"Information Overload"

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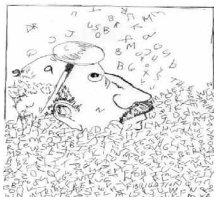
One of the things I hear constantly from peers, primary care physicians, specialists and house staff, is that everyone is experiencing *information overload.* The amount of new information that we receive online or by mailings, journals and dinners, is overwhelming, given our daily work and the time we have.



Of major concern to me is the information that is presented at dinners, lunches and conferences sponsored by various pharmaceutical companies. Representatives come armed with information about newer, more expensive drugs that frequently have not been proven more beneficial than the cheaper ones we already have. It's very comfortable for us, and it is great marketing technique by the pharmaceutical companies to get us to use their medications. Sadly it works. We start using the newer medications, leaving the cheaper, sometimes even more effective, generics by the wayside. We tend to forget that *our most important goal is achieving the best outcomes with the least possible resources for our patients.* In this *Heartbeat* we are going to discuss how to discern what information is patient-oriented and useful, and what is based on faulty assumptions or is irrelevant.

We need **P**atient **O**riented **E**vidence that **M**atters (**POEM**). This only comes from studies that evaluate what matters most to our patients—their quality and duration of life. We see a lot of **D**isease **O**riented **E**vidence (**DOE**), that is important to know, but makes no difference for our patients. We've all been presented with comparison drug studies that compare one obviously stronger dose of a lipid-lowering medication with another in the same class showing superior LDL-C lowering. This is an example of DOE. The assumption is that lowering LDL-C improves outcome in these patients, which is not necessarily true. We have to ask the pharmaceutical companies to give us a head to head comparison studies showing outcome improvements. Presently they spend much more money on marketing and marketing studies than they do on actual research.

A perfect example of POEM is PROVE-IT, the study which showed significantly lower LDL-C levels in the atorvastatin 80mg treatment group compared to pravastatin 40mg group. More importantly, it showed a 16% reduction in clinical events in the atorvastatin group. In PROVE-IT, high dose atorvastatin lowered LDL-C more effectively than moderate dose pravastatin, and this was associated with improved outcomes. This is a result that helps us treat patients, and no assumptions were involved. **The only way to distinguish between DOE and POEM is to determine whether the information requires assuming or knowing.**

A classic example of DOE with an assumption gone wrong was exemplified by the CAST study.[1] Patients with complex ventricular ectopy are at higher risk for recurrent cardiac events (DOE). But it was *assumed* that anti-arrhythmic drugs which suppressed ventricular ectopy would improve outcomes. This became standard of care, and we treated patients with anti-arrhythmic medications. When the CAST study results became available, the medications indeed decreased the ventricular ectopy, but these patients had higher rates of sudden cardiac death (SCD) secondary to the drug effects, putting them at higher risk than the complex ventricular ectopy (POEM). Counterintuitive as it may seem, the error was in assuming that treating the disease was in the best interest of the patient. The assumption that antiarrhythmic drugs decrease ventricular ectopy, and heavy pharmaceutical marketing, resulted in our treating patients inappropriately and their dying as a result. I will always remember being part of this DOE/ incorrect assumption.

Today, we know that poor left ventricular systolic function (LVEF < 35%) is the real high-risk prognosticator. We also *know, without making assumptions,* that beta-blockers, ACE inhibitors,

digoxin, aldosterone antagonists and implantable cardiac defibrillators, together and individually, improve cardiac outcomes.

Other more current examples of DOE with assumptions gone wrong or not appropriately supported:

Sulfonylureas—the mainstay of glucose control in type 2 diabetes (T2DM).

High blood sugars increase micro and macrovascular risk, and sulfonylureas lower blood sugars. The DOE here is the assumption that therefore sulfonylureas decrease cardiovascular (CV) risk by lowering blood sugar. However, a new study shows that sulfonylureas *increase* the risk of both CV and all-cause mortality.[2] This retrospective cohort study of 5795 newly diagnosed T2DM patients compared levels of exposure to monotherapy with first- and second-generation sulfonylureas and metformin to determine whether increased mortality was associated with increased drug exposure. The researchers found that higher daily doses of first and second generation sulfonylureas increased mortality risk by 30% and 40%, respectively.

Based on these results, the researchers recommend that physicians who are initiating oral anti-diabetic therapy in newly diagnosed type 2 diabetic patients use metformin over sulfonylureas—particularly the first-generation drugs. In an accompanying editorial, **Dr David Bell** (University of Alabama, Birmingham) said the study's findings warrant relegation of sulfonylureas to third-line agents, after metformin and a glitazone, in the management of T2DM.[3] "The findings of Simpson and colleagues," he writes, "add to the existing evidence that suggests that sulfonylureas increase the risk of cardiovascular events; furthermore, their study adds support to a causal link by demonstrating a dose-related effect on the risk of death." Most of us are starting new T2DM patients on the newer hypoglycemic agents. I would like to think that the change wasn't because they were newer and more expensive, but because they are truly better and associated with better outcomes compared to sulfonylureas (there is some data to support this).

Angiotensin II Blockade in Heart Failure:

Right now there is a big push, via pharmaceutical dinners and CMEs online sponsored by the pharmaceutical companies, to use angiotensin receptor blockers (ARB) in heart failure (HF) and hypertension. However, multiple ACE inhibitors have been proven beneficial in HF and are available in generic form, which are cheaper for patients and keep overall healthcare expenditures lower. ARBS have been proven equivalent, but not superior to, ACE inhibitors, but they are significantly more expensive. The pharmaceutical companies want us to ***assume*** that ARBS are better. (There's no money in advertising old generic meds.) We should ask the questions, "Are they better?" and "Where is the comparison data showing superiority?" and make no assumptions. Based on what we know, why would we use an equivalent drug that is more expensive for our patients? They are already taking multiple proven drugs, many of which aren't available in generic formulation. Healthcare expenses are already off the charts, and there is always talk about cutting reimbursement to physicians. Why would we aggravate that problem? It is our responsibility to deliver appropriate care in the most inexpensive manner possible—for our patients—and for the long term benefit of our healthcare system. We should just appreciate that ARBs, which offer equivalent benefits, give us another option for those intolerant to ACE inhibitors.

Digoxin in HF …all the wrong assumptions:

First it was *assumed* that since digoxin improved contractility of the ventricle, more was better for HF patients (we didn't know at that time that increased ionotrophy was also associated with increased SCD). A large study, the Digitalis Investigation Group [DIG] trial, using digoxin versus placebo to evaluate the long term benefits found that use was associated with decreased morbidity and hospitalization, but no decreased mortality (average doses were 0.25 to -.375 mg).[4] Perhaps it was overemphasis of this message (no decreased mortality) that lead to underutilization of digoxin. Possibly physicians were concerned about polypharmacy that is involved in treating HF patients aggressively, and therefore decided to eliminate digoxin, or maybe it was *assumed* that the morbidity benefit would be negligible once ACE inhibitors and beta-blockers were available for treatment of HF. One could even speculate that since digoxin is a low-cost medication, the lack of advertising may have played a role in forgetting the substantial non-mortality benefits—improvements in quality of life (reduced hospitalizations). For whatever reason, most physicians don't use digoxin as part of their treatment program for systolic HF. For sure, there is evidence

that physician prescribing patterns are influenced by more than evidence-base medicine.

A recent large post hoc analysis of the DIG trial involving 5,548 patients showed that digoxin in lower doses *does* decrease mortality in addition to morbidity, and also decreases cost for the management of HF (through its neuroendocrine effects)—POEM.[5] Digoxin levels above 1.0ng/mL were not associated with decreased mortality.

Unfortunately, information about a generic drug that decreases mortality and cost doesn't get a lot of press, whereas information about a drug that was found equivalent to another and is more expensive does (ARBs). I certainly hope that this new information (POEM) will contribute to the rehabilitation of digoxin in the treatment of HF. Just remember low dose is key and levels should be drawn periodically to make sure digoxin levels are < 0.9ng/mL.

Low dose aspirin and or Plavix for AF

The efficacy of anticoagulant therapy (warfarin) for primary prevention of stroke in non-valvular atrial fibrillation (AF) has been established—based on multiple studies (POEM). Stroke reduction with anti-platelet therapy (aspirin 325mg) has also been documented, but is not as effective as warfarin and is recommended for those intolerant or at too high a risk for anticoagulation (POEM). Low dose aspirin (81mg) and Plavix are other forms of excellent antiplatelet therapy effective in CAD. However, we cannot *assume* that they are just as effective in AF—no POEM yet.

Last but not least

During the last 2 decades, there have been major advances in evidence-based-medicine that can improve outcomes for patients with CV disease. The use of these therapies has improved over time, but it still remains sub-optimal. Guideline programs at the time of patient discharge from the hospital have improved physician compliance and patient adherence to these therapies, resulting in improved outcomes, but we still have a ways to go.[6] There is an unacceptable time lag between the publication of credible science that should change medical practice and its actual adoption by doctors (2 to 3 years). A current example of this is the V-HeFT II study published in the *N Engl Med J* in November of 2004. This is a study that showed a 43% mortality benefit on top of baseline treatment with ACE inhibitors, beta-blockers, aldosterone antagonists and digoxin (good compliance) in **black patients** with HF.[7] Most of our landmark evidence-based therapy trials have been completed in a mostly white population but have been applied uniformly to all populations. This new evidence is not even being applied to the black population, let alone being considered for the white population. This is at a time when it is harder and harder to prove a benefit of a new treatment modality vs placebo due to numerous background beneficial treatments. The evidence of benefit here is impressive. Why are we ignoring it?

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