**Stratifying patients for polypharmacy interventions: the case for a new biomarker?**

Commentary – BJCP – on Bengaard *et al*. Using soluble urokinase plasminogen activator receptor to stratify patients for medication review in the emergency department

The benefittoharm balance of aspirin has been further questioned

recently. What should prescribers do? The European Society of

Cardiology (ESC) Guidelines, most recently updated in 2016,

1

do

not recommend the use of aspirin for primary prevention (patients

without prior major cardiovascular or cerebrovascular event) due to

the high risk of bleeding. This position is now further supported by

the results of the Aspirin in Reducing Events in the Elderly ASPREE

trial.

2

Aspirin significantly increased the risk of major haemorrhage

without lowering the risk of cardiovascular disease, compared to

placebo.

In the British Journal of Clinical Pharmacology, Ardoino and col-

leagues found high rates of prescription of antiplatelet drugs (with

aspirin being the most frequently chosen): almost half (43.6%, 95%

CI, 41.545.7) of 959 patients aged 65 or over in Italian and Spanish

internal medicine and geriatric wards in 2012 and 2014 (as part of

the REPOSI [REgistro POliterapie SIMI] register).

3

Moreover, just over

half (52.1%) were prescribed aspirin inappropriately. In most cases,

this was overprescription (74.2%) in patients with a Systematic Coro-

nary Risk Evaluation Project (SCORE) <10%. Against this overprescrip-

tion of aspirin for primary prevention, Ardoino et al also found

substantial underprescription (30.6%) of antiplatelet agents in patients

who were secondary prevention.

3

Ardoino et al also found further inappropriate use of antiplatelets

in patients with atrial fibrillation (AF)—who should have been

anticoagulated.

The risks of major bleeding and stroke with aspirin and anticoagu-

lants used for AF has been reported in the Journal by Gieling et al,

who studied their use in 31,497 patients with AF (20082014) using

the UK Clinical Practice Research Datalink.

4

Aspirin was found to have

a similar bleeding risk to vitamin K antagonists (VKAs) but that VKAs

were more effective than aspirin (hazard ratio [HR] 2.18, 95% confi-

dence interval [95% CI], 1.832.59) in the prevention of ischaemic

stroke. Whilst Nonvitamin K antagonist oral anticoagulants (NOACs)

were similarly effective as VKA in preventing ischaemic stroke (HR

1.22, 95% CI, 0.672.19), they were associated with double the risk

of major bleeding—mainly gastrointestinal (2.07, 95% CI, 1.273.38),

a risk restricted to women (HR 3.14, 95% CI, 1.765.60). However,

caution should be applied as this was a retrospective cohort study,

albeit in a large population.

Despite this poor benefittoharm balance of aspirin, Parekh et al

found that antiplatelets agents were only 13th on a list of

medications associated with medicationrelated harms (MRH) follow-

ing hospital discharge in 1280 older adults.

5

Aspirin was behind opi-

ates, antibiotics, benzodiazepines, diuretics and antihypertensives.

The overall incidence of MRHassociated hospital readmission was

~8% (78 per 1000 discharges), at an estimated cost to the National

Health Service of £396 million annually, over 60% of which (£243 mil-

lion) was considered to be potentially preventable.

5

Therefore, whilst prescribers should remember the need for

antiplatelets in secondary prevention, they should reconsider the use of

aspirin for primary prevention and focus more on good control of the

other risk factors: blood pressure and cholesterol (the latter mainly via

use of statins). Perhaps the current success of these other interventions

now leaves little room for benefit from aspirin in primary prevention?

Authors: Christopher J D Threapleton, Tess Harris, Emma H Baker

Polypharmacy, the use of multiple medicines, is increasingly a consequence of modern healthcare. Whilst polypharmacy is often appropriate for the management of multimorbidity, it is recognised as an independent risk factor for illness, hospitalisation and death. Over the last few years there has been a surge of research into the effectiveness of interventions to improve medication appropriateness and to stop or ‘deprescribe’ certain medicines that are considered to be causing more harm than good.

Numerous studies of interventions to manage polypharmacy have been published, including several systematic reviews in the BJCP. Unfortunately, evidence of the effectiveness of such interventions has been inconclusive. Whilst improvements in the appropriateness of medications have been demonstrated, there is limited evidence that these lead to demonstrable improvements in clinically meaningful outcomes, such as in physical or cognitive function, quality of life or hospital admissions. A recent meta-analysis1 found that interventions may reduce mortality, but the certainty of evidence was low.

Huiskes and colleagues2 suggest one reason for inconclusive findings might be that trial inclusion criteria do not select patients most likely to benefit from the intervention. Interventions that work for some people might not work for others, so that selecting the wrong group of patients may result in an averaging effect of outcomes showing no overall significant effect.

Patient selection for clinical trials of polypharmacy interventions is heterogeneous and can be categorised broadly into three groups. *Patient factors* include demographics such as age, particular medical conditions or nursing home residence and may act as proxies for burden of polypharmacy or risk of harm from medicines. *Medication factors* are measures of polypharmacy burden, including the total number of prescribed medicines and the number of ‘potentially inappropriate medicines’ (PIMs) such as benzodiazepines used long term. *Harm factors* are measures of actual harm associated with polypharmacy, including falls, cognitive decline and frequent hospital attendances.

Each category has strengths and weaknesses. Some *patient factors*, such as age or the presence of a particular diagnosis, are straightforward to use, but may not adequately reflect patients who would benefit most from a polypharmacy intervention. Other factors, such as frailty or multimorbidity may be more appropriate. The Charlson Comorbidity Index, for example, can be used to predict 10 year survival based on the presence or absence of certain diagnoses3. Such tools can be tremendously helpful at prognostication but are heavily reliant on accurate medical records. Indeed, a common barrier to prescribing decisions is a lack of relevant clinical data4. *Medication factors*, such as the inclusion of patients taking a certain number of medicines, are convenient because prescription data can be obtained from medical records. However, such factors often fail to account for the appropriateness of medicines for the individual patient. For example, a certain number of medicines may be appropriate for someone with ischaemic heart disease, diabetes and COPD, but not for someone without such a high morbidity burden. Various measures of medication appropriateness, such as the Medication Appropriateness Index (MAI), are commonly used in research, but are time consuming and therefore less useful in clinical practice. Using *harm factors*, such as the inclusion of patients who frequently fall, may result in a greater reduction of harm (i.e., fall prevention) than using broader criteria. However, identifying patients for inclusion where harm has already occurred means excluding others where the risk of harm is great, but an event has yet to occur. Additionally, some harms, such as the relationship between anticholinergic drug use and the development of dementia5, may not be reversible.

An alternative approach to stratify patients is to use a biomarker as a proxy for the risk of harm from medicines. Most research on biomarkers and polypharmacy have focussed on pharmacogenomic markers, such as genetic variants that affect pharmacokinetics. In this volume, Bengaard and colleagues6 outline a novel cohort study that investigated the relationship between polypharmacy, health outcomes and soluble urokinase plasminogen activator receptor (suPAR), a non-specific biomarker that reflects immune activity. SuPAR is a marker for increasing age, impaired cardiac, renal and hepatic function, exacerbations of inflammatory conditions such as autoimmune connective tissue disorders and chronic obstructive pulmonary disease, and lifestyle factors such as smoking and obesity7,8. It has a strong positive association with the Charlson Comorbidity Index9 so could be regarded as a proxy for multimorbidity. As such, a simple blood test to measure suPAR could help stratify patients by overall health status.

Bengaard and colleagues reviewed medical records of 26,291 patients who had suPAR levels measured on admission to the acute medical unit of a large teaching hospital in Copenhagen, Denmark. They recorded the total number of prescribed medicines and PIMs taken by each patient and, in the 90 day follow up, the time to death or readmission to hospital. They found that both suPAR and the number of prescribed medicines were positively associated with hospitalisation and death. When patients were grouped by suPAR level, the number of prescribed medicines were positively associated with mortality and risk of readmission for those with lower suPAR levels, but not for those with high levels. A similar relationship was found between PIMs and readmission rates. These results indicate that the number of medicines or PIMs taken by a patient has a greater effect on mortality and readmission for patients with lower levels of morbidity. Patients with higher levels of morbidity are less affected by the number of medicines they take; mortality and admission rates are similarly high across this cohort.

The authors hypothesise that polypharmacy harms could be caused by adverse drug reactions or drug-drug interactions, but acknowledge that this doesn’t explain the smaller impact on those with high suPAR levels. They argue that polypharmacy in patients with high suPAR levels may be more appropriate given their greater burden of disease and the high base rate of hospitalisation of these patients may be more resistant to the effects of polypharmacy. Other factors may also be confounding. Prescribing levels may be impacted by variations in health literacy, language barriers or the presence (or lack) of support from family members. Extensive prescribing in patients with low suPAR levels may represent an attempt to manage symptoms of difficult life circumstances (such as social deprivation) or mental health problems, neither of which are likely to affect suPAR levels but could affect mortality or hospital admissions. The authors also acknowledge that smoking affects suPAR, but information on smoking status was not included in this study.

This was a well-designed study, but limited to a single centre in Denmark, with patients who had a recent acute admission to hospital. Different populations, such as those with more stable health conditions, or those with different ethnicities or lifestyles may yield different results. It is assumed that the number of prescriptions represents the medicines taken by each patient. It is well known that adherence to medicines is often poor and is positively associated with increasing polypharmacy – patients who take more medicines are less likely to take them correctly. It may be that multimorbidity also impacts adherence and patients with higher suPAR levels may have more varied adherence than those with lower suPAR levels.

This study raises important questions about how patients with polypharmacy are managed. Many interventions into polypharmacy have attempted to focus on older patients, or those with markers of multimorbidity, such as residents of nursing homes. Conversely, it may be that polypharmacy in patients with low morbidity causes the worst harm to benefit ratio. At present, it appears there are no published clinical trials to assess the effectiveness of polypharmacy interventions for patients stratified by suPAR level. It would be interesting to see whether there was a relationship between suPAR and the type of outcome or the degree of effect of such interventions. If a simple blood test could help determine which patients are most likely to benefit, we may be able to determine how best to improve outcomes for people with polypharmacy. Randomised controlled trials of such interventions are needed first though in order to demonstrate improvement in outcomes that are clinically meaningful.

1. Bloomfield HE, Greer N, Linsky AM, et al. Deprescribing for Community-Dwelling Older Adults: a Systematic Review and Meta-analysis. *J Gen Intern Med*. 2020;35(11):3323-3332. doi:10.1007/s11606-020-06089-2

2. Huiskes VJB, Burger DM, Van Den Ende CHM, Van Den Bemt BJF. Effectiveness of medication review: A systematic review and meta-analysis of randomized controlled trials. *BMC Fam Pract*. 2017;18(1). doi:10.1186/s12875-016-0577-x

3. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A New Method of Classifying Prognostic Comorbidity in Longitudinal Studies: Development and Validation. *J Chronic Dis*. 1987;40(5):373-383. http://www.sciencedirect.com/science/article/pii/0021968187901718

4. Threapleton CJD, Kimpton JE, Carey IM, et al. Development of a structured clinical pharmacology review for specialist support for management of complex polypharmacy in primary care. *Br J Clin Pharmacol*. 2020;(January):1-10. doi:10.1111/bcp.14243

5. Coupland CAC, Hill T, Dening T, Morriss R, Moore M, Hippisley-Cox J. Anticholinergic Drug Exposure and the Risk of Dementia: A Nested Case-Control Study. *JAMA Intern Med*. 2019;179(8):1084-1093. doi:10.1001/jamainternmed.2019.0677

6. Bengaard AK, Iversen E, Kallemose T, et al. Using soluble urokinase plasminogen activator receptor to stratify patients for medication review in the emergency department. *Br J Clin Pharmacol*. Published online 2021:1-12. doi:10.1111/bcp.14982

7. Haupt TH, Kallemose T, Ladelund S, et al. Risk factors associated with serum levels of the inflammatory biomarker soluble urokinase plasminogen activator receptor in a general population. *Biomark Insights*. 2014;9:91-100. doi:10.4137/BMI.S19876

8. Vasarhelyi B, Toldi G, Balog A. The Clinical Value of Soluble Urokinase Plasminogen Activator Receptor (suPAR) Levels in Autoimmune Connective Tissue Disorders. *EJIFCC*. 2016;27(2):122-129. http://www.ncbi.nlm.nih.gov/pubmed/27683525%0Ahttp://www.pubmedcentral.nih.gov/articlerender.fcgi?artid=PMC4975228

9. Haupt TH, Petersen J, Ellekilde G, et al. Plasma suPAR levels are associated with mortality, admission time, and Charlson Comorbidity Index in the acutely admitted medical patient: A prospective observational study. *Crit Care*. 2012;16(4):1-9. doi:10.1186/cc11434