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The multifaceted angina

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Introduction: the mutifaceted angina

The word angina describes a symptom most of the time, but not exclusively, due to myocardial ischaemia. The first, lucid, description of angina goes back to 1772 when Heberdeen wrote: 'There is a disorder of the breast... The seat of it, and sense of strangling and anxiety, with which is attended, may make it not improperly be called angina pectoris. Those, who are afflicted with it, are ceased [sic] while they are walking and most particularly when they walk soon after eating, with a painful and most disagreeable sensation in the breast, which seems as it would take their breathe away, if it were to increase or to continue; the moment they standstill, all this uneasiness vanishes'.[1]

The definition used today for angina is not very different.[2]

Whatever the definition in guidelines or text book, the reality is that angina can be perceived by patients in many different ways. This is because: (i) not all patients with angina are the same (*they might have different comorbidities, different perception of pain*); (ii) not all the anginal attacks are the same (*as they may be precipitated by several different mechanisms*); and (iii) not all the *ischaemic episodes* are the same.

The aim of this supplement of the *European Heart Journal*, *the Heart of the Matter* is to provide a spectrum of the multiple facets of angina. To this end, a group of experts with experience and interest in chronic stable angina met at the University of Ferrara, Italy to present and discuss several clinical cases which are all reported in the supplement.

It follows that, the symptomatic pharmacological treatment of patients with angina cannot be the same for all patients, instead it has to be personalized. Current clinical guidelines recommend antianginal therapy to control symptoms of angina before considering coronary artery revascularization,[3–5] following a categorical first- and second-line approach (*Figure 1*). Drugs that are classified first line are beta-blockers, calcium channel blockers, and short acting nitrates. The second line are long-acting nitrates, ivabradine, nicorandil, ranolazine, and trimetazidine. Second-line drugs are indicated for patients who have contraindications to first line agents, do not tolerate them or remain symptomatic. This categorical approach has been questioned in the past couple of years.[6–10] Newer antianginal drugs, which are classified as second choice, have more evidence-based and more contemporary data to support their use than what is available for the traditional first-choice drugs. Recently, systematic reviews covering 50 years of medical treatment of angina were performed,[10] which demonstrated an incredible scarcity of data since only 72 controlled randomized studies comparing two antianginal drugs were identified including a total of 7034 patients since 1964 to the current day.[11,12] Furthermore, only 13 studies included between 100 and 300 patients with more than 50 patients per group, a minimum number to perform a meaningful comparison among groups. The results clearly indicate that, from the little data that there is, no superiority of one antianginal agent over another has been shown and equivalence is demonstrated among beta-blockers, calcium antagonists, and I_f channel inhibitors. This, in turn, suggests that the treatment of chronic patients can be achieved with all the available class of drugs tailoring these to the patients' characteristics, comorbidities, and to the typology of resulting ischaemia. This is the reason why the authors of the present supplement decided to propose a different, more individualized approach to patients with angina, the so-called 'Diamond approach to personalized treatment of angina'.[10]

It is clear that chest pain can have different causes and mechanisms, which are summarized in *Figure 2*. The ultimate cause of pain is controversial as angina pain is complex in its quality, perception, and has a rather chaotic association with ischaemia. In the heart, several α-ganglia are present, mainly in the epicardial fat, and are supplied by proximal coronary arteries. Neurons integrate not only with those of the heart, but also with the mediastinal, cervical, dorsal, and stellate ganglia, explaining why pain can be felt differently (*or even not felt at all in the case of silent ischaemia*) and in different parts of the body,

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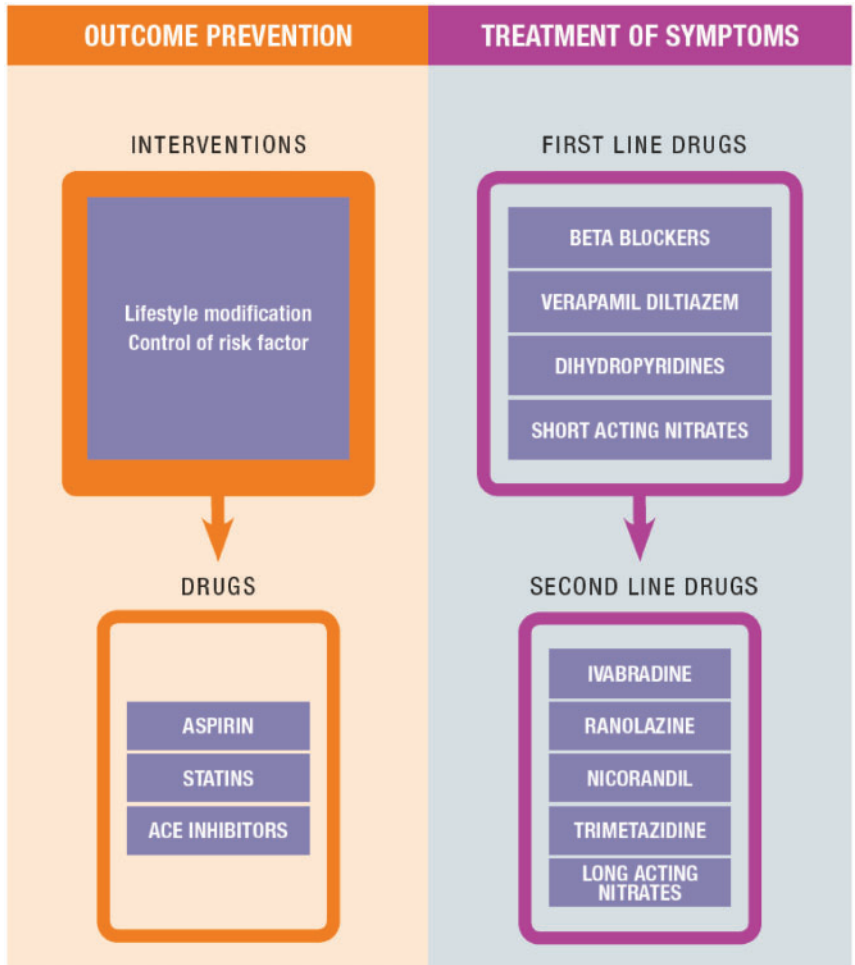

Figure 1 Current guideline suggestions for the symptomatic medical treatment of angina pectoris. ©LLS 2018[22].

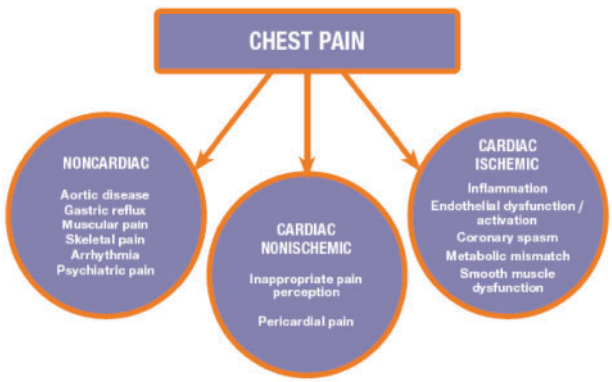

Figure 2 Pathophysiology of angina pectoris. ©LLS 2018[22].

although it most frequently occurs in the chest and/or left arm.[13]

Equally, angina might be the result of ischaemia provoked by distinct mechanisms. Usually, angina occurs when myocardial ischaemia is caused by fixed atherosclerotic narrowing of one or more epicardial coronary artery spasms, with or without endothelial dysfunction. In some circumstances, the angina is associated with a coronary spasm and a metabolic dysfunction. Vasospastic angina occurs when myocardial ischaemia is caused by a coronary artery spasm with or without endothelial dysfunction. Microvascular angina refers to the absence of an obstructed epicardial coronary artery. Myocardial ischaemia, in this case, is likely caused by microvascular and endothelial dysfunction as well as by inflammation of the coronary arteries[14,15] (*Figure 3*). The different mechanisms may also co-exist and overlap in one and the same patient, each one of them dominating to a different extent in different occasions.

The resulting ischaemia, whatever the cause which has provoked it, might be very different from patient to patient.

From a metabolic point of view, myocardial ischaemia results in anaerobic glycolysis with consequent increased concentration and release of hydrogen, potassium,

lactate, and adenosine (*the two last components causing pain*) in the venous blood draining the ischaemic territory. The resulting acidosis competes with calcium ions and freezes all its movements through the sarcolemma and sarcoplasmic reticulum, thus causing the well-known 'ischaemia-induced regional hypokinesia or akinesia'.[16] In the clinic, the existence of metabolic ischaemia is documented by a drop of pH in the venous coronary sinus blood concomitant with a release of lactate from the ischaemic myocytes, causing an inversion of the percentage of myocardial arterial venous difference of lactate, which from positive becomes negative.[17] These biochemical alterations precede the actual occurrence of the classical ECG changes and of the chest pain, as well as the regional alteration of contractility and likely are different from patient to patient. Their intensity will depend on the duration of ischaemia, the development of collateral flow and the existing metabolic turnover before ischaemia. In some cases, previous episodes of angina might precondition the heart, in others the residual flow might be sufficient to meet the energy needs of the akinetic ischaemic area, giving rise to the so-called hibernated myocardium.[18-20] Furthermore, the recent introduction of the fractional flow reserve—*FFR*—has clearly shown that coronary artery stenosis, apparently severe, might not always result in an ischaemic burden sufficient to justify revascularization.[21]

Figure 3 Determinants of myocardial ischaemia. ©LLS 2018[22].

Importantly and largely, in patients with angina, these changes are transient and normally require a trigger (*i.e. exercise, stress, exposure to cool temperature, etc.*).

Finally, patients with angina might differ because they might have different comorbidities such as atrial fibrillation, hypertension, left ventricular dysfunction, or heart failure as well as chronic obstructive pulmonary disease, diabetes, hypertrophic cardiomyopathy, or chronic kidney disease. The 'Diamond Approach' (*Figure 4*) considers all of these different facets of angina and translates them into visual coloured formats (*Figures 5 and 6*) which might capture the attention more than a grey text of the guidelines, often too long to be read in detail by the busy physicians. Here, in this Supplements, several of the facets of angina are reported in the form of clinical cases in the hope that they might help the reader to recognize the different situations of his/her patient and to make the best possible therapeutic choices, independently from whether the drugs are first- or second-line choice.

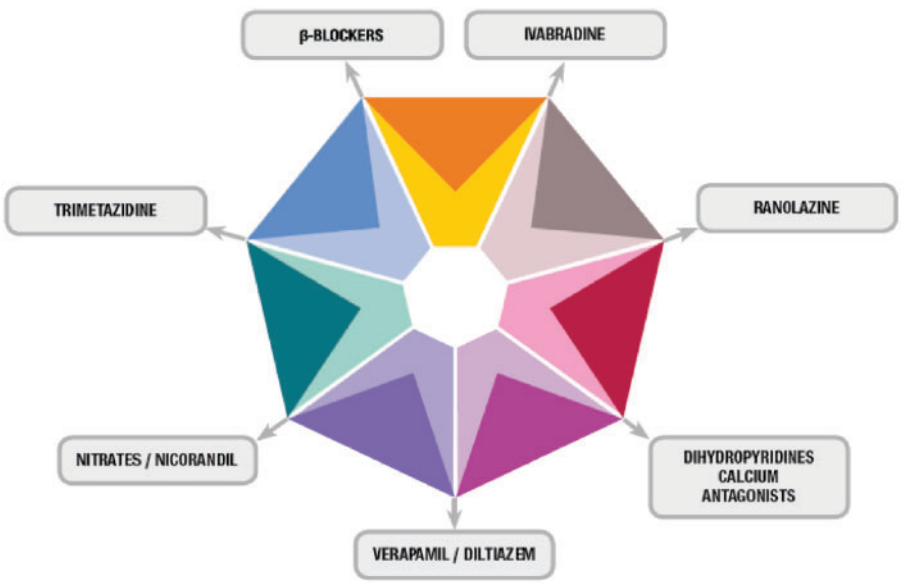

Figure 4 The 'Diamond' approach. ©LLS 2018[22].

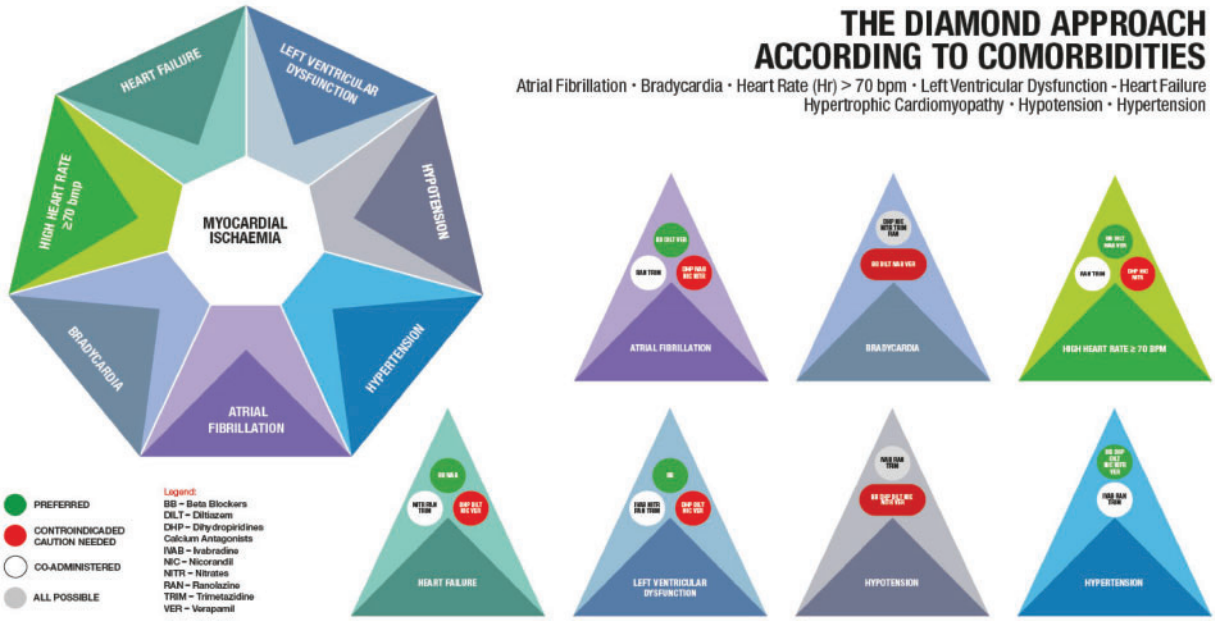

Figure 5 The 'Diamond' approach according to comorbidities. ©LLS 2018[22].

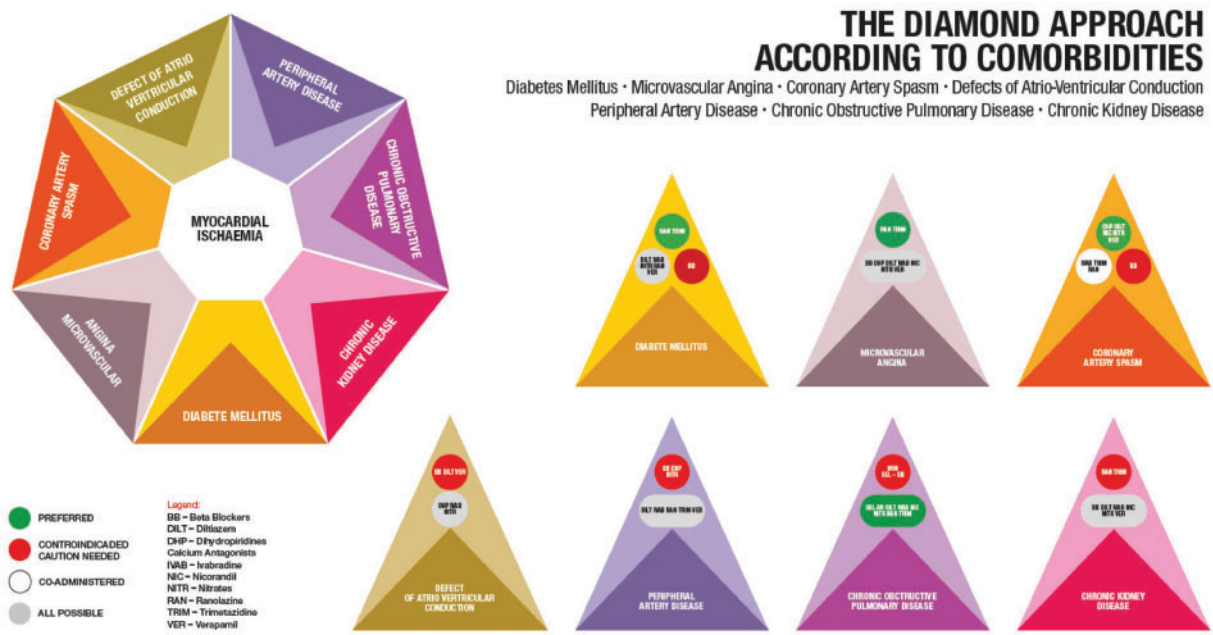

Figure 6 The 'Diamond' approach according to comorbidities. ©LLS 2018[22].

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