Internal and Emergency Medicine (2018) 13:589–591
https://doi.org/10.1007/s11739-018-1841-y

CE - COMMENTARY

Outcomes in syncope research: it is time to standardize

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Received: 14 March 2018 / Accepted: 20 March 2018 / Published online: 26 March 2018

Syncope, a common condition causing sudden and transient loss of consciousness with rapid and complete recovery, remains a huge management problem for the clinician and a potentially debilitating one for the patient. Derived from the Greek word *synkoptein* ("to cut short"), syncope, first described by Hippocrates, continues to confound us. It presently accounts for 1–2% of emergency department (ED) visits, and, due to concerns of recurrence and associated adverse consequences including death, leads commonly to hospital admission, at which time, extensive, unproductive, costly, and non-diagnostic evaluations are the rule.

The reasoning for the hospitalization decisions remains obscure, and no real, cogent, or rational outcome measure is generally considered. Benefits from hospitalization are difficult to quantitate [1, 2]. Despite the immensity of the problem, syncope evaluation and subsequent data collection for patient care and research purposes is time-consuming and tedious. Furthermore, recurrences and their severity are unpredictable. Thus, quality and outcome measures have not been collected systematically and researched scrupulously nor quantitated carefully.

Based on the totality of the data, guideline documents have developed risk assessment and diagnostic pathways [3, 4], but outcome measures remain obscure. No international consensus regarding specific outcome measures is yet within reach. Prospective studies have resulted in a confusing array of data that are heterogenous in nature, conflicting in outcomes and impossible to implement. Reasons include underlying patient characteristics, competing morbidity issues, patient age, and local hospital biases that vary from study to study.

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Reported outcomes have been simply too numerous, without clinical relevance and without direct relationship to syncope. Outcomes need to be defined carefully, remain relevant clinically, and be robust and reproducible in different settings to compare data reliably and develop prognostic risk models that are relevant, accurate, safe, and dependant on syncope itself.

Since syncope ranges from benign to life-threatening situations, risk stratification (based on prognostic models) during the initial evaluation has become important—as it should. This may be the crux of the problem. Prognosis, with regard to syncope, especially of those patients seen in the ED is difficult to determine without regard to the presence or absence of underlying diseases that essentially and specifically define the prognosis by themselves. Outcomes would not be expected to be similar for patients with ischemic heart disease and syncope compared to those with ischemic heart disease and no syncope, but, if syncope were vasovagal in origin in a patient with no heart disease, the prognosis may be the same as a control population. Thus, syncope may be defined by the disease, at least in part, or maybe not in every circumstance.

In many conditions, such as, aortic dissection, pulmonary embolism, and heart failure, the prognosis is defined further by disease acuity, severity, and progression. The prognostic impact of the underlying condition, especially in cardiac conditions or terminal illness, is the critical determinant, not the presenting symptom, e.g., syncope [5–7]. In other words, a pulmonary embolus or gastrointestinal bleed is not an outcome measure, and yet may define the prognosis. In addition, it may contribute to syncope, but syncope itself may have nothing to do with the prognosis. A critical issue in most studies is that there are no good control groups with which to compare. Even with propensity matching, determining exactly the role of syncope itself to predict any specific outcome measure is problematic.

In this issue, Solbiati et al. [8] perform a systematic review providing a critical appraisal of outcomes in syncope research. The authors screened 60,751 records of syncope research systematically, and focus on 31 studies meeting

their criteria as a prospective ED study of patients with syncope, for whom short-term outcome data regarding morbidity or mortality was available. The measured outcomes found in the studies were analysed critically by an expert group consisting of the Scientific Committee of the First and Second Workshops on Syncope Assessment. A discussion of the pros and cons of each outcome was summarized.

This important scientific contribution, following expert consensus papers and guidelines, shows the problems of outcome heterogeneity (Table 1). Considering the multiplicity of "outcomes" in Table 1, it becomes clear that many are not real outcomes. Some studies included items, such as, "acute surgical procedure or endoscopic intervention," whereas others considered pseudo-diagnoses including "structural heart disease" or "acute pulmonary edema." These are not outcome measures or even disease entities. Such data simply confuse and dilute real outcome measures including mortality and syncope recurrence.

These same authors, and an expanded expert panel, 6 years earlier [9], gave recommendations on the exact same issue; the present report is an updated review with details of the 31 published study outcomes not part of the above panel review. Solbiati et al. examine what is a clinically relevant outcome. Table 3 summarizes the strengths and weaknesses of selected outcomes according to the authors' assessments. They recommend practical solutions to standardize research, i.e., common patient datasheets, shared protocols for management of patients, emphasis on the time-dependent, cause/effect relationships between syncope and outcomes, and an independent commission to re-adjudicate outcomes.

While the review does list various outcome measures, there are so many that it does not provide guidance regarding the important measures necessary to actually consider. Despite this fine contribution, a clear critical appraisal and a consensus regarding the most important outcome measures to consider is still lacking. Unfortunately, the eminent and qualified panel did not provide their opinion on this matter.

It is also important to address the time course of the outcome measure: Why is a 30-day outcome measure of any specific value? There is no proven relationship between syncope and outcome measure that is clearly time dependant. Quite the contrary, syncope can be a sporadic condition reflecting a benign or malignant process that can be manifest in the short term or the long term. It may be important for the ED focus, but not for management of syncope at all.

It is important for clinicians to understand that clinical prediction rules should help to stratify patients with syncope after the initial evaluation when no obvious cause is present, thus reflecting the future management at time of possible discharge from the ED. The initial evaluation is physician-dependent and varies with the local availability of clinical tools including echocardiography and expert help. Limited resources and reliable, safe, robust, and credible clinical prediction tools that extend beyond the ED visit are still warranted.

Recently, results from the well-conducted and, to date, largest prospective study [10, 11] of 4030 syncope patients were published resulting in the development of the Canadian Syncope Risk Score and the Canadian Syncope Arrhythmia Risk Sore. This study incorporates many of the above points in sample size, data collection, patient inclusion, and outcomes measured that are and were criticised in the previous studies. The present paper did not include this recent important publication.

To date, these risk scores, although not yet validated, are most likely the best, clinically relevant, updated, and useful scores. Time will tell if implementation and validation of these scores actually take place has any real value or is even possible. Despite the research, it is not clear that we have been able to provide measurable improvement in syncope outcomes based on the weaknesses of the studies and the analysis of the information, no matter how well intentioned. It is difficult to see where, why, and how more prospective ED studies will help to guide clinicians. In our opinion, international efforts should focus on syncope intervention studies. Randomized, well-designed studies are needed to evaluate credible and real outcome measures agreed upon by the general community of physicians caring for syncope patients, and not based upon misguided studies and the economic efficacy of implementation of such items including early discharge. A quick review of clinicaltrials.org reveals that today at least seven prospective syncope outcomes studies are still enrolling.

Compliance with ethical standards

Conflict of interest Ruwald: none declared. Olshansky: Amarin, Boehringer Ingelheim, Lundbeck, On-X/Cryolife.

Statement of human and animal rights This article does not contain any studies with human participants or animals performed by any of the authors.

Informed consent None.

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