Critical Review Form

Therapy

Bach RG, et al. The Effect of Routine, Early Invasive Management on Outcome for Elderly Patients with NSTE ACS, *Annals IM* 2004; 141: 186-195

Objective: Non-blinded RCT of 2220 adult patients hospitalized in one of 169 hospitals in 9 countries between 1997-1999 with unstable angina or NSTEMI as part of pharmaceutical industry sponsored TACTICS-TIMI 18 trial randomized to early invasive or conservative management strategy.

Methods: Pre-specified subgroup analysis of young (< 65 years) versus old (≥ 65 years) with post-hoc analysis of multiple age-stratified subgroups for the endpoints of death, non-fatal MI, and bleeding complications. The interventional strategy group underwent coronary angiography within 4-48 hours of randomization, while those in the conservative arm were treated medically and, if stable, "underwent an exercise tolerance test before discharge" (p. 187).

Guide		Comments
I.	**Are the results valid?**	
A.	**Did experimental and control groups begin the study with a similar prognosis (answer the questions posed below)?**	
1.	Were patients randomized?	Yes (see Figure 1, p. 188, CONSORT diagram). "Through a centralized system patients were randomly assigned, stratified by center, to the early invasive or conservative strategy". (p. 187)
2.	Was randomization concealed (blinded)?	No. No ethical means to blind patients or families to the group allocation. **Note** that if you were assessing this trial on the Jadad scale (discussed in July 2004 Journal Club as only validated tool to "grade" the level of evidence in randomized, controlled trials for meta-analysis), the study would be graded 4/5 (and deemed less impressive evidence than a blinded study which would rate 5/5) and in this regard the Jadad scale is biased against studies which CANNOT be blinded.

3.	Were patients analyzed in the groups to which they were randomized?	Intent to treat not explicitly stated, but assumed based upon Table 2 (p. 189) which shows invasive versus conservative strategy stratified by age.
4.	Were patients in the treatment and control groups similar with respect to known prognostic factors?	Many significant differences noted (Table 1, p. 189) between younger & older cohorts. Of note, the authors did not compare the baseline characteristics of those > 65 years in treatment and control arms (could one group have had confounding variable to explain observed outcomes?).
B.	**Did experimental and control groups retain a similar prognosis after the study started (answer the questions posed below)?**	
1.	Were patients aware of group allocation?	Yes (see discussion above).
2.	Were clinicians aware of group allocation?	Yes.
3.	Were outcome assessors aware of group allocation?	No. "An independent committee whose members were unaware of patients' treatment assignments adjudicated all primary endpoints" (p. 188)
4.	Was follow-up complete?	1.2% (27 /2220 patients) lost to follow-up at 6 months (p. 188).
II.	**What are the results (answer the questions posed below)?**	
1.	How large was the treatment effect?	See Table 3, Figure 1, and Figure 3. a) ≥ 65 years absolute risk reduction (ARR) 4.1% (5.7% versus 9.8%, p<0.019) for composite endpoint of death or non-fatal MI at 30 days. Since NNT = 1/ARR, this translates into treating 24 patients to prevent one death or non-fatal MI at 30 days. At 6 months, ARR 4.8% for NNT 21, compared with < 65 years where NNT 250! b) Among those > 75 years ARR 10.8% (NNT 9.3). c) $39,000 per death or MI averted < 65 years c/w $9967 > 75 years.

		"Although patients 65 years or older made up 43% of study group, they accounted for 71% of all deaths and 53% of all myocardial infarctions at 6 months" (p. 190).
2.	How precise was the estimate of the treatment effect?	Confidence Intervals not provided.
III.	**How can I apply the results to patient care (answer the questions posed below)?**	
1.	Were the study patients similar to my patient?	Multiple exclusion criteria requires cautious application to general ED elderly population, but if your geriatric ED patient does not meet any of TACTIC-TIMI 18 exclusion criteria, they probably represent similar patient to this trial.
2.	Were all clinically important outcomes considered?	No functional outcomes assessed such as ability to attend to activities of daily living or quality of life.
3.	Are the likely treatment benefits worth the potential harm and costs?	It would appear so, although one would hope for further studies with less restrictive exclusion criteria. Dr. Bach stated that such trials are NOT currently underway, though, and are unlikely to be studied in the near-future, so the current trial probably represents the best-evidence for the treatment of ACS in the elderly for some time to come.

<u>Bottom Line</u>: A highly select cohort of elderly patients show a significant benefit from early (< 48 hours), invasive management of acute coronary syndrome compared with non-invasive, conservative management with a 4.8% absolute risk reduction of death or non-fatal MI at 6 months. While 250 patients under age 65 need to undergo early invasive management to prevent one death or non-fatal MI at 6 months, only 9 patients over age 75 need to be similarly treated. Future trials should analyze early invasive strategies compared with conservative strategies on an elderly population with less exclusive restriction criteria.