General

Reteplase superior to alteplase in ischemic stroke

Alteplase is typically administered to patients with ischemic stroke presenting within 4.5 hours of symptom onset, but alternative thrombolytics are needed. Researchers in this trial, conducted in China, compared reteplase to alteplase. A total of 1412 eligible patients were equally randomized to either reteplase or alteplase. The primary outcome was excellent functional outcome (mRS of 0 or 1) at 90 days. The primary outcome was seen in 80% of patients in the reteplase arm compared to 70% in the alteplase arm (RR 1.13). There was no significant difference in symptomatic intracranial hemorrhage within 36 hours between the two arms (i.e. 2.4% Vs 2.0%). The researchers concluded that double-bolus reteplase was both non-inferior and superior to alteplase as regards an excellent functional outcome at 90 days.

Reference

Li, S., et al. (2024). Reteplase versus Alteplase for Acute Ischemic Stroke. New England Journal of Medicine, 390, 2264–2273.

Updated guidelines in the management of allergic bronchopulmonary aspergillosis and allergic bronchopulmonary mycosis

An expert group of the International Society for Human and Animal Mycology recently updated guidelines on managing allergic bronchopulmonary aspergillosis (ABPA) and allergic bronchopulmonary mycosis (ABPM) after more than a decade. The group recommended screening for Aspergillus fumigatus *(A. fumigatus)* sensitization using fungus-specific IgE in all newly diagnosed asthmatic adults and only difficult-to-treat asthmatic children. ABPA is diagnosed in those with risk factors, compatible clinic-radiological presentation, evidence of fungal sensitization, serum total IgE ≥500 IU/mL, and two of; fungal-specific IgG, peripheral blood eosinophilia or suggestive imaging. ABPM is considered in an ABPA-like presentation but normal A. fumigatus-IgE. The group further recommended monotherapy with prednisolone or itraconazole therapy in acute ABPA and a combination of both therapies in recurrent exacerbations.

Reference

Agarwal, R., et al. (2024). Revised ISHAM-ABPA working group clinical practice guidelines for diagnosing, classifying, and treating allergic bronchopulmonary aspergillosis/mycoses. European Respiratory Journal, 63(4), 400061.

Dapagliflozin shows no benefit in critically ill patients with acute organ dysfunction.

Sodium-glucose cotransporter 2 (SGLT-2) inhibitors improve outcomes in patients with type 2 diabetes, heart failure, and chronic kidney disease. Researchers in this study evaluated their role in critically ill patients with organ dysfunction. A total of 507 participants admitted to three ICUs in Brazil were equally randomized to either dapagliflozin 10mg (up to 14 days or discharge whichever came first) plus standard of care or standard of care alone. The primary endpoints were mortality, kidney replacement therapy initiation, or ICU stay of up to 28 days. The researchers found that the addition of dapagliflozin to the standard of care didn't improve clinical outcomes. The highest probability of benefit was observed in the use of kidney replacement therapy (10.9% in the dapagliflozin arm versus 15.1%). Otherwise, benefit or harm couldn't be ascertained due to the wide confidence intervals.

Reference

Tavares, C. A. M., et al. (2024). Dapagliflozin for Critically Ill Patients with Acute Organ Dysfunction: The DEFENDER Randomized Clinical Trial. JAMA.

Continuous or intermittent -Lactam Antibiotic Infusions in Critically Ill Patients with Sepsis

There's conflicting evidence on which □-Lactam antibiotic infusion method is better. Researchers in this large multi-centric BLING III trial equally randomized 7031 patients with sepsis to either continuous (n = 3498) or intermittent infusions (n = 3533) of □-Lactam antibiotics (piperacillin-tazobactam or meropenem). The primary outcome was all-cause mortality at 90 days, while secondary outcomes included clinical cure up to 14 days. The researchers found no significant difference in all-cause mortality between the two infusion strategies. Clinical cure was however higher in the continuous infusion strategy versus the intermittent strategy; that is 55.7% versus 50.0% respectively. The study therefore sheds more light on the clinical dilemma of whether to administer the □-Lactam antibiotics as continuous or intermittent infusions.

Reference

Dulhunty, J. M., et al. (2024). Continuous vs Intermittent □-Lactam Antibiotic Infusions in Critically Ill Patients With Sepsis: The BLING III Randomized Clinical Trial. JAMA.

Mortality and Morbidity in Adults with Rheumatic Heart Disease

Rheumatic heart disease (RHD) remains a major public health challenge in LMICs. The INVICTUS Investigators in this large prospective observational study enrolled 13,696 RHD and followed them up for a median of 3.2 years. The primary endpoint was all-cause mortality, and other outcomes included cause-specific mortality, heart failure (HF) hospitalization, stroke, recurrent rheumatic fever, and infective endocarditis. Mortality was high, estimated at 15% (4.7% per patient-year), the majority of it from vascular causes i.e. mainly HF or sudden cardiac death. Severe valvular disease indicators including congestive HF (HR, 1.58), pulmonary hypertension (HR, 1.52), and atrial fibrillation (HR, 1.30) were associated with increased mortality. Surgery (HR, 0.23) or valvuloplasty (HR, 0.24) were associated with lower mortality. The researchers note that mortality correlated with valve disease severity and recommended improving access to surgical intervention.

Reference

Karthikeyan, G., et al. (2024). Mortality and Morbidity in Adults with Rheumatic Heart Disease. JAMA.

Metformin on the risk of cardiometabolic diseases and related mortality among US cancer survivors

Metformin has pleiotropic effects and is protective of cardiometabolic disorders in diabetic patients. Whether a similar effect could be seen in cancer survivors is not known. Researchers in this prospective cohort study used the US National Health and Nutrition Examination Survey data and identified 3995 cancer survivors who were followed up to 17 years (median duration 6.42 years). About 448 (11%) reported metformin usage. Metformin was associated with a lower risk of all-cause (HR, 0.62) and cardiometabolic death (HR, 0.65). It was also associated with a lower risk of total cardiovascular disease (odds ratio [OR], 0.41), stroke (OR, 0.44), hypertension (OR, 0.27), and coronary heart disease (OR, 0.41). Researchers concluded that metformin was associated with a lower risk of cardiometabolic diseases, all-cause, and cardiometabolic deaths.

Reference

Li, Y., Liu, X., et al. (2024). Metformin use correlated with lower risk of cardiometabolic diseases and related mortality among US cancer survivors: evidence from a nationally representative cohort study. BMC Medicine 2024 22:1, 22(1), 1–16.

Pulmonologist-directed care in undiagnosed COPD or asthma

Over 70% of patients with COPD and asthma remain undiagnosed. Researchers in this study identified and enrolled patients with undiagnosed COPD or asthma from the community, and determined if early diagnosis and treatment would reduce health-care utilization and improve outcomes. Five hundred eight (508) participants underwent randomization to either intervention (evaluation and treatment by a pulmonologist and an asthma–COPD educator) or usual care by their primary care practitioner. The primary endpoint was the annual rate of participant-initiated healthcare utilization for respiratory illness. The primary endpoint was lower in the intervention arm than usual care i.e., 0.53 versus 1.12 events per person-year; incidence rate ratio, 0.48. The researchers concluded that in a community strategy of identifying patients with undiagnosed COPD or asthma, pulmonologist-directed care reduced healthcare utilization than usual care.

Reference

Aaron, S. D., Vandemheen, K. L., et al. (2024). Early Diagnosis and Treatment of COPD and Asthma — A Randomized, Controlled Trial. New England Journal of Medicine, 390(22), 2061–2073.

Semaglutide on chronic kidney disease in type 2 diabetes mellitus

Patients with type 2 diabetes mellitus (T2DM) with chronic kidney disease (CKD) are at high risk of kidney failure. Whether semaglutide reduces this risk isn't known. This placebo-controlled trial enrolled 3,533 participants with T2DM and CKD. CKD was defined as an estimated glomerular filtration rate of 25 to 75ml per minute per 1.73 m2. They were randomized to subcutaneous semaglutide at a dose of 1.0 mg weekly or placebo, the primary outcome being major kidney disease events. The primary outcome was significantly lower in the semaglutide than in the placebo group i.e. HR, 0.76. A pattern favoring semaglutide was seen in all kidney-specific outcomes, including death from cardiovascular causes among others. They concluded that semaglutide improves kidney outcomes in T2DM patients with CKD.

Reference

Perkovic, V., Tuttle, K. R., et al. (2024). Effects of Semaglutide on Chronic Kidney Disease in Patients with Type 2 Diabetes. New England Journal of Medicine.

Combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors is better than either drug alone.

Among patients with T2DM, glucagon-like peptide-1 receptor agonists (GLP1-RA) and sodium-glucose cotransporter-2 inhibitors (SGLT2is) are second to third-line antihyperglycemic agents. Whether a combination of the two drug classes reduces the risk of major adverse cardiovascular events (MACEs), and renal events than either drug alone isn't known. The researchers matched GLP1-RA- SGLT2i combination users to single-drug users using 2 cohorts with the primary outcome being MACEs and serious renal events. Combination therapy was associated with a 30% lower risk of MACEs (HR, 0.70), and a 57% lower risk of serious renal events (HR, 0.43). GLP1-RAs were also associated with a 29% lower risk of MACEs than SGLT2i (HR, 0.71). The researchers concluded that in this study, the GLP1-RA-SGLT2i combination was associated with a reduction in MACEs and renal events than either drug alone.

Reference

Simms-Williams, N., Treves, N., et al. (2024). Effect of combination treatment with glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter-2 inhibitors on incidence of cardiovascular and serious renal events: population-based cohort study. BMJ, 385.

Comparative effectiveness of second-line oral antidiabetic agents among T2DM patients.

Researchers in this study conducted a comparative analysis of second-line oral hypoglycemic agents (OHAs) in routine clinical practice. They conducted a cohort study involving 75,739 adults with T2DM who initiated second-line oral antidiabetic treatment with a sulfonylurea, DPP-4 inhibitor, or SGLT-2 inhibitor added to metformin. The primary endpoint was an absolute change in glycated hemoglobin from baseline to 1 year. Secondary endpoints included body mass index (BMI), systolic blood pressure (SBP), and eGFR. SGLT2 inhibitors were more effective than sulfonylurea and DPP-4 inhibitors at reducing the HBA1c i.e. -2.5mmol/mol versus -3.2mmol/mol respectively. SGLT-2 inhibitors also more effectively reduced BMI and SBP. They thus concluded that SGLT-2 inhibitors were more effective than sulfonylurea and DPP-4 inhibitors as second-line OHAs.

Reference

Bidulka, P., Lugo-Palacios, D. G., et al. (2024). Comparative effectiveness of second-line oral antidiabetic treatments among people with type 2 diabetes mellitus: emulation of a target trial using routinely collected health data. BMJ, 385.

Long-acting cabotegravir and rilpivirine in virologically suppressed adults with HIV in Africa.

Long-acting cabotegravir (CBG) and rilpivirine (RPV) are licensed for HIV-1 treatment in resource-rich countries. Whether it can be used in Africa where demographics and HIV characteristics might differ wasn't clear. This study evaluated if switching to long-acting therapy with injections every 8 weeks is non-inferior to daily oral therapy. This study enrolled a total of 512 patients with HIV viral load below 50 copies per mL on oral antiretroviral therapy and no history of virological failure. These were randomized in a 1:1 ratio to CBG+RPV or to continue oral therapy. The primary outcome was week 48 viral load below 50 copies/ml. The primary outcome was observed in 96% of 255 participants in the CBG+RPV arm and 97% of 257 in the oral therapy group. The researchers reported that long-acting therapy was non-inferior compared to oral therapy.

Reference

Kityo, C., Mambule, I. K., et al. (2024). Switch to long-acting cabotegravir and rilpivirine in virologically suppressed adults with HIV in Africa (CARES): week 48 results from a randomized, multicentre, open-label, non-inferiority trial. The Lancet Infectious Diseases, 0(0).

Stress Ulcer Prophylaxis during Invasive Mechanical Ventilation

It's not clear whether stress ulcer prophylaxis in patients who are mechanically ventilated is beneficial or harmful. In this large international randomized control trial, 4821 critically ill patients undergoing invasive ventilation were randomized in a 1:1 ratio to receive intravenous pantoprazole 40mg daily or placebo. The primary endpoint was clinically significant upper gastrointestinal bleeding at 90 days, and the safety outcome was all-cause death at 90 days. The primary outcome was observed in 1.0% of patients in the pantoprazole arm compared to 3.5% in the placebo arm (HR, 0.30). There was no significant difference in mortality at 90 days. The researchers thus concluded that among invasively ventilated patients, pantoprazole resulted in a lower risk of upper gastrointestinal bleeding than placebo, but did not reduce the risk of mortality.

Reference

Cook, D., Deane, A., et al. (2024). Stress Ulcer Prophylaxis during Invasive Mechanical Ventilation. New England Journal of Medicine.

MCH

Lateral episiotomy or no episiotomy in vacuum-assisted delivery in nulliparous women

Vacuum-assisted vaginal deliveries are associated with significant maternal complications including injury to the anal sphincter. Researchers in this Swedish study determined if a pre-emptive lateral episiotomy as compared to no episiotomy could reduce obstetric anal sphincter injury. A total of 702 patients equally randomized to lateral episiotomy or no episiotomy were included in the final analysis. Fewer patients in the episiotomy arm sustained anal sphincter injury compared to no episiotomy i.e. 6% versus 13% (adjusted risk ratio, 0.47). There was no difference in postpartum pain, blood loss, neonatal outcomes, or total adverse events, though the episiotomy arm had more wound infections and dehiscence. The researchers concluded that lateral episiotomy can be recommended for nulliparous women requiring vacuum extraction to reduce the risk of anal sphincter injury.

Reference

Bergendahl, S., Jonsson, M., et al. (2024). Lateral episiotomy or no episiotomy in vacuum-assisted delivery in nulliparous women (EVA): a multicentre, open-label, randomized controlled trial. BMJ, 385, e079014.

Modifiable risk factors associated with neonatal mortality in sub-Saharan Africa.

With sub-Saharan Africa (SSA) shouldering the highest burden of neonatal mortality, knowing the modifiable risk factors is crucial to averting neonatal mortalities. Researchers in this study analyzed the demographics and health survey data sets from 35 SSA countries conducted between 2010 and 2022, and calculated the population-attributable fractions (PAF) for modifiable risk factors. The researchers found that the highest PAF was attributed to delayed initiation of breastfeeding (>1 hour after birth) (23.88%), uncleaned cooking fuel (5.27%), mothers lacking formal education (4.34%), mothers lacking tetanus vaccination (3.54%), and infrequent antenatal care visits (2.4%), and together these modifiable risk factors were associated with 40% of neonatal deaths among singleton children. The researchers thus concluded that a significant number of neonatal deaths in SSA were preventable.

Reference

Ahmed, K. Y., Thapa, S., et al. (2024). Population modifiable risk factors associated with neonatal mortality in 35 sub-Saharan African countries: analysis of data from demographic and health surveys. EClinicalMedicine, 73.

Azithromycin prophylaxis in pregnancy and labor.

Early evidence suggested that azithromycin prophylaxis in pregnant women improved maternal and neonatal outcomes. However, recent trials have yielded conflicting results. Researchers conducted a systematic review and meta-analysis to ascertain if azithromycin prophylaxis reduced neonatal or maternal mortality. The primary outcome was neonatal mortality and intrapartum, and antenatal administration were assessed separately. In the 20 RCTs reviewed, intrapartum azithromycin wasn't impactful on neonatal or maternal mortality i.e., RR, 1.02 and RR, 1.26 respectively. Antenatal azithromycin similarly didn't show any effect on neonatal or maternal outcomes. The researchers hence concluded that low to very-low certainty evidence suggests that azithromycin prophylaxis in pregnant women might not reduce neonatal or maternal mortality

Reference

Shamim, M. A., Kumar, J., et al. (2024). PeRinatal, neOnatal, and Maternal OuTcomEs with azithromycin prophylaxis in pregnancy and labor (PROMOTE-PROPHYLAXIS): systematic review and meta-analysis. EClinicalMedicine, 73.

Kangaroo mother care on early neonatal mortality.

Kangaroo mother care (KMC) is recommended by the WHO, but its effect on neonatal mortality and cost-effectiveness remains unclear. In this study conducted in Uganda, 2221 neonates with 700 to 2000 grams were enrolled and randomized to either KMC initiated before stabilization (intervention group) or standard care (incubator or radiant heater). The primary endpoint was all-cause neonatal mortality at 7 days. The researchers found no effect on early neonatal mortality as a similar number of neonates died in either group i.e., 7.5% of neonates died in either group. KMC was however found to be cost-effective from both provider and societal perspectives. The researchers thus concluded that additional investment in neonatal care is needed for further impact on SSA.

Reference

Tumukunde, V., Medvedev, M. M., et al. (2024). Effectiveness of kangaroo mother care before clinical stabilization versus standard care among neonates at five hospitals in Uganda (OMWaNA): a parallel-group, individually randomized controlled trial and economic evaluation. The Lancet, 403(10443), 2520–2532.

General Surgery

Liberal versus restrictive blood transfusion in traumatic brain injury

Most transfusion guidelines recommend a restrictive blood transfusion strategy for most patient groups. Whether this strategy is safe in patients with traumatic brain injury and anemia isn't clear. Researchers in this trial randomized 742 patients (1:1 ratio) with traumatic brain injury to a liberal or restrictive strategy, transfusing at a hemoglobin level of ≤10 or ≤7 g/dl respectively. The primary endpoint was an unfavorable outcome by the Glasgow Outcome Scale-Extended at 6 months. There was no significant difference in the rate of undesirable outcomes between liberal (68.4%) or restrictive (73.5%) transfusion strategies. They thus concluded that in critically ill patients with traumatic brain injury and anemia, the liberal transfusion strategy didn't reduce the risk of unfavorable outcomes at 6 months.

Reference

Turgeon, A. F., et al. (2024). Liberal or Restrictive Transfusion Strategy in Patients with Traumatic Brain Injury. New England Journal of Medicine.

Different antiplatelet strategies following coronary artery bypass grafting (CABG) on five-year clinical outcomes.

Dual antiplatelet therapy (DAPT) with ticagrelor is more effective than aspirin monotherapy in preventing saphenous vein graft failure after CABG. Whether DAPT has effects on long-term clinical outcomes is unclear. Researchers in this trial randomized participants (1:1:1) to ticagrelor 90 mg twice daily plus aspirin 100 mg once daily, ticagrelor monotherapy, or aspirin monotherapy for one year after surgery. The primary outcome was MACEs at 5 years. The researchers found that the primary outcome occurred in fewer patients in the dual antiplatelet arm (22.6%) than in aspirin monotherapy (29.9%) or ticagrelor monotherapy (32.9%). The researchers thus concluded that dual antiplatelet therapy for 1 year after CABG reduced major adverse cardiovascular events at 5 years than monotherapy alone.

Reference

Zhu, Y., Zhang, W., et al. (2024). Antiplatelet therapy after coronary artery bypass surgery: five-year follow-up of randomized DACAB trial. BMJ, 385.

Burr-hole drainage with or without irrigation in chronic subdural hematoma.

Chronic subdural hematoma is commonly surgically managed with burr-hole drainage, irrigation of subdural space, and insertion of subdural drain. The role of irrigation of subdural space has however not been well evidenced. Researchers in the non-inferiority trial randomized 589 adult patients with chronic subdural hematoma to either with or without subdural irrigation. The primary outcome measure was reoperation within 6 months, with the non-inferiority set at a 7.5% margin. Secondary outcomes included unfavourable outcomes (mRS 4-6), and mortality rate at 6 months. The researchers found the reoperation rate was 6.0% higher without subdural irrigation, and thus were not able to demonstrate non-inferiority of burr holes without irrigation. The researchers concluded that since there were no differences in functional outcomes or mortality between arms, subdural irrigation was better.

Reference

Raj, R., Tommiska, P., et al. (2024). Burr-hole drainage with or without irrigation for chronic subdural hematoma (FINISH): a Finnish, nationwide, parallel-group, multicentre, randomized, controlled, non-inferiority trial. The Lancet, 403(10446), 2798–2806.

Early Minimally Invasive Removal of Intracerebral Hemorrhage

For patients with spontaneous intracerebral hemorrhage (ICH), surgical evacuation is recommended as a lifesaving measure only, because of inadequate evidence for functional outcomes benefit. This trial compared early minimally invasive surgical removal of hematoma and best medical management with the latter alone. Three hundred (300) patients presenting in 24 hours with a supratentorial ICH were randomly assigned (1:1) to minimally invasive surgery and medical management or latter alone. The primary endpoint which was the mean score for disability on the utility-weighted mRS at 180 days, favored surgery with 0.458 versus 0.374 in the control arm (an estimated difference of 0.084). The surgical benefit was mostly derived from lobar hemorrhage. Death by 30 days occurred less commonly with surgery. The authors thus concluded that early minimally invasive surgery with best-medical therapy for intracerebral hemorrhage improved outcomes compared with medical management alone.

Reference

Rradilla, G., Ratcliff, J. J., et al. (2024). Trial of Early Minimally Invasive Removal of Intracerebral Hemorrhage. New England Journal of Medicine, 390(14), 1277–1289.