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Modern fixed combinations of antihypertensive drugs in the treatment of arterial hypertension and obesity: can this comorbid pathology be effectively controlled?

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Aim. To assess the effect of azilsartan/chlortalidone and irbesartan/hydrochlorothiazide fixed combinations on office, daily peripheral and central blood pressure (BP), daily parameters of aortic stiffness and structural and functional state of the left ventricle in patients with arterial hypertension (AH) and obesity.

Material and methods. The study included 46 patients with hypertension and obesity aged 35 to 55 years. In the beginning of the study and after 6 months of treatment with azilsartan/chlortalidone (AZL/C) or irbesartan/hydrochlorothiazide (IRB/H) all patients underwent a comprehensive clinical and instrumental and laboratory examination, including a general examination with anthropometric measurements, office measurement of BP, electrocardiography, echocardiography, 24-hour BP monitoring with analysis of central BP and the main parameters of aortic stiffness, biochemical blood tests.

Results. Long-term use of two fixed combinations of sartan and diuretic was accompanied by a significant decrease of office and daily BP. However, in the AZL/C use, this change was more pronounced than in the IRB/H. Also, in the AZL/H group, a significantly larger number of patients reach a normalization of 24-hour BP profile. Both studied drugs significantly reduced central BP, which indicates their positive effect on aortic stiffness. However, a significant change in the daily pulse wave velocity determined by the Vasotens system was not detected. During therapy, in both groups, a decrease in left ventricular myocardial mass indexed by body surface area was revealed. It was more noticeable in the AZL/H group and when height indexed^{2,7}. In both groups, an insignificant decrease in creatinine level and an increase in glomerular filtration rate, more noticeable with the administration of AZL/H, were noted. There were no significant fluctuations in the level of uric acid and potassium, which confirms the safety of the use of the studied combinations in patients with AH and obesity.

Conclusion. According to studies, AH in obese patients is less well controlled than in patients with normal body weight. AZL/H and IRB/H are effective and safe drugs for the treatment of AH in obese patients. However, long-term treatment of AZL/H allows reaching a more pronounced decrease in peripheral and central BP, improving the structural and functional state of the left ventricular myocardium in comparison with IRB/H.

Key words: arterial hypertension, metabolically active obesity, azilsartan/chlortalidone, left ventricular geometry, central blood pressure, daily pulse wave velocity.

Conflicts of Interest: the study was carried out with the financial support of OOO Takeda Pharmaceutical, the study was sponsored by Society of Heart Failure Specialists.

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Obesity and associated cardiovascular diseases (CVDs) pose a serious public health threat. CVDs are the leading cause of death among obese patients. Arterial hypertension (AH) is one of the most closely related to obesity disease. According to the ESSE-RF study, in the group of patients with normal body weight the AH prevalence is 32,9% and 26,0% among men and women, in the group with overweight — 45,8% and 38,5%, in the group with class 3 obesity AH is revealed in 71,9ц% and 67,8% of cases [1]. Blood pressure (BP) control is an important requirement for successful AH treatment. Research shows that people with obesity have less controlled AH. Thus, in the study by Booth HP, et al. researchers analyzed data from 153,000 patients aged 30 to 100 in the UK [2]. As the body mass index (BMI) increased, the number of patients receiving combined antihypertensive therapy was found to be increasing. At the same time, the number of patients who reached the target BP levels decreased, becoming the lowest in class 3obesity (69% in normal weight, 51% in morbid obesity).

According to ESC/ESH Arterial Hypertension (Management of) Guidelines, most patients, with the exception of patients with stage 1 AH of low cardiovascular risk, are shown to be treated with two drugs using a fixed combination of angiotensin converting enzyme inhibitors (ACEI) or an angiotensin receptor antagonist (ARA) with calcium channel blocker (CCB) or diuretic [3]. According to recent studies, azilsartan/chlorthalidone (AZL/C) is an effective and currently the only fixed combination of ARA and thiazid-like diuretic. A multicenter study by Neutel J, et al. compared the efficacy and safety of fixed combinations of AZL/C and olmesartan/hydrochlorothiazide (OLM/H) in 837 patients with stage 2 AH over 18 years of age.

The follow-up period was 52 weeks. Both drugs were effective and safe in reducing blood pressure, but lower doses of the drug were used in the AZL/C group than in the OLM/H group to achieve target levels [4]. Similar data with the same drugs were obtained in study by Bakris G, et al. involving 153 patients with stage 3 chronic kidney disease (CKD) [5]. The effect of AZL/C on renal function was evaluated in rat with metabolic syndrome or diabetes mellitus (DM). The studied combination had more pronounced nephroprotective and anti-inflammatory properties than AZL or chlortalidone monotherapy [6, 7]. In most studies with AZL/C using, the effect of the drug on office and daily peripheral BP was studied. The purpose of our study was a comparative assessment of the influence of AZL/C (Edarbi Klo, Takeda, Japan) and a fixed combination of irbesartan/hypothiazide (IRB/H, Coaprovel, Sanofi, France) on the office, daily peripheral and central BP, daily parameters of aortic stiffness and structural and functional of the left ventricle (LV) in patients with AH and obesity with long-term treatment.

Material and methods

The study included 46 patients with AH and obesity at the age of 35 to 55 years. AH was diagnosed by office BP measurements (⩾140/90 mmHg), obesity was diagnosed with an increase in BMI >30 kg/m². The exclusion criterion was the presence of acute myocardial infarction (AMI), acute cerebrovascular accident (ACA), diabetes mellitus (DM), severe renal and hepatic failure in the history. The majority of patients (43%) receive combined antihypertensive therapy before inclusion in the study, 25% — monotherapy, 31% did not take any drugs. All patients signed informed consent for voluntary participation in the study.

The combination therapies were prescribed according to the instructions for use. For comparability of the study groups, the medications were prescribed in a strict sequence: the first patient included in the study was prescribed the original AZL/C, the second — the original IRB/H. Such a sequence of prescribing two fixed combinations was maintained in the following.

The general characteristics of patients are presented in Table 1. All patients at inclusion in the study and after 6 months of therapy were carried out a comprehensive clinical, instrumental and laboratory examination, including general examination with anthropometric measurements, office BP measurement, echocardiography, 24-hour monitoring with the analysis of central BP and the main parameters of aortic stiffness.

BP measurement. The office BP measurement was carried out upon inclusion in the study, after 1, 3 and 6 months of therapy following a 10-minute sitting period using an Omron 5 automatic BP monitor. The first measurement was excluded from the analysis and the mean value between the 2nd and 3rd measurement was determined. Between visits, patients performed a BP self-monitoring using an automatic BP monitor 2 times a day (in the morning and evening), followed by a mean value between the 2nd and 3rd measurements (the first of which was excluded), which was recorded in a diary.

24-hour BP monitoring was carried out when included in the study and after 6 months of therapy using the BPLab system. The following indicators were analyzed: average daily, day and night values of systolic BP (SBP), diastolic BP (DBP), pulse pressure (PP), type of daily curve, day and night variability of SBP and DBP.

Table 1

General characteristics of the patients included in the study

Parameter	AZL/C (n=23) group	IRB/H (n=23) group
Age (years)	46,4±7,0	48,8±5,5
Sex	males. 13 (56%) females 10 (44%)	males 12 (52%) females 11 (48%)
Waist (sm)	males 113,1±12,9 females 110,6±10,9	males 113,1±12,3 females 104,8±10,3
Waist/hip width	males 0,98±0,07 females 0,95±0,09	males 0,98±0,06 females 0,89±0,06
Waist/height	0,64±0,06	0,64±0,07
AH stage, n (%)	1 — 11 (48%) 2 — 12 (52%)	1 — 13 (57%) 2 — 10 (43%)
SBP (mm Hg)	152,4±12,5	152,5±10,6
DBP (mm Hg)	100,2±9,7	100,2±8,0
Dyslipidemia, n (%)	15 (75%)	14 (70%)
Total cholesterol (mmol/L)	5,7±0,9	5,6±1,0
LDL (mmol/L)	3,6±0,8	3,4±0,7
Triglycerides (mmol/L)	2,1±0,9	1,8±0,9
Microalbuminuria, n, (%)	10 (43%)	8 (35%)
Creatinine (μmol/L)	86,1±16,4	84,9±12,3
GFR (ml/min/1,73 m2)	94,8±13,0	95,5±9,9

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure, LDL — low density lipoproteins, HDL — high density lipoproteins, GFR — glomerular filtration rate.

Aortic stiffness analysis. All patients were analyzed for aortic stiffness and central pulse wave within 24 hours using BPLab Vasotens system when including in the study and after 6 months of antihypertensive therapy. The following parameters were estimated: average values of central SBP, DBP and PP, aortic augmentation index (AIxao), pulse wave velocity (PWV).

Echocardiography. Echocardiography was performed on a VIVID 7 apparatus of General Electric (USA) in accordance with the guidelines of the American Society of Echocardiography (ASE) and the European Association of Cardiovascular Imaging (EACVI). The basic linear and volume indicators of the LV, LV mass (LVM), followed by indexing onto the body surface area or height, the relative thickness (RT) were determined and calculated. Violation of LV geometry was determined by LVM and RT. The linear and volume dimensions of the atria and the function of the right ventricle were also evaluated.

Laboratory tests. When included in the study, all patients underwent a biochemical blood test with an assessment of the lipid profile, glucose, creatinine, uric acid, electrolytes. To assess the safety of the studied combined drugs, the level of creatinine, uric acid and blood electrolytes was determined again after 3 and 6 months of antihypertensive therapy.

Statistical analysis. Statistical processing of the material was carried out with the help of the "Stastica 10.0" (Statsoft, USA) software package. When choosing the method of data comparison, the normality of distribution of a characteristic in subgroups was taken into account, considering the Shapiro-Wilk test. Under normal distribution, the mean value and standard deviation were calculated. The null hypothesis when comparing groups deviated at a significance level of $<0,05$. The comparability of the formed groups was assessed by quantitative indicators using the Student's t-test, by qualitative indicators using the Pearson's chi-squared test or the Fisher's exact test. In multiple comparisons, one-way ANOVA test was used.

The study was conducted in accordance with Good Clinical Practice standards and the principles

Table 2

Динамика офисного АД на фоне терапии исследуемыми препаратами

Visit	AZL/C (n=23) group		IRB/H (n=23) group	
	SBP (mm Hg)	DBP (mm Hg)	SBP (mm Hg)	DBP (mm Hg)
Inclusion	152,4±12,5	100,2±9,7	152,5±10,6	100,2±8,0
Visit 2 (1 month)	129,9±15,0*	87,0±9,5*	131,3±15,2*	88,5±9,7*
Visit 3 (3 months)	129,7±14,6*	86,8±9,5*	134,9±13,9*	91,9±9,6*
Visit 4 (6 months)	122,9±8,8*	84,2±6,9*	133,4±12,3*#	91,9±7,8*#

Note: * — p<0,05 in comparison with the inclusion visit, # — p <0,05 in comparison with the AZL-X group.

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure.

of the Declaration of Helsinki. The study protocol was approved by the Inter-university Ethical Committee. Prior to inclusion in the study, written informed consent was obtained from all participants.

This article is a fragment of the Prospective observational stUdy of aZilsartan/chlortalidone compared with irbesartan/hydrochlorothiaZide combination therapy in patients with arteriaL hypertension and obEsity in routine clinical practice (PUZZLE), organized by its authors. This prospective study, including the publication of its preliminary results with the above aim, objectives and design, has been approved by international experts and registered on the clinicaltrials.gov website under the number: NCT03006796.

Results

The study included patients of middle age (47,6±6,25 years) with 1-2 stage AH and metabolically active form of obesity, which was confirmed by anthropometric data, the presence of metabolic disorders in patients, in particular, dyslipidemia, which was found in most (75%) patients. Microalbuminuria (MAU) from 30 to 100 mg/dL was observed in 18 (39%) patients. No renal dysfunction was detected. When comparing the data of the patients included in the study, there were no significant differences between the group of AZL/C and IRB/H.

Over the entire follow-up period 4 visits were made, during which the office BP measurement was carried out: an inclusion visit, after 1, 3 and 6 months of therapy (Table 2). Against the background of AZL/C and IRB/H intake, a reliable decrease in the office SBP and DBP was found during the month, by an average of 22,4 and 12,3 mm Hg, respectively. After 3 months, BP in the AZL/C group was stabilized, while the IRB/H group showed an increase in BP in some patients, which required an increase of the drug dose. By the end of the observation (after 6 months of therapy), a significantly lower BP was observed against the background of AZL/C intake than in the IRB/H group (122,9 and 84,2 mm Hg vs. 133,4 and 91.9 mm Hg, respectively).

Table 3

The number of patients reached the target BP level during treatment

Visit	AZL/C (n=23) group	IRB/H (n=23) group
Visit 2 (1 month)	18 (78%)	15 (65%)
Visit 3 (3 months)	21 (91%)	18 (78%)
Visit 4 (6 months)	21 (91%)	19 (83%)

During the observation period, 21 (91%) patients reached the target values of office BP (<140/90 mm Hg) in the group of AZL/C, and 19 (83%) patients in the IRB/H group (Table 3). In the majority of patients, BP normalization occurred during the 1st month of therapy. In the IRB/H group after 3 months of therapy, 7 patients (30%) needed a dose correction to achieve the target BP levels.

For comparison, in the AZL/C group dose correction was nor requires on the 3st visit.

When analyzing the data of 24-hour BP monitoring (Table 4), in both groups, a significant decrease in the average daily, day and night values of SBP and DBP was observed, on average, by 13,5 and 11,2 mm Hg. for SBP and DBP during the day. In the analysis of daily BP variations on the background of 6-month antihypertensive therapy in both groups the increase in the number of patients with normalized daily BP profile (dipper) was revealed. However, in the AZL/C group such patients were much more than in the IRB/H group (26% of patients with dipper type before treatment, 61% — after treatment). In both groups there was a tendency to decrease the variability of SBP and DBP during day and night time, but no

Table 4

Changes in 24-hour BP monitoring in patients taking studied drugs

Parameters		AZL/C (n=23) group		IRB/H (n=23) group	
		Before treatment	After treatment	Before treatment	After treatment
av. dly SBP		140,5±12,0	126,1±6,7*	139,4±11,5	128,7±7,4*
av. dly DBP		98,1±10,8	78,7±6,5*	89,1±5,2	82,1±4,2*
av. SBP day		143,1±11,3	128,7±7,7*	143,6±10,2	134,6±8,4*
av. DBP night		93,7±10,2	82,6±9,1*	93,5±5,7	87,5±5,3*
av. SBP day		134,3±13,6	119,8±11,0*	123,8±12,9	114,2±7,9
av. DBP night		85,3±12,5	74,5±10,2*	76,7±6,8	70,1±5,7*
Type	dipper non-dipper over-dipper n.peaker	6 (26%) 13 (57%) 1 (4%) 3 (13%)	14 (61%)* 8 (35%) 1 (4%) 0	10 (43%) 11 (48%) 2 (9%) 0	15 (66%) 7 (30%) 1 (4%) 0
Variability SBP (day)		14,1±3,8	13,2±3,1	13,6±3,1	11,7±3,4
Variability SBP (night)		12,1±4,3	11,6±3,6	11,8±4,3	10,8±2,4
Variability BBP (day)		10,8±3,5	10,2±3,0	11,2±2,5	10,8±2,3
Variability BBP (night)		9,9±3,5	8,7±3,3	10,8±4,2	9,0±2,6

Note: * — p<0,05 in comparison with the data before treatment.

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure.

Table 5

Changes of central blood pressure and aortic stiffness parameters in patients taking studied drugs

Parameters	AZL/C (n=23) group		IRB/H (n=23) group	
	Before treatment	After treatment	Before treatment	After treatment
av. dly SBP (mm Hg)	131,1±10,9	116,6±7,3*	129,9±11,3	118,0±6,4*
av. dly DBP (mm Hg)	94,3±10,5	82,5±7,9*	92,9±5,1	84,4±4,3*
av. SBP day (mm Hg)	132,4±10,6	119,0±8,5*	134,2±10,7	123,1±7,2*
av. DBP day (mm Hg)	96,6±10,3	84,9±8,8*	97,7±5,7	89,8±5,5*
av. SBP night (mm Hg)	126,5±13,2	111,7±10,9*	118,6±12,6	106,6±8,2
av. DBP night (mm Hg)	87,9±12,8	76,7±10,2*	81,5±5,6	72,3±5,2*
av. dly Aix (%)	26 (18-30)	16 (12-33)	28 (19-34)	14 (9-23)
av. dly PWV (m/s)	10,4±1,0	10,3±1,1	9,9±1,1	9,8±1,4

Note: * — p <0.05 in comparison with the visit before treatment.

Abbreviations: SBP — systolic blood pressure, DBP — diastolic blood pressure, AIx — augmentation index, PWV — pulse wave velocity.

significant differences between the groups were revealed.

Against the background of 6-month combination therapy, in both groups there was a significant decrease in the central daily, day and night SBP and DBP, on average, by 13,2 and 10,2 mm Hg for SBP and DBP per day (Table. 5). One of the parameters of aortic stiffness (AIxao) also decreased in both groups; however, there was no significant difference between the groups. In addition, in both groups, there was no

Table 6

Changes of EchoCG parameters in patients taking studied drugs

Parameters		AZL/C (n=23) group		IRB/H (n=23) group	
		Before treatment	After treatment	Before treatment	After treatment
LVMI m		96,7±11,2	95,6±9,4	97,8±9,3	96,0±9,1
LVMI f		87,6±9,1	86,7±8,8	86,1±8,9	85,7±9,0
LVMH m		47,5±5,1	43,2±4,8	41,9±5,4	46,1±4,3
LVMH f		43,7±5,3	40,7±5,4	38,2±4,9	39,4±5,3
LV geometry	normal CR CH EH	6 (26%) 11 (49%) 4 (17%) 2 (8%)	12 (53%)* 7 (30%) 4 (17%) 0	8 (35%) 10 (43%) 3 (14%) 2 (8%)	11 (49%) 7 (30%) 4 (17%) 1 (4%)
LVEDVI (ml/m^2)		59,2±8,4	56,9±8,2	59,8±8,9	60,5±9,2
LVEF, %		63,7±5,7	64,4±4,4	62,7±4,2	61,3±4,9
LAVI (ml/m^2)		28,6±5,9	28,3±4,6	26,3±5,8	25,8±5,9
RAVI (ml/m^2)		22,4±5,9	20,7±3,9	20,7±5,2	22,1±3,9
LV basal diameter (sm)		3,5±0,3	3,6±0,4	3,4±0,4	3,6±0,5
TAPSE		2,2±0,2	2,3±0,3	2,3±0,4	2,4±0,3

Note: * — p<0,05 in comparison with the visit before treatment.

Abbreviations: LVMI — left ventricular mass index (f — female, m — male), CR — concentric remodeling, CG — concentric hypertrophy, EG — eccentric hypertrophy, LVEDVI — left ventricular end-diastolic volume index, LVEF — LV ejection fraction, LAVI — left atrium volume index, RAVI — right atrium volume index, TAPSE — tricuspid annular plane systolic excursion.

Table 7

Changes of creatinine levels and GFR in patients taking studied drugs

Visit	AZL/C (n=23) group		IRB/H (n=23) group	
	Creatinine (μmol/L)	GFR (ml/min/1.73 m^2)	Creatinine (μmol/L)	GFR (ml/min/1.73 m^2)
Inclusion	85,5±15,2	95,6±17,1	84,9±12,3	95,5±9,9
Visit 3 (3 months)	73,5±10,9	102,4±15,8	85,3±11,2	94,6±8,1
Visit 4 (6 months)	78,1±10,9	102,4±13,2	82,1±11,3	101,1±4,5

Abbreviation: GFR — glomerular filtration rate.

Table 8

Changes of laboratory parameters in patients taking studied drugs

Visit	AZL/C (n=23) group		IRB/H (n=23) group	
	Uric acid (μmol/L)	Potassium (mmol/L)	Uric acid (μmol/L)	Potassium (mmol/L)
Inclusion	383,8±41,1	4,4±0,5	340,8±45,3	4,7±0,4
Visit 3 (3 months)	367,2±43,1	4,6±0,4	365,4±31,6	4,3±0,6
Visit 4 (6 months)	352,9±43,0	4,5±0,3	374,5±44,2	4,4±0,3

significant change in the daily PWV during therapy, which may be related to the peculiarities of determining this indicator by Vasotens system.

When included in the study, all patients were given recommendations to reduce body weight: a diet with a calorie restriction of food to 1,500 kcal/day in women and 1800 kcal/day in men, regular exercise up to 30 minutes a day, changes in eating behavior (reduction of the portion size, restriction of food intake in the evening and night, regular frequent meals in small amounts.

In both groups there was a decrease in body weight by 7,2±2,8 kg on average. At the analysis of the structural and functional state of myocardium according to EchoCG data in dynamics (Table 6) LVM was indexed not only on the body surface area (BSA), but also on growth2,7. On the background of antihypertensive therapy in both groups there was a slight LVMi decrease.

In the analysis of LVMi dynamics, a more pronounced decrease was found in the AZL/C group, but there were no significant differences between the groups. Also, in the group of AZL/C, more patients had normalization of LV geometry: 2 patients from the subtype "eccentric hypertrophy" and 4 patients from the subtype "concentric remodeling" went to the "norm". The number of patients with LV concentric hypertrophy before and after treatment did not change in the group of AZL/C. Number of patients with LV concentric hypertrophy in the group of IRB/H increased by 1 patient, which may be related to insufficiently long period of observation and progression of AH.

In both groups, no significant dynamics of the LV, RV and atria volume were revealed.

To assess the safety of combined drugs, as well as their nephroprotective effect, we analyzed the laboratory data of patients when included in the study, after 3 and 6 months of therapy. During the whole period of observation in both groups there was a tendency to decrease the creatinine level and increase glomerular filtration rate (GFR), calculated by CKD-EPI formula (Table 7). It was more noticeable against the background of AZL/C intake. No significant variations of urine acid and potassium levels were found in both groups during therapy (Table 8), which confirms the safety of the studied combinations in patients with AH and obesity.

Discussion

An important requirement for successful AH treatment is the control of BP levels. Most patients require at least two antihypertensive drugs to achieve the target BP level. In our study, a comparative assessment of the efficacy and safety of AZL/C and IRB/H in patients with AH and obesity was carried out against a background of 6-month therapy. In the analysis of office measurements and 24-hour BP monitoring it was found that both combinations effectively reduce peripheral and central BP, but in the group of AZL/C this reduction was stronger and was achieved by taking lower doses of the drug. Possibly, the efficacy of AZL/C in patients with obesity is explained by nephroprotective and anti-inflammatory effects of azilsartan, as well as the ability to increase the sensitivity of tissues to insulin. The study by Kumar K, et al. involved 305 patients with AH and DM 2 with excess body weight (BMI 26,6±3,8 kg/m²) [8].

One hundred fifty two patients received AZL, the rest ones received telmisartan for 6 months. In the AZL group a more significant decrease in BP, as well as in the level of glucose and glycated hemoglobin (HbA1C), was observed than in the telmisartan group, which, according to the authors, is associated with the pleiotropic effect of the drug [9]. In our study, a stable BP decrease on the background of AZL/C intake resulted in a more significant decrease in LV myocardium mass and improvement of its structural and functional state than in the IRB/H group. However, no significant change in aortic stiffness parameters was revealed. This may be due to the fact that our study analyzed 24-hour PWV, and its significant variations during the day did not allow to reveal the dynamics on the background of treatment. In our study, prolonged use of AZL/C and IRB/H was not accompanied by hyperuricemia and electrolyte disorders. A more significant decrease in creatinine and an increase in GFK levels was found in the AZL/C group. Also in this group, 6 (26%) patients showed a decrease or complete absence of MAU, which may indicate the nephroprotective effect of the drug. In the IRB/H group, there were only 2 (8%) such patients.

Conclusion

According to research data, AH patients with obesity are less controlled than patients with normal weight. Combination therapy, particularly with ARA and diuretics, can help achieve targeted BP levels. AZL/C and IRB/H are effective and safe drugs for the treatment of AH in obese patients. Prolonged treatment of AZL/C allows to achieve more stable reduction of peripheral and central BP, improvement of structural and functional state of LV myocardium, than treatment of IRB/H.

Conflicts of Interest: the study was carried out with the financial support of OOO Takeda Pharmaceutical, the study was sponsored by Society of Heart Failure Specialists.

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