A Contemporary Overview of the Pathophysiology of Angina Pectoris

Firas E. Zahr, MD, Suresh R. Mulukutla, MD, Oscar C. Marroquin, MD
University of Pittsburgh Medical Center Heart and Vascular Center for Quality, Outcomes, and Clinical Research, Pittsburgh, PA

Angina pectoris, a common manifestation of stable ischemic heart disease, is a common problem that continues to grow in our society, given the aging population, the epidemic of obesity, and resultant cardiovascular risk factors. This article focuses on the pathophysiology of this disease, its epidemiology, and the goals of therapy. Although angina pectoris can present in many different ways (eg, typical, atypical, silent), correct identification requires thoughtful assessment and evaluation. It is clear that our focus in the prevention of coronary artery disease by addressing modifiable risk factors is of paramount importance. However, patients often present to physicians because of symptoms and their satisfaction with their care is often dictated by the effectiveness of the treatment for this presentation. It also requires a tailored approach, recognizing that (except in higher-risk scenarios) pharmacologic agents should be the first-line approach to treatment. The availability of newer first-line agents such as ranolazine should allow an effective trial of optimal medical therapy, which, incidentally, forms the cornerstone of many of the appropriateness criteria for revascularization for coronary disease. Coronary revascularization, either by percutaneous coronary intervention or by bypass surgery, is a reasonable option in patients whose symptoms are not adequately controlled with medical therapy alone or in those with high-risk characteristics. Even with revascularization, significant numbers of patients will continue to have (or develop over time) anginal symptoms requiring medical treatment.

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Angina pectoris is one of the classic symptoms of coronary artery disease (CAD), originally described in 1772 by the English physician William Heberden, who had encountered a group of patients with "a painful and most disagreeable sensation in the breast which seems as if [it would] extinguish life if it were to increase or to continue." He went on to describe that those suffering from these afflictions "are seized while they are walking (more especially if it is uphill and soon after eating) … but the moment they stand still all the uneasiness vanishes."[1] The term *angina* derives from the Latin (defined variably as pain in the throat), whereas *pectoris* derives from the Latin *pectus* (chest).

Although angina represents the most identifiable symptom in patients with ischemic heart disease, it is causally related to the presence and development of obstructive coronary atherosclerosis. The classic paradigm of ischemic heart disease, originally proposed by Gould and Lipscomb[2] in 1974, postulated that a reduction in coronary artery diameter to 30% to 45% resulted in a limitation of the maximal coronary adaptive vasodilatory response to exercise, whereas a reduction to 85% or more resulted in limitations of resting blood flow. In the spectrum of disorders within ischemic heart disease, particularly for patients with stable angina pectoris, this relationship between angiographic severity of coronary stenosis and its effect on coronary vasodilatory response has been the basis of recommendations for both surgical and percutaneous revascularization. However, with increasing appreciation of the limitations of visually determined angiographic severity, additional modalities that directly measure the effect of coronary stenosis on the myocardial reserve (the fractional flow reserve) have become standard.

Measurement of Angina

There are several tools that quantify angina and its impact on functional status. The Canadian Cardiovascular Society classifies angina into one of four levels, ranging from Class I (angina only with strenuous prolonged activity with no impairment on ordinary activities) to Class IV (angina at rest and inability to perform any physical activity) (Table 1).[3] This is the most commonly used tool in the clinical arena. There are other well-validated survey tools to quantify angina and its impact on quality of life that are used in research studies. The Rose Angina Questionnaire assesses several symptoms, including the location of the discomfort, its duration, and the level of stress before it develops. Symptoms can then be defined as definite angina or not; mild (grade 1) or severe (grade 2).[3] Other survey tools characterize a patient's functional status limitation induced by cardiac symptoms, including the specific activity scales in the Duke Activity Status Index. The multidimensional Seattle Angina Questionnaire assesses the effect of angina on five domains (physical limitation, angina stability, angina frequency, disease perception, and the patient's satisfaction with treatment).[4]

Prevalence of Angina

Over 400,000 new cases of stable angina occur each year on the basis of the National Health and Nutrition Examination Survey (1999-2002).[5] These rates of chronic angina pectoris in the United States are similar to that observed in other industrialized Western European countries. The prevalence of angina increases with advancing age, from being almost negligible in those < 35 years of age to almost one in five in those ≥ 75 years who report it.[6] Angina is not benign; approximately one-half of patients presenting with myocardial infarction (MI) report having antecedent angina.[7] Two older population-based studies

TABLE 1

Canadian Cardiovascular Society Classification of Angina Pectoris

Class	Description
I	Ordinary physical activity, such as walking or climbing stairs, does not cause angina. Angina occurs with strenuous, rapid, or prolonged exertion at work or during recreation.
II	Slight limitation of ordinary activity. Angina occurs on walking or climbing stairs quickly, walking uphill, walking or climbing stairs after meals, in the cold, in wind, under emotional stress, or only during the first few hours after awakening. Angina occurs after walking $>$ 2 blocks on the level and climbing $>$ 1 flight of ordinary stairs at a normal pace under normal conditions.
III	Marked limitations of ordinary physical activity. Angina occurs on walking 1–2 blocks on the level and climbing 1 flight of stairs in normal conditions and at a normal pace.
IV	Inability to carry on any physical activity without discomfort. Anginal symptoms may be present at rest.

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(from Olmsted County, MN, and Framingham, MA) examined the annual rates of MI in patients with symptoms of angina and reported similar rates of 3% to 3.5% per year. On this basis, it can be estimated that, for every 30 patients with stable angina, one is hospitalized with an MI; if there are 550,000 MIs annually, it follows that 16.5 million patients have angina in the United States—a truly staggering thought. This figure does not include patients who fail to seek medical attention for their chest pain.[8]

Prognosis of Angina

Our understanding of the prognosis of angina comes from the descriptions of the Framingham cohort. In this cohort, patients with angina had mortality rates similar to those seen in the posthospital phase of MI.[9] However, more recent studies in patients with stable angina have also added to our understanding of the prognosis in these patients.

The study by Buckley and Murphy[10] included 1609 adults with ischemic heart disease in primary care practices. Compared with patients with a previous MI, those with angina and no prior MI had a lower likelihood of dying during follow-up—hazard ratios for all-cause mortality 0.73 (95% confidence interval [CI], 0.55-0.98) and for cardiovascular mortality 0.65 (95% CI, 0.44-0.98). Physical function was consistently lower among those with angina alone. In another study, the same group examined the prognosis of 1785 patients with angina as a first manifestation of ischemic heart disease.[11] In this group, within 5 years, 6.5% had an acute MI, and 9.8% died from any cause. Male sex and older age were both associated with increased hazard for acute MI and all-cause mortality. Interestingly, acute MI after the index episode of angina greatly increased the risk of subsequent death. The authors concluded that appropriate control of risk factors and optimal use of preventive medical treatments should be aggressively pursued in patients with angina who represent a high-risk group in primary care.[11]

Similar findings have also been reported in other diverse patient populations. In the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) study, the 3-year mortality rate for patients without MI was 2.4%.[12] Variability in mortality rates between studies in the modern era almost certainly reflect differences in baseline risk and concomitant medical management.

Economic Burden

In addition to the clinical burden that chronic angina poses to the individual patient, it is also associated with enormous health care expenditures. These include both direct costs in the form of hospitalizations, surgery, and medications, and indirect costs in the form of unemployment and angina-related work limitations. Based on the prevalence of angina, the associated costs in the United States may range from $17 billion to $49 billion annually. In 2002, total health care expenditures were in excess of $1.5 billion, 1.3% (~ $20 million) of which may be associated with the direct cost of angina.[13]

These cost figures may be conservative because the majority of the studies cited in this article are based on data collected as early as the late 1980s through the late 1990s. These estimates may not reflect current changes in health care cost and practice, particularly with the advent of more complex and costly revascularization procedures and technologies. For instance, in the Randomized Intervention Treatment of Angina (RITA)-2 trial,[14] patients with stable angina treated with balloon angioplasty had better angina relief but more cardiac events than patients randomized to medical therapy. RITA-2 documented that the higher initial cost of angioplasty (£2793; ~ US $4335) was undiminished after 3 years of follow-up.[14] In contrast, the findings of the randomized Trial of Invasive Versus Medical Therapy in Elderly Patients With Chronic Angina (TIME) trial[15] reported that the higher initial costs of elderly patients randomized to percutaneous coronary intervention (PCI) were largely balanced by the higher follow-up costs in patients randomized to medical therapy. These findings suggest that the cost effectiveness of PCI depends in large part on the severity of the patient's angina; in patients with severe symptoms, PCI can improve quality of life and avert some costs (eg, emergency department and clinic visits and pharmaceuticals), whereas in patients with mild or no symptoms and low-risk characteristics there is less to gain from intervention.

Drug-eluting stents (DES) have further reduced the rate of repeat revascularization procedures in comparison with bare metal stents but are significantly more expensive. The Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions (SIRIUS) trial[16] suggests that the $2881 higher initial cost of patients assigned to a sirolimus-coated stent was partially offset during follow-up by lowering the need for costly repeat revascularization procedures. The economic impact of DES may depend critically on the rate of repeat procedures that can be achieved using alternative therapies; when repeat procedure rates are already quite low, it is difficult to lower them further and thereby recoup the added cost of a drug-coated stent. The cost

of the DES is also quite influential in this balance. In the United States the cost of DES—initially $3000 per stent—has dropped significantly since their initial introduction, but the cost of bare metal stents has also dropped dramatically, so there is still a large incremental cost difference between the two stent types. Data from the National Cardiovascular Data Registry suggest that US health care costs can be reduced by > $200 million per year with minimal impact on restenosis if bare metal stents were used in patients at low risk of target vessel revascularization.[17]

Angina in Women

Women report more chest pain despite a lower rate of obstructive CAD and better preserved left ventricular (LV) function compared with men on coronary angiography.[18] It is now recognized that the prognosis for women with chest pain, despite findings of nonobstructive CAD, is not benign, and that a significant proportion of these patients are at increased cardiovascular risk. The Women's Ischemia Syndrome Evaluation (WISE) study[19,20] observed that women with persistent chest pain demonstrate twice the rate of adverse cardiovascular events, including nonfatal MI, stroke, congestive heart failure, and cardiovascular death, compared with those without. In some women, angina is related to microvascular dysfunction and ischemia in the setting of coronary arteries without (or with minimal) angiographic disease.[21] Although this phenomenon has been attributed to both hormonal abnormalities and traditional risk factors, the association to other nontraditional risk factors, such as inflammation, cannot be discounted.[22] In this group, there is increasing evidence that a patient's symptoms due to microvascular dysfunction might benefit from antianginal and antiischemic therapy that can improve endothelial function and quality of life.[23] It may be difficult to confirm the diagnosis of microvascular dysfunction in women using conventional testing with stress echocardiography and nuclear perfusion imaging. Phosphorus-31 magnetic resonance spectroscopy is an emerging technology that assesses the ratio of high-energy phosphate (phosphocreatine) to low-energy inorganic phosphates, as well as cellular pH, and is the sine que non of an ischemic state; it may be the ideal technology to identify patients with microvascular dysfunction-induced ischemia.

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Importantly, although the clinical presentation of myocardial ischemia in women can be that of typical angina, it is not uncommon for atypical symptoms (eg, exertional dyspnea, palpitations, nausea) to be the primary presenting symptom in women with myocardial ischemia. Furthermore, despite the fact that the overall prevalence of obstructive CAD observed during coronary angiography is lower in women than in men, the morbidity and mortality associated with CAD during a woman's lifespan is similar to that observed in men. As such, the education of women presenting with chest pain and being evaluated for the presence of CAD (or, in its absence, of microvascular dysfunction) needs to be tailored toward improving their understanding of the risk factors that can serve as therapeutic targets to improve their overall cardiovascular health.[24]

Silent Ischemia

Asymptomatic myocardial ischemia has been shown to occur more often than symptomatic ischemia in patients with stable CAD; on ambulatory electrocardiographic (ECG) monitoring, nearly one-half of patients with stable CAD are shown to have transient ST-segment depressions that likely represent silent ischemic events.[25]

The Asymptomatic Cardiac Ischemia Pilot Study (ACIP)[25] tested various strategies to reduce silent ischemia. Eligible patients had evidence of asymptomatic ischemia on ambulatory ECG, an abnormal exercise ECG, and stable CAD with ≥ 50% stenosis. Although most of the patients had angina symptoms at study enrollment, approximately one-third were asymptomatic. Participants were randomized to medical therapy versus revascularization. ACIP demonstrated increased suppression of ischemic episodes and better cardiovascular outcomes in patients treated with revascularization as compared with medical therapy.

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In patients with mild-to-moderate CAD, silent ischemia provides similar prognostic information for adverse outcomes as symptomatic ischemia. In patients with medically managed CAD, the likelihood of death or MI during 7 years of follow-up was similar between patients with asymptomatic ST-segment depression with exercise and those patients

with symptomatic ST-segment depression with exercise (Figure 1). However, among patients with medically treated extensive CAD (three-vessel disease), silent ischemia is associated with worse prognosis than symptomatic ischemia.[26,27]

The more recent Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial[28] trial demonstrated similar outcomes between those patients with CAD who received revascularization and optimal medical therapy compared with optimal medical therapy alone. The medical therapy provided in COURAGE included aspirin, β-blockers, 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors, and angiotensin-converting enzyme inhibitors, which were used with greater frequency than in the ACIP study. Separate studies have demonstrated the ability of all of these different medical therapies to suppress silent ischemic episodes, which may explain why medical therapy was as effective as revascularization in these more recent studies. However, in the COURAGE trial, nearly one-third of patients reported angina despite revascularization; this was no different from those who did not undergo revascularization and were treated medically.

Medical Management of Stable Angina

The pharmacologic prevention of exertional symptoms of angina has classically involved the use of agents that reduce myocardial oxygen demand and increase myocardial oxygen supply and response to exercise. These agents include organic nitrates, β-blockers, and calcium channel antagonists, and, more recently, ranolazine. A complete review of the pharmacology of available antianginal agents is beyond the scope of this review; however, we present a general overview of the most commonly used agents.

Organic Nitrates

The primary mechanism of action relates to preload reduction mediated by venodilator effects. Preload reduction reduces myocardial oxygen consumption by reducing LV chamber size and consequently systolic and diastolic wall stress. The classic pharmacodynamic feature of the organic nitrates is the development of tolerance during sustained therapy; hence, the use of intermittent therapy, in which intermittent dosing regimens or nitrate formulations that yield low or nitrate-free concentrations in plasma for 10 to 12 hours per day, is employed.[29]

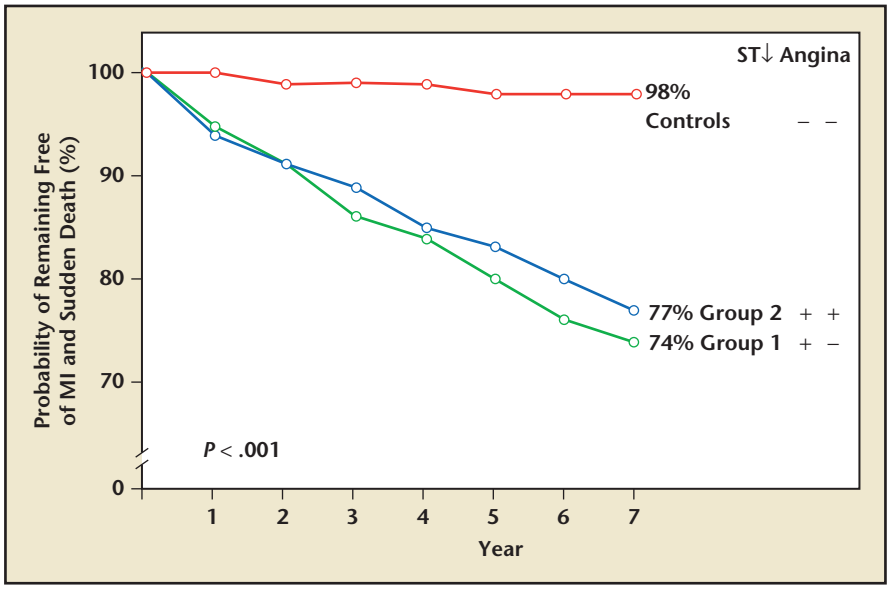
β-Blockers

β-Blockers have a long history of use in treating exertional angina. The mechanism of action is based primarily on decreasing myocardial oxygen demand following heart rate response to exercise. With the exception of patients who have suffered a previous MI or have LV systolic dysfunction, it would be useful for clinicians to have guidance from randomized clinical trials to determine which β-blockers are most effective for treating stable ischemic heart disease in patients with no history of MI or systolic dysfunction, rather than assuming (as the guidelines seem to do) that they have equal effectiveness.

Calcium Channel Blockers

Calcium channel blockers are also effective antianginal agents. Although the basic mechanism of action is similar (blockade of the L-type calcium channel and reduction of intracellular calcium concentration), there are three different classes of calcium channel antagonists that have quite different chronotropic, hemodynamic, and inotropic effects. The dihydropyridines (the prototype is nifedipine) have little effect on heart rate and atrioventricular conduction while having the most prominent defect on peripheral resistance. The benzothiazepines (the prototype is diltiazem) and the phenylalkylamines (the prototype is verapamil) also reduce peripheral vascular resistance, although both these classes

Figure 1. Prognosis of patients with exercise-induced ischemia with or without symptoms. Probability of remaining free of myocardial infarction (MI) and sudden death in control subjects who had no known history of coronary artery disease, and in patients with medically treated coronary artery disease and ST-segment depression during exercise with (Group #2) or without (Group #1) angina. Data from Weiner DA et al[26] and Conti CR et al.[27]



have prominent negative chronotropic effects and impair atrioventricular conduction. Their popular use in treating angina pectoris is often linked to their effect in reducing coronary spasm; they are generally considered less effective than other antianginal agents.

Nicorandil appears to have dual mechanisms of action; the drug increases cyclic guanosine monophosphate, presumably via a nitric oxide-mediated mechanism, but also facilitates opening of mitochondrial potassium adenosine triphosphate channels. It is not approved for use in the United States.

Ranolazine

Ranolazine, the first member of a newer class of medication, is increasingly used as a first-line agent for the treatment of stable angina. It is a piperazine derivative, first approved by the US Food and Drug Administration in 2006 for treatment of chronic angina. Ranolazine, an inhibitor of the late inward sodium current, decreases ischemia-induced myocyte sodium and calcium overload. The anti-ischemic effects occur without change in heart rate or blood pressure, making it a particularly useful antianginal agent in patients with baseline bradycardia, cardiac conduction defects, and lower blood pressures. In a large trial of patients after non–ST-elevation MI, the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST Elevation Acute Coronary Syndrome Thrombolysis in Myocardial Infarction (MERLIN-TIMI) 36 trial,[30] ranolazine did not impact the rates of major adverse cardiac events, although recurrent ischemia was reduced. In the MERLIN-TIMI 36 trial, ranolazine was also associated with a decrease in ventricular arrhythmias as detected by serial Holter monitoring, as well as a reduction in hemoglobin A_{1c} levels. The clinical implications of these effects have yet to be established.

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Coronary Revascularization for Stable Angina

Coronary revascularization provides a more rapid angina relief, lower need for drug therapy with better quality of life, and improved prognosis in selected patients. However, the prognostic benefits seen with revascularization are mainly confined to those with the most severe disease. Many of the studies that described the advantage of revascularization over medical therapy were performed when effective antianginal medications, such as ranolazine, were unavailable.

A complete description of the various revascularization modalities and the specific clinical scenarios in which such revascularization may be beneficial are beyond the scope of this review. Overall, the Coronary Artery Surgery Study (CASS), the Veterans Administrations Cooperative Study Group, and the European Coronary Surgery Study remain the pivotal studies that demonstrated the superiority of surgical revascularization over medical therapy.[31-33] Subsequently, with the advent of PCI, numerous trials have compared optimal medical therapy with percutaneous coronary revascularization. Most recently, the COURAGE[28] and BARI 2D[12] trials have brought to the forefront the limitations related to percutaneous revascularization. In these studies, although percutaneous revascularization achieved superior symptom relief, it provided no advantage over medical therapy in the freedom from death or nonfatal MI. As a result, there is renewed focus on revascularization based on extent of ischemia severity and not just symptoms. It is hoped that the large ongoing International Study of Comparative Health Effectiveness with Medical and Invasive Approaches (ISCHEMIA) trial (http://www.clinicaltrials.gov/ct2/show/NCT01471522), will definitively answer some of these questions. In this trial, patients with an ejection fraction $>$ 35% and at least moderate ischemia by single-photon emission computed tomography, echocardiography, or cardiac magnetic resonance, will be randomized to an invasive versus a noninvasive strategy (both in the background of aggressive medical therapy).

However, for patients with refractory angina, despite revascularization and maximal medical therapy, the utilization of nonpharmacologic techniques may need to be considered. The three most commonly used techniques include surgical laser transmyocardial revascularization, enhanced external counterpulsation (EECP), and spinal cord stimulation. Although there are data from relatively small clinical trials and registries suggesting their potential benefit, their utilization is recommended

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as Class IIb by the 2012 American College of Cardiology Foundation/American Heart Association guidelines for the management of patients with stable ischemic heart disease.[7] It is important to understand, however, that the presence of residual angina in patients who have undergone EECP is associated with a poor prognosis.[34]

Conclusions

Angina pectoris is a common problem that continues to grow, given the aging of our population and the epidemic of obesity and cardiovascular risk factors in our society. It is clear that our focus in the prevention of CAD by addressing modifiable risk factors is of paramount importance. However, patients often present to physicians for symptoms and their satisfaction with their care is often dictated by the effectiveness of the treatment for this presentation. Although angina pectoris can present in many different ways (typical, atypical, silent), correct identification of this problem requires thoughtful assessment and evaluation. It also requires a tailored approach, recognizing that, except in higher-risk scenarios, pharmacologic agents should be the first-line approach. The availability of newer first-line agents such as ranolazine should allow an effective trial of optimal medical therapy, which incidentally forms the cornerstone of many of the appropriateness criteria for revascularization for coronary disease. Coronary revascularization, either by PCI or by bypass surgery, is a reasonable option in patients whose symptoms are not adequately controlled with medical therapy alone, or in those with high-risk characteristics. Even with revascularization, in time, a significant number of patients will still have or develop anginal symptoms requiring medical treatment. ■

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MAIN POINTS

- The relationship between angiographic severity of coronary stenosis and its effect on coronary vasodilatory response has been the basis of recommendations for both surgical and percutaneous revascularization; however, with increasing appreciation of the limitations of visually determined angiographic severity, additional modalities that directly measure the effect of coronary stenosis on the myocardial reserve have become standard.
- Findings from several recent studies suggest that the cost effectiveness of percutaneous coronary intervention (PCI) depends in large part on the severity of the patient's angina. In patients with severe symptoms, PCI can improve quality of life and avert some costs, whereas in patients with mild or no symptoms and low-risk characteristics, there is less to gain from intervention.
- The pharmacologic prevention of exertional symptoms of angina has classically involved the use of agents that reduce myocardial oxygen demand and increase myocardial oxygen supply and response to exercise; these agents include organic nitrates, β-blockers, calcium channel antagonists, and ranolazine.
- In several recent studies, although percutaneous revascularization achieved superior symptom relief, it provided no advantage over medical therapy in the freedom from death or nonfatal myocardial infarction. As a result, there is renewed focus on revascularization based on extent of ischemia severity and not just symptoms.
- The availability of newer first-line agents such as ranolazine should allow an effective trial of optimal medical therapy, which forms the cornerstone of many of the appropriateness criteria for revascularization for coronary disease. Coronary revascularization (by PCI or bypass surgery), is a practical option in patients whose symptoms are not adequately controlled with medical therapy alone, and in those with high-risk characteristics.

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