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Potentially inappropriate medication use is associated with increased risk of incident disability in healthy older adults

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Abstract

Background: Efforts to minimize medication risks among older adults include avoidance of potentially inappropriate medications (PIMs). However, most PIMs research has focussed on older people in aged or inpatient care, creating an evidence gap for community-dwelling older adults. To address this gap we investigated the impact of PIMs use in the ASPREE clinical trial cohort.

Methods: Analysis included 19,114 community-dwelling ASPREE participants aged 70+ years (65+ if US minorities) without major cardiovascular disease, cognitive impairment, or significant physical disability. PIMs was defined according to a modified 2019 AGS Beers Criteria. Cox proportional-hazards regression models were used to estimate the association between baseline PIMs exposure, and disability-free survival, death, incident dementia, disability, and hospitalization, with adjustment for sex, age, country, years of education, frailty, average gait speed, and comorbidities.

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Authors contributions

JEL was responsible for the concept and design of work, some data analysis and interpretation and preparation of the first draft of the manuscript. TAC contributed to the data analysis, drafting and critical revision of the manuscript. MEE contributed to the design of the work and interpretation of the results. MEE, SGO, AM, MN, NS, CM, RW, and RLW critically reviewed and revised the manuscript. All authors approved the final version of this manuscript.

Conflict of interest

The authors have no conflict of interest to declare in relation to this study.

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Results: At baseline, 7396 (39% of total) participants were prescribed at least one PIM. Compared with those unexposed, participants on a PIM at baseline were at an increased risk of persistent physical disability (Adjusted HR 1.47, 95%CI 1.21, 1.80) and hospitalization (Adjusted HR 1.26, 95%CI 1.20, 1.32), but had similar rates of disability free survival (Adjusted HR 1.02; 95%CI 0.93, 1.13) and death (Adjusted HR 0.92, 95%CI 0.81, 1.05). These effects did not vary by polypharmacy status in interaction analyses. PIMs exposure was associated with higher risk of disability followed by hospitalization (Adjusted HR 1.92, 95%CI 1.25, 2.96) as well as *vice versa* (Adjusted HR 1.54, 95%CI 1.15, 2.05). PPIs, anti-psychotics and benzodiazepines were associated with increased risk of disability.

Conclusions: PIMs exposure is associated with subsequent increased risk of both incident disability and hospitalization. Increased risk of disability prior to hospitalization suggests that PIMs use may start the disability cascade in health older adults. Our findings emphasize the importance of caution when prescribing PIMs in older adults in otherwise good health.

Keywords

2019 AGS Beers Criteria; Disablement Process; Drug Related; Hospital Related

INTRODUCTION

Medications play a vital role in primary prevention and health maintenance, but any use of medication requires careful consideration of the balance between risk and benefit. This balance is particularly important in older adults, in whom physiological changes associated with aging alter the pharmacokinetic and pharmacodynamic response to medications leading to increased vulnerability to their adverse effects (1,2). Medications shown to be associated with excess morbidity (relative to potential benefit) in older adults are identified as 'potentially inappropriate medications' (PIMs) (3). Several explicit criteria, including the AGS Beers Criteria® and the STOPP criteria, have been developed to identify PIMs and guide prescribing decisions in older adults. PIMs have been associated with increased risk of hospitalization, worsening of physical function and death in vulnerable populations, such as those with cognitive impairment, or in aged care and inpatient care (4-8).

This research focus on PIMs in vulnerable populations creates an evidence-gap. Life expectancy at older ages is increasing (9) and, at the same time, the proportion of older people reporting fair or poor health status and significant functional limitations is decreasing (10). Many individuals now reach older age in relatively good health and live in the community without the confounding underlying morbidity and frailty that are prevalent in the vulernable populations where PIMs risks have been established. We have previously reported that community-dwelling 'healthy' older people have similar prevalence of PIMs to the general older population (11) but it is not known whether these medications carry increased risk of harm for healthy older adults as has been reported in those with poorer health status. Furthermore, previous research into PIMs has focussed on definitive outcomes such as mortality or hospitalization but not functional outcomes such as the ability to perform daily tasks, which are key to ongoing independence. Understanding the risk profile of PIMs in healthy older adults is necessary to determine how to balance the potential risks of certain medications against the potential benefits in this growing population group.

ASPirin in Reducing Events in the Elderly (ASPREE) was a randomized, placebo-controlled primary prevention trial of 100mg daily aspirin in community-dwelling older adults in Australia and the US (12). Participants were required to be in good health, free of pre-existing major cardiovascular disease, cognitively intact and able to independently perform basic activities of daily living. In this analysis, we aimed to determine if baseline PIMs use in community-dwelling older adults was a) associated with poorer functional outcomes (disability free survival, death, incident dementia, incident persistent disability) and hospitalization, and b) whether any risks observed were attributable to specific classes of PIMs.

METHODS

ASPREE Clinical Trial

This is a secondary analysis of data from ASPREE. Briefly, 19,114 healthy people aged 70 years or older (65 or older for US minorities) were randomized in Australia (n=16,703) and the US (n=2,411) (12). Recruitment commenced March 2010 and the trial concluded in June 2017, with a median 4.7 years of follow-up involving annual in-person study visits conducted between 2011 and 2017. At baseline, participants had lower prevalence of diabetes mellitus, osteoarthritis, chronic kidney disease, obesity, dyslipidemia and smoking and hence, were generally healthier than the broader population of a similar age (12). Furthermore, participants reported higher health-related quality of life (HRQoL) than the general older population (13). Detailed methods and results of ASPREE are described elsewhere (12,14).

Collection of medication from participants

Participants were asked to bring their medications, or a current medication list, to their baseline data collection visit. Research staff reviewed each medication and confirmed whether the medication was prescribed by the participant's doctor. All prescription medications were coded according to the World Health Organisation Anatomical and Therapeutic Chemical (ATC) coding system (https://whocc.no/atc_ddd_index/). Detailed methods of the medication collection and coding process have been described elsewhere (15).

Definitions

Potentially inappropriate medications (PIMs)—PIMs were defined as any medication where the overall risk associated with their use may outweigh possible benefit. For this analysis, any medication listed under Table 2 of the 2019 AGS Beers Criteria® for PIM use in older adults was included (3). Rather than using all the medications from the criteria, this subgroup of medications was chosen because of the strong recommendation to avoid, as opposed to other subgroups of medications that should be used with caution or avoided only for certain disease states. Where the data necessary to determine if the medication met the AGS Beers criteria® (*e.g.,* lack of dose, dosing regimen or indication data) were not collected, the medication was not considered to be PIM (*e.g.,* insulin sliding scale). Proton pump inhibitors (PPIs) were considered PIMs if they were not co-prescribed with a Non-steroidal Anti-Inflammatory Drug (NSAID). This analysis pertains to baseline medications

that were prescribed prior to the commencement of study medication (*i.e.* aspirin or placebo) for the trial. Further rationale for the choice of this criteria has been published elsewhere (11), and a full list of PIMs used in this analysis and medications that were excluded from PIMs analysis is included in Supplementary Table S1.

Covariates

Hypertension was defined as systolic blood pressure of ≥140 mmHg or diastolic blood pressure ≥ 90 mmHg or pharmaceutical treatment for high blood pressure. Diabetes was defined as self-report of diabetes or fasting blood glucose of ≥126 mg/dL or on pharmaceutical treatment for diabetes. Frailty was categorized on the basis of adapted Fried frailty criteria, which included body weight, strength, exhaustion, walking speed, and physical activity (16). The category of prefrail included participants who met one or two of these five criteria, and the category of frail included those who met three or more criteria. Polypharmacy was defined as presence of 5 or more prescription medications.

Outcomes

Loss of disability-free survival (hereafter DFS) was assessed using a composite of the first occurrence of death from any cause, dementia, or persistent physical disability. Persistent physical disability (hereafter disability) was defined as experiencing 'a lot of difficulty' or requiring assistance for any one of six basic activities of daily living for a period of at least 6 months (14). Dementia was confirmed using DSM-IV criteria by an independent adjudication committee. Details of the adjudication process have been published elsewhere (14). Incident disability and incident dementia analysis included the first occurrence of the event of interest regardless of whether it was preceded or followed by another event of interest. We also examined the association between PIMs and hospitalizations. In this analysis, incident hospitalization was defined as first admission to hospital for a period of 24 hours or more, for any reason.

Statistical analysis

Descriptive statistics (frequencies, percentages, means) were used to summarize PIMs' prevalence data. Unadjusted odds ratios (OR) were used to describe associations between baseline PIMs' exposure and each of age, study drug treatment group, polypharmacy and physical function (the ability to walk up one flight of stairs). Cox proportional-hazards regression models were used to estimate the association between baseline exposure to PIMs and DFS, and each of death, incident dementia, disability, and hospitalization. Models were then adjusted for previously identified confounders of PIMs within the ASPREE cohort (11): sex, age, country, years of education, frailty, average gait speed (usual walking speed over 3 meters), hypertension, diabetes, polypharmacy and the presence of depression (using the Center for Epidemiological Studies Depression (CESD)-10 questions score of ≥ 8) (12) at baseline. Confidence intervals were not adjusted for multiple comparisons. To disentangle the impact of PIMs from polypharmacy, a test for interaction between polypharmacy and PIM was conducted, and an analysis stratified by baseline polypharmacy is presented. To explore the relationship between disability and hospitalization we conducted sensitivity analysis in those who experienced both events.

RESULTS

At baseline, 7396 (39% of total) participants had prescription for at least one PIM (Figure 1). The proportion of participants who became lost to follow-up or died was similar between those with, and without a PIM, as was median follow-up time. Of those prescribed a PIM at baseline, 79% remained on at least one PIM throughout follow-up. Of those who were not prescribed a PIM at baseline, 46% were prescribed a PIM at some stage during follow-up. Participants who were aged 65-69 years were less likely (OR 0.72; 95%CI 0.59, 0.86) to be prescribed a PIM compared with those aged 70-74 and those aged 80-84 were more likely to be on a PIM (OR 1.22; 95%CI 1.11, 1.34), as were participants with polypharmacy or who reported any difficulty walking up a flight of stairs (Table 1). PPIs prescribed without concurrent NSAID use (54.8% of participants with PIMs use) were the most common PIMs, followed by NSAIDs without concurrent PPI use (17.3%), benzodiazepines (17%), androgens and estrogens (11.8%), and drugs with anti-cholinergic properties (11.6%) (see Table S2). With regard to PPI use, 4714 participants were prescribed PPIs at baseline(17). Of these 4054 (86%) were considered PIMs based on the 2019 AGS Beers Criteria®.

As shown in Table 2, comparing those without exposure to PIM to participants on a PIM, on adjusted analyses there was no clear evidence of a difference in risk of the loss of DFS (Adjusted HR 1.03; 95%CI 0.94, 1.13), death (Adjusted HR 0.92, 95%CI 0.81, 1.05) or incident dementia (Adjusted HR 0.93, 95%CI 0.79, 1.11). However, participants on a PIM had a higher rate of disability (7.3 per 1000 person years PIM vs 4.1 No PIM; Adjusted HR 1.47, 95%CI 1.21, 1.80) and hospitalization for any reason (126.3 per 1000 person years PIM vs 95.5 No PIM; Adjusted HR 1.26, 95%CI 1.20, 1.32). Of those who developed disability, 48% had previously reached the hospitalization outcome (n=198), 22% reached the hospitalization outcome after developing disability (n=92) and 30% were never hospitalized. For those with a prior hospitalization, the median time between hospitalization and disability was 401 days (IQR 181-857 days). For those with a subsequent hospitalization, the median time between disability and hospitalization was 247 days (IQR 73.5 – 469 days). Additional analysis of the disability and hospitalization outcomes is shown in Table S3. Those with exposure to PIM had higher risk of both hospitalization followed by disability (Adjusted HR 1.54, 95%CI 1.15, 2.05), and disability followed by hospitalization (Adjusted HR 1.92, 95%CI 1.25, 2.96).

Table 3 shows relationships between PIMs and outcomes stratified by polypharmacy. In those without polypharmacy, PIM exposure groups had similar risk for loss of DFS (Adjusted HR 0.95, 95% CI 0.83, 1.08), death (Adjusted HR 0.87, 95%CI 0.73, 1.03) and dementia (Adjusted HR 0.86, 95%CI 0.70, 1.08), but for the other outcomes participants on a PIM had a higher rates of disability (5.1 per 1000 person years PIM vs 3.4 No PIM; Adjusted HR 1.41, 95%CI 1.07, 1.86) and hospitalization (114.2 per 1000 person years PIM vs 89.2 per No PIM; Adjusted HR 1.23, 95%CI 1.16, 1.31) (Table 2 and Figure 2). However, in those with polypharmacy, similar rates of loss of DFS (Adjusted HR 0.98, 95%CI 0.84, 1.15), death (Adjusted HR 0.85, 95%CI 0.69, 1.06), disability (Adjusted HR 1.16, 95%CI 0.84, 1.57), dementia (Adjusted HR 1.07, 95%CI 0.78, 1.46) and incident hospitalization (Adjusted HR 1.04, 95%CI 0.95, 1.13) were observed between PIM exposure groups.

Supplementary Table S4 reports hazard ratios for comparison of PIM between those with and without polypharmacy, including an interaction between PIM and polypharmacy. The interaction term is significant only for hospitalization, and the relevant combination of coefficients suggests that compared to those with PIM and not polypharmacy, those with PIM and polypharmacy do not exhibit elevated risk, all other variables held constant.

Table S5 shows the relationship between the individual classes of PIM and clinical outcomes. There was an increased risk of disability associated with use of antipsychotics (Adjusted HR 1.96, 95%CI 1.17, 3.28), PPIs (Adjusted HR 1.34, 95%CI 1.07, 1.67), and benzodiazepines (Adjusted HR 1.38, 95%CI 1.01, 1.89). PPI use that met the criteria for PIM was associated with a lower risk of death following adjustment for confounders (12.1 events for 1000 person years No PIM vs 11.0 PIM, Adjusted HR 0.85, 95%CI 0.73, 0.99) and Table S6 shows cause of death within this group. No difference in rates was detected for any of the outcomes for cardiovascular PIMs or pain medications excluding NSAIDs.

DISCUSSION

Prescribing medications that have been identified as potentially inappropriate for older people requires consideration of the individual circumstances. In clinical practice, it may be deemed that the benefits outweigh the risks for a given individual, especially for adults who have reached older ages free of significant life-limiting illness or disability and therefore may be more robust. However, after adjustment for baseline comorbidities including frailty, we have found that PIM exposure in healthy older adults without major cardiovascular disease or baseline disability is associated with higher rates of incident physical disability and hospitalization. We found no difference in risk for death or dementia, both of which occurred more commonly than disability, and this resulted in a null finding for the broader category of disability free survivial.

Potential clinical impact of findings related to PIMs and physical disability

To our knowledge, this is the first study to explicitly explore associations between PIMs exposure and disability (defined as the persistent loss of at least one ADL) in community-dwelling older adults. Although there is a well-established association between specific PIMs and fracture (18-20), and fractures have been associated with disability (21), previous studies have lacked the longitudinal data required to explore disability based on persistent loss of functionality associated with activites of daily living. Recent studies of more vulnerable older people have shown that PIMs are associated with increased risk of functional decline following hospitalization (22), which suggests that hospitalization and disability may be components on a disease continuum with a hospitalization for PIMs initiating a cascade of events that results in functional decline. This raises the question as to whether hospitalization, which is a well established risk associated with PIMs use, may be driving the increased risk we observed for disability. However, this does not appear to be the case. Almost half of those who developed disability did not have a prior hospitalization. Sensitivity analysis found that PIMs exposure was associated with an increased risk of disability specifically in those for whom disability preceded hospitalization. This suggests that PIMs may increase the risk of disability through pathways that are not linked with

prior hospitalizations, and may even initiate the disability cascade in healthy older adults. Persistent loss of an ADL in older people has been associated with substantial reduction in health related quality of life (23). The ability to live independently is a critical factor in aging and loss of independence is a known fear among the general older population (24). Bearing this in mind, our findings of an almost 50% increase in the rate of persistent physical disability associated with exposure to PIMs suggests that caution is warranted when prescribing PIMs to older adults regardless of their health and function.

Context and interpretation of hospitalization and death findings

Findings of increased risk of hospitalization associated with PIMs exposure in our study were similar to those previously published (25-27), adding strength to the evidence that PIM use is associated with increased hospitalization not only in more vulnerable populations but also healthier older adults.

Overall, we did not observe any difference between the risk of death in those with PIM exposure compared to those without PIMs. While this result is consistent with recent studies in modestly sized cohorts (~500-600 people) of older people discharged from hospital or residents in nursing home who were likely to be more unwell (28,29), it contrasts with results of a larger (n=1606) study in Brazil that showed a 44% increase in the risk of death for PIMs using the 2012 AGS Beers Criteria® (30). Our study utilized the updated 2019 AGS Beers Criteria® and therefore included PPIs, which may explain the differences in results as PPIs were associated with a decreased risk of death on our cohort (see further discussion below). Notably, two recent studies have shown an association between increased risk of death and new initiation of PIMs but not longer term use (31,32). If ASPREE participants represent longer term PIMs users, then our findings would be in line with these two studies. However, ASPREE did not collect data on historical medication use and hence it was not possible to determine when those on PIMs at baseline were initially prescribed them.

Impact of polypharmacy on PIMs findings

In analysis stratified by polypharmacy, the raw rates of disability and hospitalization were higher in those with polypharmacy compared to those without polypharmacy regardless of PIM status. This is consistent with the well known risks of polypharmacy as an independent predictor of hospitalization and death in older people (33). However, we found that participants without polypharmacy who were exposed to PIMs had an increased risk of disability or hospitalization. This suggests that PIMs should still be prescribed but with caution for older people without polypharmacy.

Risk profile of individual PIMs

No single PIMs class appeared to be responsible for the increased risks we observed, and anti-psychotics, benzodiazepines and PPIs were all independently associated with increased risk of disability in our cohort. Given their established adverse effects, both antipsychotics and benzodiazepines have been consistently included on the list of PIMs from the initial publication by Beers (34) until the most recently released AGS Beers criteria (in 2019) (3). However, PPIs were only recently included. PPI use without appropriate clinical indication

or concurrent NSAID use was added to the 2019 criteria based on evidence of increased risk of Clostridium difficile infection and bone loss and fractures (3). Given that fractures are a risk factor for disability (35,36), our findings of increased risk of disability with PPI use is consistent with this rationale. However, we also observed association between PPI use and decreased risk of death. This beneficial association is in conflict with previous studies conducted in the general population and in more vulnerable older populations, where PPIs have been linked with increased risk of both mortality (37,38). The raw difference in mortality rates between those exposed to PPIs that met the criteria and those not exposed was small, and therefore it is possible that our mortality finding is an erroneous result that is attributable to adjustment for confounders. Additionally, our analysis was limited to medications that met the PIMs criteria according to Table 2 of the 2019 AGS Beers Criteria®. This meant that not all PPIs were considered to be PIMs, and examination of broader PPI use was beyond the scope of our analysis. While efforts have been made in recent years to reduce the number of older adults on high dose PPIs, longer term use of high-dose PPIs remains common in Australia, US, France and Iceland (39-43) . Therefore, we believe further investigation of the associations between PPI use and functional outcomes, and analysis of PPI use more broadly, may be warranted given the substantial proportion of older people taking this class of medication.

Potential impact of changes in prescription medication use during follow-up

Older people may change medications frequently. We chose to look at the impact of PIMs exposure at a certain point in time (baseline in the ASPREE study) rather than ongoing or time varying exposure in order to explore the simple clinical question of whether an older person who is currently on a PIM (for any reason) is at increased risk of poor functional outcomes. While the majority of participants (79%) who were on a PIM at baseline remained on a PIM throughout the entire follow-up period, many of those not prescribed PIMs at baseline commenced on a PIM at some point during follow-up (46%). If anything, initiation of PIMs in the No PIM group likely diluted the true difference between the the groups and result in an underestimation of the risk of disability associated with PIMs use. Therefore, we do not believe our findings are undermined by our chosen methodology, but instead reflect the real world prescribing environment.

Strengths & Limitations

A key strength of our study is the prospective design with regular physical disability screening and robust clinical event adjudication, which minimized ascertainment bias. We used a validated PIMs tool. We used a large sample of healthy older adults and were able to control for a wide range of demographic, lifestyle and known risk factors. Given the observational design, it is not possible to evaluate causality. Reverse causality is a major factor in measuring the association between medications and health outcomes. However, our participants were clinically free of dementia, myocardial infarction, stroke and other cardiovascular disease, such as transient ischemic attack or angina, at baseline and were independent with all ADLs. Overall, data quality was high with limited missing data (44).

This analysis accounted for a wide range of potential confounding variables, but potential for residual confounding remains. Our analysis was based on the presence of PIMs at

study entry, and we did not collect medication dose, nor did we collect non-prescription medications other than NSAID use. Length of exposure prior to randomization was not collected, and therefore we cannot rule out a selection bias caused by an impact of PIMs prior to enrollment. We could not account for changes in PIM exposure during follow-up. There was also a lack of information regarding the clinical indication surrounding the PIM, which limits the detail to which the 2019 AGS Beers Criteria® could be definitively applied. Previous research has shown that use of explicit criteria to evaluate prescribing may account for only a small portion of drugs deemed inappropriate by implicit review (45). Ascertainment of medications relied on self-report and the checking of packaging and prescriptions by study staff. However, wherever possible, medical records were used to prompt participants about medications they have may omitted, mitigating the limitations of self-report.

CONCLUSION

PIMs exposure at baseline was associated with increased the rates of incident physical disability and/or incident hospitalization in healthy older people without significant baseline cardiovascular, cognitive or physical impairment. Our findings emphasize the importance of caution when prescribing PIMs in older adults, including those in otherwise good health.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Key Points

- Among community-dwelling healthy older adults, PIMs use was associated with significantly increased risk of incident disability (defined as persistent loss of at least one ADL), and hospitalization.
- Increased risk of disability with PIMs use was evident in those for whom disability preceeded hospitalization, as well as *vice versa*.
- Polypharmacy did not modify the associations, and PIMs users without concurrent polypharmacy were at increased risk of disability and hospitalization.

What does this matter?

Our findings suggest that PIMs use may start the disability cascade among healthy community-dwelling older adults and confirm that caution is warranted when prescribing PIMs to older adults regardless of their health, function and polypharmacy status.

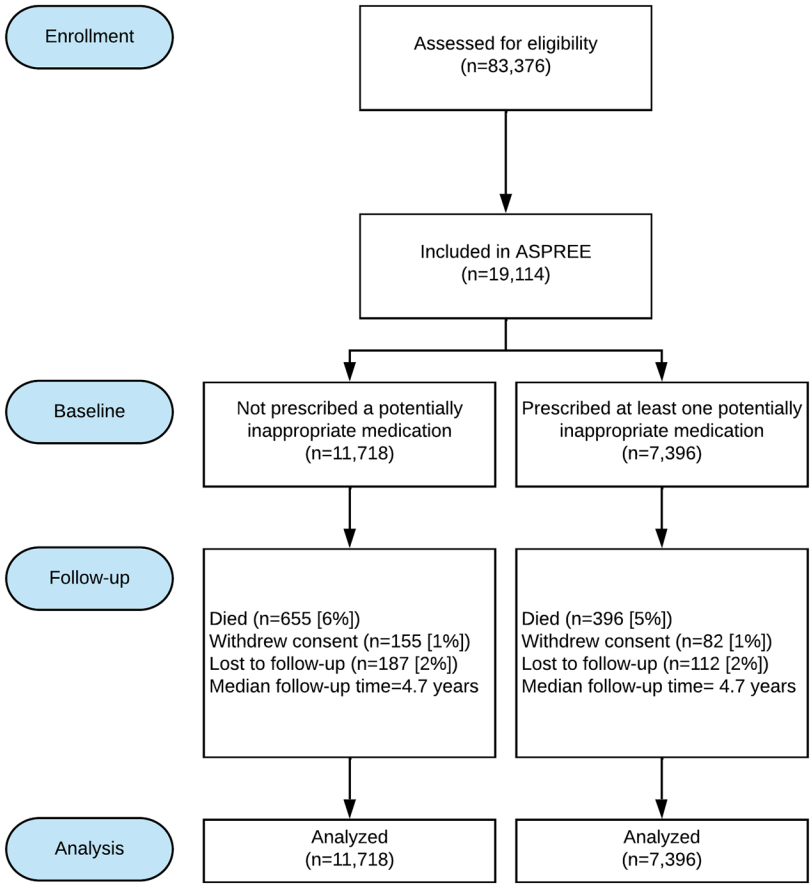

Figure 1: Participant follow-up by baseline PIMs exposure

For participants who withdrew from the trial, all information up to the point of withdrawal was included in the analysis.

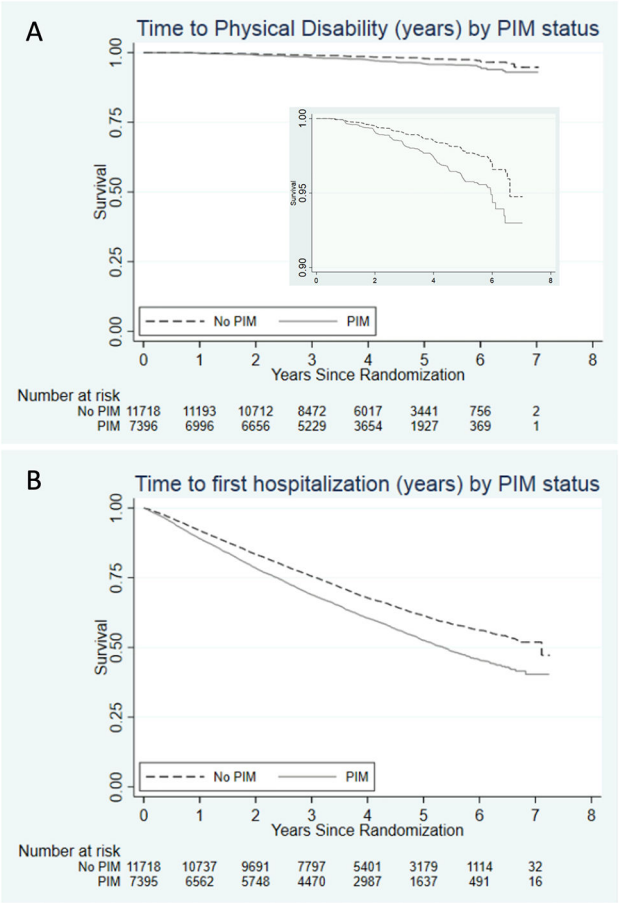

Figure 2: Kaplan-Meier curves for Disability and Hospitalization by baseline PIMs status (inset panel on figure A is the same curve with modified y-axis range of 0.90 - 1.00).

Table 1 –

Participant baseline characteristics grouped by presence or absence of PIMs, based on modified 2019 AGS Beers Criteria®

Group	No PIM (n=11,718)	PIM (n=7,396)	Odds Ratio (95% CI)
Age (n and percent)			
65-69	393 (3%)	173 (2%)	0.72 (0.59,0.86)
70-74	6,576 (56%)	4,022 (54%)	Reference
75-79	3,045 (26%)	1,977 (27%)	1.06 (0.99,1.14)
80-84	1,098 (9%)	840 (11%)	1.22 (1.11,1.34)
85+	606 (5%)	384 (5%)	1.04 (0.89,1.22)
Treatment group (n and percent)			
Placebo	5,817 (50%)	3,708 (50%)	Ref
Aspirin	5,901 (50%)	3,688 (50%)	1.02 (0.96,1.08)
Polypharmacy [a]			
No polypharmacy	9,885 (84%)	4,141 (56%)	Ref
Polypharmacy	1,833 (16%)	3,255 (44%)	4.24 (3.94,4.55)
Difficulty walking up one flight of stairs			
No difficulty	10,295 (88%)	5,970 (81%)	Ref
Any level of difficulty	1,423 (12%)	1,426 (19%)	1.72 (1.59, 1.87)

[a]Polypharmacy defined as concurrent use of 5 or more prescription medications

Table 2 –

Risk of disability free survival, death, dementia, persistent disability or hospitalization outcomes by baseline PIMs exposure, based on modified 2019 AGS Beers Criteria®

	No PIM (n=11,718)		PIM (n=7,396)		Unadjusted hazard ratio (95% CI)	Adjusted hazard ratio (95% CI)[a]
	N	Rate per 1000 person years (95% CI)	N	Rate per 1000 person years (95% CI)		
Loss of disability free survival [b]	1086	20.5 (19.3, 21.7)	749	22.7 (21.1, 24.4)	1.12 (1.02, 1.23)	1.03 (0.94, 1.13)
Death	655	12.0 (11.2, 13.0)	397	11.7 (10.6, 12.9)	0.98 (0.86, 1.11)	0.92 (0.81, 1.05)
Incident[c] disability	197	4.1 (3.6, 4.8)	215	7.3 (6.4, 8.4)	1.8 (1.50, 2.20)	1.47 (1.21, 1.80)
Incident dementia[c]	357	6.9 (6.2, 7.6)	218	6.7 (5.9, 7.7)	0.98 (0.83, 1.17)	0.93 (0.79, 1.11)
Incident Hospitalization	4196	95.5 (92.6, 98.4)	3245	126.3 (122.0, 130.1)	1.33 (1.20, 1.40)	1.26 (1.20, 1.32)

[a] Adjusted for sex, age, country, years of education (<12y, vs 12y+), frailty, average gait speed, hypertension, diabetes, and the presence of depression.

[b] Composite of first occurance of death from any cause, incident dementia or incident physical disability

[c] Incident includes the first occurance of disability or dementia regardless of whether the event was preceded by another event of interest (e.g. incident disability includes the first occurrence of disability regardless of whether that disability was preceded by dementia)

Table 3 –

Risk of disability free survival, death, dementia, disability and hospitalization outcomes by baseline PIMs exposure, based on modified 2019 AGS Beers Criteria®, stratified by polypharmacy status

	No PIM (n=11,718)		PIM (n=7,396)		Adjusted[a] Hazard Ratio
	N	Rate per 1000 person years (95% CI)	N	Rate per 1000 person years (95% CI)	HR (95%CI)
No polypharmacy (n = 14,026)					
Loss of disability free survival [b]	846	18.8 (17.6, 20.2)	341	18.2 (16.3, 20.2)	0.95 (0.83, 1.08)
Death	509	11.1 (10.1, 12.1)	188	9.8 (8.5, 11.3)	0.87 (0.73, 1.03)
Incident disability[c]	137	3.4 (2.9, 4.0)	86	5.1 (4.2, 6.4)	1.41 (1.07, 1.86)
Incident dementia[c]	297	6.8 (6.0, 7.6)	109	5.9 (4.9, 7.4)	0.86 (0.70, 1.08)
Incident Hospitalization	3368	89.2 (86.3, 92.3)	1699	114.2 (108.9, 119.7)	1.23 (1.16, 1.31)
Polypharmacy (n= 5088)					
Loss of disability free survival [b]	240	29.7 (26.2, 33.7)	408	28.7 (25.9, 31.6)	0.98 (0.84, 1.15)
Death	146	17.4 (14.8, 20.5)	209	14.1 (12.3, 16.2)	0.85 (0.69, 1.06)
Incident disability[c]	60	8.4 (6.5, 10.8)	129	10.3 (8.7, 12.2)	1.16 (0.84, 1.57)
Incident dementia[c]	60	7.6 (5.9, 9.8)	109	7.8 (6.5, 9.4)	1.07 (0.78, 1.46)
Incident Hospitalization	828	133.5 (124.8, 143.0)	1546	143.0 (136.0, 150.3)	1.04 (0.95, 1.13)

[a] Adjusted for sex, age, country, years of education (<12y, vs 12y+), frailty, average gait speed, hypertension, diabetes, and the presence of depression.

[b] Composite endpoints of death from any cause, incident dementia or incident physical disability.

[c] Incident includes the first occurance of disability or dementia regardless of whether the event was preceded by another event of interest (e.g. incident disability includes the first occurrence of disability regardless of whether that disability was preceded by dementia).