deaths with letrozole versus tamoxifen treatment (13 vs 6, respectively). Data from IES at 37.4 months' median follow-up showed a significantly greater incidence of myocardial infarction (MI) with exemestane versus tamoxifen (20 vs 8, respectively; p = 0.02). However, more mature data from ATAC at 68 months' median follow-up showed the incidence of stroke was significantly reduced with anastrozole versus tamoxifen (62 vs 88, respectively; p = 0.03). There was a difference, although not significant, between anastrozole and tamoxifen in the number of ischaemic CV events (127 vs 104, respectively; p = 0.1). The majority of these events, however, continued to be mild to moderate in severity and there was no difference in the incidence of MI (1.2% vs 1.1%, respectively). Also, the numbers of CV deaths remained low and similar for the two groups (anastrozole 49, tamoxifen 46), with the majority of these deaths occurring after completion or discontinuation of study treatment.
Conclusions: The differences in CV safety profiles between the AIs confirm that AIs are not interchangeable in clinical practice. At present, anastrozole is the only AI in the adjuvant setting with a detailed benefit risk profile from over 5 years' follow-up, from which no CV safety concerns have emerged.

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Skeletal protective effect of clodronate in primary breast cancer-bone mass, bone turnover, and skeletal-related events (SRE's)

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Breast cancer treatments that suppress ovarian function – such as hormone therapy and chemotherapy – accelerate the loss of bone mass, yet hormonal osteoporosis prophylaxis is contraindicated. Thus, anti-osteolytic agents such as bisphosphonates have been suggested to maintain bone integrity.
In a randomized, double-blind, placebo-controlled study in 1069 patients, oral clodronate (BONEFOS®, Schering AG, Berlin, Germany) 1600 mg was given daily for 2 years (medication period) followed by a 3-year follow-up period (5 years total). There was a significant reduction in the occurrence of bone metastases and improved overall survival with clodronate.
In a predefined subgroup of 498 patients, it was also shown that oral clodronate had a protective effect with regard to bone mineral content of the spine and hip. While on treatment, patients in the clodronate group either had an increase in mean bone mineral density (BMD) or maintained their baseline BMD in contrast with the placebo group, where a significant decrease in mean BMD was seen at all sites but one. During the 3-year follow-up period, the mean BMD decreased significantly for both treatment groups at all sites studied and there was no difference in the changes between the treatment groups. Therefore, clodronate had a protective effect on the loss of bone mineral content during the medication period as compared with placebo, but this effect was not maintained during the follow-up. Similar patterns of change are observed using biochemical markers of bone formation, such as serum PINP, or bone resorption such as urinary NTx excretion. Thus, the temporal courses of BMD and biochemical marker changes are similar to the effects of clodronate on the occurrence of bone metastases during treatment, with a reduction in effect when treatment is discontinued.
Over the 5-year study period, a total of 124 patients developed bone metastases: 51 patients treated with clodronate and 73 treated with placebo. In these patients, adjuvant oral clodronate treatment decreased the overall occurrence of SREs for both the 5-year study period (5.5% vs 9.8% with placebo; $P < 0.01$), with the most notable differences seen in the need for radiation (4.5% vs 8.7% with placebo) or incidence of skeletal fractures (2.3% vs 5.6% with placebo). Thus, adding clodronate to standard adjuvant therapy in primary breast cancer protects the skeleton from metastases and SREs, but the optimum duration of treatment with clodronate remains to be determined.

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Nomograms to predict outcome after preoperative chemotherapy for breast cancer

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Background: The aim of this study was to develop and validate nomograms to predict residual breast and axillary tumor, breast conservation and disease-free survival (DFS) after preoperative chemotherapy (PC) for breast cancer.
Patients and Methods: Data from 496 patients treated with anthracycline PC at the Institut Gustave Roussy was used to develop and calibrate the nomograms. These nomograms were tested on 2 independent cohorts of patients treated at MD Anderson Cancer Center. The first cohort received anthracycline (n = 337), the second a combination of paclitaxel and anthracycline (n = 237) PC.
Results: A nomogram to predict breast and axillary residual tumor had good discrimination and calibration in the training and the anthracycline-treated validation sets ($P < 0.01$). Application of the nomogram to patients treated with combination of paclitaxel and anthracycline indicated that patients with intermediate chemotherapy sensitivity benefit the most from an optimized schedule of paclitaxel whereas patients who are unlikely to achieve pCR to anthracylines remain at low probability for pCR even after inclusion of paclitaxel. The nomogram for breast conservation had a good discrimination but a poor calibration because of difference in terms of attitude toward breast conservation across countries. The nomogram for DFS had a concordance index of 0.72 ($P < 0.01$) in the validation set and outperformed commonly used prediction tools ($P = 0.02$).
Conclusions: We developed and validated several nomograms that predict outcome after preoperative chemotherapy for breast cancer. These tools will be available online.

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Taxanes as adjuvant chemotherapy for early breast cancer: pooled-analysis of 15,000 patients enrolled in 8 randomized clinical trials

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Background: The benefit of taxanes as part of adjuvant chemotherapy for early breast cancer undergone surgery is still unclear. We performed a pooled analysis of published phase III trials, to look if adjuvant chemotherapy with taxanes can add some advantage over standard chemotherapy.
Methods: All phase III trials published or presented at major meetings were considered eligible. A pooled analysis was accomplished, and event-based relative risk ratios (RR) with 95% confidence interval (CI) were derived. Both analyses were performed to look at significant differences in: disease-free survival (DFS), and overall survival (OS). The combined effect estimation was computed with both fixed- and random-effect model. For both analyses, Cochran Q heterogeneity test was applied as well. To increase the clinical meaning of that approach, a subgroup analysis considering only those trials enrolling patients with node-positive disease (9670 patients) was performed as well.
Results: Eight trials (15003 patients) were gathered; they were designed to look if chemotherapy with taxanes (paclitaxel or docetaxel) improves survival. Two out of 8 trials did not report OS results. When data were pooled and plotted, significant differences in favor of taxanes were seen in DFS in the overall population (RR = 0.84, 95%CI: 0.79–0.88, p < 0.00001, heterogeneity p = 0.55) and in node-positive group (RR = 0.84, 95%CI: 0.79–0.89, p < 0.0001, heterogeneity p = 0.57). Moreover, a significant differences in favor of taxanes were seen in OS in the overall population (13,575 patients, RR = 0.85, 95%CI: 0.78–0.92, p < 0.0001, heterogeneity p = 0.33) and in node-positive group (RR = 0.84, 95%CI: 0.77–0.91, p < 0.0001, heterogeneity p = 0.15), as well.
Conclusions: Considered the available phase III trials, taxanes-based adjuvant chemotherapy for early breast cancer seems to add a significant benefit in both disease-free and overall survival over standard chemotherapy. The lack of significant heterogeneity in both the overall population and in the node-positive group does underscore the homogenous effect through al trials.