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BMJ (5 January 2019, Vol. 364, No. 8181)

Circulating high sensitivity C reactive protein concentrations and risk of lung cancer: Nested case-control study within Lung Cancer Cohort Consortium
David C Muller, Tricia L Larose, Allison Hodge, et al.
BMJ 2019; 364 (Published 03 January 2019)
https://www.bmj.com/content/364/bmj.k4981

Abstract
Objectives To conduct a comprehensive analysis of prospectively measured circulating high sensitivity C reactive protein (hsCRP) concentration and risk of lung cancer overall, by smoking status (never, former, and current smokers), and histological sub-type.
Design Nested case-control study.
Setting 20 population based cohort studies in Asia, Europe, Australia, and the United States.
Participants 5299 patients with incident lung cancer, with individually incidence density matched controls.
Exposure Circulating hsCRP concentrations in prediagnostic serum or plasma samples.
Main outcome measure Incident lung cancer diagnosis.
Results A positive association between circulating hsCRP concentration and the risk of lung cancer for current (odds ratio associated with a doubling in hsCRP concentration 1.09, 95% confidence interval 1.05 to 1.13) and former smokers (1.09, 1.04 to 1.14) was observed, but not for never smokers (P<0.01 for interaction). This association was strong and consistent across all histological subtypes, except for adenocarcinoma, which was not strongly associated with hsCRP concentration regardless of smoking status (odds ratio for

adenocarcinoma overall 0.97, 95% confidence interval 0.94 to 1.01). The association between circulating hsCRP concentration and the risk of lung cancer was strongest in the first two years of follow-up for former and current smokers. Including hsCRP concentration in a risk model, in addition to smoking based variables, did not improve risk discrimination overall, but slightly improved discrimination for cancers diagnosed in the first two years of follow-up.
Conclusions Former and current smokers with higher circulating hsCRP concentrations had a higher risk of lung cancer overall. Circulating hsCRP concentration was not associated with the risk of lung adenocarcinoma. Circulating hsCRP concentration could be a prediagnostic marker of lung cancer rather than a causal risk factor.

Association between intake of non-sugar sweeteners and health outcomes: Systematic review and meta-analyses of randomised and non-randomised controlled trials and observational studies

Ingrid Toews, Szimonetta Lohner, Daniela Küllenberg de Gaudry, et al.
BMJ 2019; 364 (Published 02 January 2019)
https://www.bmj.com/content/364/bmj.k4718

Abstract
Objective To assess the association between intake of non-sugar sweeteners (NSS) and important health outcomes in generally healthy or overweight/obese adults and children.
Design Systematic review following standard Cochrane review methodology.
Data sources Medline (Ovid), Embase, Cochrane CENTRAL, WHO International Clinical Trials Registry Platform, Clinicaltrials.gov, and reference lists of relevant publications.
Eligibility criteria for selecting studies Studies including generally healthy adults or children with or without overweight or obesity were eligible. Included study designs allowed for a direct comparison of no intake or lower intake of NSS with higher NSS intake. NSSs had to be clearly named, the dose had to be within the acceptable daily intake, and the intervention duration had to be at least seven days.
Main outcome measures Body weight or body mass index, glycaemic control, oral health, eating behaviour, preference for sweet taste, cancer, cardiovascular disease, kidney disease, mood, behaviour, neurocognition, and adverse effects.
Results The search resulted in 13 941 unique records. Of 56 individual studies that provided data for this review, 35 were observational studies. In adults, evidence of very low and low certainty from a limited number of small studies indicated a small beneficial effect of NSSs on body mass index (mean difference −0.6, 95% confidence interval −1.19 to −0.01; two studies, n=174) and fasting blood glucose (−0.16 mmol/L, −0.26 to −0.06; two, n=52). Lower doses of NSSs were associated with lower weight gain (−0.09 kg, −0.13 to −0.05; one, n=17 934) compared with higher doses of NSSs (very low certainty of evidence). For all other outcomes, no differences were detected between the use and non-use of NSSs, or between different doses of NSSs. No evidence of any effect of NSSs was seen on overweight or obese adults or children actively trying to lose weight (very low to moderate certainty). In children, a smaller increase in body mass index z score was observed with NSS intake compared with sugar intake (−0.15, −0.17 to −0.12; two, n=528, moderate certainty of evidence), but no significant differences were observed in body weight (−0.60 kg, −1.33 to 0.14; two, n=467, low certainty of evidence), or between different doses of NSSs (very low to moderate certainty).
Conclusions Most health outcomes did not seem to have differences between the NSS exposed and unexposed groups. Of the few studies identified for each outcome, most had few participants, were of short duration, and their methodological and reporting quality was

limited; therefore, confidence in the reported results is limited. Future studies should assess the effects of NSSs with an appropriate intervention duration. Detailed descriptions of interventions, comparators, and outcomes should be included in all reports.

International variation in radiation dose for computed tomography examinations: Prospective cohort study

Rebecca Smith-Bindman, Yifei Wang, Philip Chu, et al.
BMJ 2019; 364 (Published 02 January 2019)
https://www.bmj.com/content/364/bmj.k4931

Abstract

Objective To determine patient, institution, and machine characteristics that contribute to variation in radiation doses used for computed tomography (CT).

Design Prospective cohort study.

Setting Data were assembled and analyzed from the University of California San Francisco CT International Dose Registry.

Participants Standardized data from over 2.0 million CT examinations of adults who underwent CT between November 2015 and August 2017 from 151 institutions, across seven countries (Switzerland, Netherlands, Germany, United Kingdom, United States, Israel, and Japan).

Main outcome measures Mean effective doses and proportions of high dose examinations for abdomen, chest, combined chest and abdomen, and head CT were determined by patient characteristics (sex, age, and size), type of institution (trauma center, care provision 24 hours per day and seven days per week, academic, private), institutional practice volume, machine factors (manufacturer, model), country, and how scanners were used, before and after adjustment for patient characteristics, using hierarchical linear and logistic regression. High dose examinations were defined as CT scans with doses above the 75th percentile defined during a baseline period.

Results The mean effective dose and proportion of high dose examinations varied substantially across institutions. The doses varied modestly (10-30%) by type of institution and machine characteristics after adjusting for patient characteristics. By contrast, even after adjusting for patient characteristics, wide variations in radiation doses across countries persisted, with a fourfold range in mean effective dose for abdomen CT examinations (7.0-25.7 mSv) and a 17-fold range in proportion of high dose examinations (4-69%). Similar variation across countries was observed for chest (mean effective dose 1.7-6.4 mSv, proportion of high dose examinations 1-26%) and combined chest and abdomen CT (10.0-37.9 mSv, 2-78%). Doses for head CT varied less (1.4-1.9 mSv, 8-27%). In multivariable models, the dose variation across countries was primarily attributable to institutional decisions regarding technical parameters (that is, how the scanners were used).

Conclusions CT protocols and radiation doses vary greatly across countries and are primarily attributable to local choices regarding technical parameters, rather than patient, institution, or machine characteristics. These findings suggest that the optimization of doses to a consistent standard should be possible.

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JAMA: Journal of the American Medical Association (1/8 January 2019, Vol. 321, No. 1)

Effect of Medication Co-payment Vouchers on P2Y12 Inhibitor Use and Major Adverse Cardiovascular Events Among Patients With Myocardial Infarction: The ARTEMIS Randomized Clinical Trial

Tracy Y. Wang, Lisa A. Kaltenbach, Christopher P. Cannon, et al

JAMA. 2019; 321 (1): 44-55.
https://jamanetwork.com/journals/jama/article-abstract/2720024

Abstract

Importance Despite guideline recommendations, many patients discontinue $P2Y_{12}$ inhibitor therapy earlier than the recommended 1 year after myocardial infarction (MI), and higher-potency $P2Y_{12}$ inhibitors are underutilized. Cost is frequently cited as an explanation for both of these observations.

Objective To determine whether removing co-payment barriers increases $P2Y_{12}$ inhibitor persistence and lowers risk of major adverse cardiovascular events (MACE).

Design, Setting, and Participants Cluster randomized clinical trial among 301 hospitals enrolling adult patients with acute MI (June 5, 2015, through September 30, 2016); patients were followed up for 1 year after discharge (final date of follow-up was October 23, 2017), with blinded adjudication of MACE; choice of $P2Y_{12}$ inhibitor was per clinician discretion.

Interventions Hospitals randomized to the intervention (n = 131 [6436 patients]) provided patients with co-payment vouchers for clopidogrel or ticagrelor for 1 year (median voucher value for a 30-day supply, $137 [25th-75th percentile, $20-$339]). Hospitals randomized to usual care (n = 156 [4565 patients]) did not provide study vouchers.

Main Outcomes and Measures Independent coprimary outcomes were patient-reported persistence with $P2Y_{12}$ inhibitor (defined as continued treatment without gap in use ≥30 days) and MACE (death, recurrent MI, or stroke) at 1 year among patients discharged with a prescription for clopidogrel or ticagrelor.

Results Among 11 001 enrolled patients (median age, 62 years; 3459 [31%] women), 10 102 patients were discharged with prescriptions for clopidogrel or ticagrelor (clopidogrel prescribed to 2317 [36.0%] in the intervention group and 2497 [54.7%] in the usual care group), 4393 of 6135 patients (72%) in the intervention group used the voucher, and follow-up data at 1 year were available for 10 802 patients (98.2%). Patient-reported persistence with $P2Y_{12}$ inhibitors at 1 year was higher in the intervention group than in the control group (unadjusted rates, 5340/6135 [87.0%] vs 3324/3967 [83.8%], respectively; $P < .001$; adjusted difference, 2.3% [95% CI, 0.4% to 4.1%]; adjusted odds ratio, 1.19 [95% CI, 1.02 to 1.40]). There was no significant difference in MACE at 1 year between intervention and usual care groups (unadjusted cumulative incidence, 10.2% vs 10.6%; $P = .65$; adjusted difference, 0.66% [95% CI, −0.73% to 2.06%]; adjusted hazard ratio, 1.07 [95% CI, 0.93 to 1.25]).

Conclusions and Relevance Among patients with MI, provision of vouchers to offset medication co-payments for $P2Y_{12}$ inhibitors, compared with no vouchers, resulted in a 3.3% absolute increase in patient-reported persistence with $P2Y_{12}$ inhibitors and no significant reduction in 1-year MACE outcomes.

Effect of Low-Dose Intracoronary Alteplase During Primary Percutaneous Coronary Intervention on Microvascular Obstruction in Patients With Acute Myocardial Infarction: A Randomized Clinical Trial

Peter J. McCartney, Hany Eteiba, Annette M. Maznyczka, et al

JAMA. 2019; 321 (1): 56-68.
https://jamanetwork.com/journals/jama/article-abstract/2720025

Abstract

Importance Microvascular obstruction commonly affects patients with acute ST-segment elevation myocardial infarction (STEMI) and is associated with adverse outcomes.

Objective To determine whether a therapeutic strategy involving low-dose intracoronary fibrinolytic therapy with alteplase infused early after coronary reperfusion will reduce microvascular obstruction.

Design, Setting, and Participants Between March 17, 2016, and December 21, 2017, 440 patients presenting at 11 hospitals in the United Kingdom within 6 hours of STEMI due to a proximal–mid-vessel occlusion of a major coronary artery were randomized in a 1:1:1 dose-ranging trial design. Patient follow-up to 3 months was completed on April 12, 2018.

Interventions Participants were randomly assigned to treatment with placebo (n = 151), alteplase 10 mg (n = 144), or alteplase 20 mg (n = 145) by manual infusion over 5 to 10 minutes. The intervention was scheduled to occur early during the primary PCI procedure, after reperfusion of the infarct-related coronary artery and before stent implant.

Main Outcomes and Measures The primary outcome was the amount of microvascular obstruction (% left ventricular mass) demonstrated by contrast-enhanced cardiac magnetic resonance imaging (MRI) conducted from days 2 through 7 after enrollment. The primary comparison was the alteplase 20-mg group vs the placebo group; if not significant, the alteplase 10-mg group vs the placebo group was considered a secondary analysis.

Results Recruitment stopped on December 21, 2017, because conditional power for the primary outcome based on a prespecified analysis of the first 267 randomized participants was less than 30% in both treatment groups (futility criterion). Among the 440 patients randomized (mean age, 60.5 years; 15% women), the primary end point was achieved in 396 patients (90%), 17 (3.9%) withdrew, and all others were followed up to 3 months. In the primary analysis, the mean microvascular obstruction did not differ between the 20-mg alteplase and placebo groups (3.5% vs 2.3%; estimated difference, 1.16%; 95% CI, −0.08% to 2.41%; *P* = .32) nor in the analysis of 10-mg alteplase vs placebo groups (2.6% vs 2.3%; estimated difference, 0.29%; 95% CI, −0.76% to 1.35%; *P* = .74). Major adverse cardiac events (cardiac death, nonfatal MI, unplanned hospitalization for heart failure) occurred in 15 patients (10.1%) in the placebo group, 18 (12.9%) in the 10-mg alteplase group, and 12 (8.2%) in the 20-mg alteplase group.

Conclusions and Relevance Among patients with acute STEMI presenting within 6 hours of symptoms, adjunctive low-dose intracoronary alteplase given during the primary percutaneous intervention did not reduce microvascular obstruction. The study findings do not support this treatment.

Effect of Linagliptin vs Placebo on Major Cardiovascular Events in Adults With Type 2 Diabetes and High Cardiovascular and Renal Risk: The CARMELINA Randomized Clinical Trial

Julio Rosenstock, Vlado Perkovic, Odd Erik Johansen, et al for the CARMELINA Investigators

JAMA. 2019; 321 (1): 69-79.
https://jamanetwork.com/journals/jama/article-abstract/2714646

Abstract

Importance Type 2 diabetes is associated with increased cardiovascular (CV) risk. Prior trials have demonstrated CV safety of 3 dipeptidyl peptidase 4 (DPP-4) inhibitors but have included limited numbers of patients with high CV risk and chronic kidney disease.
Objective To evaluate the effect of linagliptin, a selective DPP-4 inhibitor, on CV outcomes and kidney outcomes in patients with type 2 diabetes at high risk of CV and kidney events.
Design, Setting, and Participants Randomized, placebo-controlled, multicenter noninferiority trial conducted from August 2013 to August 2016 at 605 clinic sites in 27 countries among adults with type 2 diabetes, hemoglobin A_{1c} of 6.5% to 10.0%, high CV risk (history of vascular disease and urine-albumin creatinine ratio [UACR] >200 mg/g), and high renal risk (reduced eGFR and micro- or macroalbuminuria). Participants with end-stage renal disease (ESRD) were excluded. Final follow-up occurred on January 18, 2018.
Interventions Patients were randomized to receive linagliptin, 5 mg once daily (n = 3494), or placebo once daily (n = 3485) added to usual care. Other glucose-lowering medications or insulin could be added based on clinical need and local clinical guidelines.
Main Outcomes and Measures Primary outcome was time to first occurrence of the composite of CV death, nonfatal myocardial infarction, or nonfatal stroke. Criteria for noninferiority of linagliptin vs placebo was defined by the upper limit of the 2-sided 95% CI for the hazard ratio (HR) of linagliptin relative to placebo being less than 1.3. Secondary outcome was time to first occurrence of adjudicated death due to renal failure, ESRD, or sustained 40% or higher decrease in eGFR from baseline.
Results Of 6991 enrollees, 6979 (mean age, 65.9 years; eGFR, 54.6 mL/min/1.73 m^2; 80.1% with UACR >30 mg/g) received at least 1 dose of study medication and 98.7% completed the study. During a median follow-up of 2.2 years, the primary outcome occurred in 434 of 3494 (12.4%) and 420 of 3485 (12.1%) in the linagliptin and placebo groups, respectively, (absolute incidence rate difference, 0.13 [95% CI, −0.63 to 0.90] per 100 person-years) (HR, 1.02; 95% CI, 0.89-1.17; $P < .001$ for noninferiority). The kidney outcome occurred in 327 of 3494 (9.4%) and 306 of 3485 (8.8%), respectively (absolute incidence rate difference, 0.22 [95% CI, −0.52 to 0.97] per 100 person-years) (HR, 1.04; 95% CI, 0.89-1.22; $P = .62$). Adverse events occurred in 2697 (77.2%) and 2723 (78.1%) patients in the linagliptin and placebo groups; 1036 (29.7%) and 1024 (29.4%) had 1 or more episodes of hypoglycemia; and there were 9 (0.3%) vs 5 (0.1%) events of adjudication-confirmed acute pancreatitis.
Conclusions and Relevance Among adults with type 2 diabetes and high CV and renal risk, linagliptin added to usual care compared with placebo added to usual care resulted in a noninferior risk of a composite CV outcome over a median 2.2 years.

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The Lancet (5 January 2019, Vol. 393, No. 10166)

SGLT2 inhibitors for primary and secondary prevention of cardiovascular and renal outcomes in type 2 diabetes: A systematic review and meta-analysis of cardiovascular outcome trials

Thomas A Zelniker, Stephen D Wiviott, Itamar Raz, et al.
The Lancet: Volume 393, ISSUE 10166, P31-39, January 05, 2019
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32590-X/fulltext

Summary

Background
The magnitude of effect of sodium-glucose cotransporter-2 inhibitors (SGLT2i) on specific cardiovascular and renal outcomes and whether heterogeneity is based on key baseline characteristics remains undefined.
Methods
We did a systematic review and meta-analysis of randomised, placebo-controlled, cardiovascular outcome trials of SGLT2i in patients with type 2 diabetes. We searched PubMed and Embase for trials published up to Sept 24, 2018. Data search and extraction were completed with a standardised data form and any discrepancies were resolved by consensus. Efficacy outcomes included major adverse cardiovascular events (myocardial infarction, stroke, or cardiovascular death), the composite of cardiovascular death or hospitalisation for heart failure, and progression of renal disease. Hazard ratios (HRs) with 95% CIs were pooled across trials, and efficacy outcomes were stratified by baseline presence of atherosclerotic cardiovascular disease, heart failure, and degree of renal function.
Findings
We included data from three identified trials and 34 322 patients (60·2% with established atherosclerotic cardiovascular disease), with 3342 major adverse cardiovascular events, 2028 cardiovascular deaths or hospitalisation sfor heart failure events, and 766 renal composite outcomes. SGLT2i reduced major adverse cardiovascular events by 11% (HR 0·89 [95% CI 0·83–0·96], p=0·0014), with benefit only seen in patients with atherosclerotic cardiovascular disease (0·86 [0·80–0·93]) and not in those without (1·00 [0·87–1·16], p for interaction=0·0501). SGLT2i reduced the risk of cardiovascular death or hospitalisation for heart failure by 23% (0·77 [0·71–0·84], p<0·0001), with a similar benefit in patients with and without atherosclerotic cardiovascular disease and with and without a history of heart failure. SGLT2i reduced the risk of progression of renal disease by 45% (0·55 [0·48–0·64], p<0·0001), with a similar benefit in those with and without atherosclerotic cardiovascular disease. The magnitude of benefit of SGLT2i varied with baseline renal function, with greater reductions in hospitalisations for heart failure (p for interaction=0·0073) and lesser reductions in progression of renal disease (p for interaction=0·0258) in patients with more severe kidney disease at baseline.
Interpretation
SGLT2i have moderate benefits on atherosclerotic major adverse cardiovascular events that seem confined to patients with established atherosclerotic cardiovascular disease. However, they have robust benefits on reducing hospitalisation for heart failure and progression of renal disease regardless of existing atherosclerotic cardiovascular disease or a history of heart failure.

Radiotherapy plus cetuximab or cisplatin in human papillomavirus-positive oropharyngeal cancer (NRG Oncology RTOG 1016): A randomised, multicentre, non-inferiority trial

Maura L Gillison, Andy M Trotti, Jonathan Harris, et al.
The Lancet: Volume 393, ISSUE 10166, P40-50, January 05, 2019
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32779-X/fulltext

Summary
Background
Patients with human papillomavirus (HPV)-positive oropharyngeal squamous cell carcinoma have high survival when treated with radiotherapy plus cisplatin. Whether replacement of cisplatin with cetuximab—an antibody against the epidermal growth factor

receptor—can preserve high survival and reduce treatment toxicity is unknown. We investigated whether cetuximab would maintain a high proportion of patient survival and reduce acute and late toxicity.

Methods

RTOG 1016 was a randomised, multicentre, non-inferiority trial at 182 health-care centres in the USA and Canada. Eligibility criteria included histologically confirmed HPV-positive oropharyngeal carcinoma; American Joint Committee on Cancer 7th edition clinical categories T1–T2, N2a–N3 M0 or T3–T4, N0–N3 M0; Zubrod performance status 0 or 1; age at least 18 years; and adequate bone marrow, hepatic, and renal function. We randomly assigned patients (1:1) to receive either radiotherapy plus cetuximab or radiotherapy plus cisplatin. Randomisation was balanced by using randomly permuted blocks, and patients were stratified by T category (T1–T2 *vs* T3–T4), N category (N0–N2a *vs* N2b–N3), Zubrod performance status (0 *vs* 1), and tobacco smoking history (≤10 pack-years *vs* >10 pack-years). Patients were assigned to receive either intravenous cetuximab at a loading dose of 400 mg/m ^{2} 5–7 days before radiotherapy initiation, followed by cetuximab 250 mg/m ^{2} weekly for seven doses (total 2150 mg/m ^{2}), or cisplatin 100 mg/m ^{2} on days 1 and 22 of radiotherapy (total 200 mg/m ^{2}). All patients received accelerated intensity-modulated radiotherapy delivered at 70 Gy in 35 fractions over 6 weeks at six fractions per week (with two fractions given on one day, at least 6 h apart). The primary endpoint was overall survival, defined as time from randomisation to death from any cause, with non-inferiority margin 1·45. Primary analysis was based on the modified intention-to-treat approach, whereby all patients meeting eligibility criteria are included. This study is registered with ClinicalTrials.gov, number NCT01302834.

Findings

Between June 9, 2011, and July 31, 2014, 987 patients were enrolled, of whom 849 were randomly assigned to receive radiotherapy plus cetuximab (n=425) or radiotherapy plus cisplatin (n=424). 399 patients assigned to receive cetuximab and 406 patients assigned to receive cisplatin were subsequently eligible. After median follow-up duration of 4·5 years, radiotherapy plus cetuximab did not meet the non-inferiority criteria for overall survival (hazard ratio [HR] 1·45, one-sided 95% upper CI 1·94; p=0·5056 for non-inferiority; one-sided log-rank p=0·0163). Estimated 5-year overall survival was 77·9% (95% CI 73·4–82·5) in the cetuximab group versus 84·6% (80·6–88·6) in the cisplatin group. Progression-free survival was significantly lower in the cetuximab group compared with the cisplatin group (HR 1·72, 95% CI 1·29–2·29; p=0·0002; 5-year progression-free survival 67·3%, 95% CI 62·4–72·2 *vs* 78·4%, 73·8–83·0), and locoregional failure was significantly higher in the cetuximab group compared with the cisplatin group (HR 2·05, 95% CI 1·35–3·10; 5-year proportions 17·3%, 95% CI 13·7–21·4 *vs* 9·9%, 6·9–13·6). Proportions of acute moderate to severe toxicity (77·4%, 95% CI 73·0–81·5 *vs* 81·7%, 77·5–85·3; p=0·1586) and late moderate to severe toxicity (16·5%, 95% CI 12·9–20·7 *vs* 20·4%, 16·4–24·8; p=0·1904) were similar between the cetuximab and cisplatin groups.

Interpretation

For patients with HPV-positive oropharyngeal carcinoma, radiotherapy plus cetuximab showed inferior overall survival and progression-free survival compared with radiotherapy plus cisplatin. Radiotherapy plus cisplatin is the standard of care for eligible patients with HPV-positive oropharyngeal carcinoma.

Radiotherapy plus cisplatin or cetuximab in low-risk human papillomavirus-positive oropharyngeal cancer (De-ESCALaTE HPV): An open-label randomised controlled phase 3 trial

Hisham Mehanna, Max Robinson, Andrew Hartley, et al.

The Lancet: Volume 393, ISSUE 10166, P51-60, January 05, 2019
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32752-1/fulltext

Summary

Background

The incidence of human papillomavirus (HPV)-positive oropharyngeal cancer, a disease affecting younger patients, is rapidly increasing. Cetuximab, an epidermal growth factor receptor inhibitor, has been proposed for treatment de-escalation in this setting to reduce the toxicity of standard cisplatin treatment, but no randomised evidence exists for the efficacy of this strategy.

Methods

We did an open-label randomised controlled phase 3 trial at 32 head and neck treatment centres in Ireland, the Netherlands, and the UK, in patients aged 18 years or older with HPV-positive low-risk oropharyngeal cancer (non-smokers or lifetime smokers with a smoking history of <10 pack-years). Eligible patients were randomly assigned (1:1) to receive, in addition to radiotherapy (70 Gy in 35 fractions), either intravenous cisplatin (100 mg/m^2 on days 1, 22, and 43 of radiotherapy) or intravenous cetuximab (400 mg/m^2 loading dose followed by seven weekly infusions of 250 mg/m^2). The primary outcome was overall severe (grade 3–5) toxicity events at 24 months from the end of treatment. The primary outcome was assessed by intention-to-treat and per-protocol analyses. This trial is registered with the ISRCTN registry, number ISRCTN33522080.

Findings

Between Nov 12, 2012, and Oct 1, 2016, 334 patients were recruited (166 in the cisplatin group and 168 in the cetuximab group). Overall (acute and late) severe (grade 3–5) toxicity did not differ significantly between treatment groups at 24 months (mean number of events per patient 4·8 [95% CI 4·2–5·4] with cisplatin *vs* 4·8 [4·2–5·4] with cetuximab; p=0·98). At 24 months, overall all-grade toxicity did not differ significantly either (mean number of events per patient 29·2 [95% CI 27·3–31·0] with cisplatin *vs* 30·1 [28·3–31·9] with cetuximab; p=0·49). However, there was a significant difference between cisplatin and cetuximab in 2-year overall survival (97·5% *vs* 89·4%, hazard ratio 5·0 [95% CI 1·7–14·7]; p=0·001) and 2-year recurrence (6·0% *vs* 16·1%, 3·4 [1·6–7·2]; p=0·0007).

Interpretation

Compared with the standard cisplatin regimen, cetuximab showed no benefit in terms of reduced toxicity, but instead showed significant detriment in terms of tumour control. Cisplatin and radiotherapy should be used as the standard of care for HPV-positive low-risk patients who are able to tolerate cisplatin.

Withdrawal of pharmacological treatment for heart failure in patients with recovered dilated cardiomyopathy (TRED-HF): An open-label, pilot, randomised trial

Brian P Halliday, Rebecca Wassall, Amrit S Lota, et al

The Lancet: Volume 393, ISSUE 10166, P61-73, January 05, 2019
https://www.thelancet.com/journals/lancet/article/PIIS0140-6736(18)32484-X/fulltext

Summary

Background

Patients with dilated cardiomyopathy whose symptoms and cardiac function have recovered often ask whether their medications can be stopped. The safety of withdrawing treatment in this situation is unknown.

Methods

We did an open-label, pilot, randomised trial to examine the effect of phased withdrawal of heart failure medications in patients with previous dilated cardiomyopathy who were now asymptomatic, whose left ventricular ejection fraction (LVEF) had improved from less than 40% to 50% or greater, whose left ventricular end-diastolic volume (LVEDV) had normalised, and who had an N-terminal pro-B-type natriuretic peptide (NT-pro-BNP) concentration less than 250 ng/L. Patients were recruited from a network of hospitals in the UK, assessed at one centre (Royal Brompton and Harefield NHS Foundation Trust, London, UK), and randomly assigned (1:1) to phased withdrawal or continuation of treatment. After 6 months, patients in the continued treatment group had treatment withdrawn by the same method. The primary endpoint was a relapse of dilated cardiomyopathy within 6 months, defined by a reduction in LVEF of more than 10% and to less than 50%, an increase in LVEDV by more than 10% and to higher than the normal range, a two-fold rise in NT-pro-BNP concentration and to more than 400 ng/L, or clinical evidence of heart failure, at which point treatments were re-established. The primary analysis was by intention to treat. This trial is registered with ClinicalTrials.gov, number NCT02859311.

Findings

Between April 21, 2016, and Aug 22, 2017, 51 patients were enrolled. 25 were randomly assigned to the treatment withdrawal group and 26 to continue treatment. Over the first 6 months, 11 (44%) patients randomly assigned to treatment withdrawal met the primary endpoint of relapse compared with none of those assigned to continue treatment (Kaplan-Meier estimate of event rate 45·7% [95% CI 28·5–67·2]; p=0·0001). After 6 months, 25 (96%) of 26 patients assigned initially to continue treatment attempted its withdrawal. During the following 6 months, nine patients met the primary endpoint of relapse (Kaplan-Meier estimate of event rate 36·0% [95% CI 20·6–57·8]). No deaths were reported in either group and three serious adverse events were reported in the treatment withdrawal group: hospital admissions for non-cardiac chest pain, sepsis, and an elective procedure.

Interpretation

Many patients deemed to have recovered from dilated cardiomyopathy will relapse following treatment withdrawal. Until robust predictors of relapse are defined, treatment should continue indefinitely.

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The New England Journal of Medicine (3 January 2019, Vol. 380, No. 1)

Cardiovascular Risk Reduction with Icosapent Ethyl for Hypertriglyceridemia

Deepak L. Bhatt, P. Gabriel Steg, Michael Miller, et al. for the REDUCE-IT Investigators

N Engl J Med 2019; 380: 11-22 January 3, 2019
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Abstract

Background

Patients with elevated triglyceride levels are at increased risk for ischemic events. Icosapent ethyl, a highly purified eicosapentaenoic acid ethyl ester, lowers triglyceride levels, but data are needed to determine its effects on ischemic events.

Methods

We performed a multicenter, randomized, double-blind, placebo-controlled trial involving patients with established cardiovascular disease or with diabetes and other risk factors, who had been receiving statin therapy and who had a fasting triglyceride level of 135 to 499 mg per deciliter (1.52 to 5.63 mmol per liter) and a low-density lipoprotein cholesterol

level of 41 to 100 mg per deciliter (1.06 to 2.59 mmol per liter). The patients were randomly assigned to receive 2 g of icosapent ethyl twice daily (total daily dose, 4 g) or placebo. The primary end point was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, coronary revascularization, or unstable angina. The key secondary end point was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke.

Results

A total of 8179 patients were enrolled (70.7% for secondary prevention of cardiovascular events) and were followed for a median of 4.9 years. A primary end-point event occurred in 17.2% of the patients in the icosapent ethyl group, as compared with 22.0% of the patients in the placebo group (hazard ratio, 0.75; 95% confidence interval [CI], 0.68 to 0.83; P<0.001); the corresponding rates of the key secondary end point were 11.2% and 14.8% (hazard ratio, 0.74; 95% CI, 0.65 to 0.83; P<0.001). The rates of additional ischemic end points, as assessed according to a prespecified hierarchical schema, were significantly lower in the icosapent ethyl group than in the placebo group, including the rate of cardiovascular death (4.3% vs. 5.2%; hazard ratio, 0.80; 95% CI, 0.66 to 0.98; P=0.03). A larger percentage of patients in the icosapent ethyl group than in the placebo group were hospitalized for atrial fibrillation or flutter (3.1% vs. 2.1%, P=0.004). Serious bleeding events occurred in 2.7% of the patients in the icosapent ethyl group and in 2.1% in the placebo group (P=0.06).

Conclusions

Among patients with elevated triglyceride levels despite the use of statins, the risk of ischemic events, including cardiovascular death, was significantly lower among those who received 2 g of icosapent ethyl twice daily than among those who received placebo.

Marine n−3 Fatty Acids and Prevention of Cardiovascular Disease and Cancer

JoAnn E. Manson, Nancy R. Cook, I-Min Lee, et al. for the VITAL Research Group

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Abstract

Background

Higher intake of marine n−3 (also called omega-3) fatty acids has been associated with reduced risks of cardiovascular disease and cancer in several observational studies. Whether supplementation with n−3 fatty acids has such effects in general populations at usual risk for these end points is unclear.

Methods

We conducted a randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D3 (at a dose of 2000 IU per day) and marine n−3 fatty acids (at a dose of 1 g per day) in the primary prevention of cardiovascular disease and cancer among men 50 years of age or older and women 55 years of age or older in the United States. Primary end points were major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes) and invasive cancer of any type. Secondary end points included individual components of the composite cardiovascular end point, the composite end point plus coronary revascularization (expanded composite of cardiovascular events), site-specific cancers, and death from cancer. Safety was also assessed. This article reports the results of the comparison of n−3 fatty acids with placebo.

Results

A total of 25,871 participants, including 5106 black participants, underwent randomization. During a median follow-up of 5.3 years, a major cardiovascular event occurred in 386

participants in the n−3 group and in 419 in the placebo group (hazard ratio, 0.92; 95% confidence interval [CI], 0.80 to 1.06; P=0.24). Invasive cancer was diagnosed in 820 participants in the n−3 group and in 797 in the placebo group (hazard ratio, 1.03; 95% CI, 0.93 to 1.13; P=0.56). In the analyses of key secondary end points, the hazard ratios were as follows: for the expanded composite end point of cardiovascular events, 0.93 (95% CI, 0.82 to 1.04); for total myocardial infarction, 0.72 (95% CI, 0.59 to 0.90); for total stroke, 1.04 (95% CI, 0.83 to 1.31); for death from cardiovascular causes, 0.96 (95% CI, 0.76 to 1.21); and for death from cancer (341 deaths from cancer), 0.97 (95% CI, 0.79 to 1.20). In the analysis of death from any cause (978 deaths overall), the hazard ratio was 1.02 (95% CI, 0.90 to 1.15). No excess risks of bleeding or other serious adverse events were observed.

Conclusions

Supplementation with n−3 fatty acids did not result in a lower incidence of major cardiovascular events or cancer than placebo.

Vitamin D Supplements and Prevention of Cancer and Cardiovascular Disease

JoAnn E. Manson, Nancy R. Cook, I-Min Lee, et al. for the VITAL Research Group

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Abstract

Background

It is unclear whether supplementation with vitamin D reduces the risk of cancer or cardiovascular disease, and data from randomized trials are limited.

Methods

We conducted a nationwide, randomized, placebo-controlled trial, with a two-by-two factorial design, of vitamin D3 (cholecalciferol) at a dose of 2000 IU per day and marine n−3 (also called omega-3) fatty acids at a dose of 1 g per day for the prevention of cancer and cardiovascular disease among men 50 years of age or older and women 55 years of age or older in the United States. Primary end points were invasive cancer of any type and major cardiovascular events (a composite of myocardial infarction, stroke, or death from cardiovascular causes). Secondary end points included site-specific cancers, death from cancer, and additional cardiovascular events. This article reports the results of the comparison of vitamin D with placebo.

Results

A total of 25,871 participants, including 5106 black participants, underwent randomization. Supplementation with vitamin D was not associated with a lower risk of either of the primary end points. During a median follow-up of 5.3 years, cancer was diagnosed in 1617 participants (793 in the vitamin D group and 824 in the placebo group; hazard ratio, 0.96; 95% confidence interval [CI], 0.88 to 1.06; P=0.47). A major cardiovascular event occurred in 805 participants (396 in the vitamin D group and 409 in the placebo group; hazard ratio, 0.97; 95% CI, 0.85 to 1.12; P=0.69). In the analyses of secondary end points, the hazard ratios were as follows: for death from cancer (341 deaths), 0.83 (95% CI, 0.67 to 1.02); for breast cancer, 1.02 (95% CI, 0.79 to 1.31); for prostate cancer, 0.88 (95% CI, 0.72 to 1.07); for colorectal cancer, 1.09 (95% CI, 0.73 to 1.62); for the expanded composite end point of major cardiovascular events plus coronary revascularization, 0.96 (95% CI, 0.86 to 1.08); for myocardial infarction, 0.96 (95% CI, 0.78 to 1.19); for stroke, 0.95 (95% CI, 0.76 to 1.20); and for death from cardiovascular causes, 1.11 (95% CI, 0.88 to 1.40). In the analysis of death from any cause (978 deaths), the hazard ratio was 0.99 (95% CI, 0.87 to 1.12). No excess risks of hypercalcemia or other adverse events were identified.

Conclusions
Supplementation with vitamin D did not result in a lower incidence of invasive cancer or cardiovascular events than placebo.

Tisagenlecleucel in Adult Relapsed or Refractory Diffuse Large B-Cell Lymphoma
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Abstract
Background
Patients with diffuse large B-cell lymphoma that is refractory to primary and second-line therapies or that has relapsed after stem-cell transplantation have a poor prognosis. The chimeric antigen receptor (CAR) T-cell therapy tisagenlecleucel targets and eliminates CD19-expressing B cells and showed efficacy against B-cell lymphomas in a single-center, phase 2a study.
Methods
We conducted an international, phase 2, pivotal study of centrally manufactured tisagenlecleucel involving adult patients with relapsed or refractory diffuse large B-cell lymphoma who were ineligible for or had disease progression after autologous hematopoietic stem-cell transplantation. The primary end point was the best overall response rate (i.e., the percentage of patients who had a complete or partial response), as judged by an independent review committee.
Results
A total of 93 patients received an infusion and were included in the evaluation of efficacy. The median time from infusion to data cutoff was 14 months (range, 0.1 to 26). The best overall response rate was 52% (95% confidence interval, 41 to 62); 40% of the patients had complete responses, and 12% had partial responses. Response rates were consistent across prognostic subgroups. At 12 months after the initial response, the rate of relapse-free survival was estimated to be 65% (79% among patients with a complete response). The most common grade 3 or 4 adverse events of special interest included cytokine release syndrome (22%), neurologic events (12%), cytopenias lasting more than 28 days (32%), infections (20%), and febrile neutropenia (14%). Three patients died from disease progression within 30 days after infusion. No deaths were attributed to tisagenlecleucel, cytokine release syndrome, or cerebral edema. No differences between response groups in tumor expression of CD19 or immune checkpoint–related proteins were found.
Conclusions
In this international study of CAR T-cell therapy in relapsed or refractory diffuse large B-cell lymphoma in adults, high rates of durable responses were produced with the use of tisagenlecleucel.

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Sources

BMJ: British Medical Journal	http://www.bmj.com/theBMJ
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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/
If you have not already registered for an NHS Athens Account, please register at: NB: It is recommended that you register on a Trust (NHS) PC for speedy confirmation of your username and password. Once registered, your account can be accessed from any device with online access.	https://openathens.nice.org.uk/

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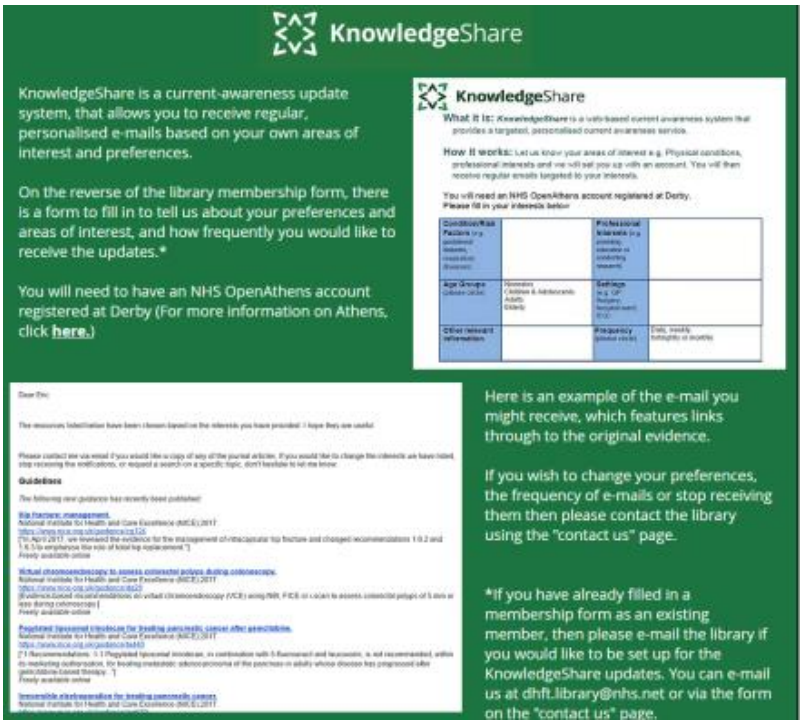

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