

Definitions and incidence of cardiac syndrome X: review and analysis of clinical data

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Abstract There is no consensus regarding the definition of cardiac syndrome X (CSX). We systematically reviewed recent literature using a standardized search strategy. We included 57 articles. A total of 47 studies mentioned a male/female distribution. A meta-analysis yielded a pooled proportion of females of 0.56 ($n = 1,934$ patients, with 95% confidence interval: 0.54–0.59). As much as 9 inclusion criteria and 43 exclusion criteria were found in the 57 articles. Applying these criteria to a population with normal coronary angiograms and treated in 1 year at a general hospital, the attributable CSX incidence varied between 3 and 11%. The many inclusion and exclusion criteria result in a wide range of definitions of CSX and these have large effects on the incidence. This shows the need for a generally accepted definition of CSX.

Keywords Cardiac syndrome X · Microvascular angina · Angina pectoris and normal coronary arteries

Introduction

The syndrome of angina pectoris with a normal coronary arteriogram, often termed cardiac syndrome X (CSX), is an important clinical entity [65]. About 20% of patients with anginal chest pain have normal coronary angiograms (CAG). Some physicians regard this as sufficient to diagnose CSX, the so-called broad diagnosis of CSX [65, 66]. However, the cause of CSX is not conclusively established and its definition is controversial. For example, a subgroup of these patients have objective signs of ischaemia, such as the classic downsloping ST-segment depression on exercise testing and/or a reversible defect detected by myocardial single-photon emission computed tomography (SPECT). Consequently, other authorities consider that CSX is discounted by a positive result from any diagnostic test for ischaemia, especially SPECT; and there is also the view that CSX might best be relabelled as one of several causes of microvascular dysfunction [37]. Furthermore, there are various exclusion criteria, such as hypertension and diabetes, that may or may not be used to discount the diagnosis of CSX. Finally, in overviews and textbooks it is often stated that (pre-menopausal) women are especially prone to developing cardiac syndrome X. In fact, some authors exclusively study female patient populations, but there is considerable variation in the proportion of women in other studies of CSX patients.

The present paper is a review to determine the gender and main definitions for CSX in the recent literature and also the effects of different definitions upon the attributable CSX incidence. To study this latter aspect we examined

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and analysed the CAG data for a population of patients treated in a general hospital in the Netherlands.

Methods

CSX definitions

The PubMed database was used to identify papers in which criteria and definitions for CSX are described. Our search consisted of '(cardiac syndrome x[tiab]) NOT (case reports[pt] OR comment[pt] OR review[pt])', with limits set to English language, humans, and publication date between June 2003 and July 2008. We limited our search strategy to cardiac syndrome X and excluded metabolic syndrome X and tako-tsubo cardiomyopathy [6, 24, 42].

This search yielded 112 references. Conference abstracts, pediatric papers, and 'e-publications ahead of print' were excluded. Of 83 articles the full text was retrieved for further analysis. Articles were independently surveyed by two authors (IV and GT) and reviewed with regard to their used definitions of CSX. The survey left 57 studies for this review.

Impact of CSX definition upon CSX incidence

All the CAGs made in 2003 in a general hospital (Spaarne Hospital Hoofddorp, The Netherlands) were collected. An extensive search was made to obtain the clinical history, physical examination, routine laboratory tests, and echocardiography results for all patients with CAGs stated to be completely normal. All CAGs were independently evaluated by two experienced observers (AK and DO).

Only patients with original angiograms and sufficient clinical data were included in the present study.

Results

CSX definitions

The 57 papers selected for determining the main definitions of CSX covered a total of 2,375 patients. A normal coronary angiogram was used in the majority of the studies. However, in a few studies minimal coronary artery disease, like atheromatous plaque without critical obstructions, is included as "normal coronary angiogram" [18, 22, 56]. A few studies state minimal coronary artery disease in the exclusion criteria [1]. But in the majority of the studies there was no statement regarding minimal artery disease. Only few studies specified the interpretation of the normal coronary angiograms, like revision of the CAG films, blinded observation, or interpretation by more reviewers.

Table 1 lists the nine CSX definitions, and hence inclusion criteria, obtained from our review of the 57 studies.

In more detail:

- Out of the 57 studies 42 required positive exercise electrocardiograms for the diagnosis of CSX. The general criterion, when given, for a positive exercise stress test result was uniform ST depression ≥ 1 mm. Only one study considered stress-induced angina without significant ST depression to be positive for ischaemia [15].
- As much as 11 studies regarded positive myocardial perfusion images to be good alternatives to a positive result from exercise testing.
- As much as 18 studies considered effort-induced angina pectoris as an inclusion criterion.
- Four studies defined CSX simply as angina pectoris and normal CAG, the so-called broad diagnosis of CSX.

Table 1 Inclusion criteria for CSX

Inclusion criteria for CSX	Number of studies
Angina pectoris	18
Positive exercise stress test	
Normal coronary arteries	
Effort induced angina pectoris	17
Positive exercise stress test	
Normal coronary arteries	
Angina pectoris	11
Positive exercise stress test OR positive SPECT	
Normal coronary arteries	
Angina pectoris	4
Normal coronary arteries	
Angina pectoris	4
Positive exercise stress test AND positive SPECT	
Normal coronary arteries	
Angina pectoris	1
Positive exercise stress test	
No significant CAD on CAG	
Effort induced AP	1
Positive exercise stress test	
Normal coronary arteries AND prolonged coronary flow on CAG	
Angina pectoris	1
Positive exercise stress test	
Normal coronary arteries AND reduced LVEF on echo	
Angina pectoris	1
Positive SPECT	
Normal coronary arteries	

CSX cardiac syndrome X; AP angina pectoris; CAG coronary angiogram; SPECT single photon emission tomography; LVEF left ventricular ejection fraction

Table 2 lists no less than 43 exclusion criteria for CSX. The most frequently used exclusion criteria are valvular heart disease, diabetes mellitus, left ventricular hypertrophy, hypertension, and cardiomyopathy.

Table 2 Exclusion criteria included studies

Exclusion criteria used in the studies for present review	<i>N</i> studies of 57 total
Valvular heart disease	33
Diabetes mellitus	32
Left ventricular hypertrophy	26
Hypertension	24
Cardiomyopathy (non specified)	23
Renal failure	22
History of myocardial infarction	15
LV dysfunction	14
Coronary spasm	13
Hepatic dysfunction	12
Arrhythmias	9
Inflammatory disease	9
Dyslipidaemia	8
Left bundle branch block	8
Cardiac disease (non specified)	7
Gastro Intestinal disorder	7
Systemic disease (non specified)	6
Smoking	6
Thyroid dysfunction	5
Obesitas	5
Non-cardiac chest pain	5
Conduction disorder (incl LBTB)	5 (13)
Hypertrophic CMP (total CMP)	5 (23)
Congestive CMP (total CMP)	5 (23)
Dilated CMP (CMP total)	4 (23)
Alcoholism	4
Metabolic syndrome	4
Dysphagia/oesophagitis	3
Malignancy	3
LVEF < 40%	2
Psychiatric illness	2
Auto immune disease	2
Estrogen replacement therapy	2
PTCA/CABG in history	2
Ectasia on CAG	2
Bridging on CAG	2
Claudicatio intermittens	2
Heart failure (non specified) (total)	1 (17)
Myocarditis	1
Congenital heart disease	1
Aortic wall diseases	1
Anaemia	1
Thrombocytopenia	1

In overviews and textbooks it is often stated that (premenopausal) women are especially prone to develop cardiac syndrome X.

In Table 3 data of individual studies are presented.

Table 3 Included studies of CSX patients

Included study of CSX patients	Year	<i>n</i>	Female (%)	Mean age (Y)
Lee [41]	2008	21	81	55
Timurkaynak [61]	2008	79	54	50
Cemin [11]	2008	11	100	59
Zorc-Pleskovic [66]	2008	31	100	55
Lanza [38]	2008	18	61	58
Altun [2]	2007	9	77	49
Cotrim [12]	2008	91	48	51
Asbury [5]	2008	64	100	58
Demir [18]	2008	17	41	57
Grabczewska [23]	2007	53	57	55
Li [44]	2007	36	100	NA
Okyay [48]	2007	32	66	53
Dabek [15]	2007	34	65	57
Yildiz [64]	2007	10	79	49
Kayikcioglu [33]	2007	30	60	46
Mao [45]	2007	51	78	21
Dabek [14]	2007	36	65	57
Vermeltoort [63]	2007	20	75	55
Galiuto [21]	2007	17	53	55
Alroy [1]	2007	42	100	52
Huang [29]	2007	12	60	63
Guzik [28]	2007	43	65	44
Gur [26]	2007	23	70	49
Gur [27]	2007	23	NA	NA
Sgueglia [59]	2007	30	73	61
Russell [55]	2007	24	89	54
Sen [56]	2007	203	58	53
Shmilovich [60]	2007	17	71	58
de Vries [17]	2006	42	26	58
Nam [47]	2006	52	NA	NA
Eskandarian [19]	2006	40	73	46
Cay [10]	2006	126	62	53
Jadhav [30]	2006	52	100	56
Czepczynski [13]	2006	68	63	45
Leu [43]	2006	92	21	64
Lanza [40]	2005	10	59	70
Cay [9]	2005	80	52	51
On [49]	2005	36	53	36
Guo [25]	2005	22	68	48
Masci [46]	2005	41	NA	53
Senen [57]	2005	21	48	56
Pasqui [51]	2005	30	60	54
Sestito [58]	2005	30	73	60

Table 3 continued

Included study of CSX patients	Year	<i>n</i>	Female (%)	Mean age (Y)
De Candia [16]	2005	21	57	55
Valeriani [62]	2005	16	50	60
Cavusoglu [8]	2005	31	45	52
Kolasinska-Kloch [36]	2004	42	52	46
Kolasilska-Kloch [35]	2004	25	36	49
Altun [3]	2004	8	75	46
Asbury [4]	2004	100	100	61
Fabian [20]	2004	40	40	55
Lanza [39]	2004	55	50	57
Qian [54]	2004	126	47	53
Osamichi [50]	2004	24	71	58
Gorgulu [22]	2003	18	44	51
Pizzi [53]	2004	NA	NA	59
Kidawa [34]	2003	50	64	49

NA not available

In 53 out of the total of 57 included studies the female/male distribution of the study population was mentioned. Six studies were focussed upon female patients with CSX. These studies were excluded for the pooling of the proportion of women in the study populations. Ultimately 47 studies with a total of 1,934 patients could be used for the meta-analysis.

The proportion of women in the 47 studies of CSX patients varied considerably ranging from 0.21 to 1.0, with a pooled estimate of 0.56 (95% confidence interval: 0.54–0.59), see also Fig. 1. Hence, there is a significantly higher proportion of woman compared to males in the group of patients with CSX.

CSX incidence

As much as 567 CAGs were performed in 1 year at a general hospital. Figure 2 is a flowchart showing how we analysed the available information. The main stages are:

- Original CAGs or clinical data could not be found for eight patients, leaving 559 cases for analysis.
- Out of the available 559 CAGs 78 (14%) were considered as absolutely normal.
- Excluding 13 cases with no angina pectoris as indication for CAG, and another 5 with an acute coronary syndrome, resulted in an incidence of 60 (11%) CSX patients according to the broad diagnosis of CSX (angina pectoris and normal coronary arteries) [17, 23, 54, 65, 66].
- Another 15 cases were excluded owing to the lack of exercise stress tests or myocardial perfusion imaging preceding the CAG.

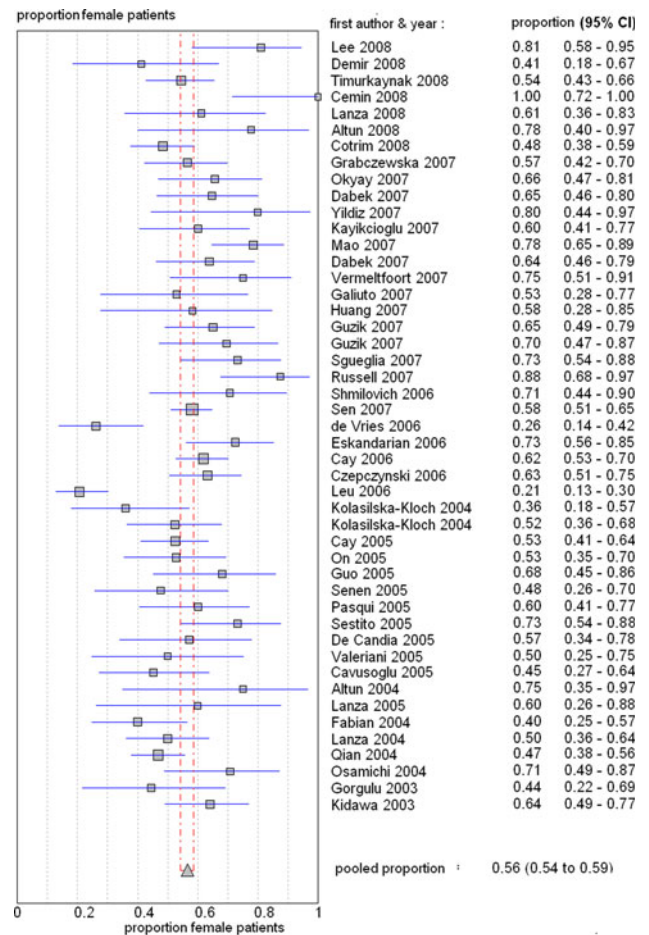


Fig. 1 Plot of proportion of women of individual studies, including 95% confidence intervals

- Of the remaining 45 cases, 28 were *included* owing to positive results for ischaemia from exercise tests or SPECT.
- Finally, a much stricter definition of CSX was obtained by using the main exclusion criteria shown in the second-to-last stage in Fig. 2. This strict definition resulted in an attributable CSX incidence of 18 (3%) patients.

Discussion

CSX definitions and incidences

The present review of recent archival literature demonstrates that there is a wide range of definitions of CSX. This wide range of definitions has a large effect on the attributable incidence of CSX, as has been shown by an analysis of all available CAGs and other clinical data for a population of patients treated in 1 year at a general hospital.

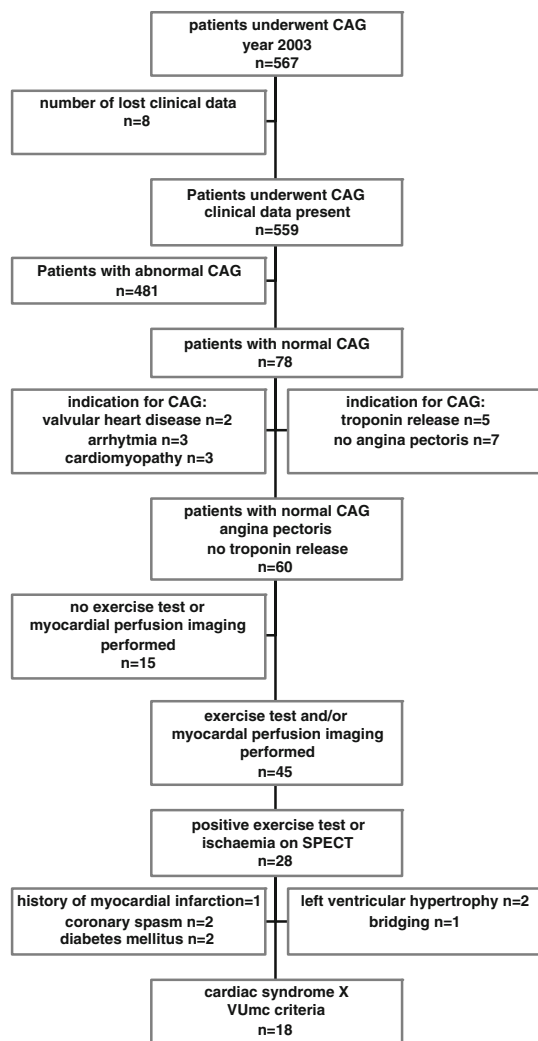


Fig. 2 Flowchart of the available information

Generally, it is stated that patients with chest pain and normal coronary arteriogram may represent 10–20% of those undergoing coronary arteriography because of clinical suspicion of angina [65]. This is in broad agreement with our analysis results that 11% of patients had a normal CAG. The rather low incidence of normal CAG can be the result of the use of rather strict criteria for a normal CAG including a consensus reading by two independent readers of the CAG's.

It is generally accepted (e.g. in authoritative textbooks) that the majority of the CSX patients are women [32, 65]. Some authors have even suggested that CSX is a women's disease. However, our review has found a pooled relative female frequency of 56% in a population of more than 1,900 CSX patients. Thus, our data do not support the assumption that CSX is a women's disease, since 44% of the population was male. Potential pathophysiological explanations, such as estrogen depletion, which are based

upon the female gender, apply only to a part of the CSX patients [31].

Inclusion and exclusion criteria

The literature survey showed that the inclusion and exclusion criteria varied. This was especially the case for the exclusion criteria.

The definition of 'normal coronary arteries' was particularly unclear. Most studies did not define a normal CAG, and some included patients with coronary artery disease (CAD) ranging from minimal to stenoses up to 50% of luminal diameter. Obviously, normal coronary arteries are the cornerstone of the diagnosis of CSX. Hence, there should be no doubt regarding the use of this inclusion criterion for studies of CSX patients. Future studies of CSX patients should make a clear description regarding the evaluation and results of the CAG studies of the coronary artery anatomy.

The so-called broad diagnosis for CSX, a combination of 2 inclusion criteria (angina pectoris and normal coronary arteries) was used only in four studies (7%).

Most studies used a combination of three inclusion criteria, namely (effort induced) angina pectoris, positive exercise test result, and a normal CAG. This definition was used in 46 out of 57 studies (81%). The use of this additional inclusion criterion resulted in a decrease of the incidence of CSX to 7% in our population. The definition of a positive exercise stress test appears to be more standardized than the definition of a normal CAG. Most publications used a ST depression ≥ 1 mm as a positive exercise stress test: only 12 out of the 57 studies did not define a positive stress test.

The use of specific exclusion criteria ranged from 2 to 58% of the selected studies of CSX patients, often depending on the main objectives of the studies, for example the use of thrombocytopenia as an exclusion criterion in a study investigating the mean platelet volume [9].

The most frequently mentioned exclusion criteria are valvular heart disease, diabetes mellitus, left ventricular hypertrophy, hypertension, and cardiomyopathy. Endothelial dysfunction has been assessed both in patients with diabetes mellitus and hypertension with normal CAG, and in patients with CSX without diabetes or hypertension. Interestingly, coronary flow reserve may be reversible in specific patient groups, e.g. in patients with hypertrophy after anti-hypertensive therapy [52]. However, we note that most international studies consider diabetes mellitus and hypertension to be exclusion criteria for CSX, thereby considering these patients as a separate group.

The existence of such a long list of exclusion criteria in the selection process of CSX patients illustrates the lack of agreement between the different research groups regarding

the origins of this syndrome. Besides the use of a standard and fixed combination of inclusion criteria future studies should apply a standard combination of exclusion criteria.

In a recent editorial, Camici proposed the following exclusion criteria in order to obtain a more homogeneous set of cardiac syndrome X patients: absence of left bundle branch block; absence of even minimal irregularities on the angiogram; no evidence of diabetes mellitus, arterial hypertension, hyperlipidaemia, valve disease, epicardial arterial spasm, and cardiomyopathy [7].

In our selection of CSX patients we decided to include only patients with completely normal coronary angiograms, effort-induced angina pectoris, positive exercise stress test and/or positive SPECT study. Furthermore, we decided to add arrhythmias, left ventricular hypertrophy, myocardial infarction in the medical history, and myocardial bridging to the exclusion criteria proposed by Camici. These inclusion and exclusion criteria resulted in an attributable CSX incidence of only 3%.

Conclusions

The wide range of definitions of CSX in recent literature and the variations in inclusion and exclusion criteria, particularly the latter, make interpretation of the results of individual studies difficult. This shows the need for a generally accepted definition of CSX.

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Conflict of interest statement None.

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