

# Noncardiac chest pain: systematic review of the literature on prognosis

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**Background:** Noncardiac chest pain (NCCP) is defined as persistent angina-like chest pain with no evidence of cardiac disease. There is some controversy about the long-term morbidity and mortality outcomes of NCCP patients. Many studies have found no significant differences in death rates in chest pain patients without coronary artery disease compared to the general population. However, studies that include longer follow-up periods and a better characterization of the NCCP population reveal a twofold elevation in the relative risk of adverse cardiac events over 5–26 years. This review sought to identify studies in relation to cardiovascular and psychological prognosis of NCCP patients.

**Methods:** PubMed database and reference lists from relevant publications were reviewed. Inclusion criteria were systematic reviews, prospective studies, and retrospective surveys from 1970 to 2011. Search terms were as follows: chest pain, noncardiac chest pain, nonspecific chest pain, unexplained chest pain, prognosis of noncardiac chest pain, prognosis of angina with normal angiography, and angina with normal coronary arteries.

**Results:** Studies supporting worse outcome (cardiac morbidity and mortality;  $n=16$ ) included 173,875 patients with mean age 57 and mean length of follow-up 7.5 years. Studies supporting good outcome ( $n=25$ ) included 244,998 patients with age 50 and length of follow-up 5 years. Articles supporting poor psychological outcome ( $n=9$ ) included 3,987 patients and length of follow-up 2 years.

**Conclusion:** There are mixed data on long-term morbidity, cardiovascular adverse events, and mortality of NCCP patients. Some studies provide supporting evidence for poor outcome, while others provide evidence for positive outcome. However, many patients with NCCP have prolonged psychosocial comorbidity. The heterogeneity of NCCP and study populations limited definitive conclusions. However, many patients with NCCP have psychiatric morbidity and poor quality of life. Several questions remain about NCCP with respect to the psychopathology and pathophysiology of this condition. Whether NCCP patients have good or bad outcome requires careful risk stratification.

**Keywords:** chest pain, noncardiac chest pain, anxiety, angina with normal coronary arteries, microvascular angina, prognosis

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## Introduction

Chest pain is a common and alarming patient complaint, amounting to more than 6 million cases in the USA annually.<sup>1</sup> After extensive and costly evaluations, many of these patients receive the diagnosis of noncardiac chest pain (NCCP), defined as persistent angina-like chest pain with no evidence of cardiac impairment after a reasonable cardiac evaluation. NCCP is a heterogeneous disorder caused by various

conditions (Table 1). Several studies have supported evidence for anxiety and mood disorders and pain perception abnormalities. Inflammation and microvascular angina are also implicated. Patients can have normal epicardial coronary arteries but still have microvascular dysfunction.<sup>2</sup> Acid reflux may induce chest pain. Gastroesophageal reflux disease, esophageal motility disorders, musculoskeletal disorders, breathing disorders, depression, and anxiety are implicated as causal factors.<sup>3,5,8</sup> Few studies support a role of antidepressants in treating pain perception and the comorbid anxiety and depression. NCCP is considered a benign problem with various psychopathological comorbidities.

While chest pain can be a bona fide symptom of coronary artery disease (CAD), not infrequently, the origin of chest pain remains elusive even after thorough cardiovascular evaluations. Approximately 30% of all coronary angiograms prove to be negative for significant CAD, and these patients are thus diagnosed with NCCP.<sup>3</sup> More than 3 million patients are admitted with NCCP each year, costing over \$10 billion annually,<sup>4</sup> and are given this “diagnosis of exclusion”<sup>5,6</sup> since no organic medical cause to explain their complaint could be ascertained. NCCP is associated with exceedingly high health-care costs due to activity limitations for the patients, health-care utilization, repeated admissions to coronary care units, and further catheterizations. Regardless of the etiology of the pain, NCCP patients suffer, and they experience poor psychological and quality-of-life outcomes.<sup>7</sup> In view of the fact that the condition is poorly understood, these patients do not receive optimal care.<sup>8</sup> A high percentage of these patients continue to experience chest pain for many years and be consumers of medical resources. The question is how many of these patients eventually develop cardiovascular morbidity and mortality.<sup>9–13</sup> Unexplained chest pain is often comorbid with anxiety, depression, and somatoform disorders.<sup>14–21</sup> In a recent study by White et al, the comorbidity of psychiatric conditions and NCCP was examined prospectively in a cohort of 231 NCCP patients free of a current or lifetime cardiac diagnosis. The authors found that 44% of the NCCP patients suffered

from a current Axis I psychiatric diagnosis, with anxiety disorders being most prevalent at 41% and mood disorders at 13%.<sup>22</sup> Patients with NCCP may also have exaggerated or abnormal cardiac pain perceptions,<sup>23</sup> visceral hyperalgesia,<sup>24</sup> and/or abnormal cardiac sensitivity to a variety of stimuli.<sup>25</sup> Treatment of NCCP includes psychotherapy and psychotropic medications, such as antidepressant and antianxiety drugs.<sup>26</sup>

Studies that include longer follow-up periods and a better characterization of the heterogeneous NCCP population reveal about a twofold elevation in the relative risk of adverse cardiac events (cardiovascular morbidity and mortality) over 5–26 years in NCCP patients.<sup>9–13</sup> Due to the frequency of significant psychiatric comorbidity associated with NCCP, could it be that the known association between anxiety, depression, panic disorder, and cardiovascular disease (CVD) is responsible for the long-term morbidity and mortality of NCCP? It has been shown that acute and chronic anxiety can be associated with sudden cardiac death and CAD.<sup>27,28</sup> Depression is an established risk factor for CVD with a 2.0 relative risk of adverse cardiovascular events.<sup>29,30</sup> Panic disorder has been associated with hypertension, small vessel cardiac ischemia, and lipid abnormalities.<sup>31,32</sup> Thus, associations could exist between NCCP, depression/anxiety, and a higher risk of cardiovascular morbidity and mortality. A large proportion of older women report levels of depressive symptoms that are significantly related to increased risk of CVD death and all-cause mortality, even after controlling for established CVD risk factors.<sup>30</sup> Elderly women diagnosed with nonspecific chest pain may be at increased cardiovascular risk.<sup>33–35</sup> In women with suspected myocardial ischemia, depression was a strong predictor of increased risk of cardiac events.<sup>36</sup> However, the causal relationship between coronary heart disease (CHD) risk factors in the psychiatric population and increased NCCP morbidity and mortality risk, if any, is unclear. It remains unknown if psychiatric disorders can contribute to NCCP and thus lead to any CAD, or if any other CVD risk factors exist that are present in the NCCP population. Between 32% and 64% of patients with chest pain

**Table 1** Causes of NCCP

Esophageal causes	GERD, esophageal dysmotility-nutcracker esophagus, achalasia, diffuse esophageal spasm, HTLES
Stomach	Peptic ulcer, gastritis
Musculoskeletal	Costochondritis, Tietze syndrome, fibromyalgia, muscle injury
Pulmonary	Pleuritis, pneumonia, intrathoracic masses
Visceral hypersensitivity	Esophageal hypersensitivity
Psychological comorbidity	Panic disorder and anxiety, depression
Malignant disease	Gastrointestinal, chest wall, breast
Miscellaneous	Drug-induced pain, sickle cell disease, herpes zoster, pericarditis, myocarditis

**Abbreviations:** GERD, gastroesophageal reflux disease; HTLES, hypertensive lower esophageal sphincter; NCCP, noncardiac chest pain.

and normal coronary angiograms are smokers.<sup>37</sup> In patients with chest pain and negative coronary angiograms, some studies have identified diminished coronary flow velocity reserve and aortic distensibility,<sup>38</sup> microvascular angina,<sup>39</sup> endothelial dysfunction,<sup>40–42</sup> aortic stiffness,<sup>43</sup> and vascular and metabolic abnormalities.<sup>44</sup> Perhaps, the best study of endothelial function in NCCP was a longitudinal study by Bugiardini et al.<sup>40</sup> Since anxiety and depression are highly comorbid with NCCP and since studies support the presence of depression and anxiety as risk factors for CAD, it is very important to know the long-term prognosis of NCCP, which at this point remains unclear. It is important to understand the long-term prognosis of NCCP so that these patients can be better treated to decrease suffering and cost. In this article, we review the literature focusing on studies that address the prognosis of NCCP patients.

## Objective

To identify studies in relation to the long-term prognosis of NCCP patients including cardiovascular health risk and psychological well-being.

## Methods

### Search strategy

Two sources of material for inclusion in the review were identified – electronic database and reference lists from the papers reviewed. We used a multistep search process to identify published research reports related to NCCP. We initially searched the PubMed (National Library of Medicine) computer database for relevant studies. This database contains MEDLINE citations along with selected other citations. Inclusion criteria were systematic reviews, prospective studies, and retrospective surveys. We conducted a search of the PubMed database from 1970 to 2011 using the following search terms: chest pain, non-cardiac chest pain, nonspecific chest pain, unexplained chest pain, prognosis of noncardiac chest pain, prognosis of angina with normal angiography, angina with normal coronary arteries, cardiac syndrome X, non-obstructive coronary disease and variant angina, and chest pain of noncardiac origin. Reference lists of published articles were also included.

### Data extraction and synthesis

A data collection sheet was designed for the review. The following data were collected: publication details, participation and setting, patient population, study design, NCCP definition, outcome measures, results, and discussion. We then manually reviewed articles obtained through the PubMed

search to identify additional articles pertinent to the topic of this review. The title and abstract of each article were read, and from that relevant studies that investigated NCCP were selected. All identified studies were imported and combined into one database.

## Results

Relevant studies that investigated NCCP were selected. Studies supporting worse outcome (cardiac morbidity and mortality; Table 2; n=16) comprised 173,875 total patients followed up, with mean age 57 and mean length of follow-up 7.5 years. Studies supporting good outcome (Table 3; n=25) comprised 2,44,998 patients with age 50 and length of follow-up 5 years. Articles indicating a poor psychological outcome (psychiatric morbidity, worse quality of life) for NCCP patients (Table 4; n=9) comprised 3,987 patients and length of follow-up 2 years.

## Discussion

In follow-up studies indicating worse outcome, patients were followed an average of 7.5 years compared with 5 years in studies indicating good prognosis. Also, the mean age is 57 years in the worse outcome group compared to 50 years in the good outcome group. There is some controversy about the long-term morbidity and mortality outcomes of NCCP patients. Many studies have found no significant differences in death rates in chest pain patients without CAD compared to those in the general population.<sup>6</sup> In one such study, the 7-year mortality rate was 4% for patients with a normal arteriogram and 8% for those whose workup had revealed mild disease.<sup>75</sup> Another study<sup>53</sup> following 173 patients for 12 years reported that patients being discharged from the ED with NCCP had as good a prognosis for cardiovascular outcomes as the general population of the same age – but the frequency and intensity of chest pains remained unchanged in a third of the patients over this lengthy time period. Dumville et al<sup>78</sup> retrospectively studied 456 consecutive patients presenting with chest pain to a Rapid-Access Chest Pain Clinic in England. Of these, 235 were discharged with a diagnosis of NCCP within 14 days of their symptoms being reported. Upon follow-up (median of 5.4 months later), nearly half of the patients still had chest pain, and amongst these, more than half remained unconvinced by their negative cardiac diagnosis.<sup>78</sup>

However, these results contrast with the number of studies,<sup>9–13</sup> which indicate that NCCP patients are at higher risk to experience adverse cardiovascular outcomes than

**Table 2** Articles supporting worse cardiovascular outcome for NCCP patients

Investigators	Participants	Months	Outcome measures	Results
Bodegard et al (2004) <sup>45</sup>	2,014	312	CABG and MI morbidity data	Had a higher incidence of CABG ( $P<0.0004$ ) and acute MI ( $P<0.026$ )
Bugiardini et al (2009) <sup>9</sup>	7,656	12	Rates of mortality and cardiovascular morbidity	2% death rate at 1-year follow-up
Eslick and Talley (2008) <sup>10</sup>	197	48	Continued chest pain, quality of life, and mortality	The cardiac mortality rate for patients with NCCP was 5.5% ( $P=0.16$ )
Johnson et al (2006) <sup>12</sup>	673	62.4	Cardiovascular mortality, MI, CHF, and stroke	More than twice the rate of composite CV events ( $P=0.03$ ).
Robinson et al (2006) <sup>35</sup>	83,622	96	CHD events in women with NCCP	Twofold higher risk of subsequent hospitalization for angina
Rutledge et al (2006) <sup>36</sup>	505	58.8	Cardiovascular mortality and morbidity	Increased incidence of death and cardiac events
Wilhelmsen et al (1998) <sup>13</sup>	6,488	192	Mortality and morbidity	The relative risk of CHD mortality among men with "nonspecific chest pain" was 2.77
McMahon et al (2008) <sup>11</sup>	786	60	Mortality	5-year mortality rate more than double the general population
Sekhri et al (2007) <sup>46</sup>	8,762 NCCP: 6,396		Death due to CAD or ACS	599,194 (32.4%) with NCCP
Bugiardini et al (2004) <sup>40</sup>	42	120	Endothelial function	Twenty-two patients with vasoconstriction, 13 patients with CAD
Herlitz et al (1998) <sup>47</sup>		60	Mortality rate	NCCP 32%
Launbjerg et al (1993) <sup>48</sup>	595	84	Cardiac death	High cardiac mortality
Ruigomez et al (2009) <sup>49</sup>	3,028	12	Morbidity and mortality	More likely to have IHD
Robinson et al (2008) <sup>50</sup>	571	85.2	Nonfatal MI	Twofold CAD
Munk et al (2008) <sup>51</sup>	386	120	IHD and mortality	Threefold high
Gilles et al (2006) <sup>52</sup>	Retrospective 3,514 men, 3,136 women		All-cause and CVD-specific death	Higher incidence of all-cause and CVD-specific death

**Abbreviations:** ACS, acute coronary syndrome; CABG, coronary artery bypass graft; CAD, coronary artery disease; CHD, coronary heart disease; CHF, congestive heart failure; CV, cardiovascular; CVD, cardiovascular disease; IHD, ischemic heart disease; MI, myocardial infarction; NCCP, noncardiac chest pain.

the general population. Geraldine et al concluded from 786 patients discharged from an ED in the UK, following an episode of acute chest pain, that they had significantly reduced 5-year survivals.<sup>11</sup> Results from a primary prevention study in Göteborg, Sweden, also indicated high cardiovascular (20%) and non-cardiovascular (18%) mortality rates amongst patients with "chest pain who had not been considered to have angina pectoris".<sup>13</sup> Bugiardini et al<sup>9</sup> pooled data from three Thrombolysis in Myocardial Infarction (TIMI) trials and found a high (12.1%) incidence of adverse (cardiac-related) events at 1 year of follow-up in those NCCP patients. That study followed 710 well-characterized NCCP patients presenting with acute chest pain but lacking obstructive CAD on angiograms and without ST segment elevations during stress tests. Likewise, a study by Johnson et al<sup>12</sup> followed 303 NCCP patients in the Women's Ischemia Syndrome Evaluation (WISE) study and reported 20% incidence of cardiovascular events (twice the incidence in women with normal angiograms and no persistent chest pain) at a median of 5.2 years of follow-up. This risk of cardiovascular events

was not as high as in patients with chest pain plus obstructive CAD ( $n=263$ ), which was 40%, but the risk was still twice as high as in healthy controls.<sup>12</sup> Verification of the findings of Johnson et al has been reported by Eslick et al<sup>10</sup> for NCCP patients under 65 years of age in Australia: higher rates of cardiac mortality over 4 years for NCCP patients (6% cardiac mortality) and also for CAD chest pain patients (11%).<sup>10</sup> The longest study was a 26-year follow-up of men with "possible angina" based on chest pain reported in a questionnaire but no abnormal stress test compared to men with negative responses on the chest pain questionnaire and a normal stress test.<sup>45</sup> At 26 years, men with this kind of NCCP had a CHD mortality of 25% compared to 14% among men with no symptoms of angina. The NCCP patients also had a higher incidence of coronary artery bypass grafting and acute myocardial infarctions (MIs).

In summary, there are studies indicating that NCCP patients are not at higher risk of cardiac events, and there are studies indicating that NCCP patients are at higher risk of cardiac events. All studies agree that the chest pain

**Table 3** Articles supporting NCCP as a benign problem or with good cardiovascular outcome

Investigators	Participants	Months	Outcome measures	Results
Scholtz et al <sup>53</sup>	185	144	Fatal or nonfatal myocardial infarction	Good long-term prognosis
Karlson et al <sup>54</sup>	2,102	12	Mortality	Mortality 3%
Walker et al <sup>55</sup>	487	1	Acute myocardial infarction, death, PCI	2.1% adverse cardiac events
Bargheer et al <sup>56</sup>	178	177.6	Mortality, MI	Excellent long-term prognosis
Voelker et al <sup>57</sup>	88	110.4	Death, MI	Three deaths, one MI
Foussas et al <sup>58</sup>	160	30	Death, MI	Excellent prognosis
Lamendola et al <sup>59</sup>	155	137	Cardiac death, AMI	Excellent long-term prognosis
Lichtlen et al <sup>60</sup>	176	148.8	Coronary event	Good long-term prognosis
Isner et al <sup>61</sup>	121	51.6	Morbidity, cardiac events	High favorable prognosis
Pasternak et al <sup>62</sup>	175	42.7	Chest pain	Low mortality and morbidity
Dart et al <sup>63</sup>	98	Retrospective review	Life expectancy	Excellent prognosis
Van Dorpe et al <sup>64</sup>	142	49.3	Cardiac death	No cardiac death, one MI
Panju et al <sup>65</sup>	158	36	Mortality	Low mortality rate
Williams et al <sup>66</sup>	161	117.6	Survival	No significant difference
Spalding et al <sup>67</sup>	250	12	Mortality rate	2.9% in NCCP
	NCCP 108			
Rey et al <sup>68</sup>	104	44.4	Pain	Favorable life prognosis
Roll et al <sup>69</sup>	64	60	Pain	Excellent prognosis
Launbjerg et al <sup>70</sup>	204	33	Cardiac death, nonfatal AMI	Three events among 140 patients
	NCCP 140			
Fagring et al <sup>71</sup>	235,855	12	1-year mortality	Similar to general population
	Registry study			
Zarauza et al <sup>72</sup>	93	12	Coronary events	Good 1-year outcome
Colon et al <sup>73</sup>	105	33.6	MI, cardiac death	Excellent 3-year prognosis
Bringager et al <sup>74</sup>	199 patients		Long-term outcome, death rate	Low death rate
Kemp et al <sup>75</sup>	21,487 consecutive coronary arteriograms	84	The effect on 7-year survival	The 7-year survival rate was 96%
Hirota et al <sup>76</sup>	274	72	Fatal or nonfatal MI	None
Prina et al <sup>77</sup>	1,973 (NCCP: 230)		Adverse cardiac event, mortality	Without risk factors, cardiac outcome is excellent

**Abbreviations:** AMI, acute myocardial infarction; MI, myocardial infarction; NCCP, noncardiac chest pain; PCI, percutaneous coronary intervention.

**Table 4** Articles supporting poor psychological outcome for NCCP patients

Investigators	Participants	Months	Outcome	Results
Bringager et al <sup>74</sup>	199	108	Mortality, health-related quality of life	Panic disorder has a negative long-term effect
Dumville et al <sup>78</sup>	235 (retrospective data)		Chest pain	Half of NCCP patients reported ongoing chest pain
Karlson et al <sup>54</sup>	2,102	12	Mortality, AMI,	More emotional and psychosomatic symptoms
Karlson et al <sup>79</sup>		12	Chest pain, well-being	More chest pain, worse quality of life
Ockene et al <sup>80</sup>	57	15	Functional status	Many patients remained limited in activity
Bass and Jackson <sup>81</sup>	30	12	Psychosocial status	Psychiatric morbidity, chronic course
Roll et al <sup>69</sup>	64	60	Chest pain, depression	High psychological symptoms
Fagring et al <sup>82</sup>	1,069		Quality of life	Poor
Jerlock et al <sup>83</sup>	231		Quality of life	Poor

**Abbreviations:** AMI, acute myocardial infarction; NCCP, noncardiac chest pain.

commonly persists in NCCP patients for many years. At least 50% of the NCCP patients have an Axis I psychiatric diagnosis. Depression is an established risk factor for CVD. By last count, 12 long-term prospective studies have clearly established that there is about a 2.0 relative risk of adverse

cardiovascular events associated with depression.<sup>29,30</sup> It is possible that NCCP patients in the long run may have poor cardiovascular outcome, and studies are needed to determine if depression and anxiety play a role. Is there an association between anxiety, depression, and CVD that could explain



the possible association of NCCP and long-term morbidity and mortality? Another important aspect is the heterogeneity of NCCP. The NCCP group includes many patients with a history of established CAD and NCCP.

## Conclusion

The literature we have searched contains mixed findings in relation to long-term medical and psychological prognosis in patients with NCCP. The findings from this review show that there are mixed data on long-term morbidity, cardiovascular adverse events, and mortality of NCCP, some supporting evidence for poor outcome and others supporting evidence for positive outcome. Articles supporting poor outcome had longer follow-ups and included patients of higher age. Bodegard et al<sup>45</sup> followed their subjects for 26 years. Articles supporting poor long-term outcome tend to include NCCP patients with high preexisting cardiac risk factors, namely, endothelial dysfunction (Bugiardini et al<sup>40</sup>), higher TIMI score family history, hypertension, hypercholesterolemia, diabetes mellitus (Bugiardini et al<sup>9</sup>), and increased cardiovascular risk factors (Wilhelmsen et al<sup>13</sup>). Studies supporting good cardiovascular outcome included young adults who had less cardiac risk factors.<sup>56</sup> Lichtlen et al<sup>60</sup> reported that NCCP patients experiencing a coronary event had significantly more risk factors like hypercholesterolemia, hypertension, smoking, and diabetes mellitus than those without a coronary event. One possible conclusion could be that age  $\geq 55$  years with increased cardiac risk factors could confer a long-term cardiovascular risk compared with NCCP patients between 45 and 50 years of age with less risk factors. More studies are needed to determine if this risk is higher than in the general population aged  $\geq 55$  years without NCCP.

It is possible that NCCP patients in the long run may have poor cardiovascular outcome, and studies are needed to determine if depression and anxiety play a role.<sup>84</sup> The heterogeneity of NCCP and the study populations included in the literature limit definitive conclusions. A number of studies have addressed cardiovascular changes in these patients. However, many patients with NCCP have prolonged psychiatric morbidity and poor quality of life. Several questions remain about NCCP with respect to the psychopathology and pathophysiology of this condition, and these patients are poorly understood leading to challenges in their care. Often labeled as “psychogenic”, these patients are dismissed without proper reassurance, education about their complaint, and specific preventive measures

they should take. This leads to further frustration, patient suffering, and cost.

Whether NCCP patients have good or bad outcome, these patients need careful risk stratification.<sup>84</sup> The following should be regularly emphasized: weight reduction, smoking cessation, diet monitoring, lipid control, and treating anxiety and depression. There is evidence supporting an association between low heart rate variability (HRV) and depression<sup>85</sup>; therefore, measuring HRV could be helpful in NCCP patients. As endothelial function, arterial compliance, and pulse wave reflections serve as independent, prognostic markers of cardiovascular morbidity and mortality,<sup>86</sup> any subclinical CVD (endothelial dysfunction) could be identified by pulse-wave analysis and velocity, a noninvasive, FDA-approved technique.<sup>87</sup> Pulse-wave velocity and HRV could be measured in conjunction with a 3-lead ECG. Personality inventories focusing on anger and anxiety such as the Spielberger State-Trait Anxiety Inventory<sup>88</sup> and Spielberger Anger Expression Inventory<sup>89</sup> would be very useful rating instruments that could provide valuable insight into the personality structure and emotional status of the patient.

## Disclosure

The authors report no conflicts of interest in this work.

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