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Contents

Original Papers

Original Paper

Efficacy of Unsupervised YouTube Dance Exercise for Patients With Hypertension: Randomized Controlled Trial

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Abstract

Background: High blood pressure (BP) is linked to unhealthy lifestyles, and its treatment includes medications and exercise therapy. Many previous studies have evaluated the effects of exercise on BP improvement; however, exercise requires securing a location, time, and staff, which can be challenging in clinical settings. The antihypertensive effects of dance exercise for patients with hypertension have already been verified, and it has been found that adherence and dropout rates are better compared to other forms of exercise. If the burden of providing dance instruction is reduced, dance exercise will become a highly useful intervention for hypertension treatment.

Objective: This study aims to investigate the effects of regular exercise therapy using dance videos on the BP of patients with hypertension, with the goal of providing a reference for prescribing exercise therapy that is highly feasible in clinical settings.

Methods: This nonblind, double-arm, randomized controlled trial was conducted at Juntendo University, Tokyo, from April to December 2023. A total of 40 patients with hypertension were randomly assigned to either an intervention group (dance) or a control group (self-selected exercise), with each group comprising 20 participants. The intervention group performed daily dance exercises using street dance videos (10 min per video) uploaded to YouTube. The control group was instructed to choose any exercise other than dance and perform it for 10 minutes each day. The activity levels of the participants were monitored using a triaxial accelerometer. BP and body composition were measured on the day of participation and after 2 months. During the intervention period, we did not provide exercise instruction or supervise participants' activities.

Results: A total of 34 patients were included in the study (16 in the intervention group and 18 in the control group). The exclusion criteria were the absence of BP data, medication changes, or withdrawal from the study. The mean age was 56 (SD 9.8) years, and 18 (53%) of the patients were female. The mean BMI was 28.0 (SD 6.3) m/kg^2, and systolic blood pressure (SBP) and diastolic blood pressure (DBP) were 139.5 (SD 17.1) mm Hg and 85.8 (SD 9.1) mm Hg, respectively. The basic characteristics did not differ between the two groups. In the multivariate analysis, SBP and DBP improved significantly in the intervention group compared to the control group (mean SBP –12.8, SD 6.1 mm Hg; *P*=.047; mean DBP –9.7, SD 3.3 mm Hg; *P*=.006).

Conclusions: This study evaluated the effects of dance exercise on patients with hypertension, as previously verified, under the additional condition of using dance videos without direct staff instruction or supervision. The results showed that dance videos were more effective in lowering BP than conventional exercise prescriptions.

Trial Registration: University Hospital Medical Information Network UMIN 000051251; https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000058446

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KEYWORDS

dance; video; exercise therapy; hypertension; blood pressure therapy; YouTube; mHealth

Introduction

High blood pressure (BP) is a major chronic disease that threatens people's health and is an important risk factor for many types of heart, brain, and kidney vascular diseases. A total of 590,000 Japanese individuals with high BP continuously receive medical care, the highest number among lifestyle-related diseases [1]. The prevalence of high BP among adults in the United States was 29% from 2011 to 2014, and the prevalence rates increased with age: 18-39 years, 7.3%; 40-59 years, 32.2%; and 60 years and older, 64.9% [2]. The global population aged older than 65 years is expected to double between 2019 and 2050 [3]. Japan has the oldest population worldwide; in 2013, those aged older than 65 years exceeded 25% of the population and are expected to exceed 40% by 2060 [4]. Therefore, high BP is a global public health problem, and the number of patients with the condition is expected to increase with the growth of the aging population.

High BP is associated with an unhealthy lifestyle. The clinical treatment of high BP involves antihypertensive medications and lifestyle interventions, such as reducing salt intake, eating a diet rich in fruits and vegetables, exercising, and maintaining a healthy body weight [5]. Although antihypertensive medications are the main treatment, exercise is also an important recommendation for patients with high BP [6-8]. It is known that regular moderate exercises, such as water walking, brisk walking, running, small-sided soccer, and swimming, have beneficial effects on BP in patients with hypertension [9-13]. The World Health Organization recommends at least 150 minutes of moderate to vigorous physical activity (MVPA) per week [14]. However, in Japan, only about half of the population (59.6% of men and 46.9% of women) meets these physical activity standards [15]. Furthermore, during the COVID-19 pandemic, restrictions on outdoor activities led to decreased physical activity levels [16]. It has also been suggested that safety concerns, especially for women when exercising alone outdoors or after sunset, as well as fear of criticism, are barriers to engaging in physical activity [17]. Challenges in securing time and space for exercise due to caregiving, childcare, employment, and pandemics hinder physical activity. Furthermore, although physical activity interventions delivered or prompted by health professionals in primary care appear effective in increasing participation in MVPA, exercise prescription training for health care professionals is inadequate [18].

Dance, a fun form of exercise that uses music and can be performed in confined spaces, remains feasible, even in situations such as the COVID-19 pandemic. Dance was part of Japan's educational curriculum in 2012 and was added as an Olympic sport starting in 2024 [19]. A survey conducted in Japan indicated that the proportion of teenagers participating in hip-hop dance at least once a week rose from 2.1% in 2015 to 3.5% in 2023 [20]. Therefore, dance has become an accessible sport, and compared to other activities such as marathon running or swimming, is easier for patients to perform in terms of space and time. A meta-analysis comparing dance to other exercises found that adherence and dropout rates for dance were better than those for other forms of exercise [21]. Previous studies have shown that regular dance therapy can benefit hypertension management in patients [22-30]. However, to the best of our knowledge, no studies in Japan have examined the effects of dance on BP. Additionally, previous studies involved direct patient monitoring during exercise or used internet-based methods for monitoring. In clinical settings, it is challenging to gather participants for regular prescribed group dance sessions or to monitor them using video chat. We, therefore, aimed to investigate the effect of regular dance therapy interventions on BP in patients with hypertension to provide a reference for prescription studies on dance exercise therapy in these patients. We hypothesized that performing the same movements without monitoring using self-made dance videos could lower BP and be useful as a nonpharmacological treatment for high BP.

Methods

Ethical Considerations

This study was approved by the Ethics Committee of Juntendo University (approval: E22-0387). The participants received written information about the trial, including its aim, expected advantages, and role, and were asked to provide written informed consent. This study was retrospectively registered with the University Hospital Medical Information Network (UMIN) under ID UMIN 000051251 and with the International Standard Randomized Controlled Trial Number registry (under ID ISRCTN46013). The UMIN is a network member of the Japan Primary Registries Network, as described in the World Health Organization registry network. All procedures were performed in accordance with relevant guidelines and regulations.

Setting and Design

This study was conducted at the Juntendo University Department of General Medicine, Tokyo, Japan, a regional core hospital that treats many patients with lifestyle-related diseases. Outpatients generally visit the hospital every 2 months.

This was a nonblind, double-arm randomized controlled trial conducted from April 1, 2023, to December 27, 2023. Based on a previous study [31], we set the intergroup difference (difference from baseline) to –9 and the SD at 9. The results of previous studies are as follows: mean difference (MD) –8.75 mm Hg; 95% CI –6.51 to –10.39 for systolic BP, and MD –8.35 mm Hg; 95% CI –6.25 to –10.45 for diastolic BP. This study anticipated a similar decrease in BP, as reported previously. With a desired power of 80%, a sample size of 34 individuals was calculated. Considering a dropout rate of 15%, we selected a sample size of 40 participants, allocated in a 1:1 ratio into two groups using a random number table: the intervention (dance)

group (n=20) and the control group (n=20). TM created the randomization table, staff members (MSakairi) conducted the recruitment, and the admin assistant conducted the group allocation.

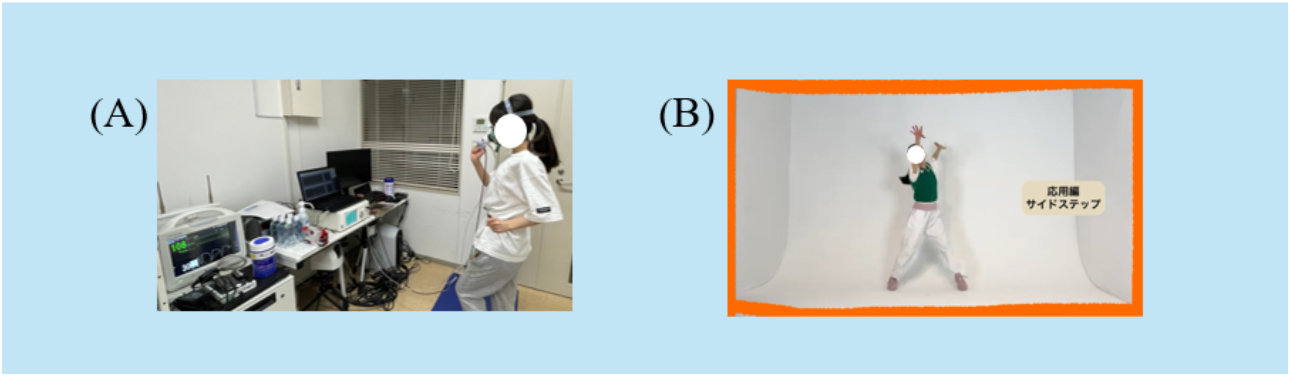
We included outpatients with high BP from the Juntendo University Department of General Medicine. These patients with hypertension had been diagnosed with hypertension and were receiving regular oral medication. The patient was invited to participate in this study by their primary physician, whom they regularly visited for hypertension management, and consent was obtained. Participants were informed that their participation in this study was voluntary and that they could withdraw if they chose to discontinue after joining. Additionally, if their primary physician determined that withdrawal was necessary due to changes in their medical condition, the study could be terminated. We excluded patients with complications rendering them unsuitable for exercise, such as cardiovascular disease, cerebral vascular disease, those unable to balance on one leg, and patients who were newly prescribed antihypertensive drugs or who were administered antihypertensives later.

Interventions

Development of Dance Videos

The intervention group watched an approximately 10-minute-long dance video and replicated the movements. The dance videos for the intervention group were created using the following materials and procedures. One of the authors (MSakairi), with 29 years of extensive experience in dance, developed a dance program based on street dance, with reference to instructional videos for school classes [32]. The music used for the dance was selected from DOVA-SYNDROME [33]. The staff used exhaled-breath analysis to measure the dance activity level and create five videos ranging from 4.5 to 7 metabolic equivalent of task (METs), measuring the intensity of physical activity that represents the metabolic rate relative to the resting metabolic rate (Figure 1). The formula used to calculate METs is expressed as follows:

Figure 1. Details about dance. (A) The process of creating the dance. We have used exhaled breath analysis to measure the activity level of dance and created five videos ranging from 4.5 to 7 METs. (B) A part of the distributed dance video. We distributed the video of the dance we created to participants using YouTube. MET: metabolic equivalent of task.



During the dance activity, METs were measured using a respiratory gas analyzer (pulmonary exercise load monitoring system: AE-310S, Minato Medical Science Co, Ltd, Osaka city, Osaka, Japan). The average METs for each dance video were as follows: (1) 4.57, (2) 4.86, (3) 4.84, (4) 6.95, and (5) 7.11 METs. Measurements were conducted using the breath-by-breath method to calculate VO_2 and VCO_2 based on signals from high-precision flow sensors [34]. We uploaded the created dance videos to YouTube with restricted access.

Intervention Group Procedures

On the day of recruitment, we provided the intervention group with a URL to access the five YouTube videos. Participants were instructed to freely select a dance from the 5 videos and perform it daily while watching the video. We did not provide any guidance on dance instruction or supervision during the dance sessions. However, we instructed the control group to freely select any exercise other than dance and perform it for 10 minutes daily. Additionally, on the day of recruitment, BP and body composition were measured, and web-based surveys were administered using Google Forms to all participants. BP was measured using an automatic medical electronic BP monitor (HBP-9035 Kentaro, OMRON Health Care Co, Ltd, Kyoto City, Kyoto Prefecture, Japan).

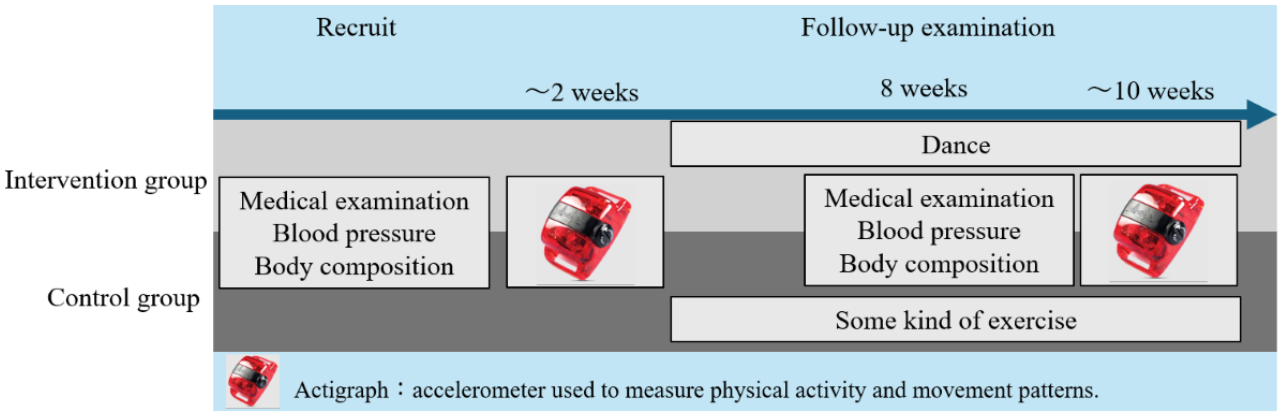
Participants from both groups were instructed not to change their lifestyle 2 weeks from the day of recruitment and to wear an ActiGraph continuously during this period, except during sleep and bathing. ActiGraph is a 3-axis accelerometer (wGT3X-BT ActiGraph, ActiGraph, LLC). Actigraph triaxial accelerometers are the most extensively used devices in numerous studies focused on monitoring human physical activity energy expenditure; they are capable of detecting changes in motion and converting them into digital signals, which can then be analyzed to estimate energy expenditure [35].

Two weeks after recruitment, both the intervention and control groups were instructed to begin their designated exercises and continue until the end of the study period.

Approximately 2 months after recruitment, during a regular outpatient visit, BP and body composition were measured again, and another web-based survey was completed. Subsequently, the participants were instructed to wear the ActiGraph continuously, except during sleep and bathing, for another 2 weeks (Figure 2). During the intervention period, participants in both the intervention and control groups did not receive

exercise guidance, nor were the frequency or manner of their exercise monitored. We did not compensate the participants of this study. The research data of patients in this study were anonymized using identification numbers; however, researchers could still identify individual patients with these numbers.

Figure 2. Research schedule. We instructed both the intervention group and the control group to exercise and measured their physical activity levels using an actigraph.



Outcome Measures

Variables

The variables used in this study were gender, age, number of antihypertensive drugs, number of lifestyle-related diseases (diabetes, dyslipidemia, and hyperuricemia), medical history (cerebral infarction and ischemic heart disease), height, body weight, body muscle mass, body fat mass, family in need of care (children and adults), the presence of cohabitants, exercise habits, systolic blood pressure (SBP), diastolic blood pressure (DBP), and MVPA per day (corresponding to activity levels that are moderate or higher in intensity, namely, a level of 3 METs or higher).

Primary Outcome

The main outcome of this study was BP. During the study period, we measured the BP and body composition of the patients twice for comparison. This was performed on the day of participation and 2 months after participation during outpatient visits.

Data Collection

We obtained the participants' gender, age, frequency of antihypertensive medication use, lifestyle-related diseases (diabetes, dyslipidemia, and hyperuricemia), and medical history (cerebral infarction, and ischemic heart disease) from medical records for both groups. The body composition measured on the day of recruitment and 2 months later included height, weight, muscle mass, and body fat mass. In addition, a web-based survey using Google Forms was conducted to inquire about the presence of cohabitants, caregivers (both children and adults), and exercise habits. The criteria of the ActiGraph for adopting the data involved confirming valid days with worn durations of 10 hours or more per day, with at least 7 such days within 2 weeks. The average value for the adopted days was calculated for each individual [36-38]. In this study, as it is exploratory research rather than a confirmatory study, we did not perform multiplicity adjustments.

Statistical Analyses

All statistical analyses were performed using JMP Pro (version 16.0; SAS Institute). All reported *P* values were 2-tailed, and *P* values <.05 were considered statistically significant. The results are presented as mean (SD) for continuous variables or as prevalence (%) for categorical variables. Comparisons between two groups were performed using the chi-square test. Multiple regression analysis was performed on both groups, with BP as the dependent variable. The other covariates were gender, age, and daily MVPA before starting exercise.

Results

A total of 40 patients participated in the study (see Multimedia Appendix 1 for CONSORT [Consolidated Standards of Reporting Trials] checklist), and 20 outpatients were evaluated in each intervention and control group. We excluded 2 patients who lacked BP data, one patient who changed medications, and 1 patient who withdrew to care for a parent from the dance group. We also excluded one patient who changed medications and one patient who took a double dose from the control group. These participants could have experienced BP changes due to antihypertensive medications, and the lack of BP data makes evaluation difficult. Including these participants may reduce validity, so it is reasonable to exclude them. Therefore, 16 patients in the intervention group and 18 patients in the control group were analyzed (Figure 3). Among the participants, 18 (53%) participants were female, 4 (12%) participants were family caregivers, and 19 (56%) participants had lifestyle diseases (diabetes, dyslipidemia, and hyperuricemia). The mean age was 56 (SD 9.8) years, the mean number of patients who took treatment with an antihypertensive drug was 1.5 (SD 0.5), the mean BMI was 28.0 (6.3) m/kg^2, the mean body muscle mass was 46.5 (SD 9.6) kg, the mean body fat mass was 25.3 (SD 13.8) kg, the mean MVPA time of per day was 20.8 (SD 14.3) minutes, and the mean SBP and DBP were 139.5 (SD 17.1) and 85.8 (SD 9.1) mm Hg (Table 1).

Figure 3. Number of participants and exclusions from the study. Four participants were excluded from the intervention group and two from the control group.

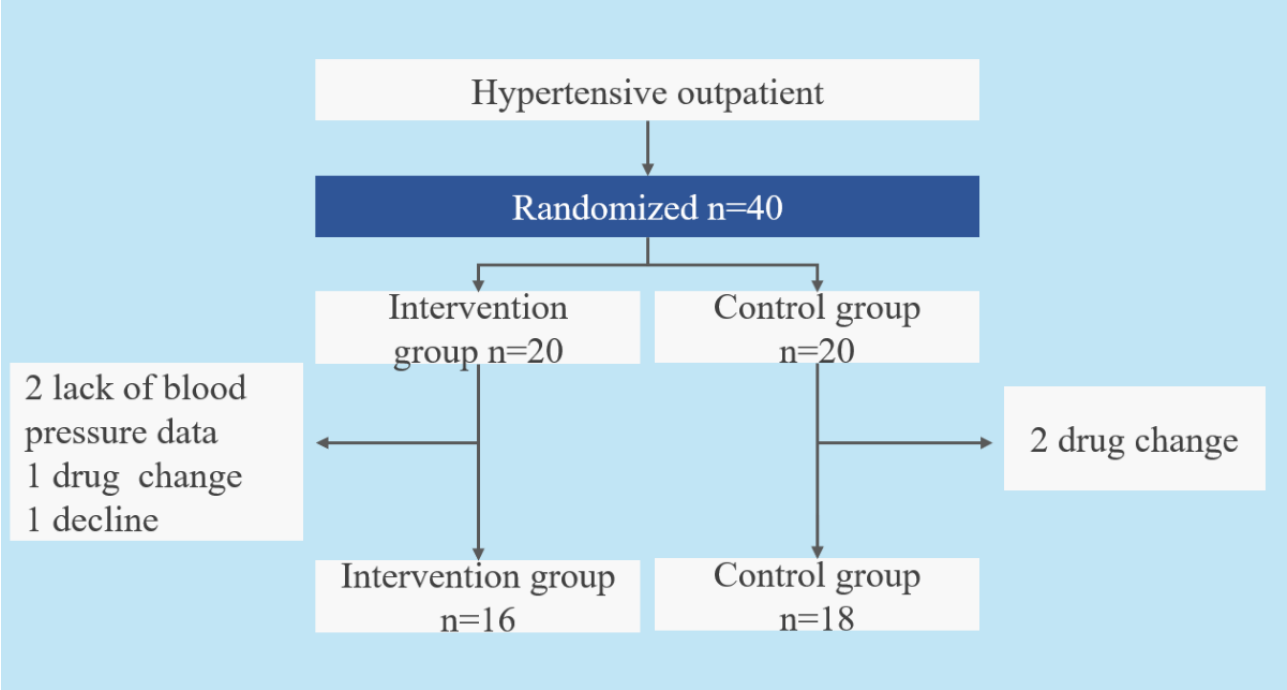


Table 1. Characteristics comparing intervention and control groups[a].

Variable	Total (n=34)	Intervention group (n=16)	Control group (n=18)	*P* value
Sex (female), n (%)	18 (53)	9 (56)	9 (50)	.70
Age (years), mean (SD)	56 (9.8)	54 (11)	59 (8)	.20
Antihypertensive drug, mean (SD)	1.5 (0.5)	1.5 (0.5)	1.5 (0.5)	.10
Lifestyle disease, n (%)	19 (56)	8 (50)	11 (61)	.50
BMI (m/kg^2), mean (SD)	28.0 (6.3)	27.2 (1.5)	29.1 (1.5)	.80
Body muscle mass (kg), mean (SD)	46.5 (9.6)	45.4 (9.7)	47.4 (9.7)	.60
Body fat mass (kg), mean (SD)	25.3 (13.8)	23.0 (14.0)	27.1 (13.9)	.40
Family caregiver, n (%)	4 (12)	2 (13)	2 (11)	.90
SBP[b] (mm Hg), mean (SD)	139.5 (17.1)	141 (4.6)	138.2 (3.8)	.60
[c]DBP (mm Hg), mean (SD)	85.8 (9.1)	86.3 (11.4)	85.4 (6.8)	.80
MVPA[d] per day (minutes), mean (SD)	20.8 (14.3)	24.7 (4.6)	17.3 (9.7)	.20

[a]This is the blood pressure measured on the first day of recruitment.

[b]SBP: systolic blood pressure.

[c]DBP: diastolic blood pressure.

[d]MVPA: moderate to vigorous physical activity (moderate intensity activities range from 3.0 to 5.9 METs, while high-intensity activities are 6.0 METs or above).

As a result, there was a difference in SBP between the 2 groups. The mean for the intervention group was –7.9 (SD 18.1) mm Hg and the mean for the control group was 3.9 (SD 14.5) mm Hg (*P*=.04). No difference was observed in DBP (mean –6.6, SD 11.1 mm Hg; mean –0.94, SD 10.6 mm Hg; *P*=.14), body weight (mean –3.5, SD 13.3 kg; mean –5.4, SD 18.7 kg; *P*=.74), body muscle mass (mean –7.9, SD 16.6 kg; mean –5.1, SD 15.6 kg; *P*=.61), body fat mass (mean –0.075, SD 1.1 kg; mean –1.0, SD 0.46 kg; *P*=.06), time of MVPA (mean 1.4, SD 7.5 min; mean –1.1, SD 6.9 min; *P*=.32) between the group and control group (Table 2).

Table 2. Amount of change before and after intervention between groups[a].

	Systolic blood pressure			Diastolic blood pressure		
	Estimate	SD	*P* value	Estimate	SD	*P* value
Dance	–12.8	6.1	.047	–9.7	3.3	.006
Sex	–2.8	5.9	.60	–1.1	3.1	.70
Age	–0.5	0.3	.10	–0.6	0.2	.001
Pre-MVPA[b] (minutes)	–0.2	0.2	.30	–0.006	0.1	.09

[a]Missing values were excluded from the analysis.

[b]SBP: systolic blood pressure.

[c]DBP: diastolic blood pressure.

[d]MVPA: moderate to vigorous physical activity.

In the multivariate analysis, SBP and DBP improved significantly in the intervention group compared with the control group (mean SBP –12.8, SD 6.1 mm Hg; *P*=.05; mean DBP 9.7, SD 3.3 mm Hg; *P*=.006). For the other covariates, only age showed a significant difference in DBP (*P*=.001; Table 3). No significant harm or unexpected effects were reported during this study.

Table 3. Multivariable analysis of systolic/diastolic blood pressure and each response variable[a].

	Systolic blood pressure			Diastolic blood pressure		
	Estimate	SD	*P* value	Estimate	SD	*P* value
Dance	–12.8	6.1	.047	–9.7	3.3	.006
Sex	–2.8	5.9	.60	–1.1	3.1	.70
Age	–0.5	0.3	.10	–0.6	0.2	.001
Pre-MVPA[b] (minutes)	–0.2	0.2	.30	–0.006	0.1	.09

[a]Missing values were excluded from the analysis.

[b]MVPA: moderate to vigorous physical activity.

Discussion

Principal Findings

Our results confirmed that regular exercise therapy using dance videos can lower the BP of patients with hypertension, even without monitoring. To the best of our knowledge, this is the first report of this finding.

BP control is crucial to maintaining health. However, various barriers, such as environmental and time constraints, prevent patients from engaging in exercise, which is a useful nonpharmacological therapy for BP control.

The Relationship Between Exercise and BP

Regarding the relationship between exercise and BP, the antihypertensive effects of aerobic exercise have been well documented in numerous meta-analyses [8,39,40]. Aerobic exercise can significantly decrease SBP and DBP, with specific reductions observed in postmenopausal women and those who participate in combined aerobic and resistance exercises [41]. The American College of Cardiology/American Heart Association guidelines report that exercise therapy can reduce SBP by 2-5 mm Hg and DBP by 1-4 mm Hg [42]. An 8-week stepping exercise program lowered SBP/DBP by 13.1/14.8 mm Hg in older women with stage 1 hypertension [43]. In another study, swimming reduced SBP and DBP by 9 mm Hg over 20 weeks [44]. A meta-analysis of 22 trials (736 participants) examining the effects of regular running on resting BP showed a significant reduction in hypertensive patients' resting BP, with a weighted MD of SBP –5.6 mm Hg (95% CI –9.1 to –2.1; *P*=.01) and DBP –5.2 mm Hg (95% CI –9.0 to –1.4; *P*<.01) [11]. A meta-analysis of 32 studies examining the effects of walking interventions on cardiovascular disease risk factors found a significant improvement in BP among patients with hypertension, with SBP –3.58 mm Hg (95% CI –5.19 to –1.97) and DBP –1.54 mm Hg (95% CI –2.83 to –0.26) [45]. Although the mechanisms underlying these effects are not fully understood, several other factors have been considered. Exercise likely reduces arterial pressure by decreasing cardiac output and total peripheral resistance [46]. Exercise reduces vascular responsiveness to norepinephrine, which increases vascular resistance, and reduces plasma endothelin-1 concentration. Furthermore, endothelium-dependent vasodilation is critically dependent on the production of nitric oxide. Exercise training has been shown to increase nitric oxide production and improve vasodilatory function in healthy participants [47-58]. Vertical head movements during moderate exercise may reduce angiotensin II type 1 receptor expression and BP [59]. Other mechanisms include structural changes in the blood vessels and genetic factors; however, more data are needed [60-62]. In this study, the dance group showed significant improvement in SBP and DBP compared to the control group (mean SBP –12.8, SD 6.1 mm Hg and mean DBP –9.7, SD 3.3 mm Hg). This

improvement is comparable to that observed with other aerobic exercises.

The Relationship Between Dance and BP and Monitoring Methods in Previous Studies

Dance is a dynamic aerobic endurance exercise that is broadly defined as moving one's body rhythmically to music, usually as a form of artistic or emotional expression. Many health benefits of dance have been realized in recent years. In a previous meta-analysis, the effects of dancing on a large variety of physical health measures were assessed in healthy adults. Studies on healthy adults have found that dance is equal to or greater than exercise in terms of its effectiveness in improving physical health [63-68]. Additionally, a meta-analysis comparing dance with other exercises showed that attrition rates from dance interventions were reported to be lower or equal to exercise, and adherence rates from dance interventions were higher or similar to exercise [21]. In a meta-analysis, dance therapy significantly reduced BP in patients with hypertension, with reductions of approximately 12 mm Hg in SBP and 3.4 mm Hg in DBP [69]. Patients with hypertension undergoing dance movement therapy experience reductions in SBP by 19.2 mm Hg and DBP by 9.5 mm Hg after 4 weeks of twice-weekly sessions [25]. Dances performed in dance movement therapy are often rooted in modern dance [26], but other dance genres also have a positive impact on BP control in patients with hypertension. In aerobic dance, participants saw a decrease in SBP by 18.8 mm Hg and DBP by 8.9 mm Hg over 12 weeks of 45-minute sessions three times a week [27]. Hula dance participants experienced a reduction in SBP by 18.3 mm Hg compared to 7.6 mm Hg in the control group after 12 weeks of 60-minute sessions twice a week [28]. In a study of older adults performing folk dance, SBP decreased from 146.8 mm Hg to 133.8 mm Hg and DBP from 78 mm Hg to 72 mm Hg over 12 weeks of 50-minute sessions three times a week [29]. Additionally, chain dance led to a decrease in SBP by 9 mm Hg and DBP by 6 mm Hg after 6 weeks of 30 to 45-minute sessions twice a week [30]. Overall, dance has been suggested to be highly effective in improving BP, and the results of this study support this.

Differences Between Previous Dance Studies and Ours

Naturally, exercise prescriptions are meaningless unless implemented by patients. The method of monitoring exercise implementation is likely an important factor in evaluating the effectiveness of exercise therapy in patients with hypertension. In previous studies investigating the relationship between dance exercise prescriptions and BP control, improvements in BP control were observed in all cases. However, as mentioned, in all these studies, the execution of dance exercises was monitored face-to-face or through other means. The most significant difference between this study and the previous research is that we tested the effectiveness of dance-based exercise prescriptions on BP without monitoring. To our knowledge, no previous study has examined the antihypertensive effects of dancing without monitoring. This study is the first to entrust everything to the patients themselves, without monitoring whether the exercise prescriptions were carried out or how accurately the participants performed the dance. In this study, we did not conduct monitoring during the dance sessions; the SBP and DBP in the dance group showed a significant improvement compared with those in the control group. General outpatient care must be carried out in a very short time, lasting only 5-10 minutes, and the existence of a fixed tool that can be used without supervision is thought to be highly effective in the management of lifestyle-related diseases.

Therefore, dance exercises using dance videos may be superior to other forms of exercise in terms of sustainability. Previous noninterventional studies have found that the primary intrinsic motivator for participation in dance was having fun [70] or improving mood [71], whereas participants also experienced significant physical benefits. This was a secondary motivator for initial and maintained participation, thereby likely demonstrating the enjoyment and adherence link that exists in dance. It is presumed that the pleasure and enjoyment experienced by many through dance offers the additional advantage of an increased likelihood of regular participation and adherence, which are essential features for achieving long-term health benefits and could explain the results seen in the included studies. This result is consistent with previous findings. Additionally, in this study, a dance exercise video posted on YouTube was provided as reference material for physical activity. This approach may have facilitated patients' access to an exercise "model," potentially leading to improved adherence to the prescribed physical activity.

The Significance of Applying This Study to Clinical Medicine

Incorporating exercise prescriptions using YouTube dance exercise videos into outpatient treatment may improve BP control in patients with hypertension, similar to other exercise prescriptions, even in busy and understaffed outpatient settings without monitoring. If video-based dance prescriptions, such as those used in this study, were put into practice, doctors would only need to provide patients with dance prescription videos. This could eliminate the need to spend valuable time during outpatient visits explaining exercises or monitoring exercise routines.

Limitations

This study had a few limitations.

First, because the patients were recruited from a single university hospital, there may be a risk of selection bias. In the future, this can be improved by recruiting more participants from additional outpatient clinics.

Second, the frequency of dance sessions and the accuracy of movements in the intervention group were unknown. Exercise therapy, intensity, and duration in the control group were also unknown because they were not measured.

Third, the timing of the outpatient visit was generally set at 8 weeks after registration for both BP and body composition measurements; however, there was some variation due to the timing of the outpatient visit.

Fourth, factors such as exercise, diet, and sleep immediately before BP measurement were not standardized because the schedule was adjusted to suit the participants' convenience.

Fifth, since three participants from each group dropped out during the observation period, BP changes in these individuals may have occurred due to antihypertensive medications, making evaluation difficult due to the absence of BP data. Including these participants could reduce the validity of the study; therefore, their exclusion is appropriate.

Despite these limitations, this study remains useful, though it faces constraints due to its focus on verifying the effectiveness of exercise prescriptions through dance videos in outpatient settings.

Conclusions

This study examined the effects of videos of unsupervised dance exercises on patients with hypertension. The results showed that dance videos were more effective in lowering BP than conventional exercise prescriptions. These results will contribute to exercise therapy for patients with lifestyle-related diseases.

Acknowledgments

We would like to thank the outpatient nurses and the doctors in charge of the outpatient department of the Department of General Medicine who cooperated with our research. No funding was provided to participants. The equipment used in this research was purchased with research funds from the Department of General Medicine at Juntendo University Hospital. Additionally, some equipment was loaned by the Sportsology Center at the Graduate School of Medicine, Juntendo University. We did not use generative artificial intelligence in our study.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

MSakairi collected the data. MSakairi analyzed the data and wrote the manuscript with feedback from TM, HT, NY, MSaita, MSuzuki, KF, HF, and TN. TM supervised the project. All authors contributed substantially to the study design and conceptualization, reviewed the manuscript, and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1123 KB - cardio_v9i1e65981_app1.pdf]

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Abbreviations

BP: blood pressure
CONSORT: Consolidated Standards of Reporting Trials
DBP: diastolic blood pressure
MD: mean difference
MET: metabolic equivalent of task
MVPA: moderate to vigorous physical activity
SBP: systolic blood pressure
UMIN: University Hospital Medical Information Network

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Application of Dragonnet and Conformal Inference for Estimating Individualized Treatment Effects for Personalized Stroke Prevention: Retrospective Cohort Study

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Abstract

Background: Stroke is a major cause of death and disability worldwide. Identifying individuals who would benefit most from preventative interventions, such as antiplatelet therapy, is critical for personalized stroke prevention. However, traditional methods for estimating treatment effects often focus on the average effect across a population and do not account for individual variations in risk and treatment response.

Objective: This study aimed to estimate the individualized treatment effects (ITEs) for stroke prevention using a novel combination of Dragonnet, a causal neural network, and conformal inference. The study also aimed to determine and validate the causal effects of known stroke risk factors—hypertension (HT), diabetes mellitus (DM), dyslipidemia (DLP), and atrial fibrillation (AF)—using both a conventional causal model and machine learning models.

Methods: A retrospective cohort study was conducted using data from 275,247 high-risk patients treated at Ramathibodi Hospital, Thailand, between 2010 and 2020. Patients aged >18 years with HT, DM, DLP, or AF were eligible. The main outcome was ischemic or hemorrhagic stroke, identified using *International Classification of Diseases, 10th Revision* (*ICD-10*) codes. Causal effects of the risk factors were estimated using a range of methods, including: (1) propensity score–based methods, such as stratified propensity scores, inverse probability weighting, and doubly robust estimation; (2) structural causal models; (3) double machine learning; and (4) Dragonnet, a causal neural network, which was used together with weighted split-conformal quantile regression to estimate ITEs.

Results: AF, HT, and DM were identified as significant stroke risk factors. Average causal risk effect estimates for these risk factors ranged from 0.075 to 0.097 for AF, 0.017 to 0.025 for HT, and 0.006 to 0.010 for DM, depending on the method used. Dragonnet yielded causal risk ratios of 4.56 for AF, 2.44 for HT, and 1.41 for DM, which is comparable to other causal models and the standard epidemiological case-control study. Mean ITE analysis indicated that several patients with DM or DM with HT, who were not receiving antiplatelet treatment at the time of data collection, showed reductions in total risk of −0.015 and −0.016, respectively.

Conclusions: This study provides a comprehensive evaluation of stroke risk factors and demonstrates the feasibility of using Dragonnet and conformal inference to estimate ITEs of antiplatelet therapy for stroke prevention. The mean ITE analysis suggested that those with DM or DM with HT, who were not receiving antiplatelet treatment at the time of data collection, could potentially benefit from this therapy. The findings highlight the potential of these advanced techniques to inform personalized treatment strategies for stroke, enabling clinicians to identify individuals who are most likely to benefit from specific interventions.

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KEYWORDS

stroke; causal effect; ITE; individual treatment effect; Dragonnet; conformal inference; mortality; hospital records; hypertension; risk factor; diabetes; dyslipidemia; atrial fibrillation; machine learning; treatment

Introduction

Stroke is a leading cause of death and disability, presenting both personal and economic burdens [1]. Astonishingly, many epidemiological studies have identified important risk factors of stroke occurrence, especially through the use of cohort studies [2], and randomized controlled trials (RCTs) have identified the impact of treating these risk factors. While RCTs control for confounding factors through study design, cohort studies attempt to address these factors using statistical methods. However, the possibility of residual confounding remains, highlighting the need for improved analysis approaches [3].

Frameworks of causal effect have largely been confined to Pearl's [4] structural causal models (SCMs) and Rubin's [5] potential outcome models (POMs) [6]. SCMs evaluate causal relationships between variables using a directed acyclic graph defined by a set of structural equations, which consider the influence of each variable by its parents, or causes, along with its probability distribution. In addition, SCMs can also assess the effect of interventions by estimating how changing one unit of treatment (or risk) leads to a change in outcome [7]. Conversely, POMs focus on the concept of counterfactuals, specifically what would have happened if an individual had been exposed to a different treatment or risk [8]. Consequently, this approach estimates 2 potential outcomes (POs) for each individual: if the individual had received the treatment and if they had not. Subsequently, Rosenbaum and Rubin [9] developed propensity scores to reflect the probability of an individual being assigned to a certain treatment group. Therefore, these estimates are only considered valid if the 2 specific conditions—strong ignorability and positivity—are met. Statistical methods have been developed based on POMs and propensity scores, including matching [10], stratified propensity score (SPS) [11], inverse probability weighting (IPW) [12,13], and doubly robust estimation (DRE) [14-16]. Recently, nonconventional statistical models such as double machine learning (DML), meta-learners, and neural networks have also been developed to estimate unbiased causal effects without requiring strong underlying assumptions [14]. Causal neural networks (NNs), including TARNet and Dragonnet, learn by sharing input data to estimate both factual and counterfactual outcomes. This approach is currently an active area of research [17-19]. Dragonnet also uses "learned data" to predict propensity scores by tradeoff with prediction quality, which yields better average treatment effect (ATE) estimates [18].

Current causal modeling has shifted its focus from the ATE, which measures the treatment effect averaged across the entire study population, to the conditional average treatment effect (CATE), which assesses the ATE conditional on particular variables, such as sex, age, and other covariates. More recently, the focus has further evolved to the individualized treatment effect (ITE), which estimates the treatment effect for a particular individual. CATE has inherent variability depending on which covariate the model is conditioned on [20]. However, estimating ITEs is challenging because it requires making assumptions about the underlying individual data-generating process and the model used to estimate the ITEs [17]. A statistical technique called conformal inference may appropriately estimate the confidence intervals of ITEs by accounting for the uncertainty in their estimation. Despite being a novel technique, it has shown promise [20]. Conformal inference uses nonconformity scores that measure the degree of disagreement between the estimated and observed outcomes, to provide a confidence interval or a precision of estimation [21-23]. Therefore, we conducted this study to estimate the CATE of stroke occurrence based on real-world clinical data using Dragonnet NN models. Additionally, ITE was estimated to identify individuals at high risk of stroke who may benefit from lowering risk factors by combining the strengths of Dragonnet and conformal inference approaches. To the best of our knowledge, no prior studies have employed these methods in combination to estimate causal effects in a clinical setting.

Methods

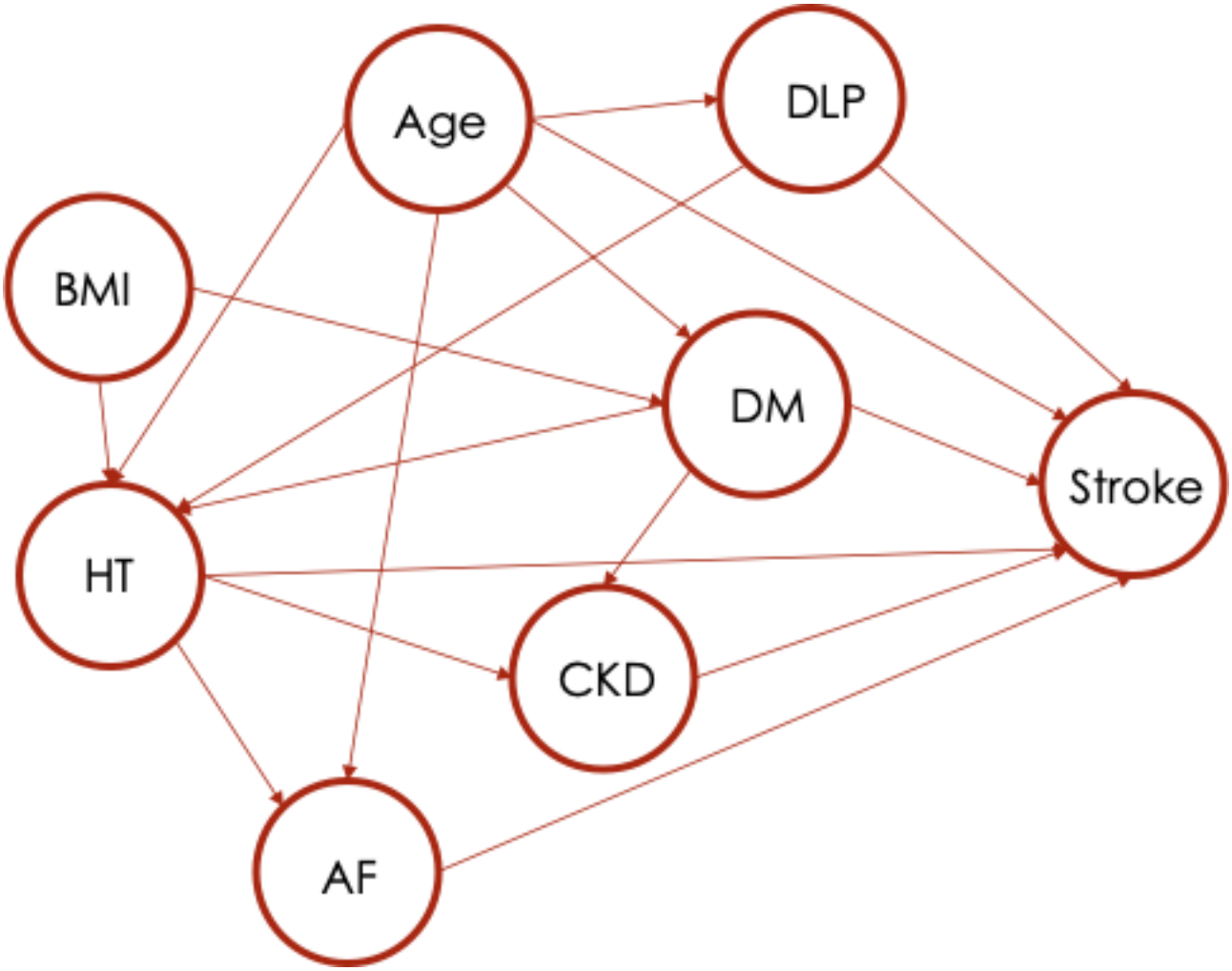
Overview

The study population included a retrospective cohort of patients who were at high risk for stroke and had been treated and followed up at Ramathibodi Hospital, Thailand, between 2010 and 2020. Hospital records and the *International Classification of Diseases, 10th Revision* (*ICD-10*) classification system were used to identify patients. Patients were eligible if they were aged >18 years and had one or more of the following conditions: hypertension (HT; *ICD-10* code I10-I16), diabetes mellitus (DM; *ICD-10* code E08-E13), dyslipidemia (DLP; *ICD-10* code E78), and atrial fibrillation (AF; *ICD-10* code I48). Patients were excluded if they had a stroke on their first visit or only had one visit during the study period. The main outcome measured in the study was the occurrence of ischemic or hemorrhagic stroke, which was identified using the *ICD-10* codes I63 and I61, respectively.

Patients were followed up from their index date (i.e., the date they were identified as high-risk patients) until they progressed to stroke, were lost to follow-up, or were stroke-free at the end of the study (December 31, 2020). Patients who were lost to follow-up or stroke-free at the end of the study period were censored on their last visit date or at the end of the study. A causal diagram was constructed (Figure 1), and potential predictors of stroke were collected, including age, sex, BMI, chronic kidney disease (CKD), AF, HT, DM, and DLP. HT, AF, and DM were considered as mediators, whereas the remaining variables were covariates in the models. A software library called DoWhy, now incorporated into PyWhy (Python Software Foundation), was used to construct models for stratification, IPW, DRE, and DML [24]. Parameters of all estimators were set by default in the DoWhy package. The number of strata in the stratification method was automatically determined [25]. The weighting scheme in IPW was set to default inverse propensity score. For DRE, the regression and propensity models were specified as lasso and logistic regression, respectively. For DML, linear and nonlinear cross-fitted models were applied to the outcome model (lasso and Extreme Gradient Boosting [XGBoost]), propensity model (logistic regression and XGBoost), and final model (linear regression and lasso). Estimands of each risk pathway were defined by PyWhy from the input causal graph. Graphical causal

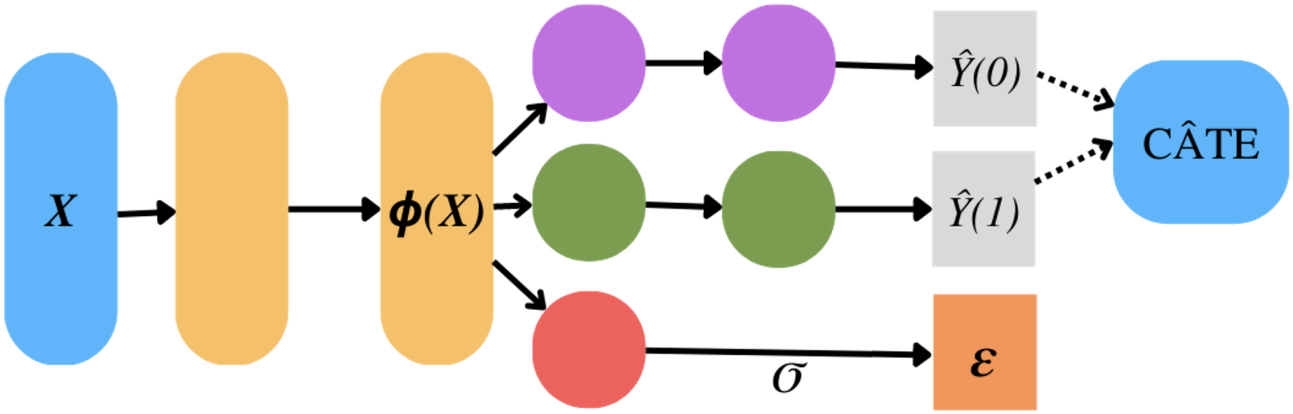
model–based inferences from the DoWhy library were used for medication analysis to quantify the causal effects of direct and indirect pathways, termed natural direct effect (NDE) and natural indirect effect (NIE), respectively [4,26]. NDE (Y1,M(0)x−Y0,M(0)x) refers to the change in the outcome of an individual when they are exposed to a specific treatment Y1, compared to another treatment Y0, while keeping the mediator variable constant at the baseline value or reference treatment *M(0)*. In contrast, NIE (Y1,M(1)x-Y1,M(0)x) refers to the difference between the counterfactual outcome value when treatment Y1 is fixed and the mediator assumes a certain value at a particular treatment *M(1)* and the counterfactual outcome value when the mediator assumes the same value at the baseline *M(0)* [27].

Figure 1. Causal diagram of patients at risk of stroke occurrence. AF: atrial fibrillation; CKD: chronic kidney disease; DLP: dyslipidemia; DM: diabetes mellitus; HT: hypertension.



The Dragonnet NN was used to estimate PO and propensity scores. The architecture of Dragonnet was based on previous work (Figure 2) [18]. It employs a deep net to create a representation layer $(X) \in$, which is used to forecast outcomes for both the treatment $\hat{Y}(1)$ and control groups $\hat{Y}(0)$. It utilizes 2 hidden layers for each outcome model while a basic fully connected layer with a sigmoid function is used for the propensity score ( ). CATE was estimated by subtracting treatment (risk) and control PO for each risk factor (Y1x−Y0x | Z) and risk ratios were estimated by division of PO (Y1xY0x|Z); Y_1 is the PO for the risk group, Y is the PO for the control group, x is an interested factor, and Z are other covariates.

Figure 2. Dragonnet architecture. *X* is the covariates, *(X)* is a learned representation of *X*. $\hat{Y}(1)$ is the predicted outcome of the treatment (risked) group. $\hat{Y}(0)$ is the predicted outcome of the control group. ε is the estimated propensity score. CÂTE is the conditional average treatment effect computed by $\hat{Y}(1)–\hat{Y}(0)$.



To accurately estimate the ITE, it is mandatory for the conditional independence assumption to hold, especially considering the unequal distribution of covariates between factual and counterfactual outcomes of the treatment and control groups, commonly known as covariate shift. To address this challenge, we employed a nested method of weighted split-conformal quantile regression (CQR) to estimate the ITE [20,23] by incorporating antiplatelet medications as a treatment for stroke prevention. POs were estimated using quantile loss setting α at .05. The dataset was split evenly into training and evaluation sets; Multimedia Appendix 1 shows the entire algorithm. All risk factors and covariates were similar between models, considering antiplatelet medication as a treatment and stratified by risk factor (Yantiplatelets=1x-Yantiplatelets=0x|Z), with *x* representing the risk factors of interest (i.e., HT, DM, and DLP) and Z representing other covariates. AF was not included as a stratum for the estimation of ITE in this example since it is not an indication for the prescription of antiplatelet therapy, but it remained a covariate.

Ethical Considerations

The data were anonymized to ensure confidentiality and privacy protection. This study was approved by the Human Research Ethics Committee, Faculty of Medicine Ramathibodi Hospital, Mahidol University (COA. MURA2021/255). The committee waived the need to obtain consent for the collection, analysis, and publication of the retrospectively obtained and anonymized data for this noninterventional study.

Results

A total of 275,247 high-risk patients were included in the cohort. Among them, 9659 patients developed stroke, resulting in an incidence of 3.5% (95% CI 3.4-3.6). The follow-up rate for the study population was 80% (7752/9659).

Baseline demographic and risk factors were compared between 9659 stroke patients and 265,588 nonstroke patients (Multimedia Appendix 2). Stroke patients had a mean age of 64.7 years and were more likely to be male. Stratification by risk indicated that 13% of AF patients, 4% of HT patients, 4% of DM patients, and 4% of DLP patients experienced stroke in contrast to only 2% of non-AF patients, 1% of non-HT patients, 3% of non-DM patients, and 3% of non-DLP patients, who developed stroke.

Causal effects of mediators including HT, DM, CKD, and AF on stroke were estimated based on the causal diagram in Figure 1. The estimands report as probability of stroke given the risk factors, *P*(*Stroke* | *risk factors*), are as follows: *P*(*Stroke* | *HT, age, DM, DLP*) for HT; *P*(*Stroke* | *AF, age, HT*) for AF; *P*(*Stroke* | *age, DLP*) for DLP; and *P*(*Stroke* | *age, DM, BMI*) for DM (Multimedia Appendix 3). For the POM approach, the SPS estimator showed AF as the highest risk of stroke, followed by HT, DM, and DLP with risk estimates of 0.084 (95% CI 0.079-0.088), 0.019 (95% CI 0.015-0.020), 0.010 (95% CI 0.008-0.010), and 0.0015 (95% CI −0.0002 to 0.0027), respectively. IPW yielded similar, albeit slightly higher, corresponding risks of 0.092 (95% CI 0.089-0.096), 0.024 (95% CI 0.022-0.025), 0.010 (95% CI 0.008-0.010), and 0.001 (95% CI −0.0005 to 0.0025), respectively. Comparable results were observed in the DRE analysis, with a similar trend of risk effect estimates of 0.082 (95% CI 0.0849-0.0871), 0.025 (95% CI 0.0243-0.0257), 0.008 (95% CI 0.0057-0.0063), and 0.0006 (95% CI 0.0001-0.0011), respectively.

The SCM estimation also yielded similar trends to the POM approach, in which the risk of stroke was 0.096 (95% CI 0.0948-0.0972), 0.021 (95% CI 0.0204-0.0216), 0.007 (95% CI 0.0067-0.0073), and 0.0005 (95% CI 0.0004-0.0006) for AF, HT, DM, and DLP, respectively. Mediation analysis indicated the NDE of HT to be 0.020 (95% CI 0.019-0.021) and the NIE to be 0.0027 (95% CI 0.0025-0.0029). NDE and NIE for DM and DLP were both modest and consistent with the findings from other models. Figure 1 illustrates the pathways through which the mediators act: HT mediates through CKD and AF, DM mediates through HT and CKD, while DLP mediates through HT.

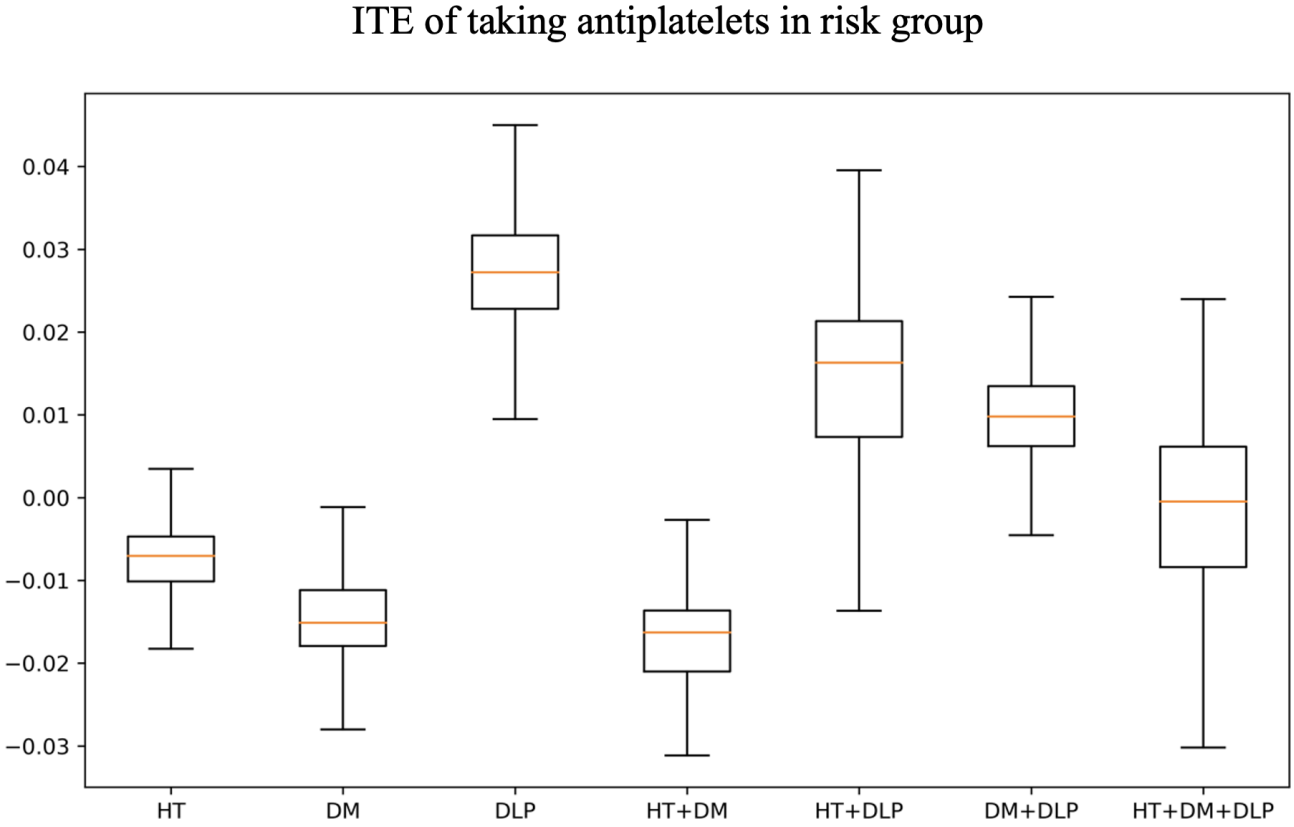
In the context of DML, the nonparametric model estimates were slightly smaller than those for the linear model, with risks of 0.086 (95% CI 0.0849-0.0871), 0.015 (95% CI 0.0145-0.0155), 0.006 (95% CI 0.0057-0.0063), and 0.0 (95% CI −0.0001 to 0.001) for AF, HT, DM, and DLP, respectively, whereas the corresponding linear model estimate risks were 0.097 (95% CI 0.096-0.098), 0.023 (95% CI 0.0223-0.0236), 0.009 (95% CI 0.0087-0.0093), and 0.002 (95% CI 0.0018-0.0022).

Dragonnet estimated the causal effects of AF, HT, DM, and DLP on stroke as 0.075 (95% CI 0.074-0.076), 0.017 (95% CI

0.0169-0.0170), 0.01 (95% CI 0.009-0.010), and −0.002 (95% CI −0.0022 to 0.0021), with causal ratios of 4.56 (95% CI 4.56-4.57), 2.44 (95% CI 2.41-2.46), 1.41 (95% CI 1.21-1.60), and 0.856 (95% CI 0.855-0.858), respectively. The odds ratios from the logistic regression models were respectively 3.34 (95% CI 2.68-3.75), 2.56 (95% CI 2.33-2.80), 1.16 (95% CI 1.05-1.30), and 1.00 (95% CI 0.8-1.4). Details are provided in Multimedia Appendix 3 for comparison.

The influence of risk reduction for individual patients who did not receive antiplatelet therapy, had they been given the medication (counterfactuals of nontreatment ITEs), was examined using weighted split-CQR. As shown in Multimedia Appendix 4, three of the samples (3/50, 6%) appear to have potentially benefited from antiplatelet treatment, indicating that a considerable number of patients might have experienced a positive impact on their stroke risk reduction had they received the medication. The mean ITEs indicated that several patients with DM or DM with HT were not currently receiving antiplatelet treatment and would be more likely to benefit if they had received it, with reduction of total risk as −0.015 (IQR −0.011 to −0.018) and −0.016 (IQR −0.015 to 0.022) among each group, respectively (Figure 3).

Figure 3. Box plot representing the mean individual treatment effect for patients with different risk factors who had not been taking antiplatelet medication, illustrating the potential impact on stroke risk reduction if they had received antiplatelet therapy. DLP: dyslipidemia; DM: diabetes mellitus; HT: hypertension; ITE: individual treatment effect.



Discussion

Principal Findings

We estimated the causal influences of risk factors associated with stroke outcomes using multiple approaches that included SPS, IPW, DRE, SCM, and mediation analysis, in addition to DML and Dragonnet NNs. Our findings indicate strong positive causal effects associated with AF and HT on stroke development, with DM exerting a weaker effect. DLP, in contrast, had little effect. Furthermore, our analysis suggests that patients with both DM and HT not currently in receipt of antiplatelet treatments would be the most likely beneficiaries of antiplatelet therapy based on the mean ITEs.

The results from the different estimators generally demonstrated consistency, although there were slight variations in specific point estimates and confidence intervals varied slightly. The estimated causal effect derived from various methods using real-world observational data is comparable with standard cohort epidemiological studies using more traditional logistic regression approaches [28,29].

Comparison to Prior Works

SPS is a widely used method that minimizes confounding bias by adjusting baseline covariates and confounding factors and estimating treatment effects by stratum. However, SPS is sensitive to the number of strata and features that affect both treatment and outcome (confounding factors), which can lead to bias in the causal effect estimate [30-33]. In addition, some strata may be sparsely populated, making the ATE hard to define and more prone to bias [34]. Rosenbaum and Rubin [9] originally proposed dividing the strata into 5 levels and then subsequently automatically splitting the strata until the balance in the numbers of treated and control observations was achieved [25].

IPW attempts to reduce confounding of the ATE by weighting the sample with the inverse propensity score and by balancing the distribution of the covariates between the treated and untreated groups [35], thereby avoiding the problem of data sparsity that may be present in SPS, particularly with small sample sizes. However, there is a reliance on the assumption that the propensity score model correctly captures all confounding factors, which, if incorrect, may bias the ATE. Additionally, IPW is more sensitive to the model and variable selection for estimating the propensity scores, with small differences in estimated propensity scores potentially leading to large differences in estimated causal effects [36]. Finally, IPW may imprecisely estimate treatment effects if a sample size is small, leading to a propensity score close to 0 or 1 [36,37].

DRE combines propensity score and outcome regression models [38], which can lead to improvements in the robustness of model specification by allowing one of the two treatment and outcome models to be miss-specified but still provide a consistent estimation [39]. The challenge is to validly model either the propensity score or the outcome model; it may be tempting to use modern machine learning approaches or nonparametric models in DRE, but this may lead to bias if the functions are too complex, leading to overfitting [40,41]. DML was developed to address the bias from regularization and overfitting in estimating the parameter of interest, which arises when naively inserting machine learning estimators into the estimation equation. This approach consists of two critical components: (1) the use of Neyman-orthogonal moments or scores to estimate the parameters and (2) the application of cross-fitting, which provides an efficient form of data-splitting. By using both elements, DML minimizes the impact of regularization bias and overfitting on parameter estimation; this also extends to nonparametric models [14].

Applying POMs (eg, SPS, IPW, DRE) relies heavily on the assumption that the treatment assignment is independent of the PO given the observed covariates, which is known as “unconfoundedness” or the conditional independence assumption. If this assumption does not hold, the estimated causal effect will be biased. In contrast, SCMs facilitate the modeling of complex relationships between multiple causes and effects in the presence of latent or unobserved variables [4,42]. In addition, SCMs can be considered as counterfactual predictions of interventions, which can be useful in applications such as causal inference in experimental or observational studies [43-46]. However, SCMs are limited by the assumption of independence between variables and may require conceptualized causal relationship mechanisms.

The benefit of using NNs to estimate causal effects is their flexibility and power to handle high-dimensional and complex data. Shalit et al [17] introduced TARNet by sharing information between the PO of treatment and control groups, which is different from the previous model that separated the training data. More recently, Dragonnet was developed by combining propensity scores with targeted regularization, resulting in more accurate inference [18]. Dragonnet is considered more robust with very low or high propensity scores but has several limitations including sensitivity to choice of architecture and hyperparameters, dealing with only a single set of features at a time, and difficulty of interpretation [18]. Despite some limitations, Dragonnet’s benefits surpass these drawbacks, making it an attractive approach for estimating causal effects in complex real-world data.

Strengths and Limitations

A critical aspect of causal inference, particularly in estimating CATE, involves certain assumptions, notably ignorability and positivity. Strong ignorability necessitates the observation and adjustment for all confounding variables that influence both the treatment and the outcome, while positivity ensures that every patient has a nonzero probability of receiving each treatment. In our study, we believe these assumptions are reasonably satisfied. We included a comprehensive set of covariates, such as age, sex, BMI, chronic kidney disease, and relevant comorbidities (HT, DM, DLP, and AF), which are well-documented factors influencing stroke risk and treatment decisions. However, we acknowledge that there might be unmeasured confounders not captured in our dataset. Regarding the decision on antiplatelet drug administration, we utilized detailed patient records from Ramathibodi Hospital, ensuring a thorough assessment of factors influencing treatment. Nonetheless, we recognize the potential for residual confounding and the inherent limitations of observational data. Future studies could benefit from incorporating more granular clinical data and leveraging advanced causal discovery methods to further validate these assumptions.

Causal effects can vary between individuals, which necessitates the estimation of ITEs. Treatment effects can vary between individual patients; therefore, applying a single treatment effect as CATE to all individual patients is inappropriate [47,48] as some patients may gain more or less benefit from treatments. Thus, the estimation of ITE to identify at-risk patients most likely to benefit from treatment is a major goal for stratified and precision medicine approaches. Estimating ITEs requires larger sample sizes, as individual-level estimates are less precise than aggregate-level estimates [49]. A covariate shift may result from unobserved counterfactual data but this is minimized using a weighted split-CQR approach [23].

We believe that the clinical implications of our study are significant, as understanding the causal relationships and individual treatment effects of stroke risk factors can directly influence patient care by providing more precise and personalized risk assessments. Additionally, we can conduct reviews and quality assessments of current patients in the clinic to determine who should receive further treatment. These methods enable clinicians to identify high-risk patients who would benefit most from targeted interventions, like antiplatelet therapy, thereby optimizing treatment strategies and improving patient outcomes. The use of real-world data ensures that our findings apply to everyday clinical practice.

Our study has some limitations. First, we used real-world data rather than RCT data, thus some important covariates were not previously planned, measured, and collected as part of routine clinical evaluation and were therefore unavailable for ITE estimation. Second, we acknowledge the possibility of unmeasured confounders in the observational dataset. Future studies could benefit from incorporating more granular clinical

data, such as detailed medication records, laboratory results, and lifestyle factors, to mitigate potential confounding. Third, the models used for estimating ITEs were trained and validated in only a single setting, thereby limiting their generalizability. Future research should focus on validating the models in diverse settings with different patient populations or hospitals. This external validation would help to determine whether the models' predictive performance and the estimated ITEs hold true across various contexts.

Conclusion

This study provides comprehensive causal estimates of AF, HT, DLP, and DM on stroke using various advanced statistical and machine learning methodologies. The consistent results across multiple analytical approaches and this study's alignment with a standard cohort study reinforce the robustness of our findings. AF and HT emerged as significant risk factors for stroke, with DM showing a moderate effect, while DLP had minimal impact. Notably, the use of Dragonnet and conformal inference techniques allowed us to accurately estimate ITEs, highlighting that several high-risk patients who did not take antiplatelets at the time of data recorded, particularly those with DM or DM combined with HT, could potentially benefit from antiplatelet therapy. This suggests that personalized treatment strategies could be pivotal in reducing stroke risk among these patients.

The findings underscore the significance of individualized risk assessment and treatment personalization in clinical settings. Future research should focus on integrating these advanced causal inference models into routine clinical practice to enhance treatment outcomes for high-risk stroke patients. Additionally, the use of real-world data provides valuable insights but also presents challenges related to unmeasured confounding and data quality. Addressing these challenges in future studies will be crucial for advancing our understanding and improving stroke management strategies.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

This study has been conceptualized by SL and AT. SL performed data management, model construction, and analysis. The manuscript was drafted by SL and revised by GJM, JA, and AT. All authors approved the final version of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Nested approach for interval estimates of individual treatment effect algorithm. α=.05 to cover 95% confidence interval.
[DOCX File, 21 KB - cardio_v9i1e50627_app1.docx]

Multimedia Appendix 2
Descriptive analysis of features between stroke and nonstroke.
[DOCX File, 23 KB - cardio_v9i1e50627_app2.docx]

Multimedia Appendix 3
Estimated causal effect from estimators. Numbers indicate conditional average treatment (risk) effect (CATE) with 95% confidence interval. * Heart disease ** top quintile low-density lipoprotein (LDL).
[DOCX File, 22 KB - cardio_v9i1e50627_app3.docx]

Multimedia Appendix 4
Sample of 50 individual treatment effects with 95% confidence intervals and stroke risk reduction who had not received antiplatelet treatment, demonstrating the potential benefits had they been given the medication. In this plot, 3 of the samples (6%) demonstrate that a considerable number of patients could have experienced a positive impact on their stroke risk reduction had they received the antiplatelet treatment. The y-axis displays the treatment effect, while the x-axis represents each individual patient in the sample.
[DOCX File, 59 KB - cardio_v9i1e50627_app4.docx]

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Abbreviations

AF: atrial fibrillation
ATE: average treatment effect
CATE: conditional average treatment effect
CKD: chronic kidney disease
CQR: conformal quantile regression
DLP: dyslipidemia
DM: diabetes mellitus
DRE: doubly robust estimation
HT: hypertension
***ICD-10*:** *International Classification of Diseases, 10th Revision*
IPW: inverse probability weighting
ITE: individualized treatment effect
NDE: natural direct effect
NIE: natural indirect effect
NN: neural network
PO: potential outcome
POM: potential outcome model

RCT: randomized controlled trial
SCM: structural causal model
SPS: stratified propensity score
XGBoost: Extreme Gradient Boosting

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