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Optimal combination treatment and vascular outcomes in recent ischemic stroke patients by premorbid risk level

Jong-Ho Park [a,b], Bruce Ovbiagele [b,*]

[a] Department of Neurology, Seonam University Myongji Hospital, Goyang, South Korea
[b] Department of Neurology, Medical University of South Carolina, Charleston, SC, United States

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ABSTRACT

Background: Optimal combination of secondary stroke prevention treatment including antihypertensives, antithrombotic agents, and lipid modifiers is associated with reduced recurrent vascular risk including stroke. It is unclear whether optimal combination treatment has a differential impact on stroke patients based on level of vascular risk.

Methods: We analyzed a clinical trial dataset comprising 3680 recent non-cardioembolic stroke patients aged ≥35 years and followed for 2 years. Patients were categorized by appropriateness levels 0 to III depending on the number of the drugs prescribed divided by the number of drugs potentially indicated for each patient (0 = none of the indicated medications prescribed and III = all indicated medications prescribed [optimal combination treatment]). High-risk was defined as having a history of stroke or coronary heart disease (CHD) prior to the index stroke event. Independent associations of medication appropriateness level with a major vascular event (stroke, CHD, or vascular death), ischemic stroke, and all-cause death were analyzed.

Results: Compared with level 0, for major vascular events, the HR of level III in the low-risk group was 0.51 (95% CI: 0.20–1.28) and 0.32 (0.14–0.70) in the high-risk group; for stroke, the HR of level III in the low-risk group was 0.54 (0.16–1.77) and 0.25 (0.08–0.85) in the high-risk group; and for all-cause death, the HR of level III in the low-risk group was 0.66 (0.09–5.00) and 0.22 (0.06–0.78) in the high-risk group.

Conclusion: Optimal combination treatment is related to a significantly lower risk of future vascular events and death among high-risk patients after a recent non-cardioembolic stroke.

1. Introduction

Vascular events including stroke are eminently preventable through optimal control of well-established risk factors [1,2]. Robust clinical trial evidence supports the use of various drug classes that specifically target stroke risk factors [3]. However, in the overwhelming majority of cases, these secondary prevention drugs were tested for efficacy in clinical trials of single agent classes [3], and so their potentially combined beneficial effects along with proven medications from other classes, has not been frequently or systematically evaluated. We recently demonstrated that optimal combination secondary prevention drug treatment after a recent stroke was broadly associated with a significantly lower risk of stroke, major vascular events, and death [4]. Little is known about whether the effect of optimal combination treatment on vascular recurrence among recent stroke patients might vary depending on the level of premorbid vascular risk.

In this study, we investigated the impact of optimal combination treatment in recent stroke patients stratified by established cerebrovascular/cardiovascular disease at the time of their index stroke.

2. Methods

2.1. Patients and study

We reviewed data from the Vitamin Intervention for Stroke Prevention (VISP) trial [5]. Details of the trial have been published elsewhere [5]. The study enrolled 3680 patients aged ≥35 years to determine whether high doses of multivitamin (folic acid, pyridoxine, and cobalamin) given to lower total homocysteine levels would reduce the risk of recurrent stroke and major vascular events in patients with a recent (within the preceding 120 days) non-disabling, non-cardioembolic stroke [5]. Demographic, clinical, and laboratory data were collected at baseline, with subsequent clinical and laboratory information obtained at follow-up visits of 1, 6, 12, 18, and 24 months. We reviewed VISP data recorded on medication use, which was collected at every 6-month interval follow-up visit. We utilized secondary prevention drug information as reported previously [4]. The trial was approved by the ethics committee or institutional review board at each national or local site [5].

* Corresponding author at: Department of Neurology, Medical University of South Carolina, 96 Jonathan Lucas St., CSB 301, MSC 606 Charleston, SC 29425-6160, United States.
E-mail address: Ovibes@musc.edu (B. Ovbiagele).

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There were three possible recommended medication classes for each patient: antihypertensive (AH), antithrombotic (AT), and lipid modifier (LM) therapy. All participants were considered to be eligible for AT and LM medications based on the fact that both strategies have been linked to a proven reduction in the risk of recurrent stroke and other cardiovascular events (Class I; Level A and Class I; Level B) [3]. Subjects with established/newly diagnosed hypertension were considered to be eligible for AH medication based on Class I; Level A evidence [3]. Evidence-based secondary prevention was defined using an appropriateness algorithm for various secondary prevention strategies based on Mukherjee et al. study [6]. Composite appropriateness level was determined for each patient as follows: Level 0, none of the indicated medications prescribed; level I, 1 medication prescribed even though 3 medications indicated; level II, 2 medications prescribed even though 3 medications indicated or 1 medication prescribed even though 2 medications indicated; and level III, all indicated medications were prescribed. If patient did not have a diagnosis of hypertension and was prescribed both of the 2 other indicated medication classes (LM + AT), that patient's appropriateness was defined as level III.

Study subjects were categorized into low- and high-risk groups. High-risk was defined as patients with a history of stroke or coronary heart disease (CHD) [7]. History of CHD included myocardial infarction, angina, coronary angioplasty/stenting, or coronary artery bypass graft surgery in the VISP database [5]. VISP qualifying stroke was not included in history of stroke.

2.2. Outcome variable(s)

The primary outcome for this analysis was major vascular events (a composite of ischemic stroke, CHD including myocardial infarction, coronary revascularization, cardiac resuscitation, and fatal CHD, or vascular death). Secondary outcome was ischemic stroke and tertiary outcome was death of any cause.

2.3. Statistical analysis

Comparisons across the groups were examined using the χ^2 test for categorical variables and Student *t* test for continuous variables. Subjects with no medication (level 0) for secondary prevention were the referent group for purposes of comparison. Cox proportional hazard regression analyses were performed to estimate the risk of outcome events on 2 years after adjusting for age, sex, systolic blood pressure (BP), hypertension, diabetes, history of carotid endarterectomy, history of congestive heart failure, history of alcohol use, mini-mental state examination (MMSE) score, high-dose B vitamin therapy, serum levels of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), creatinine (all $P < 0.01$), and body mass index, homocysteine, ethnicity, smoking and stroke severity that are potentially linked to cardiovascular recurrence or death, regardless of statistical significance. Participants not having outcome events were censored at last follow-up examination, or last visit. Participants lost to follow-up during the course of the study were included in the Cox model until the last contact. Results are given by hazard ratio (HR) and its 95% confidence interval (CI). A linear trend of adjusted HRs across a medication class (levels 0 to III) was examined using a likelihood ratio test. In addition, survival curves were fit by the log-rank tests. The interaction between vitamin therapy (high vs low dose) and each medication class in predicting the risk of vascular events and all-cause death was assessed by including the appropriate interaction terms in the model. All analyses were conducted using IBM SPSS Version 22.0 (IBM Corp., Armonk, NY) and a probability value of <0.05 was considered statistically significant.

3. Results

3.1. Patient characteristics and incidence of outcome events by risk category

In 3680 participants in the VISP trial, mean age was 66.3 ± 10.8 years, 37.5% were women and 79.5% were white. During an average 20 months of follow-up, a total of 300 (8.2%) incident stroke and 619 (16.8%) major vascular events, and 216 (5.6%) all-cause deaths were recorded. Eighty-one per cent received AH, 54.6% LM, and 93.4% AT. Overall, 51.0% of total subjects received level III therapy. High-risk group consisted of history of stroke only (n = 636); history of CHD only (n = 742); and history of coexisting stroke and CHD (n = 220). Table 1 shows baseline characteristics of low-risk group and high-risk group. High-risk group was older, had greater frequencies of men, hypertension, diabetes mellitus, history of congestive heart failure, history of carotid endarterectomy, high-dose B vitamin treatment, and optimal treatment (level III), whereas MMSE score, systolic BP, serum levels of total cholesterol, LDL-C and HDL-C, and history of alcohol use were lower. Occurrence of major vascular events (20% vs 14.4%; $P < 0.001$), stroke (8.5% vs 7.9%; $P = 0.486$), and all-cause death (7.1% vs 4.9%; $P = 0.007$) were higher in high-risk group vs low-risk group (Fig. 1).

3.2. Effect of secondary prevention medication classes on vascular outcomes and death by risk category

Table 2 shows multivariate risk adjusted effect of combination treatment on 2-year risk of vascular outcomes and all-cause death by appropriateness strata. For high-risk group, when compared with level 0, the adjusted HR for major vascular events for level II and level III was 0.38 (95% CI, 0.17–0.85; $P = 0.018$) and 0.32 (95% CI, 0.14–0.70;

Table 1
Baseline characteristics of low-risk group and high-risk group.

	Low-risk (n = 2082)	High-risk* (n = 1598)	*P*
Age, years	65.6 ± 11.0	67.2 ± 10.5	<0.001
MMSE, score	27.0 ± 3.3	26.7 ± 3.4	0.023
Systolic blood pressure, mmHg	141.4 ± 18.8	140.1 ± 18.5	0.030
Body mass index, kg/m^2	28.3 ± 5.9	28.3 ± 5.4	0.810
Total cholesterol, mg/dL	206.0 ± 47.5	196.7 ± 45.1	<0.001
LDL-C, mg/dL	124.5 ± 41.0	118.5 ± 39.8	<0.001
Triglycerides, mg/dL	174.7 ± 179.7	175.5 ± 117.9	0.884
HDL-C, mg/dL	46.4 ± 15.3	44.0 ± 15.6	<0.001
Creatinine, mg/dL	1.09 ± 0.57	1.14 ± 0.60	0.019
Homocystein, μmol/L	14.1 ± 5.9	14.2 ± 6.0	0.530
Male	1225 (58.8)	1076 (67.3)	<0.001
Non-white	322 (15.5)	223 (14.0)	0.201
Hypertension	1710 (82.1)	1388 (86.9)	<0.001
Diabetes mellitus	556 (26.7)	545 (34.1)	<0.001
Smoker	361 (17.3)	261 (16.3)	0.420
Qualifying stroke NIHSS			0.921
0	695 (33.4)	542 (33.9)	
1–4	1219 (58.5)	925 (57.9)	
≥5	168 (8.1)	131 (8.2)	
History			
Congestive heart failure	57 (2.7)	136 (8.6)	<0.001
Carotid endarterectomy	106 (5.1)	141 (8.8)	<0.001
Alcohol use	1239 (61.4)	888 (56.9)	0.006
High-dose B vitamin	1002 (48.1)	825 (51.6)	0.035
Appropriateness strata			<0.001
Level 0	37 (1.8)	26 (1.6)	
Level I	122 (5.9)	73 (4.6)	
Level II	957 (46.0)	586 (36.7)	
Level III	966 (46.4)	913 (57.1)	

Values provided are number (%) or mean ± SD, as appropriate, unless otherwise stated. MMSE indicates mini-mental state examination; LDL-C, low-density lipoprotein cholesterol; HDL-C, high-density lipoprotein cholesterol; and NIHSS, National Institutes of Health Stroke Scale.

* Defined as history of stroke or coronary heart disease.

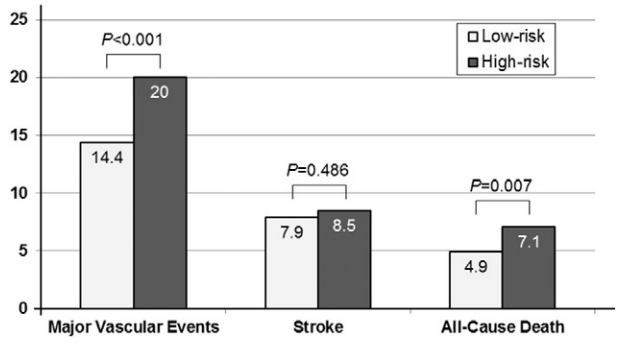

Fig. 1. Two-year vascular outcome events and all-cause death after a recent stroke (<120 days) by low- and high-risk groups. High-risk is defined as history of stroke or coronary heart disease.

$P = 0.004$), respectively. Risk of recurrent stroke was lower in the level III group (0.25, 0.08–0.85; $P = 0.026$). The adjusted HR for all-cause death was lower in the level III group (0.22, 0.06–0.78; $P = 0.019$) vs level 0. Compared to the least medication class (level 0), reverse-response relationships were observed between increasing appropriateness strata and outcome events ($P_{trend} = 0.004$ for major vascular events; $P_{trend} < 0.001$ for stroke; $P_{trend} = 0.003$ for all-cause death). For low-risk group, the adjusted HR for vascular outcomes or death was not significantly lower in the level III group, when compared with level 0.

The Kaplan–Meier curves in the high-risk group depicted low probability of major vascular events (Fig. 2A), stroke (Fig. 2B), and all-cause death (Fig. 3) over 2-year follow-up period by optimal combination treatment (level III) with $P = 0.025$, $P = 0.019$, and $P = 0.020$, respectively by log-rank test.

The interaction effect between vitamin dose and each secondary prevention medication level on risk of major vascular events, stroke, and all-cause death was not significant (high-dose B vitamin * level I, $P = 0.893/P = 0.723/P = 0.427$; high-dose B vitamin * level II, $P = 0.853/P = 0.586/P = 0.914$; and high-dose B vitamin * level III, $P = 0.759/P = 0.845/P = 0.925$, respectively; data not shown).

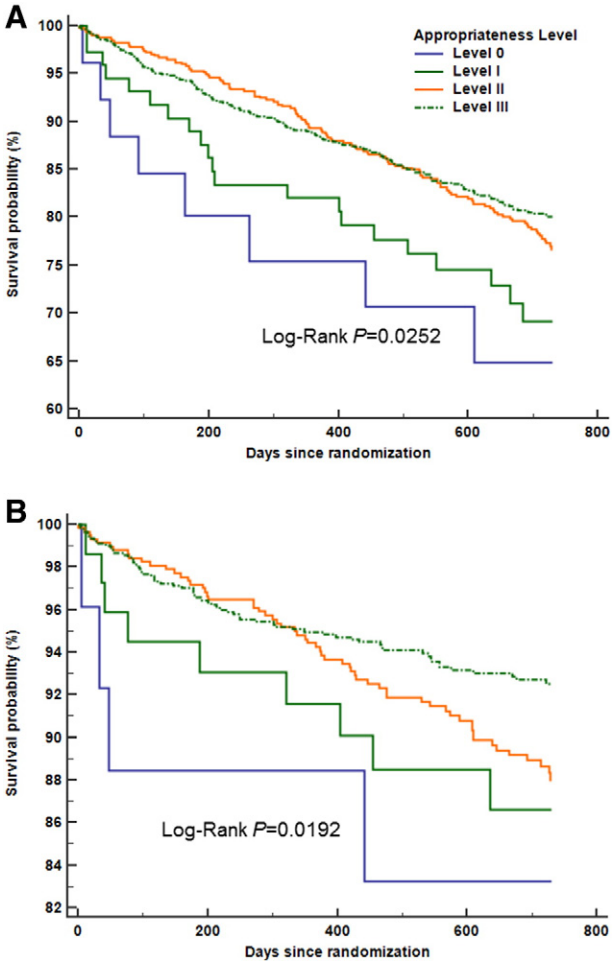

Fig. 2. Kaplan–Meier curves for the endpoint of major vascular events (A) and stroke (B) over 2 years in the high-risk* group after an ischemic stroke based on secondary prevention medication classes (levels 0 to III). Optimal combination drug treatment as level III diminishes risk of vascular events. *Defined as history of stroke or coronary heart disease.

Table 2
Multivariate risk adjusted effect of secondary prevention medication classes (levels 0 to III) on 2-year risk of vascular outcomes and death after a recent noncardioembolic stroke.

	Level of secondary prevention[c]			
	Level 0	Level I HR (95% CI)	Level II HR (95% CI)	Level III HR (95% CI)
High-risk* group	n = 26	n = 73	n = 586	n = 913
Major vascular events	1 [Reference]	0.43 (0.17–1.10)	0.38 (0.17–0.85)[b]	0.32 (0.14–0.70)[a]
Events, n (%)	8 (30.8)	21 (28.8)	122 (20.8)	169 (18.5)
Stroke	1 [Reference]	0.39 (0.10–1.60)	0.47 (0.14–1.57)	0.25 (0.08–0.85)[b]
Events, n (%)	4 (15.4)	9 (12.3)	60 (10.2)	63 (6.9)
All-cause death	1 [Reference]	0.29 (0.06–1.33)	0.38 (0.11–1.33)	0.22 (0.06–0.78)[b]
Events, n (%)	3 (11.5)	7 (9.6)	54 (9.2)	49 (5.4)
Low-risk group	n = 37	n = 122	n = 957	n = 966
Major vascular events	1 [Reference]	0.94 (0.34–2.56)	0.53 (0.21–1.33)	0.51 (0.20–1.28)
Events, n (%)	8 (21.6)	28 (23.0)	133 (13.9)	130 (13.5)
Stroke	1 [Reference]	0.69 (0.18–2.65)	0.49 (0.15–1.62)	0.54 (0.16–1.77)
Events, n (%)	6 (16.2)	11 (9.0)	72 (7.5)	75 (7.8)
All-cause death	1 [Reference]	2.37 (0.29–19.28)	1.43 (0.19–10.65)	0.66 (0.09–5.00)
Events, n (%)	2 (5.4)	15 (12.3)	57 (6.0)	29 (3.0)

Values provided are hazard ratios (HRs) with 95% confidence intervals (CIs). Results are risk adjusted for age, sex, systolic blood pressure, hypertension, diabetes mellitus, history of carotid endarterectomy, history of congestive heart failure, history of alcohol use, mini-mental state examination score, high-dose B vitamin therapy, serum levels of low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, creatinine, and homocysteine, body mass index, ethnicity, smoking, and stroke severity.

* Defined as history of stroke or coronary heart disease.

[a] $P < 0.01$.

[b] $P < 0.05$.

[c] $P = 0.004$ for lower outcome of major vascular events; $P < 0.001$ for lower outcome of stroke; $P = 0.003$ for lower outcome of all-cause of death with a linear trend test of adjusted HRs across appropriateness strata (levels 0 to III).

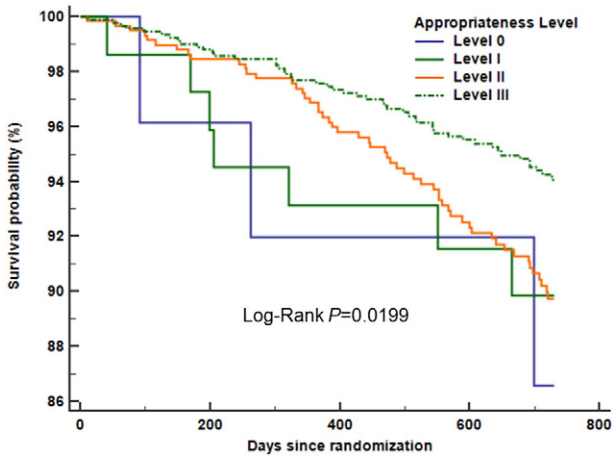

Fig. 3. Kaplan–Meier curves for the endpoint of all-cause death over 2 years in the high-risk* group after an ischemic stroke based on secondary prevention medication classes (levels 0 to III). Optimal combination drug treatment as level III reduces risk of death. *Defined as history of stroke or coronary heart disease.

4. Discussion

We observed that optimal combination treatment was significantly linked to lower rates of major vascular events, stroke, and all-cause death in a high-risk population of recent non-cardioembolic stroke patients. Only optimal combination prescription was related to substantive and significant relative risk reductions in major vascular events (68%), stroke (75%), and all-cause death (78%), when compared with level 0 (nonuse of drug classes). Major vascular events were also reduced by 62% in those with level II prescription. It should be noted that while high-risk patients with level III prescription had robustly lower vascular events and risk of dying over the 2-year period, they were at relatively higher risk of further cardiovascular events due to more risk factors and systemic comorbidities, when compared with low-risk group.

In this analysis, while the point estimates suggested benefit, optimal combination treatment in the low-risk group was not linked to a significantly lower risk of outcome events. This neutral result in the low-risk group might have been due to a relatively lower frequency of level III prescription or a higher prevalence of non-atherosclerotic stroke subtypes with comparatively fewer comorbidities. However, our findings should not be interpreted as a meaning that low-risk patients do not benefit from optimal combination treatment, but that high-risk patients more clearly benefit from this strategy. Also, it should be pointed out that optimal combination prescription itself should not be considered as an absolute secondary prevention, but as an essential part of a comprehensive stroke prevention strategy (e.g. smoking cessation, physical exercise, and diet control) [8].

While our primary study aim was to investigate the impact of optimal combination treatment (level III) on the reduction of major vascular events, we must point out that the lack of a significant difference in outcomes between non-optimal treatment (level I and level II) and no treatment at all (level 0) in the low- and high-risk groups, should not be viewed as no-treatment having the same effect as non-optimal treatment. Rather, our study was likely underpowered to investigate difference in outcomes between non-optimal treatment (level I and level II) and no treatment at all (level 0) in the low- and high-risk groups. To mitigate this challenge, we conducted a likelihood ratio analysis, which clearly revealed a decrease in vascular events with increasing treatment appropriateness levels.

This study has limitations. First, our findings cannot be necessarily extrapolated to the overall stroke population including those with cardioembolic stroke. Second, VISP was conducted over a decade ago, but baseline risk factor profiles and background treatments in VISP were not dissimilar to more contemporary large noncardioembolic stroke secondary prevention trials (i.e. PRoFESS) [9], and data from other clinical trials conducted from as far back as 20 years ago continue to steadily generate hypothesis-generating information for testing in future studies [10,11]. Finally, since the main objective of this study was to evaluate the class effect of prescribed medications on outcome events after an ischemic stroke, we did not consider the quantitative assessment of risk factor control. However, this study was strengthened by the prospective nature of data collection in VISP, rigorous trial procedures, and a fairly large sample size [5].

Despite the aforementioned limitations, our findings showed that optimal combination treatment was especially effective in high-risk patients, but it remains to be confirmed through future prospective studies.

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Disclosures

None.

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