**Clinical outcomes in patients with primary stable microvascular angina: is the Jury still out?**

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**Introduction**

Recent studies have shown that up to 50% of patients who undergo elective coronary angiography for the assessment of chest pain symptoms suggestive of coronary artery disease (CAD) may have normal coronary arteries (NCAs) or no flow-limiting stenoses (1-4). This proportion is somewhat higher than previously reported likely due to broader indications for coronary angiography worldwide. Over the past three decades many studies have documented that a large proportion of these patients have functional and/or structural coronary microcirculatory abnormalities able to trigger myocardial ischaemia and angina symptoms (5), a condition defined as “microvascular angina” (MVA) (6).

Initial studies assessing prognosis in patients with typical chest pain despite angiographically NCAs showed a very low rate of major cardiac events at long-term follow-up, with survival rates comparable to those in the general population. Quality of life, however, was often found to be markedly impaired in these individuals due to recurrent severe and prolonged chest pain symptoms (7-15). The concept that prognosis is “benign” in patients with chest pain in the absence of obstructive CAD, however, has been challenged in recent years particularly by large studies reporting increased rates of major clinical events (2,3). A recent meta-analysis (16) has shown that angina with no obstructive CAD (NO-CAD) has a heterogeneous prognosis and that a main determinant of major adverse events is the presence of ‘some’ coronary atherosclerosis. Evidence of myocardial ischaemia on imaging stress testing was also associated with worse clinical outcomes, particularly regarding re-hospitalization, recurrence of angina, repeat coronary angiography and quality of life, but it had no impact on survival (16).

Establishing the reasons for the different prognostic findings reported by older studies and more recent reports is of major clinical importance. Thus, in the present article we compared findings of studies that looked at clinical outcomes of patients with anginal pain despite NO-CAD. We looked specifically at the clinical characteristics, selection criteria and clinical events of the different patient populations assessed in these studies.

This manuscript mainly focuses on defining the prognostic impact of *primary stable MVA*, which is clinically characterized by (5): 1) episodes of anginal pain exclusively or predominantly triggered by effort 2) evidence of myocardial ischaemia on noninvasive stress testing; 3) NCAs at angiography; 4) no evidence of coronary artery spasm and 5) absence of other cardiac (e.g., myocardial, pericardial, valvular diseases) or systemic (e.g. immunologic disease) conditions that are known to be associated with an increased risk of cardiovascular events (2,17).

**The “origins” of MVA**

A brief summary as to the origins of MVA may help understand the reasons for the discrepancies between older and more recent studies regarding prognosis of patients with angina and NO-CAD. In 1967 Likoff et al. first reported the development of typical angina pectoris and ischaemic ST-segment depression at the electrocardiogram (ECG) during exercise stress testing in 15 women with NCAs at angiography (18).

Some years later, Arbogast and Bourassa showed that, contrary to CAD patients (group C), those with angina and NCAs (“group X”) showed no impairment of left ventricular (LV) function during chest pain induced by atrial pacing, despite the development of ischaemic ECG changes and myocardial lactate production, thus questioning the ischaemic nature of the symptoms (19). In an editorial comment to this paper, however, Harvey Kemp, that referred to the clinical picture of ‘group X’ as “*syndrome X”*, speculated that, despite the lack of LV dysfunction, ECG and metabolic changes could still be related to myocardial ischaemia and that the lack of LV impairment in group X could have been due to differences in the severity and/or regional distribution of ischaemia, compared with that caused by obstructive CAD (20).

Along these lines, Maseri et al. suggested that the lack of LV impairment in patients with *cardiac syndrome X* could be related to the presence of coronary microvascular dysfunction (CMD) affecting the myocardium in a “patchy” fashion and not involving large myocardial areas as those usually observed in patients with obstructive CAD (21).

The presence of CMD in patients with angina and NCAs had first been suggested by Opherk et al., who found a reduced coronary flow reserve (CFR) in response to dipyridamole (22), and also demonstrated, during the same period, by Cannon and Epstein, who coined the term “microvascular angina” to define the condition. (23,24). CMD in patients with angina and NCAs was subsequently confirmed in many other studies using various invasive and/or non-invasive diagnostic techniques (25-30).

Although patients included in these initial studies represented a relatively heterogeneous population (e.g. some had completely NCAs at angiography while others had “near-NCAs”), most included well characterized patients fulfilling stringent entry criteria for *cardiac syndrome X*, i.e., exercise-induced angina, positive exercise stress test results and “completely” NCAs at angiography; furthermore, other relevant heart conditions, including coronary artery spasm, impaired LV function, heart valve disease and LV hypertrophy, were also excluded in most, albeit not all, studies **(Table 1)**.

When this definition of syndrome X is carefully applied, a reduced coronary microvascular dilatation can be shown in up to 75% of patients (31), and the proportion of patients with evidence of CMD can be even higher if tests for coronary microvascular constriction are also associated (32). Accordingly, a very large proportion of patients with cardiac syndrome X can reasonably be considered to have primary stable MVA, when other potential cardiac and non-cardiac causes of chest pain are excluded (5).

**Follow-up studies in patients with primary stable MVA**

The initial follow-up studies carried out to assess clinical outcomes in MVA included patients with typical clinical and angiographic features of *cardiac syndrome X*, as described above. The main clinical characteristics of patients and long-term follow-up results of these studies, together with those of more recent reports, are summarized in **Table 1** (7-10,33). We excluded from this review studies of patients with chest pain and NCAs who did not have evidence of myocardial ischaemia as an inclusion criterion (34,35). Overall, 568 patients were included in the selected studies. They were followed-up for an average period of 10.9 years (range 3-16), during which only 3 cardiac deaths were reported, and global mortality was also consistently low and in line with that expected in an unselected comparable population of healthy subjects. These studies, however, consistently reported a high recurrence of chest pain episodes often leading to repeat non-invasive investigations and readmission to hospital (7-13,33,36).

While a major quality of these studies is in the rather homogeneous inclusion criteria **(Table 1)**, some limitations should be acknowledged: 1) the number of patients in the individual studies was small, thus raising some uncertainty as to the applicability of their results to larger populations of MVA patients; the very long-term follow-up recently provided in a sizeable number of patients, however, should have overcome this limitation (13); 2) no control groups were included; however, serious cardiac event rates were very low and, therefore, significant differences with the general population would have been extremely difficult to demonstrate; 3) the relation of CMD with clinical outcomes was not assessed; however, survival was excellent despite the presence of CMD in a very large proportion of patients (9,13,31), which makes it unlikely that CMD might have had a major impact on mortality.

In summary, follow-up studies including homogeneous groups of patients with clinical features typical of primary stable MVA consistently reported good long-term prognosis.

**Initial reports of worse clinical outcomes in NO-CAD patients**

In the mid-2000’s, two reports showed that patients enrolled in clinical trials of no-ST-segment elevation acute coronary syndromes (NSTE-ACS) who were found to have NO-CAD at angiography had a sizeable rate of cardiac events at follow-up, thus suggesting an impaired prognosis (37,38). Patients included in these trials, however, are clearly different from those with primary stable MVA and would require separate assessment and discussion. As demonstrated by several studies, patients with NSTE-ACSs and NO-CAD have different causes for their acute chest pain, such as epicardial coronary artery spasm, coronary thrombosis, myocarditis and tachyarrhythmias (39-41). Thus, although coronary microvascular spasm and CMD may also be responsible for NSTE-ACS, it is difficult -without specifically investigating the underlying mechanisms- to attribute to CMD the appreciable rate of events occurring in NO-CAD patients enrolled in NSTE-ACS trials.

**Follow-up studies in stable patients with NO-CAD**

Two large studies (2,3) have given support to the notion that prognosis in patients with stable MVA might be worse than that suggested by the initial studies. The prospective study Women’s Ischemia Syndrome Evaluation (WISE) assessed clinical characteristics and outcome of women who underwent “a clinically indicated angiogram for chest pain symptoms or suspected myocardial ischemia” (42). Exclusion criteria included a previously known CAD and a functional New York Heart Association (NYHA) class IV **(Table 2)**.

The 5-year follow-up of patients who showed NO-CAD at angiography was reported by Gulati et al. (2). Overall, 540 out of 936 women (57.6%) enrolled in the study showed NO-CAD, 318 (60%) having NCAs and 222 (40%) non-significant CAD (NS-CAD, defined as any coronary stenosis <50%). Clinical outcomes in these patients were compared with those of 1000 age-matched asymptomatic women enrolled in the St. James Women Take Heart Project (43). The primary end-point was a combination of cardiac death, myocardial infarction (MI), stroke and admission for heart failure (HF).

**Table 3** summarizes the main clinical characteristics of the 2 WISE subgroups and controls. Overall, women enrolled in the WISE study had higher rates of cardiovascular risk factors (CVRFs). The primary end-point was significantly increased both in patients with NS-CAD and those with NCAs, as compared with controls. However, while there were significant differences between patients with NS-CAD and controls for all individual components of the combined end-point, the increased risk of NCA patients was only driven by admission for HF and stroke, whereas no significant differences existed in survival and nonfatal AMI **(Table 3)**. Of note, the increased rate of HF in WISE patients was expected due to the inclusion of patients with NYHA class II-III (42); importantly, this finding suggests a higher rate of LV dysfunction in these patients, that might have also had a significant impact on the increased risk of stroke reported in the study (44).

In another study (3), Jespersen et al. retrospectively assessed clinical outcomes of 4711 women and 6512 men who underwent coronary angiography “for suspected stable angina” in the East of Denmark between 1998-2009 **(Table 2)**. NCAs and NS-CAD were found in 65% and 33% of patients, respectively. Patients were compared with a group of asymptomatic subjects enrolled in the Copenhagen City Heart Study (45). The primary end-point was a combination of cardiovascular mortality, hospitalization for MI, HF or stroke. All-cause mortality was assessed as a secondary end-point.

The main clinical characteristics of the 2 groups are summarized, separately for men and women, in **Table 4**. As shown, NO-CAD patients had significantly higher rates of traditional CVRFs, with the exception of smoking. Moreover, 6% of male and 2% of female patients had an LV ejection fraction (LVEF) <40%, and other heart diseases were present in 15% and 8% of men and women, respectively.

At an average follow-up of 7.5 years, the risk of events, adjusted for age, sex and CVRFs, was significantly increased both in patients with NS-CAD and those with NCAs. However, after excluding patients with other heart diseases and/or LVEF <40%, the risk of events remained increased only in NS-CAD patients; the difference between NCA patients and controls in the combined end point was indeed of borderline statistical significance only and that in mortality was no longer significant **(Table 5)**. Importantly, a further reduction of the risk estimates would be expected from excluding patients with mildly impaired LV function (i.e., LVEF >40% but <50%).

Although taken together the results of these two large studies showed impaired outcome in patients with angina and NO-CAD, clinical events seem unlikely to have been driven primarily by CMD. Firstly, patients enrolled were heterogeneous **(Table 2)**, including subgroups with cardiac conditions known to be associated with increased cardiovascular risk, such as LV dysfunction, non-ischaemic heart diseases and arrhythmias; furthermore, LV hypertrophy and coronary artery spasm do not seem to have been systematically excluded (2,3). Secondly, after adjustment for confounders, mortality was not significantly higher in the subgroups of patients with NCAs (those most likely to have primary stable MVA), as compared to the respective control groups.

In summary, there is no evidence that the worse prognosis reported in stable NO-CAD patients in large epidemiologic studies can be directly attributed to CMD.

**Follow-up studies of stable patients with NO-CAD and CMD**

The prognostic value of CMD in stable patients undergoing elective coronary angiography and showing NO-CAD was assessed in a few small studies. After excluding reports including patients with specific cardiac abnormalities (e.g., severe LV hypertrophy and/or obstructive CAD) (46,47), five studies were identified (48-52), the main characteristics and results of which are summarized in **Table 6**.

The relation with outcome of both abnormalities in endothelium-independent and endothelium-dependent coronary microvascular function was variably assessed in these studies. As known, indeed, to meet myocardial oxygen demand, coronary blood flow (CBF) is regulated by complex factors that act directly on SMCs of small resistance arteries or indirectly by inducing the release of vasodilator substances by the endothelium. Thus, an impairment of microvascular function may result from either a reduced response of SMCs to dilator stimuli, an impaired production and/or release of dilator substances by the endothelium, or both (5).

Of note, an impaired endothelium-dependent dilatation is expected to have a greater prognostic impact, as it is usually a clue to a global functional impairment of the endothelium, including its anti-atherosclerotic and anti-thrombotic actions, or may even suggest an underlying early coronary atherosclerosis, by itself associated with endothelial dysfunction (53,54).

The assessment of endothelium-dependent CMD in prognostic studies was usually assessed by intracoronary administration of acetylcholine (Ach), which causes microvascular dilatation through the release of NO by endothelial cells (26). In presence of endothelial dysfunction, resulting in reduced release of NO, Ach causes lower degrees of coronary microvascular dilatation (i.e., lower increases of CBF). Moreover, in case of severe endothelial dysfunction, Ach may actually cause microvascular constriction (i.e., reduction of CBF), as it also exerts a direct vasoconstrictor effect on SMCs through direct stimulation of muscarinic receptors, an effect that in normal conditions is masked by the predominant endothelium-dependent vasodilatation (55).

On the other side, endothelium-independent CMD in prognostic studies was predominantly assessed by adenosine, that acts through direct stimulation of A2 receptors on SMCs (56). It should be observed that an impairment of small artery vessel dilatation might depend from functional abnormalities, structural alterations (e.g., SMCs hypertrophy, medial fibrosis, intimal thickening) or both. Adenosine may in part also act through endothelial NO release, although this effect is usually of limited pathophysiologic relevance (57).

Al Suwaidi et al. (48) first assessed the prognostic impact of CMD in NO-CAD patients by studying 157 patients “referred for coronary atherosclerosis” who showed coronary stenoses <40% and no evidence of coronary spasm at angiography. Both CBF responses to intracoronary adenosine (maximal dose 36 µg) and Ach (maximal dose 54.6 µg) were assessed. At a mean follow-up of 2.3 years 6 patients had cardiac events. Adenosine CFR showed no association with outcome, whereas all events occurred in patients showing a reduction of CBF in response to Ach >20%; these patients, however, also showed an epicardial constriction >20% in response to the drug. Furthermore, the role of NS-CAD vs. NCAs in the occurrence of events was not explored in this study.

Halcox et al. (49) studied 308 patients undergoing coronary angiography for “chest pain or abnormal non-invasive cardiac investigations”, including 132 patients with any CAD and 176 with NCAs. A not specified number of patients had impaired LV function, with 8% and 6%, however, having an LVEF <40%, respectively. Endothelium-independent CMD was assessed by both adenosine (4.4 µg) and sodium-nitroprusside (SNP, 60 µg) administration; furthermore, Ach test was performed (maximal dose 30 µg). At a mean follow-up of 3.8 years, 35 patients had cardiovascular events, 13 in the NCA group. CBF response to adenosine and SNP showed no relation with events. In contrast, a lower reduction in coronary vascular resistance (CVR) in response to Ach was an independent predictor of events (p=0.019). A similar independent association with events, however, was also found for Ach-induced epicardial constriction (p=0.019). Only unadjusted survival analyses were done in the NCA group, showing a significant association with events for the 2 worse tertile CVR response to Ach (p=0.035) and a borderline association for any epicardial constriction (p=0.069).

The last three studies (50-52) included subgroups of female patients enrolled in the WISE study (see above). Von Mering et al. (50) studied 163 patients; 123 (75%) showed NO-CAD, 74 of whom had <20% stenosis (considered as NCAs) and 49 had 20-49% stenosis (“minimal CAD”). Patients underwent assessment of coronary dilator function by intracoronary adenosine (18 µg), nitroglycerin (NTG, 200 µg) and Ach (maximal dose 54.6 µg). At a median follow-up of 4 years, 58 patients had clinical events, including 5 deaths and 2 AMI. On multivariable analysis, the magnitude of the epicardial vessel constriction in response to Ach was an independent predictor of events, together with significant or minimal CAD. No independent prognostic value was found for coronary microvascular response to Ach, adenosine or NTG.

Pepine et al. (51) assessed CFR by intracoronary adenosine (18 µg) in 189 women, 152 (81%) of whom had NO-CAD at angiography. During a mean follow-up of 5.4 years, 34 patients experienced major cardiovascular events, 25 of whom were in the NO-CAD group. Adenosine CFR <2.32 was an independent predictor of events both in the whole population and in NO-CAD women. However, although HF was a relevant component of the primary end-point, NYHA class and LV function were not considered in multivariable analyses; furthermore, no separate analyses were done in the subgroup of patients with NCAs.

Finally, AlBadri et al. (52) have reported long-term follow-up (median 9.7 years) of WISE women who underwent assessment of coronary reactivity at enrolment by intracoronary adenosine (maximal dose 36 µg) and/or Ach (maximal dose 18.2 µg) and/or NTG. Although the authors report significant associations of the vascular response to adenosine and Ach with various clinical end-points in post-hoc analyses, no significant association was, in fact, found between abnormal coronary reactivity tests by pre-specified criteria (e.g., adenosine CFR <2.32; increase in CBF by Ach <50%) and major cardiovascular events (death, MI, stroke) in the NO-CAD group of patients. Again, important confounding variables (LVEF, NYHA class and NS-CAD) were not taken into adequate account in multivariable analyses (52).

In summary, although the results of invasive studies suggest an association between CMD and impaired clinical outcomes in NO-CAD patients, there are limitations that preclude categorical conclusions regarding the prognostic role of CMD in these patients and, more specifically, in those fulfilling a strict definition of primary stable MVA. Major limitations noted in these studies include the large heterogeneity of patients and the presence of confounding prognostic variables, not always adequately addressed in multivariable statistical analyses.

Importantly, epicardial coronary constriction in response to Ach also showed association with outcome, thus raising the issue of whether abnormal epicardial reactivity might be involved in the adverse prognosis reported in these patients, as recently suggested in patients with ACS with NO-CAD (58). Of note, it should be observed that while an abnormal response to Ach was always considered as an expression of an impairment of endothelium-dependent vasodilation (48-50,52), it might also be related to an abnormal constrictor response of vascular smooth cells to the drug, as hypothesized in patients with vasospastic angina (59). Unfortunately, whether patients included in these studies might have also had epicardial spasm was not adequately investigated as only small doses of acetylcholine were used (60).

Finally, the data do not support a strong association between impaired endothelium-independent coronary microvascular dilation and clinical outcomes. Of note, a prognostic role of endothelium-independent CMD was recently suggested by a large non-invasive study (61). In this study of 4029 patients followed for a median of 5.6 years, Gupta et al., extended previous findings (62), reporting that patients with reduced both CFR and maximal myocardial blood flow (mMBF), as assessed by positron emission tomography pharmacologic stress testing, had the highest annual cardiovascular mortality (3.3%) compared to those with low CFR but normal mMBF (1.7%), normal CFR but low mMBF (0.9%) or both normal CFR and mMBF (0.4%). However, patients in this study were very heterogenous, as 29.4% had reduced LVEF, 28% had a history of MI and more than one third had previous coronary revascularization; importantly, most patients did not undergo coronary angiography. Thus, the results of this study cannot be extrapolated directly to patients with NO-CAD or those with primary stable MVA, as the authors recognize in their manuscript (61).

**Summary of findings**

Most of the uncertainty regarding clinical outcomes of patients with MVA derives from the fact that different studies have included different populations, making it difficult to compare like with like, and several of these studies have methodological limitations. The early follow-up studies of patients with angina and NO-CAD that reported good prognosis included relatively homogeneous groups of patients, who were largely representative of primary stable MVA. In contrast, the most recent studies -generally reporting impaired clinical outcomes- recruited more heterogeneous patient groups, often with various degrees of CAD and other confounders, possibly including vasospastic angina that *per se* may be associated with impaired prognosis (48-50).

Importantly, in the two recent population studies on NO-CAD patients, the subgroups with NCAs at angiography showed, after appropriate correction for confounding variables, rates of survival comparable to those in control populations (2,3). Furthermore, the rates of acute MI were also not in increased in the WISE report **(table 3**) (2), while these data were unavailable for the Danish study (3). Of note, the favourable prognosis and the low rate of life-threatening cardiac events in patients with primary stable MVA is largely expected, on the basis of robust evidence that mild subendocardial ischaemia, as usually seen in MVA patients, has a very low risk of fatal arrhythmic or haemodynamic complications (63,64). However, whether repeated episodes of subendocardial ischaemia in MVA patients may lead to some form of LV failure, in particular heart failure with preserved LVEF, may require further investigation (65,66).

On the other hand, the large studies that assessed clinical outcome in patients with stable angina symptoms but NO-CAD indicate that those with some degree of CAD (stenosis <50%) are more likely to have impaired clinical outcomes (2,3), a finding confirmed by a recent meta-analysis (16). These data are in agreement with few other studies that also suggested worse clinical or angiographic outcomes in patients with stable angina and NO-CAD as compared to those with completely NCAs (67-69), although it should be noticed that patients with coronary stenosis up to 70-75% were included in the NO-CAD group in these studies (68,69).

It could be argued that the significant rate of coronary events in patients with NO-CAD can be explained by the fact that these often occur as a consequence of acute complications in nonsignificant coronary plaques (70,71), and risk may be higher in patients with extensive NO-CAD (72). Further studies should assess whether CMD may have any prognostic value in these patients. Of note, it should be observed that atherosclerotic plaques have been shown by intravascular ultrasound in a sizeable proportion of patients with MVA displaying NCAs at angiography (73,74), and therefore whether and how they may impact on clinical outcome is also an important issue that appropriate studies should answer.

Moreover, future studies should aim to clarify the pathophysiologic and prognostic role of epicardial spasm in the general population of patients with angina despite NCAs or NS-CAD, as several studies suggest a relation between coronary spasm and clinical outcomes in these patients (48-50). Coronary spasm is indeed a condition often underdiagnosed in clinical practice which is known to have prognostic implications that may differ from those of MVA (75) and, importantly, can be effectively prevented by appropriate vasodilator therapy (76).

**Conclusions**

Published data indicate that clinical outcomes are heterogeneous in patients with angina and NO-CAD. Patients with strict criteria for primary stable MVA may have a markedly impaired quality of life but, according to current evidence, they do not appear to have an increased mortality or risk of major coronary events. Patients with MVA and NS-CAD have instead an increased risk of developing cardiovascular events and may therefore require a more aggressive management. The increased rate of coronary events in the latter group is likely related to the risk of acute complications of subcritical coronary plaques. Future studies, however, should assess whether CMD has a true prognostic role in this clinical context and in other clinical settings of NO-CAD.

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**Table 1**. Main characteristics and follow-up results of studies on patients with primary stable MVA.

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | No. pts | Age | F (%) | Inclusion criteria | Exclusion criteria | FU (years) | Death | CV death | CAD death | AMI | Stroke |
| Chauhan, 19934 | 41 | 46.4 | 61 | Angina, positive exercise test and NCAs; normal LV pressures | Oesophagoeal spasm, LV hypertrophy, LBBB | 2.9 | - | - | - |  | - |
| Romeo, 19935 | 30 | 50.0 | 90 | Angina-like pain, positive exercise test and NCAs; normal LV pressures | LV hypertrophy, CAS, hypertension, diabetes, collagen disease | 5 | - | - | - | - | - |
| Kaski, 19956 | 99 | 48.5 | 79 | Exercise-induced chest pain, positive exercise testing, NCAs | CAS, LV hypertrophy, hypertension, diabetes, LBBB, osesophageal spasm | 7 | - | - | - | 5 | - |
| Radice, 19957 | 30 | 51.0 | 73 | Stable angina due to only or mainly to exertion; positive exercise test, NCAs | CAS, LV hypertrophy, hypertension, LBBB, other heart disease | 12.2 | 1 | - | - | - | 3 |
| Suzuki, 20028 | 86 | 59.0 | 59 | Chest pain, positive exercise test, NCAs small artery sclerosis at EMB | CSA, valvular disease, hypertensive heart disease, cardiomyopathy,  Collagen, endocrine, metabolic disease | 7.2 | 1 | - | - | - | 2 |
| Bugiardini, 2004\*9 | 42 | 51.6 | 100 | De novo angina, positive exercise test and ischemia at RN test, NCAs | Cardiomyopathy, valvular disease, dyslipidemia, diabetes | 10.3 | 1 | 1 | 1 | - | - |
| Lanza, 201730 | 240 | 55.5 | 76 | Angina, positive exercise test, NCAs | LV hypertrophy, LV dysfunction, any heart disease, CAS, LBBB | 16 | 26 | 9 | 2 | 8^ | 14^ |

AMI=acute myocardial infarction; CV=cardiovascular; CAD=coronary artery disease; CAS=coronary artery spasm; EMB=endomyocardial biopsy; F=female patients; LBBB=left bundle branch block; LV=left ventricle; NCAs=normal coronary arteries; pts=patients; RN=radionuclide tests. \*De novo angina; ^data on 207 patients.

**Table 2.** Main inclusion and exclusion criteria of WISE and Danish studies

on prognosis of patients with chest pain and NO-CAD.

|  |  |  |  |
| --- | --- | --- | --- |
|  | WISE study  (ref. 11) |  | Danish study  (ref. 12) |
| Inclusion criteria | Women >18 years undergoing a clinically indicated angiogram for chest pain symptoms or suspected myocardial ischemia |  | All patients having a first coronary angiography in Eastern Denmark because of suspected stable angina between 1998 and 2009 |
| Exclusion criteria | * + Comorbidity which compromised  1-year follow-up   + Pregnancy   + Contraindications to diagnostic provocative tests   + NYHA IV heart failure   + Recent AMI   + Significant valvular or congenital disease   + Language barrier to questionnaire testing   + Recent PCI or CABG |  | * + Age <20 years   + Previous AMI or unstable angina   + Previous PCI or CABG   + Aortic stenosis   + Paroxysmal atrial fibrillation/flutter   + Hypertrophic cardiomyopathy   + Myocarditis |

AMI=acute myocardial infarction; CABG=coronary artery bypass graft; NYHA=New York Heart Association; PCI=percutaneous coronary intervention.

**Table 3.** Main clinical characteristics and clinical events in WISE patients with NS-CAD or NCAs and controls

included in the 5-year follow-up study (data from ref. 11)

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | NS-CAD  (n=222) | NCAs  (n=318) | Controls  (n=1000) | P  (among groups) | P1  (NS-CAD vs. controls) | P2  (NCAs vs. controls) |
| Age (years) | 58.7 | 53.6 | 54.8 | 0.02 | - | - |
| Hypertension (%) | 61 | 50 | 18 | <0.001 | - | - |
| Diabetes (%) | 20 | 14 | 5 | <0.001 | - | - |
| Smoking (%) | 58 | 46 | 18 | <0.001 | - | - |
| LDL-cholesterol (mg/dL) | 114 | 111 | 136 | <0.001 | - | - |
| Anti-lipemic drugs (%) | 36 | 12 | 3 | <0.001 | - | - |
| Aspirin (%) | 62 | 44 | 24 | <0.001 | - | - |
| ***Clinical events*** |  |  |  |  |  |  |
| All-cause death (%) | 8.2 | 3.0 | 2.1 | - | 0.04 | 0.74 |
| Cardiovascular death (%) | 4.4 | 1.5 | 0.7 | - | 0.11 | 0.82 |
| Acute myocardial infarction (%) | 3.9 | 0.9 | 0.7 | - | 0.07 | 0.31 |
| Stroke (%) | 5.2 | 2.4 | 1.0 | - | 0.002 | 0.004 |
| Admission for heart failure (%) | 5.6 | 3.3 | 0.3 | - | <0.001 | 0.002 |
| Combined end-point (%) | 16.0 | 7.9 | 2.4 | - | <0.001 | 0.002 |

NS-CAD=nonsignificant coronary artery disease; NCAs=normal coronary arteries

**Table 4.** Main clinical characteristics of patients included in the Danish study on prognosis of patients with chest pain and NO-CAD.

(Data from Ref. 12).

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | Men | | | |  | Women | | | |
|  | NS-CAD  (n=884) | NCAs  (n=1226) | Controls  (n=2359) | P |  | NS-CAD  (n=884) | NCAs  (n=1226) | Controls  (n=2359) | P |
| Age (years | 62.8 | 55.9 | 56.5 | <0.001 |  | 65.0 | 58.5 | 58.9 | <0.001 |
| Anti-hypertensive drugs (%) | 52 | 38 | 13 | <0.001 |  | 61 | 44 | 18 | <0.001 |
| Diabetes (%) | 22 | 13 | 5 | <0.001 |  | 18 | 10 | 3 | <0.001 |
| Smoking (%) | 31 | 30 | 35 | 0.002 |  | 25 | 19 | 31 | <0.001 |
| Anti-lipemic drugs (%) | 65 | 45 | 3 | <0.001 |  | 71 | 50 | 4 | <0.001 |
| LVEF <40% (%) | 6 | 6 | 0 | 0.003 |  | 1 | 2 | 0 | 0.011 |
| Other heart disease (%) | 14 | 15 | 1 | <0.001 |  | 9 | 8 | 1 | <0.001 |

LVEF=left ventricle ejection fraction; NS-CAD=nonsignificant coronary artery disease; NCAs=normal coronary arteries

**Table 5.** Hazard ratios for the primary end-point and all-cause death in various subgroups of patients   
in the Danish study on prognosis of patients with chest pain and NO-CAD. (Data from Ref. 12).

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | NS-CAD | | |  | NCAs | | |
|  | HR | 95% C.I. | P |  | HR | 95 C.I. | P |
| **Primary end-point** |  |  |  |  |  |  |  |
| All patients | 1.83 | 1.51-2.28 | <0.001 |  | 1.52 | 1.27-1.83 | <0.001 |
| No other heart disease | 1.62 | 1.29-2.05 | <0.001 |  | 1.42 | 1.15-1.74 | 0.001 |
| Only LVEF>40% | 1.50 | 1.11-2.02 | 0.008 |  | 1.31 | 1.01-1.71 | <0.05 |
| **All-cause death** |  |  |  |  |  |  |  |
| All patients | 1.52 | 1.24-1.88 | <0.001 |  | 1.29 | 1.97-1.56 | 0.007 |
| No other heart disease | 1.43 | 1.14-1.81 | 0.002 |  | 1.33 | 1.08-1.64 | 0.008 |
| Only LVEF>40% | 1.34 | 1.00-1.79 | 0.05 |  | 1.20 | 0.92-1.55 | 0.18 |

LVEF=left ventricle ejection fraction; NS-CAD=nonsignificant coronary artery disease; NCAs=normal coronary arteries

**Table 6.** Main clinical characteristics and results of studies assessing the relation of CMD with clinical outcome in NO-CAD patients

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | No. pts | Mean age  (yrs) | Female | Inclusion criteria | Exclusion criteria | Endothelium-dependent CMD | Endothelium-independent CMD |
| Al Suwaidi, 200042 | 157 | 52.0 | 66% | Referral for coronary atherosclerosis;  any stenosis <40% | ACS, PCI/CABG, variant angina, PVD, LVEF <50%, valvular disease, systemic disease | + (Ach) | - (ADO) |
| Halcox, 200243 | 171\* | 51.1 | 60% | Referral for chest pain or abnormal non-invasive cardiac investigations | ACS, valvular disease, NYHA III-IV, not revascularized 3-vessel/LM disease | + (Ach) | - (SNP, ADO) |
| Von Mering, 200444 | 123\* | 55.6° | 100% | Those of WISE study (Table 3) | Those of WISE study (Table 3) | - (Ach) | - (ADO, NTG) |
| Pepine, 201045 | 152\* | 55.0° | 100% | Those of WISE study (Table 3) | Those of WISE study (Table 3) | n.a. | + (ADO) |
| AlBadri 201949 | 181\* | 55.0° | 100% | Those of WISE study (Table 3) | Those of WISE study (Table 3) | +/- (Ach) | - (ADO, NTG) |

\*Patients with NO-CAD included in the study; °Mean age of the whole population, including also patients with obstructive CAD.

Ach=acetylcholine; ACS=acute coronary syndrome; ADO=adenosine; CMD=coronary microvascular dysfunction; LM=left main; n.a.=not assessed; NTG=nitroglycerin; PCI=percutaneous coronary intervention; NYHA=New York Heart Association; LVEF=left ventricular ejection fraction; PVD=peripheral vascular disease; SNP=sodium nitroprusside

(+)=significant association with main clinical outcome; (-)=no significant association with main clinical outcome.