
How can clinical trialists serve the needs of clinicians and patients more effectively?

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DAVID KENT

INDIVIDUALISING TREATMENT DECISIONS FOR ACUTE VASCULAR SYNDROMES
15.15 – 15.35



BIOGRAPHY

Dr David Kent graduated from McGill University Faculty of Medicine in Montreal. After his medical internship, he was Medical Director at the maximum security prison in Walpole, Massachusetts, and then Head of Office for Médecins Sans Frontières in Central Bosnia during the war in 1994. He completed his internal medicine residency/chief residency at The Cambridge Hospital/Harvard Medical School, and was a Robert Wood Johnson Clinical Scholar at the University of Michigan, where he received his MSc in Clinical Research Design and Statistical Analysis. He is currently a practicing general internist; an Assistant Professor of Medicine at Tufts-New England Medical Center/Tufts University School of Medicine, Boston; and an Assistant Professor of Clinical Research at The Sackler School for Biomedical Sciences, Tufts University, where he is Associate Director of Clinical Research Training Programs. Dr. Kent's major research interest is in the development of predictive models for cardiovascular disease and stroke, and their application to clinical trials.

ABSTRACT

Average results of clinical trials do not apply to all patients in the trial, and sometimes trial results may be driven by a relatively small group of influential (typically high-risk) individuals. In trials testing interventions in acute myocardial infarction most of the mortality outcomes occur in patients with multiple high-risk features that are identifiable before treatment. Using easily obtainable variables to form a risk score, it can be shown that patients in the highest risk quartile have a mortality rate that is typically 10-fold to 20-fold the rate found in the lowest-risk quartile. With such outcome-risk heterogeneity, risk-benefit trade-offs for treatments, such as primary percutaneous coronary interventions or thrombolytic therapy, differ substantially between risk subgroups, and in predictable ways. Yet these subgroups would not be identified using conventional "one-variable-at-a-time" subgroup analysis.

Similar outcome-risk/treatment-benefit heterogeneity is found in trials testing interventions in acute coronary syndromes more generally. In acute ischemic stroke, the benefits of thrombolytic therapy do not appear to be modified by estimated outcome risk, since the major predictors of outcome (for example, stroke severity) are also the major predictors of thrombolytic-related intracerebral hemorrhage — the main treatment-related harm. However, several factors seem to alter a patient's risk-benefit profile for thrombolytic therapy, such as time-to-treatment, prior stroke, blood pressure and sex. Taken together as a "treatment-favorability score", these factors potentially identify large subgroups of patients for whom the benefits clearly outweigh the harms, and other large subgroups for whom the harms clearly outweigh the benefits. Much as for acute coronary syndromes, these patient subgroups cannot be identified efficiently on the basis of one variable in isolation (such as time-to-therapy). However, unlike acute coronary syndromes, because these treatment-modifying factors were initially identified by "one-variable-at-a-time" subgrouping, such a "treatment-favorability score" is prone to over-fitting, and needs to be validated on independent clinical trial data.

While stratification by predicted outcome risk should be routinely performed in clinical trials with significant outcome-risk variation (i.e. in almost all cases), substantial heterogeneity of treatment benefit which is not directly related to identified outcome-risk will typically require a redundancy of trials to validate.

RELEVANT COMPETING INTERESTS

None declared

CONTACT DETAILS

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