Section A-Research paper

Ischemic Mitral Regurgitation and Anticoagulation In STEMI

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Abstract

Background: Appropriate systolic coaptation of the anterior and posterior mitral leaflets depends on normal anatomy and function of the different components of the mitral valve apparatus: annulus, leaflets, chordae, papillary muscles, and the left ventricular (LV) wall. Mitral regurgitation (MR) consists in systolic retrograde flow from the LV to the left atrium (LA) because of the lack of adequate coaptation of the leaflets and a pressure gradient between the two cavities. It is important to distinguish between primary MR due to organic disease of one or more components of the mitral valve apparatus and secondary MR which is not a valve disease, but represents the valvular consequences of a LV disease. Secondary MR is defined as functional MR, due to LV remodelling by idiopathic cardiomyopathy or coronary artery disease. In the latter clinical setting, secondary functional MR is called ischaemic MR. Mitral valve leaflets undergo multiple changes in response to myocardial ischemia and the mechanical stretch imposed by LV remodelling The mitral valve has the possibility of increasing its surface to match LV dilation and prevent MR. Ischemic MR has the specificity of self-aggravating in a vicious circle as it promotes the dilation of the LV which, in turn, leads to additional LV remodelling and exacerbated MR. This phenomenon is facilitated by the fact that ischemic LV seems more vulnerable to MR. Early intravenous anti-coagulation along with anti-platelets is the cornerstone for the management of acute coronary syndrome patients. The primary aim of early anti-coagulation is to reduce the ischaemic burden in the myocardium without increasing the haemorrhagic events. Acute coronary syndrome (ACS) occurs due to complete or incomplete coronary thrombosis following atherosclerotic plaque rupture. ACS includes the patients having unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI).

Keywords: Mitral Regurgitation, Anticoagulation, STEMI

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Introduction

Appropriate systolic coaptation of the anterior and posterior mitral leaflets depends on normal anatomy and function of the different components of the mitral valve apparatus: annulus, leaflets, chordae, papillary muscles, and the left ventricular (LV) wall. Mitral regurgitation (MR) consists in systolic retrograde flow from the LV to the left atrium (LA) because of the lack of adequate coaptation of the leaflets and a pressure gradient between the two cavities. It is important to distinguish between primary MR due to organic disease of one or more components of the mitral valve apparatus and secondary MR which is not a valve disease, but represents the valvular consequences of a LV disease. Secondary MR is defined as functional MR, due to LV remodelling by idiopathic cardiomyopathy or coronary artery disease. In the latter clinical setting, secondary functional MR is called ischaemic MR **(1)**.

Mechanisms of ischaemic mitral regurgitation:

Reduced closing forces:

Ischaemic MR results from an unbalance between increased tethering forces and reduced closing forces, the latter including reduction in LV contractility, altered systolic annular contraction, reduced synchronicity between the two papillary muscles and global LV dyssynchrony, especially in basal segments **(1)**.

Tethering forces:

Inadequate closure of the mitral leaflets is the consequence of increased tethering forces. The most frequent pattern corresponds to a posterior infarction, usually transmural, leading to local LV pathological remodelling and distortion contributing to apical, posterior, and lateral displacement of the posterior papillary muscle. The papillary muscle contributes non-extensible chordae to both leaflets; its displacement results in a more apical position of the leaflets and their coaptation point, and a characteristic deformity of the anterior leaflet described as 'seagull sign'. The tethering process produces the shape of a tent between the annular plane and the displaced leaflets. The tenting volume relates closely to the regurgitant orifice area. In the case of posterior infarction and regional remodelling, the tenting area is asymmetric, predominates on the posterior leaflet close to the medial commissure, accompanied by reduced mobility of the posterior leaflet. In other patients, LV dilatation is more global; LV is more spherical; both papillary muscles are displaced; the tenting area is symmetric; the regurgitant jet is central; the contribution of annular dilatation and flattening is more important. This situation occurs in patients with previous anterior or both anterior and posterior infarctions **(1)**.

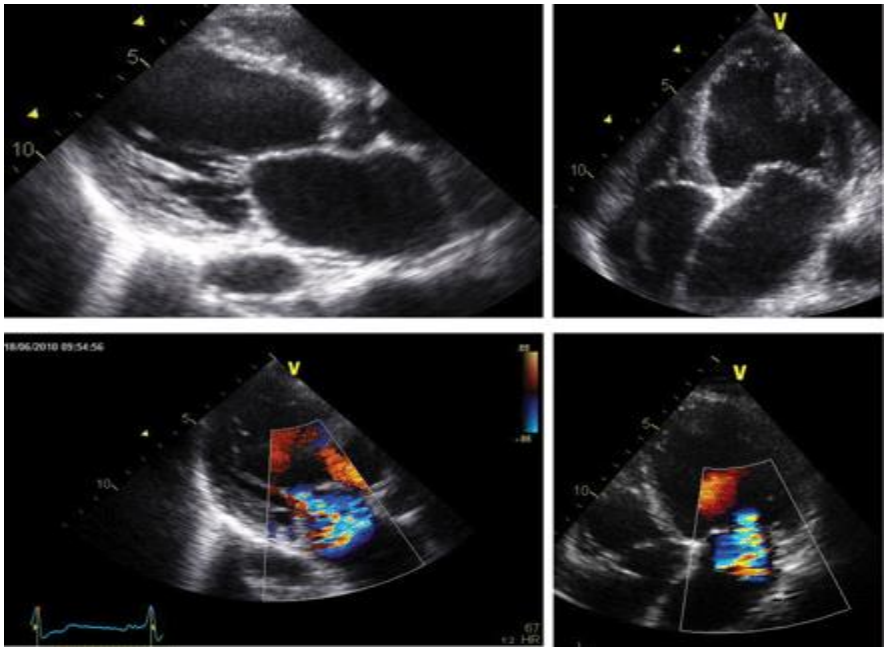

Figure 1: Symmetric mitral valvular distortion and central jet of ischaemic mitral regurgitation. Upper panel: parasternal long-axis view (left) apical four-chamber view (right). The left ventricle is dilated and spherical. Symmetric tethering of the leaflets is present, inducing large tented area and coaptation distance. Lower panel: corresponding images showing the color jet, originating and directed centrally **(2)**.

Pathophysiology:

Pathophysiology of ischaemic MR is much more complex than that of primary MR, since myocardial damage and LV dysfunction are the causes that precede MR. The consequences of MR depend on the severity of regurgitation, the driving force and the acuteness of the lesion and in turn of LA compliance. There are two relatively rare clinical entities in which MR occurs acutely with the energy generated by the regurgitation, transformed into potential energy: rupture of a papillary muscle in acute myocardial infarction and true ischaemic MR secondary to a transient active ischaemic episode. The rupture of a papillary muscle, usually a head of the postero-medial muscle, is a dramatic mechanical complication of acute myocardial infarction with a high mortality rate if surgery is not immediately performed. Acute ischaemic episodes linked to a severe stenosis of the left circumflex and/or the right coronary artery can induce 'flash pulmonary oedema' **(3)**.

In the vast majority of patients in whom ischaemic MR is chronic and complicates LV dysfunction and most often heart failure, LA is enlarged, more compliant and the driving force is relatively low. The volume overload due to MR contributes to a vicious circle: the more remodelled LV, the more severe MR which begets further LV dilatation and

thus, further MR. This cycle has important effects on LV geometry, leading to a rather spherical LV. Although MR reduces impedance and has an unloading effect, the LV dilatation increases ventricular wall stress leading to worsened LV performance. The upstream consequences are high LA pressure and pulmonary arterial hypertension **(4)**.

An important characteristic of ischaemic MR is its dynamic component. The degree of MR is best defined by the effective regurgitant orifice (ERO) area. The regurgitation area can change during systole: it is less important in mid-systole when compared with early and late systole. These changes are determined by dynamic changes of transmitral pressure contributing to valve closure. Another aspect of the dynamic characteristics of ischaemic MR is a possible reduction in regurgitant volume related to a reverse LV remodelling obtained by appropriate medical treatment. In patients with chronic ischaemic MR, the ERO area can also change dynamically in the daily life, in response to changes in loading conditions leading to transient episodes of increased regurgitant volume **(5)**.

The dynamic characteristics of MR can be appreciated during an exercise Doppler echocardiogram. The degree of MR at rest is unrelated to exercise-induced changes in ERO area or regurgitant volume. In some patients, exercise-induced changes are low. In other patients with moderate or even severe MR at rest, a decrease in ERO area can be observed with exercise and usually results from contractile reserve of the LV, in particular of the postero-basal segment and/or a reduction in intra-LV dyssynchrony. In contrast, ∼30% of patients develop a severe increase in MR and in systolic pulmonary artery pressure during exercise. The degree of exercise-induced increase or decrease in MR relates to changes in LV remodelling and valvular deformation and also to changes in LV and papillary muscles synchronicity (**6**).

Valve changes in ischemic MR:

Mitral valve leaflets undergo multiple changes in response to myocardial ischemia and the mechanical stretch imposed by LV remodelling. The mitral valve has the possibility of increasing its surface to match LV dilation and prevent MR **(7)**.

Current knowledge suggests embryonic growth process reactivation in response to mechanical stretch, increasing extracellular matrix production and resulting in larger mitral leaflets. However, mitral leaflet enlargement is often unable to keep the leaflets proportional to the dilated LV. In ovine models of MI, it was shown that infarction can modify the leaflet response to mechanical stretch by inducing significant remodelling including active leaflet thickening, excessive presence of myofibroblasts, and profibrotic signaling, such as transforming growth factor (TGF) β with subsequent collagen production **(7)**.

In a recent experimental study in which mitral valve growth was induced by aortic regurgitation, the presence of MI was associated with attenuated increase in mitral valve area, with subsequent development of MR. While precise mechanisms for those changes have yet to be elucidated, the hypothesis of angiotensin II triggering TGF-β–mediated remodelling has been explored. Interestingly, models of MI with controlled LV dilation suggest that losartan can potentially prevent post-MI adverse changes in the leaflets **(8)**.

Those experimental studies are parallelled with clinical observations. Abnormal valve biology and biomechanics have been observed in patients with advanced heart failure, suggesting an organic contribution to secondary MR. In patients followed sequentially after MI, progressive leaflet thickening as determined with the use of echocardiography was correlated with the presence of MR, independently from LV function or size. Thus, in addition to the primary LV changes, ischemic heart disease is associated with abnormal mitral leaflet biology, limiting valve adaptation to the remodelling ventricle and impairing the biomechanical properties of the valve and its normal coaptation **(9)**.

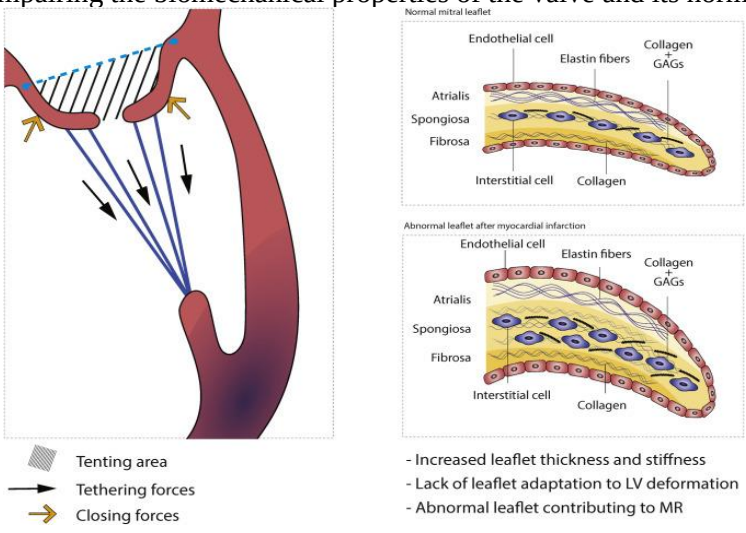

Figure 2: Current pathophysiologic concepts for ischemic mitral regurgitation (MR). (**Left**) Illustration of tethering and closing forces after myocardial infarction. This process results in an apical displacement of the coaptation. (Right) Illustration of a normal mitral valve leaflet (top) and thickened post–myocardial infarction leaflet (**bottom**). GAG, glycosaminoglycan; LV, left ventricular **(12)**.

Impact of ischemic MR on LV function and survival:

Ischemic MR has the specificity of self-aggravating in a vicious circle as it promotes the dilation of the LV which, in turn, leads to additional LV remodelling and exacerbated MR. This phenomenon is facilitated by the fact that ischemic LV seems more vulnerable to MR **(10)**.

Adverse prognosis and survival are proportionally related to increasing MR severity after MI, but in contrast to primary MR, even mild ischemic MR is associated with adverse events. The presence of nonsevere MR after MI markedly increases the occurrence of congestive heart failure at 5 years, including in patients without symptoms at baseline (rates more than doubled, despite adjustments for age and LV ejection fraction). The presence of any degree of MR has been consistently associated with reduced survival at 30 days, 1 year, and 5 years **(11)**.

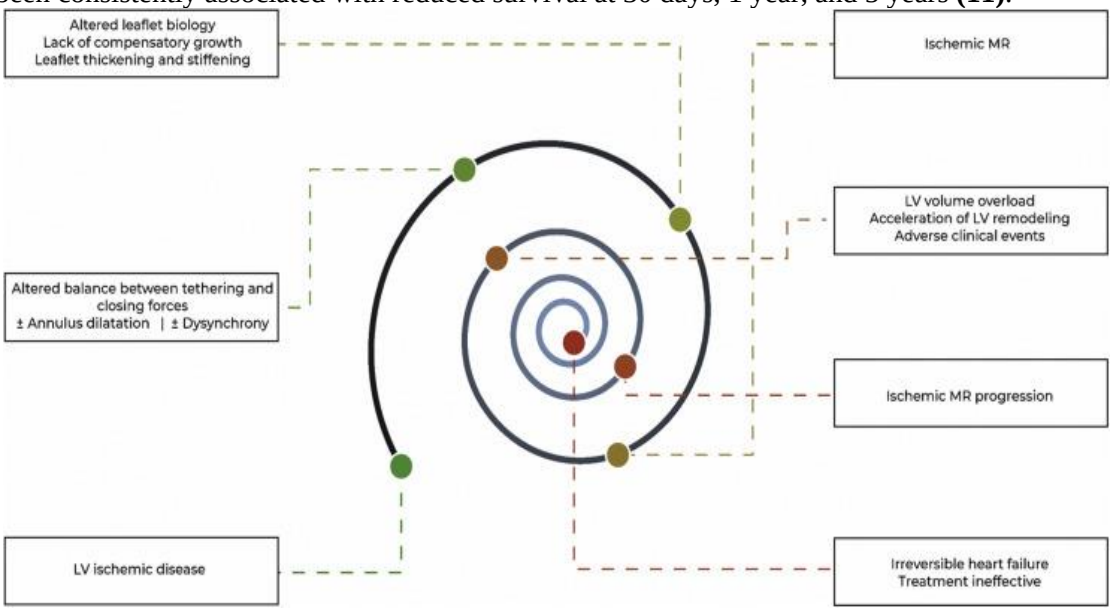

Figure 3: Interplay between ischemic mitral regurgitation (MR) and left ventricular (LV) remodelling, eventually leading to irreversible heart failure without treatment option **(12)**.

At the molecular level, combination of myocardial ischemia and volume overload is characterized by a biphasic response: transient rise in intramyocardial molecular signals promoting compensatory LV hypertrophy, followed by their decline as heart failure progresses. Those dynamic changes in LV biology in ischemic MR are highlighted by further animal experimentations showing that early MR correction can reverse LV remodelling and improve LV function, whereas the same intervention performed at a later time point has less or no effect **(9)**.

While the timing of MR correction after MI in clinical studies remains largely unexplored, recent data from percutaneous mitral repair also suggest that patients with more advanced heart failure are less likely to benefit from these procedures **(13)**.

In summary, multiple studies with different approaches and design consistently indicate that 1) ischemic MR, even if not severe, is independently associated with adverse LV remodelling and poor clinical outcomes; and 2) the level of LV remodelling and dysfunction is an important moving target to assess in order to estimate the benefits of intervention.

❖ Diagnosis and Evaluation:

Transthoracic echocardiography (TTE) is the first-line modality used to determine MR mechanism and severity because numerous quantitative and qualitative parameters can be gathered. However, TTE can sometimes be suboptimal because of poor patient echogenicity. In that case, other modalities, such as transesophageal echocardiography (TEE) or cardiac magnetic resonance imaging (CMR), can be helpful.

Echocardiographic evaluation of IMR:

Echocardiography detects mitral valve abnormalities (leaflets, subvalvular apparatus, mitral annulus and/or LV) that cause valvular regurgitation **(14)**.

Ventricular remodelling and deformation of the mitral system:

The diameters of the LV, the volume of the LV by two-dimensional (2D) biplanar imaging, or more accurately with three-dimensional (3D) imaging, and the sphericity index of the LV must be determined. The extent and location of the

segmental alterations and the parietal thinning of the LV, as well as the posterior and apical displacement of the posterior papillary muscle and the distance between the papillary muscles should also be assessed. As for the deformation of the mitral apparatus, the most commonly used parameters are the size of the ring, the distance of coaptation, the angles of the leaflets and the area of tenting. The measurements are obtained in parasternal long-axis view in mesosystole. 3D echocardiography allows us to assess the volume of tenting, which seems to provide advantages over 2D **(15)**.

Morphology of the mitral valve:

In the asymmetric closure pattern of IMR, a "hockey stick" or seagull sign is shown on the echocardiogram. The anterior leaflet in systole is below the posterior, which is also stressed, altering the coaptation. An eccentric jet of insufficiency appears, ipsilateral to the posterior leaflet, which goes to the posterior region of the left atrium (LA). This pattern is typical of inferior or inferolateral infarction **(15)**.

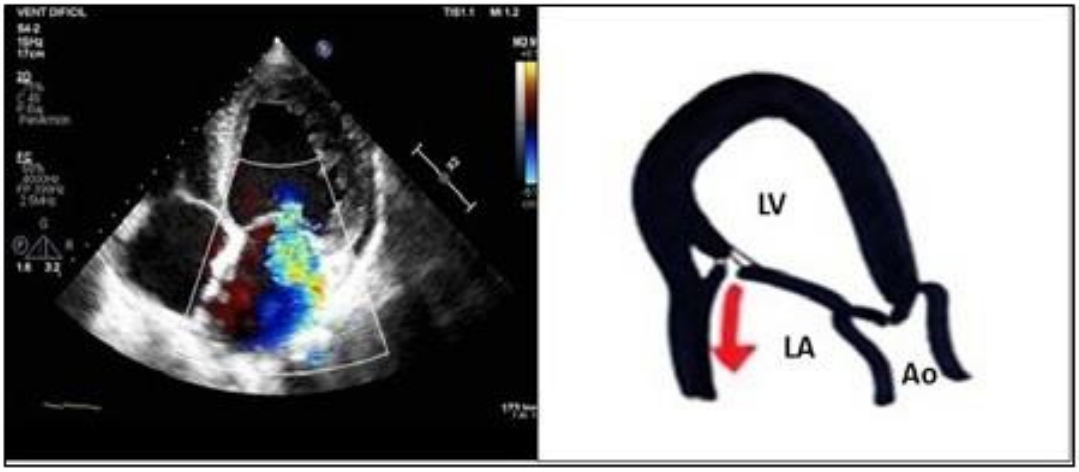

Figure 4. An apical four-chamber view, showing ischaemic mitral regurgitation with asymmetric closure: the anterior leaflet in systole is below the posterior, also stressed, altering the coaptation. The insufficiency jet is eccentric, ipsilateral to the posterior leaflet and is directed towards the posterior region of the left atrium. Echocardiographic image on the left and schematic drawing on the right. Ao: aorta; LA: left atrium; LV: left ventricle

The symmetric closure is due to a global remodelling of the LV, with a spheroidal shape and greater dysfunction. There is an apical displacement of both leaflets and the coaptation point, with greater dilation and flattening of the mitral annulus. The area and volume of tenting are greater than in the asymmetric pattern, being the origin and direction of the central regurgitation jet, by a symmetrical effect on both leaflets. It is associated more with anterior infarction or multiple infarcts **(16).**

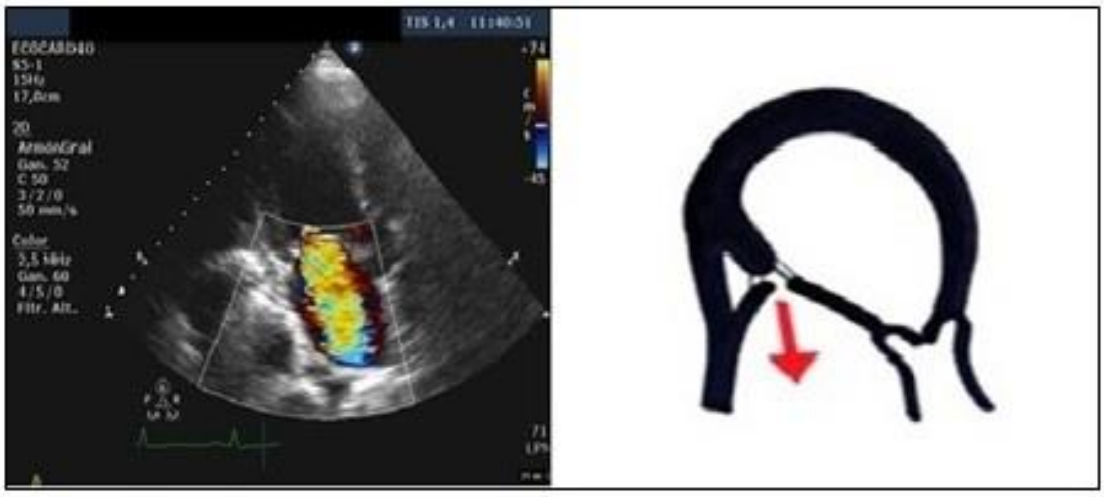

Figure 5. An apical three-chamber view, showing ischaemic mitral regurgitation with symmetrical closure: this is due to a global remodelling of the left ventricle, with apical displacement of both leaflets and the coaptation point. The insufficiency jet is central, due to a symmetrical effect on both leaflets. Echocardiographic image on the left and schematic drawing on the right. Ao: aorta; LA: left atrium; LV: left ventricle

Quantification of the severity of IMR:

Transthoracic echocardiography (TTE) is an excellent method for assessing the mechanism and severity of IMR, although with some limitations. The following methods are used **(14)**.

Color flow imaging:

This is the most used and simplest method in the evaluation of IMR. It assumes that the greater the severity of MR, the greater the size and extension of the jet within the LA. However, it is imprecise, because the relationship between the extension of the jet and the severity of regurgitation is not direct, depending on many technical and haemodynamic factors. Thus, the interaction with a wall or valvular structure conditions its area, underestimating it (Coanda effect). While central flows drag flux in their path producing overestimation, a large eccentric flow that is distributed through the posterior wall of the LA goes in favour of severe IMR. Conversely, small flows that appear just behind the mitral leaflets indicate slight insufficiencies.

Limitations: This method alone is not recommended to quantify the severity of the IMR; it should only be used to detect it. When more than just a small IMR central jet is observed, a more quantitative assessment is required.

Vena contracta width:

The vena contracta (VC) is the area of the jet as it leaves the regurgitant orifice; it thus reflects the regurgitant orifice area. The VC is typically imaged in a view perpendicular to the commissural line. Whenever possible, it is recommended to take an averaging of measurements taken over at least two to three beats and using two orthogonal planes. A VC width <3 mm indicates mild MR and a width ≥7 mm defines it as severe. In the case of IMR, the regurgitant orifice does not seem to be circular, but rather more extended along the coaptation line. Furthermore, the Doppler image does not give an appropriate orientation of the 2D planes to obtain an accurate cross-sectional view of the VC. An average 8 mm VC width in 2D has been reported as severe MR of any etiology, including IMR. The VC seems to be less influenced by the load conditions of the LV and therefore be more reproducible than the flow-imaging color methods.

Limitations: Intermediate VC values (3-7 mm) require confirmation by quantitative methods. Many times, VC is obtained in eccentric jets. In case of multiple jets, the respective values of VC are not additive. The assessment of VC by 3D echocardiography is still reserved for research.

Doppler volumetric method:

This is a method used when the proximal isovelocity surface area (PISA) and the VC are not accurately applicable. The MR volume is obtained by calculating the difference between total stroke volume (product of the mitral ring area by the velocity-time integral [VTI] of the LV input tract flow) and the systemic stroke volume (product of the LV outflow tract area by the LV outflow tract VTI).

Limitations: This is time-consuming so it is not recommended as a first-line method in the quantification of MR. Its calculation is inaccurate in the presence of significant aortic regurgitation.

The flow convergence method:

This is the most recommended quantitative method. The following is recommended: obtain a four-chamber apical view to determine the PISA, then align the flow with the ultrasound beam, adjust the gain and lower the wall filter, decrease the depth and reduce the sector size to increase the spatiotemporal resolution. Decrease the aliasing speed immediately, creating a longer PISA, moving the baseline in the direction of the MR flow, up to a speed of 20-40 cm/s. Measure the PISA radius in mesosystole, with the morphology of the flow as close to a hemisphere, in the first aliasing. Determine the VTI and peak flow velocity of MR with continuous Doppler. The effective regurgitant orifice area (EROA) is thus determined. This allows integrating the different severity indices, classifying MR into mild, moderate or severe **(14)**. The primary MR is considered severe if the EROA is ≥40 mm2 and the regurgitant volume (R Vol) ≥60 mL. In secondary MR, the severity threshold is lower, 20 mm^2 and 30 mL, respectively, indicating a subgroup of patients with an increased risk of cardiovascular events. EROA is the most robust parameter to determine the severity of the MR, being able to determine the PISA with both central and eccentric MR.

Table 1. Quantification of ischaemic mitral valve regurgitation severity **(14)**.

Parameters	**Type**	**Mild**	**Moderate**	**Severe**
MV morphology	Qualitative	Normal/abnormal	Normal/abnormal	Flail leaflet/ruptured PMs

Colour flow MR jet	Qualitative	Small, central	Intermediate	Large central jet or eccentric jet reaching the posterior wall of the LA
Flow convergence zone	Qualitative	No or small	Intermediate	Large
CW signal of MR jet	Qualitative	Faint/parabolic	Dense/parabolic	Dense/triangular
VC width (mm)	Semi-quantitative	<3	Intermediate	≥7 (>8 for biplane)
Pulmonary vein flow	Semi-quantitative	Systolic dominance	Systolic blunting	Systolic flow reversal
Mitral inflow	Semi-quantitative	A-wave dominant	Variable	E-wave dominant (1.5 m/s)
TVI mitral /TVI aortic	Semi-quantitative	<1	Intermediate	>1.4
EROA (mm^2)	Quantitative	c	20–29; 30–39*	≥40
R Vol (mL)	Quantitative	<30	30–44; 45–59*	≥60

CW: continuous wave; LA: left atrium; EROA: effective regurgitant orifice area; LV: left ventricle; MR: mitral regurgitation; R Vol: regurgitant volume; VC: vena contracta

Limitations:

In IMR there is a dynamic variation of the regurgitant orifice, with early and late systolic peaks and mesosystolic descent. Non-hemispheric PISA derived from eccentric jets, multiple or regurgitant or complex elliptical orifices may not be valid. The degree of MR could be underestimated, so a lower threshold is used in determining the severity of the functional MR.

Anterograde velocity of mitral inflow:

In the absence of mitral stenosis, a peak velocity E >1.5 m/s suggests severe MR, whereas a dominant A-wave (atrial contraction) excludes it. This is applicable in patients over 50 years of age. The VTI ratio, between the mitral inflow Doppler and the aortic flow at the level of the rings in a four-chamber view, is an additional strong parameter in the assessment of MR severity. A ratio of 1.4 suggests severe MR

Pulmonary venous flow:

When MR severity increases, there is a decrease in the S-wave velocity in the pulmonary vein flow determined by pulsed Doppler, which is a sensitive but not very specific parameter of severity, since it can also appear in atrial fibrillation, ventricular dysfunction and increased LA pressure. In the most severe forms, the S-wave can be reversed, which is a specific parameter of severe MR.

Continuous wave Doppler of MR jet:

Speed itself is not a parameter of severe MR. However, the intensity of the signal - dense, dashed ("notched"), triangular and with an early peak speed ("blunt") in its morphology - indicates greater severity. All of this indicates elevated LA pressure or a prominent regurgitant pressure wave in the LA due to severe MR. In the eccentric MR it can be difficult to obtain a complete record, although the intensity of the signal is dense. The continuous wave Doppler of an MR jet is a qualitative parameter of MR severity.

Transesophageal echocardiography

Transesophageal echocardiography (TOE) is especially useful when the quality of TTE is not optimal, since it allows a detailed evaluation of the morphology of the mitral valve and subvalvular apparatus. In 2D TOE, the diameter of the mitral annulus can be quantified, as can the height and increase of the tenting area, as well as the traction and decrease of the apposition surface. Three-dimensional TOE has been shown to be superior to 2D TOE in the measurement of the area of the VC, being useful in organic and functional MR, even with several regurgitation jets . It allows automatic measurement of the PISA area, avoiding geometric assumptions, and more accurate calculation of the R Vol and EROA. On the other hand, 3D TOE performs a direct planimetry of the anatomical regurgitant orifice in an easy and

reproducible way. In this way, both 2D and 3D TOE provide additional information in order to select the appropriate treatment strategy **(17)**.

Use of cardiac magnetic resonance to quantify ischemic MR:

CMR can help in quantifying MR. The most common and accepted approach involves comparison between LV stroke volume (obtained from short-axis images covering the entire LV) and aortic forward stroke volume (obtained by phase-contrast flow imaging): The difference between the values is assumed to be the MR volume **(18)**.

This indirect assessment does not rely on MR jet characteristics for quantification. CMR regurgitant volume is therefore completely independent from flow orientation or variations during systole. This represents a significant advantage over some static echocardiography-derived parameters, such as EROA or VC. On the other hand, CMR is more limited in assessing the dynamic nature of MR (relation to exercise), cannot be easily repeated in patients with changing volume status, is not widely available, and some patients may have contraindications. Growing data seem to support the use of CMR to quantify MR. Despite possible discordance with echocardiography (more frequently with secondary MR), CMR regurgitant volume is overall better correlated with prognosis **(19)**.

One recent CMR study shows that MR regurgitant fraction > 35% is associated with adverse outcomes in patients with ischemic MR, and better stratification can also be achieved by integrating MI size. However, most other severity data from CMR are derived from patients with primary MR, and therefore not directly applicable to the ischemic MR population **(20)**.

Assessment of LV function and viability:

LV size and systolic function represent important variables that can be assessed by TTE. In addition to LV ejection fraction, the use of more advanced techniques such as LV strain has been associated with mortality in a recent study involving patients with secondary MR (50% ischemic MR) **(21)**.

The use of strain to compute indices of LV muscle dyssynchrony can also potentially predict the likelihood of MR improvement after various interventions. Myocardial viability represents the potential of each LV segment to recover its function after revascularization. Myocardial viability can be assessed by dobutamine echocardiography or thallium or technetium radionuclide imaging. When available, CMR and fluorodeoxyglucose–positron-emission tomography can potentially improve the accuracy of viability assessment. A large extent of viable myocardium (> 5 segments) and an absence (≤ 60 ms) of anterior-posterior papillary muscle dyssynchrony have been independently associated with improvement in ischemic MR following revascularisation **(22)**.

The assessment of myocardial viability could represent a key feature in patients with ischemic MR undergoing revascularization. More data, however, are needed to support a more generalized clinical applicability.

Biomarkers:

The use of cardiac stretch biomarkers, such as B-type natriuretic peptide, can be useful to monitor patients with primary organic MR, with high values predicting mortality. Higher values are also associated with increased MR severity and mortality in patients with ischemic MR, although elevated levels in this population can also be caused by LV dysfunction and does not always reflect MR severity. Despite encouraging results in predicting secondary MR response after CRT, the clinical applicability of newer biomarkers (sST2, galectin 3) remains to be studied in larger trials **(23)**.

Therapeutic Approaches:

Treatment of the underlying LV disease with pharmacologic approaches, biventricular pacing, and revascularization are usually the first steps in patients with ischemic MR. In those with persistent MR and associated symptoms, surgical or percutaneous interventions can be considered. Many studies highlight the importance of patient selection when considering such interventions. In most advanced disease, conservative medical therapy, consideration for LV assist device, or cardiac transplantation could be more relevant than a mitral intervention, highlighting the importance of multidisciplinary heart team evaluation **(12)**.

Medical therapy:

Standard medication for LV remodelling should be given after MI, especially in patients at risk of developing ischemic MR. This includes agents blocking the renin-angiotensin system (angiotensin-converting enzyme inhibitor [ACEI] and angiotensin receptor blocker [ARB]), beta-blockers, and aldosterone antagonists. In addition to their effects on LV remodelling, the use of optimal doses of ACEI/ARB can potentially improve mitral leaflet biology. The use of adjunct neprilysin inhibitor (sacubitril-valsartan combination) has been shown to be more effective to decrease MR severity vs ARB alone and should be used when indicated. Regarding emerging new molecular targets for heart failure, the ongoing Ertugliflozin for Functional Mitral Regurgitation (EFFORT) trial is specifically exploring the potential effects of a sodium-glucose cotransporter 2 (SGLT2) inhibitor in patients with ischemic and nonischemic secondary MR. Optimization of medical therapy should be a universal first step in patients with ischemic MR **(24)**.

Cardiac resynchronization therapy:

Several studies have shown that CRT in eligible patients can help reduce the severity of secondary MR in approximately one-half of cases, with better clinical outcomes. MR response to CRT can potentially be predicted by studying mitral and LV morphology (less response with larger LV and increased valve tenting), echocardiography-derived indices of dyssynchrony, and cardiac biomarkers. Based on available data, current guidelines suggest CRT when indicated before considering any mitral procedure (surgical or transcatheter replacement or repair). Reassessing clinical status and MR severity after 3-6 months is reasonable to confirm CRT response **(9)**.

Coronary revascularization:

Percutaneous coronary revascularisation of the culprit artery is typically the first action performed at the time of an acute coronary syndrome. Outside the acute setting, indications for revascularisation depend on the underlying coronary anatomy, presence of symptoms, LV dysfunction, and viability. In appropriate cases, revascularisation may lead to reverse remodelling of the LV, which in turn may result in a reduction in MR. Patients with ischemic MR having proven ischemia should therefore undergo coronary angiography and be evaluated for myocardial revascularisation. Decision for percutaneous vs surgical revascularisation is chosen based on anatomic feasibility and risk assessment of both methods. In many cases, a multidisciplinary heart team discussion is required, because each approach can eventually be combined with mitral valve interventions (combined coronary and mitral surgery vs sequential percutaneous revascularization followed by percutaneous edge-to-edge repair). Relatively preserved annular geometry and the use of viability studies can help in predicting the likelihood of MR improvement with revascularization alone or conversely identify the patients more likely to benefit from revascularisation combined with a mitral valve intervention **(25)**.

Mitral valve surgery combined with revascularisation:

Revascularisation alone can leave a significant proportion of patients with residual MR. Thus, the question of combined mitral valve repair or replacement remains critical but is still a matter of debate in many situations. Mitral repair with a restrictive annuloplasty ring with or without subvalvular repair and mitral valve replacement can be performed alone or in combination with coronary artery bypass grafting (CABG).

In patients with moderate ischemic MR with an indication of CABG, a relevant question is whether a specific additional intervention must be performed on the mitral valve. While some studies have suggested a clear superiority of performing combined CABG and mitral valve repair in this situation, that finding has been mitigated by a trial in which 301 patients with moderate ischemic MR were randomized to CABG alone or CABG and mitral valve repair. Although the rate of moderate or severe MR was higher in the CABG-alone group (32.3% vs 11.2%; $P < 0.001$), rehospitalization and serious clinical events rate were similar (84 vs 92 events per 100 patient-years; $P = 0.35$), with higher neurologic events and arrhythmias in patients undergoing CABG and mitral repair (14 vs 4 events; $P = 0.02$). Despite this absence of net overall benefit, the option of mitral valve repair at the time of CABG has still to be prospectively studied in selected patients based on myocardial viability (odds of MR improvement with revascularisation alone) and predictors of mitral repair success. Indeed, several parameters have been associated with outcomes following mitral valve repair, including increased anterior and posterior leaflet angles, increased tenting area, larger LV diameter, annulus size, and interpapillary muscle distance, and increased sphericity **(26)**.

There is more consensus on the fact that severe ischemic MR should generally be addressed during CABG procedure. In that case, mitral repair or mitral valve replacement can both be performed. However, the benefits of mitral repair over replacement in primary organic MR are not observed in patients with ischemic MR. Observational studies have shown that recurrent MR is more frequent after mitral valve repair, leading to more reoperation and without clear benefits in LV function. This has also been highlighted in a randomized trial comparing mitral repair vs replacement in patients with severe ischemic MR. Patients with mitral repair had much higher recurrence of MR at 2-year follow-up (58.8% vs 3.8%; $P < 0.001$), along with increased heart failure (24.0 vs 15.2 per 100 patient-years; $P = 0.05$) and cardiovascular hospital readmissions (48.3 vs 32.2 per 100 patient-years; $P = 0.01$), compared with patients with mitral valve replacement. It is worth noting that the use of undersizing annuloplasty does not directly correct the main mechanism of ischemic MR. Mitral repair could potentially be optimized by using adjunct interventions on the subvalvular apparatus and correction of LV and papillary muscle position and shape **(27)**.

Surgical and percutaneous options for isolated mitral interventions:

Isolated mitral surgery in patients with ischemic MR but without the need for revascularisation should be reserved for patients with persistent symptoms despite optimal medical therapy and CRT (if indicated). Those cases should be carefully evaluated because LV systolic function is not expected to improve in the absence of revascularisation. Surgical risk should be assessed, and patients deemed at high or prohibitive surgical risk may be considered for transcatheter mitral valve repair or advanced heart failure therapies **(28).**

Edge-to-edge leaflet repair is the most widely accepted percutaneous mitral valve intervention and is a less invasive treatment option for patients with moderate-severe secondary MR who are denied surgery because of high risk. The

MitraClip device (Abbott Vascular, Santa Clara, CA) is the only system currently approved in Canada, the US, and Europe. The **E**ndovascular **V**alve **E**dge-to-Edge **Re**pair **St**udy (EVEREST) trials have demonstrated its feasibility and safety for primary and secondary MR, but resulting in a lower efficacy compared with surgery regarding the presence of residual MR **(29).**

Patient selection for edge-to-edge repair mostly depends on mitral valve anatomy: Leaflet length and mobility, mitral valve orifice area, presence of calcifications, origin of regurgitant jet(s), measurement of coaptation gap, and interatrial septum morphology represent important variables to collect. Benefits of the MitraClip device over optimal medical treatment in patients with secondary MR have been studied in 2 randomized controlled trials: COAPT (**C**ardiovascular **O**utcomes **A**ssessment of the MitraClip **P**ercutaneous **T**herapy for Heart Failure Patients With Functional Mitral Regurgitation) **(13)**. and MITRA-FR (Percutaneous Repair with the MitraClip Device for Severe Functional/Secondary Mitral Regurgitation) **(30)**.

Both studies included ~60% of patients with ischemic MR. The COAPT study demonstrated that percutaneous repair reduced the risk of all-cause mortality (29.1% vs 46,1%; $P < 0.001$) and rehospitalization (35.8% vs 67.9% per patient-year; $P < 0.001$) at 24 months and was associated with positive LV remodelling compared with medical treatment alone. These results were validated in subgroups of patients: ischemic vs nonischemic and surgical high vs low risk **(30)**.

Conversely, MITRA-FR demonstrated no benefit of percutaneous repair over medical treatment for the same primary outcomes at 12 and 24 months (all-cause mortality and rehospitalisation for HF occurred in 63.8% vs 67.1%: hazard ratio 1.01, 95% confidence interval 0.77-1.34) **(13)**.

Anticoagulation In STEMI

Early intravenous anti-coagulation along with anti-platelets is the cornerstone for the management of acute coronary syndrome patients. The primary aim of early anti-coagulation is to reduce the ischaemic burden in the myocardium without increasing the haemorrhagic events. Acute coronary syndrome (ACS) occurs due to complete or incomplete coronary thrombosis following atherosclerotic plaque rupture. ACS includes the patients having unstable angina (UA), non-ST-elevation myocardial infarction (NSTEMI) and ST-elevation myocardial infarction (STEMI). **(31)**.

Pathophysiology of ACS and role of anticoagulation:

The primary pathogenesis of ACS starts from the development of coronary atherosclerotic plaques and subsequent consequences due to rupture/erosion of unstable coronary plaques. Rupture of the plaques leads to activation of platelets and coagulation cascade as a result of injury to blood vessels. The pathophysiology of ACS includes platelet activation and thrombin production, among others. Thrombin production and generation of a prothrombotic state in ACS have paved the role for treatment with anti-coagulation during an acute stage **(31)**.

Initial management of ACS includes oxygen therapy, anti-platelets, nitrates, analgesics, beta-blockers and statins. Due to the generation of platelet-rich thrombus and prothrombotic state, anti-coagulants such as unfractionated heparin (UFH), low molecular weight heparin (LMWH) and other antithrombotic agents are indicated in these patients. Following this initial acute coronary event, thrombin remains elevated for a long time, and these patients are at risk of recurrence of ACS. Research is ongoing to determine the role of long-term anti-coagulants to prevent subsequent coronary events once the acute stage is over **(31)**.

Anticoagulants used in ACS:

The commonly used anti-coagulants in ACS include UFH, LMWH, bivalirudin and fondaparinux. **(31)**.

Table 2 | Characteristics of various anti-coagulants used in acute coronary syndrome

Anti-coagulant	Structure	Molecular weight	Onset of action	Half-life	Mechanism of action	Monitoring
Heparin	Sulfated muco-polysaccharide	15000 daltons (4000–30000 daltons)	Immediate	1 hr	Antithrombin mediated inhibition of factors II and X	aPTT, Anti-factor Xa activity, or ACT (200–250 s during PCI with GPI or 250–300 s without GPI)
Enoxaparin	Fractionation and depolymerization of heparin	5000 daltons (3000–5000 daltons)	IV: Immediate SC: 2 hrs	4 hrs	Antithrombin mediated inhibition of X≫II	No need of monitoring
Bivalirudin	Synthetic 20-amino acid analogue of hirudin	2000 daltons	Immediate	25 min	Direct thrombin (II) inhibitor	ACT
Fondaparinux	Synthetic pentasaccharide, derived from cleavage of heparin sulfate	1700 daltons	IV: Immediate SC: 2 hrs	17 hrs	Antithrombin mediated inhibitor of factor X	No need of monitoring

abbreviations: ACT, activated clotting time; aPTT, activated partial thromboplastin time; GPI, Glycoprotein IIb/IIIa inhibitor; HIT, heparin induced thrombocytopenia; hr, hour; IV, intravenous; PCI, percutaneous coronary intervention; SC, subcutaneous.

Table 3 | Duration of anti-coagulation after acute coronary syndrome

Anti-coagulant	Duration in conservative treatment (NSTE-ACS, thrombolysis)	Primary PCI
Unfractionated heparin (UFH)	Maintain for 48 hrs or until revascularization	Discontinue anti-coagulation
Enoxaparin	Maintain for 8 days or till hospitalization or revascularization	Discontinue anti-coagulation
Bivalirudin	Until diagnostic angiography or PCI is performed, in patients with early invasive strategy only	Maintain for 4 hrs after the procedure
Fondaparinux	For index hospitalization up to 8 days or until revascularization	Discontinue anti-coagulation
Warfarin	If patient has LV thrombus or LV aneurysm, 3 months to life-long therapy	

Table 4 | Dosing of anti-coagulants used in acute coronary syndrome

Anti-coagulant	NSTE ACS/Ischemia-guided therapy	Thrombolysis	Primary PCI
UFH	60 units/kg bolus (max 4000 units) + 12 units/kg/hr (max 1000 units) IV infusion titrated to therapeutic aPTT Obtain aPTT of 1.5–2.0 times control (approx. 50–70 s)	60 units/kg bolus (max 4000 units) + 12 units/kg/hr (max 1000 units) IV infusion titrated to therapeutic aPTT Obtain aPTT of 1.5–2.0 times control (approx. 50–70 s)	PCI with planned GPI: 50–70 units/kg IV bolus to achieve therapeutic ACT of 200–250 s PCI without planned GPI: 70–100 units/kg IV bolus to achieve therapeutic ACT of 250–300 s

Enoxaparin	1 mg/kg IV SC q12 hr (Reduce dose to 1 mg/kg/d SC if CrCl < 30 mL/min)	≤75 yr: 30 mg IV bolus, then 15 minute later 1 mg/kg SC q12 hr ≥75 yr: No bolus, 0.75 mg/kg SC q12 hr (Reduce dose to 1 mg/kg/d SC if CrCl < 30 mL/min)	0.5–0.75 mg IV bolus if no anti-coagulation previously or if more than 12 hrs of enoxaparin 0.3 mg/kg IV if last SC dose was between 8–12 hrs before PCI Without new dose if last dose < 8 hrs
Fondaparinux	2.5 mg SC daily	2.5 mg IV × 1, then 2.5 mg SC daily starting next day	Not recommended without additional anti-coagulant with anti-II activity
Bivalirudin	0.10 mg/kg IV loading followed by 0.25 mg/kg/hr infusion	–	0.75 mg/kg IV bolus + 1.75 mg/kg/hr infusion
Abbreviations: ACT, activated clotting time; IV, intravenous; SC, subcutaneous; GPI, glycoprotein IIb/IIIa inhibitor; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.			

UFH is the most affordable, oldest and remains the most frequently used anti-coagulant in ACS. It binds with anti-thrombin III and inhibits factors IIa (thrombin) and Xa indirectly by activation of antithrombin. Heparin requires parenteral administration and is usually given via a continuous intravenous route. Clearance of heparin is extra-renal; hence, it is safe in renal dysfunction. Levels of heparin-binding proteins vary from person to person inside the blood circulation, which results in unpredictable and variable anti-coagulant responses of heparin. Because of intra- and inter-individual variability, monitoring of the anti-coagulation effect either by aPTT, activated clotting time (ACT) or anti-factor Xa level is essential to ensure a therapeutic response . Activity of heparin may be reduced in the vicinity of platelet-rich thrombus by neutralization of heparin by high concentration of PF4 released from activated platelets. Another important limitation is risk of heparin-induced thrombocytopenia (HIT), which can paradoxically increase thromboembolic risk (arterial or venous thrombosis) in the patient. It is a serious and potentially life-threatening complication in the setting of ACS. It has also been postulated that heparin discontinuation causes biological rebound generation of thrombin and increases prothrombotic state. The most common side effect is bleeding, and the antidote protamine can be used in patients with serious bleeding. Typically, 1 mg of intravenous protamine can neutralize 100 units of heparin **(32)**.

Low molecular weight heparin (LMWH) is prepared from heparin by chemical depolymerization. It causes inhibition of factor Xa more than factor IIa because of a short pentasaccharide chain. It has better bioavailability, predictable anti-coagulant response and longer half-life than heparin. Because of the predictable anti-coagulant response, monitoring of anti-coagulation is not necessary in most patients. Other advantages include a lower risk of HIT and osteoporosis. LMWH via a subcutaneous route can be administered at home which increases patient satisfaction. Doses have to be reduced in renal dysfunction and monitoring of anti-coagulant effects is indicated in special groups of patients such as those who are pregnant and in presence of mechanical prosthetic valves **(33)**.

Fondaparinux is a synthetic analogue of antithrombin-binding sequence. It requires the presence of antithrombin for its action and causes inhibition of factor Xa only without affecting factor IIa. The drug is administered once daily by subcutaneous route. Because of its renal clearance, it should be given cautiously to patients with renal dysfunction and should be avoided when creatinine clearance is less than 20 mL/min **(34)**.

Direct thrombin inhibitors (e.g. bivalirudin) potentially have an advantage over UFH or LMWH as they inhibit clot bound thrombin. Additionally, direct thrombin inhibitors don't interact with plasma proteins, provide a stable anti-coagulation effect and do not cause thrombocytopenia. Bivalirudin is a synthetic analogue of hirudin which directly binds and inhibits thrombin (factor IIa) without activation of antithrombin. Its action can be monitored by ACT and aPTT when used in high doses and low doses, respectively. It causes less bleeding than heparin and can be safely used in patients with heparin-induced thrombocytopenia who require PCI **(34)**.

Warfarin, an oral vitamin K antagonist, interferes with synthesis of clotting factors II, VII, IX, and X. It is not indicated in acute coronary events. The only indication of warfarin is in patients requiring triple therapy (anti-coagulant and dual anti-platelet therapy), such as patients with atrial fibrillation, mechanical valves or deep venous thromboembolism. Frequent monitoring, increased drug interactions, food drug interactions and increased risk of bleeding when combined with dual anti-platelet therapy are the major limitations of warfarin for use in ACS. The development of novel anti-

coagulants has addressed some of these limitations and these novel anti-coagulants might have a potential role in the management of ACS **(34)**.

ANTI-COAGULATION IN STEMI:

STEMI is associated with a heavy thrombus burden due to activation of platelet aggregation and coagulation cascade, and immediate primary PCI or thrombolysis is required within the window period. Anti-coagulation has shown to reduce mortality and recurrent ischaemic events with both thrombolysis and primary PCI. Primary PCI is usually done in high thrombotic settings and this thrombotic risk is increased by damage of the endothelium during coronary intervention. Therefore, there is an increased risk of early ischaemic complications during PCI such as acute stent thrombosis. There is a need of early and efficient anti-coagulation therapy to block the coagulation cascade and prevent ischaemic injury to the myocardium **(35)**.

- ***UFH:***

Randomized trials conducted in the pre-fibrinolytic era showed lower risk of mortality and reinfarction in patients of STEMI treated with heparin. A meta-analysis in the fibrinolytic era suggested that for every 1000 patients of STEMI treated with heparin in addition to aspirin, five fewer deaths ($p = 0.03$) and three fewer recurrent infarctions ($p = 0.04$) occurred, but at the cost of three major bleeding events ($p = 0.001$) **(** . Guidelines support the use of heparin for at least 48 hours after fibrinolysis or until PCI is done **(36).**

- ***Enoxaparin:***

LMWH reduces the rates of re-occlusion of the infarct-related artery, reinfarction or recurrent ischaemic events. Several trials compared LMWH with UFH as part of a pharmacologic reperfusion strategy and found LMWH to be superior. The ASSENT trial showed that enoxaparin reduced 30-day mortality and in-hospital reinfarction as compared to heparin with similar rates of intracranial haemorrhage. ExTRACT-TIMI 25 was a double-blind trial which showed that enoxaparin reduced the primary end point of mortality and recurrent MI by 17% with enoxaparin but increased major bleeding significantly (1.4% vs. 2.1%) as compared to heparin. ATOLL trial found that bleeding rates and bleeding events were reduced with enoxaparin when compared with heparin in STEMI patients undergoing primary PCI **(37)**. Enoxaparin was also associated with significant reduction in recurrence or complications of MI.

Fondaparinux:

The OASIS-6 trial included 12,000 subjects with STEMI and randomized them to receive UFH or fondaparinux. Overall, it was associated with a reduced rate of death and bleeding, and it showed a high rate of periprocedural catheter thrombosis and coronary complications in the subgroup treated by primary PCI. Consequently, it has been given class III recommendation in STEMI when used as sole anti-coagulant **(36).**

Bivalirudin:

In patients undergoing fibrinolysis, bivalirudin reduced recurrent MI by 25%–30% compared with heparin without affecting mortality at the expense of higher rates of major bleeding **(38)**.

In contrast, the HORIZONS-AMI trial compared bivalirudin with UFH plus GPI in STEMI patients undergoing primary PCI. Bivalirudin reduced net adverse clinical events (rate of major bleeding or major CV events including reinfarction and target vessel revascularization) primarily driven by a significant 40% reduction in major bleeding events. However, patients in the bivalirudin group were found to have a four-fold increase in acute stent thrombosis.The EUROMAX trial in the era of radial artery PCI access also presented similar findings with reduced primary outcome of death or major bleeding events but at the expense of five-fold increase of acute stent thrombosis events in the bivalirudin group. These events led to a downgrade of recommendations in recent updates from the previous class I to class IIa **(39)**.

Newer anticoagulants in ACS:

Novel anti-coagulants such as anti-Xa therapies (apixaban, rivaroxaban, otamixaban) and direct thrombin inhibitors (dabigatran) have been tried in patients with ACS.

Anti-Xa drugs (apixaban and rivaroxaban) were found to increase the rate of bleeding in a dose-related manner when added with anti-platelet therapy in the phase III trials. The APPRAISE-2 study had to be stopped prematurely due to excessive bleeding with apixaban regimen in addition to DAPT **(40)**.

The Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Aspirin with or without Thienopyridine Therapy in Subjects with ACS Thrombolysis In MI 46 (ATLAS ACS-TIMI 46) study was done to assess the effect of rivaroxaban after ACS. It was a randomized, double-blind, placebo-controlled, phase II, dose-escalation trial in which

3491 participants were randomly assigned to rivaroxaban 5, 10, 15 or 20 mg once daily or placebo. Rivaroxaban reduced major ischaemic outcomes including death, myocardial infarction or stroke but at the cost of increased bleeding in dose dependent manner **(41)**.
In the ATLAS ACS 2- TIMI 51 study, low-dose (5 mg twice daily) and very low-dose rivaroxaban (2.5 mg twice daily) was added to double anti-platelet therapy in patients with established ACS, and rivaroxaban significantly decreased the primary composite outcomes (death, MI or stroke) by 16% in those patients **(41)**. As very low dose rivaroxaban had a more favourable safety profile, 2.5 mg twice daily rivaroxaban has been recommended by ESC in combination with aspirin and clopidogrel in patients with ACS **(41)**.

Further safety of low-dose rivaroxaban was assessed in the GEMINI-ACS-1 trial, in which 3037 patients with ACS were randomized to receive aspirin or rivaroxaban in addition to a thienopyridine (clopidogrel or ticagrelor). This trial was different as rivaroxaban was used in place of aspirin, not simultaneously. The primary end point was TIMI clinically significant bleeding; low dose rivaroxaban was found to have similar risk of clinically significant bleeding as aspirin when added to a thienopyridine ($p = 0.580$). They did not assess the efficacy of rivaroxaban in this trial **(42)**.
Dabigatran was added to DAPT in ACS patients in the RE-DEEM study and was associated with dose-dependent increase in bleeding events. A phase III trial of intravenous anti-Xa otamixaban was not found to be useful in patients with NSTE-ACS undergoing early PCI. Otamixaban did not reduce ischaemic event rates, but significantly increased bleeding rates when compared with UFH plus eptifibatide **(43)**.
The use of newer anti-coagulants in ACS is limited by increased risk of bleeding as they are given in addition to dual anti-platelet drugs. Only rivaroxaban, out of the novel anti-coagulants, has been approved in Europe at present for the use in ACS patients. Further studies are ongoing for other novel anti-coagulants.

Guidelines:
The use of various anti-coagulants has been advised in guidelines for the management of patients with STEMI but different classes of recommendations are given based on available evidence **(36).**

Table 5 | Guidelines by the American College of Cardiology (2013) and the European Society of Cardiology (2017) regarding anti-coagulation in ST-elevation myocardial infarction

	ACC guidelines Class (level)	**ESC guidelines Class (level)**
Primary PCI		
Routine use of UFH with or without GPI to achieve therapeutic ACT	I (C)	I (C)
Routine use of enoxaparin	NA	IIa (A)
Routine use of bivalirudin	I (B)	IIa (A)
Fondaparinux is not recommended for primary PCI as a sole anti-coagulant	III (B)	III (B)
Fibrinolysis		
Routine use of UFH	I (C)	I (B)
Routine use of enoxaparin	I (A)	I (A)
Routine use of fondaparinux	I (B)	IIa (B)

Abbreviations: GPI, glycoprotein IIb/IIIa inhibitor; IV, intravenous; NA, not available; NSTEMI, non-ST elevation myocardial infarction; PCI, percutaneous coronary intervention; SC, subcutaneous; UFH, unfractionated heparin.

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