

**The parallel tales of microvascular angina and heart failure with preserved ejection fraction:  
a paradigm shift**

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## **Parallel tales: microvascular angina and heart failure with preserved ejection fraction**

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2 In the past decade, a growing body of studies has clearly demonstrated that coronary microvascular  
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4 dysfunction (CMD) plays a pivotal role in several cardiovascular diseases<sup>1</sup>. In particular, emerging  
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6 evidence suggests that CMD is the main contributor to myocardial ischemia in a large subset of  
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8 patients with chronic stable angina. Indeed, non-obstructive coronary atherosclerosis is observed in  
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10 up to 50% of patients with anginal symptoms and positive stress test results, undergoing diagnostic  
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12 coronary angiography<sup>2</sup>. Thus, the prevalence of microvascular angina (MVA) is higher than  
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14 previously thought and is associated with worse clinical outcome than that observed in  
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16 asymptomatic subjects with a similar burden of risk factors<sup>3</sup>. The diagnosis of MVA is based on  
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18 the following: 1) symptoms of myocardial ischemia; 2) absence of obstructive coronary artery  
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20 disease; 3) evidence of myocardial ischemia; 4) evidence of impaired coronary microvascular  
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22 function. The reason why the clinical relevance of MVA has previously been overlooked is  
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24 probably because exploration of the coronary microcirculation has been elusive to routine  
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26 diagnostic tools until recently. A parallel “tale” could be told regarding heart failure (HF) with  
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28 preserved ejection fraction (HFpEF). Indeed, HFpEF is observed in about 50% of patients  
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30 presenting with HF symptoms and is characterized by the absence of the hallmark of HF, i.e. a  
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32 reduced EF<sup>4</sup>. As with MVA, patients with HFpEF have a worse clinical outcome compared with  
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34 asymptomatic subjects exhibiting a similar burden of risk factors. The diagnosis of HFpEF is based  
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36 on the following: 1) typical symptoms of HF, 2) typical signs of heart failure, 3) a non-dilated left  
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38 ventricle with normal or only mildly reduced EF, 4) relevant structural heart disease (i.e. left  
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40 ventricular hypertrophy, left atrial enlargement) and/or diastolic dysfunction. In both MVA and  
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42 HFpEF, no therapeutic intervention has hitherto been proven to improve patient outcome; similarly,  
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44 symptomatic treatment is largely empirical.  
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## The common soil hypothesis

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2 Based on the above considerations the question arises as to whether these parallel “tales” of MVA  
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4 and HFpEF represent two extreme clinical presentations of a disease continuum (Figure). This  
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6 tantalizing question is justified by the results of recent studies showing that CMD can be  
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8 demonstrated not only in MVA but also in HFpEF<sup>5,6</sup>. The hypothesis of a common soil for these  
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10 two conditions appears to be endorsed by the clinical observation that dyspnoea is present in a large  
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12 proportion of patients with MVA and, vice versa, angina-like symptoms are reported in about 50%  
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14 of those with HFpEF<sup>7</sup>. Several triggers have been identified to contribute to CMD, including  
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16 traditional risk factors such as smoking, hypertension and diabetes as well as chronic inflammatory  
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18 diseases, such as chronic obstructive pulmonary disease, chronic kidney disease and auto-immune  
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20 conditions. CMD has been well documented in MVA and is responsible for the reduced coronary  
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22 flow reserve (CFR) frequently observed in this condition.  
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28 Recent studies suggest that CMD might play a key role also in HFpEF. Indeed, endothelial  
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30 activation/dysfunction reduce nitric oxide (NO) bioavailability, cyclic guanosine monophosphate  
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32 content, and protein kinase G in adjacent cardiomyocytes<sup>8</sup>. These changes are known to favour  
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34 hypertrophy and fibrosis contributing to diastolic dysfunction. The importance of inflammation in  
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36 the induction of cardiac fibrosis and HF has recently been convincingly demonstrated. TGF  
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38 (transforming growth factor)- $\beta$  is likely to play a major role in this setting, as suggested by the  
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40 observation that disruption of TGF-signalling attenuates pressure overload-induced interstitial  
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42 fibrosis in the heart<sup>9</sup>. Furthermore, endothelial dysfunction contributes to cardiac fibrosis via the  
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44 reduced bioavailability of NO, known to exert direct anti-fibrotic effects involving the cyclic  
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46 guanosine monophosphate pathway<sup>10</sup>. Finally, NO deprivation favours endothelial cells conversion  
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48 to a mesenchymal cell type that can gives rise to fibroblasts<sup>11</sup>. Thus, a cross-talk between the  
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50 endothelium and the surrounding myocardium seems to play a key role in the pathogenesis of  
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58 HFpEF.  
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## Modulating factors

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2 A critical question is why if there is a “common soil” nurturing the development of MVA and  
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4 HFpEF or by the same token, a continuum of disease, angina prevails at one extreme of the  
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6 spectrum of clinical presentations (MVA) while dyspnoea prevails at the other extreme (HFpEF). A  
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8 first response to this intriguing question comes from a large body of evidence suggesting that in  
9  
10 patients with MVA two important additional alterations contributing to angina severity are: 1)  
11  
12 hyper-reactivity of smooth muscle cells to constrictor stimuli in coronary microvessels; 2) enhanced  
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14 perception of cardiac algogenic stimuli. Indeed, a large percentage of patients with MVA develop  
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16 coronary microvascular spasm, anginal pain and ST-segment depression following the  
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18 intracoronary administration of acetylcholine (ACh)<sup>12</sup>. Of note, recent clinical evidence indicates  
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20 that coronary microvascular spasm in patients with CMD can cause subtle contractile abnormalities,  
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22 and can be associated with mild elevations of high sensitivity cTn<sup>13</sup>. Although still a working  
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24 hypothesis at present, it is tempting to speculate that coronary “microvascular” and “epicardial”  
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26 spasm have a similar origin. Indeed, we have convincing experimental and clinical evidence that  
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28 enhanced Rho-kinase activity in vascular smooth muscle cells - not in endothelial cells - plays a  
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30 major pathogenic role<sup>14</sup>. In MVA, the presence of microvascular spasm helps explaining why a  
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32 sizeable proportion of patients report predominantly angina at rest, or a combination of rest and  
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34 effort-related angina. The importance of enhanced pain perception was initially proposed in 1988  
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36 by Shapiro et al. and subsequently confirmed by other investigators. Using positron emission  
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38 tomography to measure changes in regional cerebral blood flow as an index of neuronal activity,  
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40 Rosen et al. provided evidence that altered central neural handling of afferent signals may  
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42 contribute to the abnormal pain perception in patients with MVA. More recently, Valeriani et al.  
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44 demonstrated abnormal cortical pain processing in patients with MVA. This was characterized by  
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46 inadequate habituation to pain which might be the main cause of enhanced cardiac pain perception  
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48 and also account for the symptomatic improvement observed in these patients using tricyclics and  
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50 adenosine antagonists like theophylline<sup>15</sup>. It is worth noting that in MVA reduced CFR, hyper-  
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1 reactivity to constrictor stimuli, and enhanced pain perception, may combine differently in different  
2 patients thus accounting for the disappointing results of standard angina treatments in many of these  
3 patients<sup>16</sup>.

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7 What about HFpEF? Which mechanisms in addition to endothelial dysfunction might orientate  
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9 towards a phenotype characterized by dyspnoea rather than chest pain? It is conceivable that  
10 circulating factors might modulate the effects of CMD favouring the production of fibrosis and  
11 development of LVH. In this setting, fibrocytes, circulating monocyte-derived cells with tissue  
12 remodelling properties of fibroblasts, might play a modulating role<sup>17</sup>. Interestingly, in a murine  
13 model of cardiac remodelling in which fibrocytes are recruited to chronically injured myocardium,  
14 treatment of these animals with serum amyloid P decreased fibrocyte accumulation and fibrosis<sup>18</sup>.

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24 One of the main functions attributed to fibrocytes is extra-cellular matrix production, although it is  
25 possible that these cells may have other actions that are more typically associated with both  
26 macrophages and fibroblasts. Another modulating factor might be represented by atrial natriuretic  
27 peptide (ANP). Indeed, recent findings suggest that ANP signaling results in phosphorylation of  
28 Smad proteins, thus blocking their nuclear translocation and binding to TGF-Smad responsive  
29 elements in the promoter regions of extra-cellular matrix genes<sup>19</sup>. It is also worth considering that,  
30 as suggested by Pepine et al, cycles of ischemia-reperfusion might impair myocyte relaxation  
31 causing diastolic dysfunction and HFpEF<sup>20</sup>. The latter can, in turn, favor myocardial ischemia by  
32 increasing intramyocardial tension, an important determinant of myocardial oxygen consumption.  
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This vicious circle may thus explain why dyspnea is a frequent symptom also in MVA whilst, on  
the other hand, angina is frequent in HFpEF. It may also explain why cTn is occasionally elevated  
in asymptomatic patients who will later go on to develop HFpEF, thus suggesting that subclinical  
ischemia can directly contribute to the pathogenesis of HFpEF<sup>21</sup>. Interestingly, Rho kinase  
inhibition, known to prevent epicardial and microvascular coronary spasm, improves diastolic  
function in hypertensive rats<sup>22</sup>. Attesting the gradual and progressive nature of these mechanisms,  
patients exhibiting HFpEF tend to be older than those presenting MVA.

## A paradigm shift

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2 If the common soil hypothesis of MVA and HFpEF is correct, then a paradigm shift is needed, as  
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4 CMD becomes a common diagnostic and therapeutic target for both of them. These two conditions  
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6 have been identified and accepted by the scientific community only recently and rather reluctantly.  
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8 The reason for this may be that these conditions do not exhibit the classic hallmark of ischemic  
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10 heart disease (IHD) and of HF, namely epicardial stenoses and reduced EF, respectively. It is  
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12 nevertheless increasingly acknowledged by the medical community that they represent a substantial  
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14 public health burden because of their high prevalence and guarded prognosis, characterized not only  
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16 by a higher mortality risk as compared to age and sex-matched asymptomatic subjects, but also by a  
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18 high rate of hospital re-admissions.  
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24 Thus, a first important challenge facing the scientific community is to devise strategies for the early  
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26 diagnosis of CMD. The latter can be helped by the non-invasive assessment of CFR using  
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28 transthoracic Doppler echocardiography, cardiac magnetic resonance or positron emission  
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30 tomography. Furthermore, the demonstration of coronary microvascular spasm with intracoronary  
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32 Ach, as well as measurements of coronary blood flow and the index of microcirculatory resistance  
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34 during coronary angiography, may provide additional diagnostic information. A second challenge is  
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36 the standardization of the diagnostic criteria for MVA and HFpEF. Efforts should be directed  
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38 toward an accurate definition of these two conditions and this should be reflected in international  
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40 guidelines as appropriate. A third challenge is the identification of new biomarkers for the diagnosis  
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42 and risk stratification of MVA and HFpEF. Recent studies suggest that among patients with MVA,  
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44 a lower CFR is associated with worse clinical outcomes, and suitable biomarkers are needed for  
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46 prospective studies in larger cohorts of patients. Similarly, in patients with HFpEF, serum levels of  
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48 certain biomarkers appear to correlate with diastolic load, although very limited evidence is  
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50 available on the ability of such biomarkers to provide real diagnostic and prognostic information.  
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52 Analogous considerations apply to recent techniques developed for the identification of interstitial  
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54 myocardial fibrosis by cardiac magnetic resonance.  
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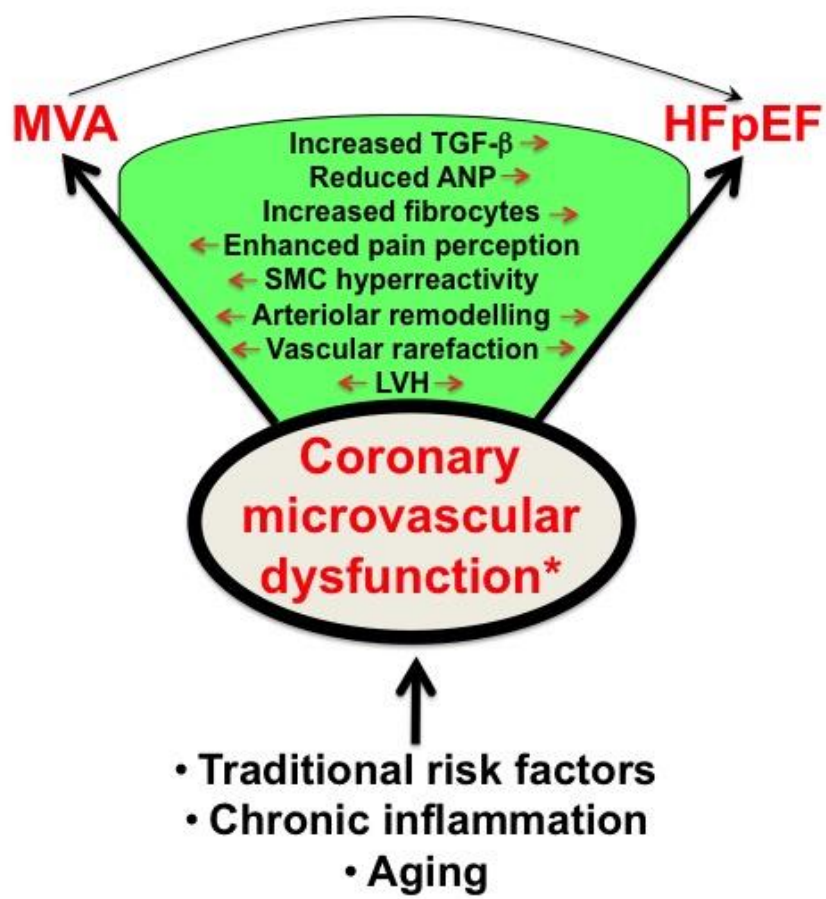
## Therapeutic implications

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2 One of the future major challenges is the identification of effective evidence-based treatments for  
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4 these conditions. Pharmacological agents currently available, that were developed to target large  
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6 epicardial vessels and left ventricular dysfunction, are generally ineffective in controlling symptoms  
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8 in patients with MVA and HFpEF and there is scarce evidence to ascertain whether they provide  
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10 prognostic benefits in these patients.  
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14 As the common soil of MVA and HFpEF is CMD, the latter should be the main therapeutic target  
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16 for both conditions. Indeed, it is unlikely that one single treatment will be beneficial in all patients  
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18 since the mechanisms of microvascular dysfunction are multiple. Consequently, it is important to  
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20 develop therapeutic strategies that tackle both the functional and structural abnormalities underlying  
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22 CMD. One crucial objective is to continue the fight against coronary risk factors both through the  
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24 implementation of lifestyle changes and the use of drugs such as statins that have been shown to  
25  
26 improve endothelial dysfunction. If the prevailing mechanism is smooth muscle cell hyper-  
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28 reactivity, then old and new vasodilators like Rho-kinase inhibitors might reduce the ischemic  
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30 burden. In the subset in which the prevailing mechanism is vascular remodelling, ACE-inhibitors  
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32 have been proved to be effective, particularly in hypertensive patients. In those cases where the  
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34 prevailing mechanism is myocardial fibrosis, aldosterone antagonists and phosphodiesterase-  
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36 5 inhibitors might be of help. Finally, in the patients in whom the prevailing mechanism is  
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38 advanced coronary microvascular rarefaction cell therapy might be considered.  
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46 In conclusion, we advocate action to develop appropriate diagnostic and therapeutic strategies for  
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48 tackling these “new” diseases in the years to come.  
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### Figure legend

1  
2 The figure summarizes the common soil hypothesis for microvascular angina (MVA) and heart failure  
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4 with preserved ejection fraction (HFpEF) including modulating factors, which can orientate at one  
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6 extreme towards MVA and at the other extreme towards. Of note, ischemia per se can promote  
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8 myocardial fibrosis. \* Coronary micorvascular dysfunction is characterized by a variable combination  
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10 of endothelial dysfunction, smooth muscle cell hyperreactivity, vascular remodeling, vascular  
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12 rarefaction.  
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15 Legend: HFpEF. ANP=atrial natriuretic peptides; LVH=left ventricular hypertrophy; SMC=smooth  
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17 muscle cells; TGF- $\beta$ =tissue growth factor-beta.  
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Figure

