Original Article

Initial expierence with Deprescribing in physically active older adults with post-COVID syndrome in Kazakhstan: A Cohort Study Investigating Transition to Simplified Treatment Regimen

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ABSTRACT

Background
Arterial hypertension (AH) and post-COVID synrome poses a rising challenge in low and middle-income countries, with uncertain prevalence in Kazakhstan's older adults population.

Objectives
This study investigates the effectiveness and safety of transitioning older adults patients (65 and older) from multiple antihypertensive medications to a "single tablet" strategy, aiming to evaluate its effect on patient conidion and identify factors influencing dose adjustments.

Design
A prospective cohort study with a follow-up of 8 week.

Participants
There were enrolled 98 patients, categorizing them by age groups 65-74 years and 75 and older.

Intervention
One-moment isolated deprescribing of hypotensive drugs to "one tablet" therapy.

Measurements
Endpoints were assessed over three visits in eight weeks, utilizing statistical analysis with significance set at $p < 0.05$.

Results
Older patients exhibited a trend of higher education, lower smoking rates, and lower average weight. Transitioning to a single-tablet strategy led to a significant reduction in hypertensive crises and adverse events. While therapy adherence improved initially, it decreased by 10% by the 8th week. Factors influencing therapy changes were identified through subgroup analysis.

Conclusion
This study provides valuable insights into transitioning older adults patients to a "single tablet" strategy, underscoring the importance of personalized approaches based on identified influencing factors.

Keywords
deprescribing, hypertension, older adults, antyhypertensive treatment.

INTRODUCTION

Countries with low and middle-income levels suffer more from arterial hypertension (AH). From 2000 to 2010, the prevalence of AH in high-income countries decreased by 2.6%, while in low and middle-income countries, it increased by 7.7% [1]. The International Mobility in Aging Study (IMIAS) focusing on older adults individuals revealed that the prevalence of AH ranged from 53.4% to 83.5% in five assessed cities: Kingston (Canada), Saint-Hyacinthe (Canada), Tirana (Albania), Manizales (Colombia), and Natal (Brazil) [2]. Although more than 80% of patients received treatment, the lowest therapy effectiveness rates were observed in Albania and Brazil [2]. This raises questions about therapy adherence in developing countries, including Kazakhstan.

European clinical guidelines describe six strategies for assessing patient adherence to treatment, including a simplified therapy model using a single administration of long-acting medications [3]. Some studies suggest that reducing blood pressure (BP) lowers the risk of stroke and cardiovascular complications in patients over 80 years old with stage 2 AH (systolic BP [SBP] >160 mm Hg) and stage 1 AH with high cardiovascular risk [4,5].

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However, these studies, like many others [6,7], were primarily conducted on non-frail older adults patients with low comorbidity and polypharmacy rates. At the same time, significant BP reduction and/or prescribing multiple antihypertensive drugs (AHDs) may be harmful to the older adults, increasing the risk of all-cause mortality [8,9] or leading to drug-induced orthostatic hypotension [10]. Observational studies also indicate that more intensive BP reduction is associated with an increased risk of falls in older adults individuals [11]. Post-COVID-19 is a clinical syndrome characterized by the onset or persistence of systemic and organ symptoms after the acute phase of COVID-19 infection, lasting more than 12 weeks and not explained by an alternative diagnosis [12]. Symptoms typically include persistent fatigue, shortness of breath, cognitive difficulties (such as brain fog and trouble concentrating), musculoskeletal pains, sleep disturbances, mood disorders (such as depression and anxiety), and various other symptoms that may affect respiratory, cardiovascular, gastrointestinal, neurological, dermatological, or other systems [13, 14].

In the context of conflicting data, a decision was made to conduct a study involving older adults patients using isolated deprescribing [15] – transitioning from multi-drug therapy or monotherapy to combination therapy in a single tablet, following European recommendations [3] to evaluate the effect of this method on physically active older adults with post-COVID syndrome.

MATERIALS AND METHODS

Design: A prospective cohort study was planned to assess the effectiveness and safety of transitioning from multiple antihypertensive medications to "single tablet" therapy in older adults (65-74 years), old (75-89 years), and long-lived (90 and older) patients. The study also aimed to identify factors leading to dose adjustments.

Participants: Inclusion criteria included (1) patients aged 65 and older with post-COVID syndrome as defined in the clinical protocols of the Republic of Kazakhstan [16], (2) expressing a desire to adjust their therapy, (3) The Short Physical Performance Battery (SPPB) 10 points or more, (4) Mini–Cog 4 points or more, (5) signed informed consent. Exclusion criteria were (1) insufficient autonomy for independent visits to the active longevity center; (2) presence of severe psychiatric or neurological disorders; (3) major cardiovascular events and transient ischemic attacks within the past 3 years leading to hospitalization; (4) ischemic heart disease (IHD) and/or heart failure (HF) stages III-IV according to NYHA; (5) life expectancy less than 6 months; (6) patients who missed appointments or failed to communicate within 7 days of missing a dose; (7) any serious adverse event requiring hospitalization. Patient recruitment took place at the active longevity center in Almaty from December 1, 2022, to January 31, 2023, and patients were scheduled for the first visit (week 0).

Intervention: At the study onset, patients' current medications were deprescibed by replacing, and therapy was initiated using the "single tablet" strategy. Patients were transitioned from multiple antihypertensive medications to a "single tablet" therapy (combination of valsartan, amlodipine, and/or hydrochlorothiazide) according to the study protocol. The switch was simultaneous, with patients advised to start the new medication the morning after the initial examination. Patients taking beta-blockers continued their medication. The three-component therapy was prescribed only to patients not taking beta-blockers.

Endpoints: The primary endpoint was the presence of hypertensive crises. Secondary endpoints included (2) blood pressure levels at visits; (3) satisfaction with therapy effect; (4) presence of adverse events unrelated to underlying conditions; (5) therapy adherence level; (6) therapy changes (escalation or de-escalation); (8) Hospital Anxiety and Depression Scale (HADS) assessment. Patient assessment occurred at three visits: at enrollment (week 0), at the 4th week, and at the 8th week. A subgroup of patients requiring therapy adjustment was planned for identification, followed by cohort analysis to determine response peculiarities.

Statistical Analysis: Statistical analysis and data visualization were performed using the R 4.3.2 statistical computing environment (R Foundation for Statistical Computing, Vienna, Austria). Descriptive statistics were presented as observed number of observations (relative frequency) for qualitative variables and mean (standard deviation) and median (1st and 3rd quartiles) for quantitative variables. Mann-Whitney test was used for comparing groups for quantitative variables, Fisher's exact test for comparing groups for categorical variables. Wilcoxon test was used to study the dynamics of quantitative variables, and generalized mixed-effects regression models and mixed models of proportional odds were used for analyzing the dynamics of binary and ordinal variables, respectively. Differences were considered statistically significant at $p < 0.05$.

RESULTS

The study included 98 patients with a mean age of 66.0 (62.3; 74.0) years. Two groups were identified: those under 75 years (N=77) and those 75 years and older (N=21), within which the tolerability of therapy transition was assessed. There was a trend indicating that older adults patients were more educated in terms of "higher education" (p = 0.121), smoked less (p = 0.116), and had a lower average weight compared to younger patients (Table 1).

Table 1. Demographics, history and anthropometry

Characteristic	All patients	Age <75 N = 77	≥ 75 years N = 21	p
Gender				0.228
woman	77/98 (78.6%)	58/77 (75.3%)	19/21 (90.5%)	
man	21/98 (21.4%)	19/77 (24.7%)	2/21 (9.5%)	
Hypertension				0.274
Grade 1	2/98 (2.0%)	2/77 (2.6%)	0/21 (0.0%)	
Grade 2	43/98 (43.9%)	34/77 (44.2%)	9/21 (42.9%)	
Grade 3	50/98 (51.0%)	40/77 (51.9%)	10/21 (47.6%)	
undefined	3/98 (3.1%)	1/77 (1.3%)	2/21 (9.5%)	
HR (bpm)	78.0 (73.3; 80.0)	78.0 (74.0; 80.0)	76.0 (73.0; 84.0)	0.502
SBP (mm.Hg.)	163.5 (160.0; 174.8)	165.0 (160.0; 174.0)	160.0 (153.0; 180.0)	0.52
DBP (mm.Hg.)	92.0 (90.0; 100.0)	92.0 (90.0; 100.0)	91.0 (90.0; 95.0)	0.243
Age	66.0 (62.3; 74.0)	64.0 (62.0; 68.0)	79.0 (75.0; 84.0)	<0.001*
Height (cm)	166.0 (162.0; 170.0)	168.0 (162.0; 171.0)	164.0 (160.0; 169.0)	0.189
Weight (cm)	79.0 (70.0; 87.0)	80.0 (72.7; 87.0)	73.0 (65.0; 84.0)	0.047*
Waist circumference (cm)	96.0 (84.3; 109.0)	96.0 (85.0; 110.0)	95.0 (82.0; 101.0)	0.267
BMI	28.3 (25.9; 30.8)	28.5 (25.9; 31.0)	27.5 (24.8; 28.7)	0.099
BMI ≥25	83/98 (84.7%)	68/77 (88.3%)	15/21 (71.4%)	0.084
BMI ≥30	29/98 (29.6%)	25/77 (32.5%)	4/21 (19.0%)	0.289
CHD	47/98 (48.0%)	37/77 (48.1%)	10/21 (47.6%)	>0.999
Heart Failure	28/98 (28.6%)	19/77 (24.7%)	9/21 (42.9%)	0.111
Stroke	9/98 (9.2%)	7/77 (9.1%)	2/21 (9.5%)	>0.999
DM 2 type	9/98 (9.2%)	7/77 (9.1%)	2/21 (9.5%)	>0.999
CKD	9/98 (9.2%)	8/77 (10.4%)	1/21 (4.8%)	0.679
Vein disease	5/98 (5.1%)	2/77 (2.6%)	3/21 (14.3%)	0.064
Other chronic diseases	50/98 (51.0%)	37/77 (48.1%)	13/21 (61.9%)	0.328
Number of AH drugs	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)	3.0 (2.0; 4.0)	0.693
ACE inhibitors	73/98 (74.5%)	61/77 (79.2%)	12/21 (57.1%)	0.051*
ARBs	16/98 (16.3%)	12/77 (15.6%)	4/21 (19.0%)	02.74
CCBs	42/98 (42.9%)	30/77 (39.0%)	12/21 (57.1%)	0.146
ß-blockers	66/98 (67.3%)	50/77 (64.9%)	16/21 (76.2%)	0.434

Endpoints:

It was observed that after transitioning to single-tablet therapy, there was a statistically significant decrease in the number of hypertensive crises in all age groups (p<0.001), as well as the number of adverse events (p<0.001). Table 2 shows the number of events from visit to visit, and the number of complaints from different organ systems significantly decreased. Regarding the endpoints of "satisfaction with the clinical effect of therapy," a statistically significant trend (p<0.001) towards increased satisfaction was noted by the third visit (Table 3).

Table 2. Endpoints: hypertensive crises and adverse events.

Hypertensive crises	1st visit	2nd visit	3rd visit	p
Patients	40/98 (40.8%)	7/98 (7.1%)	6/98 (6.1%)	<0.001
Age <75	29/77 (37.7%)	4/77 (5.2%)	3/77 (3.9%)	<0.001
Age ≥75	11/21 (52.4%)	3/21 (14.3%)	3/21 (14.3%)	<0.001
Adverse events				
All patients	86/98 (87.8%)	20/98 (20.4%)	18/98 (18.4%)	<0.001
Age <75	66/77 (85.7%)	15/77 (19.5%)	16/77 (20.8%)	<0.001
Age ≥75	20/21 (95.2%)	5/21 (23.8%)	2/21 (9.5%)	<0.001

Table 3: Satisfaction with clinical effect.

Age	Value	1st visit	2nd visit	3rd visit	p
Patients	completely no	11/93 (11.8%)	–	–	<0.001
	rather no than yes	15/93 (16.1%)	4/98 (4.1%)	4/98 (4.1%)	
	neither satisfied nor dissatisfied	52/93 (55.9%)	12/98 (12.2%)	6/98 (6.1%)	
	yes rather than no	15/93 (16.1%)	43/98 (43.9%)	21/98 (21.4%)	
	completely yes	–	39/98 (39.8%)	67/98 (68.4%)	
Age <75	completely no	9/74 (12.2%)	–	–	<0.001
	rather no than yes	12/74 (16.2%)	3/77 (3.9%)	3/77 (3.9%)	
	neither satisfied nor dissatisfied	38/74 (51.4%)	9/77 (11.7%)	6/77 (7.8%)	
	yes rather than no	15/74 (20.3%)	35/77 (45.5%)	18/77 (23.4%)	
	completely yes	–	30/77 (39%)	50/77 (64.9%)	
≥ 75 years	completely no	2/19 (10.5%)	–	–	<0.001
	rather no than yes	3/19 (15.8%)	1/21 (4.8%)	1/21 (4.8%)	
	neither satisfied nor dissatisfied	14/19 (73.7%)	3/21 (14.3%)	–	
	yes rather than no	–	8/21 (38.1%)	3/21 (14.3%)	
	completely yes	–	9/21 (42.9%)	17/21 (81%)	

In assessing treatment adherence (Table 4), it was found that 20.6% of patients used medications irregularly at the study entry. By the second visit, therapy adherence in the overall population increased by 37.2%, but by the 8th week, it decreased by 10% ($p<0.001$). A shift towards non-adherence to medication intake once a week was registered. Subgroup analysis revealed that patients aged 75-89 demonstrated a higher level of adherence compared to early older adults patients (Table 4).

Table 4: Assessment of patient adherence to treatment.

Age group	Value	1st visit	2nd visit	3rd visit	p
All patients	usually takes medications only when BP rises	20/97 (20.6%)	–	–	<0.001
	violates 1-2 times per week	8/97 (8.2%)	3/98 (3.1%)	4/98 (4.1%)	
	violates <1 time per week	18/97 (18.6%)	6/98 (6.1%)	16/98 (16.3%)	
	usually adheres to the regimen	51/97 (52.6%)	88/98 (89.8%)	78/98 (79.6%)	
	violates >2 times per week	–	1/98 (1%)	–	
< 75 years	usually takes medications only when BP rises	16/76 (21.1%)	–	–	<0.001
	violates 1-2 times per week	7/76 (9.2%)	3/77 (3.9%)	4/77 (5.2%)	
	violates <1 time per week	12/76 (15.8%)	6/77 (7.8%)	12/77 (15.6%)	
	usually always adheres to the regimen	41/76 (53.9%)	68/77 (88.3%)	61/77 (79.2%)	
≥ 75 years	usually takes medications only when BP rises	4/21 (19%)	–	–	<0.001
	violates 1-2 times per week	1/21 (4.8%)	–	–	
	violates <1 time per week	6/21 (28.6%)	–	4/21 (19%)	
	usually always adheres to the regimen	10/21 (47.6%)	20/21 (95.2%)	17/21 (81%)	
	violates >2 times per week	–	1/21 (4.8%)	–	

When evaluating patient groups requiring a change in therapy, it was found that the following patient groups were prone to therapy change (Table 5): (1) older age, (2) patients with higher education, (3) non-smokers, and (4) those with a higher number of other chronic diseases. In this group, the BMI was lower, and patients with a BMI > 25 were less common. By the 8th week (3rd visit), patients in the "therapy change" group recorded fewer adverse events (27.1% vs. 5.1%, $p < 0.007$), comparable satisfaction with the clinical effect ($p = 0.233$), and therapy adherence with a slight trend towards better compliance ($p = 0.215$).

Table 5. Demographics and clinical characteristics of patients who required an upward or downward change in drug therapy.

Characteristics	No changes, N = 59	Changes, N = 39	p
Gender			0.617
woman	45/59 (76.3%)	32/39 (82.1%)	
man	14/59 (23.7%)	7/39 (17.9%)	
Age	65.0 (62.0; 70.5)	72.0 (64.0; 75.0)	0.031*
Age group			0.081
<75 years	50/59 (84.7%)	27/39 (69.2%)	
≥75 years	9/59 (15.3%)	12/39 (30.8%)	
Patient's occupation			0.528
Retired	37/59 (62.7%)	30/39 (76.9%)	
salaried employee	11/59 (18.6%)	3/39 (7.7%)	
disability pension	7/59 (11.9%)	4/39 (10.3%)	
housewife/homemaker	3/59 (5.1%)	1/39 (2.6%)	
own business	1/59 (1.7%)	1/39 (2.6%)	
Patient's education			<0.001*
secondary	13/59 (22.0%)	2/39 (5.1%)	
special secondary	29/59 (49.2%)	9/39 (23.1%)	
incomplete higher education	0/59 (0.0%)	1/39 (2.6%)	
higher education	17/59 (28.8%)	27/39 (69.2%)	
Smoking			0.006*
never smoked	30/59 (50.8%)	32/39 (82.1%)	
doesn't smoke, used to smoke	21/59 (35.6%)	5/39 (12.8%)	
active smoker	8/59 (13.6%)	2/39 (5.1%)	
Smoking history	29/59 (49.2%)	7/39 (17.9%)	0.002*
Height (cm)	168.0 (161.0; 171.0)	165.0 (163.5; 169.5)	0.867
Weight (kg)	82.0 (73.5; 88.0)	73.0 (67.5; 85.0)	0.046*
Waist circumference (cm)	96.0 (85.0; 109.5)	96.0 (81.0; 105.0)	0.547
BMI	28.5 (26.3; 31.1)	26.8 (24.9; 29.1)	0.04*
BMI ≥25	55/59 (93.2%)	28/39 (71.8%)	0.008*
BMI ≥30	20/59 (33.9%)	9/39 (23.1%)	0.269
CHD	34/59 (57.6%)	13/39 (33.3%)	0.024*
HF	18/59 (30.5%)	10/39 (25.6%)	0.654
Stroke	7/59 (11.9%)	2/39 (5.1%)	0.31
DM 2 type	7/59 (11.9%)	2/39 (5.1%)	0.31
CKD	8/59 (13.6%)	1/39 (2.6%)	0.082
Vein disease	4/59 (6.8%)	1/39 (2.6%)	0.645
Other chronic diseases	20/59 (33.9%)	30/39 (76.9%)	<0.001*

Anxiety and depression were assessed longitudinally. Following deprescribing, depression scores in patients remained unchanged, while a statistically significant reduction in anxiety was observed across the entire population from visit to visit. The decrease in anxiety scores across the whole group was -1 (-2; 0) <0.001, in the group <75 years old -1 (-2; 0) <0.001, and in the group ≥75 years old 6 (5; 8) 5 (4; 8) -0.5 (-1.2; 0) 0.046

DISCUSSION

Interpretation: This study successfully described the tolerability of transitioning from multiple medications to a single-tablet strategy for the older adults population with post-COVID syndrome in Kazakhstan. Factors contributing to a better tolerance of the transition were identified, including patient age, smoking status, higher education, and body mass index. Education was associated with age, making it challenging to determine the direction of the influencing factors. However, after therapy adjustment and dose selection for the patient in all age groups, better treatment adherence was observed than demonstrated at the study entry. In comparison with data from other countries, systematic non-adherence was recorded in 28.8% of patients compared to rates of 41.6% and 31.5% in the UK and the Czech Republic, respectively [17]. It is worth noting that adherence decreased by 10% by the third visit, whereas in the meta-analysis by Naderi SH et al., adherence decreased by 0.15 percentage points per month (P = 0.07) and was not associated with age or whether patients paid for their tablets [18].

Notably, changes in therapy were needed in an older group of patients (p=0.031), more educated (p<0.001) and less lifetime smokers (p=0.006). This may be due to a more sensitive attitude to the state of their own body. At the same time, a change of therapy was needed in slimmer patients (p=0.046 by weight and p=0.04 by BMI) with lower prevalence of CHD (p=0.024) and more other chronic diseases (p<0.001).

Improvement in patients' mental state was also demonstrated following deprescribing and transitioning to a single-pill therapy strategy. This may underscore deficiencies in the provision of primary medical care outside of experimental conditions. This study is the first to examine groups of younger elderly patients and an older age group with post-COVID syndrome and factors influencing therapy adjustment following intervention. These parameters and the results obtained will assist physicians in better addressing patient concerns about their health.

Study Limitations

A limitation of this study was the smaller number of older adults individuals aged 75-89, which could have affected the statistical power of the study. The specific replacement algorithm, used in studies on medication withdrawal by D. Garfinkel et al. [19,20] or in the DANTE study [21,22], was not employed, however, prognostic factors for the necessity of therapy revision after transitioning from one type of antihypertensive therapy to another were identified. Another growth point is the assessment of different transition algorithms from one drug to another, with a rational focus on the early transition period — the first and second weeks. In terms of assessing therapy adherence quality, it was noted that there are no universal and reliable methods [23-25], and the group did not come closer to improving the technology of this aspect. Nonetheless, the observed improvement in adherence contributes to the prevention of associated diseases [3, 26-32].

PERSPECTIVES

Areas for future research include improving the methodology for maintaining patient adherence and incorporating elements of comprehensive geriatric assessment.

Authors's contribution:

Data gathering and idea owner of this study: **Kudabaeva Venera**

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Writing and submitting manuscript: **Kudabaeva Venera**

Editing and approval of final draft: **Kudabaeva Venera**

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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