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BMJ (31 March 2018, Vol. 360, No. 8147)

Endovascular treatment for acute ischaemic stroke in routine clinical practice: Prospective, observational cohort study (MR CLEAN Registry)
Ivo G H Jansen, Maxim J H L Mulder, Robert-Jan B Goldhoorn, for the MR CLEAN Registry investigators
BMJ 2018; 360 (Published 09 March 2018)
https://www.bmj.com/content/360/bmj.k949

Abstract
Objective To determine outcomes and safety of endovascular treatment for acute ischaemic stroke, due to proximal intracranial vessel occlusion in the anterior circulation, in routine clinical practice.
Design Ongoing, prospective, observational cohort study.
Setting 16 centres that perform endovascular treatment in the Netherlands.
Participants 1488 patients included in the Multicentre Randomised Controlled Trial of Endovascular Treatment for Acute Ischaemic Stroke in the Netherlands (MR CLEAN) Registry who had received endovascular treatment, including stent retriever thrombectomy, aspiration, and all alternative methods for acute ischaemic stroke within 6.5 hours from onset of symptoms between March 2014 and June 2016.
Main outcome measures The primary outcome was the modified Rankin Scale (mRS) score, ranging from 0 (no symptoms) to 6 (death) at 90 days after the onset of symptoms. Secondary outcomes were excellent functional outcome (mRS score 0-1), good functional outcome (mRS score 0-2), and favourable functional outcome (mRS score 0-3) at 90 days; score on the extended thrombolysis in cerebral infarction scale at the end of the intervention procedure; National Institutes of Health Stroke Scale score 24-48 hours after intervention; and complications that occurred during intervention, hospital admission, or three months' follow up period. Outcomes and safety variables in the MR CLEAN Registry were compared with the MR CLEAN trial intervention and control arms.
Results A statistically significant shift was observed towards better functional outcome in patients in the MR CLEAN Registry compared with the MR CLEAN trial intervention arm (adjusted common odds ratio 1.30, 95% confidence interval 1.02 to 1.67) and the MR CLEAN trial control arm (1.85, 1.46 to 2.34). The reperfusion rate, with successful reperfusion defined as a score of 2B-3 on the extended thrombolysis in cerebral infarction

score, was 58.7%, the same as for patients in the MR CLEAN trial. Duration from onset of stroke to start of endovascular treatment and from onset of stroke to successful reperfusion or last contrast bolus was one hour shorter for patients in the MR CLEAN Registry. Symptomatic intracranial haemorrhage occurred in 5.8% of patients in the MR CLEAN Registry compared with 7.7% in the MR CLEAN trial intervention arm and 6.4% in the MR CLEAN trial control arm.
Conclusion In routine clinical practice, endovascular treatment for patients with acute ischaemic stroke is at least as effective and safe as in the setting of a randomised controlled trial.

Socioeconomic status, non-communicable disease risk factors, and walking speed in older adults: Multi-cohort population based study
Silvia Stringhini, Cristian Carmeli, Markus Jokela, et al. for the LIFEPATH Consortium
BMJ 2018; (Published 23 March 2018)
https://www.bmj.com/content/360/bmj.k1046

Abstract
Objective To assess the association of low socioeconomic status and risk factors for non-communicable diseases (diabetes, high alcohol intake, high blood pressure, obesity, physical inactivity, smoking) with loss of physical functioning at older ages.
Design Multi-cohort population based study.
Setting 37 cohort studies from 24 countries in Europe, the United States, Latin America, Africa, and Asia, 1990-2017.
Participants 109 107 men and women aged 45-90 years.
Main outcome measure Physical functioning assessed using the walking speed test, a valid index of overall functional capacity. Years of functioning lost was computed as a metric to quantify the difference in walking speed between those exposed and unexposed to low socioeconomic status and risk factors.
Results According to mixed model estimations, men aged 60 and of low socioeconomic status had the same walking speed as men aged 66.6 of high socioeconomic status (years of functioning lost 6.6 years, 95% confidence interval 5.0 to 9.4). The years of functioning lost for women were 4.6 (3.6 to 6.2). In men and women, respectively, 5.7 (4.4 to 8.1) and 5.4 (4.3 to 7.3) years of functioning were lost by age 60 due to insufficient physical activity, 5.1 (3.9 to 7.0) and 7.5 (6.1 to 9.5) due to obesity, 2.3 (1.6 to 3.4) and 3.0 (2.3 to 4.0) due to hypertension, 5.6 (4.2 to 8.0) and 6.3 (4.9 to 8.4) due to diabetes, and 3.0 (2.2 to 4.3) and 0.7 (0.1 to 1.5) due to tobacco use. In analyses restricted to high income countries, the number of years of functioning lost attributable to low socioeconomic status by age 60 was 8.0 (5.7 to 13.1) for men and 5.4 (4.0 to 8.0) for women, whereas in low and middle income countries it was 2.6 (0.2 to 6.8) for men and 2.7 (1.0 to 5.5) for women. Within high income countries, the number of years of functioning lost attributable to low socioeconomic status by age 60 was greater in the United States than in Europe. Physical functioning continued to decline as a function of unfavourable risk factors between ages 60 and 85. Years of functioning lost were greater than years of life lost due to low socioeconomic status and non-communicable disease risk factors.
Conclusions The independent association between socioeconomic status and physical functioning in old age is comparable in strength and consistency with those for established non-communicable disease risk factors. The results of this study suggest that tackling all these risk factors might substantially increase life years spent in good physical functioning.

Affordability and availability of off-patent drugs in the United States—the case for importing from abroad: Observational study

Ravi Gupta, Thomas J Bollyky, Matthew Cohen, Joseph S Ross, Aaron S Kesselheim

BMJ 2018; 360 (Published 19 March 2018)
https://www.bmj.com/content/360/bmj.k831

Abstract

Objectives To evaluate whether off-patent prescription drugs at risk of sudden price increases or shortages in the United States are available from independent manufacturers approved in other well regulated settings around the world.

Design Observational study.

Setting Off-patent drugs in the USA and approved by the Food and Drug Administration, up to 10 April 2017.

Study cohort Novel tablet or capsule prescription drugs approved by the FDA since 1939 that were no longer protected by patents or other market exclusivity and had up to three generic versions.

Main outcome measures Number of additional manufacturers that had obtained approval from any of seven non-US regulators with similar standards (European Medicines Agency (European Union), HealthCanada (Canada), Therapeutic Goods Association (Australia), Medsafe (New Zealand), Swissmedic (Switzerland), Medicines Control Council (South Africa), and the Israel Health Ministry). Association with drug characteristics including US orphan drug designation for drugs treating rare diseases, World Health Organization essential medicine designation, treatment area, drug product complexity (that is, with attributes that could complicate establishing bioequivalence or manufacturing), and total Medicaid spending in 2015.

Results Of 170 eligible study drugs, more than half (109, 64%) had at least one manufacturer approved by a non-US regulator and 32 (19%) had four or more. Among 44 (26%) drugs with no FDA approved generic versions, 21 (48%) were available from at least one manufacturer approved by one of the seven non-US regulators, and two (5%) by four or more manufacturers. Across all drugs and regulators (including the FDA), 66 (39%) drugs were available from four or more total manufacturers. Of 109 drugs with at least one non-US regulator approved manufacturer, 12 (11%) were approved for patients with rare diseases and 29 (27%) were WHO designated essential medicines; only 12 (11%) were complex products that might be more complicated to import. The highest numbers of drugs were indicated for treating cardiovascular diseases, diabetes, or hyperlipidemia (19, 17%); psychiatric disease (16, 15%); and infectious diseases (15, 14%). In 2015, Medicaid alone spent nearly US$700m (£508m; €570m) on generic drugs without adequate US competition that could have had a manufacturer approved by non-US peer regulatory agencies.

Conclusion In this study, more than half the off-patent drugs with no generic competition in the USA had at least one independent manufacturer approved by a non-US peer regulatory agency; slightly fewer than half had four or more total manufacturers. Facilitating US patient access to such manufacturers could help sustain affordable access to essential off-patent drugs.

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Effect of Loading Dose of Atorvastatin Prior to Planned Percutaneous Coronary Intervention on Major Adverse Cardiovascular Events in Acute Coronary Syndrome: The SECURE-PCI Randomized Clinical Trial

Otavio Berwanger, Eliana Vieira Santucci, Pedro Gabriel Melo de Barros e Silva, et al. for the SECURE-PCI Investigators

JAMA. 2018; 319 (13): 1331-1340.
https://jamanetwork.com/journals/jama/article-abstract/2675023?redirect=true

Abstract

Importance The effects of loading doses of statins on clinical outcomes in patients with acute coronary syndrome (ACS) and planned invasive management remain uncertain.

Objective To determine if periprocedural loading doses of atorvastatin decrease 30-day major adverse cardiovascular events (MACE) in patients with ACS and planned invasive management.

Design, Setting, and Participants Multicenter, double-blind, placebo-controlled, randomized clinical trial conducted at 53 sites in Brazil among 4191 patients with ACS evaluated with coronary angiography to proceed with a percutaneous coronary intervention (PCI) if anatomically feasible. Enrollment occurred between April 18, 2012, and October 6, 2017. Final follow-up for 30-day outcomes was on November 6, 2017.

Interventions Patients were randomized to receive 2 loading doses of 80 mg of atorvastatin (n = 2087) or matching placebo (n = 2104) before and 24 hours after a planned PCI. All patients received 40 mg of atorvastatin for 30 days starting 24 hours after the second dose of study medication.

Main Outcomes and Measures The primary outcome was MACE, defined as a composite of all-cause mortality, myocardial infarction, stroke, and unplanned coronary revascularization through 30 days.

Results Among the 4191 patients (mean age, 61.8 [SD, 11.5] years; 1085 women [25.9%]) enrolled, 4163 (99.3%) completed 30-day follow-up. A total of 2710 (64.7%) underwent PCI, 333 (8%) underwent coronary artery bypass graft surgery, and 1144 (27.3%) had exclusively medical management. At 30 days, 130 patients in the atorvastatin group (6.2%) and 149 in the placebo group (7.1%) had a MACE (absolute difference, 0.85% [95% CI, −0.70% to 2.41%]; hazard ratio, 0.88; 95% CI, 0.69-1.11; *P* = .27). No cases of hepatic failure were reported; 3 cases of rhabdomyolysis were reported in the placebo group (0.1%) and 0 in the atorvastatin group.

Conclusions and Relevance Among patients with ACS and planned invasive management with PCI, periprocedural loading doses of atorvastatin did not reduce the rate of MACE at 30 days. These findings do not support the routine use of loading doses of atorvastatin among unselected patients with ACS and intended invasive management.

Association of a Negative Wealth Shock With All-Cause Mortality in Middle-aged and Older Adults in the United States

Lindsay R. Pool, Sarah A. Burgard, Belinda L. Needham, et al

JAMA. 2018; 319 (13): 1341-1350.
https://jamanetwork.com/journals/jama/fullarticle/2677445

Abstract

Importance A sudden loss of wealth—a negative wealth shock—may lead to a significant mental health toll and also leave fewer monetary resources for health-related expenses. With limited years remaining to regain lost wealth in older age, the health consequences of these negative wealth shocks may be long-lasting.

Objective To determine whether a negative wealth shock was associated with all-cause mortality during 20 years of follow-up.
Design, Setting, and Participant The Health and Retirement Study, a nationally representative prospective cohort study of US adults aged 51 through 61 years at study entry. The study population included 8714 adults, first assessed for a negative wealth shock in 1994 and followed biennially through 2014 (the most recent year of available data.(
Exposure Experiencing a negative wealth shock, defined as a loss of 75% or more of total net worth over a 2-year period, or asset poverty, defined as 0 or negative total net worth at study entry.
Main Outcomes and Measures Mortality data were collected from the National Death Index and postmortem interviews with family members. Marginal structural survival methods were used to account for the potential bias due to changes in health status that may both trigger negative wealth shocks and act as the mechanism through which negative wealth shocks lead to increased mortality.
Result There were 8714 participants in the study sample (mean [SD] age at study entry, 55 [3.2] years; 53% women), 2430 experienced a negative wealth shock during follow-up, 749 had asset poverty at baseline, and 5535 had continuously positive wealth without shock. A total of 2823 deaths occurred during 80 683 person-years of follow-up. There were 30.6 vs 64.9 deaths per 1000 person-years for those with continuously positive wealth vs negative wealth shock (adjusted hazard ratio [HR], 1.50; 95% CI, 1.36-1.67). There were 73.4 deaths per 1000 person-years for those with asset poverty at baseline (adjusted HR, 1.67; 95% CI, 1.44-1.94; compared with continuously positive wealth.(
Conclusions and Relevance Among US adults aged 51 years and older, loss of wealth over 2 years was associated with an increased risk of all-cause mortality. Further research is needed to better understand the possible mechanisms for this association and determine whether there is potential value for targeted interventions.

Association of Solid Fuel Use With Risk of Cardiovascular and All-Cause Mortality in Rural China

Kuai Yu, Gaokun Qiu, Ka-Hung Chan, et al
JAMA. 2018; 319 (13): 1351-1361.
https://jamanetwork.com/journals/jama/article-abstract/2677446?redirect=true

Abstract
Importance When combusted indoors, solid fuels generate a large amount of pollutants such as fine particulate matter.
Objective To assess the associations of solid fuel use for cooking and heating with cardiovascular and all-cause mortality.
Design, Setting, and Participants This nationwide prospective cohort study recruited participants from 5 rural areas across China between June 2004 and July 2008; mortality follow-up was until January 1, 2014. A total of 271 217 adults without a self-reported history of physician-diagnosed cardiovascular disease at baseline were included, with a random subset (n = 10 892) participating in a resurvey after a mean interval of 2.7 years.
Exposures Self-reported primary cooking and heating fuels (solid: coal, wood, or charcoal; clean: gas, electricity, or central heating), switching of fuel type before baseline, and use of ventilated cookstoves.
Main Outcomes and Measures Death from cardiovascular and all causes, collected through established death registries.

Results Among the 271 217 participants, the mean (SD) age was 51.0 (10.2) years, and 59% (n = 158 914) were women. A total of 66% (n = 179 952) of the participants reported regular cooking (at least weekly) and 60% (n = 163 882) reported winter heating, of whom 84% (n = 150 992) and 90% (n = 147 272) used solid fuels, respectively. There were 15 468 deaths, including 5519 from cardiovascular causes, documented during a mean (SD) of 7.2 (1.4) years of follow-up. Use of solid fuels for cooking was associated with greater risk of cardiovascular mortality (absolute rate difference [ARD] per 100 000 person-years, 135 [95% CI, 77-193]; hazard ratio [HR], 1.20 [95% CI, 1.02-1.41]) and all-cause mortality (ARD, 338 [95% CI, 249-427]; HR, 1.11 [95% CI, 1.03-1.20]). Use of solid fuels for heating was also associated with greater risk of cardiovascular mortality (ARD, 175 [95% CI, 118-231]; HR, 1.29 [95% CI, 1.06-1.55]) and all-cause mortality (ARD, 392 [95% CI, 297-487]; HR, 1.14 [95% CI, 1.03-1.26]). Compared with persistent solid fuel users, participants who reported having previously switched from solid to clean fuels for cooking had a lower risk of cardiovascular mortality (ARD, 138 [95% CI, 71-205]; HR, 0.83 [95% CI, 0.69-0.99]) and all-cause mortality (ARD, 407 [95% CI, 317-497]; HR, 0.87 [95% CI, 0.79-0.95]), while for heating, the ARDs were 193 (95% CI, 128-258) and 492 (95% CI, 383-601), and the HRs were 0.57 (95% CI, 0.42-0.77) and 0.67 (95% CI, 0.57-0.79), respectively. Among solid fuel users, use of ventilated cookstoves was also associated with lower risk of cardiovascular mortality (ARD, 33 [95% CI, −9 to 75]; HR, 0.89 [95% CI, 0.80-0.99]) and all-cause mortality (ARD, 87 [95% CI, 20-153]; HR, 0.91 [95% CI, 0.85-0.96]).
Conclusions and Relevance In rural China, solid fuel use for cooking and heating was associated with higher risks of cardiovascular and all-cause mortality. These risks may be lower among those who had previously switched to clean fuels and those who used ventilation.

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The Lancet (31 March 2018, Vol. 391, No. 10127)

Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): A double-blind, randomised, phase 3 study

Ludwig Kappos, Amit Bar-Or, Bruce A C Cree, et al. for the show EXPAND Clinical Investigators

The Lancet: Volume 391, No. 10127, p1263–1273, 31 March 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30475-6/fulltext

Summary
Background
No treatment has consistently shown efficacy in slowing disability progression in patients with secondary progressive multiple sclerosis (SPMS). We assessed the effect of siponimod, a selective sphingosine 1-phosphate (S1P) receptor$_{1,5}$ modulator, on disability progression in patients with SPMS.
Methods
This event-driven and exposure-driven, double-blind, phase 3 trial was done at 292 hospital clinics and specialised multiple sclerosis centres in 31 countries. Using interactive response technology to assign numbers linked to treatment arms, patients (age 18–60 years) with SPMS and an Expanded Disability Status Scale score of 3·0–6·5 were randomly assigned (2:1) to once daily oral siponimod 2 mg or placebo for up to 3 years or until the occurrence of a prespecified number of confirmed disability progression (CDP) events. The primary endpoint was time to 3-month CDP. Efficacy was assessed for the full

analysis set (ie, all randomly assigned and treated patients); safety was assessed for the safety set. This trial is registered with ClinicalTrials.gov, number NCT01665144.

Findings

1651 patients were randomly assigned between Feb 5, 2013, and June 2, 2015 (1105 to the siponimod group, and 546 to the placebo group). One patient did not sign the consent form, and five patients did not receive study drug, all of whom were in the siponimod group. 1645 patients were included in the analyses (1099 in the siponimod group and 546 in the placebo). At baseline, the mean time since first multiple sclerosis symptoms was 16·8 years (SD 8·3), and the mean time since conversion to SPMS was 3·8 years (SD 3·5); 1055 (64%) patients had not relapsed in the previous 2 years, and 918 (56%) of 1651 needed walking assistance. 903 (82%) patients receiving siponimod and 424 (78%) patients receiving placebo completed the study. 288 (26%) of 1096 patients receiving siponimod and 173 (32%) of 545 patients receiving placebo had 3-month CDP (hazard ratio 0·79, 95% CI 0·65–0·95; relative risk reduction 21%; p=0·013). Adverse events occurred in 975 (89%) of 1099 patients receiving siponimod versus 445 (82%) of 546 patients receiving placebo; serious adverse events were reported for 197 (18%) patients in the siponimod group versus 83 (15%) patients in the placebo group. Lymphopenia, increased liver transaminase concentration, bradycardia and bradyarrhythmia at treatment initiation, macular oedema, hypertension, varicella zoster reactivation, and convulsions occurred more frequently with siponimod than with placebo. Initial dose titration mitigated cardiac first-dose effects. Frequencies of infections, malignancies, and fatalities did not differ between groups.

Interpretation

Siponimod reduced the risk of disability progression with a safety profile similar to that of other S1P modulators and is likely to be a useful treatment for SPMS.

6-month versus 12-month or longer dual antiplatelet therapy after percutaneous coronary intervention in patients with acute coronary syndrome (SMART-DATE): A randomised, open-label, non-inferiority trial

Joo-Yong Hahn, Young Bin Song, Ju-Hyeon Oh, et al. for the show SMART-DATE investigators

The Lancet: Volume 391, No. 10127, p1274–1284, 31 March 2018
http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)30493-8/fulltext

Summary

Background

Current guidelines recommend dual antiplatelet therapy (DAPT) of aspirin plus a P2Y12 inhibitor for at least 12 months after implantation of drug-eluting stents (DES) in patients with acute coronary syndrome. However, available data about the optimal duration of DAPT in patients with acute coronary syndrome undergoing percutaneous coronary intervention are scant. We aimed to investigate whether a 6-month duration of DAPT would be non-inferior to the conventional 12-month or longer duration of DAPT in this population.

Methods

We did a randomised, open-label, non-inferiority trial at 31 centres in South Korea. Patients were eligible if they had unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction, and underwent percutaneous coronary intervention. Enrolled patients were randomly assigned, via a web-based system by computer-generated block randomisation, to either the 6-month DAPT group or to the 12-month or longer DAPT group, with stratification by site, clinical presentation, and

diabetes. Assessors were masked to treatment allocation. The primary endpoint was a composite of all-cause death, myocardial infarction, or stroke at 18 months after the index procedure in the intention-to-treat population. Secondary endpoints were the individual components of the primary endpoint; definite or probable stent thrombosis as defined by the Academic Research Consortium; and Bleeding Academic Research Consortium (BARC) type 2–5 bleeding at 18 months after the index procedure. The primary endpoint was also analysed per protocol. This trial is registered with ClinicalTrials.gov, number NCT01701453.

Findings

Between Sept 5, 2012, and Dec 31, 2015, we randomly assigned 2712 patients; 1357 to the 6-month DAPT group and 1355 to the 12-month or longer DAPT group. Clopidogrel was used as a P2Y12 inhibitor for DAPT in 1082 (79·7%) patients in the 6-month DAPT group and in 1109 (81·8%) patients in the 12-month or longer DAPT group. The primary endpoint occurred in 63 patients in the 6-month DAPT group and in 56 patients in the 12-month or longer DAPT group (cumulative event rate 4·7% *vs* 4·2%; absolute risk difference 0·5%; upper limit of one-sided 95% CI 1·8%; $p_{non\text{-}inferiority}$=0·03 with a predefined non-inferiority margin of 2·0%). Although all-cause mortality did not differ significantly between the 6-month DAPT group and the 12-month or longer DAPT group (35 [2·6%] patients *vs* 39 [2·9%]; hazard ratio [HR] 0·90 [95% CI 0·57–1·42]; p=0·90) and neither did stroke (11 [0·8%] patients *vs* 12 [0·9%]; 0·92 [0·41–2·08]; p=0·84), myocardial infarction occurred more frequently in the 6-month DAPT group than in the 12-month or longer DAPT group (24 [1·8%] patients *vs* ten [0·8%]; 2·41 [1·15–5·05]; p=0·02). 15 (1·1%) patients had stent thrombosis in the 6-month DAPT group compared with ten (0·7%) in the 12-month or longer DAPT group (HR 1·50 [95% CI 0·68–3·35]; p=0·32). The rate of BARC type 2–5 bleeding was 2·7% (35 patients) in the 6-month DAPT group and 3·9% (51 patients) in the 12-month or longer DAPT group (HR 0·69 [95% CI 0·45–1·05]; p=0·09). Results from the per-protocol analysis were similar to those from the intention-to-treat analysis.

Interpretation

The increased risk of myocardial infarction with 6-month DAPT and the wide non-inferiority margin prevent us from concluding that short-term DAPT is safe in patients with acute coronary syndrome undergoing percutaneous coronary intervention with current-generation DES. Prolonged DAPT in patients with acute coronary syndrome without excessive risk of bleeding should remain the standard of care.

Estimates of global seasonal influenza-associated respiratory mortality: A modelling study

A Danielle Iuliano, Katherine M Roguski, Howard H Chang, et al. for the show Global Seasonal Influenza-associated Mortality Collaborator Network

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http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(17)33293-2/fulltext

Summary

Background

Estimates of influenza-associated mortality are important for national and international decision making on public health priorities. Previous estimates of 250 000–500 000 annual influenza deaths are outdated. We updated the estimated number of global annual influenza-associated respiratory deaths using country-specific influenza-associated excess respiratory mortality estimates from 1999–2015.

Methods

We estimated country-specific influenza-associated respiratory excess mortality rates (EMR) for 33 countries using time series log-linear regression models with vital death records and influenza surveillance data. To extrapolate estimates to countries without data, we divided countries into three analytic divisions for three age groups (<65 years, 65–74 years, and ≥75 years) using WHO Global Health Estimate (GHE) respiratory infection mortality rates. We calculated mortality rate ratios (MRR) to account for differences in risk of influenza death across countries by comparing GHE respiratory infection mortality rates from countries without EMR estimates with those with estimates. To calculate death estimates for individual countries within each age-specific analytic division, we multiplied randomly selected mean annual EMRs by the country's MRR and population. Global 95% credible interval (CrI) estimates were obtained from the posterior distribution of the sum of country-specific estimates to represent the range of possible influenza-associated deaths in a season or year. We calculated influenza-associated deaths for children younger than 5 years for 92 countries with high rates of mortality due to respiratory infection using the same methods.

Findings

EMR-contributing countries represented 57% of the global population. The estimated mean annual influenza-associated respiratory EMR ranged from 0·1 to 6·4 per 100 000 individuals for people younger than 65 years, 2·9 to 44·0 per 100 000 individuals for people aged between 65 and 74 years, and 17·9 to 223·5 per 100 000 for people older than 75 years. We estimated that 291 243–645 832 seasonal influenza-associated respiratory deaths (4·0–8·8 per 100 000 individuals) occur annually. The highest mortality rates were estimated in sub-Saharan Africa (2·8–16·5 per 100 000 individuals), southeast Asia (3·5–9·2 per 100 000 individuals), and among people aged 75 years or older (51·3–99·4 per 100 000 individuals). For 92 countries, we estimated that among children younger than 5 years, 9243–105 690 influenza-associated respiratory deaths occur annually.

Interpretation

These global influenza-associated respiratory mortality estimates are higher than previously reported, suggesting that previous estimates might have underestimated disease burden. The contribution of non-respiratory causes of death to global influenza-associated mortality should be investigated.

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The New England Journal of Medicine (29 March 2018, Vol. 378, No. 13)

Duration of Adjuvant Chemotherapy for Stage III Colon Cancer

Axel Grothey, Alberto F. Sobrero, Anthony F. Shields, et al.

N Engl J Med 2018; 378:1177-1188 March 29, 2018
http://www.nejm.org/doi/full/10.1056/NEJMoa1713709

Abstract

Background

Since 2004, a regimen of 6 months of treatment with oxaliplatin plus a fluoropyrimidine has been standard adjuvant therapy in patients with stage III colon cancer. However, since oxaliplatin is associated with cumulative neurotoxicity, a shorter duration of therapy could spare toxic effects and health expenditures.

Methods

We performed a prospective, preplanned, pooled analysis of six randomized, phase 3 trials that were conducted concurrently to evaluate the noninferiority of adjuvant therapy with either FOLFOX (fluorouracil, leucovorin, and oxaliplatin) or CAPOX (capecitabine and

oxaliplatin) administered for 3 months, as compared with 6 months. The primary end point was the rate of disease-free survival at 3 years. Noninferiority of 3 months versus 6 months of therapy could be claimed if the upper limit of the two-sided 95% confidence interval of the hazard ratio did not exceed 1.12.

Results

After 3263 events of disease recurrence or death had been reported in 12,834 patients, the noninferiority of 3 months of treatment versus 6 months was not confirmed in the overall study population (hazard ratio, 1.07; 95% confidence interval [CI], 1.00 to 1.15). Noninferiority of the shorter regimen was seen for CAPOX (hazard ratio, 0.95; 95% CI, 0.85 to 1.06) but not for FOLFOX (hazard ratio, 1.16; 95% CI, 1.06 to 1.26). In an exploratory analysis of the combined regimens, among the patients with T1, T2, or T3 and N1 cancers, 3 months of therapy was noninferior to 6 months, with a 3-year rate of disease-free survival of 83.1% and 83.3%, respectively (hazard ratio, 1.01; 95% CI, 0.90 to 1.12). Among patients with cancers that were classified as T4, N2, or both, the disease-free survival rate for a 6-month duration of therapy was superior to that for a 3-month duration (64.4% vs. 62.7%) for the combined treatments (hazard ratio, 1.12; 95% CI, 1.03 to 1.23; P=0.01 for superiority).

Conclusions

Among patients with stage III colon cancer receiving adjuvant therapy with FOLFOX or CAPOX, noninferiority of 3 months of therapy, as compared with 6 months, was not confirmed in the overall population. However, in patients treated with CAPOX, 3 months of therapy was as effective as 6 months, particularly in the lower-risk subgroup.

Molecular Minimal Residual Disease in Acute Myeloid Leukemia

Mojca Jongen-Lavrencic, Tim Grob, Diana Hanekamp, et al.

N Engl J Med 2018; 378:1189-1199 March 29, 2018
http://www.nejm.org/doi/full/10.1056/NEJMoa1716863

Abstract

Background

Patients with acute myeloid leukemia (AML) often reach complete remission, but relapse rates remain high. Next-generation sequencing enables the detection of molecular minimal residual disease in virtually every patient, but its clinical value for the prediction of relapse has yet to be established.

Methods

We conducted a study involving patients 18 to 65 years of age who had newly diagnosed AML. Targeted next-generation sequencing was carried out at diagnosis and after induction therapy (during complete remission). End points were 4-year rates of relapse, relapse-free survival, and overall survival.

Results

At least one mutation was detected in 430 out of 482 patients (89.2%). Mutations persisted in 51.4% of those patients during complete remission and were present at various allele frequencies (range, 0.02 to 47%). The detection of persistent DTA mutations (i.e., mutations in DNMT3A, TET2, and ASXL1), which are often present in persons with age-related clonal hematopoiesis, was not correlated with an increased relapse rate. After the exclusion of persistent DTA mutations, the detection of molecular minimal residual disease was associated with a significantly higher relapse rate than no detection (55.4% vs. 31.9%; hazard ratio, 2.14; P<0.001), as well as with lower rates of relapse-free survival (36.6% vs. 58.1%; hazard ratio for relapse or death, 1.92; P<0.001) and overall survival (41.9% vs. 66.1%; hazard ratio for death, 2.06; P<0.001). Multivariate analysis confirmed that the

persistence of non-DTA mutations during complete remission conferred significant independent prognostic value with respect to the rates of relapse (hazard ratio, 1.89; P<0.001), relapse-free survival (hazard ratio for relapse or death, 1.64; P=0.001), and overall survival (hazard ratio for death, 1.64; P=0.003). A comparison of sequencing with flow cytometry for the detection of residual disease showed that sequencing had significant additive prognostic value.

Conclusions

Among patients with AML, the detection of molecular minimal residual disease during complete remission had significant independent prognostic value with respect to relapse and survival rates, but the detection of persistent mutations that are associated with clonal hematopoiesis did not have such prognostic value within a 4-year time frame.

Cardiovascular Safety of Febuxostat or Allopurinol in Patients with Gout

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http://www.nejm.org/doi/full/10.1056/NEJMoa1710895

Abstract

Background

Cardiovascular risk is increased in patients with gout. We compared cardiovascular outcomes associated with febuxostat, a nonpurine xanthine oxidase inhibitor, with those associated with allopurinol, a purine base analogue xanthine oxidase inhibitor, in patients with gout and cardiovascular disease.

Methods

We conducted a multicenter, double-blind, noninferiority trial involving patients with gout and cardiovascular disease; patients were randomly assigned to receive febuxostat or allopurinol and were stratified according to kidney function. The trial had a prespecified noninferiority margin of 1.3 for the hazard ratio for the primary end point (a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or unstable angina with urgent revascularization).

Results

In total, 6190 patients underwent randomization, received febuxostat or allopurinol, and were followed for a median of 32 months (maximum, 85 months). The trial regimen was discontinued in 56.6% of patients, and 45.0% discontinued follow-up. In the modified intention-to-treat analysis, a primary end-point event occurred in 335 patients (10.8%) in the febuxostat group and in 321 patients (10.4%) in the allopurinol group (hazard ratio, 1.03; upper limit of the one-sided 98.5% confidence interval [CI], 1.23; P=0.002 for noninferiority). All-cause and cardiovascular mortality were higher in the febuxostat group than in the allopurinol group (hazard ratio for death from any cause, 1.22 [95% CI, 1.01 to 1.47]; hazard ratio for cardiovascular death, 1.34 [95% CI, 1.03 to 1.73]). The results with regard to the primary end point and all-cause and cardiovascular mortality in the analysis of events that occurred while patients were being treated were similar to the results in the modified intention-to-treat analysis.

Conclusions

In patients with gout and major cardiovascular coexisting conditions, febuxostat was noninferior to allopurinol with respect to rates of adverse cardiovascular events. All-cause mortality and cardiovascular mortality were higher with febuxostat than with allopurinol.

Ibrutinib plus Venetoclax for the Treatment of Mantle-Cell Lymphoma
Constantine S. Tam, Mary Ann Anderson, Christiane Pott, et al.
N Engl J Med 2018; 378:1211-1223 March 29, 2018
http://www.nejm.org/doi/full/10.1056/NEJMoa1715519

Abstract

Background

Both the BTK inhibitor ibrutinib and the BCL2 inhibitor venetoclax are active as monotherapy in the treatment of mantle-cell lymphoma. Complete response rates of 21% have been observed for each agent when administered as long-term continuous therapy. Preclinical models predict synergy in combination.

Methods

We conducted a single-group, phase 2 study of daily oral ibrutinib and venetoclax in patients, as compared with historical controls. Patients commenced ibrutinib monotherapy at a dose of 560 mg per day. After 4 weeks, venetoclax was added in stepwise, weekly increasing doses to 400 mg per day. Both drugs were continued until progression or an unacceptable level of adverse events. The primary end point was the rate of complete response at week 16. Minimal residual disease (MRD) was assessed by flow cytometry in bone marrow and by allele-specific oligonucleotide–polymerase chain reaction (ASO-PCR) in blood.

Results

The study included 24 patients with relapsed or refractory mantle-cell lymphoma (23 patients) or previously untreated mantle-cell lymphoma (1 patient). Patients were 47 to 81 years of age, and the number of previous treatments ranged from none to six. Half the patients had aberrations of TP53, and 75% had a high-risk prognostic score. The complete response rate according to computed tomography at week 16 was 42%, which was higher than the historical result of 9% at this time point with ibrutinib monotherapy (P<0.001). The rate of complete response as assessed by positron-emission tomography was 62% at week 16 and 71% overall. MRD clearance was confirmed by flow cytometry in 67% of the patients and by ASO-PCR in 38%. In a time-to-event analysis, 78% of the patients with a response were estimated to have an ongoing response at 15 months. The tumor lysis syndrome occurred in 2 patients. Common side effects were generally low grade and included diarrhea (in 83% of the patients), fatigue (in 75%), and nausea or vomiting (in 71%).

Conclusions

In this study involving historical controls, dual targeting of BTK and BCL2 with ibrutinib and venetoclax was consistent with improved outcomes in patients with mantle-cell lymphoma who had been predicted to have poor outcomes with current therapy.

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
JAMA: The Journal of the American Medical Association	http://jama.ama-assn.org/
The Lancet	www.thelancet.com
The New England Journal of Medicine	http://content.nejm.org/

The British Medical Journal (BMJ), JAMA and the New England Journal of Medicine (NEJM) can be accessed in full-text through your NHS Athens account. Unfortunately the national subscription to The Lancet has been cancelled.	https://www.evidence.nhs.uk/nhs-evidence-content/journals-and-databases or http://www.openathens.net/
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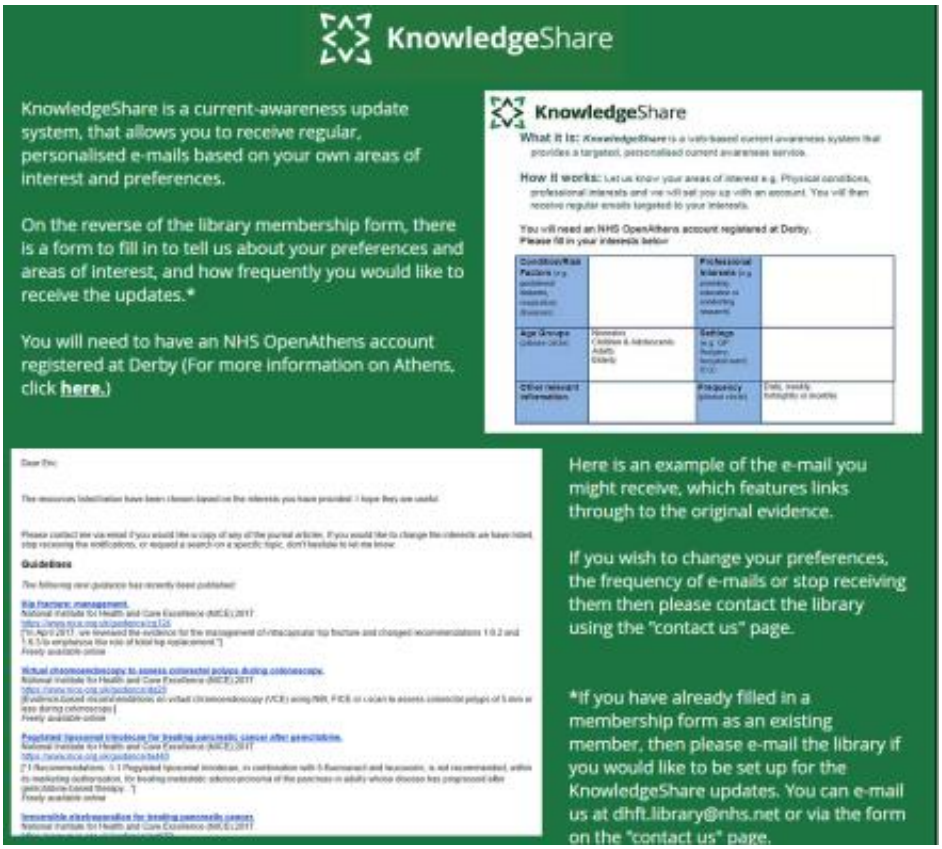

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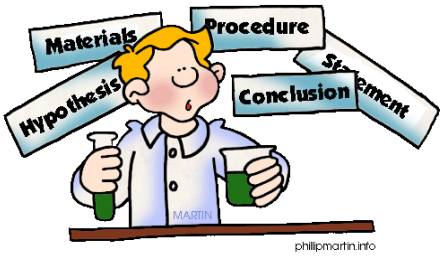

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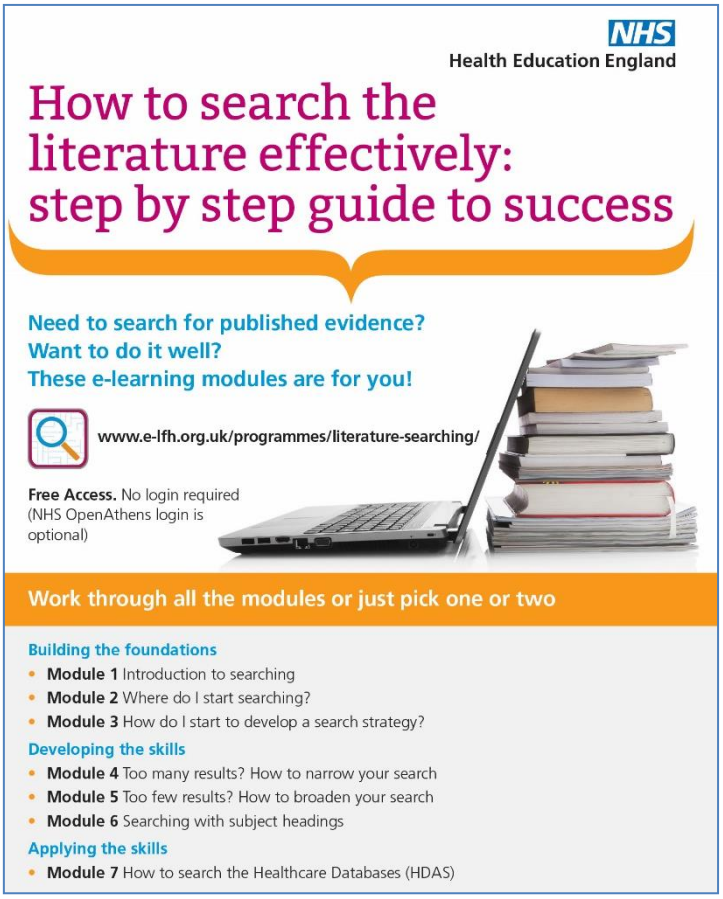

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