.3%±3% in the nifedipine group. This finding means lesion formation for a given lipid accumulation was significantly reduced in nifedipine-treated rabbits. However, the total cholesterol concentration was 48±7 mg/dL in the placebo group versus 46±6 mg/dL in the nifedipine group. These results suggest that nifedipine can suppress atherogenesis without reducing hypercholesterolemia. The PREVENT (Prospective Randomized Evaluation of the Vascular Effects of Norvasc Trial) Investigation [37] reported that amlodipine does not have a noticeable effect on the angiographic progression of coronary atherosclerosis or the risk of major CVD events. However, it is associated with fewer hospitalizations due to unstable angina and revascularization. The ELSA (European Lacidipine Study on Atherosclerosis) Trial [38] found that lacidipine, a DHP-CCB, had a greater effect on the progression of carotid intimal-medical thinness and the number of plaques per patient. Despite a smaller reduction in ambulatory BP, this suggests an anti-atherosclerotic action of this drug. Ishii et al. [39] proposed that the anti-atherosclerotic effect of DHP-CCBs is achieved by suppressing the generation of reactive oxygen species, the expression of adhesion molecules, and the progression and migration of smooth muscle cells. In macrophages, they reduce cholesterol accumulation and suppress the expression of matrix metalloproteinases, as well as activate peroxisome proliferator-activated receptor-γ. Furthermore, CCBs are highly effective in suppressing coronary vasospasm. Nishigaki et al. [40] showed that among four CCBs (benidipine, amlodipine, nifedipine, and diltiazem), major CVD events in patients with vasospastic angina were significantly lower in patients treated with benidipine. Recently, Kim et al. [41] reported that there was no difference in cardiovascular outcome occurrence in patients with vasospastic angina treated with first-generation CCBs (including diltiazem and nifedipine) and second-generation CCBs (including amlodipine and benidipine). However, the incidence rate of acute coronary syndrome was significantly lower in patients treated with second-generation CCBs. According to the 2023 ESH Guidelines [8], in patients with hypertension and CAD with angina pectoris, both DHP and non-DHP-CCB are particularly useful, and β-blockers should not usually be combined with non-DHP-CCB. Hypertension and LVH are often associated with myocardial ischemia and nonobstructive CAD. In such cases, treatment with CCBs can be beneficial.

Renal protection

Reducing albuminuria or proteinuria is a crucial surrogate goal in hypertension treatment, as it helps decrease both chronic kidney disease (CKD) and CVD. To achieve the target goal in CKD, a combination therapy is typically required, involving a RAS blocker with a CCB or a diuretic, particularly if estimated glomerular filtration rate (eGFR) levels are at CKD stages ≥3a [8]. A secondary analysis of the ACCOMPLISH (Avoiding Cardiovascular Events through Combination Therapy in Patients Living with Systolic Hypertension) Study [42,43] demonstrated the superior efficacy of combining benazepril and amlodipine over benazepril plus hydrochlorothiazide, as it slows nephropathy progression. Therefore, CCBs are generally recommended as the drug to combine with RAS blockers in high-risk patients, as this combination therapy effectively reduces BP and primary protein excretion [8]. However, the kidney protection mechanism of CCBs may vary depending on the types of calcium channels. L-type CCBs increase glomerular pressure through dilation of the afferent artery and constriction of the efferent artery. In contrast, L/N-type and L/T-CCBs decrease glomerular pressure and improve glomerular microcirculation through vasodilatory activity on both afferent and efferent arterioles [9,12,44]. Thamcharoen et al. [16] found that L/N-CCB (cilnidipine) and L/T-type CCBs (azelnidipine, efonidipine, and benidipine) combined with RAS blockers resulted in a decrease in proteinuria and an improvement in kidney function compared to standard L-type CCBs, despite no additional BP-lowering effect. Lercanidipine, an L/T channel blocker, is highly lipophilic compared to amlodipine and directly dilates both the afferent and efferent glomerular arteries without altering intraglomerular capillary pressure [17]. Burnier [45] reported that lercanidipine appears to provide renal protection similarly to an

ACEI, while amlodipine is generally less effective in terms of renal protection. The beneficial effects of amlodipine in slowing the progression of renal disease are only achievable when combined with a RAS blocker. Zhao et al. [46] reported that combined treatment with RAS blockers and L/T-type CCBs reduced proteinuria without increasing kidney function and adverse effects. This finding is independent of BP and may be associated with decreased aldosterone.

PREVENTION OF CARDIOVASCULAR EVENTS

DHP-CCBs have been extensively studied for the prevention of CVD, in comparison to various classes of antihypertensive drugs. The Sys-Eur (Systolic Hypertension in Europe) Trial [47] was a randomized, double-blind comparison of a placebo and active treatment with a CCB (nitrendipine) for older patients (>60 years, n=4,695) with isolated systolic hypertension (ISH). The group receiving active treatment with CCBs experienced a reduction in BP of 10.1 mmHg in systolic BP and 4.5 mmHg in diastolic BP, compared to the placebo group. Furthermore, active treatment led to a decrease in the rate of cardiovascular complications; total stroke was reduced by 42% (P=0.003), fatal and nonfatal cardiac endpoints by 31% (P=0.03), and cardiovascular mortality by 27% (P=0.07). The INSIGHT (Intervention as a Goal in Hypertension Treatment) Study [48] compared the effects of nifedipine, a CCB, with the diuretic combination co-amilozide on cardiovascular mortality and morbidity in high-risk patients with hypertension. The overall mean BP dropped from 173/99 mmHg to 138/82 mmHg. Nifedipine once daily and co-amilozide were equally effective in preventing overall cardiovascular or cerebrovascular complications. Based on the above studies, DHP-CCBs are recommended in elderly patients with hypertension and those with ISH [49]. The VALUE (Valsartan Antihypertensive Long-term Use Evaluation) Trial [50] was designed to test the hypothesis that valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high CVD risk. However, contrary to expectations, the results showed that the amlodipine-based regimen had a more pronounced BP-lowering effect than the valsartan-based regimen, especially during the first 6 months (BP was 4.0/2.1 mmHg lower in the amlodipine group than in the valsartan group after 1 month, 1.5/1.3 mmHg after 1 year; P<0.001 between groups). However, the primary composite endpoint was similar between the two regimens. Myocardial infarction occurred less frequently in the amlodipine group (4.1% vs. 4.8%; hazard ratio [HR], 1.19; P=0.02), and stroke trended lower (3.7% vs. 4.2%; HR, 1.15; P=0.08). New onset diabetes was higher in the amlodipine group (16.4% vs. 13.1%; HR, 0.77; P<0.0001), and HF trended higher (5.3% vs. 4.2%; HR, 0.89; P=0.12). This study emphasized that BP reduction is more important than the mechanism of action of the drug, and that amlodipine-based treatment has a powerful BP-lowering effect in the early phase. Therefore, the quicker patients can reach the target with CCBs, the better the protection they will receive. In the ASCOT-BPLA Study [25], patients were randomized to one of two BP-lowering treatments, either amlodipine with or without perindopril (amlodipine-based) or atenolol with or without bendroflumethiazide (atenolol-based). The study found that the amlodipine-based regimen prevented more major CVD events and induced less diabetes than the atenolol-based regimen. Furthermore, the ASCOT Legacy Study [51], results after a 16-year follow-up, showed that significantly fewer deaths from stroke occurred in the amlodipine-based treatment group than in the atenolol-based treatment group. Patients with combined treatment with lipid-lowering treatment had fewer CVD deaths more than 10 years after the trial closure. These studies have important implications, suggesting that combined interventions with BP-lowering CCBs and lipid-lowering treatments are associated with long-term benefits in patients with hypertension and no history of CAD events. The ACCOMPLISH Study [39] aimed to investigate the efficacy of the combination treatment of an ACEI and DHP-CCB in reducing the rate of CVD events, compared to treatment with an ACEI plus a thiazide diuretic in high-risk patients with hypertension. The combination of benazepril and amlodipine was found to be superior to the combination of benazepril and hydrochlorothiazide in reducing CVD events in high-risk patients. Therefore, the aforementioned studies suggest that DHP-CCBs can effectively reduce CVD events in ISH, elderly, and high-risk patients. Moreover, these agents, when combined with RAS blockers, can be effective in reducing CVD events.

INDICATIONS, CONTRAINDICATIONS, AND SIDE EFFECTS

CCBs are indicated for a variety of conditions, including

hypertension in the elderly, ISH, angina pectoris, and coronary vasospasm, according to the 2022 KSH Guidelines [2]. Additionally, non-DHP-CCBs such as verapamil and diltiazem are suggested for use post–myocardial infarction, as they do not cause rebound tachycardia. They are also recommended for hypertrophic cardiomyopathy due to their ability to improve diastolic filling time. The common side effects of DHP-CCBs include tachycardia, peripheral edema, headaches, and hot flashes, while non-DHP-CCBs may cause constipation and bradycardia [5]. Non-DHP-CCBs are contraindicated in cases of high-grade SA or AV block, HFrEF, bradycardia (for instance, a heart rate of less than 60 bpm), and when comedications are susceptible to significant drug interactions mediated by P-gp or CYP3A4. DHP-CCBs should be used cautiously in cases of tachyarrhythmia, HFrEF (class III or IV), and preexisting severe edema. Similarly, non-DHP-CCBs should be used with caution in cases of constipation [8].

Peripheral edema

There is no universally accepted definition of peripheral edema related to CCBs, which results in a wide range of reported incidence rates, from 5% to 70% [52]. This condition is more prevalent in women, in individuals who are often in an upright position, and in the elderly. The incidence is 2.8 times higher with high-dose CCBs than with low-dose CCBs [52,53]. Liang et al. [53] found that the incidence of peripheral edema was significantly higher with DHP-CCBs than with non-DHP-CCBs. Among DHP-CCBs, the first-generation CCB nifedipine had the highest incidence of peripheral edema, while the fourth-generation CCB lacidipine had the lowest incidence, according to the systematic review and network meta-analysis. The COHORT Study [54] revealed that amlodipine was associated with significantly more edema-related symptoms (19%) than lipophilic CCBs, lercanidipine (9%) or lacidipine (4%). The primary mechanism behind this is postulated to be an imbalance between precapillary and postcapillary tones, leading to intracapillary hypertension and fluid leakage. The rate of drug withdrawal due to edema was 2.1 times higher in the CCB group than in the placebo group [55]. Therefore, it is crucial to identify and manage peripheral edema when treating patients with CCBs. Treatment strategies for CCB-related edema may include the following: (1) reducing the dose of CCBs; (2) switching from a DHP-CCB to a non-DHP-CCB or to a lipophilic CCB such as lercardipine or lacidipine; (3) coadministration of RAS blockers; and (4) diuretic therapy. Diuretics, particularly thiazide diuretics, have been suggested as a treatment option for edema due to their ability to decrease limb volume.

However, since CCB-related edema is not associated with volume overload at a fundamental level, routine administration of diuretics is not recommended for patients with edema to reduce the edematous state [52]. Vouri et al. [56] reported that a significant proportion of patients were prescribed loop diuretics instead of having their DHP-CCB dose reduced or discontinued. This led to adverse events associated with loop diuretics in the first 4 months following initiation, highlighting the need to evaluate edema after starting CCBs. The combination of DHP-CCB and RAS blockers has been suggested to reduce edema compared to DHP-CCB monotherapy due to the balanced vasodilating effect of RAS blockers on both precapillary and postcapillary tones. For instance, a combination of amlodipine and an ACEI was found to reduce edema the most, while a combination of nifedipine and an ARB did not alleviate edema, although information on this is limited [52,53]. Therefore, the use of long-acting and lipophilic DHP-CCBs in combination with RAS blockers may decrease the likelihood of peripheral edema development compared to DHP-CCB monotherapy [53].

CONCLUSIONS

This review provides an overview of CCBs. The following major points are highlighted.

First, CCBs are categorized into two types: DHP-CCBs and non-DHP-CCBs. DHP-CCBs are further subcategorized into first-to fourth-generation based on their time of discovery, onset of drug effect, and duration of activity. They exhibit higher vascular selectivity, making them potent vasodilators. Conversely, non-DHP-CCBs have higher cardiac selectivity, making them suitable for treating tachyarrhythmia, although they should be used with caution in cases of HF and bradycardia. Traditional CCBs primarily block L-type calcium channels, while novel CCBs also block N-type and/or T-type channels, leading to organ-protective actions. Consequently, each CCB has unique pharmacokinetic profiles and side effects.

Second, DHP-CCBs have a more potent BP-lowering effect than other classes of antihypertensive drugs. They exhibit similar BP-lowering effects within their class and maintain a relatively constant BP-lowering effect throughout the day.

Third, systolic BP variability was found to be lower in patients receiving amlodipine than in those receiving atenolol or lisinopril. This finding partly explains the reduced risk of vascular events in patients treated with amlodipine.

Fourth, CCBs have protective effects against HMOD, including LVH and increased arterial stiffness. Additionally, CCBs suppress atherosclerosis and coronary vasospasm.

Fifth, L/N-CCBs and L/T-type CCBs, when combined with RAS blockers, result in decreased proteinuria and improved kidney function compared to standard L-type CCBs, despite no additional BP-lowering effect.

Sixth, large-scale trials have shown that DHP-CCBs can effectively reduce CVD events in patients with ISH, the elderly, and high-risk patients. Furthermore, these agents, when combined with RAS blockers, can effectively reduce CVD events.

Seventh, CCBs are indicated for conditions including hypertension in the elderly, ISH, angina pectoris, and coronary vasospasm. Non-DHP-CCBs are contraindicated in any high-grade SA or AV block, HFrEF, bradycardia (e.g., heart rate <60 bpm), and when comedications are susceptible to significant drug interactions mediated by P-gp or CYP3A4. DHP-CCBs should be used with caution in patients with tachyarrhythmia, HFrEF (class III or IV), and preexisting severe edema, while non-DHP-CCBs should be used with caution in patients with constipation.

Eighth, CCB-induced edema is a common side effect and is more common at higher doses. Reducing the dose, switching from DHP to non-DHP-CCBs or lipophilic CCBs, or using combined therapy with a RAS blocker instead of DHP-CCB monotherapy, can lower the risk of peripheral edema development.

Accordingly, CCBs are indicated for a variety of conditions, including hypertension in the elderly, ISH, angina pectoris, and coronary vasospasm. However, it is important to note that each CCB has unique pharmacokinetics and side effects. This necessitates careful consideration when making clinical decisions.

ARTICLE INFORMATION

Ethics statements
Not applicable.

Conflicts of interest
The author has no conflicts of interest to declare.

Funding
None.

ORCID
Eun Mi Lee, https://orcid.org/0000-0002-2447-9453

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Review Article

Cardiovasc Prev Pharmacother 2023;5(4):126-133
eISSN 2671-700X
https://doi.org/10.36011/cpp.2023.5.e18

Cardiovascular Prevention and Pharmacotherapy

Lipid variability in patients with diabetes mellitus

Jeongmin Lee[1], Seung-Hwan Lee[2,3]

[1]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Eunpyeong St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[2]*Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, Seoul, Korea*
[3]*Department of Medical Informatics, College of Medicine, The Catholic University of Korea, Seoul, Korea*

Diabetic dyslipidemia is characterized by hypertriglyceridemia, low high-density lipoprotein cholesterol (HDL-C), elevated low-density lipoprotein cholesterol (LDL-C), and the predominance of small dense LDL particles caused by insulin resistance in patients with type 2 diabetes mellitus (DM) or insulin deficiency in patients with type 1 DM. Dyslipidemia is a major risk factor for atherosclerotic cardiovascular disease in individuals with DM, and lowering lipid levels can reduce the associated morbidity and mortality. The current guidelines for dyslipidemia management recommend an LDL-C goal lower than 55 to 100 mg/dL, depending on the underlying risk factors. However, greater visit-to-visit variability in cholesterol levels might be an independent predictor of major adverse cardiovascular events, high incidence of atrial fibrillation, poor renal outcomes, and cognitive dysfunction in patients with DM. This review focuses on the clinical implications of lipid variability in patients with DM.

Keywords: LDL cholesterol; Diabetes complications; Dyslipidemias; Triglycerides

INTRODUCTION

Atherosclerotic cardiovascular disease (ASCVD), which comprises ischemic heart disease, cerebrovascular disease, and atherosclerosis, is the second leading cause of death in Korea, surpassed only by malignant neoplasms. Dyslipidemia, a condition characterized by metabolic irregularities in plasma lipids and lipoproteins such as low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglycerides, is a primary contributor to ASCVD [1]. Notably, ASCVD is a predominant cause of mortality among patients with diabetes mellitus (DM), and dyslipidemia, a significant risk factor for ASCVD, can be managed in these patients [2]. The typical dyslipidemia patterns seen in patients with DM include hypertriglyceridemia, elevated levels of small dense LDL-C (sdLDL-C), and reduced HDL-C, all of which are closely associated with hyperglycemia [3,4].

Since LDL-C has been identified as the most reliable predictor of ASCVD, statin therapy is primarily used to treat dyslipidemia and decrease the incidence and risk of ASCVD. This approach is based on prior research suggesting that "the lower, the better" [5,6]. Most earlier studies assessing lipid-lowering effects, such as those of statins, concentrated on lipid markers at the start and end of the studies. However, recent research has shed light on the connection

Received: September 11, 2023; **Revised:** October 6, 2023; **Accepted:** October 10, 2023
Correspondence to Seung-Hwan Lee, MD
Division of Endocrinology and Metabolism, Department of Internal Medicine, Seoul St. Mary's Hospital, College of Medicine, The Catholic University of Korea, 222 Banpo-daero, Seocho-gu, Seoul 06591, Korea
Email: hwanx2@catholic.ac.kr

between cholesterol variability and various diseases. Consequently, this review aims to summarize the impact of lipid variability in patients with DM.

DYSLIPIDEMIA IN DM

Hypertriglyceridemia in DM

Hypertriglyceridemia is the most prevalent form of dyslipidemia found in patients with DM. This elevation in serum triglycerides is primarily driven by insulin resistance, which is associated with hyperglycemia [7]. In patients with type 2 DM, insulin resistance results in an increase of free fatty acids due to lipolysis, which in turn leads to an increased secretion of very-low-density lipoproteins, including triglycerides. Conversely, patients with type 1 DM, which is characterized by insulin deficiency, do not see an increase in triglycerides due to the influx of free fatty acids into the liver. Instead, they develop hypertriglyceridemia as a result of impaired triglyceride clearance [3,8].

Hypercholesterolemia in DM

Severe dyslipidemia is not typically seen in the majority of patients with DM. As previously noted in the introduction, LDL-C is considered to be a predictive factor for ASCVD, and the importance of statin therapy is also underscored in patients with DM, in whom elevated levels of free fatty acids, due to insulin resistance and hypertriglyceridemia, cause an increase in LDL lipolysis. This results in the creation of smaller, denser LDL particles, referred to as sdLDL-C. Closely linked to ASCVD, sdLDL-C contributes to the higher incidence of CVD in patients with DM [9].

HDL is involved in the reverse transport of cholesterol from peripheral tissues back to the liver, and low HDL-C levels are another predictive indicator for ASCVD, in addition to high LDL-C levels. Elements such as advanced glycation end products, oxidative stress, and inflammatory responses triggered by hyperglycemia result in a reduction of HDL-C levels and interfere with cholesterol efflux [8,10].

LIPID VARIABILITY IN DM

As outlined in the introduction, the primary and secondary prevention of ASCVD relies heavily on lipid-lowering therapy, predominantly through the use of statins. Furthermore, it has been demonstrated that discontinuing statin therapy can lead to increased short- and long-term mortality rates, as well as a higher incidence of vascular events in patients with ASCVD [11–13]. Poorer outcomes have been reported in patients who discontinued statin therapy than in those who never started it [14,15]. The conversation around lipid variability originated from studies that explored the relationship between lipid variability and the prognosis of ASCVD in the context of large-scale statin trials. Research has been conducted on daily variability [16,17] and seasonal variability [18] in lipid levels in patients with type 2 DM, revealing the existence of biological variability in cholesterol levels. However, the clinical significance of short-term lipid variability remains unclear, and interest has grown in recent years in the impact of long-term (visit-to-visit) lipid variability in patients with DM.

Risk of DM incidence with lipid variability

Studies based on data from Korea have reported a correlation between lipid variability and the risk of developing DM. One study [19], which utilized the Korean National Health Insurance Service (NHIS) database, divided total cholesterol variability into deciles. The results showed that the group in the highest decile had a 1.16-fold higher risk of developing DM than the group in the lowest decile, regardless of whether they were undergoing lipid-lowering therapy (95% confidence interval [CI], 1.57–1.63). Another study [20] examined the risk of DM based on HDL-C variability. In that research, both the average HDL-C and HDL-C variability were used as variables. The findings indicated that both men and women had a higher risk of developing DM if they had lower baseline HDL-C levels and greater variability. According to a multivariate analysis model, the group with a lower average HDL-C and higher variability had a 1.40 times higher risk (95% CI, 1.38–1.42) of developing DM compared to the group with a higher average HDL-C and lower variability. Previous studies have suggested that a chronic inflammatory state and nonenzymatic apolipoprotein glycation may play a role in the impairment of HDL-C function [20,21]. Additionally, HDL-C influences glucose metabolism through both direct and indirect pathways. Several mechanisms may account for the association between elevated levels of HDL-C and a decreased risk of diabetes,

encompassing anti-inflammatory response mechanisms, enhanced insulin secretion, and improved glucose uptake by peripheral muscles [22]. However, the exact impact of HDL-C variability on subsequent type 2 DM risk remains uncertain. A separate Korean study [23] that used data from a single institution consistently found that patients with persistent hypertriglyceridemia had a 1.58-fold higher risk for newly diagnosed DM. However, after adjusting for body mass index, the study found no statistically significant link between changes in triglyceride levels and the risk of DM (hazard ratio [HR], 1.25; 95% CI, 0.86–1.80). In analyses pre-adjusting the triglyceride group (from abnormal triglyceride levels to the normal range), there was no statistically significant correlation with DM risk. Moreover, the normal-abnormal group (those with normal levels in the first examination and abnormal levels in the second examination) showed no correlation with the development of DM. This implies that the development of diabetes due to hypertriglyceridemia may span several years, with insulin resistance emerging a decade or two before the onset of the disease. Nevertheless, it remains to be clarified whether variability in triglyceride levels serves as a predictive factor for heightened DM risk.

Long-term fluctuations in total cholesterol and HDL-C may increase the risk of developing DM. Cholesterol homeostasis is vital for pancreatic β-cells, influencing their survival, proliferation, and functional maturation [24]. Therefore, imbalances in cholesterol have been linked to DM. Cholesterol distribution is considered crucial for β-cell function, rather than its total level. However, more research is required to determine whether mitigating these fluctuations can effectively lower the incidence of DM.

Lipid variability in DM and health outcomes

Overall mortality and risk of CVD

Research has consistently reported that lipid variability is associated with mortality and CVD risk since the Framingham Heart Study [25]. However, studies specifically targeting patients with DM are scarce. A recent study from Taiwan [26] identified LDL-C variability as a risk factor for CVD in patients with type 2 DM, but found no significant correlations with HDL-C or triglyceride variability. A relatively recent study conducted in Hong Kong [27] found that among type 2 patients with DM who did not have CVD, variability in LDL-C, the total cholesterol to HDL-C ratio, and triglycerides increased the risk and mortality rate of CVD by 1.27 times (95% CI, 1.20–1.34), 1.31 times (95% CI, 1.25–1.38), and 1.09 times (95% CI, 1.04– 1.15), respectively. Another study by Wang et al. [28] discovered that variability in total cholesterol excluding triglycerides increased the risk of all-cause mortality and CVD mortality. With every 10% rise in variability in HDL-C, LDL-C, and total cholesterol, the risk of all-cause mortality increased by 1.30-fold (95% CI, 1.22–1.37), 1.05-fold (95% CI, 1.01–1.09), and 1.10-fold (95% CI, 1.03–1.16), respectively. Correspondingly, the risk of CVD mortality increased by 1.27-fold (95% CI, 1.16–1.39), 1.08-fold (95% CI, 1.02–1.15), and 1.16-fold (95% CI,1.07–1.27), respectively. In the study based on the ACCORD (Action to Control Cardiovascular Risk in Diabetes)-Lipid trial in China [29], LDL-C variability was a strong predictor of both all-cause mortality and CVD mortality, showing a 1.22-fold increase (95% CI, 1.13–1.32). The study also analyzed the risk of non-CVD mortality, revealing that for every 10% increase in HDL-C variability, the risk of mortality from causes other than CVD increased by 31%. The most recent study based on the ACCORD-Lipid trial [30] revealed that variability in LDL-C within the highest quartile (Q4) was associated with a 1.61-fold increase in the risk of all-cause mortality and a 1.78-fold increase in the risk of CVD mortality compared to the lower quartiles (Q1–Q3). Notably, stratified analyses by quartiles of the variabilities and means in LDL-C, HDL-C, and triglyceride showed that higher variability in the lipid profile in the target range was a risk factor for CVD mortality. These study findings suggest that managing not only the absolute values of dyslipidemia-related parameters, but also their variability, is crucial in patients with DM.

Variability in lipid levels has the potential to harm the endothelium, and fluctuations in lipid efflux can compromise plaque stability, consequently elevating the risk of plaque rupture [31]. In turn, this leads to the release of atherogenic substances and therefore an increased mortality risk [32].

Atrial fibrillation

Although dyslipidemia is widely acknowledged as a significant risk factor for CVD, as mentioned previously, such recognition has not been equally established for atrial fibrillation (AF). Dyslipidemia appears to be associated with a lower prevalence of AF, commonly referred to as the “cholesterol paradox” in AF [33].

In contrast to the consistent research on lipid variability and CVD risk, conflicting results have been reported regarding the association between lipid variability and AF. A comprehensive Korean study involving 3,660,385 adults [34] observed that a lower incidence of AF was correlated with elevated levels of total cholesterol, LDL-C, HDL-C, and triglycerides, with approximately 22%, 19%, 6%, and 12% reductions in risk, respectively. High lipid variability was associated with a higher risk for AF. The highest variability (Q4) in total cholesterol was correlated with a 1.09-fold increase in AF risk (95% CI, 1.06–1.13), a 1.12-fold increase (95% CI, 1.08–1.16) in LDL-C variability, a 1.08-fold increase (95% CI, 1.04–1.12) in HDL-C, and a 1.05-fold increase (95% CI, 1.01–1.08) in triglycerides. In another study conducted in Hong Kong [35], which involved 23,329 patients with DM (mean glycated A1c, 8.6%), it was observed that high levels of LDL-C were associated with an approximately 21% reduction in the risk of AF (95% CI, 0.73–0.85). Similarly, high levels of HDL-C demonstrated about a 33% risk reduction (95% CI, 0.57–0.78), and high total cholesterol levels decreased the risk of AF by 13% (95% CI, 0.82–0.93). Conversely, a high total cholesterol level was correlated with an approximately 1.04-fold higher risk of developing AF (95% CI, 1.01–1.07). However, high lipid variability based on the coefficient of variation in LDL-C, HDL-C, and total cholesterol was a significant risk factor for AF. In the coefficient variation, approximately 1.02 times increased risk per increment were shown in LDL-C (95% CI, 1.01–1.02), HDL-C (95% CI, 1.02–1.03), and total cholesterol (95% CI, 1.01–1.02). In contrast, variability in triglyceride levels was not found to be associated with AF, with a corresponding risk reduction of approximately 12% (95% CI, 0.85–0.92).

Cholesterol levels and their fluctuations could be associated with the development of AF through various mechanisms. Cholesterol serves as a component of cell membranes that modulates alterations in membrane properties, impacting membrane permeability and proteins such as ion channels, pumps, and receptors. These alterations may disrupt the electrical balance and resting state of cell membranes, increasing the likelihood of arrhythmia development [36]. Inflammation is also linked to the onset and persistence of AF. Lipid variability contributes to oxidative stress and chronic inflammation. Higher levels of LDL-C and low levels of HDL-C are correlated with an increased state of inflammation [37,38].

Kidney disease

End-stage kidney disease is one of the major complications of DM and is closely linked to increased mortality rates. Variability in blood pressure and blood glucose levels are recognized risk factors for albuminuria and a reduced glomerular filtration rate [39–41]. However, there is limited research on the relationship between lipid variability and diabetic kidney disease. In a small-scale study conducted in Taiwan involving patients with type 2 DM [42], variability in HDL-C was the only lipid-related factor that was identified as a risk factor for diabetic kidney disease. An Italian study [43] found that variability in LDL-C and HDL-C in patients with type 2 DM was associated with a decrease in the glomerular filtration rate. A recent small-scale study in Japan [44] examined the risk of microalbuminuria and diabetic kidney disease in relation to postprandial triglyceride variability. The study found that the group with high postprandial triglyceride variability had a 49% increased risk of developing microalbuminuria. In a large-scale study conducted in Hong Kong [45], researchers analyzed the prognostic significance of variability in LDL-C, the total cholesterol to HDL-C ratio, and triglyceride levels for kidney disease over a median follow-up period of 66.5 months. The study found that for every 1 mmol/L increase in LDL-C variability, the incidence rate of kidney disease showed a 1.20-fold rise increase (95% CI, 1.05–1.25), and the occurrence of end-stage kidney disease increased by 2.08-fold (95% CI, 1.74–2.5). The association between variability in the total cholesterol to HDL-C ratio and kidney disease was similar to that of LDL-C variability. However, no significant correlation was found between triglyceride variability and kidney disease.

The relationship between lipid variability and kidney disease in patients with DM is predominantly attributed to fluctuations in LDL-C levels. This is due to the same pathophysiological factors that contribute to ASCVD, including disorders in lipid metabolism (specifically cholesterol and chylomicron metabolism), oxidative stress, and inflammation, all of which adversely affect the glomeruli [46]. Therefore, it may be necessary to minimize lipid variability to prevent the onset of kidney disease in patients with DM.

Cognitive dysfunction and dementia

The brain contains abundant lipids, particularly glycerophospholipids, sphingolipids, and cholesterol. Research has shown that levels of lipid oxidation products are elevated in tissues from aged mice [47]. Several studies have demonstrated that variability in the lipid profile was a risk factor for cognitive dysfunction. A cross-sectional study from PROSPER (Prospective Study of Pravastatin in the Elderly at Risk) [48] revealed that greater variability in LDL-C levels was associated with reduced cognitive function in older individuals at a high risk of vascular disease. Lee et al. [49] found that increased variability in total cholesterol levels was associated with a higher risk of developing all-cause dementia, Alzheimer disease, and vascular dementia in the general population. Another representative Korean study [50] showed that higher variability in total cholesterol was a risk factor of all-cause dementia. Abnormal lipid metabolism is a common characteristic shared by both DM and dementia. Dyslipidemia promotes amyloid-β (the main component of senile plaques and one of the histopathological markers) pathology and induces oxidative stress with mitochondrial dysfunction [51]. However, there are limited studies reporting an independent association between lipid variability and the development of cognitive dysfunction or dementia in individuals with DM. In a recent study from Hong Kong [52] including 273,876 patients with type 2 DM, lipid levels were not a significant risk factor for dementia.

Management of lipid variability

Many studies have attributed lipid variability to the use of statins. Patient nonadherence to medication is often identified as a cause of this variability, with LDL-C variability even suggested as a specific test for evaluating adherence [53]. Other elements, such as lipid variability resulting from weight changes [54], chronic kidney disease, or genetic factors, may also be linked to lipid variability and contribute to the differing responses to treatment [55].

The impact of statin therapy and dosage on lipid variability remains unclear. In the TNT (Treating to New Targets) trial [38], administering a high dose of atorvastatin (80 mg/day) significantly decreased LDL-C variability compared to a low dose of atorvastatin (10 mg/day). Intermittent statin dosing has been proposed as a way to save costs or manage statin intolerance. However, for statins with a short half-life, this approach could increase lipid variability and potentially introduce risks [56]. Research is currently being conducted on the use of long-acting proprotein convertase subtilisin kexin-9 inhibitors as a means to reduce lipid variability, but further evidence is needed to assess potential risks [57]. Therefore, maintaining stable lifestyle habits through consistent treatment, dietary modifications, and regular exercise is important.

It is imperative to underscore the significance of regular lipid profile monitoring in clinical practice, ensuring that patients prescribed statins undergo routine assessments to track lipid levels, and tailoring treatment strategies for optimal cardiovascular risk management.

CONCLUSIONS

Lipid variability in patients with DM has been shown to increase the risk of ASCVD and mortality, similar to its impact in individuals without DM. Lipid variability also has an impact on diabetic kidney disease, although the magnitude of this effect may vary depending on certain lipid parameters. The management of dyslipidemia in patients with DM should focus on both keeping LDL-C levels below the target and minimizing variability.

ARTICLE INFORMATION

Ethics statements

Not applicable.

Conflicts of interest

The authors have no conflicts of interest to declare.

Funding

None.

Author contributions

Conceptualization: all authors; Investigation: SHL; Methodology: SHL; Writing–original draft: JL; Writing–review & editing: all authors. All authors read and approved the final manuscript.

ORCID

Jeongmin Lee, https://orcid.org/0000-0001-9074-8087
Seung-Hwan Lee, https://orcid.org/0000-0002-3964-3877

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Review Article

Cardiovasc Prev Pharmacother 2023;5(4):134-143
eISSN 2671-700X
https://doi.org/10.36011/cpp.2023.5.e17

Cardiovascular Prevention and Pharmacotherapy

COVID-19 vaccination–related cardiovascular complications

Jae Yeong Cho, Kye Hun Kim

Department of Cardiovascular Medicine, Chonnam National University Hospital, Chonnam National University Medical School, Gwangju, Korea

The global response to the COVID-19 pandemic has led to rapid vaccine development and distribution. As vaccination efforts continue, concerns have arisen regarding potential adverse events associated with COVID-19 vaccination. This article examines emerging evidence on adverse events, including myocarditis, pericarditis, and thrombotic complications, in relation to COVID-19 vaccination. Reports of myocarditis and pericarditis cases following messenger RNA vaccines have sparked interest, with discussions revolving around potential mechanisms and genetic predispositions. The contrasting findings on pericarditis risk postvaccination highlight the complexity of studying this phenomenon. Thrombotic events, particularly vaccine-induced thrombotic thrombocytopenia, have garnered attention, prompting investigations into antibody responses and mechanisms. This article underscores the importance of ongoing research, collaboration, and data analysis for accurately understanding adverse events. While the COVID-19 vaccination campaign may have ended, it is still vital to maintain vigilance, collect comprehensive data and foster interdisciplinary collaboration to uphold vaccine safety and steer public health strategies in the upcoming period.

Keywords: COVID-19; Vaccination; Cardiovascular diseases; Adverse cardiac events

INTRODUCTION

The initiation of the COVID-19 vaccination in December 2020 in the United States and various other Western countries, with subsequent commencement in Korea in February 2021, engendered notable domestic and global concerns. While typical vaccination-related manifestations were documented, there were also reports of serious adverse events emerging. The initial vaccines utilized adenoviral vectors, raising concerns about thrombosis events, while the widespread distribution of messenger RNA (mRNA) vaccines has brought issues such as myocarditis and pericarditis to the forefront. It is also noteworthy that instances of vaccine-related myocarditis displayed varying clinical outcomes between countries and ethnicities [1,2], and in particular, that more adverse events occurred within the Korean context [3]. The ongoing COVID-19 pandemic has led to an unprecedented global effort to develop and distribute vaccines to combat the spread of the virus. As vaccination campaigns progress, it is crucial to closely monitor and assess potential adverse events associated with the vaccines. Among the reported adverse events, myocarditis, pericarditis, and thrombotic complications have garnered attention due to their potential links to COVID-19 vaccination (Fig. 1). This review delves into the emerging evidence surrounding these adverse events and explores their possible associations with different types of vaccines.

Received: September 14, 2023; **Revised:** October 5, 2023; **Accepted:** October 10, 2023
Correspondence to Kye Hun Kim, MD
Department of Cardiovascular Medicine, Chonnam National University Hospital, Chonnam National University Medical School, 42 Jebong-ro, Dong-gu, Gwangju 61469, Korea
Email: christiankyehun@hanmail.net

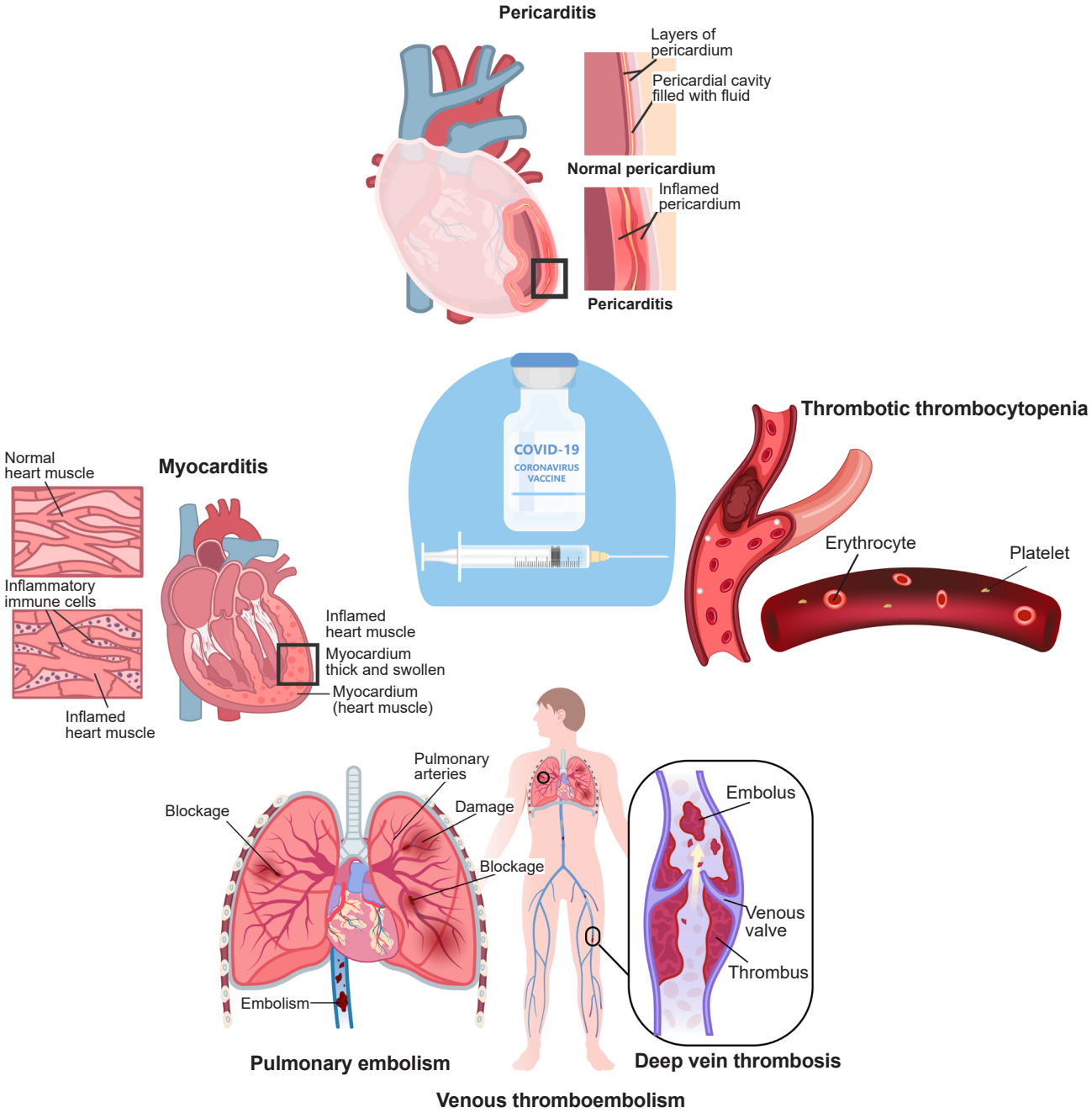

Fig. 1. COVID-19 vaccination–related cardiovascular complications.

MYOCARDITIS

There is a substantial body of evidence indicating a potential association between COVID-19 vaccination and the development of myocarditis. Myocarditis and pericarditis are known complications of mRNA vaccines, especially in young adults and teen boys aged 12 to 17 years [4], with the highest observed incidence within 2 to 7 days after the second dose at a rate of 3.5 to 140 per million doses [5,6]. The incidence of myocarditis is rare, and myocarditis oc-

curs much more frequently following COVID-19 infection than following vaccination [4]. Even in the group at highest risk, boys aged 12 to 17 years, the risk of myocarditis was 1.8 to 5.6 times higher after SARS-CoV-2 infection than after vaccination [4]. Myocarditis was estimated to develop 1 to 10 per million persons in the month following vaccination, which was substantially lower than observed after SARS-CoV-2 infection [2]. Cardiovascular events following vaccination are rare and should be considered alongside the overall benefits of COVID-19 vaccination [4,7]. General myocarditis, especially viral myocarditis, is known to have an annual incidence rate of 1 to 10 cases per 100,000 individuals. Following mRNA COVID-19 vaccination, an incidence rate of 1.4 to 5.0 cases per 100,000 individuals within 7 to 42 days has been reported [8]. A population-based cohort study in Denmark [9], analyzing myocarditis and pericarditis occurring within 28 days of vaccination in 4,931,775 vaccine recipients from October 2020 to October 2021, revealed an adjusted risk ratio of 1.34 (95% confidence interval [CI], 0.90–2.00) for myocarditis following BNT162b2 vaccination and 3.92 (95% CI, 2.30–6.68) following mRNA-1273 vaccination. In a self-controlled case series within the cohort study, the rate ratio was 1.48 (95% CI, 0.93–2.36) for BNT162b2 vaccine recipients and 6.25 (95% CI, 2.83–13.82) for mRNA-1273 vaccine recipients. An analysis of data from the largest healthcare organization in Israel (Clalit Health Services) [1], demonstrated a myocarditis incidence rate of 2.13 cases per 100,000 individuals within 42 days after the first dose of mRNA vaccines. Notably, the highest myocarditis incidence rate was observed in men aged 16 to 29 years, reaching 10.69 cases per 100,000 individuals, with rates of 4.12 and 0.23 cases per 100,000 in men and women overall, respectively. An analysis of data from the Ministry of Health of Israel [10] revealed that myocarditis occurrence after BNT162b2 vaccination exceeded the expected frequency based on 2017–2019 incidence rates. The analysis, including the 21 days after the first dose and 30 days after the second dose, showed a post–first-dose rate ratio of 1.42 (95% CI, 0.92–2.10) and a post–second-dose rate ratio of 5.34 (95% CI, 4.48–6.40) compared to the expected frequency in unvaccinated individuals. Data analysis of reports submitted to the national passive reporting system, Vaccine Adverse Event Reporting System (VAERS), in the United States [5] revealed 1,626 cases of myocarditis following mRNA vaccine administration from December 2021 to August 2022. The incidence of myocarditis within 7 days of vaccination exceeded the expected frequency based on 2017–2019 claims data in multiple age and sex strata. Notably, the frequency of myocarditis following vaccination was highest among 12- to 15-year-old boys, with 70.7 cases per million BNT162b2 doses administered, and ranged from 52.4 to 105.9 cases per million doses among other age groups and vaccines. These four studies consistently reported relatively consistent results—namely, increased rates following the second dose, higher rates in young men, and rates exceeding the expected frequency in unvaccinated individuals. A notable difference in Denmark's report [9] was the relatively lower adjusted hazard ratio (aHR) following BNT162b2 vaccination, which may be attributed to the specificity of risk in patients with no other risk factors apart from vaccination. Although different studies used varying risk intervals between 7 and 42 days after vaccination, all reported higher rates of myocarditis during the risk interval than expected. Although consistent results have been reported regarding an increased rate of myocarditis following the second dose compared to the first, interpreting this as a dose-response relationship is challenging. With ongoing third-dose vaccinations, further research is needed to determine whether the incidence of myocarditis remains higher after the second dose. However, this possibility is unlikely, and immunological attenuation may provide a more plausible explanation. SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA encoding the viral spike glycoprotein, which, when administered, generates adaptive immune responses to produce immunoglobulin G (IgG) antibodies against the viral spike protein, facilitating virus neutralization. While some RNA can stimulate the innate immune system on its own, mRNA vaccines underwent nucleoside modification to reduce innate immunogenicity. Nonetheless, in individuals with certain genetic predispositions, an immune response to mRNA could trigger proinflammatory cascades, leading to systemic reactions, including myocarditis [11].

In a large Israeli cohort study [1], only one out of 54 patients with COVID-19 vaccine–related myocarditis (VRM) developed cardiogenic shock requiring extracorporeal membrane oxygenation support. A US study involving 40 hospitals [12] reported no readmissions or deaths among COVID-19 VRM patients, with all patients discharged within a median of 2 days (interquartile range, 2–3 days). In a Korean nationwide study from our team [3], we observed 95

severe COVID-19 VRM cases (19.8% of total VRM), including 36 cases of fulminant myocarditis and 21 deaths. Additionally, we identified eight cases of sudden cardiac death confirmed through autopsy. Given our extensive dataset of over 44 million individuals, it is possible that our study observed more deaths than studies with smaller populations. However, the largest cohort in the US [5], encompassing 192,405,448 individuals, reported no COVID-19 VRM-related deaths. The discrepancy between our findings and those in the United States may be attributed to differences in case reporting systems. Most US studies utilized the VAERS, a passive reporting system susceptible to both underreporting and overreporting. In contrast, the Korean government established a comprehensive reporting system for adverse events before COVID-19 vaccination, along with a national compensation system for related medical expenses. Given that VRM is a legally mandated reportable adverse reaction to COVID-19 vaccination in Korea, the risk of underreporting is minimized. The Korean government also established a causality assessment committee to review and confirm vaccination-associated cases, further reducing the potential for overreporting of VRM.

The exact mechanisms underlying mRNA vaccine-induced myocarditis are still not fully understood. Nevertheless, some reports indicate that the mRNA-1273 vaccine may initiate a strong CD4 cytokine response, particularly involving type 1 helper T (Th1) cells. CD4 cells have been suggested as a possible contributor to the onset of myocarditis [13,14]. The detailed mechanisms warrant further clinical and basic research. Myocarditis and perimyocarditis may be caused by the direct invasion of cardiomyocytes by SARS-CoV-2 [15] and an inflammatory response. However, the fact that myocarditis occurs after vaccination, in the absence of live viruses, also points to an immune-mediated phenomenon and molecular mimicry between the spike protein (present in infection and after vaccination) and autoantigens in genetically predisposed persons, as confirmed by the discovery of autoantibodies in some patients [11]. New evidence suggests the role of endogenous autoantibodies against interleukin-1 receptor antagonist (IL-1RA) and hyperphosphorylated IL-1RA in triggering myocarditis in young male adults [16]. Further investigation into the mechanism of vaccine-related myocarditis and the development of effective treatment strategies are warranted.

PERICARDITIS

Rather than myocarditis, a notable proportion of patients have experienced chest pain after receiving the COVID-19 vaccine, leading to a diagnosis of pericarditis. Some of these instances have posed more substantial treatment challenges and involved extended recovery periods in contrast to typical viral pericarditis cases.

A study analyzing cases of pericarditis following COVID-19 vaccine administration through medical records from 40 hospitals in the United States [12] reported a total of 37 cases (15 cases after the first dose and 22 cases after the second dose) out of a total of 2,000,287 doses administered. This indicated a significantly higher incidence of pericarditis compared to the prevaccination period (prevaccination, 49.1%; postvaccination, 78.8%). A self-controlled case series conducted in the United Kingdom [2] reported a total of 1,574 cases of pericarditis between December 2020 and August 2021. Among these, 356 cases occurred within 28 days after mRNA vaccine administration, with 188 cases occurring in COVID-19–infected patients and 154 cases occurring before vaccine administration. Hospitalizations and deaths due to pericarditis increased within 14 days after COVID-19 infection (incidence rate ratio [IRR], 3.81; 95% CI, 1.90–7.63), but there was no increase in hospitalizations or deaths due to pericarditis after vaccine administration. Instead, there was a lower risk (ChAdOx1 first dose: IRR, 0.59 [95% CI, 0.37–0.94]; BNT162b2 first dose: IRR, 0.46 [95% CI, 0.24–0.90]). The risk of pericarditis within 28 days after COVID-19 infection was elevated (IRR, 2.79; 95% CI, 1.80–4.32), but the risk was lower within 28 days after ChAdOx1 first dose (IRR, 0.74; 95% CI, 0.59–0.92). A case-control study comparing hospital control participants and patients hospitalized with carditis after BNT162b2 and Sinovac-CoronaVac vaccine administration in Hong Kong [17] showed an adjusted odds ratio of 7.78 (95% CI, 3.76–16.13) for carditis within 14 days after BNT162b2 vaccine administration. In the subgroup analysis, the adjusted odds ratio was 9.29 (95% CI, 3.94–21.91) for myocarditis and 1.06 (95% CI, 0.35–3.22) for pericarditis. The results from the studies above show somewhat contradictory findings. An analysis of medical records from 40 US hospitals following vaccine administration [12] indicated an increased incidence of pericarditis after vaccine initiation compared to the prevaccination period. However, other studies did not find an increased rate of pericarditis

following vaccine administration. This could be interpreted as reflecting a specific association in patients without other risk factors, but caution is needed due to the low incidence of pericarditis itself and the possibility of its occurrence in the absence of vaccine-related factors. In the US study, there were 193 cases of pericarditis after the first dose and 374 cases after the second dose, but interpreting this in terms of a dose-response relationship is difficult. Considering the potential mechanisms of myocarditis and pericarditis, this seems to be driven more by immunological modulation rather than a straightforward dose-response relationship. Other research results outside the US [2,17] showed that the rate of pericarditis occurrence did not increase after vaccine administration.

SARS-CoV-2 mRNA vaccines contain nucleoside-modified mRNA encoding the viral spike glycoprotein of SARS-CoV-2. Delivered within lipid nanoparticles, these vaccines prompt the human cells to produce the spike protein, initiating adaptive immune responses that generate IgG antibodies targeting the viral spike protein for virus neutralization. While some RNA can independently stimulate the innate immune system, nucleoside modifications were introduced to mRNA vaccines to minimize innate immunogenicity. Nevertheless, in individuals with specific genetic predispositions, an immune response to mRNA can trigger proinflammatory pathways, potentially leading to systemic reactions like myocarditis and pericarditis. It is acknowledged that side effects resembling myocarditis and pericarditis have been observed following smallpox vaccination, although the underlying mechanisms differ from those of mRNA vaccines. This underscores the established understanding that vaccines designed to elicit immune responses can carry a risk of myocarditis and pericarditis [18].

VACCINE-INDUCED THROMBOTIC THROMBOCYTOPENIA

Vaccine-induced thrombotic thrombocytopenia (VITT) has emerged as a rare side effect of adenoviral vector–based vaccines against COVID-19 and has been most frequently reported after the use of the ChAdOx1 vaccine [19]. One of the first reports of COVID-19 VITT [20], which was released on April 9, 2021, involved five healthcare workers aged 32 to 54 years 7 to 10 days after receiving their first dose. The incidence was five out of 130,000 vaccinated persons in that report. In the same issue of the *New England Journal of Medicine*, a German and Austrian group [21] also reported 11 patients (nine women aged 22–49 years) with VITT after ChAdOx1 nCov-19 vaccination. They reported nine cases of cerebral venous thrombosis, three cases of splanchnic vein thrombosis, three cases of pulmonary embolism (PE), and four cases of other thromboses. Six of them died and five developed disseminated intravascular coagulation. Soon afterwards, a UK group [22] reported 23 VITT patients, 22 of whom tested positive for platelet factor 4 (PF4), including one equivocal test. A nonheparin anticoagulant agent and intravenous immunoglobulin were recommended for those patients. Nonetheless, intravenous immunoglobulin therapy might obscure the capacity of anti-PF4/heparin antibodies to interact with and trigger platelet activation in the presence of heparin, potentially yielding erroneous negative outcomes in immunoassay functional tests. A case of VITT and PE was reported 13 days after receiving the single dose of Ad26 vaccines [19]. Additionally, reports have surfaced regarding instances of cerebral venous sinus thrombosis (CVST) in the United States during the period from March 2 to April 21, 2021. By April 12, 2021, roughly 7 million doses of the Ad26.COV2.S vaccine had been administered in the United States, and six cases of CVST accompanied by thrombocytopenia were identified among the vaccine recipients. Consequently, a temporary nationwide halt to vaccination with this product was instituted on April 13, 2021 [23].

VITT has been reported after mRNA vaccines as well as adenoviral vector vaccines. Al-Rasbi et al. [24] presented a 37-year-old man with myocarditis, pulmonary edema, and pulmonary hemorrhage 12 days after receiving the first dose of BNT162b2 mRNA COVID-19 vaccination. He responded favorably to a 5-day course of intravenous methylprednisolone and immunoglobulin. A case series study [25] also reported a short-term risk of PE among French residents aged 75 years or older after receipt of the BNT162b2 mRNA injection. A study in Italy [26] also reported a combination of acute exacerbation of interstitial lung disease and PE in an elderly patient after booster mRNA vaccination against COVID-19. A study in Saudi Arabia [27] also reported a 78-year-old man who developed PE 1 day after receiving the second dose of the BNT162b2 vaccine. Another case of a healthy 24-year-old young man with PE due to the BNT162b2 vaccine [28] also reported that his symptoms started 6 hours after administration of the second dose of

the vaccine.

Antibodies directed against PF4, also known as CXCL4, are implicated in the pathogenesis of VITT. These antibodies, which belong to the IgG class, interact with platelet Fc γ IIa receptors with relatively low affinities, leading to platelet activation [21,29]. Ongoing research aims to elucidate the mechanisms by which the vaccines in question induce the production of new antibodies or activate preexisting ones. A developing model proposes that the vaccine initiates the generation of neoantigens as an initial step, followed by a systemic inflammatory response as a secondary step. This dual process seems to contribute to the formation of anti-PF4 antibodies. Noteworthy components of the vaccine that have the capacity to bind to PF4 and induce structural changes, thus creating neoantigens, include viral proteins originating from the HEK3 cell line and free DNA. Preliminary investigations suggest that binding of adenoviral hexon proteins to PF4 may play a role in this process [29–31].

The incidence of VITT in Korea is very low according to a report from Korea Disease Control and Prevention Agency (KDCA) [32], and VITT was considered in 214 cases in Korea, yet it has been definitively diagnosed in only four cases to date: two men in their 30s with cerebral vein thrombosis, one woman in her 70s with deep vein thrombosis, and one man in his 60s with pulmonary arterial thromboembolism.

VENOUS THROMBOEMBOLISM

In a UK study [33] from December 2020 to April 2021, involving 19,608,008 ChAdOx1 vaccine recipients, 9,513,625 BNT162b2 vaccine recipients, and 1,758,095 COVID-19 cases, venous thromboembolism risk increased 8 to 14 days post-ChAdOx1 vaccination (IRR, 1.10; 95% CI, 1.02–1.18). COVID-19 patients also had a substantial risk increase (IRR, 13.86; 95% CI, 12.76–15.05), whereas BNT162b2 vaccination did not significantly elevate the risk. Venous thromboembolism after ChAdOx1 vaccination often coincided with thrombocytopenia (IRR, 1.34; 95% CI, 0.99–1.83). Analyzing data from the EudraVigilance database [34], BNT162b2 vaccines had 33 adverse reactions per million doses, while ChAdOx1 vaccines had 151 per million. BNT162b2 recipients had lower thrombosis rates than unvaccinated individuals, but ChAdOx1 recipients had a higher PE risk ratio (18–64 years, 18.8 [95% CI, 4.3–5.1]; >65 years, 4.0 [95% CI, 3.7–4.2]). Analyzing data until June 23, 2021, for ChAdOx1, BNT162b2, and Ad26 vaccines, Cari et al. [35] found that thrombotic events of the Ad26 vaccine were comparable to ChAdOx1's, both surpassing BNT162b2, across age groups (18–64 and >65 years).

A study based on data from eight US health plans [36], spanning from December 14, 2020, to January 26, 2021, analyzed adverse reactions following the first and second doses of BNT162b2 and mRNA-1273 vaccines within 21 days. While the adjusted rate ratio for venous thromboembolism was 1.16 (95% CI, 1.00–1.34), the two-sided P-value was not statistically significant at 0.05. In a study analyzing thrombotic reactions among BNT162b2 vaccine recipients aged 75 and above in France [25], after first and second doses, PE occurrence showed no increase post–first dose (relative incidence [RI], 0.85; 95% CI, 0.75–0.96) and a slight increase post–second dose (RI, 1.10; 95% CI, 0.95–1.26). Based on a national prospective cohort study in Scotland [37], a nested incident-matched case-control study found no association between deep vein thrombosis occurrence (adjusted rate ratio [aRR], 1.21; 95% CI, 0.95–1.54) or PE occurrence (aRR, 0.78; 95% CI, 0.63–0.96) and ChAdOx1 vaccine administration. Similarly, there was no association between deep vein thrombosis occurrence (aRR, 0.79; 95% CI, 0.56–1.11) or PE occurrence (aRR, 0.35; 95% CI, 0.26–0.48) and BNT162b2 vaccine administration. In a retrospective analysis of Mayo Clinic medical records in the United States [38], venous thromboembolism occurrence within 90 days following the first vaccine dose was compared to the 90 days prior to vaccination. The BNT162b2 (aHR, 1.00; 95% CI, 0.87–1.15), mRNA-1273 (aHR, 1.02; 95% CI, 0.87–1.19), and Ad.26 (aHR, 0.97; 95% CI, 0.63–1.50) vaccines did not show an increased risk of venous thromboembolism. In a population-based cohort study in Spain [39], deep vein thrombosis occurrence (standardized incidence rate [SIR], 0.89; 95% CI, 0.65–1.22) and PE occurrence (SIR, 0.78; 95% CI, 0.52–1.16) did not increase following ChAdOx1 vaccination. Similarly, deep vein thrombosis (SIR, 1.03; 95% CI, 0.89–1.19) and PE (SIR, 0.84; 95% CI, 0.84–1.20) did not increase after the first dose of BNT162b2, but a slight increase in PE was observed after the first dose (SIR, 1.25; 95% CI, 1.07–1.46). Notably, the incidence of both deep vein thrombosis (SIR, 4.68; 95% CI, 4.07–5.38) and PE (SIR, 17.86; 95% CI, 16.37–19.50) increased significantly after COVID-19 infection. A systematic review of eight studies [40], including two randomized controlled trials, five large-scale case-control series, and

one large prospective cohort study, indicated that mRNA vaccines did not increase the risk of venous thromboembolism (RR, 0.48–1.20). In a population-based cohort study conducted in Denmark and Norway [41], individuals aged 18 to 65 years who received the ChAdOx1 vaccine were compared to the general populations of Denmark (2016–2018) and Norway (2018–2019). The study findings revealed a significant increase in venous thromboembolism cases among vaccinated people. Based on the current evidence, it is suggested that there is a slight increase in the risk of venous thromboembolism with adenovirus vector vaccines, while such a risk is less evident with mRNA vaccines.

AREA OF UNCERTAINTY

Acute myocardial infarction

Studies investigating myocardial infarction risk have yielded mixed results, emphasizing the need for thorough assessments across different vaccines and populations. In an Israeli study [42], observations were made up to 42 days after administering the BNT162b2 mRNA vaccine. Each group consisted of 890,000 individuals, with 59 myocardial infection events in the vaccine group and 60 in the control group; this yielded a risk ratio of 1.07 (95% CI, 0.74–1.60), with no significant difference. Research from medical institutions including the Kaiser Permanente group in the United States [36] examined the effects of BNT162b2 and mRNA-1273 vaccines within 21 days of administration. Among 118.4 million doses administered, the number of myocardial infarction occurrences was 935 versus 1,030 (RR, 1.02; 95% CI, 0.89–1.18), indicating no increase in postvaccination events. A study in France [25] observed patients aged 75 and above after initial BNT162b2 mRNA vaccine administration for 14 days. Among 3.2 million patients who received at least two doses, 538 incidents were observed, with an RR of 1.08 (95% CI, 0.97–1.21), indicating no significant increase in myocardial infarction occurrence. A study published in *BMJ* [41] examined arterial events, venous thromboembolism, thrombocytopenia, and bleeding occurring within 28 days after the first dose of the ChAdOx1 vaccine in Denmark and Norway, spanning from February to March 2021. Using a population-based cohort approach, the study compared event rates among vaccine recipients to the general population's expected event rates. While venous thromboembolism showed an association with vaccine administration, arterial events, including acute myocardial infection, did not increase. For acute myocardial infarction, the standardized morbidity ratio was 1.09 (95% CI, 0.66–1.68), with an expected number of 18 and an observed number of 20, showing no significant difference between groups.

The occurrence of myocardial infarction does not seem to relate to vaccination. In fact, the occurrence rate of myocardial infarction tends to increase in patients with underlying conditions like old age, hypertension, and diabetes. While myocardial infarction can occur after vaccination, acute myocardial infarction has been occurring at a consistent rate even before the era of COVID-19 vaccines. In recent years, its incidence rate has slightly increased. According to the Health Insurance Review and Assessment Service (HIRA) data [43], there has been an increase in myocardial infarction cases in Korea from 93,475 in 2016 to 121,169 in 2020, though variations exist between countries, with a decreasing trend in the United States. This increase is attributed to the rising prevalence of risk factors such as hypertension, diabetes, and dyslipidemia, which are associated with coronary artery disease.

The occurrence of ischemic heart disease as a hypersensitivity reaction following vaccination or medication is referred to as Kounis syndrome. It involves the release of mediators such as histamine, thromboxane, prostaglandins, leukotrienes, and platelet-activating factors from mast cells in response to allergic reactions, triggering vasospasms and coronary artery constriction. The syndrome is classified into three types. While cases of Kounis syndrome postvaccination have been reported, they are rare and fall within the realm of hypersensitivity reactions rather than direct vaccine side effects [44].

Heart failure

There is no documented research linking heart failure to COVID-19 vaccination. However, the emergence of myocarditis after mRNA COVID-19 vaccination is recognized, as we already mentioned in the present review. While typically mild, with no manifestation of heart failure symptoms, there have been some severe cases accompanied by acute heart failure [45]. Following myocarditis, it is conceivable for dilated cardiomyopathy, a form of heart failure, to develop as a sequela. This progression is often termed as "inflam-

matory cardiomyopathy." However, no current evidence suggests that myocarditis resulting from vaccination follows such a trajectory. The present understanding is that patients recover without significant lingering effects. While there has been no documented association between COVID-19 vaccination and heart failure, there have been recurrent reports of myocarditis following the administration of the COVID-19 vaccine. Domestic causality assessments have acknowledged this association. Although the long-term consequences of vaccine-associated myocarditis are not yet known, it is established that myocarditis caused by viral infections can progress to dilated cardiomyopathy and result in the formation of scar tissue within the heart, potentially leading to heart failure. Therefore, there exists a possibility that vaccine-associated myocarditis might demonstrate similar long-term sequelae upon prolonged observation.

The SARS-CoV-2 mRNA vaccine contains nucleoside-modified mRNA coding for the SARS-CoV-2 viral spike glycoprotein. This is encapsulated in lipid nanoparticles, and once administered, the mRNA is introduced into human cells. This prompts the cells to produce the spike protein, which in turn stimulates the adaptive immune response, facilitating the production of IgG antibodies against the viral spike protein, thereby conferring neutralizing ability against the virus. Some RNA inherently stimulates the innate immune system, leading to the premature degradation of mRNA before it reaches the target cells. As a result, the mRNA vaccines underwent nucleoside modification to reduce this innate immunogenicity. Nevertheless, in certain individuals with genetic predispositions, an immune response may be triggered against the mRNA itself, initiating proinflammatory cascades that could potentially explain some of the vaccine-associated inflammatory complications, including myocarditis and pericarditis [11]. Viral myocarditis typically undergoes three stages of reaction before reaching the recovery phase. However, in some cases, if infected cells are not entirely eliminated or immune cells with auto-reactive capabilities persist within the myocardium, chronic inflammation can occur and progress into dilated cardiomyopathy [46]. If postvaccination, the immune system activated by the mRNA itself does not stabilize after a temporary inflammatory response and continues to induce myocardial damage, there is a potential for progression similar to that observed after viral myocarditis, eventually leading to heart failure. The occurrence of heart failure potentially associated with vaccination can be largely attributed to acute heart failure due to myocarditis. Additionally, if it occurs upon subsequent tracking, it could be considered a transition from recovered myocarditis to chronic heart failure. Beyond these two scenarios, other causes are difficult to postulate.

CONCLUSIONS

The occurrence of adverse events subsequent to COVID-19 vaccination, such as myocarditis, pericarditis, and thrombotic incidents, has spurred extensive research endeavors aimed at investigating potential associations and underlying mechanisms. The existing body of evidence presents a multifaceted scenario, with certain studies indicating heightened risks and others failing to establish significant correlations. Sustained vigilance, robust data collection, and thorough investigations remain imperative to gain a comprehensive understanding of the connections between COVID-19 vaccination and adverse events.

In forthcoming vaccination campaigns, it is crucial to take into account various factors, encompassing vaccine types, patient demographics, and preexisting risk factors, when assessing adverse events. Collaborative efforts among healthcare professionals, researchers, and regulatory authorities are pivotal in making well-informed decisions and ensuring the safety of vaccine recipients. Ongoing research endeavors will further illuminate the intricacies of adverse events associated with COVID-19 vaccination and provide valuable insights to shape future vaccination strategies.

ARTICLE INFORMATION

Ethics statements
Not applicable.

Conflicts of interest
The authors have no conflicts of interest to declare.

Funding
None.

Author contributions
Conceptualization: all authors; Investigation: JYC; Methodology: KHK; Project administration: KHK; Resources: KHK;

Supervision: KHK; Validation: KHK; Visualization: JYC; Writing–original draft: JYC; Writing–review & editing: all authors. All authors read and approved the final manuscript.

ORCID
Jae Yeong Cho, https://orcid.org/0000-0002-9393-2821
Kye Hun Kim, https://orcid.org/0000-0002-6885-1501

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Original Article

Cardiovasc Prev Pharmacother 2023;5(4):144-150
eISSN 2671-700X
https://doi.org/10.36011/cpp.2023.5.e14

Cardiovascular Prevention and Pharmacotherapy

Variation in blood viscosity based on the potential cause of stroke of undetermined etiology

Jinyoung Oh, Youngchan Jung, Jin Kim, Sun Ki Min, Sang Won Han, Jong Sam Baik

Department of Neurology, Inje University Sanggye Paik Hospital, Inje University College of Medicine, Seoul, Korea

Background: This study investigated potential differences in blood viscosity (BV) among patients with stroke of undetermined etiology, negative evaluation (SUDn), specifically those with potential atherothrombosis (SUDn-AT) and those with possible embolism (SUDn-E).

Methods: This single-center study employed a retrospective observational design. The participants were patients over 20 years old with the SUDn stroke subtype who were admitted within 5 days of symptom onset. These patients were categorized as SUDn-AT or SUDn-E. Patients in the SUDn-AT group had nonsignificant stenosis (<50%) of a major brain artery relevant to their symptoms and exhibited one or more signs of systemic atherosclerosis, including atherosclerosis of at least one major brain artery other than those clinically relevant, coronary artery disease, and/or peripheral artery disease. For the SUDn-E group, the SUDn criteria from the TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system were strictly applied.

Results: The final analysis included 153 patients, with 104 (68%) classified as SUDn-E and the remaining 32% as SUDn-AT. Patients in the SUDn-AT group had a higher systolic BV (P=0.012) and diastolic BV (P=0.020) than those in the SUDn-E group. Multivariable logistic regression analysis revealed that age (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.03–1.13; P=0.003), systolic BV (OR, 3.11; 95% CI, 1.41–6.85; P=0.005), and diastolic BV (OR, 1.08; 95% CI, 1.02–1.14; P=0.009) were associated with SUDn-AT.

Conclusions: Within the TOAST system, two SUDn entities may be distinguishable, with potentially different underlying etiologies: atherothrombosis and embolic stroke of undetermined source.

Keywords: Blood viscosity; Etiology; Stroke

INTRODUCTION

The classification of stroke type is a critical component of its evaluation and treatment. The assessment and treatment of stroke depend heavily on its etiology, underscoring the importance of accurate classification. The TOAST (Trial of Org 10172 in Acute Stroke Treatment) classification system, established in 1993 for the study of low molecular weight heparinoid [1], has become the predominant method for determining the cause of ischemic stroke. Despite the trial's lack of success, the TOAST classification has been employed in numerous studies concerning stroke epidemiology, intervention, risk factors, and prognosis. However, despite its current widespread use, the TOAST system

Received: July 26, 2023; **Revised:** September 18, 2023; **Accepted:** October 4, 2023
Correspondence to Jong Sam Baik, MD
Department of Neurology, Inje University Sanggye Paik Hospital, Inje University College of Medicine, 1342 Dongil-ro, Nowon-gu, Seoul 01757, Korea
Email: jsbaik@paik.ac.kr

has several limitations. These include a high frequency of stroke of undetermined etiology, negative evaluation (SUDn), also known as cryptogenic stroke, as well as inconsistent results across observers [2,3]. Advances in imaging techniques now allow a more accurate diagnosis of strokes and identification of their underlying causes. Concurrently, new therapeutic strategies have been developed. These include medications such as statins or non–vitamin K antagonist oral anticoagulants (NOACs), which are used to prevent further vascular events in patients with systemic atherosclerosis or atrial fibrillation (AF).

The TOAST classification system defines SUDn as stroke for which the cause remains uncertain, even after a thorough evaluation. Patients diagnosed with SUDn should not exhibit significant stenosis (≥50%) of any clinically relevant artery, and no sign of embolism originating from the heart should be evident. Furthermore, even with extensive investigation, no other explanation for the stroke should be identifiable. Within the TOAST classification system, two distinct SUDn entities may be distinguishable: atherothrombosis (AT) and embolic stroke of undetermined source (ESUS). These may differ in their underlying etiology [2,4]. Blood viscosity (BV) is a crucial factor in predicting endothelial shear stress, as it represents the inherent resistance encountered by blood flow. BV refers to the thickness and stickiness of blood, and it plays a key role in determining the frictional force exerted on the blood vessel wall. BV is associated with thromboembolic events, and elevated BV levels are associated with an increased risk of cerebrovascular and cardiovascular disease [5]. Previous studies have suggested that BV levels vary across stroke subtypes [6,7]. For instance, lacunar stroke is associated with higher BV than other subtypes, such as large artery atherosclerosis and cardioembolism [8].

Given the distinct stroke mechanisms associated with AT and ESUS, we hypothesized that BV levels would vary based on the potential cause of stroke within the SUDn group. Consequently, this study was conducted to determine whether differences were present in BV levels between patients with SUDn with possible AT (SUDn-AT) and those with SUDn with possible embolism (SUDn-E).

METHODS

Ethics statement

This study was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (No. 2022-03-011). The requirement for written informed consent was waived due to the retrospective nature of the study.

Patients

This study was carried out at a single center (Inje University Sanggye Paik Hospital, Seoul, Korea), utilizing a retrospective observational design. The participants were patients exhibiting the SUDn stroke subtype, as classified using the TOAST system, between March 2017 and December 2021. The inclusion criteria were as follows: (1) having an age of over 20 years and being admitted within 5 days of stroke onset; (2) exhibiting the SUDn stroke subtype according to the TOAST classification; and (3) displaying a cortical or nonlacunar subcortical lesion on brain computed tomography (CT) or magnetic resonance imaging (MRI). Patients were excluded if they met the following criteria: (1) displayed a hematocrit (Hct) level of less than 30% or greater than 50% at baseline, due to the potential influence of Hct on BV; (2) had received intravenous thrombolysis or intra-arterial thrombectomy during admission; or (3) had taken antithrombotic medication within 5 days of stroke onset.

For the study, patients were categorized into two groups: SUDn-AT and SUDn-E. Those in the SUDn-AT group were required to have nonsignificant stenosis (less than 50%) of a major brain artery relevant to their symptoms. The major brain arteries were identified as the carotid, vertebral, and basilar arteries, along with proximal segments of the anterior, middle, and posterior cerebral arteries. Furthermore, these patients needed to exhibit one or more signs of systemic atherosclerosis, including atherosclerosis of at least one major brain artery other than those clinically relevant, coronary artery disease (CAD), and/or peripheral artery disease (PAD) [2]. For the SUDn-E group, the criteria for SUDn in the TOAST classification system were strictly applied.

During admission, all patients with SUDn underwent a thorough examination. Each patient received a brain CT or MRI scan, along with an angiographic study. Demograph-

ics, medical history, and traditional vascular risk factors were also evaluated. Additionally, measurements were taken for 12-lead electrocardiography, complete blood counts, blood lipid profiles, renal and liver function, and coagulation factors. Except for those who did not provide informed consent, the patients underwent transthoracic echocardiography and 24-hour Holter monitoring.

BV measurement

The methods employed in this study to measure BV have been previously reported [9]. From January 2017 onward, BV measurements at our institution have been taken from consecutive patients with ischemic stroke, considering the potential influence of BV on treatment. Although not obligatory, this practice was adopted to ensure the highest quality of patient care. In the present study, a scanning capillary-tube viscometer (SCTV; Hemovister, Pharmode Inc) was utilized to evaluate whole BV. The SCTV measured both systolic BV (SBV) and diastolic BV (DBV), which represent viscosities at high and low shear rates, respectively. SBV was assessed at a shear rate of 300 seconds^{-1}, while DBV was measured at 1 second^{-1}. BV samples were collected via initial blood sampling prior to hydration therapy in the emergency room or outpatient department, and all measurements were taken within 24 hours of sample collection.

Statistical analysis

Statistical analysis was performed using IBM SPSS ver. 25.0 (IBM Corp), with a two-sided P-value of less than 0.05 considered to indicate statistical significance. Descriptive analyses were expressed as number (percentage) for categorical data and as mean±standard deviation for continuous data. The Kolmogorov-Smirnov test was employed to evaluate normality. Univariate analyses were performed to identify significant factors for the SUDn-AT group. For continuous variables, either the independent samples t-test or the Mann-Whitney U-test was utilized, while the chi-square test was used to analyze categorical variables. Variables that yielded a P-value of <0.05 in the univariate analyses were incorporated into the multivariable logistic regression models. A partial correlation analysis was carried out to ascertain the differences in BV, adjusting for the effects of Hct between the two groups.

RESULTS

A total of 297 patients with the SUDn subtype of stroke, representing 25% of all consecutive patients with ischemic stroke during the study period, were considered for inclusion in the study. However, 144 of these patients (49%), were excluded from the study for various reasons: 18 patients due to the absence of BV measurements, 38 patients due to Hct levels below 30% or above 50%, 14 patients due to undergoing intravenous thrombolysis or intra-arterial treatments, and 93 patients due to prior use of antithrombotic medication. Consequently, 153 patients were selected for the final analysis.

Table 1 presents the baseline characteristics of the enrolled patients. The mean age was 69.6±12.34 years, with women constituting 47.1% of the patient population. Most patients (75.2%) had a history of hypertension, 34.6% had diabetes, 43.8% had dyslipidemia, and 27.5% were current cigarette smokers. Seven patients (4.6%) had a history of CAD, while none of the patients had PAD. The median time from the onset of symptoms to hospital arrival was 18 hours, with 61.3% of patients arriving at the hospital within 24 hours. No significant difference was observed in the time to admission between groups. Of the 153 patients, 104 (68.0%) were classified as SUDn-E and the remaining 32.0% as SUDn-AT. No significant differences were observed in the baseline characteristics between these groups, except for age, history of hypertension, and National Institutes of Health Stroke Scale (NIHSS) score at admission. The SUDn-AT group had a significantly higher age (P=0.001), more frequent history of hypertension (P=0.004), and higher NIHSS score at admission (P=0.007). These findings suggest that advanced age and a history of hypertension are major risk factors for systemic atherosclerosis.

Table 2 displays the laboratory findings from the study population. The SUDn-AT group exhibited higher levels of serum creatinine, plasma glucose at admission, and high-sensitivity C-reactive protein (hs-CRP), suggesting these results as potential risk factors for systemic atherosclerosis. Regarding BV, patients in the SUDn-AT group demonstrated higher SBV (P=0.012) and DBV (P=0.020), indicating an overall pattern of greater BV at admission relative to the SUDn-E group. In the multivariable logistic regression analysis, age (odds ratio [OR], 1.08; 95% confidence interval [CI], 1.03–1.13; P=0.003), SBV (OR, 3.11; 95% CI,

Table 1. Baseline characteristics of the study population

Characteristic	Total (n=153)	SUDn-E (n=104)	SUDn-AT (n=49)	P-value
Age (yr)	69.6±12.34	67.5±12.66	74.3±10.28	0.001*
Sex				0.984
Male	81 (52.9)	55 (52.9)	26 (53.1)	
Female	72 (47.1)	49 (47.1)	23 (46.9)	
Hypertension	115 (75.2)	71 (68.3)	44 (89.8)	0.004*
Diabetes mellitus	53 (34.6)	32 (30.8)	21 (42.9)	0.143
Dyslipidemia	67 (43.8)	43 (41.3)	24 (49.0)	0.375
Stroke	8 (5.2)	5 (4.8)	3 (6.1)	0.711
Coronary artery disease	7 (4.6)	5 (4.8)	2 (4.1)	0.841
Current smoking	42 (27.5)	32 (30.8)	10 (20.4)	0.180
Statin use	35 (22.9)	26 (25.0)	9 (18.4)	0.362
Time to admission (hr)	30.2±31.35	30.8±32.77	29.4±28.32	0.853
NIHSS score at admission	2.4±2.56	2.0±2.12	3.2±3.19	0.007*
Lesion localization				0.190
Anterior	90 (58.8)	56 (53.8)	34 (69.4)	
Posterior	59 (38.6)	45 (43.3)	14 (28.6)	
Multiple	4 (2.6)	3 (2.9)	1 (2.0)	
Systolic blood pressure (mmHg)	162±28.24	160±29.12	168±24.67	0.053
Diastolic blood pressure (mmHg)	88±17.23	87±17.92	88±15.82	0.705

Values are presented as mean±standard deviation, number (%) or mean±standard deviation.
SUDn, stroke of undetermined etiology, negative evaluation; SUDn-E, SUDn with possible embolism; SUDn-AT, SUDn with possible atherothrombosis; NIHSS, National Institutes of Health Stroke Scale.
*Statistically significant.

Table 2. Laboratory findings of the study population

Variable	Total (n=153)	SUDn-E (n=104)	SUDn-AT (n=49)	P-value
Hemoglobin (g/dL)	13.8±1.60	13.7±1.62	14.1±1.55	0.142
Hematocrit (%)	41.3±4.51	41.0±4.42	42.1±4.64	0.167
White blood cells (10^3/μL)	7.9±2.60	7.7±2.68	8.4±2.39	0.100
Platelets (10^3/μL)	236.1±66.69	237.5±66.93	233.0±66.77	0.708
Blood urea nitrogen (mg/dL)	17.2±5.74	16.9±5.41	17.8±6.39	0.432
Creatine (mg/dL)	0.86±0.28	0.83±0.23	0.93±0.37	0.045*
Random plasma glucose (mg/dL)	154.0±62.80	146.6±51.58	169.8±80.24	0.034*
Total cholesterol (mg/dL)	166.3±39.91	163.5±38.06	172.0±43.32	0.243
LDL cholesterol (mg/dL)	101.1±31.29	98.8±30.76	105.8±32.18	0.206
HDL cholesterol (mg/dL)	44.7±11.21	44.3±10.96	45.6±11.78	0.526
Triglyceride (mg/dL)	110.3±50.55	112.3±52.01	106.0±47.61	0.463
International normalized ratio	0.99±0.06	0.99±0.06	0.99±0.65	0.584
Fasting glucose	103.0±35.67	99.2±30.96	111.4±43.25	0.083
Systolic blood viscosity (cP)	4.53±0.62	4.44±0.55	4.71±0.72	0.012*
Diastolic blood viscosity (cP)	29.01±8.54	27.91±7.83	31.33±9.54	0.020*
hs-CRP (mg/dL)	0.65±1.50	0.41±0.77	1.15±2.35	0.006*

Values are presented as mean±standard deviation.
SUDn, stroke of undetermined etiology, negative evaluation; SUDn-E, SUDn with possible embolism; SUDn-AT, SUDn with possible atherothrombosis; LDL, low-density lipoprotein; HDL, high-density lipoprotein; cP, centipoise; hs-CRP, high-sensitivity C-reactive protein.
*Statistically significant.

1.41–6.85; P=0.005), and DBV (OR, 1.08; 95% CI, 1.02–1.14; P=0.009) were found to be associated with SUDn-AT. Given that Hct is a major determinant of BV, a Hct-adjusted partial correlation analysis was conducted. This analysis revealed a significant association between the SUDn-AT subtype and increases in both SBV (r=0.176, P=0.012) and DBV (r=0.165, P=0.036).

DISCUSSION

In this study, we classified the stroke subtype of SUDn within the TOAST classification system into two groups: SUDn-AT and SUDn-E. We then examined the differences in BV levels between these groups. Our findings indicated that the SUDn-AT group had significantly higher SBV and DBV levels than the SUDn-E group. Additionally, relative to the SUDn-E participants the SUDn-AT group was characterized by older age, a history of hypertension, and higher levels of serum creatinine, plasma glucose at admission, and hs-CRP. The findings suggest that these factors may be associated with the development of systemic atherosclerosis.

AT is likely the most common etiologic mechanism of ischemic stroke. However, it can sometimes be challenging to ascertain whether cerebral arterial stenosis was induced by atherosclerosis or an ESUS. According to the Reduction of Atherothrombosis for Continued Health (REACH) registry, 15.9% of patients with symptomatic AT also had symptomatic polyvascular disease [10]. One in six patients with stroke, CAD, or PAD display symptomatic involvement of one or two additional arterial beds. Consequently, the presence of other major brain arterial stenosis, CAD, and PAD was utilized as supportive evidence for the diagnosis of SUDn-AT in this study. This approach is based on the concept that atherosclerosis is a systemic disease that simultaneously affects multiple vascular beds [2].

In our study, the SUDn-AT group exhibited a higher BV than the SUDn-E group. While one study [11] indicated that higher BV levels are associated with ischemic stroke in patients with AF, no direct comparison has been made of BV measurements among the other stroke subtypes. Results have also differed based on the study design and the enrolled population [9]. Several plausible explanations support our findings of higher BV in the SUDn-AT group. First, the concept of ESUS was developed based on the hypothesis that most strokes in patients with ESUS are caused by numerous cardioembolic events, and that anticoagulation could prevent secondary ischemic events [4]. Importantly, however, two large, randomized NOAC trials have demonstrated that paroxysmal AF appears to be a rare cause of ESUS [4]. In the present study, nonstenotic atherosclerotic plaques, a major contributor to ESUS, were classified as SUDn-AT if they were associated with systemic atherosclerosis. Second, intracranial atherosclerosis (ICAS) is one of the most common causes of stroke, accounting for 30% to 50% of strokes in Asian populations [12]. The proposed stroke mechanisms of ICAS include hypoperfusion distal to the stenotic vessel, artery-to-artery embolism, and branch atheromatous disease [13]. Plaque stability may be more important than the degree of stenosis in ICAS, as artery-to-artery embolism may also occur more frequently [14]. A study investigating recurrent stroke and its mechanisms in patients initially classified as SUD based on the TOAST classification found that recurrent strokes were associated with the presence of stenosis of <50% in the relevant artery or stenosis of ≥50% in a nonrelevant artery. This underscores the importance of atherothrombotic mechanisms in these patients [15]. Endothelial damage, impaired blood flow, and hypercoagulability can trigger thrombus formation [16]. BV constitutes a primary mechanism for thrombus formation, and increased BV is a risk factor for AT [5]. Elevated BV may promote shear-mediated platelet activation; thus, it is prothrombotic and atherogenic, as it increases shear stress. One study [17] revealed that BV, Hct, and fibrinogen concentration were significantly higher in those with stenosis in two or three arteries compared to other patients. Considering the Virchow triad, thromboembolic susceptibility in ICAS may be related to endothelial damage, impaired blood flow, and hyperviscosity due to hemorheological alterations. These changes might be associated with the higher BV observed in the SUDn-AT group.

Our study did have certain limitations. First, the data were collected retrospectively from a single center, which made it impossible to establish a causal relationship between BV levels and the SUDn stroke subtype. Confounding factors may also have been present and not considered. Second, not all patients underwent transcranial Doppler or transesophageal echocardiography. Prior NOAC studies suggest that a patent foramen ovale with high-risk clinical features should not be classified as ESUS. This could suggest the presence of selection bias and may have impacted the va-

lidity of our results. Third, our conclusion was not robustly supported by statistical power due to the small sample size and the absence of age-matched controls. Finally, our findings are applicable only to Korean patients and cannot be generalized. These limitations should be taken into account when interpreting the results of the present study.

In conclusion, the findings revealed that the SUDn-AT group exhibited a higher BV than the SUDn-E group. This suggests that within the TOAST classification system, two distinct SUDn entities could be identifiable: SUDn-AT, associated with systemic atherosclerosis, and SUDn-E, associated with ESUS. These entities may have differing underlying etiologies. The role of BV in the mechanism of stroke requires further elucidation, which should be achieved through additional research involving larger patient populations.

ARTICLE INFORMATION

Ethics statements

This study was approved by the Institutional Review Board of Inje University Sanggye Paik Hospital (No. 2022-03-011). The requirement for written informed consent was waived due to the retrospective nature of the study.

Conflicts of interest

Sang Won Han is the Associate Editor of *Cardiovascular Prevention and Pharmacotherapy*, but was not involved in the peer reviewer selection, evaluation, or decision process of this article. The authors have no other conflicts of interest.

Funding

None.

Author contributions

Conceptualization: all authors; Data curation: all authors; Formal analysis: JO, SWH; Investigation: SWH, JO; Methodology: all authors; Project administration: all authors; Software: SWH, JO; Supervision: JSB; Validation: SWH, JSB; Visualization: JO; Writing–original draft: JO, JSB; Writing–review & editing: all authors. All authors read and approved the final manuscript.

ORCID

Jinyoung Oh, https://orcid.org/0000-0002-4235-8655
Youngchan Jung, https://orcid.org/0009-0004-8243-6971
Jin Kim, https://orcid.org/0000-0001-5623-981X
Sun Ki Min, https://orcid.org/0000-0002-2987-4989
Sang Won Han, https://orcid.org/0000-0002-9503-1883
Jong Sam Baik, https://orcid.org/0000-0002-5300-203X

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Cardiovascular Prevention and Pharmacotherapy
#243, Yongwon Building, 31, Seochojungang-ro 18-gil,
Seocho-gu, Seoul 06634, Korea
Tel: +82-70-8873-6030
Fax: +82-2-587-2066
Email: cpp1@e-jcpp.org

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   - Main heading should be INTRODUCTION, METHODS, RESULTS, and DISCUSSION.
   - Subheadings can be used in each section.
   - Abbreviations must be defined at first mention in the text and each table and figure.
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   - For experimental animals, state the species, strain, number used, and pertinent descriptive characteristics should be provided. When describing surgical procedures, identify the preanesthetic and anesthetic agents used and the amounts, concentrations, routes, and frequency of administration of each. Paralytic agents are not considered acceptable substitutes for anesthetics. For other invasive procedures on animals, report the analgesic or tranquilizing drugs used. If none were used, provide justification for exclusion.
   - In human studies, indicate that the study was approved by an institutional review board along with the name of the IRB, and that the participants gave written informed consent (or that no informed consent was required).
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- EndNote output styles for Journal of Cardiovascular Prevention and Pharmacotherapy is available at: https://e-jcpp.org.
- ***Journal***: Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, et al. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. Lancet 2016;387:957–67.
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- ***Chapter in book***: Hinohara T, Robertson CG, Simpson JB. Directional coronary atherectomy. In: Topol EJ, editor. Textbook of interventional cardiology. 2nd ed. W.B. Saunders Company; 1994. p. 645–57.
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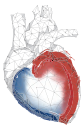

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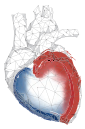

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