Supplementary Tables

ESC Working Group on Coronary Pathophysiology & Microcirculation Position paper on 'Coronary Microvascular Dysfunction in Cardiovascular Disease'

Short title: Coronary Microvascular Dysfunction

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Supplementary Table 1.- Prevalance of non-obstructive CAD and "normal" angiograms in large cohorts of stable patients

References	Registry	Period	Patients with non-obstructive angiograms			Patients with "normal" angiograms		*"normal" (% lumen stenosis)*
			All n/N (%)	Women n/N (%)	Men n/N (%)	Woman n/N (%)	Men n/N (%)	
0 to <50% lumen stenosis in any major coronary arteries								
Sharaf BL et al.[1]	WISE (USA) §	1996-99	184/323 (57.0)	184/323 (57.0)	---	110/ 323 (34)	---	*0 to <20 §*
Gulati M et al.[2]	WISE (USA) §	1997-99	540/936 (57.7)	540/936 (57.7)	---	318/936 (34)	---	*0 to <20 §*
Jespersen et al.[3]	Danish registry *	1998-09	5183/11223 (46.2)	3073/4711 (65.2)	2110/6512 (32.4)	2253/4711(48)	1226/6512 (19)	*0 †*
Sedlak TL et al.[4]	Canadian registry †	1999-02	3087/13695 (22.5)	1757/4184 (42.0)	1330/9511 (14.0)	1275/4184 (31)	804/9511 (8.5)	*0 **
Sharaf BL et al.[5]	WISE (USA) §	2001-07	567/917 (61.8)	567/917 (61.8)	---	339/917 (37)	--	*0 to <20 §*
Johnston et al.[6]	SCAAR (Sweden) †	2005-10	11127/31742 (35.1)	4517/13116 (34.4)	6610/18626 (35.5)			
Kissel et al. [7]	SCAAR (Sweden) †	1995-12	7478/18384 (40.7)	3517/6031 (58.3)	3961/12353 (32.1)			
	Total number of observations - n/N (%)		***28166 / 77220 (36.5)***	***14155 / 30218 (46.8)***	***14011 / 47002 (29.8)***			
	[% min - % max]		***[22.6 – 61.8]***	***[34.4-65.2]***	***[14.0-35.5]***			
0 to <70% lumen stenosis in any major coronary arteries								
Shaw LJ et al.[8]	NCDR (USA) †	2000-02	155305/375896 (41.3)	86186/168332 (51.2)	69119/207564 (33.3)			
Maddox TM et al.[9]	US Veterans (USA) *	2007-12	16775/37674 (44.5)	1310/1666 (78.6)	15465/36008 (42.9)	935/1666 (56)	7456/36008 (21)	*0 to <20 **
Davis MB et al.[10]	US Veterans (USA) *	2007-12	23696/48441 (48.9)	1689/2132 (79.2)	22007/46309 (47.5)	1065/2132 (50)	8534/46309 (18)	*0 to <20 **
	Total number of observations - n/N (%)		***195776 /462011 (42.4)***	***89185/172130 (51.8)***	***106591/ 289881 (36.8)***			
	[% min - % max]		***[41.3-48.9]***	***[51.2-79.2]***	***[33-48]***			

*§ quantitative coronary analysis; † visual analysis; * method used for angiograms evaluation not available*
NCDR: National Cardiovascular Data Registry; SCAAR: Swedish Coronary Angiography and Angioplasty Registry; WISE: Women's Ischemia Syndrome Evaluation.

Supplementary Table 2.- Prevalence of non-obstructive CAD (<50% lumen stenosis in any major coronary artery) in large cohorts of ACS patients

Reference	Registry/Trial and/or Country	Disease	Period	All n / N (%)	Women n / N (%)	Men n / N (%)	n-W in n-All (%)
Ramanath[11]	Michigan, USA	ACS	1999-04	123 / 2264 (5.4)	66/ 734 (9.0)	57 / 1530 (3.7)	53.7
Germing[12]	Germany	ACS	1996-00	76 / 897 (8.5)	22 /236 (9.3)	54 / 661 (8.2)	28,9
Dey[13]	GRACE	ACS	1999-06	2031 / 26755 (7.6)	921 / 7638 (12.1)	1110 / 19117 (5.8)	45.3
Manfrini[14]	EMMANCE, UK†	ACS	2003-04	350 / 1602 (21.8)	114 / 555 (20.5)	236 / 1047 (22.5)	32.6
Sun[15]	Beijing, China†	ACS	2007-08	51 / 729 (7.0)	20 / 215 (9.3)	31 / 514 (6.0)	39,2
Rossini[16]	Bergamo, Italy	ACS	2009	318 / 2438 (13.0)			
	Total number of observations - n/N (%)			***2949 / 34685 (8.5)***	***1143 / 9378 (12.2)***	***1448 / 22869 (6.5)***	***43.4***
	[% min - % max]			***[5.4-21.8]***	***[9.0- 20.5]***	***[3.7-22.5]***	
Larsen[17]	APPROACH, Canada§	MINOCA	1999-00	725 / 9796 (7.4)	283 / 2530 (11.2)	442 / 7266 (6.1)	39.0
Bainey [18]	APPROACH, Canada	MINOCA	2002-14	2092 / 35928 (5.8)	1108 / n.a. (n.a.)	984 / n.a. (n.a.)	53.0
Frycz-Kurek [19]	PL-ACS, Poland	MINOCA	2003-06	972 / 32959 (2.9)			
Agewall[20]	SMINC, Sweden	MINOCA	2003	11 / 152 (7.2)	9 / 27 (33.3)	2 / 125 (1.6)	81.8
Lindahl[21]	SWEDEHEART, Sweden	MINOCA	2003-13	9466/ 118260 (8.0)			
Baccouche[22]	Stuttgart, Germany	MINOCA	2004-07	162 / 1174 (13.8)			
Andrè[23]	FAST-MI, France	MINOCA	2005	167 / 2582 (6.5)	73 / 719 (10.2)	94 / 1863 (5.2)	43.7
Kang[24]	KAMIR, Korea	MINOCA	2005-06	372 / 8510 (4.4)	146 / 2445 (6.0)	226 / 6065 (3.7)	39.2
Johnston[6]	SCAAR, Sweden†	MINOCA	2005-10	13172 / 95846 (13.7)	7333 / 32489 (22.6)	5839 / 63357 (9.2)	55.7
Rhew[25]	Chonnam, Korea	MINOCA	2006-08	100 / 1220 (8.2)	41 / 353 (11.6)	59 / 867 (6.8)	41.0
Smilowitz[26]	ACTION, USA	MINOCA	2007-14	18918 / 322523 (5.9)	11763 / 112547 (10.5)	7155 / 209976 (3.4)	62.2
Hamdan[38]	Beirut, Lebanon	MINOCA	2008-09	11 / 124 (8.9)	7 /31 (22.6)	4 / 93 (4.3)	63.6
Hjort[27]	SWEDEHEART, Sweden	MINOCA	2009-13	1639 / 18943 (8.7)	1050 / 6125 (17.1)	589 / 12818 (4.6)	64.1
Baron[28]	SWEDEHEART, Sweden	MINOCA	2011-13	3533 / 41817 (8.4)	2086 / 12863 (16.2)	1447 / 28954 (5.0)	59.0
	Total number of observations - n/N (%)			***51340 / 689834 (7.4)***	***23899 / 170129 (14.0)***	***16841 / 331384 (5.1)***	***58.7%***
	[% min - % max]			***[2.9-13.8]***	***[6.0-33.3]***	***[1.6-9.2]***	
Larson[29]	Minneapolis, USA	STEMI	2003-06	127 / 1335 (9.5)	52 / 381 (13.6)	75/ 954 (7.9)	40.9
Johnston[6]	SCAAR, Sweden	STEMI	2005-10	2268 / 31648 (7.2)	976 / 9612 (10,2)	1292 / 22036 (5.9)	43.0
Smilowitz[26]	ACTION, USA	STEMI	2007-14	3204 / 146003 (2.2)	1611 / 44969 (3,6)	1593 / 101034 (1,6)	50,3
Andersson[30]	Denmark	STE-ACS	2009-14	554 / 4793 (11.6)	212 / 1313 (16.1)	342 / 3480 (9.8)	38.3
	Total number of observations - n/N (%)			***6153 / 183779 (3.3)***	***2851 / 56275 (5.1)***	***3302 / 127504 (2.6)***	***46.3%***
	[% min - % max]			***[2.2-11.6]***	***[3.6-16.1]***	***[1.6-9.8]***	

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Reference	Registry/Trial and/or Country	Disease	Period	All n / N (%)	Women n / N (%)	Men n / N (%)	n-W in n-All (%)
Patel [31]	CRUSADE	NSTEMI	2001-03	3306 / 38301 (8,6)	1873 / 14261 (13,1)	1433 / 24040 (6,0)	56,7
Gehrie[32]	CRUSADE	NSTEMI	2001-05	4903 / 51608 (9.5)	2882 / 19602 (14.7)	2021 / 32006 (6.3)	58.8
Planer[33]	ACUITY Trial §	NSTEMI	2003-05	197 / 2442 (8,1)	105 / 824 (12,7)	92 / 1618 (5,7)	53,3
Johnston[6]	SCAAR, Sweden	NSTEMI	2005-10	10904 / 64198 (17,0)	6357 / 22877 (27,8)	4547 / 41321 (11,0)	58,3
Smilowitz[26]	ACTION, USA	NSTEMI	2007-14	15714 / 176520 (8,9)	10152 / 67578 (15,0)	5562 / 108942 (5,1)	64,6
	Total number of observations - n/N (%)			***35024 / 333069 (10.5)***	***21369 / 125142 (17.1)***	***13655 / 207927 (6.6)***	***61.0%***
	[% min - % max]			***[8.1-17.0]***	***[12.7-27.8]***	***[5.7-11.0]***	
De Ferrari[34]	n. 8 TIMI Trial	NSTE-ACS	1994-08	3550 / 37101 (9,6)	1974 / 11823 (16,7)	1576 / 25278 (6,2)	55,6
Roe[35]	PURSUIT Trial	NSTE-ACS	1995-97	696 / 5767 (12,1)	346/ 1862 (18,6)	350 / 3905 (9,0)	49,7
Bugiardini[36]	n. 3 TIMI Trial	NSTE-ACS	1996-01	701 / 7656 (9,2)			
Glaser[37]	TIMI 18 Trial	NSTE-ACS	1997-99	194 / 1646 (11,8)	95 / 555 (17,1)	99 / 1091 (9,1)	49,0
Gehrie[32]	CRUSADE	NSTE-ACS	2001-05	5538 / 55514 (10,0)	3221/ 21294 (15,1)	2317 / 34220 (6,8)	58,2
Mega[38]	TIMI 36 Trial	NSTE-ACS	2004-07	461 / 3920 (11.8)	225 / 1162 (19.4)	236 / 2758 (8.6)	48,8
	Total number of observations - n/N (%)			***11140 / 111604 (10.0)***	***5861 / 36696 (16)***	***4578 / 67252 (6.8)***	***56.2%***
	[% min - % max]			***[9.2-12.1]***	***[15.1-19.4]***	***[6.2-9.1]***	

§ = angiograms evaluation by quantitative coronary analysis
ACTION: Registry-GWTG, Acute Coronary Treatment and Intervention Outcomes Network Registry - Get With the Guidelines;
APPROACH: Alberta Provincial Project for Outcome Assessment in Coronary Heart disease;
CASPAR: Coronary Artery Spasm in Patients with Acute Coronary Syndrome;
EMMANCE: Evaluation of Methods and Management of Acute Coronary Events;
FAST-MI: French registry of Acute ST-elevation or non-ST-elevation Myocardial Infarction;
GENESIS-PRAXY: Gender and Sex Determinants of Cardiovascular Disease: From Bench to Beyond Premature Acute Coronary Syndrome;
GRACE: Global Registry of Acute Coronary Events;
KAMIR: Korean Acute Myocardial Infarction Registry;
SCAAR: Swedish Coronary Angiography and Angioplasty Registry;
SMINC: Stockholm Myocardial Infarction with Normal Coronaries.

Supplementary Table 3.- Diagnostic evaluation of coronary microcirculation

Technique	Characteristics	Strength & Weakness
Non-invasive diagnostic tests		
SPECT	SPECT and PET use a radioactive tracer to assess the activity of the myocardial tissue, revealing areas of decreased MBF. In dynamic SPECT imaging, radionuclide tracers such as ^{99m}Tc-tetroboxime which exhibit linear uptake with flow allows more accurate assessment of MBF than ^{99m}Tc-sestamibi, ^{99m}Tc-tetrofosmin or Thallium-201.	SPECT has worse spatial and temporal resolution than PET and is associated with more radiation exposure due to the shorter half-life of PET tracers.
PET	The gold-standard tracers for quantification of MBF are the following.[39] ^{15}O-water is the ideal perfusion agent with 100% first-pass perfusion; its myocardial uptake is proportional to MBF, but due to its rapid clearance it cannot be used for visual analysis.[40] ^{13}N-ammonia diffuses across cell membranes and gets metabolically trapped in myocardial cells, but its trapping becomes rate-limiting at high MBF.[40] Rubidium-82 based tracers have the advantage of not requiring an on-site cyclotron, but they come with the disadvantage of significant roll-off at high MBF.[39]	The main disadvantage of PET imaging is the limited clinical availability and its high cost Image co-registration with the anatomical information of CT scan offers better anatomical resolution and delineation of myocardial tissue.[40]
MCE	Microbubbles are employed for the quantification of MBF.[41] Microbubbles are infused iv at a constant rate to achieve steady-state concentration and then destroyed by acoustic waves. Changes of echo-signal are used to determine MBF. CFR is calculated analyzing pulse wave Doppler in the LAD artery at baseline and under hyperemic conditions (e.g. post-adenosine).[41] in the absence of significant epicardial disease, CFR value <2.0 is indicative of microvascular dysfunction.	MCE has been widely used in clinical studies, but is technically demanding, requires relevant expertise and a slow-learning curve and may not be feasible in all patients.[40]
CMR	Perfusion CMR assesses the presence of perfusion defects due to epicardial stenoses or microvascular disease. Early or late gadolinium enhancement can be used to show the presence of microvascular obstruction in patients with ACS pre- or post-reperfusion.[42] Other newer CMR techniques, such as stress T1 mapping, may be superior to gadolinium based first-pass perfusion for assessing microvascular function.[42]	It use is increasing in clinical practice, although slowed by high costs.
CCT	Dynamic CCT imaging and myocardial attenuation gradients (endocardial versus epicardial) can be used to assess microvascular function after pharmacological vasodilation e.g. by adenosine infusion.[43]	It use is increasing in clinical practice, although slowed by the use of high dose radiation.

Technique	Characteristics	Strength & Weakness
Invasive diagnostic tests		
Coronary angiography	Widely used in ischemic heart disease, it helps physicians to decide on eventual additional local therapies to improve myocardial perfusion. After successful revascularization of an epicardial coronary stenosis, contrast medium progression impairment could reflect microcirculation damage. Several semiquantitative or quantitative indices have been validated for determining the degree of myocardial perfusion. The most common are TIMI flow grade, corrected TFC,[44] MBG,[45] TMPG.[46]	Limitations are represented by: 1) semiquantitative assessment; 2) restriction to epicardial flow evaluation of TIMI flow grade and corrected TFC; 3) interindividual high variability in the assessment of TMPG and MBG.
Doppler-flow wire.	Coronary blood flow is measured by means of an intracoronary Doppler-tipped guidewire.[47] The Doppler guidewire transmits and receives pulsed wave ultrasound signals. The wire is plugged into an external console, which analyze signals for calculating flow velocity. Characteristic of coronary microvascular obstruction are systolic flow reversal, rapid deceleration of diastolic flow (< 600 msec) and a reduced coronary flow velocity reserve.	The good point is the quantitative assessment and good reproducibility. Limitation are a potential signal instability and difficulty in guidewire positioning in complex anatomy.
CFR	The most frequent evaluation of CFR is during cardiac catheterization. CFR is ratio between resting and maximal possible coronary blood flow (hyperemia). It assesses the capacity of coronary circulation to dilate and thus increase MBF. The coronary flow velocity pattern for microcirculation impairment is defined as a diastolic deceleration time <600 ms.	CFR interrogates the overall coronary circulation without distinction between macro- and microcirculation. Other imitations are 1) high measurement variability; 2) during ACS the resting condition is highly questionable.
Thermodilution	It is a novel index based on thermodilution background.[48] This technique uses a pressure/temperature wire and an infusion microcatheter. It has already been evaluated in vivo and in vitro.	The good point is the quantitative assessment and good reproducibility. Limitations are a potential signal instability and difficulty in guidewire positioning in complex anatomy.
IMR	IMR is the ratio of distal coronary pressure and the thermodilution-derived mean transit time during maximal hyperemia, measured with a pressure/temperature wire. IMR measures the resistance to myocardial flow, specifically related to the coronary microcirculation compartment.	IMR is an objective index dedicated to the coronary microcirculation. It has some degree of variability in the measurements resulting from the manual injection of an intracoronary bolus of saline at room temperature.

ACS= acute coronary syndrome; CCT= cardiac computed tomography; CFR= coronary flow reserve; CMR = cardiac magnetic resonance; IMR= index of microvascular resistance; LAD= left anterior descending; MBF=myocardial blood flow; MBG= myocardial blush grade; MCE= myocardial contrast echocardiography; PET = positron emission tomography; SPECT= single-photon emission computed tomography; TIMI = Thrombolysis in Myocardial Infarction; TFC= TIMI frame count; TMPG= TIMI Myocardial Perfusion Grade.

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