INVITED COMMENTARY

CREST: The Twilight Zone Between (Mis)Interpretation and Deception

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What is the main message of Parakesvas and co-authors almost three years after publication of the “carotid revascularization endarterectomy versus stent trial” (CREST) main results? Was CREST a bad trial? Without hesitation, the answer should be “No”. CREST was designed in the late 1990s and started in 2000. At the time, there had been no adequate randomized comparison of carotid endarterectomy (CEA) and protected carotid angioplasty (CAS). The reason for CREST was self-evident: compare protected CAS and CEA in low-surgical-risk but symptomatic patients. It was the first trial implementing a lead-in-phase to guide interventionalist experience. CREST added substantially to the body of data comparing CEA with CAS, with the lowest death/stroke rates ever achieved in a randomized trial on carotid revascularization independent of indicative symptoms and type of intervention. So far so good, but where did it go wrong?

CREST was set-up to randomize symptomatic patients, but inclusion of asymptomatics was necessary to maintain enrollment. Although this is not a flaw per se, publicity of main results uncritically on differentiation between asymptomatics and symptomatic patients is a serious FLAW! CREST data were initially presented as showing that there were no differences in outcomes between the two procedures. The primary endpoint which included death stroke and myocardial infarction (MI) within 30 days was 4.5% for CEA and 5.2% for stenting (NS), leading the interventionists to claim equivalence of the two procedures. Subsequent “subgroup” analyses showed that CAS was associated with higher stroke and death rates in symptomatic patients, females, and patients >65 years.

By that time, the general public opinion already had been influenced and molded, and CREST and subsequent guidelines were used to “promote wider use of CAS in standard and low risk symptomatic patients”. Headlines in national newspapers concluded that “CAS and CEA were equally as safe and effective in terms of stroke prevention”. This statement was factually incorrect because CREST, as in all trials on CAS versus CEA, showed that CAS was associated with a significantly higher risk (almost twofold excess) of procedural stroke. Uncritical interpretation of the CREST data (and initially incompletely reported data) could fatally alter the opinion of the innocent physician. Accordingly, the reader should especially consider what CREST (and the other trials) did NOT tell you. The American Heart Association (AHA) guidelines undoubtedly are the cornerstone for practice worldwide. Not including any reference to ICSS (still the largest-ever randomized trial in symptomatic patients comparing CEA with CAS) in 2011 AHA guidelines received fierce criticism. Furie wrongly suggested that data were not available to the review group at that time. In reality, ICSS data were released (both on conference and ahead of print) before CREST! The complete omission of the ICSS trial by the AHA is still inexplicable. Several months later, in a revised version of the guidelines, ICSS was included, but despite this, the recommendations were identical to the first AHA guidelines! This uncritical and unbalanced positioning in selective data implementation did harm to the international credibility of the AHA. Notwithstanding the overall responsibility of the primary investigators for reporting balanced conclusions, merely the role of editors of leading journals, guideline committees, and international newspapers, should be denounced to prevent the switch from incomplete data reporting and misinterpretation into deception.

CREST initially concluded that “peri-operative MI was independently associated with increased future mortality and remained an important consideration in choosing the mode of carotid revascularization or medical therapy”. It was long assumed that the excess mortality in patients with procedural MI was largely attributable to deaths after CEA. However, it turned out to be the opposite. A greater proportion of late deaths was observed in CAS patients who had suffered a periprocedural MI. Moreover, CREST recently showed that stroke after carotid intervention was independently associated with a near threefold increase in future mortality. This led Wesley Moore, PI of the CREST trial, to state that: “The thing we learned was that the simple addition of death, stroke, and MI represents a design error!” The most important priority in any carotid intervention trial should be the prevention of stroke, and not to divert attention by risk of periprocedural MI. In essence, all primary events are important but not of equal consequence.

In conclusion, CREST’s initial report and claims of equivalence of the two therapeutic procedures in both the short and long term were unjustified. CREST, as with any other RCT comparing CEA with CAS, in fact showed us significantly higher stroke and death rate associated with CAS. Or, in the words of Wesley Moore “It should now be apparent that
the current technique employed for carotid artery stenting is not competitive with endarterectomy”.

REFERENCES