

# Potentially Inappropriate Medication Use in Older Adults Intensive Care Patients According to TIME-to-STOP Criteria

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## Abstract

**Objective:** It was aimed in this study, to determine the prevalence and pattern of potentially inappropriate medication (PIM) use according to TIME-to-STOP criteria in older adults hospitalized in the intensive care unit (ICU). In addition, the results were compared with the results of our previous study, evaluated by 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list.

**Materials and Methods:** In this descriptive study, the data of patients aged 65 and over (n=139) hospitalized in the University Hospital ICU between 8 June 2020 and 11 January 2021, were evaluated retrospectively. The relationship between dependent and independent variables was evaluated with chi-square, Mann-Whitney U and t-test analyses.

**Results:** The number of patients with at least one PIM use according to TIME-to-STOP criteria was 67 (48.2%) [80.6%, 59.7%, 48.2% in Beers, STOPP/v2 and EU(7)-PIM list, respectively]. PIM use showed no significant difference in terms of demographic and clinical characteristics. The groups causing the highest rates of PIM use were antipsychotic, propulsive and sedative-hypnotic drugs. The presence of PIM use and prognosis showed no relationship; mortality was significantly higher in patients using midazolam and digoxin.

**Conclusion:** According to TIME-to-STOP criteria, at least one PIM use was detected in approximately half of the older adults hospitalized in the ICU. In TIME-to-STOP criteria and 3 other screening criteria, there were differences between the prevalence of PIM, the drugs regarded as PIM or the PIM evaluation criteria. It is considered that there is a need to extend the scope of TIME-to-STOP criteria for ICU patients.

**Keywords:** Potentially inappropriate medication, intensive care unit, older adults, TIME-to-STOP criteria, explicit criteria

## Introduction

"Potentially inappropriate medication (PIM) use" was defined as using the drugs having a greater risk of harm in older adults than the expected benefit, which should be avoided if safer alternatives are available (1). Various criteria were developed for the evaluation of PIM use in the older adults and to guide physicians in selecting safe drugs in the clinical practice: Explicit (criteria-based) and implicit (judgment-based) criteria (2).

Physician's clinical evaluation is considered by implicit criteria, while evaluating prescriptions (3). Explicit criteria however, provide information and guidance on optimal drug use by presenting lists of drugs that should be avoided (4). The first

of such criteria developed for this purpose is "Beers criteria", defined by the American Geriatrics Society in 1991 (5).

Since then, many countries developed their own PIM use criteria. In Europe, STOPP/START criteria, EU(7)-PIM list, NORGE-PNH criteria, PRISCUS List; in Brazil CBMP-II criteria; in China, Chinese PIM criteria are some of those (6-11). Although there are many studies to date, conducted especially with Beers criteria and STOPP/START criteria in our country, considering differences in diagnosis-treatment guidelines, prescribing habits and the drug market, PIM use criteria specific to Turkey is required. Criteria Set of Turkish Inappropriate Medication Use in the Elderly (TIME-to-START and TIME-to-STOP), based on STOPP/START criteria,

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was established under the leadership of the Rational Drug Use Study Group of the Turkish Academic Geriatrics Society (12). It was developed by a multidisciplinary team of experts using the "Delphi technique". Thus, TIME criteria was enabled to be used not only in Turkey but also in other countries, especially in Europe. The criteria were presented in Turkish with a view to guide the non-geriatrician physicians while planning treatment for older adults in daily clinical practice and to make it easy to understand. Furthermore, a mobile application was developed so that healthcare professionals could easily access TIME criteria at any time (4).

Older adults ICU patients are more frail and have more comorbidities with respect to other patients. On the other hand, treatment protocols can greatly vary during ICU stay due to acute development of the diseases and their critical nature, where many drugs are used, typically for a short period of time (13). Moreover, the involvement of several physicians in treatment, with insufficient coordination between them and insufficient time for consultation may also lead to increased PIM use in older adults in the ICUs (14). Several studies conducted with this patient group using different criteria revealed the prevalence of PIM use as 48-98% (15-18).

In our previous study, a prospective study on older adults hospitalized in the ICU, we determined the prevalence of PIM use as 80.6%, 59.7% and 48.2%, according to 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list, respectively (18). In the present study, analyzing our previous study data according to the recently published TIME-to-STOP criteria. We aimed to determine a) the prevalence of PIM use in ICU patients and affecting factors, b) the drug groups most frequently evaluated as PIM, c) the relationship between the 28-day mortality rates and the length of stay in the ICU with PIM use. Another aim was to compare the PIM use results obtained by TIME-to-STOP criteria in this study with the results of our previous study, evaluated by 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list.

## Materials and Methods

This is a cross-sectional study. The data of our previous study (data of 139 patients aged 65 and over, hospitalized in Dokuz Eylül University Research and Application Hospital Internal Medicine ICU and Anesthesia ICU between 8 June 2020-11 January 2021) were evaluated retrospectively (18).

Evaluated data of patients: demographic characteristics (age, gender, body mass index, number of comorbidities), administration of mechanical ventilation (MV) and/or renal replacement therapy (RRT), mortality data (yes/no), length of ICU stay (days), laboratory findings (serum creatinine, GFR, sodium, potassium) and medication use data (active ingredients, daily dose and use number), Charlson Comorbidity Index (predicts one-year mortality), Glasgow Coma Scale (evaluates

the state of consciousness by scoring responses to eye/verbal/motor stimuli), acute physiology and chronic health evaluation II score (APACHE II, evaluates the disease severity) and mortality (death occurred in the first 28 days after ICU admission).

PIM use was evaluated by TIME-to-STOP criteria for drugs used by patients during their ICU stay (12). Polypharmacy was defined as the use of 5 or more medications.

## Statistics

Descriptive statistics were implemented for the demographic data of each hospitalization of the patients and the presence of PIM use. Results were given as number (n), percentage (%) and mean (standard deviation). The relationship between the dependent variable (presence of PIM use) and independent variables (demographic data, clinical characteristics) was evaluated by chi-square analysis. Independent variables were analyzed in two different groups according to the median values.

The relationship between the presence of PIM use, drugs, and 28-day mortality was evaluated by chi-square analysis and Fisher's Exact test. The relationship between the presence of PIM use and the average number of days of stay in the ICU was evaluated by using the Student's t-test for parametric data and the Mann-Whitney U test for non-parametric data. All data were analyzed by the SPSS-24 (SPSS INC., Chicago, IL, USA) statistical program and  $p < 0.05$  was considered statistically significant.

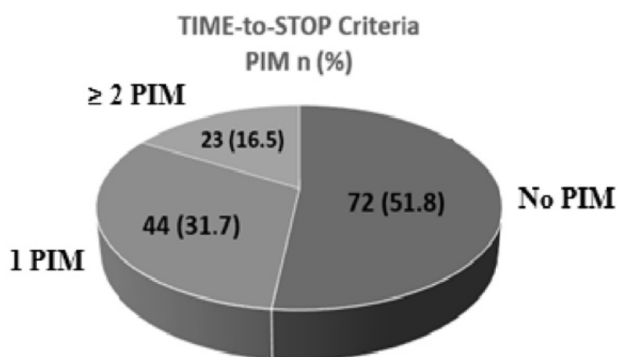
The research was initiated after the approval of the Non-Interventional Clinical Research Ethics Committee of Dokuz Eylül University and carried out in accordance with the principles of the Declaration of Helsinki.

## Results

Mean age of 139 patients included in the study was  $76.7 \pm 7.7$  (65-102) years and 51.1% (n=71) of them were male. Respiratory system diseases was the most common diagnosis of hospitalization, with a rate of 38.1%. MV support was used in 89.2% (n=124) of the patients. Mean length of ICU stay was  $12.2 \pm 9.9$  days. Polypharmacy occurred in 90.6% (n=126) of the patients. Mortality occurred in 32.4% patients in this period.

Patients with at least one PIM use according to the TIME-to-STOP criteria was 48.2% (n=67) (Figure 1). There was no statistically significant difference between the presence of PIM use and demographic and clinical characteristics, according to TIME-to-STOP criteria, ( $p > 0.05$ ) (Table 1). Polypharmacy was not statistically significantly affecting the presence of PIM according to TIME-to-STOP criteria ( $p = 0.057$ ).

According to TIME-to-STOP criteria, the most common drugs evaluated as PIM were antipsychotics (quetiapine or haloperidol)



**Figure 1.** Potentially inappropriate drug use (PIM use) in elderly patients (n=139) hospitalized in the intensive care unit, according to TIME-to-STOP criteria

**Table 1. Factors affecting PIM use according to TIME-to-STOP criteria**

	TIME-to-STOP criteria Presence of PIM use (n=67)	p-value
<b>Age (years) (n)</b>		
65-74 (65)	32 (49.2)	0.925
75-84 (50)	23 (46.0)	
≥85 (24)	12 (50.0)	
<b>Gender (n)</b>		
Female (68)	34 (50.0)	0.678
Male (71)	33 (46.5)	
<b>Body mass index (n)</b>		
<25 (62)	29 (46.8)	0.763
≥25 (77)	38 (49.4)	
<b>Mechanical ventilation (n)</b>		
Yes (124)	58 (46.8)	0.333
No (15)	9 (60.0)	
<b>Renal replacement therapy (n)</b>		
Yes (26)	13 (50.0)	0.839
No (113)	54 (47.8)	
<b>Charlson comorbidity index (n)</b>		
≤6 (65)	28 (43.1)	0.294
>6 (74)	39 (52.7)	
<b>Glasgow Coma scale (n)</b>		
≤9 (70)	33 (47.1)	0.801
>9 (69)	34 (49.3)	
<b>APACHE II (n)</b>		
≤22 (70)	28 (40.0)	0.052
>22 (69)	39 (56.5)	
<b>Number of drugs (n)</b>		
≤10 (70)	29 (41.4)	0.107
>10 (69)	38 (55.1)	

PIM: Potentially inappropriate medication, the relationship between the dependent and independent variables was evaluated by chi-square analysis

in 26.6% (n=37), propulsives (metoclopramide) in 25.2% (n=35) and sedatives-hypnotics (midazolam) in 7.2% of the patients (Figure 2).

According to TIME-to-STOP criteria, no significant relation was found in the 28-day mortality rate and length of ICU stay in the presence of PIM use (Table 2). As for the drugs evaluated as PIM according to TIME-to-STOP criteria, mortality was significantly higher in patients using midazolam and digoxin (Table 3). There was no significant difference in terms of length of ICU stay. There was no significant relation between polypharmacy and the 28-day mortality rate or length of ICU stay (p>0.05).

**Comparison of the PIM use results obtained by the TIME-to-STOP criteria with the results of our previous study, evaluated by the 2019 Beers, STOPP/v2 criteria and EU(7)-PIM List (18).**

One or more PIM use was determined in 48.2% of the patients by TIME-to-STOP criteria, in 80.6% by Beers criteria, in 59.7% by STOPP/v2 criteria and in 48.2% by EU(7)-PIM List (Supplement 1).

The presence of PIM use was not associated with demographic and clinical features according to TIME-to-STOP criteria, while receiving RRT as well as high number of drugs were the common variables significantly affecting the presence of PIM use according to the other three criteria (Supplement 2).

Antipsychotic drugs were common to all four criteria, ranking among the top three PIM. The most common drugs evaluated as PIM in intensive care patients were: Enoxaparin (29.5% of patients), metoclopramide (25.2% of patients), and antipsychotics (haloperidol or quetiapine, 24.5% of patients), according to the 2019 Beers criteria. Furthermore, benzodiazepine and opioid combinations, having clinically significant drug-drug interaction potential and should be avoided according to the Beers criteria, were used in 58.3% of the patients. According to STOPP/v2 criteria, 26.6% of the patients used haloperidol or quetiapine, 20.9% enoxaparin and 18.0% amiodarone, which were evaluated as PIM. According to EU(7)-PIM list, drugs evaluated as PIM at most were amiodarone in 23.7% of the patients, metoclopramide in 19.4%, and haloperidol in 10.8% (Supplement 3).

According to four criteria, there was no significant difference between 28-day mortality rate of the patients with and without PIM use. The length of ICU stay was significantly longer in the presence of PIM use, only in 2019 Beers criteria (Supplement 4).

**Discussion**

This is the first study evaluating prevalence of PIM use in older adults hospitalized in the ICU, by the TIME criteria. We found PIM prevalence as 48.2% according to TIME-to-STOP criteria. This value was lower than the PIM prevalence we found by the 2019 Beers and STOPP/v2 criteria in our previous study, but similar to the PIM prevalence we found by EU(7)-PIM list. However, there

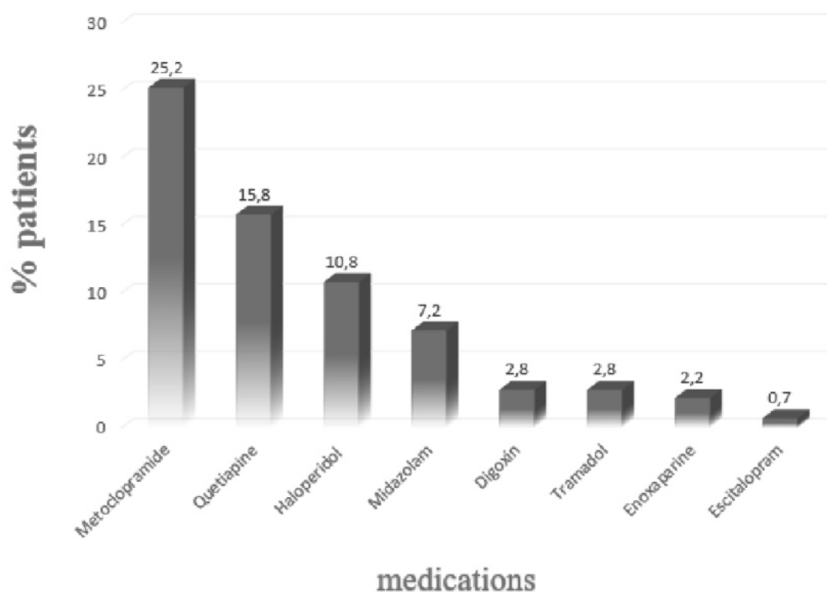


Figure 2. The most common drugs evaluated as PIM in elderly patients hospitalized in the intensive care unit, according to the TIME-to-STOP criteria

**Table 2. The relationship between the PIM use presence and 28-day mortality and length of ICU stay, according to TIME-to-STOP criteria**

		Mortality n (%)	p-value	Length of ICU stay (day) mean (SD)	p-value
TIME-to-STOP criteria	PIM (n=67)	26 (38.8)	0.743	12.6 (10.9)	0.590
	No PIM (n=72)	26 (36.1)		11.7 (9.1)	

PIM: Potentially inappropriate medication, the relationship between the presence of PIM use and 28-day mortality was evaluated by chi-square analysis. The relationship between the presence of PIM use and the average number of days of stay in the ICU was evaluated by using the Student's t-test

**Table 3. The relationship between the drugs evaluated as PIM and 28-day mortality, according to TIME-to-STOP criteria**

PIM use according to TIME-to-STOP criteria	Mortality n (%)		p-value
Metoclopramide	Yes (n=35) No (n=114)	15 (42.9) 37 (35.6)	0.441
Quetiapine	Yes (n=22) No (n=117)	6 (27.3) 46 (39.3)	0.284
Haloperidol	Yes (n=15) No (n=124)	3 (20.0) 49 (39.5)	0.140
Midazolam	Yes (n=10) No (n=129)	8 (80.0) 44 (34.1)	<b>0.006</b>
Digoxin	Yes (n=4) No (n=135)	4 (100.0) 48 (35.6)	<b>0.018</b>
Tramadol	Yes (n=4) No (n=135)	1 (25.0) 51 (37.8)	0.603
Enoxaparin	Yes (n=3) No (n=136)	2 (66.7) 50 (36.8)	0.556

PIM: Potentially inappropriate medication, the relationship between the presence of PIM use, drugs, and 28-day mortality was evaluated by chi-square analysis and Fisher's Exact test

were differences regarding the medications evaluated as PIM use and the evaluation criteria (18).

TIME criteria are recently published, so the studies using TIME for evaluating PIM use are still limited in the literature. PIM rate was 21.5-38% in older adults presented to geriatric outpatient clinics, 11.7% in older adults treated in the palliative care service (19-21). The high prevalence of PIM use and different drug groups accepted as PIM use in our study when compared to other studies in the literature were attributed to our sample group being composed of ICU inpatients.

In this study, antipsychotics were the group of drugs most frequently evaluated as PIM use according to TIME-to-STOP criteria. In our previous study, antipsychotics ranked first according to the STOPP/v2 criteria, and were among the drug groups with the most common causes of PIM use according to the 2019 Beers criteria and the EU(7)-PIM list. Using antipsychotics in the treatment of delirium in ICU inpatients is controversial. Routine use of haloperidol or atypical antipsychotics in most of the adult patients at critical state and developing delirium is conditionally recommended because their undesirable effects outweigh their potential benefits (22). Antipsychotics are considered directly as PIM use in the older adults due to their anticholinergic and extrapyramidal side effects in TIME-to-STOP, 2019 Beers and STOPP/v2 criteria, while they are considered as PIM use when received above the recommended dose in EU(7)-PIM list. PIM use rate of antipsychotics in older adults treated in the ICU was 8.3% according to 2012 Beers criteria, and 14.9% in hospitalized older adults according to CBMPLI criteria (16,23). The higher incidence of delirium in ICU patients and the frequent use of antipsychotics in such cases may be a contributing factor in increased rates of PIM use in our study (24). Antipsychotics increase ICU length of stay and mortality (25), and may cause extrapyramidal side effects (26). More effective and safe alternatives are needed (27).

Metoclopramide was one of the drugs most commonly regarded as PIM in our study. For metoclopramide, PIM use rate was about 3-22% in non-ICU patients according to Beers 2012 criteria, and 29% in ICU patients (16,28-30). The criterion for evaluating metoclopramide as PIM use is similar in TIME-to-STOP, 2012 and 2019 Beers criteria, and it is recommended to avoid using this drug due to its extrapyramidal side effects (12,31,32). However, the criterion for evaluating metoclopramide as PIM is different in EU(7)-PIM list (dose adjustment is recommended) and in STOPP/v2 criteria (in patients with Parkinsonism) (6,7). Off-label use of metoclopramide, such as facilitating enteral feeding in the ICU, is common but it may increase the risk of side effects including parkinsonism and tardive dyskinesia in older adults (33).

Midazolam was the third most common drug of PIM use. According to TIME-to-STOP criteria, using benzodiazepines in acute and chronic respiratory failure was evaluated as PIM use,

similar to STOPP/v2 criteria. Therefore, the rate of PIM use due to midazolam was the same rate found by STOPP/v2 criteria in our previous study. According to 2019 Beers criteria, under the title of drug-drug interactions, concomitant use of benzodiazepines (midazolam) and opioids (fentanyl) is accepted as PIM use due to the risk of toxicity. However, benzodiazepines and opioids are the essential drugs increasing patients' compliance with the ventilator and reducing anxiety and agitation during MV support (34). The prevalence of PIM use was found to be high according to 2019 Beers criteria, considering that approximately 90% of the patients received MV support (18). According to EU(7)-PIM list, dose adjustment is recommended for midazolam, and it was not accepted as PIM because the patients included in our study received lower doses. Midazolam is preferred over other benzodiazepines since it is short-acting (35). However, the use of midazolam in the ICU was found to cause delirium, prolongation of ICU length of stay, and an increased risk of mortality (36-38). For patients receiving mechanical ventilator support, guidelines recommend primarily propofol or dexmedetomidine instead of midazolam if analgesia and continuous sedation are required (22).

Digoxin, tramadol and enoxaparin were the other drugs accepted as PIM according to TIME-to-STOP criteria. Digoxin-related PIM use factors and the rates we obtained were similar for TIME-to-STOP and the other three criteria. It is primarily used in the treatment of atrial fibrillation, favored in heart failure with normal ejection fraction, and generally used above the recommended dose (0.125 mg/day), which were the PIM use factors for digoxin. The rate of digoxin-related PIM use (using above the recommended dose) was reported as 5.3-14.6% according to different criteria in non-ICU older adults (39-41). Lower rate (2.8%) determined in our study may be attributed to the low number of patients using digoxin. In-patients of cardiology ICU and cardiovascular surgery ICU were not included in this study.

According to TIME-to-STOP and 2019 Beers criteria, tramadol was one of the drugs to be avoided when kidney functions failed, and PIM use rate was the same in both criteria. In STOPP/v2 criteria, first choice use of opioids for pain relief was recognized as PIM use, whereas in EU(7)-PIM list, their overdose use. Two studies with older adults admitted to the hospital, the rate of tramadol-related PIM use was 7-18% (42,43). In the study by Noronha et al. (44) in the geriatric oncology clinic, the rate of tramadol-induced PIM use was found to be 30% according to Beers criteria, and this high rate of PIM use may be related to the patient group and their frequent use of analgesics. In our study, tramadol was not administered in patients with malignancy only, but with moderate to severe pain, additionally. However, opioid-related PIM use rate was lower due to using primarily paracetamol or non-steroidal anti-inflammatory drugs for pain relief.

In our previous study, amiodarone was one of the common drugs causing PIM use according to all three criteria (16-24%). It was accepted as PIM use in 2019 Beers and STOPP/v2 criteria for being used as the first treatment choice of atrial fibrillation, however, in EU(7)-PIM list, due to the need for dose adjustment. Atrial fibrillation was reported to be common in ICUs, and increasing mortality (45). Therefore, immediate control of atrial fibrillation is vital. Given that amiodarone is not common in primary care, its use was excluded from the criteria while developing TIME-to-STOP criteria. For this reason, amiodarone could not be evaluated as PIM use in our study. However, amiodarone use is quite common in the ICU. It may be suggested to add it to TIME-to-STOP criteria list in case it is desired to cover a broader scope of patient group.

The number of drugs used and having RRT were recognized as risk factors for PIM use according to 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list, and although the rate of PIM use was higher in TIME-to-STOP criteria, the difference was not significant. Renal functions and GFR decreased in patients receiving RRT (46). Using enoxaparin in patients with low GFR was the most commonly evaluated PIM use in 2019 Beers and STOPP/v2 criteria. Thus, preferring enoxaparin as an antithrombotic during RRT led to a high rate of enoxaparin-induced PIM use, leading RRT indirectly to be a risk factor for PIM use. In the TIME-to-STOP criteria, using enoxaparin under serious bleeding risks is considered as a PIM use, independent of renal function tests, which may explain low levels of enoxaparin-related PIM use rates and the reason why RRT was not a significant risk factor for PIM use. It may be recommended to add a note on dose adjustment to TIME-to-STOP criteria in patients with severe renal impairment.

In our study, the length of ICU stay and the mortality rate were found to be higher in the presence of PIM use with respect to TIME-to-STOP criteria, but not significant. In the study by Özkan (47), drugs used in cardiovascular system diseases showed a significant relationship between PIM use and mortality according to TIME-to-STOP criteria. PIM use rates due to midazolam and digoxin caused a significant increase in mortality in our study. The studies conducted on patients sedated with midazolam in the ICU, revealed significantly increased mortality with midazolam in comparison to other sedative agents (38,48). Likewise, in many large-scale studies and meta-analyses, digoxin was shown to significantly increase all-cause mortality when used for both heart failure and atrial fibrillation (49,50). Our results show similarity to the literature in this respect.

### Study Limitations

Small sample size and being conducted in a single-center are the limitations the study. Although this was a retrospective analysis, the data collection was implemented prospectively in the previous study and there was no data loss.

### Conclusion

It was determined in this study that approximately half of the older adults hospitalized in the ICU had at least one PIM use according to TIME-to-STOP criteria. Antipsychotics and propulsive drugs were the most frequently observed PIM. TIME-to-STOP criteria were not found to be effective in determining the prognosis, but there was a correlation between digoxin- and midazolam-related PIM use and mortality. Furosemide, fentanyl and amiodarone, which were among the 10 most frequently used drugs for ICU patients throughout the study period and regarded as PIM according to other three criteria along with a caution notice added for older adults in the short product information, were not included in TIME-to-STOPP criteria, indicating the need to extend the current criteria for older adults. Another recommendation would be the extension of TIME-to-STOP criteria so that the information regarding dose adjustment of enoxaparin in patients with severe renal impairment are also included.

### Ethics

**Ethics Committee Approval:** The research was initiated after the approval of the Non-Interventional Clinical Research Ethics Committee of Dokuz Eylül University and carried out in accordance with the principles of the Declaration of Helsinki.

**Informed Consent:** Our previous study (18), consent was obtained from the participants or their relatives.

**Peer-review:** Externally peer-reviewed.

### Authorship Contributions

Surgical and Medical Practices: N.M.Y., F.D.A., N.G., Concept: S.O., N.M.Y., F.D.A., N.G., A.G., Design: S.O., N.M.Y., F.D.A., N.G., A.G., Data Collection or Processing: S.O., N.M.Y., F.D.A., Analysis or Interpretation: S.O., N.M.Y., F.D.A., N.G., A.G., Literature Search: S.O., N.M.Y., F.D.A., N.G., A.G., Writing: S.O., A.G.

**Conflict of Interest:** No conflict of interest was declared by the authors.

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**Supplement 1. PIM use prevalence in ICU patients according to the TIME-to-STOP, 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list (18)**

TIME to STOP criteria (n=139)		2019 BEERs criteria (n=139)		STOPP v2 criteria (n=139)		EU(7)-PIM list (n=139)	
n (%)		n (%)		n (%)		n (%)	
No PIM	72 (51.8)	No PIM	27 (19.4)	No PIM	56 (40.3)	No PIM	72 (51.8)
1 PIM	44 (31.7)	1 PIM	45 (32.4)	1 PIM	57 (41.0)	1 PIM	47 (33.8)
≥2 PIM	23 (16.5)	≥2 PIM	67 (48.2)	≥2 PIM	26 (18.7)	2 PIM	20 (14.4)
Prevalence of PIM use	67 (48.2)	Prevalence of PIM use	112 (80.6)	Prevalence of PIM use	83 (59.7)	Prevalence of PIM use	67 (48.2)

PIM use: Potentially inappropriate medication use  
 Demirer Aydemir F, Oncu S, Yakar NM, Utkugun GA, Gokmen N, Comert B, Ucku R, Gelal A. Potentially inappropriate medication use in elderly patients treated in intensive care units: A cross-sectional study using 2019 Beers, STOPP/v2 Criteria and EU(7)-PIM List. Int J Clin Pract 2021;75:e14802.

**Supplement 2. Variables significantly affecting the presence of PIM use according TIME-to-STOP, 2019 Beers, STOPP/v2 criteria and EU(7)-PIM List**

	TIME-to-STOP criteria PIM use presence (n=67)	p-value	2019 Beers criteria PIM use presence (n=112)	p-value	STOPP/v2 criteria PIM use presence (n=83)	p-value	EU(7)-PIM List PIM use presence (n=67)	p-value
<b>Age (years) (n)</b>								
65-74 (65)	32 (49.2)	0.925	49 (75.4)	0.328	37 (56.9)	0.471	30 (46.2)	0.903
75-84 (50)	23 (46.0)		42 (84.0)		29 (58.0)		25 (50.0)	
≥85 (24)	12 (50.0)		21 (87)		17 (70.8)		12 (50.0)	
<b>Gender (n)</b>								
Female (68)	34 (50.0)	0.678	56 (82.4)	0.604	41 (60.3)	0.891	35 (51.5)	0.450
Male (71)	33 (46.5)		56 (78.9)		42 (59.2)		32 (45.1)	
<b>Body mass index (n)</b>								
<25 (62)	29 (46.8)	0.763	50 (80.6)	0.985	36 (58.1)	0.722	28 (45.2)	0.520
≥25 (77)	38 (49.4)		62 (80.5)		47 (61.0)		39 (50.6)	
<b>Mechanical ventilation (n)</b>								
Yes (124)	58 (46.8)	0.333	101 (81.5)	0.453	73 (58.9)	0.561	60 (48.4)	0.900
No (15)	9 (60.0)		11 (73.3)		10 (66.7)		7 (46.7)	
<b>Renal replacement therapy (n)</b>								
Yes (26)	13 (50.0)	0.839	26 (100.0)	0.005	21 (80.8)	0.015	19 (73.1)	0.005
No (113)	54 (47.8)		86 (76.1)		62 (54.9)		48 (42.5)	
<b>Charlson Comorbidity index (n)</b>								
≤6 (65)	28 (43.1)	0.294	44 (67.7)	<0.001	34 (52.3)	0.095	26 (40.6)	0.083
>6 (74)	39 (52.7)		68 (91.9)		49 (66.2)		41 (55.4)	
<b>Glasgow Coma scale (n)</b>								
≤9 (70)	33 (47.1)	0.801	62 (88.6)	0.016	38 (54.3)	0.189	41 (58.6)	0.014
9 (69)	34 (49.3)		50 (72.5)		45 (65.2)		26 (37.7)	
<b>APACHE II (n)</b>								
≤22 (70)	28 (40.0)	0.052	47 (67.1)	<0.001	38 (54.3)	0.189	24 (34.3)	0.001
>22 (69)	39 (56.5)		65 (94.2)		45 (65.2)		43 (62.3)	
<b>Number of drug (n)</b>								
≤10 (70)	29 (41.4)	0.107	48 (68.6)	<0.001	36 (51.4)	0.045	24 (34.3)	0.001
>10 (69)	38 (55.1)		64 (92.8)		47 (68.1)		43 (62.3)	

PIM: Potentially inappropriate medication, the relationship between the dependent and independent variables was evaluated by chi-square analysis

**Supplement 3. Drug groups evaluated as PIM in elderly ICU patients and related criteria according TIME-to-STOP, 2019 Beers, STOPP/v2 criteria and EU(7)-PIM List (18)**

Drugs	PIM use criteria according to TIME to STOPP	% (n)	PIM use criteria according to 2019 Beers	% (n)	PIM use criteria according to STOPP/v2	% (n)	PIM use criteria according to EU(7)-PIM	% (n)
<b>Antipsychotics</b> Haloperidol	Neuroleptics/antipsychotics for hypnotic purpose (increased confusion, hypotension, extrapyramidal side effects, risk of fall).	15.8% (n=22)	Avoid antipsychotics for behavioral problems of dementia or delirium unless non-pharmacological options have failed or are not possible and the older adult is threatening substantial harm to self or others	13.7% (n=19)	Neuroleptics as hypnotics, unless sleep disorder is due to psychosis or dementia	15.8% (n=22)	N/A	N/A
Quetiapine		10.8% (n=15)		10.8% (n=15)		10.8% (n=15)	Anticholinergic and extrapyramidal side effects Above the recommended dose	10.8% (n=15)
<b>Propulsives</b> Metoclopramide	Metoclopramide or trimethobenzamide as the first line antiemetic treatment of older adults (due to the extrapyramidal side effects and restlessness).	25.2% (n=35)	Metoclopramide can cause extrapyramidal effects, including tardive dyskinesia; risk may be greater in frail older adults and with prolonged exposure	25.2% (n=35)	Prochlorperazine or metoclopramide with Parkinsonism (risk of exacerbating Parkinsonian symptoms).	N/A	Antidopaminergic and anticholinergic effects, may worsen peripheral arterial blood flow and precipitate intermittent claudication, above the recommended dose	19.4% (n=27)
<b>Sedative-hypnotic</b> Midazolam	Benzodiazepines with acute or chronic respiratory failure i.e. PO <sub>2</sub> <60 mmHg and / or pCO <sub>2</sub> > 50 mmHg (risk of exacerbation of respiratory failure).	7.2% (n=10)	Midazolam and fentanyl Drug-drug interactions	58.3% (n=81)	Benzodiazepines with acute or chronic respiratory failure i.e. pO <sub>2</sub> <8.0 kPa ± pCO <sub>2</sub> >6.5 kPa (risk of exacerbation of respiratory failure).	7.2% (n=10)	N/A	N/A
<b>Glycosides</b> Digoxin	Digoxin as first line treatment for atrial fibrillation. Digoxin for heart failure with preserved EF. Digoxin at a dose greater than 0.125 mg/day	2.8% (n=4)	Digoxin for first-line treatment of atrial fibrillation or of heart failure	2.8% (n=4)	Digoxin for heart failure with preserved systolic ventricular function.	1.4% (n=2)	Elevated glycoside sensitivity in older people; risk of intoxication Above the recommended dose	2.8% (n=4)

Supplement 3. Continued								
Drugs	PIM use criteria according to TIME to STOPP	% (n)	PIM use criteria according to 2019 BEERs	% (n)	PIM use criteria according to STOPP/v2	% (n)	PIM use criteria according to EU(7)-PIM	% (n)
<b>Opioids</b> Tramadol	Extended-release tramadol if eGFR <30 mL/min/1.73 m <sup>2</sup>	2.8% (n=4)	Potentially inappropriate medications based on kidney function	2.8% (n=4)	Use of oral or transdermal strong opioids as first line therapy for mild pain	7.9% (n=11)	More adverse effects in older people above the recommended dose	4.3% (n=6)
<b>Antithrombotic</b> Enoxaparin	Factor Xa inhibitors with concurrent significant bleeding risk.	2.2% (n=3)	Potentially inappropriate medications based on kidney function	29.5% (n= 41)	Factor Xa inhibitors if eGFR <15 (risk of bleeding). Any duplicate drug class prescription. Factor Xa inhibitors with concurrent significant bleeding risk.	20.9% (n=29)	N/A	N/A
<b>Antiarrhythmics</b> Amiodarone	Excluded criteria (reason: The drugs are not commonly used in primary care in local practice)	N/A	Avoid as first-line therapy for atrial fibrillation unless patient has heart failure or substantial left ventricular hypertrophy	15.8% (n=22)	Amiodarone as first-line antiarrhythmic therapy in supraventricular tachyarrhythmias	18.0% (n=25)	Associated with QT interval problems and risk of provoking torsades de pointes Above the recommended dose	23.7% (n=33)

PIM: Potentially inappropriate medication, N/A: Not applicable  
Demirer Aydemir F, Oncu S, Yakar NM, Utkuogun GA, Gokmen N, Comert B, Ucku R, Gelal A. Potentially inappropriate medication use in elderly patients treated in intensive care units: a cross-sectional study using 2019 Beers, STOPP/v2 Criteria and EU(7)-PIM List. Int J Clin Pract. 2021; 75(11):e14802. doi:10.1111/ijcp.14802

<b>Supplement 4. Relationship of PIM use presence with 28-day mortality rate and length of ICU stay according TIME-to-STOP, 2019 Beers, STOPP/v2 criteria and EU(7)-PIM list (18)</b>					
		<b>Mortality n (%)</b>	<b>p-value</b>	<b>Length of ICU stay (day) Mean (standard deviation)</b>	<b>p-value</b>
2019 Beers criteria*	PIM (n=112)	46 (41.1)	0.069	13.1 (10.4)	0.028
	No PIM (n=27)	6 (22.2)		8.4 (6.6)	
STOPP/v2 criteria*	PIM (n=83)	33 (39.8)	0.486	11.8 (9.5)	0.660
	No PIM (n=56)	19 (33.9)		12.6 (10.6)	
EU(7)-PIM list*	PIM (n=67)	28 (41.8)	0.303	13.1 (11.1)	0.295
	No PIM (n=72)	24 (33.3)		11.3 (8.8)	
TIME to STOPP criteria	PIM (n=67)	26 (38.8)	0.743	12.6 (10.9)	0.590
	No PIM (n=72)	26 (36.1)		11.7 (9.1)	

Demirer Aydemir F, Oncu S, Yakar NM, Utkugun GA, Gokmen N, Comert B, Ucku R, Gelal A. Potentially inappropriate medication use in elderly patients treated in intensive care units: a cross-sectional study using 2019 Beers, STOPP/v2 Criteria and EU(7)-PIM List. *Int J Clin Pract.* 2021; 75(11):e14802. doi: 10.1111/ijcp.14802

The relationship between the presence of PIM use and the average number of days of stay in the ICU was evaluated by using the Student's t-test for parametric data and the Mann-Whitney U test for non-parametric data.

The relationship between the presence of PIM use and 28-day mortality was evaluated by chi-square analysis