Published in final edited form as:

J Am Geriatr Soc. 2019 December ; 67(12): 2458–2462. doi:10.1111/jgs.16243.

Medication Use Quality and Safety in Older Adults: 2018 Update

Nagham J. Ailabouni, BPharm, PhD^{*}, Zachary A. Marcum, PharmD, PhD^{*}, Kenneth E. Schmader, MD^{†,‡}, Shelly L. Gray, PharmD, MS^{*}

^{*}Department of Pharmacy, University of Washington, Seattle, Washington;

[†]Department of Medicine (Geriatrics), School of Medicine, Duke University Medical Center, Durham, North Carolina;

[‡]Geriatric Research Education and Clinical Center, Durham Veterans Affairs Medical Center, Durham, North Carolina.

Abstract

Improving the quality of medication use and medication safety is an important priority for prescribers who care for older adults. The objective of this article was to identify key articles from 2018 that address these issues. In addition, we selected four of these articles to annotate, critique, and discuss their broader implications for clinical practice. The first study highlights a cluster-randomized trial that utilized a pharmacist-led education-based intervention delivered to both patients and physicians to deprescribe four types of inappropriate medications (sedative-hypnotics, first-generation antihistamines, selective nonsteroidal anti-inflammatory drugs, and glyburide). The second study, a nested case-control study using data from within the UK Clinical Practice Research Datalink, examined the association between anticholinergic exposure, overall and by anticholinergic medication class, and dementia risk in 40 770 older adults. The third study, a longitudinal cohort study of 1028 Swedish older adults, examined the association between antihypertensive medications and incident dementia. The last study was a randomized, double-blind, placebo-controlled trial that investigated the effect of daily low-dose aspirin (100 mg) for primary prevention on cardiovascular events and major hemorrhage in 19 144 community-dwelling older adults. Collectively, this current article provides insight into the pertinent topics of medication use quality and safety in older adults and helps raise awareness about optimal prescribing in older adults.

Keywords

deprescribing; drug-related problems; inappropriate prescribing; older adults; polypharmacy

Address correspondence to Nagham J. Ailabouni, BPharm, PhD, School of Pharmacy, 1959 Northeast Pacific Street, H362 Health Sciences Building, University of Washington, Seattle, WA 98195-7630. naghamja@uw.edu.

Author Contributions: All authors contributed to the writing of this article and approved the final version before submission.

Conflict of Interest: The authors have no conflicts of interest.

SUPPORTING INFORMATION

Additional Supporting Information may be found in the online version of this article.

Supplementary Appendix S1: List of journals manually searched

Supplementary Appendix S2: List of 2018 articles that addressed medication use quality and safety

Suboptimal prescribing is prevalent in older adults and can increase the risk of adverse drug events and other drug-related morbidity and mortality.^{1–4} Aspects of suboptimal prescribing include unnecessary polypharmacy, potentially inappropriate medications (PIMs), and underuse of medications (ie, potential prescribing omissions [PPOs]). Unnecessary polypharmacy is defined as the prescription of at least one medication that is not clinically indicated.^{1,3} PIMs refer to medications where the potential harm outweighs any perceived or actual health benefits.² Last, PPOs refer to medications with known therapeutic benefits for preventing morbidity and mortality (eg, not prescribing an angiotensin-converting enzyme inhibitor [ACE-I] for an older adult following a myocardial infarction [MI]),^{1,4} hence resulting in potential therapeutic failure. All prescribers strive to avoid suboptimal prescribing and medication safety issues in older adults to achieve desired therapeutic outcomes.

Collating and summarizing the most pertinent literature related to the quality use of medications and/or medication safety among older adults can be challenging due to the lack of specific search terms available in computerized databases. Therefore, the objective of this article was to identify key articles published in 2018 that addressed these issues. We selected and summarized four articles from this list and have discussed their broader clinical implications.

METHODS

An OVID Medline search was conducted and restricted to articles published in 2018, English language, humans, and older adults (aged ≥ 65 years) to capture articles related to the following topics: adverse drug events, adverse drug withdrawal events (ADWEs), drug-related problems, medication adherence, medication administration, medication dispensing, medication errors, medication misadventures, medication monitoring, medication-related problems, polypharmacy, suboptimal prescribing, therapeutic failure, and underutilization. We also performed a manual search for additional relevant articles from select high-impact journals (Supplementary Appendix S1). A Google Scholar search using terms “inappropriate prescribing” and “deprescribing/de-prescribing” was also conducted to supplement the search.

We included articles that addressed innovative objectives and those that utilized rigorous observational or experimental designs with reliable and valid measures. We excluded studies published in journals that regularly publish articles related to the topics mentioned above and, thus, are more easily identified by readers (ie, consultant pharmacist, drugs, and aging). Additionally, we excluded review articles (except systematic reviews with a meta-analysis), cross-sectional studies, case series, case reports, and small single-center epidemiological studies.

Sixty-nine articles were identified after one author (N.A.) reviewed article titles and abstracts for relevance. Of these articles, three coauthors (N.A., S.G., and Z.M.) reviewed abstracts and full texts to determine their eligibility. Disagreements were resolved by discussion. Of the remaining 59 articles, we individually rated the top articles based on the quality of methods employed, innovativeness of the research question, and significance of

clinical impact to select the four articles to feature in this special article by consensus. We categorized the remaining articles under major headings in Supplementary Appendix S2.

SUMMARY OF STUDIES

Deprescribing Through Patient Empowerment and Physician Engagement

The developing pharmacist-led research to educate and sensitize community residents to the inappropriate prescription burden in the elderly (D-PRESCRIBE) trial compared the effectiveness of a pharmacist-led intervention that involved educating older adults and their physicians about the harms of inappropriate medications vs usual care.⁵ Martin et al⁵ achieved this by conducting a two-group, parallel, pragmatic, cluster-randomized clinical trial in Quebec, Canada, with randomization at the pharmacy level. Patients were eligible if they were aged 65 years or older and had filled a prescription for one of the target medications (sedative-hypnotics [eg, benzodiazepines, zopiclone, and zolpidem], first-generation antihistamines, glyburide, and selective nonsteroidal anti-inflammatory drugs [NSAIDs]) for at least three consecutive months before screening. The goal of the intervention was to facilitate a shared-decision conversation by conveying information related to the medications' harms to both the patient and the physician *prior* to the physician-patient encounter.⁵ Pharmacists used medication-specific brochures to educate patients and adapted evidence-based pharmaceutical opinions that were sent to physicians. A 16-week tapering schedule was recommended for sedative-hypnotic medications. Other target medications were discontinued based on provider discretion. The primary outcome was the discontinuation of a target medication at 6 months.

In total, 489 eligible patients (mean age = 75 years; 66% women) from 69 pharmacies were included. Complete discontinuation of target medications occurred in 42.7% (n = 106) of participants in the intervention group compared to 12% (n = 29) of participants in the control group (risk difference [RD] = 31%; 95% confidence interval [CI] = 23%–38%). The highest discontinuation rate occurred in NSAID users (57.6% vs 21.7% for controls; RD = 35%; 95% CI = 10%–55%), followed closely by sedative-hypnotic users (43.2% vs 9% for controls; RD = 34%; 95% CI = 25%–43%) and last by glyburide users (30.6% vs 13.8% for controls; RD = 17%; 95% CI = 2%–31%). Antihistamine discontinuation was not analyzed because of the small sample size. Of 77 patients who attempted to taper sedative-hypnotics, 29 (38%) reported ADWEs.

In the intervention group, 79% of participants (197 of 248) reported a physician encounter in which deprescribing was discussed. Of the participants who completed the 6-month follow-up (n = 219), 66% of physicians had received pharmaceutical opinions. Medication discontinuation was slightly higher for participants in whom a pharmaceutical opinion was sent relative to those in whom an opinion was not sent. This, however, was not significantly different (RD = 8%; 95% CI = –6% to 22%). Reasons why pharmacists refrained from sending these included patients' wishes and patients already stopping the medication.

A prior study conducted by these authors (Eliminating Medications Through Patient Ownership of End Results [EMPOWER]) examined the effect of patient education alone and found a discontinuation rate of 27% of participants' benzodiazepines vs 5% in controls.⁶ A

slightly higher number of EMPOWER participants (42%) experienced ADWEs in comparison to the current study. Additionally, the EMPOWER authors found that one reason that patients chose not to deprescribe medications was physician/pharmacist resistance. The current trial, therefore, overcame this by utilizing pharmacists to engage *both* patients and physicians in the deprescribing process. Other strengths include implementing a randomized study design, a low attrition rate (89% completed the trial), and a patient-centered approach integral to successful deprescribing.

A few limitations should be noted. A 6-month study period was relatively short to examine long-term discontinuation of medications. As evidenced by the variation in RDs among medication classes, the success of this approach could vary by medication type.

Several factors could help improve the uptake of deprescribing, including identifying barriers that prevent older adults from initiating a deprescribing conversation and developing and utilizing tools with high predictive validity that aim to assess older adults' willingness to deprescribe and clinician screening tools that identify older adults who would be receptive to deprescribing.⁷ Nevertheless, this study demonstrates a promising intervention to successfully deprescribe medications.

Anticholinergics and Dementia Risk

Richardson and colleagues examined the association between anticholinergic exposure and dementia risk by conducting a rigorous nested case-control study using data from within the UK Clinical Practice Research Datalink.⁸ This study included 40 770 participants, aged 65 years or older, with a diagnosis of dementia between April 2006 and July 2015 and 283 933 controls without dementia. The Anticholinergic Cognitive Burden (ACB) scale was used to define exposure from 4 to up to 20 years before a dementia diagnosis.⁹ Medications with possible anticholinergic effects (ACB score of 1 [ACB1]) were defined as those with serum anticholinergic activity or in vitro affinity to muscarinic receptors, but their clinical impact is uncertain (eg, atenolol). Medications with an ACB score of 2 (ACB2) (eg, carbamazepine) or an ACB score of 3 (ACB3) (eg, amitriptyline) are considered to have definite anticholinergic effects with established, clinically relevant cognitive effects, with ACB3 medications having reports of delirium. The primary analysis focused on number of defined daily doses (DDDs) of medications according to the ACB score.¹⁰

The most consistent findings were found with ACB3 medications. During the exposure period, 14 453 (35%) cases and 86 403 (30%) controls were prescribed at least one ACB3 medication. The adjusted odds ratio (OR) for dementia with any exposure to an ACB3 medication was 1.11 (95% CI = 1.08–1.14). Importantly, people prescribed greater dosage quantities of definite anticholinergics (ACB3) had a higher risk of dementia. Use consistent with the highest dose category (>1460 DDDs) was associated with an adjusted OR for dementia of 1.57 (95% CI = 1.18–2.09) for ACB2 medications and 1.31 (95% CI = 1.22–1.41) for ACB3 medications. A cumulative dose-response relation was not found for ACB1 medications.

In a secondary analysis examining ACB3 medication at the class level, the risk of dementia increased with greater exposure to antidepressant, urological, and antiparkinsonian

medications, but not with antipsychotics, respiratory, and gastrointestinal agents. This pattern of results was observed for exposures occurring 15 to 20 years before a dementia diagnosis. The authors concluded that “future research should examine anticholinergic drug classes as opposed to anticholinergic effects intrinsically or summing scales for anticholinergic exposure.”

The results from this large representative sample of older adults confirm mounting evidence that overall anticholinergic exposure may be associated with increased dementia risk.^{11,12} The authors carefully dealt with reverse causation bias that can occur because anticholinergics are used for early symptoms (prodromal) of dementia before the diagnosis, by excluding anticholinergics in the 4 years prior to the index date. Another strength is the long exposure window that was examined before the index date; information about medication use was available for 10 to 15 years for 59% of participants and for 15 to 20 years for 26% of participants. Last, the authors controlled for several important covariates, including indications for anticholinergic medications. Taken together, these strengths have extended research in this area.^{11–13}

A few limitations should be noted. One is that identifying dementia cases from administrative files might underestimate the true rates of the disease diagnosed compared with using a consistent prospective population-based ascertainment approach.¹³ Another concern is unmeasured or residual confounding, especially the ability to measure the severity of depression.

These findings challenge the current thinking that anticholinergic exposure should be measured using all medications with these effects. Additional research is needed to further elucidate the underlying biological mechanisms and examine dementia risk with specific anticholinergic medication classes. In the meantime, providers should consider non-pharmacological and other pharmacological alternatives instead of anticholinergics in older adults.^{2,14} As an example, for depression, citalopram and sertraline are preferred over paroxetine for depression. Also, second-generation antihistamines (eg, cetirizine) are preferred over first-generation antihistamines, such as chlorpheniramine.

Antihypertensive Medication Regimen Intensity and Incident Dementia

To assess the association between antihypertensive medication regimen intensity and risk of incident dementia, a longitudinal cohort study of Swedish older adults, aged 78 years or older, was analyzed.¹⁵ Participants included both community-dwelling and institutionalized older adults without dementia at baseline, who were followed up at 3 and 6 years. Antihypertensive use was collected by a physician’s clinical examination for community-dwelling participants and via medical records for institutionalized participants. For antihypertensive dose, the prescribed daily dose (PDD) was used, defined as the proportion of antihypertensive daily dose divided by the DDD. The PDDs were summed for those participants taking more than one antihypertensive. A total of 1208 participants (mean age = 84.1 years) were included.

The authors found that the number of antihypertensive medication use was significantly associated with reduced risk of incident dementia (adjusted hazard ratio [aHR] = 0.68; 95%

CI = 0.55–0.84) after adjusting for potential confounders. In addition, the total PDD was associated with reduced risk of incident dementia (aHR = 0.70; 95% CI = 0.57–0.86). These results were robust in comparison to analyses that adjusted for the competing risk of all-cause mortality. On the individual antihypertensive subclass level, ACE-I (aHR = 0.49; 95% CI = 0.25–0.96) and calcium channel blocker (CCB) use (aHR = 0.49; 95% CI = 0.24–0.99) were both associated with lower dementia risk. However, these results were no longer statistically significant after adjusting for the competing risk of all-cause mortality. The competing risk model, however, revealed diuretic use to be significantly associated with lower dementia risk (aHR = 0.66; 95% CI = 0.44–0.99).

This study has several strengths, including the use of longitudinal antihypertensive exposure data, with a median follow-up longer than 5 years and the assessment of antihypertensive dosage. However, there are important additional considerations. The authors had relatively small sample sizes for antihypertensive subclass use, and these results should be interpreted with caution. In particular, the finding that ACE-I and CCB use was associated with reduced dementia risk was no longer statistically significant in the competing risk model for mortality. This suggests that these results may be due to increased mortality risk. Moreover, the study had few users of angiotensin receptor blockers, which have been found to be associated with a reduced risk of clinical and neuropathological dementia outcomes.^{16–18} In addition, CCBs and diuretics were measured as singular subclasses, preventing the ability to assess potential differences across the subtypes (eg, thiazide vs loop). Finally, the analysis adjusted for baseline history of hypertension rather than time-varying blood pressure, introducing the potential for confounding.

These results are consistent with research that shows antihypertensive use is associated with a reduced risk of dementia.¹⁶ However, this literature is discrepant in terms of which individual antihypertensive subclasses are associated with a reduced risk. This is likely due to study design differences. For example, observational studies assessing dementia incidence have used baseline or short antihypertensive exposure measurement periods and enrolled older age groups. Antihypertensive use starting several years prior to subclinical cognitive impairment and continuing long-term may provide more benefits to brain health than currently described in the literature.¹⁹ Participants' mean age at baseline in this study was approximately 84 years; future research is needed on the effect of antihypertensive medications initiated in patients at midlife on late-life dementia.¹⁵

Effect of Aspirin on Cardiovascular Events and Bleeding in Healthy Elderly

This study reports secondary end points from the Aspirin in Reducing Events in the Elderly trial, which found that daily low-dose aspirin (100 mg) for primary prevention did not reduce disability-free survival in healthy older adults.²⁰ McNeil et al conducted a randomized, double-blind, placebo-controlled trial to evaluate the effect of daily use of 100 mg of enteric-coated aspirin on prespecified secondary end points of cardiovascular events and major hemorrhage in community-dwelling older adults, aged 70 years or older, from Australia and the United States (or 65 years among blacks and Hispanics in the United States).²¹ Potential participants were excluded if they had overt coronary heart disease, overt cerebrovascular disease, atrial fibrillation, dementia, clinically significant physical disability,

a high bleeding risk, anemia, a known contraindication to or inability to take aspirin, current regular use of an anticoagulant or antiplatelet medication other than aspirin, a systolic blood pressure of 180 mm Hg or higher or a diastolic blood pressure of 105 mm Hg or higher, or limited life expectancy of less than 5 years.

The cardiovascular event outcome was a composite of fatal coronary heart disease, nonfatal MI, fatal/nonfatal stroke, or hospitalization for heart failure. The major hemorrhagic event outcome was a composite of hemorrhagic stroke, symptomatic intracranial bleeding, or clinically significant extracranial bleeding, defined as bleeding that led to transfusion, hospitalization, prolongation of hospitalization, surgery, or death.

Of the 19 114 persons enrolled in the trial, 9525 were randomized to receive aspirin and 9589 were randomized to receive placebo. The demographic characteristics of the groups were well balanced. Of the population, 50% was 75 years and older; 5% was black. After a median of 4.7 years of follow-up, the rate of cardiovascular outcomes was 10.7 events per 1000 person-years in the aspirin group and 11.3 events per 1000 person-years in the placebo group (HR = 0.95; 95% CI = 0.83–1.08). The rate of major hemorrhage outcomes was 8.6 events per 1000 person-years in the aspirin group and 6.2 events per 1000 person-years in the placebo group (HR = 1.38; 95% CI = 1.18–1.62; $P < .001$). The findings for MI or stroke alone were similar.

This large, high-quality study had multiple strengths, including the randomized blinded control design, intention-to-treat analysis, groups that were similar with respect to prognostic factors, valid outcome measurement, inclusion of medication adherence measures, and excellent follow-up, with only 1.5% to 1.6% attrition. A limitation of this trial was the low adherence rate, with only two-thirds of participants still taking aspirin by the end of the trial. This possibly underestimates the benefit of aspirin on cardiovascular outcomes and its associated bleeding risks. The trial enrolled healthy community-dwelling older adults, and many eligibility criteria excluded older adults commonly encountered in clinical practice, thus limiting generalizability.

These findings have considerable public health implications as millions of older adults take aspirin for primary prevention.²¹ The results of this trial indicate that the risks of taking aspirin for primary prevention likely outweigh the benefits in healthy community-dwelling older adults. Additionally, according to the 2019 American College of Cardiology/American Heart Association guideline update on the primary prevention of cardiovascular disease, low-dose oral aspirin (ie, 75–100 mg) should not be routinely administered for the primary prevention of atherosclerotic cardiovascular disease among adults older than 70 years.²² In addition, aspirin should be avoided in older adults who are at an increased risk for bleeding (eg, warfarin/NSAID users). Prescribers should individually assess the expected benefits and bleeding risk for older adults prior to prescribing low-dose aspirin for primary cardiovascular disease prevention.

DISCUSSION

We identified and provided a critique for four studies published in 2018 articles that highlight important topics relating to medication quality and safety. The first study features a successful deprescribing pharmacist-led educational intervention targeting patients and physicians that led to a significant discontinuation of inappropriate medications, with a number needed to treat of 3.⁵ The second study confirmed results of prior research that increasing use of anticholinergics was associated with increased dementia risk; however, new findings suggest that only some anticholinergic medication classes may increase dementia risk.⁸ The third study found that the use of certain antihypertensive medications is associated with a reduced risk of developing dementia; additional comparative effectiveness research on this important emerging topic is needed before recommending specific antihypertensives.¹⁵ The last study showed that use of low-dose aspirin for primary prevention in older adults resulted in a significantly higher risk of major hemorrhage and did not result in a significantly lower risk of cardiovascular disease than placebo.²¹ Together, these studies along with the supplementary material highlight the ongoing challenge of optimizing medication quality and safety in older adults and highlight potential opportunities to improve the quality of prescribing and health of older adults.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ACKNOWLEDGMENTS

Financial Disclosure: Dr Gray received support from a National Institute on Aging National Institutes of Health grant (U01AG00678). Dr Marcum was supported by an Agency for Healthcare Research and Quality grant (K12HS022982). Dr Schmader received support from the National Institute on Aging, Duke Pepper Older Americans Independence Center (P30AG028716).

Sponsor's Role: None.

REFERENCES

1. Zullo AR, Gray SL, Holmes HM, Marcum ZA. Screening for medication appropriateness in older adults. *Clin Geriatr Med*. 2018;34:39–54. [PubMed: 29129216]
2. American Geriatrics Society. 2019 updated AGS Beers Criteria(R) for potentially inappropriate medication use in older adults. *J Am Geriatr Soc*. 2019; 67:674–694. [PubMed: 30693946]
3. Shah BM, Hajjar ER. Polypharmacy, adverse drug reactions and geriatric syndromes. *Clin Geriatr Med*. 2012;28:173–186. [PubMed: 22500537]
4. Gallagher P, Ryan C, Byrne S, Kennedy J, O'Mahony D. STOPP (Screening Tool of Older Person's Prescriptions) and START (Screening Tool to Alert doctors to Right Treatment): consensus validation. *Int J Clin Pharmacol Ther*. 2008;46:72–83. [PubMed: 18218287]
5. Martin P, Tamblyn R, Benedetti A, Ahmed S, Tannenbaum C. Effect of a pharmacist-led educational intervention on inappropriate medication prescriptions in older adults: the D-PRESCRIBE randomized clinical trial. *JAMA*. 2018;320:1889–1898. [PubMed: 30422193]
6. Tannenbaum C, Martin P, Tamblyn R, Benedetti A, Ahmed S. Reduction of inappropriate benzodiazepine prescriptions among older adults through direct patient education: the EMPOWER cluster randomized trial. *JAMA Intern Med*. 2014;174:890–898. [PubMed: 24733354]
7. Turner JP, Martin P, Zhang YZ, Tannenbaum C. Patients beliefs and attitudes toward deprescribing: can deprescribing success be predicted? *Res Soc Adm Pharm*. 2019.

8. Richardson K, Fox C, Maidment I, et al. Anticholinergic drugs and risk of dementia: case-control study. *BMJ*. 2018;361:k1315. [PubMed: 29695481]
9. Campbell NL, Maidment I, Fox C, Khan B, Boustani M. The 2012 update to the anticholinergic cognitive burden scale. *J Am Geriatr Soc*. 2013;61:142–143.
10. WHO Collaborating Centre for Drug Statistics Methodology. ATC Classification Index With DDDs Oslo, Norway 2017 https://www.whocc.no/atc_ddd_index_and_guidelines/atc_ddd_index/. Accessed June 7, 2017.
11. Carriere I, Fourrier-Reglat A, Dartigues JF, et al. Drugs with anticholinergic properties, cognitive decline, and dementia in an elderly general population: the 3-city study. *Arch Intern Med*. 2009;169:1317–1324. [PubMed: 19636034]
12. Gray SL, Hanlon JT. Anticholinergic medication use and dementia: latest evidence and clinical implications. *Ther Adv Drug Saf*. 2016;7:217–224. [PubMed: 27695623]
13. Gray SL, Anderson ML, Dublin S, et al. Cumulative use of strong anticholinergics and incident dementia: a prospective cohort study. *JAMA Intern Med*. 2015;175:401–407. [PubMed: 25621434]
14. Hanlon JT, Semla TP, Schmader KE. Alternative medications for medications in the use of high-risk medications in the elderly and potentially harmful drug-disease interactions in the elderly quality measures. *J Am Geriatr Soc*. 2015;63:e8–e18. [PubMed: 26447889]
15. Tan ECK, Qiu C, Liang Y, et al. Antihypertensive medication regimen intensity and incident dementia in an older population. *J Am Med Dir Assoc*. 2018;19:577–583. [PubMed: 29306604]
16. Levi MN, Macquin-Mavier I, Tropeano AI, Bachoud-Levi AC, Maison P. Antihypertensive classes, cognitive decline and incidence of dementia: a network meta-analysis. *J Hypertens*. 2013;31:1073–1082. [PubMed: 23552124]
17. Li NC, Lee A, Whitmer RA, et al. Use of angiotensin receptor blockers and risk of dementia in a predominantly male population: prospective cohort analysis. *BMJ*. 2010;b5465:340.
18. Hajjar I, Brown L, Mack WJ, Chui H. Impact of angiotensin receptor blockers on Alzheimer disease neuropathology in a large brain autopsy series. *Arch Neurol*. 2012;69:1632–1638. [PubMed: 22964777]
19. Livingston G, Sommerlad A, Orgeta V, et al. Dementia prevention, intervention and care. *Lancet*. 2017;390:2673–2734. [PubMed: 28735855]
20. McNeil JJ, Woods RL, Nelson MR, et al. Effect of aspirin on disability-free survival in the healthy elderly. *N Engl J Med*. 2018;379:1499–1508. [PubMed: 30221596]
21. McNeil JJ, Wolfe R, Woods RL, et al. Effect of aspirin on cardiovascular events and bleeding in the healthy elderly. *N Engl J Med*. 2018;379:1509–1518. [PubMed: 30221597]
22. Arnett DK, Blumenthal RS, Albert MA, et al. ACC/AHA guideline on the primary prevention of cardiovascular disease. *J Am Coll Cardiol*. 2019;2019:26029.