T.M.I. (Too Much Information)?

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Parents of teenagers will recognize the following scenario: parent comprehensively lecturing teenager on some topic at hand, carefully outlining the rationale for a parental decision, invoking extensive reasoning of why one option is better than another for good adolescent decision-making, etc., etc. Teenager looks away, rolls eyes (possibly, but not necessarily outside of visual field of parent), and mutters, *sotto voce,* “… T.M.I. …”

*Article see p 1719*

T.M.I. Too much information. In making clinical decisions, we as clinicians generally believe that more information characterizing our patients’ disease processes allows us to make better decisions about therapeutic direction, thereby ultimately improving their quality of life and outcomes.

Of course, like many things that we would like to believe, this is not always the case, when the concept is tested rigorously. Over the past few years, several studies have shown that providing an increment of information on which clinicians can base management—compared with management without such information—does not necessarily improve symptoms and/or outcomes. Examples include the Evaluation Study of Congestive Heart Failure and Pulmonary Artery Catheterization Effectiveness (ESCAPE) trial, a randomized trial in which in-hospital management based on invasive hemodynamic information from pulmonary artery catheterization did not improve measures of 6-month outcomes in comparison with clinically based management in decompensated heart failure (HF) patients, and the often neutral trial results reported when chronic outpatient HF management is guided according to serial measurements of natriuretic peptide levels, as well. The usual trajectory for such studies is initial validation of a marker associated with a pathophysiology of interest, subsequent demonstration of prognostic value in observational studies showing that abnormal levels of the marker are associated with increased risk of an unfavorable outcome, small studies showing that a therapy can improve the marker, and then finally, therapy directed at the marker in a more definitive study with the expectation of actual improved outcome. The trajectory of natriuretic peptide-guided therapy has certainly played out this way, with generally disappointing results at the final step.

In this issue of *Circulation,* Van Veldhuisen and colleagues report the provocative results of the Diagnostic Outcome Trial in Heart Failure (DOT-HF). They report that providing clinicians with information about intrathoracic fluid accumulation (which has been shown to be reflective of intrathoracic fluid accumulation) and basing management on that information did not lead to the hypothesized improvement in a composite of all-cause mortality or adjudicated HF hospitalizations in patients with chronic HF. In fact, the data suggest that the incremental information was associated with an increase in HF hospitalizations across the follow-up time period. In other words, more information was apparently associated with worse outcomes. How could this be?

DOT-HF enrolled patients with symptomatic chronic HF and systolic dysfunction with at least 1 prior HF hospitalization. The patients were enrolled within 6 months of implantation of a defibrillator or resynchronization device that was equipped with the ability to track intrathoracic impedance. Patients were randomly assigned to a control group, in which neither patients nor their clinicians had access to the impedance data, or to an access group, in which an alert sounded to notify the patient that impedance had fallen below a prespecified threshold, prompting an outpatient visit for assessment and potential adjustment of therapy, which to some degree was protocol-driven. The trial was powered for a 20% reduction in the composite event rate, and the enrollment of 2400 patients was planned, with the expectation of >800 primary composite events. The trial was stopped well ahead of schedule by the sponsor, on the basis of slow recruitment and advances in device technology, which, according to the authors, “… could lead to interpretation difficulties.” At that point, only ~15% of the planned enrollment had occurred, and enrolled patients were monitored for at least 6 months. Over an average of 15 months of follow-up, the primary composite end point occurred more often in the access group than in the control group, with a hazard ratio of 1.52 and near statistical significance. This finding was driven by HF hospitalizations, which were increased significantly in the access group, with a hazard ratio of 1.79 (95% confidence interval, 1.08–2.95; *P*=0.022), with relatively similar rates of all-cause death in the 2 groups. The data displayed in Figure 3 of the article suggest that the event curves began to diverge in an unfavorable direction for the access group at 3 to 4 months after randomization.

These unexpectedly negative results prompt thought about how providing information reflecting thoracic fluid accumulation to patients and clinicians, and allowing them to act on it, could lead to an increase in HF hospitalizations and, in fact, all cardiovascular hospitalizations in this trial. Negative results such as these are very important to report and publish, because we then must question all of our assumptions that
formed the rationale for such an approach. There are several potential explanations.

One possibility is that our assumptions regarding the pathophysiology or mechanism driving an episode of decompensated HF leading to hospitalization are incorrect, or in part incorrect. The use of devices that can provide ongoing readouts of pulmonary artery \(^4\) or left atrial pressures, \(^5\) or those that examine intrathoracic impedance, \(^6\) have suggested that an episode of decompensated HF leading to hospitalization is often preceded by a prolonged subclinical period of a slow increase of pulmonary pressures (suggesting increasing left atrial pressures) or reduction in impedance (suggesting slow accumulation of fluid). These studies led to the enticing possibility that targeting therapy during that subclinical period could reduce the likelihood of clinical decompensation. A close look at the data, however, suggests that the story may be more complex. In the DOT-HF trial, among the episodes of HF hospitalization, only \(\approx 60\%\) were preceded by an alert condition, where impedance readings fell below the prespecified threshold indicating risk. In other words, the sensitivity of the impedance alert to predict a HF episode was only modest. This is actually consistent with previous studies, \(^7-9\) and false-positives seem common, as well. \(^9\) Published data examining device-determined impedance or pressure measurements tend to report relative risks or hazards associated with an abnormal measurement to predict a subsequent HF episode. The actual discriminatory power may be modest, however. Stevenson and colleagues \(^10\) reported from the Chronicle Offers Management to Patients with Advanced Signs and Symptoms of Heart Failure (COMPASS-HF) trial that the distributions of estimated pulmonary artery diastolic pressures among those patients who did versus those who did not develop HF events showed substantial overlap before the event. Thus, relying on dichotomization of any such signal to trigger treatment is likely to lead to both unnecessary treatment and undertreatment.

Another possibility is that, perhaps, the inclusion of the patient as part of the information loop is an incorrect strategy. In the DOT-HF trial, an alert audible to the patient sounded when an impedance threshold had been crossed, driving a required patient-physician contact for evaluation and possible intervention. When a larger and more definitive trial was performed, \(^16,17\) the HF community certainly conceivable that a distinct result may have occurred if full enrollment were accomplished. The HF community has seen previous examples in which the results from a small study with provocative findings were found to be incorrect when a larger and more definitive trial was performed. \(^16,17\)

So what lessons have been learned? DOT-HF joins an instructive group of trials in which unexpected results cause us to question assumptions about the relation between biomarkers and outcomes, and the treatment guided by biomarkers, as well. Suppression of post-myocardial infarction premature ventricular contractions \(^18\) and elevation of high-density lipoprotein levels \(^19\) are examples of strategies that have not worked as planned, despite attractive rationales. In such cases, we are driven to reexamine the mechanistic connection between the marker and the outcome, or to reexamine specific treatment strategies. Much is learned from trials that do not achieve their hypothesized outcome, and it is important that the DOT-HF investigators moved forward with 6-month follow-up of enrolled patients and the publication of their unfavorable results, as well, despite very early termination of recruitment. That decompensation of HF is preceded by a prolonged period of a subclinical slow rise of pressure or slow accumulation of fluid that can be captured by a monitoring device, allowing potential intervention, is highly attractive mechanistically, but it is likely that the story is more
complex, and other mechanisms, such as shifts in central blood volume,\textsuperscript{20} may be at play.

The data also highlight the complexity of medical decision making and the role of providing information to drive management. What is the optimal type and amount of information to provide? What treatment algorithm should be applied? What is the role of the patient? Rigorously designed trials testing the effect of information and guided treatment on patient outcomes, as seen in the recent examples cited here, are very important for the community to assess which, if any, of the strategies should be incorporated to benefit our patients. From such trials, we may eventually learn when information may be too much information.

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**References**


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