The large, long-term ACE inhibitor trials quoted by Krum et al — SAVE,2 TRACE3 and AIRE4 — between them screened 34,037 patients with myocardial infarction and left ventricular dysfunction. Only 5986 patients (18%) met the inclusion/exclusion criteria to be enrolled in one of the trials. Unfortunately, the CAPRICORN5 (β-blocker) and EPHESUS (aldosterone antagonist) trials did not publish the number of patients screened versus the number randomised, but a glance at their exclusion criteria explains why, for some patients, it may not have been appropriate to start these medications during their hospital stay. Some of the exclusion criteria for CAPRICORN were: unstable angina, ongoing therapy with antiarrhythmics (except amiodarone), secondary or tertiary heart block or sick sinus syndrome unless paced, uncontrolled hypertension (>160/95 mmHg), bradycardia (heart rate, <60 beats/min), hypotension (systolic blood pressure, <80 mmHg), requirement for intravenous diuretics or inotropes, chronic obstructive pulmonary disease with ongoing inhaled β2-agonist or steroid therapy, and unstable insulin-dependent diabetes.

Is there any harm in prescribing outside the inclusion/exclusion criteria for clinical trials? A population-based, time-series analysis linking prescription-claims data and hospital admission records of 1.3 million adults in Canada6 showed that hyperkalaemia-related deaths in hospital doubled after the RALES trial (spironolactone) was published in 1999. There was no reduction in re-hospitalisation for heart failure or all-cause mortality. The authors speculated that part of the reason for this was spironolactone to patients who would have been excluded from the RALES trial.

While we would not advocate prescribing strictly within the boundaries of the inclusion/exclusion criteria of clinical trials, it is important to understand these criteria, so that prescribing in “real world” patients is done with care.

We are reassured that Krum et al’s study suggests there is discretion in the prescribing of drug therapy. Presumably, during ongoing medical assessment, it will be appropriate for some patients to commence some of these medications (potential benefit outweighs potential harm), while others may need to have their medications reviewed because of adverse events.

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SNAPSHOT

Lung encasement by metastatic osteoblastic sarcoma

A 21-year-old man with a high-grade osteoblastic sarcoma of the tibia had a tumour resection and adjuvant chemotherapy. Eight months later, he became dyspnoeic and a radiograph showed a large left-sided pleural effusion and a nodule in the right mid zone.

Calcified pleural metastases were confirmed on biopsy, and talc pleurodesis was performed. High-dose methotrexate was commenced, but 2 months later a chest radiograph showed marked calcification of the pleura and pulmonary metastases on the left side (Figure). The right pulmonary nodule had increased in size and the patient’s serum alkaline phosphatase level had risen to 4459 U/L (reference range, 30–130 U/L). A trial of ifosfamide transiently reduced the alkaline phosphatase level. The patient died 4 months later.

Figure: Radiograph showing diffuse dense pleural thickening encasing the left hemithorax, multiple metastatic nodules in the left lung, and a solitary deposit in the right mid zone.

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2 Moyle LA, Pfeffer MA, Braunwald E. Rationale, design and baseline characteristics of the survival and ventricular enlargement trial. SAVE Investigators. Am J Cardiol 1991; 68: 700-70D.
3 The Trace Study Group. The TRAndolapril Cardiac Evaluation (TRACE) study: rationale, design, and baseline characteristics of the screened population. Am J Cardiol 1994; 73: 44C-50C.

Henry Krum

IN REPLY: We thank Bailey and Naganathan for their thoughtful viewpoint regarding prescribing according to clinical trial criteria. We agree that prescribing in the real world often involves complex decision making, taking into account age, comorbidities, concomitant medications and other factors, whereby guidance regarding individual patients cannot readily be extracted from