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ORIGINAL RESEARCH

Representation of Women in Randomized Trials in Cardiac Surgery: A Meta-Analysis

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BACKGROUND: Women have traditionally been underrepresented in randomized clinical trials (RCTs). We performed a systematic evaluation of the inclusion of women in cardiac surgery RCTs published in the past 2 decades.

METHODS AND RESULTS: MEDLINE, EMBASE, and the Cochrane Library were searched (2000 to July 2020) for RCTs written in English, comparing ≥2 adult cardiac surgical procedures. The percentage of women enrolled and its association with year of publication, sample size, mean age, funding source, geographic location, number of sites involved, and interventions tested were analyzed using a meta-analytic approach. Fifty-one trials were included. Of 25 425 total patients, 5029 were women (20.8%; 95% CI, 17.6–24.4; range, 0.5%–57.9%). The proportion of women dropped significantly during the study period (29.6% in 2000 versus 13.1% in 2019, $P<0.001$). Women were significantly more represented in European trials (26.2%; 95% CI, 21.2–31.9), and less represented in trials of coronary bypass surgery versus other interventions (16.8%; 95% CI, 12.3–22.7 versus 33.6%; 95% CI, 27.4–40.5; $P=0.0002$) and in trials enrolling younger patients ($P=0.009$); the percentage of women was higher in industry-sponsored versus non-industry sponsored trials (31.7%; 95% CI, 27.2–36.6 versus 15.5%; 95% CI, 10.0–23.2; $P=0.0004$) and was not associated with trial sample size ($P=0.52$) or study design (multicenter versus monocenter: $P=0.22$). After exclusion of trials conducted at Veteran Affairs centers, women representation was 24.4% (95% CI, 21.1–28.0; range, 10.4%–57.9%), with no significant changes during the study period.

CONCLUSIONS: The proportion of women in cardiac surgery trials is low and likely inadequate to provide meaningful estimates of the treatment effect.

Key Words: cardiac surgery ■ RCT ■ women

Women have traditionally been underrepresented in randomized clinical trials (RCTs) and, despite the efforts of funding agencies and of the academic community, this has not improved in recent years.[1] While systematic analyses of the patients' population included in clinical trials has been published for many fields of cardiology,[1] no similar evaluation has been published for cardiac surgery.

An adequate women representation in cardiac surgical trials that supports evidence-based practice is particularly important as female subjects have specific anatomic/functional characteristics and surgical outcomes[2–4] and generalization of the surgical results obtained in a prevalently male population may be inappropriate and potentially harmful.

We have performed a systematic evaluation of the inclusion of women in the cardiac surgery trials published in the past 2 decades.

METHODS

The data that support the findings of this study are available from the corresponding author upon reasonable request. This study follows the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[5] As no individual patient was involved, ethical approval was not requested.

A comprehensive search to identify RCTs comparing ≥2 adult cardiac surgical procedures published from 2000 was performed in July 2020 (Ovid

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CLINICAL PERSPECTIVE

What Is New?

- Women inclusion in cardiac surgery trials is low and likely inadequate to provide meaningful treatment effect estimates.

What Are the Clinical Implications?

- Substantial effort must be made by surgical trialists and funding agencies to promote the inclusion of women in cardiac surgery trials.

Nonstandard Abbreviations and Acronyms

VA	Veteran Affairs

MEDLINE, Ovid EMBASE, and the Cochrane Library). The search strategy included the following terms: "CABG", "off-pump coronary surgery", "on-pump coronary surgery", "arterial grafts", "bilateral internal mammary artery", "bilateral internal thoracic artery", "radial artery", "right gastroepiploic artery", "arterial revascularization", "saphenous vein graft", "mitral valve repair", "mitral valve replacement", "tricuspid valve", "aortic valve replacement", "aortic valve repair", "heart transplant", and "ventricular assist device" (the full search strategy is reported in the Data S1). Studies performed on patients with congenital cardiac abnormalities were not included in the search.

Studies were included in the final analysis if they were RCTs written in English and compared ≥2 adult cardiac surgical procedures. In case of multiple publications from the same RCT, the report that better described the study population was selected. Two investigators (A.D.F., M.D.M.) performed data extraction independently; a third investigator (M.G.) verified data. Extracted data included publication year, sample size, mean age, number and percentage of women, funding source, geographic location, number of sites involved, interventions tested, and whether sex was tested as a potential treatment effect modifier.

Proportions were calculated using the *metaprop* function of *meta package* in R. Inverse variance method was used for data pooling. Subgroup analysis was performed using random effect. Logit-transformation was performed to calculate CIs. DerSimonian-Laird estimator was used to estimate between-study variance. The Funnel plot and Egger test were used for estimation of publication bias.

As a sensitivity analysis, all comparisons were repeated after the exclusion of trials conducted at Veteran Affairs (VA) medical centers.

RESULTS

Fifty-one trials published between 2000 and 2020 were included (Table 1).[6–55] The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flowchart is reported in Figure S1. The median sample size was 225 patients (interquartile range [IQR], 125–394); 21 trials (41.2%) were multicentric (median number of sites, 13; IQR, 7–24), 3 (5.9%) involved patients from VA medical centers, 27 (52.9%) were from Europe, 12 (23.5%) from North America, 5 (9.8%) from Asia/Australia/South America, and 7 (13.7%) involved multiple continents. The tested interventions were coronary artery bypass grafting in 37 trials (72.5%), valve surgery in 7 trials (13.7%), saphenous vein graft harvesting for bypass surgery in 2 trials (3.9%), ventricular remodeling in 2 trials (3.9%), use of mechanical assistance devices in 2 trials (3.9%), and ablation of atrial fibrillation in cardiac surgery patients in 1 trial (1.9%). Trials received institutional support in 28 cases (54.9%), private support in 6 cases (11.8%), or mixed support in 3 (5.9%) cases. Primary outcomes were clinical events in 31 trials (60.8%), patency in 12 trials (23.5%), imaging in 7 trials (13.7%), and hemodynamic data in 1 trial (1.9%).

Among the 25 425 patients included, there were 5029 women (20.8%, 95% CI, 17.6–24.4, range 0.5%–57.9%) (Figure 1).[6–55]

Women proportion dropped significantly between the first and the past year of the study period (29.6% in 2000 versus 13.1% in 2019, $P<0.001$) (Figure 2).[6–55]

Only 3 trials (5.9%) formally tested sex as treatment effect modifier.

Women were significantly more represented in trials based in Europe (26.2%; 95% CI, 21.2–31.9) versus North America (11.9%; 95% CI, 4.1–29.9), Asia/Australia/South America (16.8%; 95% CI, 12.7–21.9), and those involving multiple continents (16.4%; 95% CI, 14.1–19.9) ($P=0.003$). Women were less represented in trials of coronary bypass surgery versus other interventions (16.8%; 95% CI, 12.3–22.7 versus 33.6%; 95% CI, 27.4–40.5; $P=0.0002$) and in trials enrolling younger patients ($P=0.009$; Figure 3)[6–55]; the percentage of female patients was higher in industry-sponsored versus non-industry sponsored trials (31.7%; 95% CI, 27.2–36.6 versus 15.5%; 95% CI, 10.0–23.2; $P=0.0004$) and was not significantly associated with the trial sample size ($P=0.52$) or study design (multicenter versus monocenter: $P=0.22$). No publication bias was found (Figure S2; Egger test P value=0.55).

Table 1. Main Features of the Included Trials

Study	Y	Total Sample Size (n)	Women (n)	Women (%)	Funding Source	Geographic Location	Multicenter/ Monocenter	No. of Centers	Interventions Tested
Acker et al[6]	2014	251	96	38.2	National Institutes of Health and the Canadian Institutes of Health	United States, Canada	Multicenter	22	MV repair vs MV replacement
ACORN[7]	2006	193	105	54.4	The authors of this article received grant support (further details not specified)	United States, Canada	Multicenter	29	MV surgery+CorCap cardiac support device vs MV surgery alone
Al-Ruzzeh et al[8]	2006	168	27	16.1	NR	UK	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
ART[9]	2010	3102	446	14.3	British Heart foundation (SP/03/001) and Medical Research Council (G0200390)	UK, Poland, Australia, Brazil, Italy, Austria, India	Multicenter	28	BITA vs SITA
BBS[10]	2010	339	121	35.7	Danish Heart Foundation (08-4-R64- A2029-B948-22480), Danish Medical Research Council, Copenhagen Hospital Corporations Medical Research Council, Rigshospitalet Research Council, Aase and Ejnar Danielsens Foundation, Gangsted Foundation, and Danish Agency for Science, Technology, and Innovation	Denmark	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
BHACAS 1-2[11]	2002	401	72	17.9	Garfield Weston Trust, Sir Siegmund Warburg's Voluntary Settlement, and the British Heart Foundation	UK	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
CADENCE-MIS[12]	2015	100	46	46	Edwards Lifesciences LLC	Germany	Multicenter	5	Mini-invasive AVR vs Full sternotomy AVR
Carrier et al[13]	2003	130	15	11.5	NR	Canada	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
CARRPO[14]	2009	331	39	11.8	Danish Heart Foundation and Lundbeck Foundation	Denmark	Monocenter	1	Total arterial revascularization vs SITA+SVG
CORONARY[15]	2012	4752	909	19.1	Canadian Institutes of Health Research	Argentina, Australia, Brazil, Canada, Chile, China, Colombia, Czech Republic, Estonia, France, India, Italy, The Netherlands, Sweden, Turkey, Ukraine, UK, Uruguay, United States	Multicenter	79	OFF-PUMP vs ON-PUMP CABG
COTRIP[16]	2019	100	36	36	Before starting this study, the protocol was given to both manufacturers. The study was then supported by an unrestricted grant from St. Jude Medical, Eschborn, Germany	Germany	Monocenter	1	Trifecta valve vs Perimount Magna Ease valve
CRISP[17]	2014	106	25	23.6	Medical Research Council/NIHR Efficacy and Mechanism Evaluation programme	UK, India	Multicenter	9	OFF-PUM vs ON-PUMP
Czerny et al[18]	2001	80	13	16.2	NR	Austria	Monocenter	1	OFF-PUMP vs ON-PUMP CABG

(*Continued*)

Table 1. Continued

Study	Y	Total Sample Size (n)	Women (n)	Women (%)	Funding Source	Geographic Location	Multicenter/ Monocenter	No. of Centers	Interventions Tested
DOORS[19]	2012	900	207	23.0	Danish Heart Foundation, Danish Centre for Health Technology Assessment, Danish Research Council for Health Sciences, Tove and John Girott's Foundation, Medtronic, Guidant, and Getinge	Denmark	Multicenter	4	OFF-PUMP vs ON-PUMP CABG
Falk et al[20]	2008	129	39	30.2	NR	Germany	Multicenter	2	MV Surgery (Loop technique) vs MV Surgery (Resection)
Fattouch et al[21]	2009	128	40	31.2	NR	Italy	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
Gillinov et al[22]	2016	260	120	46.1	National Institutes of Health and the Canadian Institutes of Health Research	United States, Canada	Multicenter	20	MV Surgery+AF ablation vs MV Surgery alone
Glineur et al[23]	2016	304	40	13.1	Grant no. 3.4600.04 from the Fonds de la recherché scientifique médicale, Brussels, Belgium	Belgium	Monocenter	1	BITA Y vs BITA IN SITU
Goldman et al[24]	2011	733	6	0.8	The Veteran Affairs Cooperative Studies Program	United States	Multicenter	11	RA vs SVG
GOPCABE[25]	2013	2394	755	31.5	Unrestricted grant from Maquet	Germany	Multicenter	12	OFF-PUMP vs ON-PUMP CABG
Halfwerk et al[26]	2019	125	33	26.4	Maquet Netherlands (travel grant to present part of this work at the 2017 Society for Cardiothoracic Surgery Annual Meeting in Belfast)	The Netherlands	Monocenter	1	Minimal invasive extra corporeal circulation vs Advanced extra corporeal circulation in Aortic valve surgery
JOCRI[27]	2005	167	22	13.2	Health and Labor Science Research Grant 14-013 from the Japanese Ministry of Health, Labor, and Welfare	Japan	Multicenter	5	OFF-PUMP vs ON-PUMP CABG
Karolak et al[28]	2007	299	58	19.4	Funding Sources Division of Cardiac Surgery and the Maritime Heart Centre at Dalhousie University (Halifax, Nova Scotia)	Canada	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
Khan et al[29]	2004	103	13	12.6	The British Heart Foundation (PG/ 9912) and the Royal Brompton and Harefield National Health Service Trust Clinical Research Committee. Medtronic Inc. supplied the Octopus II equipment for the study free of cost	UK	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
Légaré et al[30]	2004	300	59	19.7	Maritime Heart Center	Canada	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
Lemma et al[31]	2012	411	126	30.7	Medtronic, Italy	Italy, Switzerland	Multicenter	8	OFF-PUMP vs ON-PUMP CABG
Lingaas et al[32]	2004	120	26	21.6	NR	Norway	Monocenter	1	OFF-PUMP vs ON-PUMP CABG

(*Continued*)

Table 1. Continued

Study	Y	Total Sample Size (n)	Women (n)	Women (%)	Funding Source	Geographic Location	Multicenter/ Monocenter	No. of Centers	Interventions Tested
MASS III[33]	2010	308	65	21.1	This work was supported partially by a research grant from the Zerbini Foundation, Sao Paulo, Brazil, and Medical School University of Sao Paulo	Brazil	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
Michaux et al[34]	2011	50	8	16	Supported in part by the Swiss Society of Anesthesiology and Reanimation	Switzerland	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
Michler et al[35]	2016	301	96	31.9	Funded by the National Institutes of Health and the Canadian Institutes of Health Research	United States , Canada	Multicenter	26	CABG+MV Repair vs CABG alone
Muneretto et al[36]	2003	176	69	39.2	NR	Italy	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
Myers et al[37]	2000	162	48	29.6	Supported in part by Marshfield Clinic Physician Research Specific Restricted Funds, and the Gwen D. Sebold Award	United States	Monocenter	1	Total arterial revascularization vs SITA+SVG
OCTOPUS[38]	2001	281	137	48.7	Funded entirely by the Netherlands National Health Insurance Council	The Netherlands	Multicenter	3	OFF-PUMP vs ON-PUMP CABG
Pegg et al[39]	2008	60	8	13.3	The British Heart Foundation, the Medical Research Council, and the Wellcome Trust	UK	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
PRAGUE-4[40]	2004	388	225	57.9	Grant NA 6569–3 of the Internal Grant Agency of the Ministry of Health of the Czech Republic	Czech Republic	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
PRAGUE-6[41]	2016	206	86	41.7	Supported by "P35 - PRVOU" - the Scientific Plan of Charles, University in Prague, the Czech Republic, granted by the Ministry of Health of the Czech Republic	Czech Republic	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
PROMISS[42]	2010	150	24	16	Merck Foundation and Sociedade de Gestao Hospitalar Cruz Vermelha Portuguesa SA	Portugal	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
RAPCO RITA[43]	2010	394	41	10.4	NR	Australia	Monocenter	1	RA vs RITA
RAPCO SVG[43]	2010	225	43	19.1	NR	Australia	Monocenter	1	RA vs SVG
RAPS[44]	2004	541	75	13.9	Grant (MT-13883) from the Canadian Institutes of Health Research	Canada, New Zealand	Multicenter	13	RA vs SVG
REGROUP[45]	2019	1150	6	0.5	Funded by the Cooperative Studies Program, Office of Research and Development, Department of Veterans Affairs	United States	Multicenter	16	Endoscopic SVG harvesting vs Open SVG harvesting
RESTOR-MV[46]	2010	147	35	23.8	The study was terminated when the sponsor failed to secure ongoing funding; Myocor, Inc., Maple Grove, Minnesota	United States , India	Multicenter	21	Coapsys ventricular reshaping vs standard surgery in patients submitted to CABG+MV Repair or CABG alone
ROOBY[47]	2009	2203	14	0.6	The Department of Veterans Affairs Cooperative Studies Program	United States	Multicenter	18	OFF-PUMP vs ON-PUMP CABG

(*Continued*)

Table 1. Continued

Study	Y	Total Sample Size (n)	Women (n)	Women (%)	Funding Source	Geographic Location	Multicenter/ Monocenter	No. of Centers	Interventions Tested
RSVP[48]	2008	103	5	4.8	The Kate Weeke's Fellowship, Royal College of Surgeon of England (Dr Chong), the Clinical Research Committee, Royal Brompton and Harefield NHS Trust (Dr Webb), the Victor Phillip Dahdaleh Charitable Foundation (Dr Webb)	UK	Monocenter	1	RA vs SVG
Shahin et al[49]	2005	96	38	39.6	NR	The Netherlands	Monocenter	1	PYSHIO Ring vs Classic Ring
SMART[50]	2004	197	45	22.8	Grants from Medtronic Inc and the Carlyle Fraser Heart Center Foundation (Atlanta, GA)	United States	Monocenter	1	OFF-PUMP vs ON-PUMP CABG
STAND-In-Y[51]	2009	409	236	57.7	NR	Italy	Monocenter	1	RA vs SVG
STICH[52]	2009	1000	147	14.7	Grants (5U01-HL-69015, 5U01-HL-69013, and 5U01-HL-69010) from the National Heart, Lung, and Blood Institute	Poland, Russia, Canada, United States, Italy, Czech Republic, Australia, Austria, Germany, Serbia, Lithuania, Singapore, Sweden, Thailand, Brazil, New Zealand, Uruguay, Norway, Hungary, Turkey, Malaysia, Greece, Belgium	Multicenter	127	CABG+Surgical ventricular reconstruction vs CABG alone
SUPERIOR SVG[53]	2019	250	31	12.4	Heart and Stroke Foundation of Canada (Grant# 7092) and the Canadian Institutes of Health Research-funded Canadian Network and Centre for Trials Internationally (CANNeCTIN)	Canada, Sweden, Israel	Multicenter	12	No touch SVG vs conventional SVG
Vukovic et al[54]	2019	100	28	28	NR	Serbia	Monocenter	1	Ministernotomy vs conventional sternotomy in aortic valve surgery
Yu et al[55]	2014	102	25	24.5	NR	China	Monocenter	1	OFF-PUMP vs ON-PUMP CABG

AF indicates atrial fibrillation; AVR, aortic valve replacement; BITA, bilateral internal thoracic artery; CABG, coronary artery bypass grafting; MV, mitral valve; NIHR, National Institute for Health Research; NR, not reported; RA, radial artery; SITA, single internal thoracic artery; and SVG, saphenous vein graft.

List of trials' acronyms: ACORN indicates Acorn Clinical Trial; ART, Arterial Revascularization Trial; BBS, Best Bypass Surgery Trial; BHACAS, Beating Heart Against Cardioplegic Arrest Studies; CADENCE-MIS, EDWARDS INTUITY Valve System CADENCE-MIS Study; CARRPO, Copenhagen Arterial Revascularization Randomized Patency and Outcome trial; CORONARY, CABG Off or On Pump Revascularization Study; COTRIP, Randomized Comparison of Trifecta and Perimount Magna Ease Supraannular Aortic Xenografts study; CRISP, Coronary Artery Bypass Grafting in High-Risk Patients Randomised to Off- or On-Pump Surgery; DOORS, Danish On-Pump Versus Off-Pump Randomization Study; GOPCABE, German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients; JOCRI, Japanese Off-Pump Coronary Revascularization Investigation; MASS III, The Medicine, Angioplasty, or Surgery Study III; OCTOPUS, Early Outcome After Off-Pump Versus On-Pump Coronary Bypass Surgery; PRAGUE-4; A randomized comparison between off-pump and on-pump surgery; PRAGUE-6, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥6; PROMISS, Prospective Randomized Comparison of Off-Pump and On-Pump Multi-Vessel Coronary Artery Bypass Surgery; RAPCO, Radial Artery Patency and Clinical Outcomes; RAPS, Radial Artery Patency Study; REGROUP, Randomized Endovein Graft Prospective Trial; RESTOR-MV, Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve; ROOBY, Veteran Affairs Randomized On/Off Bypass Study; RSVP, Radial Artery Versus Saphenous Vein Patency Trial; SMART, Surgical Management of Arterial Revascularization Therapies Trial; STAND-In-Y, Arterial revascularization in primary coronary artery bypass grafting: direct comparison of 4 strategies; STICH, Surgical Treatment for Ischemic Heart Failure Trial; and SUPERIOR SVG, Surgical and Pharmacological Novel Interventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting Surgery Trial.

Sensitivity Analysis Excluding the VA Trials

After the exclusion of the 3 trials conducted at VA centers (Goldman et al., REGROUP [Randomized Trial of Endoscopic or Open Vein-Graft Harvesting for Coronary-Artery Bypass], ROOBY [Randomized On/Off Bypass Study]),[24,45,47] women were 5003 out of 21339 total patients (24.4%; 95% CI, 21.1–28.0; range, 10.4%–57.9%). No significant difference in the

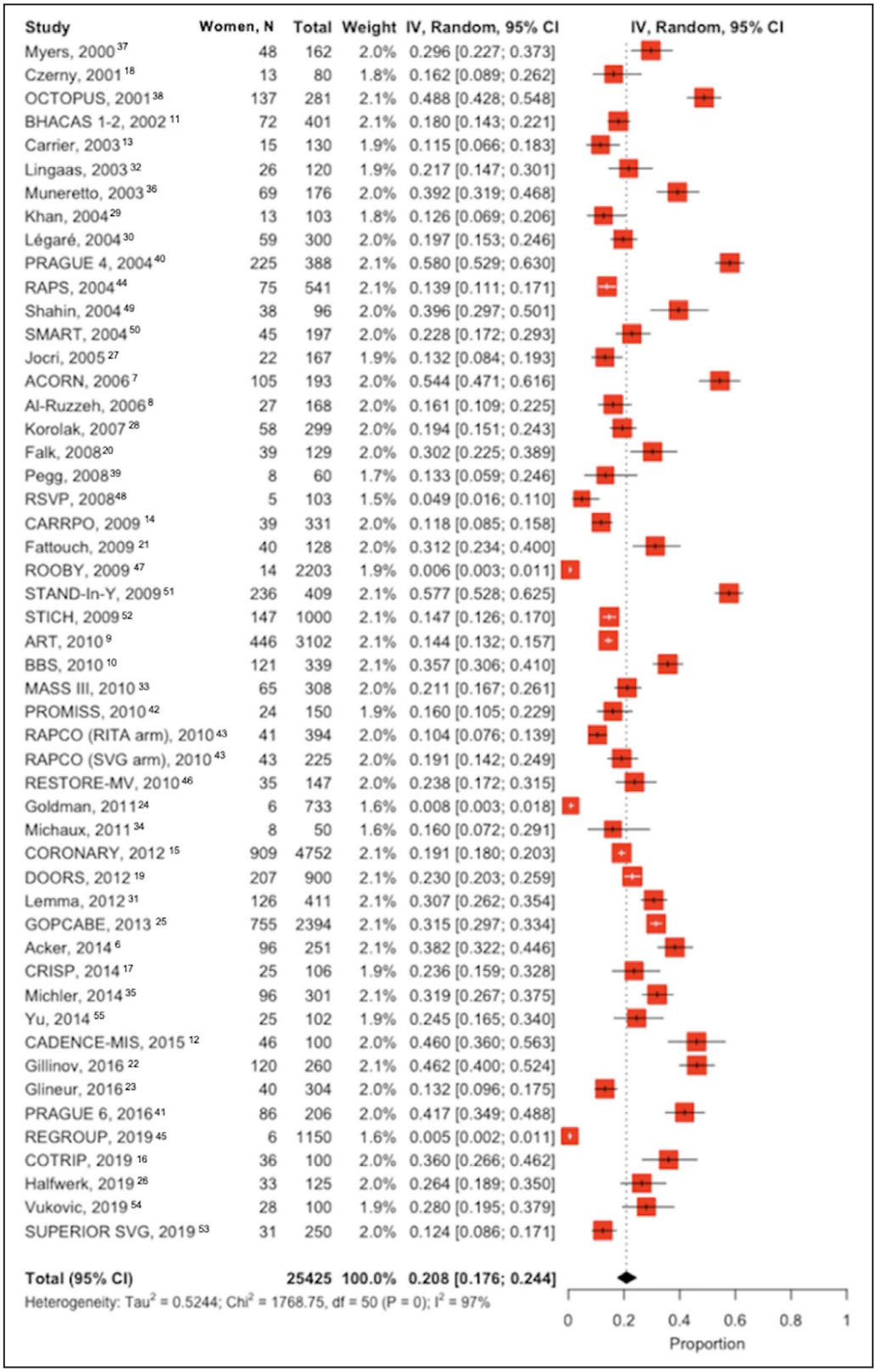


Figure 2. Proportions of women in cardiac surgery trials by study period.
ACORN indicates Acorn Clinical Trial; ART, Arterial Revascularization Trial; BBS, Best Bypass Surgery Trial; BHACAS, Beating Heart Against Cardioplegic Arrest Studies; CADENCE-MIS, EDWARDS INTUITY Valve System CADENCE-MIS Study; CARRPO, Copenhagen Arterial Revascularization Randomized Patency and Outcome trial; CORONARY, CABG Off or On Pump Revascularization Study; COTRIP, Randomized Comparison of Trifecta and Perimount Magna Ease Supraannular Aortic Xenografts study; CRISP, Coronary Artery Bypass Grafting in High-Risk Patients Randomised to Off- or On-Pump Surgery; DOORS, Danish On-Pump Versus Off-Pump Randomization Study; GOPCABE, German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients; JOCRI, Japanese Off-Pump Coronary Revascularization Investigation; MASS III, The Medicine, Angioplasty, or Surgery Study III; OCTOPUS, Early Outcome After Off-Pump Versus On-Pump Coronary Bypass Surgery; PRAGUE-4; A randomized comparison between off-pump and on-pump surgery; PRAGUE-6, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥6; PROMISS, Prospective Randomized Comparison of Off-Pump and On-Pump Multi-Vessel Coronary Artery Bypass Surgery; RAPCO, Radial Artery Patency and Clinical Outcomes; RAPS, Radial Artery Patency Study; REGROUP, Randomized Endovein Graft Prospective Trial; RESTOR-MV, Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve; ROOBY, Veteran Affairs Randomized On/Off Bypass Study; RSVP, Radial Artery Versus Saphenous Vein Patency Trial; SMART, Surgical Management of Arterial Revascularization Therapies Trial; STAND-In-Y, Arterial revascularization in primary coronary artery bypass grafting: direct comparison of 4 strategies; STICH, Surgical Treatment for Ischemic Heart Failure Trial; and SUPERIOR SVG, Surgical and Pharmacological Novel Interventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting Surgery Trial.

proportion of women was found comparing the beginning versus the end of the study period (29.6% in 2000 versus 24.4% in 2019, *P*=0.45) (Figure S3).

Women were significantly more represented in trials based in North America (29.8%; 95% CI, 21.0–40.3) and Europe (26.2%; 95% CI, 21.2–31.9) versus Asia/Australia/South America (16.8%; 95% CI, 12.7–21.9) and those involving multiple continents (16.4%; 95% CI, 14.1–19.9) (*P*=0.003).

Women were less represented in trials of coronary bypass surgery versus other interventions (21.4%; 95% CI, 17.8–25.5 versus 33.6%; 95% CI, 27.4–40.5; *P*=0.001), but not in trials enrolling younger patients (*P*=0.17); the percentage of female patients was higher in industry-sponsored versus non-industry sponsored trials (31.7%; 95% CI, 27.2–36.6 versus 21.7%; 95% CI, 17.1–27.0; *P*=0.002) and was not significantly associated with the trial sample size (*P*=0.42) or study design (multicenter versus monocenter: *P*=0.26). No publication bias was found (Figure S4; Egger test *P* value=0.66).

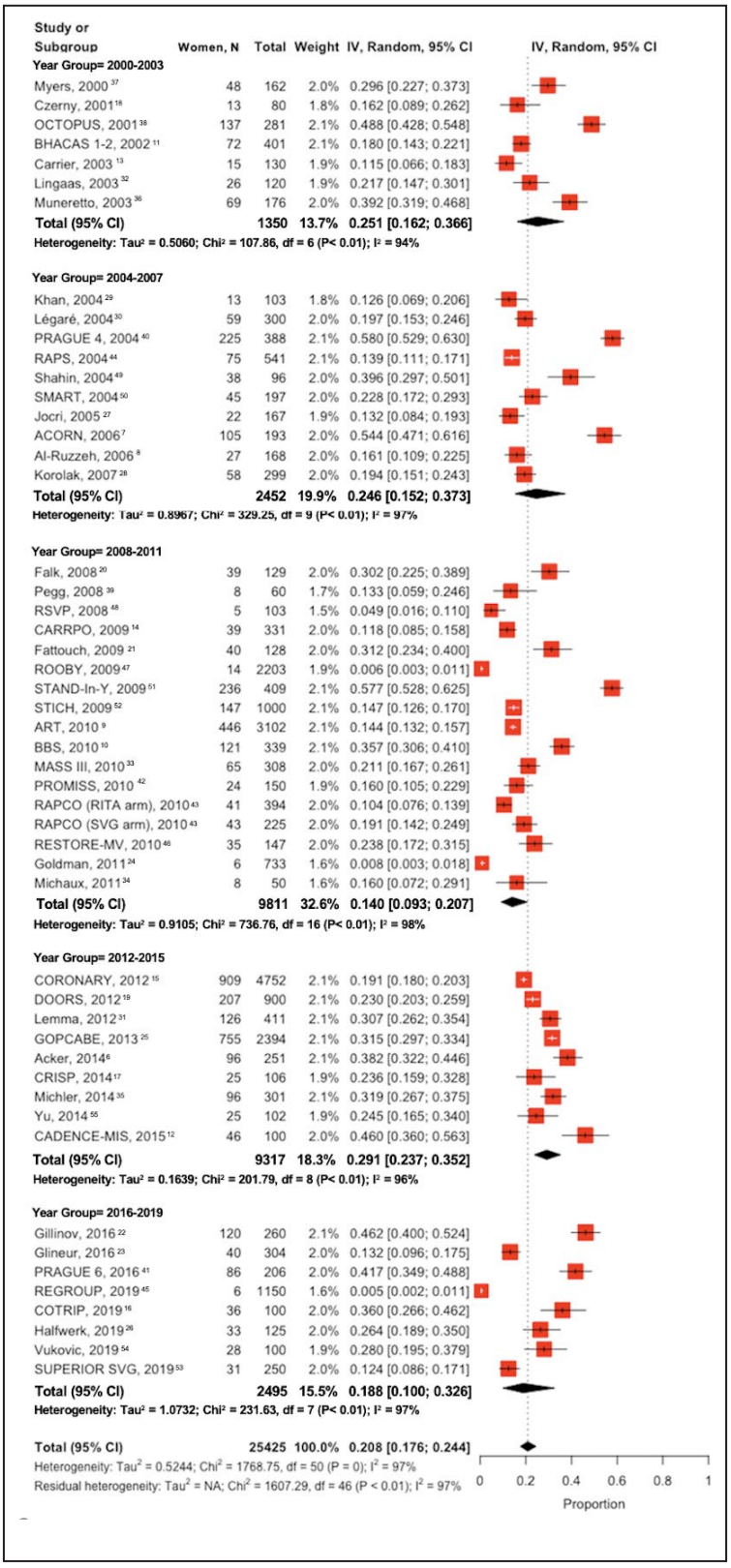
DISCUSSION

Generalizability of RCT results to both sexes depends on having a sufficient number of men and women. However, underrepresentation of women in RCTs in general, and in cardiac surgery trials in particular, remains an unsolved issue.

For example, the available observational evidence on the use of multiple arterial grafting in women is conflicting, with some studies suggesting and others refuting a clinical benefit for female patients who receive >1 arterial graft for coronary artery bypass graft (CABG).[56–60] In the only large RCT that has tested the multiple arterial grafts hypothesis (the Arterial Revascularization Trial)[61] women represented only 15% of the study population and sex was not formally tested as a treatment effect modifier in the main analysis.

Similarly, the effect of off-pump surgery for CABG in women has been associated with contradictory results.[62–64] However, the percentage of women enrolled in the largest off-pump trials was low (0.5%, 19.2%, and 31.5% in ROOBY,[47] CORONARY [CABG Off or On Pump Revascularization Study],[15] and GOPCABE [German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients Study],[25] respectively). It is noteworthy that of the 3 mentioned trials only 1 (ie, CORONARY)[15] formally tested sex as a treatment effect modifier.

Figure 1. Proportions of women in cardiac surgery trials.
Squares represent the study weight; diamonds represent the pooled proportion of each subgroup with CIs; dots in the squares represent the study proportion and bars are the CIs (white when the CI is fully within the square (ie, very small CI, otherwise black [ie, large CI]). The dotted line represents the cumulative proportion. ACORN indicates Acorn Clinical Trial; ART, Arterial Revascularization Trial; BBS, Best Bypass Surgery Trial; BHACAS, Beating Heart Against Cardioplegic Arrest Studies; CADENCE-MIS, EDWARDS INTUITY Valve System CADENCE-MIS Study; CARRPO, Copenhagen Arterial Revascularization Randomized Patency and Outcome trial; CORONARY, CABG Off or On Pump Revascularization Study; COTRIP, Randomized Comparison of Trifecta and Perimount Magna Ease Supraannular Aortic Xenografts study; CRISP, Coronary Artery Bypass Grafting in High-Risk Patients Randomised to Off- or On-Pump Surgery; DOORS, Danish On-Pump Versus Off-Pump Randomization Study; GOPCABE, German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients; IV, inverse variance; JOCRI, Japanese Off-Pump Coronary Revascularization Investigation; MASS III, The Medicine, Angioplasty, or Surgery Study III; OCTOPUS, Early Outcome After Off-Pump Versus On-Pump Coronary Bypass Surgery; PRAGUE-4; A randomized comparison between off-pump and on-pump surgery; PRAGUE-6, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥6; PROMISS, Prospective Randomized Comparison of Off-Pump and On-Pump Multi-Vessel Coronary Artery Bypass Surgery; RAPCO, Radial Artery Patency and Clinical Outcomes; RAPS, Radial Artery Patency Study; REGROUP, Randomized Endovein Graft Prospective Trial; RESTOR-MV, Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve; ROOBY, Veteran Affairs Randomized On/Off Bypass Study; RSVP, Radial Artery Versus Saphenous Vein Patency Trial; SMART, Surgical Management of Arterial Revascularization Therapies Trial; STAND-In-Y, Arterial revascularization in primary coronary artery bypass grafting: direct comparison of 4 strategies; STICH, Surgical Treatment for Ischemic Heart Failure Trial; and SUPERIOR SVG, Surgical and Pharmacological Novel Interventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting Surgery Trial.



In the valve literature, the COTRIP (Randomized Comparison of Trifecta and Perimount Magna Ease Supraannular Aortic Xenografts study) trial[16] tested the use of 2 different prosthetic aortic valves in patients with aortic stenosis undergoing aortic valve replacement. Again, the majority of included patients were men (64%) and sex was not formally tested as a treatment effect modifier.

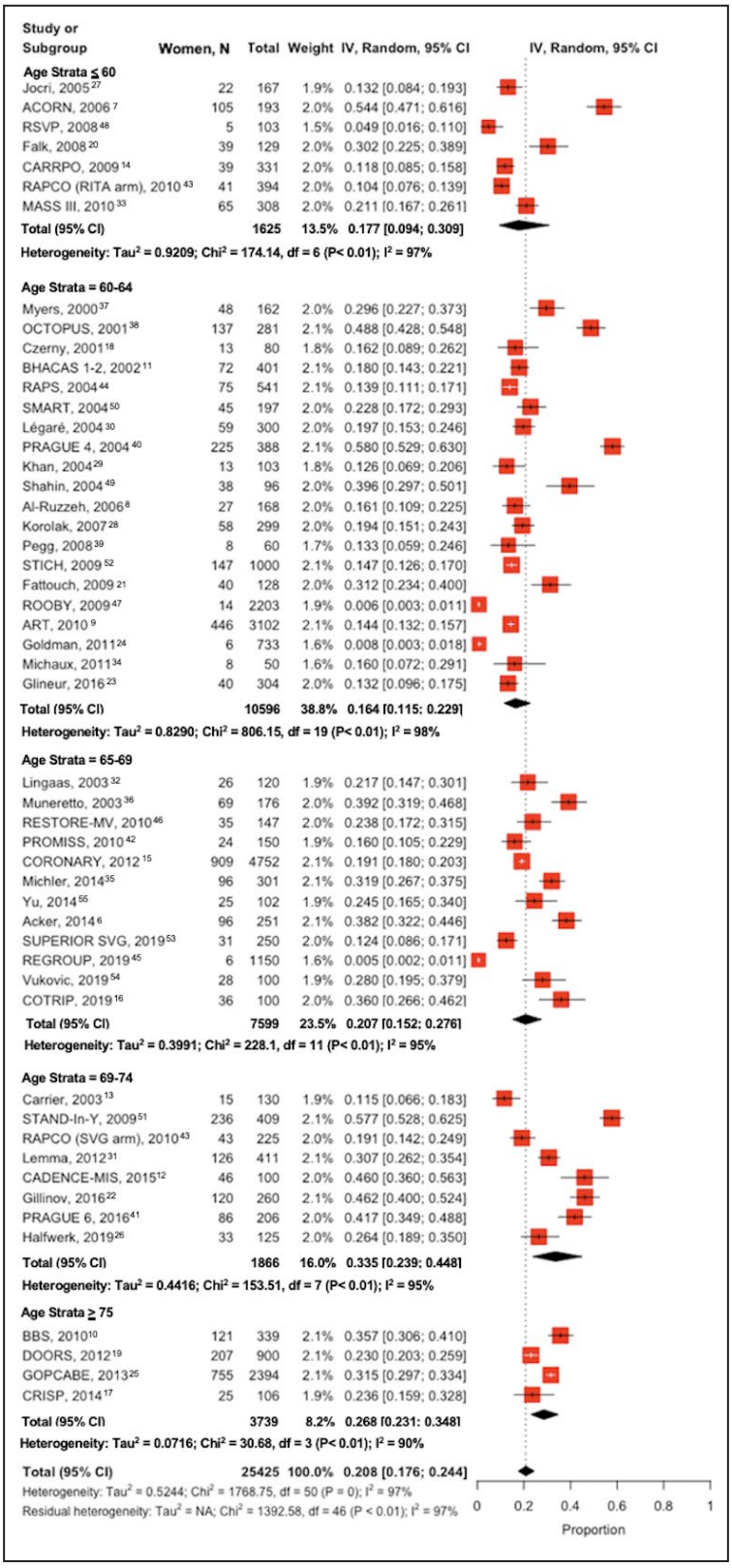

Study or Subgroup
Women, N
Total
Weight
IV, Random, 95% CI
IV, Random, 95% CI
Age Strata ≤ 60
Jocri, 2005 27 22 167 1.9% 0.132 [0.084; 0.193]
ACORN, 2006 7 105 193 2.0% 0.544 [0.471; 0.616]
RSVP, 2008 48 5 103 1.5% 0.049 [0.016; 0.110]
Falk, 2008 20 39 129 2.0% 0.302 [0.225; 0.389]
CARRPO, 2009 14 39 331 2.0% 0.118 [0.085; 0.158]
RAPCO (RITA arm), 2010 43 41 394 2.0% 0.104 [0.076; 0.139]
MASS III, 2010 33 65 308 2.0% 0.211 [0.167; 0.261]
Total (95% CI) 1625 13.5% 0.177 [0.094; 0.309]
Heterogeneity: Tau² = 0.9209; Chi² = 174.14, df = 6 (P< 0.01); I² = 97%
Age Strata = 60-64
Myers, 2000 37 48 162 2.0% 0.296 [0.227; 0.373]
OCTOPUS, 2001 38 137 281 2.1% 0.488 [0.428; 0.548]
Czerny, 2001 18 13 80 1.8% 0.162 [0.089; 0.262]
BHACAS 1-2, 2002 11 72 401 2.1% 0.180 [0.143; 0.221]
RAPS, 2004 44 75 541 2.1% 0.139 [0.111; 0.171]
SMART, 2004 50 45 197 2.0% 0.228 [0.172; 0.293]
Légaré, 2004 30 59 300 2.0% 0.197 [0.153; 0.246]
PRAGUE 4, 2004 40 225 388 2.1% 0.580 [0.529; 0.630]
Khan, 2004 29 13 103 1.8% 0.126 [0.069; 0.206]
Shahin, 2004 49 38 96 2.0% 0.396 [0.297; 0.501]
Al-Ruzzeh, 2006 8 27 168 2.0% 0.161 [0.109; 0.225]
Korolak, 2007 28 58 299 2.0% 0.194 [0.151; 0.243]
Pegg, 2008 39 8 60 1.7% 0.133 [0.059; 0.246]
STICH, 2009 52 147 1000 2.1% 0.147 [0.126; 0.170]
Fattouch, 2009 21 40 128 2.0% 0.312 [0.234; 0.400]
ROOBY, 2009 47 14 2203 1.9% 0.006 [0.003; 0.011]
ART, 2010 9 446 3102 2.1% 0.144 [0.132; 0.157]
Goldman, 2011 24 6 733 1.6% 0.008 [0.003; 0.018]
Michaux, 2011 34 8 50 1.6% 0.160 [0.072; 0.291]
Glineur, 2016 23 40 304 2.0% 0.132 [0.096; 0.175]
Total (95% CI) 10596 38.8% 0.164 [0.115; 0.229]
Heterogeneity: Tau² = 0.8290; Chi² = 806.15, df = 19 (P< 0.01); I² = 98%
Age Strata = 65-69
Lingaas, 2003 32 26 120 1.9% 0.217 [0.147; 0.301]
Muneretto, 2003 36 69 176 2.0% 0.392 [0.319; 0.468]
RESTORE-MV, 2010 46 35 147 2.0% 0.238 [0.172; 0.315]
PROMISS, 2010 42 24 150 1.9% 0.160 [0.105; 0.229]
CORONARY, 2012 15 909 4752 2.1% 0.191 [0.180; 0.203]
Michler, 2014 35 96 301 2.1% 0.319 [0.267; 0.375]
Yu, 2014 55 25 102 1.9% 0.245 [0.165; 0.340]
Acker, 2014 6 96 251 2.1% 0.382 [0.322; 0.446]
SUPERIOR SVG, 2019 53 31 250 2.0% 0.124 [0.086; 0.171]
REGROUP, 2019 45 6 1150 1.6% 0.005 [0.002; 0.011]
Vukovic, 2019 54 28 100 1.9% 0.280 [0.195; 0.379]
COTRIP, 2019 16 36 100 2.0% 0.360 [0.266; 0.462]
Total (95% CI) 7599 23.5% 0.207 [0.152; 0.276]
Heterogeneity: Tau² = 0.3991; Chi² = 228.1, df = 11 (P< 0.01); I² = 95%
Age Strata = 69-74
Carrier, 2003 13 15 130 1.9% 0.115 [0.066; 0.183]
STAND-In-Y, 2009 51 236 409 2.1% 0.577 [0.528; 0.625]
RAPCO (SVG arm), 2010 43 43 225 2.0% 0.191 [0.142; 0.249]
Lemma, 2012 31 126 411 2.1% 0.307 [0.262; 0.354]
CADENCE-MIS, 2015 12 46 100 2.0% 0.460 [0.360; 0.563]
Gillinov, 2016 22 120 260 2.1% 0.462 [0.400; 0.524]
PRAGUE 6, 2016 41 86 206 2.0% 0.417 [0.349; 0.488]
Halfwerk, 2019 26 33 125 2.0% 0.264 [0.189; 0.350]
Total (95% CI) 1866 16.0% 0.335 [0.239; 0.448]
Heterogeneity: Tau² = 0.4416; Chi² = 153.51, df = 7 (P< 0.01); I² = 95%
Age Strata ≥ 75
BBS, 2010 10 121 339 2.1% 0.357 [0.306; 0.410]
DOORS, 2012 19 207 900 2.1% 0.230 [0.203; 0.259]
GOPCABE, 2013 25 755 2394 2.1% 0.315 [0.297; 0.334]
CRISP, 2014 17 25 106 1.9% 0.236 [0.159; 0.328]
Total (95% CI) 3739 8.2% 0.268 [0.231; 0.348]
Heterogeneity: Tau² = 0.0716; Chi² = 30.68, df = 3 (P< 0.01); I² = 90%
Total (95% CI) 25425 100.0% 0.208 [0.176; 0.244]
Heterogeneity: Tau² = 0.5244; Chi² = 1768.75, df = 50 (P = 0); I² = 97%
Residual heterogeneity: Tau² = NA; Chi² = 1392.58, df = 46 (P < 0.01); I² = 97%
0
0.2
0.4
0.6
0.8
1
Proportion

Figure 3. Proportions of women in cardiac surgery trials by age groups.
ACORN indicates Acorn Clinical Trial; ART, Arterial Revascularization Trial; BBS, Best Bypass Surgery Trial; BHACAS, Beating Heart Against Cardioplegic Arrest Studies; CADENCE-MIS, EDWARDS INTUITY Valve System CADENCE-MIS Study; CARRPO, Copenhagen Arterial Revascularization Randomized Patency and Outcome trial; CORONARY, CABG Off or On Pump Revascularization Study; COTRIP, Randomized Comparison of Trifecta and Perimount Magna Ease Supraannular Aortic Xenografts study; CRISP, Coronary Artery Bypass Grafting in High-Risk Patients Randomised to Off- or On-Pump Surgery; DOORS, Danish On-Pump Versus Off-Pump Randomization Study; GOPCABE, German Off-Pump Coronary Artery Bypass Grafting in Elderly Patients; JOCRI, Japanese Off-Pump Coronary Revascularization Investigation; MASS III, The Medicine, Angioplasty, or Surgery Study III; OCTOPUS, Early Outcome After Off-Pump Versus On-Pump Coronary Bypass Surgery; PRAGUE-4; A randomized comparison between off-pump and on-pump surgery; PRAGUE-6, Off-pump versus on-pump coronary artery bypass graft surgery in patients with EuroSCORE ≥6; PROMISS, Prospective Randomized Comparison of Off-Pump and On-Pump Multi-Vessel Coronary Artery Bypass Surgery; RAPCO, Radial Artery Patency and Clinical Outcomes; RAPS, Radial Artery Patency Study; REGROUP, Randomized Endovein Graft Prospective Trial; RESTOR-MV, Randomized Evaluation of a Surgical Treatment for Off-Pump Repair of the Mitral Valve; ROOBY, Veteran Affairs Randomized On/Off Bypass Study; RSVP, Radial Artery Versus Saphenous Vein Patency Trial; SMART, Surgical Management of Arterial Revascularization Therapies Trial; STAND-In-Y, Arterial revascularization in primary coronary artery bypass grafting: direct comparison of 4 strategies; STICH, Surgical Treatment for Ischemic Heart Failure Trial; and SUPERIOR SVG, Surgical and Pharmacological Novel Interventions to Improve Overall Results of Saphenous Vein Graft Patency in Coronary Artery Bypass Grafting Surgery Trial.

Our data showed a significant drop in women proportion during the study period (2000–2020) when all trials were included in the analysis.

It is interesting to note that when trials conducted at VA medical centers were excluded from the analysis the temporal drop in women representation disappeared and North American RCTs were found to be those enrolling the highest proportion of women (29.8%). The fact that trials funded by one of the most active US agencies in cardiac surgery prevalently enroll male subjects (the mean prevalence of men in the 3 VA studies included was 99.4%) explains this result.

The lower representation of women in CABG RCTs was confirmed even after the exclusion of trials conducted at VA centers. While one might speculate that these disparities could be in part because of inherent biases within the cardiovascular care system leading to lower referral for interventions for female patients with coronary artery disease,[65] it should be noted that such proportions are similar to those reported in large national registries like the Society of Thoracic Surgeons adult cardiac surgical database,[66] where women represent ≈25% of the overall CABG population.

Nonetheless, as such percentages are likely inadequate to provide meaningful estimates of treatment effect, overrepresentation of female patients should be taken into consideration in the design of future cardiac surgical trials.

A lower proportion of women was also found in non-industry sponsored trials (irrespective of the exclusion of trials conducted at VA centers).

Limitations

The present analysis shares the limitations of meta-analyses and of pooled estimates, including the potential for methodological and clinical heterogeneity among included studies and the possibility of collinearity between tested variables. Moreover, RCTs generally capture only biologic sex and gender could not be addressed in our analysis.

CONCLUSIONS

Our study shows that the proportion of women included in cardiac surgery RCTs is low and likely inadequate to provide meaningful estimates of treatment effect. It is particularly concerning that this proportion significantly decreased over the past 2 decades, although this temporal trend was not seen when trials conducted at VA medical centers were excluded from the analysis. As important sex-related differences in cardiac surgical outcomes exist,[2,67] surgical results obtained in a prevalently male population may not apply to women and might potentially misinform surgical decision making in women. Substantial effort must be made by surgical trialists and funding agencies to promote the inclusion of women in cardiac surgery trials.

ARTICLE INFORMATION

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Disclosures

None.

Supplementary Material

Data S1
Figures S1–S4

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Supplemental Material

Data S1. Full search strategy.

Database: Ovid MEDLINE (In-Process & Other Non-Indexed Citations and Ovid MEDLINE January 2020 to July 2020), Ovid EMBASE (January 2020 to July 2020), and The Cochrane Library (Wiley) (January 2020 to July 2020). No language restriction enforced.

Ovid MEDLINE:

(CABG) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR ((off-pump coronary surgery) AND on-pump coronary surgery) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (arterial grafts) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (bilateral internal mammary artery) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (bilateral internal thoracic artery) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (radial artery) AND (CABG) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (right gastroepiploic artery) AND (CABG) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (arterial revascularization) AND (CABG) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (saphenous vein graft) AND (CABG) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (mitral valve repair) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (mitral valve replacement) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (tricuspid valve) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (aortic valve replacement) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (aortic valve repair) AND clinical trial [Publication type] AND("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (heart transplant) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication]) OR (ventricular assist device) AND clinical trial [Publication type] AND ("2000/01/01"[Date - Publication] : "2020/07/01"[Date - Publication])

Ovid EMBASE:

1 CABG.mp.
2 (off pump coronary surgery and on pump coronary surgery).mp.
3 arterial grafts.mp.
4 bilateral internal mammary artery.mp.
5 bilateral internal thoracic artery.mp.
6 radial artery.mp.
7 (right gastroepiploic artery and CABG).mp.
8 (arterial revascularization and CABG).mp.
9 (saphenous vein graft and CABG).mp.
10 mitral valve repair.mp.
11 mitral valve replacement.mp.
12 tricuspid valve.mp.
13 aortic valve replacement.mp.
14 aortic valve repair.mp.
15 heart transplant.mp.
16 ventricular assist device.mp.
17 or/1-16

18 limit 17 to ((clinical trial or randomized controlled trial or controlled clinical trial or multicenter study or phase 1 clinical trial or phase 2 clinical trial or phase 3 clinical trial or phase 4 clinical trial) and yr="2000 - 2020")

Cochrane Trials:
((CABG OR ("off pump coronary surgery" AND "on pump coronary surgery") OR arterial grafts OR bilateral internal mammary artery OR internal thoracic artery OR radial artery OR (right gastroepiploic artery AND CABG) OR (arterial revascularization AND CABG) OR (saphenous vein graft and CABG) OR mitral valve repair OR mitral valve replacement OR tricuspid valve OR aortic valve replacement OR aortic valve repair OR heart transplant OR ventricular assist device)):ti,ab

Figure S1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flowchart.

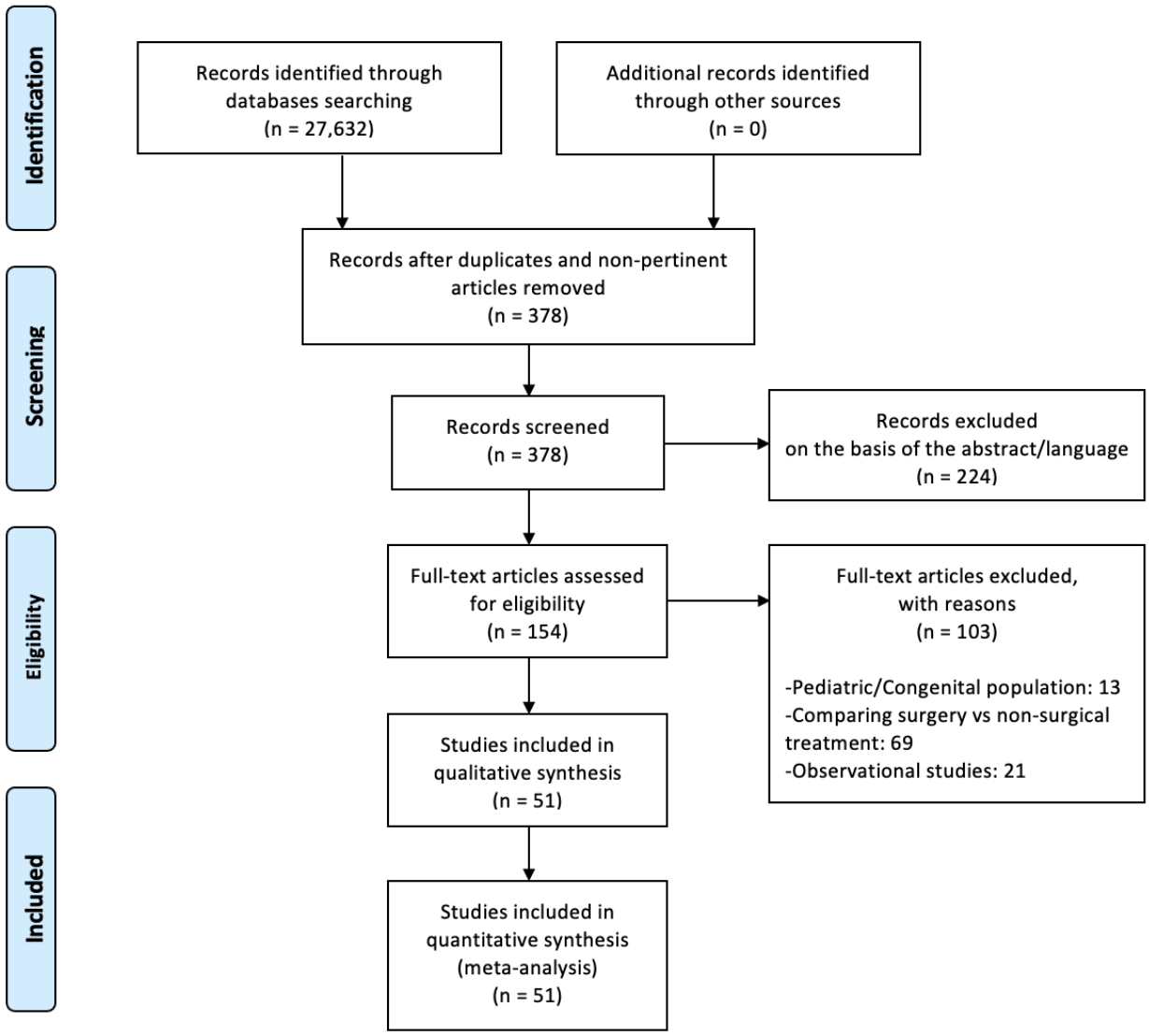

Figure S2. Funnel plot: log-transformed proportion of women versus standard error.

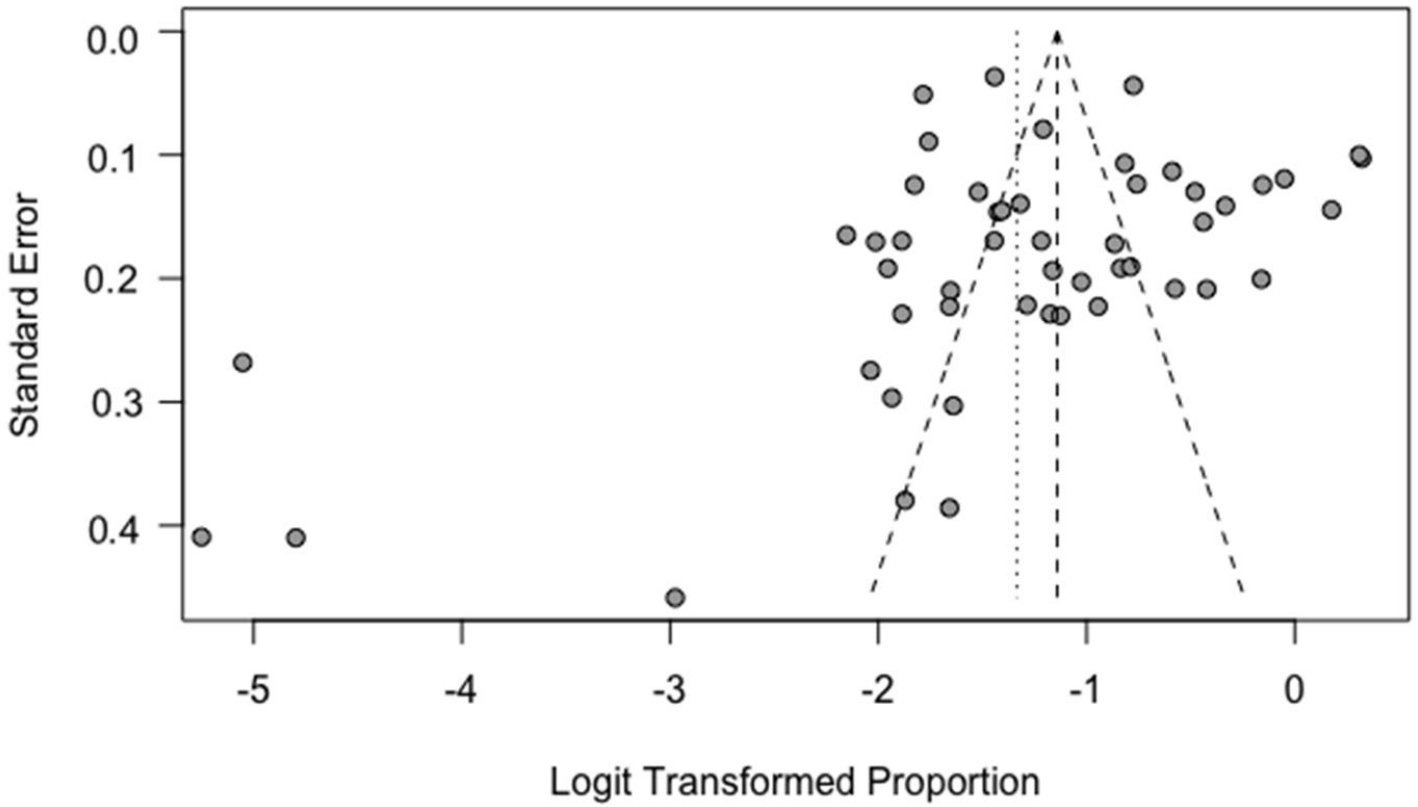

Figure S3. Proportions of women in cardiac surgery trials by study period after the exclusion of the trials conducted at Veteran Affairs (VA) centers.

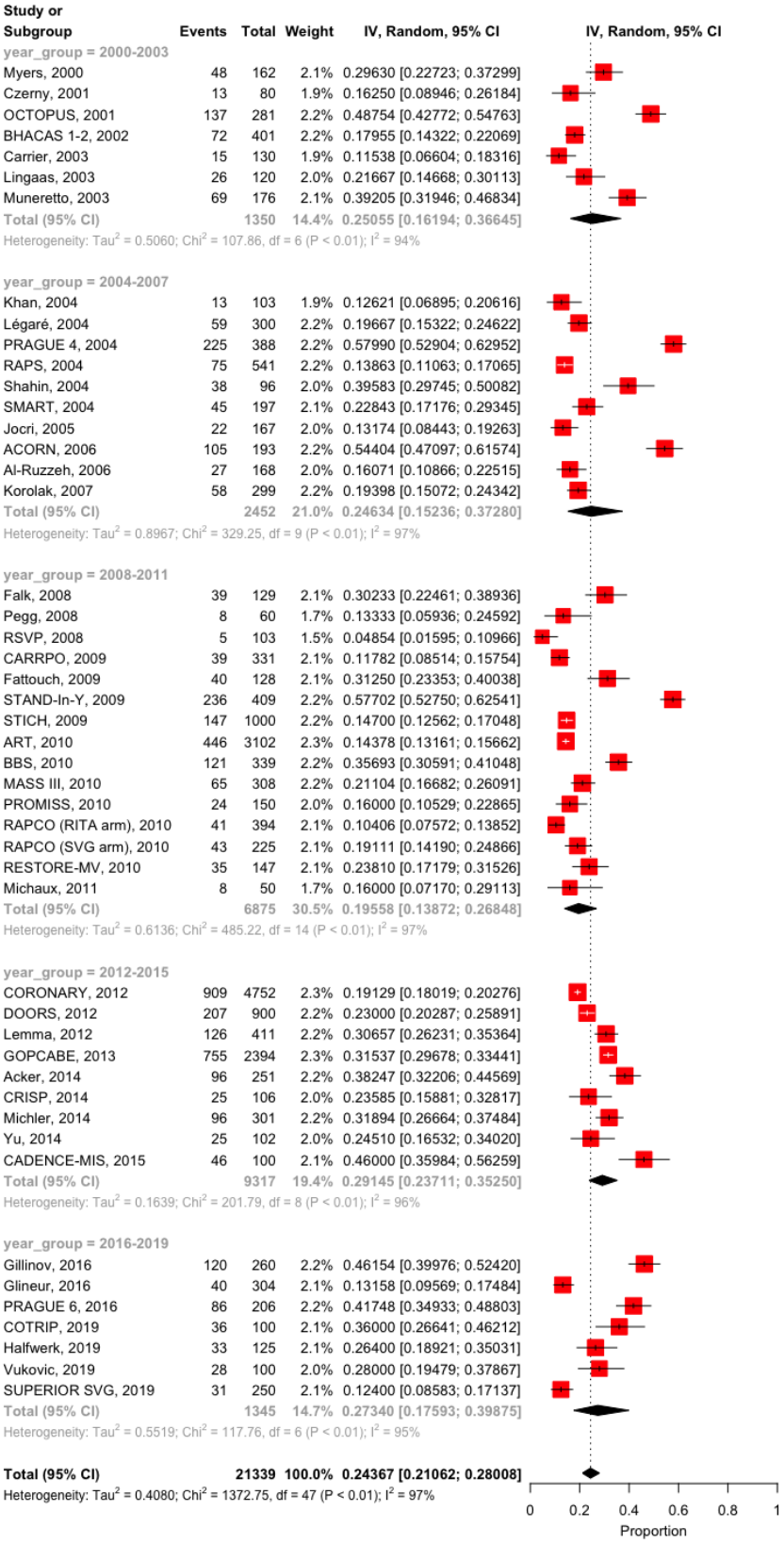

Figure S4. Funnel plot: log-transformed proportion of women versus standard error after the exclusion of the trials conducted at Veteran Affairs (VA) centers.