

General

Regular use of proton-pump inhibitors and increased risk of stroke

Proton-pump inhibitors (PPIs) are one of the most frequently prescribed drugs used for the treatment of gastric acid-related disorders. There is preliminary evidence linking long-term PPIs use to increased risk of incident stroke. Researchers recently contributed more evidence by evaluating this association and determining which population groups are at a higher risk. A prospective analysis of the UK Biobank cohort (492,479 participants) and a meta-analysis of nine (9) randomized controlled trials (RCTs) were employed to investigate this association. The study found that regular PPI users had a 16% higher risk of stroke than non-users. The absolute risk of stroke was higher in individuals with higher baseline stroke risk score. The researchers recommended caution while prescribing PPIs and assessment of stroke risk for individualised PPIs use.

Yang, M., He, Q., Gao, F. et al. Regular use of proton-pump inhibitors and risk of stroke: a population-based cohort study and meta-analysis of randomized-controlled trials. *BMC Med* 19, 316 (2021). <https://doi.org/10.1186/s12916-021-02180-5>

Causal role of high body mass index in multiple chronic diseases: a systematic review and meta-analysis of Mendelian randomisation studies

Obesity is a global public health threat that has been associated with a multitude of chronic diseases in observational studies. Researchers summarized the evidence from Mendelian randomization (MR) studies on the association between Body Mass Index (BMI) and chronic diseases. A meta-analysis of published MR studies (from PubMed and Embase) and de novo analyses of the FinnGen consortium (a public-private partnership project combining genotype data from Finnish biobanks and digital health record data from Finnish health registries) were conducted. Genetically predicted higher BMI was associated with increased risk of type 2 diabetes mellitus, 14 circulatory disease outcomes, asthma, chronic obstructive pulmonary disease, 5 digestive system

diseases, 3 musculoskeletal diseases, multiple sclerosis and several cancers. The researchers added substantial evidence in favor of a causal role of obesity in various chronic diseases and recommended continued efforts to reduce obesity prevalence.

Larsson, S.C., Burgess, S. Causal role of high body mass index in multiple chronic diseases: a systematic review and meta-analysis of Mendelian randomization studies. *BMC Med* 19, 320 (2021). <https://doi.org/10.1186/s12916-021-02188-x>

The impact of high-risk medications on mortality risk among older adults with polypharmacy

Polypharmacy is common among older adults as the burden of ageing rises globally. It's however not understood if mortality risk is related to specific medications. Researchers included 1356 older adults with polypharmacy (5+ long-term medications/day) from a longitudinal study of ageing. These were grouped according to use of high-risk medication categories, and all-cause and cause-specific mortality were assessed. Of five high-risk medication patterns, the mental health drugs cluster showed increased mortality over 6 years, while others showed no differences in mortality. Mental health drugs especially antidepressants, opioids, and muscle relaxants carried a higher risk of all-cause mortality and hence older patients on such psychotropic medications need closer attention. The researchers also recommended inclusion of opioids on structured medication reviews.

Huang Y-T, Steptoe A, et al. The impact of high-risk medications on mortality risk among older adults with polypharmacy: evidence from the English Longitudinal Study of Ageing. *BMC Medicine*. 2021 Dec 16. <https://doi.org/10.1186/s12916-021-02192-1>

Multicomponent Strategy with Decentralized Molecular Testing for Tuberculosis

In the global fight to end Tuberculosis (TB), effective strategies to aid its prompt diagnosis and treatment are paramount. In this study, researchers in Uganda, through a cluster-randomized trial involving 20 health centers from different regions in the country, compared a multi-component diagnostic strategy (on-site molecular testing for TB, guided restructuring of clinic workflows, and monthly feedback of quality metrics) to routine care (on-site sputum-smear microscopy

and referral-based molecular testing). The primary endpoint was the number of patients treated for confirmed TB within 14 days upon presentation. The intervention strategy led to significantly more patients (342) being treated for confirmed TB within 14 days than the control group (220). Other indicators measured also favoured the intervention strategy. It's evident that such multi-component strategies could yield more wins in eradicating TB.

Cattamanchi A, Reza TF et al. Multicomponent Strategy with Decentralized Molecular Testing for Tuberculosis. *N Engl J Med*. 2021 Dec 23;385(26):2441-2450. doi: 10.1056/NEJMoa2105470. PMID: 34936740.

The role of oliguria in the diagnosis and staging of acute kidney injury among patients with critical illness.

Acute kidney injury (AKI) definition includes serum creatinine (sCr) alterations and urinary output (UO). The importance of oliguria-based criteria is however challenged. Researchers through a cohort study of 15,620 adult patients admitted at an Intensive care unit determined the contribution of oliguria to AKI diagnosis, severity assessment, and outcomes. Data on daily sCr levels, hourly UO measurements, and long-term mortality was collected. Severity of AKI using sCr and UO was determined separately, and agreement assessed. sCr and UO had a poor agreement on AKI diagnosis and staging. UO criteria enabled identification of AKI in 36.0% patients compared to sCr criteria alone, and such patients had a higher 90-day mortality compared to patients without AKI. Oliguria hence has major diagnostic and prognostic value and should be accounted for by clinicians.

Bianchi NA, Stavart LL et al. Association of Oliguria With Acute Kidney Injury Diagnosis, Severity Assessment, and Mortality Among Patients With Critical Illness. *JAMA Netw Open*. 2021 Nov 1;4(11):e2133094. doi: 10.1001/jamanetworkopen.2021.33094. PMID: 34735011; PMCID: PMC8569487.

Association between Implementation of the Severe Sepsis and Septic Shock Early Management Bundle Performance Measure and Outcomes in Patients with Suspected Sepsis in US Hospitals

Sepsis remains a major cause of mortality globally with the burden being greatest in Low and Middle-income countries. Different approaches have been tried but their effectiveness

remains unclear. Researchers evaluated a Severe Sepsis and Septic Shock Early Management Bundle (SEP-1) implemented in US hospitals on sepsis outcomes. A retrospective cohort study was conducted among adults admitted in 114 hospitals with suspected sepsis within 24 hours of hospital arrival. Study endpoints included lactate testing rates, broad-spectrum antibiotic use rates, and short-term mortality rates. The researchers found implementation of SEP-1 increased lactate testing rates, however, didn't affect antibiotic use rates, or short-term mortality. They further concluded that other alternative approaches to reduce sepsis mortality maybe needed.

Rhee C, Yu T et al. Association Between Implementation of the Severe Sepsis and Septic Shock Early Management Bundle Performance Measure and Outcomes in Patients With Suspected Sepsis in US Hospitals. *JAMA Netw Open*. 2021 Dec 1;4(12):e2138596. doi: 10.1001/jamanetworkopen.2021.38596. PMID: 34928358; PMCID: PMC8689388.

Current evidence on Tuberculosis screening among ambulatory people living with HIV

For tuberculosis (TB) screening in people living with HIV (PLWHIV), the WHO recommends a four-symptom screen (W4SS) followed by a molecular test, if W4SS is positive. A team of experts assessed the diagnostic accuracy of alternative screening tests for TB in this population. A systematic review (25 studies) and individual-participant data (22 studies) meta-analysis were conducted, and found that among PLWHIV on anti-retroviral therapy (ART), a parallel strategy of W4SS with any chest x-ray abnormality offered at the same time was the best to improve sensitivity. For outpatients not on ART, C-reactive protein (≥ 10 mg/L) as a stand-alone or sequential strategy (W4SS then C-reactive protein ≥ 5 mg/L) was best to improve specificity. The current WHO-recommended algorithm wasn't sensitive enough to identify all TB cases.

Ashar Dhana, Yohhei Hamada et al. Tuberculosis screening among ambulatory people living with HIV: a systematic review and individual participant data meta-analysis; *Lancet Infect Dis* 2021 Published Online November 17, 2021 [https://doi.org/10.1016/S1473-3099\(21\)00387-X](https://doi.org/10.1016/S1473-3099(21)00387-X)

Role of thoracic ultrasonography in pleurodesis pathways for malignant pleural effusions

In this era of Medical technology innovations, ultrasonography is showing up in new medical corridors where

its utility needs validation. A team of researchers evaluated whether the use of thoracic ultrasonography in pleurodesis pathways shortened hospital stay among patients with malignant pleural effusions undergoing pleurodesis. A randomized trial involving 313 patients was conducted in 11 respiratory centers in Europe, with 159 participants assigned to ultrasonography-guided care, and 154 participants to standard care. Outcome measures included: length of hospital stay, pleurodesis failure at three months, all-cause mortality, and cost-effectiveness among others. Findings favored thoracic ultrasonography with significantly shorter length of hospital stay in the intervention arm, better cost-effectiveness compared to the standard, with no differences in pleurodesis failure at three months. The researchers hence recommended consideration of thoracic ultrasonography in patients undergoing pleurodesis.

Psallidas I, Hassan M, et al. Role of thoracic ultrasonography in pleurodesis pathways for malignant pleural effusions (SIMPLE): an open-label, randomised controlled trial. *Lancet Respir Med*. 2021 Oct 8;S2213-2600(21)00353-2. doi: 10.1016/S2213-2600(21)00353-2. Epub ahead of print. PMID: 34634246.

Pharmacotherapy for adults with overweight and obesity: a systematic review and meta-analysis

Obesity has global public health importance and despite lifestyle modifications being the mainstay of management, pharmacotherapy provides options for when these fail. Researchers conducted a systematic review and meta-analyses of randomized controlled trials and summarized the benefits and harms of weight-lowering drugs. A total of 143 trials involving 49810 participants were involved in the analysis. The study found phentermine-topiramate as the most effective in lowering weight, followed by GLP-1 receptor agonists. Naltrexone-bupropion, phentermine-topiramate, GLP-1 receptor agonists and orlistat were associated with adverse events leading to drug discontinuation. On further analysis, semaglutide, a GLP-1 receptor agonist was found most beneficial. The researchers concluded that phentermine-topiramate and GLP-1 receptor agonists, especially semaglutide were the best drugs for weight loss.

Shi Q, Wang Y, et al. Pharmacotherapy for adults

with overweight and obesity: a systematic review and network meta-analysis of randomised controlled trials. *Lancet*. 2022 Jan 15;399(10321):259-269. doi: 10.1016/S0140-6736(21)01640-8. Epub 2021 Dec 8. PMID: 34895470.

MCH

A better understanding of the association between maternal perception of foetal movements and late stillbirth

Reduced fetal movements are frequently reported by mothers prior to fetal death, but there is a poor understanding about how to manage this symptom in clinical practice. Researchers, through a meta-analysis of case-control studies of late stillbirth, sought to determine which women had the greatest odds of still birth in relation to maternal report of fetal movements in late pregnancy. The researchers found that: increased strength of fetal movements, fetal hiccups and regular episodes of vigorous movement were associated with decreased odds of late stillbirth, whereas decreased frequency, and a single episode of unusually vigorous movement were associated with increased odds of late stillbirth. These findings expound on our knowledge on the concept of fetal movements and still birth, which was not well understood.

Thompson, J.M.D., Wilson, J. et al. A better understanding of the association between maternal perception of foetal movements and late stillbirth—findings from an individual participant data meta-analysis. *BMC Med* 19, 267 (2021). <https://doi.org/10.1186/s12916-021-02140-z>

Erythromycin versus azithromycin for treatment of preterm premature rupture of membranes.

Preterm premature rupture of membranes (PPROM) complicates approximately up to 3% of pregnancies and leads to one third of preterm births. Antibiotics are used to prolong pregnancy and treat or prevent chorioamnionitis. It is not clear which one of erythromycin and azithromycin is superior. Researchers conducted a systematic review and meta-analysis of 5 trials with 1289 women comparing the duration of latency and rate of clinical chorioamnionitis in women with PPRM treated with erythromycin or azithromycin. The study found no difference in duration of latency between the two groups (6.6-6.7 days), but found a lower clinical

chorioamnionitis prevalence and rate in women treated with azithromycin. The researchers concluded that azithromycin had a similar latency period as erythromycin but lower rate of clinical chorioamnionitis.

Seaman RD, Kopkin RH, Turrentine MA. Erythromycin versus azithromycin for treatment of preterm prelabor rupture of membranes: A systematic review and meta-analysis. *Am J Obstet Gynecol.* 2021 Dec 29;S0002-9378(21)02957-4. doi: 10.1016/j.ajog.2021.12.262. Epub ahead of print. PMID: 34973176.

Dolutegravir as first- or second-line treatment for HIV-1 infection in children

Over 1.8 million children and adolescents, globally live with HIV-1 infection. Despite this significant number, treatment options for this population remain few. Researchers through a multicentric, randomized clinical trial compared the efficacy and safety of a dolutegravir-based ART (Anti-retroviral therapy) regimen (intervention) to a standard (non-dolutegravir based ART) in children and adolescents weighing at least 14 kilograms. The outcome was treatment failure at 96 weeks. Of 707 children enrolled into the study, 350 were in the intervention arm while 357 were on the standard care arm. By the end of 96 weeks, 47 participants in the dolutegravir-group and 75 in the standard care arm had treatment failure. It was concluded that a dolutegravir-based ART was superior to standard care.

Anna Turkova, Ellen White, et al. Dolutegravir as First- or Second-Line Treatment for HIV-1 Infection in Children; December 30, 2021 *N Engl J Med* 2021; 385:2531-2543 DOI: 10.1056/NEJMoa2108793

Marked reduction in antibiotic usage following intensive malaria control in a cohort of Ugandan children

Intensive malaria control may have additional benefits beyond reducing malaria incidence. Researchers compared antibiotic treatment of children before and after implementation of highly effective malaria control interventions (Long-lasting insecticidal nets and sustained indoor residual spraying of insecticide) in Tororo, Uganda; a malaria endemic area. An observational study was conducted following two successive cohorts of children aged 6 months to 10 years in a study clinic for 8 years. The adjusted incidence of both malaria and antibiotic treatments significantly reduced in the before and after period. Researchers

concluded that in malaria endemic settings, effective malaria control interventions could reduce antibiotic treatment of children which may in turn alter antibiotic prescribing practices and avert antimicrobial resistance as well as reduce health system costs.

Krezanoski PJ, Roh ME, et al. Marked reduction in antibiotic usage following intensive malaria control in a cohort of Ugandan children. *BMC Med.* 2021 Nov 30;19(1):294. doi: 10.1186/s12916-021-02167-2. PMID: 34844601; PMCID: PMC8630830.

COVID-19

Aspirin as therapy for patients admitted to hospital with COVID-19

It's generally accepted that thromboprophylaxis has a role in the treatment of hospitalized COVID-19 patients. Aspirin with its anti-thrombotic properties has been proposed as a potential therapy. Researchers through a large trial conducted in UK, Indonesia and Nepal, evaluated its safety and efficacy. A total of 14892 patients were enrolled: 7351 received 150mg aspirin daily till discharge while 7541 received standard-of-care. The outcome measure was mortality at 28 days. Researchers found a similar mortality rate in both groups (17%) with a slight reduction in hospital stay associated with aspirin, 8 days Vs 9 days in the standard-of-care group. Aspirin also resulted in a slight reduction in thrombotic events. Researchers concluded that aspirin was not beneficial in reducing mortality or mechanical ventilation amongst hospitalized COVID-19 patients.

RECOVERY Collaborative Group. Aspirin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. *Lancet.* 2022 Jan 8;399(10320):143-151. doi: 10.1016/S0140-6736(21)01825-0. Epub 2021 Nov 17. PMID: 34800427; PMCID: PMC8598213.

Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients

Remdesivir has been shown to shorten recovery time in patients hospitalized with Covid-19. However, its utility in outpatient settings hasn't been well studied. This study set out to evaluate its efficacy and safety in high-risk non-hospitalized patients with Covid-19 through a randomized, double-blind, placebo-controlled trial. Five-hundred sixty-two (562) patients were randomly assigned to receive intravenous

remdesivir or placebo; primary efficacy outcome was a composite of Covid-19-related hospitalization or death from any cause by day 28, whereas the safety outcome was any adverse event. The primary outcome occurred significantly less frequently in the remdesivir group, 2 patients (0.7%) compared to 15 (5.3%) in the placebo group.

Researchers concluded that a course of remdesivir was safe and resulted in 87% lower risk of hospitalisation or death.

Gottlieb RL, Vaca CE, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. *N Engl J Med.* 2021 Dec 22;NEJMoa2116846. doi: 10.1056/NEJMoa2116846. Epub ahead of print. PMID: 34937145; PMCID: PMC8757570.

BNT162b2 Vaccine Booster and Mortality Due to Covid-19

Disturbing evidence of the waning immunity of Covid-19 vaccines has brought to life the concept of vaccine boosters. Their effectiveness in lowering mortality isn't clear. A study conducted in Israel compared mortality due to Covid-19 among participants who received a booster and those that didn't, in an elderly population who had received two doses of BNT162b2 at least 5 months earlier. Of the 843,208 eligible participants, 758,118 (90%) received the booster during the study period. Death due to Covid-19 occurred much less frequently in the booster group, 65 participants compared to 137 participants in the non-booster group. The researchers found that the vaccine booster conferred 90% lower mortality to its recipients compared to the non-booster group.

Arbel R, Hammerman A, et al. BNT162b2 Vaccine Booster and Mortality Due to Covid-19. *N Engl J Med.* 2021 Dec 23;385(26):2413-2420. doi: 10.1056/NEJMoa2115624. Epub 2021 Dec 8. PMID: 34879190; PMCID: PMC8728797.

Effect of high-flow oxygen therapy vs conventional oxygen therapy on invasive mechanical ventilation and clinical recovery in patients with severe COVID-19

In severe COVID-19, the effect of high-flow (via nasal cannula) versus conventional oxygen therapy on outcomes hasn't been well studied. Researchers conducted an open-label randomized clinical trial in 3 hospitals in Colombia comparing the association of these two modalities with the need for intubation and recovery time until 28 days among a total of 220 patients with severe Covid-19. Significantly fewer patients were intubated in the high-flow arm, 34 (34.3%) vs 51

(51.0%) in the conventional oxygen therapy arm. Median recovery time was also shorter in the high-flow arm, 11 days vs 14 days in the conventional oxygen therapy group. Other indicators measured also favored the high-flow oxygen therapy. The researchers concluded that high-flow was superior to conventional oxygen therapy in patients with severe Covid-19.

Ospina-Tascón GA, Calderón-Tapia LE et al. Effect of High-Flow Oxygen Therapy vs Conventional Oxygen Therapy on Invasive Mechanical Ventilation and Clinical Recovery in Patients With Severe COVID-19: A Randomized Clinical Trial. *JAMA*. 2021 Dec 7;326(21):2161-2171. doi: 10.1001/jama.2021.20714. PMID: 34874419; PMCID: PMC8652598.

Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia

The role of dexamethasone in treatment of severe Covid-19 is undisputed. An optimum daily dose is however still debated, with a higher dose hypothesized to be superior. Researchers compared the association of two dexamethasone dose-regimens; that is 12mg and 6mg with the number of days alive without life support. A large randomized trial involving 1000 patients with Covid-19 and severe hypoxemia was conducted, with half being treated with 12mg/day, and the other half with 6mg/day of dexamethasone for 10 days. There was no significant difference in days alive without life support at 28 days: 12mg/day of dexamethasone resulted in 22.0 days compared to 20.5 days in those that received 6mg/day dose. The researchers concluded that a higher daily dose (12mg) wasn't superior.

COVID STEROID 2 Trial Group, Munch MW et al. Effect of 12 mg vs 6 mg of Dexamethasone on the Number of Days Alive Without Life Support in Adults With COVID-19 and Severe Hypoxemia: The COVID STEROID 2 Randomized Trial. *JAMA*. 2021 Nov 9;326(18):1807-1817. doi: 10.1001/jama.2021.18295. Erratum in: *JAMA*. 2021 Dec 14;326(22):2333. PMID: 34673895; PMCID: PMC8532039.

Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins in COVID-19 management

Thrombo-prophylaxis is a crucial component in the treatment of hospitalized patients with Covid-19. An optimum dose regimen of heparin has however not been well studied. Researchers sought to investigate

if therapeutic dose low-molecular-weight heparin reduced major thromboembolism and death compared to prophylactic/intermediate-dose heparin among hospitalized patients with Covid-19. This was achieved through a randomized trial involving 253 adults with elevated D-dimers levels. The primary efficacy endpoint was thromboembolism or death from any cause, while safety endpoint was major bleeding at 30 days. Incidence of major thromboembolism or death was much lower with therapeutic-dose (28.7%) than with prophylactic/intermediate-dose heparins (41.9%), except in critically ill patients; with no difference in safety profile. It's evident that therapeutic-dose regimen is more efficacious without increase in safety concerns.

Spyropoulos AC, Goldin M et al. Efficacy and Safety of Therapeutic-Dose Heparin vs Standard Prophylactic or Intermediate-Dose Heparins for Thromboprophylaxis in High-risk Hospitalized Patients With COVID-19: The HEP-COVID Randomized Clinical Trial. *JAMA Intern Med*. 2021 Dec 1;181(12):1612-1620. doi: 10.1001/jamainternmed.2021.6203. Erratum in: *JAMA Intern Med*. 2021 Dec 28;: PMID: 34617959; PMCID: PMC8498934.

COVID-19 Post-acute Sequelae among adults: 12 Month Mortality Risk

Complications following Covid-19 infection are a growing concern globally. It's not however understood whether Covid-19 poses a significant mortality risk downstream. In this study, researchers determined the relationship between Covid-19 infection and 12-month mortality in adult patients. An analysis of electronic medical records in the University of Florida setting was conducted for a cohort including both Covid-19 positive and negative patients. Of the 13,638 participants, 178 had severe Covid-19 (hospitalized within 30 days of test), 246 had mild/moderate Covid-19 while 13,214 were Covid-19 negative. The mortality risk was significantly higher for patients with severe Covid-19 compared to both Covid-19 negative and mild Covid-19 patients. The researchers made the following conclusion "In a time when nearly all COVID-19 hospitalizations are preventable this study points to an important and under-investigated sequela of COVID-19 and the corresponding need for prevention"

Mainous, Arch G 3rd et al. "COVID-19 Post-acute Sequelae Among Adults: 12 Month Mortality Risk." *Frontiers in medicine* vol. 8 778434. 1 Dec. 2021, doi:10.3389/fmed.2021.778434



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