

Statement of Consensus on Cognitive Difficulties Following Coronary Artery Bypass Surgery

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This Statement addresses three questions:

Question 1

Is there a broad consensus among experts that cognitive decline after coronary artery bypass graft surgery exists ?

Question 2

How should cognitive decline be assessed in studies designed to evaluate the impact of coronary artery bypass surgery?

To answer these first two questions, the Panel has based its views on the following:

- a) Many studies have documented that cardiac surgery leads to more serious consequences in a small but significant proportion of patients. This includes death through neurological consequences, non-fatal stroke, transient ischaemic attacks (TIAs), coma or stupor (Mathew et al, 2003; Roach et al, 1996; Harrison, 2000; SP Newman & Harrison 2002; The American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2004). Patients who survive these consequences are subject to significantly increased health care costs.
- b) A large number of studies that have demonstrated cognitive decline after coronary artery bypass graft (CABG) surgery and related procedures in contrasts

to the small number of studies that have failed to find a decline. The major difference between these studies is in the patient groups studied, the tools used to assess cognitive function and the methods of analysis used. Where the studies are appropriately designed and the tools of measurement appropriate and appropriately analyzed, there is a consistent finding that cognitive function is impaired.

- c) 3. Formal neuropsychological testing prior to and at various times after surgery provides a sensitive measure of cognitive function and has revealed more subtle deficits in 20 to 70% of patients undergoing cardiac surgery (The American College of Cardiology/American Heart Association Task Force on Practice Guidelines 2004). For some patients these changes are transient with assessments in the days after surgery yielding the highest number of patients with deficits. In some patients these difficulties have been shown to persist (See e.g, Stroobant 2005; MF Newman et al 2001). It is possible that in some patients the longer term changes are overwhelmed by the effects of aging and the cerebrovascular disease (Stygall et al 2003; McKhann et al 2005).
- d) Neuropsychological assessment has also been shown to be able to demonstrate differences in patients according to their biological characteristics (e.g. Endocab - Mathew et al 2003) their postoperative clinical characteristics (e.g. postoperative atrial fibrillation - Stanley et al 2002) and to be associated with aspects of the surgical or anesthetic protocols (e.g. postoperative hyperthermia - Grocott et al 2002);
- e) The clearest evidence for the impact of CABG on the brain and its possible amelioration come from randomized controlled trials that have contrasted the impact of different surgical or anesthetic procedures on neuropsychological outcome. Evidence of a difference as a result of these types of interventions attests to the fact that CABG surgery can have an impact and also in the case of positive findings, a differential impact on the brain. Examples of these studies include evidence that the pH management by alpha-stat results in less neuropsychological disturbance in comparison to pH-Stat (Patel et al 1996 ; Murkin et al 1995) ; the improved neuropsychological outcome with the use of arterial line filters (Pugsley et al 1994), suggestion of advantage using leucocyte filtration (Whitaker et al 2004), impact of neuroprotective pharmacologic agents (Arrowsmith et al 2001).
- f) Underpinning the findings of the neuropsychological impact of cardiac surgery is the evidence from:
 - i) Magnetic resonance imaging (MRI) studies which have shown that in a proportion of patients new lesions appear post CABG (Toner et al 1994; Moody et al 1995), that MRI abnormalities are clearly seen in patients in the hours post CABG surgery (Harris et al 1993) and that a relationship between MRI findings and neurocognitive deficits has been documented (see Bendszus et al 2002)
 - ii) Pathological evidence of Small Capillary Arteriolar Dilatations in animals and humans post CABG (Moody et al 1990).

- iii) Animal research that has demonstrated the differential impact of surgical manipulations and the neuroprotective impact of pharmacological interventions on animals undergoing CABG surgery. (See e.g. Ma et al 2003)
- g) The putative causes of the cognitive deterioration following coronary artery bypass surgery include the risk of atheromatous emboli, the risks of air bubbles and thrombotic emboli, the systemic inflammatory response and disturbances of cerebral perfusion. Dominant amongst these is the occurrence of microemboli the panel consider it important that some studies have demonstrated that the number of microemboli delivered during CPB is correlated with the postoperative neurocognitive decline seen immediately and 8 weeks after CPB.
- h) Changes in surgical practice to reduce embolic load and so to limit potential for cerebral injury, have been based in part on studies where the primary outcome has been post surgery cognitive loss.
- i) There is some evidence to suggest that these cognitive difficulties are associated with increased hospital stay and poorer quality of life
- j) The panel notes that the AHA / ACC Guidelines 2004 include cognitive loss into their Type II neurological injury category emphasizing, from the perspective of a senior specialist body in the USA, the clinical relevance of this neuropsychological domain as one adverse consequence of cardiac surgery.

Question 3

Is there an additional global assessment to parallel the neuropsychological assessment of change following cardiac surgery. The panel considered a number of possible global assessments.

- a) Quality of Life

The difficulty proposing a measure, is that the patients are significantly debilitated prior to their surgery that changes in quality of life are overwhelmed by the reduction in symptoms post surgery. In addition changes post CABS in quality of life are not always realized in the short term.

- b) Self reports of cognitive change

A number of studies have been performed in this area and all have demonstrated that self reports of cognition are driven by mood and in particular depression (SP Newman et al 1989; Vingerhoets et al 1995; Khatri et al 1999)

- c) General measures of mental state

Measures such as the Mini Mental State Exam have been used in this area and generally shown to be insensitive. They are in the main tests of

screening for dementia and do not have the sensitivity required when compared to neuropsychological assessment.

Conclusion.

The panel considers:

1. That cognitive decline post coronary artery bypass surgery is an entity that exists.
2. That it best assessed by an appropriate battery of neuropsychological tests.
3. That it is a problem worthy of alleviating by interventions to reduce the risk and protect the brain.
4. That neuropsychological assessment provides an appropriate, sensitive and valuable measure to assess the impact of different interventions to protect the brain.
5. That neuropsychological change is different from neurological injury and constitutes a primary outcome measure in its own right.
6. That the assessment of cognition through neuropsychological assessment should not be diluted by measures of a different type where there is no good evidence for change following cardiac surgery.
7. That a search for an additional global outcome to parallel the neuropsychological assessment will not yield a satisfactory measure that will be sensitive nor be sufficiently specific in studies of the effects of cardiac surgery on the brain.
8. That the ideal time for the assessment of the impact of coronary artery bypass graft surgery is between 6 to 12 weeks post surgery (See also Murkin et al 1995).

References

ACC/AHA 2004 guideline update for coronary artery bypass graft surgery: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Update the 1999 Guidelines for Coronary Artery Bypass Graft Surgery). 2004;100:e340-437.

Arrowsmith JE, Harrison MJG, Newman SP, Stygall J, Timberlake N, Pugsley, WB. Neuroprotection of the brain during cardiopulmonary bypass. A randomised trial of remacemide during coronary artery bypass in 171 patients. Stroke. 1998; 29: 2357-2362.

Bendszus M, Reents W, Franke D et al. Brain damage after coronary artery bypass grafting. *Arch Neurol.* 2002;59:1090-1095.

Grocott HP, Mackensen GB, Grigore AM. Postoperative hyperthermia is associated with cognitive dysfunction after coronary artery bypass graft surgery. *Stroke.* 2002;33:537-41.

Harris DN, Bailey SM, Smith PL. et al. Brain swelling in first hour after coronary artery bypass surgery. *Lancet.* 1993; 342: 586-587.

Harrison MJG. Neurological complications of cardiac surgery. In: Newman SP, Harrison MJG, editors. *The Brain and Cardiac Surgery.* Amsterdam: Harwood Academic Publishers: 2000, p.21-50.

Khatri P, Babyak M, Clancy C et al. Perception of cognitive function in older adults following coronary artery bypass surgery. *Health Psychology.* 1999;18:301-306

Ma D, Yang H, Lynch J, Franks NP, Maze M, Grocott HP. Xenon attenuates cardiopulmonary bypass-induced neurologic and neurocognitive dysfunction in the rat. *Anesthesiology.* 2003 Mar;98(3):690-8

Mathew JP, Grocott HP, Phillips-Bute B, et al. Lower endotoxin immunity predicts increased cognitive dysfunction in elderly patients after cardiac surgery. *Stroke.* 2003;34:508-513.

McKhann GM, Grega MA, Borowicz LM Jr. et al. Is there cognitive decline 1 year after CABG? Comparison with surgical and nonsurgical controls. *Neurology.* 2005; 65:991-999

Moody DM, Bell MA, Challa VR et al. Brain microemboli during cardiac surgery or aortography. *Ann Neurol.* 1990; 28:477-486.

Moody DM, Brown WR, Challa VR et al. Brain microemboli associated with cardiopulmonary bypass: A histologic and magnetic resonance imaging study. *Ann Thorac Surg.* 1995; 59:1304-1307.

Murkin JM, Newman SP, Stump DA, Blumenthal JA. Statement of consensus on assessment of neurobehavioral outcomes after cardiac surgery. *Annals of Thoracic Surgery.* 1995; 59: 1289-95.

Murkin JM, Martzke JS, Buchan AM et al. A randomized study of the influence of perfusion technique and pH management strategy in 316 patients undergoing coronary artery bypass surgery. II. Neurologic and cognitive outcomes. *J. Thorac Cardiovasc Surg.* 1995;110:349-362.

Newman MF, Kirchner JL, Phillips-Bute B, et al. Longitudinal assessment of neurocognitive function after coronary-artery bypass surgery. *New England Journal of Medicine.* 2001; 344:395-402.

Newman S, Klinger L, Venn G et al. Subjective reports of cognition in relation to assessed cognitive performance following coronary artery bypass surgery. *Journal of Psychosomatic Research* 1989; 33: 227-233.

Newman SP, Harrison MJG. Coronary-artery bypass and the brain: persisting concerns. *Lancet Neurology* 2002;1:119-125.

Patel RL, Turtle MR, Chambers DJ et al. Alpha-stat acid-base regulation during cardiopulmonary bypass improves neuro-psychologic outcome in patients undergoing coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* 1996; 111:1267-1279.

Roach GW, Kanchuger M, Mangano CM, et al. Adverse cerebral outcomes after coronary bypass surgery. *New England Journal of Medicine.* 1996;335:1857-1862

Stanley TO, Mackensen GB, Grocott HP, et al. The impact of postoperative atrial fibrillation on neurocognitive outcome after coronary artery bypass graft surgery. *Anesth Analg.* 2002;94:290-5.

Stroobant N, Van Nooten G, Van Belleghem Y, Vingerhoets G, Relation between neurocognitive impairment, embolic load, and cerebrovascular reactivity following on- and off-pump coronary artery bypass grafting. *Chest.* 2005;127:1967-1976.

Stygall J, Newman SP, Fitzgerald G et al. Cognitive change 5 years after coronary artery bypass surgery. *Health Psychology.* 2003; 22: 579-586

Toner I, Peden CJ, Hamid SK et al. Magnetic resonance imaging and neuropsychological changes after coronary artery bypass graft surgery: Preliminary findings. *Journal of Neurosurgical Anesthesiology.* 1994;6:163-169.

Vingerhoets G, De Soete G, Jannes C. Subjective complaints versus neuropsychological test performance after cardiopulmonary bypass. *Journal of Psychosomatic Research.* 1995; 39:843-853.

Whitaker DC, Newman SP, Stygall J et al. The effect of leucocyte-depleting arterial line filters on cerebral microemboli and neuropsychological outcome following coronary artery bypass surgery. *European Journal of Cardio-thoracic Surgery.* 2004; 25:267-274.