Critical Review Form
Prognosis

Objective: “To evaluate the incidence and prognosis of syncope due to specific causes among participants in the Framingham Heart Study” (p. 878)

Methods: All reports of syncope among Framingham participants between 1971 and 1998 were examined. Equivocal cases were adjudicated by a committee of physicians who excluded 275 reported possible syncope episodes if available data did not support the diagnosis, or if no evaluation within four years was available, or if a head injury was involved in the syncope episode. The cause of syncope was assigned by an Internist and Cardiologist who were blinded to outcomes, but had inpatient and outpatient medical records available for review. Causes were collapsed into four basic categories: cardiac, neurological, vasovagal/other, and unknown. Each participant with syncope was matched with two randomly selected non-syncope Framingham participants according to age and gender for comparison. Using a COX regression model and multivariable analysis, the cohort was assessed for the outcomes of all cause mortality, coronary mortality, myocardial infarction and stroke.

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<td>1. Are the results valid?</td>
<td>Framingham cohort is predominantly middle-aged to elderly Caucasians. A broad cross-section of compliant and non-compliant patients with variable levels of co-morbidity is available in this data set with lengthy, high quality follow-up. Overall, an unbiased sampling which might not be extrapolated to BJH due to racial differences alone. For the last question, there were no standardized objective diagnostic procedures detailed.</td>
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<td>A. Was the sample of patients representative? In other words, how were subjects selected and did they pass through some sort of “filtering” system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?</td>
<td>Syncope patients were matched with two non-syncope Framingham participants according to age and gender (p. 879) who should have similar morbidity and mortality. However, looking at Table 2 (p. 881), the syncope cohort appears to have an increased prevalence of smoking, coronary artery disease, strokes, atrial fibrillation, and use of cardiac medications. The</td>
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The authors attempt to correct for these differences by performing multivariable analysis.

| C. | Was follow-up sufficiently complete?  
In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up? | Yes, 7814 participants were followed for an average of 17 years for a total of 133,164 person-years with 727 syncope cases included in the analysis (p. 879). |
| D. | Were objective and unbiased outcome criteria used?  
Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures. | The outcomes were defined at the beginning of the study as “death from any cause, myocardial infarction or death from coronary artery disease…and fatal or non-fatal stroke” (p. 879). Objective measures of outcomes were not detailed in this publication. |

II. What are the results?

| A. | How likely are the outcomes over time? | The age-adjusted incidence of syncope in males and females was 7.2 per 1000 person-years or 6% every 10 years. A sharp increase in the incidence is noted over age 70 years with 11.1 per 1000 person-years and at age 80 years 19.5 per 1000 person-years in females.  
▫ 44% of syncope patients never seek medical care.  
▫ Unknown etiology is the leading cause among males and females either with or without known coronary disease, while seizure and stroke are exceedingly rare causes of syncope.  
▫ Cardiac syncope is four-fold higher in those with cardiovascular history and in those without known cardiovascular disease. There is a high risk of recurrent syncope when cardiac syncope is the etiology.  
▫ The risk of all-cause death varies from cardiac syncope (Hazards Ratio = 2.01) to neurological syncope (HR = 1.54) to idiopathic syncope (HR = 1.32), but is not increased for vasovagal syncope (HR = 1.08). |
**Limitations**

1) Recall bias may result in an underestimation of the incidence of syncope.
2) Lack of explicit diagnostic criteria.
3) Predominantly Caucasian, older population may not be extrapolated to other populations.

**Bottom Line**

Cardiac syncope patients represent a high risk group with 100% higher all-cause mortality when corrected for confounding co-morbidities. These patients should all be closely monitored. “Syncope of unknown cause” patients have 32% higher all-cause mortality and “neurological syncope” patients 54%; further diagnostic testing may be warranted in these patient populations. “Unknown cause” is the leading diagnosis in men and women both with and without known cardiovascular disease. The incidence of syncope increases markedly with age over 70 years. Almost half of patients with syncope never seek medical care. “Vasovagal syncope” is not related to increased mortality, myocardial infarctions, or stroke.