

EULAR develops guidelines for managing patients with RA

Clinical question How should patients with newly diagnosed rheumatoid arthritis (RA) be managed?

Bottom line These guidelines, from the European League Against Rheumatism (EULAR) recommend early diagnosis and rapid initiation of treatment with disease-modifying anti-rheumatic drugs (DMARDs) even before the patient's symptoms meet official criteria for RA. For most patients the initial choice of DMARD is methotrexate. Anti-inflammatory drug therapy, exercise, occupational therapy, and hydrotherapy should be used to treat pain and maintain function. (Level of evidence [LOE] = 5)

Combe B, Landewe R, Lukas C, et al. EULAR recommendations for the management of early arthritis: report of a task force of the European Standing Committee for International Clinical Studies Including Therapeutics (ESCSIT). *Ann Rheum Dis*. 2007;66(1):34-45.

Synopsis These European guidelines were developed by an expert committee of rheumatologists. The group assembled all research information after searching several databases, and attempted to answer their questions with the best available evidence, using the AGREE instrument to evaluate the relevance of the recommendations. Expert opinion was used when good research evidence was unavailable. The group focused on research evaluating the effect of management on the development of erosions and loss of function. The recommendations have not been tested in practice. The group produced 12 recommendations. They suggest treatment should begin quickly, ideally within 6 weeks of initial diagnosis (LOE: good). Prognosis should be attempted by evaluating the number of affected joints, markers of inflammation, and evidence on x-ray of erosions. The guidelines do not give specific recommendations as to how to weigh these findings when determining the need for aggressive therapy (LOE: low-quality). Based on observational studies, patients who seem to be at risk of developing persistent or erosive RA should be treated quickly with DMARDs. Based on good research showing effectiveness and safety, methotrexate should be started in most patients. Therapy should start within 6 weeks of the onset of symptoms, even if patients don't completely meet the criteria for diagnosis. NSAIDs and systemic or local corticosteroids should be used for pain control. Exercise, occupational therapy, and hydrotherapy should be used as adjuncts to drug treatment to maintain function and decrease pain (LOE: good). These guidelines are similar to the guidelines from the British Society for Rheumatism and are a little more aggressive than those from the American College of Rheumatology.

Reasoning training slows age-related functional decline

Clinical question Can cognitive training for older adults slow functional decline resulting in less difficulty with activities of daily living?

Bottom line Reasoning training (in this study, practicing strategies for finding patterns in letter series or word series) results in a slower decline of age-related functional ability as assessed by self-reported instrumental activities of daily living (IADLs) at 5 years of follow up. (Level of evidence = 2b)

Willis SL, Tennstedt SL, Marsiske M, et al, for the ACTIVE Study Group. Long-term effects of cognitive training on everyday functional outcomes in older adults. *JAMA*. 2006; 296(23):2805-2814.

Synopsis These investigators enrolled into their study 2,832 persons, aged 64 years or older, living independently with good baseline functional and cognitive status. Patients randomly received (allocation assignment concealed) one of four interventions: 10 sessions of cognitive training for memory, reasoning, or speed of processing, or no contact (the control group). Memory training consisted of teaching mnemonic strategies for remembering material such as word lists or texts; reasoning training

involved teaching strategies for finding patterns in letter series or word series; and speed of processing training consisted of improving visual search and attention skills by following objects on a computer screen. Booster training was offered at 11 months and 33 months after initial training, but only 60% of patients fully participated. Measurement of functional outcomes occurred through self-ratings of difficulties with IADLs. Assessments by individuals blinded to treatment group assignment occurred at baseline and annually for a total of 5 years. Complete follow-up occurred for only 67% of patients at 5 years. Using intention-to-treat analysis, only individuals receiving reasoning training reported significantly less difficulty in performing IADLs than control patients. No significant additional benefit occurred as a result of booster training. The effects of the training on self-reported IADL function could reflect self-report bias so the need for a placebo control group in future studies is important.

Early switch to PO is effective for severe pneumonia

Clinical question Can patients with severe pneumonia be switched to oral therapy after 3 days if clinically stable?

Bottom line Patients with severe pneumonia who are oxygenating well, have defervesce, and who can take oral medications can be switched from IV to oral therapy after 3 days. Mortality and cure rates will be the same, and hospital stays may be shorter. (Level of evidence = 1b)

Oosterheert JJ, Bonten MJ, Schneider MM, et al. Effectiveness of early switch from intravenous to oral antibiotics in severe community acquired pneumonia: multicentre randomised trial. *BMJ*. 2006;333(7580):1193.

Synopsis Rather than the usual 7 days of IV treatment, a switch to oral antibiotic treatment after 3 days has been shown to produce similar outcomes while decreasing length of stay in patients hospitalized with community-acquired pneumonia. The Dutch researchers conducting this study wished to determine whether patients with severe pneumonia would do as well with an early switch. They enrolled 302 patients admitted with severe pneumonia (average severity score = 113) to general wards of seven hospitals. The patients had typical signs and symptoms of severe pneumonia but were not immunocompromised and did not require mechanical ventilation. The patients were randomly assigned, using concealed allocation, to continued IV treatment for 7 days or a switch to oral antibiotic treatment after 3 days. The switch was done for patients who were clinically stable, had a drop in temperature, and were able to take oral medication (81% of patients in that group). Choice of antibiotic, both IV and oral, as well as determination of suitability for discharge were left to the admitting physician. Mortality within 28 days, the major end point of the study, was similar in both groups (4% vs 6%). In-house death and clinical cure rates were also similar between the 2 groups. Early-switch patients left the hospital, on average, just over 2 days earlier (9 days vs 11.3 days).

Annual mammography starting at age 40 years doesn't lower bCA mortality

Clinical question Does starting annual mammography at age 40 years decrease breast cancer (bCA) mortality?

Bottom line This study found that 10 years of annual mammography starting at age 40 years produced no statistically significant reduction in breast cancer mortality. The screening of women in this age group is controversial and the limitations of these data won't settle the arguments. (Level of evidence = 1b)

Moss SM, Cuckle H, Evans A, et al, for the Trial Management Group. Effect of mammographic screening from age 40 years on breast cancer mortality at 10 years' follow-up: a randomised controlled trial. *Lancet*. 2006;368(9552):2053-2060.

Synopsis Women in England, Scotland, and Wales aged 39 to 41 years were randomly assigned to annual mammography

(n=53,884) or usual care (n=106,956). The research team evaluated the women until they were 48 years of age (mean follow-up = 10.7 years; more than 99% accounted for). The main outcomes, breast cancer mortality and all-cause mortality, came from the National Health Service Central Register and were analyzed via intention to treat. Overall, 81% of the women had at least 1 mammogram and those screened women had, on average, 5.6 mammograms during the study period. The authors state, but give no data, that their evidence indicates that the extent of screening in the control group is small. During the study, the cost of screening in this age group was not covered by the National Health Service and would therefore be borne at personal expense. At the end of the study, the differences between groups in all-cause mortality (1.66 vs 1.72 per 1,000 person-years) and breast cancer mortality (0.18 vs 0.22 per 1,000 person years) were not statistically significant. The study was originally designed to have 80% power to detect a 20% relative reduction in breast cancer mortality. However, the study group ran out of money and didn't recruit as many women as they had planned. The final study had 72% power. In other words, although this was a well-conducted study, the statistical aspects are limited. For example, compared with usual care, we would need to screen 2,512 (95% CI, 1,149-13,544) to prevent 1 breast cancer death over 10 years.

ABCD rule predicts 7- and 30-day stroke risk in patients with TIA

Clinical question Do clinical factors reliably predict which patients with transient ischemic attacks (TIAs) will experience a stroke in the next 30 days?

Bottom line The ABCD score, determined by using clinical factors previously tested on other populations, appears to reliably predict the risk of stroke in the 30 days following hospitalization for TIA. It may not have the same validity in patients not admitted to the hospital. (Level of evidence = 1b)

Tsivgoulis G, Spengos K, Manta P, et al. Validation of the ABCD score in identifying individuals at high early risk of stroke after a transient ischemic attack: a hospital-based case series study. *Stroke*. 2006;37(12):2892-2897.

Synopsis These authors retrospectively studied 226 consecutive patients hospitalized with TIA. They compared the outcome predicted by the ABCD score with the real outcome. To determine the ABCD (for Age, BP, Clinical factors, and Duration) score, points are given as follows: 60 years or older (1 point); systolic BP greater than 140 mm Hg and/or diastolic BP greater than or equal to 90 mm Hg (1 point); unilateral weakness (2 points), speech disturbance without weakness (1 point); and a duration of symptoms of 60 minutes or more (2 points), of 10 to 59 minutes (1 point), of less than 10 minutes (0 points). The researchers calculating the ABCD score were unaware of the real outcome. Within 30 days of the index TIA, 22 (9.7%) patients had a subsequent stroke. The ABCD score was highly correlated with the risk of stroke:

ABCD score	7-day stroke risk (95% CI)	30-day stroke risk (95% CI)
2 or less	0	0
3	1.7% (0%-5.1%)	3.5% (0%-8.2%)
4	7.6% (1.2%-14%)	7.6% (1.2%-14%)
5	19.1% (7.8%-30.4%)	21.3% (10.4%-33%)
6	18.8% (0%-37.9%)	31.3% (8.6%-54%)

There is one limitation to this generally well-done study: The ABCD model was developed in an outpatient setting to predict risk for all TIA patients. This study only addresses its application to hospitalized patients.

Levels of evidence are explained at <http://www.infopeoms.com/levels.html>.

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New biomarkers add little to current predictors for CAD

Clinical question Do new biomarkers improve our ability to predict whether a patient will have an initial cardiovascular (CV) event?

Bottom line Novel biomarkers predict CV risk, but do not add to our current ability to predict risk using conventional risk factors like age, sex, cholesterol level, diabetes, tobacco use, and blood pressure. The new biomarkers should not be routinely used, given their cost and the fact that we do not know whether modifying these risk factors improves patient outcomes. (Level of evidence = 1b)

Wang TJ, Gona P, Larson MG, et al. Multiple biomarkers for the prediction of first major cardiovascular events and death. *N Engl J Med*. 2006;355(25):2631-2639.

Synopsis There is increasing attention in the popular media and among some physicians and their patients to new biomarkers for the prediction of CV risk. However, it is important to ask 2 questions: Does a biomarker significantly improve our ability to predict risk over existing risk factors; and, does this knowledge help us choose interventions that can modify risk? The authors of this study identified 3,209 men and women with a mean age of 59 years who were participating in the Framingham Offspring Study. Fasting levels of 10 biomarkers (C-reactive protein, B-type natriuretic peptide, N-terminal pro-atrial natriuretic peptide, aldosterone, renin, fibrinogen, D-dimer, plasminogen-activator inhibitor type 1, homocysteine, and the urinary albumin-to-creatinine ratio) were measured and patients were followed up for a median of 7.4 years. During that time, 207 patients died and 169 had a first major CV event (MI, prolonged angina with electrocardiographic changes, heart failure, or stroke). A pair of multivariate models were developed to predict the risk of death and initial CV event. The model developed to predict risk of death included C-reactive protein, B-type natriuretic peptide, urinary albumin-to-creatinine ratio, homocysteine, and plasma renin; the model for initial CV event included only B-type natriuretic peptide and urinary albumin-to-creatinine ratio. The "multimarker scores" generated by these models were stratified into 3 groups: low risk (bottom 40%), intermediate risk (middle 40%), and high risk (top 20%). The models were then adjusted for conventional risk factors like age, sex, cigarette use, cholesterol level, and diabetes. The multimarker scores accurately predicted CV risk, with a relative risk of death that was 4 times greater in the group with high scores than in the group with low scores. The researchers then compared risk prediction using only conventional risk factors with risk prediction using conventional risk factors plus the multimarker scores. Using the C-statistic and the area under the receiver operating characteristic curve, two overall measures of predictive accuracy, the authors found no significant difference between these sets of models (eg, C-statistic = 0.76 for conventional risk factors vs C-statistic = 0.77 when you add the multimarker score to predict CV events).