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ORIGINAL RESEARCH

Inhaled anticholinergic use and all-cause mortality among elderly Medicare beneficiaries with chronic obstructive pulmonary disease

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Background: The purpose of this study was to examine the association between use of inhaled anticholinergics and all-cause mortality among elderly individuals with chronic obstructive pulmonary disease (COPD), after controlling for demographic, socioeconomic, health, functional status, smoking, and obesity.

Methods: We used a retrospective longitudinal panel data design. Data were extracted for multiple years (2002–2009) of the Medicare Current Beneficiary Survey (MCBS) linked with fee-for-service Medicare claims. Generic and brand names of inhaled anticholinergics were used to identify inhaled anticholinergic utilization from the self-reported prescription medication files. All-cause mortality was assessed using the vital status variable. Unadjusted group differences in mortality rates were tested using the chi-square statistic. Multivariable logistic regressions with independent variables entered in separate blocks were used to analyze the association between inhaled anticholinergic use and all-cause mortality. All analyses accounted for the complex design of the MCBS.

Results: Overall, 19.4% of the elderly Medicare beneficiaries used inhaled anticholinergics. Inhaled anticholinergic use was significantly higher (28.5%) among those who reported poor health compared with those reporting excellent or very good health (12.7%). Bivariate analyses indicated that inhaled anticholinergic use was associated with significantly higher rates of all-cause mortality (18.7%) compared with nonusers (13.6%). However, multivariate analyses controlling for risk factors did not suggest an increased likelihood of all-cause mortality (adjusted odds ratio 1.26, 95% confidence interval 0.95–1.67).

Conclusion: Use of inhaled anticholinergics among elderly individuals with COPD is potentially safe in terms of all-cause mortality when we adjust for baseline risk factors.

Keywords: geriatrics, chronic obstructive pulmonary disease, inhaled anticholinergics, mortality, drug safety

Introduction

Chronic obstructive pulmonary disease (COPD) is characterized by airflow limitation due to chronic inflammation of the lungs.[1–3] Worldwide, COPD is estimated to become the third leading cause of mortality and the fifth most burdensome disease.[4–6] In the United States, COPD is the fourth leading cause of morbidity and mortality.[4,7] Individuals with COPD also suffer from extensive physical and psychological comorbidities, which worsen their health-related quality of life and pose challenges to health care management,[3,8] and can lead to increased risk of mortality in the elderly over the age of 65 years.[9]

Bronchodilators including long-acting and short-acting beta-2-agonists, inhaled anticholinergics (IAC), and combination drug therapies have been approved in the

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United States for the management of COPD.[7] Traditionally, anticholinergics agents have been linked with an increased risk of fatal and nonfatal cardiovascular adverse events, stroke, and all-cause mortality. IAC have been shown to reduce the risk of adverse events due to inclusion of a quaternary ammonium structure which inhibits gastrointestinal absorption.[10] However, other mechanisms may increase the risk of adverse events in specific subgroups. These include elevation of plasma IAC levels in elderly individuals and in those with renal impairment.[11,12]

Evidence regarding the safety of IAC in terms of all-cause mortality is inconsistent. Findings from several randomized controlled trials have indicated that IAC are as safe as placebo or active controls in terms of all-cause mortality.[13,14] Similarly, analyses of pooled data from the controlled trials show no statistically significant increase in risk of cardiovascular adverse events or all-cause mortality with IAC use.[15–17] However, these results have been contradicted in a systematic review with meta-analysis which concluded that IAC use was associated with increased risk of composite cardiovascular adverse events including stroke, myocardial infarction, and cardiovascular death.[18] Further, a nested case-control study reported a 34% increase in cardiovascular mortality and an 11% increase in all-cause mortality with IAC, specifically ipratropium bromide.[18,19] These findings cannot be generalized due to methodological shortcomings in terms of double-counting of event data (meta-analysis) and not adequately accounting for baseline differences (nested case-control study).[10,20] Subsequently, results from the four-year UPLIFT (Understanding Potential Long-term Impacts on Function with Tiotropium) trial suggested that tiotropium was not associated with adverse events and actually reduced the risk of mortality.[14] These findings were also supported by a systematic review and meta-analysis published after including data from the UPLIFT trial.[21]

None of the above-mentioned studies were specific to the elderly, so their findings may have limited applicability in the elderly population. It is reported that elderly individuals are not adequately represented in randomized controlled trials.[22] Moreover, disease management in elderly individuals with COPD is complicated by extensive coexisting chronic physical and psychiatric conditions.[23] For example, elderly individuals with COPD are at greater risk for chronic renal failure,[24] which leads to elevated plasma IAC levels that may further elevate the risk of adverse events, including all-cause mortality.[11] To date, no study has rigorously examined the association between IAC use and all-cause mortality in elderly individuals with COPD. Therefore, the primary objective of the current study was to examine the association between use of IAC and all-cause mortality in elderly individuals with COPD. For the purposes of this study, we used retrospective longitudinal data from elderly Medicare beneficiaries seeking care in the real-world setting.

Materials and methods

Study design

We adopted a longitudinal panel design with retrospective observational data to analyze the association between use of IAC and all-cause mortality using the Medicare Current Beneficiary Survey (MCBS). The MCBS is a "nationally representative sample of aged, disabled, and non-institutionalized Medicare beneficiaries" with linkage to fee-for-service Medicare claims.[25] Because individuals were followed for three years, we defined the baseline period as the first observed year of each panel. Follow-up of each panel for two years were used to assess mortality status, as discussed below.

Data source

The MCBS is a longitudinal, multipurpose survey, and is representative of the Medicare population in the United States. Medicare beneficiaries are selected using a multistage stratified random sampling design. Selected beneficiaries are followed for a period of three years. The data are continually collected for three rounds per year at four-month intervals. MCBS follows a rotating panel survey design in which each panel is interviewed 12 times.

The MCBS is divided into two modules, ie, "access to care" and "cost-and use". The access to care module contains information relating to respondents' access to medical providers and their satisfaction with health care for beneficiaries enrolled in Medicare for the entire year. In contrast with that, the cost and use file of the MCBS contains information on health care use, prescription drug use, chronic conditions, and personal health care practices.[25] Health care expenditures and utilization were obtained from personal interviews conducted every four months as well as Medicare claims. The current study utilized multiple years of cost and use files linked with fee-for-service Medicare claims data.

Analytical sample

Individuals were considered to have diagnosed COPD if they had at least one inpatient visit or two outpatient visits for COPD based on International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes for chronic bronchitis (491.xx), emphysema (492.xx),

or unspecified chronic airway obstruction (496.xx). Other inclusion criteria consisted of community-dwelling fee-for-service Medicare beneficiaries who were over 65 years of age and had full-year enrollment during the baseline period.

Using the merged data from multiple years (2002–2009), we obtained six longitudinal panels: 2002–2004 (Panel I); 2003–2005 (Panel II); 2004–2006 (Panel III); 2005–2007 (Panel IV); 2006–2008 (Panel V); and 2007–2009 (Panel VI). The final sample consisted of 2610 Medicare beneficiaries, and included 424 beneficiaries in Panel I, 458 beneficiaries in Panel II, 406 beneficiaries in Panel III, 475 beneficiaries in Panel IV, 419 beneficiaries in Panel V, and 428 beneficiaries in Panel VI.

Key independent variable: IAC use

We identified IAC use from prescription medicine events files. Prescription medicine events files contain self-reported drug utilization at the prescription level. Two IAC are approved in the United States, ie, ipratropium bromide (short-acting) and tiotropium bromide (long-acting). All generic and brand names for these two IAC were obtained from the US Food and Drug Administration register.[26] These names were then used to identify IAC use. The first year of each panel was used to measure baseline characteristics as well as IAC use. Elderly Medicare beneficiaries who reported having at least one prescription for any IAC in the baseline year of each panel were categorized as IAC users.

Dependent variable: mortality status (dead versus alive)

We defined mortality status as a dichotomous variable (yes/no) using the "vital status" variable in the MCBS data. Decedent status was derived from both survey responses and administrative claims files.[27] Medicare beneficiaries who died during the follow-up observation years were considered as decedents. For example, in the first panel (2002–2004), mortality status was determined using vital status data in follow-up years (ie, individuals who died in 2003 or 2004).

Other independent variables

All independent variables were measured in the baseline period (ie, first year of observation).

Demographic variables consisted of gender (women, men), race (white, African American, others), age in years (65–69, 70–74, and ≥75), and metropolitan status (metro, not metro). Socioeconomic status included education (less than high school, high school, and college education), poverty status (<200% versus >200% of the federal poverty line), and prescription drug coverage (yes, no).

Coexisting chronic physical and mental health conditions were identified using responses to questions about whether beneficiaries ever had the following diseases: Alzheimer's disease, arthritis, cardiovascular disease, cancer, diabetes, hypertension, mental illness, osteoporosis, and stroke. Based on three studies which analyzed multimorbidity patterns with respiratory diseases (one using Medicaid data[28] and others using expert clinical reviews),[29,30] separate indicator variables were constructed for each of the following comorbidities: cardiovascular/metabolic disorders (composite of beneficiaries with diabetes/heart disease/hypertension/stroke); mental illness; musculoskeletal disorders (composite of beneficiaries with arthritis and/or osteoporosis) and other diseases (composite of beneficiaries with cancer and/or Alzheimer's disease). Because of the potential association between chronic renal failure and adverse events with use of IAC, we also included an indicator variable for chronic renal failure. Chronic renal failure was identified using the ICD-9-CM codes in the clinical classification software[31] provided by the Agency for Healthcare Research and Quality, ie, 585.xx, 586, 792.5, V42.0, V45.1, V56.0–V56.32, and V56.8.

Personal health care practices were identified using smoking status (current, past, never) and body mass index (BMI) values categorized into five different classes: underweight (BMI < 18.5 kg/m^2); normal (BMI ≥ 18.5–25 kg/m^2); overweight (BMI ≥ 25–30 kg/m^2); and obese (BMI ≥ 30 kg/m^2).[32]

Health status was measured by self-perceived general health. In the MCBS data, the survey respondents reported their physical health status as being excellent, very good, good, fair, or poor. For the purpose of our analyses, we grouped these responses as: excellent or very good health; good health; fair health; and poor health. A panel or cohort variable was used as an additional independent variable to adjust for time effects.

Statistical methods

Chi-square tests of independence were used to determine unadjusted group differences according to IAC use. In order to understand the independent association between IAC use and other variables and all-cause mortality, independent variables were entered in separate blocks. The first model (model I) was an unconditional model with IAC use as the only independent variable. Model II adjusted for IAC use and coexisting conditions (mental illness, cardiovascular/metabolic disorders, musculoskeletal disorders, chronic renal failure, and other conditions). In model III,

we added gender, race, age, metro status, education level, and socioeconomic status. Model IV adjusted for perceived health status in addition to all the independent variables included in model III. Additionally, in model V, we included functional status, BMI category, and smoking status. All analyses controlled for the complex design of the MCBS and were conducted using survey procedures with Statistical Analysis System version 9.3 software (SAS Institute Inc, Cary, NC, USA).

Results

The final study sample obtained after applying all eligibility criteria consisted of 2610 Medicare beneficiaries. A majority (54%) of the study sample were female, 84% were white, 53% were older than 75 years, 52% were married, and 70% resided in a metropolitan area. In terms of socioeconomic status, 34% had no high school education and 42% of the sample was below 200% of the federal poverty level. Twenty-three percent of elderly individuals were obese and 20% were current smokers. The far right entries in Table 1 show the number and weighted percentages of beneficiaries with IAC use. The significance column reports the statistical significance between IAC use and beneficiary characteristics. Statistically significant differences in IAC use were observed by gender, age categories, prescription drug coverage, health status, functional status, and smoking status. IAC use was significantly higher (28.5%) among elderly Medicare beneficiaries who reported poor perceived health status as compared with those self-reporting excellent or very good health status (12.7%).

In our study sample, 19% of the elderly individuals reported IAC use in the baseline period. Table 2 summarizes unadjusted associations between selected beneficiary characteristics and all-cause mortality. We observed a statistically significant association between IAC use and all-cause mortality (odds ratio [OR] 1.46, 95% confidence interval [CI] 1.12–1.90). Elderly Medicare beneficiaries with IAC use and cardiovascular/metabolic disorder had an increased likelihood of all-cause mortality compared with those without IAC use and cardiovascular/metabolic disorder (OR 1.40, 95% CI 1.03–1.91). Medicare beneficiaries who reported their health status to be poor were five times more likely to die than those with self-reported excellent to very good health status (OR 5.69, 95% CI 3.79–8.53).

Multivariable logistic regressions with independent variables entered in separate blocks were used to examine the association between IAC use and all-cause mortality.

Table 1 Description of study sample characteristics according to IAC use among elderly Medicare beneficiaries with COPD: Medicare Current Beneficiary Survey, 2002–2009

	Total		Percentage with IAC use		
	n	wt %	n	wt %	Sig
Gender					**
Women	1390	53.7	245	17.0	
Men	1220	46.3	255	21.7	
Race					
White	2176	83.9	426	19.7	
African American	173	6.7	29	15.8	
Others	260	9.4	45	16.6	
Age, years					*
65–69	557	25.2	135	23.3	
70–74	485	21.6	81	16.4	
≥75	1568	53.2	284	18.4	
Married					
Married	1289	51.5	243	19.1	
Not married	1320	48.5	257	19.3	
Metro status					
Metro	1753	69.7	339	19.1	
Not metro	857	30.3	161	19.3	
Education					
Less than high school	924	34.3	182	19.7	
High school	966	37.6	188	19.3	
College	710	28.2	130	18.7	
Poverty status					
>200% FPL	1054	42.1	205	19.6	
<200% FPL	1556	57.9	295	18.8	
Prescription drug coverage					*
Yes	1973	75.8	405	20.2	
No	637	24.2	95	15.9	
Health status					***
Excellent/very good	740	29.6	94	12.7	
Good	876	33.6	160	18.4	
Fair	671	25.3	154	23.5	
Poor	310	11.5	88	28.5	
Functional status (ADL)					***
None	1556	62.0	257	16.4	
1–2 ADL	706	26.3	157	22.8	
3–6 ADL	344	11.8	85	25.7	
Body mass index					
Underweight	113	4.0	29	24.9	
Normal	984	37.5	179	18.2	
Overweight	930	35.7	166	17.8	
Obese	561	22.8	123	22.1	
Smoking status					***
Current smoker	498	20.0	113	22.1	
Past smoker	1437	55.4	324	22.8	
Never smoked	671	24.6	62	8.5	
Mental illness					
Yes	492	19.2	100	19.3	
No	2118	80.8	400	19.1	
CMD					
Yes	2149	81.6	407	18.9	
No	459	18.4	93	20.6	

(*Continued*)

Table 1 (*Continued*)

	Total		Percentage with IAC use		
	n	wt %	n	wt %	Sig
Musculoskeletal disorders					
Yes	1921	72.4	376	19.8	
No	687	27.6	123	17.5	
Chronic renal failure					
Yes	195	7.1	38	18.9	
No	2415	92.9	462	19.2	
Other comorbidities					
Yes	1320	49.7	262	19.2	
No	1290	50.3	238	19.1	
Cohort					
2002–2004	424	15.2	79	18.2	
2003–2005	458	17.2	85	17.4	
2004–2006	406	15.8	79	19.3	
2005–2007	475	18.1	98	21.5	
2006–2008	419	16.9	84	21.4	
2007–2009	428	16.8	75	17.0	

Notes: Based on 2610 elderly Medicare beneficiaries with COPD, who were observed between years 2002 and 2009. Asterisks represent significant association between inhaled anticholinergic use and beneficiary characteristics based on Chi-square tests. ***$P < 0.001$; **$0.001 \leq P < 0.01$; *$0.01 \leq P < 0.05$.

Abbreviations: ADL, activities of daily living; COPD, chronic obstructive pulmonary disease; FPL, federal poverty line; IAC, inhaled anticholinergics; wt, weighted; Sig, significance; CMD, cardiometabolic disorders (diabetes, heart disease, hypertension and stroke); musculoskeletal disorders, arthritis and osteoporosis; other comorbidities, cancer and Alzheimer's disease.

Even after adjusting for coexisting chronic conditions, we observed a statistically significant association between IAC use and all-cause mortality (adjusted OR 1.47, 95% CI 1.14–1.90). Similar results were observed when the analyses additionally controlled for demographic characteristics (adjusted OR 1.51, 95% CI 1.16–1.97). However, the significant association between IAC use and all-cause mortality disappeared once we controlled for health status (adjusted OR 1.32, 95% CI 1.00–1.74). Similar findings were noted in model IV, which additionally controlled for lifestyle risk factors (adjusted OR 1.26, 95% CI 0.95–1.67, Table 3).

Although, not specific to the elderly, it has been reported that IAC use is associated with increased risk of fatal and nonfatal cardiovascular events,[18,19,33,34] suggesting that among individuals with cardiovascular disease, IAC use may increase the risk of mortality. Therefore, we also included an interaction term between IAC use and the presence of cardiovascular/metabolic disorder (results not shown). After controlling for all the variables included in model IV, there was no statistically significant association between the interaction term and all-cause mortality (Wald chi-square = 2.676, $P = 0.102$).

Table 2 Description of selected characteristics according to all-cause mortality among beneficiaries: COPD Medicare Current Beneficiary Survey, 2002–2009

	wt %	Unadjusted logistic regression		
		OR	95% CI	Sig
IAC use				
Yes	18.7	1.46	(1.12–1.90)	**
No	13.6			
IAC/CMD groups				
IAC and CMD	18.9	1.40	(1.03–1.91)	*
No IAC and CMD	14.3			
IAC and no CMD	17.9	1.26	(0.69–2.28)	
No IAC and no CMD	10.2	0.68	(0.45–1.01)	
Health status				
Excellent/very good	7.2			
Good	11.7	1.71	(1.18–2.48)	**
Fair	20.2	3.24	(2.24–4.69)	***
Poor	29.9	5.69	(3.79–8.53)	***
Gender				
Women	12.8	0.73	(0.58–0.91)	**
Men	16.6			
Race/ethnicity				
White	14.2			
African American	16.7	1.11	(0.71–1.72)	
Others	16.2	1.20	(0.86–1.66)	
Age, years				
65–69	8.7			
70–74	11.2	1.41	(0.86–2.31)	
≥75	18.7	2.53	(1.74–3.69)	***

Notes: Based on 2610 elderly Medicare beneficiaries with COPD, who were observed between years 2002 and 2009. Asterisks represent significant association between inhaled anticholinergic use and beneficiary characteristics based on Chi-square tests. ***$P < 0.001$; **$0.001 \leq P < 0.01$; *$0.01 \leq P < 0.05$.

Abbreviations: COPD, chronic obstructive pulmonary disease; IAC, inhaled anticholinergics; CMD, cardiometabolic disorders (diabetes, heart disease, hypertension and stroke); Wt, weighted; CI, confidence interval; OR, odds ratio; Sig, significance.

Discussion

This study contributes to the knowledge base on the safety of IAC use in terms of all-cause mortality among elderly Medicare beneficiaries with COPD seeking care in a real world-setting, with extensive controls for demographic and socioeconomic factors, coexisting chronic conditions, personal health care practices, and self-reported health status. We observed a statistically significant association between IAC use and all-cause mortality in the bivariate analyses. However, after controlling for self-reported perceived health status in the final model, which also included coexisting conditions, and demographic, socioeconomic, and lifestyle risk factors, it was found that IAC use was no longer associated with all-cause mortality. This finding is consistent with that of the UPLIFT trial and other meta-analyses,[14,21] and can be explained using the updated evidence from this field.[15]

Table 3 Adjusted odds ratios and 95% confidence intervals from multivariable logistic regressions on all-cause mortality among elderly beneficiaries with COPD: Medicare Current Beneficiary Survey, 2002–2009

Model		OR	95% CI	Sig
I	**IAC use**			
	Yes	1.46	(1.12–1.90)	**
	No			
		AOR	**95% CI**	**Sig**
II	**IAC use**			
	Yes	1.47	(1.14–1.90)	**
	No			
III	**IAC use**			
	Yes	1.51	(1.16–1.97)	**
	No			
IV	**IAC use**			
	Yes	1.32	(1.00–1.74)	
	No			
V	**IAC use**			
	Yes	1.26	(0.95–1.67)	
	No			

Notes: Based on Medicare beneficiaries with COPD, who were observed between years 2002 and 2009. The logistic regression also includes an intercept term not presented here. Asterisks represent significant group differences compared to the reference group based on multivariable logistic regressions. Model I, included IAC use as the only independent variable; model II, additionally controlled for all coexisting conditions (mental illness, cardiovascular/metabolic disorders, musculoskeletal disorders, chronic renal failure, and other conditions); model III, controlled for all variables in model II and gender, race, age, metro status, education and poverty status; model IV, controlled for all variables in model III and perceived health status; and model V, controlled for all variables in model IV and body mass index and smoking status. **$0.001 \leq P < 0.01$.

Abbreviations: COPD, chronic obstructive pulmonary disease; IAC, inhaled anticholinergics; OR, odds ratio; AOR, adjusted odds ratios; CI, confidence interval; Sig, significance.

Previous studies have shown increased cardiovascular events and mortality due to use of IAC.[19,33,34] However, in a synthesis of available evidence on the safety of IAC use in terms of major cardiovascular events, it has been suggested that IAC may not be responsible for severe cardiovascular adverse events because of its poor gastrointestinal absorption.[35] Consistent with this medical opinion, we did not find any statistically significant association between the interaction term (ie, IAC use and cardiovascular/metabolic disorder) and all-cause mortality, suggesting that use of IAC is safe in the elderly with cardiovascular disease. Our findings are also consistent with a review of the evidence from clinical trials on IAC use and cardiovascular-related mortality which concluded that IAC is safe.[36,37] If replicated, our study findings may have significant implications for IAC treatment in the elderly with cardiovascular conditions.

An interesting observation in our study was the higher rate of IAC use among current smokers (22.1%) and former smokers (22.8%) compared with nonsmokers (8.5%). It is indeed surprising that current smokers were more likely to report IAC use compared with nonsmokers and former smokers. Current evidence on this issue has consistently indicated that, irrespective of smoking status, IAC use is associated with improved lung function.[38–40] Findings from the post hoc analysis of data from the UPLIFT by smoking status also suggested that use of tiotropium improves lung function and health status, regardless of smoking status.[40] Given these findings, one would expect no differences in IAC use by smoking status. However, one could speculate that greater IAC use among current smokers could be due to some evidence of increased lung function with tiotropium in smokers. A study reported by Moita et al indicates that the difference in lung function with tiotropium use was significantly greater for current smokers as compared with former smokers.[39]

A noteworthy finding from the current study is the disappearance of the statistically significant association between IAC use and all-cause mortality after adjusting for health status. In our study, self-reported perceived health status was also a strong predictor of all-cause mortality, consistent with prior studies. Prior research using a pooled analysis of 22 studies observed a statistically significant association between poor health status and increased risk of mortality (risk ratio 1.92, 95% CI 1.64–2.25).[41] Further, closer examination of IAC use by health status indicates that a higher proportion of elderly individuals with poor health status (28.5%) reported using IAC compared with those with excellent or very good health (12.7%). Therefore, any observed relationship between IAC and all-cause mortality may have been driven by differences in IAC use according to health status. These findings collectively highlight the importance of controlling for self-perceived health status when investigating the relationship between IAC use and all-cause mortality, because adjusting for health status may change the direction of the relationship between IAC use and mortality, as shown in our study.

The strength of this study includes its use of a nationally representative sample of elderly individuals over 65 years of age, the longitudinal study design, and the ability to ascertain the relationship between IAC use and mortality after controlling for a comprehensive list of risk factors. The study has a few limitations which should be noted. Because the MCBS data do not contain precise dates of prescription fills, it is difficult to derive data on adherence and persistence with IAC, and adherence may affect the

risk of death. Therefore, studies examining long-term persistence with use of IAC may provide a robust indication of the association between IAC use and all-cause mortality. The study may also suffer from selection bias as a result of unobserved variables, such as patient preferences that may have affected IAC use. However, we may have minimized any selection bias by controlling for a host of risk factors with the potential to impact the association between IAC use and all-cause mortality. Further, the MCBS does not collect laboratory data, so we were unable to assess and adjust for the severity of COPD in our analyses.

Despite these limitations, our study makes a unique contribution to the existing knowledge base on safety of IAC use among the elderly. Our results suggest that use of IAC may be safe in the elderly with COPD, and indicate a need to control for self-perceived health status when examining the relationship between IAC use and all-cause mortality. Given the lack of evidence related to IAC use and all-cause mortality in the elderly population, robust longitudinal studies are required in this population to derive more definitive conclusions.

Disclosure

The authors report no conflicts of interest in this work.

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