THERAPEUTICS INITIATIVE
Evidence Based Drug Therapy

The limitations and potential hazards of using surrogate markers

Clinicians are often advised to use surrogate markers to help guide drug therapy. This typically occurs with guideline-based therapy for chronic conditions, such as type II diabetes mellitus[1] and cardiovascular disease.[2] The US Food and Drug Administration defines a surrogate as "a laboratory measurement or physical sign that is used in therapeutic trials as a substitute for a clinically meaningful end point that is a direct measure of how a patient feels, functions, or survives, and that is expected to predict the effect of therapy".[3] Common surrogate markers include glycated hemoglobin (HbA1c) for diabetes mellitus, low-density lipoprotein cholesterol (LDL-C) and blood pressure for cardiovascular disease, and bone mineral density (BMD) for osteoporosis.

Surrogate markers can lead to misuse of scarce healthcare resources if a decision to initiate treatment is based on a "threshold" level of the surrogate marker without clinical relevance. Once drug therapy is started, surrogate markers are often used to monitor drug effectiveness and modify pharmacotherapy. We assume that the surrogate marker tells us whether or not drug therapy is reducing risks of morbidity or mortality.

This approach can be hazardous as shown in the examples below.

This Letter suggests an approach to the use of surrogate markers. It also considers the utility of treating to surrogate marker "targets" and the use of surrogates in risk prediction scores. When using surrogates to make recommendations for individual patients, clinicians should ask **FOUR** important questions:

1. Does "worsening" of a surrogate marker reliably indicate an increased risk of morbidity and mortality?

Using total cholesterol (TC) as an example, despite the widespread view that elevated TC is a risk factor for death, a number of studies have found that elevated TC is either associated with decreased mortality or not associated with mortality.[4-7] Thus TC is not a reliable marker for increased risk.

Lesson: A worsening surrogate marker does **not** always indicate increasing risk of morbidity and mortality.
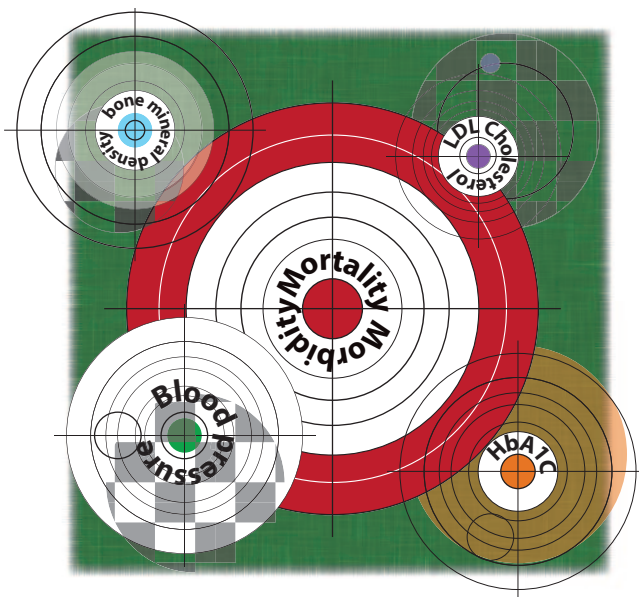
2. Does "improving" a specific surrogate marker lead to less morbidity and mortality?

There are numerous examples where improving a surrogate marker is associated with harm as opposed to benefit. A few of these are as follows. Torcetrapib substantially reduced LDL-C and substantially increased high-density lipoprotein cholesterol (HDL-C), yet it increased mortality and cardiovascular morbidity.[8] Rosiglitazone lowered HbA1c in Type II diabetes but increased the incidence of myocardial infarction.[9,10] Fluoride increased BMD, but increased the incidence of fractures.[11] Erythropoiesis-stimulating agents (e.g. darbepoetin) increased hemoglobin levels in chronic kidney disease patients but increased stroke and vascular access thrombosis.[12] Furthermore, the magnitude of change to a surrogate marker does not necessarily predict the magnitude of clinical benefit. In the largest statin trial, the patient group achieving the most reduction in LDL-C had the same relative benefit (RR 0.79) as the group with the least reduction (RR 0.78).[13]

Lesson: "Improvement" of popular surrogate markers due to drug therapy failed to predict better health outcomes in these examples. Using drug therapy to "improve" surrogate markers may be harmful, not helpful. Once such "contrary" evidence exists for a particular surrogate, clinicians should question its application in other settings. Understanding this can free both the clinician and patient from chasing numbers at the expense of the patient's health.

3. Do benefits of using surrogate markers as targets for drug therapy outweigh the harms?

Clinicians are frequently advised in guidelines to adjust drug treatment to achieve surrogate outcome targets (e.g. blood pressure, LDL-C, or HbA1c). The scientific way to test whether "better" surrogate targets are indeed better for patients is to randomize patients to groups with the intent to achieve different surrogate marker targets and measure clinical outcomes. For LDL-C targets, this approach has never been tested in a randomized controlled trial (RCT).[14] RCTs comparing the benefits of lower blood pressure targets (<135/85 vs. standard <140-160/90) have **not** shown that the benefits of attempting to achieve lower blood pressure targets outweigh the harms.[15,16] A new US blood pressure guideline developed according to the Institute of Medicine's recommendations to avoid conflicts of interest recognized this evidence by revising "target" systolic BP upwards in 2014.[17] In type 2 diabetes, the ACCORD trial demonstrated that attempting to achieve a lower HbA1C target (<6.0%), as compared to a standard target (7.0-7.9%) increased mortality and did not significantly decrease cardiovascular adverse events.[18] The ADVANCE[19] and VADT[20] trials also demonstrated disadvantages to the lower surrogate targets, also leading to changes in the relevant guidelines.

Lesson: Aiming for surrogate targets that are either unproven, or have been proven harmful, is not consistent with evidence-based principles.

References

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4. Is it useful to employ surrogate marker values in risk prediction tools?

Some clinicians regularly employ risk prediction tools (e.g. Reynolds Risk Score[21]) to estimate or predict the risk of morbidity and mortality in an individual patient. Risk prediction tools include surrogate markers to calculate risk estimates in individuals. There is increasing concern that such prediction tools cannot even predict risk accurately for a population, let alone for an individual.[22, 23] When a surrogate marker is not a reliable predictor of risk, this problem should not be surprising.

Lesson: When there is evidence that a "worsening" surrogate marker does not reliably predict risk, using risk prediction tools that incorporate the surrogate marker is potentially misleading.

Conclusion

• Most commonly used surrogate markers have not been proven to be consistently predictive of morbidity or mortality risk thus their use in risk calculators is questionable.

• Relying on surrogate markers to assess effectiveness of drug therapy has not been proven to yield clinically meaningful benefits and there are important examples where that strategy was harmful.

• **Avoid chasing surrogate targets (e.g. LDL-C targets) that have not been proven to have a net health benefit.**

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