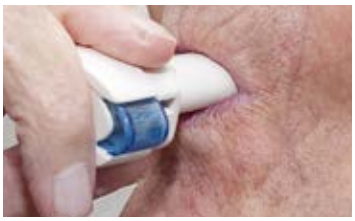
# research

SGLT2 inhibitor use associated with increased risk of lower limb amputation p 271

Hospital admission of older people linked to increased rate of potentially inappropriate prescriptions at discharge p 272



Triple therapy better than dual therapy at reducing risk of COPD exacerbations p 274

**ORIGINAL RESEARCH** Nationwide register based cohort study

## Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events

Ueda P, Svanström H, Melbye M, et al

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**Study question** Is there an association between the use of sodium glucose cotransporter 2 (SGLT2) inhibitors and seven serious adverse events of current concern?

**Methods** This register based study in Sweden and Denmark, from July 2013 to December 2016, used data from a propensity score matched cohort of 17 213 new users of SGLT2 inhibitors (dapagliflozin, 61%; empagliflozin, 38%; canagliflozin, 1%) and 17 213 new users of the active comparator, glucagon-like peptide 1 (GLP1) receptor agonists. The primary outcomes were lower limb amputation, bone fracture, diabetic ketoacidosis, acute kidney injury, serious urinary tract infection, venous thromboembolism, and acute pancreatitis, as identified from hospital records. Hazard ratios and 95% confidence intervals were estimated using Cox proportional hazards models.

**Study answer and limitations** Use of SGLT2 inhibitors, as compared with GLP1 receptor agonists, was associated with an increased risk of lower limb amputation (incidence rate 2.7 *v* 1.1 events per 1000 person years, hazard ratio 2.32, 95% confidence interval 1.37 to 3.91) and diabetic ketoacidosis (1.3 *v* 0.6, 2.14, 1.01 to 4.52), but not with bone fracture (15.4 *v* 13.9, 1.11, 0.93 to 1.33), acute kidney injury (2.3 *v* 3.2, 0.69, 0.45 to 1.05), serious urinary tract infection (5.4 *v* 6.0, 0.89, 0.67 to 1.19), venous thromboembolism (4.2 *v* 4.1, 0.99, 0.71 to 1.38), or acute pancreatitis (1.3 *v* 1.2, 1.16, 0.64 to 2.12). Limitations include the potential of unmeasured and residual confounding and the misclassification of outcome and exposure.

**What this study adds** The use of SGLT2 inhibitors is associated with twofold increases in the risk of lower limb amputation and diabetic ketoacidosis.

**Funding, competing interests, and data sharing** See bmj.com for funding and competing interests. No additional data are available.

**Primary outcome analyses of association between use of sodium glucose cotransporter 2 (SGLT2) inhibitors compared with glucagon-like peptide 1 (GLP1) receptor agonists and risk of serious adverse events**

| | SGLT2 inhibitors (n=17 213) | | GLP1 receptor agonists (n=17 213) | | | |
|---|---|---|---|---|---|---|
| Adverse event | No of events | No of events per 1000 person years | No of events | No of events per 1000 person years | Hazard ratio (95% CI) | Absolute risk difference (95% CI) |
| Lower limb amputation | 40 | 2.7 | 22 | 1.1 | 2.32 (1.37 to 3.91) | 1.5 (0.4 to 3.3) |
| Bone fracture | 228 | 15.4 | 263 | 13.9 | 1.11 (0.93 to 1.33) | 1.5 (−1.0 to 4.6) |
| Diabetic ketoacidosis | 19 | 1.3 | 11 | 0.6 | 2.14 (1.01 to 4.52) | 0.7 (0.0 to 2.0) |
| Acute kidney injury | 34 | 2.3 | 62 | 3.2 | 0.69 (0.45 to 1.05) | −1.0 (−1.8 to 0.2) |
| Serious urinary tract infection | 80 | 5.4 | 114 | 6.0 | 0.89 (0.67 to 1.19) | −0.7 (−2.0 to 1.1) |
| Venous thromboembolism | 63 | 4.2 | 79 | 4.1 | 0.99 (0.71 to 1.38) | 0.0 (−1.2 to 1.6) |
| Acute pancreatitis | 20 | 1.3 | 23 | 1.2 | 1.16 (0.64 to 2.12) | 0.2 (−0.4 to 1.3) |

# Tackling potentially inappropriate prescribing

**ORIGINAL RESEARCH** Longitudinal study

## Prevalence of potentially inappropriate prescribing in older people in primary care and its association with hospital admission

Pérez T, Moriarty F, Wallace E, McDowell R, Redmond P, Fahey T

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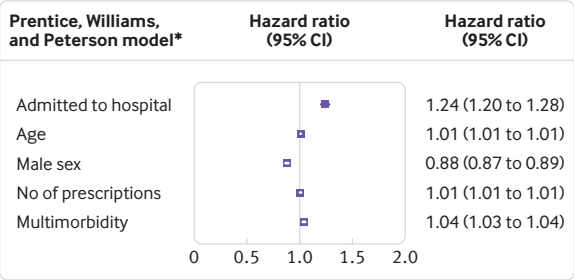


*Estimated hazard ratios (95% CI) for rate of distinct potentially inappropriate prescribing criteria met among all participants. Reference groups were no hospital admission and female sex . In this model, the outcome is time from beginning of year to a new potentially inappropriate prescribing criterion observed in each patient per calendar year

**Study question** Is admission to hospital associated with potentially inappropriate prescribing among older primary care patients?

**Methods** This was a longitudinal study of retrospectively extracted data from general practice records from 44 general practices in the Republic of Ireland in 2012-15. Participants were adults aged 65 years or over attending participating practices. The relation between hospital admission (both any admission versus none and after admission versus before) and the outcome of prevalence of potentially inappropriate prescribing (assessed using 45 criteria from the Screening Tool for Older Persons' Prescription (STOPP) version 2) was analysed both as rate of distinct potentially inappropriate prescribing criteria met (stratified Cox regression) and binary presence of potentially inappropriate prescribing (logistic regression). Analyses were adjusted for patients' characteristics, and a sensitivity analysis used propensity score matching based on patients' characteristics and diagnoses.

**Study answer and limitations** The overall prevalence of potentially inappropriate prescribing ranged from 45.3% (13 940/30 789) of patients in 2012 to 51.0% (14 823/29 077) in 2015. Independently of age, sex, number of prescription items, comorbidity, and type of health cover, hospital admission was associated with a higher rate of distinct potentially inappropriate

**COMMENTARY** Opportunities to intervene are often missed

In 2017 the World Health Organization launched its third global patient safety challenge with the aim of reducing severe avoidable medication related harm by 50% over a five year period.[1]

One important approach is to identify potentially inappropriate prescribing and correct it where necessary, with the expectation that this will avoid serious harm. Primary care in the UK is well placed to do this using electronic searches to identify patients at risk: effective interventions are available to reduce hazardous prescribing,[2] and some evidence shows that this can also reduce associated hospital admissions.[3] Secondary care is also increasingly enabled to tackle potentially inappropriate prescribing as electronic prescribing becomes more commonplace and pharmacists have a greater role in the prescribing and monitoring of medication.[4 5]

Nevertheless, the size and scale of the problem is considerable, as confirmed by Pérez and colleagues. Potentially inappropriate prescribing is associated with subsequent adverse drug events and hospital admissions, as well as reduced quality of life,[6] but what the new study also shows is that the risk of potentially inappropriate prescribing is increased after hospital admission.[6]

Pérez and colleagues analysed data from general practices before and after discharge from hospital, and their findings therefore reflect prescriptions issued by those general practices (and not necessarily the drugs that patients were receiving at the point of discharge). The authors note several important reasons for the increase in potentially inappropriate prescribing, such as the intensification of existing drug regimens and the failure to stop certain drugs (or reduce doses) after discharge from hospital. A recent English observational study reported that 17% of medication changes suggested at hospital discharge are not actioned by general practices (without a documented reason).[8]

### Holistic approach

Although a hospital admission is clearly an opportunity for a more holistic approach to a patient's drug treatment, this does not always happen. Specialists view evidence based guidelines as an important part of their practice, and new diagnoses usually lead to new drug therapy. Despite efforts to avoid inappropriate polypharmacy, additional comorbidities often lead to potentially inappropriate prescribing.[9] Some specialists may not feel empowered to change or stop pre-admission medicines when they prescribe for new conditions.

**Reducing potentially inappropriate prescribing requires interventions grounded in primary care, in secondary care, and at the interface between the two**

In the past, the routine outpatient appointment after discharge from hospital was another opportunity for medication review, but outpatient follow-up is no longer routine practice.

All of these factors help to explain why potentially inappropriate prescribing is more common after hospital discharge. They also highlight the importance of interventions known to improve outcomes at discharge, including better communication between secondary and primary care, involvement of pharmacists, closer monitoring of patients, and better self management.[10]

Secondary care clearly has an important role in both avoiding and tackling potentially inappropriate prescribing. In the modern

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prescribing criteria met (adjusted hazard ratio 1.24, 95% confidence interval 1.20 to 1.28). Among admitted participants, the likelihood of potentially inappropriate prescribing after admission was higher than before admission independent of patients' characteristics (adjusted odds ratio 1.72, 1.63 to 1.84). Potential exists for unmeasured confounding that might partly or fully explain the relation between hospital admission and potentially inappropriate prescribing, and examination of whether cases of potentially inappropriate prescribing might have been clinically justified was not possible.

**What this study adds** Hospital admission was independently associated with an increased rate of potentially inappropriate prescriptions after discharge back to primary care.

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era of increased specialisation and intensive treatment schedules, all healthcare episodes should include a more generalist review and an opportunity to stop any inappropriate polypharmacy.

Comprehensive hospital care models are becoming more popular and are often set up for people with complex healthcare needs, especially older patients.[11] Medication reviews can be an important part of this process, often leading to the withdrawal of prescribed drugs ("deprescribing" (https://deprescribing.org/)). New protocols and guidelines are being evaluated to improve the safety and effectiveness of deprescribing—for example, by avoiding drug withdrawal states. The deprescribing process can be further supported by written or electronic algorithms, and computerised interventions seem to be particularly effective.[12]

Reducing potentially inappropriate prescribing requires interventions grounded in primary care, in secondary care, and at the interface between the two. Effective multidisciplinary working, particularly involving pharmacists, is important, as is making the best use of electronic health records for identifying patients at risk and providing decision support.

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# Triple therapy in the management of chronic obstructive pulmonary disease

Zheng Y, Zhu J, Liu Y, et al

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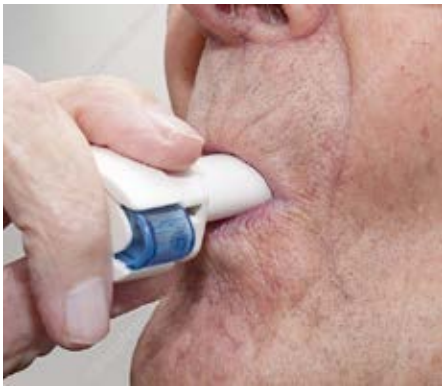
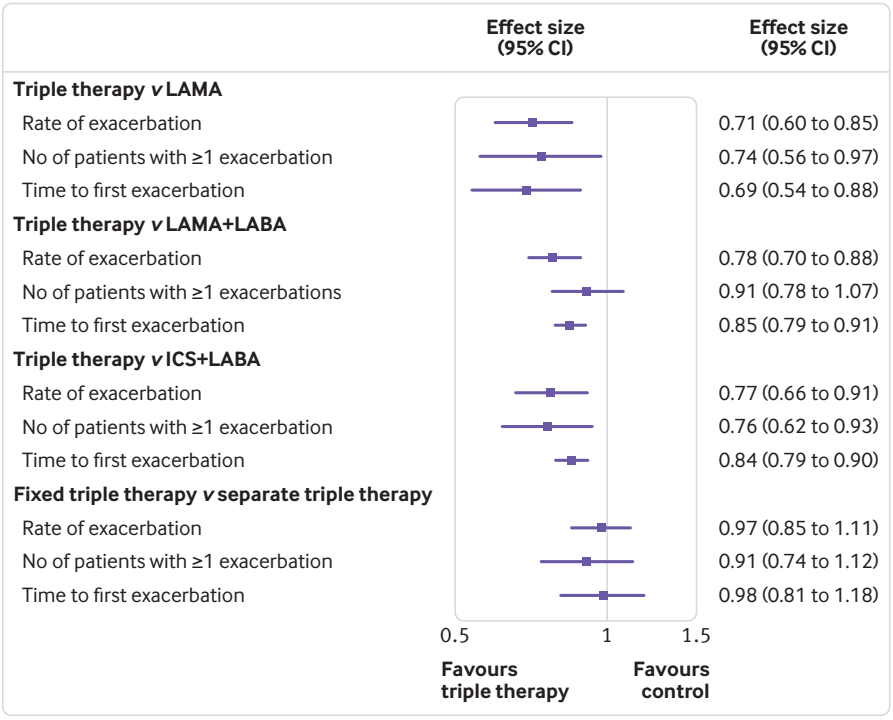
**Study question** How do the efficacy and safety of triple therapy (containing a long acting muscarinic receptor antagonist (LAMA), long acting β2 adrenoreceptor agonist (LABA), and inhaled corticosteroid (ICS)) compare with that of dual therapy or monotherapy in patients with chronic obstructive pulmonary disease (COPD)?

**Methods** Randomised controlled trials comparing triple therapy with dual therapy or monotherapy in patients with COPD were identified by searching PubMed, Embase, Cochrane databases, and clinical trial registries, from inception to April 2018. The primary outcome was the risk of moderate or severe exacerbations. Relevant studies were systematically reviewed, and outcomes of interest were analysed by meta-analysis.






Association of triple therapy with the risk of moderate or severe exacerbations. Fixed=treatments given in one inhaler; separate=treatments given in different inhalers

**Study answer and limitations** Compared with dual therapy or monotherapy, use of triple inhaler therapy resulted in a lower rate of moderate or severe COPD exacerbations, together with improvements in lung function and health related quality of life. However, triple therapy was shown to significantly increase the risk of pneumonia (relative risk 1.53, 95% confidence interval 1.25 to 1.87). All the included studies were efficacy trials rather than effectiveness trials; future trials are needed to clarify the effectiveness or cost effectiveness of triple therapy in COPD.

**What this study adds** Our results suggest that use of triple therapy significantly reduced the risk of moderate or severe COPD exacerbations compared with dual therapy (of ICS and LABA or LAMA and LABA) or LAMA monotherapy. In addition, a single inhaler regimen of triple therapy was non-inferior to triple therapy administered with multiple inhalers.

Competing interests, funding, and data sharing
No funding was provided for the study, and no additional data are available. The authors declare no competing interests.