

# What dictates prognosis in myocardial ischemic syndromes: myocardial ischemia or coronary atherosclerosis?

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**Abstract:** Myocardial ischemic syndromes are the main cause of death worldwide, with a rising incidence in developing countries. But why and how people with myocardial ischemic syndromes die or suffer major adverse cardiovascular events, namely myocardial infarction and sudden cardiac death, is still an incompletely resolved question. The intricacy of the issue arises at least somewhat from the relationship between angina pectoris, coronary atherosclerosis, and transient myocardial ischemia on the one hand and subsequent myocardial infarction, ischemic heart failure, and death on the other; a cause-effect relationship is not necessarily implied. The question has important prognostic and therapeutic implications because a proper identification of causes and mechanisms allows us to optimize the workup of patients and the therapeutic targets. Studies of conditions of myocardial infarction with normal coronary arteries (MINOCA) and angina with normal coronary arteries can be instrumental to resolving some of these unknowns. Such analyses convey the concept that coronary atherosclerosis, even when subclinical and usually considered prognostically irrelevant, has, conversely, important adverse prognostic implications. They also highlight, however, an important role for myocardial ischemia, which—when appropriately detected—alters prognosis unfavorably on top of coronary atherosclerosis. ■ *Heart Metab.* 2020;81:23-26

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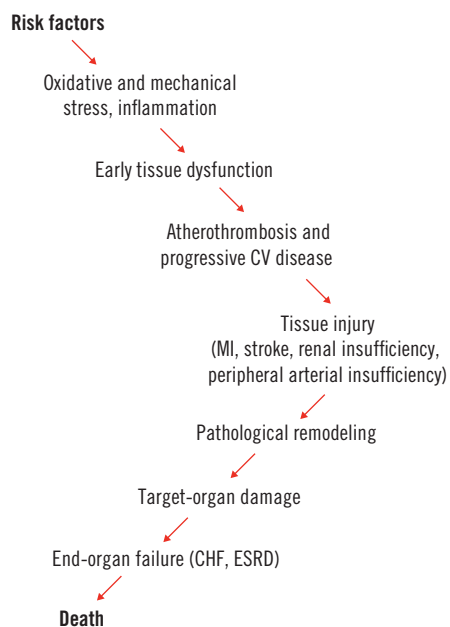
““Myocardial ischemic syndromes” is the terminology we use to encompass the various manifestations of ischemic heart disease, from angina pectoris to myocardial infarction to sudden cardiac death. We have recently written why such terminology is preferable over the terms of “coronary artery disease” (CAD), which focuses on the pathology of coronary arteries, and of “coronary heart disease,” which focuses on the heart but omits the various noncoronary causes of myocardial ischemia.<sup>1</sup> Independently of this semantic foreword, we all recognize that myocardial ischemic syndromes are

the main causes of death worldwide, with incidences particularly on the rise in developing countries.<sup>2</sup> But why and how do people with myocardial ischemic syndromes die or suffer major adverse cardiovascular (CV) events, namely myocardial infarction? The issue is not easy to resolve because the relationship between angina pectoris, coronary atherosclerosis, and transient myocardial ischemia on the one hand and subsequent myocardial infarction, ischemic heart failure, and death on the other, is not necessarily one of cause and effect. The question has important prognostic and therapeutic implications because

proper identification of causes and mechanisms allows tailoring of the optimal workup of patients and optimal therapeutic targets.

### The vascular disease continuum

In the early 1990s, experts on various manifestations of CV disease (CVD) proposed a view of CVD as a chain of events initiated by risk factors (multiple and unrelated) and linearly progressing to end-stage heart disease (Figure 1).<sup>3,4</sup> The anticipation was that intervention any-



**Figure 1** The cardiovascular disease continuum.<sup>4</sup>  
Abbreviations: CHF, congestive heart failure; CV, cardiovascular; ESRD, end-stage renal disease; MI, myocardial infarction

where along the chain would confer cardioprotection. Clinical disease is considered the final step of progressive processes occurring at molecular and cellular levels. CV risk factors, including elevated cholesterol, diabetes, hypertension, and cigarette smoking initiate a cascade of events, including endothelial dysfunction, activation of vasoactive mediators, inflammation, and vascular remodeling, eventually resulting in target-organ damage and in the development of coronary atherosclerotic plaques. These processes, starting very early in life, produce clinically overt cardiac disease after decades. The paradigm described in Figure 1 identifies atherosclerosis as a key step in this process that may eventually lead to myocardial infarction, heart failure, and sudden death. But is coronary atherosclerosis a necessary and suffi-

cient step toward progression in the CVD continuum? Can nonvascular mechanisms precipitate myocardial ischemic syndromes in isolated fashion or in combination with atherosclerotic plaques?

### Myocardial infarction and angina “without atherosclerosis”

The dogma of a close link between coronary atherosclerosis and myocardial ischemic syndromes has been strongly challenged. It has been repeatedly reported that 10% to 15% of acute myocardial infarctions occur in patients without coronary atherosclerotic obstructions, an entity now referred to as myocardial infarction with normal coronary arteries (MINOCA),<sup>5</sup> proving that atherosclerosis—no matter how prevalent—is not a sine qua non condition for the progression along the CVD continuum.

Additional evidence has been offered by studies on late outcomes of angina with “normal coronary arteries.” The absence of a stenosis  $\geq 50\%$  is common, reported in 20% to 30% of patients undergoing coronary angiography<sup>6,7</sup> regardless of previous report of myocardial ischemia.<sup>7,8</sup> The prognostic implications of this condition, defined often as “angina without obstructive CAD” and referred to sometimes as “angina with normal coronary arteries,” are controversial. The condition is associated with a high incidence of adverse events in many studies, whereas other studies have only reported an impaired quality of life. These inconclusive results derive from the heterogeneity of the inclusion criteria, with regard to the inclusion of symptomatic or asymptomatic subjects, the qualification of “angina” (ie, typical or atypical), and the definition of “absence of obstructive CAD” (ie, “less-than-obstructive CAD” or normal coronary arteries). Recent meta-analyses<sup>9,10</sup> included highly heterogeneous patients; subjects ranged from asymptomatic to those admitted for an acute coronary syndrome. Angina with normal coronary arteries offers the unique opportunity to assess the prognostic impact of coronary atherosclerosis as distinct from the impact of myocardial ischemia.

We therefore assessed long-term clinical outcomes during the follow-up of symptomatic patients that had stable angina without obstructive CAD via a systematic review and meta-analysis of 54 observational studies.<sup>11</sup> Data on all-cause death and nonfatal infarction were reported in 49 of these studies, including 29 335 patients followed-up for a median period of 5 years (interquartile range, 3 to 7 years). The remaining five

studies reported data on mortality only. The main findings of this meta-analysis were as follows:

- (i) on univariate meta-regression analyses, major adverse CV events were significantly associated with dyslipidemia ( $P=0.011$ ), diabetes ( $P=0.049$ ), and hypertension ( $P=0.038$ )
- (ii) incidence of primary outcome was significantly higher in studies including patients with non-obstructive coronary atherosclerosis (1.32 per 100 person-years; 95% confidence interval [CI], 1.02–1.62;  $I^2=93%$ ,  $P<0.01$ ) than in those including only patients with completely normal coronary arteries (0.52 per 100 person-years; 95% CI, 0.34–0.71)
- (iii) incidence of adverse events were not significantly different ( $P=0.09$ ) between studies including patients with documented myocardial ischemia (0.80 per 100 person-years; 95% CI, 0.52–1.07;  $I^2=85%$ ,  $P<0.01$ ) and studies that included patients regardless of documentation of myocardial ischemia (1.13 per 100 person-years; 95% CI, 0.81–1.44;  $I^2=93%$ ,  $P<0.01$ )
- (iv) incidence of events were much lower ( $P=0.02$ ) in studies that based patient enrollment on exercise electrocardiographic (ECG) stress testing (0.56 per 100 person-years; 95% CI, 0.23–0.88;  $I^2=84%$ ,  $P<0.01$ ) than in studies enrolling patients on the basis of imaging techniques (stress echocardiography or nuclear imaging) (1.52 per 100 person-years; 95% CI, 0.45–2.58;  $I^2=82%$ ,  $P<0.01$ )
- (v) a trend toward incidence of primary outcome ( $P=0.10$ ) in patients with “typical” angina (1.27 per 100 patient-years; 95% CI, 0.34–2.19;  $I^2=82%$ ,  $P<0.01$ ) was higher than in patients with “undefined” angina (0.93 per 100 patient-years; 95% CI, 0.68–1.19;  $I^2=92%$ ,  $P<0.01$ )
- (vi) the incidence of events in patients with vasospastic angina (0.94 per 100 patient-years; 95% CI, 0.69–1.20;  $I^2=48%$ ,  $P<0.01$ ) was similar ( $P=0.83$ ) to that in studies excluding such patients (1.00 per 100 patient-years; 95% CI, 0.76–1.25;  $I^2=93%$ ,  $P<0.01$ )
- (vii) there was higher all-cause mortality ( $P<0.01$ ) associated with nonobstructive CAD (0.74 per 100 person-years; 95% CI, 0.56–0.93;  $I^2=92%$ ,  $P<0.01$ ) than complete absence of CAD (0.28 per 100 person-years; 95% CI, 0.17–0.39;  $I^2=55%$ ,  $P<0.01$ )
- (viii) all-cause mortality was similar ( $P=0.21$ ) in patients with documented myocardial ischemia (0.45 per

100 person-years; 95% CI, 0.27–0.62%;  $I^2=78%$ ,  $P<0.01$ ) and those where ischemia was not an inclusion criterion (0.69 per 100 person-years; 95% CI, 0.49–0.89;  $I^2=92%$ ,  $P<0.01$ ).

In summary, based on these observations, the presence of coronary atherosclerosis, even when it does not attain “hemodynamic significance,” adversely affects outcome, but myocardial ischemia per se has prognostic implications, and the coexistence of the two portends the highest incidence of major adverse CV events and mortality.

### New paths to the cardiovascular disease continuum and conclusions

These analyses convey the concept that coronary atherosclerosis, even when subclinical, and usually considered prognostically irrelevant and in any case not addressable by current therapies, has relevant prognostic implications, probably because plaque complications causing coronary thrombosis may occur with any degree of lumen reduction and therefore also in the presence of mild, nonobstructive coronary plaques.<sup>12</sup> Such lesions appear to be responsive to preventive therapies, such as aspirin and statins, as shown by recent literature.<sup>13,14</sup> They also highlight an important role for myocardial ischemia, which—when appropriately detected—alters prognosis unfavorably and on top of coronary atherosclerosis. Thus, it would seem that therapeutic efforts should tackle the important anatomic substrate of most myocardial ischemic syndromes (coronary atherosclerosis) within the path described above of the CV continuum, and that the occurrence of myocardial ischemia, also by mechanisms different from obstructive coronary atherosclerosis, contributes to the occurrence of major adverse events, including mortality. ■

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