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Effects of the vasopeptidase inhibitor, omapatrilat, in 723 patients with coronary heart disease

*Pacific study group**

Abstract

Introduction

Among individuals with a history of myocardial infarction (MI), higher levels of blood pressure (BP) are associated with increased long-term risks of death from coronary heart disease. Treatment with a BP-lowering regimen, based on omapatrilat may result in greater clinical benefits than treatment with a regimen based on a regular angiotensin-converting enzyme (ACE) inhibitor because of more favourable effects on the renin-angiotensin-aldosterone system.

Methods

Seven hundred and twenty-three clinically stable patients with a history of MI or unstable angina, and a mean entry BP of 134/77 mmHg, were randomised to six months treatment with omapatrilat 40 mg, omapatrilat 20 mg, or matching placebo.

Results

After six months, mean BP levels (systolic/diastolic) in the omapatrilat 40 mg group were reduced by 4.3/2.9 mmHg (95% confidence interval 1.3 to 7.2/1.2 to 4.6). Mean BP levels in the omapatrilat 20 mg group were reduced by 4.6/1.0 mmHg (1.6 to 7.6/-0.7 to 2.6) in comparison with the placebo group. Both doses of omapatrilat also produced significant decreases in plasma ACE activity and significant increases in levels of plasma renin activity, atrial natriuretic peptide, endothelin and homocysteine ($p < 0.05$ for all). Premature discontinuations were more frequent with omapatrilat than with placebo ($p < 0.001$ for 20 mg and 40 mg).

Conclusions

Omapatrilat produced changes in BP, neurohormone and biochemical parameters that were similar for the two doses. The long-term clinical implications of the observed effects are uncertain and a large-scale randomised trial would be required to reliably establish the effects of omapatrilat on the risks of major vascular disease events among patients with coronary heart disease.

Introduction

Among individuals with a history of myocardial infarction (MI), higher levels of blood pressure (BP) are associated with increased long-term risks of death from coronary heart disease,¹ an association that appears to be continuous across a wide range of BP levels. Randomised trials involving patients with a history of coronary heart disease have provided

clear evidence of the beneficial effects of agents that lower BP in both hypertensive and non-hypertensive individuals.^{2,3} In some studies, benefits have been achieved with only small changes in BP,⁴ suggesting that ancillary drug properties, such as inhibition of the renin-angiotensin system (RAS), may have important independent effects. Conversely, other evidence suggests that the sizes of the benefits conferred are proportional to the magnitude of the BP reduction achieved.³

Vasopeptidase inhibitors (VPIs) are a novel class of BP-lowering agent that appear to simultaneously inhibit the RAS and potentiate the natriuretic peptide system.⁵ Preliminary data from small, short-term trials suggest that the VPI, omapatrilat, may reduce BP more than regular angiotensin-converting enzyme (ACE) inhibitors.⁵ There is also some limited evidence that treatment with a regimen based on omapatrilat may result in greater clinical benefits than treatment with a regimen based on a regular ACE inhibitor (ACE-I).^{6,7} The Prevention with A Combined Inhibitor and Folic acid In Coronary heart disease (PACIFIC) Study was conducted to assess the effects of omapatrilat on BP and on neurohormone and biochemical parameters, and to assess treatment tolerability, among patients with a history of coronary heart disease. Using a factorial design, the study simultaneously investigated the effects of folic acid on homocysteine levels: the results for the folic acid comparisons have been reported separately.⁸

Materials and methods

Study participants

Participants were recruited to the trial from 28 hospitals in Australia and New Zealand. At each hospital, an ethics committee approved the conduct of the study and all participants provided written informed consent. Individuals were potentially eligible for inclusion in the trial if they had: (i) a history of acute MI or a hospital admission for the treatment or investigation of unstable angina two weeks or more prior to registration; (ii) a left ventricular ejection fraction (LVEF) of 40% or more; and (iii) a high risk of subsequent MI or coronary heart disease (CHD) death (estimated risk 3% per year or greater). Individuals were deemed to be at high risk if they had one or more of the following five characteristics: age 65 years or older; current cigarette smoking; a history of diabetes; more than one prior MI; or Canadian Cardiovascular Society angina grade 2 or higher.

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Exclusion criteria were: current treatment with an ACE-I or angiotensin II (Ang II) antagonist; a definite indication for, or contra-indication to, treatment with an ACE-I; a definite indication for, or contra-indication to, treatment with folic acid; a sustained systolic BP (SBP) > 180 mmHg or < 100 mmHg or a sustained diastolic BP (DBP) > 100 mmHg or < 65 mmHg; MI or unstable angina in the previous two weeks or clinical instability following a recent CHD event or myocardial revascularisation procedure; severe mental illness; recent epileptic seizure; current treatment with a potassium-sparing diuretic, anabolic steroids, colchicine or bile acid-binding resins; child-bearing potential; seriously abnormal laboratory test results; or any other life-threatening non-cardiac disease.

Design and study treatment

Prior to randomisation, all potentially eligible individuals received four-weeks of single-blind treatment with placebo-omapatrilat and placebo-folic acid. Individuals that successfully completed this run-in phase then received a test dose of 20 mg active omapatrilat. Those that tolerated the 20 mg test dose were then randomised, double-blind in a 3x3 factorial design, to one of three omapatrilat treatment groups (omapatrilat 40 mg, omapatrilat 20 mg or omapatrilat-placebo) and to one of three folic acid treatment groups (folic acid 2.0 mg, folic acid 0.2 mg or folic acid-placebo). Study treatment was assigned by a central computerised randomisation service. For participants assigned omapatrilat 40 mg or placebo, randomised treatment was initiated with omapatrilat 20 mg or placebo daily for two weeks, followed by omapatrilat 40 mg or placebo daily for the remainder of the six-month treatment period. Participants assigned omapatrilat 20 mg or placebo commenced immediately on this regimen. Follow-up visits were scheduled for one month, three months and six months after randomisation, with a final post-study visit at seven months.

Study outcomes

The primary outcome for the omapatrilat comparisons was BP. Secondary outcomes were neurohormone levels (plasma ACE, plasma renin activity [PRA], Ang II, aldosterone, neutral endopeptidase [NEP], atrial natriuretic peptide [ANP], aminoterminal ANP, brain natriuretic peptide [BNP], aminoterminal BNP, norepinephrine, epinephrine), and levels of plasma endothelin. Treatment tolerability assessed from the numbers discontinuing randomised study treatment was also a secondary outcome. The primary outcome for the folic acid comparisons was plasma homocysteine levels. All BP, neurohormone and biochemical measurements were made at trough drug levels. BP was measured at all visits in triplicate to the nearest 2 mmHg, using a standard mercury sphygmomanometer. Neurohormone and biochemical parameters were measured at baseline and at six months from samples of venous blood collected at a comparable time of day after the participant had fasted for at least four hours. Samples were collected and analysed using established methods.^{7,9,21}

Figure 1 Trial profile

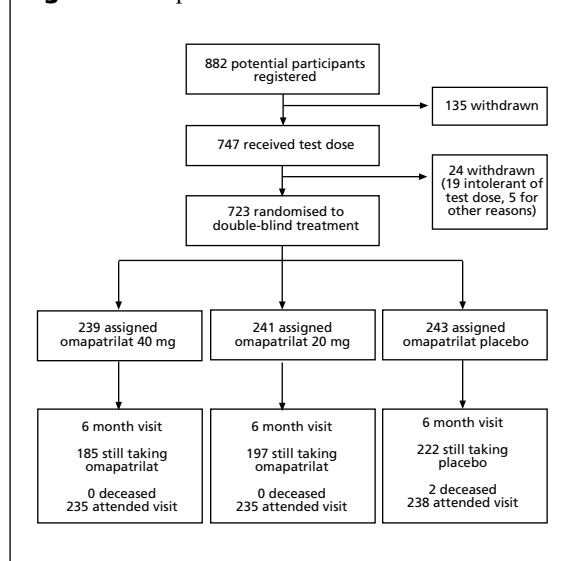


Table 1 Primary reasons for withdrawal before randomisation

Reason for withdrawal	n
Ejection fraction < 40%	36
Adverse event during run-in	26
Seriously abnormal blood test result	20
Participant decision	11
No blood sample for neurohormones	8
Poor adherence during run-in	8
Intolerant of 20 mg test dose of omapatrilat*	19
Hypotension	12
Angioedema	1
Other side-effect	6
Died during run-in period	3
Other reason	28
Total not randomised*	159

*Four other patients were judged to be intolerant of the test dose as a consequence of delayed adverse reactions to omapatrilat that occurred after randomisation (two episodes of syncope and one each of hypotension and diarrhoea)

†Five of the 159 individuals not randomised received the test dose of omapatrilat but were excluded prior to randomisation for reasons other than intolerance of the test dose

Statistics

The study sample size of 723 patients provided 80% power with $p=0.05$ to detect a 3.8/2.4 mmHg difference between each of the groups in the change in BP levels (SBP/DBP) from baseline to six months (assuming a standard deviation for changes in SBP of 15 mmHg and in DBP of 10 mmHg).²² All primary analyses were conducted according to the intention-to-treat principle. The effects of treatment on normally distributed data were tested using analysis of variance (ANOVA) to estimate main and interaction effects. A non-parametric conditional re-sampling test was used to test data that were not normally distributed.^{23,24} Possible effects of covariates on the treatment

Table 2 Effects of 20 mg omapatrilat test dose on blood pressure and heart rate [mean (standard error)]

	Systolic blood pressure (mmHg)	Diastolic blood pressure (mmHg)	Heart rate (bpm)
Baseline	132 (0.6)	76 (0.3)	63 (0.4)
1 hour	120 (0.6)	69 (0.3)	63 (0.4)
2 hours	115 (0.6)	68 (0.3)	63 (0.4)
3 hours	114 (0.6)	68 (0.3)	62 (0.4)

Table 3 Baseline characteristics of randomised participants

	Omapatrilat 40 mg (n=239)	Omapatrilat 20 mg (n=241)	Placebo (n=243)
Risk factors			
Age, years (SD)	67 (7.8)	68 (7.8)	68 (7.6)
Male (%)	197 (82)	201 (83)	192 (79)
Current smoker (%)	37 (15)	30 (12)	36 (15)
Body mass index, kg/cm ² (SD)	28 (4.1)	27 (3.8)	28 (4.8)
Ejection fraction (%)	58 (9.4)	56 (9.2)	58 (8.5)
Medical history			
Myocardial infarction (%)	181 (76)	185 (77)	157 (65)
Unstable angina (%)	135 (56)	126 (52)	159 (65)
CABG or PTCA (%)	76 (32)	74 (31)	79 (33)
Diabetes (%)	36 (15)	34 (14)	35 (14)
Drug treated hypertension	52 (22)	54 (22)	72 (30)
Current treatments			
Aspirin (%)	216 (90)	220 (91)	220 (91)
β-blocker (%)	136 (57)	143 (59)	167 (69)
Calcium antagonist (%)	32 (13)	26 (11)	43 (18)
Chronic nitrate (%)	105 (44)	87 (36)	109 (45)
HMG Co-A reductase inhibitor (%)	182 (76)	170 (71)	179 (74)

CABG = coronary artery bypass graft; HMG Co-A reductase inhibitor = 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor; PTCA = percutaneous transluminal coronary angioplasty.

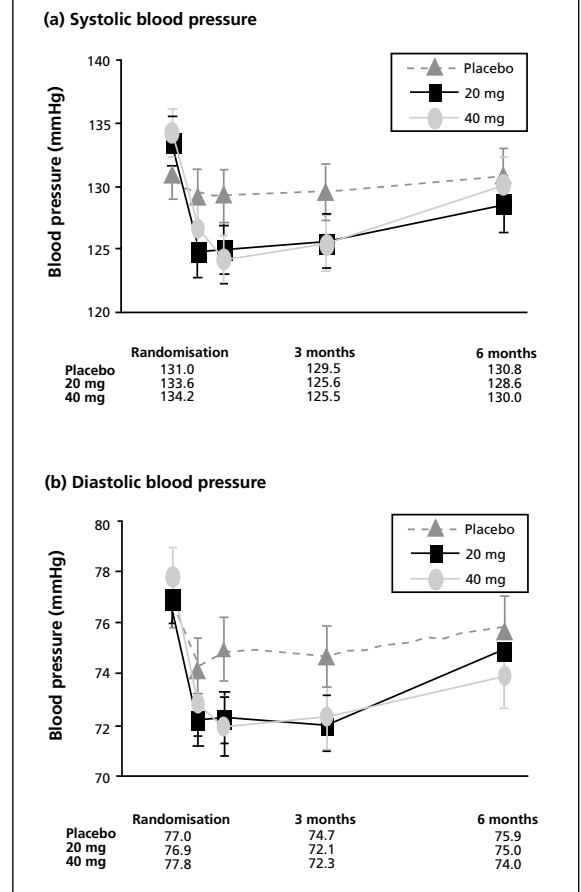
effects observed in the univariate analyses were investigated using analysis of covariance. All p-values were calculated from two-tailed tests of statistical significance.

Results

Registration, randomisation and follow-up

Eight hundred and eighty-two potentially eligible participants commenced the run-in phase. A total of 159 did not proceed to randomisation (Figure 1 and Table 1). Of the 723 randomised participants, 721 survived to the end of the scheduled six months of treatment and 708 (98%) attended the six-month follow-up visit. Among the 747 individ-

Figure 2 Mean systolic and diastolic blood pressure levels at randomisation and during follow-up (two weeks, one month, three months and six months) by randomised group. Error bars represent 95% confidence intervals



uals that received the 20 mg omapatrilat test dose, there was a mean decrease in SBP of 18 mmHg and a mean decrease in DBP of 8 mmHg after three hours (Table 2). Nineteen potential participants were intolerant of the test dose (Table 1) and were not randomised. The baseline characteristics of randomised participants are shown in Table 3 and Figure 2. One-quarter had a history of drug-treated hypertension and, in total, 68% were receiving agents that have BP-lowering effects (for hypertension or for other indications, such as angina).

Adherence to randomised treatment

Premature withdrawals from randomised treatment (Figure 1 and Table 4) were more common in each of the omapatrilat groups (40 mg, 22%; 20 mg, 18%) than in the placebo group (8%) (both p<0.001), but there was no significant difference between the two omapatrilat groups (p=0.2). Much of the excess of withdrawals in the omapatrilat groups was due to cough, dizziness or hypotension.

Effects of omapatrilat on blood pressure

There was a 4.3/2.9 mmHg (95% confidence interval 1.3 to 7.2/1.2 to 4.6) reduction in BP in the

Table 4 Principal reasons for premature discontinuation of randomised treatment

Principal reason for discontinuation	Omapatrilat 40 mg (n=239)	Omapatrilat 20 mg (n=241)	Placebo (n=243)
Cough	13	7	0
Dizziness	8	8	1
Hypotension	5	5	1
Angioedema	1	3	0
Participant decision	4	3	1
Other reason*†	23	18	16
Total discontinuations†	54	44	19

*Includes one participant taking placebo that experienced angioedema, for whom the cited principal reason for discontinuation was not angioedema

† Excludes two participants in the placebo group that died before completion of scheduled follow-up

omapatrilat 40 mg group compared with placebo ($p=0.005$ for SBP and $p<0.001$ for DBP) and a 4.6/1.0 mmHg (1.6 to 7.6/-0.7 to 2.6) reduction in BP in the omapatrilat 20 mg group compared with placebo ($p=0.003$ for SBP and $p=0.3$ for DBP). Over the same period, the reduction in BP in the omapatrilat 40 mg group compared with that in the omapatrilat 20 mg group was -0.3/1.9 mmHg (-2.7 to 3.7/0.3 to 3.6; $p=0.8$ for SBP and $p=0.02$ for DBP). The sizes of the reductions in SBP and DBP appeared smaller at six months than at three months (Figure 2), but for none of the comparisons did the differences reach conventional levels of statistical significance ($p>0.05$ for all).

The magnitude of the BP reduction did not appear to be related to initial levels of SBP or DBP ($p>0.6$ for both). Nor were there clear associations between most other patient characteristics and the size of the effects of treatment on BP ($p>0.3$ for age, gender, LVEF, ACE I/D polymorphism, angiotensinogen M235T polymorphism and concomitant therapy with another BP-lowering drug). Analyses that included a term for adherence to randomised treatment identified no interaction between adherence and the effects of study treatment on BP ($p>0.7$). Similarly, analyses of participant subgroups defined *post hoc* on the basis of full versus incomplete adherence to randomised therapy, failed to identify adherence as a determinant of the apparent difference in the effects of omapatrilat on BP after three months and six months of follow-up ($p>0.2$).

Effects of omapatrilat on neurohormones, endothelin and homocysteine

From baseline to six months, both doses of omapatrilat significantly reduced ACE activity and increased levels of PRA, ANP and endothelin, compared with placebo (Table 5). There were borderline significant decreases in BNP and aminoterminal BNP in the omapatrilat 40 mg group compared with placebo only. There were no clear differences between omapatrilat and placebo groups in

the changes in levels of Ang II, aldosterone, NEP activity, aminoterminal ANP, epinephrine or norepinephrine. Plasma homocysteine levels were significantly increased by both doses of omapatrilat (Table 5).

Discussion

The results of this study demonstrate a large effect of omapatrilat 20 mg on BP measured at peak drug levels following the initial test dose. However, the long-term effects measured at trough drug levels were more modest, and smaller than those reported by previous shorter-term studies of omapatrilat in patients with hypertension.^{5,25} While the low mean entry BP of study participants might be predicted to result in smaller absolute BP reductions, there was no evidence from this study of any association between entry BP levels and the size of the BP reductions observed. Moreover, neither withdrawal from study treatment nor the use of non-study BP-lowering drugs appeared to have an important influence on the estimates of treatment effect obtained.

Tolerability

The excess of premature withdrawals among omapatrilat-treated patients was due principally to cough, dizziness and hypotension. Each of these is a recognised adverse effect of agents that inhibit ACE.²⁶ There were six reported cases of possible angioedema, one at the time of the test dose and five during follow-up (one of which occurred in a patient receiving treatment with placebo). None of the cases of angioedema resulted in death or required endotracheal intubation. The rate of angioedema among patients treated with omapatrilat in the PACIFIC study appears similar to that observed in other studies of the drug.²⁷

Inhibitory effects on the renin-angiotensin system

Omapatrilat exerted significant effects on renin, the natriuretic peptides and endothelin. The observed decrease in ACE and increase in PRA are consistent with the established effects of ACE-Is.²⁸ The elevation in PRA indicates reduced levels of intra-renal Ang II (with loss of feedback inhibition), although no clear effect of treatment on systemic plasma Ang II levels was observed. This finding is consistent with the results of longer-term studies of ACE-Is²⁸ and with the anticipated effects of inhibition of NEP.²⁹ There was no observed effect of treatment on plasma NEP activity. However, this may be a consequence of the assay being of limited sensitivity and conducted at trough drug levels. An increase in ANP levels has been observed in previous studies of omapatrilat and pure NEP inhibitors.^{7,30,31} The increase in ANP in the absence of an increase in BNP is most likely a consequence of the much greater affinity of ANP for NEP and of the greater role of NEP in the breakdown of ANP. In addition, the fall in BP may have resulted in a reduction in BNP secretion (through unloading of the left ventricle) while a similar effect on ANP (through a reduction in atrial

Table 5 Effects of omapatrilat on neurohormone, endothelin and homocysteine levels

	Mean (standard error)			P value		
	Omapatrilat 40 mg	Omapatrilat 20 mg	Placebo	40 mg vs. placebo	20 mg vs. placebo	40 mg vs. 20 mg
ACE (IU/l)						
Baseline	23.5 (0.4)	23.7 (0.5)	23.4 (0.5)	<0.001	<0.001	0.3
6 months	11.5 (0.6)	12.7 (0.6)	23.1 (0.4)			
PRA (ng/ml/h)						
Baseline	0.82 (0.04)	0.79 (0.04)	0.86 (0.06)	<0.001	<0.001	0.04
6 months	2.21 (0.15)	1.82 (0.12)	0.88 (0.07)			
Angiotensin II (pmol/L)						
Baseline	7.5 (0.3)	7.5 (0.3)	7.3 (0.3)	0.3	0.9	0.3
6 months	8.4 (0.4)	7.9 (0.3)	7.8 (0.3)			
Aldosterone (pmol/L)						
Baseline	143.2 (5.2)	143.3 (5.0)	164.9 (7.5)	1.0	0.6	0.6
6 months	138.7 (7.2)	136.0 (5.6)	163.5 (7.5)			
NEP (pmol/L)*						
Baseline	0.79 (0.06)	0.85 (0.07)	0.78 (0.05)	0.2	0.9	0.3
6 months	0.74 (0.04)	0.86 (0.08)	0.81 (0.06)			
ANP (pmol/L)						
Baseline	15.6 (0.6)	15.3 (0.6)	15.1 (0.5)	0.002	0.05	0.2
6 months	17.7 (0.7)	16.8 (0.6)	15.2 (0.5)			
Aminoterminal ANP (pmol/L)						
Baseline	0.78 (0.03)	0.76 (0.03)	0.77 (0.03)	0.8	0.2	0.3
6 months	0.81 (0.03)	0.83 (0.03)	0.79 (0.03)			
BNP (pmol/L)						
Baseline	12.4 (0.6)	11.9 (0.5)	12.0 (0.5)	0.04	0.4	0.1
6 months	11.8 (0.5)	11.9 (0.5)	12.6 (0.6)			
Aminoterminal BNP (pmol/L)*						
Baseline	51.7 (3.3)	49.9 (2.9)	48.5 (2.8)	0.01	0.4	0.05
6 months	46.8 (2.8)	50.7 (3.2)	52.0 (3.5)			
Norepinephrine (pmol/L)						
Baseline	3193 (109)	3022 (84)	3327 (113)	0.2	0.09	0.7
6 months	3342 (105)	3258 (104)	3275 (99)			
Epinephrine (pmol/L)						
Baseline	204 (10.8)	190 (10.1)	200 (9.1)	0.9	1.0	0.9
6 months	199 (10.2)	184 (10.3)	197 (9.7)			
Endothelin (pmol/L)*						
Baseline	1.4 (0.03)	1.4 (0.03)	1.4 (0.03)	<0.001	0.005	0.2
6 months	1.6 (0.03)	1.5 (0.03)	1.4 (0.03)			
Homocysteine (micromol/L)*						
Baseline	10.6 (0.2)	11.1 (0.3)	11.2 (0.3)	<0.001	0.006	0.5
6 months	10.6 (0.2)	10.9 (0.3)	10.4 (0.3)			

See text for abbreviations. p-values calculated using a conditional resampling test of the differences between groups in changes from baseline to six months, except *: p-values calculated using ANOVA.

distending pressure) is less likely. The observed reduction in levels of aminoterminal BNP provides evidence of reduced secretion of BNP. Plasma catecholamine levels did not rise, in spite of the fall in BP, and this may reflect either baroreceptor resetting or sympathoinhibitory effects of cardiac peptides.

Increases in endothelin and homocysteine

The 10% increase in endothelin levels following treatment with omapatrilat therapy has not previously been documented and is not typical of the effects of ACE-Is.³² However, NEP is in part responsible for the degradation of endothelin and inhibition of NEP could therefore explain the observed increase.^{33,34} In a previous study conducted among patients with heart failure, there was a significant fall in endothelin I in patients receiving omapatrilat, 5–10 mg daily, (at which dose the drug is predominantly an inhibitor of ACE), compared with patients receiving omapatrilat 20–40 mg daily (at which dose inhibition of NEP is more pronounced).^{6,7} The effects of omapatrilat on plasma homocysteine were identified *post hoc*, but the 5–10% higher homocysteine levels among omapatrilat-treated participants are

unlikely to be the consequence of chance. Cross-reactivity of omapatrilat with the homocysteine assay is unlikely, but altered renal metabolism of homocysteine is a possible explanation.³⁵

Conclusions

This randomised trial is a large detailed study of the effects of a VPI, but while much new information is provided, the implications of the findings for the risks of major cardiovascular events remain uncertain. The BP-lowering effect would be anticipated to reduce the risk of major vascular events, as would the inhibitory effects on the RAS. In contrast, the increases in endothelin and plasma homocysteine might have adverse consequences. When published, the results of the Omapatrilat Cardiovascular Treatment Assessment Versus Enalapril (OCTAVE) Study, comparing omapatrilat and lisinopril, will provide more reliable information about the safety and tolerability of omapatrilat compared with a regular ACE-I. However, before omapatrilat could be recommended for patients with coronary heart disease, other large-scale, long-term studies would be required to assess the

comparative efficacy of omapatrilat and ACE-Is for the prevention of major vascular events.

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