## TCTAP 2019

### Elderly or Fragile Patients with Complex CAD: CABG or PCI ?

**David P Taggart** MD PhD FRCS FESC Professor of Cardiovascular Surgery, University of Oxford



Conflicts of Interest:

(i) Clinical: Cardiac Surgeon

(ii) Commercial: Consultant to Medistim, Medtronic, VGS, Stryker (iii) Chairman of Surgical Committee of the EXCEL trial

# Elderly or Fragile Patients with Complex CAD: CABG or PCI ? Elderly (>80)

(i) Is there an Evidence Basis for CABG (and PCI) in >80s?
(ii) Mortality and Morbidity of CABG (and PCI) in >80s?
(iii) Quality of Life/Independent Living after CABG in >80s?

# Fragility

(i) Formal testing (?) but 'eyeball' or 'end of bed test' crucial
(ii) If Frail: PCI (For CABG a 'good 80' is better than a 'bad 60')

Elderly or Fragile Patients with Complex CAD: CABG or PCI **Problems with Available Data !!** 

(i) All Anecdotal (No specific RCTs of PCI/CABG > 80 years)
(ii) In existing <u>RCTs of PCI/CABG very few patients >80 yrs</u>
(iii) In <u>observational studies</u> usually few patients >80 years
(iv) Often short duration of follow-up (< 5 years)</li>

### [JACC 2018]

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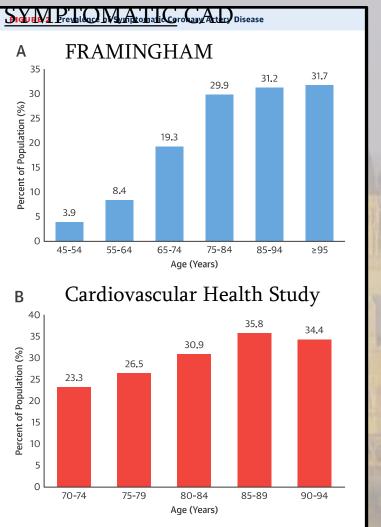
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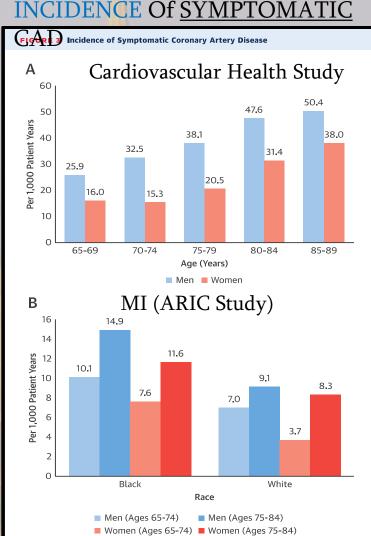
# Coronary Artery Disease in Patients $\geq$ 80 Years of Age

Mahesh V. Madhavan, MD,<sup>a</sup> Bernard J. Gersh, MB, СнВ, DPhil,<sup>b</sup> Karen P. Alexander, MD,<sup>c</sup> Christopher B. Granger, MD,<sup>c</sup> Gregg W. Stone, MD<sup>a,d</sup>

### **PREVALENCE Of**

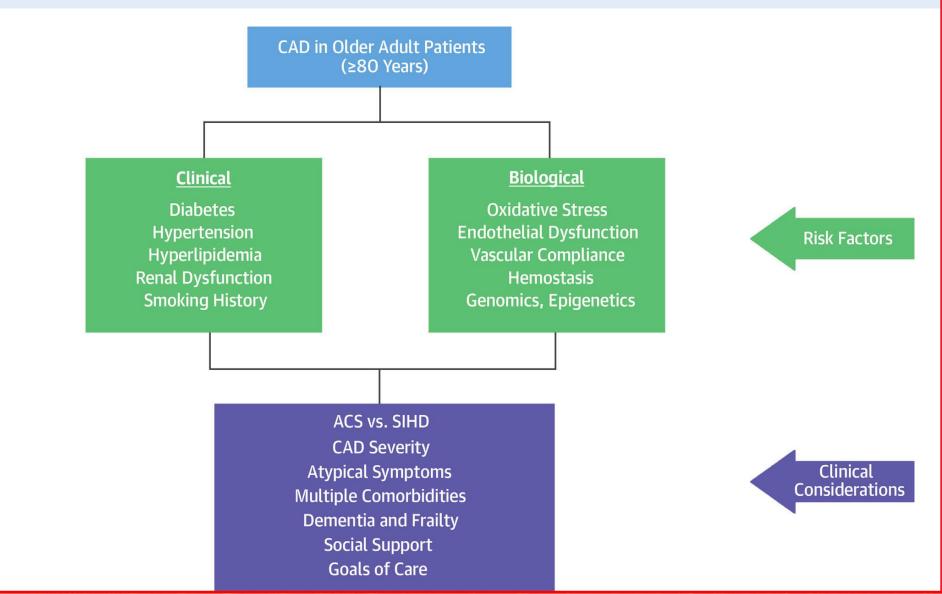


- >80 are fastest growing population in industrialized societies
- Age : strongest predictive factor for both CAD and death
- Elderly have more severe CAD (LM) and major comorbidities
- CAD often presents as vague/non-specific symptoms
- Asymptomatic disease x2 symptomatic disease



### General Considerations for Treating CAD in Octogenarians [JACC 20]

**CENTRAL ILLUSTRATION** Risk Factors, Clinical Influences, and Treatment Considerations in Older Patients With Coronary Artery Disease



# Quality of life after coronary revascularization in the elderly [EH] 2006]

Michelle M. Graham<sup>1</sup>\*, Colleen M. Norris<sup>1,2</sup>, P. Diane Galbraith<sup>6</sup>, Merril L. Knudtson<sup>3,5</sup>, and William A. Ghali<sup>3,4,6</sup> for the APPROACH Investigators<sup>6</sup>

< 70 years: 7783 70-79 years: 2940 > 80 years: 439

Aims To describe health status outcomes at 4 years for a cohort of elderly patients with cardiac disease. Methods and results Using the Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease, an outcomes initiative capturing all patients undergoing cardiac catheterization in Alberta, Canada, health status was measured using the Seattle Angina Questionnaire (SAQ) and crude and risk-adjusted outcomes were determined and compared for patients treated with percutaneous coronary intervention or coronary artery bypass surgery (CABG) vs. medical therapy. Response rates among surviving, consenting patients were 64.8% for patients, 70 years (n  $\frac{1}{4}$  7883), 77.3% for patients aged 70–79 years (n  $\frac{1}{2}$  2940), and 77.7% for patients  $\geq$ 80 years of age (n  $\frac{1}{4}$  439). For patients aged , 70 years, and those aged 70–79 years, for all dimensions of the SAQ, scores were significantly better for patients treated with revascularization procedures than with medical therapy. For patients over the age of 80 years, scores for patients treated with CABG in particular were significantly better, with the exception of exertional capacity. At 3 years, all scores remained stable or improved, and continued to favour revascularization.

Conclusion Elderly patients undergoing revascularization have better health status at 4 years than do those in the same age group who do not undergo revascularization. These findings suggest that age should not deter against revascularization given the combined survival and quality-of-life benefits.

#### **RESEARCH ARTICLE**

#### Open <u>Access</u>



### Predicting operative mortality in octogenarians for isolated coronary artery bypass grafting surgery: a retrospective study

Jessica G. Y. Luc<sup>1</sup>, Michelle M. Graham<sup>2,3</sup>, Colleen M. Norris<sup>1,2,3</sup>, Sadek Al Shouli<sup>1,2</sup>, Yugmel S. Nijjar<sup>1</sup>2018 and Steven R. Meyer<sup>1,2\*</sup>

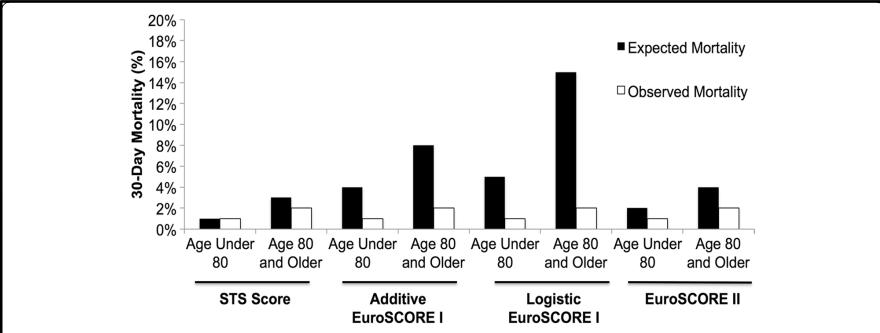


Fig. 1 STS risk score, additive EuroSCORE, logistic EuroSCORE, and EuroSCORE II overestimates operative mortality in patients age 80 and older. Expected 30-day mortality was compared to observed 30-day mortality in patients under the age of 80 and patients age 80 and older who underwent isolated CABG

# STS score most accurate at predicting mortality in both </> 80 (Followed by EuroSCORE II)

#### Comparison of Intermediate-Term Outcomes of Coronary Artery Bypass Grafting Versus Drug-Eluting Stents for Patients ≥75 Years of Age

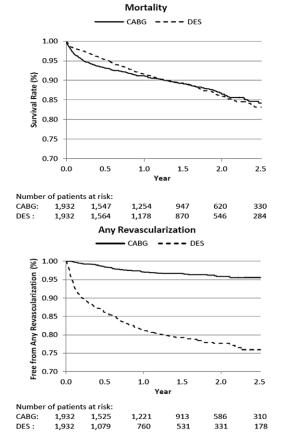
Edward L. Hannan, PhD<sup>a,\*</sup>, Ye Zhong, MD, MS<sup>a</sup>, Peter B. Berger, MD<sup>b</sup>, Gary Walford, MD<sup>c</sup>, Jeptha P. Curtis, MD<sup>d</sup>, Chuntao Wu, MD<sup>e</sup>, Ferdinand J. Venditti, MD<sup>f</sup>, Robert S.D. Higgins, MD<sup>g</sup>, Craig R. Smith, MD<sup>h</sup>, Stephen J. Lahey, MD<sup>i</sup>, and Spencer B. King III, MD<sup>j</sup>

Table 3

2.5-Year outcomes for propensity-matched patients aged  $\geq$ 75 years receiving coronary artery bypass grafting (CABG) and drug-eluting stents (DES) in New York State: January 1, 2008 to December 31, 2010

Long-Term Outcomes	Observed Rate		Kaplan-Meier S	urvival Estimates	Adjusted HR (95% CI) DES/CABG	p Value
	CABG	DES	CABG	DES		
Mortality	11.3	10.7	15.8	16.9	1.06 (0.87-1.30)	0.58
Stroke/MI/Mortality	14.3	14.7	19.8	21.9	1.15 (0.97-1.38)	0.12
Repeat revascularization	3.0	15.7	4.5	24.1	7.48 (5.61–9.98)	< 0.0001

Data are presented as percentage.



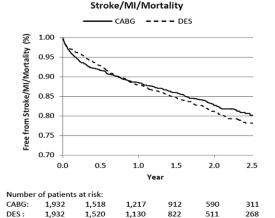


Figure 1. Kaplan-Meier survival curves for propensity-matched CABG and DES patients during 2.5-year follow-up.

3864 patients, Ο vears  $\bigcirc$ propensity Ο matched <u>@ mean of 18</u>  $\bigcirc$ months mortality and composite of mortality, stroke, MI cross in favour of CABG and also with greatly reduced risk of repeat revasc.

What would the results look like at 5 years ?

Comparison of coronary revascularization procedures in octogenarians: a systematic review and meta-analysis <u>Stephen H McKellar</u>, <u>Morgan L Brown</u>, <u>Robert L Fry</u>, <u>Hartzell V Schaff</u>, <u>Thoralf M Sundt III</u> *Nature Reviews* volume5, pages738-746 (2008)

- o 67 studies (35 PCI, 32 CABG) with 65,376 patients
- No baseline characteristics (presumably CABG patients had more severe CAD but otherwise highly selected as 'low-risk' for CABG ?)

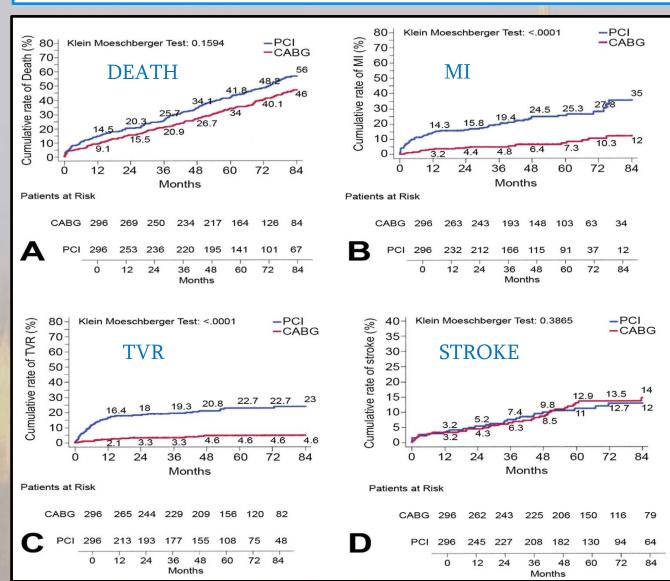
• Only 3 studies had 5-yr follow-up (presumably those with best results ?)

%	PCI	CABG
30 Day Mortality	5.4 (4.4-6.4)	7.2 (6.3-8.2)
1 year Survival	87 (84-91)	86 (83-88)
3 years Survival	78 (68-87)	78 (74-82)
5 years Survival	62 (46-77)	68 (62-73)

Survival data similar between PCI and CABG at 1 and 3 years (limited data !) BUT presumably (i) CABG patients had more severe CAD but (ii) 'highly selected'

#### Coronary Artery Surgery Versus Percutaneous Coronary Intervention in Octogenarians: [ATS 2015] Long-Term Results

Francesco Nicolini, MD, PhD, Giovanni Andrea Contini, MD, Daniela Fortuna, MS, Davide Pacini, MD, Davide Gabbieri, MD, Luigi Vignali, MD, Gianluca Campo, MD, Antonio Manari, MD, Claudio Zussa, MD, Paolo Guastaroba, MS, Rossana De Palma, MD, PhD, and Tiziano Gherli, MD



N= 592 patients

### Patient Selection ?

CABG at 7 yrs: significantly reduced mortality, MI, repeat Revasc and similar incidence of stroke !! Very similar to results in younger patients !!

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# Coronary Artery Bypass Grafting With and Without Manipulation of the Ascending Aorta



### A Network Meta-Analysis

Dong Fang Zhao, BA,<sup>a,b</sup> J. James Edelman, PhD,<sup>a,b,c</sup> Michael Seco, MBBS,<sup>a,b,c</sup> Paul G. Bannon, PhD,<sup>a,b,c,d,e</sup> Michael K. Wilson, MBBS,<sup>b,c,e</sup> Michael J. Byrom, PhD,<sup>a,b,c,d,e</sup> Vinod Thourani, MD,<sup>f</sup> Andre Lamy, MD, MHSc,<sup>g</sup> David P. Taggart, PhD,<sup>h</sup> John D. Puskas, MD,<sup>i</sup> Michael P. Vallely, PhD<sup>a,b,c,d,e</sup>

013 studies: 37,720 patients with 4 Techniques

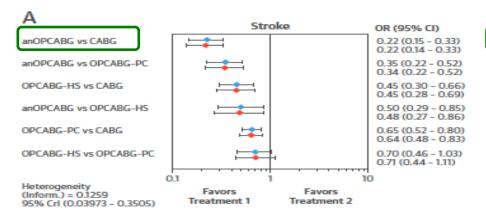
o(i) ONCABG (On-Pump)

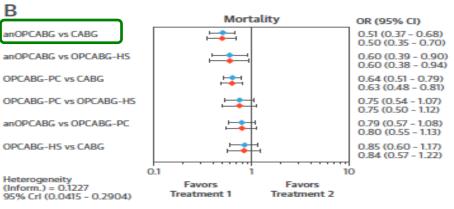
o(ii) OPCABG-PC (Off-Pump, Partial Clamp),

o(iii) OPCABG-HS (Off-Pump, Heartstring),

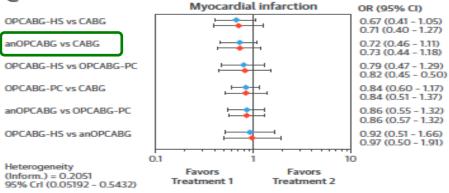
o(iv) ANOPCABG (Off-Pump, NTAT: No Touch Aortic Technique)

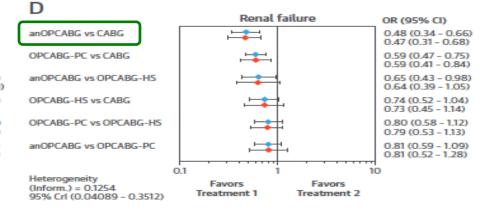
Effects on Death, Stroke, MI, Renal Failure, AF, Bleeding

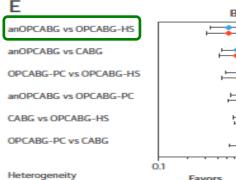




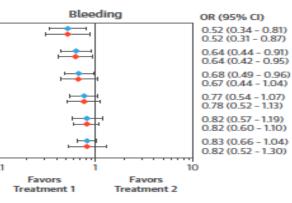
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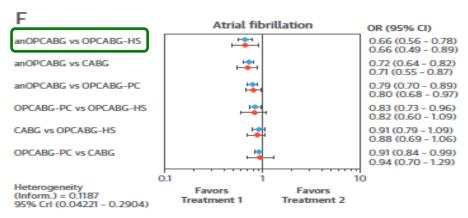






(Inform.) = 0.1143 95% Crl (0.03745 - 0.3146)





—•— Fixed Effects

— Random Effects (Informative Prior)

Challenges and Outcomes in Elderly/Fragile after CABG

## Problems with Available Data !!

(i) All Anecdotal (No specific RCTs of PCI/CABG > 80 years) (ii) In existing RCTs of PCI/CABG very few >80 years (iii) In observational studies usually few patients >80 years (iv) Often short duration of follow-up? ✓ Medical evaluation essential (Patient Selection !!!) Patient/Family decision essential

Prof DT Opinion: 'I prefer to operate on a 'good' 80 year old than a 'bad' 60 year old







### National Inpatient Sample Database 786,747 CABG 2010-14

### Acute and Stable Ischemic Heart Disease

#### CORONARY ARTERY BYPASS GRAFTING IN OCTOGENARIANS: MORBIDITY AND MORTALITY

Poster Contributions Poster Hall, Hall A/B Sunday, March 11, 2018, 3:45 p.m.-4:30 p.m.

Session Title: Special Populations: The Good, the Bad, the Old, the Young and the Sweet Ones (and Others Too!) Abstract Category: 02. Acute and Stable Ischemic Heart Disease: Clinical Presentation Number: 1262-455

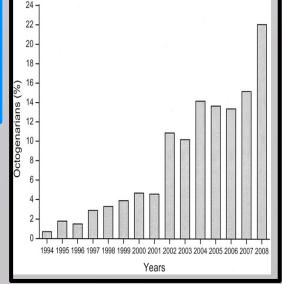
Authors: <u>Thaer Musa</u>, Gbolahan Ogunbayo, Naoki Misumida, Ahmed Abdel-Latif, Adrian Messerli, University of Kentucky, Lexington, KY, USA

	>80	<80	р
Mean age	82.9+/- 2.5		<0.1
female	34%	25%	<0.1
Caucasian	86%	79%	<0.1
CCF (%)	1.6%	0.7%	<0.05
CRF (%)	24.6%	13.9	<0.05
Anaemia (%)	32.2	19	<0.05

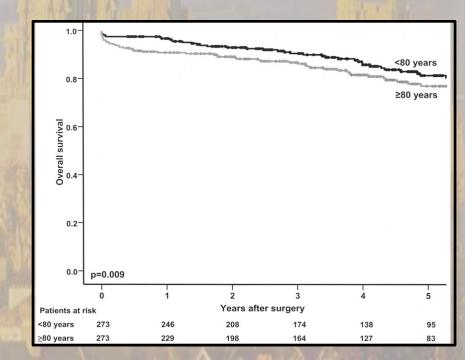
PPM	>80	<80	р
Mortality	4.1	1.4	
Length of Stay	9(6)	7(5)	
Shock (%)	6	4.4	
IABP	10.2	8.8	
Heart Block (%)	2	0.9	
PPM	2.7	0.8	
Tamponade (%)	0.6	0.3	
Shock (%)	6	4.4	
Acute Renal Failure	25.6	13.8	
Nursing Dacility	49.8	15.4	

### Coronary Artery Bypass Surgery in Octogenarians: Long-Term Outcome Can Be Better Than Expected

Juha Nissinen, MD, Jan-Ola Wistbacka, MD, PhD, Pertti Loponen, MD, Kari Korpilahti, MD, PhD, Kari Teittinen, MD, Markku Virkkilä, MD, PhD, Matti Tarkka, MD, PhD, and Fausto Biancari, MD, PhD



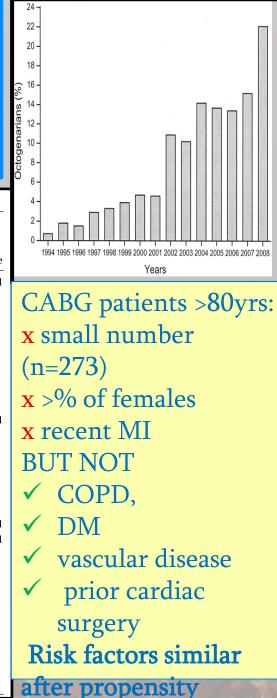
546 Propensity matched patients >80 CABG had increased
X Post op mortality (4.8% vs 2.6%; p=0.17)
X Atrial Fibrillation (55% vs 43%; p=0.008)
X Delirium (19% vs 11%; p=0.009)
But a similar incidence of
✓ Stroke (2.6% vs 2.2%; p=0.78)
✓ IABP use (2.2% vs 1.8%; p=0.76)
✓ Renal failure (2.6% vs 1.1%; p=0.34)
✓ ICU stay (2 vs 1.9 day; p=0.21)
✓ 5-year survival (77% vs 81%)



# Coronary Artery Bypass Surgery in Octogenarians: Long-Term Outcome Can Be Better Than Expected

Juha Nissinen, MD, Jan-Ola Wistbacka, MD, PhD, Pertti Loponen, MD, Kari Korpilahti, MD, PhD, Kari Teittinen, MD, Markku Virkkilä, MD, PhD, Matti Tarkka, MD, PhD, and Fausto Biancari, MD, PhD

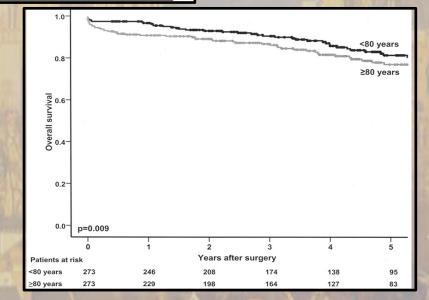
	Overall	Series	Propensity Score-Matched Pairs			
Variable	Octogenarian Patients (n = 274) (%)	Younger Patients (n = 3,200) (%)	p Value	Octogenarian Patients (n = 273) (%)	Younger Patients (n = 273) (%)	p Value
Age (years)	$82.5\pm1.9$	$66.6 \pm 8.8$	< 0.0001	$82.5\pm1.9$	$70.5\pm 6.8$	< 0.0001
Females	110 (40.1)	761 (23.8)	< 0.0001	109 (39.9)	109 (39.9)	1.00
Pulmonary disease	24 (8.8)	356 (11.1)	0.23	24 (8.8)	37 (13.6)	0.08
Diabetes	63 (23.0)	618 (19.3)	0.14	63 (23.1)	69 (25.3)	0.55
Renal failure	3 (1.1)	28 (0.9)	0.73	3 (1.1)	4 (1.5)	0.73
Cerebrovascular disease	42 (15.3)	373 (11.7)	0.07	41 (15.0)	43 (15.8)	0.81
Neurologic dysfunction	5 (1.8)	34 (1.1)	0.25	5 (1.8)	3 (1.1)	0.73
Myocardial infarction<3 months	106 (38.7)	628 (19.6)	< 0.0001	105 (38.5)	105 (38.5)	1.00
Extracardiac arteriopathy	30 (10.9)	270 (8.4)	0.16	30 (11.0)	26 (9.5)	0.57
Previous cardiac surgery	0 (0)	126 (3.9)	< 0.0001	0 (0)	17 (6.2)	< 0.0001
$LVEF \le 0.50$	89 (0.325)	10 (0.342)	0.56	89 (0.326)	98 (0.359)	0.42
Unstable angina pectoris	53 (19.3)	417 (13.0)	0.003	53 (19.4)	58 (21.2)	0.60
Critical preoperative status	6 (2.2)	33 (1.0)	0.08	6 (2.2)	11 (4.0)	0.22
Systolic pulmonary a. pressure >60 mm Hg	2 (0.7)	18 (0.6)	0.67	2 (0.7)	3 (1.1)	0.69
Emergency operation	21 (7.7)	180 (5.6)	0.17	21 (7.7)	29 (10.6)	0.24
Additive EuroSCORE	$7.6\pm2.4$	$3.9\pm2.7$	< 0.0001	$7.6\pm2.4$	$5.6\pm3.0$	< 0.0001
Logistic EuroSCORE (%)	$10.6\pm9.3$	$4.3\pm5.6$	< 0.0001	$10.6\pm9.6$	$7.0\pm8.2$	< 0.0001
Higgins score	$3.8\pm2.2$	$\textbf{2.4} \pm \textbf{2.4}$	< 0.0001	$3.8\pm2.2$	$3.5\pm2.8$	0.002
At least one mammary artery graft	220 (80.3)	2986 (93.3)	<0.0001	219 (80.2)	219 (80.2)	1.00
Bilateral mammary artery graft	3 (1.1)	515 (16.1)	< 0.0001	2 (0.2)	2 (0.2)	1.00
No. of distal anastomosis	$4.1 \pm 1.1$	$4.1\pm1.3$	0.61	$4.1 \pm 1.1$	$3.9\pm1.2$	0.13
Beating heart surgery	54 (19.7)	288 (9.0)	< 0.0001	53 (19.4)	53 (19.4)	1.00
Aortic cross-clamping time (minutes)	$71\pm30$	$80\pm28$	<0.0001	$71\pm30$	73 ± 31	0.50
Cardiopulmonary bypass time (minutes)	$101\pm 24$	103 ± 31	0.44	$101\pm24$	$105\pm34$	0.45



	C	Overall Series	Propensity Score-Matched Pairs			
Variable	Octogenarian Patients (n = 274) (%)	Younger Patients (n = 3,200) (%)	p Value	Octogenarian Patients (n = 273) (%)	Younger Patients (n = 273) (%)	p Value
Immediate postoperative outcome:						
30-day mortality	13 (4.7)	40 (1.3)	< 0.0001	13 (4.8)	7 (2.6)	0.17
Reoperation	18 (6.6)	161 (5.0)	0.27	18 (6.6)	20 (7.3)	0.74
Reoperation for bleeding	9 (3.3)	106 (3.3)	0.99	9 (3.3)	16 (5.9)	0.22
Stroke	7 (2.4)	7 (2.6)	0.88	7 (2.6)	6 (2.2)	0.78
Intraaortic balloon pump	6 (2.2)	26 (0.8)	0.02	6 (2.2)	5 (1.8)	0.76
Acute renal failure requiring dialysis	7 (2.6)	28 (0.9)	0.008	7 (2.6)	3 (1.1)	0.34
ICU stay (days)	$2.0\pm2.7$	$1.6\pm3.5$	< 0.0001	$2.0\pm2.7$	$1.9\pm3.2$	0.21
ICU stay $\geq$ 5 days	24 (8.8)	121 (3.8)	< 0.0001	24 (8.8)	19 (7.0)	0.43
Delirium	52 (19.0)	254 (8.0)	< 0.0001	52 (19.1)	30 (11.1)	0.009
Pneumonia	21 (7.7)	177 (5.5)	0.14	21 (7.7)	18 (6.6)	0.62
Atrial fibrillation	143 (55.4)	1142 (36.5)	< 0.0001	142 (55.3)	113 (43.6)	0.008
Combined adverse endpoint <sup>a</sup>	36 (13.1)	211 (6.6)	< 0.0001	36 (13.2)	29 (10.6)	0.36
Late postoperative outcome:			< 0.0001			0.009
1-year overall survival	90.8%	97.3%		90.8%	96.7%	
3-year overall survival	86.3%	93.9%		86.7%	90.5%	
5-year overall survival	76.6%	90.4%		77.0%	81.3%	
10-year overall survival	34.9%	76.1%		35.0%	55.3%	

Propensity matched patients >80 had increased X Post op mortality (4.8% vs 2.6%; p=0.17) X Atrial Fibrillation (55% vs 43%; p=.0.008) X Delirium (19% vs 11%; p=0.009) But a similar incidence of

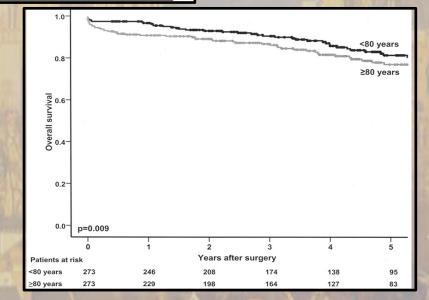
- ✓ Stroke (2.6% vs 2.2%; p=0.78)
- ✓ IABP use (2.2% vs 1.8%; p=0.76)
- ✓ Renal failure (2.6% vs 1.1%; p=0.34)
- ✓ ICU stay (2 vs 1.9 day; p=0.21)
- ✓ 5-year survival (77% vs 81%)



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Reoperation	18 (6.6)	161 (5.0)	0.27	18 (6.6)	20 (7.3)	0.74
Reoperation for bleeding	9 (3.3)	106 (3.3)	0.99	9 (3.3)	16 (5.9)	0.22
Stroke	7 (2.4)	7 (2.6)	0.88	7 (2.6)	6 (2.2)	0.78
Intraaortic balloon pump	6 (2.2)	26 (0.8)	0.02	6 (2.2)	5 (1.8)	0.76
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ICU stay (days)	$2.0\pm2.7$	$1.6\pm3.5$	< 0.0001	$2.0\pm2.7$	$1.9\pm3.2$	0.21
ICU stay $\geq$ 5 days	24 (8.8)	121 (3.8)	< 0.0001	24 (8.8)	19 (7.0)	0.43
Delirium	52 (19.0)	254 (8.0)	< 0.0001	52 (19.1)	30 (11.1)	0.009
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Late postoperative outcome:			< 0.0001			0.009
1-year overall survival	90.8%	97.3%		90.8%	96.7%	
3-year overall survival	86.3%	93.9%		86.7%	90.5%	
5-year overall survival	76.6%	90.4%		77.0%	81.3%	
10-year overall survival	34.9%	76.1%		35.0%	55.3%	

Propensity matched patients >80 had increased X Post op mortality (4.8% vs 2.6%; p=0.17) X Atrial Fibrillation (55% vs 43%; p=.0.008) X Delirium (19% vs 11%; p=0.009) But a similar incidence of

- ✓ Stroke (2.6% vs 2.2%; p=0.78)
- ✓ IABP use (2.2% vs 1.8%; p=0.76)
- ✓ Renal failure (2.6% vs 1.1%; p=0.34)
- ✓ ICU stay (2 vs 1.9 day; p=0.21)
- ✓ 5-year survival (77% vs 81%)



#### Long-term survival after use of internal thoracic artery in octogenarians is gender related [JTCVS 2015]

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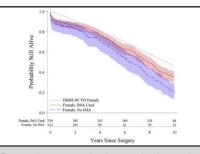
#### ABSTRACT

**Objective:** The goal of this study is to assess the benefits of a left internal thoracic artery as a bypass conduit in octogenarians undergoing elective coronary artery bypass grafting. We hypothesize that there is no survival advantage and that outcome may be gender related.

**Methods:** In a retrospective analysis of 1141 octogenarians (aged >80 years) undergoing isolated coronary artery bypass grafting from 1996 to 2012, patients were divided into 2 groups: Group I (coronary artery bypass grafting–left internal thoracic artery) included 870 patients (339 female/531 male), and group II (coronary artery bypass grafting–saphenous vein graft) included 271 patients (131 female/140 male).

Results: The overall 30-day mortality was 5.7%: 4.3% in group I and 7.0% in group II (P = .1). Group II had a lower trend of any postoperative complication (P = .05) and pneumonia (P = .05). When analyzed by gender, there were no discernable differences in long-term survival for male patients in group I (65% at 5 years and 29% at 10 years) versus male patients in group II (65% at 5 years and 31% at 10 years) (P = .2). However, survival was significantly greater for female patients in group I (70% at 5 years and 35% at 10 years) versus female patients in group II (63% at 5 years and 21% at 19 years) (P = .01). Multiple logistic and Cox regression analysis showed that left internal thoracic artery use is associated with improved survival in female patients (hazard ratio [HR], 0.72; confidence interval [CI], 0.56-0.93) but not in male patients (HR, 1.14; CI, 0.9-1.4). Advanced age was associated with an increased risk of mortality (HR, 1.08 per year; CI, 1.05-1.1). Both patient age (P = .01) and Society of Thoracic Surgeons-predicted 30-day mortality (P = .03) remain in the final model for 30-day mortality. The benefit of the left internal thoracic artery after coronary artery bypass grafting in octogenarians may be gender related.

**Conclusions:** This study shows that the benefit of the left internal thoracic artery in the octogenarian population undergoing coronary artery bypass grafting may be gender related. For elderly female patients, the use of the left internal thoracic artery as a bypass conduit was associated with better long-term survival, whereas no significant difference was found among the male population. The use of the left internal thoracic artery was associated with a greater postoperative pulmonary morbidity for the study population as a whole. The present study does not refute the benefit of the left internal thoracic artery–left anterior descending graft, but instead distinguishes a subset who might benefit more. (J Thorac Cardiovasc Surg 2015;150:891-9)



Time-varying outcome (survival curve): 10 years in female patient with ITA versus SVG.

#### Central Message

The benefit of the ITA after CABG in octogenarians may be gender related.

#### Perspective

In octogenarians, ITA use may improve longterm survival benefits in women but not in men. Use of the ITA in this population is associated with increased pulmonary complications. In frail octogenarians, use of an SVG instead of an ITA may be a justified alternative. The benefit of the ITA after CABG in octogenarians may be gender related.

See Editorial Commentary page 900.

