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TITLE: **Off-pump versus on-pump coronary artery bypass grafting for ischemic heart disease**

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CALIFORNIA TECHNOLOGY ASSESSMENT FORUM®

OFF-PUMP VERSUS ON-PUMP CORONARY ARTERY BYPASS GRAFTING FOR ISCHEMIC HEART DISEASE

A Technology Assessment

INTRODUCTION

The California Technology Assessment Forum (CTAF) was asked to update its assessment of the evidence for the use of off-pump coronary artery bypass grafting (CABG) surgery. The Forum reviewed off-pump CABG on February 13, 2002 and found that it met criteria at that time. However, recent publication of the results of the Randomized On/Off Bypass (ROOBY) trial raised concerns about the original assessment. The following is an update of the earlier technology assessment and focuses primarily on Technology Assessment Criterion 4: is off-pump CABG as beneficial as the established alternative, on-pump CABG using cardiopulmonary bypass.

BACKGROUND

In 2006 approximately 425,000 people died from coronary heart disease in the United States: one of every six deaths.[1] The American Heart Association estimates that 1,450,000 Americans will have a heart attack in 2010. Clinical trials have demonstrated that CABG, which uses arteries and/or veins to route blood around narrowed or blocked coronary arteries, can increase patient survival compared with medical therapy.[2] The standard approach to CABG is to use cardiopulmonary bypass to circulate blood throughout the body, thus allowing the heart to be stopped so that bypasses can safely be performed. Approximately 448,000 CABG procedures were performed in 2006 with in-hospital mortality falling to 3.5% from 4.3% approximately ten years earlier in spite of an increase in the preoperative surgical risk in the patients undergoing surgery.[1]

The earliest CABG procedures were done on a beating heart, including Sabiston's original aortocornary bypass in 1962.[3] However, the advent of cardiopulmonary bypass and cardioplegic arrest through a full sternotomy allowed for full access to the coronary arteries in a quiescent and bloodless field, which made the procedure technically much easier. Thus, "beating heart" or "off-pump" coronary artery bypass grafting was abandoned for some time.

In the early 1980's, several investigators revived interest in off-pump CABG.[4, 5] The primary benefit ascribed to off-pump CABG was a reduction in the neurocognitive deficits thought to occur after cardiopulmonary bypass. These investigators and others suggested that off-pump procedures would avoid known adverse effects of cardiopulmonary bypass (increased inflammatory response, clotting, and microemboli), thus

potentially reducing patient morbidity and mortality. Subsequent improvements in cardiac retractor and stabilization systems allowed for exposure of all surfaces of the heart and made it technically possible to perform multi-vessel coronary bypass on the beating heart.[6, 7]

Off-pump coronary artery bypass grafting

Off-pump CABG is primarily performed using a standard median sternotomy incision. Surgeons use stabilizers to steady the heart and intracoronary shunts to permit continued myocardial perfusion during the construction of the distal anastomoses. Target artery immobilization is accomplished with proprietary stabilizing retractor systems offered by several manufacturers.[6-8]

There are many potential advantages of off-pump CABG over the on-pump procedure. Aortic cross clamping and cannulation for cardiopulmonary bypass increases the risk for bleeding and for embolization (platelet emboli, air emboli, atherosclerotic emboli). Key short-term patient outcomes related to these complications include the potential for death, strokes, heart attacks, renal failure, and a return to the operating room for bleeding. Avoiding the trauma of cardiopulmonary bypass may also shorten the length of the surgery and the post-operative recovery time resulting in shorter intensive care unit (ICU) stays and shorter hospitalizations. Intermediate term outcomes may include improved neurocognitive outcomes and quality of life through a reduction in microemboli to the brain.

However, off-pump CABG is a technically more demanding procedure than on-pump CABG. Constant heart motion, fluctuating hemodynamics during the manipulation of the heart, regional ischemia, and difficult access to the coronary arteries (particularly the left circumflex artery) all contribute to the potential for sub-optimal construction of the arterial anastomoses and may influence decision-making about the number of bypass grafts performed during surgery.[9, 10] Induced bradycardia and improvements in surgical devices for local tissue stabilization are attempts to minimize these difficulties. It is known that the completeness of revascularization correlates with long term survival. Thus, two important outcomes to assess when comparing off-pump to on-pump CABG are the number of grafts performed and the long-term patency of the grafts.

Overall the most important outcome to assess is long-term mortality as bypass surgery is primarily performed to reduce mortality from coronary artery disease. Ideally outcomes would be assessed over a five to ten year time-frame to adequately assess the durability of the anastomoses. Other essential long-term

outcomes include rates of myocardial infarction (MI), stroke, the need for repeat revascularization, cognitive function and quality of life.

TECHNOLOGY ASSESSMENT (TA)

TA Criterion 1: The technology must have final approval from the appropriate government regulatory bodies.

Off-pump CABG is a procedure and therefore is not regulated by the Food and Drug Administration (FDA). Several manufacturers have developed the specialized devices to perform off-pump CABG. These devices have received FDA clearance through the 510(k) process.

TA Criterion 1 is met.

TA Criterion 2: The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.

The Medline database, Cochrane clinical trials database, Cochrane reviews database and the Database of Abstracts of Reviews of Effects (DARE) were searched using the key words “coronary artery bypass, off-pump,” “beating heart,” “opcab,” “op-cab” and “octopus.” These were cross-referenced with the keyword “coronary artery bypass”. The search was performed for the period from 1966 through January 2010. The bibliographies of systematic reviews and key articles were manually searched for additional references. References were also solicited from the manufacturers and local experts. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. This review focuses on the essential patient oriented outcomes: death, myocardial infarctions, strokes, revascularization, bleeding requiring re-operation, renal injury requiring dialysis, cognitive function and quality of life. These outcomes are relatively uncommon and require time to observe. Given the prior CTAF assessment, the large number of randomized trials, the large number of prior meta-analyses, and the potential for selection and information bias in observational trials, this assessment includes only trials that randomized at least one hundred participants or followed participants for at least one year.

The search identified 2135 potentially relevant trials. After elimination of duplicate and non-relevant references, 197 articles were reviewed in full. A large number of randomized trials were excluded because of small size, limited follow-up, specialized patient populations, and lack of any of the essential clinical outcomes.[11-91] The remaining 51 references describe sixteen randomized trials in detail.[92-142] The characteristics of the trials are summarized in Table 1 below. Details that are relevant for the assessment of the quality of randomized trials are described in Table 2. The peri-operative outcomes are summarized in Table 3 and the intermediate outcomes are summarized in Table 4. No trials adequately described the five and ten year outcomes for patients.

The search also identified nineteen systematic reviews and meta-analyses comparing the results of off-pump to on-pump CABG.[9, 10, 143-159] Many of the small randomized trials excluded from this review are included in these meta-analyses, though the most recent only included ten trials in their meta-analysis.[146]

Level of Evidence: 1, 2, 3, 4, and 5.

TA Criterion 2 is met.

TA Criterion 3: The technology must improve net health outcomes.

As noted in the introduction, there is no question that off-pump CABG improves net health outcomes compared with no surgery in patients with indications for CABG. Approximately 20% of all CABG procedures in the United States are performed using the off-pump approach and there is a large body of observational evidence demonstrating outcomes that are close to those achieved by on-pump CABG.[153, 159-162] The primary question that remains open is whether the net health outcomes achieved by off-pump CABG are comparable to or indeed better than those achieved with on-pump CABG.

TA Criterion 3 is met.

TA Criterion 4: The technology must be as beneficial as any established alternatives.

The primary value of CABG is the reduction in mortality achieved with surgery when compared to medical therapy or percutaneous coronary interventions (PCI) such as angioplasty and the placement of coronary

artery stents. Thus, the most important outcome to assess is long-term mortality following CABG. A minimum of five years and ideally ten years would be required to fully assess the impact of off-pump CABG on mortality. One of the key benefits cited in favor of off-pump CABG is better neurocognitive function in patients following surgery, including a reduction in strokes. CABG also treats angina. Thus, the key outcomes focused on in this assessment include mortality, strokes, heart attacks, and neurocognitive function. Since few studies had more than one-year follow-up, we focused on outcomes through one year. Because of concerns that off-pump surgery may result in insufficient or poor quality revascularization, important secondary outcomes included the completeness of revascularization and the rate of repeat procedures for revascularization. Perioperative outcomes such as atrial fibrillation, bleeding, renal dysfunction, and reoperations are important, but primarily as reflected in overall mortality, strokes, and heart attacks as these are the clinical outcomes that matter most to patients.

Table 1 describes the characteristics of the randomized trials directly comparing off-pump to on-pump surgery. Most of the trials were performed in Europe, though Brazil, Japan, Canada, and the United States are represented. The average age of participants in the trials ranged from 59 to 67 years old and 10% to 34% were female with the exception of the ROOBY trial described in detail below. The trials randomized 5031 patients with the ROOBY trial contributing 44% of the patients. All but two of the trials were single center trials at centers with one or a few surgeons with special expertise in performing off-pump surgery. Essentially all trials excluded patients who required emergent surgery, had undergone prior bypass surgery, or who required additional surgery at the same time as the CABG such as cardiac valve surgery or repair of aortic aneurysms. The oldest patients, those with significant heart failure, and those with significant renal disease were also generally excluded from the trials. Thus the patient population is somewhat lower risk than the larger population of patients undergoing CABG and this is reflected in the overall good outcomes reported in the trials relative to national averages.

The criteria for the quality of the randomized trials are summarized in Table 2. All were randomized, but the method of randomization was often not described in detail, nor was the method of allocation concealment. Ideally the blind would not have been broken for the operating surgeons until the day of the operation and the study participants could have remained blinded throughout the trial. Information bias is less likely to play a major role in studies with hard outcomes like mortality and stroke as long as the outcome assessment was performed by someone blinded to treatment allocation. None of the studies described blinded evaluation and outcome adjudication for outcomes with some potential for subjectivity such as stroke and MI.

Physicians reading and scoring post-CABG angiograms were usually blinded, but this is not one of the key outcomes. In general, the studies were balanced after randomization, loss to follow-up was minimal and balanced, and the results were analyzed and presented as intention to treat.

The peri-operative outcomes through thirty days are summarized in Table 3. Among patients randomized to off-pump bypass, the surgeon elected to convert to an on-pump procedure in up to 22% of the surgeries[106], though several studies reported no conversions.[93, 95, 112, 113] It is unclear why there is such heterogeneity in conversion rates. The largest and most recent series reported a conversion rate of just over 12%.[132] The majority of the trials reporting the operative time, noted shorter operative times with the off-pump approach. However, several trials reported equivalent or shorter operative times with the on-pump procedure, including the largest and most recent trial.[132] In all studies, the average number of grafts performed was lower in surgeries performed off-pump, although the differences were small. For instance in the large ROOBY trial, patients in the off-pump group received an average of 2.9 grafts per surgery compared with 3.0 grafts for patients in the on-pump group ($p = 0.002$) and the off-pump group received significantly fewer grafts than planned prior to surgery ($p<0.001$).

In the earliest trials, the time spent in the ICU and hospital were shorter following off-pump surgery, but this has not been true in the more recent trials. In the ROOBY trial there were no significant differences in time in the ICU or hospital with a trend towards almost a half-day longer average hospitalization for patients in the off-pump group. Across the studies, there were no clear differences in peri-operative mortality, MI's, strokes, reoperations or renal failure requiring dialysis. As noted in prior meta-analyses[145, 148, 153, 159], there was a significant reduction in peri-operative atrial fibrillation, but this did not appear to result in shorter hospitalizations or fewer strokes.

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Table 1: **Description of Study Procedures and Participants**

Study Key authors Location	Years performed	N	Follow-up (years)	Age, yrs Sex, %F	%DM EF	Inclusion criteria	Exclusion criteria	Comment
Czerny 2001 Vienna, Austria	Before 2001	80	1.1	64 16	NR 0.64	≥ 2 vessels Normal EF Elective, low risk	Diffuse disease LVH	Single center
BHACAS 1 Angelini; Ascione Bristol, UK	1997-1998	200	2.0	62 20	20 80% > 0.50	≥ 1 vessel 1st CABG	EF<30%, recent MI COPD, CVA, Renal dz, circumflex dz	Single center
BHACAS 2 Angelini; Ascione Bristol, UK	1998-1999	201	1.2	63 16	31 77% >0.50	≥ 1 vessel 1st CABG	EF<30%, COPD, CVA, renal disease	Single center
OCTOPUS Van Dijk; Nathoe Utrecht, Netherlands	1998-2000	281	5.0	61 31	13 78% > 0.50	≥ 1 vessel 1st CABG	Emergency CABG. EF<30% Recent MI	Single center
Lee 2003 Honolulu, Hawaii	1999-2001	60	1.0	66 18	NR 0.55	≥ 1 vessel "Safe" for both procedures.	Creatinine ≥ 2.0 Re-operation	Single center, two surgeons
Muneretto 2003 Brescia, Italy	2000-2002	176	1.0	67 39	41 NR	≥ 2 vessels	Age > 75 years COPD, CVA, Renal dz, carotid dz.	Single center
Gerola 2004 Sao Paulo, Brazil	Before 2004	160	0.1	59 34	21 NR	≥ 1 vessel	Emergency CABG. Age > 70 years, EF < 35%, AIDS, circumflex disease	Single center
Khan 2004 London, UK	2000-2002	103	0.25	63 13	27 67% > 0.50	≥ 3 vessels 1st CABG	<30, > 80 years CAS > 70%, EF < 20%, recent CVA	Single center, two surgeons
Legare 2004 Karolak 2007 Halifax, Canada	1999-2003	300	3.8	63 20	33 86% > 0.50	≥ 1 vessel 1st CABG	Emergency CABG. EF<30%	Single center, six surgeons
SMART Puskas 2004 Atlanta, Georgia	2000-2001	197	1.0	62 23	31 49% > 0.45	≥ 1 vessel	Emergency CABG.	Single surgeon
PRAGUE-4 Widimsky; Straka 2004 Prague, Czech Rep.	2000-2002	400	1.0	63 19	28 0.58	≥ 1 vessel	Emergency CABG. Significant valvular disease.	Single center
JOCRI Kobayashi 5 centers Japan	2002-2004	147	0.1	60 15	60 0.56	≥ 2 vessels 1st CABG	> 70 years CAS, recent stroke	5 centers, 5 surgeons
Al Ruzzeh 2006, 2008 Middlesex, UK	Before 2006	168	0.5	63 17	21 68% > 0.50	≥ 2 vessels	Emergency CABG. EF<30%, renal failure	Single surgeon
Lingaas 2006 Oslo, Norway	Before 2005	120	1.0	65 22	17 0.72	≥ 1 vessel	EF<30% Renal failure	Single center, four surgeons
Motallebzadeh 2006, 2007 London, UK	2002-2004	212	0.5	65 11	24 48% > 0.50	1st CABG	Prior cardiac surgery, CAS>50%, recent MI, prior CVA, EF < 20%, renal failure	Single center
ROOBY Shroyer 2009 18 centers, USA	2002-2008	2203	1.0	63 0.6	43 59% > 0.54	Elective or urgent CABG. ≥ 1 vessel	Emergent surgery, Significant valvular disease, small target vessels	18 centers, 53 surgeons

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Table 2: **Quality of the Randomized Clinical Trials Comparing Off-pump to On-pump coronary artery bypass grafting**

Study	Randomization	Allocation concealment	Comparable groups at randomization	Loss to follow-up comparable?	Blinded outcome assessment	Patient blinding	ITT (lost to follow-up included?)
Czerny 2001 Vienna, Austria	NR	NR	Yes	NR	NR	NR	NR
BHACAS 1 Angelini; Ascione Bristol, UK	Yes	Yes	Yes	Yes	Yes	Yes	Yes
BHACAS 2 Angelini; Ascione Bristol, UK	Yes	Yes	Yes	Yes	Yes	Yes	Yes
OCTOPUS Van Dijk; Nathoe Utrecht, Netherlands	Yes	Yes	Yes	Yes	Yes	NR	NR
Lee 2003 Honolulu, Hawaii	NR	Yes	Yes	Yes	Yes	NR	Yes
Muneretto 2003 Brescia, Italy	NR	NR	Yes	Yes	NR	NR	Yes
Gerola 2004 Sao Paulo, Brazil	Yes	NR	Yes except prior MI 24 vs. 45, p=0.001	Yes	NR	NR	Yes
Khan 2004 London, UK	NR	NR	Yes except planned grafts greater in off-pump (3.6 vs. 3.2, p=0.003)	Yes	NR	NR	Yes
Legare 2004 Karolak 2007 Halifax, Canada	Yes	Yes	Yes	Yes	NR	NR	Yes
SMART Puskas 2004 Atlanta, Georgia	Yes	Yes	Yes, except fewer prior strokes in off-pump, 1 vs. 9, p=0.02	Yes, but high	Partial	Yes	Yes
PRAGUE-4 Widimsky; Straka 2004 Prague, Czech Rep.	Yes	Yes	Yes	No	NR	NR	Yes
JOCRI Kobayashi 5 centers Japan	Yes	NR	Yes	Yes	NR	NR	Yes
Al Ruzzeh 2006, 2008 Middlesex, UK	Yes	Yes	Yes	Yes	Yes	Yes	NR
Lingaas 2006 Oslo, Norway	Yes	NR	Yes	Yes	Partial	NR	Yes
Motallebzadeh 2006, 2007 London, UK	Yes	Yes	Yes	Yes	NR	NR	NR
ROOBY Shroyer 2009 18 centers, USA	Yes	Yes	Yes	Yes	Partial	NR	Yes

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Table 3: **Peri-operative and thirty day outcomes**

Study	Study group	N	Conversion to on pump (n, %)	Op time (minutes)	Mean number of grafts	ICU stay (days)	Hospital LOS (days)	Death (n)	Cardiac arrest (n)	MI (n)	Stroke (n)	Atrial fibrillation (n)	Re-operation for bleeding (n)	Renal failure requiring dialysis (n)
Czerny 2001	Off-pump	40	9 (22.5%)	178	2.6	1.2	13.5	0		0	0	5	1	
									NR					NR
Vienna, Austria	On-pump	40		254	3.1	2.0	12.6	0		0	0	7	2	
BHACAS 1	Off-pump	100	2 (2.0%)	177	2.3	1.1	6.3	0		1	0	11		
Angelini; Ascione									NR				NR	NR
Bristol, UK	On-pump	100		186	2.5	1.3	7.2	2		4	0	45		
BHACAS 2	Off-pump	100	0 (0%)		2.9			0		0	0	14		
Angelini; Ascione				NR		NR	NR		NR				NR	NR
Bristol, UK	On-pump	101			3.0			0		1	0	29		
OCTOPUS	Off-pump	142	5 (3.5%)	250	2.4	1.4	8.1	0		7	1	28		
Van Dijk; Nathoe									NR				NR	NR
Utrecht, Netherlands	On-pump	139		229	2.6	1.6	8.6	0		7	2	29		
Lee 2003	Off-pump	30	0 (0%)	246	3.1		5.0	1	1			7		
						NR				NR	NR		NR	NR
Honolulu, Hawaii	On-pump	30		246	3.6		6.0	0	0			12		
Muneretto 2003	Off-pump	88	8 (9.1%)		2.7	0.9	5.0	3	1	1	0	19		
				NR									NR	NR
Brescia, Italy	On-pump	88			2.8	1.85.0	7.0	2	0	2	2	31		
Gerola 2004	Off-pump	80	NR	190	1.8	2.3	7.6	1	0	3	0	7	0	
														NR
Sao Paulo, Brazil	On-pump	80		205	1.8	2.4	8.0	3	0	6	0	4	0	
Khan 2004	Off-pump	54	2 (3.7%)	238	3.1	1.0	7.0	0		1	0		0	
									NR			NR		NR
London, UK	On-pump	49		238	3.4	1.0	7.0	0		0	0		2	
Legare 2004	Off-pump	150	20 (13.3%)		2.8	0.9	5.0	2	0	4	2	38	2	
Karolak 2007				NR										NR
Halifax, Canada	On-pump	150			3.0	0.9	5.0	1	0	1	0	48	3	
SMART	Off-pump	100	1 (1.0%)		2.3		5.1	1		1	1	16	1	2
Puskas 2004				NR		NR			NR					
Atlanta, Georgia	On-pump	100			2.7		6.1	2		2	2	22	2	0
PRAGUE-4	Off-pump	208	31 (14.9%)			1.0	5.0	4		4	0	41		2
Widimsky; Straka 2004				NR	NR				NR				NR	
Prague, Czech Rep.	On-pump	192				1.0	5.0	2		3	2	44		2
JOCRI	Off-pump	81	0 (0%)	267	3.5	1.3		0	0	2	0	19		
Kobayashi							NR						NR	NR
5 centers Japan	On-pump	86		307	3.6	1.6		0	0	2	1	19		
Al Ruzzeh 2006, 2008	Off-pump	84	0 (0%)	179		1.4	10.0	1		1	2	28	3	2
					NR				NR					
Middlesex, UK	On-pump	84		222		2.3	10.0	0		1	1	22	2	5
Lingaas 2006	Off-pump	60	7 (11.7%)		2.6			1				18		
				NR		NR	NR		NR	NR	NR		NR	NR
Oslo, Norway	On-pump	60			2.8			1				20		
Motallebzadeh 2006,	Off-pump	108	0 (0%)					2			1			
2007				NR	NR	NR	NR		NR	NR		NR	NR	NR
	On-pump	104						1			4			
London, UK														
ROOBY	Off-pump	1104	137 (12.4%)	270	2.9	3.7	8.2	18	20		14		30	9
Shroyer 2009										NR		NR		
18 centers, USA	On-pump	1099		264	3.0	3.8	7.8	13	12		8		23	10

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Table 4: **Intermediate term / one year outcomes**

Study	Study group	N	Death (n, %)	Revascularization (n, %)	Patency (%)	MI (n, %))	Stroke (n, %))	Cognitive function	Quality of life
Czerny 2001	Off-pump	40	0 (0%)	3 (7.5%)	NR	0 (0%)	0 (0%)	NR	NR
Vienna, Austria	On-pump	40	0 (0%)	0 (0%)		0 (0%)	0 (0%)		
BHACAS 1 Angelini; Ascione	Off-pump	100	3 (3.0%)	3 (3.0%)	NR	2 (2.0%)	2 (2.0%)	NR	No difference at 3 years
Bristol, UK	On-pump	100	4 (4.0%)	3 (3.0%)		5 (5.0%)	3 (3.0%)		
BHACAS 2 Angelini; Ascione	Off-pump	100	1 (1%)	1 (1.0%)	NR	2 (2.0%)	1 (1.0%)	NR	No difference at 3 years
Bristol, UK	On-pump	101	3 (3.0%)	1 (1.0%)		3 (3.0%)	3 (3.0%)		
OCTOPUS Van Dijk; Nathoe	Off-pump	142	12 (8.5%)	11 (7.7%)	91%	7 (4.9%)	2 (1.4%)	No difference at 1 year	EuroQol: No difference at 1 year
Utrecht, Netherlands	On-pump	139	9 (6.5%)	7 (5.0%)	93%	9 (6.5%)	5 (3.6%)		
Lee 2003	Off-pump	30	1 (3.3%)	NR	NR	NR	0 (0%)	No difference at 1 year	NR
Honolulu, Hawaii	On-pump	30	0 (0%)				1 (3.3%)		
Muneretto 2003	Off-pump	88	4 (4.5%)	0 (0%)	NR	2 (2.3%)	0 (0%)	NR	NR
Brescia, Italy	On-pump	88	4 (4.5%)	0 (0%)		4 (4.5%)	2 (2.3%)		
Gerola 2004	Off-pump	80	1 (1.3%)	NR	NR	6 (7.5%)	0 (0%)	NR	NR
Sao Paulo, Brazil	On-pump	80	3 (3.8%)			3 (3.8%)	0 (0%)		
Khan 2004	Off-pump	54	0 (0%)	0 (0%)	88%	1 (1.9%)	0 (0%)	NR	NR
London, UK	On-pump	49	0 (0%)	0 (0%)	98%	0 (0%)	0 (0%)		
Legare 2004 Karolak 2007	Off-pump	150	10 (6.7%)	2 (1.3%)	NR	4 (2.7%)	2 (1.3%)	NR	No difference on 5 scales
Halifax, Canada	On-pump	150	5 (3.3%)	4 (2.7%)		1 (0.7%)	0 (0%)		
SMART Puskas 2004	Off-pump	100	4 (4.0%)	2 (2.0%)	94%	2 (2.0%)	2 (2.0%)	NR	SF36 and EuroQol: no difference
Atlanta, Georgia	On-pump	100	4 (4.0%)	1 (1.0%)	96%	3 (3.0%)	2 (2.0%)		
PRAGUE-4 Widimsky; Straka 2004	Off-pump	208	4 (1.9%)	NR	70%	4 (1.9%)	0 (0%)	NR	NR
Prague, Czech Repub.	On-pump	192	2 (1.0%)		74%	3 (1.6%)	2 (1.0%)		
JOCRI Kobayashi	Off-pump	81	0 (0%)	NR	NR	NR	NR	NR	NR
5 centers Japan	On-pump	86	0 (0%)						
Al Ruzzeh 2006, 2008	Off-pump	84	2 (2.4%)	NR	93%	NR	NR	Off pump better on 3 scales at 6 weeks; 2 at 6 months	Trend towards better off pump
Middlesex, UK	On-pump	84	3 (3.6%)		94%				
Lingaas 2006	Off-pump	60	1 (1.7%)	7 (11.7%)	85%	NR	NR	NR	NR
Oslo, Norway	On-pump	60	1 (1.7%)	3 (5.0%)	90%				
Motallebzadeh 2006, 2007	Off-pump	108	3 (2.8%)	NR	NR	NR	1 (0.9%)	No difference at 6 months	SF36: No difference at 6 or 18 months
London, UK	On-pump	104	4 (3.8%)				5 (4.8%)		
ROOBY Shroyer 2009	Off-pump	1104	43 (4.1%)	49 (4.6%)	83%	41 (3.7%)	14 (1.3%)	Both groups improved; 1/11 significant in favor of off pump	NR
18 centers, USA	On-pump	1099	30 (2.9%)	36 (3.4%)	88%	35 (3.2%)	8 (0.7%)		

The more important outcomes are summarized in Table 4. Ideally there would be longer follow-up, but one year is sufficient to evaluate the neurocognitive and quality of life outcomes. The trends in the other major cardiovascular events serve as intermediate outcomes for event rates expected with longer follow-up. If the events are pooled across studies, 3.5% of patients randomized to off-pump groups died compared with 2.9% of patients randomized to on-pump surgery. There was a trend towards increased mortality in patients randomized to off-pump CABG (RR 1.29, 95% CI 0.94 to 1.76, Figure 1). There was little unexplained heterogeneity in this meta-analysis (I^2 = 0%, p= 0.94). There was a trend towards fewer strokes in the off-pump group (Figure 2, RR 0.78, 95% CI 0.47 to 1.30), but more revascularizations (Figure 3, RR 1.36, 95% CI 0.96 to 1.91). There were no differences in the rate of MI (Figure 4). If all four major outcomes are combined, there was a trend towards more events in the off-pump group (Figure 5, RR 1.15, 95% CI 0.97 to 1.36), but it did not achieve statistical significance. In the studies that evaluated graft patency, the percentage of grafts that were open was consistently lower in the off-pump group, particularly when saphenous vein grafts were used. The combination of less complete revascularization and increased graft failure may explain the trend towards greater mortality in the off-pump group.

Early reports suggested that neurocognitive function was better following off-pump surgery and was one of the major motivations to perform large randomized trials.[23, 138] However, as seen in Table 4, most trials found no difference in neurocognitive outcomes at one year and in general both groups scored higher on the neurocognitive scales than they did at baseline. Several studies found differences in the first few months following surgery, but those differences were no longer clinically significant by one year. Two recent meta-analyses of the randomized trials focused exclusively on cognitive function.[147, 157] Both concluded that there were not significant neurocognitive benefits when comparing off-pump to on-pump CABG. Similarly, almost all trials evaluating quality of life outcomes reported equivalent outcomes in both groups.

Figure 1: Total mortality in the randomized trials of off-pump CABG with at least one year follow-up

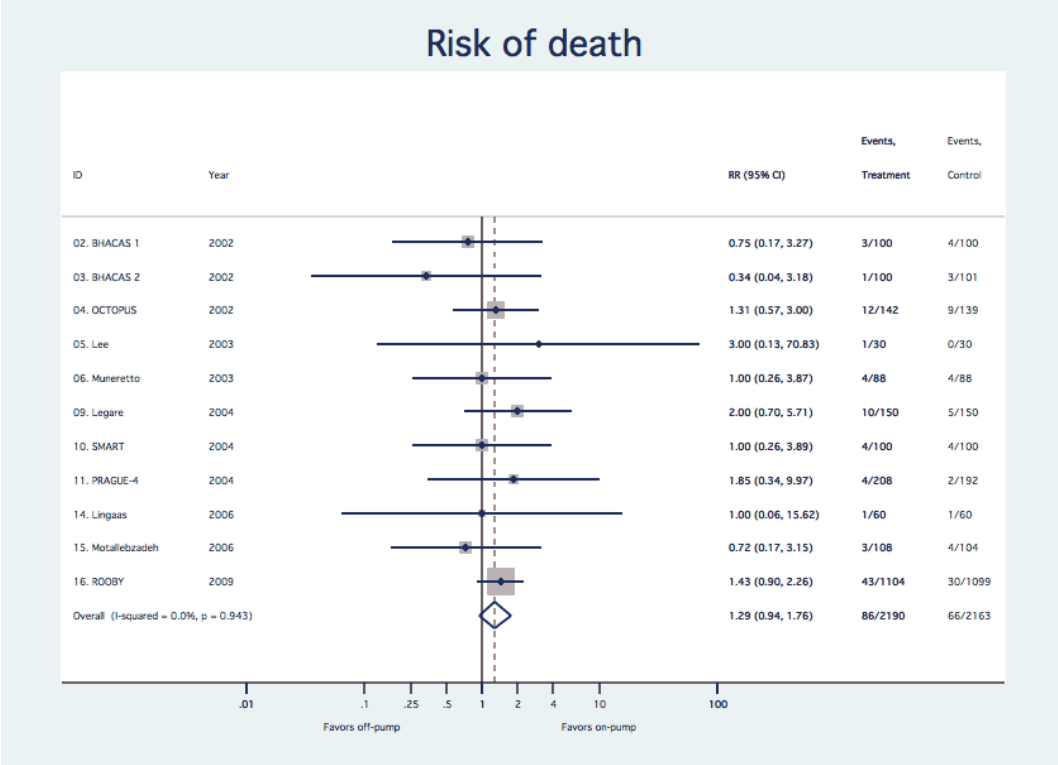


Figure 2: Strokes in the randomized trials of off-pump CABG with at least one year follow-up

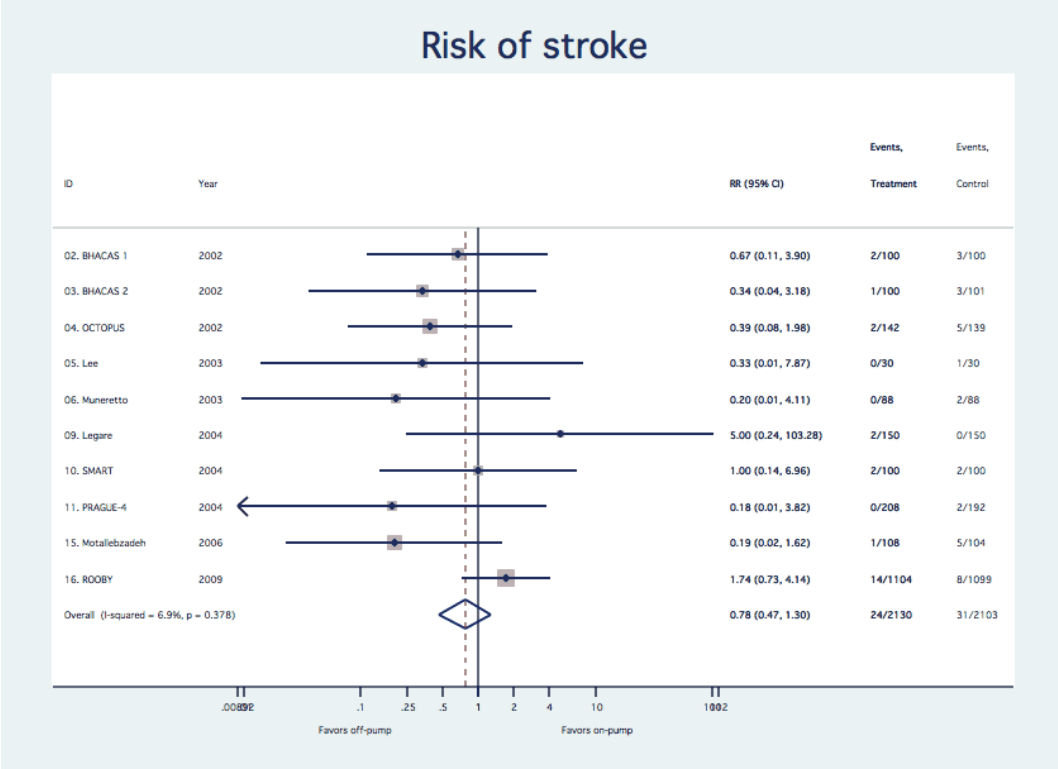


Figure 3: Revascularization in the randomized trials of off-pump CABG with at least one year follow-up

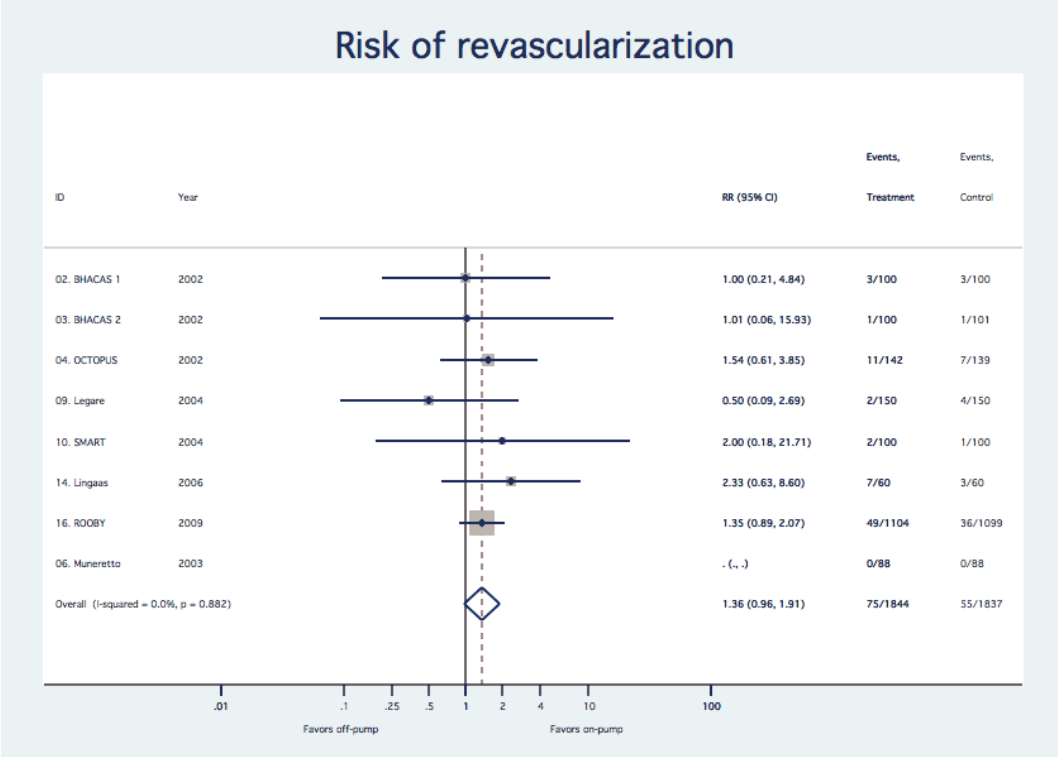


Figure 4: MIs in the randomized trials of off-pump CABG with at least one year follow-up

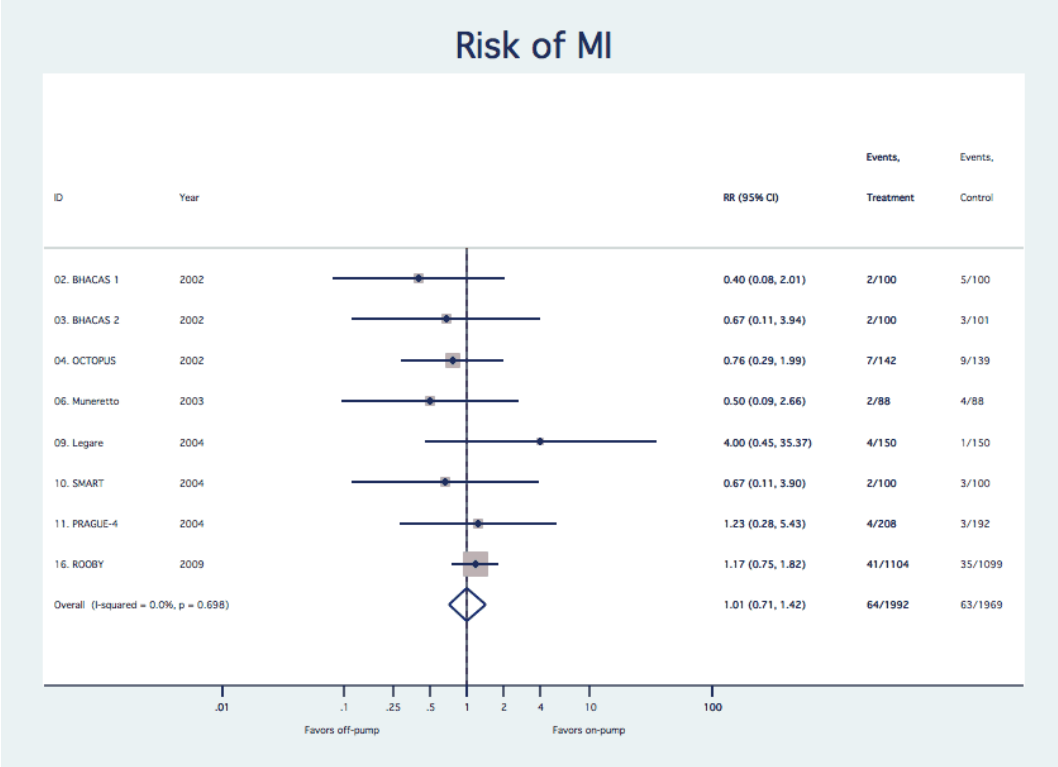
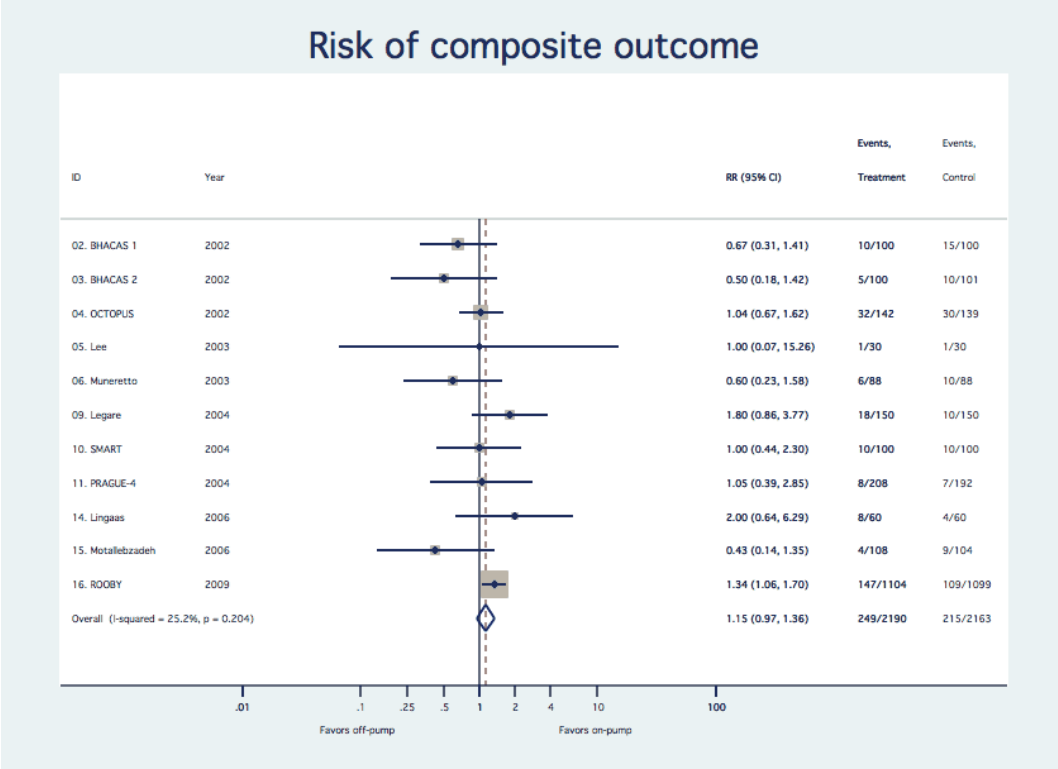


Figure 5: Total events in the randomized trials of off-pump CABG with at least one year follow-up



The Veterans Affairs (VA) ROOBY study[132] is by far the largest and best quality randomized trial directly comparing on-pump to off-pump CABG. It is also one of the few studies done in the United States and is the most recent study, thus it more closely represents current surgical techniques. Therefore, it will be described in greater detail below.

To be eligible, participating surgeons were required to have performed a minimum of 20 off-pump CABGs, although most had performed many more (mean 120, median 50). The investigators randomized 2203 patients at 18 VA medical centers between 2002 and 2007. The study followed the patients every two months for one year. The trial had two primary composite outcomes. The first combined the following short-term events: death or major complications (re-operation, cardiac arrest, coma, stroke, renal failure requiring dialysis) within 30 days. The second combined the following intermediate-term events: any death within one year; nonfatal MI between 30 days and one year; or repeat revascularization between 30 days and one year. Important secondary outcomes included the completeness of revascularization, graft patency at one year, and change in neuropsychological tests between baseline and one year.

The ROOBY trial included all patients scheduled for urgent or elective CABG without additional planned surgery, though very few women were included because of the relatively small numbers of women receiving their care at VA medical centers. It excluded patients undergoing immediate surgery and those with significant valve disease, small target vessels, or diffuse coronary disease. There were no significant differences in the baseline characteristics of the participants. Their average age was 63 years, more than 99% were male, 8% black, 5% Hispanic, and 84% white. Almost half of the participants were diabetic (44%), one-third were current smokers, and two-thirds had triple vessel disease.

The 30-day primary outcome occurred in 7.0% of patients in the off-pump group and 5.6% of patients in the on-pump group (RR 1.26, 95% CI 0.9 to 1.7, p = 0.19). Among patients in the off pump group, 1.6% died in the first 30 days, 1.8% had a cardiac arrest, 1.3% had a stroke, 2.7% were re-operated for bleeding, and 0.8% had renal failure requiring dialysis. Among patients in the on pump group, 1.2% died in the first 30 days, 1.1% had a cardiac arrest, 0.7% had a stroke, 2.1% were re-operated for bleeding, and 0.9% had renal failure requiring dialysis. Most major short-term complications were more common in the off-pump group, but none of the differences were statistically significant. None of the other peri-operative outcomes favored the off-pump group including length of time in the operating room, time spent in the intensive care unit, or length of stay in the hospital.

The one-year primary outcome occurred in 9.9% of patients in the off-pump group and 7.4% of patients in the on-pump group (RR 1.33, 95% CI 1.01 to 1.8, p = 0.04). Among patients in the off pump group 4.1% died, 4.6% underwent repeat revascularization, and 2.0% had a non-fatal MI. Among patients in the on pump group 2.9% died, 3.4% underwent repeat revascularization, and 2.2% had a non-fatal MI. When the 30-day and one-year outcomes were combined, the results even more strongly favored the on-pump group (14.6% versus 9.9%, RR 1.47, 95% CI 1.2-1.9, p = 0.001).

One of the major reasons for the development and promotion of off-pump bypass surgery was the concern that cognitive function declined significantly after surgery. Thus, the results of the neuropsychological tests represent important secondary outcome. Both the off-pump and on-pump groups improved on all ten tests at one year compared with baseline. For five of the tests, the trend was for greater improvement in the off-pump group, for the other five tests trend was for greater improvement in the on-pump group. For one test, the clock drawing test, the improvement in the off-pump group was significantly greater than that of the on-

pump group (p=0.001). There was no significant difference in the summary score for the neuropsychological testing (0.19 versus 0.17, p = 0.21).

The other secondary outcomes addressed the concern that the technical difficulties in performing anastomoses on a beating heart might lead to less complete revascularization and a higher rate of anastomotic failure. In the ROOBY trial, the proportion of patients who received fewer grafts than planned was higher in the off-pump group (17.8% versus 11.1%, p<0.01). The off-pump group had a lower proportion of grafts that were open at one year (82.6% versus 87.8%, p<0.01) and a higher proportion of occluded grafts (36.5% versus 28.7%, p<0.01).

The ROOBY trial was high quality. It was a large, multi-center trial with many surgeons, thus addressing the results from other small trials which may be more representative of a single surgeon or center's results than true differences between the two procedures. There was central randomization that occurred when the patient was in the pre-operative holding area, limiting concerns about selection bias. Outcome assessment was standardized and blinded for some outcomes, thus limiting concerns about information bias. The analysis was intention to treat with excellent follow-up (100% included in 30 day analyses, 96% included in one year analyses).

The ROOBY trial has some important limitations. Since it was primarily performed in men, the results may not apply to women. There was some cross-over in the trial (137 (12%) off-pump converted to on-pump; 43 (4%) on-pump converted to off-pump). However the primary results did not change when a per-protocol analysis was done. In addition, the majority of the sites were teaching hospitals and more patients in the on-pump group had the cardiothoracic resident as the primary surgeon (64% versus 55%, p<0.001). If this imbalance influenced the results, it would likely bias the results in favor of the off-pump group.

There are at least three on-going, large randomized trials (total n=7600) directly comparing off-pump to on-pump CABG that have yet to publish results (ClinicalTrials.gov, accessed February 1, 2010). Two of the trials are focused on older patients and should be completed in 2011. The third is randomizing over 4000 patients and following them for five years for their primary endpoint (Coronary Artery Bypass Surgery Off or On Pump Revascularization Study (CORONARY)).

Summary

Early studies suggested that by avoiding cardiopulmonary bypass off-pump CABG could reduce thromboembolic and inflammatory complications leading to more rapid recovery from surgery with fewer cognitive complications. However, the recent randomized trials and meta-analyses have failed to demonstrate improvements in neurocognitive function and quality of life compared with standard on-pump CABG. Furthermore, revascularization is consistently less complete with off-pump CABG and there is a trend towards increased mortality and decreased graft viability during the first year after surgery. The most recent trial, with the largest number of centers and surgeons, found off-pump CABG to be inferior to on-pump CABG at one year. Thus, the best evidence fails to demonstrate equivalence of off-pump CABG to the currently accepted alternative.

TA Criterion 4 is not met.

TA Criterion 5: The improvement must be attainable outside of the investigational setting.

Off-pump or beating heart CABG is a technically challenging surgical procedure that requires special equipment and highly trained surgeons and staff. To date, equivalent outcomes compared with standard surgery have not been clearly demonstrated outside of the investigational setting. Favorable results in single-center studies likely represents the special expertise of the surgeons and support staff at that institution. While off-pump CABG has been performed in many centers for several years, TA criterion 4 must be met for TA criterion 5 to be considered met.

TA Criterion 5 is not met.

CONCLUSION

The goal of this technology assessment was to compare the efficacy and safety of off-pump CABG to that of conventional “on-pump” CABG using cardiopulmonary bypass when used to treat patients with coronary artery disease requiring non-emergent revascularization. As noted in the prior assessment, non-randomized trials suggested that off-pump CABG might have lower peri-operative morbidity and mortality, shorter ICU stays, shorter hospitalizations, lower resource utilization with the additional benefit of improved neurocognitive outcomes. Because of the technical difficulty of creating anastomoses between blood vessels on a beating heart, there remained concerns about long-term outcomes including graft patency,

which could result in increased rates of recurrent angina, MI's, and the need for repeated revascularization procedures. Furthermore, the results of observational studies may suffer from significant selection bias.

This assessment focused on the sixteen trials comparing off-pump to on-pump CABG that randomized at least 100 patients or followed patients for at least one year. Nineteen systematic reviews and meta-analyses comparing the two surgeries were also reviewed in detail. The trials were of moderate quality, but were consistent in their findings. There was no overall reduction in the length of time in the ICU after surgery, nor was their any reduction in the average length of the hospitalization. More importantly, cognitive outcomes and quality of life for patients was better for patients randomized to off-pump surgery. Furthermore, there was no reduction in MI's, strokes, or overall mortality. However revascularization was less complete in off-pump surgery and the patency rate in the bypass grafts over the first year of follow-up was consistently lower. There were also strong trends towards increased mortality and increased repeat revascularization in patients randomized to off-pump surgery. Finally, the ROOBY trial, the most recent and largest study, had more outcomes than the sum of all prior studies. Both the 30-day and one year summary outcomes favored traditional on-pump CABG. Both groups improved on a battery of ten neurocognitive tests without any significant trend in favor of the off-pump procedure. The off-pump group received fewer grafts than planned, had more occluded grafts, and needed more revascularization during the first year following surgery. Finally, for the most important outcome, the trend was for higher one-year total mortality in the off-pump group (4.1% versus 2.9%, p=0.15).

In summary, the randomized trial data fail to confirm any advantages for off-pump CABG over the conventional on-pump procedure, while suggesting that long term graft patency is inferior. Two meta-analyses focusing specifically on neurocognitive outcomes failed to find any benefits in favor of off-pump CABG. The results of the large ROOBY trial dominated the summary estimates in the meta-analysis performed as part of the current assessment, but there was no evidence for heterogeneity in the data for any of the major outcomes that were analyzed. The ROOBY trial randomized predominantly men at lower risk for surgical complications. Thus, there may be subgroups such as women, older patients, or higher risk patients who would show benefit from off-pump CABG, but randomized trial data in those subgroups have not been presented in detail. The current data do not support performing the technically more difficult off-pump CABG procedure. There are at least three large, ongoing randomized trials that may identify subgroups of patients with better outcomes using the off-pump technique, but until those results are available, the off-pump technique should be considered investigational.

RECOMMENDATION

It is recommended that off-pump coronary artery bypass grafting does not meet California Technology Assessment Forum TA Criterion 4 through 5 for improvement in health outcomes.

February 17, 2010

The last review of this technology by this body was February 2002.

The California Technology Assessment Forum panel voted in favor of the recommendation.

RECOMMENDATIONS OF OTHERS

Blue Cross Blue Shield Association (BCBSA)

The BCBSA Technology Evaluation Center (TEC) conducted reviews of this technology in 1997 and 1998. TEC determined that criteria were not met. A more current assessment has not been conducted.

Centers for Medicare and Medicaid Services (CMS)

Neither a National Coverage Determination (NCD) nor a Local Coverage Determination (LCD) was found for Coronary Artery Bypass Graft surgery through a search of the CMS web site.

Society of Thoracic Surgeons (STS)

The STS has been invited to provide an opinion and have a representative attend the meeting.

American Association for Thoracic Surgery (AATS)

The AATS declined the opportunity to provide an opinion regarding this technology and to have a representative attend the meeting.

American College of Cardiology, California Chapter (CA ACC)

The CA ACC declined the opportunity to provide an opinion regarding this technology and to have a representative attend the meeting.

California Society of Thoracic Surgeons (CA STS)

A CA STS representative attended the meeting to provide testimony.

ABBREVIATIONS USED IN THIS REVIEW

CTAF	California Technology Assessment Forum
CABG	Coronary artery bypass grafting
ROOBY	Randomized On/Off Bypass
ICU	Intensive care unit
MI	Myocardial infarction
FDA	Food and Drug Administration
DARE	Database of Abstracts of Reviews of Effects
PCI	Percutaneous coronary interventions
DM	Diabetes Mellitus
EF	Ejection Fraction
NR	Not reported
BHACAS	Beating Heart Against Cardioplegic Arrest Study
COPD	Chronic obstructive pulmonary disease
CVA	Cerebrovascular accident
OCTOPUS	Octopus Study
AIDS	Acquired immune deficiency syndrome
SMART	Surgical Management of Arterial Revascularization Therapies
PRAGUE	Prague
JOCRI	Japanese Off-pump Coronary Revascularization Investigation
VA	Veterans Affairs
CAS	Coronary artery stenting
ITT	Intent to treat
CORONARY	Coronary Artery Bypass Surgery Off or On Pump Revascularization Study

REFERENCES

1. Lloyd-Jones D, Adams RJ, Brown TM, et al. Heart Disease and Stroke Statistics--2010 Update. A Report From the American Heart Association. *Circulation.* Dec 17 2009.

2. Yusuf S, Zucker D, Chalmers TC. Ten-year results of the randomized control trials of coronary artery bypass graft surgery: tabular data compiled by the collaborative effort of the original trial investigators. Part 1 of 2. *Online J Curr Clin Trials.* Oct 14 1994;Doc No 145:[3987 words; 3938 paragraphs].

3. Sabiston DC, Jr. The William F. Rienhoff, Jr. lecture. The coronary circulation. *Johns Hopkins Med J.* Jun 1974;134(6):314-329.

4. Benetti FJ. Direct coronary surgery with saphenous vein bypass without either cardiopulmonary bypass or cardiac arrest. *J Cardiovasc Surg (Torino).* May-Jun 1985;26(3):217-222.

5. Buffolo E, Andrade JC, Succi J, Leao LE, Gallucci C. Direct myocardial revascularization without cardiopulmonary bypass. *Thorac Cardiovasc Surg.* Feb 1985;33(1):26-29.

6. Arom KV, Flavin TF, Emery RW, Kshettry VR, Janey PA, Petersen RJ. Safety and efficacy of off-pump coronary artery bypass grafting. *Ann Thorac Surg.* Mar 2000;69(3):704-710.

7. Subramanian VA, Patel N. New minimal access approaches to multivessel coronary artery bypass grafting without pump. *Curr Cardiol Rep.* Nov 1999;1(4):311-312.

8. Koutlas TC, Elbeery JR, Williams JM, Moran JF, Francalancia NA, Chitwood WR, Jr. Myocardial revascularization in the elderly using beating heart coronary artery bypass surgery. *Ann Thorac Surg.* Apr 2000;69(4):1042-1047.

9. Lim E, Drain A, Davies W, Edmonds L, Rosengard BR. A systematic review of randomized trials comparing revascularization rate and graft patency of off-pump and conventional coronary surgery. *J Thorac Cardiovasc Surg.* Dec 2006;132(6):1409-1413.

10. Takagi H, Tanabashi T, Kawai N, Kato T, Umemoto T. Off-pump coronary artery bypass sacrifices graft patency: meta-analysis of randomized trials. *J Thorac Cardiovasc Surg.* Jan 2007;133(1):e2-3.

11. Al-Ruzzeh S, Hoare G, Marczin N, et al. Off-pump coronary artery bypass surgery is associated with reduced neutrophil activation as measured by the expression of CD11b: a prospective randomized study. *Heart Surg Forum.* 2003;6(2):89-93.

12. Alwan K, Falcoz PE, Alwan J, et al. Beating versus arrested heart coronary revascularization: evaluation by cardiac troponin I release. *Ann Thorac Surg.* Jun 2004;77(6):2051-2055.

13. Anderson RE, Brismar K, Barr G, Ivert T. Effects of cardiopulmonary bypass on glucose homeostasis after coronary artery bypass surgery. *Eur J Cardiothorac Surg.* Sep 2005;28(3):425-430.

14. Baker RA, Andrew MJ, Ross IK, Knight JL. The Octopus II stabilizing system: biochemical and neuropsychological outcomes in coronary artery bypass surgery. *Heart Surg Forum.* 2001;4 Suppl 1:S19-23.

15. Blacher C, Neumann J, Jung LA, Lucchese FA, Ribeiro JP. Off-pump coronary artery bypass grafting does not reduce lymphocyte activation. *Int J Cardiol.* Jun 8 2005;101(3):473-479.

16. Caputo M, Yeatman M, Narayan P, et al. Effect of off-pump coronary surgery with right ventricular assist device on organ function and inflammatory response: a randomized controlled trial. *Ann Thorac Surg.* Dec 2002;74(6):2088-2095; discussion 2095-2086.

17. Carrier M, Perrault LP, Jeanmart H, Martineau R, Cartier R, Page P. Randomized trial comparing off-pump to on-pump coronary artery bypass grafting in high-risk patients. *Heart Surg Forum.* 2003;6(6):E89-92.

18. Castellheim A, Hoel TN, Videm V, et al. Biomarker profile in off-pump and on-pump coronary artery bypass grafting surgery in low-risk patients. *Ann Thorac Surg.* Jun 2008;85(6):1994-2002.

19. Cavalca V, Sisillo E, Veglia F, et al. Isoprostanes and oxidative stress in off-pump and on-pump coronary bypass surgery. *Ann Thorac Surg.* Feb 2006;81(2):562-567.

20. Celik JB, Gormus N, Topal A, Okesli S, Solak H. Effect of off-pump and on-pump coronary artery bypass grafting on renal function. *Ren Fail.* 2005;27(2):183-188.

21. Chowdhury UK, Malik V, Yadav R, et al. Myocardial injury in coronary artery bypass grafting: on-pump versus off-pump comparison by measuring high-sensitivity C-reactive protein, cardiac troponin I, heart-type fatty acid-binding protein, creatine kinase-MB, and myoglobin release. *J Thorac Cardiovasc Surg.* May 2008;135(5):1110-1119, 1119 e1111-1110.

22. Covino E, Santise G, Di Lello F, et al. Surgical myocardial revascularization (CABG) in patients with pulmonary disease: beating heart versus cardiopulmonary bypass. *J Cardiovasc Surg (Torino).* Feb 2001;42(1):23-26.

23. Diegeler A, Hirsch R, Schneider F, et al. Neuromonitoring and neurocognitive outcome in off-pump versus conventional coronary bypass operation. *Ann Thorac Surg.* Apr 2000;69(4):1162-1166.

24. Diephuis JC, Moons KG, Nierich AN, Bruens M, van Dijk D, Kalkman CJ. Jugular bulb desaturation during coronary artery surgery: a comparison of off-pump and on-pump procedures. *Br J Anaesth.* Jun 2005;94(6):715-720.

25. Dorman BH, Kratz JM, Multani MM, et al. A prospective, randomized study of endothelin and postoperative recovery in off-pump versus conventional coronary artery bypass surgery. *J Cardiothorac Vasc Anesth.* Feb 2004;18(1):25-29.

26. Ernest CS, Murphy BM, Worcester MU, et al. Cognitive function in candidates for coronary artery bypass graft surgery. *Ann Thorac Surg.* Sep 2006;82(3):812-818.

27. Ernest CS, Worcester MU, Tatoulis J, et al. Neurocognitive outcomes in off-pump versus on-pump bypass surgery: a randomized controlled trial. *Ann Thorac Surg.* Jun 2006;81(6):2105-2114.

28. Fattouch K, Guccione F, Dioguardi P, et al. Off-pump versus on-pump myocardial revascularization in patients with ST-segment elevation myocardial infarction: a randomized trial. *J Thorac Cardiovasc Surg.* Mar 2009;137(3):650-656; discussion 656-657.

29. Formica F, Broccolo F, Martino A, et al. Myocardial revascularization with miniaturized extracorporeal circulation versus off pump: Evaluation of systemic and myocardial inflammatory response in a prospective randomized study. *J Thorac Cardiovasc Surg.* May 2009;137(5):1206-1212.

30. Gasz B, Benko L, Jancso G, et al. Comparison of inflammatory response following coronary revascularization with or without cardiopulmonary bypass. *Exp Clin Cardiol.* Spring 2004;9(1):26-30.

31. Gonenc A, Hacisevki A, Bakkaloglu B, et al. Oxidative stress is decreased in off-pump versus on-pump coronary artery surgery. *J Biochem Mol Biol.* Jul 31 2006;39(4):377-382.

32. Gu YJ, Mariani MA, van Oeveren W, Grandjean JG, Boonstra PW. Reduction of the inflammatory response in patients undergoing minimally invasive coronary artery bypass grafting. *Ann Thorac Surg.* Feb 1998;65(2):420-424.

33. Guler M, Kirali K, Toker ME, et al. Different CABG methods in patients with chronic obstructive pulmonary disease. *Ann Thorac Surg.* Jan 2001;71(1):152-157.

34. Gulielmos V, Eller M, Thiele S, et al. Influence of median sternotomy on the psychosomatic outcome in coronary artery single-vessel bypass grafting. *Eur J Cardiothorac Surg.* Nov 1999;16 Suppl 2:S34-38.

35. Gulielmos V, Menschikowski M, Dill H, et al. Interleukin-1, interleukin-6 and myocardial enzyme response after coronary artery bypass grafting - a prospective randomized comparison of the conventional and three minimally invasive surgical techniques. *Eur J Cardiothorac Surg.* Nov 2000;18(5):594-601.

36. Hoel TN, Videm V, Mollnes TE, et al. Off-pump cardiac surgery abolishes complement activation. *Perfusion.* Jul 2007;22(4):251-256.

37. Jalal A, Yunus A, Abualazm AM, et al. Coronary artery bypass grafting on beating heart. Does it provide superior myocardial preservation than conventional technique? *Saudi Med J.* Jun 2007;28(6):848-854.

38. Jares M, Vanek T, Bednar F, Maly M, Snircova J, Straka Z. Off-pump versus on-pump coronary artery surgery. *Int Heart J.* Jan 2007;48(1):57-67.

39. Jensen BO, Rasmussen LS, Steinbruchel DA. Cognitive outcomes in elderly high-risk patients 1 year after off-pump versus on-pump coronary artery bypass grafting. A randomized trial. *Eur J Cardiothorac Surg.* Nov 2008;34(5):1016-1021.

40. Johansson-Synnergren M, Nilsson F, Bengtsson A, Jeppsson A, Wiklund L. Off-pump CABG reduces complement activation but does not significantly affect peripheral endothelial function: a prospective randomized study. *Scand Cardiovasc J.* Mar 2004;38(1):53-58.

41. Kochamba GS, Yun KL, Pfeffer TA, Sintek CF, Khonsari S. Pulmonary abnormalities after coronary arterial bypass grafting operation: cardiopulmonary bypass versus mechanical stabilization. *Ann Thorac Surg.* May 2000;69(5):1466-1470.

42. Krejca M, Skiba J, Szmagala P, Gburek T, Bochenek A. Cardiac troponin T release during coronary surgery using intermittent cross-clamp with fibrillation, on-pump and off-pump beating heart. *Eur J Cardiothorac Surg.* Sep 1999;16(3):337-341.

43. Kunes P, Lonsky V, Mandak J, et al. The long pentraxin 3 in cardiac surgery: distinct responses in "on-pump" and "off-pump" patients. *Scand Cardiovasc J.* Jun 2007;41(3):171-179.

44. Lamy A, Farrokhyar F, Kent R, et al. The Canadian off-pump coronary artery bypass graft registry: a one-year prospective comparison with on-pump coronary artery bypass grafting. *Can J Cardiol.* Nov 2005;21(13):1175-1181.

45. Lonn U, Peterzen B, Carnstam B, Casimir-Ahn H. Beating heart coronary surgery supported by an axial blood flow pump. *Ann Thorac Surg.* Jan 1999;67(1):99-104.

46. Lund C, Hol PK, Lundblad R, et al. Comparison of cerebral embolization during off-pump and on-pump coronary artery bypass surgery. *Ann Thorac Surg.* Sep 2003;76(3):765-770; discussion 770.

47. Lund C, Sundet K, Tennoe B, et al. Cerebral ischemic injury and cognitive impairment after off-pump and on-pump coronary artery bypass grafting surgery. *Ann Thorac Surg.* Dec 2005;80(6):2126-2131.

48. Malheiros SM, Massaro AR, Gabbai AA, et al. Is the number of microembolic signals related to neurologic outcome in coronary bypass surgery? *Arq Neuropsiquiatr.* Mar 2001;59(1):1-5.

49. Malik V, Kale SC, Chowdhury UK, Ramakrishnan L, Chauhan S, Kiran U. Myocardial injury in coronary artery bypass grafting: On-pump versus off-pump comparison by measuring heart-type fatty-acid-binding protein release. *Tex Heart Inst J.* 2006;33(3):321-327.

50. Mandak J, Pojar M, Cibicek N, et al. Impact of cardiopulmonary bypass on peripheral tissue metabolism and microvascular blood flow. *Perfusion.* Nov 2008;23(6):339-346.

51. Mariscalco G, Engstrom KG, Ferrarese S, et al. Relationship between atrial histopathology and atrial fibrillation after coronary bypass surgery. *J Thorac Cardiovasc Surg.* Jun 2006;131(6):1364-1372.

52. Masoumi M, Saidi MR, Rostami F, Sepahi H, Roushani D. Off-pump coronary artery bypass grafting in left ventricular dysfunction. *Asian Cardiovasc Thorac Ann.* Jan 2008;16(1):16-20.

53. Matata BM, Sosnowski AW, Galinanes M. Off-pump bypass graft operation significantly reduces oxidative stress and inflammation. *Ann Thorac Surg.* Mar 2000;69(3):785-791.

54. Mathisen L, Andersen MH, Hol PK, et al. Patient-reported outcome after randomization to on-pump versus off-pump coronary artery surgery. *Ann Thorac Surg.* May 2005;79(5):1584-1589.

55. Mathisen L, Andersen MH, Hol PK, et al. Preoperative cerebral ischemic lesions predict physical health status after on-pump coronary artery bypass surgery. *J Thorac Cardiovasc Surg.* Dec 2005;130(6):1691-1697.

56. Mathisen L, Lingaas PS, Andersen MH, et al. Changes in cardiac and cognitive function and self-reported outcomes at one year after coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* Dec 15 2009.

57. Medved I, Anic D, Zrnic B, Ostric M, Saftic I. Off-pump versus on-pump--intermittent aortic cross clamping--myocardial revascularisation: single center expirience. *Coll Antropol.* Jun 2008;32(2):381-384.

58. Michaux I, Filipovic M, Skarvan K, et al. Effects of on-pump versus off-pump coronary artery bypass graft surgery on right ventricular function. *J Thorac Cardiovasc Surg.* Jun 2006;131(6):1281-1288.

59. Nesher N, Frolkis I, Vardi M, et al. Higher levels of serum cytokines and myocardial tissue markers during on-pump versus off-pump coronary artery bypass surgery. *J Card Surg.* Jul-Aug 2006;21(4):395-402.

60. Ozkara C, Guler N, Batyraliev T, Okut H, Agirbasli M. Does off-pump coronary artery bypass surgery reduce secretion of plasminogen activator inhibitor-1? *Int J Clin Pract.* May 2007;61(5):763-767.

61. Paparella D, Galeone A, Venneri MT, et al. Activation of the coagulation system during coronary artery bypass grafting: comparison between on-pump and off-pump techniques. *J Thorac Cardiovasc Surg.* Feb 2006;131(2):290-297.

62. Parolari A, Alamanni F, Juliano G, et al. Oxygen metabolism during and after cardiac surgery: role of CPB. *Ann Thorac Surg.* Sep 2003;76(3):737-743; discussion 743.

63. Parolari A, Camera M, Alamanni F, et al. Systemic inflammation after on-pump and off-pump coronary bypass surgery: a one-month follow-up. *Ann Thorac Surg.* Sep 2007;84(3):823-828.

64. Parolari A, Mussoni L, Frigerio M, et al. Increased prothrombotic state lasting as long as one month after on-pump and off-pump coronary surgery. *J Thorac Cardiovasc Surg.* Aug 2005;130(2):303-308.

65. Penttila HJ, Lepojarvi MV, Kiviluoma KT, Kaukoranta PK, Hassinen IE, Peuhkurinen KJ. Myocardial preservation during coronary surgery with and without cardiopulmonary bypass. *Ann Thorac Surg.* Feb 2001;71(2):565-571.

66. Pojar M, Mand'ak J, Cibicek N, et al. Peripheral tissue metabolism during off-pump versus on-pump coronary artery bypass graft surgery: the microdialysis study. *Eur J Cardiothorac Surg.* May 2008;33(5):899-905.

67. Quaniers JM, Leruth J, Albert A, Limet RR, Defraigne JO. Comparison of inflammatory responses after off-pump and on-pump coronary surgery using surface modifying additives circuit. *Ann Thorac Surg.* May 2006;81(5):1683-1690.

68. Rainio A, Hautala N, Pelkonen O, et al. Risk of retinal microembolism after off-pump and on-pump coronary artery bypass surgery. *J Cardiovasc Surg (Torino).* Dec 2007;48(6):773-779.

69. Raja SG, Haider Z, Ahmad M. Predictors of gastrointestinal complications after conventional and beating heart coronary surgery. *Surgeon.* Aug 2003;1(4):221-228.

70. Rasmussen BS, Laugesen H, Sollid J, et al. Oxygenation and release of inflammatory mediators after off-pump compared with after on-pump coronary artery bypass surgery. *Acta Anaesthesiol Scand.* Oct 2007;51(9):1202-1210.

71. Rastan AJ, Bittner HB, Gummert JF, et al. On-pump beating heart versus off-pump coronary artery bypass surgery-evidence of pump-induced myocardial injury. *Eur J Cardiothorac Surg.* Jun 2005;27(6):1057-1064.

72. Sahlman A, Ahonen J, Nemlander A, et al. Myocardial metabolism on off-pump surgery; a randomized study of 50 cases. *Scand Cardiovasc J.* Sep 2003;37(4):211-215.

73. Schmid FX, Vudattu N, Floerchinger B, et al. Endothelial apoptosis and circulating endothelial cells after bypass grafting with and without cardiopulmonary bypass. *Eur J Cardiothorac Surg.* Apr 2006;29(4):496-500.

74. Schulze C, Conrad N, Schutz A, et al. Reduced expression of systemic proinflammatory cytokines after off-pump versus conventional coronary artery bypass grafting. *Thorac Cardiovasc Surg.* Dec 2000;48(6):364-369.

75. Selvanayagam JB, Kardos A, Francis JM, et al. Value of delayed-enhancement cardiovascular magnetic resonance imaging in predicting myocardial viability after surgical revascularization. *Circulation.* Sep 21 2004;110(12):1535-1541.

76. Selvanayagam JB, Petersen SE, Francis JM, et al. Effects of off-pump versus on-pump coronary surgery on reversible and irreversible myocardial injury: a randomized trial using cardiovascular magnetic resonance imaging and biochemical markers. *Circulation.* Jan 27 2004;109(3):345-350.

77. Stassano P, Di Tommaso L, Monaco M, et al. Myocardial revascularization by left ventricular assisted beating heart is associated with reduced systemic inflammatory response. *Ann Thorac Surg.* Jan 2009;87(1):46-52.

78. Tang AT, Knott J, Nanson J, Hsu J, Haw MP, Ohri SK. A prospective randomized study to evaluate the renoprotective action of beating heart coronary surgery in low risk patients. *Eur J Cardiothorac Surg.* Jul 2002;22(1):118-123.

79. Tatoulis J, Rice S, Davis P, Goldblatt JC, Marasco S. Patterns of postoperative systemic vascular resistance in a randomized trial of conventional on-pump versus off-pump coronary artery bypass graft surgery. *Ann Thorac Surg.* Oct 2006;82(4):1436-1444.

80. Vedin J, Antovic A, Ericsson A, Vaage J. Hemostasis in off-pump compared to on-pump coronary artery bypass grafting: a prospective, randomized study. *Ann Thorac Surg.* Aug 2005;80(2):586-593.

81. Vedin J, Jensen U, Ericsson A, et al. Cardiovascular function during the first 24 hours after off pump coronary artery bypass grafting--a prospective, randomized study. *Interact Cardiovasc Thorac Surg.* Dec 2003;2(4):489-494.

82. Vedin J, Jensen U, Ericsson A, Samuelsson S, Vaage J. Pulmonary hemodynamics and gas exchange in off pump coronary artery bypass grafting. *Interact Cardiovasc Thorac Surg.* Oct 2005;4(5):493-497.

83. Vedin J, Nyman H, Ericsson A, Hylander S, Vaage J. Cognitive function after on or off pump coronary artery bypass grafting. *Eur J Cardiothorac Surg.* Aug 2006;30(2):305-310.

84. Velissaris T, Tang A, Murray M, El-Minshawy A, Hett D, Ohri S. A prospective randomized study to evaluate splanchnic hypoxia during beating-heart and conventional coronary revascularization. *Eur J Cardiothorac Surg.* Jun 2003;23(6):917-924; discussion 924.

85. Velissaris T, Tang AT, Murray M, et al. A prospective randomized study to evaluate stress response during beating-heart and conventional coronary revascularization. *Ann Thorac Surg.* Aug 2004;78(2):506-512; discussion 506-512.

86. Vural KM, Tasdemir O, Karagoz H, Emir M, Tarcan O, Bayazit K. Comparison of the early results of coronary artery bypass grafting with and without extracorporeal circulation. *Thorac Cardiovasc Surg.* Dec 1995;43(6):320-325.

87. Wandschneider W, Thalmann M, Trampitsch E, Ziervogel G, Kobinia G. Off-pump coronary bypass operations significantly reduce S100 release: an indicator for less cerebral damage? *Ann Thorac Surg.* Nov 2000;70(5):1577-1579.

88. Wehlin L, Vedin J, Vaage J, Lundahl J. Activation of complement and leukocyte receptors during on- and off pump coronary artery bypass surgery. *Eur J Cardiothorac Surg.* Jan 2004;25(1):35-42.

89. Wehlin L, Vedin J, Vaage J, Lundahl J. Peripheral blood monocyte activation during coronary artery bypass grafting with or without cardiopulmonary bypass. *Scand Cardiovasc J.* Apr 2005;39(1-2):78-86.

90. Wildhirt SM, Schulze C, Conrad N, et al. Reduced myocardial cellular damage and lipid peroxidation in off-pump versus conventional coronary artery bypass grafting. *Eur J Med Res.* May 23 2000;5(5):222-228.

91. Wildhirt SM, Schulze C, Schulz C, et al. Reduction of systemic and cardiac adhesion molecule expression after off-pump versus conventional coronary artery bypass grafting. *Shock.* 2001;16 Suppl 1:55-59.

92. Al-Ruzzeh S, Epstein D, George S, et al. Economic evaluation of coronary artery bypass grafting surgery with and without cardiopulmonary bypass: cost-effectiveness and quality-adjusted life years in a randomized controlled trial. *Artif Organs.* Nov 2008;32(11):891-897.

93. Al-Ruzzeh S, George S, Bustami M, et al. Effect of off-pump coronary artery bypass surgery on clinical, angiographic, neurocognitive, and quality of life outcomes: randomised controlled trial. *BMJ.* Jun 10 2006;332(7554):1365.

94. Angelini GD, Culliford L, Smith DK, et al. Effects of on- and off-pump coronary artery surgery on graft patency, survival, and health-related quality of life: long-term follow-up of 2 randomized controlled trials. *J Thorac Cardiovasc Surg.* Feb 2009;137(2):295-303.

95. Angelini GD, Taylor FC, Reeves BC, Ascione R. Early and midterm outcome after off-pump and on-pump surgery in Beating Heart Against Cardioplegic Arrest Studies (BHACAS 1 and 2): a pooled analysis of two randomised controlled trials. *Lancet.* Apr 6 2002;359(9313):1194-1199.

96. Ascione R, Caputo M, Calori G, Lloyd CT, Underwood MJ, Angelini GD. Predictors of atrial fibrillation after conventional and beating heart coronary surgery: A prospective, randomized study. *Circulation.* Sep 26 2000;102(13):1530-1535.

97. Ascione R, Ghosh A, Reeves BC, et al. Retinal and cerebral microembolization during coronary artery bypass surgery: a randomized, controlled trial. *Circulation.* Dec 20 2005;112(25):3833-3838.

98. Ascione R, Lloyd CT, Gomes WJ, Caputo M, Bryan AJ, Angelini GD. Beating versus arrested heart revascularization: evaluation of myocardial function in a prospective randomized study. *Eur J Cardiothorac Surg.* May 1999;15(5):685-690.

99. Ascione R, Lloyd CT, Underwood MJ, Gomes WJ, Angelini GD. On-pump versus off-pump coronary revascularization: evaluation of renal function. *Ann Thorac Surg.* Aug 1999;68(2):493-498.

100. Ascione R, Lloyd CT, Underwood MJ, Lotto AA, Pitsis AA, Angelini GD. Economic outcome of off-pump coronary artery bypass surgery: a prospective randomized study. *Ann Thorac Surg.* Dec 1999;68(6):2237-2242.

101. Ascione R, Lloyd CT, Underwood MJ, Lotto AA, Pitsis AA, Angelini GD. Inflammatory response after coronary revascularization with or without cardiopulmonary bypass. *Ann Thorac Surg.* Apr 2000;69(4):1198-1204.

102. Ascione R, Reeves BC, Taylor FC, Seehra HK, Angelini GD. Beating heart against cardioplegic arrest studies (BHACAS 1 and 2): quality of life at mid-term follow-up in two randomised controlled trials. *Eur Heart J.* May 2004;25(9):765-770.

103. Ascione R, Talpahewa S, Rajakaruna C, et al. Splanchnic organ injury during coronary surgery with or without cardiopulmonary bypass: a randomized, controlled trial. *Ann Thorac Surg.* Jan 2006;81(1):97-103.

104. Ascione R, Williams S, Lloyd CT, Sundaramoorthi T, Pitsis AA, Angelini GD. Reduced postoperative blood loss and transfusion requirement after beating-heart coronary operations: a prospective randomized study. *J Thorac Cardiovasc Surg.* Apr 2001;121(4):689-696.

105. Cox CM, Ascione R, Cohen AM, Davies IM, Ryder IG, Angelini GD. Effect of cardiopulmonary bypass on pulmonary gas exchange: a prospective randomized study. *Ann Thorac Surg.* Jan 2000;69(1):140-145.

106. Czerny M, Baumer H, Kilo J, et al. Inflammatory response and myocardial injury following coronary artery bypass grafting with or without cardiopulmonary bypass. *Eur J Cardiothorac Surg.* Jun 2000;17(6):737-742.

107. Czerny M, Baumer H, Kilo J, et al. Complete revascularization in coronary artery bypass grafting with and without cardiopulmonary bypass. *Ann Thorac Surg.* Jan 2001;71(1):165-169.

108. Gerola LR, Buffolo E, Jasbik W, et al. Off-pump versus on-pump myocardial revascularization in low-risk patients with one or two vessel disease: perioperative results in a multicenter randomized controlled trial. *Ann Thorac Surg.* Feb 2004;77(2):569-573.

109. Karolak W, Hirsch G, Buth K, Legare JF. Medium-term outcomes of coronary artery bypass graft surgery on pump versus off pump: results from a randomized controlled trial. *Am Heart J.* Apr 2007;153(4):689-695.

110. Keizer AM, Hijman R, van Dijk D, Kalkman CJ, Kahn RS. Cognitive self-assessment one year after on-pump and off-pump coronary artery bypass grafting. *Ann Thorac Surg.* Mar 2003;75(3):835-838; discussion 838-839.

111. Khan NE, De Souza A, Mister R, et al. A randomized comparison of off-pump and on-pump multivessel coronary-artery bypass surgery. *N Engl J Med.* Jan 1 2004;350(1):21-28.

112. Kobayashi J, Tashiro T, Ochi M, et al. Early outcome of a randomized comparison of off-pump and on-pump multiple arterial coronary revascularization. *Circulation.* Aug 30 2005;112(9 Suppl):I338-343.

113. Lee JD, Lee SJ, Tsushima WT, et al. Benefits of off-pump bypass on neurologic and clinical morbidity: a prospective randomized trial. *Ann Thorac Surg.* Jul 2003;76(1):18-25; discussion 25-16.

114. Legare JF, Buth KJ, Hirsch GM. Conversion to on pump from OPCAB is associated with increased mortality: results from a randomized controlled trial. *Eur J Cardiothorac Surg.* Feb 2005;27(2):296-301.

115. Legare JF, Buth KJ, King S, et al. Coronary bypass surgery performed off pump does not result in lower in-hospital morbidity than coronary artery bypass grafting performed on pump. *Circulation.* Feb 24 2004;109(7):887-892.

116. Lingaas PS, Hol PK, Lundblad R, et al. Clinical and radiologic outcome of off-pump coronary surgery at 12 months follow-up: a prospective randomized trial. *Ann Thorac Surg.* Jun 2006;81(6):2089-2095.

117. Lingaas PS, Hol PK, Lundblad R, et al. Clinical and Angiographic Outcome of Coronary Surgery with and without Cardiopulmonary Bypass: A Prospective Randomized Trial. *Heart Surg Forum.* Jan 2004;7(1):37-41.

118. Lloyd CT, Ascione R, Underwood MJ, Gardner F, Black A, Angelini GD. Serum S-100 protein release and neuropsychologic outcome during coronary revascularization on the beating heart: a prospective randomized study. *J Thorac Cardiovasc Surg.* Jan 2000;119(1):148-154.

119. Lo B, Fijnheer R, Castigliego D, Borst C, Kalkman CJ, Nierich AP. Activation of hemostasis after coronary artery bypass grafting with or without cardiopulmonary bypass. *Anesth Analg.* Sep 2004;99(3):634-640, table of contents.

120. Motallebzadeh R, Bland JM, Markus HS, Kaski JC, Jahangiri M. Health-related quality of life outcome after on-pump versus off-pump coronary artery bypass graft surgery: a prospective randomized study. *Ann Thorac Surg.* Aug 2006;82(2):615-619.

121. Motallebzadeh R, Bland JM, Markus HS, Kaski JC, Jahangiri M. Neurocognitive function and cerebral emboli: randomized study of on-pump versus off-pump coronary artery bypass surgery. *Ann Thorac Surg.* Feb 2007;83(2):475-482.

122. Motallebzadeh R, Kanagasabay R, Bland M, Kaski JC, Jahangiri M. S100 protein and its relation to cerebral microemboli in on-pump and off-pump coronary artery bypass surgery. *Eur J Cardiothorac Surg.* Mar 2004;25(3):409-414.

123. Muneretto C, Bisleri G, Negri A, et al. Off-pump coronary artery bypass surgery technique for total arterial myocardial revascularization: a prospective randomized study. *Ann Thorac Surg.* Sep 2003;76(3):778-782; discussion 783.

124. Narayan P, Caputo M, Jones J, Al-Tai S, Angelini GD, Wilde P. Postoperative chest radiographic changes after on- and off-pump coronary surgery. *Clin Radiol.* Jun 2005;60(6):693-699.

125. Nathoe HM, Buskens E, Jansen EW, et al. Role of coronary collaterals in off-pump and on-pump coronary bypass surgery. *Circulation.* Sep 28 2004;110(13):1738-1742.

126. Nathoe HM, Koerselman J, Buskens E, et al. Determinants and prognostic significance of collaterals in patients undergoing coronary revascularization. *Am J Cardiol.* Jul 1 2006;98(1):31-35.

127. Nathoe HM, Moons KG, van Dijk D, et al. Risk and determinants of myocardial injury during off-pump coronary artery bypass grafting. *Am J Cardiol.* May 15 2006;97(10):1482-1486.

128. Nathoe HM, van Dijk D, Jansen EW, et al. A comparison of on-pump and off-pump coronary bypass surgery in low-risk patients. *N Engl J Med.* Jan 30 2003;348(5):394-402.

129. Novitzky D, Shroyer AL, Collins JF, et al. A study design to assess the safety and efficacy of on-pump versus off-pump coronary bypass grafting: the ROOBY trial. *Clin Trials.* 2007;4(1):81-91.

130. Puskas JD, Williams WH, Duke PG, et al. Off-pump coronary artery bypass grafting provides complete revascularization with reduced myocardial injury, transfusion requirements, and length of stay: a prospective randomized comparison of two hundred unselected patients undergoing off-pump versus conventional coronary artery bypass grafting. *J Thorac Cardiovasc Surg.* Apr 2003;125(4):797-808.

131. Puskas JD, Williams WH, Mahoney EM, et al. Off-pump vs conventional coronary artery bypass grafting: early and 1-year graft patency, cost, and quality-of-life outcomes: a randomized trial. *JAMA.* Apr 21 2004;291(15):1841-1849.

132. Shroyer AL, Grover FL, Hattler B, et al. On-pump versus off-pump coronary-artery bypass surgery. *N Engl J Med.* Nov 5 2009;361(19):1827-1837.

133. Staton GW, Williams WH, Mahoney EM, et al. Pulmonary outcomes of off-pump vs on-pump coronary artery bypass surgery in a randomized trial. *Chest.* Mar 2005;127(3):892-901.

134. Straka Z, Widimsky P, Jirasek K, et al. Off-pump versus on-pump coronary surgery: final results from a prospective randomized study PRAGUE-4. *Ann Thorac Surg.* Mar 2004;77(3):789-793.

135. van Dijk D, Diephuis JC, Nierich AP, Keizer AM, Kalkman CJ. Beating heart versus conventional cardiopulmonary bypass: the octopus experience: a randomized comparison of 281 patients undergoing coronary artery bypass surgery with or without cardiopulmonary bypass. *Semin Cardiothorac Vasc Anesth.* Jun 2006;10(2):167-170.

136. Van Dijk D, Jansen EW, Hijman R, et al. Cognitive outcome after off-pump and on-pump coronary artery bypass graft surgery: a randomized trial. *JAMA.* Mar 20 2002;287(11):1405-1412.

137. van Dijk D, Moons KG, Keizer AM, et al. Association between early and three month cognitive outcome after off-pump and on-pump coronary bypass surgery. *Heart.* Apr 2004;90(4):431-434.

138. van Dijk D, Nierich AP, Eefting FD, et al. The Octopus Study: rationale and design of two randomized trials on medical effectiveness, safety, and cost-effectiveness of bypass surgery on the beating heart. *Control Clin Trials.* Dec 2000;21(6):595-609.

139. van Dijk D, Nierich AP, Jansen EW, et al. Early outcome after off-pump versus on-pump coronary bypass surgery: results from a randomized study. *Circulation.* Oct 9 2001;104(15):1761-1766.

140. van Dijk D, Spoor M, Hijman R, et al. Cognitive and cardiac outcomes 5 years after off-pump vs on-pump coronary artery bypass graft surgery. *JAMA.* Feb 21 2007;297(7):701-708.

141. Widimsky P, Straka Z, Stros P, et al. One-year coronary bypass graft patency: a randomized comparison between off-pump and on-pump surgery angiographic results of the PRAGUE-4 trial. *Circulation.* Nov 30 2004;110(22):3418-3423.

142. Zamvar V, Williams D, Hall J, et al. Assessment of neurocognitive impairment after off-pump and on-pump techniques for coronary artery bypass graft surgery: prospective randomised controlled trial. *BMJ.* Nov 30 2002;325(7375):1268.

143. Athanasiou T, Aziz O, Mangoush O, et al. Do off-pump techniques reduce the incidence of postoperative atrial fibrillation in elderly patients undergoing coronary artery bypass grafting? *Ann Thorac Surg.* May 2004;77(5):1567-1574.

144. Bainbridge D, Martin J, Cheng D. Off pump coronary artery bypass graft surgery versus conventional coronary artery bypass graft surgery: a systematic review of the literature. *Semin Cardiothorac Vasc Anesth.* Mar 2005;9(1):105-111.

145. Cheng DC, Bainbridge D, Martin JE, Novick RJ. Does off-pump coronary artery bypass reduce mortality, morbidity, and resource utilization when compared with conventional coronary artery bypass? A meta-analysis of randomized trials. *Anesthesiology.* Jan 2005;102(1):188-203.

146. Feng ZZ, Shi J, Zhao XW, Xu ZF. Meta-analysis of on-pump and off-pump coronary arterial revascularization. *Ann Thorac Surg.* Mar 2009;87(3):757-765.

147. Marasco SF, Sharwood LN, Abramson MJ. No improvement in neurocognitive outcomes after off-pump versus on-pump coronary revascularisation: a meta-analysis. *Eur J Cardiothorac Surg.* Jun 2008;33(6):961-970.

148. Moller CH, Penninga L, Wetterslev J, Steinbruchel DA, Gluud C. Clinical outcomes in randomized trials of off- vs. on-pump coronary artery bypass surgery: systematic review with meta-analyses and trial sequential analyses. *Eur Heart J.* Nov 2008;29(21):2601-2616.

149. Nigwekar SU, Kandula P, Hix JK, Thakar CV. Off-pump coronary artery bypass surgery and acute kidney injury: a meta-analysis of randomized and observational studies. *Am J Kidney Dis.* Sep 2009;54(3):413-423.

150. Panesar SS, Athanasiou T, Nair S, et al. Early outcomes in the elderly: a meta-analysis of 4921 patients undergoing coronary artery bypass grafting--comparison between off-pump and on-pump techniques. *Heart.* Dec 2006;92(12):1808-1816.

151. Parolari A, Alamanni F, Cannata A, et al. Off-pump versus on-pump coronary artery bypass: meta-analysis of currently available randomized trials. *Ann Thorac Surg.* Jul 2003;76(1):37-40.

152. Parolari A, Alamanni F, Polvani G, et al. Meta-analysis of randomized trials comparing off-pump with on-pump coronary artery bypass graft patency. *Ann Thorac Surg.* Dec 2005;80(6):2121-2125.

153. Reston JT, Tregear SJ, Turkelson CM. Meta-analysis of short-term and mid-term outcomes following off-pump coronary artery bypass grafting. *Ann Thorac Surg.* Nov 2003;76(5):1510-1515.

154. Sedrakyan A, Wu AW, Parashar A, Bass EB, Treasure T. Off-pump surgery is associated with reduced occurrence of stroke and other morbidity as compared with traditional coronary artery bypass grafting: a meta-analysis of systematically reviewed trials. *Stroke.* Nov 2006;37(11):2759-2769.

155. Sellke FW, DiMaio JM, Caplan LR, et al. Comparing on-pump and off-pump coronary artery bypass grafting: numerous studies but few conclusions: a scientific statement from the American Heart Association council on cardiovascular surgery and anesthesia in collaboration with the interdisciplinary working group on quality of care and outcomes research. *Circulation.* May 31 2005;111(21):2858-2864.

156. Takagi H, Tanabashi T, Kawai N, Umemoto T. Off-pump surgery does not reduce stroke, compared with results of on-pump coronary artery bypass grafting: a meta-analysis of randomized clinical trials. *J Thorac Cardiovasc Surg.* Oct 2007;134(4):1059-1060.

157. Takagi H, Tanabashi T, Kawai N, Umemoto T. Cognitive decline after off-pump versus on-pump coronary artery bypass graft surgery: meta-analysis of randomized controlled trials. *J Thorac Cardiovasc Surg.* Aug 2007;134(2):512-513.

158. van der Heijden GJ, Nathoe HM, Jansen EW, Grobbee DE. Meta-analysis on the effect of off-pump coronary bypass surgery. *Eur J Cardiothorac Surg.* Jul 2004;26(1):81-84.

159. Wijeysundera DN, Beattie WS, Djaiani G, et al. Off-pump coronary artery surgery for reducing mortality and morbidity: meta-analysis of randomized and observational studies. *J Am Coll Cardiol.* Sep 6 2005;46(5):872-882.

160. Hannan EL, Wu C, Smith CR, et al. Off-pump versus on-pump coronary artery bypass graft surgery: differences in short-term outcomes and in long-term mortality and need for subsequent revascularization. *Circulation.* Sep 4 2007;116(10):1145-1152.

161. Magee MJ, Coombs LP, Peterson ED, Mack MJ. Patient selection and current practice strategy for off-pump coronary artery bypass surgery. *Circulation.* Sep 9 2003;108 Suppl 1:II9-14.

162. Racz MJ, Hannan EL, Isom OW, et al. A comparison of short- and long-term outcomes after off-pump and on-pump coronary artery bypass graft surgery with sternotomy. *J Am Coll Cardiol.* Feb 18 2004;43(4):557-564.