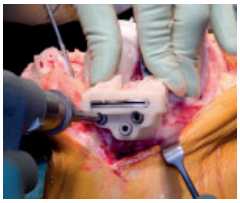
research

Pathological complete response as surrogate endpoint in breast cancer trials p 17



Perioperative iv dexamethasone in patients undergoing knee arthroplasty p 18

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ORIGINAL RESEARCH Systematic review and meta-analysis

Evaluation of pathological complete response as surrogate endpoint in neoadjuvant randomised clinical trials of early stage breast cancer

Conforti F, Pala L, Sala I, et al

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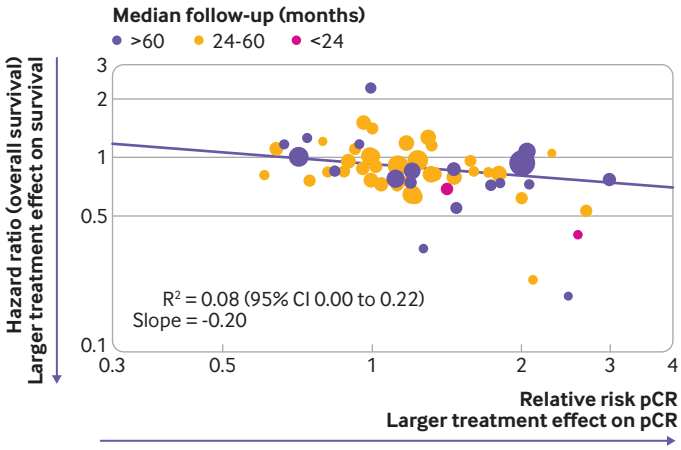
Study question Is the pathological complete response a reliable surrogate endpoint for disease-free survival and overall survival in neoadjuvant randomised clinical trials of early breast cancer?

Methods A systematic review and meta-analysis was performed of all randomised clinical trials of early breast cancer that tested neoadjuvant chemotherapy given alone or combined with other treatments, including anti-human epidermal growth factor 2 drugs, targeted treatments, antivascular agents, bisphosphonates, and immune checkpoint inhibitors. The primary objective was to assess trial level associations between the surrogate endpoint pathological complete response and both disease-free survival and overall survival.



Correlation between effects of breast cancer treatment on pathological complete response (pCR) and overall survival. Each circle represents a trial, and the surface area of the circle is proportional to the number of events observed in the corresponding trial. Straight lines represent weighted regression lines

Study answer and limitations 54 trials with a total of 32 611 patients were included in the analysis. A weak association was observed between the pathological complete response and both disease-free survival (R^2=0.14, 95% confidence interval 0.00 to 0.29) and overall survival (R^2=0.08, 0.00 to 0.22). Consistent results were confirmed across all subgroups evaluated, independently of the definition for pathological complete response, type of treatment in the experimental arm, and biological features of the disease.

What this study adds This meta-analysis showed a weak association between pathological complete response and disease-free survival and overall survival at trial level and therefore pathological complete response should not be used as primary endpoint in regulatory neoadjuvant trials of early breast cancer.

Funding, competing interests, and data sharing No funding provided. No competing interests declared. Data are available on reasonable request to the corresponding author.

Effect of dexamethasone as an analgesic adjuvant to multimodal pain treatment after total knee arthroplasty

Gasbjerg KS, Hägi-Pedersen D, Lunn TH, et al

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Study question What are the potential effects of one and two doses of intravenous dexamethasone (24 mg) as an analgesic adjuvant to multimodal pain treatment in adults after primary total knee arthroplasty?

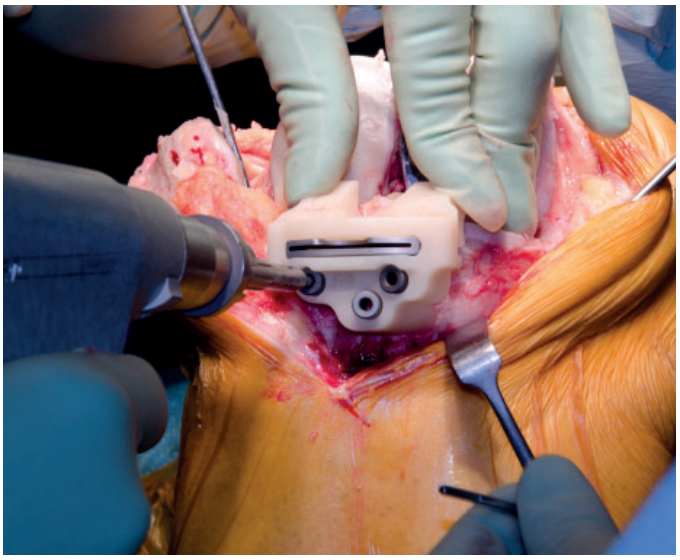
Methods The DEXamethasone twice for pain treatment after Total Knee Arthroplasty (DEX-2-TKA) trial, a randomised, blinded, placebo controlled trial with 90 days' follow-up, was conducted at five hospitals in Denmark. Between September 2018 and March 2020, 485 participants undergoing primary total knee arthroplasty were included in the trial. A computer generated randomised sequence stratified for site was used to allocate participants to one of three groups: DX1 (dexamethasone (24 mg)+placebo), DX2 (dexamethasone (24 mg)+dexamethasone (24 mg)), or placebo (placebo+placebo). The intervention was administered intravenously before, and 24 hours after, surgery. The primary outcome was total intravenous morphine consumption 0 to 48 hours postoperatively; secondary outcomes included levels of pain and adverse effects.

Study answer and limitations 485 participants were randomised: 161 to DX1, 162 to DX2, and 162 to placebo. Data from 472 participants (97.3%) were included in the primary outcome analysis. The median (interquartile range) 0 to 48 hours morphine consumptions were: DX1 37.9 mg (20.7 to 56.7), DX2 35.0 mg (20.6 to 52.0), and placebo 43.0 mg (28.7 to 64.0). Hodges-Lehmann median differences between groups were: −2.7 mg (98.3% confidence interval −9.3 to 3.7), P=0.30 between DX1 and DX2; 7.8 mg (0.7 to 14.7), P=0.008 between DX1 and placebo; and 10.7 mg (4.0 to 17.3), P<0.001 between DX2 and placebo. Postoperative pain was reduced at 24 hours with one dose and at 48 hours with two doses of dexamethasone. A limitation of the trial is the restriction of results on opioid consumption and pain levels to the first 48 hours after surgery.

What this study adds The results showed that, compared with placebo, two doses of 24 mg intravenous dexamethasone administered perioperatively as an adjuvant to multimodal pain treatment were associated with a reduction in morphine consumption and levels of pain.

Funding, competing interests, and data sharing This trial was funded by Næstved, Slagelse and Ringsted Hospitals' research fund, and received support from the Department of Anaesthesiology, Næstved, Slagelse and Ringsted Hospitals, Denmark. No competing interests declared. Trial data are available on request to the corresponding author.

Trial registration ClinicalTrials.gov NCT03506789.



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Primary outcome			
Intervention group	**DX1**	**DX2**	**Placebo**
Median (IQR) morphine consumption at 0-48 hours (mg)	37.9 (20.7-56.7)	35.0 (20.6-52.0)	43.0 (28.7-64.0)
DX2 and placebo compared with DX1:			
Difference (98.3% CI), mg	NA	−2.7 (−9.3 to 3.7)	7.8 (0.7 to 14.7)
P value	—	0.30	0.008
Placebo compared with DX2:			
Difference (98.3% CI), mg	NA	NA	10.7 (4.0 to 17.3)
P value	—	—	<0.001

DX1=dexamethasone (24 mg)+placebo; DX2=dexamethasone (24 mg)+dexamethasone (24 mg); NA=not available; placebo=placebo+placebo.
Differences between medians are calculated using Hodges-Lehmann. P values are calculated using the van Elteren test.

GP consultation rates for sequelae after acute covid-19 in patients managed in the community or hospital in the UK

Whittaker HR, Gulea C, Koteci A, et al

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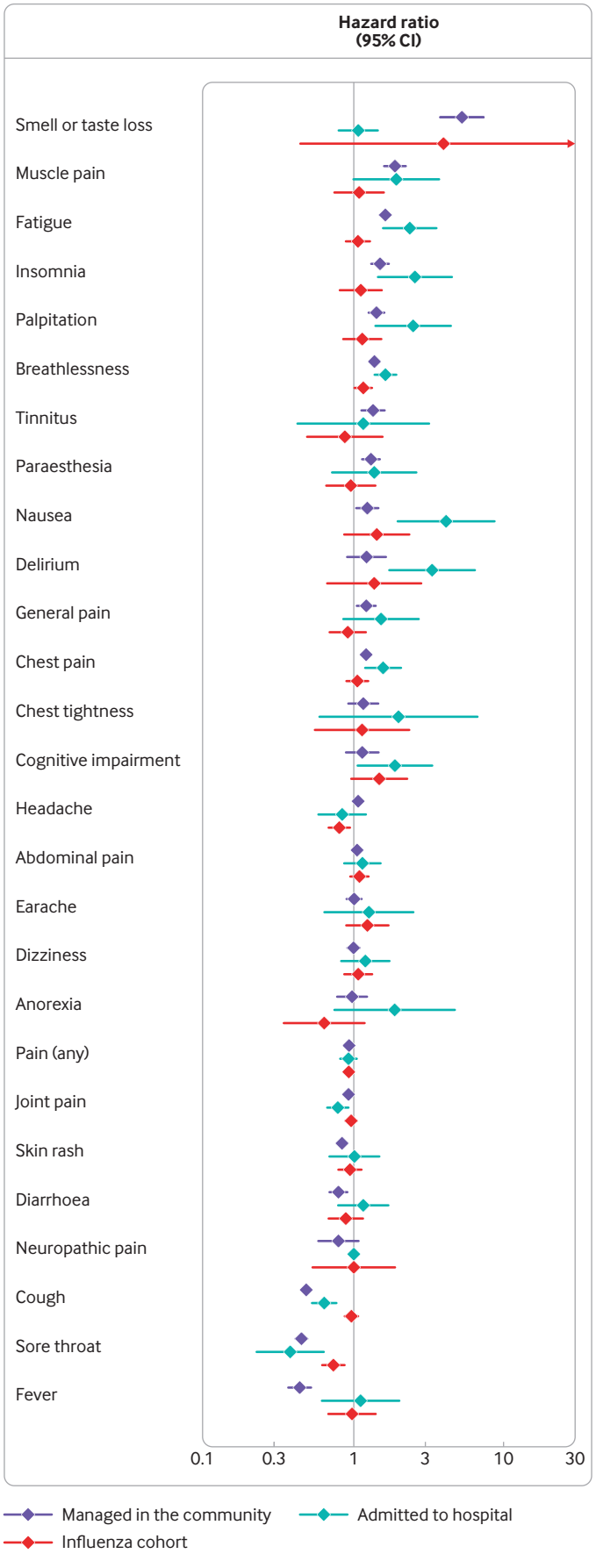
Study question Are rates for consulting a general practitioner (GP) for sequelae after acute covid-19 infection different in patients admitted to hospital with covid-19 and those managed in the community?

Methods A population based cohort study was carried out with the Clinical Practice Research Datalink (CPRD) Aurum database. 456 002 patients with a diagnosis of covid-19 between 1 August 2020 and 14 February 2021 were included and followed up for a maximum of 9.2 months. The main outcome measure was comparison of GP consultation rates for new symptoms, diseases, prescriptions, and healthcare use in individuals admitted to hospital and those managed in the community, separately, before and after covid-19 infection. For comparison, a negative control group of individuals without covid-19 (n=38 511) and patients with influenza before the pandemic (n=21 803) were included.

Study answer and limitations Relative to the negative control and influenza cohorts, patients with covid-19 in the community (n=437 943) had significantly higher GP consultation rates for multiple sequelae, and the most common were loss of smell or taste, or both (adjusted hazard ratio 5.28, 95% confidence interval 3.89 to 7.17, P<0.001), venous thromboembolism (3.35, 2.87 to 3.91, P<0.001), lung fibrosis (2.41, 1.37 to 4.25, P=0.002), and muscle pain (1.89, 1.63 to 2.20, P<0.001), and also for healthcare use after a diagnosis of covid-19 compared with 12 months before infection. For patients with covid-19 in the community, GP consultation rates were reduced for chest tightness, anorexia, loss of smell or taste, or both, tinnitus, chest pain, ischaemic heart disease, asthma, gastro-oesophageal reflux, prescriptions, and healthcare use after the first vaccination dose for covid-19. GP consultation rates over a longer follow up-period were not assessed.

What this study adds The results suggest that GP consultation rates for sequelae after acute covid-19 are different in patients with covid-19 admitted to hospital and those managed in the community. Patients in the community had higher GP consultation rates for multiple sequelae, which were comparatively more prevalent than those after viral respiratory infections, such as influenza. In individuals managed in the community, some sequelae decreased over time and with vaccination, but others such as anxiety and depression persisted.

Funding, competing interests, and data sharing Supported by BREATHE-The Health Data Research Hub for Respiratory Health (MC_PC_19004). No competing interests declared. This study used existing data from the UK CPRD electronic health record database; this data resource is accessible only to researchers with protocols approved by the CPRD's independent scientific advisory committee.



GP consultation rates for symptoms after covid-19 compared with 12 months before covid-19, in patients admitted to hospital with covid-19 and those managed in the community, and in the influenza cohort. Forest plots for each outcome developed versus each outcome not developed, separately, during follow-up. Analyses were adjusted for age, sex, body mass index, Charlson comorbidity index, and smoking status

Respiratory tract infection and risk of bleeding during oral anticoagulant treatment

Ahmed H, Whitaker H, Farewell D, Hippisley-Cox J, Noble S

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Study question Does respiratory tract infection without immediate antibiotic treatment increase the incidence of bleeding in oral anticoagulant users?

Methods This study design included individuals who act as their own controls. Only those participants who had both a general practice consultation for a community acquired respiratory tract infection that was untreated (that is, for which immediate antibiotics were not prescribed) and a major bleeding event were included. Linked general practice and hospital admission data from England were used. The study included 1208 adults with incident use of warfarin or direct oral anticoagulants between January 2010 and December 2019. The incidence of major bleeding and clinically relevant non-major bleeding in the 0-14 days after an untreated respiratory tract infection was estimated and compared with incidence during times without an untreated respiratory tract infection.

Study answer and limitations Of 1208 study participants, 58% (n=701) were male, median age at time of first bleed was 79 years (interquartile range 72-85), with a median observation period of 2.4 years (interquartile range 1.3-3.8). 292 major bleeds occurred outside the risk period and 41 in the 0-14 day risk period after consultation for an untreated respiratory tract infection. 1003 clinically relevant non-major bleeds occurred outside the risk period and 81 occurred in the 0-14 day risk period. After adjustment for age, season, and calendar year, the relative incidence of major bleeding (incidence rate ratio 2.68, 95% confidence interval 1.83 to 3.93) and clinically relevant non-major bleeding (2.32, 1.82 to 2.94) increased by more than twofold in the 0-14 days after consultation for an untreated respiratory tract infection. Findings were robust to several sensitivity analyses and did not differ by sex or type of oral anticoagulant. Respiratory tract infection was ascertained from general practice records, and does not capture self-managed infection or those infections treated elsewhere. Use of over-the-counter drugs, such as non-steroidal anti-inflammatory drugs, was not captured. With a smaller than expected population sample, the study could have been underpowered to detect significant associations beyond the 14 day risk period.

What this study adds This study observed an association between untreated respiratory tract infection and bleeding among oral anticoagulant users. There are potential implications for the management of oral anticoagulant use during an acute intercurrent illness, but further work is needed before any clinical recommendations are made.

Funding, competing interests, and data sharing This report is independent research arising from a National Institute for Health Research advanced fellowship awarded to HA and funded by Health and Care Research Wales.

No competing interests declared. The Clinical Practice Research Datalink (CPRD) data agreement prevents data sharing, but researchers can apply directly to CPRD for a dataset.

Incidence rate ratios (IRR) for major bleeding and clinically relevant non-major bleeding (CRNMB) in people who had at least one untreated respiratory tract infection during the observation period

Time period	No of events	Total No of days of observation	Crude IRR (95% CI)	Age adjusted IRR (95% CI)	Age, season, and year (adjusted IRR (95% CI))
Major bleeding:					
Baseline	292	287 579	1	1	1
Pre-risk*	4	3332	0.60 (0.22 to 1.63)	0.60 (0.22 to 1.63)	0.62 (0.22 to 1.63)
0-14 days	41	6710	2.70 (1.85 to 3.94)	2.68 (1.83 to 3.92)	2.68 (1.83 to 3.93)
15-30 days	12	5899	0.64 (0.28 to 1.46)	0.62 (0.27 to 1.42)	0.62 (0.27 to 1.42)
31-60 days	22	9667	0.76 (0.41 to 1.41)	0.72 (0.38 to 1.34)	0.72 (0.38 to 1.35)
61-90 days	24	7825	1.41 (0.82 to 2.43)	1.34 (0.77 to 2.31)	1.35 (0.78 to 2.34)
CRNMB:					
Baseline	1003	827 042	1	1	1
Pre-risk*	17	9114	1.00 (0.61 to 1.62)	1.00 (0.61 to 1.61)	0.99 (0.61 to 1.60)
0-14 days	81	23 166	2.33 (1.83 to 2.96)	2.33 (1.84 to 2.97)	2.32 (1.82 to 2.94)
15-30 days	49	21 149	1.39 (0.99 to 1.94)	1.39 (0.99 to 1.96)	1.38 (0.98 to 1.94)
31-60 days	66	34 767	1.09 (0.80 to 1.48)	1.09 (0.80 to 1.49)	1.08 (0.79 to 1.47)
61-90 days	56	28 188	0.91 (0.62 to 1.33)	0.91 (0.63 to 1.34)	0.90 (0.62 to 1.32)

*Pre-risk refers to the seven day period before a general practice consultation for a respiratory tract infection.